REAL-WORLD CHARACTERIZATION OF IBRUTINIB THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA IN BRITISH COLUMBIA

by

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Abstract

Background: Ibrutinib therapy has quickly become standard of care in Canada for CLL/SLL patients, due to its proven survival benefits. Real-world studies, however, have unveiled that ibrutinib therapy is also associated with higher rates of discontinuations and toxicities in patients. It is predicted that patients on ibrutinib therapy incur high costs to the healthcare system due to these toxicities. One potential solution includes testing for immunoglobulin heavy chain variable region (IGHV) mutations. IGHV has the potential to inform treatment-decisions, allowing for the appropriate administration of ibrutinib and improved outcomes in patients.

Objectives: The global objective was to complete a comprehensive real-world population-level observational study to characterize ibrutinib treatment in CLL/SLL patients in BC. The specific aims were as follows: i) to assess the rates of adverse events, discontinuations, dose modifications, and survival outcomes ii) to characterize the healthcare utilization and associated costs of ibrutinib therapy, and iii) to assess the impact of IGHV genomic testing, costs, resource use, and challenges of this testing and impact on survival.

Methods: Provincial cancer and administrative databases were used to collate the data required. Each objective was addressed using three unique cohorts. Specific inclusion and exclusion criteria were set, and strict data cleaning procedures were followed.

Results: Ibrutinib therapy led to good survival outcomes in the first-line and relapse/refractory settings; however, a high proportion of patients (35.1%) discontinued their ibrutinib treatment due to toxicities or disease progression. Survival outcomes were not maintained for patients who discontinued treatment regardless of reason. In the first 3 years of its use, ibrutinib cost a mean of $68,266.31 per patient per

year. From time of diagnosis, patients with unmutated IGHV had worse overall survival (OS) compared to patients with mutated IGHV (P<0.001). However, when IGHV testing was used to inform treatment selection, there was no difference in survival, with 24-month OS 88.7% vs 91.3% for patients with unmutated and mutated IGHV status respectively, (P=0.785).

Conclusions: Ibrutinib and IGHV testing have the potential to improve survival outcomes of CLL/SLL patients overall, however the drug cost of ibrutinib is a major burden to the healthcare system.

Lay Summary

Chronic lymphocytic leukemia (CLL) is seen predominantly in older adults and is the most common leukemia in the western world. Ibrutinib has demonstrated improved survival outcomes in a range of CLL patients. Increasingly more patients are being administered ibrutinib in routine practice. Real-world studies, however, have started demonstrating high discontinuation rates due to severe toxicities. Despite the high rates of toxicities, few studies have examined the costs and resource use burden on the healthcare system associated with ibrutinib therapy. A solution includes testing for immunoglobulin heavy chain variable region (IGHV) mutations. Previously, patients with unmutated IGHV status suffered poor survival outcomes compared to patients with mutated status. IGHV testing has the potential to inform treatment-decisions resulting in improved administration of therapy and outcomes in patients. We completed a population-level study assessing the toxicities, healthcare costs and resource utilization and IGHV testing outcomes of CLL/SLL patients on ibrutinib in British Columbia.

Preface

The work for this thesis was conducted at The Gordon and Leslie Diamond Health Care Centre and remotely. This study received approval from the University of British Columbia, the BC Cancer Research Ethics Board (UBC BC Cancer REB; REB #: H19-03272) and the Vancouver Coast Health Certificate of Operational Approval (V19-03272). The following certifications were completed prior to initiation of research: VCH & PHC Confidentiality Undertaking for Researchers and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics (TCPS 2: CORE).

Dr. Alina Gerrie and Rania Khelifi developed the aims of the thesis. Dr. Dean Regier and Dr. Cynthia Toze provided feedback on the aims, study methodology and statistical analysis on the supervisory committee. Steven Huang and Rania Khelifi completed the data collection from the BC CLL Database pertaining to this study. Rania Khelifi conducted all data cleaning and analysis, with statistical consultation assistance by, Dr. Deirdre Weymann and Dr. Samantha Pollard from Imprint Research. Rania Khelifi completed all thesis writing.

Population Data BC disclaimer for the work completed in Objective 2: access to data provided by the Data Steward(s) is subject to approval but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s).

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List of Abbreviations

1L – First-line

2L – Second-line

3L+ – Third line or higher

AE – Adverse event

AF – Atrial fibrillation

BC – British Columbia

BC Cancer REB – BC Cancer Research Ethics Board

BCR – B cell receptor

BR – Bendamustine, rituximab

BTK – Bruton tyrosine kinase

CAD – Canadian dollar

CAIS – BC Cancer Agency Information System

CBC – Complete blood cell count

CEOP-R – Cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab

CHOP-R – Cyclophosphamide, etoposide, vincristine, prednisone, and rituximab

CIT – Chemoimmunotherapy

CLL – Chronic lymphocytic leukemia

CLL DB – BC Provincial CLL Database

CTCAE – Common Terminology Criteria for Adverse Events

CVPR – Cyclophosphamide, vincristine, prednisone, and rituximab

DAD – Discharge abstract database

DAR – Data access request

Del(11q) – Deletion 11q

Del(13q) – Deletion 13q

Del(17p) – Deletion 17p

ED – Emergency department

ER – Emergency room

ERIC – European Research Initiative on CLL

FCR – Fludarabine, cyclophosphamide, and rituximab

FISH – Fluorescence *in situ* hybridization

FR – Fludarabine and rituximab

HCU – Healthcare utilization

ICD10-CA – 10th version of the International Classification of Disease coding system with Canadian Enhancements

ICU – Intensive care unit

IGHV – Immunoglobulin heavy chain variable region

IWCLL – International Workshop on CLL

LSARP – Large-Scale Applied Research Project

LYMASTER – BC Cancer Lymphoid Cancer Database

MMCD – Mean monthly cost difference

MSP – Medical services plan

NACRS – National ambulatory care reporting system

ORR – Overall response rate

OS – Overall survival

pCODR – pan-Canadian Oncology Drug Review

PFS – Progression free survival

PHN – Personal Health Number

PI3K – Phosphatidalyinositol-3-kinase

PLC-$\gamma 2$ – Phospholipase C- $\gamma 2$

PPPM – Per patient per month

PPPY – Per patient per year

R/R – Relapse/refractory

SAP – Statistical analysis plan

SD – Standard deviation

sDAR – Student data access request

SLL – Small lymphocytic lymphoma

SRE – Secure research environment

Study ID – Study identification number

TFS – Treatment-free survival

Tris12 – Trisomy 12

TTNT – Time to next treatment

UHN – University Health Network

USA – United States of America

USD – United States dollar

VGH – Vancouver General Hospital

Y1 – Year 1

Y2 – Year 2

Y3 – Year 3

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To all those who have lost loved ones to leukemia.

Chapter 1: Introduction

1.1 Chronic lymphocytic leukemia and small lymphocytic lymphoma

1.1.1 Incidence

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western hemisphere.[1,2] CLL is observed more commonly in men than women and affects predominantly the older adult population with a median age at diagnosis of 70.[3] In the United States of America (USA), the age adjusted rate of new cases between 2014-2018 per 100,000 men and women per year was 4.9.[3] It was estimated that in 2021, there were over 21,000 new cases of CLL and over 4000 deaths.[3] CLL therefore comprised 1.1% of all new cancer cases in the USA.[3] In Canada, the Canadian Cancer Society reported that 1,745 Canadians were diagnosed and 611 Canadians died from CLL in 2016 and 2017, respectively.[4]

1.1.2 Diagnosis

CLL is defined by the "clonal proliferation and accumulation of mature neoplastic B lymphocytes, usually of CD5-positive nature in the blood, bone marrow, lymph nodes and the spleen".[1,2] CLL is therefore diagnosed when the following is observed: $\geq 5 \times 10^9$ /L B lymphocytes in the peripheral blood, clonality of the B lymphocytes that is confirmed by flow cytometry and distinct morphological features ("small, narrow border of cytoplasm, dense nucleus lacking discernable nucleoli and partially aggregated chromatin") in the CLL cells seen in a blood smear.[5] Small lymphocytic lymphoma (SLL) falls in the same disease category as CLL however diagnostic criteria differ slightly.[5,6] For an SLL diagnosis, lymphadenopathy needs to be confirmed via a lymph node

biopsy or a biopsy of other relevant tissues, cytopenias caused by a clonal marrow infiltrate confirmed as absent and the peripheral blood contains a B lymphocyte count of $<5 \times 10^9$ /L.[5]

1.1.3 Risk classification and treatment administration

Prognosis and course of treatment are determined through clinical staging of the disease using the Rai staging system and genetic testing.[5] The Rai classification places patients on a scale that includes low risk disease (Rai stage 0), intermediate-risk disease (Rai stage I or II) and high-risk disease (Rai stage III or IV).[5] However, additional genomic testing for specific chromosomal aberrations can provide key insight into treatment options that would produce the best outcomes in different patients.[5] Often, genomic testing is done to assess for immunoglobulin heavy chain variable region (IGHV) mutational status, serum β_2-microglobulin, and the status of deletion 17p (del(17p)) and/or TP53 mutations.[5]

In routine setting, patients with asymptomatic and low risk disease (Rai stage 0) are not administered therapy and instead are put on observation until disease progression or symptoms start to appear.[5] However, upon confirmation of active disease, a plethora of treatment options are currently available and are administered based on disease stage, genetic results and comorbidities.[2] Treatment options include chemoimmunotherapies (CIT) (alkylating agents, purine analogs and anti-CD20 monoclonal antibodies), targeted therapies (Bruton tyrosine kinase (BTK) inhibitors, BCL-2 inhibitors) and cellular therapies.[7] Patients with high risk disease (Rai stage III-IV) are administered treatment based on physical fitness (comorbidities).[2] Patients with good fitness are often administered in first line setting (1L) combination CITs such as fludarabine, cyclophosphamide, and rituximab (FCR) (mutated IGHV) or bendamustine plus rituximab (BR) (>65 years), whereas those with poor fitness are typically administered venetoclax plus obinutuzumab, BTK inhibitor monotherapy or chlorambucil plus

obinutuzumab.[2] A separate grouping is created for patients with del(17p) or TP53 mutations, as CIT is not recommended, and instead targeted therapies such as venetoclax plus obinutuzumab, BTK inhibitors or idelalisib plus rituximab are all valid options to pursue.[2] In the case of relapse, patients are offered second line (2L) therapies based on type of first line therapy, fitness and duration of remission, where those who achieved a remission of greater than 36 months may repeat 1L treatment.[2]

1.2 CLL/SLL therapy timeline

As early as 2010, combinations of CIT with an anti-CD20 monoclonal antibody quickly became gold standard as they were shown to be safe and capable of improving survival in treatment naïve patients.[8–11] In the recent past however, patients harbouring certain genetic aberrations have shown poorer progression-free survival (PFS) and survival when administered a range of CITs, like, FCR and other combinations.[12–14] Similarly, older adults often with poor fitness and many comorbidities cannot tolerate a number of full-dose CITs.[15] As a result, it is now widely known that CIT results in a vast majority of patients relapsing, which previously, would have left patients at a standstill with little options for treatment moving forward. This was mitigated through advancements made in CLL pathogenesis including the elucidation of signalling molecules and pathways involved, allowing for the realization of several therapies that target these pathways.[8,16] One such therapy is ibrutinib.

1.3 Ibrutinib

1.3.1 Mechanism of action

Ibrutinib is an orally bioavailable small molecule that targets the BTK by covalently and irreversibly binding to its cysteine residue at the 481 position and inhibiting its downstream effects.[16–18] Normally, BTK's main role involves amplifying the B cell receptor (BCR) signal.[19] CLL B cells, exploit the mechanisms detailed below through constitutive activation in order to ensure their survival

and proliferation.[17,19,20] Through a series of phosphorylation events and the ligation of the BCR, BTK is recruited amongst other proteins essential for signalling.[19] The three main pathways through which signalling is propagated occurs through phospholipase C-γ2 (PLC- γ2), phosphatidalyinositol-3-kinase (PI3K) and BTK signalling.[19] BTK phosphorylates PLC- γ2 allowing for the downstream activation of protein kinase C and the release of calcium through the binding of inositol-1,4,5-triphosphate to receptors on the endoplasmic reticulum.[19,21] With respect to the PI3K pathway, continual activation of BCR is the result of downstream recruitment of BTK among additional kinases.[19] BTK, works to amplify the BCR signal, through undergoing autophosphorylation and the recruitment of phosphatidylinositol-4-phosphate 5-kinases ensuring its continual activation.[19,22] BTK is further capable of activating IκB kinase for NF-κB translocation to the nucleus.[19,23] These pathways feed into and impact one another to promote BCR survival, proliferation and maturation and as such ibrutinib works to inhibit these outcomes through targeting BTK.[19] Furthermore, CLL cells thrive through interacting with their microenvironment.[16,17] Ibrutinib has inhibitory effects resulting in reduced adhesion and migration of CLL cells, as well as the downregulation of chemokines, cytokines and other immune cells in the tumor microenvironment responsible for B cell trafficking and homing.[16,17,24–26] Based on these promising findings and further research in model organisms, clinical trials were later conducted to assess whether ibrutinib was a safe and efficacious candidate for therapy in human patients.[27,28]

1.3.2 Approval in Canada

The RESONATE trial, was a multicentre, phase 3 randomized controlled trial that compared the outcomes of patients with relapsed/refractory (R/R) CLL on either ibrutinib or ofatumumab monotherapy.[27] The study demonstrated that patients on ibrutinib had significantly ameliorated survival (PFS and overall survival (OS)) compared to those on ofatumumab.[27] Based on these findings, Health

Canada first approved ibrutinib in 2014 for select patients. These patients had to meet one of the following criteria: harboured a del(17p) mutation, had at least one prior line of therapy or were previously untreated and harboured a del(17p) mutation. In 2016, Health Canada broadened the eligibility criteria to include CLL patients that had no prior line of therapy. This approval came following the results of the RESONATE-2 trial that randomized older treatment naïve patients to receive either ibrutinib or chlorambucil.[28] When compared to chlorambucil, ibrutinib was shown to confer significantly superior PFS, OS and overall response rate (ORR).[28] Focusing specifically on the province of British Columbia (BC), ibrutinib has been accessible through compassionate access programs since 2014. In 2016, it was then publicly funded for R/R patients or in 1L for patients with del(17p). Since 2018, it has also been accessible in 1L for fludarabine-ineligible patients. Ibrutinib's widespread uptake can therefore be attributed to its generalizability and efficacy.

1.3.3 Survival outcomes

Ibrutinib has demonstrated excellent survival outcomes in both clinical trial and real-world settings. Early phase 1b-2 clinical trials have shown that ibrutinib is safe and capable of improving survival outcomes in a variety of patients including those who are R/R, older and those harbouring poor prognosis genetic aberrations making them ineligible for CIT.[18,29,30] Phase 3 trials further confirmed these survival benefits. The RESONATE trial with initial short-term follow-up (median 9.4 months) showed an OS at 12 months of 90%[27] and excellence was maintained with longer term follow-up (median 65.3 months) with a median OS reached at 67.7 months.[31] Similarly the RESONATE-2 trial presented a similar trend, with initial short-term follow-up (median 18.4 months) and a 24 month OS of 98%[28] that remained high with longer-term follow-up (median 60 months) at 83% after 5 years.[32] Real-world studies also reported a 12–24-month OS rate ranging from 69%-100%[33–38] confirming ibrutinib's

survival benefits in routine practice. Although previous studies demonstrated improved outcomes in patients, real-world studies brought to light several issues associated with ibrutinib therapy.

1.3.4 Adverse events

Adverse events (AE) have emerged as a major problem with ibrutinib therapy. Initially, phase 1b-2 trials determined that ibrutinib therapy was safe with minimal toxic effects.[18,29,30] They reported that most AEs were of low grade (Common Terminology Criteria for Adverse Events (CTCAE) grades 1-2 (CTCAE v5.0, latest file available))[39] severity and were commonly: diarrhea, fatigue, arthralgias and rash.[18,29,30] Later phase 3 trials, similarly, reported common AEs to be diarrhea, fatigue, cough, nausea, even with longer term follow-up.[27,28,32,40] They however also demonstrated a higher frequency of grade ≥ 3 AEs but maintained the position that ibrutinib was safe.[27,28,32,40] On the other hand, real-world studies recently have unveiled the higher rates of more serious AEs such as hypertension, bleeding/hemorrhaging, atrial fibrillation (AF), cytopenias and infections occurring frequently in patients.[33,35,37,41–44] Particularly, AF has emerged as a serious threat in patients administered ibrutinib, occurring at higher frequencies than initially reported in clinical trials.[35] Due to the frequency of severe AEs in patients, many are required to reduce and/or hold their current dose to manage symptoms or discontinue treatment all together.

1.3.5 Dose modification, interruption, and discontinuation

High rates of dose reductions are seen in the real-world.[45] A meta-analysis that reviewed 4458 titles and abstracts determined that the rate of dose reductions ranged between 15.1 to 26.8 events/100 person-years.[45] This is in line with a recent review article that summarized that approximately a third of all CLL patients on ibrutinib therapy are going to require a dose reduction sometime during their treatment.[46] Furthermore, intolerable AEs are consistently emerging as the culprits leading to dose

reductions in patients in the real-world.[41,47,48] Interestingly, treatment interruptions are also starting to emerge as an issue.[37] Rates as high as 55%[37] have been reported in a real-world study (with small sample size) and such interruptions are often prescribed due to intolerable AEs.[37,38,41]

Moreover, it is now well-known that ibrutinib therapy results in a large proportion of patients discontinuing treatment in the real-world. Initially with short-term follow-up (9.4 – 18.4 months) the RESONATE and RESONATE-2 trials reported low discontinuation rates and only with regards to AEs at 4%[27] and 9%[28], respectively. However, with longer term follow-up (44-60 months), the RESONATE and the RESONATE-2 trials reported a much higher rate of treatment discontinuation (39% and 41%, respectively) mirroring those seen in recent real-world studies.[32,40] The same meta-analysis by Cheung et al, reported that the rate of discontinuation in the real-world was as high as 55.2 events/100 person-year, with the most common reason for ibrutinib discontinuation being AEs across the studies included in their analysis.[45]

It is thus evident that AEs are resulting in a large percentage of ibrutinib treated patients reducing, holding, or discontinuing treatment. It can therefore only be expected that ibrutinib treated patients facing complications are incurring large costs and using a large proportion of healthcare resources and services.

1.3.6 Healthcare utilization and costs

Currently, it is unknown whether ibrutinib treatment is costly to the healthcare system in Canada. It is predicted to be so, as Ibrutinib is estimated to cost $110,000 Canadian dollars per patient per year. In BC, there are about 220 patients on ibrutinib per year (data based on 2018 estimates from the BC Provincial CLL Database, cross-referenced with the BC Cancer Pharmacy Database). The cost

of ibrutinib treatment alone for these patients comes out to more than 24 million dollars per year. These values are predicted to only increase with more and more patients each year on ibrutinib because of its uptake in routine practice. Looking towards the literature, the majority of the ibrutinib cost-effectiveness studies were completed using real-world retrospective data from the USA with varying conclusions. On one end, when ibrutinib is compared to CIT, ibrutinib was associated with significantly lower monthly medical costs but higher pharmacy costs resulting in similar or even lower monthly total healthcare costs for ibrutinib versus CIT 1L treated patients.[49–51] On the other end, studies also show the opposite, where ibrutinib treated patients suffered higher healthcare services costs due to AEs[33] (general trend for both treatment types), all-cause and CLL-related inpatient costs[52], all-cause outpatient pharmacy costs[52] and total all-cause costs per patient per month (PPPM)[44] compared to CIT treated patients. In Canada, to date, the only study assessing healthcare system burden is a study published by Lachaine et al, that used a model to estimate future costs comparing CIT to continuous oral targeted therapy.[53] As of now, there are no real-world population-level cost-effectiveness analyses completed in Canada. With the possibility of high costs in Canada, a potential mechanism to make informed treatment decisions, improve patient outcomes and possibly reduce healthcare costs involves genetic testing.

1.3.7 Genetic testing

Fluorescence in situ hybridization (FISH) is capable of differentiating CLL/SLL from other lymphoproliferative diseases such as mantle cell lymphoma.[5] FISH is particularly used for CLL/SLL patients prior to any line of therapy as it helps to establish disease risk, prognosis and treatment options for patients.[5,54] About 80% of CLL/SLL patients harbour one of the following types of genetic aberrations: deletion 13q (del(13q)), deletion 11q (del(11q)), trisomy 12 (tris 12) and del(17p).[54–57] In

BC, testing for these four aberrations is completed at one of five cytogenetic laboratories across the province.

FISH testing across BC has been validated to guarantee standardization of results.[55] Using pooled data from the different laboratories across the province and a 10% universal cut-off implemented, Gerrie et al, determined that CLL genetic aberrations were seen in 74.9%[55]: 54.9% del(13q), 18.8% tris 12, 8.5% del(11q), and 7.7% del(17p), matching the literature.[54,56,57] Del(13q) is associated with a good prognosis, trisomy 12 and normal an intermediate prognosis, and del(11q) and del(17p) a poor prognosis.[5,54] Prognosis was established based on the approximated median survival times from diagnosis (median follow-up of 70 months): del(17p), 32 months; del(11q), 79 months; tris 12, 114 months; normal, 111 months; and del(13q), 133 months.[54]

IGHV mutational status is another important prognostic marker for CLL/SLL patients.[58] Chromosomal recombination of the variable (V), diversity (D) and junctional (J) segments of the heavy and light immunoglobulin chains occurs during B-cell maturation to ensure a strong humoral immune response.[58] A number of other modifications occur, including somatic hypermutations that ensure the production of immunoglobulins with the highest selectivity through careful and specific selection of B-cells.[58] Leukemia cells can choose to use IGHV genes that have sustained mutations or not.[5,59] Using the European Research Initiative on CLL (ERIC) recommendations, unmutated status requires a $\geq$ 98% and a mutated status requires <98% nucleotide identity to germ line, respectively.[60] Currently, subsets with firmly set prognostic implications include subsets 1, 2, 4 and 8.[60] Interestingly, certain subsets such as subset 2 can confer poor prognosis and aggressive disease despite having a mutated IGHV status typically associated with better prognosis.[61] Early studies assessing IGHV status, demonstrated poorer outcomes and worse survival for IGHV unmutated patients.[12,62] In the setting of CIT, it has been show that patients with unmutated IGHV have both worse PFS and OS compared to patients with

mutated IGHV, leaving little options for treatment moving forward.[14] Recently, however, with the emergence of several targeted therapies like ibrutinib, providing treatment options for patients with unmutated IGHV, IGHV mutational status testing has become a prognostic and predictive test. Since November 2019, provincial funding for IGHV mutational status testing for CLL/SLL BC patients has been available thanks to the efforts of the Vancouver General Hospital (VGH) Cytogenetics Laboratory validating IGHV mutational status testing using a next-generation sequencing platform. Because of their efforts, BC was one of the first provinces in Canada to have this test funded for clinical care. Now, all cases in the province of BC are sent to the VGH Cytogenetics Laboratory for this specialized test. Available treatment options for patients with unmutated IGHV status are now abundant with the emergence of second and third generation BTK inhibitors beyond ibrutinib.

1.3.8 Second and third generation BTK inhibitors

Since ibrutinib has been associated with high rates of toxicities and discontinuations, more precise second generation BTK inhibitors have been developed.[63] Second generation BTK inhibitors include acalabrutinib, zanubrutinib, tirabrutinib and orelabrutinib that were developed in hopes of reducing off-target effects thought to cause toxicities in patients on ibrutinib.[63] A recent, phase 3 clinical trial comparing ibrutinib to acalabrutinib reported that acalabrutinib had survival outcomes matching those of ibrutinib, with fewer discontinuations of treatment due to AEs and lower rates of cardiovascular events.[64] Even more recently, third-generation BTK inhibitors such as the non-covalent pirtobrutinib and nemtabrutinib have entered later stages of preclinical trials and early phase clinical trials.[63,65,66]

1.4 Summary

In summary, ibrutinib therapy has become standard of care in routine practice. However, due to the emergence of AEs, high discontinuation and reduction rates and potentially high costs associated with treatment and hospitalizations seen in the real-world, we decided to complete a comprehensive real-world population-level observational study to characterize ibrutinib's effects on CLL/SLL patients in BC.

Chapter 2: Methods

2.1 Global objective and specific aims

Global objective: To comprehensively characterize on a population-level the impact and outcomes of ibrutinib therapy in CLL/SLL patients in BC

Specific aims:

1. To assess the impact of introduction of ibrutinib on CLL/SLL patients on a population-level in terms of toxicities, dose modifications (reductions and holds), discontinuations and survival outcomes

2. To characterize healthcare utilization (HCU) and costs among ibrutinib treated CLL/SLL patients in BC: ibrutinib therapy costs, practitioner costs (general practitioners and specialists), hospital services used and lengths of stay in different units throughout the hospital

3. To estimate IGHV mutational status testing outcomes detected by next-generation sequencing for BC CLL/SLL patients: (i) summarize genomic testing results and survival outcomes by IGHV status, (ii) costs, resource utilization and IGHV testing challenges and (iii) to determine if genomic testing led to informed decision-making and improved patient outcomes

2.2 Data approval and preparation

2.2.1 Student data access request

A student data access request (sDAR) submitted to Population Data BC was required to provide myself, as a student, access to a project from the already submitted and approved multi-year study, 2017 Large-Scale Applied Research Project Competition in Genomics and Precision Health study's (LSARP) data access request (DAR), titled "Deciphering the genome biology of relapsed lymphoid cancers to improve patient management" (BC Cancer REB, REB #: H18-00490). The sDAR detailed the research objectives, benefits to the public, measures to protect confidentiality (particularly with

respect to small cell sizes), the relationship to the main DAR and the methodology employed. Population Data BC approved the sDAR September 2021.

2.2.2 Data access request amendment

The LSARP project is investigating the clinical and economic impacts of four lymphoid cancer subtypes, where CLL and SLL make up one of the four categories. I completed an amendment to the LSARP DAR so that I may complete the following: use the data already extracted for CLL/SLL patients, add additional CLL/SLL patients and fields not already listed in the current DAR and request access to specific administrative databases (Table 1). The amendment detailed the currently approved data request and study population description, as well as a clear description of the updates requested and rationale for the project. I requested access to specific fields in the National Ambulatory Care Reporting System (NACRS) (Table 1), the addition of external data linkages – data fields extracted from the BC Cancer Lymphoid Cancer Database (LYMASTER) (Table 2) and updates to the current cohort with supplementary patients. Population Data BC approved the amendment September 2021.

Table 1. Administrative and cancer databases

Database	Data points
BC Provincial CLL Database	Patient identification (ibrutinib and controls), disease characteristics including Rai stage, CBC at diagnosis, FISH abnormalities, dates last follow-up
BC Cancer Lymphoid Cancer Database	To cross-compare with above, patient identification, disease characteristics, dates of follow-up
BC Cancer Provincial Systemic Therapy Program	Systemic cancer therapy, including dose reductions and interruptions
BC Cancer Registry	ICD-O site, histology, diagnosis date, date of progression
BC Cancer Agency Information System (CAIS)	Chemotherapy dispensing records, radiotherapy treatment records, diagnostic and imaging procedures, and ambulatory care services delivered at BC Cancer centres.

Database	Data points
Canadian Institute of Health Information Discharge Abstract Database (DAD)	Acute care, emergency visits, ICU days, hospitalizations, day surgeries, procedures and interventions, ICD-9 and ICD-10 codes
Medical Services Plan (MSP)	Physician services, diagnostic tests
PharmaNet	Full list of medications at baseline (at initiation of ibrutinib or alternate therapy), and medications prescribed in follow-up after initiation of therapy
Vital Statistics	Date and cause of death using ICD-10 codes
National Ambulatory Care Reporting System (NACRS)	Registration Date/Time, Date/Time Patient Left ED, ED Discharge Diagnosis 1/2/3, ED Visit Indicator, Admit via Ambulance

Table 2. Requested additional fields extracted from the BC Cancer Lymphoid Cancer Database (LYMASTER) for the data access request

Field Name	Description
Primary Dx	CLL or SLL
Date Dx	Date of diagnosis
Status	Status at last follow-up (alive or dead)
LastContact	Date last known to be alive or date of death
CauseofDeath	Cause of death
RAI STAGE_DX	Rai stage at diagnosis (0,1,2,3,4)
RAI STAGE GRP_DX	LOW (0), INT (1-2), HIGH (3-4)
BSYM_DX	B-symptoms at diagnosis – Y, N, N/A
TxPrimary	First treatment administered (even if only received one cycle)
DateStrtTx	Date started primary treatment
BMTYN	Y/N - received stem cell transplant
DateBMT	date of first stem cell transplant
TypeBMT	Type of stem cell transplant: ALLO= allogenic or AUTO=autologous
CLLRICH	Richter's transformation 1=yes 0=no
DateTrans	Date of Richter's transformation
OTHERDX	Other diagnoses – text field for other malignancies and autoimmune diseases
HB_DX	Hemoglobin at diagnosis
WBC_DX	White blood cell count at diagnosis
LYMPHS_DX	Lymphocyte count at diagnosis
PLTS_DX	Platelets at diagnosis
LDH_DX	LDH at diagnosis, units
LDHratio	LDH result/upper limit of normal
LDH ABN DX (ratio>1) (Y/N)	LDH ratio > 1, Y/N
B2M_DX	Beta 2 microglobulin at diagnosis, units

Field Name	Description
IGHVmutationstatus	0=Mutated, 1=unmutated or unknown/not documented
IGHVmutationdate	Date of IGHV mutation test
Tx preibr	Previous treatments prior to ibrutinib
Tx_modification Y/N	Y/N if treatment dose modified
Ibrut dose mods	Dose modifications of ibrutinib - No change in dose, at least one dose reduction; at least one dose escalation; at least one reduction and escalation
Ibrut dose mod_reasons	Reasons for dose modifications - comorbidities; toxicity; incorrect starting dose; concurrent med use; other; unknown/not documented
Ibrut hold	If ibrutinib was held during course of treatment – Y=Yes
Ibrutinib held	Reason for hold – free text
Reason for hold	Reasons for treatment hold: multiple toxicities, toxicity, other reasons
Ibrutinib discontinued	Reason for ibrutinib discontinuation – free text
zibrdcrecalc	Discontinued ibrutinib – Y/N
Ibrut Reason for dc_code	Coded reason for discontinuation: blank – ongoing; 1 - toxicity; 2 – progression; 3 - other
Concomitant meds ibr	concomitant medications with ibrutinib
Comorb_ibrstart	Comorbidities prior to ibrutinib start date/ at ibrutinib initiation
Ibrutinib Toxicity	Toxicities that occur during ibrutinib treatment
WBCcountatIbrutinib	WBC count prior to, at or after ibrutinib initiation
LymphcountatIbrutinib	Lymphocyte count prior to, at or after ibruitnib initiation
HgbatIbrutinib	Hemoglobin count prior to, at or after ibrutinib initiation
PltatIbrutinib	Platelet count prior to, at or after ibrutinib initiation
CBCdateIbrutinib	Date of CBC prior to, at or after ibrutinib initiation
LDHatIbrutinib	LDH count prior to, at or after Ibrutinib initiation
LDHdateIbrutinib	Date of LDH at ibrutinib
creatinineatibrutinib	Creatinine count prior to, at or after Ibrutinib initiation
CreatininedateIbrutinib	Date of creatinine at ibrutinib
RaistageatIbrutinibtx	Rai stage prior to, at or after ibrutinib initiation

Field Name	Description
FISHdateatIbrutinib	Date of FISH test closest to ibrutinib start date
del17pYNatIbr	deletion 17p status at ibrutinib initiation (Y/N)
del11qYNatIbr	deletion 11q status at ibrutinib initiation (Y/N)
tris12YNatIbr	trisomy 12 status at ibrutinib initiation (Y/N)
del13qYNatIbr	deletion 13q status at ibrutinib initiation (Y/N)
OtherTx	List of treatments administered
TxpostibrY	Treatment after ibrutinib treatment (Y=yes)
Tx_No	Line of treatment
Tx_Name	Name of therapy
No_Cycles	Number of cycles
Tx_dose	Dose of treatment (text description)
Tx_StartDate	Treatment start date
Tx_EndDate	Treatment end date
Notes	Free text notes regarding treatment
FISHTESTTYPE	Type of FISH test: SINGLE - one or two probes; PRETX (if first FISH test was prior to any treatment); POSTTX (if first FISH test was after treatment); FU - follow-up test (FU1, FU2, FU3...); NR - no result; UNK - unknown; CHIMER - FISH for XY chimerism; CG - cytogenetic banding
@1STFISHPANELYN	Y- if patient's first FISH panel (not single probes), may or may not have IGH
CollectionDate	Date of FISH test
TP53	% of abnormal cells with TP53
DEL17PYN	Deletion 17P Y/N
ATM	% of abnormal cells with ATM
DEL11QYN	Deletion 11Q Y/N
@12 CENYN	12 CEN Y/N
DEL13QYN	Deletion 13Q Y/N
FISHHIER	FISH classification based on hierarchy
CONSFISHClassification	Same as FISH classification but using conservative 11% cut-off
STUDY	Field to selectively identify cohort
IBRSTUDY	Field to selectively identify cohort

2.2.3 Administrative and cancer data

We accessed data from several databases to complete the objectives of this project. Below are descriptions of the databases and the relevant data/outcomes extracted from each.

2.2.3.1 Cancer databases

The BC Provincial CLL Database (CLL DB) is a comprehensive and extensive database that contains clinical and laboratory data on greater than 5000 CLL/SLL patients in BC. It has previously been used successfully to complete population-level analyses, assessing treatment patterns, outcomes, and genetic abnormalities in CLL/SLL patients.[55,67,68] This database was used to identify relevant patients for all objectives and to collect information on disease characteristics. The LYMASTER, is an extensive database on patients with lymphoid cancers. The initial purpose of this database was to cross-reference information with the CLL DB, however due to delays in obtaining data, described further in section 2.2.5, the LYMASTER dataset was used to define and characterize the ibrutinib cohort for objective 2 (described further in section 2.4.2). The BC Cancer Agency Information System/ BC Cancer charts (CAIS) contains records pertaining to chemotherapy dispensing, radiotherapy treatment, diagnostic and imaging procedures at BC Cancer centres. CAIS was used primarily for patient chart review and to update the CLL DB as required. Pharmacy data contains prescription records dispensed by BC Cancer pharmacies.[69] "All approved systemic therapy that is administered in regional cancer centers, community hospitals as well as administered at home across BC are dispensed by BC Cancer pharmacies".[69] This dataset was used to obtain all records of ibrutinib administration and its associated costs for the ibrutinib cohort of Objective 2.

2.2.3.2 Administrative databases

We requested the following administrative databases from Population Data BC to complete objective 2 of this project. Descriptions of contents of each dataset was obtained from the Population Data BC website.[70] The Canadian Institute of Health Information Discharge Abstract Database (DAD) dataset contains administrative and clinical data for hospital discharges (inpatient acute, chronic, rehabilitation) and day surgeries of in-patients and day surgery patients from acute care hospitals in BC.[71] This data was used to determine hospital services and lengths of in-patient stays within different hospital units for the ibrutinib cohort. The Medical Services Plan (MSP) dataset contains information on medically necessary services provided by fee-for-service practitioners to patients covered by MSP.[72] MSP is the universal insurance program of BC. We obtained costs of services incurred by ibrutinib patients for general practitioner and specialist services. The PharmatNet dataset contains all prescriptions for drugs and medical supplies dispensed from community pharmacies in BC as well as prescriptions dispensed from hospital outpatient pharmacies for patients to use at home.[73] We obtained this data but did not use it for any analysis included in this thesis. The NACRS dataset contains information on all levels of ambulatory care within Canada including emergency departments (ED), day surgery, and medical and surgical day clinics within hospitals, the community, and private clinics.[74] We used this data to obtain all visits to the ED (including those leading to inpatient admissions), as well as the use of ambulance services. The Central Demographics File (Consolidation File) was also requested and contains basic demographic information.[75] Lastly, the Vital Events and Statistics Deaths dataset contains all deaths registered in BC.[76] This data was used to determine which patients died during our study period (January 1, 2014 – December 31, 2018), as well as dates and causes of death using the 10th version of the International Classification of Disease Coding System with Canadian Enhancements (ICD10-CA).

2.2.4 Data file preparation and linking

A query in the CLL DB was created to gather all the additional patients and fields (Table 2) detailed in the amendment. The query was exported as an excel file, cleaned, and uploaded to LYMASTER prior to submission to Population Data BC for linking. Cleaning of the dataset involved transposing/re-structuring the file from long to wide format using SPSS statistical software package to get only one line per unique patient. This was required as the therapy and FISH specific fields for each new entry in the CLL DB were coded as separate lines for each patient (long format). Additionally, we ensured removal of patients who met the following exclusion criteria: those without a CLL or SLL primary diagnosis, those who had not received any CLL/SLL directed therapy and those without a valid Personal Health Number (PHN). Once cleaned, Population Data BC was responsible for de-identifying the data and then linking patient-level records with administrative health care databases obtained from Population Data BC (Table 1) using PHN's. Once completely anonymized and assigned a unique identification number, data was accessible through PopData's Secure Research Environment (SRE). The SRE is highly secure as it contains numerous steps for login, ensuring confidentiality and privacy.

2.2.5 Population Data BC data preparation

We received access to some of the data requested from Population Data BC in March 2022. Namely, we received data for our additional patient cohort from the following sources (as seen in Table 1): Consolidation files, DAD, MSP, PharmaNet, Vital Events and Statistics Deaths, and NACRS. We did not receive access to our BC Cancer data fields (CLL DB) requested in time for analysis. The data received was provided in a zipped and condensed format, separated by year e.g., MSP 2014 and by cohort (original vs. amended patients) except in the case of the NACRS data. Several steps were completed to access the data. Firstly, 7-Zip File Manager software was used to unzip every data file provided and files were converted to text format. Each text file was then read into the Stata software

packaging in fixed format for ease of use and interpretation. Stata was then used to append different years of data together and to bring the two cohorts together to form our entire cohort (note: not yet filtering out non CLL/SLL patients). This was done so that our administrative data contained the entire cohort assembled and ready for when the BC Cancer data (from CLL DB) was received. After appending all the administrative data files based on type, they were then merged, i.e., joined onto the original cohort data file obtained from LYMASTER containing study identification number (Study ID) and diagnosis. This was done as we had not received our BC Cancer data (from CLL DB) in time. The BC Cancer data contained additional patients identified and fields required for the larger analysis. As this was not received in time, we opted to move forward with identifying an ibrutinib cohort using the original DAR's data, patients, and disease characteristics available from the LYMASTER data file. We created a clinical characteristic master data file and four (explained in section 2.4.2 below) costing and HCU master data files for analysis.

2.3 Patient eligibility and criteria

2.3.1 Objective 1: Impact of ibrutinib therapy in BC

Patients were identified from the CLL DB, with supplemental information obtained from hospital records. Patients were included in this cohort if they were diagnosed with either CLL or SLL, they were ≥ 18 years of age at the time of diagnosis and they had started monotherapy ibrutinib in clinical practice in BC between November 19, 2014 – June 30, 2018, with follow-up through to December 31, 2018. Patients were excluded from this analysis if it was observed in their records that they had participated in a clinical trial during the study period, had a malignancy prior to CLL excluding non-melanomatous skin cancer, had a missing value for the date of CLL diagnosis or ibrutinib initiation and if they did not reside in BC.

2.3.2 Objective 2: Healthcare utilization and costs of ibrutinib treated patients in BC

Patients were identified using LYMASTER. They were included if they met the inclusion criteria for this objective. They had to be ≥ 18 years of age, diagnosed with CLL/SLL and initiated ibrutinib therapy between January 1, 2014 - December 31, 2018. As per the LSARP inclusion criteria, patients had to also have been diagnosed with CLL or SLL between January 1, 2000 – December 31, 2016. Patients were excluded if they lacked a valid PHN, were not diagnosed, or treated in BC, were missing a value for the date of CLL diagnosis and were missing a value for ibrutinib therapy initiation. Follow-up was until December 31, 2018.

2.3.3 Objective 3: IGHV and FISH testing in CLL/SLL patients in BC

Patients were identified using the CLL DB and data from the VGH Cytogenetics Laboratory with supplemental information obtained from hospital records. The study population included patients with a documented IGHV test completed from June 6, 2019 – May 18, 2021. A total of 63 IGHV tests were completed between June 2019 and October 2019, prior to BC provincial funding in November 2019 for IGHV testing. These samples were completed for a pilot study of well-characterized CLL/SLL patients and were included in this analysis. Patients were included if they had a valid PHN, had their IGHV test completed through the VGH Cytogenetics Laboratory, and had a CLL/SLL diagnosis. FISH was included if it was taken 1-year prior to or after the IGHV test date. Treatment was included if it was administered within one year after IGHV test date. Follow-up was until February 22, 2022.

2.4 Data cleaning

2.4.1 Objective 1: Impact of ibrutinib therapy in BC

Patients were identified using the CLL DB and the LYMASTER Database. They were also cross-referenced with the BC Cancer Pharmacy Database. The BC Cancer Pharmacy database was used to collect patient-level information on dates of ibrutinib and dose modifications. Supplementary information was obtained from hospital records when required. A thorough review of the data on ibrutinib treated patients was completed for this objective. Updates were made to the CLL DB based on chart review and numerous additional variables were created to categorize dose modification, discontinuation, and survival outcomes of patients. This also ensured the accuracy and validity of data for the patients submitted in the amendment to Population Data BC. Notable variables that were created included: line of therapy categorized as 1L, 2L and third line or higher (3L+), reasons for discontinuation (including and excluding death), discontinuation status (yes or no), categorization of any toxicities experienced during ibrutinib treatment, last treatment prior to ibrutinib and its associated start date, causes of death during ibrutinib therapy, next treatment after ibrutinib where available, FISH at time of ibrutinib, OS from time of ibrutinib initiation, OS from discontinuation of ibrutinib (including and excluding death), treatment-free survival (TFS) and TFS status. Definitions are found in section 3.2.1.

2.4.2 Objective 2: Healthcare utilization and costs of ibrutinib treated patients in BC

2.4.2.1 Clinical characteristics master file

A copy of the LYMASTER data file was created and sorted to remove all patients not diagnosed with CLL/SLL and to create a field labelling CLL/SLL drug vs. non CLL/SLL drug. To clean the LYMASTER data file, a few patients were dropped for the following reasons: a diagnosis of both CLL and diffuse large B cell lymphoma, death the following day after receiving ibrutinib

treatment since they would not have had enough time on ibrutinib to determine our outcomes of interest and lacking costing and HCU data in other administrative databases. Furthermore, ten patients repeated in the data file as they had received ibrutinib through more than one route. Some initially received ibrutinib as part of the Special Access Program, meaning that they were able to receive ibrutinib prior to its approval or funding through Health Canada and then received it through BC Cancer once funded. Others received ibrutinib through a clinical trial and later through BC Cancer. We opted to include only the earliest date of ibrutinib receipt regardless of means of receipt.

The edited LYMASTER data file was then merged with the other data required to compute clinical characteristics. Each relevant fully appended data file, namely, Demographics (consolidation files) and Deaths (vital statistics deaths), were merged on Study ID and diagnosis only obtained from the LYMASTER edited data file. Only Study ID's that matched or were originally from the edited LYMASTER data file were kept in each data file. The pharmacy, Demographics and Deaths data files were then all merged onto the edited LYMASTER file to create a clinical characteristics master data file ready for cleaning and analysis.

Date variables were converted from string format or other formats to a date format understood by Stata. Date variables converted included: date of follow-up, date of birth, date of diagnosis, prescription date and year of death, month of death, day of death, that were then combined to create a full death date. After re-formatting the date fields, all lines of non CLL/SLL drugs were dropped from the file, keeping only CLL/SLL relevant drugs in the master file. Patients were then sorted by Study ID, drug name and prescription date to generate a count field labelling each record of treatment that reset to one each time a new drug type or patient was encountered. All records that were not recorded as one were dropped, allowing us to identify the first ever prescription date for each drug a patient was prescribed. Again, through sorting by Study ID and prescription date, we were able to generate a count

field numbering each unique treatment a patient received in order of prescription date. This was necessary to determine in which line of therapy the cohort received their ibrutinib (1L vs. R/R). This was also cross-referenced with the equivalent field originally found in the LYMASTER data file. Having labelled all the treatments received by the patients, we needed to check to ensure that our inclusion criteria were met. All prescription dates prior to January 1, 2014, were dropped from the master file. As the data provided was only up to December 31, 2018, we did not have to specify dropping prescription dates after December 31, 2018. We therefore captured only prescription dates between January 1, 2014 – December 31, 2018, as defined by our inclusion criteria. The last step involved identifying the ibrutinib cohort. To identify all the patients who had received ibrutinib for their CLL/SLL, we generated a flag field in Stata, flagging all ibrutinib prescription records and dropping all patients and lines of patients without ibrutinib. With the creation of new variables for categorization and the completion of data checks for missing information, the data file was now ready for analysis.

2.4.2.2 Healthcare utilization and costing master files

A total of four separate master sheets were created using: Pharmacy, MSP, DAD and NACRS data sheets that were merged on select fields from the fully cleaned and prepared clinical characteristics master data file described in section 2.4.2.1. Methods and cleaning completed for each sheet will be described in detail below.

The pharmacy dataset was merged on a Stata data file that contained the following variables from the fully cleaned clinical characteristics master data file: Study ID, date of last follow-up, date of death, date of birth, date of diagnosis, line of therapy and status fields. This was done to create a pharmacy master sheet with only the ibrutinib patient cohort. This data file was then ready for cleaning.

Several variables found in the pharmacy data that were not required for this analysis were dropped. Similarly, as described above, dates were re-formatted into the date format understood by Stata. The cost field was also converted from string to numeric format for ease of calculation. In this data file, we now had all drug prescriptions again, and so we needed to number and count each prescription line per treatment. We did this employing similar methodology as described in the clinical characteristics' methods described above in section 2.4.2.1. In summary, we sorted the data file by Study ID, name of drug and prescription date fields and then generated a count that re-started at one every time a new Study ID or drug name was encountered. We were then able to flag all the ibrutinib prescriptions and drop the rest. We now had all the ibrutinib prescriptions in order of date prescribed for each patient. Since this also includes prescriptions prior to our January 1, 2014, initiation criteria we did the following to keep only prescriptions on or after January 1, 2014, per patient. We merged in the prescription date field from the clinical characteristics master data file and renamed it index therapy start date. Since our clinical characteristics master data file only contains the earliest ibrutinib prescription date and this was refined to remove any prescription dates prior to January 1, 2014, we used this date to define start of ibrutinib therapy. Using the index therapy start date field and the prescription field from the pharmacy data, we were able to define a difference from index field. Anything less than 0 in the difference from index field was dropped, indicating a prescription start date before January 1, 2014. We generated additional variables such as prescription year and others required for costing calculations and defined our 6-month cohort described further in statistical analysis section 3.2.2. Checks were completed throughout cleaning and analysis to ensure all patients were accounted for.

The MSP data file was merged on a Stata data file that contained the same fields as described in the section on the pharmacy master data file with the added field of ibrutinib start date. All patients that were solely found in the MSP master were dropped, to capture only the ibrutinib cohort. The data file

was then ready for cleaning. Several variables that were not necessary for the analysis were dropped. Dates were re-formatted into the date format understood by Stata. To capture only MSP claims during our study period criteria (January 1, 2014 – December 31, 2018), a field taking the difference between service date and ibrutinib start date was created. Any difference less than 0, indicating a service date prior to their ibrutinib start date was dropped from the file. Importantly, we used the specialty field available in the MSP data file that contains a code for each speciality to define a new field categorizing type of practitioner. We categorized general practitioners as 1 and all other specialties as 0, allowing us to determine costs associated with each. We also generated additional variables such as service year and others needed for costing calculations and defining our 6-month cohort described further in statistical analysis section 3.2.2. Checks were completed throughout cleaning and analysis to ensure all patients were accounted for.

Four separate hospital files that contained all patients identified in the DAR and amendment to the DAR were appended together using Stata to create one large master hospital file. This master data file was then merged on a Stata data file that contained the same fields as described in the section on the pharmacy master data file with the added field of ibrutinib start date. All patients that were solely found in the hospital master were dropped, to capture only the ibrutinib cohort. The data file was now ready for cleaning. Several variables that were not necessary or were found empty for our cohort were dropped. As previously described dates were converted into a date format understood by Stata. Patients who were admitted to hospital prior to January 1, 2014, were filtered out by generating a field that took the difference between admission date and ibrutinib start date. Any negative value was dropped, indicating an admission date prior their ibrutinib start date, except in the case of patients who did not have any admissions. For the patients with no admissions, we manually had to remove data from the hospital data fields. This was done to ensure that patients who were not admitted were still captured when data was collapsed to calculate per patient per year (PPPY) results, by changing admit year from

missing to 0. We generated additional variables such as admit year and others needed for counts and defining our 6-month cohort described further in statistical analysis section 3.2.2. Checks were completed throughout cleaning and analysis to ensure all patients were accounted for.

The NACRS data file was merged on a Stata data file that contained the same fields as described in the section on the pharmacy master data file with the added field of ibrutinib start date. All patients that were solely found in the NACRS master data file were dropped, to capture only the ibrutinib cohort. The data file was then ready for cleaning. Several variables that were not necessary for the analysis were dropped. Dates were re-formatted into the date format understood by Stata. To capture only emergency visits that occurred during our study period (January 1, 2014 – December 31, 2018), a difference between ED registration and the ibrutinib start date field was created. The ED registration field captured all ED visits including those that did not lead to an inpatient stay. Those with a negative difference were dropped, as that would indicate an ED visit prior to their ibrutinib start date, except in two cases. Firstly, patients with no different computed represented cases where patients did not visit the ED. Secondly, patients with a negative difference computed. Dropping these patients would result in the complete loss of the patient from the data file. A variable to flag these patients to keep them in the data file was created and patient data for these exceptions were deleted manually to ensure no loss of patients that comprised the cohort. For calculations, those without ED visits had their registration year changed to 0 to capture them when data was collapsed to calculate PPPY results. We generated additional variables such as registration year and others needed for counts and defining our 6-month cohort described further in statistical analysis section 3.2.2. Checks were completed throughout cleaning and analysis to ensure all patients were accounted for.

2.4.3 Objective 3: IGHV and FISH testing in CLL/SLL patients in BC

A thorough review of IGHV mutational testing patterns and results were computed using data obtained from the VGH Cytogenetics Laboratory, and hospital records compiled and extracted from the CLL DB. Importantly, charts were reviewed thoroughly to determine the reason for IGHV testing, which was categorized as either for baseline/prognostication or for treatment planning purposes. Several additional variables were created to categorize testing purpose, testing results and outcomes. Notable variables included homology categorization, stereotype prognosis, year of implementation, OS, treatment received, testing reason, and whether testing influenced treatment decision and what test (IGHV, FISH or both) influenced the treatment decision. Definitions are found in section 3.2.3.

2.4.3.1 IGHV testing methodology

Mutational testing involves the following steps to be completed as per the protocol used at the VGH Cytogenetics Laboratory (Helene Bruyere, email communication, March 2022). Polymerase chain reaction amplifies the IGHV-IGHD-IGHJ gene rearrangements using the LymphoTrack ® IGHV Leader Somatic Hypermutation Assay (Invivoscribe, San Diego, CA, USA). Massively parallel sequencing is then completed using a MiSeq ® platform (illumine, San Diego, CA, USA), followed by immunoinformatics that requires the use of LymphoTrack IGHV Somatic Hypermutation Data analysis (Invivoscribe, San Diego, CA, USA) and the IMGT/VQUEST[77] application. Results reported include the closest matching germline IGHV gene and allele, as well as the associated percent identity. The germline identity cut-off is 98% for categorization.[60] CLL cases are therefore separated into two main categories: immunoglobulin with somatic hypermutation (mutated) or immunoglobulin without somatic hypermutation (unmutated).[60] A total of 19 major stereotype subsets are assigned using the ARResT/AssignSubsets application.[78] A prognosis is determined using the ERIC guidelines.[60] In cases,

where status remains undetermined, samples are sent to the University Health Network (UHN) Genetic Diagnostics Laboratory for reflex testing with the Invivoscribe Lymphotrack IGH FR1 assay.

2.5 Complete analysis limitations

Due to delays in receiving the required data for this analysis, we had to modify our objectives and overall analysis plans. We faced delays in receiving our data due to the difficulties and impact of COVID-19 on Population Data BC's ability to provide timely access to data. Due to these complications, we had to modify our Population Data BC cohort (as described in section 2.2.5) and eliminate one of our objectives. The eliminated objective was to compare AEs, HCU and costs among CLL/SLL patients receiving ibrutinib to a matched control group of CLL/SLL patients receiving alternate therapy.

Therefore, this master's thesis focuses on comprehensively characterizing and describing the impact of ibrutinib therapy on the outcomes of CLL/SLL patients in BC and the burden of ibrutinib use on the Canadian healthcare system.

Chapter 3: Statistical Analysis

3.1 Statistical analysis plan

Prior to any data analysis, statistical analysis plans (SAP) were composed for objectives 2 and 3. The SAP detailed the study methods, timelines, project population and statistical principles and analysis proposed to accomplish our aims. The SAP for objective 2 was reviewed by Dr. Alina Gerrie (supervisor), Dr. Dean Regier and Dr. Cynthia Toze (supervisory committee) and a statistical consultation team, Dr. Samantha Pollard, and Dr. Deirdre Weymann from Imprint Research. The SAP for objective 3 was reviewed by Dr. Alina Gerrie. Based on their feedback and comments, the SAPs was continually updated throughout the analysis portion of this project and used as a guide for all portions of the analysis. Section 3.2 details the statistical analyses used to accomplish each objective.

3.2 Statistical analysis by objective

3.2.1 Objective 1: Impact of ibrutinib therapy in BC

The aim was to assess discontinuation rates, reasons for discontinuations, dose modifications and the impact on population-level survival outcomes of CLL/SLL patients on ibrutinib monotherapy using BC Cancer databases available.

Patients were divided into three categories based on line of treatment with ibrutinib: 1L, 2L and 3L+. Descriptive statistics (count, median, and range) were used to describe cohort characteristics, toxicities, dose modifications, holds, and discontinuations. Reasons for discontinuation were categorized as due to toxicity, progression or other. Given the challenges of assigning death to ibrutinib toxicity in a non-clinical trial setting, a separate toxicity analysis was conducted with deaths on ibrutinib excluded. TFS was defined as date of ibrutinib initiation to start of next line of therapy, last follow-up or death, and OS was calculated from date of ibrutinib initiation to date of last follow-up or

death. In the case of OS and TFS from time of discontinuation of ibrutinib, this was calculated from date of ibrutinib discontinuation. Comparing lines of therapy, categorical variables were compared using a Chi-squared test or a Fisher's exact test when Chi-squared parametric assumptions were not met. Numeric continuous variables were compared using the Kruskal-Wallis test. Survival parameters were depicted graphically using Kaplan-Meier survival plots and compared using the log-rank test.

3.2.2 Objective 2: Healthcare utilization and costs of ibrutinib treated patients in BC

The aim was to determine HCU, and costs involved with ibrutinib therapy in BC. Clinical characteristics describing the ibrutinib cohort of this objective were computed using descriptive statistics (count, median and range). OS was calculated from date of ibrutinib initiation to date of last follow-up or death and survival parameters were depicted graphically using Kaplan-Meier survival plots and compared using the log-rank test.

For costing and HCU, results were reported based on two separate treatment periods: (i) time from treatment initiation until 6 months post-initiation, death, or last follow-up and (ii) time from treatment initiation until death, or last follow-up. For the 6-month period, only complete cases were included. A sensitivity analysis was completed to verify how estimated costs and HCU varied based on adjusting for censoring (complete versus incomplete cases). We chose to include only complete cases as we would be certain all patients in this group would have received ibrutinib for at least 6 months allowing us to report on a total of 6-months of costs and HCU. We chose to complete a 6-month analysis as our next step includes comparing HCU and costs of ibrutinib treated patients to a matched control group of patients on CIT. CIT is only administered for a 6-month period while ibrutinib is considered indefinite therapy. The 6-month analysis will allow us to complete a direct comparison of costs and HCU while both groups are on therapy.

We were interested in determining ibrutinib costs and practitioner service costs covered by MSP. Costing data was corrected for inflation using the Canada's consumer price index from Statistics Canada.[79] Costing was reported for the entire ibrutinib cohort and by line of therapy (1L vs. R/R). Specific to ibrutinib therapy costs, the year 2014 was omitted from the analysis as patients were receiving ibrutinib through the Special Access Program or a clinical trial and so no costs were recorded in the pharmacy records. Having included these patients would have skewed the mean, as it is highly sensitive to outliers resulting in values that do not accurately represent the mean ibrutinib therapy cost. Practitioner service costs were also further stratified by practitioner type (general practitioner vs. specialist). Descriptive statistics were computed (count, mean, standard deviation, median and interquartile range) and results were presented in three ways: (i) PPPY (ii) total costs to the healthcare system and (iii) total per patient costs to the healthcare system.

Furthermore, we were interested in categorizing and quantifying HCU, particularly hospital services used by our ibrutinib cohort (Table 3). Important definitions on how certain statistics were calculated are as follows (obtained from the DAD data dictionary)[71]: total length of stay per admission was determined by taking the difference of discharge date and admission date; alternative care days refers to time spent in an acute bed by patients who had finished the acute care phase of treatment but were waiting for a placement in an extended care unit, nursing home, home care program, or other; acute/rehabilitation care days were obtained from the BC Ministry of Health and included days spent in the acute and rehabilitation level of a hospital; rehabilitation days indicated the number of days spent in the rehabilitation care unit in an Acute Care Hospital. The intensive care unit (ICU) calculation comprised any time that was spent in all special care units during a hospital stay. Emergency room (ER) visits only including those that led to inpatient admissions was calculated using data from the

DAD, however all ER visits (including those not leading to admissions) was calculated using data from the NACRS.

Table 3. Healthcare resource utilization outcomes of interest

Outcome measure
Number of hospitalized patients
Number of patients using ambulance services
Number of inpatient admissions
Number of emergency room visits (only those leading to inpatient admission)
Number of emergency room visits (including those not leading to inpatient admission)
Number of other services • Procedures/interventions • Surgeries • Ambulance use
Number of days of inpatient stays (length of stay)
Number of days in alternative care
Number of days in acute/rehabilitation care
Number of days in intensive care unit (ICU)
Number of days in rehabilitation care

HCU was reported for the entire ibrutinib cohort and by line of therapy. Descriptive statistics (count, mean, range, standard deviation (SD)) were calculated. Results were reported in two ways: (i) total HCU and (ii) PPPY for length of stays and number of events.

3.2.3 Objective 3: IGHV and FISH testing in CLL/SLL patients in BC

This objective focused on whether IGHV testing led to informed decision-making, specifically personalized treatment decisions based on genetic/genomic risk profile, HCU, costs, testing challenges, and improved survival outcomes.

IGHV test results were compared between patients based on the year of implementation (IGHV test collection date): Y1 (June 2019 – May 2020) and Y2 (June 2020 – May 2021). Descriptive statistics (count, median, range) were used to describe cohort characteristics, testing characteristics and treatments received. Categorical variables were compared using a Chi-squared test or a Fisher's exact test when Chi-squared parametric assumptions were not met. Numeric continuous variables were compared using the Kruskal-Wallis test. Treatment planning was defined as testing that directly influenced treatment decision as stated in patient charts and that resulted in the initiation of treatment within one year of the test. Baseline/prognostication involved any other case where treatment was not initiated within one year of test, completed as stated for prognostication or at baseline, or requested but no further comments in charts about use or result. Given the importance of FISH testing for CLL/SLL prognosis and treatment planning, both FISH and IGHV test results were evaluated together to determine how they influenced treatment decisions. For any treatment that was initiated within 1 year of the IGHV test result, the tests that influenced treatment decisions were documented as either IGHV, FISH or both. OS was analyzed both from the date of diagnosis and from the date of treatment initiation until date of last follow-up or death. Survival outcomes were compared based on IGHV mutational status using the log-rank test and graphically summarized using Kaplan-Meier survival plots. Cost was estimated by the MSP fee code for IGHV mutational status. Feedback from the director of the VGH Cytogenetics Laboratory was elicited to determine resource utilization and overall challenges with the testing during the first 2 years of implementation.

3.3 Other considerations

3.3.1 Confidence intervals and p-values

Standard and generally acceptable p-values and confidence intervals were used. Two-tailed significance was used with a p-value of less than 0.05 implying significance ($\propto = 0.05$). Where applicable, 95% confidence interval were reported.

3.3.2 Data cleaning and analysis software

We used two software packages for data analysis. Objectives 1 and 3 were completed using IBM SPSS Statistics version 27, while analysis for Objective 2 was completed using Stata version SE16.1 statistics/data analysis. Stata was selected for Objective 2 for its easy-to-use user interface and numerous packages allowing for the data cleaning steps required, such as appending and merging data.

3.3.3 Missing data

Where data was missing, patients with missing data were either excluded from that given analysis or reported as missing. In the case of HCU or costing, missing data was replaced with 0 for the year variable indicating that no service or cost was incurred by that patient when data was collapsed for analysis. Changes in the sample size were reported at each instance when one or more patients were removed from the analysis.

Chapter 4: Results

4.1 Impact of ibrutinib therapy in BC

4.1.1 Cohort characteristics

A total of 370 CLL/SLL patients were identified using the CLL DB who obtained ibrutinib in first line (1L, n= 35) or in a R/R (2L, n= 182; 3L+, n= 153) setting. The median time from diagnosis was 7.3 years (range, 0.0 – 30.0 years). Baseline characteristics are shown in Table 4. The median time from diagnosis to ibrutinib initiation was 4.5 years (range, 0.0 – 18.3), 5.4 years (range, 0.2 – 24.4) and 9.7 years (range, 0.7 – 30.0) for 1L, 2L and 3L+, respectively. Patients were predominantly male (68.4%), with a median age at diagnosis of 62.5 years (range, 33-89 years), and the majority (80.8%, 299/370) had low-intermediate Rai stage at time of diagnosis. Baseline FISH prior to any form of therapy (n=213) were: 16.9% del(17p), 21.1% del(11q), 22.5% tris 12, 49.3% del(13q) and 19.7% had none of the four above abnormalities. The median follow-up from CLL/SLL diagnosis for living patients (n=311) was 10.0 years (range, 0.8 – 27.5 years).

At ibrutinib initiation, the median age was 71 years (range, 41 – 94 years) and majority of the patients, 58.1% (215/370), had low-intermediate Rai stage. A median of 2 prior lines of therapy (range, 2-13), and a median time of 2.0 years (range, 0.1 – 15.8 years) from last treatment to ibrutinib with no significant differences when stratified by 2L and 3L+ lines of therapy *(P*=0.309) was observed in R/R (n=335) patients. Prevalence of FISH abnormalities at time of ibrutinib initiation, (n=189) were: 23.9% del(17p), 27.3% del(11q), 21.8% tris 12, 51.3% del(13q) and 15.4% had none of the four above abnormalities.

Table 4. Clinical characteristics of BC CLL/SLL cohort treated with ibrutinib

Baseline Characteristic N (%)	Total N=370	1L N=35	2L N=182	3L+ N=153	P-value
Male	253 (68.4)	24 (68.6)	123 (67.6)	106 (69.3)	0.946
At time of diagnosis					
Median age, yrs (range)	62.5 (33-89)	69 (50-88)	64 (33-88)	61 (34-89)	<0.001
Rai stage 3-4	35 (9.5)	4 (11.4)	16 (8.8)	15 (9.8)	0.676*
Baseline FISH prevalence	**N=213**	**N=33**	**N=130**	**N=50**	
Deletion 17p	36 (16.9)	17 (51.5)	15 (11.5)	4 (8.0)	
Deletion 11q	45 (21.1)	5 (15.2)	28 (21.5)	12 (24.0)	
Trisomy 12	48 (22.5)	4 (12.1)	29 (22.3)	15 (30.0)	
Deletion 13q	105 (49.3)	17 (51.5)	68 (52.3)	20 (40.0)	
Normal (none of above)	42 (19.7)	4 (12.1)	27 (20.8)	11 (22.0)	
Median time from diagnosis to ibrutinib, yrs (range)	7.3 (0.0-30.0)	4.5 (0.0-18.3)	5.4 (0.2-24.4)	9.7 (0.7-30.0)	<0.001
At ibrutinib initiation					
Median age, yrs (range)	71 (41-94)	74 (54-94)	71 (41-89)	71 (41-93)	0.163
Rai stage 3-4	134 (36.2)	15 (42.9)	68 (37.4)	51 (33.3)	
FISH prevalence	**N=189**	**N=28**	**N=93**	**N=67[a]**	
Deletion 17p (n=188)	45 (23.9)	14 (50.0)	19 (20.4)	12 (17.9)	
Deletion 11q (n=187)	51 (27.3)	6 (21.4)	25 (26.9)	20 (30.3)	
Trisomy 12 (n=188)	41 (21.8)	4 (14.3)	20 (21.5)	17 (25.4)	
Deletion 13q (n=187)	96 (51.3)	14 (50.0)	49 (52.7)	33 (50.0)	
Normal (none of above) (n=188)	29 (15.4)	2 (7.1)	15 (16.1)	12 (17.9)	
Median laboratory values (n=318), range					
White blood cell count, $x10^9$/L	33.5 (2-399)	96 (6-399)	30.5 (2-361)	32 (2-343)	
Lymphocytes, $x10^9$/L (n=317)	28 (0.3-379)	91 (2-379)	25.5 (0.5-356)	24 (0.3-338)	
Hemoglobin, g/L	119 (49-168)	110 (49-154)	124 (70-168)	119 (65-162)	
Platelets, $x10^9$/L (n=317)	126 (5-456)	137 (21-374)	131.5 (5-386)	122 (9-456)	

1L, first-line; 2L, second-line; 3L+, third line or greater; FISH, fluorescence *in situ* hybridization; L, liter; N, number of patients; yrs, years; [a]3L+ FISH at ibrutinib: deletion 13q and deletion 11q had an n=66
*Chi-square analysis assumptions were not met, Fisher's exact test was computed in its place

The most common comorbidities in patients prior to ibrutinib initiation were hypertension (32.7%), diabetes (14.3%), coronary artery disease (12.2%), rheumatologic disease (10.0%) and AF/flutter (8.6%), and 10.0% of patients were on anticoagulation at initiation of ibrutinib (Table 5). From the start of ibrutinib therapy, the median follow-up was 27.2 months (range, 6.1 – 49.4 months) for living patients (n=311). The median duration of ibrutinib treatment was 21.6 months (range, 0.1-49.4 months). At last follow-up, 205 patients (55.4%) were still alive and remained on ibrutinib therapy. Comparing lines of therapy, median duration of ibrutinib was 17.7 months (range, 0.1 – 47.4), 19.2 months (range, 0.8 – 49.4) and 24.2 months (range, 0.6 – 48.5) for 1L, 2L and 3L+, respectively (*P*=0.012).

Table 5. Comorbidities prior to ibrutinib initiation (N=370)

Comorbidity	N (%)*
Hypertension	121 (32.7)
Diabetes without complications	53 (14.3)
Coronary artery disease	45 (12.2)
Anticoagulation	37 (10.0)
Rheumatologic disease	37 (10.0)
Atrial Fibrillation/flutter	32 (8.6)
Chronic pulmonary disease	27 (7.3)
Moderate/Severe renal disease	24 (6.5)
Deep vein thrombosis	20 (5.4)
Cerebrovascular disease or Stroke	19 (5.1)
Myocardial infarction	19 (5.1)
Congestive Heart Failure	15 (4.1)
Pulmonary embolism	14 (3.8)
Peripheral vascular disease	11 (3.0)
Bleeding	8 (2.2)
Mild Liver Disease	8 (2.2)
Ulcer	6 (1.6)
Diabetes with sequelae	2 (0.5)

Comorbidity	N (%)*
Dementia	1 (0.3)
Unknown (no available information)	20 (5.4)

N, number of patients
Total of 350 patients had information available
*Values do not add to 100% as patients may have had more than one comorbidity

4.1.2 Dose modification patterns

The median starting dose of ibrutinib was the standard 420 mg daily (range, 140-560 mg), with 43 patients starting at a lower dose (140 or 280 mg daily), generally due to comorbidities. Dose reductions over the course of therapy were observed in 31.7% of patients (110/347, 23 patients had missing detailed dosing information), with 12.5% (4/32) in 1L, 33.3% (57/171) in 2L, and 34.0% (49/144) in 3L+ (*P*=0.049). For patients who had a dose reduction (n=110), the most common reason was due to toxicity in 92 patients (83.6%). Other reasons for reductions included new comorbidities, n=2; medication interactions, n=3; other causes, n=10 (8 non-ibrutinib related toxicities, and 1 of incorrect starting dose and patient choice each); and unknown, n=3. Temporary treatment holds were recorded by physicians in 101 patients (27.3%), with a median hold time of 0.5 months (range, 0.1 – 28.9 months). The most common reasons resulting in a treatment hold were cytopenias (7.3%), infection (3.5%), pneumonia (1.9%), and AF (1.9%). Additionally, 23 patients (6.2%) had greater than one toxicity resulting in a treatment hold and multiple holds were observed in 20 patients (5.4%).

4.1.3 Discontinuation patterns

A total of 106 patients (28.6%) discontinued therapy for reasons apart from death as shown in Table 6 including toxicity (including infections and/or cardiac events), n=53 (53/106, 50.0%); progression, n=33 (33/106, 31.1%); and other reasons, n=20 (20/106, 18.9%) (7 patient/physician choice, 4 stem cell transplant, 5 new comorbidity/drug interaction, 2 change in goals of care and 2 unknown). By line of therapy, 37.1% (13/35), 26.9% (49/182) and 28.8% (44/153) of patients

discontinued ibrutinib during 1L, 2L and 3L+ treatment, respectively (*P*=0.472). The median exposure time for patients who discontinued ibrutinib due to toxicities and progression was 8.9 months (range, 0.1 – 38.5) and 11.8 months (range, 0.9 – 45.1), respectively, which did not differ based on line of therapy.

Table 6. Reasons for ibrutinib discontinuation, excluding death

Reason for Discontinuation N (%)	Total N= 106	1L N=13	2L N=49	3L+ N=44
Toxicity	53 (50.0)	7 (53.8)	25 (51.0)	21 (47.7)
Progression	33 (31.1)	3 (23.1)	15 (30.6)	15 (34.1)
Other	20 (18.9)	3 (23.1)	9 (18.4)	8 (18.2)
Patient/physician choice*	7 (6.6)	1 (7.7)	2 (4.1)	4 (9.1)
Stem cell transplant	4 (3.8)	0	2 (4.1)	2 (4.5)
New comorbidity/drug interaction	5 (4.7)	1 (7.7)	3 (6.1)	1 (2.3)
Changes in goals of care	2 (1.9)	1 (7.7)	1 (2.0)	0
Unknown	2 (1.9)	0	1 (2.0)	1 (2.3)

1L, first-line; 2L, second-line; 3L+, third line or greater; N, number of patients
*Patient/physician choice includes adequate response achieved

Including patients who died on ibrutinib, 130 patients (35.1%) discontinued ibrutinib as shown in Table 7. Reasons for discontinuation included toxicity (including infections and/or cardiac events), n=63 (63/130, 48.5%); progression, n=43 (43/130, 33.1%); and other reasons, n=24 (24/130, 18.4%) (7 patient/physician choice, 4 stem cell transplant, 5 new comorbidity/drug interaction, 2 change in goals of care, 3 unrelated toxicity/malignancy, 2 unknown and 1 unrelated). By line of therapy, 42.9% (15/35), 30.8% (56/182) and 38.6% (59/153) of patients discontinued ibrutinib during 1L, 2L and 3L+ treatment, respectively (*P*=0.199). The median exposure time for patients who discontinued ibrutinib due to toxicities and progression was 8.9 months (range, 0.1 – 38.5) and 11.5 months (range, 0.9 – 45.1), respectively, which did not differ based on line of therapy.

Table 7. Reasons for ibrutinib discontinuation, including death

Reason for Discontinuation N (%)	Total N= 130	1L N=15	2L N=56	3L+ N=59
Toxicity	63 (48.5)	7 (46.7)	26 (46.4)	30 (50.8)
Progression	43 (33.1)	5 (33.3)	19 (33.9)	19 (32.2)
Other	24 (18.4)	3 (20.0)	11 (19.7)	10 (17.0)
Patient/physician choice*	7 (5.4)	1 (6.7)	2 (3.6)	4 (6.8)
Stem cell transplant	4 (3.1)	0	2 (3.6)	2 (3.4)
New comorbidity/drug interaction	5 (3.8)	1 (6.7)	3 (5.4)	1 (1.7)
Changes in goals of care	2 (1.5)	1 (6.7)	1 (1.8)	0
Unrelated toxicity/malignancy	3 (2.3)	0	1 (1.8)	2 (3.4)
Unrelated	1 (0.8)	0	1 (1.8)	0
Unknown	2 (1.5)	0	1 (1.8)	1 (1.7)

1L, first-line; 2L, second-line; 3L+, third line or greater; N, number of patients
*Patient/physician choice includes adequate response achieved

For the 53 patients who discontinued ibrutinib due to toxicity (not including those who died on ibrutinib), the most common reason was for cardiac causes in 10 patients (2.7%): 7 AF/flutter, 2 angina, 2 cardiac arrhythmia and 1 of each, congestive heart failure, pericardial effusion, and pleural effusion (Table 8). Other commonly observed toxicities leading to discontinuation were infections (2.2%), musculoskeletal symptoms (1.6%), fatigue (1.6%) and bleeding/hemorrhage (1.4%) (Table 8). Furthermore, 22 patients (5.9%) had greater than one toxicity resulting in a discontinuation.

Table 8. Toxicities leading to ibrutinib discontinuation, excluding death

Toxicity N (%)	Total N=370*	1L N=35*	2L N=182*	3L N=153*
Cardiac events	10 (2.7)	4 (11.4)	5 (2.7)	1 (0.7)
Atrial fibrillation/flutter	7 (1.9)	3 (8.6)	3 (1.6)	1 (0.7)
Angina	2 (0.5)	1 (2.9)	1 (0.5)	0
Cardiac arrhythmia	2 (0.5)	1 (2.9)	1 (0.5)	0
Congestive heart failure	1 (0.3)	0	1 (0.5)	0
Pericardial effusion	1 (0.3)	0	1 (0.5)	0
Pleural effusion	1 (0.3)	0	0	1 (0.7)
Infections	8 (2.2)	0	3 (1.6)	5 (3.3)
Musculoskeletal symptoms	6 (1.6)	1 (2.9)	4 (2.2)	1 (0.7)
Fatigue	6 (1.6)	1 (2.9)	5 (2.7)	0
Bleeding/Hemorrhage	5 (1.4)	1 (2.9)	4 (2.2)	0
Diarrhea	4 (1.1)	0	1 (0.5)	3 (2.0)
Pneumonia	3 (0.8)	0	2 (1.1)	1 (0.7)
Rash	3 (0.8)	0	2 (1.1)	1 (0.7)
Cytopenias	2 (0.5)	0	1 (0.5)	1 (0.7)
Headache	2 (0.5)	0	2 (1.1)	0
Hypertension	2 (0.5)	1 (2.9)	1 (0.5)	0
Nausea and Vomiting	2 (0.5)	0	0	2 (1.3)
Bruising	1 (0.3)	0	1 (0.5)	0
Other**	19 (5.1)	1 (2.9)	8 (4.4)	10 (6.5)

N, number of patients
Cardiac arrhythmia: ventricular tachycardia, tachyarrhythmia
Cytopenias: neutropenia, thrombocytopenia
Total of 53 patients, excluding death discontinued treatment ((1L, n=7; 2L, n=25; and 3L+, n=21)
*Values do not add to 100% as patients may have had more than one toxicity leading to discontinuation
**Other, any toxicity not listed in table

A total of 24 patients in the whole cohort (6.5%) died during the time they were on ibrutinib due to CLL progression in 10 (41.7% of all deaths), cardiac causes in 7 (29.2%) (3 cardiac arrest, 3 heart disease, 2 congestive heart failure, 1 acute myocardial infarction and 1 ventricular tachycardia), infections in 3 (12.5%), unrelated causes in 3 (12.5%) and a malignancy in 1 (4.1%) patient (Table 9).

Table 9. Patients who died while on ibrutinib therapy (N=24)

Cause of Death	N (%)
CLL	10 (41.7)
Cardiac*	7 (29.2)
Cardiac arrest	3 (12.5)
Heart disease	3 (12.5)
Congestive heart failure	2 (8.3)
Acute Myocardial infarction	1 (4.1)
Ventricular tachycardia	1 (4.1)
Infections	3 (12.5)
Unrelated	3 (12.5)
Malignancy	1 (4.1)

N, number of patients
Heart disease: atherosclerotic heart disease, ischemic cardiomyopathy
Infections: acute lower respiratory infection, clostridioides difficile and methicillin-susceptible Staphylococcus aureus sepsis, Escherichia coli sepsis
*Values do not add up to total as patients may have had more than one type of cardiac toxicity resulting in death

Overall, when deaths were included, the total number of patients who discontinued ibrutinib over the median follow-up (living patients only) from time of ibrutinib initiation of 27.2 months (range, 6.1 – 49.4) for the entire cohort was 130/370 (35.1%). When all cardiac and infectious causes of death are attributed to ibrutinib toxicity, the number of patients who discontinued ibrutinib due to AEs was 63/130 (48.5% of all discontinuations, 17.0% of the whole cohort) and due to progression was 43/130 (33.1% of all discontinuations, 11.6% of the whole cohort).

4.1.4 Toxicities

We observed that 323 (87.3%) patients experienced a toxicity during their ibrutinib treatment, including toxicities leading to dose reductions, holds and discontinuations. Detailed toxicities are shown in Table 10, and mostly included: bruising (17.6%), musculoskeletal symptoms (12.7%), fatigue

(12.2%), bleeding (10.8%), AF/flutter (10.3%) and cytopenias (9.7%). Greater than one toxicity was observed in 154/323 (47.7%) patients.

Table 10. Any toxicities reported during ibrutinib therapy (N=370)

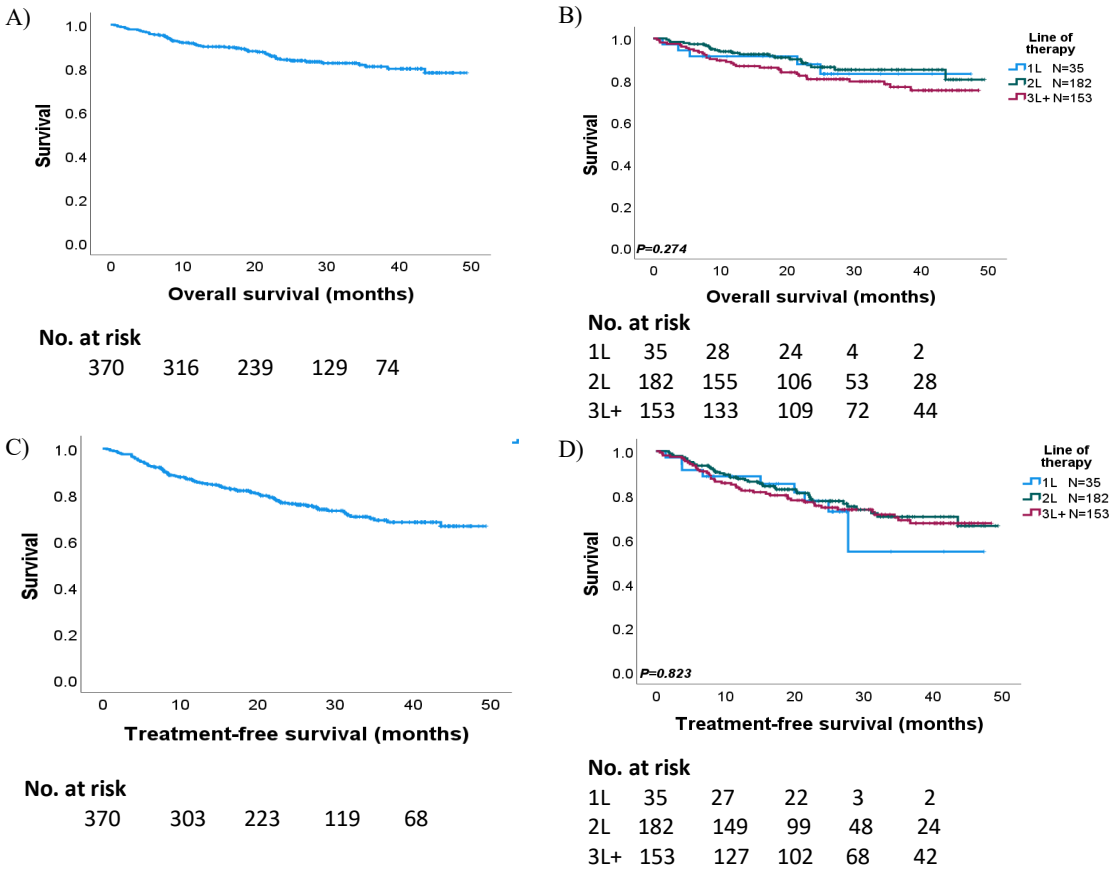
Toxicity, N (%)	Total N=370*	1L N=35*	2L N=182*	3L+ N=153*
Bruising	65 (17.6)	5 (14.3)	39 (21.4)	21 (13.7)
Musculoskeletal symptoms	47 (12.7)	4 (11.4)	26 (14.3)	17 (11.1)
Fatigue	45 (12.2)	3 (8.6)	28 (15.4)	14 (9.2)
Bleeding	40 (10.8)	4 (11.4)	24 (13.2)	12 (7.8)
Atrial fibrillation/flutter	38 (10.3)	4 (11.4)	19 (10.4)	15 (9.8)
Cytopenias	36 (9.7)	1 (2.9)	15 (8.2)	20 (13.1)
Diarrhea	26 (7.0)	1 (2.9)	10 (5.5)	15 (9.8)
Infection	23 (6.2)	1 (2.9)	7 (3.8)	15 (9.8)
Rash	22 (5.9)	2 (5.7)	8 (4.4)	12 (7.8)
Nausea and Vomiting	21 (5.7)	2 (5.7)	9 (4.9)	10 (6.5)
Other Cardiac events	14 (3.8)	3 (8.6)	8 (4.4)	3 (2.0)
Angina/palpitations	8 (2.2)	2 (5.7)	4 (2.2)	2 (1.3)
Cardiac arrhythmia	5 (1.4)	1 (2.9)	4 (2.2)	0
Congestive heart failure	2 (0.5)	0	1 (0.5)	1 (0.7)
Other Gastrointestinal	12 (3.2)	0	7 (3.8)	5 (3.3)
Headache	10 (2.7)	0	7 (3.8)	3 (2.0)
Hypertension	9 (2.4)	1 (2.9)	4 (2.2)	4 (2.6)
Pneumonia	9 (2.4)	1 (2.9)	3 (1.6)	5 (3.3)
Other**	88 (23.8)	11 (31.4)	40 (22.0)	37 (24.2)

1L, first-line; 2L, second-line; 3L+, third line or greater; N, number of patients
Cytopenias: anemia, thrombocytopenia, neutropenia
Cardiac arrhythmia: irregular heartbeat and ventricular tachycardia
Total of 323 patients had information available (1L, n=30; 2L, n=158; and 3L+, n=135)
*Values do not add to 100% as patients may have had more than one toxicity during treatment
**Other, any toxicity not listed in table

4.1.5 Survival outcomes

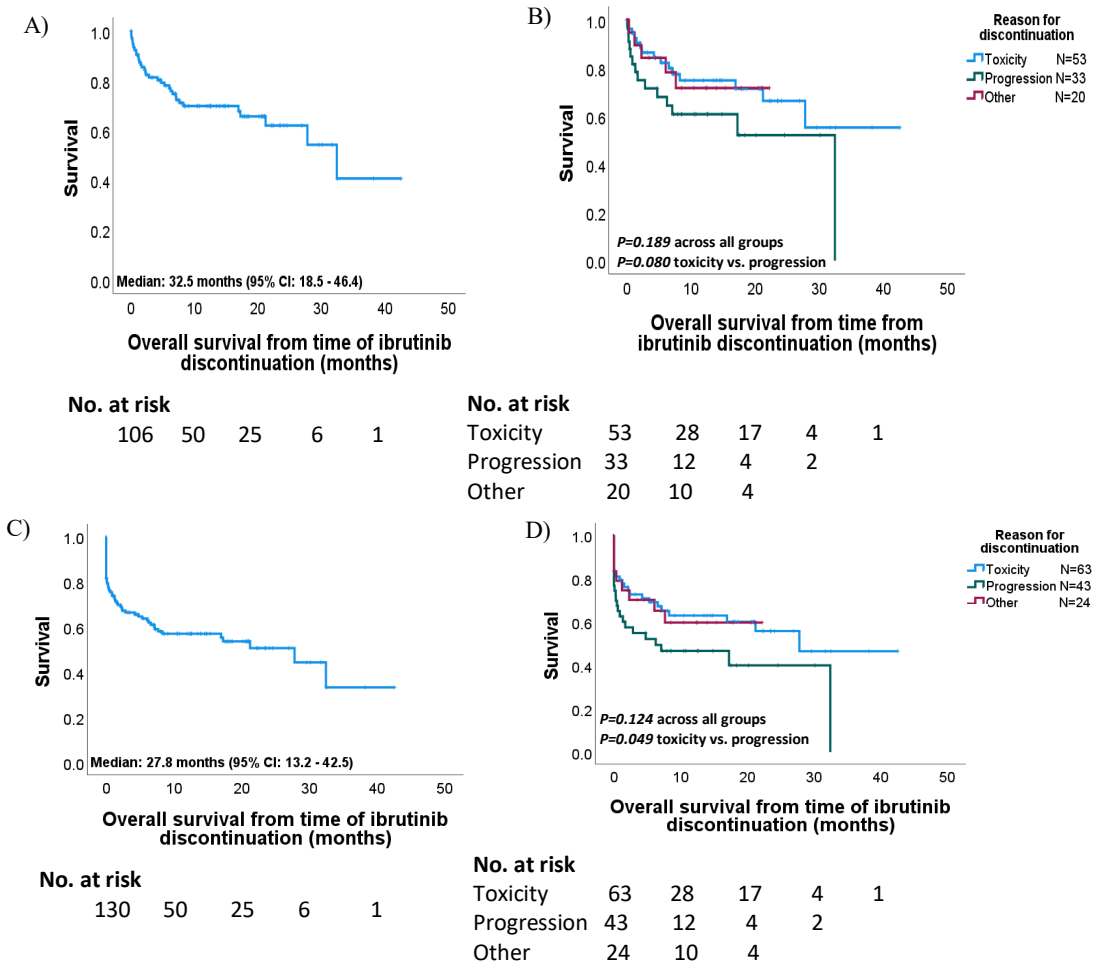
A total of 59 patients (15.9%) died at last follow-up. From the start of ibrutinib therapy, 24-month OS for the whole cohort was 83.9% with the median not reached (Figure 1A). Stratifying by line of therapy, 24-month OS from ibrutinib therapy was 83.0% for 1L, 86.2% for 2L, and 80.5% for 3L+, showing no significant differences between the lines (*P*=0.274) (Figure 1B). The most common next line of therapy after ibrutinib was venetoclax or a venetoclax-rituximab combination (n=17). Other next lines of therapy included, allogeneic stem cell transplant (n=3); idelalisib-rituximab (n=6); re-trial on ibrutinib (n=2); FR (n=2); cyclophosphamide, vincristine, prednisone and rituximab (CVP-R) (n=2); cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R) or with etoposide substituted for doxorubicin (CEOP-R) (n=7); chlorambucil-rituximab (n=1); chlorambucil alone (n=1); BR (n=4) and bendamustine alone (n=1). The 24-month TFS for the whole cohort was 76.1%, with the median not reached (Figure 1C). Stratifying by line of therapy, 24-month TFS was 72.6% for 1L, 77.3% for 2L, and 74.4% for 3L+, showing no significant differences between the lines (*P*=0.823) (Figure 1D).

Figure 1. Survival outcomes from time of ibrutinib initiation. A) Unadjusted overall survival for the whole cohort (N=370), B) Unadjusted overall survival by line of therapy. C) Unadjusted treatment-free survival for the whole cohort (N=370), D) Unadjusted treatment-free survival by line of therapy



Patients who discontinued ibrutinib therapy, not including those who died while still taking ibrutinib (n=106), had a median OS from discontinuation of 32.5 months (95% CI: 18.5-46.4) (Figure 2A). There were no significant differences observed when patients who discontinued ibrutinib were compared based on reasons for discontinuation, with 24-month OS from time of discontinuation for toxicity, progression or other 66.3%, 52.1%, and 71.7%, respectively (*P*=0.189) (Figure 2B). When those who died on ibrutinib treatment were included in this analysis (n=130), the median OS from time of discontinuation was 27.8 months (95% CI: 13.2 – 42.5) (Figure 2C), showing no significant difference when stratified by reasons for discontinuation (24-month OS from time of discontinuation for toxicity, progression or other was 55.8%, 40.0%, and 59.7%, respectively (*P*=0.124) (Figure 2D)).

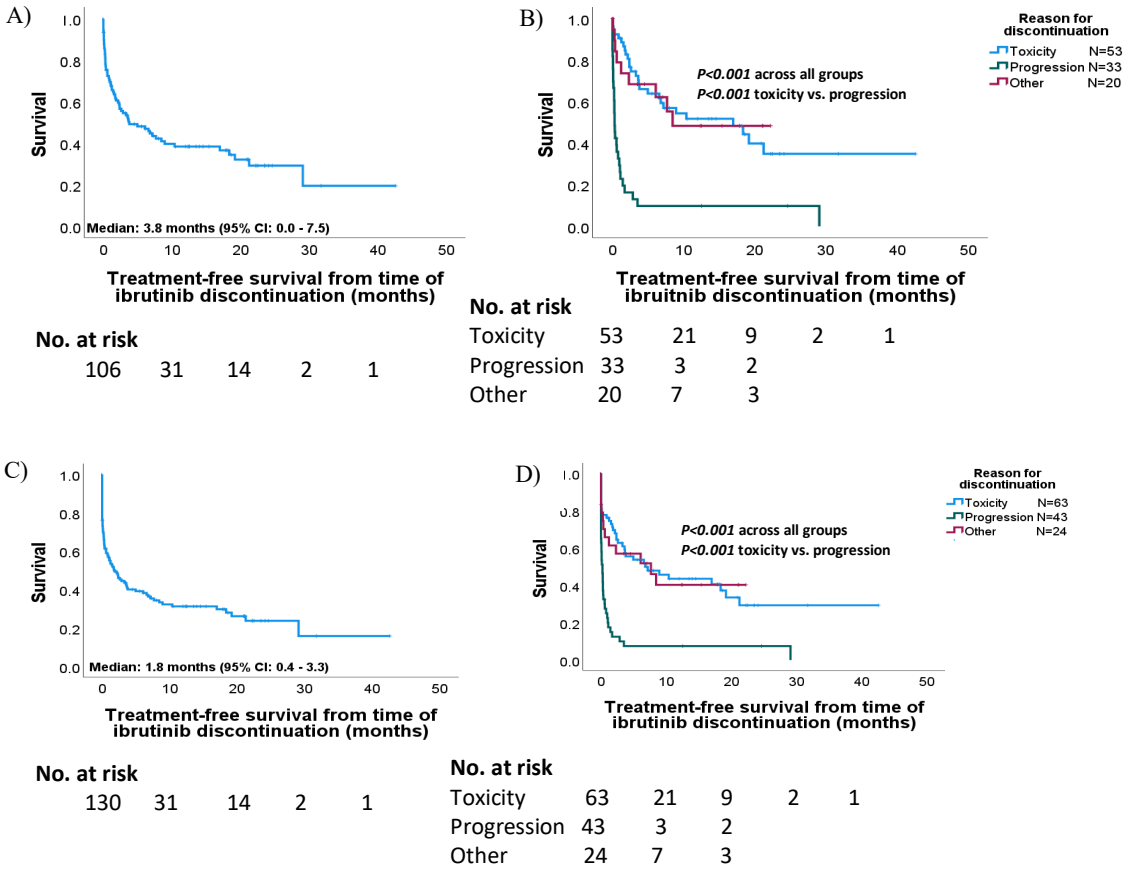
Figure 2. Unadjusted overall survival from time of discontinuation of ibrutinib. A-B) All patients who discontinued ibrutinib (not including patients who died on ibrutinib, N=106), whole cohort (A) and by reason for discontinuation (B). C-D) All patients who discontinued ibrutinib (including patients who had died on ibrutinib, N=130), whole cohort (C) and by reason for discontinuation (D)



Patients who discontinued ibrutinib, not including those who died while still taking ibrutinib (n=106), had a median TFS from time of ibrutinib discontinuation of 3.8 months (95% CI: 0.0 – 7.5) (Figure 3A). There was a significant difference observed when patients who discontinued ibrutinib were compared based on reasons for discontinuation, with 24-month TFS from time of discontinuation for toxicity, progression or other at 34.9%, 9.8%, and 48.4%, respectively (P<0.001) (Figure 3B). When those who died on ibrutinib treatment were included in this analysis (n=130), the median TFS

from time of discontinuation was 1.8 months (95% CI: 0.4 – 3.3) (Figure 3C), showing a significant difference when stratified by reasons for discontinuation (24-month TFS from time of discontinuation for toxicity, progression or other was 29.4%, 7.5%, and 40.3%, respectively (P<0.001) (Figure 3D)).

Figure 3. Unadjusted treatment-free survival from time of discontinuation of ibrutinib. A-B) All patients who discontinued ibrutinib (not including patients who died on ibrutinib, N=106), whole cohort (A) and by reason for discontinuation (B). C-D) All patients who discontinued ibrutinib (including patients who had died on ibrutinib, N=130), whole cohort (C) and by reason for discontinuation (D)



4.2 Healthcare utilization and costs of ibrutinib treated patients in BC

4.2.1 Clinical characteristics and survival

For HCU analyses, we identified a cohort of 181 CLL/SLL patients (1L, 9; R/R, 172) treated with ibrutinib in BC where we had complete data from Population Data BC. Clinical characteristics can

be found in Table 11. In brief, most patients were diagnosed with CLL (82.32%) and were of male sex (65.75%). At diagnosis, for the entire cohort the median age was 63 years (range, 25-92 years) and where data was available patients had predominantly low-intermediate (stage 0 – 2) Rai stage (39.78%, 72/181). The median follow-up time from CLL/SLL diagnosis for living patients (n=145) was 9.02 years (range, 2.15 – 17.40 years) and the median time from diagnosis to the start of ibrutinib therapy was 6.52 years (range, 0.17-15.88). At ibrutinib therapy start, patients were older at a median age of 70 years (range, 34-97) and predominantly had started their treatment at the standard dose of 420 mg (87.29%).

Table 11. Clinical characteristics of BC CLL/SLL patients treated with ibrutinib until death or last follow-up

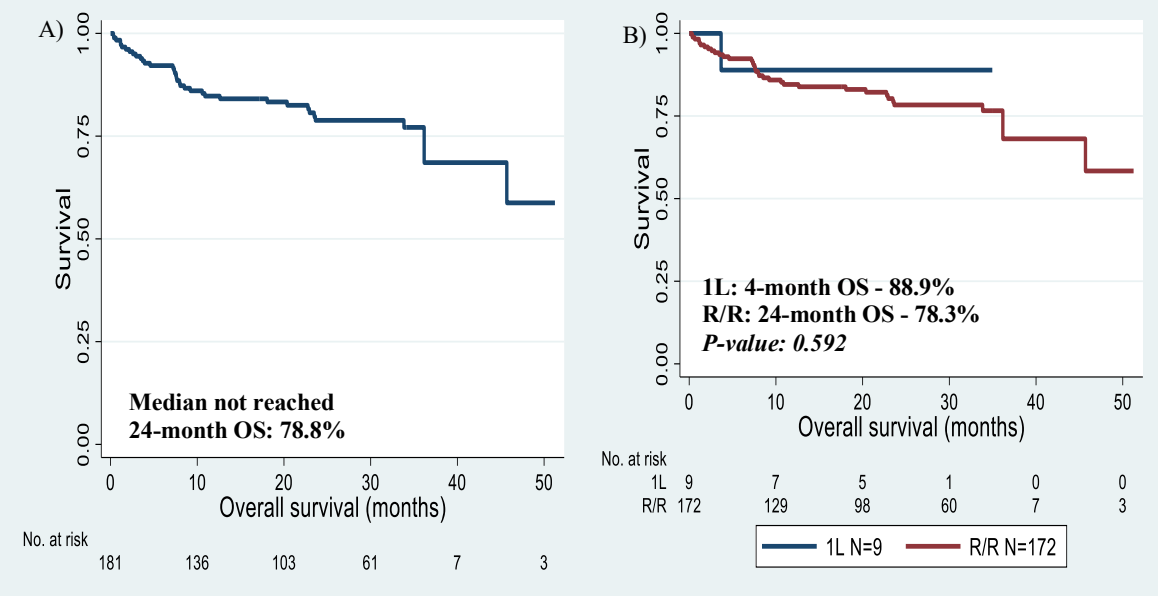
Clinical characteristics, N (%)	**Total N=181**	**1L N=9**	**R/R N=172**
CLL	149 (82.32)	8 (88.89)	141 (81.98)
Sex (Male)	119 (65.75)	6 (66.67)	113 (65.70)
Median age at dx, yrs (range)	63 (25-92)	69 (55-86)	63 (25-92)
Rai Stage			
Stage 0	40 (22.10)	<5*	38 (22.09)
Stage 1	22 (12.16)	<5*	19 (11.05)
Stage 2	10 (5.52)	0	10 (5.81)
Stage 3	10 (5.52)	0	10 (5.81)
Stage 4	27 (14.92)	<5*	26 (15.12)
Missing	72 (39.78)	<5*	69 (40.12)
Median age at index therapy, yrs (range)	70 (34-97)	74 (61-94)	70 (34-97)
Median time from diagnosis to index therapy, yrs (range)	6.52 (0.17-15.88)	5.54 (0.76-9.10)	6.69 (0.17-15.88)
Ibrutinib starting dose (mg)			
140	5 (2.76)	0	5 (2.91)
280	18 (9.95)	0	18 (10.46)
420	158 (87.29)	9 (100)	149 (86.63)

Clinical characteristics, N (%)	Total N=181	1L N=9	R/R N=172
Bone marrow transplant	9 (4.97)	0	9 (5.23)
Died by last follow-up	36 (19.89)	<5*	35 (20.35)

1L, first-line; dx, diagnosis; N, number of patients; R/R, relapsed/refractory; yrs, years
Date of last follow-up: December 31, 2018
*Due to small sample sizes, any value less than 5 will be represented in tables with (<5)

From time of ibrutinib initiation, 24-month OS for the entire cohort was 78.8% with the median not reached (Figure 4A). By line of therapy, 24-month OS was 88.9% and 78.3% for 1L and R/R respectively, with no significant differences between the lines (*P*=0.592) (Figure 4B).

Figure 4. Unadjusted overall survival from time of ibrutinib initiation. A) Whole cohort (N=181), B) By line of therapy (1L vs R/R)



A total of 36 (19.89%) patients died at last follow-up. The most common causes of death categorized using ICD10-CA codes were chronic lymphocytic leukemia of B-cell type (58.33%), leukemia/lymphoma (16.67%) and cardiac reasons (16.67%) (Table 12).

Table 12. Causes of death for ibrutinib treated patients (N=36)

Cause of death	N (%)
Chronic lymphocytic leukemia of B-cell type	21 (58.33)
Leukemia/Lymphoma	6 (16.67)
Cardiac reasons	6 (16.67)
Chronic obstructive pulmonary disease	<5*
Other ill-defined and unspecified causes	<5*

N, number of patients
Date of last follow-up: December 31, 2018
Causes of death defined based on the 10th version of the International Classification of Disease coding system with Canadian Enhancements (ICD10-CA)
Cardiac reasons: acute myocardial infarction, unspecified; atherosclerotic heart disease of native coronary artery; cardiac arrhythmia, unspecified; ischemic cardiomyopathy; aortic (valve) stenosis
Leukemia/Lymphoma reasons: chronic leukemia of unspecified cell type; leukemia, unspecified; non-Hodgkin lymphoma, unspecified; small cell B-cell lymphoma; B-cell lymphoma, unspecified
*Due to small sample sizes, any value less than 5 will be represented in tables with (<5)

4.2.2 Ibrutinib therapy costs

The mean PPPY cost of ibrutinib spanning 3 full years (January 1, 2016 – December 31, 2018) up to death or last follow-up for the entire cohort (n=174) was $68,266.31 (SD, $35, 021.86). The mean PPPY ibrutinib cost continued to increase each year: 2016 $63,345.40 (SD, $35,030.44); 2017, $68,595.10 (SD, $35,207.50), and 2018, $71,606.52 (SD, $34,674.75), respectively (Table 13).

Table 13. Mean and median annual per patient cost (Canadian dollar, $) of ibrutinib until death or last follow-up (N=174), by calendar year

Prescription Year	N	Mean (SD)	Median (IQR)
2015*	6	8,341.31 (5,776.57)	8,639.21 (2,979.04)
2016	101	63,345.40 (35,030.44)	66,389.60 (62,276.97)
2017	130	68,595.10 (35,207.50)	70,342.13 (65,055.42)
2018	136	71,606.52 (34,674.75)	72,652.21 (60,629.52)
Overall[a]	174	68,266.31 (35,021.86)	70,502.23 (63,884.92)

IQR, interquartile range; N, number of patients; SD, standard deviation
Adjusted for inflation Year 2021; Date of last follow-up: December 31, 2018
Cases where prescription costs were covered ($0) through the special access program or a clinical trial were excluded from this analysis
*All patients had only one prescription dispensed each spanning the month of December
[a]The year 2015 was omitted from the overall mean and median annual per patient cost of ibrutinib due to the small sample size. The overall spans January 1, 2016 – December 31, 2018

From time of ibrutinib start date up to and including 6 months post-ibrutinib initiation, the mean PPPY ibrutinib cost was $41,719.83 (SD, $19,483.30) (Table 14). This included only patients who had at a minimum 6 months of therapy (n=140). The mean PPPY for this cohort fluctuated every year between 2016 and 2018: 2016, $44,671.71 (SD, $16,691.00); 2017, $37,694.85 (SD; $19,867.96) and 2018, $41,172.89 (SD, $25,139.32), respectively (Table 14).

Table 14. Mean and median annual per patient cost (Canadian dollar, $) of ibrutinib up to and including 6 months from therapy initiation, complete cases only (N=140)

Prescription Year	N	Mean (SD)	Median (IQR)
2015*	6	8,341.31 (5,776.57)	8,639.21 (2,979.04)
2016	87	44,671.71 (16,691.00)	44,259.74 (25,654.98)
2017	60	37,694.85 (19,867.96)	39,276.32 (37,217.04)
2018	28	41,172.89 (25,139.32)	38,117.55 (42,237.72)
Overall[a]	140	41,719.83 (19,483.30)	43,672.22 (32,908.38)

IQR, interquartile range; N, number of patients; SD, standard deviation
Adjusted for inflation Year 2021
Cases where prescription costs were covered ($0) through the special access program or a clinical trial were excluded from this analysis
*All patients had only one prescription dispensed each spanning the month of December
[a]The year 2015 was omitted from the overall mean and median annual per patient cost of ibrutinib due to the small sample size. The overall spans January 1, 2016 – December 31, 2018

Total costs of ibrutinib over the 3 years amounted to $25,053,734.91 (Table 15). For the 6-month period, the total cost of ibrutinib was $7,300,970.79 (Table 15). The total costs over the 3 years and the 6-month period per patient were $143,986.98 and $52,149.79, respectively (Table 15).

Table 15. Total ibrutinib therapy cost (Canadian dollar, $) and total per patient ibrutinib therapy cost (Canadian dollar, $) to the healthcare system from January 1, 2016 – December 31, 2018

	Total N=174	**1L N=9**	**R/R N=165**
Total ibrutinib costs from index therapy start date to death or date of last follow-up			
Total	25,053,734.91	1,380,369.21	23,673,365.70
Total per patient	143,986.98	153,374.36	143,474.94
Total ibrutinib costs from index therapy start date up to and including 6 months post-initiation (complete cases only)			
	N=140	**N=7**	**N=133**
Total	7,300,970.79	407,107.09	6,893,863.70
Total per patient	52,149.79	58,158.16	51,833.56

N, number of patients
Adjusted for inflation Year 2021
Cases where prescription costs were covered ($0) through the special access program or a clinical trial were excluded from this analysis

4.2.3 Practitioner services costs

Over a 5-year period, from ibrutinib initiation up to last follow-up or death (January 1, 2014 – December 31, 2018), the total mean PPPY practitioner service costs were $2,917.57 (SD, $2,933.67) for the entire cohort (n=181) (Table 16). The total mean PPPY practitioner service costs for 1L patients was lower $2,414.03 (SD, $2,044.63) compared to R/R patients $2,943.75 (SD, 2,972.12) (Table 16). When stratified by practitioner type, mean PPPY was $674.98 (SD, $769.91) and $2,288.93 (SD, $2,647.50) for general practitioner and specialist services, respectively (Table 16). Total practitioner costs over the 5 years totalled to $1,239,968.87, with $274,041.91 and $965,926.98 for general practitioner and specialist services, respectively (Table 17). On a per patient basis, this amounts to

$6,850.66 over 5 years for all practitioner services, and $1,530.96 and $5,336.61 for general practitioner and specialist services, respectively (Supplementary Table 1, appendix A).

Table 16. Mean annual per patient practitioner service costs covered by MSP (Canadian dollar, $) from January 1, 2014 – December 31, 2018

Mean (SD)	Total	1L	R/R
	N=181	**N=9**	**N=172**
Mean practitioner service costs from index therapy start date to death or date of last follow-up			
All	2,917.57 (2,933.67)	2,414.03 (2,044.63)	2,943.75 (2,972.12)
	N=179	**N=9**	**N=170**
General	674.98 (769.91)	715.50 (527.48)	672.99 (780.31)
	N=181	**N=9**	**N=172**
Specialist	2,288.93 (2,647.50)	1,855.01 (1,646.71)	2,310.52 (2,687.10)
Mean practitioner service costs from index therapy start date up to and including 6 months post-initiation (complete cases only)			
	N=154	**N=7**	**N=147**
All	1,359.94 (1,508.54)	959.72 (978.27)	1,382.18 (1,531.26)
	N=148	**N=7**	**N=141**
General	332.89 (384.89)	258.55 (295.29)	336.57 (389.06)
	N=152	**N=7**	**N=145**
Specialist	1,086.93 (1,291.24)	823.00 (878.96)	1,100.60 (1,309.23)

MSP, medical services plan; N, number of patients; SD, standard deviation
Adjusted for inflation Year 2021; All includes both services completed by general and specialist practitioners
Field used to determine cost may or may not include adjustments made and may not always accurately reflect the total amount paid by MSP for a claim

For the 6-month period (n=154), the total mean PPPY practitioner service costs were $1,359.94 (SD, $1,508.54) (Table 16). The total mean PPPY practitioner service costs for 1L patients was lower $959.72 (SD, $978.27) compared to R/R patients $1,382.18 (SD, $1,531.26) (Table 16). When stratified by practitioner type, mean PPPY was $332.89 (SD, $384.89) and $1,086.93 (SD, $1,291.24) for general practitioner services and specialist services, respectively (Table 16). Total practitioner costs over the 6-month period amounted to $284,227.88 (Table 17). This came to $63,581.91 and $220,645.97 for general practitioner and specialist services, respectively (Table 17). On a per patient

basis, this amounts to $1,845.64 for all practitioner services, and $429.61 and $1,451.62 for general practitioner and specialist services, respectively (Supplementary Table 1, appendix A).

Table 17. Total practitioner service costs covered by MSP (Canadian dollar, $) from January 1, 2014 – December 31, 2018

Mean (SD)	Total	1L	R/R
	N=181	**N=9**	**N=172**
Total practitioner service costs from index therapy start date to death or date of last follow-up			
All	1,239,968.87	50,694.67	1,189,274.20
	N=179	**N=9**	**N=170**
General	274,041.91	13,594.54	260,447.37
	N=181	**N=9**	**N=172**
Specialist	965,926.98	37,100.14	928,826.84
Total practitioner service costs from index therapy start date up to and including 6 months post-initiation (complete cases only)			
	N=154	**N=7**	**N=147**
All	284,227.88	10,556.97	273,670.91
	N=148	**N=7**	**N=141**
General	63,581.91	2,326.98	61,254.93
	N=152	**N=7**	**N=145**
Specialist	220,645.97	8,229.99	212,415.98

MSP, medical services plan; N, number of patients; SD, standard deviation
Adjusted for inflation Year 2021; All includes both services completed by general and specialist practitioners
Field used to determine cost may or may not include adjustments made and may not always accurately reflect the total amount paid by MSP for a claim

The ibrutinib cohort of 181 patients had a total of 67,514 practitioner visits or services rendered. The most common practitioners consulted, or expertise used were by pathologists (56.48%), medical microbiologists (20.17%), general practitioners (9.27%), radiologists (1.87%), internal medicine specialists (1.81%) and cardiologists (1.23%) (Table 18).

Table 18. All practitioner specialties consulted by ibrutinib treated patients from January 1, 2014 – December 31, 2018 (N=67,514)

Practitioners	N (%)
Pathology	38,135 (56.48)
Medical Microbiology	13,620 (20.17)

Practitioners	N (%)
General Practice	6,259 (9.27)
Radiology	1,263 (1.87)
Internal Medicine	1,222 (1.81)
Cardiology	829 (1.23)
Ophthalmology	824 (1.22)
Respirology	679 (1.01)
Dermatology	673 (1.00)
Otolaryngology	491 (0.73)
Infectious Diseases	425 (0.63)
Hematology/oncology	379 (0.56)
Other*	2,715 (4.02)

N, total number of visits
*Any practitioner specialty frequented less than 0.5% of all practitioner visits

4.2.4 Healthcare utilization

During the 5-year study period, 117 (64.64%) patients were hospitalized. Of these 117 patients, 6 (5.13%) received ibrutinib in 1L and 111 (94.87%) in a R/R setting. Total HCU are listed in Table 19. This amounted to 362 admissions for the entire cohort, 14 for 1L and 348 for R/R patients. Over the entire study period, 21 (11.60%) patients used ambulance services a total of 79 times, all of whom received ibrutinib in a R/R setting. The total number of ER visits leading to inpatient admissions were 153, of which 7 and 146 were in patients who had received ibrutinib in a 1L and R/R setting, respectively. The total number of ER visits was higher when including those that did not necessarily result in an inpatient stay. A total of 443 were recorded for the entire cohort, of which 17 were for patients who received ibrutinib in a 1L and 426 in a R/R setting. For patients who were admitted, 234 interventions/procedures were performed, 8 for 1L and 226 for R/R patients. A total of 82 surgeries were completed of which 79 were in patients who received ibrutinib in a R/R setting.

Table 19. Total hospitalizations HCU from ibrutinib therapy initiation until death or date of last follow-up

HCU Type, N (%)	Total N=181	1L N=9	R/R N=172
Total number of admissions	362	14	348
Total number of hospitalized patients	117 (64.64)	6 (66.67)	111 (64.53)
Total number of interventions/procedures during stays	234	8	226
Total number of surgical cases	82	<5*	79
Total number of patients using ambulance services	21 (11.60)	0	21 (12.21)
Total number of times ambulance services were used	79	0	79
Total number of ER visits (including those not leading to admission)	443	17	426
Total number of ER visits (only those leading to inpatient admission)	153	7	146

ER, emergency room; HCU, health care utilization; N, number
Date of last follow-up: December 31, 2018
*Due to small sample sizes, any value less than 5 will be represented in tables with (<5)

Over the 5-year study period, the mean PPPY number of total admissions for the entire cohort was 1.47 (SD, 1.41), which appeared to be higher in R/R patients at 1.48 (SD, 1.42) compared to 1L patients at 1.17 (SD, 1.11). The 1L vs. R/R comparisons are shown in Table 20. The mean PPPY number of total ER visits (only those leading to inpatient admission) and all ER visits were 0.62 (SD, 0.96) and 1.80 (SD, 2.60), respectively. The mean PPPY total times ambulance services were used was 0.32 (SD, 0.72). The mean PPPY total number of interventions/procedures and surgical cases were 0.95 (SD, 1.08) and 0.33 (SD, 0.61), respectively. The mean PPPY length of stays (days) were as follows: total inpatient days, 8.32 days (range, 0-115); alternative care days, 0.22 days (range, 0-28); acute/rehabilitation care, 8.11 days (range, 0-103); intensive care unit, 0.39 days (range, 0-16); and rehabilitation care, 0.48 days (range, 0-58).

Table 20. Mean annual per patient hospitalizations HCU among the entire ibrutinib cohort from January 1, 2014 – December 31, 2018

HCU type, Mean (SD)	HCU from index therapy start date to death or date of last follow-up			HCU from index therapy start date up to and including 6 months post-initiation (complete cases only)		
	Total	**1L**	**R/R**	**Total**	**1L**	**R/R**
	N=181	**N=9**	**N=172**	**N=52**	**N=2**	**N=50**
Average number of total admissions	1.47 (1.41)	1.17 (1.11)	1.48 (1.42)	1.48 (0.79)	1 (1.41)	1.5 (0.78)
Average number of total interventions/procedures during stays	0.95 (1.08)	0.67 (1.15)	0.96 (1.08)	0.91 (0.71)	0	0.94 (0.70)
Average number of total surgical cases	0.33 (0.61)	0.25 (0.45)	0.34 (0.61)	0.41 (0.60)	0	0.42 (0.61)
Average number of total ER visits (only those leading to inpatient admission)	0.62 (0.96)	0.58 (0.67)	0.62 (0.98)	0.67 (0.78)	1 (1.41)	0.65 (0.76)
Average length of stay, days, mean (SD; range)	8.32 (15.88; 0 – 115)	4.42 (7.68; 0 – 25)	8.52 (16.17; 0 – 115)	7.87 (18.09; 0 – 115)	3.5 (4.95; 0 – 7)	8.04 (18.41; 0 – 115)
Average length of stay in alternative care, days, mean (SD; range)	0.22 (2.08; 0 – 28)	0	0.23 (2.14; 0 – 28)	0.22 (1.63; 0 – 12)	0	0.23 (1.66; 0 – 12)
Average length of stay in acute/rehabilitation care, days, mean (SD; range)	8.11 (15.23; 0 – 103)	4.5 (7.63; 0 – 25)	8.30 (15.51; 0 – 103)	7.67 (16.77; 0 – 103)	3.5 (4.95; 0 – 7)	7.83 (17.06; 0 – 103)
Average length of stay in intensive care unit, days, mean (SD; range)	0.39 (1.82; 0 – 16)	0	0.41 (1.87; 0 – 16)	0.44 (1.54; 0 – 8)	0	0.46 (1.57; 0 – 8)
Average length of stay in rehabilitation care, days, mean (SD; range)	0.48 (4.63; 0 – 58)	0	0.50 (4.74; 0 – 58)	1.46 (8.34; 0 – 58)	0	1.52 (8.50; 0 – 58)
	Total	**1L**	**R/R**	**Total**	**1L**	**R/R**
	N=181	**N=9**	**N=172**	**N=114**	**N=5**	**N=109**
Average number of total times ambulance services used	0.32 (0.72)	0	0.34 (0.74)	0.16 (0.47)	0	0.17 (0.48)
Average number of total ER visits (including those not leading to admission)	1.80 (2.60)	1.42 (1.16)	1.82 (2.65)	1.06 (2.04)	0.8 (0.84)	1.07 (2.08)

ER, emergency room; HCU, health care utilization; N, number; SD, standard deviation
Date of last follow-up: December 31, 2018

For the 6-month period, the mean PPPY number of total admissions for the cohort (n=52) was 1.48 (SD, 0.79). The mean PPPY number of total admissions was higher in R/R patients 1.5 (SD, 0.78)

compared to 1L patients 1 (SD, 1.41). The 1L vs. R/R comparisons are shown in Table 20. The mean PPPY number of total ER visits (only those leading to inpatient admission) and all ER visits (n=114) were 0.67 (SD, 0.78) and 1.06 (SD, 2.04), respectively. The mean PPPY total times ambulance services (n=114) were used was 0.16 (SD, 0.47). The mean PPPY total number of interventions/procedures and surgical cases were 0.91 (SD, 0.71) and 0.41 (SD, 0.60), respectively. The mean PPPY length of stays (days) were as follows: total inpatient days, 7.87 days (range, 0-115); alternative care days, 0.22 days (range, 0-12); acute/rehabilitation care, 7.67 days (range, 0-103); intensive care unit, 0.44 days (range, 0-8); and rehabilitation care, 1.46 days (range, 0-58).

During the entire 5-year study period, the most common diagnoses resulting in a hospital stay were as follows: leukemia/lymphoma (11.05%), cardiac events (8.56%), infections (5.80%), pneumonia (5.80%), cytopenias (5.52%) and inflammation/swelling (4.14%) (Table 21). The top cardiac events included AF/flutter (1.66%) and pleural effusion (1.66%) (Table 21).

Table 21. Most significant diagnosis resulting in a hospital stay for the ibrutinib cohort until death or date of last follow-up (N=362 admissions)

Diagnosis	N (%)
Leukemia/lymphoma	40 (11.05)
Cardiac events	31 (8.56)
Atrial fibrillation/flutter	6 (1.66)
Pleural effusion	6 (1.66)
Congestive heart failure	<5*
Acute subendocardial myocardial infarction	<5*
Aortic (valve) stenosis	<5*
Bradycardia, unspecified	<5*
Disease of pericardium, unspecified	<5*
Atherosclerotic heart disease of native coronary artery	<5*
Endocarditis, valve unspecified	<5*
Other cardiomyopathies	<5*
Sick sinus syndrome	<5*
Ventricular tachycardia	<5*
Infections	21 (5.80)

Diagnosis	N (%)
Pneumonia	21 (5.80)
Cytopenias	20 (5.52)
Inflammation/swelling	15 (4.14)
Sepsis	14 (3.87)
Cataract	10 (2.76)
Chemotherapy session for neoplasm	10 (2.76)
Bleeding	9 (2.49)
Chronic obstructive pulmonary disorder	9 (2.49)
Observation for suspected malignant neoplasm	9 (2.49)
Renal failure	7 (1.93)
Follow-up examination after surgery for malignant neoplasm	6 (1.66)
Other chemotherapy	5 (1.38)
Abnormal findings on diagnostic imagine of lung	<5*
Malignant neoplasm of prostate	<5*
Other disorders of lung	<5*
Other[a]	123 (33.98)

N, number of admissions
Date of last follow-up: December 31, 2018
The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD10-CA) was used to classify diagnosis
[a]Any condition in less than 1% of patients
*Due to small sample sizes, any value less than 5 will be represented in table with (<5)
Renal failure: acute renal failure with tubular necrosis; acute renal failure, unspecified; chronic kidney disease, stage 5
Cardiac: acute subendocardial myocardial infarction; aortic (valve) stenosis; atherosclerotic heart disease of native coronary artery; atrial fibrillation/flutter; congestive heart failure; bradycardia, unspecified; disease of pericardium, unspecified; endocarditis, valve unspecified; other cardiomyopathies; pleural effusion; sick sinus syndrome; ventricular tachycardia
Leukemia: chronic lymphocytic leukemia of B-cell type; diffuse large B-cell lymphoma; Hodgkin lymphoma, unspecified; lymphoid leukemia, unspecified; non-Hodgkin lymphoma, unspecified; small cell B-cell lymphoma
Cataract: cataract, unspecified; other senile cataract; senile nuclear cataract
Infections: acute bronchiolitis due to respiratory syncytial virus; acute upper respiratory infection, unspecified; cellulitis of lower limb and face; disseminated cryptococcosis; gastroenteritis and colitis of unspecified origin; mastoiditis, unspecified; other pulmonary aspergillosis; other bacterial infections of unspecified sites; pulmonary cryptococcosis; pulmonary nocardiosis; urinary tract infection
Inflammation: acute appendicitis; acute pharyngitis, unspecified; acute tubule-interstitial nephritis; biliary acute pancreatitis; bronchiectasis; chronic pansinusitis; chronic sinusitis, unspecified; enterocolitis; hemorrhoids; infective myositis, pelvic region, and thigh; inflammatory disorders of scrotum
Bleeding: gastric ulcer, acute with hemorrhage; gastrointestinal hemorrhage, unspecified; hemorrhage and hematoma complicating a procedure; hemorrhage of anus and rectum
Cytopenias: anemias; neutropenias; thrombocytopenias
Pneumonia: includes Legionnaires' disease

The most common diagnoses of patients visiting the ED were as follows: infections (15.54%), pneumonia (8.78%), cardiac events (8.45%), cytopenias (6.08%), inflammation/swelling (5.07%) and bleeding (3.38%) (Table 22). The top cardiac event was AF/flutter (3.72%), (Table 22).

Table 22. Emergency department discharge diagnosis by physicians for the ibrutinib treated cohort until death or date of last follow-up (where available; N=296 visits)

ED Discharge diagnosis	N (%)
Infections	46 (15.54)
Pneumonia	26 (8.78)
Cardiac events	25 (8.45)
Atrial fibrillation/flutter	11 (3.72)
Congestive heart failure	<5*
Palpitations/unstable angina	<5*
Pleural effusion	<5*
Acute myocardial infarct	<5*
Pulmonary embolism	<5*
Acute pericarditis	<5*
Cardiovascular system disorder	<5*
Bradycardia	<5*
Cytopenias	18 (6.08)
Medical care, other	16 (5.41)
Inflammation/swelling	15 (5.07)
Bleeding	10 (3.38)
Chest pain	9 (3.04)
Fever	9 (3.04)
Abscess	7 (2.36)
Chronic obstructive pulmonary disease exacerbation	6 (2.03)
Weakness/ Fatigue	6 (2.03)
Leukemia	5 (1.69)
Abdominal pain/ Colic	<5*
Syncope/Vasovagal	<5*
Left without being seen/against medical device with no diagnosis	<5*
Back pain	<5*
Cough	<5*
Abnormal results blood chemistry	<5*
Superficial injury head	<5*
Complication prosthetic/ implant/ graft	<5*
Other[a]	71 (23.99)

N, number of emergency department visits
Diagnostic groupings were determined using The Canadian Emergency Department Diagnosis Shortlist (CED-DxS), version 7.2 (March 2021)
Superficial injury: abrasion/contusion/superficial hematoma
[a]Any condition in less than 1% of patients
*Due to small sample sizes, any value less than 5 will be represented in table with (<5)
Cytopenias: anemia, neutropenia; Infections: septicemia; cellulitis; urinary tract infection; upper respiratory tract infection; bacteremia; mastoiditis; viral infection; paronychia finger; Cardiac: atrial fibrillation/flutter; congestive heart failure; palpitations/unstable angina; pleural effusion; acute myocardial infarct; pulmonary embolism; acute pericarditis; cardiovascular system disorder and bradycardia; Bleeding: epistaxis; coagulation defect; conjunctival hemorrhage; hemoptysis; Inflammation/ swelling: pharyngitis, acute; swelling, mass, and lump; conjunctivitis; otitis media; bronchiectasis; hemorrhoids; acute pancreatitis; arthritis, unspecified; Abscess: abscess/ furuncle/ carbuncle; anorectal abscess

4.3 IGHV and FISH testing in CLL/SLL patients in BC

4.3.1 Clinical characteristics

A total of 411 CLL/SLL patients had an IGHV test completed at VGH from June 2019 to May 2021, with 195 and 216 patients tested in Y1 andY2, respectively. Patients were predominantly male (62.3%), with a median age at diagnosis of 63 years (range, 31-92 years). Baseline characteristics are listed in Table 23. Where date of diagnosis was available (98.8%, 406/411), the median time from diagnosis until IGHV test date was 3.3 years (range, 0.0-22.8 years). Prevalence of FISH (n=282) abnormalities at time of IGHV test were: 8.9% del(17p), 9.6% del(11q), 16.0% tris 12, 54.6% del(13q), and 29.1% had none of the 4 FISH abnormalities.

Table 23. Clinical characteristics of BC CLL/SLL patients with IGHV mutational testing completed (N=411)

Baseline, N (%)	**Total**	**Y1 N=195**	**Y2 N=216**	**P-value**
Male	256 (62.3)	121 (62.1)	135 (62.5)	0.925
At time of diagnosis				
Rai stage 3-4	17 (4.1)	11 (5.6)	6 (2.8)	0.629*
Median age, yrs (range)	**N=409**	**N=195**	**N=214**	
	63 (31-92)	62 (31-92)	64 (40-91)	0.012
Time to IGHV test, yrs (range)	**N=406**	**N=194**	**N=212**	
	3.3 (0.0-22.8)	3.2 (0.0-22.8)	3.3 (0.0-20.6)	0.849
At IGHV test date				
FISH prevalence	**N=282**	**N=142**	**N=140**	
Deletion 17p	25 (8.9)	11 (7.7)	14 (10.0)	0.506
Deletion 11q	27 (9.6)	17 (12.0)	10 (7.1)	0.168
Trisomy 12	45 (16.0)	27 (19.0)	18 (12.9)	0.158
Deletion 13q	154 (54.6)	81 (57.0)	73 (52.1)	0.409
Normal (or None of the above)	82 (29.1)	34 (23.9)	48 (34.3)	0.056

FISH, fluorescence *in situ* hybridization; N, number of patients; Y, year; yrs, years
*Chi-square analysis assumptions were not met, Fisher's exact test was computed in its place

4.3.2 IGHV mutation status

A total of 396 (96.4%) patients had a mutational status defined. Within the entire cohort, 58.2% had a mutated IGHV, 38.2% had an unmutated IGHV and 3.6% had an undetermined/failed status

reported. IGHV test characteristics by year of implementation are shown in Table 24. There were no differences in test results (mutated, unmutated, or undetermined) based on year of testing (*P*=0.549). A total of 301 (73.2%) patients had information available pertaining to reasoning behind genomic testing (FISH and IGHV). Where reason for testing was available (n=301), 233 (77.4%) patients completed testing for baseline/prognostication reasons and 68 (22.6%) patients had genomic testing for treatment planning purposes.

Table 24. IGHV mutational status results and testing characteristics (N=411)

Variable, N (%)	Total	Y1 N=195	Y2 N=216	P-value
Mutational status				
Unmutated	157 (38.2)	76 (39.0)	81 (37.5)	0.549
Mutated	239 (58.2)	110 (56.4)	129 (59.7)	
Undetermined	15 (3.6)	9 (4.6)	6 (2.8)	
Reason for test				
Baseline/prognostication	233 (56.7)	104 (53.3)	129 (59.7)	<0.001
Treatment planning	68 (16.5)	49 (25.1)	19 (8.8)	
Missing/unknown	110 (26.8)	42 (21.6)	68 (31.5)	
Test that influenced treatment decision	**N=68**	**N=49**	**N=19**	
IGHV	27 (39.7)	21 (42.9)	6 (31.6)	0.546*
FISH	11 (16.2)	7 (14.2)	4 (21.0)	
Both	30 (44.1)	21 (42.9)	9 (47.4)	

FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable region; N, number of patients; Y, year

*Chi-square analysis assumptions were not met, Fisher's exact test was computed in its place

Stereotype subsets were available for 388 (94.4%) patients. They were as follows: 1.0% good prognosis, 3.6% poor prognosis, 89.8% no prognosis, and 5.6% undetermined. This was further stratified by IGHV mutation status as seen in Table 25.

Table 25. Homology and subsets by IGHV mutational status

N (%)	Mutated N=239	Unmutated N=157	P-value*
Homology identity			
<97.00% (Mutated)	220 (92.1)	0	<0.001
97.00-97.99% (Borderline mutated)	19 (7.9)	0	
≥98.00% (Unmutated)	0	157 (100.0)	
Stereotype prognosis based on subset			
Good	3 (1.3)	1 (0.6)	<0.001
Poor	2 (0.8)	13 (8.3)	
None	226 (94.6)	135 (86.0)	
Undetermined	8 (3.3)	8 (5.1)	

N, number of patients
Good: subset 4
Poor: subsets 1, 2 and 8
None: unassigned, subset not defined as per ERIC guidelines
Undetermined: missing or blank
*Chi-square analysis assumptions were not met, Fisher's exact test was computed in its place

Of the 68 patients who had IGHV testing for treatment planning purposes, 55 (80.9%) were treated in 1L, 7 (10.3%) in 2L and 6 (8.8%) in 3L+. The median age of patients at treatment was 68.5 years (range, 39-92 years). When both FISH and IGHV test results were assessed together for the treated cohort (n=68), 27 (39.7%) patients had their treatment decision influenced primarily by their IGHV status, 11 (16.2%) by their FISH status and 30 (44.1%) by both their IGHV and FISH results. The most common treatment type for both those with mutated (13/23, 56.6%) and unmutated (36/45, 80.0%) IGHV status was ibrutinib, with a larger majority in the unmutated group (Table 26). In addition to ibrutinib, 34.8% (8/23) of patients with mutated IGHV status were prescribed CIT (BR or FCR/FR), while 15.6% (7/45) of patients with unmutated IGHV status were prescribed other novel agents including acalabrutinib or venetoclax-based therapy, while 4.4% went onto allogeneic stem cell transplant (Table 26).

Table 26. Treatment type stratified by IGHV mutation status

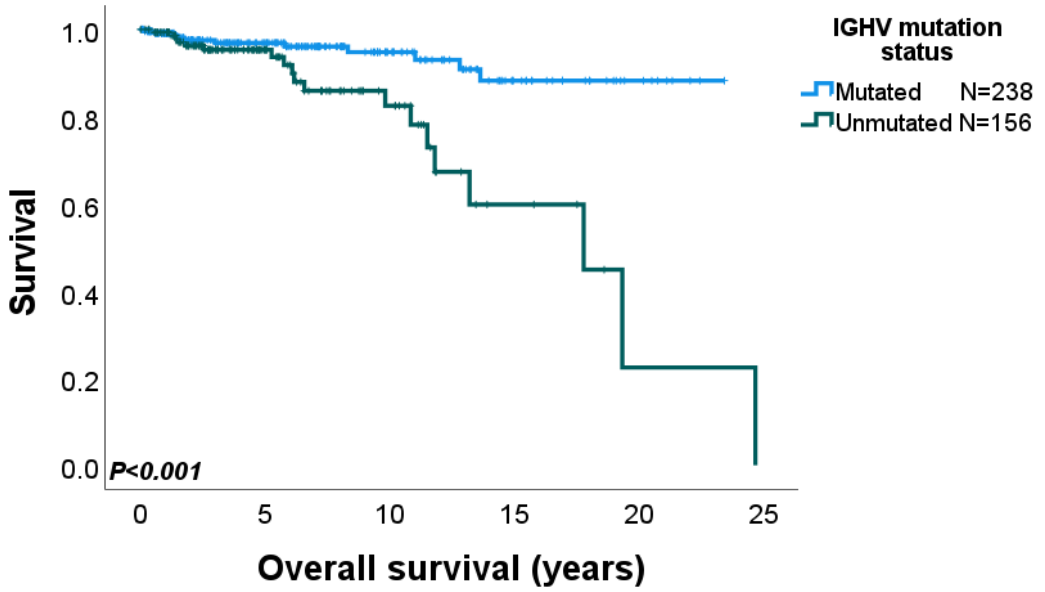
Treatment, N (%)	Mutated N=23	Unmutated N=45
Ibrutinib	13 (56.6)	36 (80.0)
BR	6 (26.1)	0
Acalabrutinib	0	5 (11.2)
Allogeneic stem cell transplant	0	2 (4.4)
FCR/FR	2 (8.7)	0
Venetoclax-rituximab	0	2 (4.4)
Rituximab	1 (4.3)	0
Acalabrutinib-obinutuzumab-venetoclax	1 (4.3)	0

N, number; BR, Bendamustine and Rituximab; FCR, Fludarabine, Cyclophosphamide and Rituximab; FR, Fludarabine and Rituximab

4.3.3 Survival outcomes

A total of 7.8% (32/411) of patients died at the time of last follow-up. Median follow-up for patients alive (n=377) at last follow-up from time of diagnosis was 4.6 years (range, 0.0-23.4 years). The 36-month OS from time of diagnosis was significantly different between patients with mutated (96.9%) and unmutated (95.3%) IGHV status (P<0.001) (Figure 5).

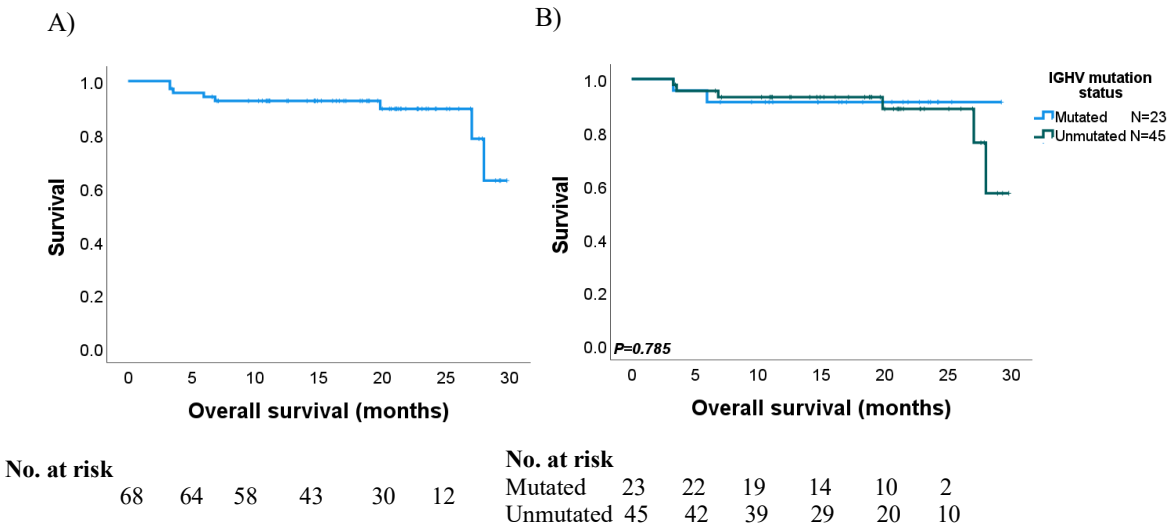
Figure 5. Unadjusted overall survival from time of diagnosis stratified by IGHV mutation status



No. at risk					
Mutated	238	129	62	25	8
Unmutated	156	60	24	6	1

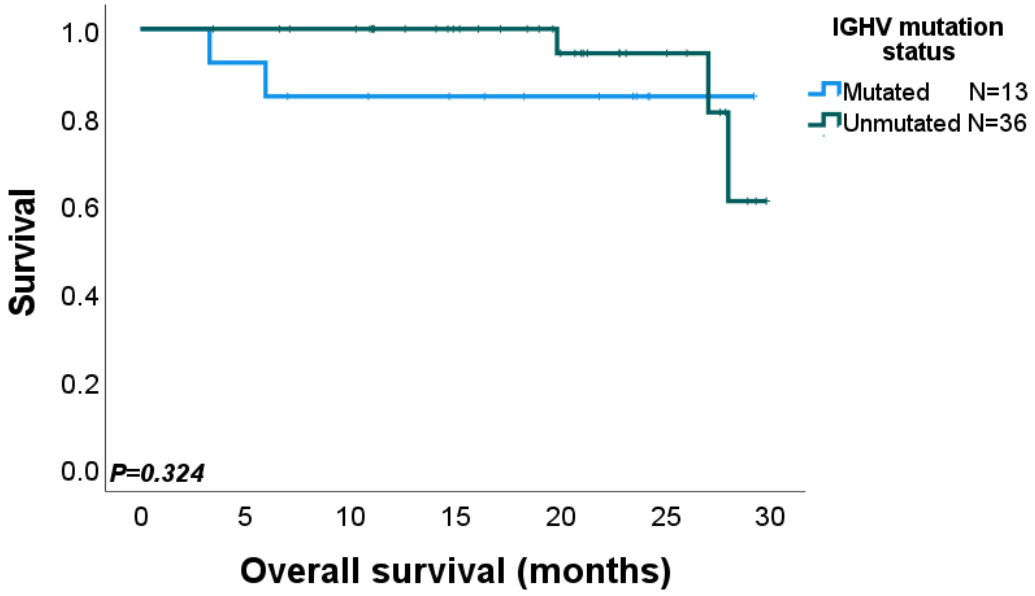
For the cohort of patients who received treatment based on their IGHV test, medial follow-up for living patients (88.2%, 60/68) from treatment initiation was 18.9 months (range, 3.5-29.8 months). The 24-month OS from time of therapy initiation was 89.6% for the treated cohort of patients (n=68), with the median not reached (Figure 6A). When stratified by mutational status, 24-month OS was not significantly different for patients with mutated (91.3%) and unmutated (88.7%) IGHV status (*P*=0.785) (Figure 6B).

Figure 6. Unadjusted overall survival from time of treatment initiation. A) Whole treated cohort (N=68), B) By IGHV mutation status



Including only patients treated with ibrutinib (n=49), 24-month OS from time of therapy initiation was not significantly different between patients with mutated (84.6%) and unmutated (94.4%) IGHV status (*P*=0.324) (Figure 7).

Figure 7. Unadjusted overall survival from ibrutinib therapy initiation stratified by IGHV mutation status



No. at risk						
Mutated	13	12	10	8	6	1
Unmutated	36	35	33	24	17	9

4.3.4 Cost analysis, resource utilization and testing challenges

Information in this section was provided by the Director of the VGH Cytogenetics Laboratory (Helene Bruyere, email communication, March 2022). The MSP fee in BC is $296.18 per IGHV test. This includes technician labour and medical interpretation. This fee was set in 2018. This value does not include the cost of having to send samples for further analysis at UHN. In addition, since this time, the protocol has been altered and costs of laboratory reagents have increased due to the impact of the COVID-19 pandemic on the economy.

Based on the current MSP fee of $296.18/test, for a total of 411 tests, the cost for IGHV testing in BC was $121,729.98 between June 2019 – May 2021, for 2 years. For 195 tests in Y1 this amounts to a total of $57,755.10 and in Y2, we recorded 216 tests, amounting to $63,974.88. This results in an

average total cost of $60,864.99 per year on the healthcare system. Concerning resource utilizations, testing is split into three main components: (i) library preparation, (ii) sequencing and (iii) analysis. Key expertise is required to complete testing and as a result, training is completed for the different components of the protocol. There is currently 1 technologist trained on part one only, 3 trained on parts one to three, and 2 technologists trained solely on part three.

Feedback from the director of the VGH Cytogenetics Laboratory identified three areas of difficulty when conducting IGHV testing. The solutions that have been adopted or were proposed will be discussed in section 5.3.4. Firstly, about 1 sample in every couple of batches (20 samples/batch) does not identify a productive clone, thus status remains undetermined. The FR1 assay required to determine the status is designed to run 5 samples. The main problem with conducting the FR1 assay locally in BC is that it would be a long time before 5 samples are collected to run a batch, resulting in a turnaround time of about 6 months. In addition, the FR1 assay has not yet been validated at VGH, unlike the IGHV mutational status test, which has undergone validation.

The second challenge is the timing of testing. Samples are batched (20 samples/batch) to decrease overall costs. However, at times, the VGH Cytogenetics Laboratory had to wait over 1 month to run a batch, while at other times, they receive more than 20 samples within a 3-week period. With about 200 samples being tested each year, this phenomenon makes it difficult for tests to be completed at set intervals, for personnel to plan and results in an increased turnaround time for samples that arrive during the slower periods.

The last challenge identified involves the testing protocol. IGHV testing requires repetitive pipetting of very miniscule quantities completed manually by lab personnel. Such a repetitive task can be time consuming and can introduce error when reporting results due to human limitations.

Chapter 5: Discussion

In this comprehensive characterization of the population-level impact of the introduction of ibrutinib for CLL/SLL patients in BC, we have demonstrated the following: (i) high rates of discontinuations due to AEs in a real-world setting, (ii) average costs and HCU associated with ibrutinib therapy, and (iii) the potential for IGHV testing to help guide treatment decisions and improve patient outcomes. This section will compare our results in light of the current understanding in the literature.

5.1 Impact of ibrutinib therapy in BC

In this real-world, population-based cohort of patients with CLL/SLL, treatment with ibrutinib led to good survival outcomes in both the 1L and R/R settings; however, a high-proportion of patients, 35.1%, discontinued ibrutinib (including death) during the median 27.2 months of follow up for living patients, primarily due to toxicities. Those who discontinued ibrutinib had poor survival outcomes, which were not different whether ibrutinib was discontinued due to drug-related toxicities or due to progressive disease.

5.1.1 Dose reductions, holds and discontinuations of ibrutinib therapy

We demonstrated that 31.7% of patients on ibrutinib in our cohort required a dose reduction, primarily for toxicities. This is a higher rate than that reported in clinical trials, where dose reductions are reported in 13-20% of patients.[32,40] Our results, on the other hand, match those of other real-world studies conducted with similar median follow-up times and cohort makeup (majority R/R patients), which report rates of dose reduction on ibrutinib of 24-33%.[47,48,80,81] Real-world studies are thus consistently demonstrating that approximately a third of all patients on ibrutinib are going to require a dose reduction during the course of their treatment.[46] In our study, dose reductions were less frequent in

the 1L setting, with only 12.5% of patients requiring a dose reduction compared to 33.7% in the R/R setting. Although lower reduction rates in 1L are seen in other studies, the difference is not as striking as what we demonstrate in this analysis, for example, Frei et al (25% 1L vs 33% R/R) and Hou et al (25% 1L vs. 27% R/R) saw similar rates in both settings.[47,80] Higher rates of dose reductions are expected in the R/R setting however, as R/R patients are generally older with numerous comorbidities (as seen in this study) and have been exposed to prior toxic therapies, making them more prone to adverse effects associated with subsequent treatment.

For dose holds, 27.3% of patients in our cohort held their ibrutinib at some point during their therapy, as recorded by physicians, with the most common reasons for dose holds being cytopenias, infections, pneumonia, and AF. In comparison, the RESONATE-2 study reported 51% of ibrutinib-treated CLL patients holding treatment due to any grade AE[32], however this was over 5 years of follow-up compared to our median follow-up of just over 2 years. Our results more closely match other real-world studies, such as a French Innovative Leukemia Organization group study which reported a hold in ibrutinib among 27% of patients during the first year of therapy[38] and Hou et al, that reported a rate of dose holds at 34% in 1L and 40% in R/R patients.[80] As a result of these high rates of dose reductions and dose holds in the real-world setting, investigators have been prompted to evaluate alternative dosing regimens to minimize toxicity.[82,83] For example, Chen et al, conducted a pilot study where they systematically lowered the ibrutinib dose (cycle 1: 420 mg/d, cycle 2: 280mg/d and cycle 3: 140 mg/d) over the span of three cycles (28 days/cycle).[83] They demonstrated that after only one cycle of ibrutinib at the standard dosage of 420 mg per day, the dose could be lowered without compromising biological activity.[83] These promising studies and results urge for more research focused on assessing different dosing regimens with ibrutinib, which may lead to the need for fewer dose reductions and holds.

Concerning discontinuations, we observed 106 patients (28.6%) discontinue ibrutinib (excluding death) due to toxicity (50.0%), progression (31.1%), and other reasons (18.9%). Most of the patients who discontinued ibrutinib had R/R disease, n=49/106 (46.2%) and n=44/106 (41.5%), 2L and 3L+ patients, respectively. Initially, the RESONATE and RESONATE-2 clinical trials with short median follow-up times (9.4 – 18.4 months) and very few patients discontinuing ibrutinib, reported discontinuation due to AEs at low rates of 4% and 9%, respectively.[27,28] With longer follow-up, however, the RESONATE (44 months) and the RESONATE-2 (60 months) studies reported higher discontinuation rates mimicking those reported by other real-world studies.[32,40] The former, saw disease progression and AEs result in 27% and 12% of ibrutinib discontinuations, respectively, totaling a 39% discontinuation rate.[40] The latter, reported a 41% discontinuation rate (including death) in the ibrutinib treated patients, with AEs emerging as the most common reason for discontinuation in 21% of patients followed by progressive disease in 6% of patients.[32] Winqvist et al, similarly to the RESONATE and RESONATE -2 trials after longer median follow-up time (30 months) saw the discontinuation rate jump from 24% to 49% in the real-world.[42,81] Following this trend, real-world studies conducted with large sample sizes and comparable median follow-up times to our study, reported high discontinuation rates (26% - 42%).[35,47,80,84–86] The rate of discontinuation seen in these real-world studies matches more closely our analysis where we included death as a reason for discontinuation (35.1%).

In our cohort, 130 patients (35.1%, including death) discontinued ibrutinib due to toxicity (48.5%), progression (33.1%), and other reasons (18.4%). Given the challenges of attributing death due to toxicity in a non-clinical trial setting, we conducted a separate toxicity analysis with deaths on ibrutinib excluded. Even in this analysis, toxicity remained the most common reason for discontinuation, with 53 of 106 patients (50.0%) discontinuing due to toxicities. This is consistent across the vast majority of the real-world studies, whereby toxicity (37%-63%) is the most common reason for discontinuing ibrutinib therapy.[35,47,80,85–88] In contrast, studies using clinical trial patients

reported disease progression as the main reason for ibrutinib discontinuation.[89,90] This highlights the importance of toxicity in the setting of ibrutinib discontinuation in the real-world that was previously underestimated by clinical trials. The most prevalent toxicities leading to discontinuation in our cohort were infections, musculoskeletal symptoms, fatigue, and bleeding/hemorrhage. Consistently, across real-world studies assessing toxicities resulting in discontinuations, infections are one of the most common toxicities observed.[35,41,47,80,81,84–87] We also reported 10/53 (18.9%) patients discontinuing due to any cardiac condition, with 7/53 (13.2%) due to AF/flutter, which is in line with prior studies which report 10-25% of patients discontinuing due to AF and other arrhythmias.[35,47,80,84–87] However, at ibrutinib initiation, we reported 8.6% of patients with a history of AF/flutter, making a considerable amount of our patients in this analysis susceptible to future events of AF. Toxicities, however, were not only limited to patients who had to discontinue or modify their dose.

5.1.2 Toxicities on ibrutinib therapy

In our cohort of primarily older CLL/SLL patients with underlying comorbidities, the majority of whom (90.5%) were on ibrutinib for R/R disease, we observed that (n=323/370) 87.3% of patients experienced at least one toxicity anytime during their exposure to ibrutinib. The most common toxicities were bruising, musculoskeletal symptoms, fatigue, bleeding, AF/flutter and cytopenias. Although, very high rates of toxicities are observed in clinical trials with virtually every patient experiencing a toxicity sometime during their treatment, the more frequent types of toxicities reported differ, such as diarrhea, fatigue, nausea and cough predominating even with longer median follow-up time.[27,28,32,40] Mirroring what we observed, real-world studies reported similar toxicities as seen in our study more frequently such as bleeding/hemorrhage, bruising, AF, cytopenias and infections.[33,35,37,41–43,91] It appears that more serious toxicities are the more frequent toxicity types reported in the real-world compared to in clinical trial settings. This discrepancy in types of toxicities noted however may

be due to the way toxicities are documented in clinical trials. Due to the careful follow-up and observation conducted in clinical trials, more minor toxicities may be better documented in clinical trial notes compared to those available in clinical notes from non-clinical trial settings.

In our study, we reported AF/flutter in 10.3% of all patients during their ibrutinib treatment, which is in line with other real-world studies that also reported high rates of AF (9%-16%).[33,35,41,43,81] Fradley et al, recently highlighted in their study comparing patients with B-cell malignancies on either ibrutinib or chemotherapy, that ibrutinib treated patients are 5 times more likely to develop atrial arrhythmias compared to patients treated with chemotherapy.[92] Avalon et al, also demonstrated that in their study of 217 patients on ibrutinib (median follow-up of 1.1 years), the group with a history of cardiovascular disease had almost a 3-fold higher rate of new-onset AF compared to the group with no prior history.[93] These studies suggest that patients with a prior history of cardiovascular disease or events, like our cohort have a higher likelihood of experiencing atrial arrhythmias because of their ibrutinib treatment. Toxicity as a reason for discontinuation also resulted in poorer survival outcomes for patients compared to the whole cohort as reported in section 5.1.3.

5.1.3 Survival outcomes on ibrutinib therapy

Our results demonstrated a good 24-month OS from time of ibrutinib initiation for the entire cohort at 83.9% with the median not reached. This is lower than what is reported in the RESONATE-2 trial that showed a 24-month OS of 98%.[28] Our cohort however was comprised of mainly R/R patients and a higher than normal number of patients with del(17p) at time of therapy (23.9%), likely explaining the lower OS. Similarly, stratifying by line of therapy 24-month OS remained good (81%-86%) for all three lines of therapy. These results are consistent with those of clinical trials with longer-term median follow-up, for example the RESONATE and RESONATE-2 trials reported 74% and 83% alive at 36

and 60 months, respectively.[32,40] Similar to our study, real-world studies by Aarup et al. reported a 24-month OS of 76.8%[35], Visentin et al. reported a 24 month OS of 95% (1L patients only)[34] and Mato et al. reported that median OS was not reached (median follow-up of 17 months).[84] Mato et al, using the Connect CLL Registry with comprehensive data from 199 US sites, demonstrated that, compared to other CITs, ibrutinib proved beneficial in the R/R setting.[94] OS was improved for patients receiving ibrutinib in 2L and in all other lines of therapy after 1L.[94] Additionally, ibrutinib resulted in improved OS in patients receiving it in 2L after 1L treatment with FCR or BR compared to patients receiving FCR or BR instead of ibrutinib in 2L.[94] Considering our cohort is comprised primarily of R/R patients, this confirms the reasonable OS reported in this study and provides compelling evidence for the continued use of ibrutinib routinely in a clinical setting in R/R patients. Our results also demonstrated a good 24-month TFS from time of ibrutinib initiation for the entire cohort at 76.1%, with the median not reached. Similarly, stratifying by line of therapy 24-month TFS remained good (73%-77%) for all three lines of therapy. Visentin et al, demonstrated a high 24-month time to next treatment (TTNT) of 97% in the ibrutinib cohort, however the study only included 1L patients, and TTNT was defined using the International Workshop on CLL (IWCLL) 2018 guidelines.[5,34] It is important to note however that the IWCLL definitions of TTNT does not count death as an event, whereas our TFS calculation did, potentially accounting for some of the differences observed. We opted to report TFS instead of PFS, as we believe it to be more clinically relevant and accurate in observational studies. In the real-world, unlike clinical trial settings, we do not know exactly when patients have progressed due to inconsistencies in follow-up visits, laboratory tests and imaging, however we are able to track accurately when patients have gone on to a new line of therapy. Clinical trials on the other hand can systematically document progression due to consistent follow-up with patients.

From time of ibrutinib discontinuation, excluding death, median OS for the entire cohort was reached at 32.5 months. Comparing lines of therapy, 24-month OS was lower for progression (52.1%)

compared to toxicity (66.3%), however differences were not found to be significant (*P*=0.080). When death was included, median OS from time of discontinuation for the entire cohort was reached earlier at 27.8 months and there was a borderline significant difference (*P*=0.049) between 24-month OS when comparing discontinuation due to toxicity (55.8%) and progression (40.0%). Aarup et al, reported a median OS from time of discontinuation of 18.2 months.[35] We surprisingly reported a longer median OS for the entire cohort compared to Aarup et al. An even shorter median survival after discontinuation of 7.8 months and 17.6 months for non-infectious AEs or other reasons and CLL progression, respectively was reported by Maddocks et al (median follow-up of 20 months).[95] This was a clinical trial that was completed early on in the development of ibrutinib and included high-risk patients who were multiply relapsed and had many lines of therapy prior to their ibrutinib.[95] Hampel et al, similarly to Aarup et al, reported a median OS post ibrutinib discontinuation of 18.5 months with significant differences (*P*=0.04) comparing median OS due to toxicity (27.8 months) and progression (11.5 months).[85] Only our analysis including death reached median OS, with a borderline significantly greater median OS for toxicity than progression (*P*=0.049) which is in line with the Hampel et al study. Our results also demonstrated from time of discontinuation (including death), a median TFS of 1.8 months and a significant difference when comparing discontinuation for toxicity (median 6.8 months) and progression (median 0.2 months) (*P*<0.001). This is also in line with the Hampel et al study, that reported a median TTNT of 2.7 months, similarly with a significant difference when comparing toxicity (median 6.5 months) and progression (median 0.3 months) as reasons for discontinuation (*P*<0.0001).[85] It is important to note that we included death as an event in our TFS calculations.

5.1.4 Limitations

Limitations of this analysis include those common to observational retrospective studies. Researchers completing retrospective studies do not have access to data collected for the purposes of

research.[96,97] Our analysis used data that was obtained via chart reviews of hospital records, was then entered into several clinical databases and was not collected by researchers specifically for this study.[97] The data available therefore may not be complete and lack information.[96,97] This resulted in us having to go back to the charts at different times to try to fill in missing data introducing the potential for error.[97] Further retrospective studies cannot be used to demonstrate causation between exposure and outcome variables.[98] This is due to two main reasons: (i) patients are not randomly distributed among the different groups and (ii) the associations determined may be due to confounders that have not been adjusted for in the analysis.[98] The CLL/SLL population is also highly heterogeneous, where a number of factors can influence outcomes. Specific CLL factors of importance include del(17p) status (absent or present), line of therapy (1L vs. R/R), age, Rai stage and AEs where applicable. We did not complete any adjustments for confounders in this analysis and as a result this may lead to incorrect associations between exposure and outcome variables.[97,98]

5.2 Healthcare utilization and costs of ibrutinib treated patients in BC

In this observational real-world analysis of 181 ibrutinib treated patients with CLL/SLL in BC, ibrutinib drug costs proved to be the primary cost to the Canadian healthcare system when compared to practitioner service costs, including either general practitioners or specialists. Ibrutinib treated patients were also shown on average be admitted to a hospital 1.5 times per year and visit the ER on average 2 times per year.

5.2.1 Ibrutinib therapy costs

We reported a mean PPPY cost of ibrutinib at $68,266.31. This amounted to a total of $25,053,734.91 for 174 patients, or $143,986.98 per patient, over the span of 3 years. The literature that surrounds economic burden of ibrutinib patients on the healthcare system were for the most part

completed in the USA.[49–51] American studies rely heavily on insurance (medical and pharmacy) claims as they do not have a publicly funded healthcare system like the one available in Canada. These studies consistently reported that pharmacy costs are the main drivers of high costs to the healthcare system in ibrutinib treated patients.[49–51] For ibrutinib costs specifically, an Italian study conducted by Ronconi et al, demonstrated that during both their first and second year of follow-up ibrutinib costs drove up the pharmaceutical costs making it the greatest expense when compared to other drugs, hospitalizations and outpatient specialist care.[99] They reported a mean ibrutinib per patient cost at €31,249 (~$42,143.18 Canadian dollars (CAD)) in the first year of follow-up and €38,816 (~$52,348.23 CAD) in the second year of follow-up for the second or later line users.[99] When converted to Canadian dollars this approaches what we saw over three years despite them not including 1L patients in this value for whom they saw higher mean costs in their study.[99] Irwin et al, also demonstrated that for their CLL-specific costs category, their ibrutinib cohort had a mean of $8,358 United States dollar (USD) (~$10,769.16 CAD) PPPM prescription/outpatient medical costs over a 12 month follow-up period.[52] Two potential explanations for why our result was lower than that reported by Irwin et al are: (i) their cohort was composed of solely 1L patients, whereas our cohort was primarily R/R patients, and (ii) ibrutinib drug costs in the USA are likely higher and so patients pay more for each ibrutinib prescription.

Specific to Canada, the pan-Canadian Oncology Drug Review (pCODR) final economic guidance report also described monthly ibrutinib costs.[100] The pCODR report was completed in 2015 based on data provided by the pharmaceutical company, Janssen, comparing the economic burden and benefits of ibrutinib and chlorambucil previously untreated CLL/SLL patients.[100] Using a partitioned survival model, they estimated ibrutinib and chlorambucil to cost over a 28-day period per patient at standard dose, $7,614.60 and $50.22, respectively.[100] Similar to this analysis, next we plan to compare

costs and HCU of our ibrutinib treated patients to a matched cohort of CIT treated patients to ascertain the costs and HCU associated with ibrutinib therapy on the healthcare system in the context of other approved therapies in Canada.

5.2.2 Practitioner services costs incurred by ibrutinib treated patients

Over 5 years, the total mean PPPY practitioner service costs were $2,917.57 for the entire cohort (n=181). When this was stratified by practitioner type, mean PPPY was $674.98 for general practitioner services and $2,288.93 for specialist services. Due to the nature of the healthcare system in Canada, we had access to the fee-for-service practitioners' data through MSP allowing us to determine costs for general practitioner versus specialist services. The current state of the literature includes predominantly studies completed in the USA.[49–51] As researchers relied heavily on insurance claims, they were able to further categorize costing into groups such as medical costs, pharmacy costs, inpatient costs, outpatient costs, ER costs and other services costs.[50,51] Studies have demonstrated the following when it came to different services costs. Kabadi et al, for example, reported that for their entire cohort of CLL patients on treatment (including BR, single-agent rituximab and FCR), the mean PPPM office visit costs was $236 USD (~$304.08 CAD) and for other services (including: laboratory and pathology, radiology, surgery, ancillary and others) was $1,832 USD (~$2,360.50 CAD).[44] Considering patients often relapse on other CLL treatments, especially CIT, it would follow that CIT treated patients would incur high costs associated with obtaining services and this is what is generally observed in US studies.[49–51] Irwin et al, reported a mean PPPM total outpatient medical costs of $2,809 (~$3,619.35 CAD) in the all-cause healthcare costs category for ibrutinib treated patients over a follow-up period of 12-months.[52] While, Ronconi et al, reported on outpatient specialist care, where they showed over the first year of follow-up a mean per patient cost of €711 (~$958.80 CAD) and €1,062 (~$1432.13 CAD) over the second year of follow-up in second or later line users.[99] This last study's

specialist care cost lines up with our specialist services costs and discrepancies may be attributed to what was included in each definition.

We reported out of a total 67,514 visits only 379 (0.56%) were completed by hematologists/oncologists. Considering our cohort is comprised of CLL/SLL patients, we would expect that hematologist/oncologist visits made up the bulk of the healthcare practitioner costs. The reason behind this discrepancy is that most hematologists/oncologists in BC including those employed at BC Cancer are not paid via the fee-for-service plan available in the MSP dataset, but rather through alternate payment plans (Deirdre Weymann, email communication, May 2022). Data received from Population Data BC only includes MSP billing codes. For our final objective, we plan to use similar methodology employed by Weymann et al.[69] Upon receiving the full Population Data BC dataset, we will proceed by identifying all hematologist/oncologist visits using BC Cancer scheduling data and then use published MSP fees to assign unit costs to visits (Deirdre Weymann, email communication, May 2022).[69]

5.2.3 Healthcare utilization in ibrutinib treated patients

With few studies available for comparison, we will compare our results to that completed by Irwin et al.[52] In their pharmaceutical sponsored study, Irwin et al used a large USA administrative claims database to compare costs and HCU of CLL patients treated 1L with ibrutinib or BR.[52]

Irwin et al, reported only 34% of their ibrutinib cohort had at least one all-cause inpatient admission.[52] Whereas in our study, over a 5-year study period we reported 64.6% of our cohort being hospitalized. The mean PPPY number of total admissions for the entire cohort in our study was 1.47. While they reported a mean PPPM number of all-cause inpatient admissions of 0.13.[52] This is in line

with what we reported on PPPY basis. Furthermore, we reported a mean inpatient length of stay PPPY of 8.32 days. Their study reported a mean all-cause inpatient length of stay of 5.3 days.[52] This is similar to what we reported and discrepancies may be attributed to the cohort makeup in each analysis. Continuing with admissions, we reported on the most common diagnoses resulting in an admission. We found the following to be the most common: leukemia/lymphoma (11.05%), cardiac events (8.56%), infections (5.80%), pneumonia (5.80%) and cytopenias (5.52%). These are all common AEs associated with ibrutinib therapy. Unfortunately, due to the nature of the data used, we were unable to comment on whether the admissions and the AEs that resulted in an inpatient admission were ibrutinib-related.

Over 5 years, we reported a mean PPPY of 1.80 for all ER visits (including those not leading to an inpatient admission). They similarly reported on this and determined a mean PPPM of 0.18 for all-cause ER visits.[52] This approximates our results on a PPPY basis. In our study, we also reported on the most common diagnoses received by patients visiting the ER and they included infections (15.54%), pneumonia (8.78%), cardiac events (8.45%) and cytopenias (6.08%), all common AEs associated with ibrutinib therapy. Due to the nature of the data used, we were unable to comment on whether the diagnoses during ER visits were ibrutinib-related.

The overall conclusion of the Irwin et al study was that ibrutinib resulted in higher rates of inpatient admissions, longer lengths of stays, more ER visits and higher costs (except for outpatient medical costs) compared to BR.[52] Future directions for our group includes conducting a comparative matched analysis assessing HCU and costs for ibrutinib patients compared to CIT treated patients using Population data BC administrative databases.

5.2.4 Limitations

For Objective 2 we relied heavily on the data available through the administrative databases requested from Population Data BC. Due to the publicly funded healthcare system in Canada, we had access to data on patients treated in BC allowing us to complete population-level HCU and costing analysis. Because of the nature of the data, we were subject to the same observational retrospective study limitations described in detail in section 5.1.4.

In addition, due to the nature of the data we were unable to comment on ibrutinib-specific HCU and costs. The data provided contained all costs and healthcare resources used by our cohort regardless of whether they were ibrutinib-related or not. Therefore, our results and analysis cover healthcare costs and utilization of ibrutinib treated patients and not ibrutinib specific outcomes. Similarly, we could not further filter the diagnosis of patients during inpatient admission and at the ER into only ibrutinib-related events. These parameters limited our ability to analyze specific outcomes related to the ibrutinib treatment itself. Another limitation included the nature of the costing data. Costing data is largely skewed, typically does not meet the assumption of constant variance (homoscedasticity) during analysis and for patients who incurred no costs during the study timeframe contains zeros.[101–103] In this study, the data was right-censored as some patients had to stop treatment earlier for whatever reason. To address this issue, we implemented a time limit.[104] We chose to limit part of our analysis to only patients with a minimum of 6-months therapy (complete cases) to ensure that we captured all costs for patients known to have been on treatment for a full 6 months.

Due to delays in obtaining data for the remainder of our cohort, there are other limitations of importance to note. We had a very small sample size, notably for patients receiving ibrutinib in a 1L setting. Due to the small sample size, we were unable to control/adjust for confounders and missing data as described in section 5.1.4. We were also unable to link the administrative data with CLL

specific data including FISH testing and other important clinical parameters required to comprehensively characterize the cohort.

5.3 IGHV and FISH testing in CLL/SLL patients in BC

In this analysis, we assessed the impact of IGHV mutational status genomic testing on CLL/SLL patient outcomes, survival and whether the testing led to informed decision making in routine practice for patients tested in BC, Canada. We also evaluated the costs, resource use and testing challenges associated with completing IGHV testing in BC. Many of the patients had mutated IGHV status and testing completed for baseline/prognostication purposes. Where available, genomic testing appeared to result in improved patient outcomes for those whose test influenced their treatment decision as survival outcomes were similar between IGHV mutated and unmutated patients, albeit follow-up was short.

5.3.1 Cohort testing characteristics

Overall, in this population-based cohort, 58.2% of patients had mutated IGHV while 38.2% had unmutated IGHV. This matches the results of Aarup et al, where they reported a rate of 27.2% of patients with unmutated IGHV status[35] but does not match those of other comparable retrospective studies that show higher rates of unmutated IGHV status (68%-79%) patients.[85,86,105] It is difficult to ascertain the reasons behind this difference, considering the literature is not conclusive at this time. Currently, subsets with firmly set prognostic implications include subsets 1, 2, 4 and 8.[60] Most tests completed (89.8%) had no prognosis assigned. Of those that were assigned more patients with mutated IGHV (1.3%) status had a good prognosis subset compared to those in the unmutated group (0.6%), which is expected. More patients in the unmutated group (8.3%) had a poorer prognosis subset

compared to those in the mutated group (0.8%), which is also to be expected. Two patients, however, had a poor prognosis subset in the mutated group, despite having a mutated IGHV status.

Our results further demonstrate that the uptake of the test increased in Y2 compared to Y1. The increase in uptake observed can be attributed to physicians over time becoming more familiar with ordering the test and it quickly becoming standard of care in BC to order IGHV testing prior to initiating treatment to help guide therapy decisions. Within the entire cohort, 22.6% (68/301) of patients had genomic testing influence the type of treatment they received. Interestingly, fewer patients in Y2 compared to Y1 had their test affect treatment decisions despite having more patients in Y2 compared to Y1. We would expect that with greater understanding of IGHV testing and results that more physicians would use the IGHV result to guide treatment. This may be the case due to our definitions associated with baseline/prognostication and treatment planning as very specific definitions were used to classify patients.

5.3.2 Treatment planning

In the entire cohort, the vast majority (80.9%, 55/68) of patients who had their genomic testing completed for treatment planning were treatment naïve. Patients with unmutated IGHV were predominantly prescribed ibrutinib and acalabrutinib (91.1%) rather than standard CIT because of their IGHV status. Patients with mutated IGHV also had a higher proportion of patients prescribed ibrutinib (56.6%), however, they also had a higher percentage of patients prescribed CIT, 34.8%, compared to 0% in the unmutated IGHV group. The results of this study thus demonstrated how knowledge of the IGHV mutational status led to informed decision-making and therapy selection. High rates of ibrutinib administration in the mutated IGHV group is most likely the result of the other criteria considered when administering ibrutinib, such as age and comorbidities. The median age of patients initiating

treatment was 68.5 years compared to 63 years for the entire cohort likely explaining the higher rate of ibrutinib administration in the mutated IGHV sub-group.

5.3.3 Survival outcomes

The entire treated cohort (n=68) had excellent survival with 24-month OS from time of treatment initiation of 89.6% with the median not reached. Interestingly, when we compared patients with unmutated IGHV and mutated IGHV, OS was significant between the groups from time of diagnosis (P<0.001); however, it was not significant from the time of IGHV-informed treatment initiation (P=0.785). In a systematic review published in 2016 compiling results from studies assessing IGHV prognostic merit, they determined that over all the studies they examined, patients with unmutated IGHV has significantly poorer median OS (range, 3.2-10 years) compared to those with mutated IGHV (range, 17.9-25.8 years).[106] Since our OS from time of diagnosis included all patients with IGHV mutation status and not only those whose tests were used to inform treatment decisions, it would follow that OS was shorter in patients with unmutated compared to mutated IGHV status. When we look at only patients whose tests affected their treatment decision, although follow-up is short, our results provided early evidence that IGHV testing led to informed decision making and improved patient outcomes, as patients with unmutated IGHV were administered treatment that led to similar survival compared to patients with mutated IGHV. This finding in our cohort can most likely be attributed to IGHV mutational status becoming a part of standard procedure for prognosis and to inform treatment decisions in BC patients.

Additionally, when we assessed only patients treated with ibrutinib (n=49), 24-month OS from ibrutinib initiation was not significantly different between IGHV mutated (84.6%) and unmutated IGHV (94.4%) patients (P=0.324). This finding also demonstrated the improved outcomes of

unmutated IGHV patients, as their 24-month survival rate matched that of real-world studies of mostly 1L patients on ibrutinib (69%-95%).[33–35] The 5-year follow-up of the RESONATE 2 trial similarly showed no significant difference in survival between unmutated and mutated IGHV patients on ibrutinib.[32] This was however done looking at PFS and not OS.[32] We thus provide compelling evidence that IGHV testing has led to informed decision making as OS was comparable between mutated and unmutated IGHV patients when the test affected their treatment administration, but longer follow-up is required to confirm this result.

5.3.4 Cost analysis, resource utilization and solutions to testing challenges

IGHV testing costs our provincial healthcare system approximately $296.18/test, summing to $121,729.98 between June 2019 – May 2021, which equated to an average of $60,864.99 per year on the healthcare system. Considering the one time test cost per patient is $296.18 and the average yearly per patient ibrutinib cost for the drug alone is $68,266.31, the cost of this test is highly reasonable, especially since it is typically a stable prognostic marker and testing is completed only once per patient.[58] In our analysis, we were also able to demonstrate the good usage of this test in informing treatment decisions and the good survival outcomes in real-world IGHV unmutated BC patients. With longer-term systematic data collection and larger sample sizes, this trend may be further elucidated. At this time, the clinical use and good outcomes demonstrated in this analysis provides further proof of the benefits associated with IGHV testing, justifying the costs involved.

In terms of the current challenges with the IGHV mutational status test, some solutions have been proposed (Helene Bruyere, email communication, March 2022). To address the issue of supplemental testing when status remains undetermined, the VGH Cytogenetics Laboratory chose to immediately ship samples to UHN each time an unproductive clone is discovered. Compared to VGH,

UHN collects samples from different labs to run the FR1 assay allowing them to process a greater number of IGHV samples and to provide a more reasonable turnaround time of about 4-5 weeks. For the fiscal year of 2022 (April 1, 2021 – March 31, 2022) the average turnaround time was 30 days for analysis completed at the VGH Cytogenetics Laboratory. To address the issue of testing timing intervals, the VGH Cytogenetics Laboratory has implemented a reduction in the number of samples per batch to 18 from 20. Although this will slightly increase the cost for the laboratory, the benefits will be a reduced turnaround time, resolution of the batch intervals issues and long wait times for laboratory personnel. Moreover, to address the testing protocol issue of repetitive pipetting, automation is being explored through the investment in a liquid handler. This will render testing more efficient and with fewer opportunities for human error.

5.3.5 Limitations

Due to the nature of the data, we were subject to the same observational retrospective study limitations described in detail in section 5.1.4. The primary limitation of this objective included the small sample size. As IGHV had only become routine practice in recent years, data available in the real-world is not yet comprehensive and available for large scale analysis. Secondly, we only had information for 73.2% (301/411) of patients available in their hospital charts to answer the specific aim of this objective relating to informed treatment decision making. Lastly, our criteria for treatment planning, involved patients starting treatment within one year of their IGHV test and needing to also have their FISH and/or IGHV results directly influence the decisions being made as identified through patient records. Generally, we found several factors such as age, comorbidities, CIT-ineligibility, and others collectively alongside FISH and/or IGHV to influence treatment decisions. Intent of treatment without further rationale provided was not considered as treatment planning or informing decisions.

Chapter 6: Concluding Remarks

To the best our knowledge, this is the first of its kind, real world, study to comprehensively characterize the impact of the introduction of ibrutinib for CLL/SLL patients on a population-level. We integrated data from 3 different cohorts to assess ibrutinib uptake, patterns of use, frequency of toxicities, survival outcomes, costs and healthcare utilization, and the ability of genomic-based testing to influence treatment decisions.

We demonstrated high rates of discontinuation and dose modifications in ibrutinib-treated patients matching the high rates seen in other real-world studies published to date. We also reported good survival outcomes in both the 1L and R/R setting, but these survival outcomes were not maintained for patients who had to discontinue their treatment particularly due to drug-related toxicities and progressive disease that were both similarly poor. Our results complement the current literature in providing further evidence for the high rates of discontinuations, dose modifications and toxicities as well as shed light on the poorer survival outcomes experienced by patients who discontinue ibrutinib on a large-scale population-level. Considering the important role BTK inhibitors play in the R/R setting, future clinical directions should focus their efforts on assessing altered ibrutinib dosing regiments and newer generation BTK inhibitors with less off-target effects[107], due to their potential to lower rates of dose modifications, discontinuations, and toxicities.

Furthermore, we were in a unique position to complete a population-level analysis of costs and HCU of ibrutinib treated patients, with access to multiple provincial databases with detailed clinical, laboratory, and healthcare resource information. We showed that ibrutinib costs made up most of the costs to the Canadian healthcare system by ibrutinib treated patients. In general, practitioner service costs were shown to be higher for specialist compared to general practitioner services. Ibrutinib treated

patients also visited the ER and were admitted to hospital about 2 times per year. Due to the nature of the data, we were unable to limit costs and HCU to only ibrutinib-related AEs. Additionally, non CLL/SLL medication costs were not evaluated in our current analysis. Considering ibrutinib is associated with high rates of AEs, medications for toxicities may be an important cost associated with ibrutinib treatment to investigate. Recently, newer targeted therapies have emerged such as acalabrutinib, that demonstrate fewer off-target effects and greater selectivity for BTK than ibrutinib.[107] Likely due to the fewer off-target effects, acalabrutinib results in fewer therapy discontinuations due to AEs and lower rates of cardiovascular events.[64] With a higher healthcare system burden particularly due to AEs resulting in hospitalizations and increased medication use, treatment of patients may transition completely from ibrutinib towards less toxic BTK inhibitors like acalabrutinib.

Lastly, we demonstrated early evidence for the potential benefits and reasons for implementing IGHV testing at a provincial level. We showed that IGHV mutational testing was both affordable on a provincial level and easy to implement with few drawbacks. Despite much of our cohort completing IGHV testing for baseline/prognostication, we still highlighted early evidence for improved patient outcomes in IGHV unmutated patients who had their test influence the type of treatment they were administered. Our study provides a benchmark for future similar analyses. With longer-term systematic data collection, this trend may be fully elucidated. In the meantime, this analysis provides reason for other provinces in Canada to explore the inclusion of IGHV testing as standard of care and provides evidence in BC for continued funding of this test.

This study serves as a baseline for future studies despite the short follow-up. We acknowledge the lack of comparators in this analysis. In terms of future directions, as mentioned previously in this thesis, we plan to complete a comparative analysis for the same outcomes with a larger sample size.

We plan to compare the outcomes of ibrutinib treated patients to those of a matched control group of CIT treated patients.

In conclusion, ibrutinib leads to good survival outcomes in CLL/SLL patients, particularly those in the R/R setting; however, is associated with significant toxicity in the real-world, leading to requirements for dose holds and early discontinuation of therapy, which can compromise outcomes. We demonstrated the high-cost burden of ibrutinib on the Canadian healthcare system, highlighting the need to select the right patients for this costly treatment. Genomic-based testing with predictive markers can assist with this selection, and IGHV testing can play an important role in tailoring treatment for patients.

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Appendix

Supplementary Table 1. Total per patient practitioner service costs covered by MSP (Canadian dollar, $) from January 1, 2014 – December 31, 2018

Mean (SD)	Total N=181	1L N=9	R/R N=172
Total practitioner service costs from index therapy start date to death or date of last follow-up			
All	6,850.66	5,632.74	6,914.38
	N=179	**N=9**	**N=170**
General	1,530.96	1,510.50	1,532.04
	N=181	**N=9**	**N=172**
Specialist	5,336.61	4,122.24	5,400.16
	N=154	**N=7**	**N=147**
Total practitioner service costs from index therapy start date up to and including 6 months post-initiation (complete cases only)			
All	1,845.64	1,508.14	1,861.71
	N=148	**N=7**	**N=141**
General	429.61	332.43	434.43
	N=152	**N=7**	**N=145**
Specialist	1,451.62	1,175.71	1,464.94

MSP, medical services plan; N, number; SD, standard deviation
Adjusted for inflation Year 2021; All includes both services completed by general and specialist practitioners
Field used to determine cost may or may not include adjustments made and may not always accurately reflect the total amount paid by MSP for a claim