STUDIES ON SURVIVAL, EFFECTIVENESS, AND COST OUTCOMES OF FIRST LINE TREATMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA

by

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Dedication

This dissertation is dedicated to my beloved parents for their love and support throughout my life, and for giving me strength to reach the stars and chase my dreams. To my husband, Mohamad, for his patience, love, and unlimited support and for making everything possible. To my kids, Masa and Idrees, for making me stronger, better fulfilled than I could have ever imagined, and for their warm hugs, smiles and pure love that people freely die for.

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ABSTRACT

With the approval of targeted therapies as first line treatments in patients with chronic lymphocytic leukemia (CLL), the National Comprehensive Cancer Network (NCCN) guidelines list these agents as monotherapy or combined with immunotherapy as the preferred front-line regimens regardless of age, comorbidity, and 17p deletion/TP53 mutation or IGHV mutation status. Therefore, more challenges in choosing between treatments has been in the clinical practices especially by the absence of direct evidence or real-world data that compare between all treatments. We sought in this research to establish evidence that compares between all treatments in regards of effectiveness, survival, and costs. In an analysis of evaluating survival outcomes using the Surveillance, Epidemiology, and End Results (SEER) database (1985-2017), the relative survival rates, cure proportions and hazard of death rates were significantly improved for patients who followed to the era of advanced therapies. A second analysis of network meta-analysis on all survival curves of the published trials revealed that acalabrutinib-plus-obinutuzumab showed significant differences in the progression free survival (PFS) outcomes when compared with ibrutinib. While ibrutinib was not statistically significant from the other targeted therapies. Among patients with low-risk disease, there was no difference between the PFS of targeted therapies and chemoimmunotherapies, but probable gain in the time-to-next-treatment (TTNT) after administering targeted therapies can be achieved. In last analysis that compared the relative effectiveness with treatment's costs found that patients who are treated with targeted therapy "venetoclax-plus-obinutuzumab" gain more health benefits and less cost when compared with all chemoimmunotherapies, while the other targeted therapies achieve higher benefits than venetoclax-plus-obinutuzumab but with higher costs. Overall, there are

always superiority of targeted agents over chemoimmunotherapies in treating CLL patients, who are older than 65 years or having comorbidities, especially in patients with high-risk disease as having unmutated IGHV or del 17p. Acalabrutinib-plus-obinutuzumab is the combination that achieved the highest effectiveness outcomes in term of PFS and TTNT but with higher costs than others.

1.0 INTRODUCTION

Chronic lymphocytic leukemia (CLL) is an indolent malignancy characterized by increased production of mature but dysfunctional B lymphocytes. CLL accounts for 25–30% of total leukemias in the United States (U.S.) [1]. According to the National Cancer institute (NCI), approximately 21,250 new CLL cases and 4,320 deaths are expected in 2021 in the U.S. [2]. CLL is most frequently diagnosed in people between 65 and 74 years of age, and the median age at diagnosis is 70 years [3]. CLL has a higher incidence by 37% in male than female populations [4].

Overall, CLL has a higher relative survival than many other cancers. The 5-year survival rate can reach 86.1% [3]; that is, 86.1 out of 100 CLL patients will still be alive 5 years after the diagnosis. The presentation of CLL is diverse. Many patients have no clinical symptoms at the time of diagnosis, and require no or delayed treatment; however, some patients present with palpable lymphadenopathy, splenomegaly, and early aggressive disease, and require immediate treatment [5].

1.1 Prognostic Factors

Several prognostic factors may help predict the clinical outcomes in patients with CLL, including genetic abnormalities [6, 7]:

- Immunoglobulin heavy chain (IGHV) mutation status: mutations in this region are associated with better survival outcomes; the median overall survival (OS) exceeds 20–25 year, whereas patients with unmutated IGHV have a median OS of 8–10 years.
- Fluorescence in situ hybridization (FISH) chromosomal abnormalities: examples include del13q, which is associated with a favorable prognosis in CLL and a median OS of 17 years; del11 or trisomy 12, which are unfavorable factors associated with a median OS of 9 to 11 years; and del17p or mutation of TP53, which are associated with unfavorable prognosis, a median OS of 7 years, a poor response to therapeutic options, and a short response duration.
- Increased age: age is associated with poorer prognosis.
- Stage of disease: disease stage is discussed later in more detail.
- Lymphocyte doubling time: a doubling of white blood cells less than 1 year after diagnosis is associated with poorer prognosis.
- Minimal residual disease (MRD): MRD refers to the small number of cancer cells that remains after treatment in the blood or the bone marrow; a negative MRD implies a favorable disease prognosis.

1.2 Risk Stratification

Two clinical staging systems (Rai and Binet) are currently available to stratify CLL. Both systems describe three major prognostic groups and their clinical outcomes. The revised Rai staging system defines low-risk disease by lymphocytosis with a presence of >40% of lymphocytes in the bone marrow; intermediate stage by lymphocytosis with enlarged nodes at any site, and/or splenomegaly and/or hepatomegaly; and high-risk disease by lymphocytosis with disease related anemia or thrombocytopenia [8]. The Binet staging system defines stages on the basis of the number of involved sites: stage A is defined by anemia (hemoglobin ≥10 g/dL), thrombocytopenia (platelets ≥100,000/mm^3), and fewer than three enlarged areas; stage B is defined by anemia (hemoglobin ≥10 g/dL), thrombocytopenia (platelets ≥100,000/mm^3), and three or more enlarged areas; and stage C is defined by anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets <100,000/mm^3) and any number of enlarged sites [9]. Because of progress in CLL therapy, the two staging systems have become insufficient. The CLL International Prognostic Index (CLL-IPI) is currently the most relevant prognostic system. It uses five independent prognostic factors: TP53 mutation/17p deletion, IGHV mutational status, serum β_2-microglobulin, clinical stage, and age. Table 1 shows the point distributions for each prognostic factor with risk stratification from low to very high [10, 11]. The OS varies among patients and is lowest in high-risk CLL-IPI groups.

Because most patients are diagnosed in early stages of the disease, their management involves active surveillance or watchful waiting until they develop symptomatic disease. Several clinical trials enrolling patients in early stages have not shown any differences in outcomes if patients are treated [12, 13]. However, patients with early-stage CLL still have a variable clinical disease course or genetic status, and thus treatment initiation is scarcely anticipated at diagnosis.

The CLL-IPI score for early-stage disease (IPS-E) was developed in 2020 to predict the time to first treatment (TTFT). Data for individual patients were collected from 11 international cohorts and analyzed to develop a prognostic score to predict the TTFT. Three covariates were consistently and independently correlated with the TTFT: unmutated IGHV, lymphocyte count $>15 \times 10^9$/L, and presence of palpable lymph nodes. The presence of each covariate adds one point to the score. Summing the points yields three possible risk categories: low risk (score 0), intermediate risk (score 1), and high risk (score 2–3). The 5-year cumulative risk for initiating the first treatment for each risk category was 8.4%, 28.4%, and 61.2% for low-risk, intermediate-risk, and high-risk patients, respectively [14-16]. Therefore, all patients with early stage disease should be followed every 3–12 months, depending on the dynamics and burden of the disease, in the first year after diagnosis; the history should be collected; the physical examination should include careful palpation of all lymph nodes areas, spleen and liver; and the complete blood count (CBC) and differential count should be determined [5].

1.3 Treatments

Because most CLL cases remain incurable, the main goal of therapy is to improve patient quality-of-life and prolong survival. In clinical trials, the most important end points for any treatment are the rate of response, progression free survival (PFS), and the MRD, which may be more relevant to young, fit patients than older patients or those with comorbidities. Ultimately, survival depends on the choice of therapy and the consequences of therapy during the disease's course.

Because most patients do not need immediate treatment because the disease is asymptomatic, the standard treatment for these patients is the watch and wait strategy. When patients develop marked signs of disease progression, CLL treatments are indicated. At least one of the following criteria should be met to consider the disease as active and initiate treatment: (1) evidence of bone marrow suppression (anemia or thrombocytopenia); (2) massive, progressive, or symptomatic splenomegaly or lymphadenopathy; (3) progressive lymphocytosis with an increase ≥50% over a 2-month period, or a lymphocyte doubling time <6 months; (4) autoimmune complications due to anemia or thrombocytopenia which are poorly responsive to corticosteroids; (5) symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, or spine); and (6) development of disease related signs, such as fatigue and B symptoms (night sweats, fever, or weight loss) [5, 15].

The introduction of targeted therapies in the past few years has led to a breakthrough in CLL management. Here, we discuss the history of advancements in CLL treatments:

a. Chemotherapy and chemoimmunotherapy: For many decades, chlorambucil was considered the standard of care in patients with CLL, until the year 2000, when the German CLL study group showed that fludarabine monotherapy is more effective than chlorambucil (fludarabine resulted in a significantly higher overall and complete remission rate [72% vs 51%, P = .003; 7% vs 0%, P = .011]) [17]. Subsequently, the CLL4 trial showed that a combination of fludarabine and cyclophosphamide (FC), compared with fludarabine alone, is associated with improved quality and duration of response in (fit) patients younger than 65 years (FC treatment resulted in longer median PFS [48 vs. 20 months; P = 0.001] and longer treatment-free survival [37 vs. 25 months; P < 0.001]) [18]. The CLL8 trial found that FC combined with rituximab, an anti-CD20 monoclonal antibody (FCR), versus FC, significantly improves

PFS and OS. Since then, FCR has become the standard treatment for young patients with CLL without comorbidities [19]. In the CLL10 trials, bendamustine-plus-rituximab was compared with FCR and found to be clearly less effective than FCR, with a median PFS of 41.7 months (95% CI: 34.9–45.3) with BR and 55.2 months (95% CI not evaluable) with FCR; the hazard ratio (HR) was 1.643, 90.4% CI: 1.3–2.1 [20]. However, bendamustine-plus-rituximab was considered the treatment of choice for patients >65 years old or (unfit) patients with comorbidities with Comorbidity Illness Rating Scale (CIRS) scores >6, because FCR is associated with a significant increase in bone marrow toxicity and higher rates of infection in these patients. In 2010, a significant improvement in PFS was achieved in these patients when anti-CD20 antibody (obinutuzumab, ofatumumab, or rituximab) was combined with chlorambucil. On the basis of these results, FCR and anti-CD20 antibody plus chlorambucil were considered the first line treatments in fit and unfit patients, respectively, until 2018. Subsequently, a marked shift in CLL treatment occurred with the introduction of targeted therapies as front-line treatments.

b. Targeted therapy: Although chemoimmunotherapies achieved survival improvements in the CLL clinical outcomes, it did not cause a significant improvement in unfit patients or patients with defined genetic factors, such as TP53 mutation/del17p or unmutated IGHV, until new inhibitors of the signal transduction pathway downstream of the B cell antigen receptor (Bruton's tyrosine kinase inhibitors [BTKi]) and B-cell lymphoma-2 protein (BCL-2 inhibitors) were approved to treat CLL. The management of CLL subsequently changed.

    1- BTKi: Ibrutinib, the first generation BTKi, was made available to treat CLL in late 2017. It showed improved in PFS, particularly in patients with genetic abnormalities (del17p) [21]. Consequently, treatment of CLL patients with TP53 mutations was

recommended. The effectiveness of ibrutinib combined with rituximab or obinutuzumab has been evaluated in two trials and found to result in significant improvement. The first trial evaluated ibrutinib-plus-rituximab vs. ibrutinib vs. bendamustine-plus-rituximab in unfit patients and detected in no differences in OS and PFS between ibrutinib and ibrutinib plus rituximab, but confirmed their superiority to chemoimmunotherapies, with a PFS HR of 0.38, 95%CI=0.25–0.59 [22]. The second trial compared ibrutinib-plus-obinutuzumab and obinutuzumab-plus-chlorambucil and showed a significant difference in PFS, with an HR of 0.23, 95%CI=0.15–0.37 [23]. In 2020, the second generation BTKi acalabrutinib was approved as a monotherapy or combination therapy with obinutuzumab for previously untreated patients with CLL. In the ELEVATE-TN trial, acalabrutinib and acalabrutinib plus obinutuzumab were associated with a PFS HR, 95%CI of 0.20, 0.13–0.30 and 0.10, 0.06–0.17, respectively, when compared with obinutuzumab-plus-chlorambucil [24].

2- BCL-2 inhibitors: Venetoclax plus obinutuzumab is used as a first line treatment, particularly if patients have contraindications for ibrutinib use, such as a history of severe hemorrhage or atrial fibrillation. Studies have shown that treatment with venetoclax plus obinutuzumab results in a higher PFS and OS than chemoimmunotherapies [25].

3- Combination of BTKi and BCL-2 inhibitor and obinutuzumab: According to the CLL2GIVe phase 2 trial, triple therapy with ibrutinib, venetoclax, and obinutuzumab has demonstrated an encouraging response in treatment naïve patients with high risk CLL [26].

In cases with symptomatic relapse within 3 years after fixed-duration treatment or non-response to treatment, the choice of therapy should be changed regardless the type of previous therapy (targeted therapy or chemoimmunotherapies). One of the following therapies can be considered: venetoclax plus rituximab for 24 months [27], BTKi monotherapy as a continuous therapy [28, 29], and idelalisib in combination with rituximab [30]. To choose among these treatments, different aspects should be discussed with patients, including the treatment duration (continuous versus the fixed duration), the administration route (oral versus intravenously), the current evidence for each possible consequence, and the risk of complications or experiencing adverse events (e.g., in the presence of comorbidities, the chance of developing bleeding and cardiac comorbidities in BTKi is greater than that for other therapies, whereas tumor lysis syndrome, renal failure, and neutropenia are more frequent in patients treated with venetoclax).

On the basis of the current National Comprehensive Cancer Network (NCCN) guidelines, targeted agents as monotherapies or combination therapies with monoclonal antibodies are considered, without preference, as the first line treatments regardless of the age, TP53/ IGHV status, and comorbidity of patients with CLL, and targeted therapies followed by chemoimmunotherapies or immunotherapy are choices to treat patients with relapsed disease [31]. Given the impressive number of treatment choices, the selection of the optimal treatment for CLL has become a challenging task in clinical practice, especially in the absence of further evidence comparing targeted therapies together. Providers must be able to weigh the pros and cons of each therapy, and to consider the efficacy, safety, and cost of each therapy.

1.4 Economic Implications

Although targeted therapies, compared with chemoimmunotherapies, have achieved significant improvement in PFS, the high costs of these agents have been concerning for both payers and patients in the past few years. Targeted agents are recommended until patients experience disease progression or toxicity. However, most chemoimmunotherapies are administered for approximately 6 months. Shanafelt and colleagues have assessed the 10-year pharmaceutical cost of CLL treatment for 100 newly diagnosed hypothetical patients in three scenarios; the historical scenario implies using chemoimmunotherapies in treating naïve and relapsed patients; combined scenario at which patients treated with targeted therapies of ibrutinib or idelalisib in relapsed disease after the front line treatment with chemoimmunotherapies; and targeted scenario at which targeted agents such as ibrutinib are used in naïve and relapsed disease. The estimated cost over a 10 year time horizon for the 100 newly diagnosed patients reached $4.5 M, $7.8 M, and $16.4 M for historical, targeted agents in relapse, and targeted agents in front-line treatments, respectively [32]. Financial hardship has been reported in many cancer survivors after cancer treatments, particularly those 18–64 years of age. Cancer survivors who are insured and have a family face more psychological financial hardship [33]. Adding targeted agents, given these high costs, would further increase the burden.

1.5 Objectives

Currently, no research evidence has compared all available targeted therapies to establish facts or conclusions or develop clear guidelines. “Expert opinions” are the primary driver in the selection of therapies for patients, considering costs.

In this research, we aimed to:

1) Use the population-based, Surveillance, Epidemiology, and End Results (SEER) database to evaluate survival in patients diagnosed with CLL between 1985 and 2017 in 5- and 10-year relative survival analyses, by applying mixture cure models and running survival analyses to distinguish between the cohort of patients diagnosed before and after the era of advanced therapies in CLL treatment.
2) Establish evidence comparing all first line treatments in CLL by conducting a systematic review and network meta-analyses on all efficacy measures of PFS, OS, time to next treatment after the first relapse (TTNT), and PFS among specific populations with un-mutated/mutated IGHV and 17p deletion in all treatments.
3) Assess the cost and effectiveness of all first line therapies and compute the budget required to treat patients with CLL who were diagnosed in 2020 and followed for the next 10 years.

Table 1.1: CLL-IPI scoring system**.**

Prognostic factor	**Points**	
Deletion 17p/TP53	4	
Unmutated IGHV genes	2	
Serum B2 microglobulin>3.5 mg/L	2	
Rai stage I-IV	1	
Age >65 years	1	
Cumulative CLL-IPI score	**Risk Category**	**5-yr OS**
0-1	low	93.2%
2-3	intermediate	79.3%
4-6	High	63.3%
7-10	Very high	23.3%

2.0 SURVIVAL TRENDS IN CHRONIC LYMPHOCYTIC LEUKEMIA ACROSS TREATMENT ERAS: US SEER DATABASE ANALYSIS (1973–2017)

Manuscript in submission process

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2.1 Abstract

Purpose: In this population-based study, we used the SEER database (1973–2017) to examine survival outcomes in chronic lymphocytic leukemia (CLL) patients followed to the era of advanced treatments including targeted therapies.

Methods: Data were extracted for patients 15 years or older with a primary diagnosis of CLL. A period analysis was performed to estimate 5- and 10-year relative survival rates for patients diagnosed during different calendar periods from 1985 to 2015. A mixture cure model was used to examine long-term survivors' proportions among patients diagnosed in 1985–2015 and for two cohorts diagnosed in 2000–2003, followed to 2012 and 2004–2007, followed to 2015. Cox-proportional hazard modeling was used for the two cohorts to estimate hazard ratios (HRs) of death adjusted for gender and age.

Results: The 5-year and 10-year age-adjusted relative survival rate ranged between 73.7% and 89.4%, and from 51.6% to "not reached", respectively, for calendar periods of 1985–2014. The long-term survivor proportions varied by age and gender from 0% to 59%. The HRs (95%CI) for the 2004–2007 cohort in comparison to the 2000–2003 cohort were 0.58 (0.43–0.78), 0.58 (0.48–0.70), 0.57 (0.49–0.0.67), 0.68 (0.54–0.85), and 0.83 (0.68–1.02) for the age categories of 45–54, 55–64, 65–74, 75–84, and ≥85 years, respectively.

Conclusion: Overall, the survival was significantly improved for patients who followed to 2015. Future studies are needed with detailed information about treatment type and such other covariates as disease stage and genetic background.

2.2 Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults, with a median age at diagnosis of 70 years for men and 73 years for women. In the United States, (U.S.), 21,250 new cases of CLL were expected for 2021[2]. In 2017, 186,422 patients were living with CLL in the U.S.[3]. Although CLL is an incurable disease, the majority of patients who are diagnosed in the early stages can live without treatment until they develop clinical symptoms[34].

Since 2010 advances in treatments have improved survival in CLL patients. Until recently, anti-CD20-based chemoimmunotherapy, including bendamustine and rituximab (BR) or fludarabine, cyclophosphamide, and rituximab (FCR), has been the mainstay treatment for previously untreated patients[8, 31]. Despite this progress, BR and FCR have had a limited effect in high-risk patients with TP53 mutation and/or del17p and in elderly patients. Targeted therapies, including Bruton's tyrosine kinase inhibitors (ibrutinib and acalabrutinib) and a BCL2 inhibitor (venetoclax) as single agents or in combination with monoclonal antibodies, have greatly improved the prognosis of CLL patients[23-25, 29, 35, 36]. The National Comprehensive Cancer Network guidelines consider targeted agents as first-line treatment for CLL patients, regardless of age, TP53/immunoglobulin heavy chain variable (IGHV) status, or comorbidity[31]. In addition to marked changes in CLL treatment, a greater understanding of the biology of this disease since 1999 allowed the stratification of patients from low to high risk based on clinical, biological, and prognostic factors (including disease stage, genetic abnormalities such as TP53 mutation and/or del17p, and IGHV abnormalities). This has enabled early disease detection and treatment initiation[37-39]. In turn, this has markedly improved survival outcomes among CLL patients over the last decade.

Recent studies have examined overall survival in CLL patients. Brenner and colleagues evaluated the relative survival among CLL patients in the U.S. using the Surveillance, Epidemiology, and End Results (SEER) database for the period of 1973–2004 and found a significant improvement in the survival of patients diagnosed since 2000. The 5- and 10-year relative survival rates were significantly higher in women than in men and in patients aged 15–59 years than in those who were older at the time of diagnosis[40]. Weide et al. conducted a retrospective cohort study to examine the overall survival (OS) of CLL patients in Germany since the start of first treatment. OS was significantly improved for patients treated between 2009 and 2017, and this was strongly correlated to improved standard of care and the use of new treatments based on chemoimmunotherapy and targeted agents (ibrutinib and idelalisib)[7].

Compared to patients with other cancers, CLL patients live longer, with a 5-year relative survival rate of 86.1%[1], and therefore can be considered long-term survivors. The probability of being a long-term survivor may vary with age at diagnosis, prognostic factors, and treatment but this has not yet been studied in CLL patients. We report on analyses utilizing the population-based SEER database to evaluate survival in patients diagnosed with CLL from 1985 to 2017. First, we estimated the 5- and 10-year relative survival rates for 5-year intervals from the time of diagnosis. Second, we performed time-to-event analyses to indirectly distinguish the extent of improved survival in the era of new treatments, particularly for elderly (frail) patients. In these analyses, the proportions of long-term survivors were calculated using a mixture cure model (MCM) based on age and gender.

2.3 Methods

2.3.1 Study Population

Data were extracted from the National Cancer Institute's SEER database. The patients were identified using SEER*Stat, version 8.3.8, with multiple primary standardized incidence ratios and frequency sessions to identify each patient cohort[41]. Eligible individuals were patients aged 15 years or older with a primary diagnosis of pathologically confirmed CLL (no previous cancer diagnoses) (ICD-0-3) between 1985 and 2017, with or without subsequent cancers. Demographic data (gender; age at diagnosis; year of diagnosis; survival status [alive, dead, or censored], and cause of death) were extracted for each patient. Based on the year of diagnosis, the calendar periods of 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2017 were used to evaluate and compare incidence and survival rates among patients. All analyses were conducted separately based on gender and the following age categories: 15–44, 45–54, 55–64, 65–74, 75–84, and 85 years or older.

2.3.2 Statistical Analyses

The crude number of incident cases was obtained from frequency tables for each period stratified by gender and age groups. The annual age-adjusted incidence rates per 100,000 were estimated for 1985 to 2017.

For each calendar period, 5- and 10-year relative survival rates were estimated for all cohorts by means of period analysis, which provides a more up-to-date estimate for long-term survival in cancer patients[42]. Unlike the traditional method that calculates survival regardless years following the diagnosis, this method accurately predicts long-term survival rates for patients diagnosed later in the calendar periods using the period-based survival probabilities in

defined years following diagnosis[43-45]. Age-adjusted relative survival estimates were obtained by dividing the weighted sum of age-specific survival estimates of the observed all-cause survival in the CLL sample by the expected all-cause survival in the general population. This expected survival was determined using the Ederer II method[46], in which the matched individual is followed and considered to be at risk until the corresponding cancer patient dies or is censored. Because survival in CLL patients may vary by age and gender, relative survival rates stratified by these two variables were also examined. An actuarial analysis of survival was performed using a semi-parametric distribution to plot 10-year relative survival curves using CanSurv software (Information Management Services Inc., Calverton, NY, U.S) for two intervals of diagnosis (1985–1999 and 2000–2015). These too were stratified by gender[47].

To assess heterogeneity between CLL patients who are long-term survivors (cure) and those who are not after a long follow-up, an MCM was specified to calculate the cure percentage[48]. MCM can aid in interpreting the plateau of survival over time (if found), which indicates the presence of long-term survivors. Moreover, two different models can be included to explain the survival in non-cured and cured patients. In MCM, the net survival at time t is defined as

$$c+(1-c)\times S(t)$$

where c is the probability of being cured, $1-c$ is the probability of not being cured, and $S(t)$ is a cumulative survival function indicating the probability of being alive at time t if the patient is not cured.

Cause-specific life tables were extracted from the life table session of SEER*Stat for all patients who received a primary diagnosis of CLL between 1985 and 2015 (survival data was not

available for years after 2015). Each patient was considered to have an event if the patient died due to cancer; the status was considered as censored if the patient was alive or died due to other causes. Using R software (R Foundation for Statistical Computing, Vienna, Austria), the probability of a patient being cured was modeled using log-logistic regression. Gompertz, lognormal, Weibull, and exponential models were tested using the Akaike information criterion to fit the second component of the model, i.e., the survival function for patients who were not cured. A cure model was considered valid if it met the following criteria: (1) follow-up time >2/3 median survival time of uncured status and (2) cure percentage < most recent observed survival estimate. Cure models were tested for the entire cohort of patients that were followed to 2015 and for two cohorts of patients who were diagnosed in 2000–2003 and 2004–2007 and followed to 2012 and 2015, respectively. The length of follow-up ranged from 8 to 12 years after diagnosis. The lengths for both groups overlapped up to 2012, at which time the second cohort was distinguished and was followed from 2013 to 2015 – an interval during which more effective therapies were introduced.

To examine the possible effect of advanced CLL treatments, life tables were generated for the two cohorts of patients diagnosed 2000–2003 and diagnosed 2004–2007 and followed to 2012 and 2015, respectively. Time-to-event analyses were conducted to generate Kaplan–Meier curves for each age category in each cohort. The Cox proportional hazard model was tested and used to calculate the hazard ratio (HR) of death with a corresponding 95% confidence interval (CI). The assumptions of hazard proportionality using Schoenfeld residuals and global tests, interaction, and confounding were tested. A multivariate Cox proportional hazard model adjusted for age and gender was specified. For cases in which the Cox proportional hazard assumption was violated (e.g., hazard rates are not proportional over time), the weighted Cox regression

model introduced by Schemper in 2009 was used; this method computes the value of average hazard ratios over the observed period[49].

2.4 Results

Overall, 36,007 cases diagnosed primarily with CLL were identified in the SEER database for the period of 1985–2017 (Table 1). Males accounted for approximately 60% of the cohort of CLL patients and the age categories of 15-44, 45-54, 55-64, 65-74, 75-84, and +85 years accounted for 2.1%, 9.0%, 20.9%, 29.6%, 26.2%, and 11.1% of patients, respectively. Table 1 shows the details of characteristics of incident cases based on year-of-diagnosis intervals. The demographic proportions were approximately consistent over calendar periods with no statistically significant differences. The annual age-adjusted incidence rate per 100,000 varied by year of diagnosis from 4.5 to 5.9 (Figure 1).

2.4.1 Relative Survival

Overall, the 5-year age-adjusted relative survival rates by calendar periods were 73.7% (1985-1989), 76.7% (1990–1994), 77.1% (1995–1999), 83.6% (2000–2004), 87.1% (2005–2009), and 89.4% (2010–2014). Table 2 presents the relative survival rates for each period by gender and age. Figure 2 shows the 5-year and 10-year relative survival with 95%CI in each calendar period; comparing the calendars with prior ones, there was a statistically significant improvement in relative survival in the calendar periods after year 2000. These results were confirmed by the actuarial analysis for up to 10-year age-adjusted relative survival rates among the CLL patients diagnosed in the periods of 2000–2015 and 1985–1999 in Figure 3.

2.4.2 Mixture Cure Model

A cure model was built and tested for the cohort of CLL patients diagnosed between 1985 and 2015. Because covariates may affect the survival rate, the cure fraction was calculated per gender and age category (45–54, 55–64, 65–74, 75–84, >85 years). The long-term survival proportions decreased as patient age increased as patients age ≥75 years were found to be without cure. Females had higher proportions for being long-term survivors than males across all age categories (Table 3).

The secondary analysis of cure probability with the year of diagnosis as an additional covariate to indirectly evaluated differences in treatment between the two cohorts (diagnosed 2000-2003) and (diagnosed 2004-2007). It revealed higher cure fractions in the second cohort (diagnosed 2004-2007), which was followed until 2015 (Table 3B).

2.4.3 Cox Proportional Hazard Model

Kaplan–Meier curves are plotted for the two cohorts (diagnosed 2000-2003 and diagnosed 2004-2007) in Figure 4. The median survival for each age category in each cohort ranged from 5.9 years in patients age >85 years to 12.9 years in patients 45-54 years old in the cohort diagnosed in the 2000-2003 period). Median survival was not reached for all age categories in the cohort diagnosed 2004-2007, except for patients age >85 years where the median survival was 7 years (Table 4).

The HR of death adjusted for age and gender was 0.58 (95%CI; 0.43–0.78), 0.58 (95%CI; 0.48–0.70), and 0.57 (95%CI; 0.49–0.67) for age groups of 45–54, 55–64, and 65–74 years, respectively, when the second cohort (diagnosed 2004-2007) is compared with the first cohort (diagnosed 2000-2003). The Cox proportional hazard model assumption of hazard

proportionality was not met for patients aged 75–84 years; thus, weighted Cox regression was applied, resulting in an HR of 0.68 (95%CI; 0.54–0.85). For the last category, i.e., patients age 85 years or older, the HR was 0.83 (95%CI; 0.68–1.02).

2.5 Discussion

The principal findings of our analyses revealed continuous improvements in the 5-year and 10-year age-adjusted relative survival rates across all calendar periods between 1985 and 2015. The long-term survival (cured) proportions increased by decreasing age at diagnosis and being female. The point estimates for cured proportions were higher in the cohort diagnosed 2004-2007 that was followed into the era that targeted therapies were introduced. However, their 95% confidence intervals overlapped with those of the cured proportions of the cohort diagnosed 2000-2003 for all age categories with the exception of female patients in the cohort diagnosed in 2004-2007 and aged between 65-74 years. Compared to the 2000–2003 cohort, the HRs of death for the 2004–2007 showed significant survival improvement in all age categories, except among patients over the age of 85 years where no difference was observed.

Survival among CLL patients has been shown to increase in most population-based studies[40, 50]. Our study suggests that improvements in survival have continued in the period from 2000 to 2015. We noted significant increases in the 5- and 10-year relative survival rates after 2000 compared with the prior decades and this for all age and gender categories, and this trend is attributable to different factors.

First, several changes in CLL treatments have occurred since 2000. Response rate and PFS were shown to be better in patients treated with fludarabine versus alkylating agents[51].

The monoclonal antibody rituximab in combination with fludarabine improved survival outcomes especially in fit young patients[52]. Since 2010, CLL treatment has evolved markedly due to highly effective drugs and drug combinations, often incorporating on patient health data and genetic status. New chemoimmunotherapy combinations such as FCR, obinutuzumab plus chlorambucil, and bendamustine plus rituximab significantly changed PFS and OS in CLL patients. This was followed by the advent of targeted therapy with ibrutinib and idelalisib in 2014 for relapsed disease, which manifestly changed the natural history of the disease[19, 20, 53, 54].

Second, our understanding of the genetics of CLL and the association with patient outcomes accelerated around 2000. In this context, four genetic lesions (17p12, 11q23, 13q14, and 12q) were identified as prognostic predictors of disease and treatment. More aggressive treatment courses were initiated for patients with these lesions to achieve better outcomes, especially in high-risk patients. Other major indicators include CD38 and the presence or absence of IGHV mutation, which were reported as important markers in diagnosis and therapy choice in 1999[38].

Third, better screening and earlier diagnosis in the time period since 2000 have increased the proportion of incident cases with low-risk and early-stage disease and enabled earlier intervention with better prognosis. Better health care, especially for elderly patients, lengthened the potential survival range and actual OS duration and rates[55, 56].

Lastly, and more generally, the greater availability, affordability, and use of health insurance supported by government programs (such as Medicare and Medicaid) and private health insurance plans in U.S. has improved treatment access[57].

The survival outcomes were characterized by some gender dynamics. For instance, in the calendar periods after 2000, the 5-year and 10-year age-adjusted relative survival improved significantly in the 2005–2009 calendar period when compared to the 2000–2004, however this was observed for males but not for females. Positively so, however, females had higher survival estimates than men in all calendar periods. Hence the lack of an increase in 2005-2009 over 2000-2004 was a sign that the better survival outcomes for women remained at their relatively higher level over men in 2005-2009, while the men improved. This finding is consistent with prior studies, which have shown that women with CLL respond better to treatment and survive longer than men[58-60]. Importantly, this trend persisted through the period 2005–2009. Subsequently, the 5-year relative survival for both men and women were approximately the same at 86.9% (95%CI; 84.9–88.6) for men and 87.5% (95%CI; 85.1–89.5) for women, suggesting that the men "caught up" in terms of survival during the 2005-2009 time period. While, the 10-year relative survival rate improved for both genders, women still showed a significantly higher survival rate than men (Table 2).

Although, survival rates decreased with age, the 5- and 10-year relative survival rates in patients aged 45–54 years were higher than those of patients aged 15–45 years in all calendar periods after year 2000. This trend is opposite to the trend observed for periods prior to year 2000. Because relative survival rates reflect excess mortality attributable to CLL, improvements in relative survival for the calendar periods of 2000–2004, 2005–2009, and 2010–2014 suggest a better understanding of prognosis, changes and advances in first-line therapies as well as the treatment of recurrent disease, and improvements in supportive care plans for CLL[61, 62].

CLL primarily affects the elderly, with most patients being age 65 and older at diagnosis. Moreover, most patients are monitored with a "wait and watch" approach first until they develop

symptoms, at which time therapy is initiated. By this time patients present with more comorbidities and/or are older than 65 years and therefore less able to tolerate aggressive chemotherapies and the associated (severe) toxicity[62]. Chemoimmunotherapy was not an option for these patients until 2013, when Goede et al. reported the benefit of combining chlorambucil and obinutuzumab in treating frail patients as a standard therapy[54]. In 2014, new targeted therapies including ibrutinib and idelalisib[30, 63] showed remarkable outcomes in relapsed CLL patients, though long-term data are limited.

In order to investigate changes in survival stratified by the advent of novel treatment regimens since 2013, we selected two cohorts diagnosed between 2000–2003 and followed to 2012 and between 2004–2007 and followed to 2015 respectively. Focusing further on patients 65 and older, time-to-event analyses revealed significant improvements in survival and a decreased death hazard in the latter cohort, which was followed into the era of targeted therapies.

Considering that the average time to first-line treatment in the U.S. is four to five years from the time of diagnosis[10, 64, 65], we examined more closely the patients diagnosed 2004-2007 as these patients are likely to have started first-line therapy after active surveillance or experienced relapses after receiving first-line therapy during the follow-up period. Probably, these patients benefitted from newer therapies such as chlorambucil plus obinutuzumab (in 2013) for first-line treatment or targeted therapies such as ibrutinib or idelalisib (in 2014) for second-line treatment. In contrast, treatment options for patients in the 2000-2003 cohort were limited to those introduced up to 2012. Indeed, for patients aged 65-74 and 75-84, the HRs of approximately 0.57 and 0.68 indicated better survival for patients in the 2004-2007 cohort compared to those in the 2000-2003 cohort. However, the survival benefit was similar between

the 2000-2003 and 2004-2007 cohorts for patients aged 85 years and older, though all-cause mortality may be influenced by concurrent natural aging.

We considered another possible factor for the observed difference between the 2000-2003 and 2004-2007 cohorts. Patients in the 2000–2003 cohort, particularly those who needed to be initiated on treatment right before 2004 because of advanced disease (Rai III-IV, Binet C) and progressive cytopenia[31] had different treatment options. Satram-Hoang et al.[66]investigated treatment patterns in 2,985 elderly patients with primary CLL diagnosed between 1998 and 2009 using the SEER-Medicare database. Comparing treatment patterns between 2004 and 2007 to those up to 2003 revealed that fludarabine monotherapy decreased from 26% to 10%, while rituximab monotherapy increased from 9% to 27% and the combination of both rose from 13% to 20%; to which, in 2007 chlorambucil monotherapy was added. Applied to our study, this implies marked changes in first-line treatments between 2000–2003 and 2004–2007 for patients requiring immediate treatment, a segment that, according to data from a Mayo Clinic study[67], could reach 5.2% of the patients in our analyses.

Further support for our conclusion that the changes in treatment options around 2013 had a critical impact on survival comes from our stratification. Recall in this regard that the 2000-2003 was followed through 2012 and thus covered the phases of treatment with chemotherapy regimens and the introduction of chemoimmunotherapy regimens. The 2004-2007 cohort overlapped with the 2000-2003 cohort in terms of the chemoimmunotherapy treatment options,. However, by being followed to 2015, it differentiated itself in terms of access to the recent targeted treatments. Therefore, the incremental survival outcomes observed in the 2004-2007 cohort could be attributed to access to these targeted treatments. Note that the HRs ranged

between 0.57 to 0.83 across the age categories confirmed the likely effect of the gradual shift to advanced treatments.

Our real-world SEER results align with the improved OS outcomes reported in the clinical trials of chemoimmunotherapy with the combination of obinutuzumab and chlorambucil and the subsequent trial evidence for ibrutinib and idelalisib. The OS HR of obinutuzumab and chlorambucil when compared with chlorambucil therapy was 0.41 (95%CI=0.23-0.74)[54]. Ibrutinib was associated with an OS HR of 0.64 (95% CI=0.42-0.98) when compared with the monoclonal antibody ofatumumab in relapsed CLL[28]; while idelalisib plus rituximab was associated with an OS HR of 0.28 (95%CI=0.09-0.86) when compared with rituximab in relapsed CLL[30].

OS outcomes may continue to improve among all age and gender categories. In 2018 additional targeted therapies, combinations of targeted therapies with obinutuzumab, and BCL2 inhibitors were approved as first line therapies. Their clinical trials showed significant improvements in the response and PFS among naïve CLL patients when compared with chemoimmunotherapy[23-25, 36].

Our analyses have some limitations while also suggesting areas of future research. The SEER database does not include information on prognostic markers, including cytogenetic profiles and disease stage, which are directly related to survival in CLL patients. Therefore, we could not adjust for these factors, and future studies would benefit from more comprehensive clinical data sets. Neither does SEER include data on treatment type and duration, which makes it difficult to relate improved survival to a specific treatment; nor does it contain information about tumor recurrence, which would have enabled us to assess the relative role of first-line versus relapse treatment in the observed survival. Cure models applied to patients diagnosed in

2000 or later are susceptible to possible overestimation of the cure fraction. Although patients were followed for up to 13 years from diagnosis, 5%–12% of patients may still have been treatment-free and under active surveillance ("watchful waiting")[68, 69]. Therefore, our parametric distributions fitted to the survival curves might slightly overestimate survival. Being limited to data up to 2015 implies the need for replication of our study in a few years to capture the long-term benefit of targeted therapies.

2.6 Conclusion

In summary, our analyses suggest an increase in survival among CLL patients over 2000-2015, with an increasing proportion of long-term survivors among patients who were diagnosed after 2000 and followed until the introduction of new chemoimmunotherapy options and targeted agents for treating relapsed disease. Our analyses demonstrated that survival in men improved significantly, reaching approximately the same level as that of women, for those who were diagnosed in 2004 or later.

Table 2.1: Number (proportion) of incident cases of CLL per calendar period.

	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2017*
N	4079	4439	4544	5576	6361	6854	4154
Male	2410 (0.59)	2562 (0.58)	2686 (0.59)	3294 (0.59)	3754 (0.59)	4135 (0.60)	2528 (0.61)
Female	1669 (0.41)	1877 (0.42)	1858 (0.41)	2282 (0.41)	2607 (0.41)	2719 (0.40)	1626 (0.39)
Age at diagnosis							
15–44	113 (0.03)	133 (0.03)	149 (0.03)	134 (0.02)	132 (0.02)	141 (0.02)	98 (0.02)
45–54	326 (0.08)	402 (0.09)	520 (0.11)	627 (0.11)	652 (0.10)	722 (0.11)	415 (0.10)
55–64	919 (0.23)	885 (0.20)	835 (0.18)	1184 (0.21)	1505 (0.24)	1738 (0.25)	1090 (0.26)
65–74	1309 (0.32)	1436 (0.32)	1389 (0.31)	1512 (0.27)	1698 (0.27)	1995 (0.29)	1280 (0.31)
75-84	989 (0.24)	1136 (0.26)	1164 (0.26)	1487 (0.27)	1601 (0.25)	1475 (0.22)	828 (0.20)
85+	423 (0.10)	446 (0.10)	487 (0.11)	631 (0.11)	770 (0.12)	783 (0.11)	443 (0.11)
Race							
White	3754 (0.92)	4077 (0.92)	4157 (0.91)	5850 (0.89)	5732 (0.90)	7144 (0.86)	3580 (0.86)
African American	258 (0.06)	279 (0.06)	272 (0.06)	393 (0.07)	367 (0.06)	545 (0.08)	302 (0.07)
Others/unknown	67 (0.02)	83 (0.02)	115 (0.02)	199 (0.03)	262 (0.04)	444 (0.06)	272 (0.07)

Table 2.2: Age-adjusted 5- and 10- year relative survival (RS) percent.

	1985-1989		1990-1994		1995-1999		2000-2004		2005-2009		2010-2014*
	5-yr RS (95%CI)	10-yr RS (95%CI)	5-yr RS (95%CI)	10-yr RS (95%CI)	5-yr RS (95%CI)	10-yr RS (95%CI)	5-yr RS (95%CI)	10-yr RS (95%CI)	5-yr RS (95%CI)	10-yr RS (95%CI)	5-yr RS (95%CI)
ALL	73.7 (71.7-75.5)	51.6 (49.2-54.0)	76.7 (74.6-78.2)	55.3 (52.9-57.7)	77.1 (75.3-78.7)	58.4 (56.2-60.6)	83.6 (82.0-85.0)	67.4 (65.2-69.4)	87.1 (85.6-88.5)	75.0 (72.9-77.0)	89.4 (88.0-90.7)
Male	72.0 (69.3-74.6)	47.3 (43.9-50.5)	74.1 (71.6-76.5)	53.2 (49.7-56.6)	73.3 (70.9-75.5)	54.4 (51.4-57.4)	81.9 (79.8-83.9)	63.2 (60.1-66.1)	86.9 (84.9-88.6)	72.5 (69.8-75.1)	88.2 (86.2-90.0)
Female	76.8 (74.0-79.4)	58.2 (54.6-61.7)	79 (76.3-81.4)	59.5 (56.1-62.7)	82.4 (79.9-84.7)	64.7 (61.3-67.9)	86.0 (83.8-87.9)	73.6 (70.5-76.5)	87.5 (85.1-89.5)	78.7 (75.3-81.6)	90.8 (88.6-92.5)
Age Categories											
15–44	82.9 (74.0-89.0)	65.6 (55.3-74.0)	86.2 (78.4-91.3)	61.2 (51.7-69.4)	86.3 (79.2-91.2)	75.4 (66.9-82.0)	89.2 (81.9-93.7)	75.2 (66.1-82.1)	90.3 (82.9-94.5)	83.5 (74.7-89.4)	93.8 (86.9-97.1)
45–54	81.4 (76.2-85.6)	63.9 (57.6-69.5)	83.4 (79.0-87.1)	62.3 (56.7-67.3)	85.9 (82.1-89.0)	71.3 (66.5-75.5)	91.8 (88.9-94.1)	79.1 (75.0-82.6)	96.6 (94.0-98.1)	86.5 (82.4-89.6)	94.5 (91.6-96.4)
55–64	79.8 (76.4-82.7)	55.0 (50.9-58.9)	83.4 (80.1-86.3)	64.2 (60.0-68.1)	86.7 (83.5-89.3)	68.3 (64.1-72.1)	88.8 (86.2-90.0)	74.2 (70.0-77.3)	91.4 (89.2-93.1)	82.7 (79.6-85.3)	96.1 (94.2-97.4)
65–74	76.3 (73.0-79.3)	53.0 (48.9-57.0)	78.6 (75.5-81.4)	57.0 (53.1-60.8)	78.6 (75.4-81.4)	60.9 (56.8-72.1)	86.8 (83.9-89.1)	69.6 (65.7-73.1)	88.6 (86.0-90.7)	76.2 (72.4-79.6)	89.4 (86.9-91.5)
75-84	63.4 (58.5-68.0)	42.8 (36.5-49.0)	66.8 (62.1-71.1)	46.1 (40.0-52.1)	66.7 (62.1-70.9)	44.1 (38.3-49.8)	73.5 (69.4-77.1)	57.9 (52.2-63.2)	81.2 (77.4-84.5)	62.7 (56.7-68.1)	83.5 (79.3-87.0)
85+	49.7 (39.0-59.5)	23.6 (12.3-37.0)	50.3 (40.0-59.8)	25.4 (11.9-41.4)	42.1 (32.9-51.1)	17.5 (8.8-28.7)	61 (50.9-69.6)	29.3 (16.1-43.8)	70.2 (60.3-78.0)	46.1 (33.4-57.9)	69.5 (58.9-77.8)

*The 10- years relative survival is not available for this calendar.

CI: Confidence interval

Table 2.3: Results of mixture cure models.

3A: Estimated cure proportions for CLL patients diagnosed between 1985-2015.				
Age	Overall cured proportion (95%CI)	Cured proportion in males (95%CI)	Cured proportion in females (95%CI)	
45-54	0.43 (0.38-0.49)	0.35 (0.29-0.42)	0.59 (0.52-0.64)	
55-64	0.41 (0.37-0.44)	0.35 (0.32-0.39)	0.50 (0.46-0.54)	
65-74	0.12 (0.10-0.70)*	0.08 (0.007-0.98)	0.16 (0.12-0.22)	
75-84	0.003 (0.001-0.98)*	no cure	0.14 (0.11-0.20)	
85+	0.02 (0.001-0.99)*	no cure	0.06 (0.02-0.26)	
3B: Estimated cure fractions for CLL patients diagnosed between 2000-2003 and 2004-2007.				
	Patients diagnosed in 2004-2007 and followed-up to 2015		Patients diagnosed in 2000-2003 and followed-up to 2012	
Age	Cured proportion in males (95%CI)	Cured proportion in females (95%CI)	Cured proportion in males (95%CI)	Cured proportion in females (95%CI)
45-54	0.54 (0.30-0.75)	0.78 (0.62-0.88)	0.30 (0.09-0.63)	0.56 (0.32-0.78)
55-64	0.46 (0.29-0.65)	0.65 (0.52-0.77)	0.16 (0.04-0.46)	0.30 (0.11-0.61)
65-74	0.33 (0.22-0.46)	0.58 (0.47-0.68)	0.05 (0.01-0.25)	0.13 (0.03-0.46)
75-84	0.22 (0.12-0.37)	0.44 (0.34-0.54)	0.06 (0.02-0.19)	0.14 (0.05-0.35)
85+	no cure	0.11 (0.04-0.38)	no cure	no cure

*Wide confidence interval indicates a high variation in CLL survival per gender.

Table 2.4: Median survival time (months) outputs.

	Cohort 1 (diagnosed in 2000-2003)		Cohort 2 (diagnosed in 2004-2007)	
Age Category at diagnosis	N	Median (95%CI)	N	Median (95%CI)
45-54	492	155 (145-NR)	489	NR
55-64	884	154 (152-NR)	1181	NR
65-74	1156	136 (131-143)	1292	NR
75-84	1142	110 (105-119)	1267	NR
85+	462	71 (60-85)	513	84 (68-93)

NR: Not reached

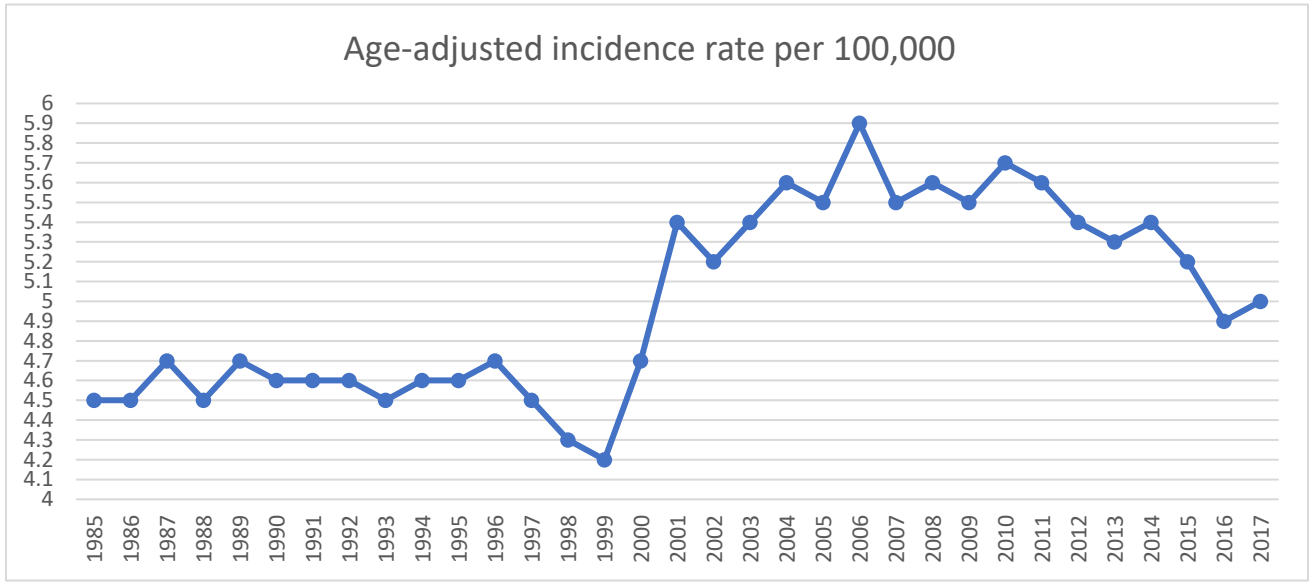
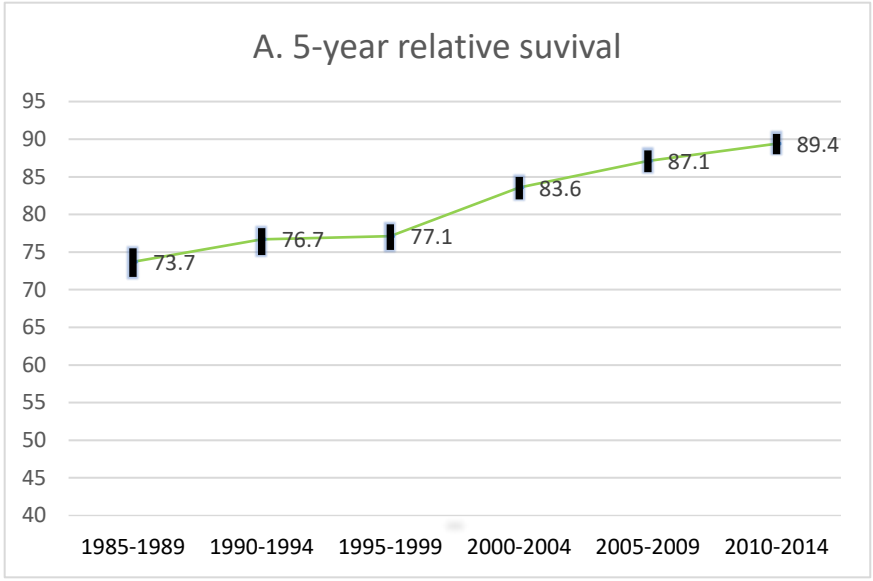


Figure 2.1: Age-adjusted incidence rate per 100,000 population.



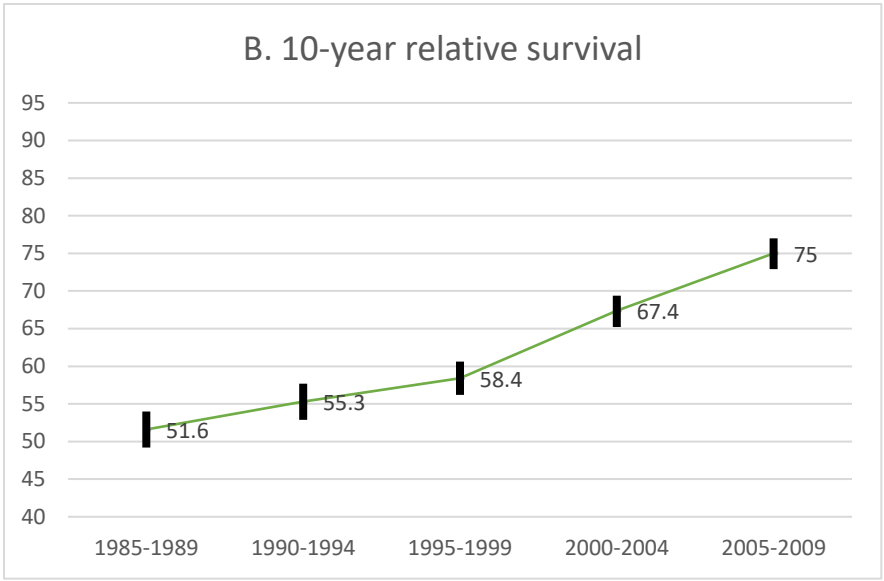


Figure 2.2: Point estimates of A) 5-year relative survival and B) 10-year relative survival with 95%CI by year of disease diagnosis.

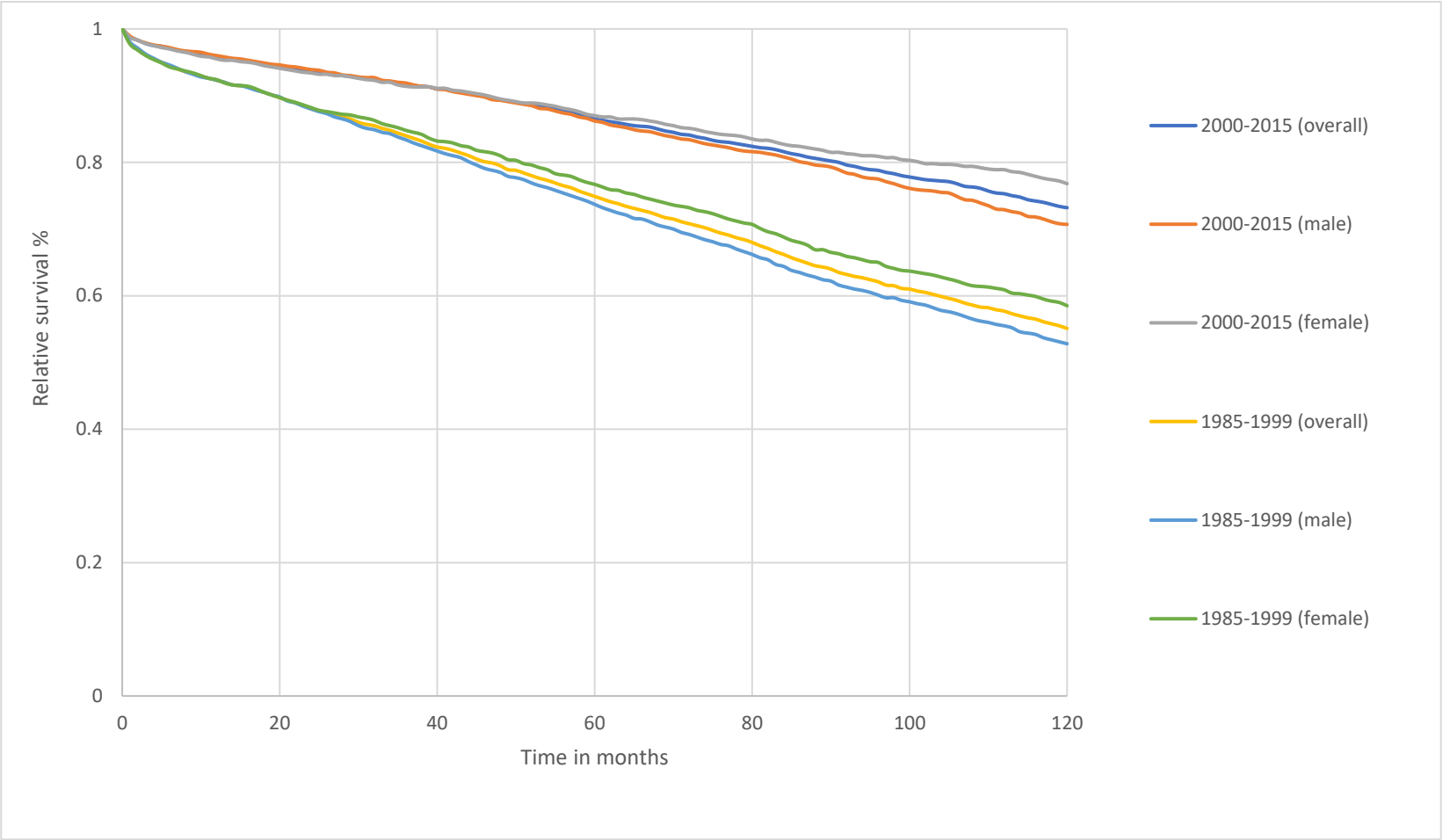
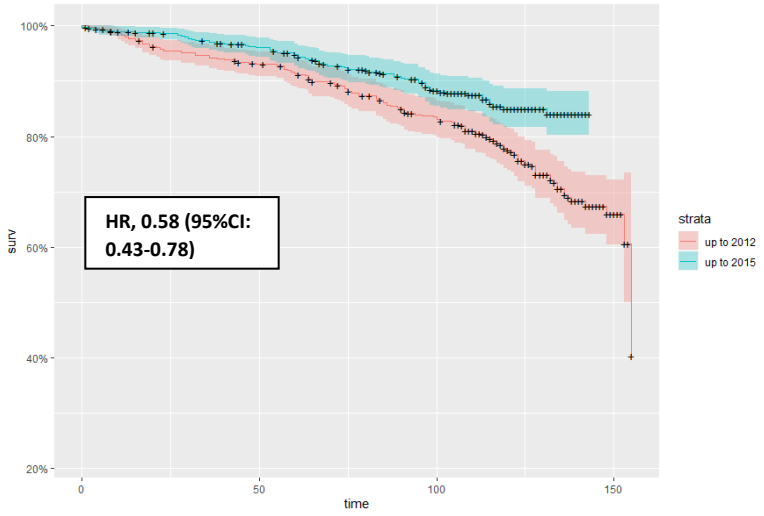
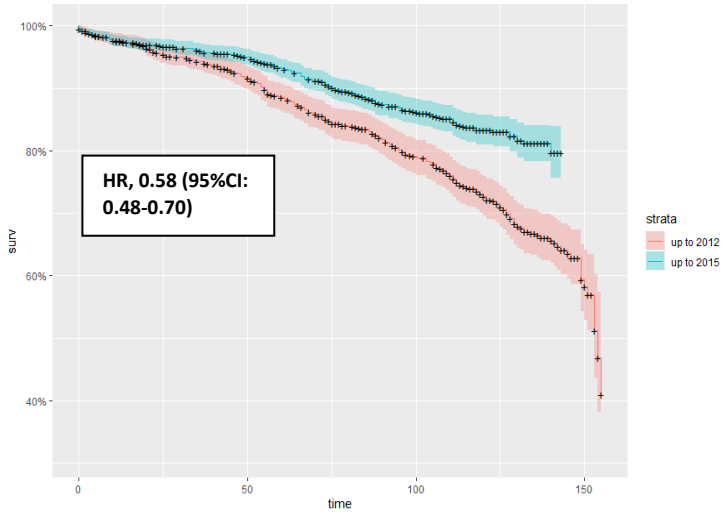


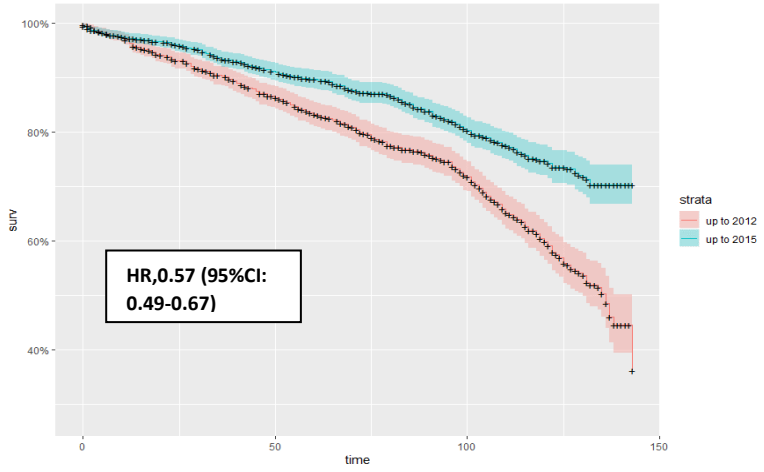
Figure 2.3: Relative survival curves for up to 120 months of follow-up for patients' cohorts diagnosed between 1985-1999 and 2000-2015.


HR, 0.58 (95%CI: 0.43-0.78)
surv
time
strata
up to 2012
up to 2015

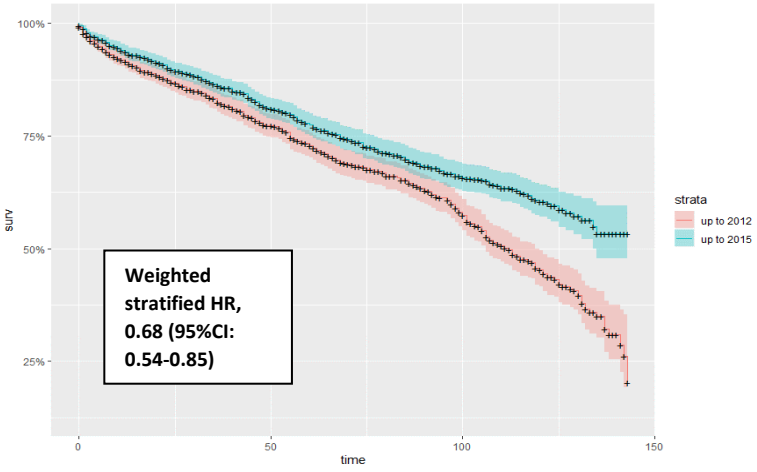
(A)


HR, 0.58 (95%CI: 0.48-0.70)
surv
time
strata
up to 2012
up to 2015

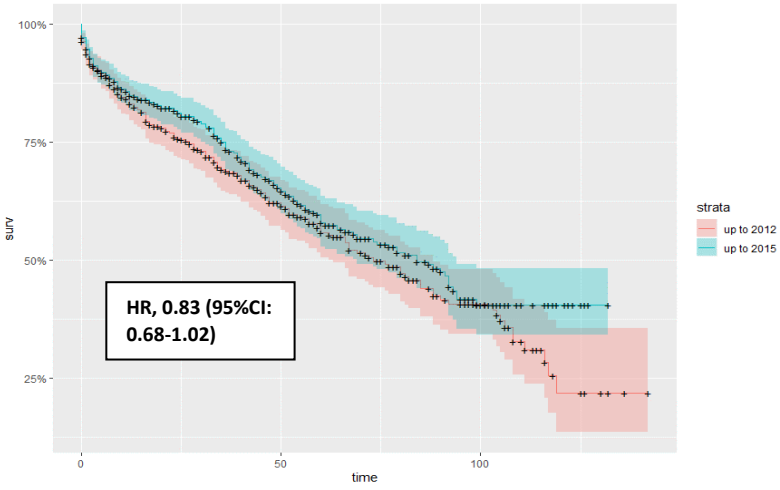
(B)


HR,0.57 (95%CI: 0.49-0.67)
surv
time
strata
up to 2012
up to 2015

(C)


Weighted stratified HR, 0.68 (95%CI: 0.54-0.85)
surv
time
strata
up to 2012
up to 2015

(D)


HR, 0.83 (95%CI: 0.68-1.02)
surv
time
strata
up to 2012
up to 2015

(E)

Figure 2.4: Kaplan-Meier curves of overall survival in both cohorts (patients diagnosed between 2000-2003 and followed to 2012 versus patients diagnosed between 2004-2007 and followed to 2015). (A) OS curves for patients ages at diagnosis 45-54, (B) patients ages 55-64 years, (C) patients ages 65-74, (D) patients ages 75-84 years, (E) patients ages 85 years or more.

3.0 COMPARATIVE EFFICACY OF FIRST-LINE TREATMENTS OF CHRONIC LYMPHOCYTIC LEUKEMIA: NETWORK META-ANALYSES OF SURVIVAL CURVES

Manuscript in submission process

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3.1 Abstract

Multiple treatment options in first-line chronic lymphocytic leukemia (CLL) pose a challenge in identifying the best treatment. We performed novel network meta-analyses (NMA; 8 trials, 11 treatments) on the Kaplan-Meier curves to compare treatments for fludarabine-ineligible patients on progression-free survival (PFS), time-to-next-treatment (TTNT) and overall survival (OS). Using the Guyot method of enhanced secondary analysis of digitized survival data and applying the fixed lognormal distribution model, we extracted the survival proportions and hazard ratios (HR) over 60 months of follow-up, including PFS comparisons by unmutated/mutated IGHV and del 17p. Acalabrutinib-plus-obinutuzumab was associated with higher 5-year PFS proportions than ibrutinib (HR=0.42, 95%CrI=0.25-0.63) but not acalabrutinib, ibrutinib-plus-obinutuzumab, ibrutinib-plus-rituximab or venetoclax-plus-obinutuzumab. In patients with un-mutated (but not with mutated) IGHV higher PFS proportions and favorable HRs were observed for acalabrutinib, acalabrutinib-plus-obinutuzumab, and ibrutinib-plus-obinutuzumab relative to ibrutinib; and targeted therapies were superior over chemoimmunotherapies in patients with del 17p. Targeted therapies containing ibrutinib or acalabrutinib regimens were associated with superior TTNT over venetoclax-plus-obinutuzumab and all chemoimmunotherapies. OS NMA generally found no difference between therapies except for some chemoimmunotherapies. Overall, only acalabrutinib-plus-obinutuzumab was associated with superior 5-year PFS gains over ibrutinib, which in turn was similar or superior in PFS benefit over other targeted therapies. Acalabrutinib and ibrutinib with obinutuzumab and acalabrutinib monotherapy were associated with greater 5-year TTNT benefits. Despite marked 5-year OS for many regimens, a differential 5-year OS benefit could not be ascertained.

3.2 Introduction

The advent of anti-CD20-based chemoimmunotherapy over the past decade has been a breakthrough in the treatment of chronic lymphocytic leukemia (CLL). For un-fit (frail) patients who are ineligible for fludarabine-based therapies (age 65 or older or comorbidities), the combination therapies obinutuzumab-plus-chlorambucil, ofatumumab-plus-chlorambucil, bendamustine-plus-rituximab and rituximab-plus-chlorambucil have become first-line treatments in CLL[8, 70, 71]. These chemoimmunotherapy regimens have shown significant improvements in terms of progression-free (PFS) and overall survival (OS) outcomes when compared to standard chemotherapy[72, 73]. Despite this progress, chemoimmunotherapies such as bendamustine-plus-rituximab and fludarabine-plus-cyclophosphamide-plus-rituximab (FCR) may be associated with developing secondary malignancies and Richter's transformation[74, 75] and may be of limited efficacy in high-risk patients with un-mutated IGHV or TP53 mutation/deletions[10, 76, 77].

The approval of new targeted therapies for the front-line treatments of CLL, such as the Bruton's tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib either as monotherapy or in combination regimens such as ibrutinib-plus-rituximab, ibrutinib-plus-obinutuzumab, acalabrutinib-plus-obinutuzumab, and the BCL-2 inhibitor venetoclax combined with obinutuzumab, have greatly improved prognosis in CLL patients regardless of TP53 status[78]. Another important recent development concerns the emergence of the time-to-next-treatment (TTNT) outcome in several recent CLL clinical trials to complement the standard outcomes of PFS, OS, and response rate[22-24].

The current National Comprehensive Cancer Network (NCCN) guidelines list ibrutinib, acalabrutinib with or without obinutuzumab, and venetoclax-plus-obinutuzumab as the preferred

front-line regimens regardless of age, comorbidity, and 17p deletion/TP53 mutation or IGHV mutation status[31]. The multiple options for mono- or combination therapy in first-line CLL, compounded by the fact that chemoimmunotherapy may still have a role in the management of CLL[79, 80], may pose a challenge to hematologists in terms of identifying the best treatment options for their CLL patients, especially since no comprehensive trials are available that compare therapeutic options head-to-head. Further, the optimal first-line treatment in un-fit patients is still unclear[8].

Network meta-analysis, a class of procedures to indirectly compare treatments, offers a statistical approach to comparing treatment options head-to-head. Here, we report on a network meta-analysis of trials that evaluated all front-line treatments in un-fit CLL patients, focusing on the efficacy measures of PFS, TTNT, and OS, as well as PFS within populations with un-mutated/mutated IGHV and deletion 17p. Whereas most network meta-analyses use the log hazard ratio (HR) method, which assumes the proportionality of all hazards in the network meta-analysis, our analyses applied the novel method proposed by Jansen and Ouwens et al. that uses the actual survival curves[81, 82].

3.3 Methods

3.3.1 Search Strategy, Eligibility Criteria, and Study Selection

A literature search was performed in Medline (PubMed), Embase, Cochrane Library, and Google Scholar to identify all phase III randomized clinical trials (RCT) evaluating first-line treatments in CLL. Additionally, the reference lists of the guidelines published by the National Cancer Institute (NCI) and the National Comprehensive Cancer Network (NCCN) were reviewed, as were the conference abstracts of the annual meetings of the American Society of Clinical Oncology (ASCO 2019-2020), American Society of Hematology (ASH 2019-2021) and European Hematology Association (EHA 2019-2020). The search, which was limited to English-language publications, included the terms “chronic lymphocytic leukemia”, “leukemia”, “previously untreated” , “first-line treatment”, and the names of agents for first-line CLL treatment. Studies had to include previously untreated patients with CLL who required treatment (i.e., symptomatic disease or Binet stage C) and were ineligible for fludarabine-based therapy because of old age or having co-existing conditions reflected by a Cumulative Illness Rating Scale (CIRS) score of 6 or more. Studies had to be a phase III (blinded or unblinded) randomized controlled trial comparing monotherapies or combination therapies including ibrutinib, acalabrutinib, obinutuzumab, venetoclax, ofatumumab, alemtuzumab, chlorambucil, rituximab, and/or bendamustine with PFS as the primary outcome and, as available, OS and TTNT as secondary outcomes. Excluded were reports of single-arm trials; trials with previously-treated patients; trials including fludarabine eligible patients; and trials not using at least PFS as an outcome.

Two independent reviewers performed the screening and evaluation of the data. Any differences were first addressed by discussion; if no consensus was achieved, the issue was escalated to a third reviewer.

3.3.2 Data Extraction

For each selected study, the patients' age, gender, ECOG performance status, Binet and Rai stage, genetic abnormalities, median follow-up, and sample size were extracted. Also extracted were the outcomes of median PFS; the hazard ratios (HR) of PFS and OS with 95% confidence interval (95%CI); complete and partial response proportions (CR/PR); and negative minimal residual disease proportion. For the network meta-analysis, the Kaplan-Meier survival curves of PFS, OS, TTNT, as well as PFS stratified by IGHV and del 17 status (if reported), were digitized using Engauge digitizer software version 10.11[83].

3.3.3 NMA of Survival Data

Network meta-analyses for time-to-event outcomes such as PFS and OS that use the HRs to synthesize the evidence across different studies require meeting the proportional hazard assumption between all competing treatments. The assumption is violated if any of the survival curves are crossed[81, 82]. Further, important time-dependent information is lost in HR-based analyses. Applying a constant HR implies that a given treatment has only an effect on the scale parameter of its survival curve and ignores the shape of this curve over time. In contrast, if one first fits parametric distributions to the respective survival curves, the shape parameter can be estimated so that both the scale and shape of the outcome over time can be used in the meta-analysis. The additional information provided by the shape parameter allows for more flexible and more realistic models and predictions of the effect of a treatment over time[84].

Procedurally, we first digitized the Kaplan-Meier curves of PFS, OS, and TTNT. Next, using the Guyot et al. method[85], we combined the digitized survival proportions with the number of patients at risk at each time-point to reconstruct the individual patient-level data. Next, Kaplan-Meier curves were established for all the treatments evaluated in the trials and plotted in one figure to check for evidence of non-proportionality. As multiple crossings were observed, we considered the assumption of proportionality of the hazard rates violated (Figure 2) and therefore applied the meta-analysis method proposed by Jansen and Ouwens et al.[81, 82] that uses the reconstructed survival curves without relying on the proportional hazards assumption. For each treatment in the network meta-analysis, we tested the goodness-of-fit of the survival data in each Kaplan-Meier curve with fixed or random parametric distributions based on the Weibull, lognormal, loglogistic, Gompertz, exponential, and generalized gamma functions. The best-fitting distribution for each treatment was selected using the deviance information criterion (DIC), the Akaike information criterion (AIC), and the Bayesian information criterion (BIC). The scale and shape were allowed to vary between treatments and trials, and the differences in the survival functions were described by the scale and shape parameters. The network meta-analysis was conducted using the survivalnma and survfelx packages in R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGs software (The BUGs project, London, United Kingdom).

A Bayesian approach was used to estimate the parameters in the network meta-analysis models to allow for uncertainty in prediction and extrapolation of the curves beyond the follow-up periods. The survival curves were plotted and hazard ratios with their 95% credible interval (CrI) compared to ibrutinib estimated for all treatments. As each possible pairwise comparison between treatments in the network meta-analysis was either direct or indirect, it was not possible

to apply the node-splitting method to evaluate the consistency of the network. However, we ran both fixed-effect and random-effect analyses on survival curves. According to the DIC, the fixed models fit the predictions better and therefore these models were retained.

In addition to the overall network meta-analysis, we also conducted sub-analyses on PFS among patients with mutated and unmutated IGHV, as well as del 17p patients. As Kaplan-Meier curves were not available for some of the studies, we used the log HR method (netmeta package in R) for these sub-analyses. The Surface Under the Cumulative Ranking (SUCRA) values were used to rank treatments. A higher SUCRA value indicates that the treatment is more likely to improve the survival outcome of interest when compared to other treatments.

3.4 Results

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Figure 1)[86, 87], we identified eight publications that met the inclusion criteria. Of these, one study[54] compared obinutuzumab-plus-chlorambucil with chlorambucil or rituximab-plus-chlorambucil; one[88] compared ofatumumab-plus-chlorambucil with chlorambucil; one[21] compared ibrutinib with chlorambucil; one[22] compared ibrutinib with ibrutinib-plus-rituximab or bendamustine-plus-rituximab; one[89] compared bendamustine-plus-rituximab with rituximab-plus-chlorambucil; one[25] compared venetoclax-plus-obinutuzumab with obinutuzumab-plus-chlorambucil; one study[23] compared ibrutinib-plus-obinutuzumab with obinutuzumab-plus-chlorambucil; and one study[24] compared acalabrutinib with acalabrutinib-plus-obinutuzumab or obinutuzumab-plus-chlorambucil. Table 1 shows for each study the patient characteristics and the outcomes reported. The networks for each outcome of interest are shown in Figure 3.

3.4.1 Progression-free Survival

The fixed-effect lognormal distribution was the best-fitting model to estimate the PFS proportions for the eleven treatments against a 60-month follow-up time horizon (Figure 4A) . As Table 2A shows, consistently at each of the 5 time points, acalabrutinib-plus-obinutuzumab was associated with the highest expected proportion of PFS compared to the other regimens; with moreover the narrowest 95%CrI and thus greater precision of the estimate. At 12 months, its expected PFS proportion of 0.99 was the highest and most precise (95%CrI=0.97-1.00) and prevailed over the ensuing years to end at 0.78 (95%CrI=0.56-0.90) at 5 years. This was markedly better than the 5-year expected PFS proportions for the three ibrutinib regimens (range: 0.56-0.58) and for venetoclax-plus-obinutuzumab (0.43); while the chemo- and chemoimmunotherapy regimens were associated with 5-year expected PFS proportions between 0.00 and 0.09.

As to the HRs, only acalabrutinib monotherapy and acalabrutinib-plus-obinutuzumab showed statistically significant superior HRs over ibrutinib at 36 months (respectively, HR=0.67, 95%CrI=0.49-0.98; HR=0.34, 95%CrI=0.23-0.47), after which only acalabrutinib-plus-obinutuzumab was superior with HR of 0.39 (95%CrI=0.25-0.57) at 48 and HR of 0.42 (95%CrI=0.25-0.63) at 60 months. Further, at 5 years ibrutinib was associated with a significantly lower hazard of progression or death when compared to the chemo- and chemoimmunotherapy regimens of, in ascending order, obinutuzumab-plus-chlorambucil (HR=4.17, 95%CrI=3.40-4.95), bendamustine-plus-rituximab (HR=7.48, 95%CrI=3.57-13.90), rituximab-plus-chlorambucil (HR=9.14, 95%CrI=7.13-11.25), ofatumumab-plus-chlorambucil (HR=9.56, 95%CrI=6.71-12.07), as well as chlorambucil monotherapy (HR=25.00, 95%CrI=14.28-33.34). Neither ibrutinib-plus-rituximab nor venetoclax-plus-obinutuzumab were

statistically significant beyond the first year (Figure 4B, Table 2B). The median PFS (95%CrI) for each treatment option after extrapolating the fitted lognormal distribution to 100 months are listed in Table 3. Acalabrutinib-plus-obinutuzumab and acalabrutinib monotherapy were estimated to have the best PFS outcome, followed by ibrutinib mono- and combination therapies, and venetoclax-plus-obinutuzumab therapy, with the remaining chlorambucil and chemoimmunotherapies showing comparably low estimated PFS.

3.4.2 Progression-free Survival by IGHV Status

All studies except Hillmen and Michallet et al. were evaluated in the PFS network meta-analysis stratified by IGHV status (Figure 3B). Compared with ibrutinib, acalabrutinib-plus-obinutuzumab (HR=0.46, 95%CrI=0.30-0.70; SUCRA=0.96) followed by acalabrutinib (HR=0.53, 95%CrI=0.37-0.76; SUCRA=0.89) and ibrutinib-plus-obinutuzumab (HR=0.60, 95%CrI=0.41-0.90; SUCRA=0.79) were associated with statistically significant lower HRs of progression or death in patients with un-mutated IGHV(Figure 5A). This was not the case for venetoclax-plus-obinutuzumab (HR=0.71, 95%CrI=0.48-1.05; SUCRA=0.69) and ibrutinib-plus-rituximab (HR=1.24, 95%CrI=0.88-1.73; SUCRA=0.42). Ibrutinib was associated significantly with a lower hazard of progression or death when compared to, in ascending order, obinutuzumab-plus-chlorambucil (HR=1.38, 95%CrI=1.02-1.86), rituximab-plus-chlorambucil (HR=2.00, 95%CI=1.49-2.67), and bendamustine-plus-rituximab (HR=2.06, 95%CrI=1.60-2.64).

The network meta-analysis in cohorts of patients with IGHV mutation found no differences in PFS between targeted therapies or chemoimmunotherapies over ibrutinib (Figure 3B). SUCRA results are presented in Table 4.

3.4.3 Progression-free Survival in Patients with Del 17p

The network meta-analysis of PFS in patients with deletion 17p included four studies (Goede et al, Fischer et al, Moreno et al, Sharman et al) (Figure 3C). Using ibrutinib-plus-obinutuzumab as the reference, targeted therapies (acalabrutinib-plus-obinutuzumab, acalabrutinib, venetoclax-plus-obinutuzumab) did not differ from ibrutinib-plus-obinutuzumab; while the latter regimen was associated with significant lower hazards than obinutuzumab-plus-chlorambucil (HR=2.35, 95%CrI=1.35-4.08), rituximab-plus-chlorambucil (HR=3.00, 95%CrI=1.34-6.74) and chlorambucil (HR=3.42, 95%CrI=1.74-6.75) (Figure 5C).

3.4.4 Time-to-next-treatment

The fixed-effect lognormal distribution was the best-fitting model to estimate the TTNT proportions over 60-months of follow-up. The TTNT network meta-analysis included five studies (Sharman et al, Hillmen et al, Fischer et al, Moreno et al, Goede et al) (Figure 3D). As no TTNT data were available for ibrutinib, the HRs were calculated compared to ibrutinib-plus-obinutuzumab.

As Table 5A shows, at each of the 5 time points, acalabrutinib-plus-obinutuzumab and acalabrutinib monotherapy, followed by ibrutinib-plus-obinutuzumab, were associated consistently with the highest proportions of TTNT compared to the other regimens. The proportions of patients without next treatment after 60 months following the first progression were 0.99 (95%CrI=0.71-1.00), 0.94 (95%CrI=0.74-0.96), and 0.93 (95%CrI=0.83-0.96), respectively. At this time point, the TTNT proportion for venetoclax-plus-obinutuzumab was 0.74 (95%CrI=0.65-0.80), while the TTNT proportions were the lowest in the remaining regimens, ranging between 0.25 and 0.38 (Figure 6).

The HRs at 60 months showed that no differences between acalabrutinib-plus-obinutuzumab (HR=0.07, 95%CrI=0.05-1.50) or acalabrutinib (HR=0.46, 95%=0.09-1.00) over ibrutinib-plus-obinutuzumab. Ibrutinib-plus-obinutuzumab was associated with a lower hazard of needing to initiate second-line therapy when compared to, in ascending order, venetoclax-plus-obinutuzumab (HR=3.00, 95%CrI=1.92-4.98), obinutuzumab-plus-chlorambucil (HR=13.50, 95%CI=5.97-29.91), rituximab-plus-chlorambucil (HR=21.14, 95%CrI=11.44-38.57), chlorambucil (HR=21.51, 95%CrI=9.91-45.52), and ofatumumab-plus-chlorambucil (HR=28.59, 95%CrI=19.52-50.30).

3.4.5 Overall Survival

The fixed-effect lognormal distribution was the best-fitting model to estimate the OS proportions for the eleven treatments against a 60-month follow-up time horizon. As Table 6A shows, the regimens of acalabrutinib-plus-obinutuzumab, acalabrutinib, ibrutinib, ibrutinib-plus-obinutuzumab, ibrutinib-plus-rituximab, and bendamustine-plus-rituximab were associated with expected OS proportions of 0.90 (95%CrI=0.74-0.96, ibrutinib-plus-obinutuzumab) to 0.95% (95%CrI=0.89-0.98, acalabrutinib-plus-obinutuzumab) at 5 years of follow-up. These 5-year proportions were higher than those for the other regimens, which ranged from 0.62 (95%CrI=0.45-0.72, rituximab-plus-chlorambucil) to 0.89 (95%CrI=0.85-0.92, Obinutuzumab-plus-chlorambucil) (Figure 7). The HRs at 60 months showed no differences between ibrutinib and other regimens, with the exception of a higher 5-year risk of death in patients treated with chlorambucil (HR=6.46, 95%CrI=1.47-12.66), ofatumumab-plus-chlorambucil (HR=7.01, 95%CrI=1.90-12.52), and rituximab-plus-chlorambucil (HR=10.32, 95%CrI=3.10-17.10) (Table 6B).

3.5 Discussion

The principal findings of our independent (i.e., not industry-sponsored) network meta-analysis of survival outcomes extrapolated beyond the follow-up periods of the respective clinical trials, are four-fold. First, consistently the acalabrutinib-plus-obinutuzumab regimen was associated with superior progression-free survival across a 5-year period, while acalabrutinib and ibrutinib monotherapy, ibrutinib-based combination therapies, and venetoclax-plus-obinutuzumab evidenced modest PFS benefits. Especially acalabrutinib-plus-obinutuzumab but also acalabrutinib monotherapy were the only treatments that, when compared to ibrutinib, evidenced a PFS benefit for up to 3 years, with the former extending this benefit to 5 years. All other treatments had either a lesser or similar PFS benefit as ibrutinib after the second year of treatment. In parallel, when extrapolating PFS curves to 100 months, acalabrutinib was projected to yield a median PFS of 87 months (95%CI=46.0-NR) while the median PFS for acalabrutinib-plus-obinutuzumab could not be estimated within this frame and therefore is likely to exceed 100 months.

Second, these PFS results were validated in the time-to-next-treatment analyses. Over 90% of patients were projected to not require second-line treatment within 5 years if treated with acalabrutinib-plus-obinutuzumab (99%), acalabrutinib monotherapy (94%), ibrutinib-plus-obinutuzumab (93%), or, to a lesser extent, venetoclax-plus-obinutuzumab (74%). Compared to the TTNT for ibrutinib-plus-obinutuzumab (as no data were available for ibrutinib), the likelihood of requiring second-line treatment within 5 years was nominally but not statistically lower for acalabrutinib and acalabrutinib-plus-obinutuzumab, indicating the efficacy of all three treatment options in delaying follow-on treatment for at least 5 years.

Third, the OS proportions by year and cumulatively over up to 5 years for all treatment options were statistically significant, signaling that all treatments had a statistically significant survival benefit. However, this was particularly the case for regimens, mono or in combination, that included acalabrutinib and/or ibrutinib and/or obinutuzumab. However, when compared to ibrutinib monotherapy, three regimens (chlorambucil, ofatumumab-plus-chlorambucil, rituximab-plus-chlorambucil) showed a markedly higher 5-year likelihood of death.

Lastly, the PFS sub-analyses for patients with IGHV mutation revealed no significant differences between the HRs of PFS among targeted therapies and chemoimmunotherapy when compared with ibrutinib. However, the PFS analysis on patients with un-mutated IGHV showed that acalabrutinib-plus-obinutuzumab, acalabrutinib monotherapy, and ibrutinib-plus-obinutuzumab were associated with significantly higher PFS than ibrutinib monotherapy. The del 17p sub-analysis yielded no significant PFS differences between the targeted therapies while the PFS HRs of chemoimmunotherapies were significantly higher compared to ibrutinib-plus-obinutuzumab. Thus, the targeted therapies of acalabrutinib-plus-obinutuzumab, acalabrutinib, ibrutinib-plus-obinutuzumab, and to a lesser extent venetoclax-plus-obinutuzumab emerged as preferred treatments in patients with high-risk disease.

Of note, we obtained our results by applying novel methods for network meta-analysis. Most network meta-analyses of cancer treatments use the HR as the metric for comparing treatments. Being a constant estimate, this supports inferences about the overall statistical significance of differences between treatments but does not reflect how these differences occur over time nor how the survival outcomes of interests manifest themselves as time evolves. In addition, it also requires the proportional hazard assumption to be met. Therefore, and not having access to the patient-level trial data, we opted to apply the Guyot method[85] to the digitized

survival curves and the subjects-at-risk to extract the estimated patient-level data; to fit parametric functions to the survival curves so as to extrapolate the survival benefits beyond the trial observation periods; and to use novel methods[81, 82] to perform a network meta-analysis of extrapolated survival curves against a 5-year time horizon.

While, ideally, treatment decisions should be made on the basis of efficacy and safety, other factors may affect the choice of therapy, especially in low-risk patients. One potential factor is the high cost of targeted therapies. Chen et al. estimated that the lifetime treatment cost for a CLL patient will increase from $147,000 to $604,000 (310% increase) if oral targeted therapies are used as first-line treatment instead of chemoimmunotherapy. This includes an increase by 520% from $9,200 to $57,000 in the total out-of-pocket cost of Medicare patients[90]. In contrast, in a study assessing the time-to-next-treatment in the real-world setting, Emond et al. demonstrated that healthcare costs during front-line CLL treatment with ibrutinib monotherapy were lower by $3,766 compared to chemoimmunotherapy due to fewer monthly days with outpatient visits and despite higher pharmacy costs[91].

Another potential factor is the TTNT after the first progression. In our analyses, patients treated with acalabrutinib, with or without obinutuzumab, and ibrutinib-plus-obinutuzumab had a similar hazard of needing to initiate the next treatment – all lower than the other treatment options. Some caution is in order, however, in that all trials estimated the TTNT for all patients without differentiating between those with genetic mutations/deletions. It may be that low-risk patients may gain better TTNT benefits from targeted therapies. In a study[92] of first-line ibrutinib therapy in patients with or without del 17p, no differences were observed in TTNT and time to discontinuation between both groups.

In part because of the innovation afforded by the statistical comparison of the actual and extrapolated survival curves, our study confirms but also substantially extends three prior network meta-analyses on first-line treatments in CLL. A 2015 network meta-analysis[72] was limited to chemoimmunotherapies in un-fit CLL patients and concluded that obinutuzumab-plus-chlorambucil demonstrated better PFS and OS outcomes compared with chlorambucil combination regimens with either fludarabine, ofatumumab, or rituximab. Our analysis included several additional regimens.

A 2017 analysis[93] using the log HR method revealed improvements in PFS and OS of ibrutinib monotherapy relative to ofatumumab-plus-chlorambucil, obinutuzumab-plus-chlorambucil, bendamustine-plus-rituximab, and rituximab-plus-chlorambucil. However, this study did not include more recent targeted therapies and regimens such as acalabrutinib with or without obinutuzumab, venetoclax-plus-obinutuzumab, or ibrutinib combined with rituximab or obinutuzumab.

A recent network meta-analysis by Davids et al[94]., sponsored by the manufacturer of acalabrutinib and, unsurprisingly, using this second-generation and not a first-generation BTK inhibitor as comparator, focused on PFS and OS outcomes in first-line CLL treatments in fludarabine-ineligible patients. It included the same trials as our network meta-analysis but also an additional trial of alemtuzumab and chlorambucil[95]. Several differences with our network meta-analyses should be noted. First, we excluded the latter trial because it was not restricted to frail patients ($\geq$65 years old or having comorbidities) and therefore might have imputed heterogeneity. Secondly, this third meta-analysis used the log HR method and thus assumed, but did not provide evidence, that the proportional hazards assumptions between all treatments was met. Our plots of the reconstructed Kaplan-Meier curves showed multiple curve crossings with a

Schoenfeld residuals *P*-value of <0.0001 and thus violating the proportionality assumption (Figure S2). Thirdly, by using the log HR method the analyses assumed a constant time-to-event pattern (expressed as the scale parameters), regardless of the actual shape of the Kaplan-Meier curves. Our approach of using fitted parametric functions with both scale and shape parameters enabled survival predictions that consider the time-dependent pattern of the survival outcomes. This lent a marked degree of ecological validity to our analyses and results. Fourthly, we included TTNT as an efficacy outcome. The TTNT metric is clinically a highly meaningful endpoint because it uniquely reflects not only the duration of treatment efficacy on the disease, but also incorporates the patient experience by accounting for patient adherence to and tolerance of the therapy. Fifthly, we included sub-analyses on such important prognostic factors as IGHV status and deletion 17p that may affect treatment response and survival outcomes as well as treatment response. Lastly, by fitting parametric functions to the survival outcomes, we were able to extrapolate the likely various survival patterns well beyond the limits of the trial data and the many "not reached" or "not estimable" medians that were reported.

While confirming the results of this third prior meta-analysis, our analyses revealed several additional findings. Our analyses confirmed the PFS HRs for all treatments versus ibrutinib for the first and third year of follow-up: that ibrutinib is superior in PFS to all chemoimmunotherapies; lower in PFS than acalabrutinib-plus-obinutuzumab, acalabrutinib, and ibrutinib-plus obinutuzumab; and similar in PFS to ibrutinib-plus-rituximab or venetoclax-plus-obinutuzumab. However, our analyses of the PFS curves showed no statistically significant differences between ibrutinib and acalabrutinib after the third year and between ibrutinib and ibrutinib-plus-obinutuzumab after the second year. Further, our OS analyses showed that in each year of follow-up, the credible interval of the respective HRs in the comparisons of acalabrutinib

and acalabrutinib-plus-obinutuzumab to ibrutinib crossed unity and therefore were not statistically significant, indicating no differential OS benefit. This challenges Davids et al.'s assertion that acalabrutinib "ranked highest in treatment efficacy over the other comparators" (p.1956). Our results confirm the superior PFS benefit of acalabrutinib monotherapy and acalabrutinib-plus-obinutuzumab over ibrutinib but do not support a claim of superior OS benefit. In addition, though in comparison to ibrutinib-plus-obinutuzumab as no ibrutinib comparisons were possible, the acalabrutinib regimens have a statistically similar TTNT benefit.

Our network meta-analysis has limitations while also suggesting areas for future research. By including new therapies introduced since 2010 clinical trials compared different treatments and the effect estimates relative to ibrutinib were gained from either direct or indirect pairwise comparisons, which may add uncertainty to the results. Therefore, we did not assess heterogeneity and consistency by the node-splitting method but instead tested each parametric distribution in random and fixed effects and used information criterion statistics to evaluate goodness-of-fit. The use of a fixed effect model was further supported by limiting the trials to those with patients age 65 year and older or with comorbidities, thus excluding potential confounding; and the fact that all trials had similar patient distributions of prognostic factors. Our study does not address the relative impact on quality-of-life due to treatment or toxicity effects. As the median follow-up times in the trials ranged from 13.6 to 60 months there may have been some uncertainty in the extrapolation of survival curves, especially in those trials with shorter follow-up.

3.6 Conclusion

In this independent network meta-analysis with reconstructed Kaplan-Meier curves and extrapolation to 5 years using fitted survival curves, acalabrutinib monotherapy, as well as the regimens of acalabrutinib and ibrutinib with obinutuzumab were associated with superior 5-year PFS gains over ibrutinib, which in turn was similar or superior in PFS benefit over other treatments. These three regimens were also associated with greater 5-year TTNT benefits. Despite marked 5-year OS for many regimens, a differential 5-year OS benefit could not be ascertained.

Table 3.1A: Summary of baseline characteristics for the included studies.

Study name	Interventions	Number of patients randomized	Median follow-up (months)	Male (%)	Median age, range	CIRS* median, range	ECOG % (0, 1, ≥2)	Binet % (A, B, C)	Rai % (stage III or IV)	Del 17p%, del 11q%, del 13q%, unmutated IGHV %
Goede et al, 2014	Obinutuzumab-chlorambucil	238	14.5	59	74, 39-88	8, 1-20	NA	23, 41, 36	NA	8, 16, 29, 61
	Rituximab-chlorambucil	233	15.3	64	73, 40-90	8, 0-18	NA	21, 43, 36	NA	5, 15, 28, 62
	Chlorambucil	118	13.6	64	72, 43-87	8, 0-18	NA	20, 42, 37	NA	10, 19 , 33, 59
Hillmen et al, 2015	Ofatumumab-chlorambucil	221	NA	64	69, 35-92	9, 4-21	39, 53, 8	35, 33, 32	NA	5, 19, NA, 57
	Chlorambucil	226	NA	62	70, 36-91	8, 4-19	38, 54, 8	31, 38, 31	NA	8, 11, NA, 56
Woyach et al, 2018	Ibrutinib-rituximab	182	38	69	71, 65–86	NA	47, 52, 1	NA	54	6, 21, 36, 61
	Ibrutinib	182	38	68	71, 65–89	NA	48, 49, 3	NA	54	5, 19, 36, 63
	Bendamustine-rituximab	183	38	65	70, 65–86	NA	54, 41, 5	NA	54	8, 18, 36, 58
Burger et al, 2018	Ibrutinib	136	60	65	73, 65-89	NA	44, 48,8	NA	44	0, 22, 22, 48
	Chlorambucil	133	60	61	72, 65-90	NA	41, 50, 9	NA	47	0, 21, 30, 47
Michallet et al*, 2018	Bendamustine-rituximab	121	23.5	58	72, 41-86	NA	51, 41, 7	5, 60, 31	NA	8, 20, 35, 60
	Rituximab-chlorambucil	120	23.3	67	72, 38-91	NA	49, 43, 7	7, 55, 36	NA	3, 16, 4, 49
Moreno et al, 2019	Ibrutinib-obinutuzumab	113	29.6	59	70, 66-75	4, 2-7	50, 46, 4	NA	53	12, 12, NA, 62
	Obinutuzumab-chlorambucil	116	36.5	68	72, 66-77	4, 2-7	46, 48, 6	NA	51	16, 19, NA, 53
Fischer et al, 2019	Venetoclax-obinutuzumab	216	28.1	67.6	72, 43–89	9, 0–23	41.2, 45.8, 13.0	21.3, 35.6, 43.1	NA	8.5, 18, 30.5, 60.5
	Obinutuzumab-chlorambucil	216	28.1	66.2	71, 41–89	8, 1–28	47.9, 40.5, 11.6	20.4, 37.0, 42.6	NA	7.3, 19.7, 30.6, 59.1
Sharman et al, 2020	Acalabrutinib-obinutuzumab	179	28.3	62	70, 65-75	6, 3-8	94.4, 5.6	NA	48	9.5, 17.3, NA, 57.5
	Acalabrutinib	179	28.3	62	70, 66-75	6, 3-8	92.2, 7.8	NA	48.6	8.9, 17.3, NA, 66.5
	Obinutuzumab-chlorambucil	177	28.3	59.9	71, 67-76	5.5, 4-8	94.4, 5.6	NA	44.1	9.0, 18.6, NA, 65.5

*This study included patients previously untreated or treated, however, the data and outcomes for the previously untreated were only used in this study.

Table 3.1B: Reported outcomes of included studies.

Study name	Interventions	Median PFS, 95%CI	PFS HR, 95%CI	OS HR, 95%CI	CR%, PR%	Peripheral blood, bone marrow -ve MRD %	HR, 95%CI in un-mutated IGHV	HR. 95%CI in del 17
Goede et al, 2014	Obinutuzumab-chlorambucil	26.7, NA	0.18, 0.13-0.24	0.41 0.23-0.74	22.3, 55.0	37.7, 19.5	0.23 0.16-0.34	0.42 0.17-1.04
	Rituximab-chlorambucil	16.3, NA	0.44, 0.34-0.57	0.66 0.39-1.11	7.3, 58.4	3.3, 2.6	0.54 0.38-0.76	0.74 0.27-2.04
	Chlorambucil	11.1, NA	Reference	Reference	0, 31.4	0, 0	Reference	Reference
Hillmen et al, 2015	Ofatumumab - chlorambucil	22.4, 19.0-25.2	0.57, 0.45-0.72	0.91 0.57-1.43	14, 68	8, 2	NA	NA
	Chlorambucil	13.1, 10.6-13.8	Reference	Reference	1, 68	<1, 0	NA	NA
Woyach et al, 2018	Ibrutinib-rituximab	NR	0.38, 0.25-0.59	No differences	12, NA	NA, 4	0.31 0.18–0.51	NA
	Ibrutinib	NR	0.39, 0.26-0.58		7, NA	NA, 1	0.19 0.11–0.35	NA
	Bendamustine-rituximab	43, 38-NR	Reference		26, NA	NA, 8	Reference	NA
Burger et al, 2018	Ibrutinib	NR	0.146, 0.098-0.218	0.450 0.266-0.671	18, 71	NA	0.11 0.06-0.19	NA
	Chlorambucil	15, NA	Reference	Reference	NA	NA	Reference	NA
Michallet et al, 2018	Bendamustine-rituximab	39.6, NA	0.523, 0.339-0.806	0.975, 0.505-1.880	24, 50	41*		
	Rituximab-chlorambucil	29.9, NA	Reference	Reference	9, 66	13*		
Moreno et al, 2019	Ibrutinib-obinutuzumab	NR, 33.6-NR	0.23, 0.15-0.37	0.92 0.48-1.77	19, 65	30, 20	0.15 0.08–0.27	0.14 0.04-0.51
	Obinutuzumab-chlorambucil	19, 15.1-22.1	Reference	Reference	8, 66	20, 17	Reference	Reference
Fischer et al, 2019	Venetoclax-obinutuzumab	NA	0.35, 0.23-0.53	1.24 0.64-2.40	49.5, 35.2	75.5, 56.9	0.22 0.12-0.38	0.33 0.12-0.89
	Obinutuzumab-chlorambucil	NA	Reference	Reference	23.1, 48.1	35.2, 17.1	Reference	Reference
Sharman et al, 2020	Acalabrutinib-obinutuzumab	NR	0.10, 0.06-0.17	0.47 0.21-1.06	24.6, 65.4	49, 26	0.08 0.04–0.16	0.10 0.03-0.34
	Acalabrutinib	NR, 43.2-NR	0.20, 0.13-0.30	0.60 0.28-1.27	8, 77	7, NA	0.11 0.07–0.19	0.23 0.09-0.61
	Obinutuzumab-chlorambucil	22.6, 20.2-27.6	Reference	Reference	13, 63	61, 22	Reference	Reference

Abbreviations: CIRS, Cumulative Illness Rating Scale; ECOG, Eastern Cooperative Oncology Group; NA, Not Available; PFS, Progression-free Survival; OS, Overall Survival; CR, Complete Response; PR, Partial Response; MRD, Minimal Residual Disease; NR, Not Reached.

*MRD was assessed in the bone marrow or peripheral blood if the bone marrow was not available.

Table 3.2: Progression-free survival proportions and hazard ratios at different time points as obtained from the fixed lognormal network meta-analysis.

	12 months	24 months	36 months	48 months	60 months
Table 3.2A: Progression-free survival proportions.					
	PFS proportion (95%CrI)				
Acalabrutinib	0.99 (0.95-1.00)	0.92 (0.84-0.96)	0.80 (0.65-0.89)	0.70 (0.48-0.83)	0.62 (0.35-0.80)
Acalabrutinib-plus-obinutuzumab	0.99 (0.97-1.00)	0.95 (0.91-0.98)	0.89 (0.79-0.95)	0.84 (0.66-0.92)	0.78 (0.56-0.90)
Bendamustine-plus-rituximab	0.89 (0.56-0.98)	0.44 (0.11-0.75)	0.14 (0.004-0.45)	0.04 (0.001-0.31)	0.01 (0.00-0.23)
Chlorambucil	0.69 (0.31-0.93)	0.07 (0.01-0.25)	0.002 (0.00-0.02)	0.00 (0.00-0.003)	0.00 (0.00-0.0006)
Ibrutinib	0.93 (0.90-0.96)	0.82 (0.75-0.86)	0.72 (0.60-0.78)	0.63 (0.48-0.71)	0.56 (0.39-0.66)
Ibrutinib-plus-rituximab	0.93 (0.78-0.98)	0.82 (0.52-0.94)	0.72 (0.32-0.90)	0.64 (0.19-0.86)	0.57 (0.12-0.83)
Ibrutinib-plus-obinutuzumab	0.98 (0.94-1.00)	0.90 (0.81-0.95)	0.77 (0.59-0.87)	0.66 (0.40-0.81)	0.58 (0.28-0.77)
Obinutuzumab-plus-chlorambucil	0.94 (0.86-0.99)	0.63 (0.56-0.72)	0.33 (0.24-0.39)	0.17 (0.09-0.25)	0.09 (0.03-0.17)
Ofatumumab-plus-chlorambucil	0.86 (0.60-0.97)	0.35 (0.15-0.58)	0.08 (0.009-0.23)	0.02 (0.001-0.11)	0.004 (0.00-0.06)
Rituximab-plus-chlorambucil	0.86 (0.65-0.97)	0.36 (0.20-0.57)	0.09 (0.02-0.21)	0.02 (0.001-0.10)	0.005 (0.00-0.05)
Venetoclax-plus-obinutuzumab	0.98 (0.92-1.00)	0.85 (0.74-0.93)	0.68 (0.47-0.81)	0.54 (0.27-0.73)	0.43 (0.16-0.67)
Table 3.2B: Hazard ratios of progression or death compared with ibrutinib.					
	HR (95%CrI) compared with ibrutinib				
Acalabrutinib	0.18 (0.05-0.43)	0.46 (0.30-0.60)	0.67 (0.49-0.98)	0.78 (0.53-1.01)	0.83 (0.55-1.10)
Acalabrutinib-plus-obinutuzumab	0.13 (0.05-0.27)	0.23 (0.14-0.34)	0.34 (0.23-0.47)	0.39 (0.25-0.57)	0.42 (0.25-0.63)
Bendamustine-plus-rituximab	1.66 (0.35-5.39)	4.14 (1.96-7.55)	6.05 (3.23-10.62)	7.04 (3.47-12.81)	7.48 (3.57-13.90)
Chlorambucil	5.00 (1.72-11.11)	12.50 (10.0-16.67)	20.00 (14.29-25.0)	20.00 (16.67-33.33)	25.00 (14.28-33.34)
Ibrutinib-plus-rituximab	0.88 (0.43-2.27)	0.90 (0.43-2.27)	0.97 (0.43-2.27)	0.98 (0.43-2.27)	1.00 (0.40-3.03)
Ibrutinib-plus-obinutuzumab	0.29 (0.13-0.58)	0.53 (0.35-0.74)	0.78 (0.57-1.04)	0.90 (0.61-1.25)	0.96 (0.54-1.35)
Obinutuzumab-plus-chlorambucil	0.93(0.49-1.43)	2.27 (1.90-2.33)	3.33 (2.78-3.85)	3.85 (3.33-4.17)	4.17 (3.40-4.95)
Ofatumumab-plus-chlorambucil	2.12 (0.66-4.68)	5.28 (3.69-6.58)	7.73 (6.07-9.22)	8.99 (6.54-11.12)	9.56 (6.71-12.07)
Rituximab-plus-chlorambucil	2.03 (0.71-3.97)	5.05 (3.92-5.56)	7.39 (6.45-7.83)	8.61 (6.95-9.44)	9.14 (7.13-11.25)
Venetoclax-plus-obinutuzumab	0.36 (0.14-0.81)	0.81 (0.53-1.05)	1.18 (0.87-1.47)	1.37 (0.94-1.79)	1.45 (0.97-1.92)

Abbreviations: CrI, Credible Interval; HR, Hazard ratio.

Table 3.3: Estimated median progression-free survival as obtained from the fitted fixed lognormal model in the net-work meta-analysis**.**

Treatment	**Median PFS in months (95%CrI)**
Acalabrutinib	87 (46.0-NR)
Acalabrutinib-plus-obinutuzumab	NR (70.0-NR)
Bendamustine-plus-rituximab	24.4 (13.1-37.0)
Chlorambucil	14.6 (9.1-20.0)
Ibrutinib	73 (46-NR)
Ibrutinib-plus-obinutuzumab	75 (41.0-NR)
Ibrutinib-plus-rituximab	75 (25-NR)
Obinutuzumab-plus-chlorambucil	28.5 (26.3-35.7)
Ofatumumab-plus-chlorambucil	20.5 (14.1-26.0)
Rituximab-plus-chlorambucil	20.6 (15.2-27.4)
Venetoclax-plus-obinutuzumab	51.8 (35.0- NR)

NR, not reached; PFS, progression free survival

Table 3.4: SUCRA of progression-free survival of the sub network meta-analyses (A) based on the IGHV mutation status, (B) among patients with deletion 17p.

Un-mutated IGHV		**Mutated IGHV**	
	P-score (fixed)		**P-score (fixed)**
Acalabrutinib_obinutuzumab	0.9625	Acalabrutinib_obinutuzumab	0.9052
Acalabrutinib	0.886	Ibrutinib_obinutuzumab	0.7821
Ibrutinib_obinutuzumab	0.7906	Ibrutinib_rituximab	0.6036
Venetoclax_obinutuzumab	0.6859	Venetoclax_obinutuzumab	0.5644
Ibrutinib	0.5473	Acalabrutinib	0.5403
Ibrutinib_rituximab	0.4215	Ibrutinib	0.4825
Obinutuzumab_chlorambucil	0.3684	Obinutuzumab_chlorambucil	0.3931
Rituximab_chlorambucil	0.1755	Bendamustine_rituximab	0.3736
Bendamustine_rituximab	0.1518	Rituximab_chlorambucil	0.3111
Chlorambucil	0.0106	Chlorambucil	0.0442

17p deletion	**P-score (fixed)**
Acalabrutinib_obinutuzumab	0.9052
Ibrutinib_obinutuzumab	0.8214
Acalabrutinib	0.6836
Venetoclax_obinutuzumab	0.5800
Obinutuzumab_chlorambucil	0.2968
Rituximab_chlorambucil	0.1610
Chlorambucil	0.0521

Table 3.5: Time-to-next-treatment proportions and hazard ratios at different time points as obtained from the fixed lognormal network meta-analysis.

	12 months	24 months	36 months	48 months	60 months
Table 3.5A: Time-to-next-treatment proportions					
	Proportion without next treatment (95%CrI)				
Ibrutinib-plus-obinutuzumab	0.99 (0.97-1.00)	0.97 (0.93-0.99)	0.96 (0.89-0.98)	0.94 (0.86-0.97)	0.93 (0.83-0.96)
Acalabrutinib	0.98 (0.91-0.99)	0.96 (0.85-0.98)	0.95 (0.81-0.97)	0.95 (0.77-0.97)	0.94 (0.74-0.96)
Acalabrutinib-plus-obinutuzumab	0.99 (0.96-1.00)	0.99 (0.90-1.00)	0.99 (0.84-1.00)	0.99 (0.78-1.00)	0.99 (0.71-1.00)
Chlorambucil	0.73 (0.69-0.78)	0.47 (0.41-0.53)	0.31 (0.25-0.37)	0.22 (0.16-0.28)	0.15 (0.10-0.21)
Obinutuzumab-plus-chlorambucil	0.90 (0.88-0.92)	0.73 (0.70-0.76)	0.58 (0.54-0.62)	0.47 (0.42-0.51)	0.38 (0.33-0.42)
Ofatumumab-plus-chlorambucil	0.91 (0.87-0.94)	0.75 (0.69-0.80)	0.58 (0.48-0.64)	0.42 (0.28-0.51)	0.28 (0.14-0.38)
Rituximab-plus-chlorambucil	0.90 (0.87-0.93)	0.68 (0.61-0.73)	0.48 (0.38-0.56)	0.35 (0.24-0.44)	0.25 (0.15-0.35)
Venetoclax-plus-obinutuzumab	0.94 (0.92-0.96)	0.87 (0.84-0.92)	0.83 (0.78-0.88)	0.78 (0.71-0.84)	0.74 (0.65-0.80)
Table 3.5B: Hazard ratios for next treatment after the first progression					
	HRs (95%CrI) compared with ibrutinib-plus-obinutuzumab				
Acalabrutinib	1.11 (0.23-1.81)	0.78 (0.16-1.49)	0.62 (0.13-1.25)	0.53 (0.11-1.09)	0.46 (0.09-1.00)
Acalabrutinib-plus-obinutuzumab	0.20 (0.14-5.42)	0.13 (0.09-3.27)	0.09 (0.07-2.38)	0.08 (0.06-1.91)	0.07 (0.05-1.50)
Chlorambucil	30.81 (13.65-68.46)	29.57 (13.26-46.70)	26.45 (12.06-56.55)	23.73(10.88-50.02)	21.51 (9.91-45.52)
Obinutuzumab-plus-chlorambucil	12.91 (5.47-29.99)	15.38 (6.57-35.30)	15.13 (6.56-34.05)	14.35 (6.32-31.97)	13.50 (5.97-29.91)
Ofatumumab-plus-chlorambucil	10.11 (4.96-21.29)	15.82 (7.98-33.17)	20.56 (11.68-40.56)	24.76 (15.63-45.72)	28.59 (19.52-50.30)
Rituximab-plus-chlorambucil	15.72 (7.51-31.97)	22.22 (11.35-43.55)	22.94 (12.09-42.97)	22.22 (11.87-40.95)	21.14 (11.44-38.57)
Venetoclax-plus-obinutuzumab	4.69 (2.64-8.66)	4.11 (2.45-7.40)	3.64 (2.24-6.26)	3.29 (2.06-5.55)	3.00 (1.92-4.98)

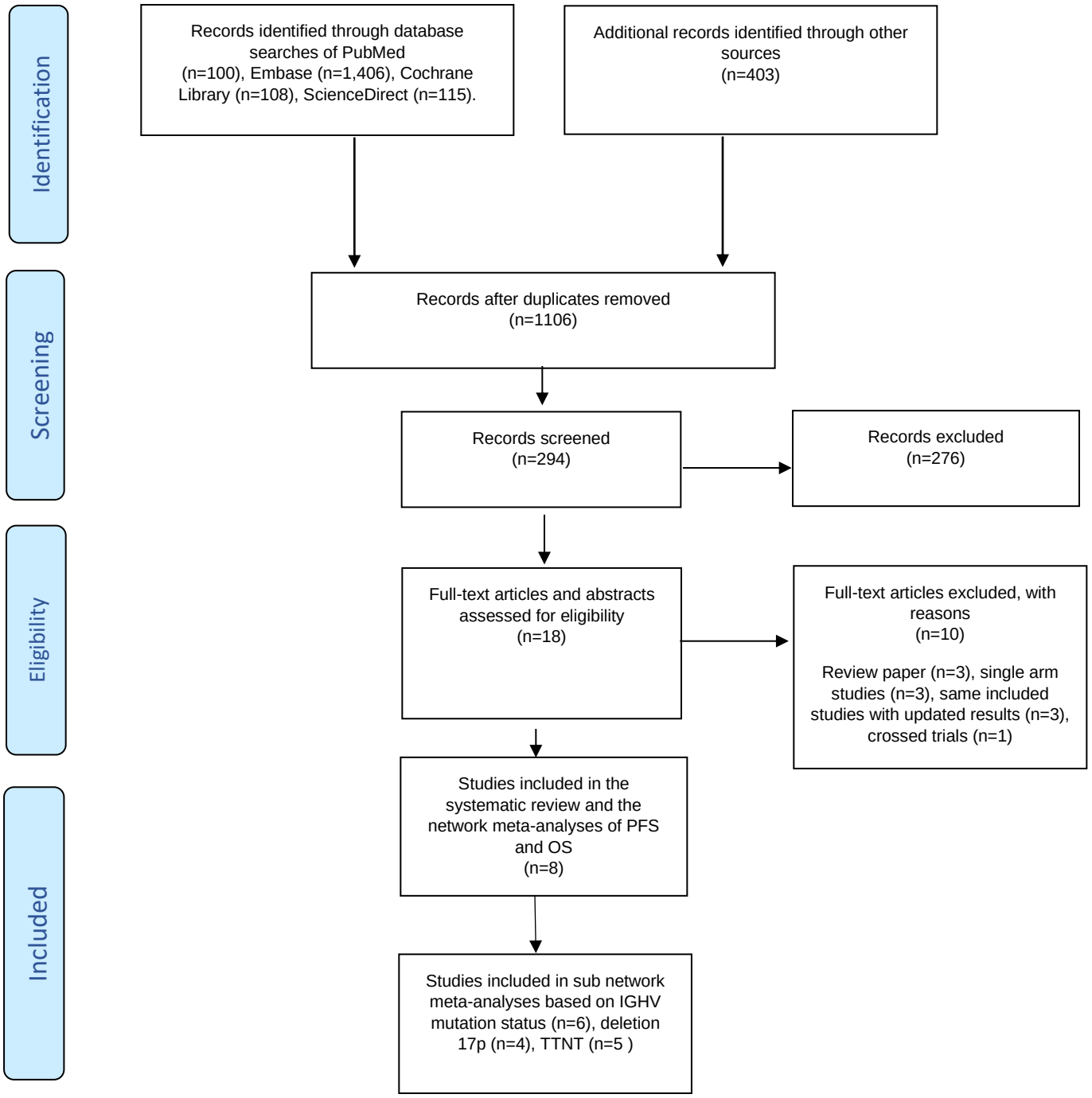
Abbreviations: CrI, Credible Interval; HR, Hazard ratio

Table 3.6: Overall survival proportions and hazard ratios at different time points as obtained from the fixed lognormal network meta-analysis.

	12 months	24 months	36 months	48 months	60 months
Table 3.6A: Overall survival proportions.					
	Survival proportion (95%CrI)				
Acalabrutinib	0.98 (0.96-0.99)	0.96 (0.93-0.98)	0.95 (0.91-0.98)	0.94 (0.88-0.97)	0.93 (0.86-0.97)
Acalabrutinib-plus-obinutuzumab	0.99 (0.97-0.99)	0.98 (0.94-0.99)	0.96 (0.92-0.98)	0.96 (0.90-0.98)	0.95 (0.89-0.98)
Bendamustine-plus-rituximab	0.98 (0.91-0.99)	0.96 (0.83-0.98)	0.94 (0.77-0.97)	0.93 (0.73-0.96)	0.92 (0.67-0.96)
Chlorambucil adjusted	0.94 (0.92-0.96)	0.86 (0.82-0.89)	0.80 (0.73-0.84)	0.74 (0.66-0.79)	0.69 (0.59-0.75)
Ibrutinib	0.98 (0.92-0.99)	0.97 (0.83-0.98)	0.95 (0.76-0.97)	0.94 (0.70-0.97)	0.93 (0.65-0.96)
Ibrutinib-plus-rituximab	0.98 (0.87-0.99)	0.97 (0.73-0.99)	0.96 (0.62-0.99)	0.94 (0.54-0.98)	0.93 (0.48-0.98)
Ibrutinib-plus-obinutuzumab	0.97 (0.93-0.99)	0.95 (0.87-0.98)	0.93 (0.82-0.97)	0.91 (0.78-0.96)	0.90 (0.74-0.96)
Obinutuzumab-plus-chlorambucil	0.97 (0.96-0.98)	0.95 (0.93-0.96)	0.93 (0.90-0.94)	0.91 (0.87-0.93)	0.89 (0.85-0.92)
Ofatumumab-plus-chlorambucil	0.96 (0.93-0.98)	0.89 (0.85-0.92)	0.82 (0.75-0.86)	0.76 (0.66-0.82)	0.70 (0.58-0.77)
Rituximab-plus-chlorambucil	0.96 (0.93-0.98)	0.87 (0.82-0.91)	0.78 (0.68-0.84)	0.70 (0.56-0.78)	0.62 (0.45-0.72)
Venetoclax-plus-obinutuzumab	0.96 (0.93-0.98)	0.93 (0.87-0.96)	0.91 (0.83-0.95)	0.89 (0.79-0.94)	0.87 (0.76-0.93)
Table 3.6B: Hazard ratios of death for each treatment compared with ibrutinib.					
	HR (95%CrI) compared with ibrutinib				
Acalabrutinib	0.82 (0.36-1.97)	1.20 (0.69-4.45)	1.35 (0.76-6.07)	1.41 (0.73-6.76)	1.43 (0.69-7.07)
Acalabrutinib-plus-obinutuzumab	0.79 (0.07-3.21)	0.78 (0.06-3.12)	0.77 (0.06-3.06)	0.77 (0.06-3.07)	0.76 (0.06-3.13)
Bendamustine-plus-rituximab	1.25 (1.15-9.63)	1.23 (0.96-9.31)	1.22 (0.91-9.25)	1.21 (0.90-9.58)	1.19 (0.89-9.94)
Chlorambucil adjusted	4.84 (1.01-10.34)	5.78 (1.26-11.96)	6.16 (1.41-12.39)	6.35 (1.46-12.56)	6.46 (1.47-12.66)
Ibrutinib-plus-rituximab	0.97 (0.53-1.73)	0.97 (0.55-1.71)	0.98 (0.52-1.71)	0.99 (0.56-1.77)	1.00 (0.51-1.87)
Ibrutinib-plus-obinutuzumab	1.03 (0.30-3.08)	1.14 (0.32-3.54)	1.32 (0.35-4.07)	1.45 (0.37-4.61)	1.52 (0.40-5.14)
Obinutuzumab-plus-chlorambucil	1.65 (0.19-6.73)	1.61 (0.18-6.77)	1.59 (0.18-6.89)	1.57 (0.16-7.02)	1.56 (0.16-7.02)
Ofatumumab-plus-chlorambucil	3.94 (0.86-7.20)	5.50 (1.31-10.73)	6.27 (1.63-11.92)	6.72 (1.80-12.29)	7.01 (1.90-12.52)
Rituximab-plus-chlorambucil	4.51 (1.02-8.56)	7.34 (1.94-13.65)	8.84 (2.59-15.36)	9.74 (2.94-16.41)	10.32 (3.10-17.10)
Venetoclax-plus-obinutuzumab	0.93 (0.08-5.03)	1.10 (0.10-5.89)	1.26 (0.11-6.74)	1.39 (0.11-7.48)	1.52 (0.12-8.19)

Abbreviations: CrI, Credible Interval; HR, Hazard ratio

Figure 3.1: PRISMA flow diagram**.**



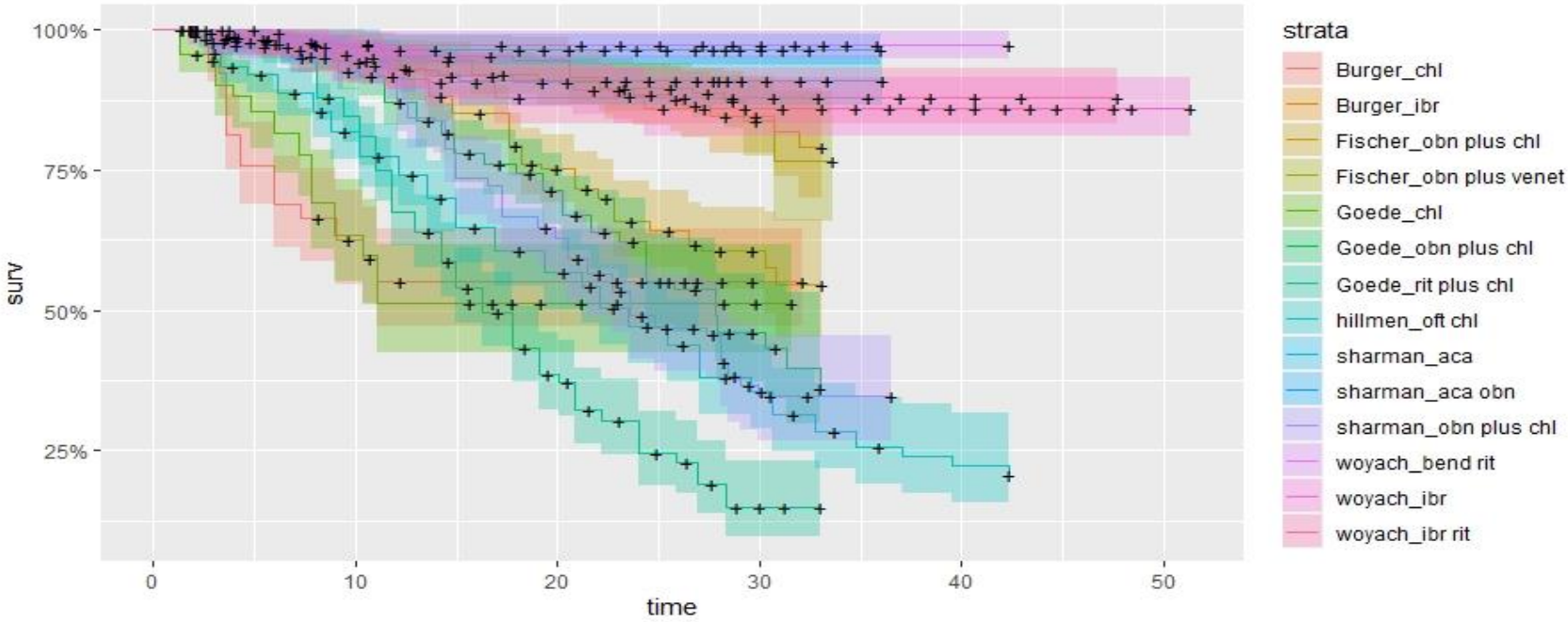


Figure 3.2A: Reconstructed Kaplan-Meier curves for most trials.

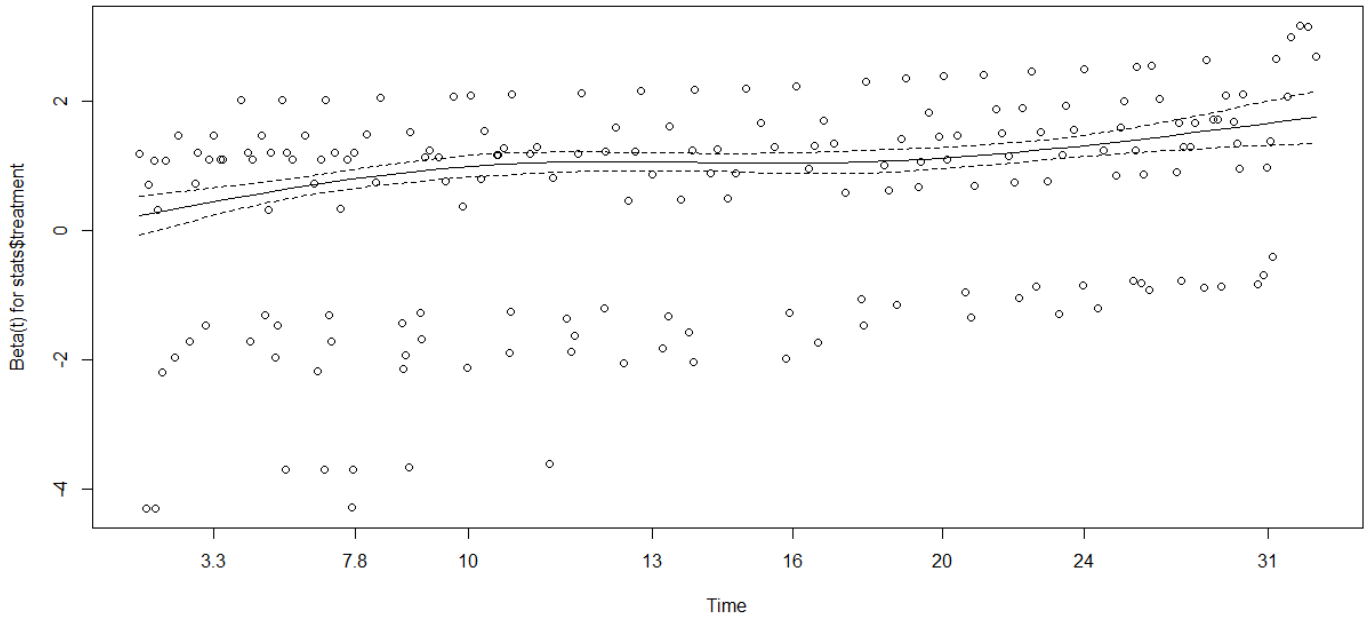
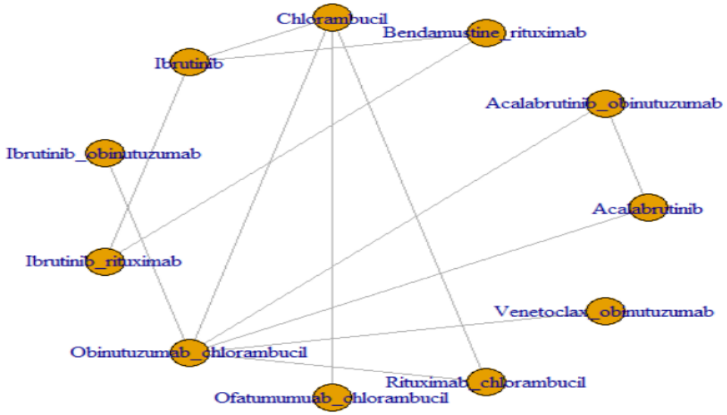
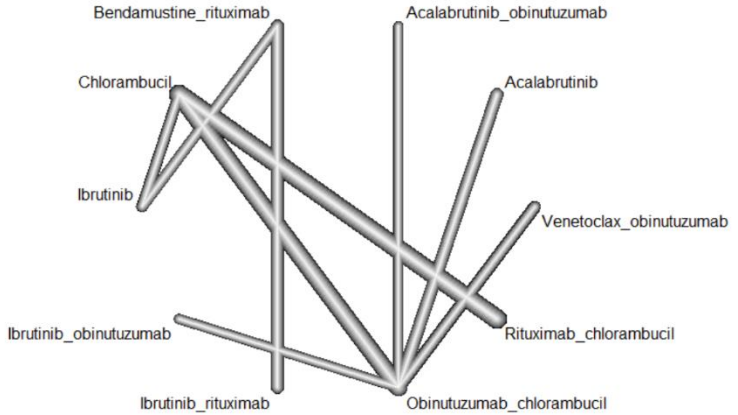


Figure 3.2B: Schoenfeld residuals against the transformed time with P-value of <2e-16.

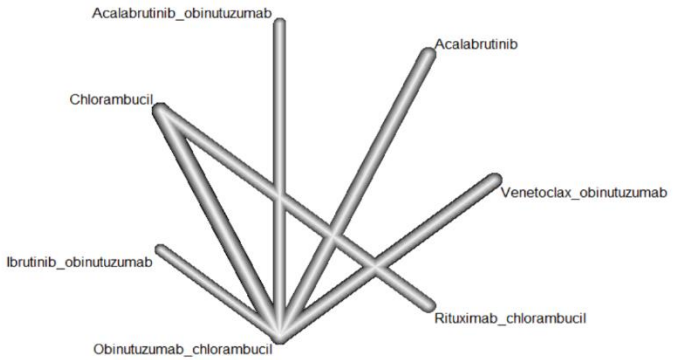
A)



B)



C)



D)

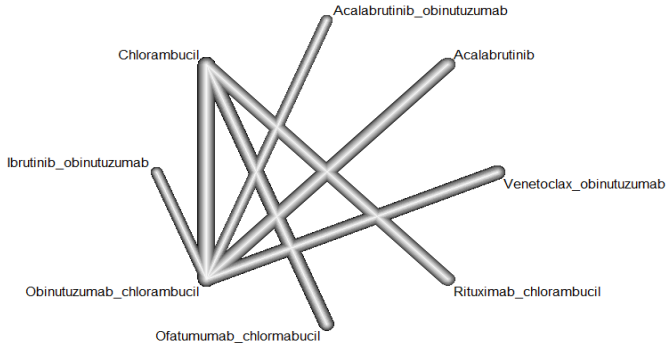


Figure 3.3: Network of (A) PFS and OS network meta-analyses, (B) PFS based on IGHV mutation status, (C) PFS in deletion 17p, (D) TTNT after the first progression.

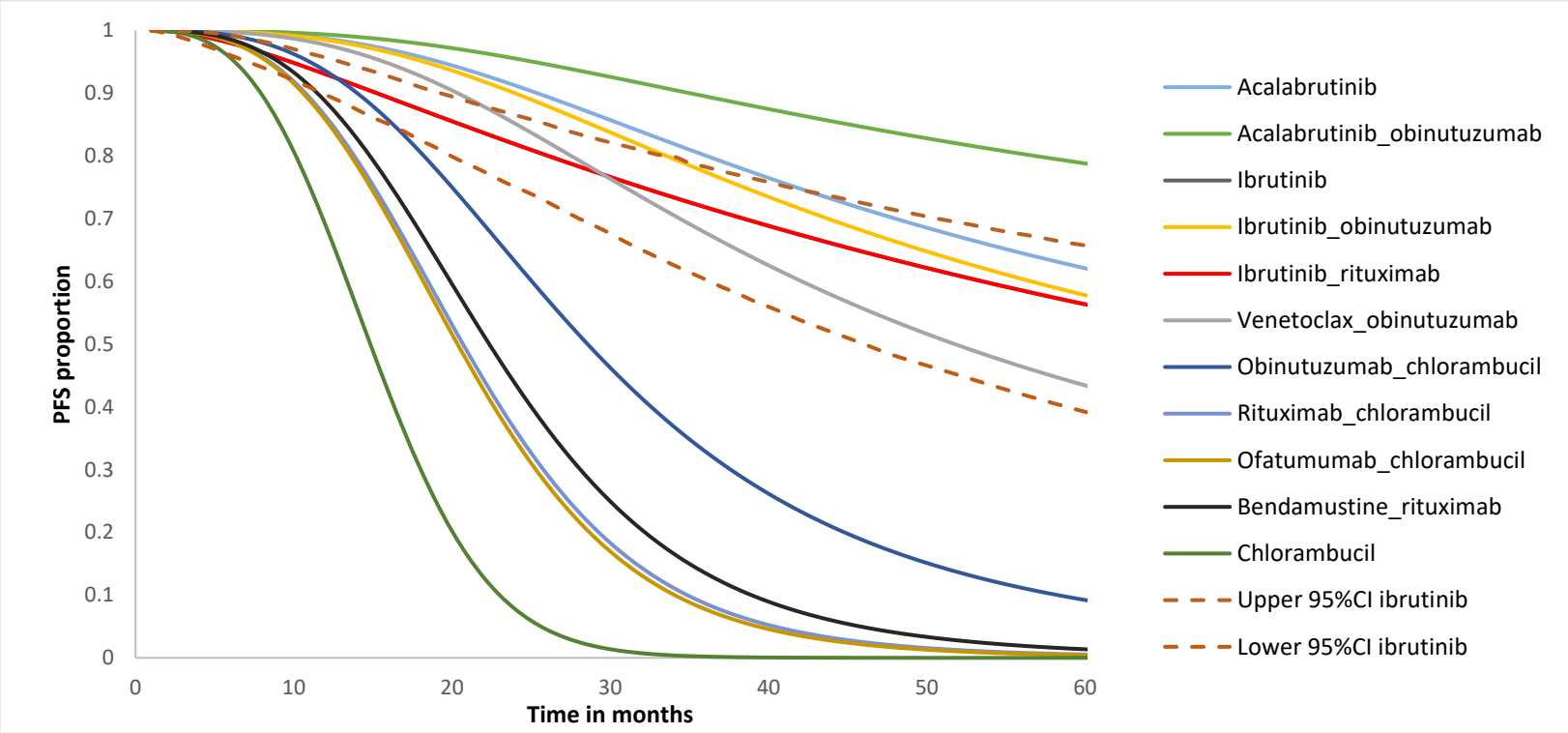


Figure 3.4A: Progression-free survival proportions over 5-years of follow-up as obtained from the fixed lognormal network meta-analysis.

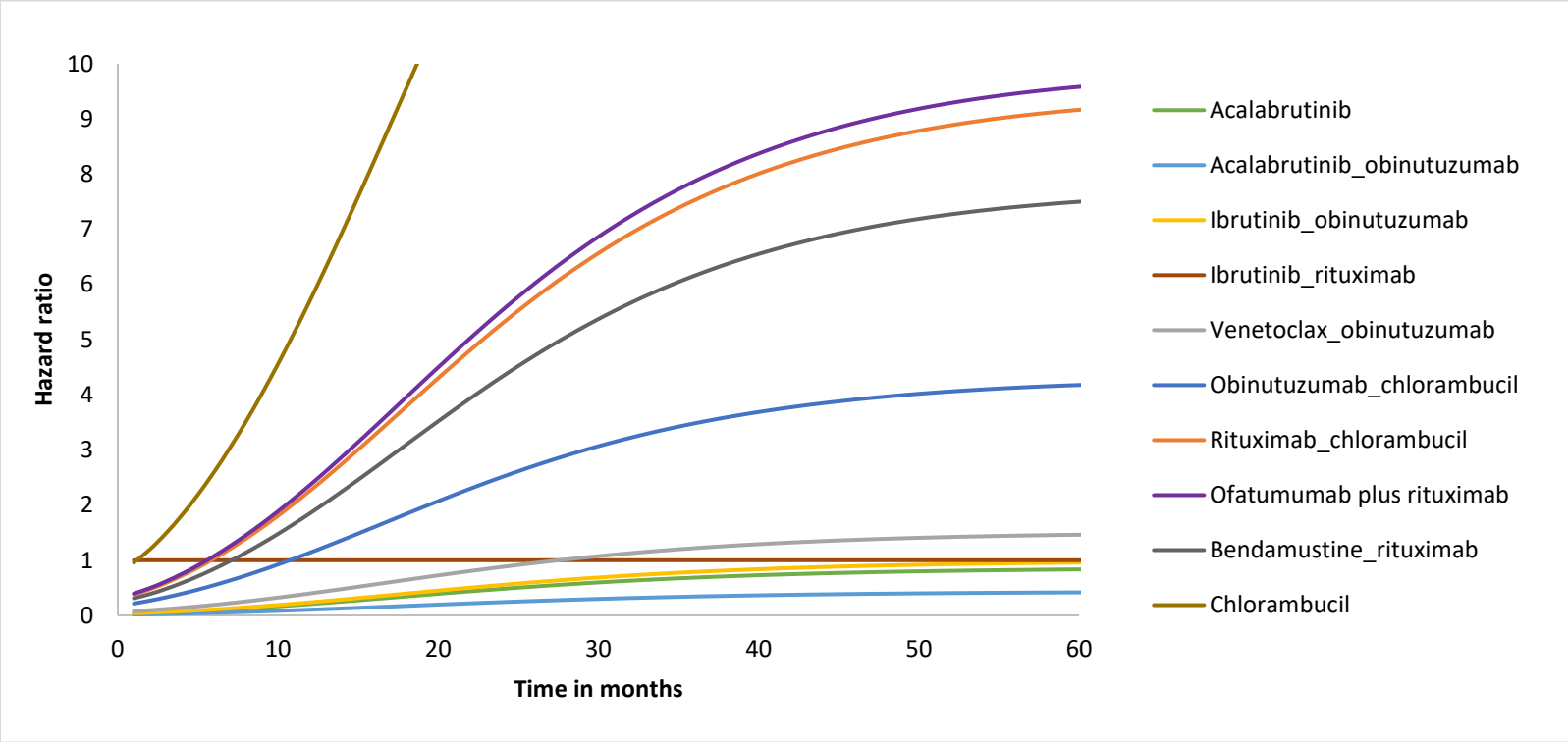
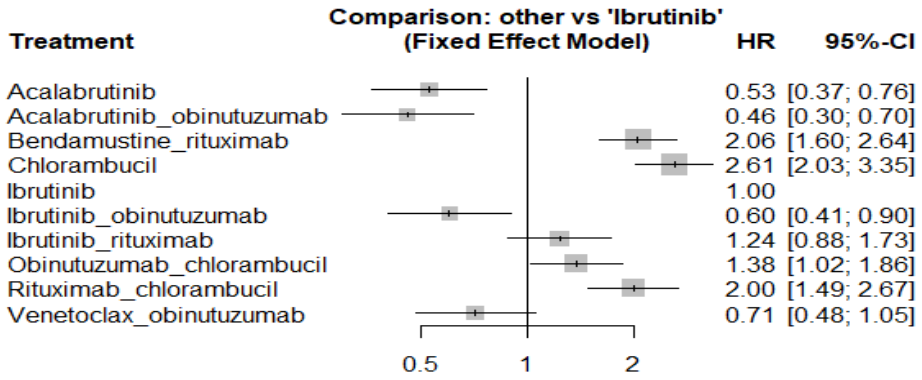
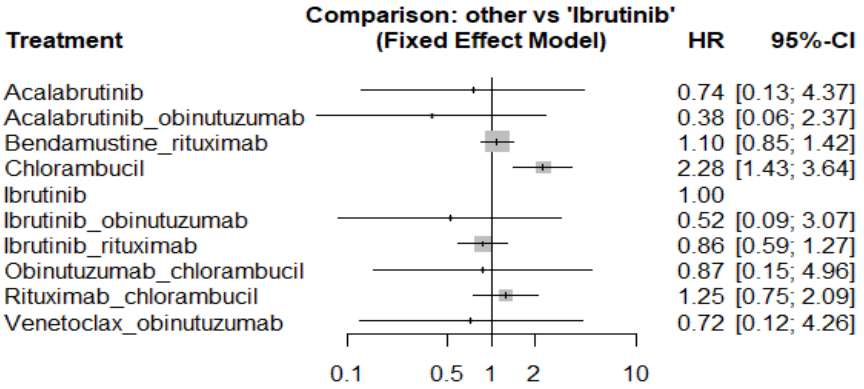


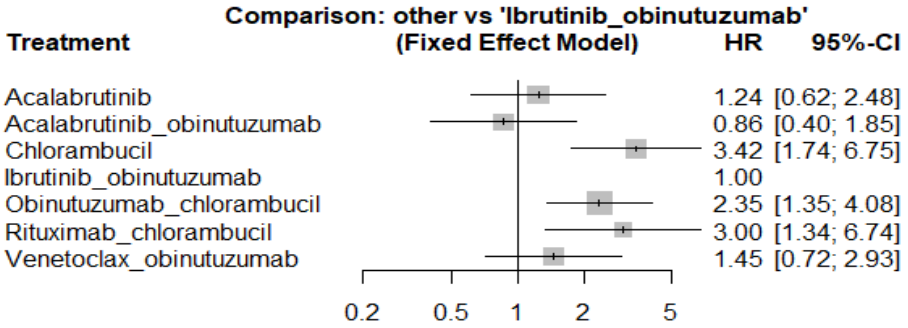
Figure 3.4B: HRs of progression or death for each treatment compared with Ibrutinib over time as obtained from as obtained from the fixed lognormal network meta-analysis.



(A)



(B)



(C)

Figure 3.5: Forests plots of hazard ratios of progression or death for each treatment compared with ibrutinib in patients (A) with un-mutated IGHV and (B) with mutated IGHV. (C) Forest's plot of hazard ratios of progression or death for each treatment compared with ibrutinib plus obinutuzumab in patients with deletion 17p.

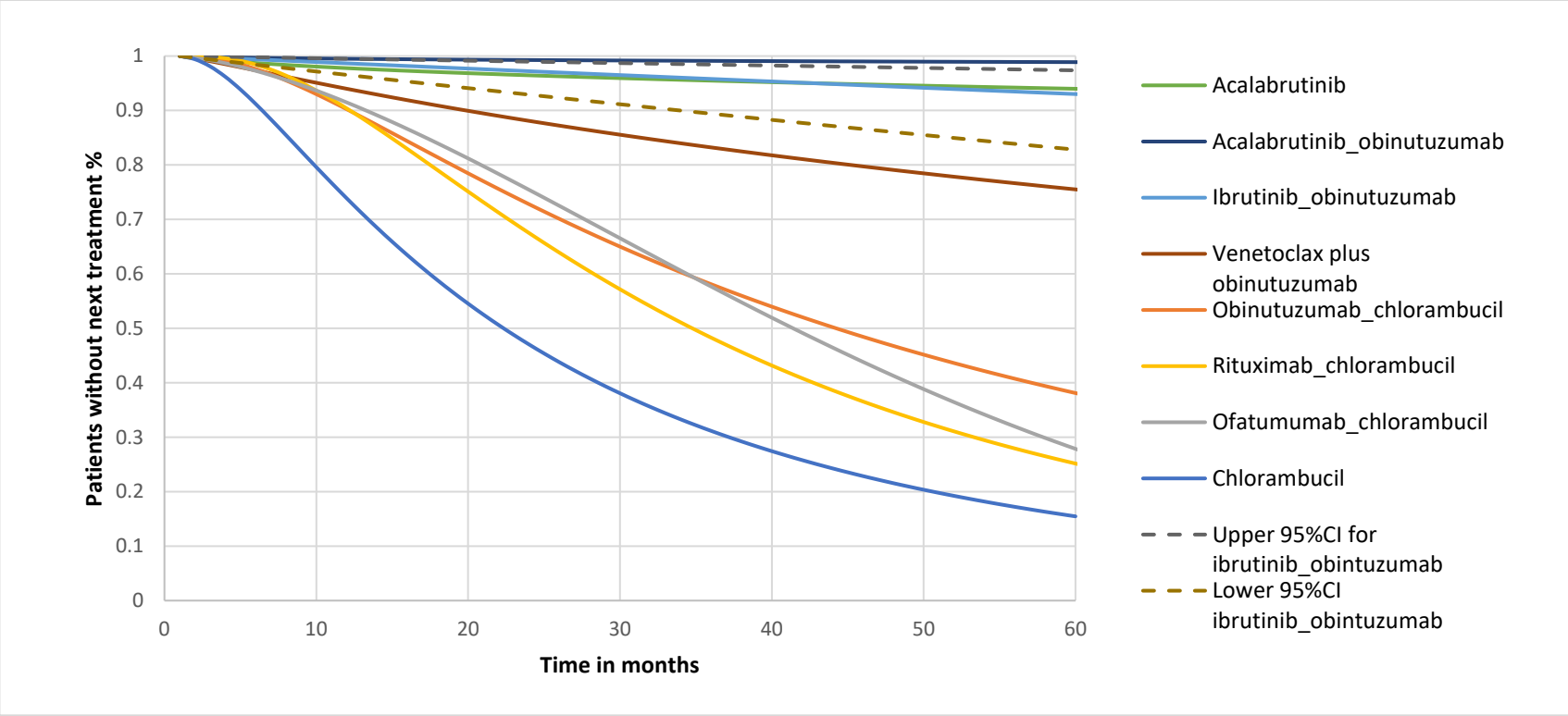


Figure 3.6: Proportions of patients without next treatment over 5-years of follow-up as obtained from the fixed lognormal network meta-analysis.

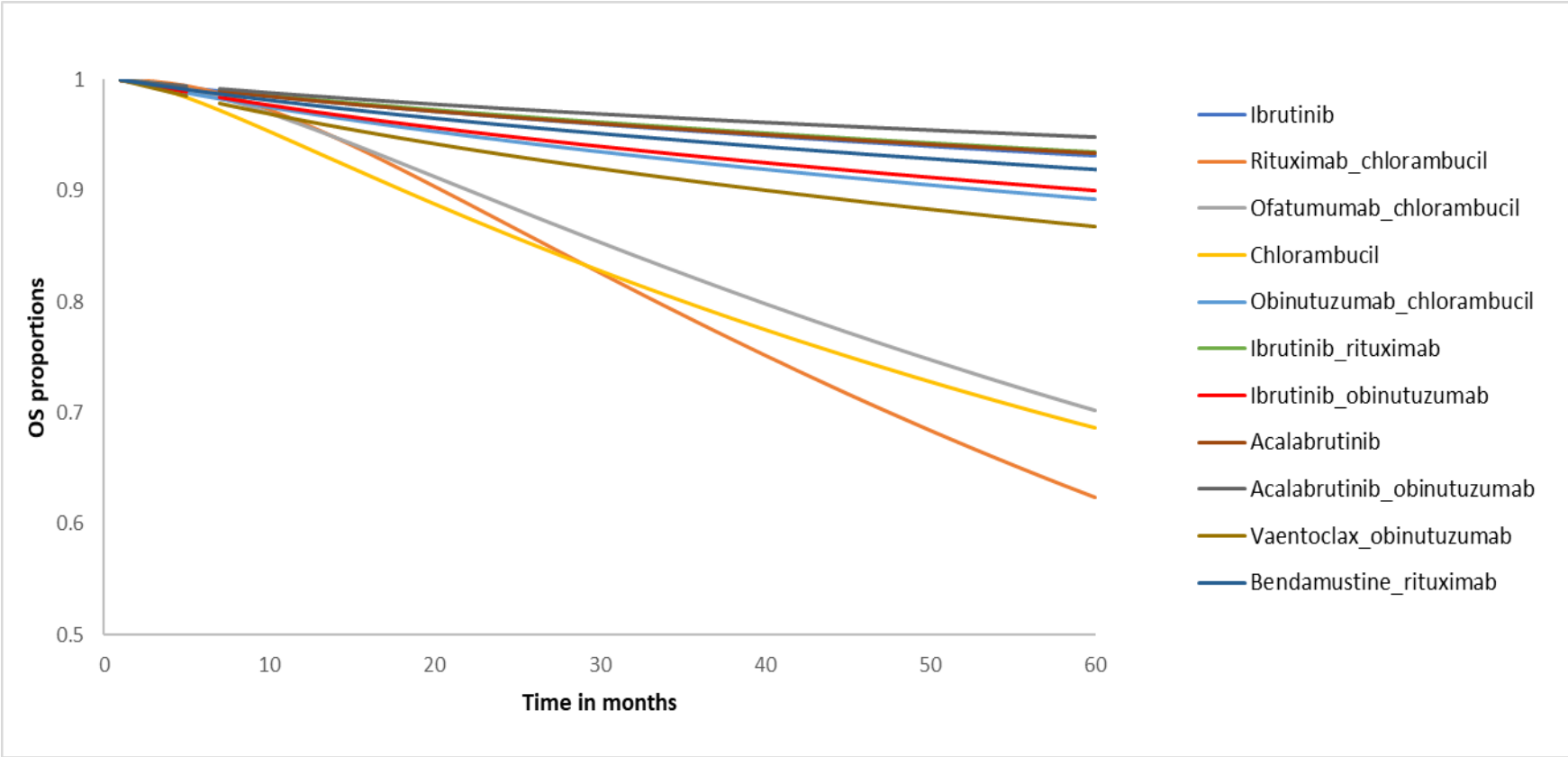


Figure 3.7: Overall survival proportions over 5-years of follow-up as obtained from the fixed lognormal network meta-analysis.

4.0 COMPARATIVE ECONOMIC EVALUATIONS FOR THE US OF FIRST-LINE TREATMENTS OF CHRONIC LYMPHOCYTIC LEUKEMIA

Manuscript in preparation process

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4.1 Abstract:

Purpose: Several chemoimmunotherapy and targeted treatment regimens are approved as front-line therapies in chronic lymphocytic leukemia (CLL). We estimated for the 10-year cost-effectiveness of these treatment regimens; and the economic burden of following the estimated risk-stratified 21,040 CLL patients diagnosed in 2020 for 10 years.

Methods: A Markov model with six exclusive health states was specified over a 10-year time horizon. Treatment effectiveness inputs were obtained from a novel network meta-analysis on the progression-free, overall survival curves, and time-to-next-treatment. Other inputs included costs of treatments and pre-medications, administration, adverse event management, emergency and outpatient clinic visits and utilities for each health state for each treatment, discounted at 3.0%/year. Life-years (LY) and quality-adjusted LYs (QALY) for each treatment were determined. Using the lowest cost regimen as reference, the incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) were estimated. The 10-year per-patient cost was determined by risk status and by initial treatment.

Results: Venetoclax-plus-obinutuzumab was the lowest cost regimen, hence the reference. Superior in effectiveness to all chemoimmunotherapies, it was cost-saving. With the highest effectiveness gains at 6.26 LYs and 5.01 QALYs, and despite being the most expensive regimen ($1,298,638/patient), acalabrutinib-plus-obinutuzumab yielded the best ICER ($409,343/LYg) and ICUR ($501,236/QALYg). The remaining ICERs of targeted therapies ranged from $512,101 /LYg to $793,236 /LYg and the ICURs from $579,737/QALYg to $869,300/QALYg. The 10-year post-diagnosis low/high (venetoclax-plus-obinutuzumab/acalabrutinib-plus-

obinutuzumab) economic burden ranges were $42,690-$98,665 for low-risk, $141,339-$326,660 for intermediate-risk, and $273,650-$632,453 for high-risk patients.

Conclusions: Compared to venetoclax-plus-obinutuzumab, chemoimmunotherapies are associated with less health benefits at higher cost. The targeted therapies achieve greater benefits at higher cost. Acalabrutinib-plus-obinutuzumab is the most cost-effective targeted regimen.

4.2 Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults in the United States (US), with an expected 21,250 new cases in 2021[2]. Most patients are diagnosed at an early stage and are monitored with a watchful-waiting approach until the balance of risk and benefit favors initiating treatment[62]. This time-to-first-treatment (TTFT) as well as life expectancy vary significantly by disease stage and disease risk stratification[69, 77]. Using the risk categories of the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI), patients with one or more high-risk markers such as del 17p, del 11q or unmutated immunoglobulin heavy-chain variable (IGHV) have a shorter TTFT than patients without risk markers when treated with standard chemoimmunotherapy[10, 77].

Although several chemoimmunotherapy regimens such as obinutuzumab-plus-chlorambucil[54], ofatumumab-plus-chlorambucil[88], bendamustine-plus-rituximab[22, 89], and rituximab-plus-chlorambucil[54, 89] have been approved to treat patients who are ineligible for fludarabine-based therapies (age 65 or older and/or comorbidities), they have not achieved the same level of improvements in survival outcomes as fludarabine-based chemoimmunotherapy regimen in younger patients[8, 70, 71]. A breakthrough in CLL management occurred with the 2014 approval of the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib and the phosphoinositide 3-kinase inhibitor idelalisib for treatment of relapsed disease[30, 63]. This was followed by the introduction in first-line therapy of ibrutinib and the second-generation BTKi acalabrutinib as monotherapy[21, 24] or in combination with monoclonal antibody agents (ibrutinib-plus-rituximab, ibrutinib-plus-obinutuzumab[22, 23], acalabrutinib-plus-obinutuzumab[24]); as well as the B-cell leukemia/lymphoma-2 (BCL-2) inhibitor venetoclax combined with obinutuzumab[25]. In addition to benefiting CLL patients in

general, these treatments have significantly improved the prognosis of CLL patients with high-risk disease and patients who are ineligible for fludarabine-based chemoimmunotherapy[96-98]. Note that the National Comprehensive Cancer Network (NCCN) guidelines list the regimens of ibrutinib monotherapy, acalabrutinib with or without obinutuzumab, or venetoclax-plus-obinutuzumab as the preferred first-line treatments for CLL patients regardless of patients' risk status, disease stage, or age[31].

Considering all available treatment options tested in trials, the relative latitude of the NCCN guidelines, and the lack of head-to-head trials, clinicians may be challenged in their decision-making about which treatment is most appropriate for a given patient and this before relative costs are taken into consideration[98-100]. We recently performed a network meta-analysis to indirectly compare the above regimens[101]. Unlike most network meta-analyses, it was not based exclusively on the constant hazard ratios and therefore the scale parameters of the Kaplan-Meier curves. Instead, we applied novel techniques for data extraction from published Kaplan-Meier curves; new methods for parametric model fitting to estimate transition probabilities that better reflect the actual time-dependent shape of these curves; and advanced approaches for comparative analysis of survival curves using both the scale and shape parameters of these curves[81, 82, 85]. This indirect treatment comparison revealed that monotherapy and/or therapies that combine acalabrutinib or ibrutinib with monoclonal agents are associated with better progression-free survival (PFS) and time-to-next-treatment (TTNT) outcomes – something observed, though to a lesser extent, for venetoclax in combination with obinutuzumab, while not being the case for the remaining regimens. No statistically significant differential long-term overall survival (OS) benefit among these various treatment options could be ascertained.

In this paper, we apply the efficacy results of this novel network meta-analysis in a set of economic evaluations to assess, from the US payer perspective, the cost-effectiveness, cost-utility, and net monetary benefit of the above regimens in terms of PFS, OS, and TTNT benefit under consideration of the associated treatment-related and health-related costs. We complement this further with a burden of treatment cost-analysis estimating the total cost of managing all CLL patients diagnosed in 2020 and followed for the next ten years, and this proportionate to the number of patients assumed to low-, intermediate-, and high-risk and considering the TTFT for each risk category.

4.3 Methods

4.3.1 Cost-effectiveness Model and Treatment Efficacy Inputs

We specified a Markov model to assess the cost and effectiveness of the ten different first-line options to treating CLL patients. Consistent with NCCN guidelines and most built models in the literature[102-104], the model consists of six exclusive health states: progression-free after initiating first-line treatment with targeted therapy or chemoimmunotherapy (state 1); progression without initiating second-line therapy (state 2); progression-free after initiating second-line therapy (state 3), further progression (state 4), progression-free on third line therapy (state 5), and death (state 6; Figure 1).

State 1 was partitioned into the sub-states of "targeted treatment" and "chemoimmunotherapy". We assumed that patients in the "targeted treatment" substate received any of the targeted regimens until disease progression or toxicity. We further assumed that patients in the "chemoimmunotherapy" substate could be either "on chemoimmunotherapy" for up to 6 cycles until progression or "off chemoimmunotherapy" without active treatment but still

progression-free. Patients who progressed after first-line treatment did not move directly to second-line therapy (state 2) until there were symptomatic indications to initiate therapy (state 3), which could vary depending on the type of first-line treatment received. We further assumed that second-line therapy post-progression consisted of idelalisib-plus-rituximab for all patients regardless of prior-line treatment; and that third-line treatment after secondary progression consisted of ofatumumab.

The transition probabilities from state 1 to state 2, to next treatment (state 3) or death (state 6) were extracted from our network meta-analysis[101]. Using the Guyot et al. method of data extraction from Kaplan-Meier curves[85], individual patient data were re-estimated and the corresponding Kaplan-Meier curves re-plotted. We then applied the method proposed by Jansen and Ouwens et al.[81, 82] that uses the reconstructed survival curves, including their scale and shape parameters, without relying on the proportional hazards assumption. We tested the goodness-of-fit of the survival data in the network with fixed or random parametric distributions based on the Weibull, lognormal, loglogistic, Gompertz, exponential, and generalized gamma functions. The best-fitting model was selected using the deviance information criterion (DIC). While in our network meta-analysis we used an empirical 60 months of follow-up, for purposes of our economic evaluation we extended the fitted curve extrapolations to a 120-month time horizon (Figure 2).

The transition probabilities from state 3 to state 4 or state 6 were derived from published Kaplan-Meier curves of idelalisib-plus-rituximab[30], while transition probabilities from state 5 to state 4 or 6 were derived from Kaplan-Meier curves of ofatumumab[105, 106]. All transition probabilities were calculated for each cycle against a 10-year time-horizon. We applied a 28-day cycle length with a half cycle correction on the first and final cycles.

4.3.2 Cost and Health-related Utility Inputs

The direct costs associated with the progression-free health states included the costs of treatments and pre-medications, administration, adverse event management[90, 107-110], emergency treatments and outpatient clinic visits[91]. After extracting the wholesale acquisition costs (WAC) from REDBOOK 2020[111], we calculated the per-cycle cost of each treatment regimen using the dosing of the standard regimen (Table 1, 2). Administration costs were based on the Medicare physician fee schedule[112] and other cost entries were retrieved from literature. For the progression health states, we estimated a cost of progression based on the requisite screening and follow-up tests per cycle[113]. Costs not reported in 2020 USD were inflation-adjusted to the third quarter of 2020 using the medical consumer price index[114] (Table 2). All outcomes and costs were discounted at 3.0% per year beyond the first year of follow-up over the time horizon of the model.

We consulted the literature for utility values of patients in each health state and for each treatment cohort [115, 116] (Table 2). We also accounted for the impact of on/off treatment, oral versus IV treatment, and treatments requiring more frequent hospital visits on quality of life . We extracted the probabilities of adverse events grade 3/4 from the source clinical trial reports and assigned these to each cohort in the model. The utility decrements for each adverse event were identified from literature[110, 117-121].

4.3.3 Cost-effectiveness Analysis

In the deterministic (base-case) analysis, we first calculated the total cost for each therapy over the 10-year time-horizon; retaining the regimen with the lowest cost as the reference treatment against which other treatments were compared. We computed the health benefit

outcomes associated with each therapy over this time-horizon as life years (LY) and quality-adjusted LYs (QALYs). For each therapy, we determined the difference (incremental or decremental) in costs and outcomes when compared to the reference treatment to obtain the incremental cost-effectiveness ratios (ICER; incremental cost to gain 1 LY over reference) and incremental cost-utility ratios (ICUR; incremental cost to gain 1 QALY over reference).

Setting the value of one LY at a cost-effectiveness threshold of $100,000, we rescaled the health benefit gain associated with each therapy into monetary value by calculating the net monetary benefit (NMB). A positive NMB specifies that the additional value of a given therapy expressed in monetary terms exceeds a given willingness-to-pay (WTP) threshold (here $100,000 per LY). Conversely, a negative NMB indicates that the value of the therapy is less than the WTP threshold.

To quantify the uncertainty in our deterministic analyses, we performed probabilistic sensitivity analyses (PSA) by means of a Monte Carlo simulation with 10,000 iterations using the variability around the parameter inputs in the model. The transition probabilities, costs, and utilities were varied using the lognormal, gamma, and beta distributions, respectively. For the cost inputs, a standard error of ±20% of the mean value was considered. For utility values, the standard deviation for each entry as extracted from literature was applied (Table 1). Both cost and effectiveness (LYs and QALYs gained) were computed in each iteration and results of the 10,000 iterations were scattered to form a cost-effectiveness scatter plot. The mean effectiveness and cost values were determined for each therapy to estimate the PSA ICERs and ICURs. A cost-effectiveness acceptability curve (CEAC) was plotted to determine the probability that a given treatment would be cost-effective at different WTP thresholds.

4.3.4 Economic Burden Across 10-years From Diagnosis

We estimated the budget implications of managing the 21,040 patients estimated to be diagnosed with CLL in 2020 using a dynamic Markov model with the same health states used in the cost-effectiveness analyses. As CLL patients are not started on treatment at the time of diagnosis but when their disease becomes symptomatic, we determined the start of first-line treatment on the basis of the transition probabilities extracted from the Kaplan-Meier curves of TTFT[122] and differentiated the TTFT probabilities by the risk stratification of the disease (low, intermediate, and high). To determine the economic burden for managing CLL patients, we computed for each expected risk category in the 2020 cohort the cumulative costs as well as the cumulative costs per individual patient for the 10-year period from 2021 to 2030 based on the regimen used as first-line therapy.

4.4 Results

4.4.1 Treatment Comparisons

The fixed-effect lognormal distribution was the best-fitting model to estimate the PFS, OS and TTNT proportions for the ten treatments and was used to extrapolate the survival curves up to 120 months of follow-up (Figure 2). Table 3 shows the survival percentages in the different health states of the Markov model at 10 years following the start of treatment by type of first-line therapy as obtained from the probabilistic sensitivity analyses. At 10 years, the percentages of patients who were progression-free following first-line treatment ranged from 0% for those treated with bendamustine-plus-rituximab to 66.1% for those administered acalabrutinib-plus-obinutuzumab. Of the 33.9% of patients initially treated with acalabrutinib-plus-obinutuzumab

who progressed within the 10-year period, 11.4% were progression-free following second- or third-line treatment with idelalisib-plus-rituximab or ofatumumab, and 10.2% required more than two or three lines of treatment. At 10 years, 87.8% of patients started on acalabrutinib-plus-obinutuzumab in first-line were still alive.

Acalabrutinib and ibrutinib monotherapy, as well as ibrutinib combination therapies showed similar (though lower compared to acalabrutinib-plus-obinutuzumab) patterns at 10 years, with 34.2% to 40.6% being progression-free on first-line treatment, 18.5% to 24.4% being progression-free after second- or third-line therapy, 17.9% to 22.3% having progressed after second- or third-line therapy, yet between 19.0% and 24.3% having died at the 10-year time point. The corresponding percentages for venetoclax-plus-obinutuzumab were 31.1%, 19.4%, 22.2%, and 27.1%. In contrast, the chemoimmunotherapy regimens had low progression-free efficacy in first-line (0.0% to 7.5%), about a quarter (23.3% to 27.0%) requiring second- or third-line treatment, over one-third (34.8% to 44.1%) requiring treatment beyond third-line, and a large number of these patients (27.6% to 39.1%) not surviving to the 10-year time point.

4.4.2 Cost-effectiveness Analysis

Cost of treatment ranged from $561,821 for venetoclax-plus-obinutuzumab to $1,298,638 for acalabrutinib-plus-obinutuzumab (Table 4). Hence, we used the cost of the venetoclax-plus-obinutuzumab regimen as the reference treatment. In terms of health benefit outcomes, LYs achieved ranged from 2.74 for bendamustine-plus-rituximab to 6.29 for acalabrutinib-plus-obinutuzumab, while QALYs gained extended from 2.09 for rituximab-plus-chlorambucil to 5.01 for acalabrutinib-plus-obinutuzumab. These deterministic costs, LY and QALY estimates were confirmed in the PSAs.

The ICERs for each of the chemoimmunotherapy regimens were negative due to higher costs but less LY benefits, ranging from an additional cost of $5,622 per LY lost (LYl) for rituximab-plus-chlorambucil to an additional $95,981/LYl for bendamustine-plus-rituximab. In contrast, the ICERs for the targeted therapies ranged from an additional $409,343 per LY gained (LYg) for acalabrutinib-plus-obinutuzumab to $793,236/LYg for ibrutinib-plus-rituximab. ICERs were confirmed in the PSAs.

Similarly, the ICURs for the chemoimmunotherapy regimens were negative due to higher costs but less QALY benefits, ranging from an incremental cost of $6,630/QALYl for rituximab-plus-chlorambucil to an additional $117,459/QALYl for bendamustine-plus-rituximab. The ICURs for the targeted therapies ranged from an additional $501,236/QALYg gained for acalabrutinib-plus-obinutuzumab to $869,300/QALYg for ibrutinib-plus-rituximab. These ICURs were confirmed in the PSAs.

Using a WTP of $100,000, all the computed NMBs were negative, ranging from $-112,821 for venetoclax-plus-obinutuzumab to $-669,638 for acalabrutinib-plus-obinutuzumab and indicating the excess costs associated with each treatment regimen. NMB estimates were confirmed in the PSAs.

The CEACs (Figure 3) depict the probabilities of reference venetoclax-plus-obinutuzumab being cost-effective when compared to all other regimens (panel A) and to the targeted therapies (panel B) while panel C shows the CEAC comparing BTKi therapies to each other. Venetoclax-plus-obinutuzumab is the only regimen that is cost-effective at a WTP threshold of $100,000/QALYg. Increasing the threshold to $500,000/QALYg, the probability of venetoclax-plus-obinutuzumab to be cost-effective declined to 51%, and the probability of acalabrutinib-plus-obinutuzumab being cost-effective increased to 46%. Acalabrutinib-plus-

obinutuzumab had a 75% probability of being cost-effective at a WTP threshold of $530,000/QALYg and a 90% probability at $590,000/QALYg.

4.4.3 Economic Burden Over 10-years From Diagnosis

Of the 21,040 patients believed to have been diagnosed with CLL in the US in 2020, an estimated 6,312, 7,574 and 7,154 patients had low-, intermediate-, and high-risk disease, respectively (Table 5). Of these, 1,118, 4,306 and 5,568 patients, respectively, are estimated to have treatment initiated at different points in time over the ensuing ten years. If all 1,118 low-risk patients were to be started on the same regimen, the 10-year cost burden would range from $269,461,597 for venetoclax-plus-obinutuzumab to $622,773,156 for acalabrutinib-plus-obinutuzumab. The corresponding 10-year burden estimates for the 4,306 intermediate-risk patients would extend from $1,070,560,441 to $2,474,253,515; rising to $1,957,581,686 and $4,524,315,660 for the 5,568 high-risk patients. The total 10-year cost across risk categories for all patients needing treatment would be between $3,297,603,724 for venetoclax-plus-obinutuzumab and $7,621,342,330 for acalabrutinib-plus-obinutuzumab.

At the patient level, the 10-year cost to treat one low-risk CLL patient would range from $42,690 if venetoclax-plus-obinutuzumab were the treatment of choice to $98,665 if treated with acalabrutinib-plus-obinutuzumab. The corresponding costs for an intermediate-risk patient are $141,339 and $326,660; and $273,650 and $632,453 for a high-risk patient.

4.5 Discussion

Recent treatment regimens for CLL involving BTK or BCL2 inhibitors in monotherapy or in combination with monoclonal antibodies have been shown to be superior in clinical benefit to prior chemoimmunotherapy regimens, but at marked additional cost. Therefore, it is critical to conduct comparative economic evaluations that quantify the cost-to-outcome association of these regimens. Equally important is to determine the economic burden of following CLL patients diagnosed in a given year over extended periods of time because of the possible need for additional lines of treatment beyond the initial regimen. Our cost-effectiveness and economic burden evaluations reported here built on a network meta-analysis simulating the comparative efficacy of various chemoimmunotherapy and targeted treatment options for CLL[101]. The principal findings of our economic evaluation are three-fold.

First, with LYs achieved ranging from 5.26 for ibrutinib to 6.29 for acalabrutinib-plus-obinutuzumab, targeted therapies are associated with marked improvements over chemoimmunotherapies, where the observed range was from 2.74 for bendamustine-plus-rituximab to 3.33 LYs for obinutuzumab-plus-chlorambucil. Venetoclax-plus-obinutuzumab bridged chemoimmunotherapies and targeted regimens at 4.49 LYs. Similarly, QALYs extended from 4.26 for ibrutinib to 5.01 for acalabrutinib-plus-obinutuzumab, clearly better than the chemoimmunotherapies, where estimates ranged from 2.09 for rituximab-plus-chlorambucil to 2.47 QLYs for obinutuzumab-plus-chlorambucil; with venetoclax-plus-obinutuzumab at 3.54 QALYs.

Second, considering that the 10-year cost of the ten regimens extended from $561,821 (venetoclax-plus-obinutuzumab) to $1,298,638 (acalabrutinib-plus-obinutuzumab), the incremental cost for the remaining nine regimens over venetoclax-plus-obinutuzumab varied

between $9,614 (rituximab-plus-chlorambucil) and $736,817 (acalabrutinib-plus-obinutuzumab). In terms of ICER and ICUR, having the lowest cost but better outcomes than the chemoimmunotherapies made venetoclax-plus-obinutuzumab cost-saving up to $-95,981/LYg and $-117,459/QALYg. Conversely, with the lower cost of venetoclax-plus-obinutuzumab but also with its lesser clinical benefit compared to the targeted therapies, the incremental cost over venetoclax-plus-obinutuzumab ranged from $582,500 (ibrutinib) to $736,817 (acalabrutinib-plus-obinutuzumab). Acalabrutinib-plus-obinutuzumab was associated with gains of 1.80 LYs and 1.47 QALYs and, despite being the highest-cost regimen, yielded the most favorable ICER at $409,343/LYg and $502,236/QALYg. Acalabrutinib monotherapy, while being associated with a difference of -0.60 LY and -0.41 QALY over its combination therapy, was economically the next best option at $512,101/LYg and $579,737/QALYg. All other targeted therapies showed ICERs exceeding $700,00/LYg and ICURs in excess of $800,000/QALYg. Summarized, compared to venetoclax-plus-obinutuzumab, all chemoimmunotherapy treatments cost more for less LY and QALY benefit, while all targeted therapy regimens cost more for better LY and QALY benefit.

Third, our economic burden analyses illustrate the long-term financial commitments associated with CLL, considering the varying lag times from diagnosis to first treatment, the distribution of patients in terms of risk, the diverging patterns of (non-)progression, and the subsequent need for additional lines of treatment. For the 21,040 CLL patients diagnosed in 2020, the expected ten-year cost following diagnosis ranged from $1.96 billion to $4.52 billion for the estimated 7,154 patients with high-risk disease, declining to between $1.07 billion to $2.47 billion for the 7,574 patients at intermediate risk, and further to $269 million to $623 million for the 6,312 low-risk patients, depending on first-line treatment administered.

Unsurprisingly, certainly if using a $100,000 per unit of benefit gained as the WTP threshold, all absolute NMB estimates were negative, indicating that the value of each treatment was not worth its cost at the $100,000 resource constraint. This raises the larger issue of the relevance of adopting a priori fixed WTP thresholds to judge whether a treatment is cost-effective. The empirical base for WTP thresholds is limited. The $50,000 per QALY threshold, though widely advocated, is an "arbitrary rule of thumb" and "convenient round number"[123] with "murky origins"[124] that "developed into a folk tradition"[123] if not "urban legend"[125] and has left "experts unclear as to how the practice emerged and spread"[123]. Neumann et al.[125] suggested using $100,000 or $150,000 (in 2014 USD) "if one had to select a single threshold outside the context of an explicit resource constraint or opportunity cost", but do not provide much of an empirical base. These estimates flow from an era of small molecules for high-prevalence diseases and/or generalized (including systemic) cancer treatments, not from the highly targeted biological treatments with complex molecules for defined and smaller populations that have significantly improved cancer patient outcomes. Therefore, our perspective is that pharmacoeconomic evaluations should inform policy, not set policy – leaving WTP threshold decisions to the payer.

An important factor to consider is the relative probability that a particular regimen will achieve the desired clinical outcome at a given investment level. Having the most favorable ICER and ICUR relative to venetoclax-plus-obinutuzumab, acalabrutinib-plus-obinutuzumab has a 94% probability of achieving its projected clinical benefit at a WTP threshold of $600,000 – a threshold at which the remaining targeted regimens have at most a 5% probability (acalabrutinib) and venetoclax-plus-obinutuzumab has a 1% probability.

Further, first-line treatment with acalabrutinib-plus-obinutuzumab was associated with 66.1% of patients being progression-free in first-line and an additional 11.4% being progression-free after second- or third-line treatment, which accounts for a combined 77.5% of patients being progression-free over ten years. The corresponding percentages for venetoclax-plus-obinutuzumab were 31.1% and 19.4% for a total of 50.5% of patients thus treated, for a difference of 25% of patients. The incremental cost of acalabrutinib-plus-obinutuzumab over venetoclax-plus-obinutuzumab translates into a cost of $27,283 to achieve a 1% gain in the probability of staying progression-free at ten years from initiating the therapy.

We included all possible factors that may affect the costs so as to establish a unique model that considers the time-to-next-treatment following progression. This is a driving factor of medical costs. Using 2014-2017 US commercial insurance data on CLL patients, Emond et al.[91] reported that front-line single-agent treatment with ibrutinib, despite being more expensive, was associated with lower total health costs compared to chemoimmunotherapy. This lower medical cost was attributed to the longer time-o-next-treatment and the lower follow-up costs including clinic and emergency visits in ibrutinib-treated patients. While not directly comparable to our cost structures and outcomes, the Emond et al. findings align with our observation of greater clinical benefit associated with targeted treatment regimens.

Our results are more encouraging than those in a study by Chen et al[90], which evaluated the economic burden of treating CLL patients from 2011 to 2025 with targeted therapies versus chemoimmunotherapy. The authors estimated that the lifetime cost per patient diagnosed following the 2016 approval of ibrutinib as first-line treatment and followed up to ten years (to 2025) would increase from $147,000 to $604,000 (410% increase) when patients were treated in first- and second-line with ibrutinib and idelalisib-plus-rituximab, respectively, instead

of chemoimmunotherapy and idelalisib-plus-rituximab regimens. We used a different model as we aimed to differentiate between all benefits that could be gained by the different first-line therapies, including the efficacy measures of PFS and OS (as extracted from fitted parametric survival curves), TTFT, TTNT, and all health-related costs. In our analyses, using ibrutinib therapy in first-line was associated with an increase in the 10-year per-patient cost by 187% compared with patients administered obinutuzumab-plus-chlorambucil.

Our study has limitations while also identifying areas for future research. The model included one scenario for second- and third-line therapy, while in the real-world setting clinicians may try other regimens. Medication costs were calculated using the WAC, which may not reflect the actual cost to payers as it does not include payer incentives; while no average sales price (ASP) is available. However, to buffer against this, we varied the cost of drugs by 20% to 30% in the PSAs. We did not consider the availability of biosimilar rituximab. While this might have lowered some estimates, there is emerging evidence that, certainly in as far as the CMS ASP is concerned, the ASPs for reference and biosimilar tend to converge as time-on-market progresses. Because no Kaplan-Meier curves were available for patients with del17p or unmutated IGHV, we could not replicate the analyses for these risk groups. We corrected for this by considering the differences in TTFT and using the mean survival in CLL patients among the different treatments.

4.6 Conclusions

Our study provides a comprehensive comparative economic evaluation of the cost-effectiveness and cost-utility of possible chemoimmunotherapy and targeted therapy regimens for fludarabine ineligible CLL patients from time of initiation of first-line treatment to death, across different states of progression and second- and third-line treatment, and against a ten-year time horizon. Regimens including the BTK inhibitors acalabrutinib and ibrutinib in mono- or various combination therapies showed the best outcomes relative to the combination of the BCL2 inhibitor venetoclax with obinutuzumab though at incremental cost. Venetoclax-plus-obinutuzumab yielded better outcomes at lower cost compared to the chemoimmunotherapy regimens, and thus was cost-saving over these regimens. Acalabrutinib-plus-obinutuzumab in first-line treatment is associated with the greatest gains in clinical effectiveness, the best cost-to-outcome ratio among targeted treatments but requiring a marked investment.

Table 4.1: Dosing of regimens per cycle

I. Dosing (mg) of first-line treatments						
	Cycle 1	Cycle 2	Cycle 3-6	Cycle 7	Cycle 8-12	13 or more
Obinutuzumab -plus-Chlorambucil	CHL= 70 mg PO, OBN= 3,000 mg IV	CHL= 70 mg PO, OBN= 1,000 mg IV	CHL= 70 mg PO, OBN= 1,000mg IV	No treatment		
Bendamustine -plus-Rituximab	BEND= 306 mg IV, RIT= 637.5 mg IV	BEND= 306 mg IV, RIT= 850 mg IV	BEND= 306 mg IV, RIT= 850 mg IV	No treatment		
Ofatumumab -plus-Chlorambucil	OFA= 1,300 mg IV, CHL= 119 mg PO	OFA= 1,000 mg IV, CHL= 119 mg PO	OFA= 1,000 mg IV, CHL= 119 mg PO	OFA= 1,000 mg IV, CHL= 119 mg PO	OFA= 1,000 mg IV, CHL= 119 mg PO	No treatment
Rituximab -plus-Chlorambucil	RIT= 637.5 mg IV, CHL= 70 mg PO	RIT= 850 mg IV, CHL= 70 mg PO	RIT= 850 mg IV, CHL= 70 mg PO	No treatment		
Venetoclax -plus-Obinutuzumab	VNT= 140 mg PO, OBN= 3,000 mg IV	VNT= 5250 mg PO, OBN= 1,000 mg IV	VNT= 11,200 mg PO, OBN= 1,000 mg IV	VNT= 11,200 mg PO	VNT= 11,200 mg PO	No treatment
Ibrutinib	11,760 mg PO	11,760 mg PO	11,760 mg PO	11,760 mg PO	11,760 mg PO	11,760 mg PO
Ibrutinib -plus-Rituximab	IBR= 11,760 mg PO	IBR= 11,760 mg PO, RIT= 2,550 mg IV	IBR= 11,760 mg PO, RIT= 637.5 mg IV	IBR= 11,760 mg PO	IBR= 11,760 mg PO	IBR= 11,760 mg PO
Ibrutinib -plus-Obinutuzumab	IBR= 11,760 mg PO, OBN= 3,000 mg IV	IBR= 11,760 mg PO, OBN= 1,000 mg IV	IBR= 11,760 mg PO, OBN= 1,000 mg IV	11,760 mg PO	11,760 mg PO	11,760 mg PO
Acalabrutinib	5600 mg PO	5,600 mg PO	5,600 mg PO	5,600 mg PO	5,600 mg PO	5,600 mg PO
Acalabrutinib -plus-Obinutuzumab	ACA= 5,600 mg PO, OBN= 3,000 mg IV	ACA= 5,600 mg PO, OBN= 1,000 mg IV	ACA= 5,600 mg PO, OBN= 1,000 mg IV	ACA= 5,600 mg PO, OBN= 1000 mg IV	ACA= 5,600 mg PO	ACA= 5,600 mg PO
II. Subsequent line therapies						
	Cycle 1	Cycle 2	Cycle 3	Cycle 4-6	Cycle 7 or more	
Idelalisib -plus-Rituximab	IDL= 8,400 mg PO, RIT= 673.5 mg IV	IDL= 8,400 mg PO, RIT= 1,700 mg IV	IDL= 8,400 mg PO, RIT= 1,700 mg IV	IDL= 8,400 mg PO, RIT= 850 mg IV	IDL= 8,400 mg PO	
Ofatumumab	300 mg IV	1000 mg IV every other cycle (every 8 weeks) up to 2 years				

III. Premedication for Obinutuzumab, Ofatumumab, Rituximab	Dosage	
Acetaminophen 650 mg po pre-infusion medications	650 mg PO	used before each cycle
Diphenhydramine 50 mg iv pre-infusion medications	50 mg IV	used before each cycle
Methylprednisolone 800 mg	800 mg IV	used before the first cycle

Table 4.2: Model inputs

I. Cost of treatment						
Cost of first-line therapies	**Cycle 1**	**Cycle 2**	**Cycle 3-6**	**Cycle 7**	**Cycle 8-12**	**Cycle ≥13**
Obinutuzumab-plus-chlorambucil	$20,799.28	$7,500.74	$7,500.74			
Bendamustine-plus-rituximab*	$14,454.93	$16,442.42	$16,442.42			
Ofatumumab-plus-chlorambucil	$9,291.30	$7,481.19	$7,481.19	$7,481.19	$7,481.19	
Rituximab*-plus-chlorambucil	$6,840.91	$8,837.39	$8,837.39			
Venetoclax-plus-obinutuzumab	$20,091.23	$12,027.66	$18,123.18	$11,473.91	$11,473.91	
Ibrutinib	$12,966.10	$12,966.10	$12,966.10	$12,966.10	$12,966.10	$12,966.10
Ibrutinib-plus-rituximab*	$12,966.10	$36,923.86	$18,955.54	$12,966.10	$12,966.10	$12,966.10
Ibrutinib-plus-obinutuzumab	$32,913.91	$19,615.37	$19,615.37	$12,966.10	$12,966.10	$12,966.10
Acalabrutinib	$13,126.40	$13,126.40	$13,126.40	$13,126.40	$13,126.40	$13,126.40
Acalabrutinib-plus-obinutuzumab	$33,074.21	$19,775.67	$19,775.67	$19,775.67	$13,126.40	$13,126.40
Cost of subsequent lines of therapy						
	Cycle 1	Cycle 2	Cycle 3	Cycle 4-6	Cycle 7 or more	
Ibrutinib	$12,966.10	$12,966.10	$12,966.10	$12,966.10	$12,966.10	
Idelalisib-plus-Rituximab	$16,472.23	$26,454.63	$26,454.63	$18,468.71	$10,482.79	
Ofatumumab	$ 1,810.11	$6,033.70 every other cycle for 2 years				
II. Medication administration costs	**Costs**	**Reference**				
IV infusion, for premedication, initial, up to 1 hour (CPT 96365)	$72.18	[126]				
Chemo or immunotherapy administration, intravenous infusion; up to 1 hour, single or initial substance or drug (CPT 96413)	$142.55	[126]				
Chemo administration, intravenous infusion; each additional hour (CPT 96415)	$30.68	[126]				
III. Premeditations for monoclonal antibodies	**Cost**					
Acetaminophen 650 mg po pre-infusion medications	$0.0382					
Diphenhydramine 50 mg iv pre-infusion medications	$0.82					

Methylprednisolone 800 mg	$8.992	
IV. Other incremental costs of chemoimmunotherapy vs. targeted therapy	**Monthly Mean Costs (10 years)**	**Reference**
Inpatient treatment	$305.29	[91]
Outpatient costs	$1,127.90	[91]
Emergency visits costs	$153.20	[91]
Other services costs	$118.78	[91]
V. Cost of disease progression	$4,231.68	[113]
VI. Cost of non-progressed disease	$2,235.54	[113]
VII. Adverse events management cost	**Cost per event**	**Reference**
Neutropenia	$3,506.00	[90]
Anemia	$2,150.00	[90]
Thrombocytopenia	$1,242.00	[90]
Leukopenia	$192.62	[107]
Febrile neutropenia	$31,028.40	[108]
Pneumonia	$17,236.88	[107]
Infusion related reaction	$2,000.00	Assumed
Tumor lysis syndrome	$43,925.00	[109]
Atrial fibrillation	$19,472.00	[107]
Diarrhea	$11,287.00	[107]
Hemorrhage	$28,126.00	[110]
VIII. Health related utility values		
Utility	**Mean value (SD)**	**Reference**
PFS without therapy	0.82 (0.17)	[115]
PFS without second-line therapy	0.71 (0.23)	[115]
PFS on initial therapy oral treatment	0.71 (0.20)	[115]
PFS on initial therapy IV treatment	0.67 (0.22)	[115]
PFS on targeted therapy	0.799 (0.20)	[127]
Progression after first-line treatment	0.66 (0.22)	[115]
PFS on second-line therapy	0.55 (0.25)	[115]
PFS on initial therapy with increased hospital visits	0.55 (0.26)	[115]

Relapsed lines of treatment	0.42 (0.25)	[115]

Utility decrement due to adverse event	**Mean decrement (SD)**	**Reference**
Neutropenia	-0.16 (0.05)	[117]
Anemia	-0.09 (0.03)	[118]
Thrombocytopenia	-0.11 (0.03)	[117]
Leukopenia	-0.01 (0.003)	[117]
Febrile neutropenia	-0.27 (0.08)	[119]
Pneumonia	-0.19 (0.06)	[118]
Infusion related reaction	-0.05 (0.02)	Assumed
Tumor lysis syndrome	-0.218 (0.07)	Assumed
Atrial fibrillation	-0.24 (0.07)	[120]
Diarrhea	-0.09 (0.03)	[121]
Hemorrhage	-0.29	[110]

* Rituximab biosimilars, possibly with lower cost, are available but were not considered here.

Abbreviations: PFS, progression free survival; SD, standard deviation.

Table 4.3: Survival proportions as resulted from the probabilistic sensitivity analyses in different health states at ten years of follow-up.

10 years model	% PFS on first-line treatment	% PFS on second- or third-line treatments	% Further progression	Death
Venetoclax-plus-obinutuzumab	31.1	19.4	22.2	27.1
Rituximab-plus-chlorambucil	2.7	23.3	34.8	39.1
Obinutuzumab-plus- chlorambucil	7.5	25.8	39.1	27.6
Ofatumumab-plus- chlorambucil	2.4	25.4	36.5	35.7
Bendamustine-plus-rituximab	0	27	44.1	28.9
Ibrutinib	34.2	24.4	22.3	19
Acalabrutinib	40.6	18.5	18.5	22.2
Ibrutinib-plus-obinutuzumab	36.8	20.8	17.9	24.3
Ibrutinib-plus-rituximab	35.4	24	21.3	19.2
Acalabrutinib-plus-obinutuzumab	66.1	11.4	10.2	12.2

Abbreviations: PFS, progression free survival**.**

Table 4.4: Deterministic and probabilistic (in parentheses) cost-effectiveness and cost-utility results (10-year time horizon) by first-line regimen

	Deterministic analyses (PSA)					
Regimen	**Cost ($)**	**LY**	**QALY**	**ICER**	**ICUR**	**NMB**
Venetoclax-plus-obinutuzumab	561,821 (561,808)	4.49 (4.50)	3.54 (3.55)	Reference	Reference	-112,821 (-111,808)
Rituximab-plus-chlorambucil	571,435 (571,273)	2.78 (2.78)	2.09 (2.09)	-5,622 (-5,503)	-6,630 (-6,483)	-293,435 (-293,273)
Obinutuzumab-plus-chlorambucil	611,192 (611,204)	3.33 (3.34)	2.47 (2.48)	-42,561 (-42,583)	-46,141 (-46,164)	-278,192 (-277,204)
Ofatumumab-plus-chlorambucil	626,977 (626,934)	2.86 (2.85)	2.17 (2.17)	-39,973 (-39,470)	-47,559 (-47,193)	-340,977 (-341,934)
Bendamustine-plus-rituximab	729,787 (729,884)	2.74 (2.74)	2.11 (2.11)	-95,981 (-95,498)	-117,459 (-116,719)	-455,787 (-455,884)
Ibrutinib	1,144,321 (1,144,058)	5.26 (5.25)	4.26 (4.27)	756,494 (776,333)	809,028 (808,681)	-618,321 (-619,058)
Acalabrutinib	1,176,342 (1,176,465)	5.69 (5.69)	4.60 (4.61)	512,101 (516,518)	579,737 (579,865)	-607,342 (-607,465)
Ibrutinib-plus-obinutuzumab	1,184,957 (1,184,457)	5.36 (5.37)	4.29 (4.29)	716,248 (715,689)	830,848 (841,418)	-648,957 (-647,457)
Ibrutinib-plus-rituximab	1,196,410 (1,196,747)	5.29 (5.29)	4.27 (4.27)	793,236 (803,720)	869,300 (881,860)	-667,410 (-667,747)
Acalabrutinib-plus-obinutuzumab	1,298,638 (1,298,437)	6.29 (6.30)	5.01 (5.02)	409,343 (409,238)	501,236 (501,108)	-669,638 (-668,437)

Notes: The ICER is expressed as the differential cost (incremental or decremental) per LY gained (Δ$/LYg). The ICUR is expressed as the differential cost (incremental or decremental) per QALY gained (Δ$/QALYg).
Abbreviations; PSA, Probabilistic sensitivity analyses; LY, Life year; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; ICUR; Incremental cost-utility ratio; NMB, Net monetary benefit.

Table 4.5: Economic burden for CLL patients for ten years following diagnosis.

Estimated 10-year budget for 2020 cohort of newly diagnosed CLL patients				
	Low risk	**Intermediate risk**	**High risk**	**Total**
	6,312	7,574	7,154	21,040
Proportion of CLL patients estimated to need treatment in the next 10 years within each risk category	0.18	0.57	0.80	
	Cost ($) of first-line treatment when initiated			
Venetoclax-plus-obinutuzumab	269,461,597	1,070,560,441	1,957,581,686	3,297,603,724
Rituximab-plus-chlorambucil	274,001,503	1,088,597,311	1,990,563,146	3,353,161,961
Obinutuzumab-plus-chlorambucil	293,153,326	1,164,686,756	2,129,697,098	3,587,537,180
Ofatumumab-plus-chlorambucil	300,698,096	1,194,661,835	2,184,508,264	3,679,868,195
Bendamustine-plus-rituximab	350,076,339	1,390,839,671	2,543,230,783	4,284,146,793
Ibrutinib	548,727,951	2,180,074,799	3,986,392,863	6,715,195,613
Acalabrutinib	564,271,558	2,241,828,943	4,099,313,887	6,905,414,387
Ibrutinib-plus-obinutuzumab	568,104,512	2,257,057,120	4,127,159,488	6,952,321,120
Ibrutinib-plus-rituximab	573,999,165	2,280,476,348	4,169,982,902	7,024,458,414
Acalabrutinib-plus-obinutuzumab	622,773,156	2,474,253,515	4,524,315,660	7,621,342,330
Estimated 10-year per-patient cost for newly diagnosed CLL patient				
	Low risk	**Intermediate risk**	**High risk**	
	Cost ($) of first-line treatment when initiated			
Venetoclax-plus-obinutuzumab	42,690	141,339	273,650	
Rituximab-plus-chlorambucil	43,410	143,721	278,260	
Obinutuzumab-plus-chlorambucil	46,444	153,766	297,710	
Ofatumumab-plus-chlorambucil	47,639	157,724	305,372	
Bendamustine-plus-rituximab	55,462	183,624	355,518	
Ibrutinib	86,934	287,821	557,257	
Acalabrutinib	89,397	295,974	573,042	
Ibrutinib-plus-obinutuzumab	90,004	297,985	576,935	
Ibrutinib-plus-rituximab	90,938	301,077	582,921	
Acalabrutinib-plus-obinutuzumab	98,665	326,660	632,453	

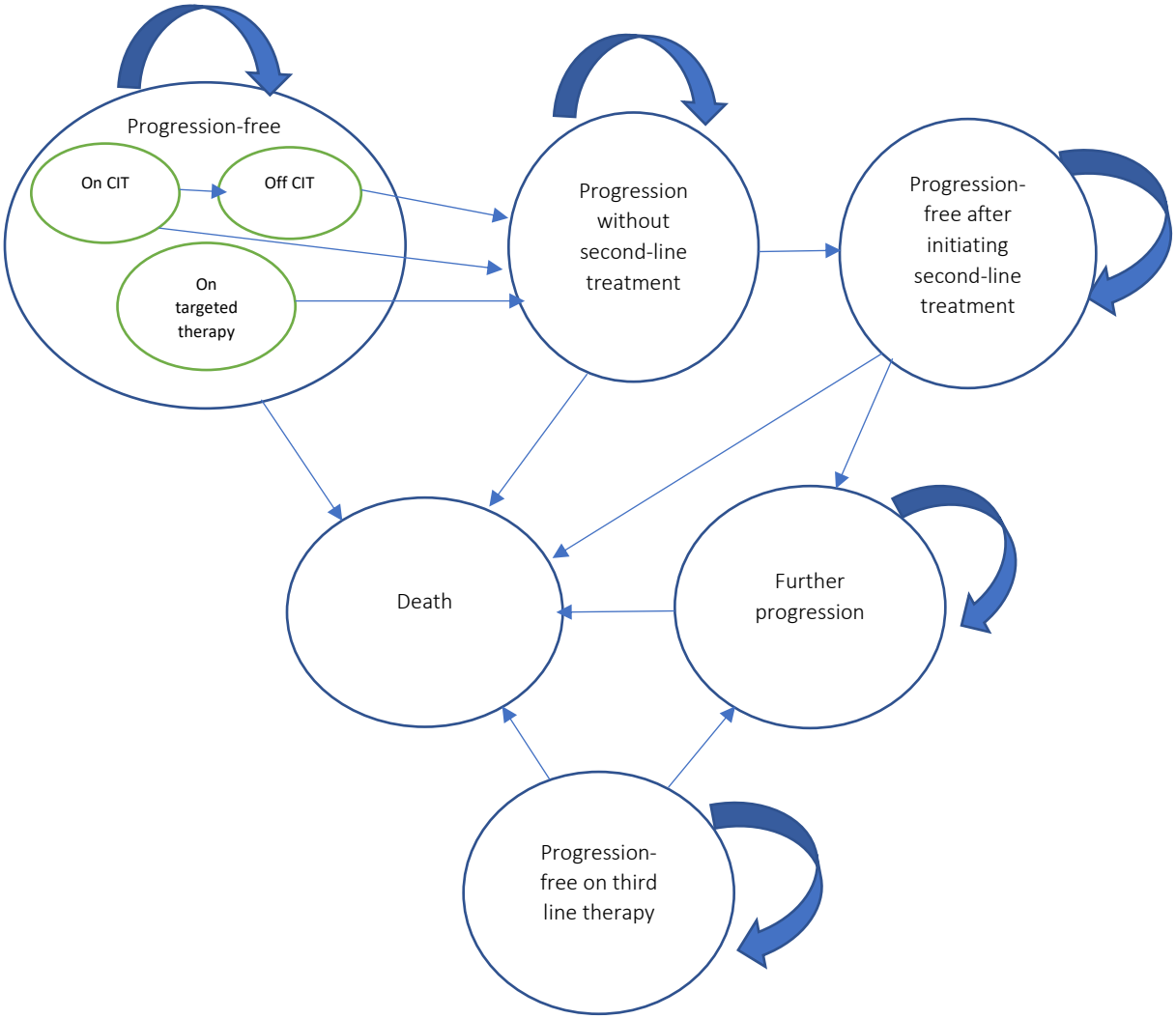
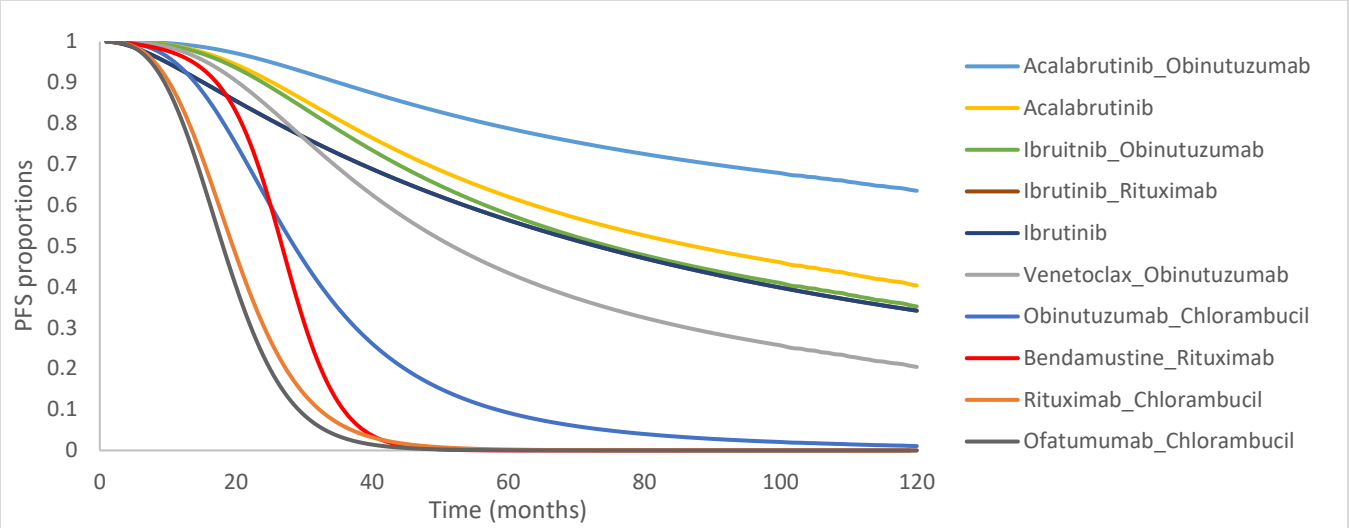


Figure 4.1: Markov Model Structure.

Abbreviation: CIT, chemoimmunotherapy.



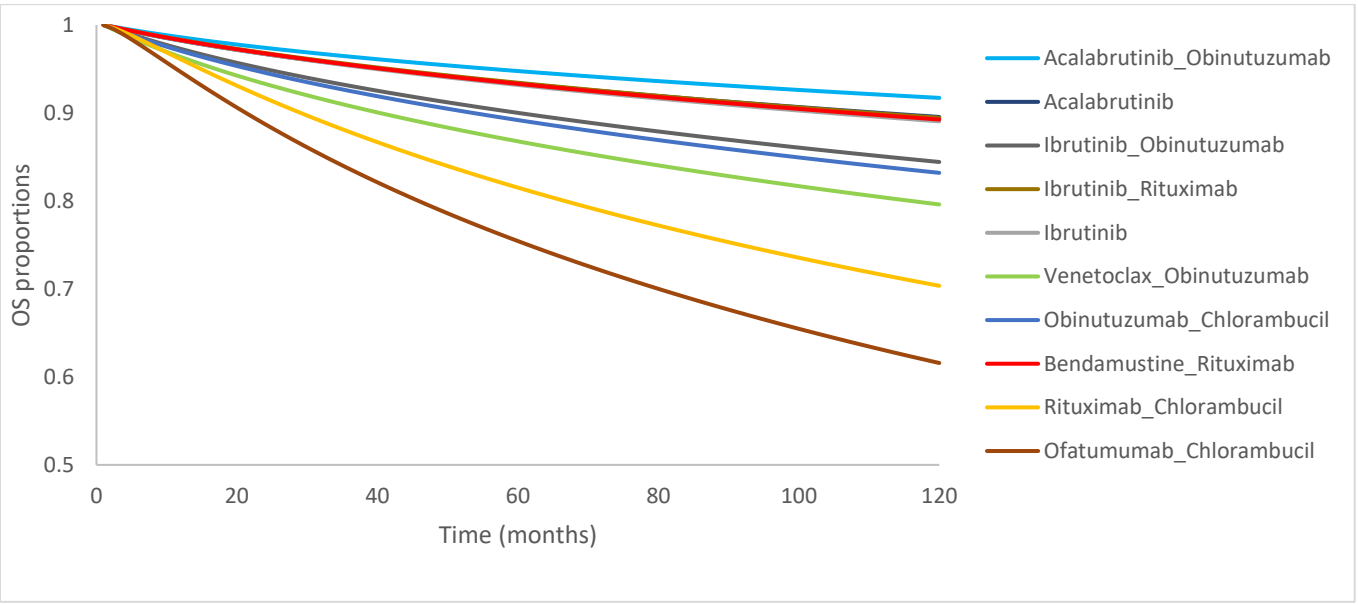
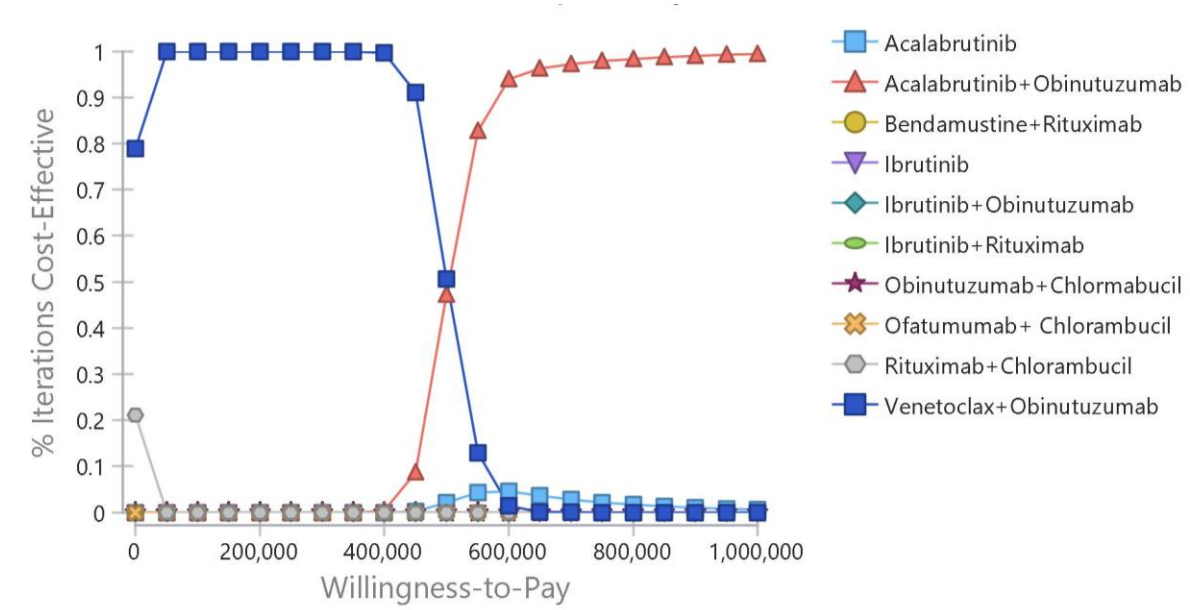


Figure 4.2: (A) Progression-free and (B) overall survival proportions as obtained from the fixed lognormal network meta-analyses.

The Y axis of the OS plot starts at 0.5 to facilitate visual recognition.

Ibrutinib and ibrutinib-plus-rituximab PFS ad OS curves overlapped and may not be discernible.

*Bendamustine-plus-rituximab and acalabrutinib OS curves overlapped and may not be discernible.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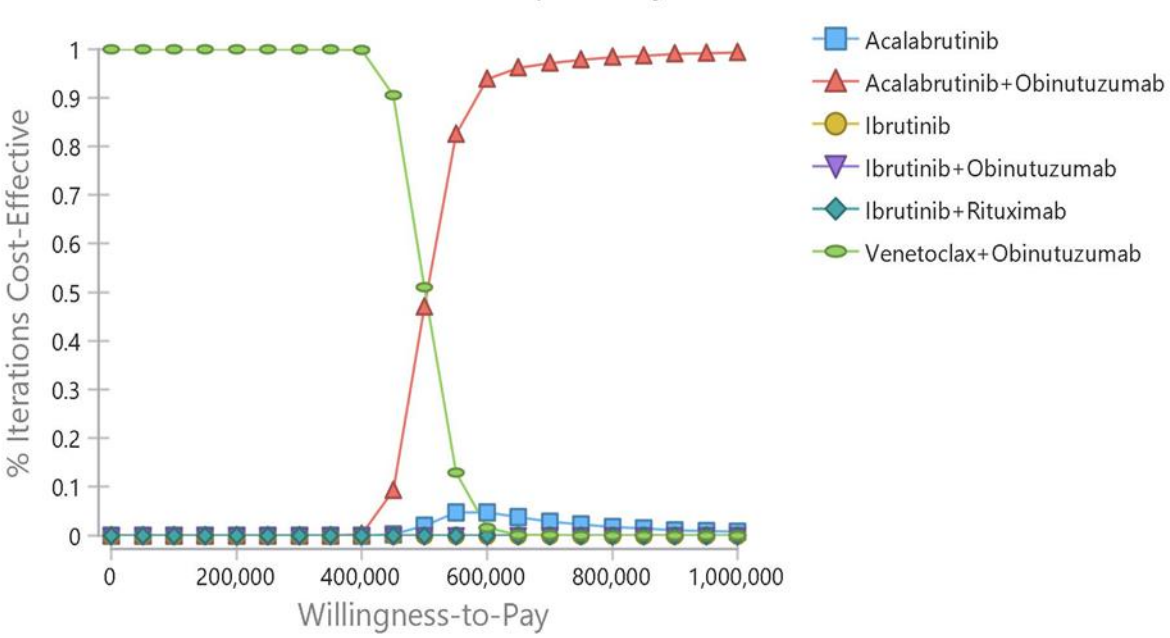
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200,000
400,000
600,000
800,000
1,000,000
Willingness-to-Pay
Acalabrutinib
Acalabrutinib+Obinutuzumab
Bendamustine+Rituximab
Ibrutinib
Ibrutinib+Obinutuzumab
Ibrutinib+Rituximab
Obinutuzumab+Chlormabucil
Ofatumumab+ Chlorambucil
Rituximab+Chlorambucil
Venetoclax+Obinutuzumab


% Iterations Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200,000
400,000
600,000
800,000
1,000,000
Willingness-to-Pay
Acalabrutinib
Acalabrutinib+Obinutuzumab
Ibrutinib
Ibrutinib+Obinutuzumab
Ibrutinib+Rituximab
Venetoclax+Obinutuzumab

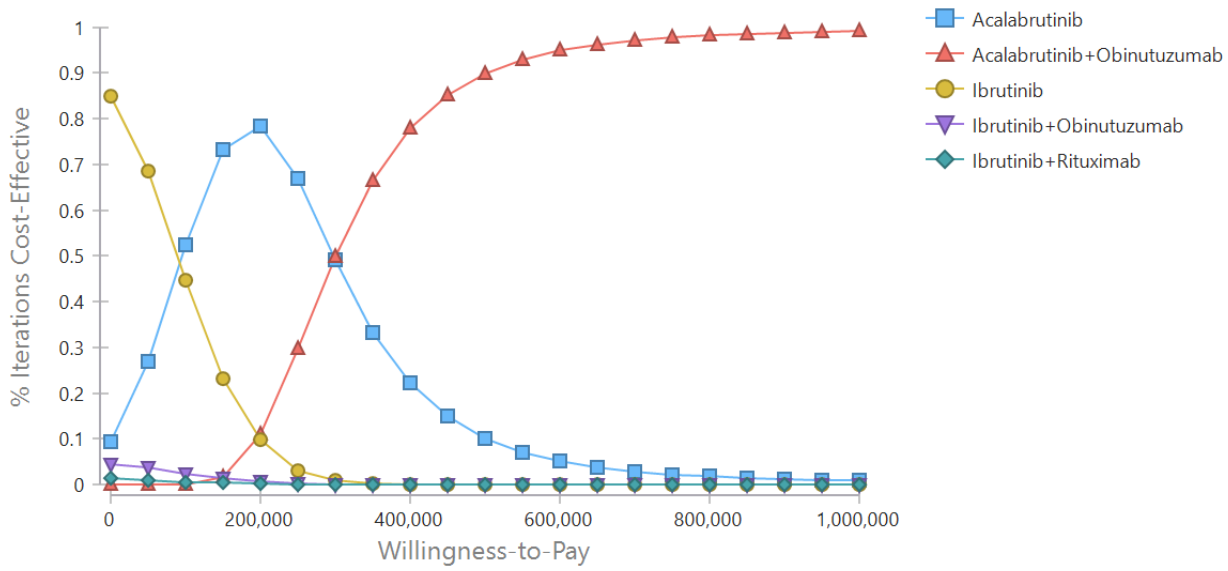


Figure 4.3: Cost-effectiveness acceptability curves when (A) all treatment, (B) targeted therapies compared with each other**, (**C) BTK inhibitors regimens compared with each other.

5.0 DISCUSSION

5.1 Summary of Findings

Over the past two decades, advances in understanding of CLL biology have facilitated the discovery of chromosomal abnormalities and genetic mutations that contribute to survival outcomes, thus aiding in the discovery of drugs that disrupt the signaling pathways of B-cells. Subsequently, the survival of patients with CLL has progressively improved. With the approval of new targeted therapies for first line and relapsed (recurrent) disease, the expected survival in high-risk groups unable to tolerate chemoimmunotherapy (patients above 65 years of age or with comorbidities) has improved significantly. We analyzed data from the large US population-based SEER database over the past three decades to explore the trends in survival and the advances in CLL treatment have affected OS in patients with CLL. We found continuous improvements in 5-year and 10-year age-adjusted relative survival across all calendar periods between 1985 and 2014. The proportions of long-term survivors varied by age, sex, and year of diagnosis. The HRs of death for patients diagnosed between 2004 and 2007 and followed up to 2015 (to the era of targeted therapies), compared with the cohort of patients diagnosed in 2000–2003 and followed up to 2012 (before the era of targeted therapies) showed a significant improvement in all age categories except 85 years of age and older. To precisely differentiate between treatments, we searched the literature for all available clinical trials of front-line therapies used to treat fludarabine ineligible patients with CLL, to establish evidence comparing efficacy in terms of the

PFS, OS, and TTNT for all treatments by conducting network meta-analyses. Eight studies with 11 regimens (obinutuzumab-plus-chlorambucil, rituximab-plus-chlorambucil, bendamustine-plus-rituximab, chlorambucil, ofatumumab-plus-chlorambucil, venetoclax-plus-obinutuzumab, ibrutinib, ibrutinib-plus-rituximab, ibrutinib-plus-obinutuzumab, acalabrutinib, and acalabrutinib-plus-obinutuzumab) were included in the NMA. All chemoimmunotherapies in the NMA, compared with ibrutinib treatment, was significantly associated with lower PFS. When other targeted therapies were compared with ibrutinib, venetoclax plus obinutuzumab, and ibrutinib plus rituximab were not associated with any significant differences at all time points. However, acalabrutinib showed significant differences compared with ibrutinib, with an HR of 0.18–0.67 within the first 3 years (up to 36 months after starting the therapy). However, this difference became insignificant after the third year. Similarly, ibrutinib-plus-obinutuzumab was significantly different from ibrutinib in the first 2 years (HR between 0.29 and 0.53), but the difference subsequently became insignificant. Acalabrutinib-plus-obinutuzumab was the only therapy associated with a significant improvement in PFS over all periods, with HRs of 0.13–0.42. Among patients with high-risk disease, such as that with del17p and unmutated IGHV, targeted therapy, compared with chemoimmunotherapies, significantly improved the PFS. The NMA of TTNT displayed longer treatment-free times after the first progression in patients treated with BTKi with or without obinutuzumab, whereas the venetoclax-plus-obinutuzumab was associated with significantly higher risk for initiating the next treatment than ibrutinib-plus-obinutuzumab (HR=3.00; 95%CI=1.92–4.98). All targeted therapies, compared with chemoimmunotherapies, were associated with a significantly prolonged TTNT interval. Because the high cost of targeted therapies may influence the decision-making process in the clinical practice, we included the relative costs and effectiveness in our third level of analyses,

considering all possible differences among treatments in terms of PFS, OS, TTNT, and quality of life for each treatment. Venetoclax plus obinutuzumab had a cost-saving effect over chemoimmunotherapies during a 10-year time horizon, whereas the other targeted therapies were associated with more gains in the LY and QALY but with incremental costs between $582,500 and $736,817, thus resulting in ICURs between 502,213 and 875,350 $/QALY.

5.2 Pharmaco-economic Significance

With the availability of different targeted therapies that can be used as monotherapies or in combination with immunotherapies, providers increasingly face challenges in choosing therapies; some physicians believe that chemoimmunotherapies still has a role in treating patients with CLL, whereas others adopt targeted therapies in treating all cases. Therefore, the optimal first line treatment in unfit patients remains unclear. Head-to-head comparisons of all available treatments are not available, and database studies to compare these treatments are not possible, because most treatments were introduced in 2018 or later. The rapid progress in the oncology field led to detection of cancer in earlier stages and the introduction of advanced treatments as targeted therapies, which have been adopted as the standard of care for many cancer types; however, specifically in CLL treatment, the costs of cancer care have escalated in the past few years. Several reports have discussed the economic and societal burden of cancer care in the U.S., with a focus on the importance of finding strategies to save costs and maintain the level of patient care. The heavy financial burdens and their consequences experienced by cancer patients have been addressed in several studies.

In this research, we analyzed all possible benefits and all health-related costs of first line therapies for treating fludarabine ineligible patients with CLL. Targeted regimens that include BTKi are associated with greater efficacy, effectiveness gains, and higher costs than those of

chemoimmunotherapies. However, treatment with venetoclax-plus-obinutuzumab is associated with greater effectiveness and lower cost than those of chemoimmunotherapies. This evidence may support clinical practice by helping decision-makers determine treatments for their patients.

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