

Application to add ibrutinib to WHO Model List of Essential Medicines

As a Medicine for Treatment of Chronic Lymphocytic Leukaemia

Submitted by:

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Potential conflicts of interest

All the authors declare no conflict of interest

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General items

1. Summary statement of the proposal for inclusion, change or deletion.

This application proposes to add ibrutinib to the list of WHO Essential Medicine as treatment for individuals with chronic lymphocytic leukaemia/small lymphocytic lymphoma and high risk of progressing to an aggressive disease and for patients with a relapsed refractory chronic lymphocytic leukaemia.

Chronic lymphocytic leukaemia is the most common form of leukaemia in western countries. In adults older than 19, it accounts for approximately 40% of the new cases. Globally, the number of deaths due to chronic lymphocytic leukaemia has increased in 70% from 1990 to 2017. However, the age-adjusted death rates have decreased in high - income regions while increased in Central Sub - Saharan Africa, East Asia, and Southeast Asia.

Ibrutinib is a first-in-class agent that binds permanently to the Bruton's tyrosine kinase, a protein downstream of the B-cell receptor that is critical for B-cell survival and proliferation. Its use in individuals with chronic lymphocytic leukaemia probably increases the overall survival (HR 0.44, 95% CI 0.20 - 0.97; moderate certainty evidence) and the progression free survival (HR 0.20, 95% CI 0.15 - 0.27; high certainty evidence). In terms of absolute effect, the use of ibrutinib prolongs progression free survival in at least 50 months (approximately 4 years), which is an effect relatively large in comparison with targeted therapies for other cancers.

One of the main barriers to a more widespread use of ibrutinib is cost. Economic evidence shows that at the current price, ibrutinib is unlikely to be a cost-effective medication. Agencies that have recommended it for coverage, have done so for specific sub-groups and with prices that were not disclosed. Adding ibrutinib to the WHO essential list of medications might help to boost its use, especially in low- and middle-income countries. Also, might help to promote mechanisms that may enhance its accessibility and affordability, such as pooled procurement or inclusion in the Medicines Patent Pool and Prequalification Program.

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	Anatomical Therapeutic Chemical (ATC) code
Ibrutinib	L01XE27

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The recommended dose for the treatment, either as a single agent or in combination, is 420 mg (three capsules) once daily.

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). It is not recommended to administer Ibrutinib to patients with severe hepatic impairment (Child-Pugh class C).

The safety and efficacy of ibrutinib in patients with renal impairment have not been established.

There are no data in pregnant women. However, animal studies have shown important toxicity and therefore ibrutinib should not be used during pregnancy.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

The clinical presentation of chronic lymphocytic leukaemia is highly heterogeneous: while some patients present with an indolent disease that may never require therapy, others may progress rapidly and may require therapy shortly after the diagnosis.

Ibrutinib is a therapeutic alternative for patients at high risk of progressing to an aggressive disease and for patients with a relapsed refractory chronic lymphocytic leukaemia.

8. Information supporting the public health relevance.

Chronic lymphocytic leukaemia is the most common form of leukaemia in western countries. In adults older than 19, it accounts for approximately 40% of the new cases.¹ Its incidence is higher in North America and Europe and lower in Latin America and Asia. In males, the age-adjusted incidence rate ranges from 4.5 per 100.000 in Canada to 0.1 per 100.000 in Japan. While in females, rates go from 2.3 per 100.000 in Canada to 0.1 per 100.000 in Japan.² Globally, the number of deaths due to chronic lymphocytic leukaemia has increased in 70% from 1990 to 2017. However, the age-adjusted death rates have decreased in high - income regions while increased in Central Sub - Saharan Africa, East Asia, and Southeast Asia.³

Additionally, chronic lymphocytic leukaemia poses a significant burden to patients and health systems: annual direct costs per person ranged from US\$4491 in Germany to US\$43,913 in the USA.⁴

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for randomized trials up to December 2020 on MEDLINE and EMBASE, from date of inception and without language limits. Additionally, we searched for up-to-date systematic reviews in MEDLINE, EMBASE and The Cochrane Library (see appendix). We used the systematic reviews as a way to identify relevant studies but conducted our own meta-analysis.

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Individuals with chronic lymphocytic leukaemia
3. Intervention: Ibrutinib
4. Comparison: No targeted therapy

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analysed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I² statistic. All the meta-analyses were conducted using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Results

We identified 4 recent systematic reviews⁵⁻⁸ and 5 randomized trials.⁹⁻¹³ Two of these trials^{9,13} compared head-to-head ibrutinib with another targeted therapy and thus were not included in the analysis. The remaining 3 trials provided data regarding the effect of ibrutinib as a first or second line of treatment in patients with chronic lymphocytic leukaemia.

Two trials were conducted in treatment-naïve patients with chronic lymphocytic leukaemia /small lymphocytic lymphoma. One trial compared ibrutinib versus chlorambucil for 12 cycles,⁹ while the other trial evaluated ibrutinib associated with obinutuzumab versus chlorambucil plus obinutuzumab for 6 cycles.¹¹ The third trial enrolled patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma and assessed the effect of ibrutinib in addition to bendamustine plus rituximab versus bendamustine plus rituximab alone.¹² In two trials, individuals with deletion of 17p were explicitly excluded, while in the remaining trial were not, although only represented a small proportion of the included patients. All the trials recruited more males than females (ratio 60:40 approximately) and the median age of participants ranged from 63 to 73 years. Overall, the majority of included patients were over 65 years old.

The meta-analysis of these three studies showed that the use of ibrutinib as a first or second line of treatment probably increases the overall survival and the progression free survival (moderate an high certainty evidence respectively). The patients enrolled in these three trials have not reached yet the median overall survival, thus, with the information available, it was not possible to provide an estimation of the time gained with ibrutinib. Regarding the progression free survival, only in one study the median survival time was reached. In this case, the use of ibrutinib probably increases the progression free survival in 50.8 more months (approximately 4 years). It is important to note that this trial recruited patients with relapsed/refractory disease, therefore, the effect of ibrutinib may be larger in treatment-naïve patients.

Finally, one trial reported the effect of ibrutinib in quality of life and found that the use of ibrutinib resulted in a statistically significant improvement of FACIT-Fatigue and EORTC QLQ-C30 scores. The mean difference observed in FACIT-Fatigue score was 2.6 (95% CI 0.4 to 4.9) however, this is under the minimal important differences reported for this scale.¹⁴ Additionally, the mean difference reported in the physical functioning score of EORTC QLQ-C30 was 5.0 (95% CI 0.75-9.25), which is also under the reported minimal important difference for this domain.¹⁵

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Ibrutinib	WITHOUT Ibrutinib	Difference (CI 95%)	
Overall survival 3 RCTs (n=1,076)	HR 0.44 (0.20 - 0.97)	Not reached	Not reached	Not estimable	⊕⊕⊕○ ^{a, b} MODERATE
Progression free survival 3 RCTs (n=1,076)	HR 0.20 (0.15 - 0.27)	65.1 months	14.3 months	50.8 months more ^c	⊕⊕⊕⊕ HIGH
Quality of life ^d 1 RCT (n=269)	Not estimable	Statistically significant differences were reported in favor of the group that received ibrutinib on the FACIT-Fatigue scale and EORTC QLQ-C30. These differences may not be important to patients since are under the reported minimal important differences.			⊕⊕○○ ^{e, f} LOW

Abbreviations: RR: Risk ratio; HR: Hazard ratio; CI: Confidence interval

- We rated down the certainty of the evidence due to inconsistency. A significant heterogeneity was observed on the meta-analysis
- Although the included trials were not blinded, the overall risk of bias was considered low for mortality and survival outcomes
- The anticipated absolute effect was estimated from the median observed in the HELIOS trial. In the other 2 trials, the progression free survival median has not been reached yet, thus it was not possible to estimate the absolute effect.
- Measured with the FACIT-Fatigue scale and EORTC QLQ-C30. FACIT-Fatigue scale is a 13-item instrument to specifically assess aspects of fatigue and tiredness, including impact on daily activities and functioning. EORTC QLQ-C30 comprises 30 items, 24 of which are aggregated into 9 multi-item scales: 5 functioning scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and/or vomiting); and 1 global health-status scale.
- We rated down the certainty of the evidence due to risk of bias. All the trial were open-label, which may have affected the measurement of a patient-reported outcome
- We rated down the certainty of the evidence due to imprecision. Only one trial provided data for this outcome. The number of participants analyzed was relatively small and the confidence interval around the mean differences probably crosses the decision thresholds

10. Review of harms and toxicity: summary of evidence of safety.

Only one of the included trials reported adverse events in both groups.¹¹ The frequency of adverse events grade 3 and 4 was similar in both arms: ibrutinib plus obinutuzumab and

chlorambucil plus obinutuzumab (RR 0.98, 95% CI 0.82-1.17, low certainty evidence). Common adverse events with ibrutinib included: neutropenia, pneumonia, hypertension, anemia, hyponatremia and atrial fibrillation.

However, recent systematic reviews have linked the use of ibrutinib with an increased risk of hypertension, atrial fibrillation and major bleeding.^{7,8}

The use of ibrutinib (in comparison with regimens without ibrutinib) probably results in 60 more cases of hypertension (95% CI from 20 to 160 more, moderate certainty evidence); 19 more cases of atrial fibrillation (95% CI from 10 to 58 more, high certainty evidence); and 122 more bleeding events (95% CI from 8 fewer to 370 more, moderate certainty evidence).

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Ibrutinib	WITHOUT Ibrutinib	Difference (CI 95%)	
Hypertension 8 RCTs (n= 2,580)	RR 2.82 (1.52-5.22)	107 per 1000	38 per 1000	69 more (20 to 160 more)	⊕⊕⊕○ ^a MODERATE
Atrial fibrillation 8 RCTs (n= 2,580)	RR 4.68 (2.36-9.28)	26 per 1000	7 per 1000	19 more (10 to 58 more)	⊕⊕⊕⊕ HIGH
Major bleeding 4 RCTs (n=1,518)	RR 1.66 (0.96-2.85)	322 per 1000	200 per 1000	122 more (8 fewer to 370 more)	⊕⊕⊕○ ^b MODERATE

Abbreviations: RR: Risk ratio; CI: Confidence interval

- We rated down the certainty of the evidence due to inconsistency. A significant heterogeneity was observed on the meta-analysis ($I^2=66\%$)
- We rated down the certainty of the evidence due to imprecision. The confidence interval around the absolute effects probably crosses the decisions thresholds.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to December 2020 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Center of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also, we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified a total of six studies/reports. Three were cost-effectiveness studies¹⁶⁻¹⁸ and 3 were reports from different agencies.

The first study, was a cost-utility analysis from the Swedish health system perspective in a population of patients with refractory or relapsed chronic lymphocytic leukemia.¹⁶ The study was based on the initial findings of the RESONATE trial, which compared ibrutinib vs the anti-CD20 agent ofatumumab. The authors concluded that ibrutinib was cost-effective in comparison with ofatumumab. However, the incremental cost-effectiveness ratio (ICER) was

around 60.000 euros per quality-adjusted life year (QALY), which is higher than the thresholds most commonly used in European countries.

A second study, was cost-utility analysis from the US Medicare perspective, using ibrutinib as first-line therapy vs obinutuzumab and chlorambucil. In a cohort of patients older than age 65 years without the 17p deletion mutation, the ICER was \$US189.326 per QALY, showing that at the current price, ibrutinib was not a cost-effective alternative.¹⁷

The last study identified was cost-utility analysis from the UK health system perspective in adults with untreated chronic lymphocytic leukaemia. The model compared ibrutinib against obinutuzumab plus chlorambucil, and showed an ICER of £75,648 per QALY, which is over the regular threshold of £20.000- £30.000 and the end-of-life threshold of £50.000. As before, this study also shows that at the current price, ibrutinib may not be a cost-effective alternative.¹⁸

Three agencies, The Canadian Agency for Drugs and Technologies in Health (CADTH, <https://www.cadth.ca>; Canada), The National Institute for Health and Care Excellence (NICE, <https://www.nice.org.uk>; UK) and The Pharmaceutical Benefits Advisory Committee (PBAC, <https://www.pbs.gov.au/pbs/home>; Australia), published a report evaluating ibrutinib. All three recommended covering the medication but only in specific subgroups of patients and with costs that are secret to public.

Summary of Economic Evaluations

Study	Limitations	Description		Cost-effectiveness	Uncertainty
Sorensen SV 2016 ¹⁶	Potentially serious limitations ^a	Model	Three-stage state transition	For Ibrutinib Incremental costs per QALYs gained were 546,904 SEK vs. ofatumumab, 556,976 SEK vs. IO, and 562,450 SEK vs. PC, which is equivalent to €58,911, €59,996, and €60,586 vs. ofatumumab, IO, and PC, respectively	A Deterministic sensitivity Analysis (DSA) was run to explore the impact on results of changes in key parameters. The time horizon and the discount rate shown to be more important. A Probabilistic Sensitivity Analysis (PSA) was also conducted for 1,000 replications. The CEACs show that ibrutinib has a greater than 50% probability of being cost-effective at WTP thresholds higher than 550,000 SEK per QALY vs. ofatumumab a greater than 50% probability of being cost-effective at Willingness-To-Pay (WTP) thresholds higher than 560,000 SEK
		Population	Refractory or relapsed chronic lymphocytic leukaemia		
		Time horizon	30 years		
		Costs	All the items and events that occurred in the trial and clinical guidelines		
		Benefits	Baseline health state utility values were based on an analysis of EQ-5D data from RESONATE. Utility increments due to response to treatment and PFS		
		Perspective	Health system		
		Others	A Swedish study, the country has no threshold		

					per QALY vs. IO and vs. PC.
Study	Limitations	Description		Cost-effectiveness (ICER)	Uncertainty
Barnes,J 2018 ¹⁷	Potentially serious limitations ^b	Model	Discrete-time semi-Markov model comprising	For Ibrutinib as first-line therapy vs obinutuzumab and chlorambucil, ICER was \$US189.326 per QALY	In 1-way sensitivity analyses, the results of altering key model parameters are presented in a tornado diagram. The authors conclude that considering even a threshold of \$US150.000 per QALY, ibrutinib would not be cost-effective in a first-line therapy when compared to obinutuzumab and chlorambucil. This is also shown in the different deterministic sensitivity analysis
		Population	A cohort of patients older than age 65 years without the 17p deletion mutation		
		Time horizon	Lifetime		
		Costs	Drug use, Events, supportive care, additional health cost (not specified)		
		Utilities	Quality-of-life weights for each health state-specific to CLL were derived from a different study that used TTO from the UK		
		Perspective	US Medicare health care perspective		
		Others	In the comparator arm, ibrutinib is used as second-line therapy. Methods, Costs and health outcomes were discounted at 3% annually. Obinutuzumab and chlorambucil are the first line comparator		
Study	Limitations	Description		Cost-effectiveness (ICER)	Uncertainty
Sinha. R 2018 ¹⁸	Potentially serious limitations ^c	Model	Three-state semi-Markov model	The ICER was £75,648, which is over the threshold of £20.000 and the end of life threshold £50.000	Probabilistic sensitivity analyses were performed using the variability around base-case estimates of the model input parameters. In the PSA only at a £100.000 threshold ibrutinib had a 50% of being cost-effective. The authors conclude that the treatment can be cost-effective at certain discount rates
		Population	A sub-population from an open-label phase III trial. 18 years or older untreated chronic lymphocytic leukaemia patients		
		Time horizon	Lifetime		
		Costs	Costs related to medical management required during treatment and follow-up, treatment of adverse-events and end-of-life costs have been included		
		Utilities	TTO UK societal utility values for the different health states associated with CLL		
		Perspective	UK health care system		
		Other	The comparator was obinutuzumab in combination with chlorambucil		

Abbreviations: IO: Idelalisib ofatumumab PC: Physician's choice, TTO: time-trade-off, CLL: Chronic Lymphocytic Leukemia

- There is a high dependency in the overall survival data. The PSA shows relevant results, however, do not compare all the alternatives at the same moment or show the probability of error, and the possible net monetary benefit of the intervention.
- The real effectiveness of the intervention is only until three years, for the lifetime simulation use some no explicit assumptions. The utilities were taken from a UK population, not the USA. Some of the costs are based on expert opinions. The paper did not show a probabilistic sensitivity analysis.
- There is a high dependency in the overall survival as an outcome on the model. The data from the outcomes were only 3 years and some important assumptions were made that could benefit the intervention.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Ibrutinib

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

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Appendix

Appendix 1: Search strategies

Search strategy for randomized trials in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Protein Kinase Inhibitors/
2. ibrutinib.mp.
3. exp Leukemia, Lymphocytic, Chronic, B-Cell/
4. Chronic Lymphocytic Leukemia.mp.
5. randomized controlled trial.pt.
6. random allocation/
7. double-blind method/
8. single-blind method/
9. randomi?ed controlled trial\$.mp.
10. Randomi?ed clinical trial\$.mp.
11. controlled clinical trial.pt.
12. ((singl\$ or double\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp.
13. random\$.mp.
14. placebo\$.mp.
15. cross-over studies.sh.
16. latin square.tw.
17. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animals/ not humans/
19. 17 not 18
20. 1 and 2
21. 3 and 4
22. 19 and 20 and 21

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Protein Kinase Inhibitors/
2. ibrutinib.mp.
3. exp Leukemia, Lymphocytic, Chronic, B-Cell/
4. Chronic Lymphocytic Leukemia.mp.
5. systematic review/
6. meta-analysis/
7. (meta analy* or metanaly* or metaanaly*).ti,ab.
8. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.

9. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
10. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
11. cochrane.jw.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 or 2
14. 3 or 4
15. 12 and 13 and 14

Search strategy for economic evaluations in MEDLINE (via OVID)

DATE: December 2020

(Ibrutinib OR kinase inhibitors)

AND

("Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh] OR chronic lymphocytic leukaemia)

AND

(Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab])

Search strategy for economic evaluations in EMBASE (via OVID)

DATE: December 2020

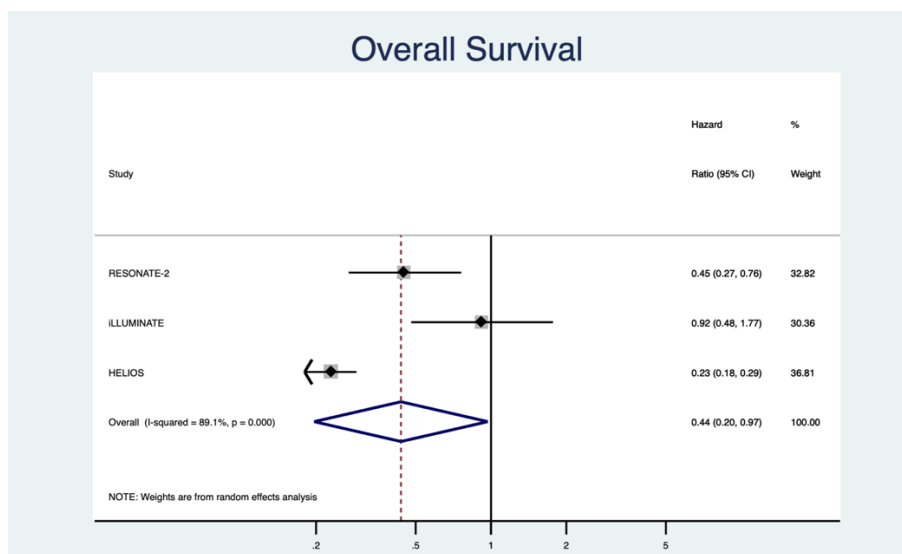
Ibrutinib OR ibrutinib.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, tc, id, tm, mh]

chronic lymphatic leukemia/

(Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/)

Appendix 2: Forest plots

Ibrutinib as a first or second line of treatment in patients with chronic lymphocytic leukaemia - Overall survival.



Ibrutinib as a first or second line of treatment in patients with chronic lymphocytic leukaemia - Progression Free Survival

