# NEW APPROACH TO BUDGET IMPACT ANALYSIS – IBRUTINIB IN TREATMENT OF RELAPSED/REFRACTORY CLL PATIENTS IN THE CZECH REPUBLIC

Přibylová L.[1], Pásztor B.[1], Veselá Š.[2], Vyhnánková M.[2], Dolečková J.[1], Duba J.[1], Kolek M.[1]

1) OAKS Consulting s.r.o. Czech Republic 2) Janssen – Cilag s.r.o. Czech Republic

## OBJECTIVES

Chronic lymphocytic leukemia (CLL) is a life-threatening disease causing formation of cytopenia and reduced immunoglobulin production. CLL represents 25 to 30% of all leukemia and is thus the most common type of adult leukemia in the Western countries (1; 2). Prevalence in Europe is estimated at 27 cases per 100,000 people (3). Incidence of CLL in Europe is about 4.92 cases per 100,000 persons per year, but significantly varies in different parts of the continent (4). Nearly 70% of newly diagnosed patients are aged 65 years or more thus CLL affects mostly older patients.

Median age of newly diagnosed patients is 72 years (5; 6). Current standard of care does not provide patients with sufficient response to treatment, progression free period and overall survival.

**Ibrutinib is an oral, first-in class once-daily Bruton's tyrosine kinase inhibitor approved for treatment of relapsed/refractory (R/R) CLL. The aim of this paper was to estimate the 5-year budget impact of ibrutinib in the treatment of R/R CLL in the Czech Republic from a payer's perspective and to show ibrutinib's benefits.**

## METHODS

**Budget impact analysis (BIA) was performed from the healthcare payers' perspective. A patient-flow model was developed based on real-world data from the University Hospital Brno** (7).

It was assumed that this patient population represents approximately 25% of all CLL patients in the Czech Republic and **number of patients was extrapolated accordingly**. The estimated number of patients starting treatment in all lines of CLL treatment is 524 per year.

The structure of current treatment mix used in the budget impact model was also based on data from the University Hospital Brno (7). Only the most common and reimbursed treatment regimens of R/R CLL were considered and its use was recalculated to form 100 % of treatments. It is FCR – fludarabine + cyclophosphamide + rituximab (82 %) and BR – bendamustine + rituximab (18 %).

Basic idea of the BI model was the construction of a Markov-state structure (see figure 2). Three health states in line with real clinical practice of R/R CLL treatment in the Czech Republic were considered:

- treatment (patient meets the criteria for treatment initiation);
- without treatment (patient does not meet the criteria for treatment initiation);
- death.

Figure 1 • Real-world CLL R/R patient population structure

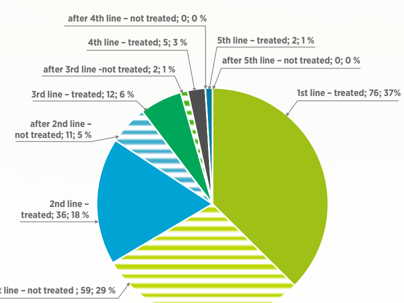
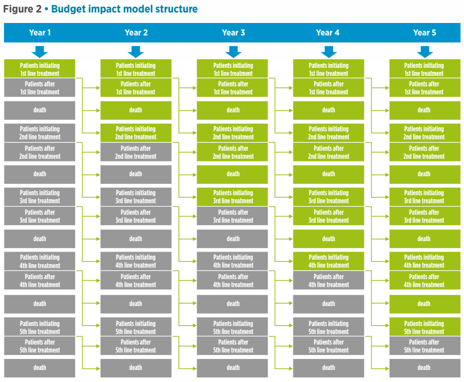



Figure 2 • Budget impact model structure




**The model works with yearly probabilities of relapse and death calculated from real-world data.** It was assumed that each patient can be in each year of the modelling exactly in one health state. This was a simplistic assumption of the BI model.

Yearly transition probabilities were assumed to be constant in time. This assumption was adopted as only cross-sectional data for the period 2009–2015 (7), not time-dependent data for specific cohorts of patients initiating treatment in each year, were available. Thus it was not possible to make conclusions about changes of the transition probabilities in time.

Exponential distribution was used to model disease progression probabilities. Exponential survival curve construction was based on the medians of time between initiating subsequent treatment lines which were available from real-world data analysis (7). Median times between initiating each pairs of subsequent treatment lines and calculated yearly transition probabilities are summarized in Table 1.

Table 1 • Median times between treatment line initiation based on real-world data

| | Median time (months) | Annual probability of initiating next treatment line |
|---|---|---|
| From initiation of 1st line Tx to 2nd line Tx | 25,7 | 27,6 % |
| From initiation of 2nd line Tx to 3rd line Tx | 13,7 | 45,5 % |
| From initiation of 3rd line Tx to 4th line Tx | 2,30 | 97,3 % |
| From initiation of 4th line Tx to 5th line Tx | 2,70 | 95,4 % |

Table 2 • Resulting transition probabilities between treatment lines for Standard of Care based on RWD

| | 1st line | 2nd line | 3rd line | 4th line | 5th line | death |
|---|---|---|---|---|---|---|
| 1st line | 49,1 % | 18,8 % | 0,0 % | 0,0 % | 0,0 % | 32,1 % |
| 2nd line | 0,0 % | 34,3 % | 28,6 % | 0,0 % | 0,0 % | 37,0 % |
| 3rd line | 0,0 % | 0,0 % | 1,6 % | 57,9 % | 0,0 % | 40,5 % |
| 4th line | 0,0 % | 0,0 % | 0,0 % | 1,5 % | 31,1 % | 67,4 % |
| 5th line | 0,0 % | 0,0 % | 0,0 % | 0,0 % | 1,0 % | 99,0 % |
| Death | 0,0 % | 0,0 % | 0,0 % | 0,0 % | 0,0 % | 100,0 % |

Another assumption of the BI model was to preserve stable structure of R/R CLL population (as stated in (7)) in the model. Disease progression probabilities were calibrated to find balance between real and modelled proportions of the population treated in each treatment line and between real modelled times between each pairs of subsequent treatment lines. Calibration of the transition probabilities was provided by MS Excel Solver using a linear model. Resulting transition probabilities used in BI model are listed in Table 2.

**The BI model using these calibrated probabilities keeps a stable structure of patient population corresponding with the real-world data** (7).

After inclusion of ibrutinib to the treatment mix the above described structure of R/R CLL population will change significantly because of differences in progression-free survival (PFS) and overall survival (OS) between current treatment options (median times between subsequent treatment line initiations on current treatment mix are shorter than PFS of ibrutinib). PFS and OS of ibrutinib were based on clinical study of ibrutinib in the R/R setting (8). Median PFS of ibrutinib was 31.6 months, median OS was not reached. OS curve was modelled using best fit estimation by Weibull distribution. Median OS was estimated at 70.9 months.

Additionally, ibrutinib is administered until disease progression, not only over several cycles of limited duration as the vast majority of current standard of care. For this reason, ibrutinib treatment costs were counted continuously until disease progression or death. Given that no data are available for PFS and OS separately in different treatment lines, the same median values of PFS and OS for all lines of treatment with ibrutinib were considered. Annual transition probabilities resulting from median PFS and OS of ibrutinib were the following: probability of death – 11.1 %, probability of continuing treatment – 70.7 %, disease progression (treatment termination) – 18.2 %. 92 % probability of treatment adherence based on ibrutinib clinical study (8) was applied in the model.

Market share of ibrutinib was assumed at 10 % in 2nd line of CLL treatment (after first relapse) and 50 % in further treatment lines during the whole 5-year time horizon of the BI model.

**Drug acquisition costs, hospital admission costs, administration costs, follow-up care and Best Supportive Care (BSC) costs were considered.** Costing was provided based on expert opinion (frequency of resource use) and the list of reimbursed medicines and resource use costs in the Czech Republic (9); (10); (11).

Table 3 • Costs of treatment

| Treatment regimen | Drug costs | Resource use costs – cycle 1 initiation | Resource use costs – cycle 2+ initiation | Administration costs | Resource use costs during treatment | Concommitant medication | Total |
|---|---|---|---|---|---|---|---|
| Ibrutinib | 75 042 EUR | 0 EUR | 0 EUR | 0 EUR | 405 EUR | 0 EUR | **75 447 EUR** |
| FCR | 14 826 EUR | 620 EUR | 184 EUR | 925 EUR | 186 EUR | 109 EUR | **16 851 EUR** |
| BR | 16 432 EUR | 620 EUR | 184 EUR | 1 064 EUR | 186 EUR | 103 EUR | **18 590 EUR** |

## RESULTS

The structure of patient population after ibrutinib entry significantly differs from the current patient flow as it is illustrated in Figure 3.

The numbers in Figure 3 are presented in detail in Table 4. Numbers from Figure 3 are highlighted.

Figure 3 • Patient flow model structure

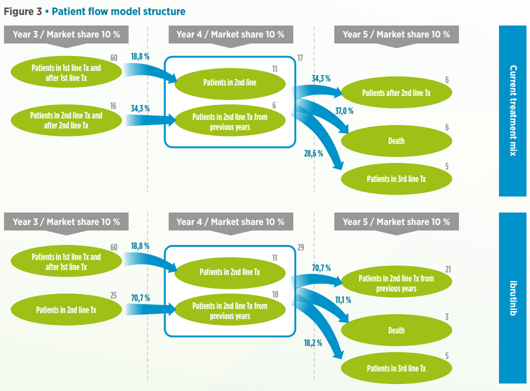



Table 4 • Detailed patient flow

| Row | Parameter | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Source, calculation |
|---|---|---|---|---|---|---|---|
| A | potential patients from 1st line | 597 | 597 | 597 | 597 | 597 | real-world data |
| B | potential patients from 2nd line | 112 | 112 | 112 | 112 | 112 | real-world data |
| C | potential patients from 3rd line | 49 | 49 | 49 | 49 | 49 | real-world data |
| D | potential patients from 4th line | 29 | 29 | 29 | 29 | 29 | real-world data |
| E | potential patients from 5th line | 9 | 9 | 9 | 9 | 9 | real-world data |
| F | ibrutinib market share in 2nd-5th line | | 10 % | 10 % | 10 % | 10 % | assumption |
| G | 1st line patients potentially treated in 2L in T+1 | 60 | 60 | 60 | 60 | | A(t)*F(t+1) |
| **Current treatment mix** | | | | | | | |
| H | annual probability of transition from 1L to 2L | 18,8 % | 18,8 % | 18,8 % | 18,8 % | 18,8 % | real-world data |
| I | 2nd line patients from 1st line in T-1 | | 11 | 11 | 11 | 11 | F(t-1)*G(t) |
| J | annual probability of transition from 2L to 2L | 34,3 % | 34,3 % | 34,3 % | 34,3 % | 34,3 % | real-world data |
| K | 2nd line patients from 2nd line in T-1 | | 4 | 5 | 6 | 6 | L(t-1)*J(t) |
| L | all patients treated in 2nd line | 11 | 15 | 16 | 17 | 17 | I(t)+H(t) |
| M | probability of death in 2nd line | 37,0 % | 37,0 % | 37,0 % | 37,0 % | 37,0 % | real-world data |
| N | deaths after 2nd line Tx | | 6 | 6 | 6 | 6 | L(t)*M(t) |
| O | annual probability of transition from 2L to 3L | 28,6 % | 28,6 % | 28,6 % | 28,6 % | 28,6 % | real-world data |
| P | patients treated in 3rd line | | 3 | 4 | 5 | 5 | L(t-1)*O(t) |
| **Ibrutinib** | | | | | | | |
| Q | annual probability of transition from 1L to 2L | 18,8 % | 18,8 % | 18,8 % | 18,8 % | 18,8 % | real-world data |
| R | 2nd line patients from 1st line in T-1 | | 11 | 11 | 11 | 11 | F(t-1)*G(t) |
| S | annual probability of transition from 2L to 2L | 70,7 % | 70,7 % | 70,7 % | 70,7 % | 70,7 % | Byrd et al., 2014 [8 |
| T | 2nd line patients from 2nd line in T-1 | | 8 | 14 | 18 | 21 | U(t-1)*S(t) |
| U | all patients treated in 2nd line | 11 | 19 | 25 | 29 | 32 | R(t)+T(t) |
| V | probability of death in 2nd line | 11,1 % | 11,1 % | 11,1 % | 11,1 % | 11,1 % | Byrd et al., 2014 [8] |
| W | deaths after 2nd line Tx | | 2 | 3 | 3 | 3 | U(t)*V(t) |
| X | annual probability of transition from 2L to 3L | 18,2 % | 18,2 % | 18,2 % | 18,2 % | 18,2 % | Byrd et al., 2014 [8] |
| Y | patients treated in 3rd line | | 2 | 3 | 5 | 5 | U(t-1)*X(t) |
| | all patients treated in 3rd line | 24 | 40 | 51 | 58 | 63 | calculation as in row Q-Y |
| | all patients treated in 4th line | 14 | 18 | 19 | 20 | 21 | calculation as in row Q-Y |
| | all patients treated in 5th line | 5 | 5 | 4 | 3 | 3 | calculation as in row Q-Y |
| **Treatment mix after ibrutinib entry without ibrutinib** | | | | | | | |
| Z | potential patients from 2nd line | 101 | 101 | 101 | 101 | 101 | B-U |
| | all patients treated in 2nd line | 11 | 19 | 25 | 29 | 32 | calculation as in row Q-Y |
| | all patients treated in 3rd line | 24 | 40 | 51 | 58 | 63 | calculation as in row Q-Y |
| | all patients treated in 4th line | 14 | 18 | 19 | 20 | 21 | calculation as in row Q-Y |
| | all patients treated in 5th line | 5 | 5 | 4 | 3 | 3 | calculation as in row Q-Y |

**Net budget impact of ibrutinib in R/R CLL in first year was estimated at EUR 1.116 mil. which represents 0.009 % of the national health care expenditure budget and 0.118 % of the oncology budget. Cumulative budget impact during five years was estimated at EUR 23.786 mil. which is 0.034 % of the national health care expenditure budget and 0.368 % of the oncology budget. Over a 5-year period, 222 patients will be treated with ibrutinib. Of these, 149 patients (67 %) would remain alive after 5 years. Without ibrutinib, only 75 patients (34 %) would remain alive after 5 years. Total number of treatments administered in each year and detailed results are presented in** Table 5.

**Graphical representation of the development of ibrutinib budget impact in time in the Czech Republic is provided in** Figure 4.

In order to determine parameters with the greatest influence on the BIA outcomes deterministic sensitivity analysis (DSA) was performed where changes of ± 25 % of model parameters were applied.

Minimum and maximum values of BIA are illustrated in Figure 6. The interval of ibrutinib budget impact stated by DSA in first year of BIA is between 612,035 EUR and 1,639,810 EUR.

Table 5 • BIA results

| Intervention | Item | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| ibrutinib | Drug costs | 2 055 550 | 4 787 530 | 6 257 658 | 7 204 545 | 7 860 840 |
| | Other costs | 11 098 | 25 847 | 33 785 | 38 897 | 42 440 |
| | **Overall costs** | **2 066 647** | **4 813 377** | **6 291 442** | **7 243 442** | **7 903 280** |
| | Number of treated patients | 55 | 82 | 99 | 110 | 118 |
| Treatment mix without ibrutinib | Drug costs | 2 190 221 | 2 162 269 | 2 240 423 | 2 319 914 | 2 384 056 |
| | Other costs | 312 488 | 306 183 | 316 429 | 327 456 | 336 552 |
| | **Overall costs** | **2 502 710** | **2 468 452** | **2 556 852** | **2 647 369** | **2 720 608** |
| | Number of treated patients | 144 | 143 | 148 | 153 | 157 |
| **Overall number of treated patients** | | **199** | **224** | **246** | **263** | **276** |
| **Overall costs** | | **4 569 357** | **7 281 829** | **8 848 295** | **9 890 811** | **10 623 888** |
| Current treatment mix | Drug costs | 3 018 656 | 3 017 582 | 3 017 040 | 3 016 768 | 3 016 633 |
| | Other costs | 424 779 | 424 623 | 424 544 | 424 505 | 424 485 |
| | **Overall costs** | **3 443 435** | **3 442 205** | **3 441 584** | **3 441 273** | **3 441 118** |
| | **Number of treated patients** | **199** | **199** | **199** | **199** | **199** |
| | **Budget impact** | **1 125 922** | **3 839 624** | **5 406 711** | **6 449 538** | **7 182 770** |

Figure 4 • Budget impact development in time

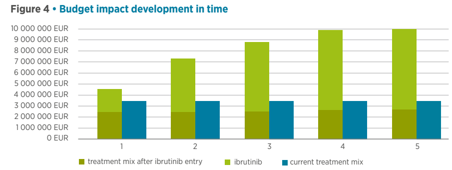



Figure 5 • Comparison of the proportions of populations alive during 5-year horizon

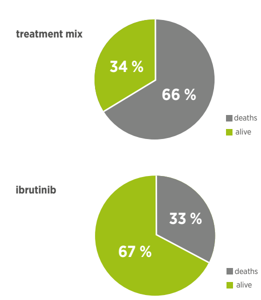
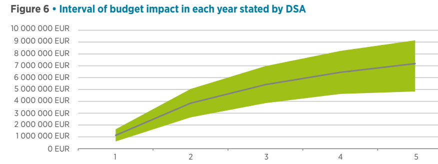
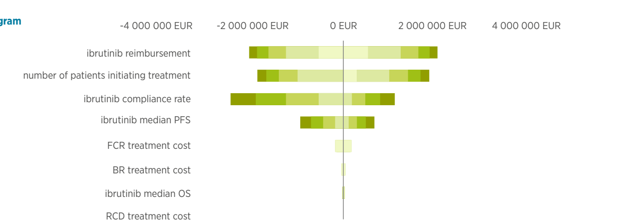



Figure 6 • Interval of budget impact in each year stated by DSA




For a more detailed comparison of the influence of each parameter BIA outcomes a tornado diagram was constructed (Figure 7). The graph shows the absolute difference relative to the baseline scenario of BIA in each year. The lightest colour on the chart shows the influence in year 1 while the darkest expresses year 5. When comparing the variance in year 5, the graph shows that the greatest impact on the BI have the following parameters: cost of ibrutinib treatment, the number of patients initiating treatment and compliance rate.

Figure 7 • Tornado diagram




## CONCLUSIONS

**Ibrutinib treatment is associated with significantly prolonged survival, decreased risk of progression and higher total costs, largely due to ibrutinib continuous administration which enables patients to remain much longer in progression-free state. CLL is an orphan indication and Ibrutinib's budget impact in the Czech Republic is negligible compared to total healthcare or oncology expenditures.**

Novel approaches of budget impact modelling (including real-world data and transition-state modelling) provide more reliable and more precise budget impact estimation and are thus extremely important for high value drugs where the budget impact is expected to be considerable compared to less effective and more outdated standards of therapy. Proper estimation of patient numbers is critical for payers and manufacturers also as basis for risk sharing negotiations which can speed up the market access process of these high value drugs. Balancing between real-world data and clinical efficacy study outcomes should be a new trend in modelling budget impact of these interventions.

## DISCUSSION

This budget impact model incorporated some assumptions which can increase the uncertainty of the results. These are incorporation of real-world data which were available only in limited quality. A deeper analysis of the real-world data would increase the accuracy of this model. The data could be taken from the whole Czech Republic and instead of time between initiating subsequent treatment lines, dates of disease progressions in separate lines of individual treatments could be analysed.

Also the ibrutinib data could be evaluated separately in specific lines of treatment to get more reliable results.

All of these proposed changes in the input data of this analysis were not available at the time of analysis so these estimated results are the most reliable to date. The model was calibrated to give estimates which correspond to the real world data available at the time of the analysis.

**References: 1. Lamanna, N, Weiss, MA a Dunleavy, K.** Chronic lymphocytic leukemia and hairy-cell leukemia. *Haller DG, Wagman LD, Camphausen KA, Hoskins WJ, editors. Cancer management: a multidisciplinary approach.* 2013. **2. Zelenetz, AD a Gordon, LI.** Non-Hodgkin's lymphomas, version 1.2014. National Comprehensive Cancer Network (NCCN) Guidelines. *Fort Washington, PA National Comprehensive Cancer Network.* 2014. **3. Orphanet.** Prevalence of rare diseases: Bibliographic data. Orphanet Report Series, Rare Diseases collection. [Online] 2012. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=52416. **4.** Sant, M, a další. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 116(19). Epub 2010/07/29 2010, stránky 3724-34. **5. Eichhorst, B, et al.** ESMO Guidelines Working Group. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO.* 2011;22 Suppl 6:vi50-4. 2011. **6. National Cancer Institute.** SEER Cancer Statistics Review, 1975-2010. [Online] 2013. http://seer.cancer.gov/csr/1975_2009_pops09/. **7. University Hospital Brno.** Collection of real world data from University Hospital Brno. 2015. **8. Byrd, JC, a další.** Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med 371(3).* 17. Jul 2014, stránky 213-23. **9. Panel, Expert.** Prim. MUDr. Martin Špaček, MUDr. Peter Turcsányi (FN Olomouc). 2015. **10. SCAU.** List of reimbursed medicinal products - version 1/4/2016. [Online] 2016. http://www.sukl.cz/sukl/seznam-cen-a-uhrad-lp-pzlu-k-1-2-2016. **11. List of reimbursed resource use items. Olomouc : EZ Centrum, 2016. 978-80-905236-0-9.**