PCN155

COST-EFFECTIVENESS ANALYSIS OF BENDAMUSTIN-RITUXIMAB COMPARED TO CHOP-RITUXIMAB IN THE TREATMENT OF INDOLENT FOLLICULAR NON-HODGKIN LYMHOMA IN THE CZECH REPUBLIC

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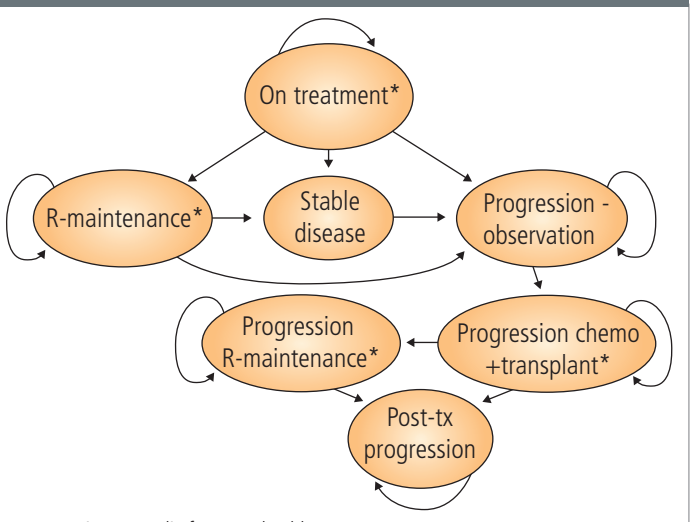
[1]VALUE OUTCOMES, s.r.o.

BACKGROUND and OBJECTIVES

There is RCT phase III clinical evidence that bendamustin-rituximab (B-R) is more effective in terms of progression free survival compared to the standard of care cyclophosphamide-doxorubicin-vincristine-prednisone-rituximab (CHOP-R) in indolent non-Hodgkin lymphoma (iNHL) patients [1].

Based on this RCT, we performed a cost-utility analysis of B-R compared to CHOP-R in the treatment of follicular iNHL (stage III and IV) in the Czech Republic.

Figure 1. Markov model scheme



Notes: Patients can die from any health state.
*Patients in these states may have adverse events.

Table 1. Summary of the model settings

Perspective	Payer's, Public health insurance
Assessed intervention	bendamustin + rituximab
Comparator	CHOP + rituximab
Time horizon	lifetime (99,9% dead after 35 years)
The target population	Adult patients with follicular non-Hodgkin's lymphoma stage 3 and 4 untreated by chemotherapy
Outcomes	Quality-adjusted life year; QALY
Discount rate	3.5% for costs and outcomes
Sensitivity analysis	Probabilistic (PSA), Scenario analyses (SA)

METHODS

We developed a life-time Markov cohort model in TreeAge Pro 2014 with 28-day cycle length and 5 health states, i.e. on treatment, rituximab maintenance (R-M) (90% of patients receive R-M for maximum of 2 years), stable disease, progression and death (see **Figure 1** for the model structure). Additionally, we modelled adverse events (AEs) of the treatment, and four sub-states during progression: 1) one year observation during progression, 2) the next line of treatment during progression (imunochemotherapy/transplantation: CHOP-R 50.0%, CVP-R 25.0%, Fludarabin-R 16.6%, Oxaliplatine-R 8.3% and 15.0% patients receive autologous bone marrow transplant), 3) 2-year R-M period (80% of patients receive R-M in the subsequent line) and 4) post R-M period. This treatment sequence was identified based on discussion with local clinical experts that it maximally reflects the Czech clinical practice [2].

Probability of progression was derived from the Kaplan-Maier curves from RCT [1] and extrapolated using survival analysis. Based on Akaike information criterion, concordance with real clinical practice and visual fit, we chose log-normal distribution for modelling of both interventions' (B-R, CHOP-R) disease progression (**Figure 2**). Probabilities of AEs come from the RCT too [1]. Hazard ratio of 0.55 was applied during stable disease to probability of progression if patient underwent R-M, which is the literature base data – Salles et al. 2010 [3]. Utilities/quality of life (QoL) data were derived from literature and equal to 0.805 (without progression), 0.618 (in progression) [4], 0.018 (an adverse event utility decrement) [5]. Due the lack of data about specific mortality, we use general Czech population mortality adjusted with specific mortality of patients in progressive disease. This approach is in line with previously published models in this disease area [4]. Resource use and costs were calculated from the healthcare payer's perspective, based on expert opinion of Czech hemato-oncology clinical specialists [2] and using the current unit costs based on legislation and code lists. Costs and outcomes were discounted by 3.5% and converted to EUR from CZK using exchange rate of 27.44 CZK/EUR [6]. **Table 1** summarizes the model settings.

Probabilistic sensitivity analysis (PSA) was performed with 1,000 iterations using a willingness to pay (WTP) threshold equal to 3-times GDP per capita in the Czech Republic (40,100 EUR/QALY) [7]; the PSA setting is shown in **Table 2**. Lastly, scenario analyses of key model parameters (discount rate and time horizon) were performed.

Figure 2. Survival analysis (data source: Rummel et al. [1])

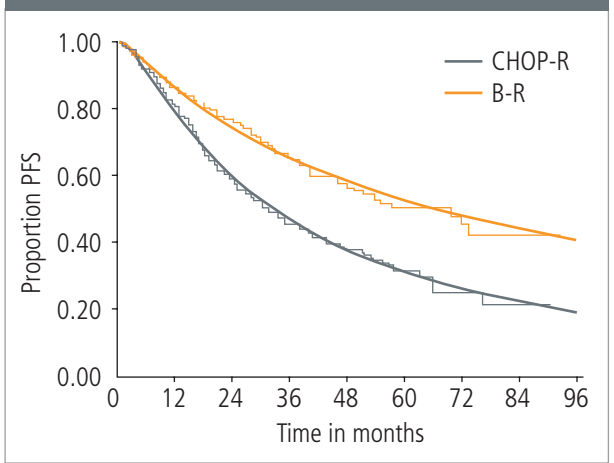


Table 2. Input parameters to PSA

Input	Distribution	Range
Probability of progression	Normal	±10%
Body surface area	Normal	±10%
Probability of AE	Beta	±10%
General Czech population mortality	Beta	±10%
Specific mortality during progression	Beta	±0.0004 [4]
Share of patients on R-M and with transplantation	Beta	±10%
Hazard ratio R-M	Beta	± 0.14 [3]
Utilities	Beta	±10% AE, ±0.056 progression [4], ± 0.018 w/o progression [4]
Costs	Gamma	±10%
Start age	Uniform	±10%

RESULTS

Over a life-time horizon, B-R compared to CHOP-R brings additional 1.21 QALY (7.47 vs. 6.26) and 1.31 LYG (9.74 vs. 8.43), discounted. The incremental total costs were 1,368 EUR (total life time costs for B-R and CHOP-R were 43,080 EUR and 41,712 EUR, respectively). ICUR and ICER thus equal to 1,133 EUR/QALY and 1,044 EUR/LYG (see **Table 3**).

The results of the PSA show that B-R is cost-effective in 100% iterations under the WTP threshold 40,100 EUR; and simultaneously in 99.3% iterations is cost-effective while using threshold equal to 7,300 EUR (see **Figure 3** and **4**).

The results of scenario analyses reveal high robustness of the model results (**Table 4**). When using the discount rate equal to 0% and 5%, the ICUR was equal to 567 and 1,466 EUR/QALY, respectively. When using the time horizon equal to 20 and 10 years, the ICUR was equal to 1,261 and 2,977 EUR/QALY, respectively.

Figure 3. Cost-effectiveness acceptability curve

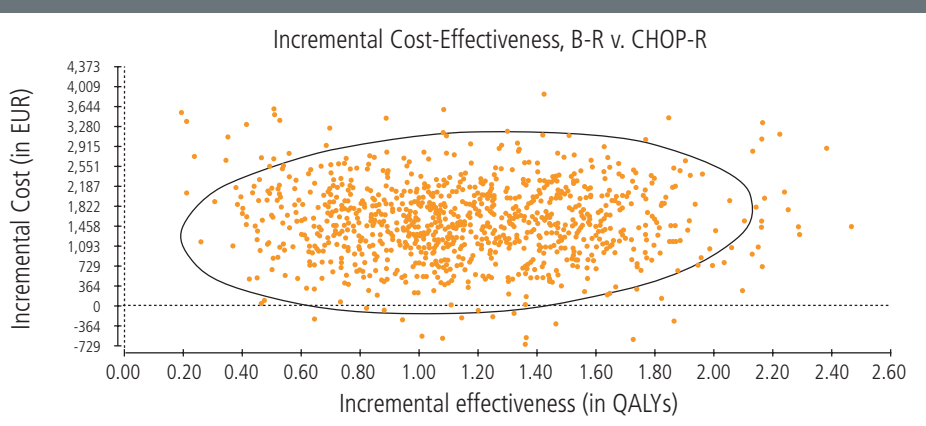
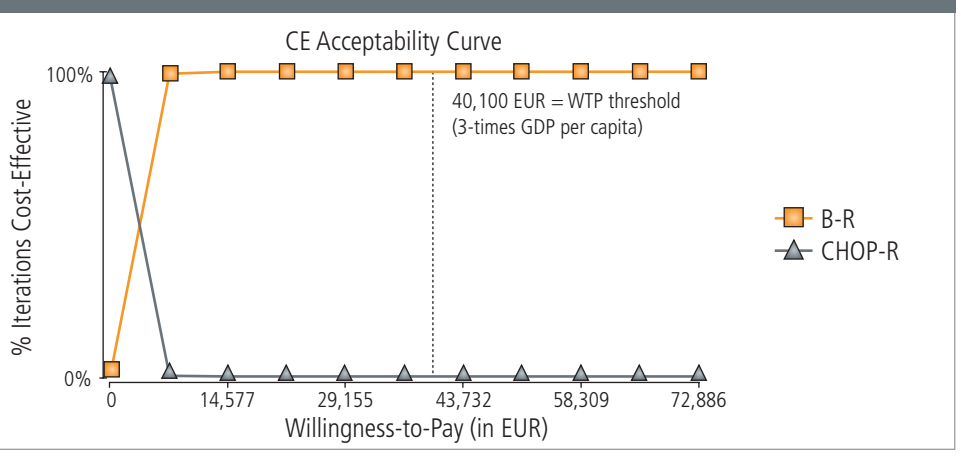


Figure 4. Cost-effectiveness acceptability curve



CONCLUSIONS

Intervention of B-R proved that it is a highly cost-effective therapy in patients with follicular iNHL stage III and IV in the Czech Republic. The higher costs of initial bendamustin treatment are in the long-term horizon offset by substantial savings of progression costs. There is 100% probability of B-R being cost-effective at the selected WTP threshold (3-times GDP per capita). Consequently, the scenario analysis confirmed the results from the base-case scenarios when the changes in key parameters changed the final ICUR result only very slightly.

The limitation of our analysis could be the absence of the Czech local utility data, as the UK published QoL data were used as the proxy. On the other hand, the results are still more than positive in terms of the cost per LYG.

Table 3. The results of cost-effectiveness analysis, base-case

	B-R	CHOP-R	Incremental
Total lifetime costs (in EUR)	43,084	41,715	1,368
Medication costs (B-R, CHOP-R)	14,798	10,180	4,617
Costs of AE of imunochemotheraphy	451	759	-308
Other care during the initial imunochemotherapy (B-R, CHOP-R)	3,651	3,699	-47
Total costs of imunochemotherapy*	18,900	14,638	4,262
Costs of rituximab maintenance therapy	14,648	14,208	440
Costs of PFS state	720	478	242
Costs of progression (including chemotherapy, transplantation)	8,813	12,386	-3,574
LYG	9.74	8.43	1.31
QALY	7.47	6.26	1.21
ICER (CZK/LYG)			1,044
ICUR (CZK/QALY)			1,133

*The sum of costs of initial imunochemotherapy (B-R, CHOP-R), AE of imunochemotherapy and other care during initial immunochemotherapy.

Table 4. The results of scenario analysis

	Incremental QALY	Incremental costs (EUR)	ICUR (EUR/QALY)
Discount rate; 0%	1.92	1,091	567
Discount rate; 5%	1.01	1,479	1,466
Time horizon: 20 years	1.03	1,300	1,261
Time horizon: 10 years	0.45	1,343	2,977

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[2] Expert panel conducted for the purposes of the model, available on request.
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[6] Czech National Bank. Average from the respective period (January-May 2014). Available online on [https://www.cnb.cz/cs/financni_trhy/devizovy_trh/kurzy_devizoveho_trhu/prumerne_mena.jsp?mena=EUR] to 6th October 2014.
[7] State Institute of Drug Control (SÚKL) recommends, based on WHO recommendation, using 3-times GDP per capita as a willingness to pay threshold (see http://www.sukl.cz/file/73935_1_1/, translation available on request).

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