COST-EFFECTIVENESS OF ZANUBRUTINIB VERSUS IBRUTINIB IN ADULT PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

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INTRODUCTION

- Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoma, commonly treated with rituximab-based regimens or Bruton tyrosine kinase inhibitors (BTKi)
- In June 2020, the European Medicines Agency accepted a marketing authorization application for Zanubrutinib (Brukinsa®), an orally administered BTK inhibitor, for the treatment of adult patients who have received at least one prior therapy or as first-line treatment for patients unsuitable for chemoimmunotherapies, based on the results of the ASPEN trial (NCT03053440) in which adult patients with WM were randomized to zanubrutinib or ibrutinib.

OBJECTIVE

- This analysis aimed to assess the cost-effectiveness of zanubrutinib versus ibrutinib in patients who have received ≥1 prior therapy or as first-line treatment for patients unsuitable for chemoimmunotherapies

METHODS

- A 3-state (pre-progression, post-progression, and death) partitioned survival model (PSM) was used to estimate the life years (LYs), quality-adjusted life years (QALYs), and costs for each treatment over a 30-year lifetime horizon
- The overall survival (OS), progression-free survival (PFS), and time-to-discontinuation (TTD) were based on the ASPEN trial data (data cut: August 2019)
- OS, PFS, and TTD curves were fitted using six parametric distributions (exponential, Weibull, Gompertz, gamma, log-logistic and log-normal) to extrapolate long-term survival outcomes. Selection of the parametric models for each outcome and treatment was based on assessments of 1) the proportional hazard assumption, 2) goodness-of-fit, and 3) clinical plausibility of extrapolated mean OS and associated hazard patterns (based on literature and US clinical expert input) and the alignment between PFS and TTD
- The OS and PFS curves were applied to determine the proportion of patients in each health state (pre-progression, post-progression and death). The TTD curve was used to estimate the total drug costs
- Background US mortality was accounted for in the model such that the mortality rates for the modelled population should not be lower than the mortality rates for the US general population
- Costs included drug acquisition, adverse event (AE) management routine care and terminal care, reported in 2020 US dollars. Drug wholesale acquisition costs were obtained from RED BOOK Online. Unit costs for the management of AEs and resource use were obtained from Healthcare Cost and Utilization Project (HCUPnet) database. The terminal care cost was obtained from published literature (***Table 1***)
- Utilities were based on the ASPEN EQ-5D data and assumptions (***Table 1***). Incidences of AE were obtained from the ASPEN trial
- All outcomes were discounted at 3% annually
- Sensitivity analyses were conducted to evaluate the impact of parameter uncertainty or structural uncertainty on model outcomes, including one-way sensitivity analyses, (OWSA), probabilistic sensitivity analyses (PSA) with 1000 runs, and scenario analyses

METHODS (CONT'D)

Table 1. Key model inputs

Parameter	Value	Reference
Key cost inputs		
Drug acquisition, zanubrutinib	$12,935.00 per 120 80mg capsules	RED BOOK Online (2020)[1]
Drug acquisition, ibrutinib	$12,966.10 per 28 420mg tablets	RED BOOK Online (2020)[1]
Routine care, pre progression (per month)	$3,155.74	Lyengar et al. (2019)[3]
Routine care, post progression (per month)	$6,490.76	Lyengar et al. (2019)[3]
Terminal care (one-time cost)	$102,517.29	Chastek et al. (2012)[2]
Utility inputs		
Progression-free survival	0.791	APSEN trial EQ-5D data
Post-progression survival	0.691	Assuming disutility of 0.100 due to progression

RESULTS

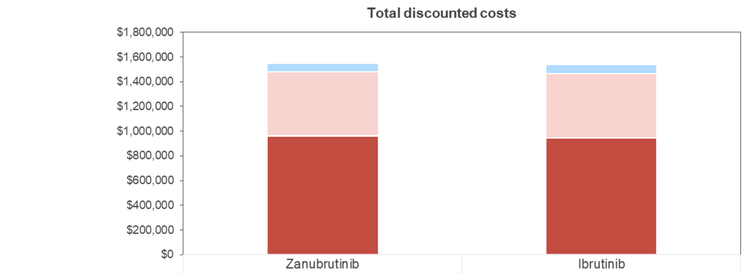
- In the base case analyses using the dependent exponential model for all outcomes over a 30-year time horizon, zanubrutinib led to 0.94 LY and 0.84 QALY gained with an additional total cost of $11,132, leading to an incremental cost-effectiveness ratio (ICER) of $13,205 per QALY gained (***Table 2***)
- The additional cost was primarily driven by patients staying on zanubrutinib treatment longer as zanubrutinib has longer time to treatment failure. However, this is partially offset by zanubrutinib's lower monthly drug acquisition, reduced cost of disease management (–$2,935) and other direct costs (–$2,964) compared to ibrutinib (***Figure 1***)

Table 2. Cost-effectiveness model results, base case analysis

Outcome	Zanubrutinib	Ibrutinib	Incremental
Total LYs (discounted)	11.33	10.39	0.94
Total QALYs (discounted)	8.75	7.90	0.84
Total costs (discounted)	$1,547,630	$1,536,498	$11,132
Incremental cost per QALY gained	-	-	$13,205

Abbreviations: LYs, life years; QALYs, quality-adjusted life years

Figure 1. Total discounted costs for zanubrutinib and ibrutinib by cost category, base case analysis



	Zanubrutinib	Ibrutinib
Other direct costs	$68,668	$71,632
Total disease management	$516,094	$519,029
Adverse events	$3,983	$3,480
Total drug acquisition	$958,885	$942,356
Total discounted costs	$1,547,630	$1,536,498

RESULTS (CONT'D)

- The results of OWSA showed that ICER was most sensitive to the monthly costs of routine care. The PSA showed that the mean probabilistic ICER was $16,804, and that the probability of zanubrutinib being cost-effective was 61% at a willingness-to-pay threshold of $100,000 per QALY gained
- Varying the time horizon to 5, 10, or 15 years consistently led to zanubrutinib being dominant (i.e., greater QALYs but lower costs) (***Table 3***)

Table 3. Cost-effectiveness model results, scenario analyses

Outcome	Incremental LYs (discounted)	Incremental QALYs (discounted)	Incremental costs (discounted)	Incremental cost per QALY gained
5 years	0.14	0.13	-$28,238	Dominant
10 years	0.44	0.39	-$18,443	Dominant
15 years	0.71	0.63	-$3,886	Dominant

Abbreviations: LYs, life years; QALYs, quality-adjusted life years

CONCLUSION

- **Zanubrutinib** appears to be **cost-effective compared with ibrutinib** for the treatment of patients with WM in the United States

DISCUSSION

- The main limitation of the economic analysis lies with the immaturity of the survival data from the relatively short follow-up in ASPEN trial, which causes uncertainties of the results of long-term survival extrapolation. To mitigate the limitation, clinical experts were consulted as to the clinical plausibility of the extrapolated survival
- Updated analysis is warranted upon availability of long-term survival data

REFERENCES

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