Economic evaluation of acalabrutinib for previously-treated patients with mantle cell lymphoma in Mexico

M. Naranjo[1], R. Rubio Ponce[1]
[1]AstraZeneca S.A de C.V ("AstraZeneca")

Introduction and objective

Mantle cell lymphoma (MCL) is a type of aggressive B-cell non-Hodgkin lymphoma (NHL). Most patients with this disease are elderly, although it also affects young adults[1]. In 2018, in Mexico, a total of 5,174 new cases of non-Hodking lymphomas and 2,741 deaths due to this disease were reported[2], reflecting the high mortality for this group of patients. Bruton's tyrosine kinase (BTK) inhibitors are the emerging standard treatment for relapsed or refractory (RR) Mantle Cell Lymphoma (MCL). In Mexico, the approved therapies for the treatment of this group of patients are acalabrutinib and ibrutinib. Despite belonging to the same therapeutic family (BTK inhibitors), studies have shown acalabrutinib to be a safer alternative due to high molecular selectivity[3,4].

The objective was to perform an economic evaluation of acalabrutinib use in adult patients with RR MCL who have received at least one previous therapy from the perspective of public health institutions in Mexico.

Methodology

A cost-effectiveness analysis of acalabrutinib compared to ibrutinib was performed using a partitioned survival Markov model consisting of three health states: progression-free survival, post-progression, and death. The proportion of patients in each state was calculated based on parametric distributions fitted independently to PFS data from ACE-LY-004[5] for acalabrutinib and PCYC-1104-CA[6] for Ibrutinib. Based on this and on the number of deaths due to progression, the post-progression survival was constructed for each treatment arm, so that the overall survival is expressed as the sum of the time in the progression-free and post-progression state. Through this model, the Life Years (LYs) Gained were calculated for each of the interventions considering a time horizon of 15 years. The perspective of the public health sector as payer was considered, so only direct medical costs associated with each intervention were calculated, including drug acquisition, adverse events management and subsequent therapies. The cost of treatment considered the usual posology of the interventions according to clinical trials: 100 mg twice a day for acalabrutinib and 560 mg for ibrutinib. The management of adverse events was validated and funded by a panel of experts, as well as the frequency and use of post-progression therapies used in routine clinical practice. Health costs and outcomes were discounted at a rate of 5%, aligned to local guidelines. All cost are expressed in US dollars[7]. Deterministic and probabilistic sensitivity analyses were carried out.

Figure 1: Average total costs per patient

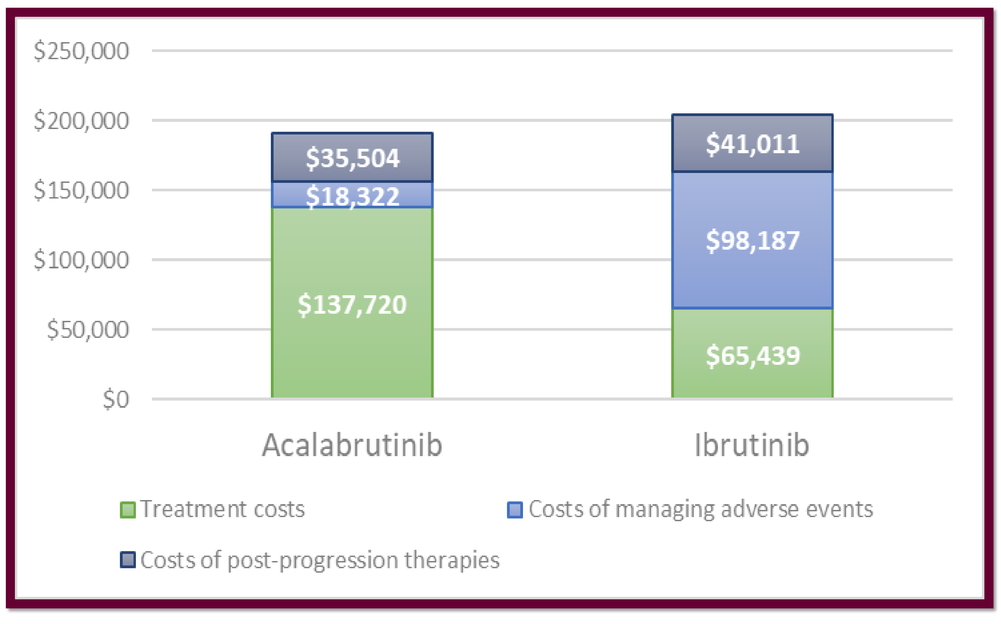


Table 1: Percentage costs for subsequent therapies and adverse events

Treatment	% costs for subsequent therapies and adverse events	Amount
Ibrutinib	68%	$139,198
Acalabrutinib	28%	$53,826
Difference	**40%**	**$85,372**

1. Jurczak, W., Długosz-Danecka, M., & Wang, M. (2019). Acalabrutinib for adults with mantle cell lymphoma. Expert Rev Clin Pharmacol, 12(3):179-187.
2. Globocan. (2018). México globocan 2018. The Global Cancer Observatory. Hendriks, R., Yuvaraj, S., & Kil, L. (2014). Targeting Bruton's tyrosine kinase in B cell malignancies. Nat Rev Cancer, 219-32.
3. Sharman, J. P., Egyed, M., Jurczak, W., Skarbnik, A., Pagel, J. M., Flinn, I. W., Kamdar, K. (2020). Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised controlled, phase 3 trial. Lancet.
4. Barf, T., Covey, T., Izumi, R., van de Kar, B., Gulrajani, M., van Lith, B., Kaptein, A. (2017). Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS.
5. Wang, M., & et al. (2018). Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet , 391: 659–67.
6. Wang, M. L., Blum, K. A., Martin, P., Goy, A., Auer, R., Kahl, B. S., Romaguera, J. E. (2015). Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results.
7. Exchange rate from peso to dollars. Cut to June 8, 2021. https://www.banxico.org.mx/tipcamb/main.do?page=tip&idioma=sp.
8. Salem, J., Manouchehri, A., Bretagne, M., Lebrun-Vignes, B., Groarke, J., Johnson, D., Moslehi, J. (2019). Cardiovascular Toxicities Associated With Ibrutinib. Journal of the american college of cardiology.
9. Berglöf, A., Hamasy, A., Meinke, S., M, P., Krstic, A., Mansson, R., Smith, C. (2015). Targets for Ibrutinib Beyond B Cell Malignancies. Scandinavian Journal of Immunology.

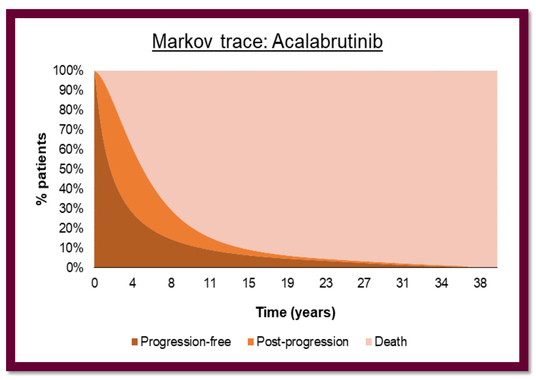
Results

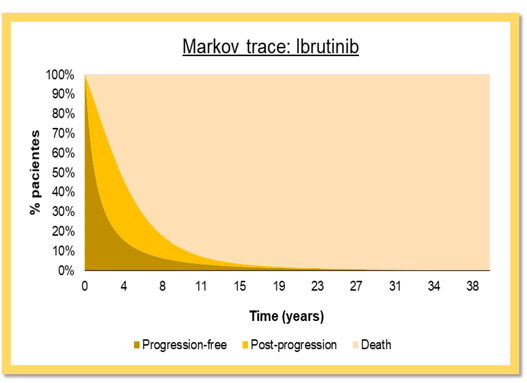
The cost-effectiveness analysis showed that the use of acalabrutinib is associated with a gain of 4.95 LYs (of which 2.86 are progression-free life years), this, compared to 3.88 LYs (of which 1.91 are progression-free life years) that showed ibrutinib means an additional gain of 1.07 LYs (Table 2). In terms of costs, acalabrutinib generates savings due to a lower incidence of grade 3 or higher adverse events, presumably due to the higher selectivity of the molecule. Savings amount to $79,865 per patient. Cost analysis showed that, the use of acalabrutinib generates a total cost of $ 191,546 per patient versus $ 204,636 per patient generated with ibrutinib, which implies a saving of $13,090 per patient, which, in combination with the superiority in efficacy of acalabrutinib, leads to in a negative incremental cost-effectiveness ratio of -$12,233.

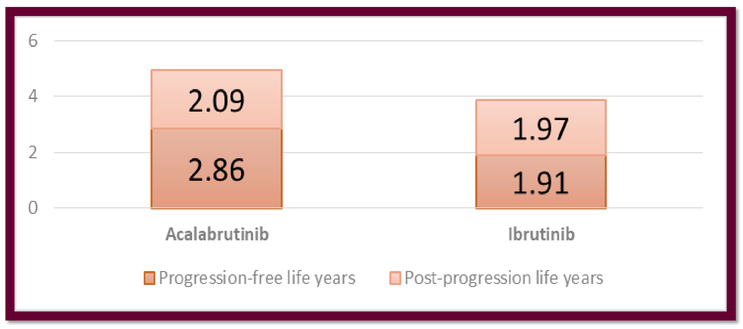
Table 2: Cost Effectiveness Analysis Results

Treatment	Average cost per patient	Incremental cost	LYs	Incremental LYs	ICER
Ibrutinib	$204,636		3.88		
Acalabrutinib	$191,546	-$13,090	4.95	1.07	$-12,233

Figure 1: Markov traces







Conclusions

Given a willingness-to-pay (WTP) threshold of $8,472 in Mexico, acalabrutinib compared to ibrutinib is a dominant alternative in the treatment of patients with RR MCL who have received at least one previous therapy due to a better clinical effectiveness profile and savings generated from reduced costs of managing adverse events.

Discussion and limitations

One of the main limitations of the study is the immaturity of the overall survival results (with a median not reached with acalabrutinib). In this regard, a model was built to estimate overall survival from deaths and progression-free survival curves, due to the maturity of the data in both studies when this measure of efficacy was considered. The dominance of acalabrutinib stems from the greater economic burden of managing adverse events in the ibrutinib arm, which is consistent with real-life studies that have reported serious and occasionally fatal cardiac adverse events in patients exposed to ibrutinib, including supraventricular arrhythmias, central nervous system hemorrhagic events, heart failure, and ventricular arrhythmias[8]. A possible cause of these AEs is off-target drug interactions by the ibrutinib mechanism of action, since in addition to inhibiting BTK, ibrutinib is a potent covalent inhibitor of other kinases, including lymphoid tyrosine kinase B, the receptor for the factor of epidermal growth, interleukin-2 inducible T-cell kinase and tyrosine-protein kinase[9]. In contrast, acalabrutinib has been shown to be a more selective molecule[3,4].