Poster Code: EE177

Cost of Adverse Events with the Bruton Tyrosine Kinase Inhibitors Ibrutinib and Acalabrutinib in the First-Line Treatment of Chronic Lymphocytic Leukaemia in Brazil

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Why did we perform this research?

- Bruton tyrosine kinase inhibitors (BTKis) have revolutionised the first-line (1L) treatment of chronic lymphocytic leukaemia (CLL) and are well-established in clinical practice[1,2,3]
- Second-generation BTKis such as acalabrutinib are now available and offer reduced off-target effects compared to the first-generation BTKi, ibrutinib[1]

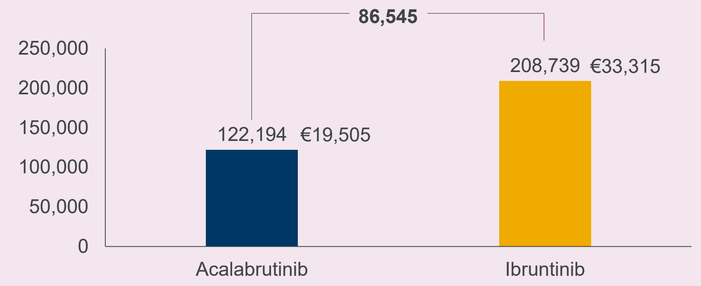
This study assesses the cost of adverse events with acalabrutinib *versus* ibrutinib in 1L treatment of CLL to determine the financial impact of these clinical differences in the Brazilian private healthcare context

Summary

BTKi binding to non-target kinases can result in adverse events; data suggest acalabrutinib may be more specific for BTK than ibrutinib, resulting in a decreased incidence of AEs, including cardiovascular events[1]

The adverse event rates reported in ELEVATE-TN[4] were combined with available cost data to estimate the financial impact on the private healthcare system in Brazil

Results demonstrated savings with acalabrutinib versus ibrutinib (100 patients)



Key takeaways

- Observed differences in the adverse event profile of ibrutinib and acalabrutinib can translate into meaningful differences in healthcare expenditure from the Brazilian private healthcare perspective
- These benefits should be considered alongside related advantages including longer treatment duration[4]

What did we find?

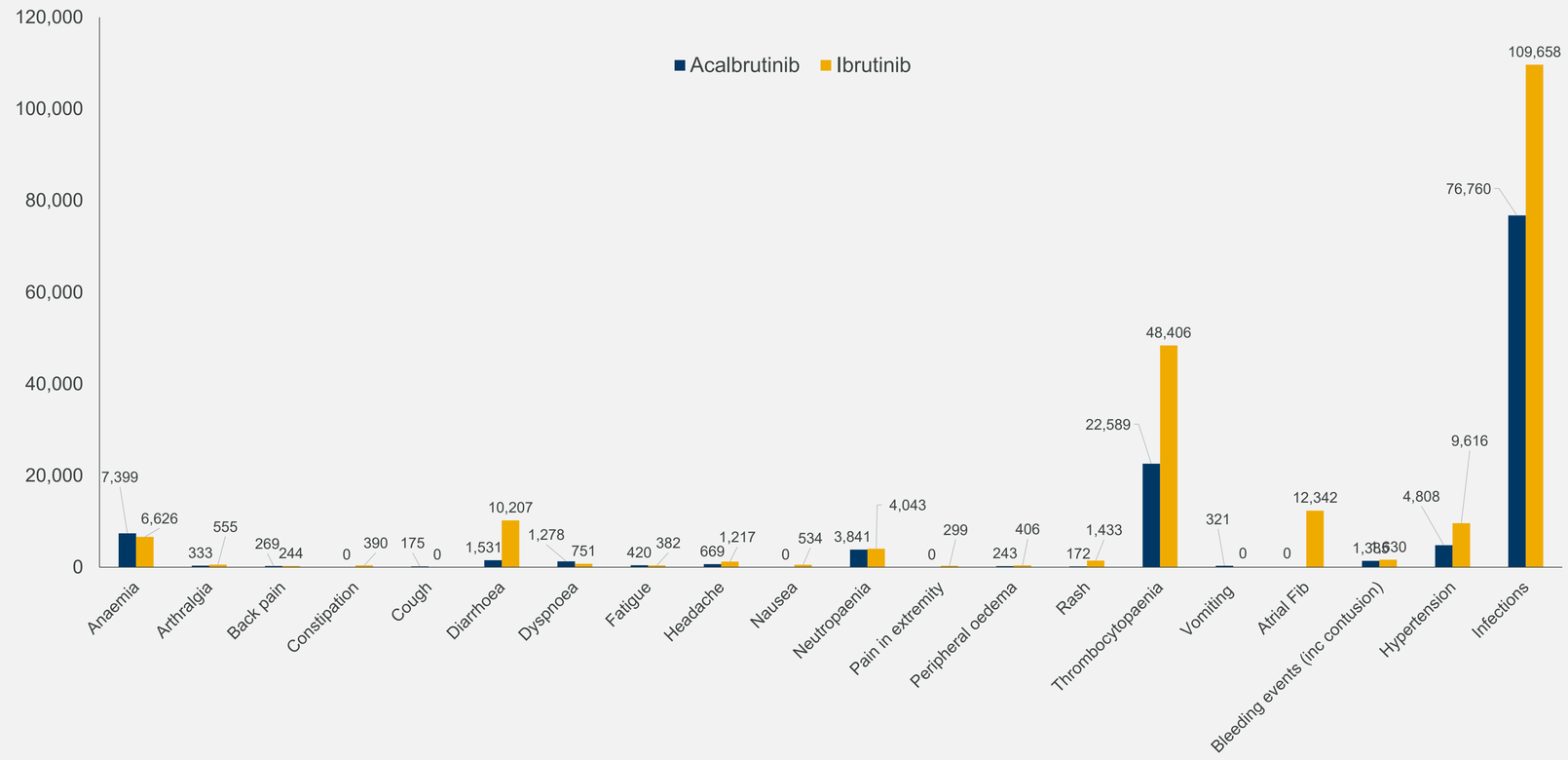
Base case

- Assuming a cohort of 100 patients, the base case analysis showed that the cost of managing AEs with acalabrutinib was R$122,194 (€19,502) *versus* R$208,739 (€33,315) with ibrutinib, a reduction of 41.5% (R$86,545 [€13,813]) in favour of acalabrutinib
  - These savings were primarily driven by the costs of managing atrial fibrillation, thrombocytopaenia, and infections (Figure 1)
  - Savings with acalabrutinib remained evident when adverse events of special interest identified in ELEVATE-TN and other adverse events were considered separately (adverse events of special interest: R$50,292 [€8,027]; other adverse events: R$36,254 [€5,786])

Scenario analysis

- In the scenario analysis, savings with acalabrutinib increased to R$207,904 (€33,181), the cost of managing the adverse events calculated as R$122,194 (€19,502) for acalabrutinib *versus* R$330,097 (€52,683)
  - The increased savings were driven by the higher rates of atrial fibrillation and hypertension for ibrutinib reported in the A041202 trial as compared to RESONATE-02

Figure 1. Estimated costs of managing adverse events per 100 patients



How did we perform this research?

Model inputs – adverse event rates

- The base case considered grade ≥3 AEs and AEs of special interest, as reported in the relevant monotherapy arms of the ELEVATE-TN[5] (acalabrutinib) and RESONATE-02[6] (ibrutinib) trials (Table 1)
  - The median duration of treatment was 27.7 months with acalabrutinib monotherapy[5] and 18.4 months with ibrutinib[6]
  - ELEVATE-TN reported on all AEs that occurred in 10% of patients in any treatment group,[5] whilst RESONATE-02 those reported adverse that occurred in 15% of patients in any treatment group;[6] therefore ELEVATE-TN provided the broadest range of AEs for inclusion
  - ELEVATE-TN[5] also specified and reported on several AEs of special interest that were not recognised as such when RESONATE-02[6] was carried out
- As RESONATE-02[6] did not report on some the AEs included in ELEVATE-TN[5] due to differences in reporting criteria combined with the subsequent recognition of the AEs of special interest, a scenario analysis that uses the A041202 trial[7] as the primary source of data for ibrutinib adverse event rates was carried out (Table 1)
  - The median duration of treatment was 32 months with ibrutinib monotherapy

Model inputs – costs

- The cost of treating AEs was estimated using a micro-costing approach (Table 1)
  - Expected healthcare utilisation to treat a particular AE was identified and validated with clinical experts (this included consideration of medical appointments/consultations, hospitals stay, investigational procedures/tests and clinical interventions)
  - Costs associated with these procedures were extracted from available Brazilian data[8–11]
  - All costs were uplifted to 2025 R$[12]

Table 1. Frequency and costs of included adverse events

Adverse event	Rate all grade ≥3 adverse events			Cost of treatment (2025 R$)
	Acalabrutinib	Ibrutinib (base case)	Ibrutinib (scenario)	
Anaemia	6.7%	6.0%	11.0%	1,104.34
Arthralgia	0.6%	1.0%	1.0%	555.27
Back pain	1.1%	1.0%	1.0%	244.31
Constipation	0.0%	1.0%	0.0%	389.53
Cough	0.6%	0.0%	1.0%	291.62
Diarrhoea	0.6%	4.0%	3.0%	2,551.85
Dyspnoea	1.7%	1.0%	1.0%	751.50
Fatigue	1.1%	1.0%	5.0%	381.83
Headache	1.1%	2.0%	2.0%	608.27
Nausea	0.0%	1.0%	0.0%	534.31
Neutropenia	9.5%	10.0%	15.0%	404.34
Pain in extremity	0.0%	1.0%	1.0%	299.35
Peripheral oedema	0.6%	1.0%	1.0%	405.64
Rash	0.6%	5.0%	5.0%	286.56
Thrombocytopaenia	2.8%	6.0%	6.0%	8,067.66
Vomiting	0.6%	0.0%	0.0%	534.31
Atrial fibrillation*	0.0%	1.5%	9.0%	8,228.03
Bleeding events* (incl contusion)	1.7%	2.0%	2.0%	814.77
Hypertension*	2.2%	4.4%	29.0%	2,185.42
Infections*	14.0%	20.0%	20.0%	5,482.88

*Adverse evens of special interest as identified in ELEVATE-TN

Limitations

- AE rates are drawn from different studies with different reporting thresholds and potentially different patient populations and trial procedures
- Definitive AE costs are lacking in Brazil and costs of management may vary across different hospitals
- Rates of AEs observed in clinical trials may not reflect rates encountered in clinical practice

What are the implications for payors?

The improved safety profile of second- *versus* first-generation BTKis can result in savings in healthcare costs

Adverse event costs should be considered as part of a holistic decision-making process for reimbursement/funding of 1L CLL treatments

Acknowledgments

Financial support for this study was provided by AstraZeneca. All authors contributed to the development of the publication and maintained control over the final content

Disclosures

BRG, IK, and JF employers have received payment from AstraZeneca for work on various projects. MH, CMT, RPPM, MD, SPM, FF and DT are employees of AZ

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Presented at ISPOR Europe 2025, Glasgow, United Kingdom, 9–12 November