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BUDGETARY IMPACT OF VENETOCLAX WITH RITUXIMAB VERSUS IBRUTINIB IN R/R CLL IN THE BRAZILIAN PRIVATE HEALTHCARE SYSTEM

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INTRODUCTION

- CLL is a lymphproliferative disease caracterized by the persistency of a minimum of 5 × 10^9/L type B monoclonal lymphocytes. These lymphocytes can accumulate in periferal blood, lymph nodes, blood marrow and spleen. More frequent in elders and considered a rare disease, CLL has a global incidence between <1 and 5.5 cases per 100,000 inhabitants. (1,2)
- Althought a rare disease, CLL is the most common type of of leukemia in adults, being reponsible for about 32% of total leukemias. (3)
- It is an indolent disease in which about 60% of patients, at the time of diagnosis, may be assymtomatic while the other 40% of patients may have several inespecific clinical and laboratory changes. (4,5)
- The presence of 17p deletion (17p Del), TP53 mutation and IGHV unmutated indicate worse clinical results with fast disease evolution. The 17p Del varies between 30% to 50% in R/R CLL patients. (6)
- A commonly used regimen for chronic lymphocitic leukemia used to be bendamustine in combination with rituximab. Recently novel targeted oral agents, such as venetoclax and ibrutinib, have provited greater survival with modest toxicity. (7)
- Venetoclax is an orally administered potent and selective BH3 mimetic that targets the BCL-2 (B-Cell Leukemia/Lymphoma 2 Gene) inhibitor, exhibiting significant apoptotic activity. While Ibrutinib is an oral covalent inhibitor of Bruton's tyrosine kinase which inhibits B-cell receptor signaling. (7)
- During NICE's appraisal about venetoclax + rituximab its committee stated that venetoclax plus rituximabe (V+R) to have similar, or better, efficacy to ibrutinib and that it was unlikely to be inferior to ibrutinib. (8)
- According to ANS' rol (mandatory list of drugs and procedures) for the private healthcare system, only R/R CLL patients with 17p Del have access to novel oral targeted agends. In which ibrutinib is the only option.

OBJECTIVE

Develop a budget-impact analysis to simulate the financial consequences of incorporating venetoclax in combination with rituximab (V+R) *versus* ibrutinib to the minimum mandatory coverage list of the National Supplementary Health Agency (ANS' rol) for treating adult relapsed or refractory Chronic Lymphocytic Leukemia (R/R CLL) patients in a 5 years-time horizon.

METHODS

- Elegible population for V+R and ibrutinib was calculated based on epidemiological premises. Starting by the total number of adults covereded by health insurance companies (HMOs) in Brazil, according the flow presented on Figure 01, and specified in Table 01.

Figure 1. Flow to define the eligible population for treatment.

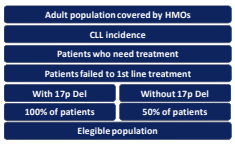


Table 1. Parameters for defining treatment eligible population (2018).

Parameter	Value
HMOs' beneficiaries (≥18 years of age)	36,340,289 (9)
CLL incidence (per 100 thousand inhabitants)	4.7 (10)
Patients who need treatment (no watch & wait indication)	66.7% (11)
Patients who have failed to 1st line treatment	44.7% (12)
Presence of 17p deletion (with 17p Del)	30% (6)
No presence of 17p deletion (without 17p Del)	70% (6)
Patients whithout 17p Del treated with ibrutinib - premise	50%*
Crescimento populacional brasileiro (13)	
2018-2019	0.79%
2019-2020	0.77%
2020-2021	0.74%
2021-2022	0.71%
2022-2023	0.68%

*Market premise

- Based on parameters defined in Table 1, it was calculated the R/R CLL population elegible for treatment with venetoclax + rituximab and ibrutinib (Table 2)

Table 2. Projection of eligible population (2020-2024).

Year	2020	2021	2022	2023	2024
General population	517	521	524	528	531
With 17p deletion	155	156	157	158	159
Without 17p deletion	362	365	367	370	372

- Once ibrutinib is only included for R/R CLL patients with 17p Del in ANS' rol, this analysis has assumed the market premise that only 50% of non-17p Del patients are currently reimbursed by health insurance companies.

Table 3. Projection of eligible population starting treatment (2020-2024).

Year	2020	2020	2020	2020	2020
General population	336	338	341	343	345
With 17p deletion	155	156	157	158	159
Without 17p deletion*	181	182	184	185	186

* 50% of total os patients without 17p Del presented in Table 2.

- A reference scenario was defined in which ibrutinib has 100% market share in R/R CLL patients (Table 4). A projected scenario assumes a gradual market penetration for venetoclax + rituximab, in which V+R reaches 25% market penetration in the end of the first year of incorporation, and finally reaching 100% market share in the fifth year (Table 4).

METHODS (CONTINUED)

Table 4. Market share – reference and projected scenarios.

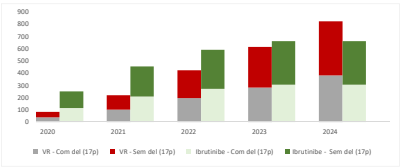
Year	2020	2021	2022	2023	2024
Reference scenario					
Venetoclax	0%	0%	0%	0%	0%
Ibrutinib	100%	100%	100%	100%	100%
Projected scenario					
Venetoclax	25%	40%	60%	80%	100%
ibrutinib	75%	60%	40%	20%	0%

- For all patients starting treatment (Table 3) it was considered full-cost of treatment in the first year for both comaprators. In the following years it was considered that 83% and 86,5% of patients treated in the previous year with V+R and ibrutinib, respectively, remained in tratment in the subsequent year. Theses values of descontinuation were based on the descontinuation rates presented in each respective phase III randomized clinical trial (33% for V+R in 2 years follow-up; and 54% for ibrutinib in 4 years follow-up). It was adopted an anualization of tratment discontinuation rates, meaning 16.5% descontinuation for V+R from year 2020 to 2021 and another 16.5% from 2021 to 2023. For ibrutinib it was assumed yearly discontinuation of 13.5% from 2020 to 2024. (14,15)
- It is important to highlight that V+R offers a fix treatment duration of 24 months after ramp-up dose (total of 25 months), while patients on ibrutinib will remain in therapy until disease progression or unbearable toxicity.
- Tabe 5 presents the cascade of patients in treatment each year.

Table 5. Treated population.

Population	2020	2021	2022	2023	2024
Venetoclax + rituximab	84	206	377	540	717
With 17p Del	39	95	174	249	331
Without 17p Del	45	111	203	291	386
Ibrutinib	252	421	501	502	434
With 17p Del	116	194	231	232	200
Without 17p Del	136	227	270	270	234

Figure 2. Patients treated with V+R and ibrutinib, per year and mutational status.



- Drugs' purchasing costs were based on dosages defined by respective labels and price-reference list, published by the Brazilian Regulatory Agency (ANVISA's list price - PF) with 18% tax (PF18%) over the circulation of merchandise and services (ICMS). Prices are based on April 2019 edition (16).
- Monthly costs are presented in Table 6 and yearly costs in Table 7 (16). A detailed description on V+R and ibrutinib costs can also be found at ISPOR Europe 2019 PCN243 poster.
- Costs were presented in US dollars (USD). Exchange rate was R$3.92 to USD 1.00. It represents the average rate of the last 60 days (07/08/2019 to 09/06/2019).

Table 6. Monthly treatment cost.

Drugs	Dosage Forms	List Price (PF18%)
Venetoclax	1st month (start-kit)	$ 1,899.27
Venetoclax	Following months (maitenance dosage)	$ 8,799.67
Rituximab	1st Cicle: 375 mg/m² (month 1)	$ 2,293.46
	2-6 Cicles: 500 mg/m² (months 2-6)	$ 3,057.94
Ibrutinib	30 days (bottle with 90 tablets)	$ 9,852.72

Table 7. Yearly treatment cost.

	2020	2021	2022	2023	2024
Venetoclax + rituximab	$ 116.279	$ 105.596	$ 8.800	$ -	$ -
Ibrutinib	$ 118.233	$ 118.233	$ 118.233	$ 118.233	$ 118.233

- An additional coverage expansion analysis was developed to assess the cost-relation of V+R *versus* ibrutinib considering the current scenario in which only one therapy (ibrutinib) is offered to 17p Del patients (Table 11), according to current ANS' rol.
- Besides cost parameter, it was considered the avarage duration of treatment for both drugs according to NICE's appraisal of venetoclax + rituximab. According to Nice the average duraation of treatment with ibrutinib was 56 months and 22 months for V+R).
- However, it was adpted a more conservative approach for V+R, assuming 25 months (ramp-up plus 24 months of maintanance) according to product label. Results in Tables 11 and 12.

RESULTS

- Results of budgetary impact analysis estimate resource savings around $164,000 already in the first year with the incorporation of venetoclax + rituximab. In five years resource savings can reach around $56,5 million dollars, being $37 million from R/R CLL patients without 17 Del and $19.5 million from patients with 17p Del (Tables 9, 10 and 11).

Table 8. Budget impact (in USD) – Patients with 17p Del

	2020	2021	2022	2023	2024
Projected	$ 18.260.089	$ 33.662.885	$ 44.041.314	$ 50.816.278	$ 53.969.119
Reference	$ 18.335.840	$ 34.194.071	$ 47.843.307	$ 56.827.929	$ 62.820.347
Incremental	$ -75.750	$ -531.186	$ -3.801.992	$ -6.011.651	$ -8.851.228

RESULTS (CONTINUED)

Table 9. Budget impact (in USD) – Patients without 17p Del

	2020	2021	2022	2023	2024
Projected	$ 21,303,438	$ 39,273,366	$ 51,381,533	$ 59,285,658	$ 62,963,972
Reference	$ 21,391,813	$ 40,053,521	$ 56,348,532	$ 70,590,776	$ 83,051,766
Incremental	$ -88,376	$ -780,155	$ -4,966,999	$ -11,305,118	$ -20,087,793

Table 10. Budget impact (in USD) – Total population

	2020	2021	2022	2023	2024
Projected	$ 39,563,527	$ 72,936,252	$ 95,422,848	$ 110,101,936	$ 116,933,091
Reference	$ 39,727,653	$ 74,247,593	$ 104,191,839	$ 127,418,704	$ 145,872,113
Incremental	$ -164,126	$ -1,311,341	$ -8,768,991	$ -17,316,769	$ -28,939,022

- According to coverage expansion analysis around 60% of the population without 17p Del could be treated with no extra costs, only with resource savings generated by treating the population with 17p Del with V+R, instead of ibrutinib (Table 11).

Table 11. Additional patients without 17p Del.

Year	Additional patients without 17p Del	Total of patients without 17p Del*	% of 17p Del patients additionaly covered
2020	216	362	60%
2021	217	365	60%
2022	219	367	60%
2023	220	370	60%
2024	222	372	60%

*According to Table 2..

- Table 12 compares the costs for treating all R/R CLL patients with 17p Del with venetoclax + rituximab *versus* ibrutinib. It also shows the absolute number of patients without 17p Del whom would be treated only by the resoruces saved by the choice of treating the population with 17p Del with venetoclax + rituximab.

Table 12. Costs per drug related to additional patients without 17p Del.

Year	Patients with 17p Del	Venetoclax + rituximab	Ibrutinib	Additional patients without 17p Del
2020	155	$ 35,773,638	$ 85,567,253	216
2021	156	$ 36,037,511	$ 86,198,412	217
2022	157	$ 36,292,760	$ 86,808,944	219
2023	158	$ 36,538,688	$ 87,397,182	220
2024	159	$ 36,775,235	$ 87,962,979	222

CONCLUSIONS

- Results of the budgetary analysis estimate savings of approximately $56,5 million dollars in 5 years with the incorporation of venetoclax + rituximab in ANS' rol for the treatment of R/R CLL patients – independently of the presence of the 17p deletion. The analysis indicates that resource savings are generated already in the first year of incorporation, being approximately $164 thousand dollars.
- According to an expansion coverage analysis, the Brazilian private health care system would be able to treat around 60% of R/R CLL patients without 17p Del only with recoruces saved by treating the 17p population with V+R.

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DISCLOSURES

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