THE ECONOMIC IMPACT OF TREATMENT SEQUENCES FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN THE UNITED STATES (US): A COST OF CARE AND BUDGET IMPACT MODEL OF VENETOCLAX PLUS OBINUTUZUMAB SEQUENCES FOR CLL PATIENTS

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Presented at the Journal of the Advanced Practitioner in Oncology (JADPRO) Live, the Advanced Practitioner Society for Hematology and Oncology (APSHO) Annual Meeting, October 20–23, 2022

BACKGROUND

- Venetoclax is a selective oral small-molecule inhibitor of B-cell lymphoma-2 (BCL-2) that restores apoptosis in cancer cells; it has been indicated as monotherapy (V mono) and in combination with rituximab (V+R) to treat relapsed/refractory patients with CLL since 2016 and 2018, respectively, and was more recently approved in combination with obinutuzumab (V+O) for use in previously untreated patients with CLL in 2019.[1]
- Other novel oral agents for CLL were also approved in the US over the past few years, including idelalisib (2014), ibrutinib (2014), duvelisib (2018), and acalabrutinib (2019).[2]
- The availability of oral targeted therapies has transformed the treatment paradigm in CLL but there is a paucity of literature pertaining to optimal sequencing.
- While other novel agents are indicated for treatment until progression, V+O is the only novel targeted combination therapy providing a 12-month fixed treatment duration for previously untreated adults with CLL.
- Long-term costs and budget impact of sequences with V+O as first-line treatment for CLL in the US remain unknown.

OBJECTIVES

- To estimate the total cumulative costs per patient of treatment sequences for adults with CLL, with and without 17p deletion.
- To evaluate the budget impact of introducing sequences with V+O as first-line therapy for CLL from a US payer perspective, based on the estimated costs of treatment sequences.

METHODS

- A partitioned survival model was developed to assess costs of treatment sequences with up to three lines of therapy. Venetoclax-based therapies can be used in first-line and retreatment.
- A total of 249 sequences were included based on NCCN guidelines and validation by clinical experts.[3]
- The model adopted a US payer perspective with a 10-year time horizon.
- Patients were distributed into five states based on efficacy data from clinical trials and real-world data: first-line, second-line, third-line, later-line (i.e., best supportive care) and death.
  - Due to the lack of long-term efficacy data, constant annual rates of progression and death were applied.
  - Efficacy data were stratified by patients' 17p deletion status.
- Key model assumptions were:
  - The efficacy of a therapy was assumed to be independent of the prior therapy received.
  - Patients would receive a second-line therapy before death, and a proportion of patients on second-line would progress to third-line and/or later lines before death.
  - Patients would be treated until progression or maximum duration specified in the label; treatment discontinuation due to reasons other than disease progression was not considered.
  - There was no treatment gap between progression and initiation of next line treatment.

METHODS (CONT.)

- Cost components included: treatment and administration, monitoring, terminal care, tumor lysis syndrome (TLS) prophylaxis (venetoclax-based therapies) and adverse event (AE)-related costs. All costs are presented in 2020 US dollars (USD).
  - Treatment and administration costs were estimated based on unit costs of drug acquisition, drug administration (for intravenous [IV] drugs), and dosing schedules. Drug wastage was considered for IV drugs. Different annual costs in the first and subsequent years were applied for therapies with a fixed duration or ramp-up period. (**Table 1**)
  - Monitoring costs included treatment-specific and all-cause healthcare costs, which totaled $37,098 for chemoimmunotherapies and $37,221 for oral targeted therapies, annually.
  - Terminal care costs ($23,093), TLS prophylaxis costs ($17,627) and AE-related costs (estimated based on unit costs from HCUPnet[4] and AE incidence rates for each therapy by line) were applied as one-time costs.

Table 1: Annual treatment and administration cost inputs

Therapy[a]	Annual treatment and administration costs (2020 USD)		Sources and notes
	First-year	Subsequent years (years 2-10)	
V+O[b]	$180,791	$0	Drug acquisition unit costs: Truven Red Book;[5] Drug administration unit costs: weighted average of Commercial and Medicare costs; Dosing schedules: Corresponding FDA drug labels/clinical trials.
Acalabrutinib (Acala)	$170,643	$170,643	
Acalabrutinib + Obinutuzumab (Acala+O)	$231,173	$170,643	
Bendamustine + Rituximab (B+R)	$112,671	$0	
Chlorambucil + Obinutuzumab (C+O)	$71,623	$0	
Duvelisib (D mono)	$161,070	$161,070	
Fludarabine + Cyclophosphamide + Rituximab (FCR)	$74,144	$0	
Ibrutinib (I mono)	$168,559	$168,559	
Ibrutinib + Obinutuzumab (I+O)	$229,089	$168,559	
Ibrutinib + Rituximab (I+R)	$234,017	$168,559	
Idelalisib + Rituximab (Ide+R)	$195,659	$136,276	
Venetoclax (V mono)	$131,735	$149,161	
Venetoclax + Rituximab (V+R)[c]	$191,117	$149,161	

Notes:
[a] Obinutuzumab, bendamustine and rituximab are administered for the first 6 cycles only. Chlorambucil is administered for the first 12 cycles only.
[b] V+O is a fixed duration therapy for 1 year including a 5-week ramp-up period for venetoclax.
[c] V+R is a fixed duration therapy for 2 years, including a 5-week ramp-up period for venetoclax in the first year.

- In the budget impact analysis, a hypothetical cohort of 1 million persons was assumed for the total health plan (Commercial and Medicare) and the target population eligible for treatment were estimated based on published epidemiological data. (**Table 2**) Market share estimates before and after market entry of sequences with first-line V+O were informed by expert clinical input.

Table 2: Epidemiological inputs for target population in budget impact analysis

Parameters	Commercial	Medicare	Sources and Notes
Plan total	1,000,000		Hypothetical plan size
Proportion of coverage	80%	20%	Kaiser Family Foundation[6]
CLL incidence rate	0.0030%	0.0275%	NIH SEER statistics,[7] US Census Bureau[8]
Proportion of first-line CLL patients treated with drug treatment	55%		AbbVie/Genentech business insights
Proportion of CLL patients with 17p deletion	6.7%		Seymour 2019[9]
Eligible patients each year	With 17p deletion: 3 Without 17p deletion: 41		Calculation

- Model outputs included 10-year cumulative costs per patient and 5- and 10-year budget impact after market entry of sequences with first-line V+O.

RESULTS

- Overall, sequences with first-line V+O combination had lower 10-year cumulative costs compared to sequences starting with other novel agents (i.e. ibrutinib monotherapy, acalabrutinib monotherapy). (**Table 3**)

Table 3: Total costs of treatment sequences starting with each first-line therapy over 10 years

Treatment sequence	Total costs (2020 USD)	
	With 17p deletion	Without 17p deletion
V+O in the first-line[a]	$935,781 - $1,345,961	$690,346 - $951,633
Acala in the first-line	$1,426,924 - $1,711,123	$1,742,308 - $1,900,689
Acala+O in the first-line	$1,829,240 - $1,970,910	$1,952,306 - $2,044,727
B+R in the first-line	$770,258 - $1,563,291	$663,890 - $1,121,592
C+O in the first-line	$658,960 - $1,475,007	$666,206 - $1,364,189
I+O in the first-line	$1,704,321 - $2,012,814	$1,701,463 - $2,018,418
I mono in the first-line	$1,504,835 - $1,906,544	$1,720,745 - $1,976,767
I+R in the first-line	$1,250,889 - $1,858,610	$1,929,611 - $2,077,936
FCR in the first-line	*	$627,028 - $1,063,972

Notes:
[a] **The lowest cost sequences starting with V+O in the first-line were V+O -> Ide+R -> V+R among patients with 17p deletion and V+O -> B+R -> V+R among patients without 17p deletion.**
* Not commonly used in patients with 17p deletion.

- Among patients with 17p deletion, cumulative costs per patient of sequences starting with V+O combination ranged from $935,781 to $1,345,961; whereas sequences starting with ibrutinib monotherapy or acalabrutinib monotherapy ranged from $1,426,924 to $1,906,544.
- Similarly, in adults without 17p deletion, cumulative costs per patient of sequences starting with V+O combination ranged from $690,346 to $951,633; and sequences starting with ibrutinib monotherapy or acalabrutinib monotherapy ranged from $1,720,745 to $1,976,767.
- Additionally, among sequences starting with V+O combination, retreatment with a venetoclax-based regimen in second-line often resulted in relatively low cumulative costs ($990,209 - $1,214,456 for patients with 17p deletion and $759,634 - $913,475 for patients without 17p deletion).
- Cumulative costs for treatment sequences were largely determined by the first two lines. When comparing treatment sequences with the same first-line therapy (e.g., sequences starting with ibrutinib monotherapy), sequences with continuous novel therapies in second-line (e.g., acalabrutinib monotherapy) resulted in higher costs compared to sequences with fixed duration novel therapies (e.g. V+R) in second-line. (**Figure 1**)
- Total budget impact of introducing sequences with V+O combination in first-line led to cost savings of $12.5 million over 5 years and $56.4 million over 10 years for a health plan of 1 million US members. (**Figure 2**)

Figure 2: Budget impact over 5 and 10 years in the overall CLL population

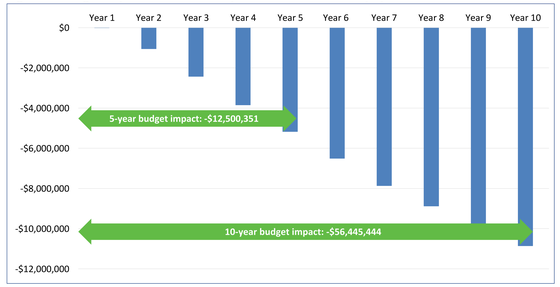
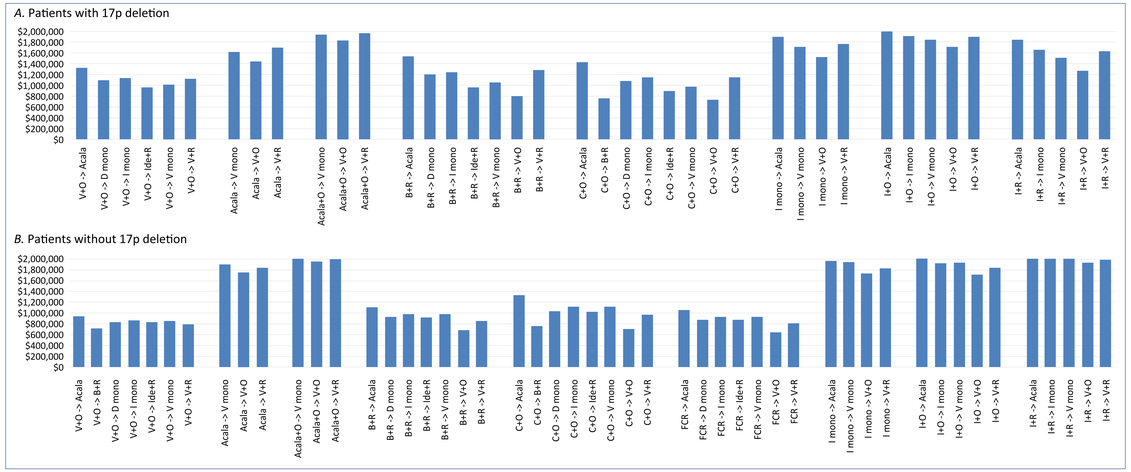


Figure 1: Average total costs of treatment sequences summarized by first two lines over 10 years



CONCLUSIONS

- Sequences starting with V+O combination resulted in considerably lower costs in our model compared to sequences starting with other novel agents (monotherapy and combination) administered until disease progression.
- Sequences including retreatment with a venetoclax-based regimen also leads to cost savings.
- The budget impact of sequences with V+O combination in first-line is cost saving due to substantial reductions in treatment costs associated with a fixed duration of therapy.

REFERENCES

1. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med.* 2013;19(2):202–208.
2. Lymphoma Research Foundation. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: FDA Updates. 2019; https://lymphoma.org/aboutlymphoma/cll/cllfdaupdates/. Accessed 13 January 2021.
3. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.* 2019.
4. HCUPnet. 2016/2017; https://hcupnet.ahrq.gov/. Accessed March 24, August 21, and November 12, 2020.
5. Truven Health Analytics. Micromedex Red Book Online Search. 2020; http://www.micromedexsolutions.com/micromedex2/librarian/. Accessed January 28 and July 9, 2020.
6. Kaiser Family Foundation. Health Insurance Coverage of the Total Population. 2018; https://www.kff.org/other/state-indicator/total-population/?currentTimeframe=0&selectedRows=%7B%22wrapups%22:%7B%22united-states%22:%7B%7D%7D%7D&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Accessed July 21, 2020.
7. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016. 2019; https://seer.cancer.gov/archive/csr/1975_2016/. Accessed April 2019.
8. U.S. Census Bureau. National Population Projections Datasets, Table 1. Projected Population by Single Year of Age, Sex, Race, and Hispanic Origin for the United States: 2016 to 2060. 2017; https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html. Accessed July 21, 2020.
9. Seymour EK, Ruterbusch JJ, Beebe-Dimmer JL, Schiffer CA. Real-world testing and treatment patterns in chronic lymphocytic leukemia: A SEER patterns of care analysis. *Cancer.* 2019;125(1):135–143.

ACKNOWLEDGEMENTS AND DISCLOSURE

Data first presented at the national meeting of the Academy of Managed Care Pharmacy, 2021.

Design, study conduct and financial support for the study were provided by AbbVie Inc. and Genentech. Genentech is a member of the Roche group.

AbbVie Inc. and Genentech participated in the interpretation of data, and review and approval of the poster. All authors contributed to the development of the abstract and maintained control over the final content.

Medical writing assistance was provided by Shelley Batts, PhD, an employee of Analysis Group, Inc. Third-party editorial assistance was provided by Jeanne Esteves, MSc, of Ashfield MedComms, an Inizio Company, and was funded by Genentech.

Beenish S. Manzoor and Kavita Sail are employees of AbbVie Inc. and may own stocks and/or options of the company.

Zhou Zhou, Nisha C. Hazra and Honghao Fang are employees of Analysis Group, Inc, which has received consulting fees from AbbVie for this study.

Arliene Ravelo and Sheila Shapouri are employees of Genentech, Inc. and may own stocks/and or options from Roche.

Matthew S. Davids is an employee of the Dana Farber Cancer Institute. **Consultation or Advisory Boards:** Genentech, Janssen, Astra-Zeneca, Verastem, MEI Pharma, AbbVie, TG Therapeutics, Pharmacyclics, Adaptive Biotechnologies, Celgene, BeiGene, Eli Lilly, and Novartis. **Research Funding:** Pharmacyclics, TG Therapeutics, Genentech, Astra-Zeneca, Verastem, BMS, MEI Pharma, Novartis, and Surface Oncology.

Mazyar Shadman is an employee of Fred Hutchinson Cancer Research Center. **Consultation and Advisory Boards:** Abbvie, Genentech, Astra Zeneca, Sound Biologics, Pharmacyclics, Beigene, Cellectar, BMS, Morphosys, TG Therapeutics. **Research Funding:** Mustang Bio, Celgene, Pharmacyclics, Genentech, Abbvie, TG therapeutics, Beigene, AstraZeneca, and Sunesis.