Premature Treatment Discontinuation among Previously Untreated Medicare Beneficiaries with Chronic Lymphocytic Leukemia Treated with Oral Targeted Therapies: A Real-World Analysis

Scott F. Huntington[1], Justin T. Puckett[2], Dureshahwar Jawaid[3], Beenish S. Manzoor[3], Sophia S. Li[4], Nnadozie Emechebe[3], Holly Budlong[3], Sachin Kamal-Bahl[2], Jalpa A. Doshi[5]

[1] Yale University, New Haven, CT, USA; [2] COVIA Health Solutions, Ambler, PA, USA; [3] AbbVie Inc., North Chicago, IL, USA; [4] Genentech Inc., South San Francisco, CA, USA; [5] University of Pennsylvania, Philadelphia, PA, USA

OBJECTIVE

To examine premature treatment discontinuation among patients initiating oral targeted agents, BTKis (ibrutinib, acalabrutinib) or BCL2is (venetoclax), for chronic lymphocytic leukemia (CLL) in the frontline setting

CONCLUSIONS

This real-world analysis found VEN-O and ACA patients had lower rates of premature discontinuation compared to IBR.

VEN-O patients had lower rates of post-discontinuation death and three-to-four times lower rate of treatment switching compared to ACA and IBR. VEN patients also had lower healthcare costs post-discontinuation compared to both IBR and ACA patients.

Future work is needed to examine factors associated with premature discontinuation of targeted treatments and potential differences in treatment outcomes.

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INTRODUCTION

- BTK inhibitors such as ibrutinib (IBR) and acalabrutinib (ACA) and BCL-2 inhibitors such as venetoclax (VEN) have become important chemotherapy-free treatment options for patients (pts) with chronic lymphocytic leukemia (CLL) in the front-line (1L) setting
  - VEN in combination with anti-CD20 immunotherapy obinutuzumab (VEN-O) is a fixed-duration therapy
  - IBR and ACA treatment continues until progression or intolerance
- There is limited real-world evidence on premature treatment discontinuation and subsequent outcomes among 1L pts
- Evidence is particularly lacking in the U.S. Medicare program, which represents a major gap in the literature and an important gap in evidence to inform clinical practice:
  - CLL is most prevalent in the elderly population, who primarily receive coverage through the Medicare program
  - Significantly older patients may be excluded from clinical trials owing to frailty

METHODS

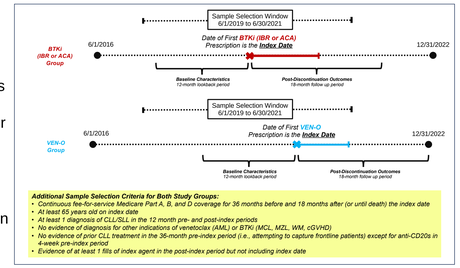
Study Design

- Retrospective cohort study using 2016-2022 Medicare 100% CCW claims data

Sample Selection

- All fee-for-service Medicare beneficiaries age ≥66 years newly initiating an available BTKi treatment (IBR or ACA) or VEN in combination with obinutuzumab (VEN-O) between 6/1/2019 and 6/30/2021 were identified
- Index date for VEN-O was first VEN fill date; obinutuzumab use was assessed in 4-weeks pre- and 8-weeks post VEN fill
- Index date for IBR and ACA was first treatment fill date
- See **Figure 1** for additional sample selection criteria

Figure 1. Study Schematic



Outcomes

- Discontinuation (i.e., consecutive 90-day gap in treatment) was assessed using the Kaplan-Meier method and considered premature if it occurred within 12 months of treatment initiation of the continuous treat-to-progression BTKis (IBR and ACA) or fixed-duration treatment for VEN-O (i.e., twelve 28-day cycles).
- Potential reasons for discontinuation were identified using ≥1 medical claim with an ICD-10 code for a diagnosis of interest 30 days before or after the discontinuation date.
- All patients had ≥6 months of follow-up after discontinuation to assess post-discontinuation outcomes:
  - All-cause death
  - Switching to alternative treatment
  - Healthcare costs

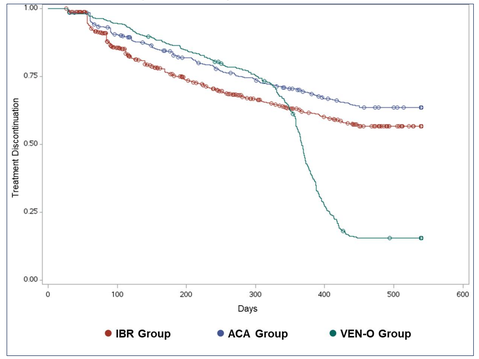
Analysis

- All outcomes were assessed descriptively.

RESULTS

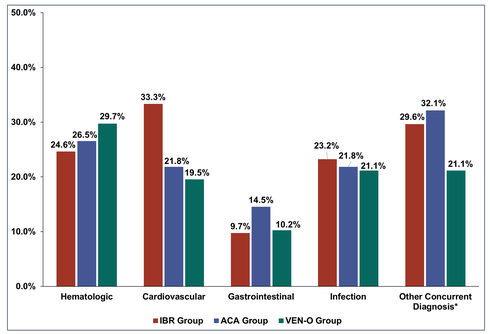
- The full study sample contained 3,653 beneficiaries (2,412 IBR; 808 ACA; 433 VEN-O).
- **Figure 2** presents a Kaplan-Meier curve for time to treatment discontinuation for IBR, ACA, and VEN-O (all patients).

Figure 2. Kaplan-Meier Curve for Time to Treatment Discontinuation (All Patients)



- Premature discontinuation rates were 35.9% (IBR), 29.0% (ACA) and 29.6% (VEN-O) with median time (IQR) to discontinuation of 4.0 (2.7,7.2), 5.1 (3.0,8.1) and 6.5 (4.0,9.3) months, respectively.
  - Potential reasons for discontinuations shown in **Figure 3**.
- Among the subset of premature discontinuers, the VEN-O group had a slightly younger mean age (76.9 years) than the IBR (79.1 years) and ACA (79.5 years) groups, and had a higher number of Elixhauser comorbidities (**Table 1**)

Figure 3. Potential Reasons for Discontinuation (Concurrent Diagnoses Surrounding Treatment Discontinuation Date^)



^30 days before or after treatment discontinuation; Other concurrent diagnoses included arthralgia/myalgia, bleeding, hepatotoxicity, renal toxicity, adverse drug event, and/or tumor lysis syndrome.*

Table 1. Sample Characteristics of Premature Discontinuers

	IBR Group	ACA Group	VEN-O Group
Characteristic			
N	867	234	128
Age, mean (SD)	79.1 (6.7)	79.5 (6.6)	76.9 (5.7)
Male	55.8%	60.3%	64.1%
White	90.9%	87.6%	>91.4%[d]
South	39.6%	40.2%	35.9%
Urban	74.7%	83.3%	82.8%
Receiving Part D Low-Income Subsidy	12.9%	12.0%	8.6%
Enhanced alternative Part D benefit	49.9%	55.1%	57.8%
Number of Elixhauser comorbidities[a]			
0-2	8.8%	9.8%	10.2%
3-4	13.6%	14.1%	9.4%
5-7	24.2%	19.2%	19.5%
8-10	35.2%	32.9%	35.9%
11+	18.2%	23.9%	25.0%
CLL treatments around index drug initiation[b]			
None (i.e. index agent only and none of the drugs below)	95.6%	88.0%	0.0%
Anti-CD20	3.3%	12.0%	100.0%
Other CLL treatments[c]	4.6%	13.6%	100.0%
All-cause hospitalization[a]	28.4%	35.0%	31.3%
CLL-related hospitalization[a]	24.1%	28.2%	27.3%
All-cause total costs[a]	$27,531 ($30,934)	$35,022 ($5,0651)	$37,358 ($35,747)
Index year			
2019	37.3%	<4.7%[d]	21.1%
2020	44.9%	>51.7%[d]	50.8%
2021	17.9%	43.6%	28.1%
Any Concurrent Diagnoses[e] (N)	63.7% (552)	57.3% (134)	56.3% (72)

[a] Assessed in 12-month pre-index period
[b] Assessed in the 4-week pre-index and 8-weeks post-index periods
[c] Patients were not permitted to have any CLL treatment in the 36-month pre-index period (other than obinutuzumab or rituximab in the 4-week pre-index period). Hence, this row denotes patients who received another CLL agent in the 8-week post-index period.
[d] Estimates based on cell sizes <11 or that would permit calculation of a cell size <11 cannot be reported per CMS policy.
e Reported 30 days before or after the discontinuation date

- Among premature discontinuers, VEN-O had a lower rate of all-cause death (26.6%) compared to IBR (31.4%) and ACA (32.5%) over follow-up (**Figure 4**).
- Premature VEN-O discontinuers also had lower rates of switching (<8.6%) compared to IBR (35.3%) and ACA (26.9%) (**Figure 5**).
  - Among IBR switchers, 37.9% and 30.1% switched to another BTKi or VEN, respectively
  - Among ACA switchers, 38.1% and 33.3% switched to VEN or chemotherapy, respectively.
  - Among VEN switchers, <8.6% switched to traditional chemo or other regimen
- In the 6-months after discontinuation, all-cause healthcare costs were lower for VEN-O ($30,452) compared to IBR ($43,315) and ACA ($46,923) (**Figure 6**).

Figure 4. Death after Premature Treatment Discontinuation

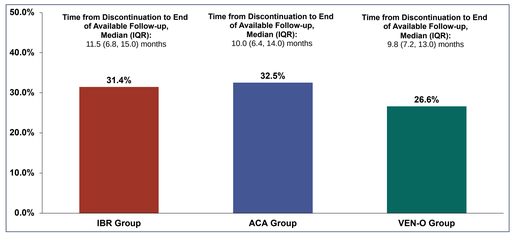


Figure 5. Switching after Premature Treatment Discontinuation

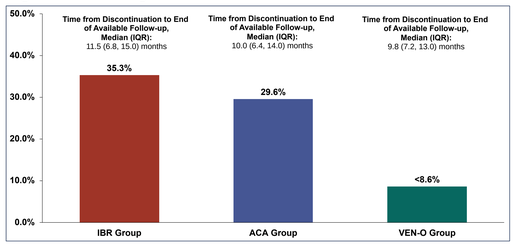
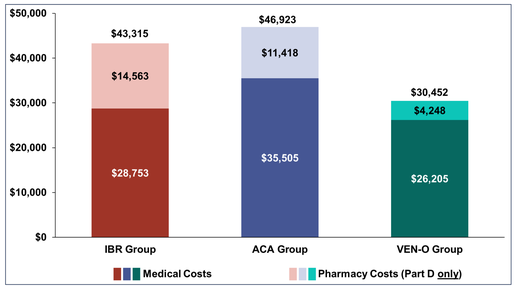


Figure 6. Healthcare Costs in the 6-months after Premature Treatment Discontinuation



LIMITATIONS

- As a claims-based study, medical coding errors are possible.
- Findings from this analysis were descriptive.
- We are unable to ascertain from the claims data the reason for premature discontinuation.
- Study is generalizable only to the fee-for-service US Medicare population.