A retrospective study evaluating the sequence of BTKi and venetoclax for relapsed/refractory CLL/SLL, with a focus on toxicity – Abstract #1554137

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Background

- Consensus treatment guidelines in the United States endorse Bruton's Tyrosine Kinase inhibitors (BTKi) and venetoclax (VEN) as preferred regimens in the first- and second-line settings[1]
  - Acalabrutinib +/- obinutuzumab
  - Zanubrutinib
  - Ibrutinib
  - Venetoclax +/- anti-CD20 monoclonal antibody
- The efficacy of venetoclax after progression on a BTKi has been established by existing literature[2]
- Real-world safety and survival data analyzing sequential venetoclax after a BTKi is lacking

Objective & Outcomes

To evaluate the toxicity and efficacy of venetoclax after progression on a BTKi for the treatment of CLL/SLL in a real-world setting.

Primary Endpoint:

- To compare the rate of grade 3 or higher toxicities in patients receiving venetoclax after a BTKi

Secondary Endpoints:

- Median Progression-Free Survival (mPFS)
- Median Overall Survival (mOS)
- Median rate of grade 3 or higher toxicities
- Incidence of dose reduction or treatment discontinuation
- Median time to next line of therapy

Study Design & Eligibility

- Single-center, retrospective, chart-review study
- Study Period: December 31, 2009 to October 20, 2022

Inclusion:

- Age 18 years and older with a diagnosis of CLL/SLL
- Receipt of sequential BTKi then venetoclax

Exclusion:

- Protected patient populations (pregnancy, prisoners)
- Receipt of concurrent BTKi and venetoclax for ≥ 3 months

Methods

- Data were collected by manual chart review of provider documentation and clinical, laboratory, and radiographic data
- Study data were collected and managed using REDCap electronic data capture tools hosted at The Ohio State University
- Baseline characteristics collected at initiation date of venetoclax
- PFS and OS data based upon date of venetoclax initiation
- Date of progression was determined by treating physician documentation of disease progression

Statistical Analysis

- Descriptive statistics utilized for patient characteristics and outcomes
  - Categorical variables presented as counts (percentages)
  - Continuous variable presented as a median +/- standard deviation
- Kaplan-Meier curves were generated for mPFS and mOS with corresponding 95% confidence intervals
  - SAS version 9.4 (SAS Institute, Inc., Cary, NC)

Patients and Baseline Characteristics

278 patients identified

215 patients excluded

- 178 BTKi + Venetoclax
- 13 mantle cell lymphoma
- 24 excluded for:
  - Concomitant anti-cancer therapy
  - Line of therapy between BTKi and venetoclax

60 patients included

Baseline Characteristics	n = 60
Male, n (%)	40 (66.7)
White/Caucasian, n (%)	56 (93.3)
Age at diagnosis	58.7 ± 9.7
Previous BTKi: Ibrutinib, n (%) Acalabrutinib, n (%)	 36 (60) 24 (40)
Previous line of therapy, n (%)	45 (75)
Median lines of therapy	2 (0-9)
Concurrent anti-CD20 None, n (%) Rituximab, n (%) Obinutuzumab, n (%)	 45 (75) 10 (16.7) 5 (8.3)

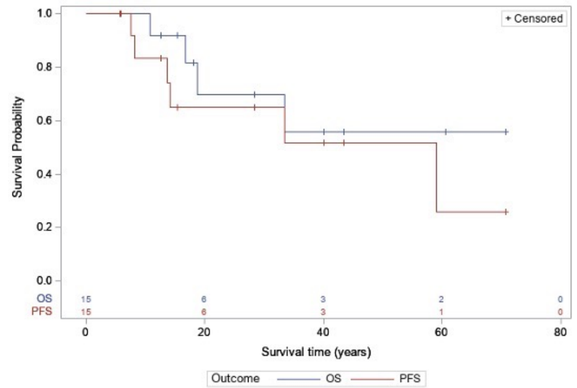
Primary Outcome

- **46 patients (76.7%) experienced a grade 3 or higher toxicity**
- Median exposure to venetoclax was 15 months (range: 1-48)
- Median follow-up was 23 months (range: 1-91)

Toxicity	n (%)	Toxicity	n (%)
Neutropenia	31 (54.4)	MACE	3 (5.0)
Thrombocytopenia	19 (32.2)	ISTH major bleed	2 (3.3)
Laboratory TLS	9 (15.0)	Nausea	2 (3.3)
ISTH minor bleed	7 (11.7)	Vomiting	1 (1.7)
Hypertension	6 (10.0)	Arthralgia/Myalgia	1 (1.7)
Clinical TLS	4 (6.7)	Other (renal caliculi)	1 (1.7)
Diarrhea	3 (5.0)	Anemia	0 (0)

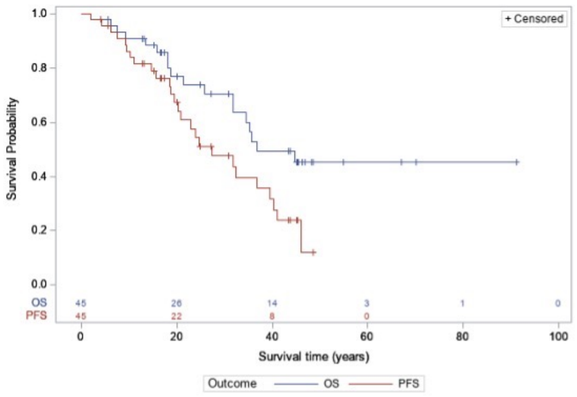
- MACE – Myocardial infarction, stroke, atrial fibrillation, cardiac death
- ISTH bleeding – International Society of Thrombosis & Haemostasis
- TLS – Defined by Cairo-Bishop criteria

Survival – Treatment naïve prior to BTKi / VEN



- Median PFS: 59.0 months (95% CI, 8.1 – NR)
- Median OS: Not Reached (95% CI, 16.7 – NR)

Survival – R/R prior to BTKi / VEN



- Median PFS: 27.3 months (95% CI, 19.4 – 39.6)
- Median OS: 36.9 months (95% CI, 31.8 – NR)

Secondary Outcomes

- Median rate of grade 3 or higher toxicity was 1 (range: 1-4)

Venetoclax Dose Reduction	N=17
Cytochrome P450 interactions	4
Toxicity	
Neutropenia	6
Thrombocytopenia	2
Nausea/vomiting	2
Diarrhea	2
Elevated AST/ALT	1
Venetoclax Discontinuation	**N=41**
Progression	16
Patient preference	9
Toxicity	7
Completion of therapy	6
Death	3

- Median time to next line of therapy (n=22) was 21.5 months (range: 2-43)

Discussion

- Real world composite ≥ grade 3 toxicity rate compares similarly with existing data for venetoclax in the R/R and first-line settings
  - MURANO: Toxicity ≥ grade 3 rate 82%, median exposure of 22.1 months[3]
  - CLL14: Toxicity ≥ grade 3 rate 78.8%, median exposure of 11.1 months[4]
- For PFS based on VEN initiation, patients who were treatment naïve prior to the BTKi/VEN sequence experienced a numerically longer mPFS with VEN than patients who were already R/R prior to the BTKi/VEN sequence
- Our mPFS of 27.3 months for R/R patients compares similarly with results from Jones JA, et al. which demonstrated a mPFS of 24.7 months in a largely R/R patient population[3]
- Future retrospective studies comparing the safety of the BTKi/VEN sequence versus BTKi plus venetoclax are warranted and ongoing.

References

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3. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med*. 2018;378(12):1107-1120. doi:10.1056/NEJMoa1713976
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