Real-world Treatment Outcomes among Patients with High-Risk CLL/SLL Receiving Venetoclax-Based Therapy in 1L or 2L: An Updated International Study

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OBJECTIVE

This study evaluated clinical outcomes in patients with high-risk CLL/SLL who initiated venetoclax in first-line (1L) or second-line (2L) settings as venetoclax monotherapy (Vmono) or venetoclax combination therapy (Vcombo)

CONCLUSIONS

This study is one of the largest investigating high-risk CLL/SLL patients who initiated venetoclax, and particularly patients with both uIGHV and del[17p]/TP53 aberrations

These findings highlight the effectiveness of venetoclax in a 1L/2L setting for patients with high-risk CLL/SLL, and are aligned with prior clinical trials and real-world analyses

The use of venetoclax in treating patients with other forms of high-risk features should be explored in future research

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INTRODUCTION

- Deep responses and long survival times have been noted in clinical trial data for patients with high-risk (i.e., unmutated immunoglobulin heavy chain variable [uIGHV] and/or del[17p]/TP53) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who initiated venetoclax-based therapy[1-3]
- However, real-world data on clinical outcomes in patients with high-risk CLL/SLL remain limited, particularly for those with both uIGHV+del(17p)/TP53[4-7]

METHODS

- Data from 25 sites participating in the CLL Collaborative Study of Real-World Evidence (CORE), a global, retrospective, observational study were used for this study
- Adult patients with CLL/SLL were included if they had del(17p)/TP53 and/or uIGHV prior to the initiation of venetoclax in 1L or 2L
- Clinical outcomes assessed were:
  - Overall response rate (ORR; proportion of patients with a documented physician-defined complete/partial response)
  - Progression-free survival (PFS; time from venetoclax initiation to disease progression/death [i.e., event] or end of follow-up [i.e., censor])
  - Overall survival (OS; time from venetoclax initiation to death [i.e., event] or end of follow-up [i.e., censor])
- Patient characteristics and clinical outcomes were stratified by high-risk feature (non-mutually exclusive: del[17p]/TP53; uIGHV (i.e., with or without confirmed del[17p/TP53]); uIGHV-only (i.e., without confirmed del[17p/TP53]; see supplemental appendices); both uIGHV+del[17p]/TP53), line of therapy (1L; 2L), and venetoclax regimen (VMono; Vcombo; see supplemental appendices)
- For PFS, TTNT-D, and OS, estimates of median survival time, and 36-month rates were reported using the Kaplan-Meier methodology

RESULTS

Patient characteristics

- Of 2,696 patients in the CORE study, 317 patients (11.8%) were included in the analyses **(Table 1)**
- Among the 317 patients:
  - 87 (27.4%) had del(17p)/TP53 (1L: 39; 2L: 48)
  - 272 (85.8%) had uIGHV (1L: 191; 2L: 81)
  - 42 (13.2%) had both uIGHV+del(17p)/TP53(1L: 24; 2L: 18)

Table 1: Patient and clinical characteristics

Subject characteristics	Total	Line of therapy		High-risk feature[1]		
		1L	2L	del(17p)/TP53	uIGHV	uIGHV+ del(17p)/TP53
	N (%) (n=317)	N (%) (n=206)	N (%) (n=111)	N (%) (n=87)	N (%) (n=272)	N (%) (n=42)
Age at initiation of line of therapy (years), mean ± SD [median]	64.9 ± 11.0 [64.9]	63.4 ± 11.3 [64.0]	66.8 ± 10.0 [67.6]	67.3 ± 11.4 [67.6]	63.8 ± 10.7 [64.1]	65.4 ± 11.2 [66.0]
Male sex, N (%)	218 (68.8%)	140 (68.0%)	78 (70.3%)	55 (63.2%)	191 (70.2%)	28 (66.7%)
Time from diagnosis to venetoclax initiation (months), mean ± SD [median]	45.6 ± 44.9 [31.4]	38.2 ± 41.3 [24.6]	59.3 ± 48.2 [45.9]	52.0 ± 47.2 [40.2]	42.6 ± 43.4 [29.7]	39.2 ± 41.2 [29.6]
ECOG assessed, N (%)	287 (90.5%)	188 (91.3%)	99 (89.2%)	79 (90.8%)	248 (91.2%)	40 (95.2%)
Grade 0	174 (60.6%)	125 (66.5%)	49 (49.5%)	39 (49.4%)	158 (63.7%)	23 (57.5%)
Grade 1 - 2	110 (38.3%)	61 (32.4%)	49 (49.5%)	40 (50.6%)	87 (35.1%)	17 (42.5%)
Grade 3 - 4	3 (1.0%)	2 (1.1%)	1 (1.0%)	0 (0.0%)	3 (1.2%)	0 (0.0%)
Rai stage assessed, N (%)	246 (77.6%)	161 (78.2%)	85 (76.6%)	69 (79.3%)	210 (77.2%)	33 (78.6%)
Stage 0 - II	150 (61.0%)	109 (67.7%)	41 (48.2%)	34 (49.3%)	137 (65.2%)	21 (63.6%)
Chromosomal abnormality tested[2], N (%)	308 (97.2%)	198 (96.1%)	110 (99.1%)	87 (100.0%)	263 (96.7%)	42 (100.0%)
At least one chromosomal abnormality detected	266 (86.4%)	167 (84.3%)	99 (90.0%)	87 (100.0%)	221 (84.0%)	42 (100.0%)
17p deletion or TP53 mutation	87 (28.2%)	39 (19.7%)	48 (43.6%)	87 (100.0%)	42 (16.0%)	42 (100.0%)
Complex karyotype	30 (9.7%)	5 (2.5%)	25 (22.7%)	17 (19.5%)	18 (6.8%)	5 (11.9%)
No chromosomal abnormality detected	42 (13.6%)	31 (15.7%)	11 (10.0%)	0 (0.0%)	42 (16.0%)	0 (0.0%)
IGHV mutation status tested, N (%)	286 (90.2%)	199 (96.6%)	87 (78.4%)	56 (64.4%)	272 (100.0%)	42 (100.0%)
Unmutated IGHV, N (%)	272 (95.1%)	191 (96.0%)	81 (93.1%)	42 (75.0%)	272 (100.0%)	42 (100.0%)
Comorbidity burden, mean ± SD [median]	1.9 ± 1.7 [2.0]	1.8 ± 1.6 [2.0]	2.1 ± 1.8 [2.0]	1.8 ± 1.6 [2.0]	1.9 ± 1.7 [2.0]	2.0 ± 1.7 [2.0]

Abbreviations: 1L: first-line; 2L: second-line; del: deletion; CLL: chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; IGHV: immunoglobulin heavy chain variable; IQR: interquartile range; SD: standard deviation; SLL: small lymphocytic lymphoma
Notes: [1] Mutations were not considered mutually exclusive. As such, patients may have had other mutations or chromosomal abnormalities in addition to del(17p)/TP53 and/or uIGHV. [2] Categories are not mutually exclusive.

Treatment characteristics

- Of 317 patients, 206 patients initiated venetoclax-based therapy in 1L (65.0%), and 111 (35.0%) in 2L **(Table 2)**
- Although Vmono was initiated by 45 (14.2%) patients, most initiated Vcombo (272 [85.8%])

Table 2: Treatment characteristics

Subject characteristics	Total	Line of therapy		High-risk feature[1]		
		1L	2L	del(17p)/TP53	uIGHV	uIGHV+ del(17p)/TP53
	N (%) (n=317)	N (%) (n=206)	N (%) (n=111)	N (%) (n=87)	N (%) (n=272)	N (%) (n=42)
Length of follow-up (months), mean ± SD [median]	26.4 ± 19.9 [24.0]	25.7 ± 18.7 [24.0]	27.9 ± 22.0 [24.0]	27.7 ± 23.7 [24.2]	25.5 ± 18.3 [23.6]	23.0 ± 17.9 [23.1]
Venetoclax treatment duration (months)[2,3] mean ± SD [median]	24.4 ± 17.7 [22.8]	24.5 ± 16.8 [23.3]	24.2 ± 19.4 [19.9]	23.3 ± 19.4 [20.2]	24.3 ± 17.1 [22.7]	21.5 ± 17.6 [17.6]
Time between first and last dose of venetoclax (months), mean ± SD [median]	13.7 ± 12.5 [11.5]	11.7 ± 9.6 [11.1]	17.5 ± 16.0 [13.6]	15.9 ± 16.6 [11.0]	13.2 ± 11.6 [11.5]	14.8 ± 16.0 [11.0]
Line of venetoclax initiation, N (%)						
1	206 (65.0%)	206 (100.0%)	0 (0.0%)	39 (44.8%)	191 (70.2%)	24 (57.1%)
2	111 (35.0%)	0 (0.0%)	111 (100.0%)	48 (55.2%)	81 (29.8%)	18 (42.9%)
Venetoclax regimen, N (%)						
Vmono	45 (14.2%)	6 (2.9%)	39 (35.1%)	25 (28.7%)	27 (9.9%)	7 (16.7%)
Vcombo[4]	272 (85.8%)	200 (97.1%)	72 (64.9%)	62 (71.3%)	245 (90.1%)	35 (83.3%)
Patients still on venetoclax therapy, N (%)	100 (31.5%)	52 (25.2%)	48 (43.2%)	29 (33.3%)	88 (32.4%)	17 (40.5%)
Patients who ended the venetoclax therapy, N (%)	217 (68.5%)	154 (74.8%)	63 (56.8%)	58 (66.7%)	184 (67.6%)	25 (59.5%)
Reasons for ending venetoclax[5,6], N (%)						
Patient completed the scheduled duration of therapy	129 (59.4%)	98 (63.6%)	31 (49.2%)	27 (46.6%)	113 (61.4%)	11 (44.0%)
Based on MRD information available at this time	62 (28.6%)	58 (37.7%)	4 (6.3%)	8 (13.8%)	61 (33.2%)	7 (28.0%)
Watchful waiting due to low or no disease activity	22 (10.1%)	14 (9.1%)	8 (12.7%)	3 (5.2%)	21 (11.4%)	2 (8.0%)

Abbreviations: 1L: first line; 2L: second line; BCRi: B-cell receptor inhibitor; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; CT/CIT: chemotherapy/chemoimmunotherapy; IQR: interquartile range; MRD: minimal residual disease; SD: standard deviation; uIGHV: unmutated immunoglobulin heavy chain variable
Notes: [1] Mutations were not considered mutually exclusive. As such, patients may have had other mutations or chromosomal abnormalities in addition to del(17p)/TP53 and/or uIGHV. [2] Duration based on the study design was calculated as the time from initiation of the line of therapy until the earliest date of (i) next line of therapy, or (ii) end of follow-up or death. [3] For Vmono, treatment duration was 27.4 ± 22.8 [23.3], for Vcombo 23.9 ± 16.7 [22.6]. [4] Venetoclax combinations included: venetoclax + obinutuzumab (N=199), venetoclax + rituximab (N=56), venetoclax + CT/CIT (N=9), venetoclax + umbralisib-based (N=7), and venetoclax + epcoritamab (N=1). [5] Categories are not mutually exclusive. [6] Proportions were computed among patients who stopped their venetoclax therapy for the 3 most common reasons for stopping therapy.

Clinical outcomes

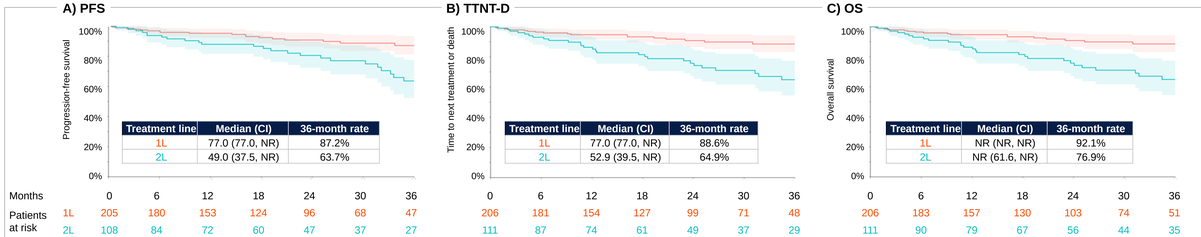
ORR

- Among the 246/317 patients with available response data, ORR results were as follows:
  - Overall, and by line of therapy: 89.4% (1L: 92.0%; 2L: 84.3%)
  - By high-risk feature, and line of therapy:
    - del(17p)/TP53 (N = 66): 87.9% (1L: 89.7%; 2L: 86.5%)
    - uIGHV (N = 213): 90.1% (1L: 92.8%; 2L: 83.3%)
    - del(17p)/TP53+uIGHV (N = 33): 90.9% (1L: 94.7%; 2L: 85.7%)

LIMITATIONS

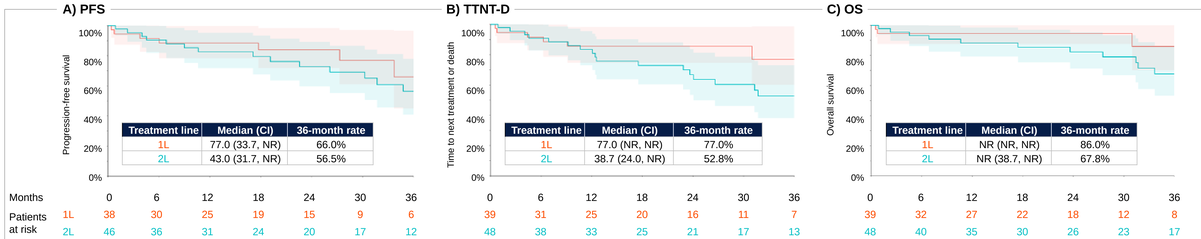
- Given that this was a retrospective chart review conducted across multiple centers, variations in clinical data interpretation and the potential for data entry errors may exist
- Although the abstractors were provided with the 2018 International Workshop on CLL (iwCLL) criteria for response reporting, physician-reported responses were documented and analyzed. Consequently, variations may exist across sites regarding the interpretation of patient response data
- The generalizability of these results to patients with high-risk CLL/SLL may be limited due to incomplete mutation testing data for some patients

Figure 1: Clinical outcomes for patients with high-risk CLL initiating venetoclax, by line of therapy



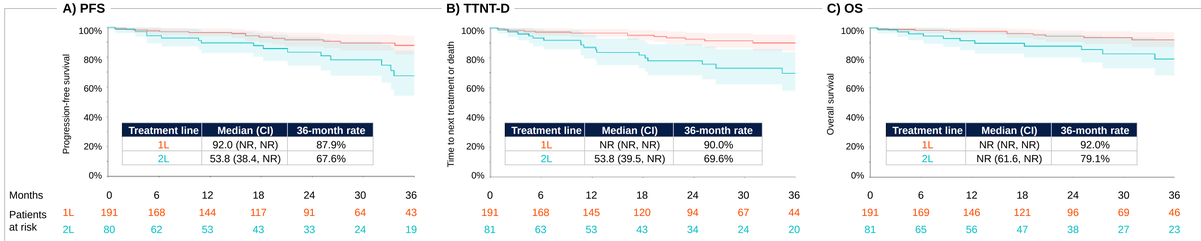
Notes: [1] 53 of 317 patients had a PFS event (deaths: 20; progression first: 33). 55 of 317 patients had a TTNT-D event (deaths: 24; next treatment: 31). A total of 24 patients died during their venetoclax line of therapy. [2] Of the 317 patients included, median PFS was 77.0 (62.9, NR) with a 36-month rate of 78.4%, median TTNT-D was 77.0 (63.3, NR) with a 36-month rate of 79.8%, and median OS was NR (NR, NR) with a 36-month rate of 86.4%. [3] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Figure 2: Clinical outcomes for patients with del(17p)/TP53 initiating venetoclax, by line of therapy



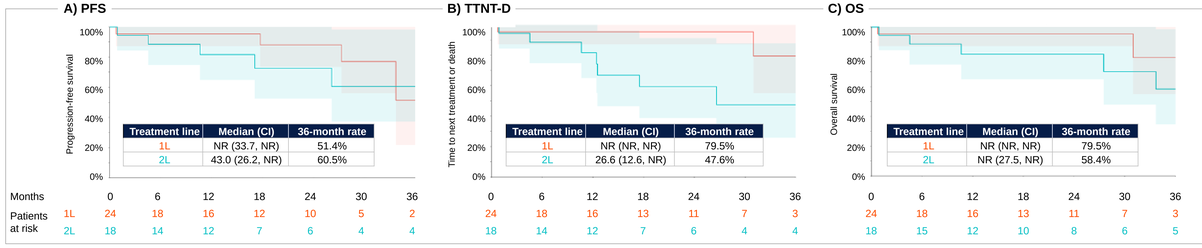
Notes: [1] 26 of 87 patients had a PFS event (deaths: 8; progression first: 18). 27 of 87 patients had a TTNT-D event (deaths: 11; next treatment: 16). A total of 11 patients died during their venetoclax line of therapy. [2] Of the 87 patients included, median PFS was 49.0 (34.8, NR) with a 36-month rate of 60.7%, median TTNT-D was 77.0 (38.7, NR) with a 36-month rate of 62.3%, and median OS was NR (NR, NR) with a 36-month rate of 74.5%. [3] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Figure 3: Clinical outcomes for patients with uIGHV initiating venetoclax, by line of therapy



Notes: [1] 37 of 272 patients had a PFS event (deaths: 16; progression first: 21). 37 of 272 patients had a TTNT-D event (deaths: 18; next treatment: 19). A total of 18 patients died during their venetoclax line of therapy. [2] Of the 272 patients included, median PFS was 92.0 (62.9, NR) with a 36-month rate of 81.8%, median TTNT-D was NR (63.3, NR) with a 36-month rate of 83.9%, and median OS was NR (NR, NR) with a 36-month rate of 88.2%. [3] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Figure 4: Clinical outcomes for patients with uIGHV + del(17p)/TP53 initiating venetoclax, by line of therapy



Notes: [1] 10 of 42 patients had a PFS event (deaths: 4; progression first: 6). 9 of 42 patients had a TTNT-D event (deaths: 5; next treatment: 4). A total of 5 patients died during their venetoclax line of therapy. [2] Of the 42 patients included, median PFS was 43.0 (33.7, NR) with a 36-month rate of 59.7%, median TTNT-D was NR (31.0, NR) with a 36-month rate of 66.5%, and median OS was NR (33.7, NR) with a 36-month rate of 68.1%. [3] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Abbreviations: 1L/2L: first/second line; CI: confidence interval; NR: not reached; OS: overall survival; PFS: progression-free survival; TTNT-D: time to next treatment or death