Association between treatment response and progression-free survival and overall survival in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a 12-month landmark meta-analysis

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Background

- Despite advances in treatment for R/R chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), CR is infrequently achieved with currently available standard therapies[1–3]
- This meta-analysis aimed to evaluate the association between response after the initiation of treatment and survival outcomes in patients with R/R CLL/SLL

Methods

Figure 1. Study design

SOURCE: Medidata Enterprise Data Store[a]
- 30,000 historical trials with 7 million patients
- 1400 customers in approximately 100 countries over 20 years

STUDY PERIOD:
- January 2012 to December 2022

KEY STUDY DEFINITIONS:
- Index date: start of first investigative/control treatment
- Baseline period: time before index date
- Follow-up period: time from index date until death or end of patient follow-up in the trial

POPULATION:
- Adult patients with confirmed R/R CLL/SLL diagnosis
- Received ≥ 1 prior line of therapy (LOT)

[a]Database contained patients' demographics, medical history, prior medications, longitudinal treatment and procedures, clinical assessment (eg, labs, vital signs, etc), investigator-assessed efficacy outcomes, adverse clinical events, and death details.

- The database included adult patients with R/R CLL/SLL who received ≥ 1 prior LOT enrolled in 6 randomized clinical trials or single-arm studies initiated after January 2012 and completed before December 2022 (**Figure 1**)
- Patients were followed from the index date until the end of patient follow-up or participation in the trial or death, whichever came first
- Best overall response (BOR), CR rate (CRR), overall response rate (ORR), duration of complete response (DOCR), and duration of response (DOR) were estimated by Medidata based on original reads from independent review committees
- Survival outcomes of PFS and OS were evaluated
- For PFS, patients alive without progression were censored on the last documented disease evaluation before the start of the new anticancer treatment or the end of follow-up, whichever occurred first
- For OS, patients alive at the end of follow-up were censored on the last day of follow-up
- Date of the last disease response assessment was determined by selecting the last available date of response assessments, clinical assessments of progression (ie, hematology), and posttreatment telephonic assessments of progression before a patient starting a new anticancer therapy or the end of follow-up (whichever occurred first)

Statistical analysis

- Patient demographics and clinical response were summarized using descriptive statistics
- Clopper-Pearson's exact 95% CI was calculated for all dichotomous outcomes
- Kaplan-Meier curve was estimated to assess the time-to-event outcomes

Landmark analysis

- Landmark analysis was performed to assess the association between treatment response at the landmark time point (set at 12 months after the index date) and survival outcomes
- A subset of patients (without PD, death, or censored before landmark time point for PFS and without death or censored before the landmark time point for OS) still in the analysis at 12 months were retained and categorized into the following cohorts:
  - CR/CR with incomplete blood marrow recovery (CRi) cohort: patients who achieved CR/CRi and whose disease did not progress before the landmark time point
  - Non-CR/non-CRi cohort: patients included in PR/nodular PR (nPR) cohort and non-CR/non-PR cohort:
    - PR/nPR cohort: patients who achieved PR/nPR but not CR/CRi and whose disease did not progress before the landmark time point
    - Non-CR/non-PR cohort: patients who did not achieve CR/CRi or PR/nPR before the landmark time point or who achieved CR/CRi or PR/nPR but progressed before landmark, and those who were never evaluated before landmark
- Survival outcomes were compared between cohorts using the Kaplan-Meier approach and Cox proportional hazard model
- Unadjusted Cox proportional hazards model was estimated with only 1 independent variable corresponding to the response before the landmark time point for both approaches listed above
- Adjusted models were estimated where indication, age, gender, race, ethnicity, ECOG PS, number of prior LOTs, and study treatment class were assessed for inclusion in the Cox proportional hazards model. Stepwise variable selection was utilized. A significance level of 0.20 was used for a variable to enter the model, and 0.15 was used to stay in the model

Patients with R/R CLL/SLL achieving and maintaining CR/CRi 12 months after treatment had significantly longer PFS than patients in other response groups

Figure 4. Landmark analysis: PFS (n = 1178)

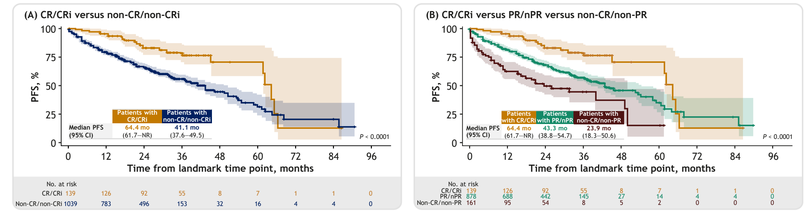


Figure 5. Landmark analysis: OS (n = 1404)

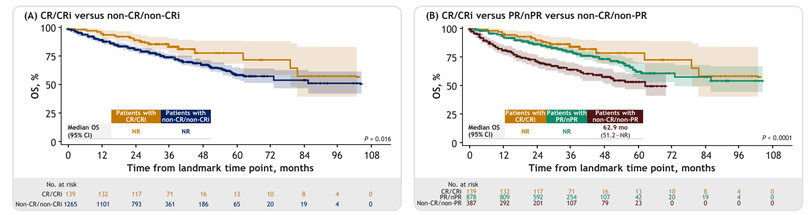
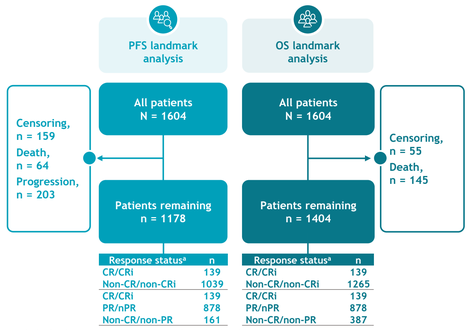


Table 3. Adjusted landmark analysis: PFS and OS

	PFS (n = 1178)		OS (n = 1404)	
Adjusted HR (95% CI)	CR/CRi versus non-CR/non-CRi	CR/CRi versus PR/nPR versus non-CR/non-PR	CR/CRi versus non-CR/non-CRi	CR/CRi versus PR/nPR versus non-CR/non-PR
Variable (vs reference population)				
CR/CRi at landmark (non-CR/non-CRi)	**0.62 (0.42–0.90)**	–	0.73 (0.47–1.12)	–
CR/CRi at landmark (non-CR/non-PR)	–	**0.41 (0.27–0.64)**	–	**0.39 (0.25–0.60)**
CR/CRi at landmark (PR/nPR)	–	**0.64 (0.44–0.93)**	–	0.77 (0.51–1.18)
PR/nPR at landmark (non-CR/non-PR)	–	**0.65 (0.50–0.84)**	–	**0.50 (0.40–0.63)**
Age > 65 y (≤ 65 y)	–	–	**1.49 (1.18–1.89)**	**1.52 (1.20–1.92)**
Male gender (female)	–	–	**1.30 (1.02–1.65)**	1.27 (1.00–1.61)
Asian (White)	0.68 (0.45–1.03)	0.67 (0.44–1.02)	**0.50 (0.26–0.98)**	0.57 (0.29–1.12)
Black or African American (White)	1.11 (0.52–2.38)	1.17 (0.55–2.51)	0.86 (0.35–2.11)	0.88 (0.36–2.14)
Missing race (White)	0.88 (0.48–1.60)	0.88 (0.48–1.62)	1.08 (0.59–1.96)	1.08 (0.60–1.96)
Other race (White)	**2.66 (1.36–5.21)**	**2.47 (1.26–4.83)**	**3.09 (1.52–6.30)**	**3.04 (1.49–6.19)**
Hispanic or Latino (Not Hispanic or Latino)	1.48 (0.96–2.29)	1.45 (0.94–2.24)	–	–
Missing ethnicity (Not Hispanic or Latino)	**1.72 (1.26–2.34)**	**1.71 (1.25–2.33)**	–	–
ECOG PS 1 (0)	1.16 (0.95–1.42)	1.18 (0.96–1.44)	**1.61 (1.27–2.05)**	**1.63 (1.28–2.07)**
ECOG PS 2 (0)	**2.06 (1.38–3.09)**	**2.14 (1.43–3.21)**	**2.78 (1.87–4.14)**	**2.70 (1.81–4.01)**
2 prior LOTs (1)	1.15 (0.90–1.48)	1.11 (0.86–1.43)	1.34 (1.00–1.80)	1.24 (0.93–1.67)
3 prior LOTs (1)	**1.88 (1.43–2.48)**	**1.88 (1.42–2.47)**	**2.11 (1.53–2.90)**	**2.05 (1.49–2.82)**
≥ 4 prior LOTs (1)	**1.96 (1.50–2.56)**	**1.88 (1.44–2.45)**	**2.24 (1.67–3.01)**	**2.02 (1.51–2.69)**
Study treatment with BCL2i (non-BCL2i)	**0.38 (0.30–0.49)**	**0.42 (0.32–0.54)**	**0.71 (0.56–0.92)**	–

Bold blue text denotes statistical significance (nominal $P < 0.05$). Candidate variables used initially to build the model included: indication, age, gender, race, ECOG PS, ethnicity, prior LOTs, and study treatment.

Figure 3. Landmark cohort disposition



[a]At the landmark time point, which was set at 12 months after the index date.

Landmark analysis

- Of the 1604 patients, 1178 and 1404 were included in the PFS and OS landmark analyses, respectively (**Figure 3**)
- Patients who achieved and maintained CR/CRi by landmark had significantly longer PFS versus:
  - Non-CR/non-CRi cohort, with an adjusted HR of 0.62 ($P = 0.01$) (**Table 3**)
  - PR/nPR cohort, with an adjusted HR of 0.64 ($P = 0.02$) and non-CR/non-PR cohort, with an adjusted HR of 0.41 ($P < 0.001$)
- At 24 months from landmark time point, 90% (85%–95%) of patients with CR/CRi, 87% (84%–89%) with PR/nPR, and 72% (67%–77%) with non-CR/non-PR were still alive (**Figure 5**)
- Patients who achieved and maintained CR/CRi by landmark had statistically longer OS versus the non-CR/non-PR cohort, with an adjusted HR of 0.39 ($P < 0.001$; **Table 3**)
- Patients who achieved and maintained CR/CRi by landmark had numerically (although not statistically significant) longer OS versus:
  - Non-CR/non-CRi cohort, with an adjusted HR of 0.73 ($P = 0.15$)
  - PR/nPR cohort, with an adjusted HR of 0.77 ($P = 0.24$)
- Limitations include limited dataset representation (6 clinical trials with only currently available standard treatment classes), residual confounding (inclusion of only the factors available in the database with relatively low missingness rates), and the requirement to exclude patients who experienced the primary endpoint of interest before landmark (patients with shorter PFS/OS durations were excluded, potentially affecting generalizability of results)

Results

Table 1. Baseline demographic and clinical characteristics

	N = 1604
Median (Q1, Q3) age, y	68 (61, 74)
Age ≤ 65 y, n (%)	672 (42)
Age > 65 y, n (%)	932 (58)
Male, n (%)	1069 (67)
Race, n (%)	
White	1409 (88)
Asian	111 (7)
Black or African American	21 (1)
Other[a]	20 (1)
Missing	43 (3)
Ethnicity	
Not Hispanic or Latino	1302 (81)
Hispanic or Latino	72 (4)
Missing	230 (14)
Median (Q1, Q3) follow-up period, y	3.4 (2.2, 4.1)
ECOG PS, n (%)	
0	678 (42)
1	817 (51)
2	109 (7)
Prior BTKi exposure, n (%)	185 (12)
Prior venetoclax exposure, n (%)	13 (1)
Mean (SD) normalized LDH[b,c]	1.2 (0.9)
Study treatment class, n (%)[d]	
Anti-CD20 monoclonal antibody	201 (13)
BTKi	648 (40)
PI3Ki	158 (10)
BCL2i	643 (40)
Prior lines of therapy	
1	720 (45)
2	395 (25)
3	226 (14)
4 or higher	263 (16)

[a]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, South African, European, Armenian, New Zealand Māori, and Arabic; [b]Ratio of serum LDH divided by serum LDH ULN measured at time point before and closest to the index date; [c]Data were missing in 639 patients; [d]Percentages do not sum up 100% because some patients received > 1 study treatment class. BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; Q1, first quartile; Q3, third quartile; SD, standard deviation.

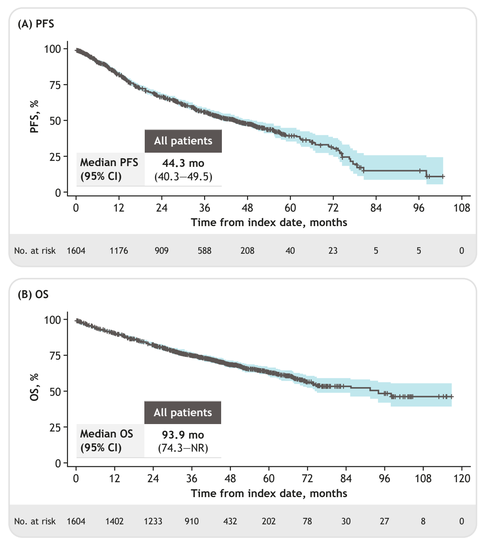
Table 2. Response outcomes

	N = 1604
BOR, n (%)[a]	
CR/CRi	242 (15)
PR/nPR	990 (62)
Stable disease	212 (13)
PD	51 (3)
Missing	109 (7)
CRR, % (95% CI)	15.1 (13.4–16.9)
ORR, % (95% CI)[b]	76.8 (74.7–78.9)
DOCR, months (95% CI)[c,d]	
Median (50% continued survival)	65.7 (54.3–70.0)
DOR, months (95% CI)[d,e]	
Median (50% continued survival)	49.9 (45.6–55.3)

[a]Best response (CR/CRi > PR/nPR > SD > PD), measured from the index date until death or PD or the start of new anticancer therapy or end of the follow-up, whichever occurred first (inclusive). Patients without evidence of response assessment at the end of follow-up were assessed as "Missing". New anticancer therapy was defined as any therapy starting after the end of the study treatment. If a patient restarted study treatment within 1 year of the end of the study treatment, it was not considered a new anticancer therapy. Anticancer therapies were identified using WHODrug codes starting with "L"; [b]Defined as the proportion of patients who attain CR/CRi or PR/nPR; [c]Defined among patients with BOR of CR/CRi as the time from initial CR/CRi to PD or death due to any cause, whichever occurred earlier; [d]Patients were censored on the last documented disease evaluation before the start of the new anticancer therapy or the end of follow-up, whichever occurred first; [e]Defined among patients with BOR of CR/CRi or PR/nPR as the time from initial CR/CRi or PR/nPR to PD or death due to any cause, whichever occurred earlier.

- There were 1604 patients across all eligible clinical trials who met the patient selection criteria (**Table 1**)
- CRR was 15.1% with a median DOCR of 65.7 months; ORR was 76.8% with a median DOR of 49.9 months (**Table 2**)
- Survival outcomes in the 1604 patients are shown in **Figure 2**
  - Median PFS was 44.3 months and median OS was 93.9 months

Figure 2. Survival outcomes (N = 1604)



Conclusions

- Among patients with R/R CLL/SLL, achieving and maintaining CR/CRi by 12 months after the start of treatment (without progression or censoring) was associated with significantly improved PFS versus achieving and maintaining PR/nPR, which was also better than not achieving/not maintaining any response
- Results show that ongoing CR/CRi by 12 months may be an informative early response endpoint for assessing the PFS in this patient population

References

1. Jones JA, et al. *Lancet Oncol* 2018;19:65–75.
2. Lew TE, et al. *Blood Adv* 2021;5:4054–4058.
3. Mato AR, et al. *Clin Cancer Res* 2020;26:3589–3596.

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