Decoding the Predictive Role of Complete Response/Remission Rate (CR) for Overall Survival (OS) in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

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Background

- Patients with R/R CLL face increasingly poor outcomes as treatment options are exhausted. This creates a significant unmet need for effective, innovative treatments.
- While OS is considered the gold-standard endpoint by regulatory agencies for the evaluation of new treatments in solid and liquid tumors,[1] evaluating OS in clinical trials can be inefficient due to the need for long follow-up or large sample sizes to capture a statistically adequate level of efficacy. This creates a barrier for patients' access to potentially life-saving treatments.
- Surrogate endpoints are intermediate outcomes that allow for earlier data collection and prediction of long-term clinical benefits for new treatments in randomized and real-world settings.[2]
- Achieving CR by International Workshop on CLL 2018 criteria indicates complete eradication of CLL/SLL in all disease compartments, including resolution of lymphadenopathy and organomegaly, clearance of bone marrow disease, and full recovery of peripheral blood counts.[3]
- As response to treatment is observed much earlier than OS, and CR may strongly predict durable remission, CR rate can provide early insights into the long-term efficacy of curative treatments for CLL. CR rate has been used to support expedited regulatory approvals for modern treatments in R/R CLL. For example, the US FDA recently approved lisocabtagene maraleucel based on CR results from the TRANSCEND CLL 004 trial.[4,5]
- Although a recent study[6] investigated the association between the improvements in CR rates and PFS in R/R CLL, the use of CR rate as a predictor or surrogate endpoint for OS in R/R CLL is not yet fully established.
- Study level association between CR-OS in R/R CLL has previously been studied using aggregate level CR and reconstructed survival data from clinical trials and real-world evidence studies,[7] but the evidence base of this existing study does not reflect recent transformations in the treatment landscape of the disease. Moreover, this study did not incorporate the effect of PR and prior lines of therapy (LoT) into correlation assessment.

Objectives

- **Primary Objectives:** To quantify the association between CR and OS in R/R CLL and investigate the impact of class of therapy on this association
- **Secondary Objectives**: To assess the auxiliary impact of PR and LoT information on the CR-OS association.

Methods

- Randomized controlled trials (RCTs) were identified from a previously published systematic review in R/R CLL.[6]
- Pseudo-individual patient data (IPD) for OS were reconstructed[8] from 19 RCTs reporting arm-specific CR rates and prior LoT distribution.
- Proportional hazards (PH) models (Cox, exponential, Weibull, and Gompertz) using arm-specific CR and partial response (PR) rates and fraction of patients with >2 prior LoT (hereafter "fraction of 3L+ patients") as covariates (i.e., predictors) were fitted to pooled pseudo-IPD for OS across RCTs, and the best fitting model was selected based on Akaike information criterion.
- The association between each covariate and OS was evaluated by the impact of 20% increase in each covariate (unilaterally) on the risk of death, and on median and mean OS—calculated over a 30-year time horizon. Sensitivity of the results with respect to model choice and therapies' mechanism of action (classified as non-targeted and targeted) was also assessed.

Results

- For each analysis, numbers of patients and observed numbers of deaths along with the mean values and ranges of each covariate across the evidence base of each analysis are summarized in **Table 1**. Mean CR rate (9%) and mean fraction of 3L+ patients (34% to 36%) were both similar across targeted and non-targeted therapies, but the mean PR rate was higher among targeted therapies compared to non-targeted therapies (62% vs. 40%).
- The Weibull PH model was the best fit to the data from all therapies and non-targeted therapies, and the exponential model was the best fit to the data from the targeted therapies. However, regardless of therapy class, reductions in mortality risks and magnitude of extensions of median and mean OS with respect to improvements in CR rates were only marginally sensitive to model choice.
- Estimated reductions in mortality risk for 20% unilateral increase in each of the covariates (PR, CR, and fraction of 3L+ patients) are summarized in **Table 2**. Compared to PR and fraction of 3L+ patients, CR was estimated to have a greater impact on mortality risk. Consistent with clinical intuition, while increases in CR and PR rates were estimated to reduce mortality risk, increase in the fraction of 3L+ patients was estimated to increase mortality risk at the population level.
- Impact of 20% increase in each covariate with respect to pre-specified null values on median and mean OS is summarized in **Table 3.** In particular, **Figure 1** displays the predicted OS trends from the best-fitting PH models for all therapies as well as subpopulations of targeted and non-targeted therapies.

Table 1: Summary of prior LoT, response and survival outcomes across studies

Studies	N, Patients	n (%), Deaths	Mean CR Rate (Range)	Mean PR Rate (Range)	Mean 3L+ Fraction (Range)
All	5,180	1,279 (24.7%)	8.9% (0%, 40.8%)	47.1% (4.0%, 81.0%)	34.9% (0.0%, 100.0%)
Targeted Therapies	2,064	433 (21.0%)	9.0% (0.0%, 40.8%)	61.5% (40.0%, 81.0%)	36.2% (0.0%, 81.9%)
Non-Targeted Therapies	3,116	846 (27.2%)	8.9% (0.0%, 36.8%)	40.0% (4.0%, 71.0%)	34.3% (0.0%, 100.0%)

Abbreviations: 3L+ = Third-line or greater, CR = Complete Response, LoT = Lines of Therapy, OS = Overall Survival, PR = Partial Response.

Table 2: Summary of percent changes in the risk of death for each 20% increase in each covariate

Covariate	All	Targeted Therapies	Non-targeted Therapies
PR	−18% (95% CI: −23%, −12%)	3% (95% CI: −12%, 20%)	−17% (95% CI: −24%, −9%)
CR	−33% (95% CI: −39%, −26%)	−32% (95% CI: −41%, −22%)	−20% (95% CI: −33%, −4%)
Fraction of 3L+ patients	6% (95% CI: 1%, 12%)	29% (95% CI: 18%, 41%)	6% (95% CI: 0%, 13%)

Abbreviations: CI = Confidence Interval, CR = Complete Response, LoT = Prior Lines of Therapy, PR = Partial Response.

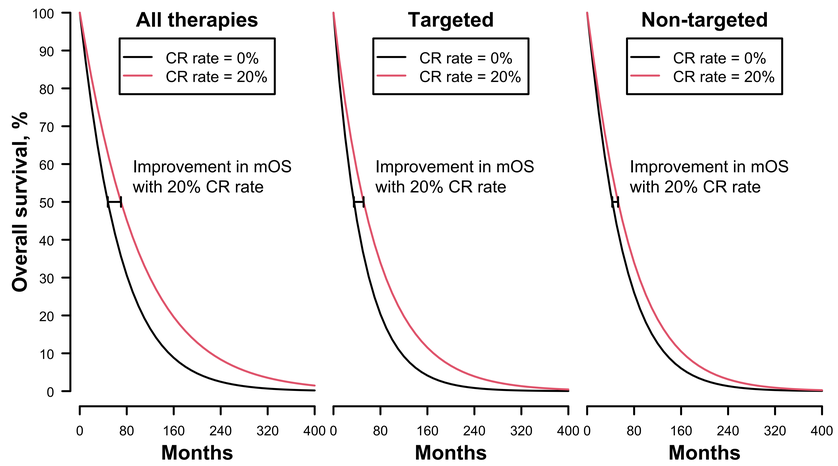
Table 3: Predicted median and mean OS from the best-fitting PH models under two different scenarios for each covariate

Therapies	Covariate	Covariate = 0%		Covariate = 20%	
		Median (months)	Mean (months)	Median (months)	Mean (months)
All	CR	47.8	67.3	70.2	96.9
	PR	34.7	49.2	41.8	59.1
	Fraction of 3L+ pts.	77.2	106	72.7	100.0
Targeted	CR	34.8	50.7	51.3	73.9
	PR	46.8	67.7	45.6	66.0
	Fraction of 3L+ pts.	154.4	179.0	119.5	152.0
Non-targeted	CR	42.8	59.5	52.7	72.9
	PR	30.9	43.2	36.8	51.3
	Fraction of 3L+ pts.	61.7	84.8	58.3	80.5

Note: In the prediction of median and mean OS under varying levels of each covariate, values of other two covariates were held constant at prespecified values. For CR and PR, these prespecified values were the observed means across the evidence base (i.e. 8.9% for CR and 47.1% for PR in the all-therapy analysis) and fraction of 3L+ patients was held constant at 100%. Baseline characteristics in the hypothetical populations for which mean and median OS are calculated were assumed to be identical to those in the observed data.

Abbreviations: 3L+ = Third-line or greater, CR = Complete Response, PH = Proportional Hazards, PR = Partial response, pts. = Patients.

Figure 1: Estimated OS curves from the best-fitting PH models under two different CR scenarios



Note: In the prediction of median and mean OS under varying levels of each covariate, values of other two covariates were held constant at prespecified values. For CR and PR, these prespecified values were the observed means across the evidence base (i.e. 8.9% for CR and 47.1% for PR in the all-therapy analysis) and fraction of 3L+ patients was held constant at 100%. Each hypothetical population was assumed to have the same baseline characteristics as in their respective evidence base except CR.

Abbreviations: CR = Complete Response, mOS = Median OS, OS = Overall Survival. PH = Proportional Hazards.

Conclusions

- Improvements in CR rates were consistently associated with clinically meaningful gains in OS in R/R CLL, regardless of therapy class and model choice.
- Association between PR and OS was more meaningful in the overall evidence base across all therapies and among non-targeted therapies compared to the association among targeted therapies.
- Impact of fraction of 3L+ patients on OS was stronger for targeted therapies compared to the impact for all therapies and non-targeted therapies.
- Findings support the potential use of CR rate as a surrogate endpoint for OS in R/R CLL. Complementing existing evidence with trial-level CR-OS surrogacy using established frameworks such as bivariate meta-analysis would strengthen CR as a surrogate endpoint for OS. The relevance of PR as a surrogate endpoint for OS may vary by therapy class.
- The main limitation of this survival analytic approach is the use of study-level covariate data where heterogeneity across patients and collinearity among covariates could not be accounted for. Inclusion of real-world evidence and single-arm studies in the evidence base in future research can reduce the uncertainty around the association between each covariate and OS.

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