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# POSTER ABSTRACTS

## 642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

### A Long-Term Analysis of Lenalidomide and Rituximab (R $^2$) for the Treatment of Chronic Lymphocytic Leukemia

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**Background:**Lenalidomide (len) is an immunomodulator that binds cereblon and alters protein degradation of Ikaros and Alios via E3 ligase. The R $^2$ regimen (len paired with Rituximab (R)) is an effective treatment (tx) for lymphoid malignancies, and its promise in patients (pts) with chronic lymphocytic leukemia (CLL) has been previously reported (James et al, JCO 2014). We performed a long-term, single-center follow-up (f/u) analysis of pts previously enrolled in two phase 2 open-label studies evaluating R $^2$ in both treatment naïve (TN) and relapsed-refractory (R/R) CLL pts.
**Methods:** The CLL Research Consortium (CRC)-014 trial enrolled TN pts. Pts initiated 2.5 mg of len daily for 21 days (D) out of a 35-day cycle (C) for C1, then 28d cycles for C2-C7. Len was escalated to 10 mg daily as tolerated. R was initiated in a dose-intensive manner: 50 mg/m $^2$ on C1D29; 325 mg/m $^2$ on C1D31 and C1D33; 375 mg/m $^2$ weekly for C2; then 375 mg/m $^2$ on D1 for C3-C7. R $^2$ was stopped after 7C.
The CRC-022 trial enrolled R/R pts. Pts initiated 5 mg of len daily for 21 days of each 28d cycle, with escalation to 25 mg daily as tolerated. R was initiated weekly at 375 mg/m2 for C1, then 375 mg/m2 on D1 for C2-C6. R/R pts could continue len for up to 6 consolidative cycles after completion of 6C of R $^2$.
Response assessment was performed using iwCLL criteria and minimal residual disease (MRD) was assessed by multi-parametric flow cytometry of the bone marrow with a sensitivity of 10 $^{-4}$. Time-to-event analyses were performed with the Kaplan-Meier method.
**Results:** We identified 43 TN pts and 25 R/R pts. Notably, 6 pts enrolled in both studies sequentially. The median age for all pts was 62.5 years (range 45-82). Rai staging at time of tx initiation was: 2 38.7%; 3 24.2%; 4: 37.1%. The profile of cytogenetic abnormalities was: 54.8% del(13q); 17.7% del(11q); 16.1% trisomy 12; 9.7% del(17p); 19.4% normal; and 1.6% complex karyotype. 69.4% of pts had unmutated immunoglobulin heavy chain. The median number of prior tx for R/R pts was 2 (range:1-6).
The overall response profile was: CR 13.2%; PR 69.1%; SD 2.9%, PD 1.5%. No pts had undetectable MRD. At median f/u time of 129 months (mo), median progression-free survival (PFS) was 15.7 mo in the TN pts and 25.4 mo in the R/R pts ($p = 0.11$, Figure 1A). The trend towards improvement may reflect len consolidation available to the R/R pts. Median time to next treatment (TTNT) was also not significantly different between the TN pts and the R/R pts (29.5 mo vs. 29.0 mo, $p = 0.56$). Median OS was significantly higher for the TN pts than the R/R pts (164.8 mo vs. 108.0 mo, $p = 0.0001$, Figure 1B). This likely reflects heavy pre-treatment in the R/R pts. Across both TN and R/R groups, 21 pts died: 8 deaths (38.1%) were related to CLL, none were related to R $^2$ treatment, and 13 (61.9%) were related to other causes or unknown.
Adverse events included: 30.9% of pts with Grade (Gr) 3-4 neutropenia, 58.8% of pts with Gr ≥2 thrombocytopenia, and 30.9% of pts with Gr ≥2 anemia. During the extended f/u period, 16.2% of pts developed pneumonia and 13.2% developed viral infections. Through the extended f/u, venous thromboembolism (VTE) developed in 9 (14.5%) pts. Only 2 pts developed VTE during active R $^2$ and both were not taking prophylactic aspirin. Five other pts developed VTE >6 mo after stopping R $^2$ and had other provoking factors. Four pts (6.5%) developed Richter transformation lymphoma. 43.5% of pts developed cutaneous neoplasms and 12.9% of pts developed non-cutaneous solid neoplasms. No pts developed secondary myeloid neoplasms.
**Conclusions:** In this long-term pooled f/u analysis of CLL pts, we found that R $^2$ provided high ORR, modest PFS and OS benefit, and tolerable long-term toxicities. The ORR of R $^2$ in this study (82.3%) compares favorably to ORR of R monotherapy in previous studies (51%, Hainsworth et al, JCO 2003). The absence of secondary myeloid neoplasms suggests that len may not substantially increase cumulative secondary malignancy risk-the cumulative cutaneous neoplasm incidence may reflect elevated baseline risk in CLL pts. Importantly, we found no increased risk in deaths attributed to therapy. The demonstrated activity of R $^2$ in CLL warrants further investigation of len in combination with other agents. Currently, new immunotherapeutic

approaches-such as bispecific antibodies and CAR-T cell therapy-are being investigated in CLL. Given len's immunomodulatory properties, combination approaches with these treatments should be explored in future trials.

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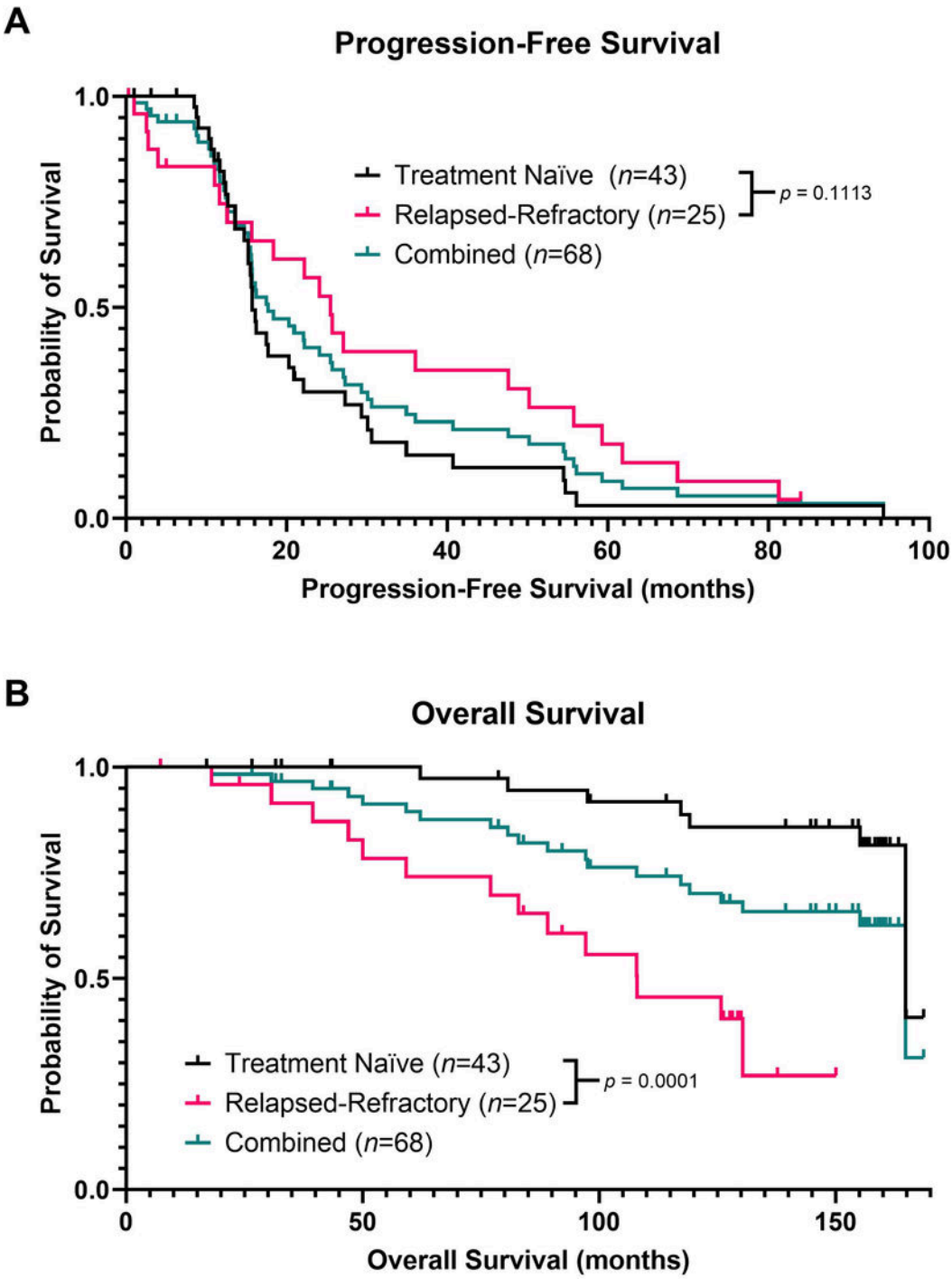


*Figure 1: Progression-free survival (A) and overall survival (B) Kaplan-Meier curves stratified by cohort: treatment naïve (black),relapsed-refractory (red), and combined (green).*

**Figure 1**

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