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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Targeted Agents in Chronic Lymphocytic Leukemia (CLL): Advancements in Overall Survival Outcomes?

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The impact of targeted agents (TAs) in fully mitigating the detrimental effects of CLL on overall survival (OS) remains uncertain. To address this, we compared the 5-year OS of treatment-naïve CLL pts who received targeted agents (TAs) in phase 3 clinical trials with the 5-year OS of age- and gender-matched general population (AGMGP) in Italy and the US. For this analysis, we included clinical trials that involved elderly or unfit pts (RESONATE2, ILLUMINATE, ALLIANCE, ELEVATE-TN, CLL14, and GLOW). We also considered trials enrolling fit pts eligible for FCR (Fludarabine, Cyclophosphamide, and Rituximab) treatment (ECOG1912, FLAIR, and CLL13).

We used the method proposed by Liu et al. [BMC Med Res Methodol 2021;21(1):111] to reconstruct individual patient data (IPD) from published Kaplan-Meier survival curves. The expected OS rate for the control population was calculated using 2019 Italian data from the Istituto Nazionale di Statistica (ISTAT) and the 2019 US database. OS of CLL pts and AGMGP were compared for restricted mean overall survival time (RMOST). The treatment effect on OS was then measured as the difference of RMOST and expressed in months.

The elderly CLL trial analysis group (2,222 pts) received TAs (58.1%) or chemo-(immunotherapy)(CT/CIT) (41.8%). TAs included Bruton Kinase inhibitors (BTKis) (i.e., ibrutinib [I] or acalabrutinib [A]) alone or with anti-CD20 (75%) or fixed-duration (FD) venetoclax [V] combos (25%). The control CT/CIT arm mainly consisted of CLB+Obinu (66%). The median age of pts was 70 years (range 47-93). The prevalence of del(17p)/mutated *TP53*, unmutated *IGHV*, or CIRS score>6 were 9.1% (0-16%), 62.4% (43-66.5%), and 48.6% (11.7-86.1%), respectively.

In the aggregate analysis, the 5-year RMOST of elderly pts treated with CT/CIT (RESONATE2, ILLUMINATE, ALLIANCE, ELEVATE-TN, CLL14, and GLOW) was found to be inferior compared to the 5-year RMOST of Italian [Difference (D), -4.2 months; 95% CI: -5.3 to -3.0; $P < 0.0001$] and US [D, -3.6 months; 95% CI: -4.7 to -2.4; $P < 0.001$] AGMGP (Fig 1).

The analysis of pts treated with TAs provided conflicting results. In the cross-matched comparison between Italian AGMGP and pts treated with BTKi single-agent or combined with anti-CD20, the 5-year RMOST difference indicates an OS advantage for the former (Fig 1). The same applied in the comparison between pts who received FD V-based therapies and Italian or US AGMGP. Notably, the 5-year RMOST of elderly CLL pts treated with BTKi single-agent (RESONATE2, ALLIANCE, ELEVATE-TN) or combined with anti-CD20 (ILLUMINATE, ALLIANCE, ELEVATE-TN) was similar to the 5-year RMOST of US AGMGP [D, -1.2 mo. (-2.5 to 0.1); $P = 0.07$ for both](Fig 1).

OS comparisons between elderly CLL pts and control populations, although controlled for age and gender, do not account for the interaction between comorbidity burden and OS. The proportion of pts with CIRS score > 6 varied widely across trials: RESONATE2, 31%; ELEVATE-TN, 11.1% in the A-arm and 16.8% in the AO-arm; ILLUMINATE, 32.7%; CLL14, 86.1%; and GLOW, 69.0%.

Since CLL pts eligible for FCR enrolled in the ECOG1912, FLAIR, and CLL13 trials typically have fewer comorbidities, they enable a clearer evaluation of the TA's impact on OS. Overall, 1,437 patients (64.5%) received TAs, and 789 (35.4%) received CIT. TAs consisted of I+R (51.5%) or FD V-based combinations (VO, VI, VO+Ibr) (48.5%). The median age of pts was 62 years (range 27-84). The prevalence of ECOG PS 0 and unmutated IGHV were 68% and 56%, respectively.

The 5-year RMOST of younger/fit pts treated with FCR was inferior to the 5-year RMOST of Italian AGMGP [D, -1.1 mo; 95% CI: -1.8 to -0.3; $P = 0.003$] but similar to the 5-year RMOST of US AGMGP [D, -0.4 mo; 95% CI, -1.1 to 0.4; $P = 0.28$]. Interestingly, no significant difference could be observed between the 5-year RMOST of younger/fit pts treated with TAs (IR or Ven-based) and the 5-year RMOST of Italian or US AGMGP (Fig 2).

In conclusion, our results suggest that in comparison to CIT, TAs mitigate but do not fully abrogate the detrimental impact of CLL on OS. The intricate interaction between CLL characteristics and the burden of comorbidities can potentially lead to misleading results in clinical trials of elderly pts. The extent of OS improvement obtained with TAs seems higher in younger/fit CLL pts who have fewer comorbidities. However, longer follow-up is needed to discern the ability of these treatments to mitigate the impact of CLL on OS over longer time intervals.

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5-year Restricted Mean Overall Survival Time (RMOST) difference between Elderly CLL pts and AGMGP.

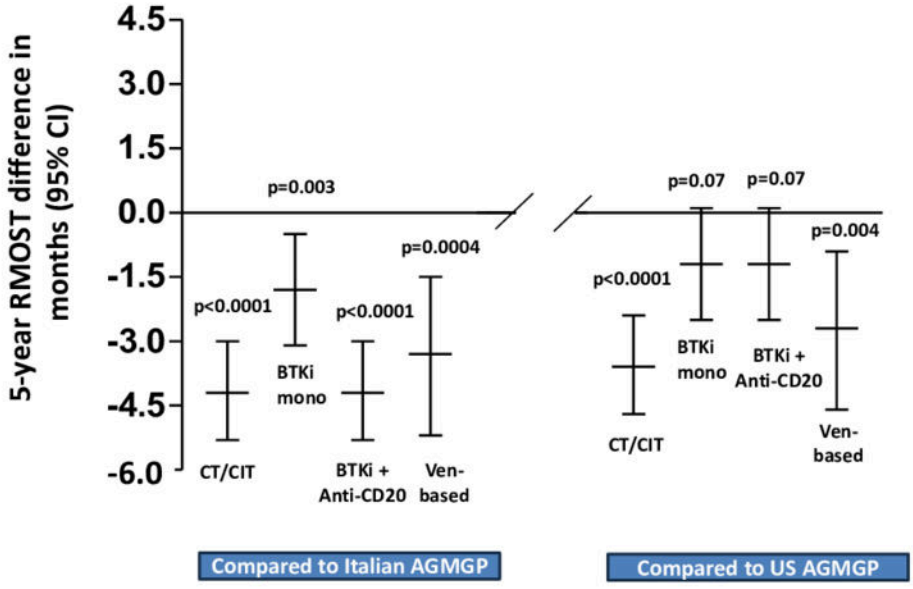

Fig 1

5-year Restricted Mean Overall Survival Time (RMOST) difference between Fit CLL pts and AGMGP.

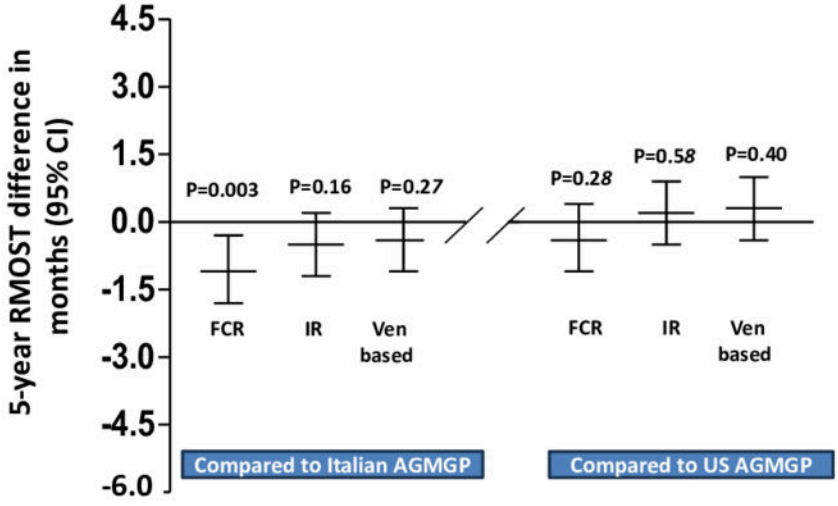

Fig 2

Figure 1

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