Meta-analysis estimating the impact on Progression-Free Survival (PFS) after front line CLL fludarabine-based treatment according to the presence of high-risk biomarkers

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Objective

- **To determine the impact of high-risk biomarkers on Progression-Free Survival (PFS) after a first-line fludarabine-based treatment in patients with chronic Lymphocytic Leukemia (CLL).**

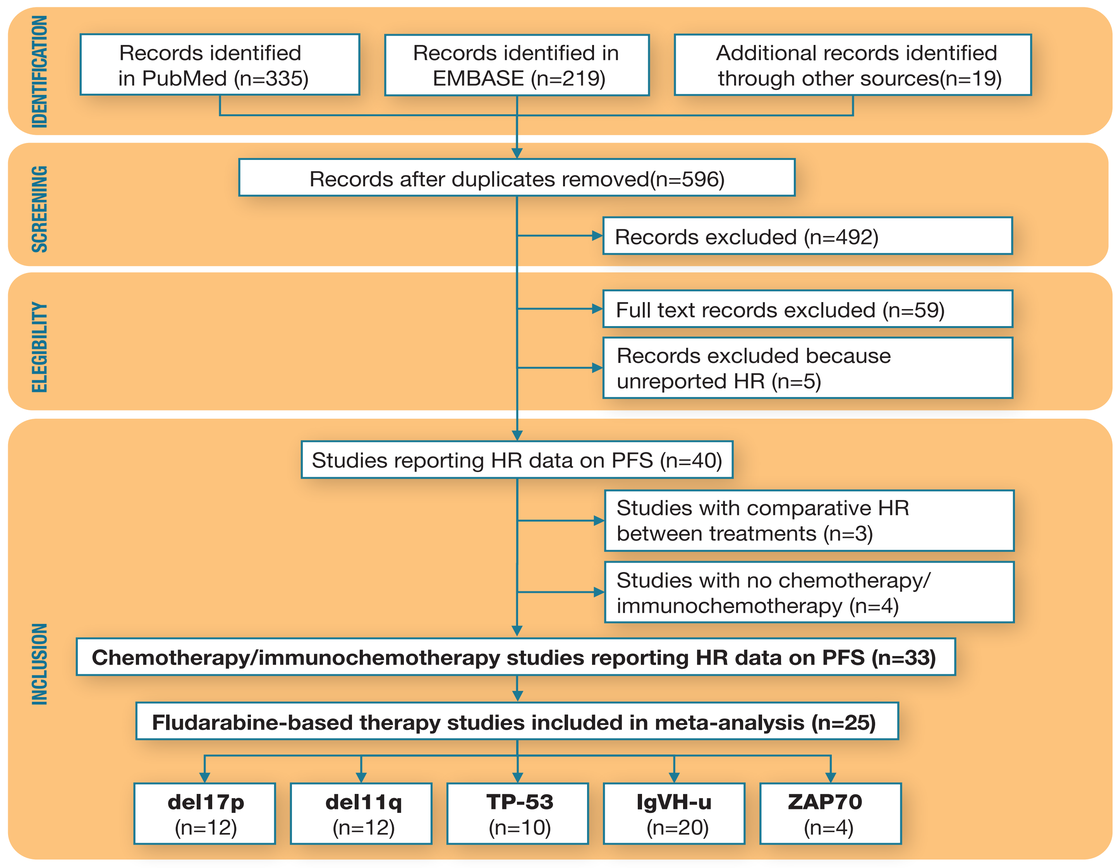
Methods

- A meta-analysis of 25 studies that relate treatment-specific PFS with the presence of different high-risk biomarkers in CLL patients treated with fludarabine-based therapies was conducted[1-25].
- The studies were previously identified through a systematic literature review using Medline and EMBASE databases and additional sources (scientific conferences) (January 2007-November 2017)[26]. The search was focused on studies that relate the response to CLL treatments in term of PFS to the presence of high-risk prognostic biomarkers **(Fig 1)**.
- The high-risk biomarkers considered were:
  - 17p deletion (del17p)
  - 11q deletion (del11q)
  - TP53 mutated gene (TP-53m)
  - unmutated immunoglobulin variable heavy-chain gene status (IgHV-u)
  - ZAP-70 expression
- The meta-analysis considered the Hazard Ratio (HR), comparing the presence (+) versus the absence (-) or the mutated/unmutated status (m/u) of each marker over the result in terms of PFS for each treatment.
- A random-effects model was used for the analysis. Cochran's Q test and I2 statistic were used to analyze heterogeneity[27].
- To assess the potential impact on results of different heterogeneity sources, models of meta-regression were set considering whether:
  1) the studies had imbalances in staging (RAI or Binet)
  2) the results originated from a multivariate analysis, and
  3) chlorambucil was the comparator arm in the clinical trial

Ibrutinib RESONATE-2 subanalysis (IGHV, del11q)

- Ibrutinib appears to have comparable efficacy independent of high-risk prognostic factors.
- For this purpose, a subanalysis of RESONATE-2 trial[28] was performed to calculate the impact of IgHV status and the presence of del11q on ibrutinib efficacy in terms of PFS.

Figure 1. Systematic review diagram



Inclusion criteria

- Spanish and/or English publications.
- Randomized Clinical Trials and/or Observational Studies.

The following high-risk prognostic factors should be included in the identified publications: del17p, TP53 status, del11q, IgHV, ZAP70.

Exclusion criteria

- Case reports, editorial letters, SLRs and letters to the editor.
- Studies referring to non-human species.
- Comments on studies.

Results

- From the 596 non-duplicated articles obtained from the systematic review, 25 studies including fludarabine-based therapies were analyzed using meta-analysis:12 had information about del17p, 12 of del11q, 10 of TP-53, 20 of IgHV and 4 of ZAP70 **(Fig. 1)**.
- The results from the meta-analysis showed that **(Fig. 2-6)**:
  - For **del17p**, the estimated joint HR for the effect on PFS comparing the presence vs the absence of this biomarker was 0.28 (CI 95% 0.20-0.39), with significant results Q test (p<0.01) and I2 = 71 %. The meta-regression indicated that all studies, including those with chlorambucil as a comparator, were a source of heterogeneity (p=0.005).
  - For **del11q**, the aggregated HR was 0.51 (CI 95% 0.44-0.59), with a non-significant grade of heterogeneity (p=0.09) and I2=38%.
  - For **IgHV**, aggregated HR for fludarabine-based therapies is estimated in 0.48 (CI 95% 0.40-0.58), with significant contrast of heterogeneity (p<0.01) and I2 = 84%.
  - For **ZAP-70**, the aggregated estimation for HR was 0.50 (CI 95% 0.27-0.53) with a significant contrast of heterogeneity (p<0.01) and I2 = 82%.
  - For **TP53**, HR was 0.41 (CI 95% 0.34-0.51), with a non-significant grade of heterogeneity (p=0.07) and I2=42%.

Ibrutinib RESONATE-2 subanalysis (IGHV, del11q)

- The subanalysis of RESONATE-2 study (median follow-up 29 months)[28] for del11q patients demonstrated a HR of 0.582 (CI 95% 0.223-1.521) with ibrutinib.
- The HR in IgHV subpopulations for ibrutinib was 1.198 (IC 95% 0.478-3.002) in the RESONATE-2 study.

Figure 2. Meta-analysis forest plot for del17p-/+ effect on PFS

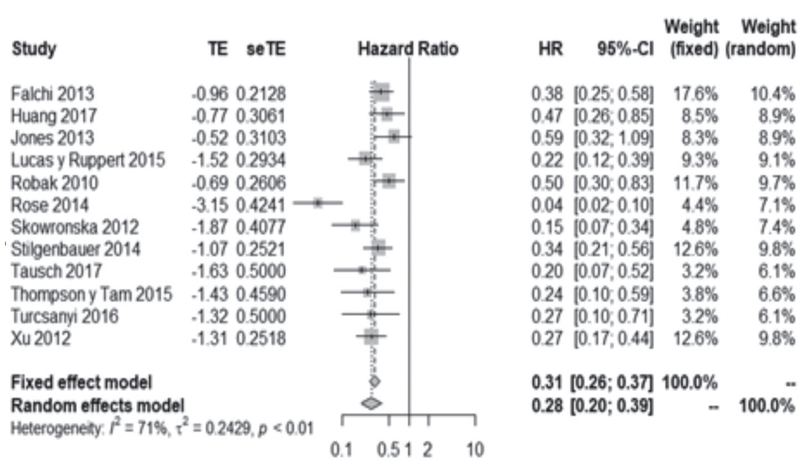


Figure 3. Meta-analysis forest plot for del11q-/+ effect on PFS

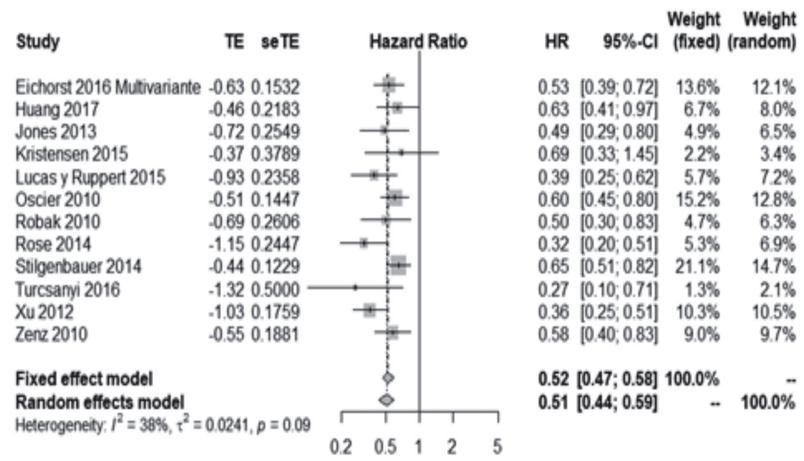


Figure 4. Meta-analysis forest plot for TP53 effect on PFS

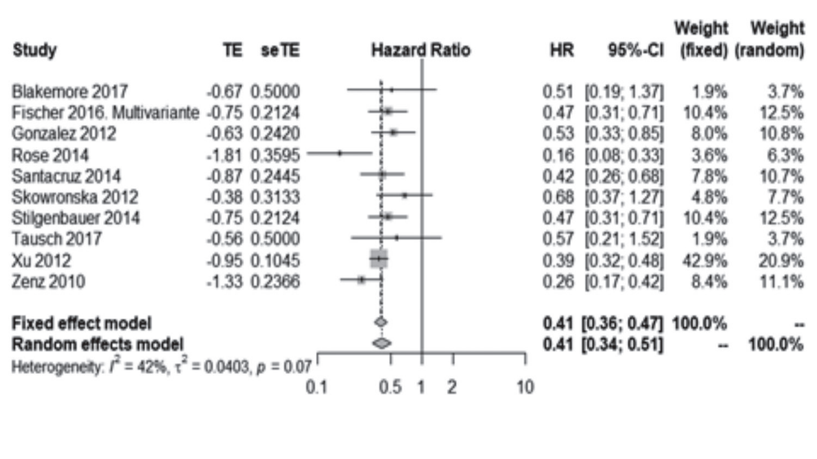


Figure 5. Meta-analysis forest plot for IgHV effect on PFS

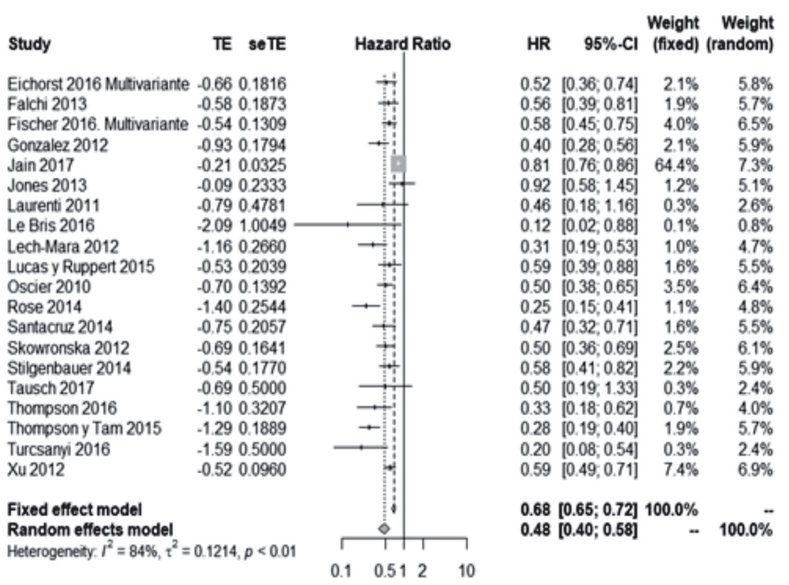
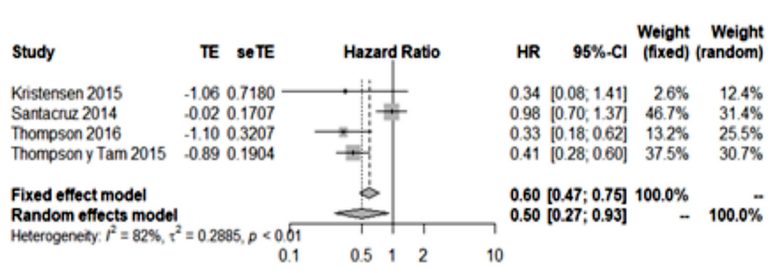


Figure 6. Meta-analysis forest plot for ZAP70-/+ effect on PFS



Conclusions

- **The presence of del17p, del11q, IgHV-u, TP53m or ZAP-70 are associated with poor survival prognosis owing to a lower PFS for fludarabine-based therapies in front-line CLL patients.**
- **On the contrary, the effect on PFS of ibrutinib is independent of the presence of del11q and IgHV-u (RESONATE-2 subanalysis).**
- **Recently, the ECOG1912 trial comparing ibrutinib based therapy (ibrutinib + rituximab) versus FCR (fludarabine + cyclophosphamide + rituximab) showed an increased efficacy in terms of PFS in the ibrutinib arm compared to FCR arm, especially in the IGHV-u patients.**

References

1. Blakemore S, et al. Blood. 2017;130:259.
2. Eichhorst B, et al. Lancet Oncol. 2016;17(7):928-942.
3. Falchi L, et al. Cancer. 2013;119(17):3177-85.
4. Fischer K, et al. Blood. 2016;127(2):208-15.
5. Gonzalez D, et al. Haematologica. 2013;98(2):274-8.
6. Huang SJ, et al. Leuk Res. 2017;55:79-90.
7. Jain P, et al. Blood 2017;130:3006.
8. Jones JA, et al. Leuk Lymphoma. 2013;54(12):2654-9.
9. Kristensen L, et al. Eur J Haematol. 2016;97(2):175-82.
10. Laurenti L, et al. Ann Hematol. 2011;90(1):59-65.
11. Le Bris Y, et al. Hematol Oncol. 2017;35(4):664-670.
12. Lech-Maranda E, et al. Arch Immunol Ther Exp (Warsz). 2012;60(6):477-86.
13. Lucas DM, et al. Leuk Lymphoma. 2015;56(11):3031-7.
14. Oscier D, et al. Haematologica. 2010;95(10):1705-12.
15. Robak T, et al. J Clin Oncol. 2010;28(11):1863-9.
16. Rose-Zerilli MJ, et al. Haematologica. 2014;99(4):736-42.
17. Santacruz R, et al. Haematologica. 2014;99(5):873-80.
18. Skowronska A, et al. J Clin Oncol. 2012;30(36):4524-32.
19. Stilgenbauer S, et al. Blood. 2014;123(21):3247-54.
20. Tausch E, et al. Haematologica. 2017;102(s2):70.
21. Thompson PA, et al. Blood 2016;128:232.
22. Thompson PA, Tam CS, et al. Blood. 2016;127(3):303-9.
23. Turcsanyi P, et al. Leuk Lymphoma. 2015;56(S1):1-166.
24. Xu M, et al. Med Oncol. 2012;29(3):2102-10.
25. Zenz T, et al. J Clin Oncol. 2010;28(29):4473-9.
26. Moher D, et al. PLoS Med 6(7):e1000097.
27. Higgins JP, et al. BMJ. 2003;327(7414):557-60.
28. Barr P, et al. Blood 2016 128:234

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