A Systematic Literature Review and Quality of Evidence Assessment of the Impact of high-risk biomarkers in progression-free survival associated with a first-line treatment in Chronic Lymphocytic Leukemia

Fernandez de la Mata M[1], Bello JL[2], Mosquera A[2], Antelo B[2], Sabater E[3], Burgos-Pol, R[3], Parra Gabilondo R[4], Climent JV[4], Casado MA[3], Gros B[5]

[1] Hospital Universitario Reina Sofía, Córdoba, Spain; [2] Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain; [3] Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid, Spain; [4] Janssen-Cilag, Madrid, Spain; [5] Janssen EMEA, Madrid, Spain

Objective

- **The aim is to identify and assess the quality of the available publications describing the relationship between high-risk prognostic biomarkers in Chronic Lymphocytic Leukemia (CLL) and the treatment response in first-line, measured in terms of Progression-Free Survival (PFS).**

Methods

- A systematic literature review was conducted using the Medline and Embase databases, considering a time frame from January 2007 to November 2017. The research was focused on studies that relate PFS to the presence of high-risk prognostic biomarkers: 17p deletion (del17p), 11q deletion (del11q), TP53 mutant gene (TP-53m), unmutated immunoglobulin heavy chain (IgVH-u) and ZAP-70.
- The strategy applied for the research follows the PRISMA international recommendations[1]. The scope included randomized clinical trials, observational and/or retrospective studies written in English and Spanish. Single-case design studies, systematic reviews, letters to the Editor, editorials, and studies concerning non-human species were excluded.
- The selection of the articles was done independently by two researchers who reached a consensus when one or more studies were only identified by one researcher. Additional studies identified in the bibliographic citations of the reviewed articles were incorporated to the analysis under reviewer's criteria.
- A descriptive table for each publication, including the Hazard Ratio results, median age and Rai and Binet distribution was built and the GRADE evaluation frame was used to analyze and standardize the quality of the evidence of these studies based on four fundamental domains: risk of bias, consistency, transparency and precision of results[2].

Results

- Three hundred thirty-five records were identified in PubMed, 219 records in Embase and 19 records were identified from other sources. After the systematic review process, 40 studies had PFS information related to the high-risk prognostic biomarkers considered[3-42]. Out of those, 22 (55%) had information about del17p subgroup, 20 (50%) informed about del11q-, 27 (68%) analyzed IgVH-u, 10 (25%) had information about TP-53m and 6 (15%) about ZAP-70 expression **(Fig. 1)**.
- Based on the GRADE scale, the quality of the evidence of the studies for all biomarkers was moderate, which means that the evidence may reflect the true effect but further research may change our confidence in the estimate of effect and may change the estimate. Expanding on these results, evidence for del11q-, del17p- and IGHV-u studies was moderate (3 points) including low rated studies (2 and 1 point) to studies with the highest scores (5 points), except for TP-53m and ZAP-70 which did not include low score evidence **(Fig. 2)**.

Figure 1. Systematic review diagram

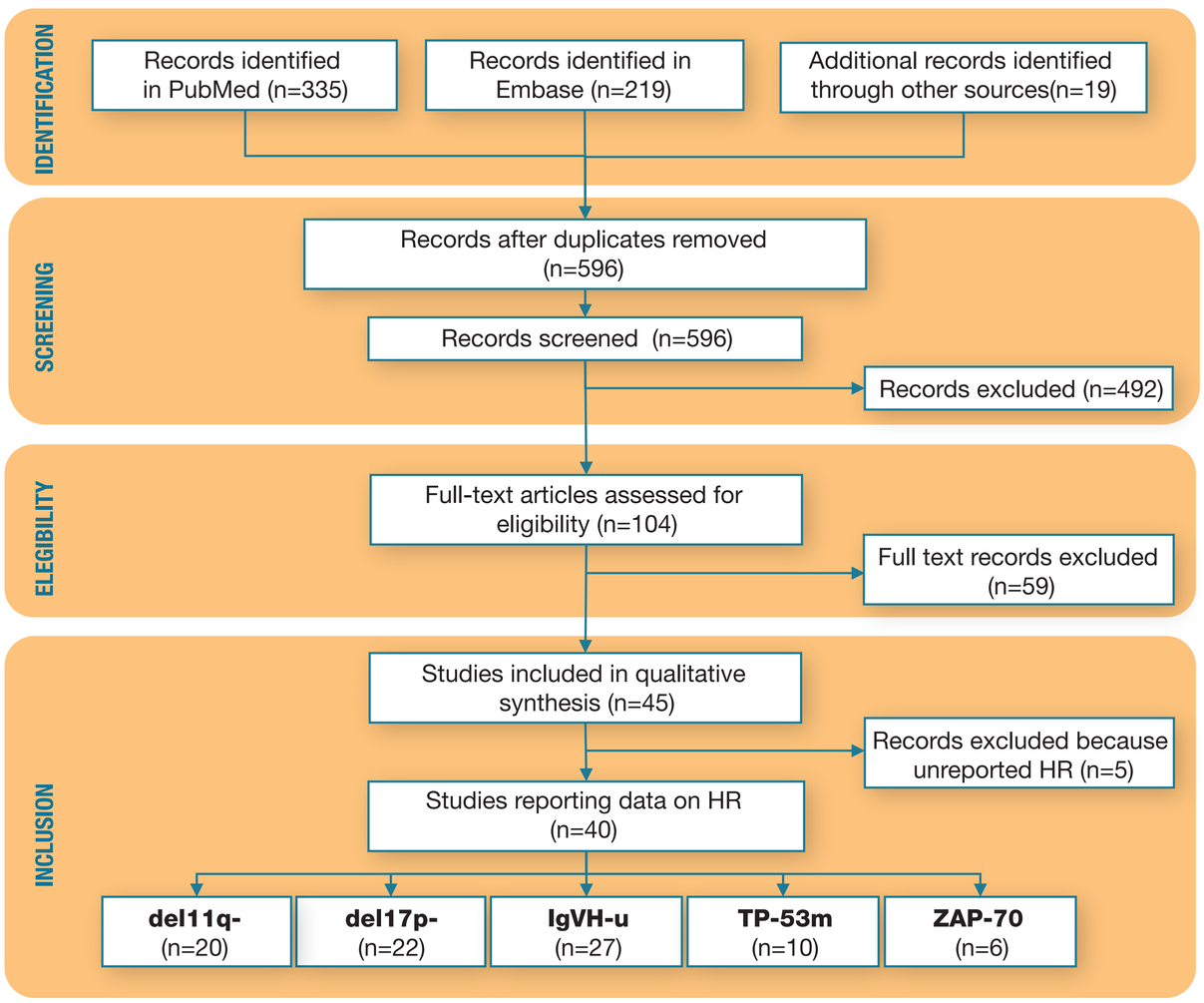

Figure 2. GRADE scale score in the studies that met the inclusion criteria

	del11q-	del17p-	IGHVu	TP-53m	ZAP-70e
Barrientos 2016	●●●	●●●	●●●		
Blakemore 2017				●●	
Eichhorst 2016	●●●●		●●●●		
Falchi 2015		●●	●●		
Farrooqui 2015			●●●		
Fischer 2011			●●●●		
Fischer 2016	●●●	●●●	●●●	●●●	
Gentile 2016	●●●	●●●	●●●		
Goede 2014	●●●●	●●●●	●●●●		
Gonzalez 2012			●●●●●	●●●●●	
Huang 2017	●●●	●●●			
Jain 2017			●●●●		
Jones 2013	●●	●●	●●		
Kipps 2017	●●●				
Kristensen 2015	●●				●●
Laurenti 2011			●●●		
Laurenti 2013					●●●
Le Bris 2016			●●		
Lech-Maranda 2012			●●●		
Lin 2009	●●●●●	●●●●●			
Lucas y Ruppert 2015	●●●	●●●	●●●		
Mato 2017		●●●●●			
O' Brien 2016			●●●●●		
Optarna 2017		●●●			
Oscier 2010	●●●		●●●		
Robak 2010	●●●	●●●			
Rose 2014	●●	●●	●●	●●	
Santacruz 2014			●●●	●●●	●●●
Sciumè 2015					●●●
Skowronska 2012		●●●	●●●	●●●	
Stilgenbauer 2014	●●●	●●●	●●●	●●●	
Tausch 2017		●●●●●	●●●●●	●●●●●	
Thompson 2016			●●		●●
Thompson, OBrien 2016		●●●			
Thompson, Tam 2016		●●●	●●●		●●●
Turcsanyi 2016	●	●	●		
Van Oers 2015	●●●●●	●●●●●	●●●●●		
Xu 2012	●●●	●●●	●●●	●●●	
Zent 2008	●●●●●	●●●●●			
Zenz 2010	●●●			●●●	
Median GRADE scale score	●●●	●●●	●●●	●●●	●●●

Quality of evidence was assessed based on the rating of the fundamental domains: risk of bias (from +2 to +4), consistency (from -1 to +1), transparency (from 0 to -1) and precision of results (from -3 to 0). The resulting scores provided the following levels of evidence: high (≥ ●●●●), moderate (●●●), low (●● and ●) and insufficient (no points or negative).

Conclusions

- **There were a considerable number of studies that evaluated the relationship between the biologic profile and the response to first-line treatment in terms of PFS in CLL.**
- **The quality of the evidence in the identified studies was moderate. This may be due to the inclusion of observational studies, which get lower rating on the GRADE scale.**

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Contact email: jcliment@its.jnj.com

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