A meta-analytic endpoint validation of surrogates used in clinical trials evaluating the efficacy of therapies in patients with chronic lymphocytic leukemia (CLL)

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Introduction: Regulatory bodies can approve treatments based on surrogate endpoints, which can be measured earlier than true endpoints. While approvals based on surrogate endpoints are increasing, many have not demonstrated a correlation with clinically meaningful outcomes. This study evaluated the validity of objective response rate (ORR) as a surrogate endpoint for progression-free survival (PFS) and overall survival (OS), and PFS as a surrogate endpoint for OS in CLL.

Methods: A systematic literature review of randomized controlled trials (RCTs) for CLL published between January 2015 and January 2022 was conducted in line with NICE (2022) requirements and Cochrane methodology. RCTs reporting at least 2 endpoints of interest (ORR, PFS, OS) were included. Two independent reviewers extracted relevant data on comparative effectiveness measures reported in the trial publications, which were used in a surrogate endpoint validation in alignment with health technology assessment guidelines. Two-stage validation was used: the overall magnitude of the comparative effect of the surrogates was estimated using a bootstrapped DerSimonian-Laird random-effects model, then correlation and regression analyses assessed the association between surrogate and final endpoints. Analyses were performed across all trials and separately across trials investigating either kinase inhibitor (Ki) or Bruton tyrosine Ki (BTKi).

Results: A total of 69 RCTs were identified; 28, 25, and 29 trials were available for the ORR vs PFS, ORR vs OS, and PFS vs OS comparisons, respectively. Respective numbers for Ki/BTKi trials within each comparison were 14/10, 13/10, and 13/11. Based on all trials, the overall magnitudes of the comparative effect of the surrogate were 0.18 (95% CI: 0.13, 0.23) for the absolute difference in ORR, 0.52 (0.41, 0.64) for the hazard ratio for PFS, and 0.80 (0.72, 0.89) for the hazard ratio for OS. Significant treatment effects were also observed in the Ki and BTKi subgroups. Statistically significant correlations for ORR vs PFS were found across all therapies (r=0.67; 95% CI: 0.40, 0.84), as well as in the Ki (0.68; 0.24, 0.89) and BTKi (0.75; 0.22, 0.94) subgroups (Figure). The correlation observed between ORR and PFS was categorized as moderate in the BTKi trials. No clear correlation between the comparative effect on ORR and OS was observed. A statistically significant association between the comparative effect on PFS and on OS based on all trials was shown (r=0.58; 0.27, 0.78). For Ki and BTKi subgroups, significant associations between comparative effects on PFS and OS were observed after weighting the regression by patient number.

Conclusions: We found robust evidence that ORR serves as a surrogate for PFS in CLL, especially when evaluating the treatment effect of BTKis, some evidence of an association between PFS and OS, and no clear evidence of ORR as a surrogate for OS.

Figure. Scatterplot displaying the correlation between ORR and PFS