Bruton Tyrosine Kinase Inhibitor (BTKi) Monotherapy for the Treatment of 'High-Risk' Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL): A Systematic Literature Review (SLR)

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OBJECTIVES: The course of CLL is heterogeneous and driven by cytogenetic factors, which can be used to predict a poor prognosis. Specifically, the presence of *TP53* mutation or 17p deletion has been shown to impact treatment response, and patients with these factors are classified as 'high risk.' BTKi monotherapies (zanubrutinib, acalabrutinib, and ibrutinib) are mainstay treatment options for 'high-risk' patients. A clinical SLR was conducted to characterize the efficacy evidence supporting the use of BTKi monotherapy in previously untreated 'high-risk' patients.

METHODS: Searches were conducted in Embase, MEDLINE (EMBASE interface), and CENTRAL (Cochrane Library) from 2007 to 2022. Searches were supplemented with grey literature. Two reviewers screened abstracts (first pass) and full-text publications (second pass). Accepted studies were extracted by one reviewer and quality assessed by a second reviewer. Disagreements were resolved by a third reviewer.

RESULTS: Five trials evaluating BTKi monotherapy in patients with previously untreated CLL (including 'high risk') were identified (SEQUOIA, CLL12, RESONATE-2, ALLIANCE, ELEVATE-TN). The only study with a prospectively defined 'high-risk' cohort was SEQUOIA (Cohort 2; n=111 patients with 17p deletion). Outcomes in patients with 'high-risk' factors treated with zanubrutinib were comparable to those in patients without 'high-risk' factors (SEQUOIA; Cohort 1). The remaining four trials included mixed populations (with and without 'high-risk' factors) for ibrutinib (CLL12, RESONATE-2, ALLIANCE) and acalabrutinib (ELEVATE-TN). Prespecified subgroup analyses demonstrated comparable outcomes in patients with and without 'high-risk' factors in these trials, although 'high-risk' patient numbers were small (<30).

CONCLUSIONS: There is limited clinical evidence in patients with 'high-risk' factors. Due to the high unmet need in these patients, ibrutinib and acalabrutinib were licensed for use in these patient populations despite small 'high-risk' subgroups. SEQUOIA (Cohort 2) is the only prospective body of evidence in a relatively large group of previously untreated 'high-risk' patients treated with BTKi monotherapy.