Targeted Treatments for Patients with Relapsed and/or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): A Systematic Literature Review (SLR) of Randomized Clinical Trials (RCTs)

Leyla Mohseninejad, PhD[1], Lydia Walder, MSc[2], Sundeep Ubi, BSc[2], Abbie Malyon, MSc[2], Keri Yang, PhD, MBA, MPH, MS, CPM, BSPharm[3], Robert Ollie, PhD[4]

[1]BeiGene Switzerland, GmbH, Basel, Switzerland; [2]FIECON, St Albans, UK; [3]BeiGene USA Inc, San Mateo, CA, USA; [4]BeiGene, Basel, Switzerland

OBJECTIVES: Targeted therapies have greatly improved outcomes in CLL, reducing rates of disease progression and mortality. Following initial response, most patients still experience relapse or become refractory to initial treatment (Moreno 2020). A clinical SLR was conducted to characterize the efficacy and safety evidence supporting the use of targeted therapies in R/R CLL.

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. A third reviewer resolved disagreements.

RESULTS: Six RCTs were identified for R/R CLL treated with Bruton tyrosine kinase inhibitor (BTKi) monotherapy (ALPINE [NCT03734016], ELEVATE-RR [NCT02477696], ASCEND [NCT02970318], RESONATE [NCT01578707], NCT01973387, and GENUINE [NCT02301156]). ALPINE and ELEVATE-RR provided head-to-head comparisons between BTKis. ALPINE demonstrated superior efficacy and cardiac safety of zanubrutinib versus ibrutinib. ELEVATE-RR demonstrated non-inferior efficacy and improved cardiac safety of acalabrutinib versus ibrutinib. ASCEND (acalabrutinib), RESONATE (ibrutinib), and NCT01973387 (ibrutinib) demonstrated superior outcomes with BTKi monotherapy compared with non-targeted treatment options. GENUINE demonstrated improved response and consistent safety with ibrutinib-ublituximab versus ibrutinib monotherapy. Three RCTs assessed combination therapies: MURANO (NCT02005471), HELIOS (NCT01611090), and HOVON-141/VISION (NCT03226301). MURANO and HELIOS demonstrated improved outcomes with venetoclax-rituximab and ibrutinib-rituximab, respectively, versus bendamustine-rituximab. HOVON-141/VISION demonstrated comparable outcomes with ibrutinib monotherapy versus no treatment following initial ibrutinib-venetoclax treatment.

CONCLUSIONS: Multiple treatments are available for R/R CLL, but there are limited data directly comparing outcomes with targeted therapies. All except three RCTs (ALPINE, ELEVATE-RR, GENUINE) compared targeted and non-targeted therapies. ALPINE was the first and only RCT powered to detect differences between BTKis. With increased use of targeted therapies, more head-to-head comparisons are required between targeted treatments to aid patient and clinician treatment decisions.