Trial in progress: A phase III, randomized, open-label study comparing zanubrutinib plus rituximab versus bendamustine plus rituximab in patients with previously untreated mantle cell lymphoma (MCL).

Authors:
Martin H. Dreyling, Constantine Si Lun Tam, Michael Wang, Stephen Douglas Smith, Marco Ladetto, Huiqiang Huang, Rebecca L. Elstrom, Melannie Co, Eric Holmgren, Jane Huang, Steven Le Gouill; University Hospital Groβhadern, Ludwig Maximilians-University, Munich, Germany; Peter MacCallum Cancer Centre, Melbourne, St Vincent's Hospital, Fitzroy, University of Melbourne, Parkville and...

Background:
Bruton tyrosine kinase (BTK) mediates B-cell proliferation, migration, and adhesion. BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MCL. Zanubrutinib is a next-generation BTK inhibitor that was designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases, with favorable pharmacokinetic and pharmacodynamic properties. Zanubrutinib monotherapy has been evaluated in 118 patients (pts) with relapsed/refractory MCL in 2 single-arm studies: BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120]. The overall response rate (ORR) by independent review committee (IRC) in both trials was 84% with median durations of response of 19.5 and 18.5 months, respectively. First-line treatment for MCL has failed to cure most pts, particularly elderly or transplant-ineligible groups, and chemotherapy-based approaches result in cumulative, long-term risks. The study described herein is designed to evaluate the safety and efficacy of zanubrutinib plus rituximab versus bendamustine plus rituximab in elderly pts and pts with comorbidities with previously untreated MCL who are ineligible for stem cell transplant.

Methods:
This ongoing phase 3, open-label study will enroll ≈500 pts to be randomized 1:1, stratified by MCL International Prognostic Index score (low vs intermediate/high), age (< 70 vs ≥70 years), and geographic region (North America/Europe vs Asia-Pacific). In arm A, pts will receive up to six 28-day cycles of oral zanubrutinib 160 mg twice daily in combination with intravenous (IV) rituximab 375 mg/m^2 on day 1 of each cycle. After 6 cycles, zanubrutinib will continue as a monotherapy until progressive disease, unacceptable toxicity, or withdrawal of consent. In arm B, pts will receive up to six 28-day cycles of IV bendamustine 90 mg/m^2 on days 1 and 2 of each cycle and rituximab 375 mg/m^2 on day 1 of each cycle, followed by observation. Eligible pts must have histologically confirmed MCL and be aged ≥70 years, or 65-69 years with defined comorbidities. Disease response will be assessed per the 2014 Lugano Classification for non-Hodgkin lymphoma. The primary endpoint is progression-free survival (PFS) determined by IRC. Key secondary end points include PFS by investigator assessment, ORR, time to and duration of response, overall survival, and safety. Recruitment is ongoing. Clinical trial information: NCT04002297.