Phase 2 study of zanubrutinib (BGB-3111) in patients with relapsed/refractory marginal zone lymphoma (R/R MZL).

Authors:
Stephen Opat, Robert Marcus, Craig Anthony Portell, William Reed, Melannie Co, Jane Huang, Judith Trotman; Monash Health, Monash University, Clayton, Victoria, Australia; Sarah Cannon Research Institute, London, United Kingdom; University of Virginia Health System, Charlottesville, VA; BeiGene USA, Inc., San Mateo, CA; Concord Repatriation Hospital, The University of Sydney, Sydney, New South...

Background:
Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, mediating B-cell proliferation, migration, adhesion and survival. BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MZL. In preclinical studies, zanubrutinib was shown to be a potent, irreversible, highly specific BTK inhibitor with excellent oral bio-availability and favorable pharmacokinetic/pharmacodynamic properties. Clinical data to date have shown that complete and sustained 24-hour BTK occupancy is associated with durable responses and suggested that zanubrutinib is generally well tolerated with low rates of serious adverse events. Preliminary results from the MZL cohort enrolled in the open-label, multicenter, phase 1 study demonstrated responses in 7 of 9 patients for an overall response rate (ORR) of 78%. Cumulative safety data also showed that zanubrutinib monotherapy was associated with infrequent incidence of atrial fibrillation and major hemorrhage and infrequent drug discontinuation due to treatment-related adverse events. This study is designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL.

Methods:
This ongoing global phase 2, single-arm, open-label study is examining zanubrutinib monotherapy in patients with R/R MZL who have received one or more prior lines of systemic therapy. Patients are treated with oral zanubrutinib at 160 mg twice-daily until progressive disease, unacceptable toxicity, or withdrawal of consent. Eligible patients must have histologically confirmed MZL, have received prior anti-CD20 antibody therapy, and have measurable disease. Disease response is assessed per the 2014 Lugano Classification for non-Hodgkin lymphoma. The primary endpoint is ORR determined by independent review committee (IRC). Key secondary endpoints include ORR by investigator assessment, time to and duration of response, time to treatment discontinuation, progression-free survival (all determined by IRC and investigator assessments), and overall survival and safety. Recruitment is ongoing.