MAHOGANY: A phase 3 trial of zanubrutinib plus anti-CD20 antibodies vs lenalidomide plus rituximab in patients with relapsed or refractory follicular or marginal zone lymphoma

Authors: Wojciech Jurczak,[1] Loretta J. Nastoupil,[2] Yuqin Song,[3] Laurie H. Sehn,[4] Clémentine Sarkozy,[5] Pier Luigi Zinzani,[6] Antonio Salar,[7] Wanhua Zhang,[8] Sha Huang,[8] Julie Wang,[9] Richard Delarue,[10] Judith Trotman[11]

Institution: [1]Maria Sklodowska-Curie National Research Institute of Oncology in Kraków, Poland; [2]MD Anderson Cancer Center, Houston, TX; [3]Peking University Cancer Hospital and Institute, Beijing, China; [4]University of British Columbia, Vancouver, BC, Canada; [5]Institut Curie, Saint Cloud, Paris, France; [6]University of Bologna, Bologna, Italy; [7]Hospital del Mar, Barcelona, Spain; [8]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [9]BeiGene USA, Inc, San Mateo, CA, USA; [10]BeiGene Switzerland GmbH, Basel, Switzerland; [11]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia

Introduction: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for treatment of patients with B-cell malignancies, including indolent non-Hodgkin lymphomas. Zanubrutinib is a second-generation, potent, and specific BTK inhibitor and has shown to be more effective and better tolerated than first-generation BTK inhibitors in several diseases, including chronic lymphocytic leukemia/small lymphocytic lymphoma and Waldenström macroglobulinemia. Zanubrutinib is approved in >15 countries, including the United States and countries in the European Union, for patients with relapsed or refractory (R/R) marginal zone lymphoma (MZL) who received ≥1 anti-CD20-based regimen, based on the single-arm MAGNOLIA trial (Opat et al. *Clin Cancer Res* 2021;27[23]:6323-32). In R/R follicular lymphoma (FL), ROSEWOOD, a phase 2 randomized study of zanubrutinib plus obinutuzumab vs obinutuzumab, met its primary endpoint of increased overall response rate (ORR) at primary analysis (Zinzani et al. *J Clin Oncol* 2022;40[suppl 16]:7510). In this trial, zanubrutinib plus obinutuzumab in patients with R/R FL demonstrated deep and durable responses with a favorable safety profile.

Material and Method: MAHOGANY (BGB-3111-308, NCT05100862) is a phase 3, randomized, open-label trial that compares the efficacy and safety of zanubrutinib plus an anti-CD20 monoclonal antibody vs lenalidomide plus rituximab in 2 independent cohorts, for patients with either R/R FL or MZL. Key eligibility criteria include histologically confirmed FL (grades 1-3A) or MZL, previous treatment with ≥1 anti-CD20–based regimen, disease relapsed after or refractory to the most recent systemic therapy, need for treatment, no prior BTK inhibitor exposure, and no prior resistance to a lenalidomide-based regimen. In the FL cohort, patients will be randomized 1:1 to zanubrutinib plus obinutuzumab (n=300) and lenalidomide plus rituximab (n=300). Randomization is stratified by age (≥60 years vs <60 years), number of prior lines of therapy (1-2 vs >2), and rituximab-refractory status (yes vs no). The primary endpoint is progression-free survival (PFS) assessed by an independent review committee (IRC), according to the Lugano 2014 criteria. Key secondary endpoints are ORR by IRC assessment and overall survival. In the MZL cohort, patients will be randomized 1:1 to zanubrutinib plus rituximab (n=75) and lenalidomide plus rituximab (n=75). Randomization is stratified by age (≥60 years vs <60 years) and number of prior lines of therapy (1–2 vs >2). The primary endpoint is PFS assessed by IRC according to the Lugano 2014 criteria. The key secondary endpoint is ORR by IRC assessment. Zanubrutinib is given at 160 mg twice daily or 320 mg once daily according to investigator, until disease progression or unacceptable toxicity. Obinutuzumab or rituximab are given for up to 8 infusions. Lenalidomide is given according to approved label for up to 12 cycles. Recruitment is ongoing.