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

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Background: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for treatment of patients (pts) 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 European Union, for pts 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). In R/R follicular lymphoma (FL), ROSEWOOD, a phase 2 randomized study of zanubrutinib plus obinutuzumab (ZO) vs obinutuzumab, met its primary endpoint of increased overall response rate (ORR) at primary analysis (Zinzani et al. *J Clin Oncol* 2022). In this trial, ZO in pts with R/R FL demonstrated deep and durable responses with a favorable safety profile.

Methods: MAHOGANY (BGB-3111-308, NCT05100862) is a phase 3 randomized, open-label trial that compares efficacy and safety of a combination of zanubrutinib plus anti-CD20 monoclonal antibody vs lenalidomide plus rituximab in 2 independent cohorts, for pts with either R/R FL or MZL. Key eligibility criteria include histologically confirmed FL (grades 1-3A) or MZL, previously treated with ≥1 anti-CD20–based regimen, relapsed after or refractory to the most recent systemic therapy, in need of treatment, no prior BTK inhibitor exposure, and no prior resistance to a lenalidomide-based regimen. In the FL cohort, pts will be randomized 1:1 to ZO (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 Lugano 2014 criteria. Key secondary endpoints are ORR by IRC assessment and overall survival. In the MZL cohort, pts 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 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 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.