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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ABSTRACT

Objective: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for the treatment of patients with B-cell malignancies, including indolent non-Hodgkin lymphomas. MAHOGANY (BGB-3111-308, NCT05100862) is a phase 3, randomized, open-label trial that will compare the efficacy and safety of zanubrutinib combination therapy (zanubrutinib combined either with the anti-CD20 monoclonal antibody obinutuzumab in patients with follicular lymphoma [FL] or with rituximab in patients with marginal zone lymphoma [MZL]) with that of the standard combination therapy, lenalidomide plus rituximab, in 2 independent cohorts of patients with relapsed/refractory (R/R) FL or MZL. Zanubrutinib is a second-generation, potent, and specific BTK inhibitor that has been 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 US and countries in the EU, for patients with R/R MZL who received ≥1 anti-CD20–based regimen, based on the single-arm MAGNOLIA trial (Opat et al. *Clin Cancer Res*. 2021;27[23]:6323-6332). In R/R FL, ROSEWOOD, a phase 2 randomized study of zanubrutinib plus obinutuzumab vs obinutuzumab monotherapy, 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 demonstrated deep and durable responses with a favorable safety profile in patients with R/R FL.

Methods: Key eligibility criteria include histologically confirmed FL (grades 1-3A) or MZL, previous treatment with ≥1 anti-CD20–based regimen, disease that relapsed after or was 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) or lenalidomide plus rituximab (n=300). Randomization is stratified by age (≥60 years vs <60 years), number of prior lines of therapy (1 or 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) or lenalidomide plus rituximab (n=75). Randomization is stratified by age (≥60 years vs <60 years) and number of prior lines of therapy (1 or 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 is given for up to 8 infusions. Lenalidomide is given according to the approved label for up to 12 cycles. Recruitment is ongoing.

Results: Not applicable—trial is ongoing.

Conclusion: Not applicable—trial is ongoing.