***Title (Italian)*:** MAHOGANY: STUDIO DI FASE 3 DI ZANUBRUTINIB PIÙ ANTICORPI ANTI-CD20 VS LENALIDOMIDE PIÙ RITUXIMAB IN PAZIENTI CON LINFOMA FOLLICOLARE O LINFOMA DELLA ZONA MARGINALE RECIDIVATO O REFRATTARIO

***Title (English)*:** MAHOGANY: A PHASE 3 TRIAL OF ZANUBRUTINIB PLUS ANTI-CD20 ANTIBODIES VS LENALIDOMIDE PLUS RITUXIMAB IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR OR MARGINAL ZONE LYMPHOMA (FL or MZL)

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Introduction: Bruton tyrosine kinase inhibitors (BTKis) have emerged as a treatment strategy for pts with B-cell malignancies, including indolent non-Hodgkin lymphomas. Zanubrutinib, a potent and specific second-generation BTKi, has demonstrated higher efficacy and tolerability than first-generation BTKis 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 pts 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]:6323-32). In ROSEWOOD, a phase 2 randomized study in R/R FL, zanubrutinib plus obinutuzumab demonstrated an increased overall response rate (ORR) vs obinutuzumab alone and had a favorable safety profile (Zinzani et al. *J Clin Oncol*. 2022;40[suppl 16]:7510).

Trial design: MAHOGANY (BGB-3111-308; NCT05100862), a randomized, open-label phase 3 trial, will compare the efficacy and safety of zanubrutinib plus an anti-CD20 monoclonal antibody vs lenalidomide plus rituximab in 2 independent cohorts of pts with R/R FL or MZL. Key eligibility criteria include histologically confirmed FL (grades 1-3A) or MZL, ≥1 prior anti-CD20–based regimen, disease that relapsed after or is refractory to the most recent systemic therapy, need for treatment, naivety to BTKi treatment, and no prior resistance to a lenalidomide-based regimen. In the FL cohort, 600 pts will be randomized 1:1 to zanubrutinib plus obinutuzumab or lenalidomide plus rituximab. In the MZL cohort, 150 pts will be randomized 1:1 to zanubrutinib plus rituximab or lenalidomide plus rituximab. Randomization for both cohorts is stratified by age (≥60 vs <60 years) and number of prior lines of therapy (1-2 vs >2), with the FL cohort also stratified by rituximab-refractory status (yes vs no). The primary endpoint in both cohorts is progression-free survival as assessed by an independent review committee (IRC), according to Lugano 2014 criteria. Key secondary endpoints are ORR by IRC assessment (both cohorts) and overall survival (FL cohort). Zanubrutinib is given at 160 mg twice daily or 320 mg once daily, according to investigator, until progression or unacceptable toxicity. Obinutuzumab or rituximab

is given for up to 8 infusions. Lenalidomide is given following the approved label for up to 12 cycles. Recruitment is ongoing.