MAHOGANY: PHASE III TRIAL OF ZANUBRUTINIB (Z) PLUS ANTI-CD20 ANTIBODIES AGAINST LENALIDOMIDE PLUS RITUXIMAB (L+R) IN PATIENTS (PTS.) WITH REFLECTED/REFRACTORY FOLLICULAR LYMPHOMA (FL) OR MARGINAL ZONE LYMPHOMA (MZL) (R/R)

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Introduction: Inhibitors of Bruton's tyrosine kinase (iBTK) have emerged as a treatment strategy for patients with B cell malignancies. Z, a potent and selective second-generation iBTK, has shown greater efficacy and tolerability than iBTK first-generation in several B-lymphocyte malignancies. Z is approved in >15 countries for patients with R/R MZL who received ≥1 line of therapy that included anti-CD20, based on the single-arm MAGNOLIA trial (Opat et al. *Clin Cancer Res*. 2021). In the ROSEWOOD study, a randomized phase II study in LF R/R, Z plus obinutuzumab (O) demonstrated increased overall response rate (ORR) versus O alone and had a favorable safety profile (Zinzani et al. *J. Clin Oncol.* 2022).

Objective: To compare the efficacy and safety of Z plus an anti-CD20 monoclonal antibody versus L+R treatment in 2 independent cohorts of pts. with LF or LZM R/R.

Method: Primary inclusion criteria for the MAHOGANY study (BGB-3111-308; NCT05100862), a phase III, randomized, open-label trial, include histologically confirmed FL (grades 1-3A) or MZL, ≥1 prior anti-CD20-based regimen , R/R disease after most recent systemic treatment, treatment need, iBTK naive, and no prior resistance to an L-based regimen. In the LF cohort, 600 patients will be randomized in a 1:1 ratio to receive Z+O or L+R. In the LZM cohort, 150 patients will be randomized in a 1:1 ratio to receive Z+R or L+R. Randomization for both cohorts is stratified by age (≥60 vs <60 years) and number of prior lines of treatment (1-2 vs >2), with the LF cohort also stratified by treatment resistance status (yes versus not). The primary endpoint in both cohorts is PFS as assessed by an independent review committee (IRC), according to the 2014 Lugano criteria. Key secondary endpoints are IRC-assessed ORR (both cohorts) and overall survival (FL cohort). Z is administered 160 mg twice daily or 320 mg once daily, depending on the investigator, until progression or unacceptable toxicity. O or R are administered up to a maximum of 8 infusions. L is administered following the approved SmPC for a maximum of 12 cycles. Recruitment is ongoing.