MAHOGANY: A PHASE 3 TRIAL OF ZANUBRUTINIB+ANTI-CD20 ANTIBODIES VS LENALIDOMIDE+RITUXIMAB IN RELAPSED/REFRACTORY FOLLICULAR OR MARGINAL ZONE LYMPHOMA

Authors: Jose Mario Mariz[1], Antonio Salar[2], Judith Trotman[3], Clémentine Sarkozy[4], Yuqin Song[5], Laurie Sehn[6], Loretta J. Nastoupil[7], Wanhua Zhang[8], Pierre Fustier[9], Richard Delarue[9], Pier Luigi Zinzani[10]

Affiliations: [1]CUF Porto Hospital, Porto, Portugal; [2]Hospital Virgen de la Arrixaca, Murcia, Spain; [3]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [4]Institut Curie, Saint-Cloud Hospital, Paris, France; [5]Peking University Cancer Hospital and Institute, Beijing, China; [6]University of British Columbia, Vancouver, BC, Canada; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]BeiGene (Beijing) Co., Ltd., Beijing, China; [9]BeiGene Switzerland, GmbH, Basel, Switzerland; [10]University of Bologna, Bologna, Italy

Introduction: Bruton tyrosine kinase inhibitors (BTKis) have emerged as a treatment strategy for patients (pts) with B-cell malignancies. Zanubrutinib (Z), a potent and specific next-generation BTKi, has demonstrated higher efficacy and tolerability than the first-generation BTKi, ibrutinib, in several B-cell malignancies. Z is approved in >15 countries for pts with relapsed/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 ROSEWOOD, a phase 2 randomized study in R/R follicular lymphoma (FL), Z plus obinutuzumab (O) demonstrated an increased overall response rate (ORR) vs O alone and had a favorable safety profile (Zinzani et al. *J Clin Oncol*. 2023).

Objective: To compare the efficacy and safety of Z plus an anti-CD20 monoclonal antibody vs lenalidomide plus rituximab (L+R) treatment in 2 independent cohorts of pts with R/R FL or MZL.

Materials and Methods: Key eligibility criteria of MAHOGANY (BGB-3111-308; NCT05100862), a randomized, open-label phase 3 trial, include histologically confirmed FL (grades 1-3A) or MZL, ≥1 prior anti-CD20–based regimen, R/R disease after the most recent systemic therapy, need for treatment, naivety to BTKi treatment, and no prior resistance to a L-based regimen. In the FL cohort, 600 pts will be randomized 1:1 to Z+O or L+R. In the MZL cohort, 150 pts will be randomized 1:1 to Z+R or L+R. 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 R-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). Z is given at 160 mg twice daily or 320 mg once daily, according to investigator, until progression or unacceptable toxicity. O or R is given for up to 8 infusions. L is given following the approved label for up to 12 cycles. Recruitment is ongoing.