Poster P02

MAHOGANY: A Phase 3 Trial of Zanubrutinib+Anti-CD20 Antibodies vs Lenalidomide+Rituximab in Relapsed/Refractory Follicular or Marginal Zone Lymphoma

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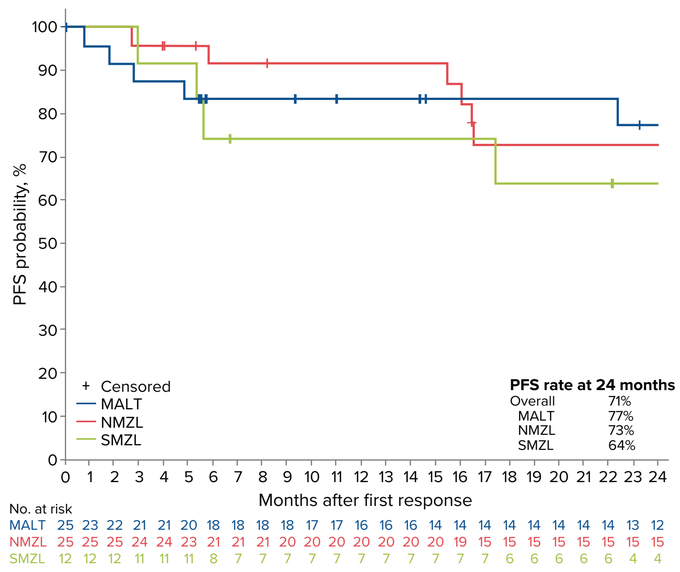
BACKGROUND

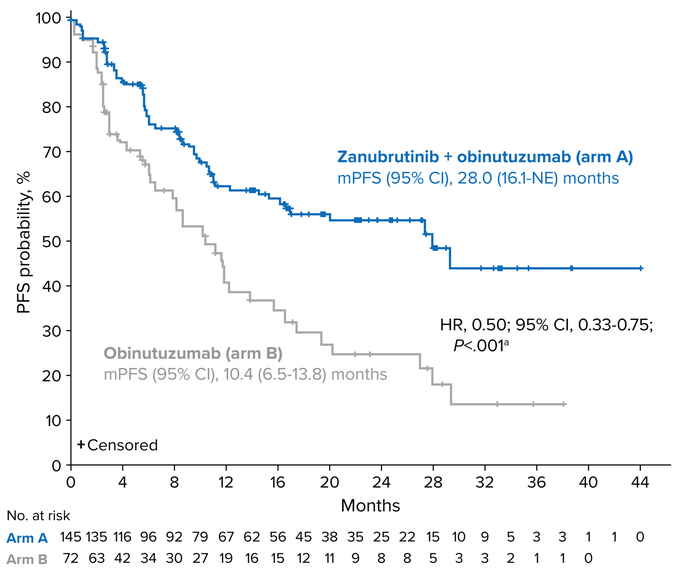
- Relapsed/refractory (R/R) disease is common in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL)
- Treatment of FL and MZL largely relies on immunochemotherapy, and additional novel therapies are greatly needed
- Zanubrutinib is a next-generation, potent, specific Bruton tyrosine kinase (BTK) inhibitor approved in the EU and US for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), and MZL[1,2] and in the US for previously treated mantle cell lymphoma[1]
  - Zanubrutinib demonstrated clinically meaningful benefit (not statistically significant) in patients with WM[3] and superior efficacy over ibrutinib in patients with R/R CLL/SLL[4]
  - In both WM[3] and CLL/SLL,[4] zanubrutinib was better tolerated than ibrutinib
- Previous findings have suggested that zanubrutinib may lead to high response rates and durable responses in R/R MZL and FL[5,6]
  - In the phase 2 MAGNOLIA study in R/R MZL (NCT03846427), zanubrutinib led to an overall response rate (ORR) of 68.2% (complete response [CR] rate, 25.8%) as assessed by an independent review committee (IRC); the progression-free survival (PFS) rate at 24 months was 71% (**Figure 1**)[5]
  - In the randomized phase 2 ROSEWOOD study in R/R FL (NCT03332017), zanubrutinib + obinutuzumab led to an IRC-assessed ORR of 69.0% (CR rate, 39.3%); the PFS rate at 24 months was 54.8% (**Figure 2**)[6]

Figure 1. PFS by IRC in the Phase 2 MAGNOLIA R/R MZL Trial[5]



MALT, mucosa-associated lymphoid tissue; NMZL, nodal marginal zone lymphoma; PFS, progression-free survival; SMZL, splenic marginal zone lymphoma.

Figure 2. PFS by IRC in the Phase 2 ROSEWOOD R/R FL Trial[6]



Median follow-up, 20.2 months.
HR, hazard ratio; IRC, independent review committee; mPFS, median progression-free survival; NE, not estimable.
[a] Descriptive 2-sided *P* value.

METHODS

- MAHOGANY (BGB-3111-308; NCT05100862) is a randomized (1:1), open-label, multicenter phase 3 trial evaluating zanubrutinib combined with the anti-CD20 antibody obinutuzumab in patients with R/R FL or rituximab in patients with R/R MZL vs lenalidomide combined with rituximab (**Figure 3**)

Figure 3. Study Design

Key eligibility criteria

- Age ≥18 years
- Histologically confirmed R/R FL (grade 1-3a) or MZL (extranodal, nodal, or splenic)
- Previous treatment with ≥1 prior line of systemic therapy, including an anti-CD20–based regimen
- Need for treatment according to modified GELF criteria[7]
- Adequate bone marrow and organ function
- No prior treatment with BTK inhibitor
- Prior lenalidomide treatment allowed unless no response or short remission (DOR <24 months)
- No clinically significant cardiovascular disease; severe or debilitating pulmonary disease; and/or history of a severe bleeding disorder

FL cohort n=600 → R 1:1

Randomization stratified by:
- Age (≥60 years, <60 years)
- Prior lines of therapy (1 or 2, >2)
- Anti-CD20–refractory status (yes, no)

Arm A (n=300)
Zanubrutinib 160 mg BID or 320 mg QD[a]
+ Obinutuzumab 1000 mg
Cycle 1: days 1, 8, and 15
Cycles 2-6: day 1

Arm B (n=300)
Lenalidomide 20 mg QD[b]
Cycles 1-12: days 1-21
+ Rituximab 375 mg/m²
Cycle 1: days 1, 8, 15, and 22
Cycles 2-5: day 1

Primary endpoint:
- PFS per IRC using PET/CT-based Lugano 2014 criteria[8]

Key secondary endpoints:
- ORR per IRC using PET/CT-based Lugano 2014 criteria[8]
- OS

Secondary endpoints:
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using PET/CT-based Lugano 2014 criteria[8])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

MZL cohort n=150 → R 1:1

Randomization stratified by:
- Age (≥60 years, <60 years)
- Prior lines of therapy (1 or 2, >2)

Arm C (n=75)
Zanubrutinib 160 mg BID or 320 mg QD[a]
+ Rituximab 375 mg/m²
Cycle 1: days 1, 8, 15, and 22
Cycles 2-5: day 1

Arm D (n=75)
Lenalidomide 20 mg QD[b]
Cycles 1-12: days 1-21
+ Rituximab 375 mg/m²
Cycle 1: days 1, 8, 15, and 22
Cycles 2-5: day 1

Primary endpoint:
- PFS per IRC using CT-based Lugano 2014 criteria[8]

Key secondary endpoint:
- ORR per IRC using CT-based Lugano 2014 criteria[8]

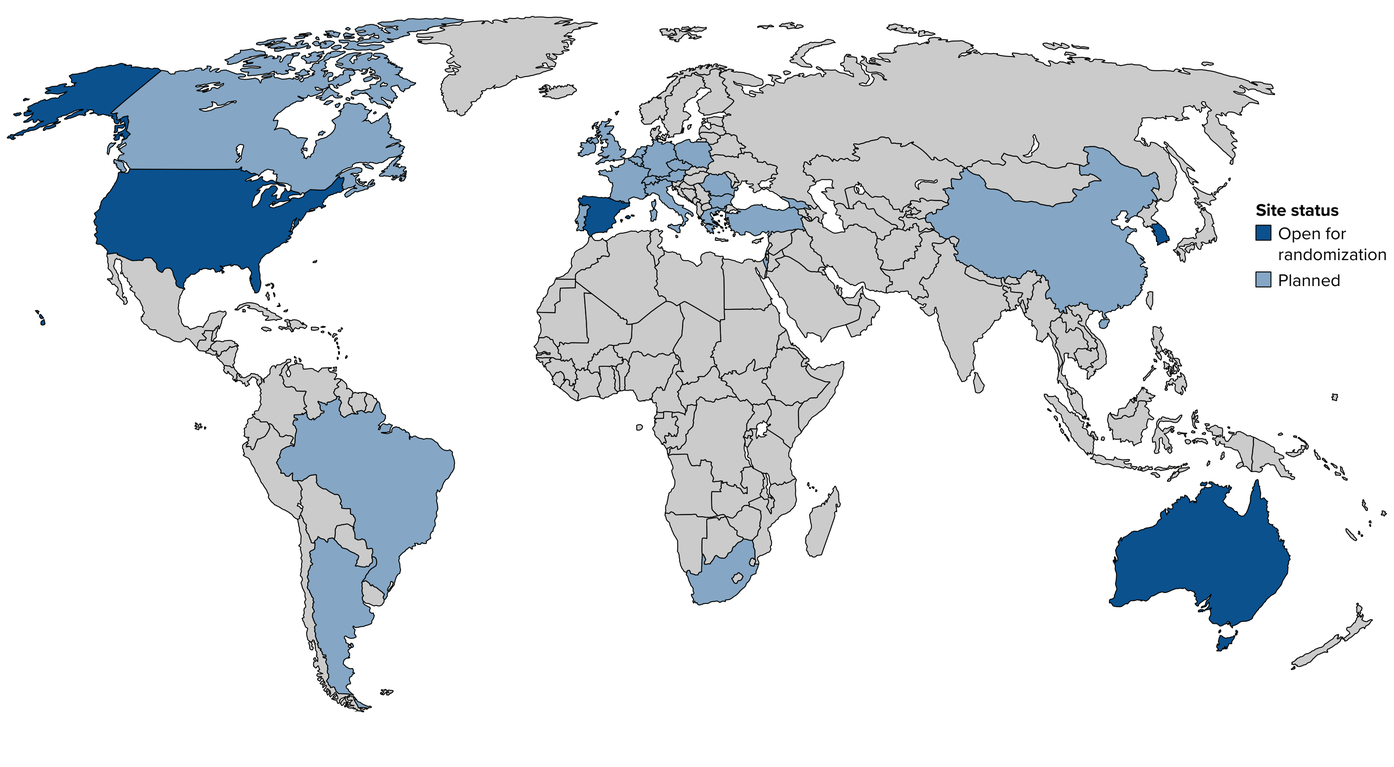
Secondary endpoints:
- OS
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using CT- and PET/CT-based Lugano 2014 criteria[8])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

One cycle is 28 days.
BID, twice daily; CRR, complete response rate; CT, computed tomography; DOR, duration of response; FL, follicular lymphoma; IA, investigator assessment; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; QD, once daily; QOL, quality of life; R, randomized; R/R, relapsed/refractory; TTR, time to response.
[a] After completion of combination treatment, patients will receive zanubrutinib monotherapy until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination, whichever comes first. [b] Patients with creatinine clearance ≥30 mL/min but <60 mL/min will receive 10 mg QD. If the patient remains free of lenalidomide-related grade 3 or 4 toxicities for ≥2 cycles, the dose may be increased to 15 mg QD on days 1-21 of a 28-day cycle at the discretion of the treating physician from cycles 3-12.

Study status

- Enrollment for MAHOGANY began in March 2022, and the study is currently recruiting
- Approximately 300 study sites in 25 countries are planned (**Figure 4**), with an estimated enrollment of 750 patients

Figure 4. Planned Study Sites



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DISCLOSURES

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