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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Background

- Relapsed/refractory (R/R) disease is common in patients with FL and MZL
- Treatment of FL and MZL largely relies on immunochemotherapy, and additional novel therapies are greatly needed
- Zanubrutinib is a second-generation, potent, specific BTK inhibitor approved in the EU and US for the treatment of CLL/SLL, WM, and MZL,\(^1,2\) and in the US for previously treated MCL\(^1\)
  - Zanubrutinib was shown to be more effective than ibrutinib, a first-generation BTK inhibitor, in patients with CLL/SLL\(^3\) and showed clinically meaningful efficacy in patients with WM\(^4\)
  - In both CLL/SLL\(^3\) and WM,\(^4\) 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\(^5,6\)

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

PFS by IRC in the Phase 2 MAGNOLIA R/R MZL Trial

- In the phase 2 MAGNOLIA study in R/R MZL (NCT03846427), zanubrutinib led to an ORR of 68% (CR rate, 26%) as assessed by an IRC; the PFS rate at 24 months was 71%.

CR, complete response; IRC, independent review committee; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SMZL, splenic marginal zone lymphoma.


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PFS by IRC in the Phase 2 ROSEWOOD R/R FL Trial

• 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%

Median follow-up, 20.2 months.

CR, complete response; FL, follicular lymphoma; HR, hazard ratio; IRC, independent review committee; mPFS, median progression-free survival; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.

Study Design: Overview

- **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.

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
- In need of treatment according to modified GELF criteria
- Adequate bone marrow and organ functions
- 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, or history of a severe bleeding disorder

2 independent cohorts

- FL cohort n=600
- MZL cohort n=150

BTK, Bruton tyrosine kinase; DOR, duration of response; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; MZL, marginal zone lymphoma; R/R, relapsed/refractory.


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### Study Design: FL Cohort

**Arm A (n=300)**
- **Zanubrutinib 160 mg BID or 320 mg QDa**
- + obinutuzumab 1000 mg
- Cycle 1: days 1, 8, and 15
- Cycles 2-6: day 1

**Arm B (n=300)**
- **Lenalidomide 20 mg QDb**
- + 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

### Key secondary endpoints
- ORR per IRC using PET/CT-based Lugano 2014 criteria
- OS

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

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**FL cohort**
- **n=600**

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

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; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; QD, once daily; QOL, quality of life; R, randomized; 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. Patients with creatinine clearance of ≥30 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. 1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

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Study Design: MZL Cohort

MZL cohort
n=150

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/m\(^2\)
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/m\(^2\)
Cycle 1: days 1, 8, 15, and 22
Cycles 2-5: day 1

Primary endpoint
• PFS per IRC using CT-based Lugano 2014 criteria\(^1\)

Key secondary endpoint
• ORR per IRC using CT-based Lugano 2014 criteria\(^1\)

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\(^1\))
• 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; 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; 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 of ≥30 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. 1. Cheson BD, et al. J Clin Oncol. 2014;32(27):3059-3068.

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Study Status

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

• Previously published work has demonstrated that zanubrutinib leads to high response rates and durable responses in patients with R/R FL and MZL

• MAHOGANY will compare the efficacy and safety of zanubrutinib in combination with obinutuzumab in R/R FL and zanubrutinib in combination with rituximab in R/R MZL with that of the well-established standard of care, lenalidomide plus rituximab

• Independent cohorts for patients with R/R FL and MZL will allow specific evaluation of zanubrutinib combination therapy in each disease

FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory.
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