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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

MAHOGANY
Phase 3 Relapsed/Refractory FL/MZL

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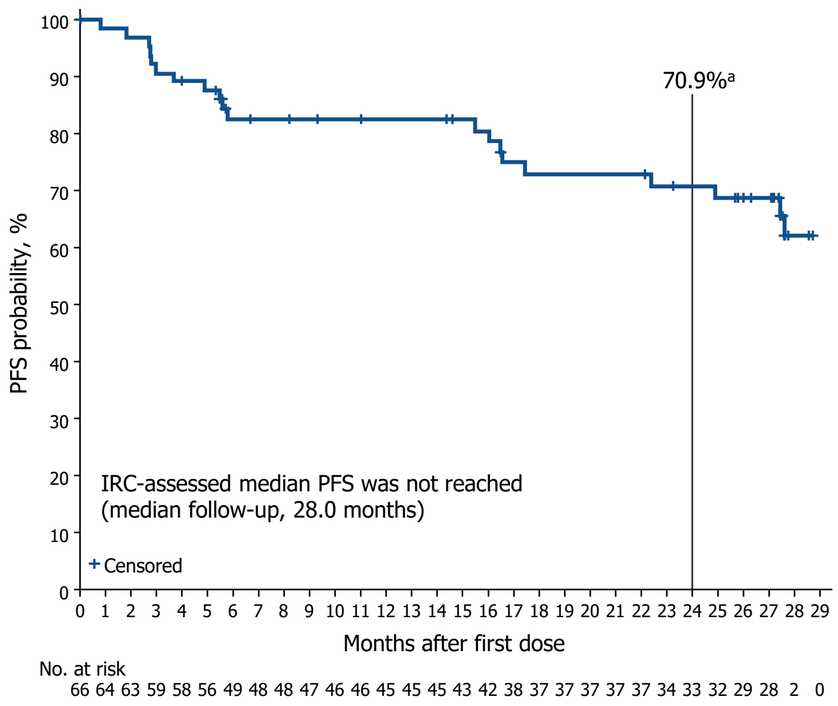
BACKGROUND

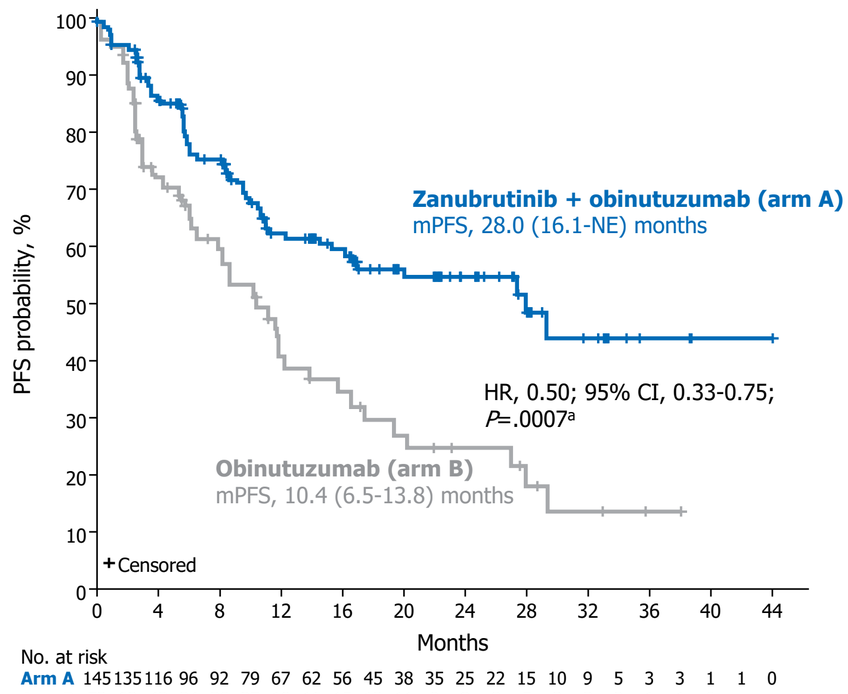
- Relapsed/refractory (R/R) disease is common in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL)
- Zanubrutinib is a second-generation, potent, specific Bruton tyrosine kinase (BTK) inhibitor approved in the US for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), MZL, and mantle cell lymphoma[1]
  - In patients with CLL/SLL[2] and WM,[3] zanubrutinib was shown to be more effective and better tolerated than ibrutinib, a first-generation BTK inhibitor
- Previous findings have suggested that zanubrutinib may lead to improved responses in R/R MZL and FL
  - 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); median progression-free survival (PFS) was not reached (**Figure 1**)[4]
  - 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%) and prolonged PFS (**Figure 2**)[5]

Figure 1. PFS by IRC in the Phase 2 MAGNOLIA R/R MZL Trial[4]



Adapted from Opat S, et al. *Blood*. 2022;140(suppl 1). Abstract 623. Data cutoff: May 4, 2022.
IRC, independent review committee.
[a] By PET and/or CT.

Figure 2. PFS by IRC in the Phase 2 ROSEWOOD R/R FL Trial[5]



IRC, independent review committee.
[a] Descriptive 2-sided *P* value.

METHODS

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

Figure 3. Study Design

Key eligibility criteria

- Age ≥18 years
- Histologically confirmed R/R FL (grade 1-3a) or MZL previously treated with ≥1 prior line of systemic anti-CD20–based therapy
- 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)
- Rituximab-refractory status (yes, no)

n=300: **Zanubrutinib 160 mg BID or 320 mg QD[a] + obinutuzumab 1000 mg**
Days 1, 8, and 15 of C1 and day 1 of C2-C6

n=300: **Lenalidomide 20 mg QD[b]**
Days 1-21 for 12 cycles
+ Rituximab 375 mg/m²
Days 1, 8, 15, and 22 of C1 and day 1 of C2-C5

MZL cohort — N=150 — R 1:1

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

n=75: **Zanubrutinib 160 mg BID or 320 mg QD[a] + rituximab 375 mg/m²**
Days 1, 8, 15, and 22 of C1 and day 1 of C2-C5

n=75: **Lenalidomide 20 mg QD[b]**
Days 1-21 for 12 cycles
+ Rituximab 375 mg/m²
Days 1, 8, 15, and 22 of C1 and day 1 of C2-C5

Primary endpoint:
- PFS per IRC using PET/CT-based Lugano 2014 criteria[6]

Key secondary endpoints:
- ORR per IRC using PET/CT-based Lugano 2014 criteria[6]
- OS

Secondary endpoints:
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using PET/CT-based Lugano 2014 criteria[6])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

Primary endpoint:
- PFS per IRC using CT-based Lugano 2014 criteria[6]

Key secondary endpoint:
- ORR per IRC using CT-based Lugano 2014 criteria[6]

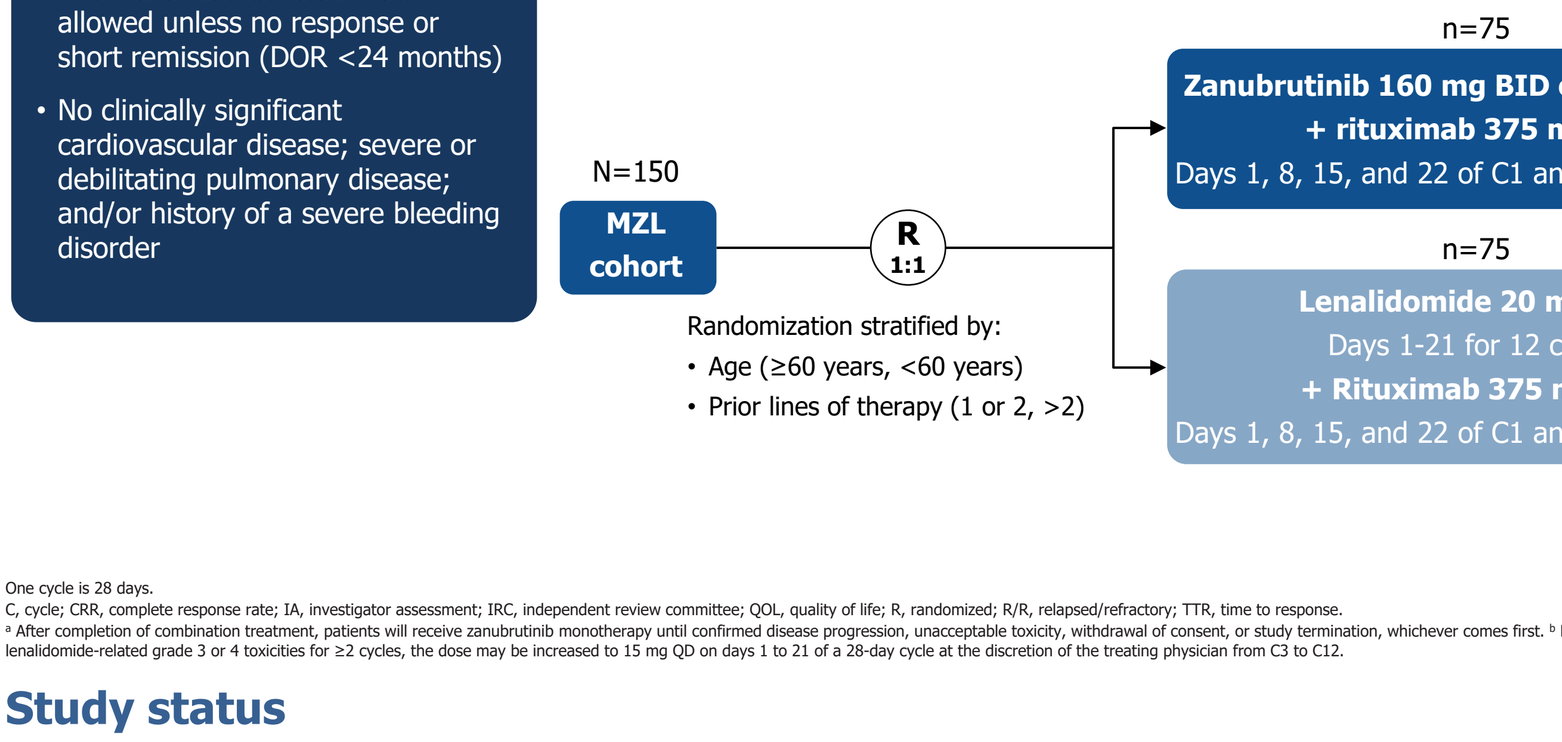
Secondary endpoints:
- OS
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using CT-based and PET/CT-based Lugano 2014 criteria[6])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

One cycle is 28 days.
C, cycle; CRR, complete response rate; IA, investigator assessment; IRC, independent review committee; 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 to 21 of a 28-day cycle at the discretion of the treating physician from C3 to C12.

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

WJ had a consulting or advisory role with AbbVie, AstraZeneca, BeiGene, Lilly, Pfizer, Roche, SOBI, and Takeda; and research funding from AbbVie, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Celgene, Janssen, Lilly, Merck, Pfizer, Roche, SOBI, and Takeda. **LJN** received research funding from Janssen Biotech, Genentech/Roche, Epizyme, IGM Biosciences, Novartis, Caribou Biosciences, Gilead Sciences, Allogene Therapeutics, BMS/Celgene, and Takeda; honoraria from Gilead/Kite, Novartis, Janssen Oncology, TG Therapeutics, BMS, ADC Therapeutics, MorphoSys, Epizyme, Genmab, Takeda, Genentech/Roche, Caribou Biosciences, Medscape, Neil Love, and PeerView; and travel support from Roche/Genentech; and had a consulting or advisory role with LRF Scientific, SIRPant, Interius Bio, ADC Therapeutics, AbbVie, Genentech, MEI, Denovo, Takeda, Caribou Biosciences, Incyte, and Janssen. **YS** has nothing to disclose. **LHS** had a consulting or advisory role with AbbVie, Seagen, Janssen, Amgen, Roche/Genentech, Gilead Sciences, Kite, Merck, Teva, TG Therapeutics, AstraZeneca, Incyte, Sandoz-Novartis, Genmab, Celgene/BMS, and BeiGene; honoraria from Amgen, AbbVie, Gilead Sciences, Janssen-Ortho, Kite, Merck, Roche/Genentech, Seagen, Teva, AstraZeneca, Incyte, Sandoz-Novartis, Genmab, Celgene/BMS, and BeiGene; and research funding from Roche/Genentech and Teva paid to their institution. **CS** received honoraria from AbbVie; research funding from Roche; and travel support from Roche and Incyte; provided expert testimony on behalf of Incyte; and had a consulting or advisory role with Janssen, GSK, Incyte, and BMS. **PLZ** had a consulting or advisory role with Celltrion, Gilead Sciences, Janssen-Cilag, BMS, Servier, Sandoz, MSD, Roche, EUSA Pharma, Kyowa Kirin, AstraZeneca, Takeda, Secura Bio, TG Therapeutics, Novartis, ADC Therapeutics, Incyte, and BeiGene and participated in speakers bureaus for Celltrion, Gilead, Janssen-Cilag, BMS, MSD, AstraZeneca, Takeda, Roche, EUSA Pharma, Kyowa Kirin, Incyte, BeiGene, and Novartis. **AS** received research funding from AbbVie and Roche; participated in speakers bureaus for BeiGene and Roche; and received travel funds from Kite and Janssen. **WZ** and **SH** are employees of BeiGene and own stock in BeiGene. **JW** is an employee of BeiGene, has received travel funds from BeiGene, and owns stock in BeiGene and BMS. **RD** has been an employee of Celgene/BMS, is an employee of BeiGene, and owns stock in Celgene/BMS and BeiGene. **JT** has received research funding from BeiGene, Janssen, Pharmacyclics, Roche, Celgene/BMS, and Selectar and has served on an advisory board for BeiGene.

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