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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Abstract 994

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Speaker Disclosures

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Background

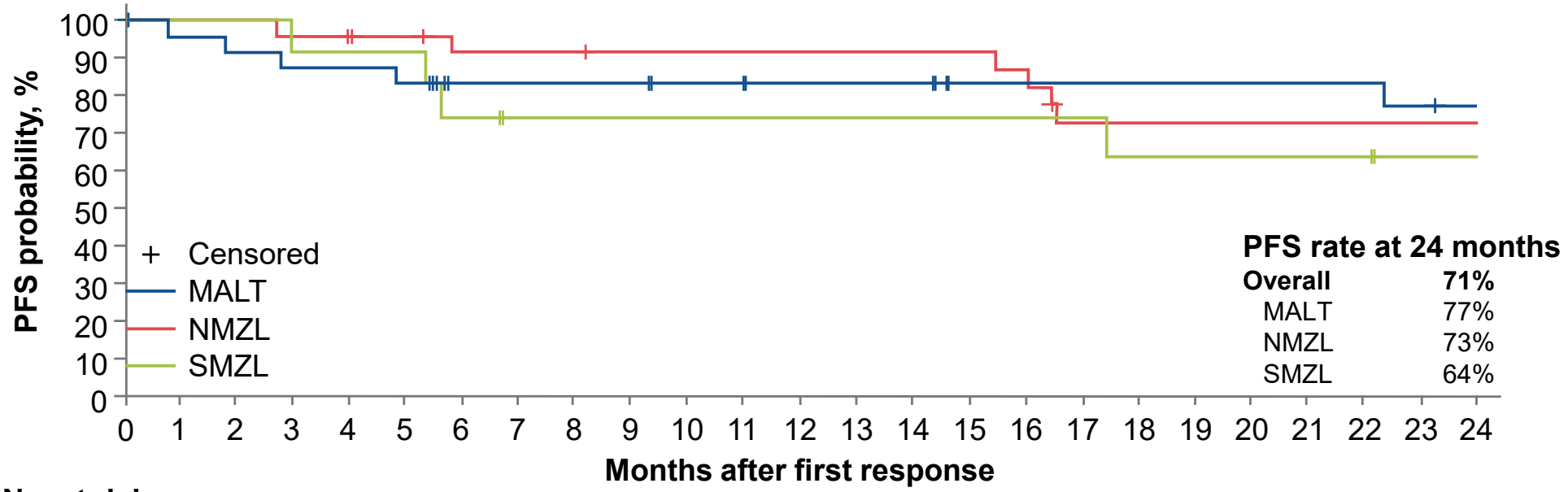
- Relapsed/refractory (R/R) disease is common in patients with FL and MZL
- Treatment of FL and MZL largely relies on immunochemotherapy, and additional novel therapies are greatly needed
- Zanubrutinib is a second-generation, potent, specific BTK inhibitor approved in the EU and US for the treatment 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.

1. Brukinsa (zanubrutinib). Prescribing information. BeiGene, Ltd; 2023. 2. Brukinsa (zanubrutinib). Summary of product characteristics. BeiGene Ireland, Ltd; 2023. 3. Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332. 4. Tam CS, et al. *J Clin Oncol*. 2022;40(suppl 16). Abstract 7521. 5. Opat S, et al. *Blood*. 2022;140(suppl 1). Abstract 623. 6. Flowers CR, et al. Presented at: 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL, USA. Abstract 7545.

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%



No. at risk

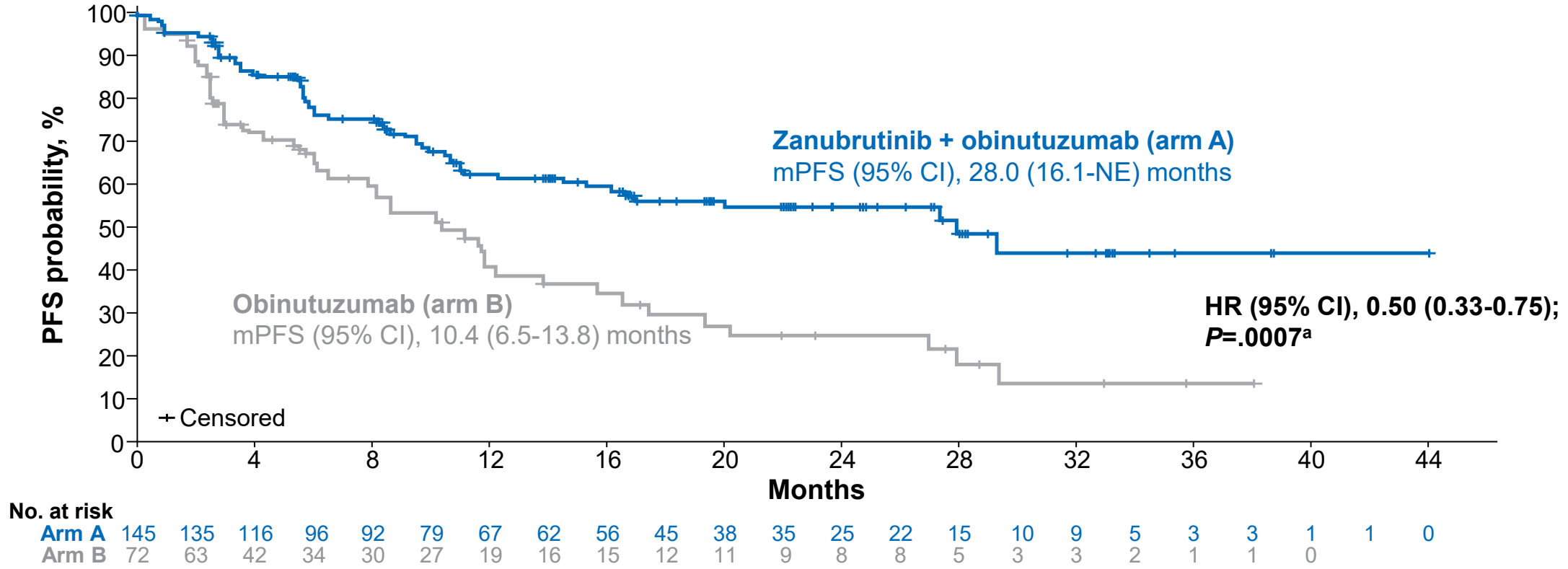
MALT	25	23	22	21	21	20	18	18	18	18	17	17	16	16	16	14	14	14	14	14	14	14	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	20	20	20	20	20	20	19	15	15	15	15	15	15	15	15
SMZL	12	12	12	11	11	11	8	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	4	4

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.

Trotman J, et al. Presented at: 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Abstract 284.

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.

[a] Descriptive 2-sided *P* value. Zinzani PL, et al. Presented at: 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Abstract 81.

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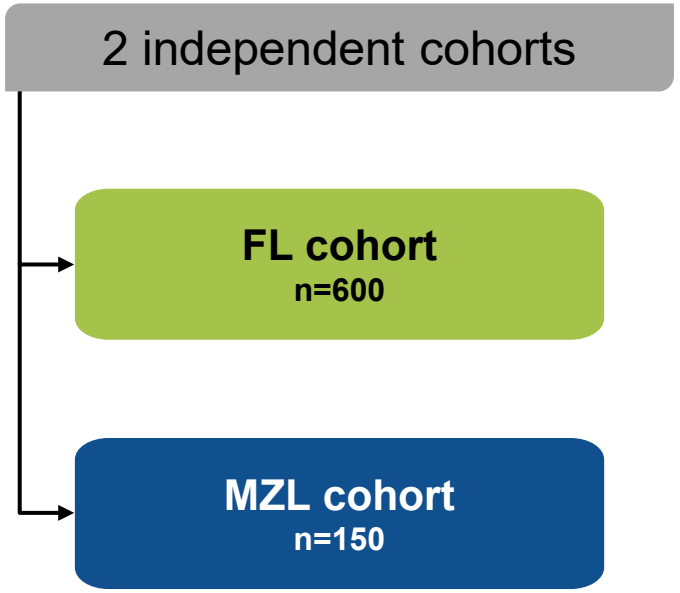
Study Design: Overview

- 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[1]
- 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



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.

1. Brice P, et al. *J Clin Oncol.* 1997;15(3):1110-1117.

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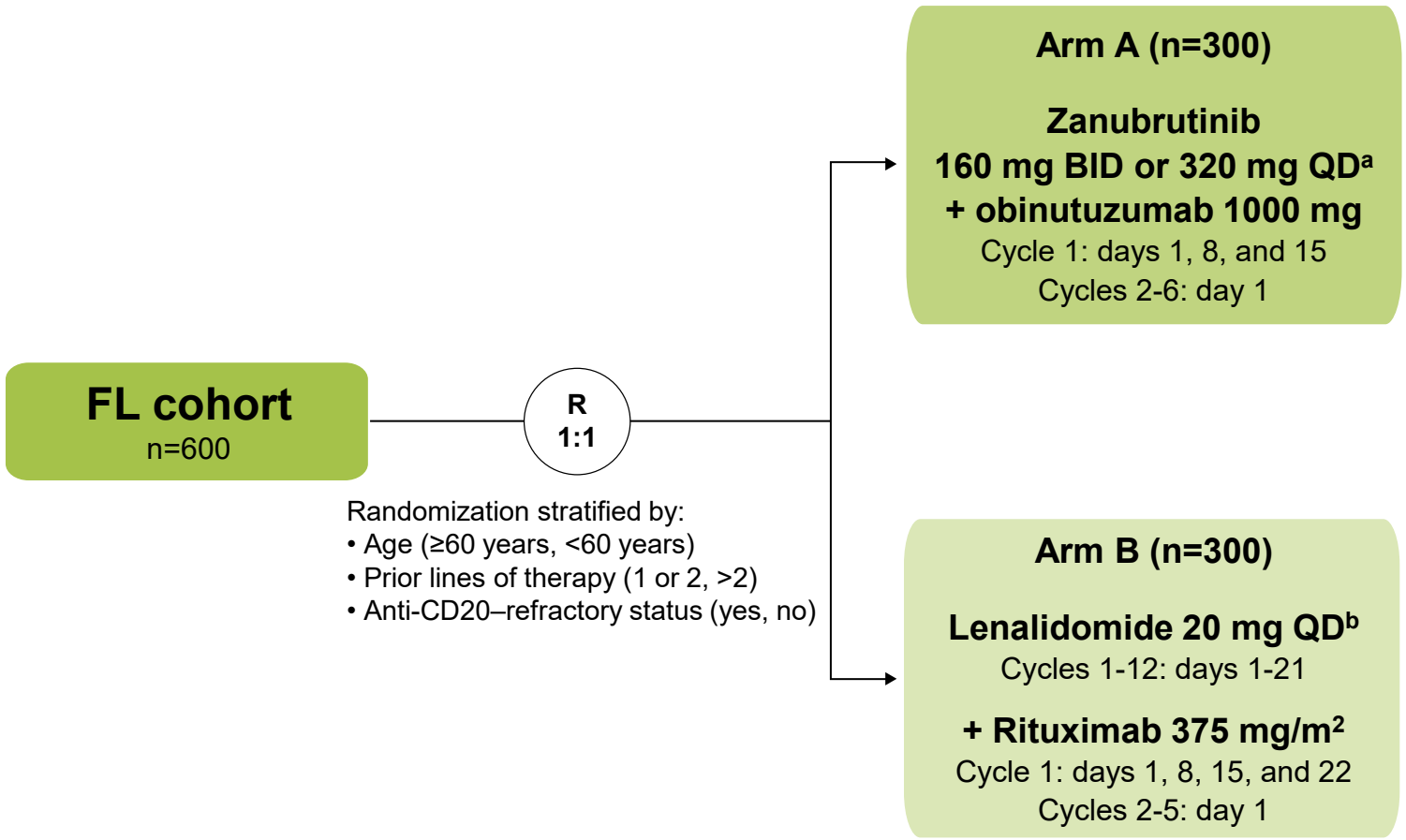
Study Design: FL Cohort



Primary endpoint

- PFS per IRC using PET/CT-based Lugano 2014 criteria[1]

Key secondary endpoints

- ORR per IRC using PET/CT-based Lugano 2014 criteria[1]
- OS

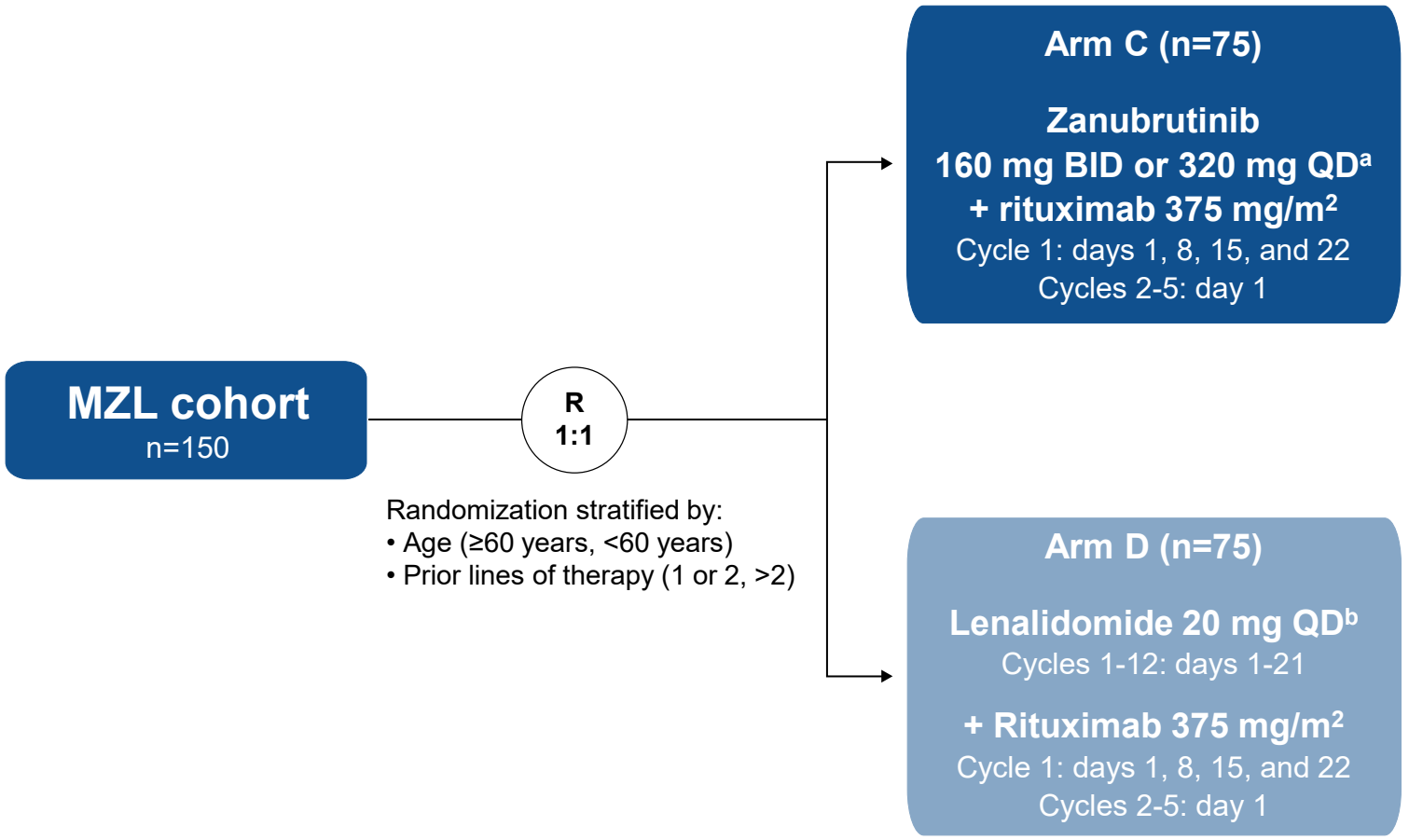
Secondary endpoints

- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using 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; 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. [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.

Study Design: MZL Cohort



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

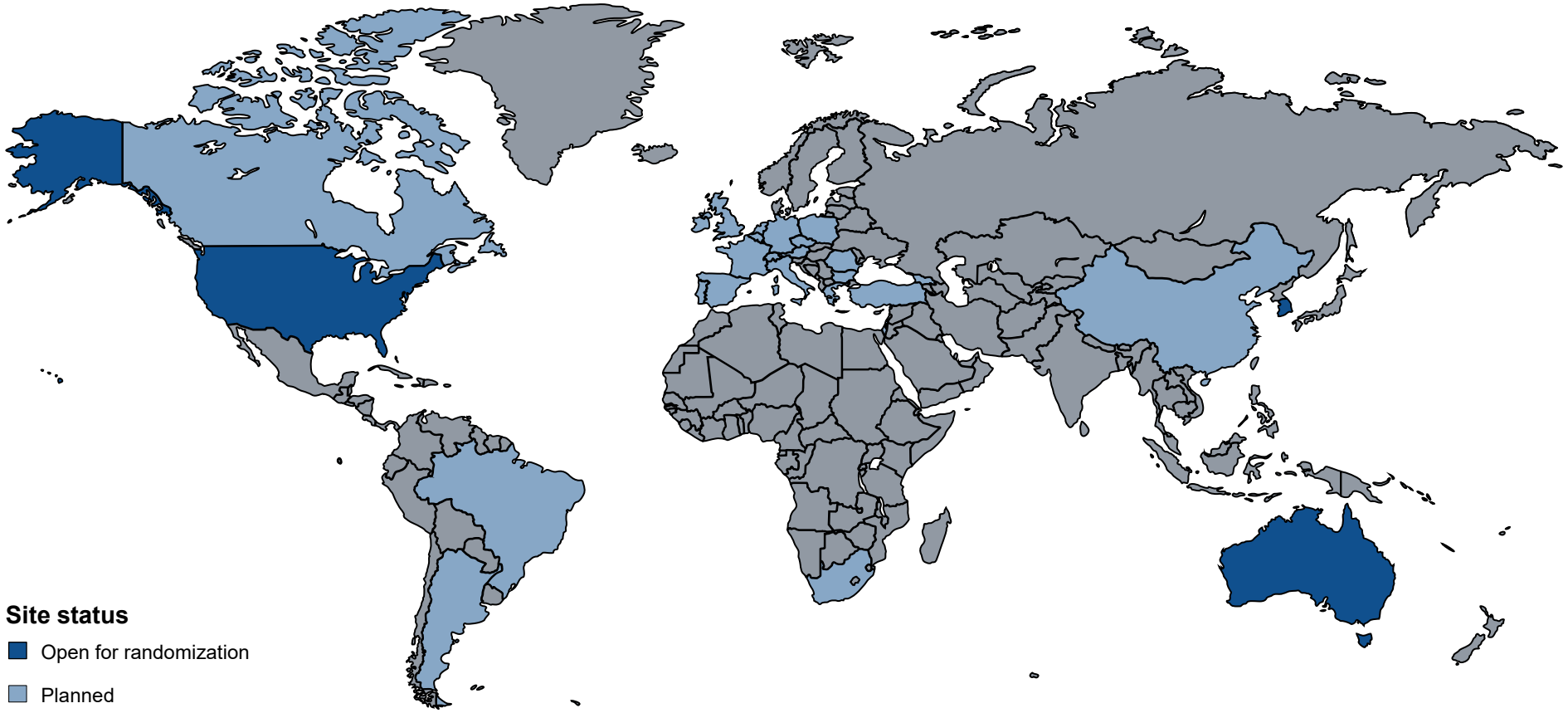
- OS
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using CT- and PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

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.

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



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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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