A Phase III study of zanubrutinib plus rituximab versus bendamustine plus rituximab in transplant-ineligible, untreated mantle cell lymphoma

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Mantle cell lymphoma is an aggressive B-cell malignancy. Current frontline chemoimmunotherapies produce high response rates but relapse is inevitable. Furthermore, the elderly and those with comorbidities are precluded from standard regimens and stem cell transplant, leaving them with limited options. Targeted therapies, including Bruton tyrosine kinase inhibitors, are an effective treatment strategy in mantle cell lymphoma. Zanubrutinib is a potent next-generation Bruton tyrosine kinase inhibitor that has demonstrated complete and sustained Bruton tyrosine kinase occupancy, minimal off-target effects and favorable pharmacokinetic/pharmacodynamic properties. Described herein is an ongoing Phase III study comparing the efficacy and safety of zanubrutinib plus rituximab followed by zanubrutinib monotherapy versus bendamustine plus rituximab followed by observation in transplant-ineligible patients with previously untreated mantle cell lymphoma.

Clinical Trial Registration: NCT04002297 (ClinicalTrials.gov)

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Here we describe an ongoing, head-to-head, randomized Phase III study comparing the efficacy of zanubrutinib (BGB-3111) and rituximab followed by zanubrutinib monotherapy with that of bendamustine plus rituximab followed by observation in patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for stem cell transplantation (SCT) as measured by progression-free survival (PFS) determined by an independent review committee (IRC). Secondary end points include PFS determined by investigator assessment (IA), overall response rate (ORR), duration of response (DOR) and overall survival (OS). This study also includes an exploratory analysis of clinical outcomes according to prognostic and predictive biomarkers, pharmacokinetic (PK) parameters and mechanisms of resistance (ClinicalTrials.gov: NCT04002297).

Background & rationale

MCL is one of the most challenging hematologic malignancies to manage owing to its aggressive clinical course and relative lack of effective cure. MCL accounts for 6% of all non-Hodgkin lymphoma (NHL) cases [1,2]. MCL is diagnosed in 0.51–0.55/100,000 persons per year in the USA with a similar incidence rate worldwide [3,4].

Table 1. BGB-3111-AU-003: overall response rate based on investigator's assessment in patients with mantle cell lymphoma.

Best response	Treatment naive (n = 11)	Relapsed/refractory (n = 37)	Efficacy evaluable (n = 48)
ORR, n (%) (95% CI)	9 (81.8) (48.2–97.7)	32 (86.5) (71.2–95.5)	41 (85.4) (72.2–93.9)
CR [†] , n (%) (95% CI)	3 (27.3) (6.0–61.0)	11 (29.7) (15.9–47.0)	14 (29.2) (17.0–44.1)
PR, n (%)	6 (54.5)	21 (56.8)	27 (56.3)
DOR median, months (95% CI)	NE (9.2–NE)	15.4 (11.5–28.2)	16.2 (11.5–28.2)
Follow-up median, months (range)	8.3 (1.6–27.9)	19.4 (1.9–38.2)	16.7 (1.6–38.2)

[†]PET scan is optional in this study and majority was per CT-based assessment.
CR: Complete response; CT: Computerized tomography; DOR: Duration of response; MCL: Mantle cell lymphoma; NE: Not estimable; ORR: Overall response rate; PET: Positron emission tomography; PR: Partial response.
Table created using data from [20].

The median age at diagnosis is 70 years and it is three-times more common in men than in women [5,6]. The majority of patients present with advanced-stage disease, including lymphadenopathy, organomegaly and bone marrow involvement and they frequently require immediate treatment [2]. The pathognomonic feature of MCL is overexpression of cyclin D1, which is a consequence of juxtaposition of the proto-oncogene *CCND1* on chromosome 11q13 to the immunoglobulin heavy chain gene at chromosome 14q32 [7].

Current frontline treatment usually includes chemo-immunotherapeutic options, most commonly rituximab–cyclophosphamide–doxorubicin hydrochloride–vincristine–prednisolone or bendamustine–rituximab. While response rates are often high, with duration of response varying from 18–30 months [8], multiple relapses are common [9,10]. Younger, fit patients have the option of high-intensity induction chemotherapy, such as hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD) followed by SCT, which results in prolonged remission for many patients [11,12]. However, the elderly and those with comorbidities are precluded from standard chemo-immunotherapeutic regimens and SCT. These patients have limited options and treatment is largely palliative. No standard treatment approach has been defined for these patients [5].

Bruton tyrosine kinase (BTK) mediates B-cell proliferation, migration, adhesion and survival and is constitutively active in MCL [7,13]. A number of BTK inhibitors, including zanubrutinib, have shown activity in relapsed/refractory (R/R) MCL and are approved by the US FDA [14–16].

Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy. In preclinical studies, zanubrutinib has been shown to be a highly potent, selective, bioavailable and irreversible BTK inhibitor [17]. Zanubrutinib has greater selectivity for BTK versus off-target TEC- and EGFR-family kinases which are thought to cause adverse events (AEs) such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash and fatigue, which can be associated with BTK inhibitor therapy [18,19]. Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes was achieved in all patients in the first-in-human Phase I study BGB-3111-AU-003 at the 160 mg twice-daily therapeutic dose (ClinicalTrials.gov: NCT02343120) [17]. Achieving complete BTK inhibition in both blood and lymph nodes is hypothesized to help provide meaningful and sustained responses in MCL and other hematologic malignancies. Based on drug–drug interaction studies and PK/pharmacodynamic analyses, proton pump inhibitors or other acid-reducing agents do not affect zanubrutinib exposure [16]. Zanubrutinib may be coadministered with strong or moderate CYP3A inhibitors at a reduced dose. In addition, antiplatelet medications and anticoagulants including warfarin have been allowed on zanubrutinib trials. There is now extensive clinical experience at the 160-mg twice-daily and 320-mg once-daily doses of zanubrutinib. Both dosing schedules have shown a high level of activity without compromising the tolerability profile.

Zanubrutinib monotherapy has been shown to be highly active and well tolerated in patients with MCL in two single-arm studies (BGB-3111-AU-003 [NCT02343120] and BGB-3111-206 [NCT03206970]) [20,21]. In BGB-3111-AU-003, 53 patients with MCL (37 R/R and 16 treatment-naïve) were dosed. The investigator-assessed ORR was 85.4% with a median DOR of 16.2 months (Table 1) [20]. The most common AEs were contusion (39.6%), diarrhea (34%), upper respiratory tract infection (26.4%) and constipation and fatigue (22.6% each). The majority of AEs were grade 1/2, with anemia as the most common grade ≥3 AE (9.4%). Ten patients (18.9%) discontinued treatment due to AEs; major hemorrhage and atrial fibrillation/flutter occurred in four patients (7.5%) [20].

Table 2. BGB-3111-206: overall response rate based on independent review committee's assessment in patients with relapsed/refractory mantle cell lymphoma.

Best response	n = 86
ORR, n (%) (95% CI)	72 (84) (74–91)
CR, n (%)	59 (68.6)
PR, n (%)	13 (15.1)
DOR median, months (range) (95% CI)	19.5 (0.9–19.5) (16.6–NE)
Follow-up median, months (range)	18.4 (0.3–23.5)
PFS median, months (range) (95% CI)	22.1 (0.0–22.3) (17.4–NE)
CR: Complete response; DOR: Duration of response; MCL: Mantle cell lymphoma; NE: Not estimable; ORR: Overall response rate; PFS: Progression-free survival; PR: Partial response. Table created using data from [21].	

In the BGB-3111-206 study, 86 patients with R/R MCL were enrolled. The IRC-assessed ORR was 84% with a median DOR of 19.5 months (Table 2) [21]. The most common adverse events were neutropenia (48.8%), leukopenia and upper respiratory tract infection (34.9% each), rash (33.7%) and thrombocytopenia (32.6%). The majority of AEs were grade 1/2; neutropenia was the most common grade ≥ 3 AE (19.8%). Eight patients (9%) discontinued treatment due to AEs. Three patients (3%) had major bleeding events. No patient experienced atrial fibrillation/flutter [21].

In a pooled safety analysis from six zanubrutinib monotherapy studies (n = 682), including patients with NHL, the most common AEs that occurred in $\geq 20\%$ of patients were upper respiratory tract infection and neutropenia [16]. The majority of AEs were grade 1/2, with neutrophil count decreased as the most common grade ≥ 3 AE (14%) [16]. Toxicities that are often associated with BTK inhibitors were infrequent, including grade ≥ 3 atrial fibrillation/flutter (0.6%), grade ≥ 3 major hemorrhage (2.1%), grade ≥ 3 thrombocytopenia (6.6%) and grade ≥ 3 diarrhea (0.9%). AEs leading to study drug discontinuation occurred in 9% of patients [22].

Rituximab, an anti-CD20 monoclonal antibody, is widely used in the treatment of different types of B-cell malignancies both as a single agent and in combination regimens. Rituximab has been demonstrated to be a key component in treatment of patients with MCL and is standardly used as part of frontline chemotherapy [5,23]. The addition of rituximab (375 mg/m²) to other agents in frontline treatment has shown an improvement in OS [24]. Clinical experiences with ibrutinib in combination with rituximab have demonstrated that the combinations are active, lack overlapping toxicity and can be combined at full monotherapy doses of the respective agents [25–27]. In preclinical studies, zanubrutinib was shown to be at least tenfold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity, consistent with its more selective activity against BTK and weaker inducible T-cell kinase inhibitory activity than ibrutinib [28]. In preclinical xenograft models, zanubrutinib has also demonstrated good combination activity with rituximab. Since rituximab is a monoclonal antibody (biologic), no PK drug–drug interaction between zanubrutinib and rituximab is expected.

Given the encouraging clinical activity and tolerability of zanubrutinib in R/R MCL and the need for more frontline treatment options for the elderly and those with comorbidities, chemotherapy-free investigation of zanubrutinib in combination with rituximab for patients with previously untreated MCL who are ineligible for SCT is warranted.

Design

Study design

This Phase III, global, multicenter, randomized, open-label, active-control study compares zanubrutinib plus rituximab followed by zanubrutinib monotherapy versus bendamustine plus rituximab followed by observation in approximately 500 adult patients with previously untreated MCL who are ineligible for SCT. The primary objective of the study is to compare efficacy of the treatment arms, as measured by PFS determined by IRC.

This study opened to accrual in July 2019 and will be recruiting patients from approximately 200 sites in Australia, Austria, Belgium, China, France, Germany, Italy, Ireland, Japan, the Netherlands, New Zealand, Poland, Portugal, Romania, Russia, Spain, Taiwan, Turkey, Ukraine, UK and the USA.

Figure 1. Study design.

Bid: Twice daily; MCL: Mantle cell lymphoma; PD: Progressive disease; R: Randomized.

Key eligibility criteria

Eligible patients must have histologically confirmed MCL with measurable disease by computed tomography/magnetic resonance imaging scan, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function. Patients must not have received prior systemic treatments for MCL. Patients must be ineligible for SCT, aged ≥ 70 years, or aged ≥ 65 and < 70 years with comorbidities precluding autologous SCT including at least one of the following: cardiac ejection fraction $\leq 40\%$, diffusing capacity for carbon monoxide $\leq 60\%$ predicted and/or creatinine clearance < 70 but ≥ 30 ml/min.

Patients will be excluded for any of the following reasons: known central nervous system involvement by lymphoma, prior hematopoietic SCT, prior treatment with a BTK inhibitor, patients for whom the goal of therapy is tumor debulking prior to SCT, clinically significant cardiovascular disease, history of severe bleeding, known infection with HIV or active hepatitis B or C viruses, or prior malignancy within the past 3 years except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma *in situ* of the cervix or breast, or localized Gleason score 6 prostate cancer.

Planned sample size

Approximately 500 patients will be enrolled and randomized in a 1:1 ratio to receive either zanubrutinib plus rituximab followed by zanubrutinib monotherapy or bendamustine plus rituximab followed by observation. Randomization will be stratified by age (< 70 vs ≥ 70 years), geographic region (Asia Pacific vs North America/Europe) and MCL International Prognostic Index Score (low vs intermediate/high).

Planned study period

All study treatments will be administered open label. The first patient was dosed on 21 August 2019. Based on enrollment projections, the study duration is estimated to be approximately 84 months (7 years). Recruitment is ongoing.

Study procedures

Patients will receive either zanubrutinib 160 mg (80 mg $\times$ two capsules) by mouth twice daily (with interval of ≥ 8 hours) plus intravenous (iv.) rituximab 375 mg/m² on day 1 of cycles 1–6, followed by zanubrutinib monotherapy at the same dose (arm A) or iv. bendamustine 90 mg/m²/day on days 1 and 2 plus iv. rituximab 375 mg/m² on day 1 of cycles 1–6 followed by observation (arm B; Figure 1). Each treatment cycle consists of 28 days. Patients will remain on the study drugs until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination.

In the event of grade ≥ 3 nonhematologic toxicities, grade ≥ 3 febrile neutropenia, grade 3 thrombocytopenia associated with bleeding, or grade 4 thrombocytopenia or neutropenia lasting for more than ten consecutive days

considered to be related to zanubrutinib, drug will be withheld until resolution of any related toxicities. Dosing can be resumed following an interruption of up to 28 days but at a reduced dose following the second and third AE (80 mg twice daily and once daily, respectively). Zanubrutinib is to be discontinued in patients who experience their fourth drug-related AE. The local rituximab and bendamustine labels should be followed for the management of toxicities. In general, no dose reductions for rituximab will be allowed; a dose delay of up to 28 days is acceptable. In arm B, if rituximab or bendamustine is delayed, then the initiation of the entire cycle should be delayed.

Outcome measures/end points

The primary objective of the study is to compare the efficacy of the treatment arms, as measured by PFS determined by IRC using the Lugano classification for NHL. Secondary objectives include PFS determined by IA, ORR (proportion of patients achieving complete response or partial response) determined by IRC and IA, DOR determined by IRC and IA, OS, rate of complete response or complete metabolic response, time to response determined by IRC and IA, patient-reported outcomes as measured by the 5-level EQ-5D (EQ-5D-5L) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) and safety parameters. Exploratory end points include PK parameters of zanubrutinib, a correlation analysis of clinical outcomes with prognostic and predictive biomarkers and an evaluation of the mechanisms of resistance to zanubrutinib.

Assessments of safety will include AEs, serious AEs, clinical laboratory tests, physical examinations, electrocardiograms and vital signs. AEs will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. An independent data monitoring committee will periodically monitor safety data and perform the interim efficacy analysis.

Statistics

The primary analysis set for all efficacy analyses is the intent-to-treat analysis set (all randomized patients). The safety analysis set will include all patients who receive any dose of study drug. The PK analysis set will include all zanubrutinib-treated patients who have at least one post-dose drug concentration measurement.

Approximately 500 patients will be enrolled and randomized in a 1:1 ratio to receive either zanubrutinib plus rituximab followed by zanubrutinib monotherapy or bendamustine plus rituximab followed by observation. The primary efficacy analysis comparing PFS assessed by IRC between the two arms will be based on a log-rank test stratified by randomization stratification factors age (<70 vs ≥ 70 years), geographic region (Asia Pacific vs North America/Europe) and MCL International Prognostic Index Score (low vs intermediate/high) in the intent-to-treat analysis set.

There will be planned analyses based on the number of PFS events as determined by IRC. The p-value will be based on Wald test for the treatment effect from the Cox regression. The hazard ratio and its two-sided 95% CI will be estimated from a stratified Cox regression model. The distribution of PFS, including median PFS and PFS rate at selected timepoints, will be estimated using the Kaplan–Meier method for each arm.

Conclusion

Targeting the BTK signaling pathway has proven to be efficacious in patients with R/R MCL. Zanubrutinib, a next-generation BTK inhibitor, has been shown to be highly active and well tolerated in R/R MCL. Rituximab has been a key component in the treatment of MCL. The combination of zanubrutinib with rituximab has the potential for improved outcomes in patients with previously untreated MCL who are ineligible for SCT and currently have limited treatment options.

Executive summary

Background & rationale

- Current frontline chemo-immunotherapeutic options can produce high response rates in mantle cell lymphoma (MCL) but relapse is inevitable for most patients.
- Furthermore, the elderly and those with comorbidities are precluded from standard regimens and stem cell transplantation (SCT), leaving them with limited treatment options.
- Targeting the B-cell receptor with Bruton tyrosine kinase (BTK) inhibitors, including zanubrutinib, has demonstrated clinical activity and has been approved by the US FDA in patients with relapsed/refractory MCL.
- Rituximab has demonstrated clinical benefits and has been standardly used in first-line MCL patients.

Zanubrutinib

- Zanubrutinib is a next-generation irreversible BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases.
- In clinical studies of relapsed/refractory MCL, zanubrutinib monotherapy has been shown to be active and well tolerated.

Phase III trial

- This Phase III, global, multicenter, randomized, open-label, active-control study compares zanubrutinib plus rituximab followed by zanubrutinib monotherapy versus bendamustine plus rituximab followed by observation in approximately 500 adult patients with previously untreated MCL who are ineligible for SCT.

Objectives

- The primary objective of the study is to compare the efficacy of the treatment arms, as measured by progression-free survival (PFS) determined by an independent review committee.
- Key secondary end points include PFS determined by investigator assessment, overall response rate, duration of response, overall survival and safety.

Statistics

- The primary efficacy analysis comparing PFS assessed by independent review committee between the two arms will be based on a log-rank test stratified by randomization stratification factors age (<70 vs ≥70 years), geographic region (Asia Pacific vs North America/Europe) and MCL International Prognostic Index Score (low vs intermediate/high) in the intent-to-treat analysis set.

Conclusion

- Zanubrutinib is a next-generation BTK inhibitor designed to be highly selective with fewer off-target effects.
- Zanubrutinib was shown to be at least tenfold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity consistent with its more selective activity against BTK.
- Zanubrutinib in combination with rituximab has the potential to further improve outcomes with a chemotherapy-free approach in patients with previously untreated MCL who are ineligible for SCT and currently have limited treatment options.

Author contributions

M Dreyling, CS Tam, M Wang, SD Smith, M Ladetto, H Huang and S Le Gouill have contributed or will contribute to patient enrollment. BeiGene was involved in study design, compilation of data and statistical analysis. All authors had full access to all of the data, contributed to data interpretation and analysis, carefully reviewed the manuscript and approved the final version. The corresponding author, M Dreyling, had final responsibility to submit for publication.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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