Protocol Title

A phase II study of bendamustine plus rituximab (BR) in patients with relapsed or progressive marginal zone B-cell lymphoma (MZBCL)

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PROTOCOL SYNOPSIS	
Study Owner:	Seoul National University Hospital
Protocol Title:	A phase II study of bendamustine plus rituximab (BR) in patients with relapsed or progressive marginal zone B-cell lymphoma (MZBCL)
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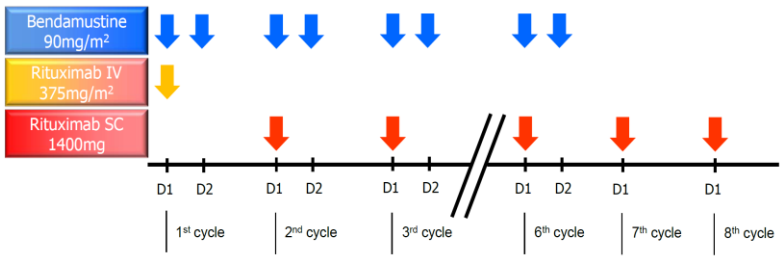
Institution Name(s):	Seoul National University Hospital
Sub-Investigator Name(s), if applicable:	☑ No ☐ Yes
Plan on using other Institutions or centers to conduct study: **If yes, please list name(s) and address(es):**	☐ No ☑ Yes Seoul National University Hospital, Seoul National University Bundang Hospital, Korean Cancer Study Group, the Lymphoma subcommittee
Rationale:	Bendamustine consists of a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain and shows both alkyla ting and antimetabolite properties. Bendamustine confers a progression-free survival (PFS) benefit in indolent B-cell lymphoid malignancies. In addition, bendamustine plus rituximab (BR) is highly active against relapsed/refractory indolent B-cell and mantle cell lymphomas (overall response rate [ORR]=92% and complete remission [CR]=55%) and chronic lymphocytic leukemia (CLL) (ORR=59% and CR=9%). Furthermore, a front-line BR demonstrates a significant PFS benefit and tolerability compared with R-CHOP in untreated indolent and mantle cell lymphomas except marginal zone B-cell lymphoma (MZBCL) (StiL NHL1 study). The 3rd nationwide study with 3,998 lymphoma patients between 2005 and 2006 revealed a relatively higher rates and

	increasing incidence of MZBCL (769 [19%] of 3,998) as compared with the 2nd nationwide study (252 [16%] of 1,548) in Korea. Although 1st-line R-CVP is the standard treatment of advanced MZBCL in Korea (ORR=88% and CR=60%), nearly 40% of MZBCL progress at 3 years. Bendamustine alone is effective against rituximab-refractory MZBCL (ORR=81% [13/16] and CR=25% [4/16]) and 1st-line BR shows similar outcome to R-CHOP (N=67, median PFS 57.2 vs 47.2 month; *P*=.3249) as a subgroup population analysis. However, the efficacy of BR has not been well elucidated in relapsed or progressive MZBCL. Therefore, this study will be conducted to evaluate the efficacy of BR in patients with relapsed or progressive MZBCL.
Study Design:	Multi-center trial, Phase II, non-randomized, open-label, single-arm study with combined therapy of bendamustine and rituximab in patients with MZBCL who has relapsed or progressive to prior chemotherapy or chemo-radiotherapy. **Bendamustine + rituximab combination chemotherapy** • Bendamustine 90mg/m2 IV on days 1-2 up to 6th cycle • Rituximab 375mg/m2 IV on day 1 at 1st cycle • Rituximab 1400mg SC on day 1 from 2nd cycle every 4 weeks up to 8th cycle, disease progression, or intolerable toxicities. 
Objectives:	Primary: ORR Secondary: CR rate, ORR according to prior chemo-sensitivity (CR+PR vs. SD+PD), PFS, OS, safety, response duration, biomarker correlative study
Subjects:	Total patients: 24 +3 (10% drop-out rate) = 27patients

Inclusion Criteria:	1. Histologically confirmed CD20-positive nodal or extranodal MZBCL 2. MZBCL patients who relapsed or progressed: have to meet a+b or a+c of the following criteria: a. At least one and a maximum of four prior lines of chemotherapy b. progression or relapsed during or after previous chemotherapy, except for rituximab treatment. c. progression or relapsed after 6 months of the last dose of previous chemotherapy including rituximab treatment. 3. Patients age ≥ 18 years 4. ECOG PS 0-2 (appendix A) 5. At least one bidimensionally measurable disease (>1.5cm defined by CT scan) 6. Adequate hematologic, renal, and hepatic functions as defined by: 1) hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1.5 x 10^9/L, and platelets ≥ 75 x 10^9/L (absolute neutrophil count ≥ 1.0 x 10^9/L, platelets ≥ 50 x 10^9/L if bone marrow involvement or hypersplenism due to the splenic involvement present) 2) Serum creatinine ≤ 1.5 x ULN or calculated CrCL ≥ 40 mL/min (Cockcroft Gault fomula) 3) Total bilirubin ≤ 1.5 x ULN (total bilirubin ≤ 3.0 x ULN in patient with Gilbert's syndrome) 7. Women of child-bearing potential should use two appropriate methods of contraception during the study (diaphragm, use of condom by partner, intrauterine contraceptive device, sponge or spermicide) or in the status of surgical sterilization or maintain abstinence. Men should use appropriate method of contraception; such as use of condom and etc. 8. Written informed consent
Exclusion Criteria:	1. Not all of the above inclusion criteria are met. 2. Prior chemotherapy within 4 weeks or radiotherapy within 6 weeks 3.Corticosteroids during last 28 days except chronic

	administration of prednisolone at a dose of < 20mg/day for indications other than lymphomas 4. Evidence of CNS involvement by lymphomas 5. Active HBV/HCV infections, known HIV infection. However, HBsAg-positive subject must be under the standard antiviral agent treatment and under the condition that HBV DNA should not be detected. HBcAb-positive subject should be checked the condition closely through trial period. 6. Prior diagnosis of cancers within 5 years, except cervical intraepithelial neoplasia type 1, localized non-melanoma skin cancer, or small differentiated thyroid cancer 7. Serious concurrent disease: 1) myocardial infarction and any cardiovascular events within 6 months prior to enrollment 2) uncontrolled hypertension despite adequate medication 3) serious congestive heart failure (NYHA functional classification III or V) 8. Patients who are pregnant or lactating
Study Drug Regimens:	Bendamustine 90mg/m2 on days 1and 2 plus subcutaneous Rituximab 1,400mg on day 1 every 4 weeks as a cycle up to 8th cycles (rituximab 375mg/m2 IV on day 1 at 1st cycle only)
Other Therapy:	N/A
Efficacy Measures:	Response evaluation every 8 weeks during BR chemotherapy, and followed by every 3 months after completion of last BR chemotherapy for 2 years, and then every 6 months after 2 years using revised response criteria for malignant lymphoma
Safety Measures:	Adverse events using NCI CTCAE version 4.03: treatment-emergent and treatment-related / discontinuation
Correlative Science:	FcγRIII polymorphism and baseline NK cell quantification before BR

Statistical Analysis:	MinMax Simon's two-stage design α **P0=0.60; P1=0.80 (ORR)** **Significant level=0.05; power=0.80** **Stage 1: 8/13 (≥9 responses are required to move to stage 2)** **Stage 2: 25/35 (26 or more responses are required to reject the null hypothesis)** **Total expected number of subjects (dropout rate: 10%) = 35 + 4 = 39 patients** **At least 35 subjects are required to achieve 80% of the power (39 in consideration of dropout rate).** **However the target number of trial is difficult to practice.**
Data Collection:	CRF
Estimated Start Date:	Activation: Feb 2015
Estimated Length of Enrollment:	First patient in: Mar 2015 Last patient in: Apr 2018 Last patient out: Apr 2020
Description of Site Enrollment Capabilities:	Most sites use first-line R-CVP in stage III/IV MALT lymphoma in Korea. Nearly 90 patients with stage IV disease might receive R-CVP per year in this center. However, some disease relapsed or progressed after prior chemotherapy or chemo-radiotherapy.
Estimated Study Duration:	65 months
Planned Written Outcomes of This Study (check all that apply):	☐ Final Study Report ☐ Submit for presentation at scientific conference ☑ Submit for full publication ☐ Submit abstract/poster at scientific conference
Publication Plan (if applicable):	Jun 2020/ J Clin Oncol
Intellectual Property Disclosure:	☑ No ☐ Yes
Study Insurance:	Covered by the study site as the local/national requirements for conducting clinical trial in Korea.

Past History and Experience:	☐ No ☑ Yes BR regimen is used in relapsed DLBCL and MCL patients in Korea. This center has many experiences in rituximab-based trials in malignant lymphomas. It also has bendamustine experience in treating indolent lymphoma.
STUDY DRUG SUPPLY	
Study Drug Requested <u>from Roche</u> Per Patient:	Mabthera IV/SC - maximum 1/7 cycles treatment per patients - 500mg/vial x1 + 200mg/vial x 1 (or 2) = 1 cycle per patient (IV) - 1400mg/vial x 7 cycles = 7 vials per patient (SC) 39 planned patients x 8 vials/patient = 312 vials (total)
Other Sources of Study Drug(s):	Bendamustine 100mg/vial by Eisai Korea