Bendamustine treatment of Chinese patients with relapsed indolent non-Hodgkin lymphoma: a multicenter, open-label, single-arm, phase 3 study

Yuan-Kai Shi[1], Xiao-Nan Hong[2], Jian-Liang Yang[1], Wei Xu[3], Hui-Qiang Huang[4], Xiu-Bin Xiao[5], Jun Zhu[6], Dao-Bin Zhou[7], Xiao-Hong Han[1], Jian-Qiu Wu[8], Ming-Zhi Zhang[9], Jie Jin[10], Xiao-Yan Ke[11], Wei Li[12], De-Pei Wu[13], Shen-Miao Yang[14], Xin Du[15], Yong-Qian Jia[16], Ai-Chun Liu[17], Dai-Hong Liu[18], Zhi-Xiang Shen[19], Lian-Sheng Zhang[20], Leonard James[21], Edward Hellriegel[21]

[1]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing 100021, China;
[2]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai 200030, China;
[3]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China;
[4]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, China;
[5]Department of Medical Oncology, 307 Hospital of Chinese People's Liberation Army, Beijing 100071, China;
[6]Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing 100142, China;
[7]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China;
[8]Department of Oncology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer, Nanjing, Jiangsu 210009, China;
[9]Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China;
[10]Department of Hematology, The First Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, Zhejiang 310003, China;
[11]Department of Hematology, Peking University Third Hospital, Beijing 100191, China;
[12]Department of Oncology, Jilin University First Affiliated Hospital, Changchun, Jilin 130021, China;
[13]Department of Hematology, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China;
[14]Department of Hematology, Peking University Institute of Hematology, Peking University People's Hospital, Beijing 100044, China;
[15]Department of Hematology, Guangdong General Hospital, Guangzhou, Guangdong 510062, China;
[16]Department of Hematology and Research Laboratory of Hematology, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, China;
[17]Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang 150001, China;
[18]Department of Hematology, Chinese PLA General Hospital, Beijing 100038, China;
[19]Department of Hematology, Shanghai Ruijin Hospital, Shanghai 200020, China;
[20]Department of Hematology, The Second Hospital of Lanzhou University, Lanzhou, Gansu 730030, China;
[21]Department of Drug Metabolism and Pharmacokinetics, Teva Branded Pharmaceutical Products R&D Inc., West Chester, PA 19380, USA.

Abstract

Background: Bendamustine was approved in China on May 26th, 2019 by the National Medical Product Administration for the treatment of indolent B-cell non-Hodgkin lymphoma (NHL). The current study was the registration trial and the first reported evaluation of the efficacy, safety, and pharmacokinetics of bendamustine in Chinese adult patients with indolent B-cell NHL following relapse after chemotherapy and rituximab treatment.

Methods: This was a prospective, multicenter, open-label, single-arm, phase 3 study (NCT01596621; C18083/3076) with a 2-year follow-up period. Eligible patients received bendamustine hydrochloride 120 mg/m^2 infused intravenously on days 1 and 2 of each 21-day treatment cycle for at least six planned cycles (and up to eight cycles). The primary endpoint was the overall response rate (ORR); and secondary endpoints were duration of response (DoR), progression-free survival (PFS), safety, and pharmacokinetics. Patients were classified according to their best overall response after initiation of therapy. Proportions of patients in each response category (complete response [CR], partial response [PR], stable disease, or progressive disease) were summarized along with a two-sided binomial exact 95% confidence intervals (CIs) for the ORR.

Results: A total of 102 patients were enrolled from 20 centers between August 6th, 2012, and June 18th, 2015. At the time of the primary analysis, the ORR was 73% (95% CI: 63%–81%) per Independent Review Committee (IRC) including 19% CR and 54%

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Correspondence to: Prof. Yuan-Kai Shi, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China
E-Mail: syuankai@cicams.ac.cn

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PR. With the follow-up period, the median DoR was 16.2 months by IRC and 13.4 months by investigator assessment; the median PFS was 18.6 months and 15.3 months, respectively. The most common non-hematologic adverse events (AEs) were gastrointestinal toxicity, pyrexia, and rash. Grade 3/4 neutropenia was reported in 76% of patients. Serious AEs were reported in 29 patients and five patients died during the study. Pharmacokinetic analysis indicated that the characteristics of bendamustine and its metabolites M3 and M4 were generally consistent with those reported for other ethnicities.

Conclusion: Bendamustine is an active and effective therapy in Chinese patients with relapsed, indolent B-cell NHL, with a comparable risk/benefit relationship to that reported in North American patients.

Clinical trial registration: ClinicalTrials.gov, No. NCT01596621; https://clinicaltrials.gov/ct2/show/NCT01596621

Keywords: Bendamustine; Non-Hodgkin lymphoma; B-cell malignancy; Relapsed disease; Clinical trial

Introduction

Non-Hodgkin lymphomas (NHLs) are a group of lymphoid malignancies that accounted for an estimated 510,000 new cases worldwide in 2018.[1] Indolent NHLs, comprising nearly 40% of all NHL cases, are a heterogeneous subgroup that tends to be slow in development and progression and may not require treatment at the time of diagnosis.[2-4] Ultimately, most patients will require treatment; although indolent NHLs are treatable, they are generally not considered curable outside of the option of hematopoietic stem cell transplantation. Patients with indolent NHLs who begin therapy follow a long-term treatment schedule that is characterized by a high frequency of relapses and eventually become refractory to standard therapies.[3]

Due to the chronic nature of indolent NHL and the need for successive rounds of therapy, agents that are active in extensively treated patients are of particular value; these treatments include chemotherapies as well as anti-CD20 monoclonal antibodies, such as rituximab.[5] Bendamustine hydrochloride (Treanda®; Teva Pharmaceuticals Industries Ltd, Petah Tikva, Israel)[6] is an alkylator with a unique structure and properties that are distinct from other commonly used alkylators, such as cyclophosphamide and chlorambucil.[7] The cellular uptake and action of bendamustine are more rapid than that of cyclophosphamide and chlorambucil and may be related to its benzimidazole ring structure and uptake by nucleoside transporters.[8]

In the USA, bendamustine is indicated as a first-line option for patients with chronic lymphocytic leukemia and as a later treatment for patients with indolent NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[6,9] Clinical studies in Europe and North America have shown that bendamustine monotherapy is effective in the treatment of patients with indolent NHL who have failed in multiple prior therapies, including other alkylators and rituximab.[10-14] The pharmacokinetic profile of bendamustine and the exposure-response relationships in these predominantly Caucasian patient populations have also been described.[15]

In China, NHLs accounted for an estimated 88,200 new cases and 52,100 deaths in 2015.[16] Furthermore, the age-standardized incidence rate and mortality rate of NHLs in China are estimated to be 4.29 and 2.45 per 100,000 person-years, respectively.[17] The preferred treatment strategies for patients with advanced-stage follicular lymphoma comprise rituximab regimens.[18,19] On May 26th, 2019, bendamustine was approved in China by National Medical Product Administration for the treatment of indolent B-cell NHL; however, the clinical data that formed the basis for this approval have not been published. While bendamustine has demonstrated effectiveness in predominantly Caucasian patients,[10-14] ethnic differences may affect a medication's safety and efficacy. As such, the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use provides guidance on characterizing ethnic factor influences.[20]

The current multicenter, open-label, single-arm, phase 3 study was the basis for the recent approval of bendamustine in China and was the first report of the efficacy, safety, and pharmacokinetics of bendamustine monotherapy in Chinese patients with relapsed, indolent B-cell NHL.

Methods

Ethical approval

The study was approved by the Institutional Review Board (IRB) of the Cancer Hospital, Chinese Academy of Medical Sciences (No. 12-016/550), and other participating centers, according to national and local regulations, and an IRB-approved consent form was signed by each patient before study enrollment.

Study design

This prospective, multicenter, open-label, single-arm, phase 3 study (NCT01596621; C18083/3076) was designed to investigate the efficacy, safety, and pharmacokinetics of bendamustine monotherapy in Chinese patients with relapsed, indolent B-cell NHL. The study was conducted between August 6th, 2012, and April 24th, 2017. Two years of patient follow-up data were collected. Patients were enrolled at 20 centers in China [Table S1 in Supplementary Materials, http://links.lww.com/CM9/A523].

Eligibility

Patients aged ≥18 years with the World Health Organization performance status of 0 to 2 were eligible if they had an initial diagnosis of indolent NHL (follicular, small lymphocytic, lymphoplasmacytic, or marginal zone lymphoma). Patients were required to have received prior rituximab (alone or combined with other treatment) with a minimum exposure of two doses of 375 mg/m^2 (or a

therapeutically active dose) and subsequent documented relapse to prior rituximab with progressive disease (PD). Disease progression was defined as the appearance of any new lesion >1.5 cm in any axis during or at the end of therapy, at least a 50% increase from the nadir in the sum of the product of the diameters (SPD) of any previously involved nodes or single involved node, or at least a 50% increase in the longest diameter of any single previously defined node >1 cm in its short axis.

Patients were required to have received treatment with at least one, but no more than three, distinct chemotherapy regimens and have bidimensionally measurable disease. Baseline laboratory parameters included an absolute neutrophil count (ANC) of at least 1000 cells/mm^3, platelet count of at least 85,000 cells/mm^3, and adequate renal and hepatic function.

Patients were excluded for the following conditions: previous radiotherapy, chemotherapy, or immunotherapy within 4 weeks before study entry or failure to recover from associated adverse events (AEs); any investigational treatment within 4 weeks; any prior bendamustine treatment; hematopoietic growth factor treatment within 4 weeks (chronic erythropoietin was allowed); therapeutic doses of systemic steroids; allogeneic transplant; transformed disease; concurrent active malignancy (except prostate cancer with a Gleason grade <6 and normal range prostate-specific antigen, excised non-melanoma skin cancer, or *in situ* cervical or bladder cancer); central nervous system lymphoma; serious infection or other medical or psychiatric condition that might interfere with achieving study objectives; pregnancy or lactation; or expected survival <3 months.

Treatment

Bendamustine hydrochloride 120 mg/m^2 was infused intravenously over 60 to 120 min on days 1 and 2 of each 21-day treatment cycle for six planned cycles (and up to eight cycles at the discretion of the physician). The administration of bendamustine hydrochloride was supervised by the investigator and sub-investigators in the clinic, thereby ensuring compliance. On day 1 of the second and subsequent treatment cycles, the patient's blood cell counts must have recovered to an ANC of at least 1000 cells/mm^3 and a platelet count of at least 75,000 cells/mm^3 to continue bendamustine therapy. If recovery criteria (including the recovery of non-hematologic toxicities to Grade 1 or less according to the National Cancer Institute Common Terminology Criteria for AEs [NCI CTCAE], version 4.0) were not met within 4 weeks following a treatment cycle, study treatment was discontinued. Patients who experienced Grade 3 or greater hematologic AEs had treatment delayed until their blood cell counts had recovered and then treatment with bendamustine was reinitiated with a dose reduction. Patients who experienced Grade 3 or 4 AEs at the dose of 120 mg/m^2 had their dose decreased to 90 mg/m^2 for the next cycle, provided they had recovered and the AEs were at baseline values or of Grade 1 for non-hematologic and platelet counts and Grade 2 or less for ANC toxicity. If Grade 3 or 4 AEs were experienced at the dose of 90 mg/m^2, the dose was further decreased to 60 mg/m^2 for the next cycle. Patients who continued to experience Grade 3 or 4 AEs at the 60 mg/m^2 dose discontinued study treatment. If a study treatment dose was reduced due to toxicity, it remained at the decreased dose for all subsequent treatment cycles.

Supportive therapy was provided according to the standard of care. Supportive therapy included anti-emetics, anti-diarrheal, antipyretic, analgesics, anti-allergic, antibiotics, and other treatments such as blood products. The administration of cytokines followed the standard of care. The following medications were not allowed during the study: therapeutic doses of systemic steroids (low doses of chronic steroids [prednisone or equivalent] up to 20 mg/day for non-neoplastic disorders or indications other than lymphoma or lymphoma-related complications were permitted), other anti-cancer medications, or palliative radiation.

Study outcomes

The primary endpoint was the overall response rate (ORR) assessed by the independent review committee (IRC), defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) as their best response by the end of therapy. The response was evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) scans and based on the definitions as described by the modified International Workshop Response Criteria.[21] CR was defined as the disappearance of all detectable clinical evidence of disease. PR required all of the following: at least a 50% decrease in SPD of up to six of the largest dominant nodes or nodal masses; no increase in the size of other nodes, liver, or spleen; splenic and hepatic nodule regression by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter; no measurable disease present in other organs, excluding splenic and hepatic nodules; and no observable new sites of disease.[21] Patients were defined as having stable disease (SD) if they did not meet the criteria for CR or PR while also not experiencing disease progression.

Within the 6 weeks before the start of treatment, CT or MRI scans and physical disease assessments were performed and used as a baseline for response and disease progression. Assessments were performed at the end of cycles 3, 6, and 8 during treatment, at the end-of-treatment visit, and every 12 weeks (±2 weeks) during follow-up after treatment completion until disease progression, initiation of another treatment for the disease, or death. Efficacy was assessed by comparing baseline scans and physical disease assessment with those performed during and following treatment. Additionally, patients underwent bone marrow aspiration and biopsy to confirm a CR if the patient's bone marrow had initially been positive for lymphoma. Lymphoma response was assessed by investigators and also by IRC.

Secondary endpoints included the duration of response (DoR), progression-free survival (PFS), safety, and pharmacokinetics. DoR was defined as the time from the first documentation of response until disease progression, death from any cause, or the start of new anti-cancer therapy. PFS

was calculated as the time from the first dose of bendamustine administered until disease progression, death from any cause, or the start of new anti-cancer therapy.

Safety was monitored by the recording of AEs with terms and severity assigned according to NCI CTCAE 4.0. Hematologic laboratory abnormalities are shown in preference to hematologic AEs because they give a more complete picture of decreased blood counts. Serious AEs (SAEs) were defined as those that were life-threatening, required or prolonged hospitalization were considered medically important, or resulted in significant disability, congenital anomaly of offspring, or death.

Pharmacokinetic parameters included maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) and to time of the last measurable concentration (AUC_{0-t}), plasma clearance, terminal elimination rate constant (λ_z), steady-state volume of distribution (V_{ss}), and apparent volume of distribution (V_z). Blood samples for pharmacokinetics were obtained before the start of the infusion, at the midpoint and end of the infusion, and at predetermined time points through approximately 24 h after completion of the infusion on day 1 of cycle 1 from a subset of 15 patients. The concentrations of bendamustine and two circulating metabolites, γ-hydroxybendamustine (M3) and N-desmethylbendamustine (M4) were simultaneously determined in plasma samples using a validated ultra-performance liquid chromatography method with tandem mass spectrometric detection. The quantifiable range of the assay was 0.100 to 100 ng/mL for bendamustine, 0.106 to 106 ng/mL for M3, and 0.095 to 95 ng/mL for M4. Pharmacokinetic parameters for bendamustine, M3, and M4 were estimated by non-compartmental methods using validated software (Pharsight® Knowledgebase Server™, version 4.0.3, in conjunction with Phoenix® WinNonlin® version 6.3 software [Certara, Princeton, NJ, USA]).

Statistical analyses

The efficacy and safety analyses were performed on all patients who received treatment with bendamustine (the primary analysis set). The primary analysis was performed on July 15, 2015. For the additional follow-up period, the date of the last patient, last follow-up visit was April 24, 2017. Patients were classified according to their best overall response after therapy, with response assessments made by the IRC informing the primary endpoint analysis. The number and percentage of patients in each response category (CR, PR, SD, or PD) were summarized along with a two-sided binomial exact 95% confidence intervals (CIs) for the ORR. All data were processed and summarized using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Data handling, including data quality assurance, was conducted according to the *Declaration of Helsinki* and ICH of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines.

ORR was calculated as the number of patients with the best response of CR or PR, divided by the number of patients. Patients who were treated but had no response data were considered non-responders in the analysis. Exact 95% CIs based on the binomial distribution were calculated for ORR. The exact *P* value to test against the null hypothesis of ORR = 50% at a two-sided alpha 5% was calculated using the binomial distribution method. For the study to be successful, the lower bound of the 95% CI for the ORR of bendamustine was required to be greater than 50%, the latter rate being the most optimistic assumption for the ORR of salvage chemotherapy in this patient population. The median DoR and PFS were assessed using the Kaplan-Meier method. If the patient had not died, progressed, or started new anti-cancer therapy at the time of the analysis, then a censored observation at the date of the most recent progression-free visit was assigned.

ORR was examined in the primary analysis set (IRC and investigator assessment) and by patient subgroups according to baseline characteristics (IRC assessment only). Baseline characteristics assessed included sex (male or female); age (<65 or ≥65 years); the number of prior chemotherapy regimens (<3 or ≥3 courses), sensitivity to last alkylator therapy (refractory, sensitive, or unknown); and the number of Follicular Lymphoma International Prognostic Index (FLIPI) nodal sites (>4 or ≤4 involved lymph nodes, or missing).

Results

Patient characteristics

A total of 102 patients with documented relapsed, indolent B-cell NHL were enrolled in the study between August 6th, 2012, and June 18th, 2015, and received at least one dose of bendamustine; these patients comprised the primary analysis set [Figure 1]. A total of 56 patients completed treatment; 46 patients (45%) discontinued treatment early due to: AEs ($n = 25$), patient or physician decision ($n = 12$), disease progression ($n = 7$), lost to follow-up ($n = 1$), and death ($n = 1$) [Figure 1]. The number of patients treated in each treatment cycle is shown in Table S2, http://links.lww.com/CM9/A523.

Demographics and disease characteristics are summarized in Table 1. The median age of patients was 53 (range 27–81) years and the majority (61%) were male. Most (82%) patients had advanced-stage disease at enrollment. Histologies included follicular lymphoma (59%; $n = 60$), small lymphocytic lymphoma (24%; $n = 24$), marginal zone lymphoma (17%; $n = 17$), and follicle center lymphoma ($n = 1$). Of 102 enrolled patients, 11 (11%) received ≥3 prior chemotherapy regimens; 91 (89%) received ≥3 doses of rituximab, and 31 (30%) were refractory to prior alkylator therapy. No patients received chemotherapy only before the study [Table 1]. The mean cumulative exposure to prior rituximab was 4517 mg.

Efficacy

Overall response rate

Responses to therapy at the primary analysis cut-off date of July 15th, 2015, are summarized in Table 2. Of the 102

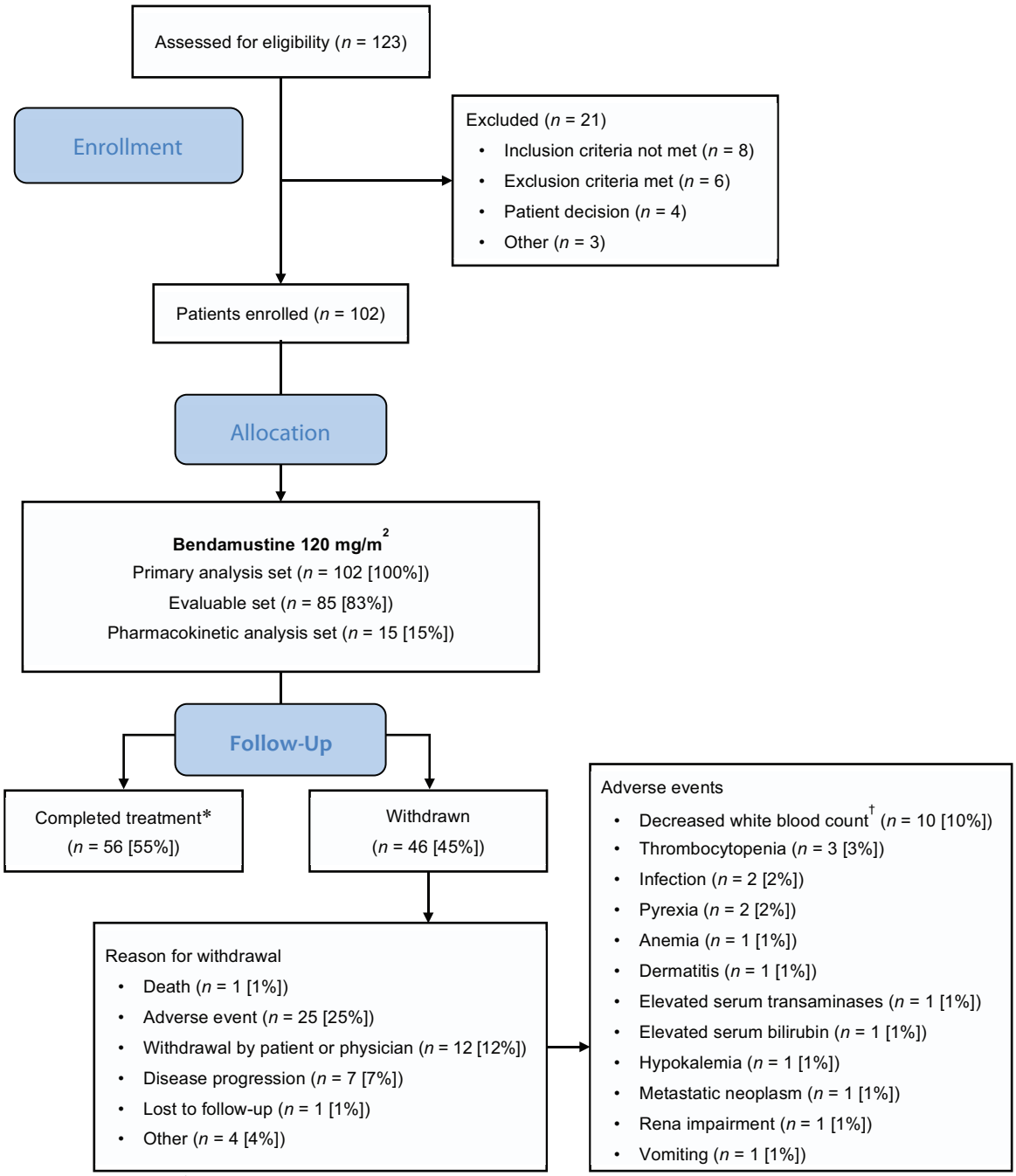

Figure 1: Patient disposition ($N = 102$). *Includes patients who withdrew during cycles 7 and 8. †Includes leukopenia, lymphocytopenia, and neutropenia.

patients who received ≥1 dose of bendamustine, the primary endpoint of the study was met with an ORR of 73% (95% CI: 63%–81%) assessed by IRC, which was significantly greater than the null rate of 50% ($P < 0.0001$). IRC and investigator assessments gave similar ORRs but differed in the relative proportions of CR and PR [Table 2]. ORRs were similar by sex (71% male *vs*. 75% female), age group (73% <65 years *vs*. 73% ≥65 years), and number of FLIPI nodal sites (72% >4 involved *vs*. 75% ≤4 involved) [Table 3]. The ORR in the subgroup of 11 patients who had received ≥3 prior chemotherapy regimens was 82% [Table 3]. Furthermore, the ORR of patients refractory to their last alkylator therapy (68%) was only modestly lower than the ORR in the overall study population [Table 3].

DoR and PFS

Kaplan-Meier curves for DoR and PFS are shown in Figure 2. With the additional follow-up period, the median DoRs were 16.2 months (95% CI: 9.3–not reached) by IRC assessment and 13.4 months (95% CI: 8.8–22.0) by investigator assessment. The DoR was shorter for patients aged ≥65 years (median 6.9 months) and the subgroup of patients who had received ≥3 prior chemotherapy

Table 1: Baseline characteristics of patients with relapsed, indolent B-cell NHL who had received at least one dose of bendamustine hydrochloride 120 mg/m^2 ($n = 102$).

Characteristics	Value
Age (years)	53 (27–81)
Men	62 (61)
Ann Arbor stage	
Stage I	2 (2)
Stage II	16 (16)
Stage III	43 (42)
Stage IV	41 (40)
Pathological type	
Follicular lymphoma	60 (59)
Grade 1	15 (15)
Grade 2	35 (34)
Grade 3	10 (10)
Small lymphocytic lymphoma	24 (24)
Marginal zone lymphoma	17 (17)
Follicle center lymphoma	1 (1)
Mean time since primary diagnosis (months)	36.7 (3.0–276.4)
Prior treatment	
Three or more prior chemotherapy regimens	11 (11)
Three or more doses of rituximab	91 (89)
Mean cumulative dose rituximab (mg)	4517
Refractory to prior alkylator therapy	31 (30)

Data are presented as *n* (%) or median (range). NHL: Non-Hodgkin lymphoma.

Table 2: ORR by IRC and investigator in patients with relapsed, indolent B-cell NHL who had received at least one dose of bendamustine hydrochloride 120 mg/m^2 ($n = 102$).

Parameters	IRC assessment	Investigator assessment
ORR	74 (73)	80 (78)
95% confidence interval*	63–81	69–86
Two-sided *P* value†	<0.0001	<0.0001
Responses		
CR	19 (19)	31 (30)
PR	55 (54)	49 (48)
SD	15 (15)	9 (9)
Disease progression‡	13 (13)	13 (13)

Data are presented as *n* (%). *95% CI calculated using binomial parameter exact method. †*P* value calculated against the null hypothesis of a response rate of 50%. ‡Includes clinical disease progression not specified in response criteria, unknown, and not assessed. CR: Complete response; CI: Confidence interval; IRC: Independent review committee; NHL: Non-Hodgkin lymphoma; ORR: Overall response rate; PR: Partial response; SD: Stable disease.

regimens (median 8.9 months), but not for patients refractory to their last alkylator therapy (median not reached) [Table 3].

With the additional follow-up period, the median PFS was 18.6 months (95% CI: 12.3–not reached) by IRC assessment and 15.3 months (95% CI: 11.3–19.4) by investigator assessment. PFS was shorter for patients aged ≥65 years (median 16.2 months) and the subgroup of patients who had received ≥3 prior chemotherapy regimens (median 11.0 months), but not for patients refractory to their last alkylator therapy (median not reached) [Table 3]. The median follow-up time was 29.5 months (95% CI: 28.6–30.1) by investigator assessment.

To explore the relationship between efficacy and cumulative dose of bendamustine, the population was divided into quintiles. The quintile with the highest cumulative dose received between 1443.12 and 1951.24 mg/m^2, equivalent to 6 to 8 cycles of treatment with full doses administered. The quintile with the second-highest cumulative dose received between 1322.08 and 1443.12 mg/m^2, equivalent to 5.5 to 6 cycles of treatment with full doses administered. The quintile with the third-highest cumulative dose received between 1081.8 and 1322.08 mg/m^2, equivalent to 4.5 to 5.5 cycles of treatment with full doses administered. The quintile with the fourth-highest cumulative dose received between 660.6 and 1081.8 mg/m^2, equivalent to 2.75 to 4.50 cycles of treatment with full doses administered. The quintile with the lowest cumulative dose received between 118.5 and 660.6 mg/m^2, the equivalent of <2.75 cycles of treatment. By IRC assessment, the ORR in the highest quintile was 95% (95% CI: 75–100), median DoR was 8.9 months (95% CI: 4.1–16.5), and median PFS was 11.2 months (95% CI: 8.8–24.9). The second-highest quintile had an ORR of 95% (95% CI: 75–100), median DoR was not reached (95% CI: 15.3–not reached), and median PFS was not reached (95% CI: 29.4–not reached). The third highest quintile had an ORR of 76% (95% CI: 53–92), median DoR of 11.6 months (95% CI: 5.8–not reached), and median PFS was 18.2 months (95% CI: 9.4–not reached). The fourth highest quintile had an ORR of 60% (95% CI: 36–81), median DoR of 9.6 months (95% CI: 1.6–not reached), and median PFS was 12.3 months (95% CI: 5.6–not reached). For the lowest quintile, the ORR was 38% (95% CI: 18–62), median DoR was not reached (95% CI: not reached–not reached), and median PFS was not reached (95% CI: 2.4–not reached). The proportion of patients not evaluated for the response was 38% for the lowest quintile, which is not unexpected. The "evaluable" response rate in this quintile was 61%. Efficacy by lymphoma subtype was also explored. Subtypes were grouped together with the marginal zone ($N = 17$), follicular ($N = 60$), and small lymphocytic ($N = 24$), and ORRs were 94%, 72%, and 58% respectively in these subgroups. Median DoR by IRC assessment was not reached (95% CI: 8.5–not reached) for the marginal zone subtype, 9.8 months (95% CI: 6.9–not reached) for the follicular subtype, and 16.2 months (95% CI: 10.9–23.5) for the small lymphocytic subtype. PFS reflected the differences in the natural course of the different subtypes.

Safety

The median number of cycles completed was six (range, 1–8 cycles). Fifty-nine patients (58%) received ≥6 cycles of bendamustine. Forty-two patients (41%) had ≥1 cycle delayed; overall 12% of all cycles administered were

Table 3: Efficacy by IRC according to baseline characteristics of patients with relapsed, indolent B-cell NHL who had received at least one dose of bendamustine hydrochloride 120 mg/m^2 ($n = 102$).

	ORR*		DoR		PFS†	
Baseline characteristics	***n***	**% (95% CI)**	***n***	**Median, months (95% CI)**	***n***	**Median, months (95% CI)**
Sex						
Male	62	71 (58–82)	44	12.5 (7.2–27.5)	62	17.2 (9.5–25.4)
Female	40	75 (59–87)	30	16.8 (9.3–NR)	40	NR (11.6–NR)
Age						
<65 years	80	73 (61–82)	58	16.8 (10.9–NR)	80	19.4 (12.9–NR)
≥65 years	22	73 (50–89)	16	6.9 (1.9–NR)	22	16.2 (5.8–NR)
Number of prior chemotherapy regimens						
<3	91	71 (61–80)	65	16.5 (9.8–NR)	91	19.4 (12.9–NR)
≥3	11	82 (48–98)	9	8.9 (2.7–NR)	11	11.0 (5.6–NR)
Sensitivity to last alkylator therapy						
Refractory	31	68 (49–83)	21	NR (11.9–NR)	31	NR (18.2–NR)
Sensitive	64	77 (64–86)	49	10.9 (7.9–23.5)	64	15.2 (10.9–29.4)
Unknown	7	57 (18–90)	4	9.8 (4.1–NR)	7	10.8 (6.0–NR)
Number of FLIPI nodal sites						
>4 involved lymph nodes	79	72 (61–82)	57	12.5 (8.9–27.5)	79	16.2 (11.0–29.4)
≤4 involved lymph nodes	16	75 (48–93)	12	16.8 (4.2–NR)	16	23.1 (9.4–NR)
Missing	7	71 (29–96)	5	NR (1.6–NR)	7	NR (3.7–NR)

*95% CI calculated using binomial parameter exact method. †Patients who were progression-free at the time of data analysis were censored at the time of their last valid assessment. CI: Confidence interval; DoR: Duration of response; FLIPI: Follicular lymphoma international prognostic index; IRC: Independent review committee; NHL: Non-Hodgkin lymphoma; NR: Not reached; ORR: Overall response rate; PFS: Progression-free survival.

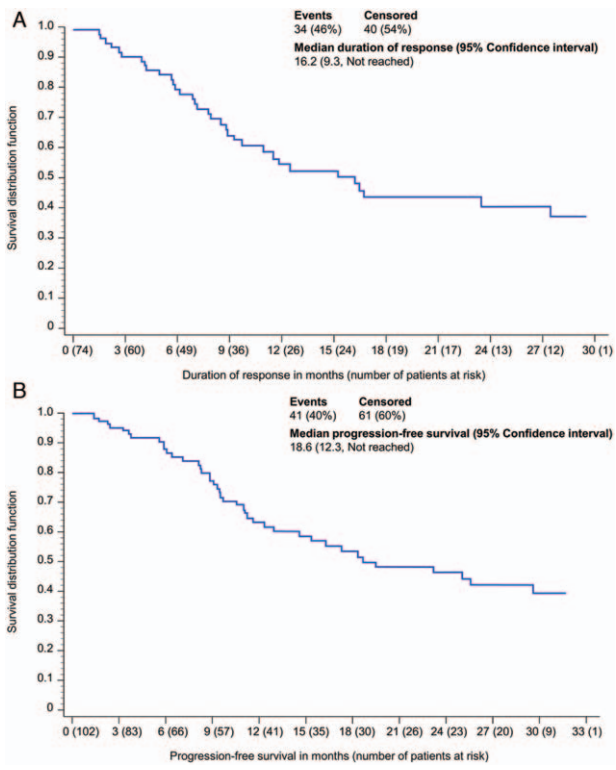

Figure 2: Kaplan-Meier curves for (A) DoR and (B) PFS by IRC in patients with relapsed, indolent B-cell NHL who had received at least one dose of bendamustine hydrochloride 120 mg/m^2; for patients with a CR or PR. CR: Complete response; DoR: Duration of response; IRC: Independent review committee; NHL: Non-Hodgkin lymphoma; PFS: Progression-free survival; PR: Partial response.

delayed. Forty-nine (48%) patients had ≥1 dose reduced; overall 13% of cycles administered had a dose reduction. Neutropenia and thrombocytopenia were the most common reasons for dose reductions or delays. The mean relative dose intensity was 82%.

Of the 102 patients, 101 (>99%) reported ≥1 AE. The incidence of non-hematologic AEs and hematologic laboratory abnormalities are shown in Table 4. The most common non-hematologic AEs were gastrointestinal: nausea ($n = 45$ [44%]), vomiting ($n = 33$ [32%]), decreased appetite ($n = 26$ [25%]); followed by pyrexia ($n = 26$ [25%]), and rash ($n = 17$ [17%]). Drug reactions occurring within 24 h of administration (eg, chills, pyrexia, rash) were all Grade 1/2 with the exception of a single event of Grade 3 pyrexia. There were no events of tumor lysis syndrome. Laboratory values revealed Grade 3/4 neutropenia in 76% of patients over the course of the study and led to recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration in 69 (68%) patients. Overall, rhG-CSF was administered in 37% of cycles. Twenty-five (25%) patients had AEs that led to study drug withdrawal; hematologic AEs accounted for 14 of these withdrawals.

Infections (any grade) were reported in 27 (26%) patients, with 16 of these patients having infections of at least Grade 3. Upper respiratory tract infections ($n = 12$ [12%]) and pneumonia ($n = 6$ [6%]) were the most commonly reported infections. One patient had a diagnosis of metastatic adenocarcinoma (paravertebral, primary unknown) on day 135 of the study. The event was considered serious and the patient was withdrawn from the study due to the event. A second malignancy, acute myeloid leukemia

Table 4: Incidence of non-hematologic AEs and hematologic laboratory abnormalities in patients with relapsed, indolent B-cell NHL who had received at least one dose of bendamustine hydrochloride 120 mg/m^2* ($n = 102$).

Parameters	All grades†	Grade 3	Grade 4	Grade 5
Non-hematologic AEs				
Nausea	45 (44)	1 (1)	0	0
Vomiting	33 (32)	6 (6)	1 (1)	0
Pyrexia	26 (25)	2 (2)	1 (1)	0
Decreased appetite	26 (25)	0	0	0
Rash	17 (17)	1 (1)	1 (1)	0
Alanine aminotransferase increased	14 (14)	1 (1)	1 (1)	0
Upper respiratory tract infection	12 (12)	2 (2)	0	0
Hypokalemia	8 (8)	2 (2)	1 (1)	0
Pneumonia	6 (6)	5 (5)	0	0
Lung infection	4 (4)	3 (3)	0	1 (1)
Respiratory failure	4 (4)	1 (1)	1 (1)	2 (2)
Herpes zoster	3 (3)	2 (2)	0	0
Febrile neutropenia	2 (2)	2 (2)	0	0
Gastrointestinal infection	1 (1)	0	0	1 (1)
Hemoptysis	1 (1)	0	0	1 (1)
Multiorgan failure	1 (1)	0	0	1 (1)
Hematologic laboratory findings				
Hemoglobin decreased	83 (82)	9 (9)	9 (9)	0
Lymphocytes decreased	97 (96)	40 (40)	43 (43)	0
Neutrophils decreased	95 (94)	46 (46)	31 (31)	0
Platelets decreased	83 (82)	22 (22)	5 (5)	0
White blood cell count decreased	96 (95)	55 (54)	12 (12)	0

Data are presented as *n* (%). *Listed are AEs or laboratory findings that occurred in >20% of patients, all Grade 3/4 events or findings that occurred in >1 patient, and all fatal AEs. †Severity grade was determined using the National Cancer Institute Common Toxicity Criteria for AEs (version 4.0). AEs: Adverse events; NHL: Non-Hodgkin lymphoma.

(transformed from myelodysplastic syndrome), was reported for a patient during the follow-up period (day 655).

One or more SAEs were reported in 29 (28%) patients and five (5%) patients died during the study. One patient developed severe thrombocytopenia after their first cycle of bendamustine that persisted despite platelet transfusion, thrombopoietin, and interleukin-11; the patient died 110 days after the last dose from hemorrhage (hemoptysis) considered related to bendamustine treatment. A second patient developed gastrointestinal and respiratory infections during the fifth cycle of bendamustine with severe lymphopenia, thrombocytopenia, and anemia. The patient's subsequent death from multiorgan failure was considered related to bendamustine treatment (45 days after the last dose). A third patient died from respiratory failure during the second cycle of treatment following treatment-related events of pancytopenia and pneumonia (30 days after the last dose). A fourth patient died during the seventh cycle of treatment due to a lung infection considered related to bendamustine treatment (56 days after the last dose). The fifth patient death (due to a cerebrovascular AE) occurred approximately 17 months after the patient's last dose of bendamustine and after the development of acute myeloid leukemia.

Pharmacokinetics

The mean pharmacokinetic parameters for bendamustine and the two active circulating metabolites, M3 and M4, in 15 patients following intravenous infusion of 120 mg/m^2 on day 1 of cycle 1 are shown in Table 5. The corresponding mean plasma concentration-versus-time profiles for bendamustine, M3, and M4 are shown in Figure 3. The duration of bendamustine infusions ranged from 1.2 to 2.0 h with a mean of 1.7 h. The mean C_{max} of bendamustine was 3909.9 ng/mL and the median t_{max} was 1.33 h. The subsequent decrease in the concentrations of bendamustine in plasma occurred in a multiphasic manner and was characterized by an initial rapid decrease, followed by a slower second phase. The mean $t_{1/2}$ in this second phase was 1.83 h. The plasma concentrations of bendamustine were below the lower limit of quantitation of the assay (<0.100 ng/mL) at or before the 24-h time point in all but one patient. The mean $AUC_{0-\infty}$ of bendamustine was 6279 ng h/mL. The mean plasma clearance of bendamustine was 392 mL/min/m^2 and the mean V_{ss} was 13.6 L/m^2. The plasma concentrations of the M3 and M4 metabolites were substantially lower than those of the parent compound. The mean $AUC_{0-\infty}$ of M3 was approximately one-tenth of that for bendamustine and approximately ten-fold higher than M4.

Discussion

Bendamustine was initially approved in the USA in 2008 as a treatment option for patients with chronic lymphocytic leukemia and subsequently as a treatment for patients with rituximab-refractory indolent NHL. The current study was the basis for the first approval of bendamustine in China

Table 5: The mean pharmacokinetic parameters for bendamustine and the two active circulating metabolites, M3 and M4, in 15 patients following bendamustine 120 mg/m^2 on day 1 of cycle 1.

Parameters	Bendamustine	M3	M4
C_{max} (ng/mL)	3909.859 ± 995.828	270.809 ± 131.805	31.896 ± 20.288
T_{max} (h)	1.33 (0.58–1.97)	1.75 (0.98–2.17)	1.75 (0.98–2.25)
AUC_{0-t} (μg h/mL)	5661 ± 3932	410 ± 194	56 ± 36
$AUC_{0-\infty}$ (μg h/mL)	6279 ± 4725*	425 ± 199†	57 ± 36
λ_z (h^{-1})	0.4525 ± 0.2424*	0.3188 ± 0.0948†	1.5692 ± 0.3271
$t_{1/2}$ (h^{-1})	1.83 ± 0.68*	2.37 ± 0.73†	0.46 ± 0.08
V_z (L/m^2)	55.1 ± 23.6*	NA	NA
V_{ss} (L/m^2)	13.6 ± 5.3*	NA	NA
Plasma clearance (mL/min/m^2)	392 ± 192*	NA	NA

Data are presented as mean ± standard deviation or median (range). *$n = 10$; the terminal elimination rate constant (λ_z) could not be reliably estimated for five patients. †$n = 13$; the terminal elimination rate constant (λ_z) could not be reliably estimated for two patients. $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to time of the last measurable concentration; C_{max}: Maximum observed plasma concentration; λ_z: Terminal elimination rate constant; NA: Not applicable; $t_{1/2}$: Terminal elimination half-life; t_{max}: Time to C_{max}; V_{ss}: Steady-state volume of distribution; V_z: Apparent volume of distribution.

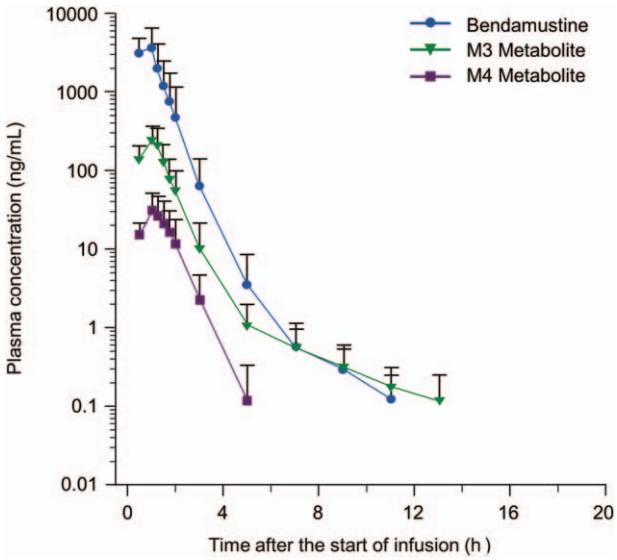

Figure 3: Mean (standard deviation) plasma concentration-*vs.*-time profiles of bendamustine and the metabolites, M3 and M4, in patients with relapsed, indolent B-cell NHL following bendamustine 120 mg/m^2 on day 1 of cycle 1 (n = 15). NHL: Non-Hodgkin lymphoma.

and was the first report of this novel chemotherapy in Chinese patients. The results of this study demonstrated the efficacy and safety of bendamustine monotherapy in Chinese patients with relapsed, indolent B-cell NHL after chemotherapy and rituximab treatment.

The results of this study in Chinese patients are similar to those of the previous clinical trials conducted in Western patients. Specifically, the ORR of 73% by IRC in this study was similar to the 75% ORR by IRC from the pivotal North American study.[11] The median DOR of 16.2 months in this study was longer than the 9.2 months from the North American study. The median PFS in this study was twice as long (18.6 months) compared with the North American study (9.3 months).[11] It should be noted, however, that these longer durations may reflect the fact that patients in the North American study had several baseline and disease characteristics that indicated they were at higher risk for relapse. Compared with this study, the North American study population was older (median age 60 *vs.* 53 years) and had a longer period since their initial diagnosis (mean 57 *vs.* 37 months).[11] In many other respects, the populations were similar, with similar proportions of follicular lymphomas (62% *vs.* 59%) and similar prior exposure to rituximab (mean prior cumulative dose 4701 *vs.* 4517 mg in the North American and Chinese studies, respectively). Furthermore, the proportions of patients who were refractory to their prior alkylator therapy were the same (30%). In both this and previous studies, the activity of bendamustine was only moderately reduced in these alkylator-refractory patients. In this study, 68% of patients refractory to their last alkylator achieved a response to bendamustine, with a median DoR that appeared to be at least as long as that for the population as a whole. It is bendamustine's distinct therapeutic profile that is of particular value in indolent lymphoma, wherein patients will require multiple lines of therapy over the course of their disease. Rates of treatment discontinuation observed in this study were similar to those reported in the North American study.[11]

The major toxicities observed for bendamustine in this study (myelosuppression, gastrointestinal toxicity, and infection) were broadly similar to those described in the North American study.[11] Overall, the incidence of individual AEs was lower in the population of this study than that in the North American study population, most notably for events such as fatigue (8% in this study *vs.* 64% in the North American study); this may be a reflection of cultural differences in the way that patients report symptoms. The incidence of infections was also lower in this study (26% *vs.* 69%).[11] The greater use of dose reductions and hematopoietic growth factor support may account for the lower incidence of infections in this study. These dose reductions did not appear to result in any reduction in efficacy compared with the experience in the North American study.[11] Although the number of SAEs resulting in death in this study ($n = 5$) was not higher than that observed in the North American study ($n = 7$),[11] the preponderance of respiratory events highlights the impor-

tance of careful monitoring patients for the risks of lung injury and myelosuppression. Further research on the mechanisms of these events is warranted. Herpes zoster was reported in three patients in this study compared with 12 patients in the North American study[11]; five North American patients reported cytomegalovirus reactivation, which was not observed in this study population.

Management of toxicities by dose modification also differed between the North American study and this study. Fewer patients in this study had a dose delay than that in the North American study (41% *vs.* 64%), with a slightly lower proportion of total cycles with a delay (12% *vs.* 17%).[11] Conversely, more patients in this study had a dose reduction (48% *vs.* 24%) although the proportion of total cycles with a reduced dose was the same in both studies (13%).[11] It is also notable that a higher proportion of patients in this study had hematopoietic growth factor support at some point in their course of bendamustine compared with the North American study population (68% *vs.* 38%).[11] Due to the low incidence of toxicity across the age range in this study population, analysis of safety by age was not performed. Notably, it remains unclear whether the toxicity of bendamustine would be affected by age. In a subgroup analysis of patients with chronic lymphocytic leukemia receiving bendamustine, there was no numerically significant difference regarding AEs between patients aged <65 years and those aged ≥65 years.[22] However, in a subgroup analysis of pooled data from patients with rituximab-refractory, indolent NHL, grade 3 or 4 treatment-emergent AEs occurred in numerically more patients aged ≥65 years than <65 years (81% *vs.* 66%).[23] Generally, the tolerability of bendamustine in elderly patients would be diminished. Thus, dose adjustments might be necessary for elderly patients in clinical practice, based on the individual's physical condition.

The pharmacokinetics of bendamustine in Chinese patients in this study were comparable with those reported for Caucasian[15] and Japanese patients with hematologic or non-hematologic malignancies.[24-26] The mean C_{max} of bendamustine was slightly lower in Chinese patients (ie, 3.9 *vs.* 5.3–5.8 μg/mL in Caucasian patients and 5.4 to 8.6 μg/mL in Japanese patients); this is likely attributable to the longer actual infusion duration reported for the individual Chinese patients in this study. The mean total systemic exposures (AUC) to bendamustine, which would not be expected to be influenced by infusion duration, were largely overlapping between Chinese patients and other ethnicities (ie, 6.3 μg h/mL in Chinese patients *vs.* 6.4–13.6 μg h/mL in Caucasian patients and 6.1–10.2 μg h/mL in Japanese patients). It is important to note, however, that the pharmacokinetic analysis performed by Owen *et al*[15] used a population approach rather than a non-compartmental approach, as in other studies, which may have contributed to the apparently higher AUC value (13.6 μg h/mL) generated for Caucasian patients from that study. Nevertheless, there was large interpatient variability in the pharmacokinetics of bendamustine across the different studies such that any observed differences are within the variability of the results.

The limitation of this study was that it was an open-label single-arm design. However, there are also several strengths of this study. The study was a large, prospective study performed across multiple centers, which, therefore, reduces the risk of bias from a single center. Furthermore, this study had well-defined methods, multiple predefined efficacy, safety, and pharmacokinetic endpoints, and statistical sample size calculations to ensure adequate statistical power.

In conclusion, this study is the first report of bendamustine monotherapy in Chinese patients with relapsed, indolent B-cell NHL. The results of this study show bendamustine to be an active and effective therapy in Chinese patients with relapsed, indolent B-cell NHL, with a comparable risk/benefit relationship to that reported in North American patients.

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Conflicts of interest

Teva employees were involved in the study design, data collection and analysis, and in the writing of this manuscript. All authors had full access to all the study data and had final responsibility for the decision to submit for publication. Leonard James and Edward Hellriegel are former employees of Teva Pharmaceuticals.

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