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Efficacy and safety assessment of prolonged maintenance with subcutaneous rituximab in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results of the phase III MabCute study

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ABSTRACT

Rituximab plus chemotherapy induction followed by rituximab maintenance for up to 2 years confers a long-term benefit in terms of progression-free survival in patients with indolent non-Hodgkin lymphoma. It is not known whether further prolonged maintenance with rituximab provides additional benefit. The phase III MabCute study enrolled 692 patients with relapsed or refractory indolent non-Hodgkin lymphoma. Patients who responded to induction with rituximab plus chemotherapy and were still responding after up to 2 years' initial maintenance with subcutaneous rituximab were randomized to extended maintenance with subcutaneous rituximab (n=138) or observation only (n=138). The primary endpoint of investigator-assessed progression-free survival in the randomized population was un-addressed by the end of study because of an insufficient number of events (129 events were needed for 80% power at 5% significance if approximately 330 patients were randomized). In total, there were 46 progression-free survival events, 19 and 27 in the rituximab and observation arms, respectively (P=0.410 by stratified log-rank test; hazard ratio 0.76 [95% confidence interval: 0.37–1.53]). The median progression-free survival was not reached in either randomized arm. There were no new safety signals; however, adverse events were seen slightly more frequently with rituximab than with observation during extended maintenance. Maintenance for up to 2 years with rituximab after response to initial induction therefore remains the standard of care in patients with relapsed or refractory indolent non-Hodgkin lymphoma. (Clinicaltrials.gov identifier: NCT01461928)

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Introduction

Non-Hodgkin lymphoma (NHL) accounts for approximately 85% of lymphomas.[1] Indolent forms include follicular lymphoma (FL), Waldenström macroglobulinemia/lymphoplasmacytic lymphoma and marginal zone lymphoma. Of these, FL is the most common,[1,2] accounting for 5/100,000 cases in Western Europe.[3] Indolent NHL usually develops slowly (and may not need immediate treatment), follows a relapsing-remitting course, and is often incurable.[1]

Chemoimmunotherapy based on the human/murine chimeric anti-CD20 monoclonal antibody rituximab is standard treatment for a range of B-cell malignancies, including indolent and aggressive forms of NHL.[3-7] Intravenously administered ritux-

imab prolongs time to disease progression and increases overall survival (OS),[8] but is associated with infusion reactions, which can be severe.[9,10] Thus, a slow infusion is required during the first antibody administration, which generally takes at least 3.5–4 h.[9-11] Faster infusion rates are used for subsequent infusions;[10,11] nevertheless, infusion duration remains a challenge for patients and healthcare providers, particularly when multi-agent chemotherapy is being used.[11]

A subcutaneous (SC) formulation of rituximab and recombinant human hyaluronidase has been developed to address this concern.[12] At fixed doses, rituximab SC has shown comparable efficacy and safety to intravenous rituximab in patients with NHL or chronic lymphocytic leukemia, with non-inferior serum trough rituximab concentrations.[12-16] Additionally, patients' preference/satisfaction and time and motion data (active healthcare practitioner time and chair time for patients) favor the use of the SC formulation,[17,18] which is currently approved in Europe, the USA and numerous other countries for multiple indications (chronic lymphocytic leukemia, diffuse large B-cell lymphoma and FL).[9,19] Dosing advantages over intravenous treatment include administration over 5–7 minutes, with a requirement for only 15 minutes of monitoring.[9,19]

Rituximab plus chemotherapy induction followed by rituximab maintenance is an approved treatment in FL,[9,19] and has shown long-term progression-free survival (PFS) benefit in patients with indolent NHL.[20-27] Tumor response and survival data show improvements in outcomes that persist over the longer term when rituximab maintenance therapy is given for up to 2 years.[27,28] Whether further and prolonged maintenance therapy (beyond 2 years) would benefit patients with relapsed/refractory (R/R) indolent NHL who have maintained their response to treatment remains unknown. MabCute (NCT01469128) is a phase III trial in which patients with R/R indolent NHL were randomized to prolonged rituximab SC maintenance or observation after completing rituximab SC-based induction and 2 years maintenance therapy, provided that they were in response and willing to continue treatment.

Methods

Study design

This was a phase III, open-label, multicenter, international, randomized interventional study enrolling patients from 141 centers worldwide (mostly in Europe). MabCute was divided into Induction (6–8 months), Maintenance I (24 months) and Maintenance II (minimum 15 months) phases (Figure 1).

The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice, local legislation and the approval of institutional review boards. Written informed consent was obtained from participants.

Study population

Adults aged ≥18 years with R/R CD20$^+$ grade 1, 2 or 3a FL or other CD20$^+$ indolent NHL (Waldenström macroglobulinemia/lymphoplasmacytic lymphoma or marginal zone lymphoma), and Eastern Cooperative Oncology Group (ECOG) performance status ≤2 were recruited. Details of the baseline assessments are provided in the *Online Supplementary Appendix*.

Study treatments

Eligible patients received eight rituximab cycles, one intravenous (375 mg/m^2) and seven SC (1,400 mg fixed-dose) with six to eight chemotherapy cycles as induction (Figure 1; further information is available in the *Online Supplementary Appendix*). Patients with complete or partial response received 2 years' maintenance with rituximab SC (Maintenance I). Patients with continuing response at the end of Maintenance I were randomized to prolonged maintenance with rituximab SC or to observation (Maintenance II).

Study endpoints and procedures

The primary endpoint was PFS from the time of randomization to extended maintenance with rituximab SC or observation in Maintenance II (PFS_{rand} in the randomized intent-to-treat [ITT_{rand}] population). Secondary endpoints included OS from the time of randomization in Maintenance II (OS_{rand}), overall response rate (Cheson criteria[29]) at end of Induction, and partial response to complete response conversion rate at the end of Maintenance I. An exploratory analysis of PFS and OS from enrollment to end of Maintenance I (i.e., the non-randomized part of the study; PFS_{reg}, OS_{reg}) according to induction chemotherapy was also performed.

Safety was assessed in all patients who received at least one dose of study medication and included adverse events (using National Cancer Institute Common Toxicity Criteria Version 4.0 and coded with Medical Dictionary for Regulatory Activities version 2.0), laboratory tests and vital signs.

Analytical plan

Sample size was based on a phase III randomized study of 465 R/R FL patients. Overall, 129 PFS_{rand} events were required to achieve 80% power for the log-rank-test at a two-sided significance level of 5%; therefore, approximately 700 patients needed to be enrolled to randomize 330 patients (allowing for a 10% dropout) after the 2.5-year Induction plus Maintenance I. Randomization to Maintenance II was 1:1, stratified by indolent NHL subtype and Follicular Lymphoma International Prognostic Index (FLIPI) category.[30] The end of study was defined as the time when all patients randomized into Maintenance II had been followed up for ≥15 months, or earlier if at least 129 PFS events had been observed.

PFS_{rand}, OS_{rand}, PFS_{reg} and OS_{reg} were reported with medians, 95% confidence intervals (95% CI), and Kaplan-Meier estimates and their 95% CI. The randomized treatment arms (prolonged rituximab maintenance *vs*. observation in Maintenance II) were compared using log-rank testing stratified according in indolent NHL subtype and FLIPI category. Cox regression was used to estimate hazard ratios (HR).

Results

Patients

In total, 692 patients received rituximab plus chemotherapy as induction (ITT population for Induction); 60.5% of patients received bendamustine, 12.4% received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and 11.8% received cyclophosphamide, vincristine and prednisone (CVP) (*Online Supplementary Table S1*); very small numbers received fludarabine, cyclophosphamide and mitoxantrone (FCM) or mitoxantrone, chlorambucil and prednisone (MCP). The distribution of patients who received each induction regimen was maintained out to Maintenance II (*Online Supplementary Table S1*). Of the patients who received induction therapy, 148 discontinued treatment because of adverse events (70 patients; 10.1%), disease progression (29; 4.2%), patients' request (16; 2.3%), investigators' request (7; 1.0%), loss to

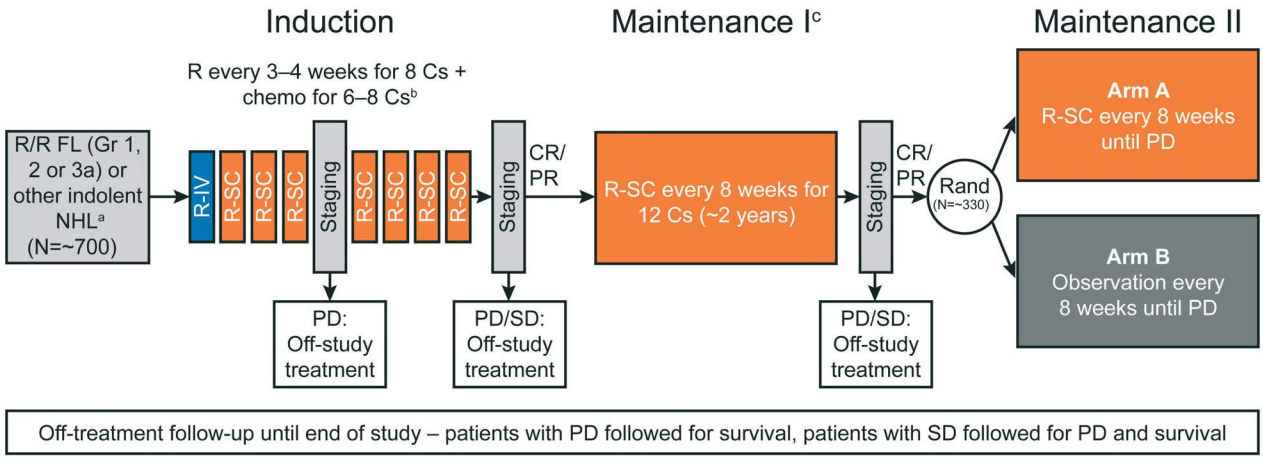

Figure 1. Study design. [a]Waldenström macroglobulinemia/lymphoplasmacytic lymphoma or marginal zone lymphoma. [b]Chemotherapy options included bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil, fludarabine-containing regimen or GIFOX. [c]Maintenance started within 8–12 weeks of completion of induction. R/R: relapsed or refractory; FL: follicular lymphoma; Gr: grade; NHL: non-Hodgkin lymphoma; R: rituximab; Cs: cycles; PD: disease progression; CR: complete response; PR: partial response; SD: stable disease; SC: subcutaneous; IV: intravenous; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone; FCM: fludarabine, cyclophosphamide and mitoxantrone; MCP: mitoxantrone, chlorambucil and prednisone; CHVP-IFN: cyclophosphamide, doxorubicin, etoposide and prednisone + interferon-α; GIFOX: gemcitabine, ifosfamide and oxaliplatin.

follow-up (4; 0.6%), death (2; 0.3%) or other reasons (20; 2.9%) (*Online Supplementary Figure S1A, B*, *Online Supplementary Table S2*). A further 39 patients withdrew after Induction and before Maintenance I because of disease progression (16; 2.3%), adverse events (6; 0.9%), patients' request (2; 0.3%), investigators' request (2; 0.3%), death (1; 0.1%), loss to follow-up (1; 0.1%) or other reasons (11; 1.6%, all with stable disease).

Of the 505 patients who continued to Maintenance I, 494 were treated (ITT population for Maintenance I; treatment was not given because of adverse events in 5 patients, disease progression in 2, investigator's request or death in 1 each, and other reasons in 2). During Maintenance I, 188 patients (38.1%) discontinued study treatment because of disease progression (82; 16.6%), adverse events (66; 13.4%), patients' request (20; 4.0%), investigators' request (8; 1.6%), death (3; 0.6%), loss to follow-up (2; 0.4%) or other reasons (7; 1.4%: 2 with stable disease) (*Online Supplementary Figure S1C*). A further 28 patients (5.7%) completed Maintenance I but discontinued before Maintenance II. Reasons were patients' request (12; 2.4%), disease progression (9; 1.8%), adverse events (4; 0.8%), investigator's request (1; 0.2%) and other reasons (2; 0.4%). Two other patients (0.4%) failed to meet randomization criteria; the remaining 276 patients were randomized to Maintenance II (Figure 2).

The median durations of the Induction and Maintenance I periods were 8.2 (range 0–18) months and 22.1 (range 0–31) months, respectively.

The primary ITT_{mnd} population included 276 patients who were randomized into Maintenance II (138 each in the rituximab and observation arms). Two further patients were initially planned for randomization but were subsequently found to be ineligible: one had disease progression and one had stable disease. Just over half of all patients were male and approximately two-thirds had Ann Arbor stage IV disease (Table 1). Patients were evenly distributed across FLIPI score categories in both arms. Approximately 40% of patients had bone marrow involvement, and just over half of all patients had FL. Nearly 60% overall had received rituximab plus bendamustine at Induction. Of the ITT population for Induction (n=692), patients receiving bendamustine were older than those receiving CHOP or CVP, and a greater proportion had a high FLIPI score and Ann Arbor stage III/IV disease at screening (*Online Supplementary Table S3*). More patients receiving bendamustine and CHOP had FL compared with those receiving CVP.

Six of 138 patients in the Maintenance II rituximab arm discontinued before the start of treatment (Figure 2). Maintenance II was completed thereafter by 109 patients randomized to rituximab and 111 randomized to observation; 23 patients (16.7%) randomized to rituximab and 27 (19.6%) randomized to observation discontinued during Maintenance II (Figure 2). The median follow-up time was 28.1 (range, 0–46) months. A single patient had progressive disease at the end of Maintenance I but was randomized to rituximab in error. This was subsequently recorded as a protocol violation.

Rituximab exposure

The median duration of exposure to rituximab during Induction was 6.4 (range, 0–11) months. The median number of rituximab cycles was 8.0 (range, 1–9); 522 patients (75.4%) received the planned eight cycles.

In Maintenance I, the median duration of exposure to rituximab was 20.3 (range, 0–28) months, with a median of 12.0 (range, 1–12) cycles being given. Of the 494 patients, 295 (59.7%) received the planned maximum 12 injections every 8 weeks for 24 months.

The median duration of exposure during Maintenance II treatment was 24.8 (range, 0–43) months, and the median number of rituximab cycles was 14.0 (range, 1–24).

Three patients received the highest number of rituximab treatments (44 cycles across the entire study), while two received the lowest (21 cycles).

Safety and tolerability

Induction

Treatment-emergent adverse events and serious adverse events were reported during Induction in 89.0% (616/692) and 30.1% (208/692) of patients, respectively. Half of all patients experienced at least one treatment-emergent

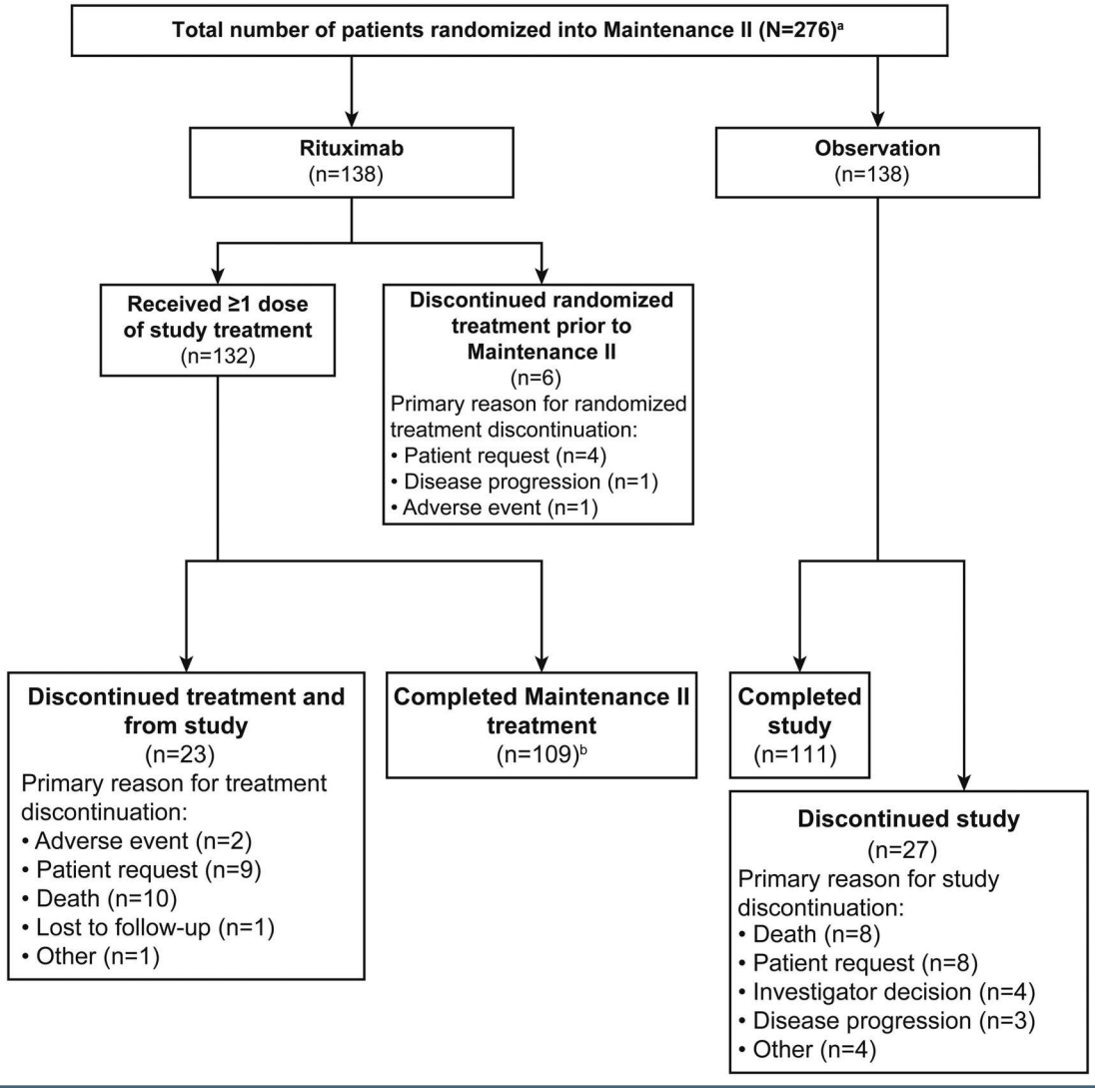

Figure 2. Patients' disposition during Maintenance II. [a]Two additional patients originally intended for randomization failed to meet continuation criteria and were consequently not treated in Maintenance II. [b]Derived by subtracting patients who discontinued from treated patients.

adverse event of grade ≥3 intensity (n=344; 49.7%), most commonly neutropenia (n=160; 23.1%). Febrile neutropenia (n=31; 4.5%), pneumonia (n=28; 4.0%) and neutropenia (n=16; 2.3%) were the most commonly reported serious adverse events (occurring in >2% of patients). Infusion/administration-related reactions were reported in 330 patients (47.7%) during Induction; 54 patients (7.8%) had a grade ≥3 event. The most common infusion/administration-related reaction of any grade during Induction was nausea (n=57; 8.2%); neutropenia was the most common grade ≥3 infusion/administration-related reaction (n=15; 2.2%). At least one treatment-emergent adverse event leading to rituximab discontinuation was reported in 66 patients (9.5%) during Induction, most frequently neutropenia (7 patients; 1.0%). At least one treatment-emergent adverse event leading to death was reported in 12 patients (1.7%).

Similar incidences of treatment-emergent adverse events were seen across induction chemotherapy regimens (*Online Supplementary Table S4*). Patients receiving bendamustine experienced more general disorders and administration site conditions overall than those in other groups. Frequencies of neutropenia reported as an adverse event were similar across induction chemotherapy regimens.

Maintenance I

Treatment-emergent adverse events and serious adverse events were reported in 380/494 (76.9%) and 134/494 (27.1%) patients, respectively, during Maintenance I. At least one treatment-emergent adverse event of grade ≥3 intensity was reported in 163 patients (33.0%), most commonly neutropenia (n=59; 11.9%). Pneumonia was the most commonly reported serious adverse event affecting >2% of patients during Maintenance I (n=17; 3.4%). Infusion/administration-related reactions were reported in 75 patients (15.2%), with 20 (4.0%) experiencing at least one grade ≥3 event. The most common infusion/administration-related reaction of any grade was decreased neutrophil count (n=14; 2.8%). Neutropenia was the most commonly reported grade ≥3 infusion/administration-related reaction during Maintenance I (9 patients; 1.8%). Rituximab discontinuation due to a treatment-emergent adverse event was reported in 28 patients (5.7%) during Maintenance I. Of these, only neutropenia and pneumonia

Table 1. Patient and disease characteristics at the start of Maintenance II.

Characteristic	Number of patients (%) R-SC n=138	Observation n=138
Median age, years (range)	64 (26-89)	65 (34-86)
Male, n (%)	74 (53.6)	68 (49.3)
Ann Arbor stage at diagnosis, n/N (%)		
I	13/134 (9.7)	8/135 (5.9)
II	12/134 (9.0)	19/135 (14.1)
III	21/134 (15.7)	30/135 (22.2)
IV	88/134 (65.7)	78/135 (57.8)
FLIPI score, n (%)		
Low	25 (34.2)	28 (36.4)
Intermediate	22 (30.1)	27 (35.1)
High	26 (35.6)	22 (28.6)
Bone marrow involvement, n (%)	60 (43.5)	59 (42.8)
Median lactate dehydrogenase, ukat/L (range)	3.26 (1.30-11.77)	3.32 (1.40-9.15)
Type of NHL at screening, n (%)		
FL	73 (52.9)	77 (55.8)
WM/LPL	28 (20.3)	25 (18.1)
MZL	36 (26.1)	35 (25.4)
Induction chemotherapy regimen		
Bendamustine	80 (58.0)	79 (57.2)
CHOP	20 (14.5)	19 (13.8)
CVP	26 (18.8)	22 (15.9)
Other	12 (8.6)	18 (13.0)

R-SC: subcutaneous rituximab; FLIPI: Follicular Lymphoma International Prognostic Index; NHL: non-Hodgkin lymphoma; FL: follicular lymphoma; WM/LPL: Waldenström macroglobulinemia/lymphoplasmacytic lymphoma; MZL: marginal zone lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone.

Table 2. Summary of adverse events occurring during extended maintenance.

Patients with ≥1 event, n (%)	R-SC n=138	Observation n=138
≥1 AE	111 (80.4)	80 (58.0)
Grade ≥3 AE affecting ≥1% patients in either arm	48 (34.8)	40 (29.0)
Neutropenia	12 (8.7)	8 (5.8)
Pneumonia	7 (5.1)	4 (2.9)
Hypertension	3 (2.2)	0
Neutrophil count decreased	3 (2.2)	0
Acute kidney injury	0	2 (1.4)
Febrile neutropenia	2 (1.4)	0
Leukopenia	0	2 (1.4)
Myelodysplastic syndrome	1 (0.7)	2 (1.4)
Upper respiratory tract infection	0	2 (1.4)
Sepsis	2 (1.4)	2 (1.4)
Thrombocytopenia	1 (0.7)	2 (1.4)
Vomiting	2 (1.4)	0
Serious AE affecting ≥1% patients in either arm	31 (22.5)	32 (23.2)
Pneumonia	8 (5.8)	4 (2.9)
Acute kidney injury	0	2 (1.4)
Appendicitis	2 (1.4)	0
Bronchitis	0	2 (1.4)
Fall	0	2 (1.4)
Febrile neutropenia	2 (1.4)	0
Myelodysplastic syndrome	1 (0.7)	2 (1.4)
Neutropenia	0	2 (1.4)
Sepsis	2 (1.4)	2 (1.4)
Squamous cell carcinoma of skin	1 (0.7)	2 (1.4)
Grade 5 (fatal) AE	5 (3.6)	5 (3.6)
AE leading to treatment discontinuation	10 (7.2)	0

R-SC: subcutaneous rituximab; AE: adverse event.

were seen in more than one patient (2 patients each). At least one treatment-emergent adverse event leading to death was reported in eight patients (1.6%).

Adverse events were the most common reason for death during Induction and Maintenance I (40/692; 5.8% and 32/494; 6.5%, respectively). Sepsis was the most frequent event leading to death during these phases (7 patients [1.0%] and 2 patients [0.4%], respectively). Rituximab-related sepsis was associated with death in four patients (0.6%) during Induction and one patient (0.2%) during Maintenance I.

Maintenance II

The original wording of the study protocol led to differences in adverse event reporting between the rituximab and observation arms in Maintenance II (see the *Online Supplementary Appendix* for details). After a protocol amendment to permit retrospective collection of adverse events of grade ≥3 during this phase (allowing adverse event reporting to be consistent between the rituximab and observation arms), neutropenia and pneumonia were the most frequently reported grade ≥3 adverse events in both the rituximab arm (8.7% and 5.1%, respectively) and the observation arm (5.8% and 2.9%, respectively) (Table 2). However, when looking at median neutrophil counts (based on laboratory data), similar values were observed in both treatment arms in Maintenance II. There were three grade ≥3 infusion/administration-related reactions (1 each of lymphopenia, urinary tract infection and hypertensive crisis). There were no reports of grade ≥3 rash, erythema or skin reaction during Maintenance II. The incidence of serious adverse events was similar for both arms (22.5% with rituximab and 23.2% for observation) (Table 2), with pneumonia (5.8% and 2.9%, respectively) and sepsis (1.4% for both arms) being most commonly reported. All fatal adverse events (5 in each arm) were considered unrelated to study treatment by the investigators. These events were pneumonia, septic shock, acute myocardial infarction, Crohn disease, abdominal infection and diverticulitis (same patient) in the rituximab arm, and acute myeloid leukemia, cardiopulmonary failure, ventricular tachycardia, pneumonia and lung disorder in the observation arm. Five further deaths in the rituximab arm and two in the observation arm were due to disease progression; a single additional death with unknown cause was recorded in the observation arm.

There were no safety concerns or new signals related to hematology, biochemistry or immunological parameters in any phase of the study, and no meaningful changes from baseline in vital signs. There were also no unexpected changes from baseline in worst-on-treatment ECOG scores, and no noteworthy differences in score shifts between the rituximab and observation arms in Maintenance II.

Efficacy

The overall response rate at the end of Induction was 84.7% (95% CI: 81.1–87.3), and was similar across different chemotherapies: 86.4% (95% CI: 82.7–89.5) for bendamustine; 87.2% (95% CI: 78.3–93.4) for CHOP; 84.1% (95% CI: 74.4–91.3) for CVP; and 76.9% (95% CI: 67.6–

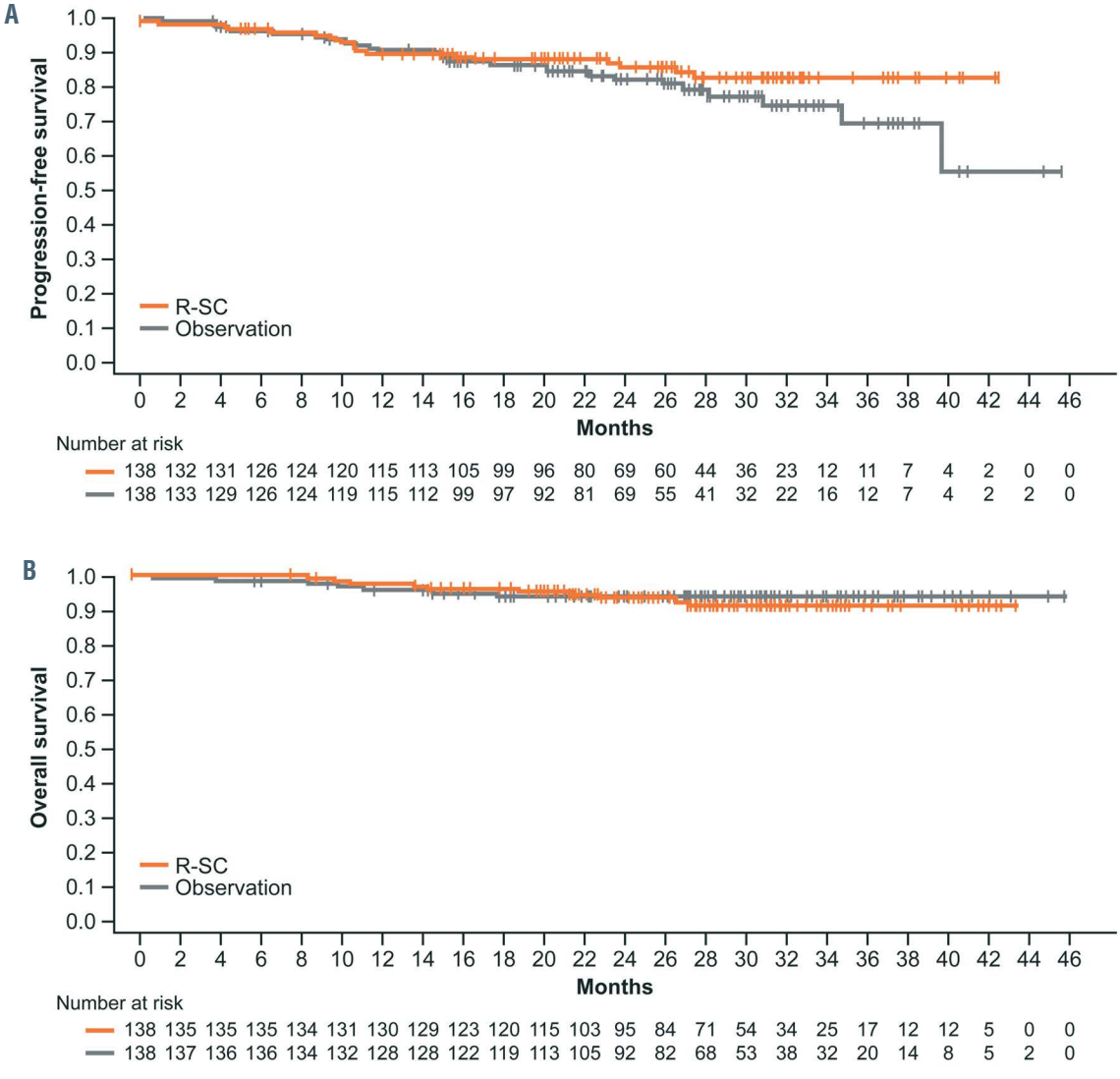

Figure 3. Survival outcomes during the randomized Maintenance II period. Kaplan-Meier analysis of progression-free (A) and overall survival (B) during the randomized Maintenance II period. R-SC: subcutaneous rituximab.

84.6) for other regimens (including FCM and MCP). All but one patient per arm among the 276 who were randomized in Maintenance II were responders after Induction (*Online Supplementary Table S5*). Proportions of patients in complete response or partial response at the end of Maintenance I were also comparable between arms among the 276 patients who were randomized (*Online Supplementary Table S5*).

Of the 357 patients who achieved a partial response at the end of Induction, 77 achieved a complete response by the end of Maintenance I, providing a conversion rate of 21.6% (95% CI: 17.4–26.2).

The MabCute study was unable to address its primary endpoint (investigator-assessed PFS_{ind}) because the number of events reported was insufficient: 129 PFS_{ind} events were needed for 80% power at 5% significance, with approximately 700 patients needed initially to yield the 330 required for randomization. There were 46 PFS_{ind} events at the end of study: 19 and 27 in the rituximab and observation arms, respectively: P=0.410 by log-rank test stratified by FLIPI risk category and NHL subtype; HR 0.76 (95% CI: 0.37–1.53), estimated using a Cox regression model with FLIPI risk category and NHL subtype as stratification factors. PFS_{ind} rates at 6, 9, 12, 15 and 18 months (Kaplan-Meier estimates) were similar for both arms (between 0.97 at 6 months and 0.88 at 18 months for rituximab, and between 0.96 at 6 months and 0.87 at 18 months for observation). The median PFS_{ind} was not reached in either arm (Figure 3A).

One patient, randomized to observation, discontinued from the study and subsequently died 2 months later. This event was not taken into consideration in the primary analysis due to a recording issue. It had no effect on the overall results or conclusions of the study.

The median PFS_{reg} (from enrollment to end of Maintenance I) (Figure 4A) was 46.32 months (95% CI: 42.87–60.02) in patients receiving bendamustine, 39.62 months (95% CI: 27.86–not reached) in patients receiving CHOP, and 37.03 months (95% CI: 33.87–74.12) in patients receiving CVP. Three-year PFS estimates for patients receiving bendamustine, CHOP, and CVP were 0.63 (95% CI: 0.57–0.69), 0.58 (0.46–0.68), and 0.59 (0.28–0.80), respectively. The median OS_{reg} (from enrollment to end of Maintenance I) (Figure 4B) was not reached in patients receiving bendamustine (95% CI: 66.86–not

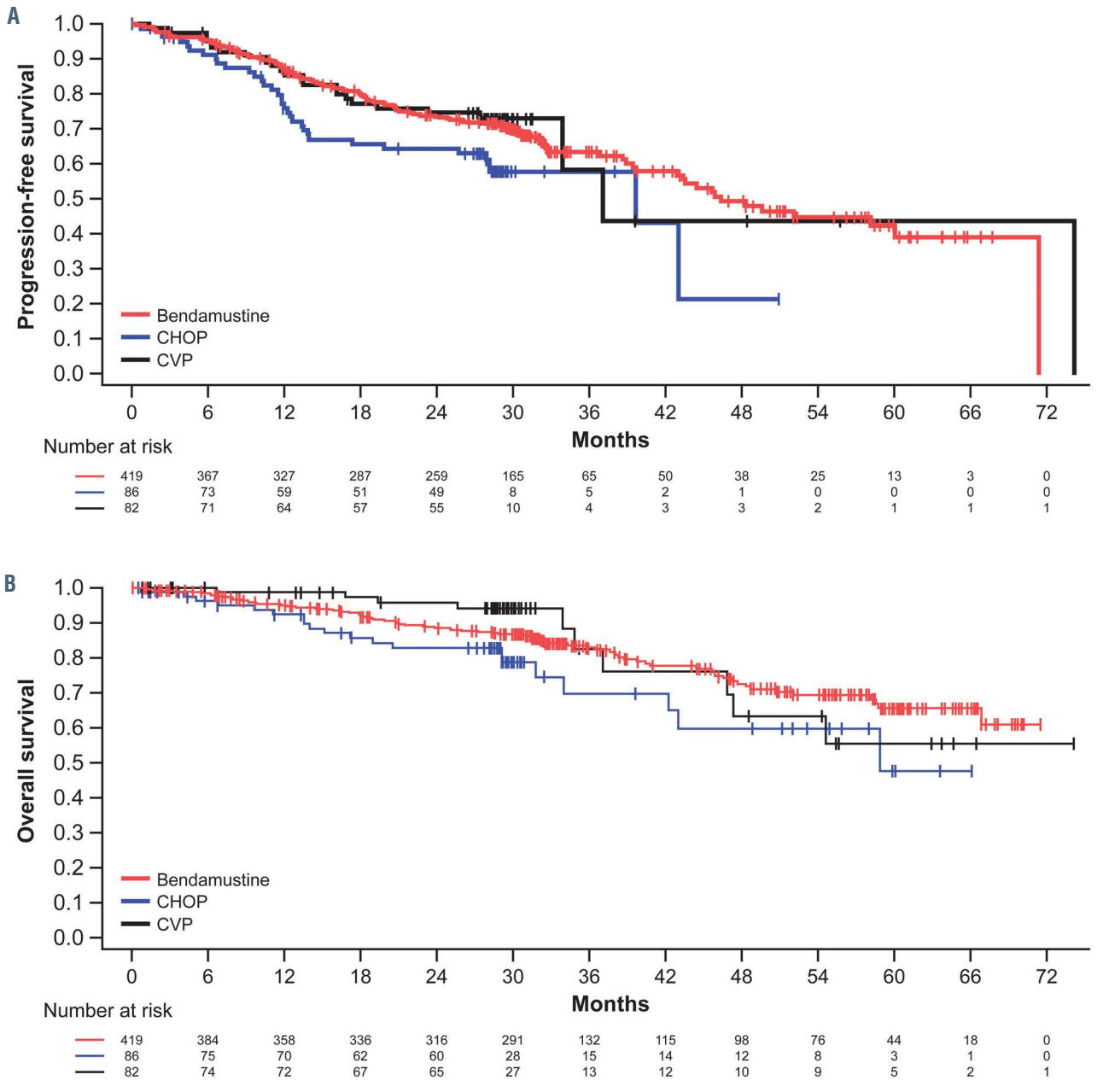

Figure 4. Survival outcomes from enrollment to end of Maintenance I, according to induction chemotherapy. Kaplan-Meier analysis of progression-free (A) and overall survival (B) from enrollment to end of Maintenance I, according to induction chemotherapy received (bendamustine *vs.* CHOP and CVP). [a]Intent to treat population for Induction. Time to event calculated from first induction therapy up to the earliest date of event until randomization; data censored after randomization. CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone.

reached) or CVP (95% CI: 46.82–not reached). The median OS_{ITT} was 58.84 months (95% CI: 42.22-not reached) in patients receiving CHOP induction. Three-year OS estimates for patients receiving bendamustine, CHOP, and CVP were 0.83 (95% CI: 0.78–0.87), 0.70 (95% CI: 0.53–0.82), and 0.82 (95% CI: 0.59–0.93), respectively. PFS_{ITT} and OS_{ITT} by NHL subtype are available in *Online Supplementary Table S6*. Unfortunately, due to the low numbers no conclusion can be drawn from these data.

Response rates at the end of Induction by both chemotherapy regimen and patients remaining at the start of each subsequent study phase showed that 56.9% of patients (157/276) who responded and who ultimately entered Maintenance II had received bendamustine as induction therapy (*Online Supplementary Table S7*).

There were 18 deaths (OS_{mnd} events) in total, ten in the rituximab arm and eight in the observation arm (not including the patient with a retrospective record of death). The median OS_{mnd} was not reached (Figure 3B).

Discussion

The benefit of 2 years of maintenance therapy with rituximab after response to frontline induction in patients with indolent NHL is well established in terms of significantly improved PFS. Early trials of rituximab maintenance in patients with R/R indolent NHL indicated effica-

cy in this setting too.[23,24,31,32] The findings prompt the question of whether further and prolonged maintenance therapy (beyond 2 years) would benefit patients with R/R indolent NHL who have maintained their response to treatment.

The overall tumor response rate after induction (~85%) in MabCute was consistent with rates observed in previous studies in R/R indolent NHL (75-95%).[22-24,31,32] These trials showed significant improvements in response duration and median PFS when rituximab maintenance therapy was given for up to 2 years compared with observation alone, and are supported by a meta-analysis of 2,586 patients participating in nine randomized trials which showed a significant improvement of median OS with rituximab maintenance therapy *versus* observation only in patients with R/R FL (HR 0.72, 95% CI: 0.57–0.91).[28] Maintenance with rituximab for 2 years following the end of Induction in the current study was associated with a rate of partial response to complete response conversion similar to that observed in previous studies.[21]

Although an OS benefit has been observed following rituximab maintenance in the R/R setting, it has not been demonstrated in the frontline setting. A 10-year follow-up of the PRIMA study in 1,018 patients with high tumor burden, previously untreated FL showed a significant long-term PFS benefit of rituximab maintenance over observation for 2 years after response to induction with rituximab and chemotherapy.[27] Although there was no significant OS benefit, the authors noted that over half of patients in the rituximab arm had not had disease progression over the 10 years, and had not required new anti-lymphoma treatment. Similar findings (significant PFS improvement but no significant effect on OS) were reported by the ECOG-ACRIN group after a median 11.5 years of follow-up of 387 patients who attained at least stable disease after CVP induction.[33] In addition, a prior study by the German STIL group confirmed the benefit of rituximab maintenance in R/R indolent NHL after a bendamustine or fludarabine salvage therapy.[34]

The key benefits of SC rituximab, with its short administration time, are linked to reductions in healthcare resource utilization[18,35] and patients' preference[15,36] relative to the intravenous formulation, particularly for long-term therapy.

Unfortunately, MabCute was unable to address its primary endpoint of investigator-assessed PFS in the randomized population. This was due to a much lower than anticipated number of PFS_{rand} events, representing only a third of the required events to have a power of 80% with a hazard ratio of 0.605. The reason for the low rate of PFS_{rand} events was not clear, but may have been related to the effectiveness of supportive care and treatment delivery under the study protocol.

There were 18 deaths in total, ten in the rituximab arm and eight in the observation arm (not including the patient with a retrospective record of death). This study was not powered to evaluate survival, and follow-up was relatively short at the time of the analysis.

The exploratory analysis of PFS_{reg} and OS_{reg} from enrollment to end of Maintenance I (i.e. the non-randomized part of the study) showed 3-year PFS_{reg} and OS_{reg} rates of 63% and 83%, respectively in patients treated with bendamustine, 58% and 70%, respectively, in those treated with CHOP, and 59% and 82%, respectively, in those treated with CVP. It should be noted that there was a bias in patients' selection; the investigator could decide what regimens to give to which patients – most patients were treated with bendamustine in the Induction period, and the size of the subgroups is very different. Therefore, a direct comparison between treatment regimens is not appropriate. In MabCute, approximately 60% of patients received bendamustine at Induction, and this proportion of patients was maintained out to the Maintenance II phase. There are few data available on the use of bendamustine in R/R NHL. A study by Sakai *et al.* recently reported 3-year PFS and OS rates of 71% and 89%, respectively, in a population of patients with R/R FL,[37] while the STIL group reported a 1-year PFS of 76% and median OS of 109.7 months in patients with R/R indolent NHL or mantle cell lymphoma.[34] However, comparison between these trials is difficult; the PFS_{reg} survival data from the current study were censored after Maintenance I, and are therefore not comparable with general PFS data.

No unexpected toxicities were reported during Maintenance II, and good tolerability and safety were maintained throughout follow-up. The proportion of patients who experienced adverse events during long-term maintenance was slightly greater in the rituximab arm than in the observation arm. These observations were as expected, given the known profile of rituximab SC.[12] Rituximab is always given by intravenous infusion for the first cycle, when the risk of infusion-related reactions is greatest, to allow slowing or stopping of the infusion (as a preventative measure). The incidence of infusion-related reactions decreases with subsequent infusions. The overall safety profile of rituximab SC is similar to that of the intravenous formulation, but with a greater incidence of mostly mild-to-moderate infusion/administration-related reactions, primarily injection-site reactions, which decrease in frequency over time.[14,15,17,38] This pattern was observed in the current study (i.e. from 47.7% of patients during Induction to 15.2% during Maintenance I and 10.1% of rituximab patients in Maintenance II). Interestingly, in line with prior publications on frontline therapy of FL, a bendamustine-based induction resulted in more frequent pyrexia and neutropenia (*Online Supplementary Table S5*).

In conclusion, the MabCute study was unable to address the question of whether prolonged (beyond 2 years) maintenance therapy with rituximab adds any clear benefit compared with observation only in patients with R/R indolent NHL (who have responded to induction therapy with rituximab plus chemotherapy), due to a low number of PFS events. Extension of treatment was not associated with any important additional toxicity (in particular no additional neutropenia or infection), and no new safety signals were observed. Two years of maintenance with rituximab after response to initial induction therapy therefore remains the standard of care in these patients.

Disclosures

SR declares a consultation or advisory role for Janssen, AstraZeneca, F. Hoffmann-La Roche Ltd, Sunesis, Pharmacyclics, Celgene, Celltrion, Kite; speakers bureau for Janssen; and research funding from Janssen. WGB declares no conflict of interest. JB declares honoraria from F. Hoffmann-La Roche Ltd, Takeda, Celgene, Novartis, and Gilead; consultation or advisory role for Takeda, Janssen, Celgene, and Gilead; research funding from F. Hoffmann-La Roche Ltd; and travel and/or accommodation expenses from F. Hoffmann La-Roche

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Contributions

SR, WGB, JB, AMC, OC, CP, C-MW, FZ and MD were involved in accrual and treatment of patients. SR analyzed data. All authors were involved in interpreting the data, critically reviewing the manuscript, approved the manuscript for submission and agree to be accountable for the accuracy and integrity of the study.

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Data-sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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