Lenalidomide-rituximab or lenalidomide-rituximab-bendamustine for relapsed/refractory follicular lymphoma: primary and final analysis of the randomized phase II HOVON110/ReBeL study

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Abstract

The R^2 (lenalidomide-rituximab) and R^2 with bendamustine (R^2B) regimens are both feasible in relapsed/refractory follicular lymphoma (R/R FL), but prospective phase II data on R^2B are lacking. In this multinational, prospective, randomized, non-comparative trial, patients with R/R FL were randomized 1:1 to R^2 (arm A) or R^2B (arm B). Patients achieving computed tomography-based partial or complete remission (PR/CR) received rituximab maintenance every 3 months for 2 years. Co-primary endpoints were investigator-assessed CR rates at end-of-induction (EOI) and severe toxicity rates. Between December 2014 and July 2019, 92 patients were randomized. The trial was stopped prematurely due to slow accrual. CR rates at EOI were 11.4% (95% confidence interval [CI]: 3.8-24.6%) for R^2 and 15.2% (95% CI: 6.3-28.9%) for R^2B. With a median follow-up of 74 months, predefined severe toxicities occurred in three (6.8%; 95% CI: 1.4-18.7%) and six patients (13.0%; 95% CI: 4.9-26.3%) in arm A and arm B respectively, with two pneumonia-related deaths in arm A and no treatment-related deaths in arm B; 43% and 66% experienced any grade 3-4 adverse events (2%/7% grade 4). At 60 months, in arms A and B event-free survival was 39.5% (95% CI: 25.1-53.6%) and 56.4% (95% CI: 40.1-69.3%). Overall survival was excellent at 72.1% and 86.3%, respectively. R^2 and R^2B are both effective treatment regimens for R/R FL. While computed tomography-based CR rates were low, treatment with R^2B resulted in numerically longer median event-free survival and overall survival, but this was associated with higher toxicity.

Introduction

Follicular lymphoma (FL) is the most frequent type of indolent lymphoma, with a rate of 2.5-5 new cases per 100.000 persons per year.[1,2] Most patients present with advanced-stage disease. Advanced-stage FL is considered incurable, even though the disease is initially highly sensitive to chemotherapy, radiotherapy and immunotherapy, with a median survival of approximately 20 years.[3] The disease course is characterized by relapses with shortening remission durations following each line of treatment.[4] First-line treatment often consists of chemotherapy such as CVP (rituximab, cyclophosphamide, vincristine, prednisolone), CHOP (CVP with the addition of doxorubicin) or bendamustine, in combination with a CD20 directed monoclonal antibody - until recently mainly rituximab and nowadays either rituximab or obinutuzumab (O). R-Bendamustine and R-CHOP are highly effective regimens delivering prolonged progression-free survival (PFS) in comparison to R-CVP,[5,6,7] and the use of rituximab maintenance (RM) for 2 years has been shown to further significantly increase PFS, but not overall survival (OS).[8,9]

The choice of treatment for relapsed disease depends on the type and duration of response to first line treatment and other patient- and disease-related factors. There are few randomized controlled trials in the relapse setting. The lenalidomide-rituximab combination (R^2 regimen) has been shown to be effective in both treatment-naive and relapsed/refractory follicular lymphoma (R/R FL).[10,11] We hypothesized that combining R^2 with bendamustine (R^2B) could deepen remission and prolong event-free survival (EFS) compared to standard R^2 treatment in patients with relapsed FL. We previously demonstrated the feasibility of the R^2B combination in the phase I dose escalation part of the HOVON110/ReBeL trial, which evaluated four dose levels in a 3+3 design and identified the recommended phase II dose level at rituximab 375 mg/m^2 intravenously on day 1, bendamustine 90 mg/m^2 intravenously on day 1,2 and lenalidomide 20 mg orally on day 3-21 of six 28-day cycles.[12] Here, we describe the prospective, randomized non-blinded phase II part of this trial (Dutch Clinical Trial Register NTR3028; (see *Online Supplementary Appendix, page 10* for the full study protocol), in which patients with R/R FL were randomized 1:1 to either R^2 or R^2B, aiming to identify the most favorable regimen considering both efficacy and tolerability to take forward for a phase III study. Rituximab maintenance for 2 years was added to both arms of the study following the significant increase in PFS demonstrated in patients with R/R FL in the EORTC 20981 phase III randomized intergroup study[13] and in the PRIMA study[8] and the increase in OS observed in a meta-analysis which analyzed individual patient level data from 11 randomized controlled trials comparing RM therapy with no maintenance for patients with FL.[14]

Methods

Study design and participants

Randomization was stratified for: Follicular Lymphoma International Prognostic Index (FLIPI) score at enrolment (0-2 *vs*. 3-5), number of prior treatments (1 *vs*. 2-5), prior bendamustine and relapse during RM. The study was conducted in accordance with the Guidelines on Good Clinical Practice from the International Conference on Harmonization and the Declaration of Helsinki. The study protocol and amendments were approved by the Ethics Committee of Amsterdam UMC and subsequently by EC for the 39 participating sites. A data and safety monitoring board was installed.

Main eligibility criteria included relapsed FL grade 1/2/3a,[15] measurable disease, ≤5 prior lines of systemic treatment,

including prior bendamustine if delivered at least 24 months previously and had resulted in a response. Main exclusion criteria included rituximab-refractory disease (relapse during RM however was allowed) and prior lenalidomide.

Procedures

Patients in arm A received six cycles of R^2 q28 days (lenalidomide orally 20 mg day [d]1-21, rituximab 375 mg/m^2 intravenously (iv) d1); patients in arm B six cycles of R^2B q28 days (lenalidomide orally 20 mg d3-21, rituximab 375 mg/m^2 iv d1, bendamustine 90 mg/m^2 iv d1, 2). Patients with PR/CR received 2 years of RM (375 mg/m^2 q3 months). Rituximab subcutaneously (flat dose, 1,400 mg) was allowed. Supportive care comprised aspirin 80 mg in both arms and co-trimoxazole 480 mg once daily and valaciclovir 500 mg twice daily in the R^2B arm until recovery of CD4-cells to >0.2x10^9/L.[15]

Patients were assessed monthly during induction and subsequently every 3 months for 5 years. Computed tomography (CT) scans were performed prior to treatment, after three cycles of induction therapy and at end-of-induction (EOI). For details on (central review of) ^{18}F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-CT scans, performed at baseline and at EOI, and central pathology review, see *Online Supplementary Appendix; Online Supplementary Methods, page 3*).

Adverse events (AE, ≥grade 2) and serious adverse events (SAE) were reported according to Common Terminology Criteria for Adverse Events version 4.0 (CTC-AE 4.0) from the first study-related procedure until 30 days following the last dose of any protocol drug. AE were also reported beyond 30 days if considered related. Second primary malignancies were reported during the entire follow-up.

Outcomes

Co-primary endpoints were CT-based CR rates (CRR) at EOI according to Cheson 2007, and rate of severe toxicities (ST), (grade ≥3 non-hematologic toxicity and specified grade 4 hematologic toxicities or treatment-related death) in the modified-ITT population (all eligible patients), with separate evaluation of both arms. Secondary endpoints included overall response rate (ORR) at EOI and at the end of RM, event-free survival (EFS), progression-free survival (PFS), disease-free survival (DFS), time to next lymphoma treatment (TTnT), overall survival (OS) and relative dose intensity of lenalidomide and bendamustine. Prespecified exploratory analyses assessed the prognostic value of TMTV at baseline and the centrally reviewed FDG PET-CT response at EOI for EFS and OS, as well as comparison of the prognostic value of CT- *versus* PET-based response evaluation. For definitions of the endpoints, sample size calculation and statistical analysis, see *Online Supplementary Appendix; Online Supplementary Methods, page 3*; and *Online Statistical Analysis Plan, page 10*).

Results

Between December 31, 2014 and July 16, 2019, 92 of 150 planned patients were enrolled. Due to slow accrual, despite several attempts to identify hurdles to enrollment and after consultation with the data and safety monitoring board, the trial was stopped prematurely and the primary and final analysis of the study was performed on the 92 patients enrolled on the phase II part of the trial with a data cutoff of December 31, 2024. Two patients were considered ineligible, one in arm A due to a diagnosis other than FL on pathology review (chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]), the other in arm B due to rituximab refractoriness (see Figure 1 for a Consort diagram of the trial). All 90 remaining patients were included in the modified intention-to-treat (mITT) analysis.

Baseline characteristics are presented in Table 1 and were comparable between arm A and B in terms of sex and median age (64/62 years). Most patients had stage III/IV disease (85%/80%), an intermediate or high-risk FLIPI score at relapse (78%/89%) and the majority had received one prior systemic line of treatment (75%/76%; range, 1-5). The median time from FL first diagnosis to enrolment in the HOVON110 study was 7.3 years (interquartile range [IQR], 4.6-11.4) for arm A and 5.1 years (IQR, 3.7-8.6) for arm B. Most patients were either treated with R-CVP or R-CHOP in the first line (R-CVP 50% arm A and 63% arm B arm; R-CHOP 27% arm A and 13% arm B). RM was given in the first line to 16 patients in arm A and 17 patients in arm B. Eighteen percent of patients in arm A and 22% of patients in arm B had progression of disease within 24 months after first line treatment (POD24). There were no statistically significant differences in the four stratification factors between the arms (FLIPI, number of prior treatments, prior bendamustine treatment and relapse during rituximab maintenance). Because of the low number of patients we did not analyze outcomes based on the stratification factors.

For 81 of 92 enrolled patients (89%), sufficient material was available for central pathology review, which confirmed a diagnosis of FL in 74 of these 81 cases (91%). In one patient a diagnosis of CLL/SLL was made and in the remaining six cases a diagnosis of FL was considered highly likely, but this could not be fully confirmed due to limited biopsy material. The vast majority of patients had grade 1/2 FL (91% in arm A and 94% in arm B).

For patients in arms A/B, 79.5%/76.1% completed all six induction cycles and 38.6%/43.5% completed both induction and eight administrations of RM (q3 months). Main reasons for discontinuation during induction were progressive disease (PD) (N=8 arm A, N=6 arm B), toxicity (N=1 arm A, N=6 arm B), or other reasons (N=5 arm A, N=2 patients arm B) (Figure 1). The median relative dose intensity (RDI) for doses administered for lenalidomide was 100% in both arms, and 100% for bendamustine in arm B.

For a complete overview of the main study outcomes, see

Online Supplementary Table S2; Online Supplementary Appendix, page 5. Based on mITT and local CT assessment (efficacy co-primary endpoint), 11.4% (95% CI: 3.8-24.6%) of patients treated in arm A and 15.2% (95% CI: 6.3-28.9) of patients treated in arm B achieved a CR at EOI; the overall response rate (ORR) was 66% and 65%, respectively. When responses assessed outside the prespecified window (8 weeks after last induction cycle) were taken into account, the CT-based CRR were 16% and 22%, respectively. An EOI FDG PET-scan was available for 34 patients (77%) in arm A and 28 patients (61%) in arm B. The complete metabolic response rate (CMR) by central PET-CT review at EOI was 48% (95% CI: 32.5-63.3%) and 50% (95% CI: 34.9-65.1%), respectively, and metabolic ORR (CMR + PMR) was 64% and 63% (*Online Supplementary Figure S1; Online Supplementary Appendix, page 7*). The CR rate at the end of maintenance (EOM) based on local investigator-assessed CT assessment was 18% and 22%, respectively, with an ORR at EOM of 32% and 37%.

At the data cutoff for the analysis of December 31, 2024, the median follow-up of the trial was 74 months. EFS at 60 months for arm A *versus* B was 39.5% (95% CI: 25.1-53.6%)

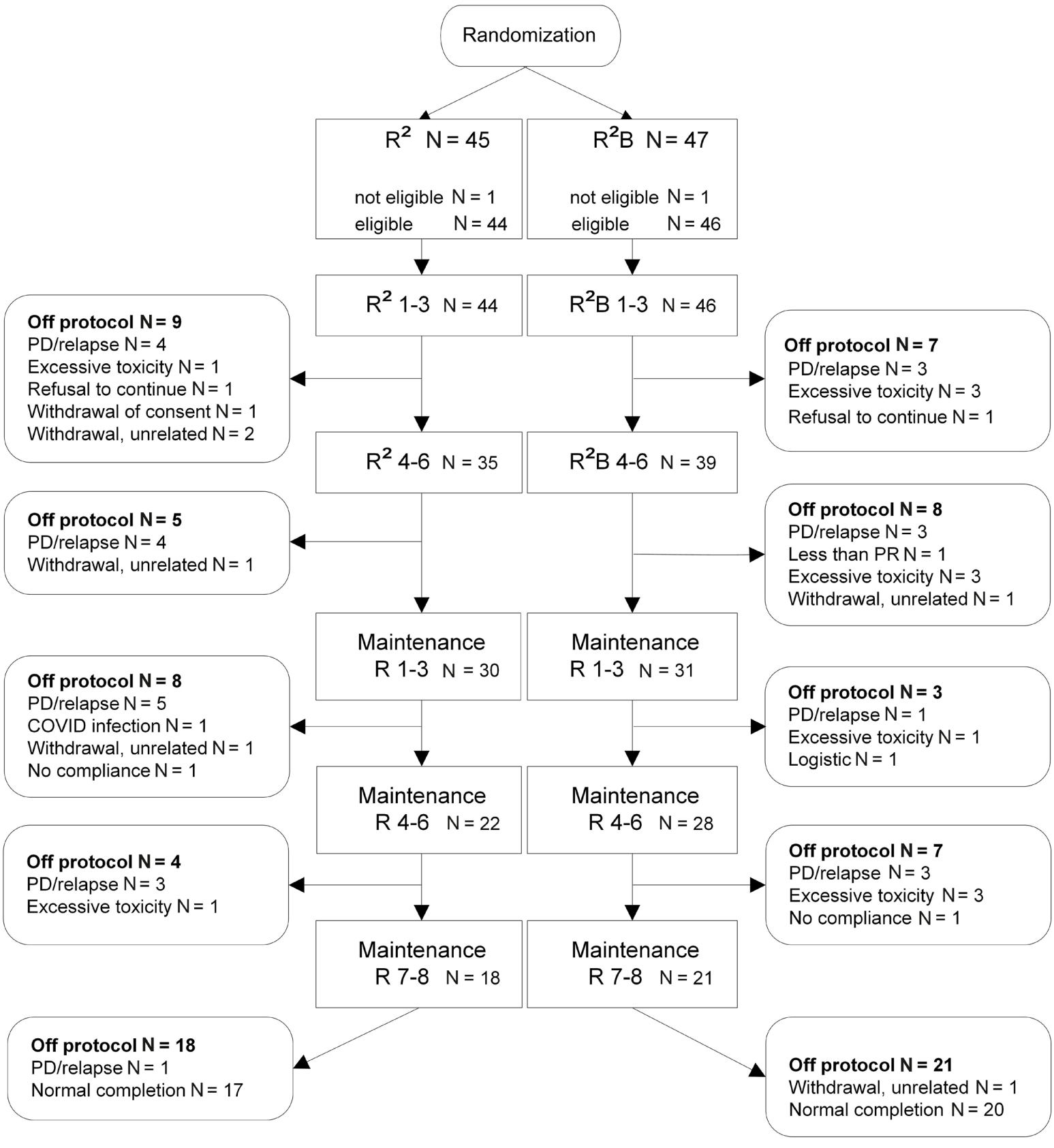


Figure 1. Consort diagram. Enrolment, randomization and reasons for going off-protocol during treatment in both arms (total population 92 patients). PD: progressive disease; PR: partial remission; R²: rituximab, lenalidomide; R²B: rituximab, lenalidomide, bendamustine.

and 56.4% (95% CI: 40.1-69.3%) respectively; median EFS was 24.6 month (range, 6.2-not reached [NR] and NR) (Figure 2A). Results for PFS were almost identical (see Figure 2; *Online Supplementary Table S2*; *Online Supplementary Appendix, page 5* for an overview of all outcomes). Importantly, at 60 months, 64% of patients in arm A and 70% of patients in arm B had not yet received any subsequent salvage treatment and the median time to next treatment (TTnT) was NR for both arms. These probabilities were derived from the KM analysis, with overlapping 95% CI.

OS was excellent in both arms, with 72% and 86% of patients alive at the end of follow-up in arms A and B, respectively; therefore, median OS was not reached in either arm (Figure 2B). Of the 21 patients with a CMR at EOI in arm A, 20 (95%) were still alive at the database lock, *versus* 20/23 patients (87%) in arm B.

Causes of death during the study were progression of FL (N=8), infectious toxicity (N=3), euthanasia in the context of subsequent metastatic prostate cancer (N=1) and unknown (N=1) in arm A; progression of FL (N=6), infectious toxicity (N=2), suicide (N=1) and unknown (N=1) in arm B.

Severe toxicity (ST) during induction (defined in line with the DLT definition as grade ≥3 non-hematologic toxicity, grade 4 neutropenia lasting ≥7 days (unless due to bone marrow [BM] infiltration and despite the use of granulocyte colony-stimutaling factor [G-CSF]) with some exceptions, e.g., grade 3 infections requiring antibiotic treatment did not qualify as ST) occurred in three patients in arm A (6.8%; 95% CI: 1.4-18.7%; two fatal pneumonia cases) and in six patients (9 ST) in arm B (13.0%; 95% CI: 4.9, 26.3%; no fatalities). For the nine patients who experienced ST, there were no differences in number of prior treatment lines compared to the whole study population: most patients had received only one prior treatment (R-CVP (N=4), R-CHOP (N=2), R-benda (N=1), or two prior treatments (chlorambucil first line, R-CVP second line and

Table 1. Patient characteristics at baseline.

Characteristics	Arm A: R^2	Arm A: R^2B	Total
Total, N (%)	44 (49)	46 (51)	90
Male, N (%)	27 (61)	31 (67)	58 (64)
Age, years, median (IQR)	64 (56-70)	62 (55-68)	63 (56-69)
Time from FL diagnosis to enrolment, years, median (IQR)	7.3 (4.6-11.4)	5.1 (3.7-8.6)	6.3 (3.7-9.7)
Stage III/IV, N (%)	35 (85)	37 (80)	74 (82)
LDH >ULN, N (%)	10 (23)	9 (20)	19 (21)
FLIPI ≥2, N (%)	34 (78)	41 (89)	75 (83)
B-symptoms, N (%)	10 (23)	8 (17)	18 (20)
Met ≥1 GELF criteria, N (%) FL grade 1/2 FL grade 3a	 41 (93) 3 (7)	 44 (96) 2 (4)	 85 (94) 5 (6)
Prior Rx lines, median (range)	1 (1-4)	1 (1-3)	1 (1-4)
Prior Rx, N (%) 1 2 3 4	 33 (75) 5 (11) 5 (11) 1 (2)	 35 (76) 9 (20) 2 (4) -	 68 (76) 14 (16) 7 (8) 1 (1)
First-line therapy, N (%) R-CVP R-CHOP R-bendamustine	 22 (50) 12 (27) 1 (2)	 29 (63) 6 (13) 2 (4)	 51 (57) 18 (20) 3 (3)
Rituximab maintenance first line, N (%)	16 (36)	17 (37)	33 (37)
Prior autologous SCT, N (%)	5 (11)	2 (4)	7 (8)
POD24, N (%) No Yes	 36 (82) 8 (18)	 36 (78) 10 (22)	 72 (80) 18 (20)

FLIPI: follicular lymphoma prognostic index; GELF: Groupe d'Etude des Lymphomes Folliculaires; IQR: interquartile range; LDH: lactate dehydrogenase; R^2: rituximab, lenalidomide; R^2B: rituximab, lenalidomide, bendamustine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisolone; Rx: systemic treatment line; POD24: progression of disease within 24 months after start of first- line treatment; SCT: stem cell transplantation; ULN: upper limit of normal.

Obinutuzumab-CHOP first line and R-bendamustine second line). Of the two patients with fatal pneumonia, one had only received one prior line (R-CHOP) and the other patient had received obinutuzumab-CHOP first line and R-bendamustine second line. Interestingly, two of the three patients who had received bendamustine as a prior treatment line, developed an ST.

Fourty three percent/66% of patients experienced any grade 3-4 AE (2%/7% grade 4) (Table 2). These comprised mainly skin toxicity, infections and gastrointestinal toxicity. More patients in arm B needed G-CSF support during induction (N=2 arm A, N=14 arm B). Interestingly, the rate of TLS was low and similar in both arms, whereas four cases of tumor flare reaction (TFR) were seen only in arm A. Symptoms of TFR included hypercalcemia, painful lymph nodes, increase in skin lesion and pseudo-progression of lesions during the first cycle of therapy. In arm A, 23 SAE were reported in 44 patients during induction, 66% were serious because of hospitalization. 60% were possibly or probably related to study drug and 87% resolved completely. In arm B, 34 SAE occurred in 46 patients, mostly due to hospitalization, with 73% possibly or probably related and 100% completely resolved.

During rituximab maintenance, the number of grade 3/4 AE was six (20%) in arm A (all grade 3) and seven in arm B (22.5%, also all grade 3). These toxicities mainly comprised infections. In arm B, 1 patient developed *Pneumocystis carinii* pneumonia during RM, after stopping co-trimoxazole prophylaxis (*Online Supplementary Table S3; Online Supplementary Appendix, page 6*). In arm A seven SAE were

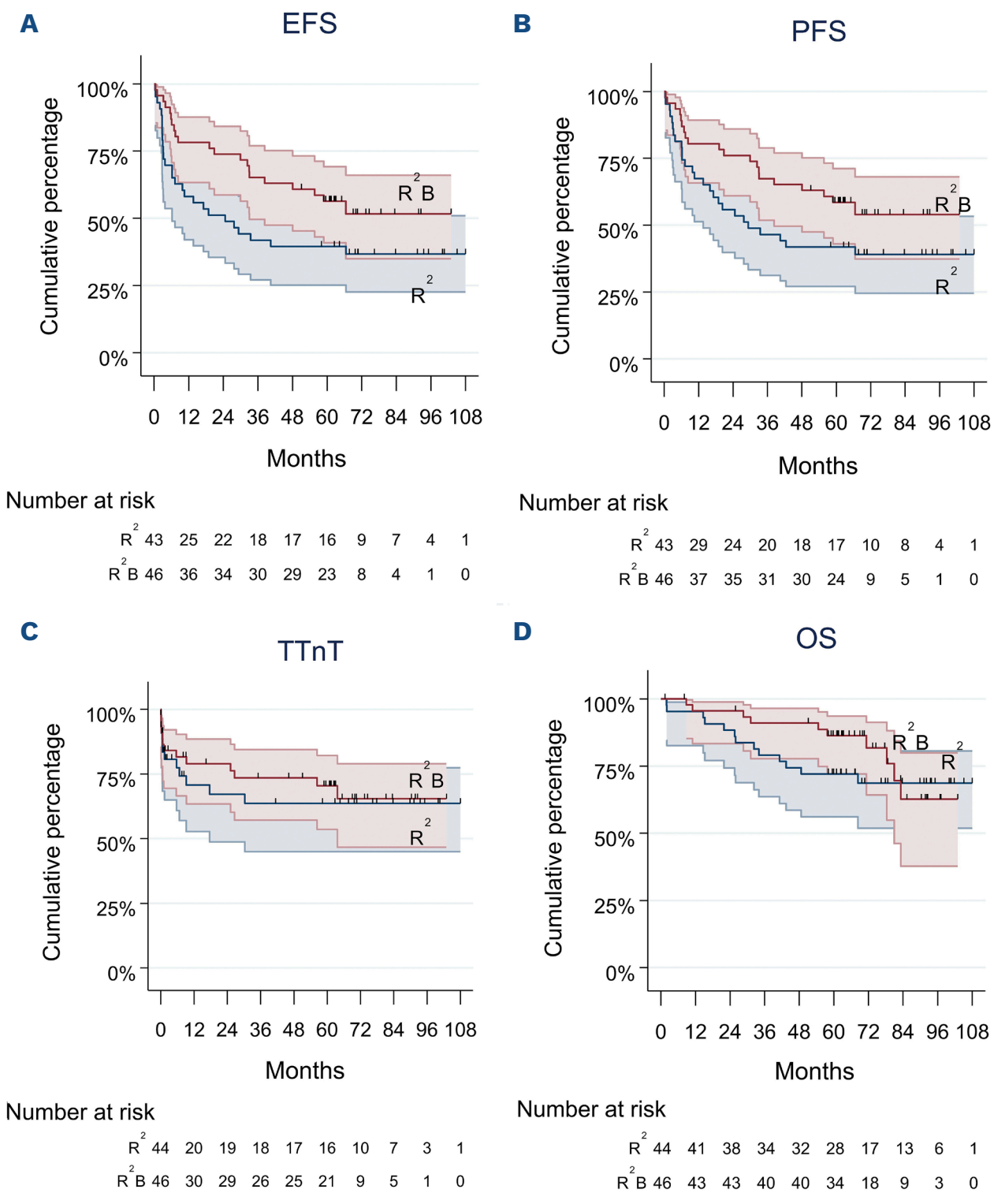


Figure 2. Kaplan Meier survival curves for both treatment arms. (A) Event-free survival (EFS). (B) Progression-free survival (PFS). (C) Time to next treatment (TTnT). (D) Overall survival (OS). Tick marks indicate censored cases. Pink shading represents 95% confidence interval (CI) for rituximab, lenalidomide, bendamustine (R^2B), blue shading for rituximab, lenalidomide (R^2).

reported in 31 patients who started with maintenance, *versus* eight SAE in 30 patients who started RM in arm B. Again, most AE were serious because of hospitalization. Thirteen second primary malignancies (SPM) in eight patients in arm A and 11 SPM in nine patients in arm B were observed during the follow-up period. These consisted of nine non-melanoma skin cancers and four solid tumors (prostate, thymic, thyroid, cervical cancer) in arm A and eight non-melanoma skin cancers and three solid tumors (prostate cancer N=2, anorectal carcinoma N=1) in arm B. None of the patients developed secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

Regarding response assessment at EOI, PET-CT seems to demonstrate more accurate response assessment and prognostic utility over conventional CT. While CT-based CR predicted excellent outcomes (PFS at 60 months 81.3%, OS 93.8%), it identified only 13.3% of patients in CR, leaving a large, heterogeneous group of non-CR patients with widely variable prognoses. In contrast, PET-CT identified CMR in a larger fraction of patients (48% in arm A, 50% in arm B), reclassifying patients with residual CT lesions but no metabolic activity, and more accurately stratifying outcomes (CMR *vs*. non-CMR PFS: 65.9% *vs*. 26.1%; OS: 88.6% *vs*. 50.0%) (Figure 3).

Baseline total metabolic tumor volume (TMTV) demonstrated substantial heterogeneity (range, 5.3-2,399.5 mL; median 234.3 mL; IQR, 113.6-471.9 mL) without significant differences between treatment arms (arm A: median 2,45.0 mL; IQR, 160.3-460.7 mL; arm B: median 234.3 mL; IQR, 113.0-635.8 mL; *P*=0.426). Median-based TMTV dichotomization revealed only a trend toward inferior PFS (HR=1.57; 95% CI: 0.86-2.87; *P*=0.139) and OS (HR=2.14; 95% CI: 0.90-5.11; *P*=0.086) in high-TMTV patients; results were pooled for both arms of the study because of low patient numbers) (*Online Supplementary Figure S2*; *Online Supplementary Appendix, page 8*). In stratified analyses, the treatment effect (arm B *vs*. A) revealed distinct patterns. Treatment in arm B resulted in a numerically but statistically not significantly higher PFS benefit in both TMTV groups (low TMTV: HR=0.60; 95% CI: 0.25-1.44; *P*=0.25; high TMTV: HR=0.73; 95% CI: 0.16-3.24; *P*=0.68), with 63.6% *versus* 45.0% in low-TMTV and 47.6% *versus* 36.8% in high-TMTV patients for arms B and A, respectively (*Online Supplementary Figure S2A*). Median PFS was 59 *versus* 25 months (low TMTV) and 19 *versus* 10 months (high TMTV) for arms B and A.

In contrast, treatment in arm B resulted in a numerically higher but not statistically significantly higher OS benefit only in high TMTV patients (HR=0.58; 95% CI: 0.06-5.39; *P*=0.64; 81.0% *vs*. 60.0%) while showing less advantage in low TMTV patients (HR=1.04; 95% CI: 0.26-4.17; *P*=0.96; 90.9% *vs*. 85.0%) (*Online Supplementary Figure S2B*). High TMTV status impacted OS in arm A patients (60.0% *vs*. 85.0% (high *vs*. low TMTV), whereas this negative prognostic effect was less pronounced in arm B patients (81.0% *vs*. 90.9%). Consequently, the absolute OS benefit of arm B was greater in high TMTV patients (21.0% difference) versus low TMTV patients (5.9% difference). However, neither

Table 2. Toxicity during induction treatment.

Toxicity	Arm A: R^2 N=44 N of patients experiencing AE (%)				Arm B: R^2B N=46 N of patients experiencing AE (%)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Infections	19 (43)	9 (20)	1 (2)	2 (4)	23 (50)	11 (24)	2 (4)	0
Gastrointestinal	12 (27)	2 (5)	0	0	18 (39)	7 (15)	0	0
Metabolic	1 (2)	2 (5)	0	0	3 (7)	1 (2)	0	0
Neurologic	4 (9)	0	0	0	5 (11)	2 (4)	0	0
Skin disorders	13 (30)	2 (5)	0	0	13 (28)	7 (15)	0	0
Vascular disorders	1 (2)	2 (5)	0	0	6 (13)	1 (2)	0	0
Cardiovascular disorders	1 (2)	2 (5)	0	0	1 (2)	4 (9)	0	0
General disorders	9 (20)	2 (5)	0	0	21 (46)	3 (7)	0	0
Musculoskeletal and connective tissue disorders	4 (9)	0	0	0	4 (9)	1 (2)	0	0
Infusion-related reaction	5 (11)	0	0	0	3 (7)	0	0	0
Other	20 (45)	8 (18)	0	0	20 (43)	11 (24	1 (2)	0

AE: adverse events; N: number; R^2: rituximab, lenalidomide; R2B: rituximab, lenalidomide, bendamustine.

interaction reached statistical significance (PFS: *P*=0.744; OS: *P*=0.510), likely due to limited sample size and low event rates (23 OS events total). Additional quantitative PET analyses (radiomics) including maximal standardized uptake value (SUV_{max}), SUV_{peak} and total lesion glycolysis (TLG) have been performed and the results can be found in *Online Supplementary Table S1; Online Supplementary Appendix, page 5*. Cox regression analyses of baseline SUV_{max} and treatment arms *versus* PFS and OS also did not show significantly different effects, although patients with an SUV_{max} below the median seem to have a more favorable PFS (*Online Supplementary Figure S3*), this was not statistically significant, probably due to low numbers of patients.

Discussion

We previously demonstrated in the phase I dose escalation

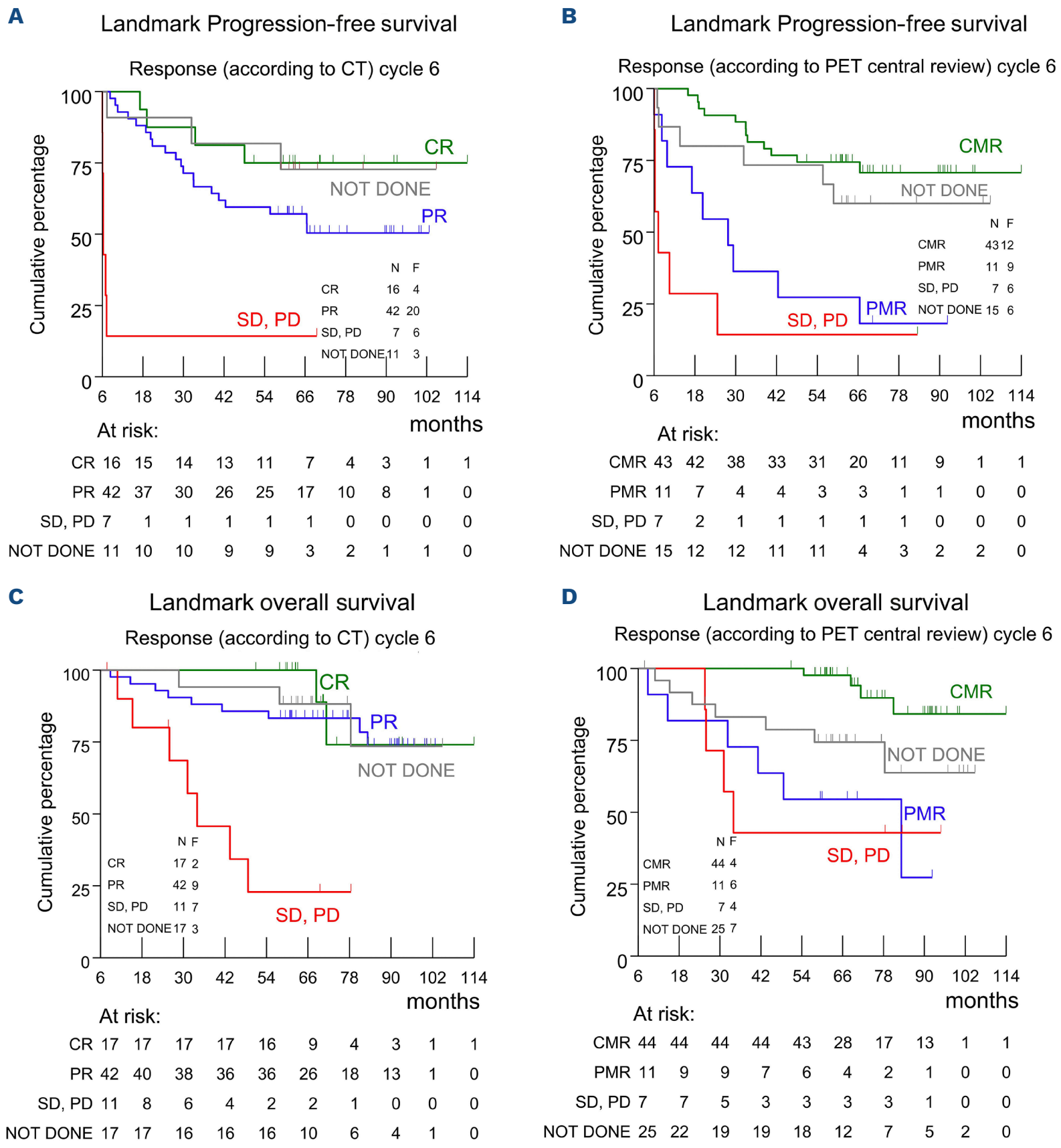


Figure 3. Kaplan Meier curves according to response (all patients, landmark analysis at end of induction). (A) Progression-free survival (PFS) based on the results of end of induction (EOI) computed tomography (CT) scan. (B) PFS based on the results of EOI positron emission tomography (PET)-CT scan. (C) Overall survival (OS) based on the results of EOI CT scan. (D) OS based on the results of EOI PET-CT scan. CMR: complete metabolic response rate; CR: complete remission; PD: disease progression; PMR: partial metabolic response; PR: partial remission; SD: stable disease.

part of this trial that rituximab-lenalidomide can be safely combined with bendamustine in the standard dose of lenalidomide 20 mg daily for 21/28 days and bendamustine 90 mg/m^2 day 1 and 2.[12] We subsequently evaluated this combination in a randomized non-comparative phase II trial of R^2 and R^{2}B in R/R FL patients, with the hypothesis that adding bendamustine to the R^2 regimen could result in a higher percentage of complete responses and potentially longer PFS. Efficacy and toxicity were however analyzed separately for both arms and any comparisons are of an exploratory nature.

We here report high CT-based OR rates and PET-CT based CMR rates, but low CT-based CR rates for both treatment arms. At a median follow-up of 74 months, 39% of R^2 treated patients and 61% of R^{2}B treated patients were still alive without progression and the median OS was not reached for either regimen. This compares favorably with historic real-world controls and is in line with long-term outcomes of the R^2 arm of the AUGMENT trial, which also enrolled a non-rituximab-refractory cohort.[4,17]

Both R^2 and R^{2}B regimens demonstrated lower-than-expected rates of severe toxicity, remaining below the protocol-defined threshold of 20%. However, the R^{2}B arm did show a higher frequency of grade 3/4 adverse events (mostly infections), and more G-CSF was needed to manage neutropenia, with cumulative use reaching 30% of patients by cycle 6, compared to 5% in the R^2 arm. Only one case of PCP was reported in the R^{2}B arm with the recommended primary antibiotic prophylaxis using co-trimoxazole and valaciclovir until recovery of CD4 T cells to >0.2x10^9/L.[16] This occurred during rituximab maintenance. No cases of varicella zoster reactivation or other opportunistic infections were observed. Taken together, the safety results of this study suggest that while R^2-based combinations merit further evaluation in phase III trials, additional toxicity may preclude further development of R^{2}B. A previously published study also highlighted the increased risk of infections in patients treated with RM after R-bendamustine in first line, which underlines the need for increased vigilance in these patients, including monitoring of the CD4 T-cell count and careful consideration of continued infection prophylaxis in patients with low CD4 T-cell counts.[18]

The treatment landscape for R/R FL has evolved considerably since the initiation of this trial and now includes CD19 CAR T-cell therapies, a novel CD19-directed monoclonal antibody (tafasitamab) and bispecific antibodies targeting CD20xCD3, such as epcoritamab and mosunetuzumab.[19,20] It has recently been shown that prior use of bendamustine could negatively affect T-cell function and impair the efficacy of chimeric antigen receptor (CAR) T-cell therapy, which could dissuade clinicians from using bendamustine-based therapies in the future.[21-23] Furthermore, novel antibodies are under investigation in combination with lenalidomide and other immunomodulatory drugs to generate effective, and potentially safer, chemotherapy-free options.[24] The combination of rituximab and lenalidomide with the novel CD19 antibody tafasitamab is a recent example of this, demonstrating safety and significantly improving PFS compared to R^2 in patients with R/R FL.[25] Novel antibodies and T-cell engaging therapies however add considerably to the cost of treatment and are therefore not (yet) widely available in various countries, as well as being associated with short- and long-term toxicities including cytokine release syndrome, neurotoxicity and infections. Comparing the R^2 arm of our study with the R^2 arm of AUGMENT, InMIND en EPCORE-FL1 is hindered by differences in baseline characteristics and treatment duration (6 cycles in our study *vs.* 12 cycles in the other studies). For example, the percentage of patients with POD24 was 18%/22% for arm A and B in our study, *versus* 31%, 32% and 38% in AUGMENT, InMind and EPCORE-FL1. There were no major differences in ORR (66% in our study *vs*. 70%, 72% and 79% for the other studies). The median PFS for our study was 29 months for the R2 arm and not reached for the R^{2}B arm, *versus* 39.4 months, 13.9 months and 11.7 months for the R^2 arm in the other studies. The higher PFS for the R^2 arm in our study and AUGMENT may be due to a more favorable selection of patients, with exclusion of rituximab-refractory cases.[17,25,26] Treatment discontinuations due to toxicity in our study were similar to those in AUGMENT, InMind and EPCORE-FL1 (*data not shown*).

An important finding in our study is that with extended follow-up we confirmed a high incidence of secondary malignancies, particularly non-melanoma skin cancer. This highlights the need for increased vigilance and routine assessment of skin lesions in all patients receiving lenalidomide-containing treatment. Previously, this was described mostly in patients with multiple myeloma receiving lenalidomide maintenance treatment.[27,28]

Our exploratory analyses of baseline TMTV and other quantitative PET-based response assessments yielded several noteworthy observations. Although more definitively demonstrated in prior larger studies,[29,30] baseline TMTV showed a trend toward prognostic value in lenalidomide-containing regimens, with high tumor burden associated with inferior outcomes across treatment arms. The stratified analysis indicates that adding bendamustine to rituximab-lenalidomide improved PFS regardless of tumor burden, while its beneficial effect on OS appeared potentially limited to patients with high TMTV. While these results are preliminary and failed to show statistical significance, probably due to the small sample size, they raise the question whether TMTV might serve not only as a prognostic biomarker, but potentially also as a predictive marker to guide therapy selection, particularly with respect to treatment intensification decisions in patients with high TMTV.

Beyond baseline TMTV, our findings also underscore the clinical relevance of employing PET-based response evaluation at EOI in relapsed FL. PET-CT can outperform conventional CT in more accurately distinguishing metabolically

inactive residual lesions from persistent viable lymphoma, thereby improving outcome prediction. The advantage of PET-CT evaluation has already been shown in other lymphomas and forms the basis for the shift from primarily CT-based to PET-based response evaluation as the current standard in diffuse large B-cell lymphoma and Hodgkin lymphoma, both in clinical trials and in clinical practice.[13,31] The main limitation of our study is the low statistical power due to slow accrual and early discontinuation of the trial. This includes limiting our ability to assess the prognostic value of TMTV which, with larger numbers, could have been evaluated as a continuous value instead of a dichotomous parameter. Additionally, the benefit of PET response assessment over CT at EOI may be underestimated. When restricting the analysis to patients who underwent both CT and PET-CT, PET-defined CMR had a higher negative predictive value (NPV) than CT-defined CR. Finally, it is important to note that the treatment landscape for R/R FL, characterized by the absence of a clear standard of care and the emergence of multiple active new drugs, challenges the design and conduct of any randomized trial of novel combinations. In this study, these factors contributed both to slow accrual and limit extrapolation of study findings to a new treatment era.

In conclusion, the combination of rituximab, lenalidomide and bendamustine is effective in relapsed FL, but, as can be expected, was associated with more toxicity than the R^2 regimen, especially more infectious complications. In countries/regions where novel immunotherapies such as T-cell engagers, chimeric antigen receptor T-cell therapy and tafasitamab are not (yet) reimbursed, or in case of medical contraindications for T-cell redirecting therapies, both R^2 and R^2B can be considered as they achieve prolonged PFS and OS. Finally, assessment of remission status by FDG PET-CT potentially improves the prognostic stratification in relapsed FL with longer PFS/EFS in patients with CMR, regardless of treatment arm, adding to the growing body of data that suggest that FDG PET-CT should be considered as the response assessment tool in patients with R/R FL.[32]

Disclosures

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Contributions

MJK, MD, KML, and JKD designed the clinical trial. DC performed the statistical analysis. MK was the central data-manager for the trial. JMZ, NT, CM, AA, and GJCZ performed the central PET review. SEW and GJCZ performed the TMTV analysis. WK, SEC, and DdJ performed the central pathology review. All other authors enrolled patients and provided data. MJK wrote the first draft of the report with input from JKD, MD, KML, DC, and JMZ, who also had direct access to the underlying data. All authors approved the final version of the manuscript.

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Data-sharing statement

The data presented in this study are available on request, check the HOVON website (www.hovon.nl) for HOVON Policy Trial Data Sharing. The data are not publicly available due to specific conditions extended by the HOVON foundation, as owner of data collected in HOVON studies.

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