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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma

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KEY POINTS

- **Chemotherapy-free VEN + R had modest efficacy and acceptable toxicity in relapsed/refractory disease warranting further study.**
- **VEN + BR led to increased toxicity; optimized chemotherapeutic dosing and/or combinations remain to be explored.**

This open-label phase 2 study (CONTRALTO) assessed the safety and efficacy of BCL-2 inhibitor venetoclax (VEN) plus rituximab (R), and VEN plus bendamustine (B) and R, vs B + R (BR) alone in relapsed/refractory (R/R) follicular lymphoma. Patients in the chemotherapy-free arm (arm A: VEN + R) received VEN 800 mg/d plus R 375 mg/m² on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 4, 6, 8, 10, and 12. After a safety run-in with VEN 600 mg, patients in the chemotherapy-containing cohort were randomized to either VEN + BR (arm B; VEN 800 mg/d for 1 year + 6 cycles of BR [B 90 mg/m² on days 1 and 2 and R 375 mg/m² on day 1]) or 6 cycles of BR (arm C). Overall, 163 patients were analyzed (9 in the safety run-in and 52, 51, and 51 in arms A, B, and C, respectively). Complete metabolic/complete response rates were 17% (arm A), 75% (arm B), and 69% (arm C). Of patients in arm B, only 61% received ≥90% of the planned B dose vs 96% of patients in arm C. More frequent hematologic toxicity resulted in more reduced dosing/treatment discontinuation in arm B vs arm C. Rates of grade 3/4 adverse events were 51.9%, 93.9%, and 60.0% in arms A, B, and C, respectively. VEN + BR led to increased toxicity and lower dose intensity of BR than in arm C, but efficacy was similar. Optimizing dose and schedule to maintain BR dose intensity may improve efficacy and tolerability of VEN + BR, while VEN + R data warrant further study. This study was registered at www.clinical trials.gov as #NCT02187861. (*Blood*. 2020;136(23):2628-2637)

Introduction

Follicular lymphoma (FL) is typically treated by combining an anti-CD20 antibody with chemotherapy, which improves response rates, progression-free survival (PFS), and overall survival compared with chemotherapy alone.[1-5] However, many patients relapse repeatedly, with progressively increasing resistance to therapy.[6,7] Use of targeted agents such as BCL-2 inhibitors may enhance antitumor therapy by acting as chemosensitizers.[8-10]

Venetoclax (VEN) is a highly selective, potent oral BCL-2 inhibitor, approved globally in multiple indications, including use in chronic lymphocytic leukemia (CLL) patients who have received ≥1 previous therapy, either in combination with rituximab (R) or as monotherapy in Europe.[11] In the United States, approval is for the treatment of adult patients with CLL or small lymphocytic lymphoma and patients with previously untreated acute myeloid leukemia who are ineligible for intensive chemotherapy, in combination with hypomethylating agents or cytarabine.[12] Preclinical data in CLL and non-Hodgkin lymphoma suggest that VEN + R or VEN + bendamustine and R (BR) may improve response compared with R or chemotherapy alone.[10,13] Early clinical data also support the safety and efficacy of VEN in FL as monotherapy or combined with BR.[13,14] The present study (CONTRALTO; NCT02187861) assessed VEN + R and VEN + BR vs BR alone in patients with relapsed or refractory FL.

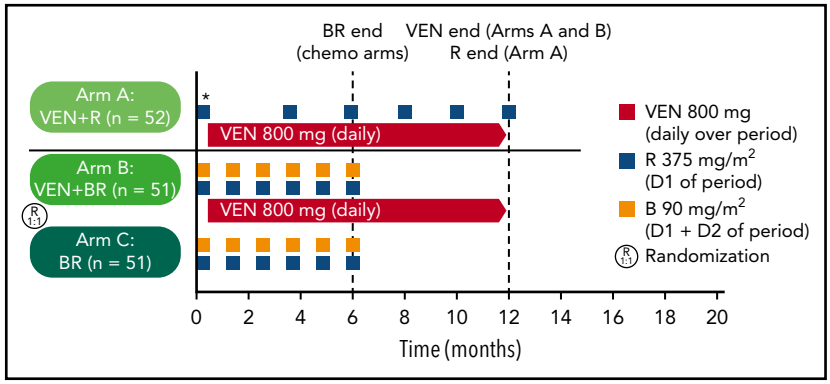

Figure 1. Dosing schedule by arm and time on study. Arm A (chemotherapy-free): VEN (800 mg daily) + R (375 mg/m^2). Arm B (chemotherapy containing): VEN (800 mg daily) + B (90 mg/m^2) + R (375 mg/m^2). Arm C (chemotherapy containing): B (90 mg/m^2) + R (375 mg/m^2). *R administered on days 1, 8, 15, and 22. Safety run-in arm (not displayed above) consisted of 9 patients that received VEN (600 mg daily for 1 year) + B (90 mg/m^2 on days 1 and 2 of each 28-day cycle) + R (375 mg/m^2 on day 1 of each cycle). D, day.

Methods

Study design and treatment

This open-label, international, multicenter phase 2 study comprised a safety run-in plus 3 treatment arms. Patients were enrolled into a chemotherapy-free (arm A: VEN + R) or chemotherapy-containing cohort at the investigator's (INV's) discretion. In the chemotherapy-containing cohort, patients were randomized 1:1 to arm B (VEN + BR) or arm C (BR only; Figure 1) using stratified permuted block randomization following a safety run-in (first 9 patients enrolled into the chemotherapy-containing cohort). Stratification was according to duration of response (DOR) to prior therapy (≤12 months/>12 months) and disease burden (high/low), according to modified Groupe d'Etude des Lymphomes Folliculaires criteria.[15] Patients enrolled to the safety run-in received VEN 600 mg orally daily during 6 28-day cycles of standard BR (B 90 mg/m^2 IV on days 1 and 2 and R 375 mg/m^2 IV on day 1) and then continued VEN alone for 1 year. Following a safety review of the safety run-in and data from another phase 1 study[13] by an internal monitoring committee and scientific oversight committee, the VEN dose for arm B during randomization was selected as 800 mg, given orally daily for 1 year, plus 6 28-day cycles of standard BR. Patients in arm C received 6 28-day cycles of standard BR. Patients chosen for arm A received VEN 800 mg orally daily + R (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 4, 6, 8, 10, and 12) for 1 year (Figure 1). VEN treatment commenced on day 1 cycle 1 in study arms A and B.

All patients received prophylaxis for tumor lysis syndrome (TLS) before first dose of VEN + R or VEN + BR, including hydration and a uric acid–reducing agent.[16]

Institutional review boards/ethics committees at all participating institutions approved the protocol. The study was conducted in accordance with International Conference on Harmonization guidelines, including Good Clinical Practice, and the principles of the Declaration of Helsinki.[17] All patients provided written informed consent.

Patient population

Eligible patients were aged ≥18 years with histologically confirmed FL (grade 1-3a); adequate coagulation, renal, and hepatic function; and had ≥1 prior FL therapy. Response duration of prior B, if received, had to be >1 year in patients receiving chemotherapy. Refractoriness to last line of prior treatment was defined as progressive disease (PD) within 6 months of last dose or no response to treatment if no PD was reported and resistance to R was defined as lack of response to or progression within 6 months of R-containing therapy. Exclusion criteria included primary central nervous system lymphoma, live vaccines within 28 days, and chemotherapy within 28 days of initiating study treatment.

Study objectives and end points

The primary efficacy objectives were to evaluate the activity of VEN + BR compared with BR and VEN + R, as measured by 18-fluorodeoxyglucose positron emission tomography (PET)-assessed complete metabolic response (CMR) rate 6 to 8 weeks after C6D1 (primary response assessment [PRA]), defined by the independent review committee (IRC) and in accordance with Lugano 2014 criteria.[18]

Secondary efficacy end points included PET-assessed CMR rate at PRA, as defined by the INV, PET-assessed CMR at 1 year from C1D1 (IRC and INV), computed tomography (CT)-assessed complete response (CR) at PRA and at 1 year from C1D1 (IRC and INV), overall response rate (ORR; IRC and INV), INV-assessed DOR (from first partial response or CR until PD or death), and PFS.

Safety objectives were to evaluate the safety and tolerability of (1) VEN 600 mg + BR in the safety run-in, (2) VEN+BR vs BR, and (3) VEN + R. Safety end points included the incidence, severity, and outcome of adverse events (AEs), changes in clinical laboratory results, and maintenance of relative dose intensity of B. Patients were followed for safety outcomes until at least 30 days after the last dose of VEN or B, at least 90 days since the last dose of R, and until study discontinuation or termination.

PET and CT imaging

Imaging at PRA and at 1 year included PET and CT scan with oral and IV contrast. Combined PET/CT scans were encouraged.

Biomarker analysis

BCL-2 immunohistochemistry (IHC) and *BCL-2* fluorescence in situ hybridization (FISH) were performed, and minimal residual disease (MRD) negativity (per million count below the limit of detection) was evaluated in peripheral blood. See supplemental Appendix (available on the *Blood* Web site) for detailed methodology.

Data analysis and statistical methods

Efficacy analyses were conducted on the intent-to-treat population (enrolled patients). The safety population comprised patients who received ≥1 dose of any study treatment. The pharmacokinetic (PK)-evaluable population comprised patients who received ≥1 dose of VEN with ≥1 PK parameter estimated using noncompartmental analysis.

CMR rate and INV-based PET and CT response rates at PRA (and corresponding 95% confidence intervals [CIs]) were constructed according to the Clopper-Pearson method.[19] The difference in CMR rates between arms B and C was calculated and the approximate 95% CI was determined using the Wald method.[20] Time-to-event end points were estimated using Kaplan-Meier methodology.[21] Cox regression and logistic regression were used for exploratory analyses of potential biomarker effects on response probability and risk of progression.

Dose intensities were calculated as (actual dose/actual time)/(planned dose/planned time) × 100%. For patients who discontinued treatment due to AEs, actual time was calculated to the time of planned treatment. For all other patients, including those with PD or those who died, actual time was calculated to the time of actual treatment.

Following an amendment to the statistical analysis plan due to the number of scans outside the prespecified window and missing data for the analysis period, an additional analysis of all available response assessments was conducted, and an extended analysis period of 42 to 65 weeks was used (see supplemental Appendix for details). Here, we focus on INV-assessed response assessment according to this updated statistical analysis plan for a more comprehensive efficacy assessment.

Expected sample size was ~156 patients (50 patients in each arm plus at least 6 patients in the safety run-in). Under a binomial distribution assumption, which was based on a 40% to 50% CMR rate as per historical BR data,[22,23] this would allow 95% CIs for estimation of CMR to have a margin of error ~15%.

Unless otherwise stated, baseline was defined as the last value obtained before the first dose of study drug.

Statistical analyses were performed using SAS version 9.4.

Results

Patient population

Patients (N = 163) were enrolled at 57 sites across 8 countries and followed between 13 November 2014 and 16 March 2018 (last patient, last visit), of whom 9 entered the safety run-in, 52 entered arm A (VEN + R), 51 entered arm B (VEN + BR), and 51 entered arm C (BR) (Figure 2). Three patients (2 in arm B and 1 in arm C) did not receive study treatment; therefore, the safety population comprised 160 patients.

Patient demographics and baseline clinical characteristics are summarized in Table 1. Demographics for patients from the safety run-in and patients who completed VEN + BR therapy are shown in supplemental Tables 1 and 2, respectively. At baseline, 120 out of 137 patients (87.6%) had BCL-2–positive disease (IHC score ≥2/3), with similar proportions noted across the study arms (Table 1). In 86 out of 106 patients with available data (81.1%), *BCL-2* rearrangement was present, with similar proportions across all study arms.

Ten patients (4 in arm A, 5 in arm B, and 1 in arm C) had received an autologous stem cell transplant (supplemental Table 3). One patient in each arm was initially treated for diffuse large B-cell lymphoma and relapsed with diagnosis of FL.

A greater proportion of VEN + R patients (arm A; 92.3%) discontinued the study compared with VEN + BR (arm B; 62.7%) or BR (arm C: 62.7%), primarily due to a higher percentage with PD (80.8% vs 37.3% and 43.2%, respectively). Four patients discontinued the study due to an AE (1, 2, and 1 in arms A, B, and C, respectively), and 6 died (3, 1, and 2 in arms A, B, and C, respectively). Overall, 80 out of 103 patients with baseline samples (77.7%) tested MRD positive and represented the MRD-evaluable cohort.

Efficacy

Per the updated statistical analysis plan described above in "Methods," INV-assessed CMR/CR rates by PET + CT at the PRA were 75% (95% CI, 60.37 to 85.67) for arm B and 69% (95% CI, 54.11 to 80.89) for arm C (difference: 5.88 [95% CI, −11.59 to 23.35], $P = .51$), and at 1 year were 43% (95% CI, 29.35 to 57.75) and 51% (95% CI, 36.60 to 65.25), respectively (difference: −7.84 [95% CI, −27.16 to 11.47], $P = .43$) (Table 2). ORR by PET + CT was 84% for both arms B and C at the PRA and 49% and 57%, respectively, at 1 year. In comparison, the INV-assessed ORR by PET + CT was lower with VEN + R (arm A) at the PRA (35%) and at 1 year (27%) (Table 2); 17% of patients in arm A reached CMR at the PRA. Response rates were higher in a subgroup of 26 patients in arm A with nonrefractory FL vs those with refractory FL (ORR as best overall response [BOR] 54% vs 19%, respectively). In a subgroup of patients who were R refractory, INV-assessed CMR/CR rates by PET + CT at the PRA were 64% (95% CI, 35.14 to 87.24) for arm B, 67% (95% CI, 43.03 to 85.41) for arm C, and 11.8% (95% CI, 1.46 to 36.44), respectively. CMR as BOR by INV-assessed PET + CT was 25% in arm A (35% in nonrefractory and 15% in refractory FL patients) (Table 2). No significant differences in response between patients with refractory and nonrefractory FL were observed in arms B and C. IRC- and INV-assessed response rates in all study arms using PET + CT scans at the PRA and after 1 year of treatment were consistent (supplemental Table 4). INV-assessed responses at 1 year in the 19 patients who completed arm B (VEN + BR) are listed in supplemental Table 5.

With median follow-up of 18 months in arms B and C, the hazard ratio (HR) for DOR for arm B vs C was 0.69 (95% CI, 0.38 to 1.27; Figure 3A); INV-assessed median PFS was similar (HR, 0.69; 95% CI, 0.38 to 1.24) (Figure 3B). Median PFS was 6.6 months for arm A. Landmark analysis of PFS is shown in supplemental Figure 1.

Nearly all patients were positive by BCL-2 IHC and by *BCL-2* FISH and negative by MCL-1 IHC (Table 1), limiting the ability to perform subgroup analysis for these biomarkers. PFS was not differentiated by BCL-XL IHC status (BCL-XL high: HR, 0.37 [95% CI, 0.11 to 1.2]; BCL-XL low: HR, 0.9 [95% CI, 0.43 to 1.9]). Analysis of response by expression of *BCL-2* family genes showed no clear differences in response between arm A, and arm B vs C (supplemental Figure 2).

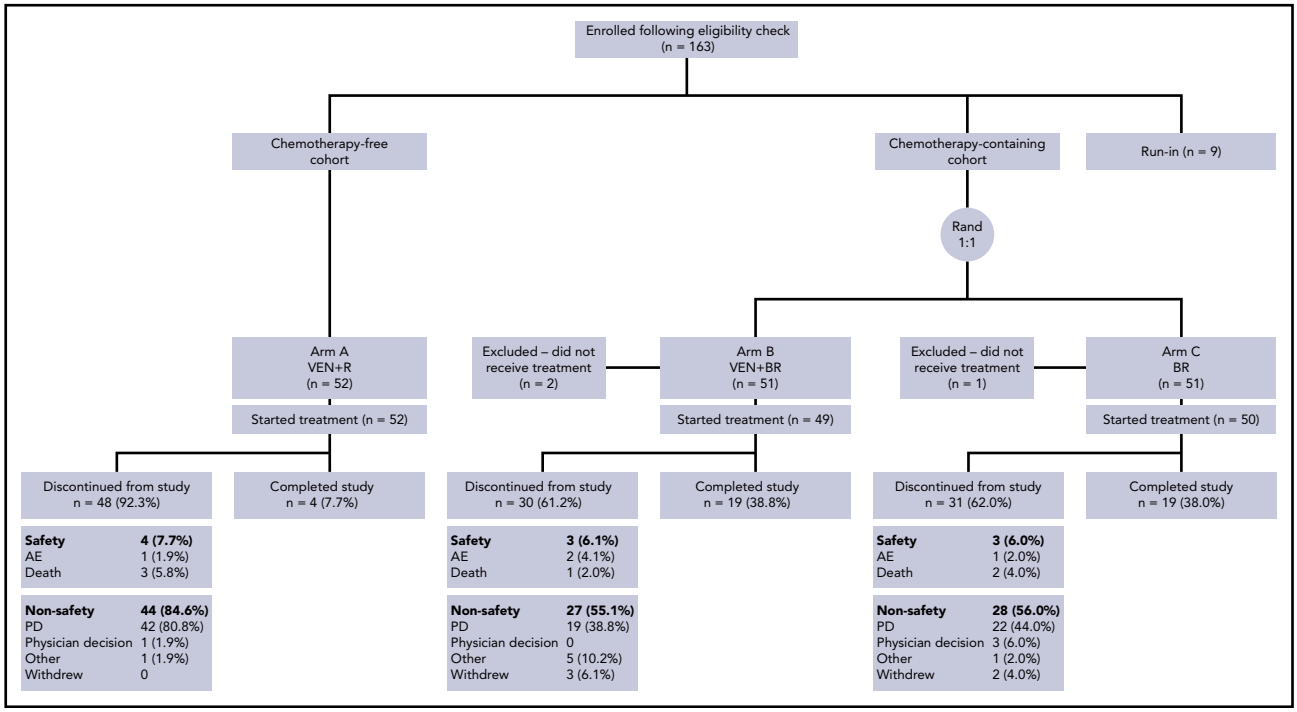

Figure 2. Patient flow. Rand, randomization.

In VEN + R responders (CMR/partial metabolic response as BOR), the rate of undetectable MRD at mid-induction (cycle 4) was 90% (9/10 MRD-evaluable patients), comparable with that of BR patients (100%; 7/7 MRD-evaluable patients).

Safety

Ninety-eight percent of patients in arm A and all patients in arms B and C had ≥1 AE (Table 3). Fifty-two patients had ≥1 serious AE, with the highest incidence in arm B (53.1%). A total of 103 patients (68.2%) had ≥1 grade 3/4 AE, most commonly neutropenia and thrombocytopenia.

In total, 41 patients (27.2%) received ≥1 course of granulocyte-colony stimulating factor for neutropenia prophylaxis: 3 (5.8%) patients in arm A, 21 (42.9%) in arm B, and 17 (34.0%) in arm C (supplemental Table 6). More patients in arm B received platelet transfusions (14.3%) compared with arm A (3.8%) and arm C (2.0%; supplemental Table 6).

Of 5 fatal AEs (Table 3), 3 were in arm A (pulmonary hemorrhage, colitis, myocardial infarction; all considered unrelated to study treatment); 1 in arm B (pneumonia, considered related to study treatment); and 1 in arm C (hypoxia in the context of pulmonary embolism, considered unrelated to study treatment).

No clinical TLS occurred. Four patients experienced grade 3/4 laboratory TLS: 1 (1.9%) in arm A and 3 (6.1%) in arm B. All patients were able to restart treatment.

AEs led to treatment discontinuation in 25 patients: 3 (5.8%) in arm A (2 VEN and 2 R discontinuations), 20 (40.8%) in arm B (17 VEN, 10 B, and 7 R discontinuations), and 2 (4.0%) in arm C (1 B and 1 B + R discontinuation). For details, see supplemental Table 7.

AE-related VEN dose modification or interruption occurred in 63 patients (20 in arm A and 43 in arm B), mostly due to neutropenia (n = 6) and diarrhea (n = 5) with VEN + R and neutropenia (n = 26) and thrombocytopenia (n = 18) with VEN + BR. Safety summaries for patients who completed VEN + BR and patients in the safety run-in are presented in supplemental Tables 8 and 9, respectively.

PK assessments

Ninety percent or more of the planned dose was received by 76.9% (VEN) and 90.4% (R) of patients in arm A; by 26.5% (VEN), 85.7% (R), and 61.2% (B) in arm B; and by 97.9% (R) and 95.8% (B) in arm C. Drug exposure data are shown in supplemental Table 10.

VEN PK parameters, available in 97 patients, were similar across arms A and B, suggesting no marked effect of BR or R co-administration (supplemental Table 11).

Discussion

CONTRALTO investigated the safety and efficacy of VEN in a chemotherapy-free regimen (VEN + R) and a B-containing regimen (VEN + BR) vs BR in patients with relapsed or refractory FL. VEN + R was associated with acceptable toxicity but modest activity. Most VEN + R–treated patients had advanced stage disease, were refractory to last treatment, or were heavily pretreated, and approximately one-third of them were refractory to R. However, responding patients had deep and sustained responses, similar to those receiving B-containing regimens. Patients receiving VEN + R who were nonrefractory to last treatment had superior response rates and MRD negativity compared with the total arm A population.

Table 1. Patient demographics and baseline clinical characteristics

Characteristic	Arm A: VEN + R (n = 52)	Arm B: VEN + BR (n = 51)	Arm C: BR (n = 51)
Median age, y (range)	63 (40-84)	66 (43-82)	61 (35-80)
Age ≥65 y, n (%)	23 (44.2)	29 (56.9)	22 (43.1)
Male, n (%)	27 (51.9)	35 (68.6)	30 (58.8)
Lymph node ≥10 cm, n (%)	5 (9.6)	4 (7.8)	7 (13.7)
Ann Arbor stage, n (%)	n = 50	n = 49	n = 51
I	2 (4.0)	5 (10.2)	4 (7.8)
II	4 (8.0)	8 (16.3)	10 (19.6)
III	9 (18.0)	13 (26.5)	7 (13.7)
IV	35 (70.0)	23 (46.9)	30 (58.8)
ECOG performance status, n (%)	n = 52	n = 48	n = 50
0	36 (69.2)	28 (58.3)	34 (68.0)
1	16 (30.8)	19 (39.6)	16 (32.0)
2	0	1 (2.1)	0
FL grade 3a, n (%)	n = 52 7 (13.5)	n = 50 7 (14.0)	n = 50 9 (18.0)
Bone marrow infiltration, n (%)	n = 51	n = 51	n = 49
Yes	18 (35.3)	19 (37.3)	13 (26.5)
No	32 (62.7)	31 (60.8)	35 (71.4)
Unknown	1 (2.0)	1 (2.0)	1 (2.0)
Extranodal involvement, n (%)			
Yes	31 (59.6)	30 (58.8)	27 (52.9)
No	21 (40.4)	21 (41.2)	24 (47.1)
Prior therapies, n			
Minimum to maximum	1-6	1-6	1-4
Median	3	3	2
Refractory* to last treatment, n (%)	26 (50.0)	19 (37.3)	23 (45.1)
Refractory to R, n (%)	17 (32.7)	14 (27.5)	21 (41.2)
Duration of prior therapy response, n (%)	n = 49	n = 51	n = 50
≤12 mo	29 (59.2)	22 (43.1)	26 (52.0)
>12 mo	20 (40.8)	29 (56.9)	24 (48.0)
Disease burden (GELF), n (%)	n = 52	n = 51	n = 51
Low	9 (17.3)	14 (27.5)	17 (33.3)
High	43 (82.7)	37 (72.5)	34 (66.7)
BCL-2 IHC evaluable, n (%)	n = 48	n = 46	n = 43
Negative (0-1)	6 (12.5)	4 (8.7)	7 (16.3)
Positive (2-3)	42 (87.5)	42 (91.3)	36 (83.7)
***BCL-2* FISH evaluable, n (%)**	n = 40	n = 33	n = 33
Negative	3 (7.5)	4 (12.1)	3 (9.1)
Positive	35 (87.5)	24 (72.7)	27 (81.8)
Undetermined	2 (5.0)	5 (15.2)	3 (9.1)
BCL-XL IHC evaluable, n (%)	n = 42	n = 46	n = 42
IHC score ≥2,3	9 (21)	15 (33)	14 (33)
MCL-1 IHC evaluable, n (%)	n = 37	n = 38	n = 38
IHC score† ≥2	0 (0)	0 (0)	2 (5)

ECOG, Eastern Cooperative Oncology Group; GELF, Groupe d'Etude des Lymphomes Folliculaires.

*Refractoriness to last line of prior treatment was defined as PD within 6 mo of last dose received or no response to treatment (if no PD was reported).

†No IHC scores ≥3 were observed for MCL-1.

Table 2. Investigator-assessed response rates in the chemotherapy-free cohort (arm A) and chemotherapy-containing cohort (arms B and C) using PET + CT scan (intent-to-treat population) and BOR in arm A (refractory and nonrefractory patient subgroups)

N (%)	Arm A: VEN + R (n = 52)	Arm B: VEN + BR (n = 51)	Arm C: BR (n = 51)
Primary response assessment*			
ORR	18 (35)	43 (84)	43 (84)
CMR/CR	9 (17)	38 (75)	35 (69)
95% CI (Clopper-Pearson)	8.23, 30.33	60.37, 85.67	54.11, 80.89
Difference (95% CI)	NA	5.88 (−11.59 to 23.35), $P = .51$	
PMR/PR	9 (17)	5 (10)	8 (16)
NMR/SD	7 (14)	0	1 (2)
PMD/PD	23 (44)	2 (4)	5 (10)
Response data missing†	3 (6)	4 (8)	2 (4)
1 y follow-up‡			
ORR	14 (27)	25 (49)	29 (57)
CMR/CR	10 (19)	22 (43)	26 (51)
95% CI (Clopper-Pearson)	9.63, 32.53	29.35, 57.75	36.60, 65.25
Difference (95% CI)	NA	−7.84 (−27.16 to 11.47), $P = .43$	
PMR/PR	4 (8)	3 (6)	3 (6)
NMR/SD	3 (6)	0	0
PMD/PD	32 (62)	12 (24)	15 (29)
Response data missing†	3 (6)	14 (28)	7 (14)

BOR, n (%)	Arm A: VEN + R (n = 52)	Arm A: VEN + R refractory§ (n = 26)	Arm A: VEN + R nonrefractory§ (n = 26)
ORR	19 (37)	5 (19)	14 (54)
CMR	13 (25)	4 (15)	9 (35)
PMR	6 (12)	1 (4)	5 (19)
NMR	6 (12)	4 (15)	2 (8)
PD	13 (25)	6 (23)	7 (27)
Response data missing†	14 (27)	11 (42)	3 (12)

NA, not applicable; NMR, no metabolic response; PMR, partial metabolic response; PR, partial response; SD, stable disease.

*Primary response evaluated from mid-induction visit to 10 weeks after C6D1 or 10 weeks after day 1 of the last cycle.

†Includes off study early for toxicity, off study early for not meeting inclusion/exclusion criteria, off study for death, withdrawal of consent, or unreadable scans. Responses were evaluated by PET/CT scan first; if missing, CT scan response was imputed. All patients with PD prior to or during the observation period were included as PD.

‡The 12-month responses were evaluated 42 to 65 weeks after C1D1.

§Refractoriness to last line of prior treatment was defined as PD within 6 months of last dose received or no responses to treatment (if no PD was reported).

Arms B and C showed similar CMR/CR rates and response durability; however, toxicity was higher with VEN + BR than with BR. More patients receiving VEN + BR than BR withdrew from study treatments or underwent dose modification, driven by hematologic and gastrointestinal toxicities. Only 27% of patients achieved ≥90% VEN dose intensity in the VEN + BR arm, showing the limited tolerability of this regimen at the given dose and schedule. It is worth noting that patients in arm C on average were younger and had fewer prior lines of therapy compared with arm B. Indeed, the heavier pretreatment history of patients in arm B vs C may have had a compounding effect on the efficacy and tolerability/safety of VEN + BR. Despite the increased toxicity in arm B vs C, leading to lower BR exposure, similar efficacy outcomes were seen between the 2 arms. Further investigation is needed to determine the optimal dose and schedule of BR in combination with VEN for relapsed or refractory FL in order to maximize efficacy while minimizing toxicity. Indeed, the combination of VEN plus other chemotherapy regimens may offer a different safety profile and is worthy of further exploration.

The most important toxicities in the VEN-containing arms were grade 3/4 neutropenia and thrombocytopenia. The rate of neutropenia in the VEN + BR arm was similar to previously reported data for BR.[24] The rate of thrombocytopenia in the VEN + BR arm was notably higher than previously reported for BR.[24,25] Incidences of gastrointestinal toxicities were consistent with the safety profile of VEN in other trials.[14,26-29] TLS risk was mitigated by prophylaxis, and no cases of clinical TLS were reported. No new safety signals were reported with VEN treatment.

Limitations of the study design and conduct preclude precise conclusions on the efficacy of adding VEN to BR or R, but the benefit should not be dismissed. The dosing schedule used in this study was based on encouraging results from the phase 1 study,[14] with doses as high as 1200 mg and also clearing the safety run-in. However, more toxicity was seen in the current study with the VEN + BR combination, and this led to increased dose modification. In the CAVALLI study, VEN was administered on a noncontinuous dosing schedule in combination with R plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in diffuse large

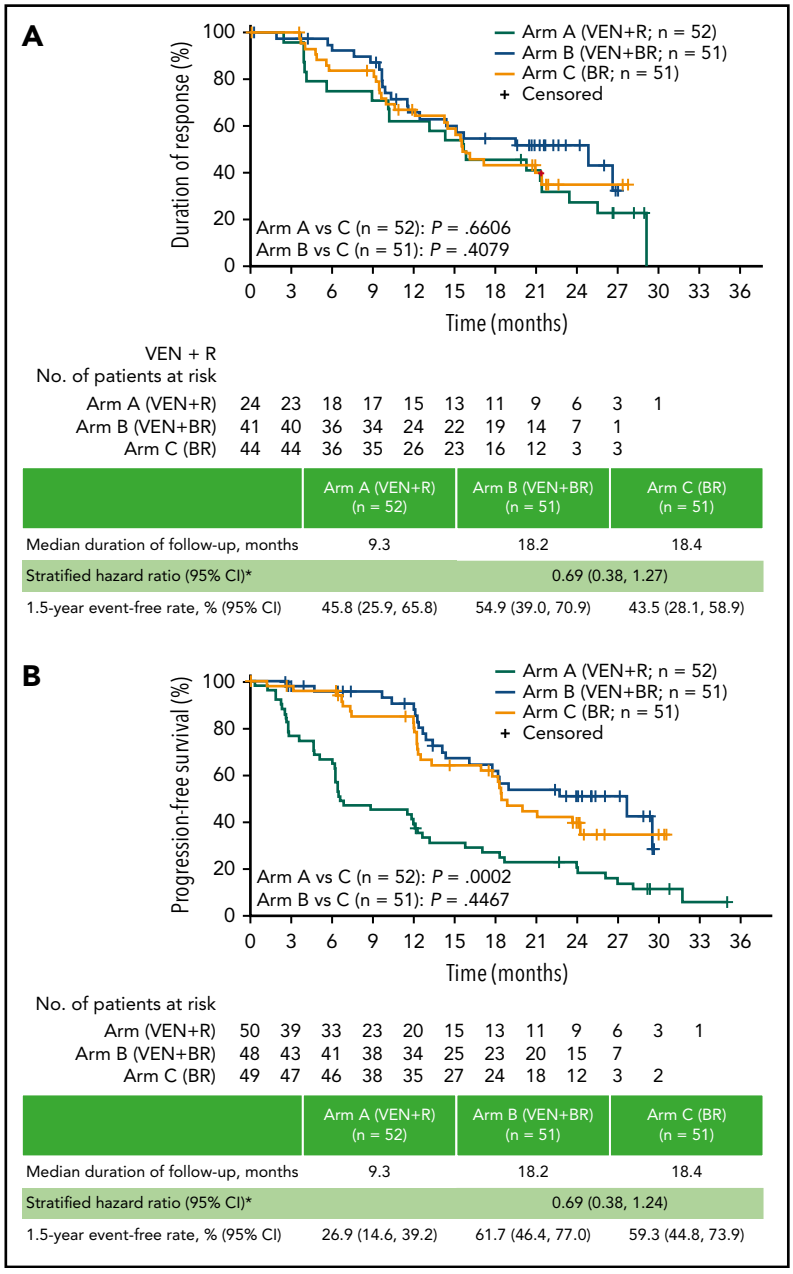

Figure 3. Kaplan-Meier plot of DOR and PFS. DOR (A) and PFS (B) *Stratified by DOR to prior therapy (≤12 months/>12 months) and disease burden (high/low), according to modified Groupe d'Etude des Lymphomes Folliculaires criteria.[15]

B-cell lymphoma and FL patients.[30,31] On this schedule, VEN was associated with a higher rate of AEs; however, R-CHOP dose intensity was maintained at a similar rate to the historical comparator (R-CHOP arm of the GOYA study[32]) with improved efficacy in the BCL-2–positive population.[31] While comparisons are limited by different chemotherapy backbones, they highlight the potential of intermittent VEN administration over a longer treatment period to improve efficacy and tolerability of chemotherapy combination regimens. An important limitation of the protocol was the lack of mandatory guidance on dose reduction and discontinuation, and doses were modified at the INV's discretion at a higher rate than the historical comparator. Furthermore, VEN treatment was limited to 1 year, whereas targeted therapies have typically been administered until progression in other trials.

In conclusion, our data suggest that further investigation is warranted to confirm the clinical effects of adding VEN to chemoimmunotherapy regimens or monoclonal antibodies in FL patients. In particular, optimization of VEN dosing and scheduling is needed, perhaps with noncontinuous dosing schedules being of particular interest in distinct populations. Several studies are now underway exploring VEN in various combination strategies in FL patients (NCT02956382, NCT03113422, NCT03135262, NCT02611323, and NCT02877550), with both continuous and noncontinuous schedules being assessed in first-line and relapsed/refractory settings. Notably, a phase 2 study is exploring obinutuzumab + B in combination with a noncontinuous dosing schedule of VEN (induction therapy) in previously untreated patients with high tumor burden FL (NCT03113422). The results of this study will help clarify how best to deliver VEN in B-containing regimens to maximize efficacy. The potential of VEN + R as a chemotherapy-free option for patients with nonrefractory FL also merits further exploration, particularly in earlier-line or frail populations who cannot tolerate chemotherapy. In addition, further

Table 3. Summary of safety (safety population)

	Arm A: VEN + R (n = 52)	Arm B: VEN + BR (n = 49)	Arm C: BR (n = 50)
Total number of AEs	425	936	502
Patients with ≥1 event, n (%)			
Any grade AE	51 (98.1)	49 (100.0)	50 (100.0)
Grade 3/4 AE	26 (50.0)	45 (91.9)	29 (58.0)
AE with fatal outcome (grade 5)	3 (5.8)	1 (2.0)	1 (2.0)
SAE	16 (30.8)	26 (53.1)	10 (20.0)
AE leading to dose modification/ interruption from any treatment	30 (57.7)	44 (89.8)	21 (42.0)
AE leading to VEN dose modification/ interruption	20 (38.5)	43 (87.8)	NA
AE leading to withdrawal from any treatment	3 (5.8)	20 (40.8)	2 (4.0)
AE leading to withdrawal of VEN	2 (3.8)	17 (34.7)	NA
All AEs occurring in ≥20% of patients in any treatment arm, n (%)			
Nausea	14 (26.9)	32 (65.3)	22 (44.0)
Neutropenia	14 (26.9)	30 (61.2)	17 (34.0)
Thrombocytopenia	7 (13.5)	28 (57.1)	8 (16.0)
Diarrhea	21 (40.4)	24 (49.0)	11 (22.0)
Vomiting	7 (13.5)	24 (49.0)	13 (26.0)
Fatigue	13 (25.0)	21 (42.9)	15 (30.0)
Anemia	3 (5.8)	19 (38.8)	7 (14.0)
Infusion-related reaction	18 (34.6)	10 (20.4)	7 (14.0)
Constipation	5 (9.6)	10 (20.4)	17 (34.0)
Cough	6 (11.5)	12 (24.5)	12 (24.0)
Pyrexia	5 (9.6)	10 (20.4)	9 (18.0)
Hypokalemia	6 (11.5)	13 (26.5)	4 (8.0)
Decreased appetite	5 (9.6)	10 (20.4)	6 (12.0)
Grade 3/4 AEs occurring in ≥10% of patients in any treatment arm, n (%)			
Neutropenia	13 (25.0)	29 (59.2)	14 (28.0)
Thrombocytopenia	4 (7.7)	22 (44.9)	3 (6.0)
Anemia	3 (5.8)	7 (14.3)	1 (2.0)
Leukopenia	2 (3.8)	5 (10.2)	2 (4.0)
Febrile neutropenia	0	6 (12.2)	3 (6.0)
Vomiting	0	5 (10.2)	0
Hypokalemia	1 (1.9)	6 (12.2)	1 (2.0)
SAEs occurring in ≥3% of patients in any treatment arm, n (%)			
Febrile neutropenia	0	6 (12.2)	3 (6.0)
Pneumonia	2 (3.8)	3 (6.1)	0
Pneumocystis jirovecii pneumonia	0	3 (6.1)	0
Myelodysplastic syndrome	0	3 (6.1)	0
Lung infection	0	2 (4.1)	1 (2.0)
Cellulitis	0	0	2 (4.0)
Increased blood lactate dehydrogenase	2 (3.8)	0	0

SAE, serious AE.

investigation of predictive markers of VEN efficacy in FL is warranted.

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Authorship

Contribution: All authors were involved with the acquisition of the data; contributed to the analysis and interpretation of the data; provided administrative, technical, or material support or were involved with study supervision; and participated in manuscript development and final approval.

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Footnotes

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The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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