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Phase II study of venetoclax added to bendamustine and obinutuzumab in patients with high-risk follicular lymphoma as front-line therapy: PrE0403

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Over-expression of BCL-2 defines follicular lymphoma (FL). Venetoclax (VEN), a selective BCL-2 inhibitor, has previously been evaluated with bendamustine-based chemoimmunotherapy. VEN was given continuously, resulting in promising efficacy but unacceptable toxicity. The Phase II PrE0403 study was designed to evaluate intermittent dosing of VEN (10 days per cycle) combined with obinutuzumab and bendamustine (VEN-OB) in untreated FL subjects with high-risk features defined as a FLIPI-1 score of ≥3 and/or high tumor burden by GELF criteria. A total of 56 subjects were planned to be accrued with a goal of having 51 subjects eligible to improve the historical 50% CR rate to 65% with an 85% power and 15% type I error rate. Immunohistochemistry (IHC) expression of 3 antiapoptotic proteins (BCL-xL, MCL-1, and BCL-2) was performed and correlated with clinical outcomes. All 56 subjects were eligible and treated. CR rate was 41/56 (73.2%) and ORR was 52/56 (92.5%) meeting the primary endpoint. 2-year estimated PFS was 87.5% (90% CI: 75.3,93.9%) and 2-year estimated OS was 94.6% (90% CI: 86.7, 97.9%). However, the incidence of treatment-related adverse events ≥ grade 3 was 83.9% and serious adverse events were seen in 57.1%. After induction, atypical infections, including Grade 5 events, occurred. Anti-apoptotic protein expression by IHC was not correlated with clinical outcomes. Thus, while meeting the primary efficacy end point, VEN-OB is considered overly toxic in high-risk FL.

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INTRODUCTION

Follicular lymphoma (FL) is an indolent form of non-Hodgkin lymphoma with an incidence rate of 13,000-15,000 new cases per year in the United States [1]. FL can often be observed at diagnosis, particularly if asymptomatic and with low tumor burden by GELF criteria [2]. Treatment with chemoimmunotherapy is often considered when patients meet high tumor burden by GELF criteria [2] or have a high FLIPI score [3].

Translocation between the immunoglobulin heavy chain gene promoter/enhancer on chromosome 14 and the antiapoptotic gene, *BCL2*, on chromosome 18, is the genetic hallmark of FL and results in over-expression of the BCL-2 oncoprotein. Venetoclax (VEN) is a selective, orally bioavailable, small molecule inhibitor of BCL-2. Single agent activity of VEN is low in FL (ORR 38%) [4] and when VEN was combined with rituximab there was no change in response rate (ORR 35%) [5]. In one arm of the CONTRALTO study, chemotherapy with bendamustine was combined with VEN and rituximab in relapsed FL [5]. VEN was given continuously at 800 mg with each cycle of chemoimmunotherapy. A high rate of non-completion of chemotherapy cycles due to an overly high rate of adverse events was seen for this regimen. ORR with the combination was promising at 84%, however, response rates were similar to the arm treated with bendamustine and rituximab without VEN. Further, the bendamustine, rituximab, VEN arm had only 64% of patients receiving at least 90% dose intensity. Thus, modifications to the treatment schema were thought to be needed to improve tolerance.

It was hypothesized that intermittent dosing of VEN would be better tolerated than continuous dosing when given in combination. Pre-clinical studies suggest that VEN can induce chemotherapy sensitization [6, 7], thus rationalizing the dosing around chemotherapy administration. At the time of study conception, given promising early studies with obinutuzumab [7] and an improved pre-clinical activation of antibody dependent cytotoxicity over rituximab [8], obinutuzumab was chosen to partner with the standard chemotherapy backbone of bendamustine [9]. Thus, we conducted a Phase II study evaluating VEN given intermittently with obinutuzumab and bendamustine (VEN-OB) in PrE0403.

SUBJECTS AND METHODS

Ethics approval and consent to participate

The PrE0403 study was conducted in 10 US centers and was approved by Institutional Review Boards at each institution. Institutional Review Board

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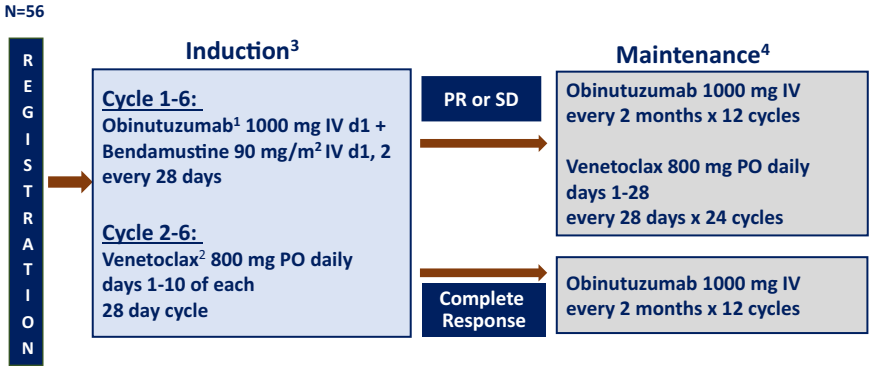

Fig. 1 Final Treatment Schema. [1] Cycle 1 only: Obinutuzumab 100 mg IV day 1 and 900 mg on day 2 followed by day 8 and day 15, 1000 mg IV. [2] In the initial design VEN 800 mg PO daily D1-10 was given with cycle 1. Due to high rate of laboratory TLS in first 21 patients, the study was amended to give venetoclax at cycle 2 through 6 only. [3] Growth Factor was required during induction cycles. [4] Maintenance phase begins 8-12 weeks after induction. Maintenance for 2 years after induction.

names and registration numbers are listed in the supplement. All potential subjects signed informed consent prior to enrollment, and the study was conducted according to the International Conference of Harmonization guidelines for Good Clinical Practice. The study was registered at clinicaltrials.gov, number NCT03113422.

Eligibility

Patients ≥ 18 years of age with biopsy proven FL were eligible if they had either high tumor burden by GELF [2] or high risk by FLIPI-1 (≥ 3 risk factors) [3]. Potential subjects were required to be at least stage II and have good performance status (ECOG 0-2) with adequate organ function. Prior treatment for FL was not allowed, except for a short course of steroids for symptomatic control.

Treatment Plan

Eligible subjects were treated with obinutuzumab 1000 mg IV day 1 and bendamustine 90 mg/m^2 IV day 1 and 2 every 28 days for 6 cycles. With the first cycle of treatment, Obinutuzumab 1000 mg was given as split dose on D1 (100 mg) and D2 (900 mg) as well as D8 and D15. Fixed dose VEN was given at 800 mg PO daily, without dose ramp up with C1, on days 1-10 of each cycle. Monitoring for tumor lysis syndrome (TLS) was performed after completion of bendamustine and rituximab, approximately 6-8 h after venetoclax dosing on day 1 and prior to treatment on day 2 during cycle 1. Chemotherapy and TLS monitoring with C1 could have been performed in the hospital, per investigator discretion; however, no patients were admitted for TLS monitoring with C1. On planned interim analysis, a high rate of laboratory TLS was identified (38%, 8 of 21 subjects) during cycle 1 and the study was amended for the subsequent 36 patients to receive VEN 800 mg PO daily on days 1–10 for cycles 2-6 only.

After completion of induction therapy, maintenance obinutuzumab at 1000 mg IV every 2 months for 2 years or 12 doses was planned to start 8–12 weeks after completing induction for all responding or stable patients. For those that only achieved a partial response (PR) or stable disease (SD), VEN 800 mg PO daily was planned for two years in addition to obinutuzumab. Treatment schema is presented in Fig. 1.

Allopurinol was not required, but allowed if the risk of TLS was thought to be higher than that of Stevens-Johnson Syndrome when given with bendamustine [10]. IV and oral hydration was mandated per protocol. Rasburicase was allowed per institutional standards. Primary prophylaxis with granulocyte stimulating growth factors was administered in all subjects. Viral and *Pneumocystis jiroveci* (PJP) prophylaxis was not mandated at study initiation, but after atypical infections developed, these were mandated on amendment.

Statistical design

The primary objective of the study was to improve the historical induction CR rate of obinutuzumab and bendamustine from 50% to 65% with the addition of VEN. Historical CR rate was based on results from EA2408 (bendamustine and rituximab in frontline FL) [11] and GADOLIN (bendamustine and obinutuzumab in relapsed NHL) [12]. CR was assessed after induction therapy and defined per Lugano criteria [13] including negative bone marrow biopsy, if bone marrow was involved at screening. To achieve a power of 85% with a 15% type I error (using a binomial test) to test the hypothesis of improved CR rate with VEN, 51 eligible subjects were needed; the null hypothesis was to be rejected and this regimen considered promising if 30 or more subjects achieve a CR. To allow for 10% ineligibility, the study planned to enroll 56 subjects overall.

Secondary objectives included overall response rate (ORR), conversion of PR patients to CR with maintenance therapy, progression-free and overall survival (PFS and OS), and adverse events. Efficacy analysis for the primary objective included all eligible and treated patients. Kaplan-Meier method was used to estimate and visualize PFS and OS. Subjects were followed for a minimum of 2 years for progression and survival outcomes.

A planned safety analysis, assessing all treatment-related grade 3 or higher AEs and AEs in specific categories, was performed after the first 21 subjects were treated and received 3 cycles of therapy. Data cut off for final analysis was May 2023.

Expression of antiapoptotic proteins

At screening, formalin fixed paraffin embedded (FFPE) tumor specimens were analyzed by traditional immunohistochemistry (IHC) methods to assess for expression of three antiapoptotic proteins, BCL-2, BCL-xL and MCL-1. Each specimen was assessed for the proportion of cells with positive staining along with the corresponding intensity of staining, and a traditional H-score [14] was then calculated. Correlations between the markers were analyzed with Spearman's correlations.

See Supplement for further IHC methods.

RESULTS

Subject enrollment, characteristics and treatment

Fifty-seven subjects with untreated follicular lymphoma were enrolled from December 2017 to November 2020 and all 57 were eligible. One eligible subject withdrew consent prior to starting treatment. Fifty-six eligible and treated subjects were included in safety and efficacy assessments. Subject characteristics are listed in Table 1. Ninety-six percent of subjects were high tumor burden by GELF.

Figure 2 shows patient flow through the study. Eleven subjects did not complete 6 cycles of VEN-OB and 11 did not start maintenance therapy. Only 5 subjects completed all 12 cycles of maintenance therapy (Supplement Table 1). Reasons for discontinuation are presented in Fig. 2.

Efficacy assessments

The observed CR rate with VEN-OB induction was 73.2% (41/56), achieving the primary endpoint. ORR was 92.9% (52/56) with 11 subjects (19.6%) achieving PR, and 1 subject (1.8%) achieving stable disease (SD). Of the 12 patients with PR or SD, 4 (33.3%) did not undergo maintenance due to investigator discretion ($n = 1$), AE [$n = 2$], or disease progression [$n = 1$], and 1 (8.3%) underwent maintenance but stopped treatment prior to disease assessment.

Table 1. Baseline Characteristics.

	N = 56	(%)
Median Age in Years (range)	62 (33–79)	
Sex		
Male	35	62%
Female	21	38%
Race		
Asian	1	2%
Black	5	9%
White	50	89%
ECOG Performance Status		
0	35	62%
1	21	38%
Histologic Grade		
I/II	42	75%
IIIa	9	16%
Missing	5	9%
Ann Arbor Stage		
II	2	4%
III	16	29%
IV	38	68%
B-symptoms present		
Yes	21	38%
Risk Profile		
High Tumor Burden by GELF	54	96%
High Risk FLIPI-1 (≥3)	33	59%
*HTB GELF AND High risk FLIPI-1	30	54%

Thus, 7 (58.3%) were evaluable for improvement in response with maintenance; 3 of these 7 received obinutuzumab only due to prior AEs with VEN and 4 of the 7 received both obinutuzumab and VEN maintenance. Three of these 7 converted from PR to CR, and the single patient with SD converted to PR. The 4 subjects with deepening response were evenly split between receiving obinutuzumab only ($n = 2$) and obinutuzumab and VEN ($n = 2$) maintenance.

At the time of data cut-off, median (Q1, Q3) follow up was 34.9 months (29.3, 43.6) and all subjects had completed planned 2 year follow up. The estimated 2-year (90% confidence interval) PFS and OS were 87.5% (75.3, 93.9%) and 94.6% (86.7, 97.9%). (see Fig. 3).

Adverse events

Table 2 lists Treatment Related Adverse events (TRAEs) occurring in ≥10% of subjects during induction and maintenance. Of note, laboratory TLS was observed in 8 of 21 (38.1%) subjects at planned interim analysis, when VEN was administered with cycle 1. All episodes of TLS were laboratory; no clinical TLS was seen [15]. After amending the protocol to initiating VEN with C2, no TLS was identified in the 35 additional treated subjects.

All but 1 subject experienced a TRAE of any grade and 83.9% (90% CI: 73.6; 91.4%) (47/56) developed a Grade ≥ 3 TRAE during induction therapy. Excluding the expected AE of lymphopenia, Grade ≥3 TRAE of any grade was 75% (42/56) during induction therapy. Serious adverse events (SAE) occurred in 32 (57.1%) unique subjects during induction. Of the 34 subjects who entered maintenance therapy, 14.7% ($n = 5$) did not experience any TRAE while 85.3% (90% CI: 71.5, 94.0) (29/34) developed Grade ≥ 3 TRAE and 16 (47.1%) unique patients experienced a SAE.

Four atypical infections were noted at the end of induction or during maintenance therapy. One subject developed PJP at the end of treatment, prior to maintenance therapy and subsequently developed a Grade 5, cytomegalovirus (CMV) encephalitis event thought to be related to treatment. At the time of this event, the

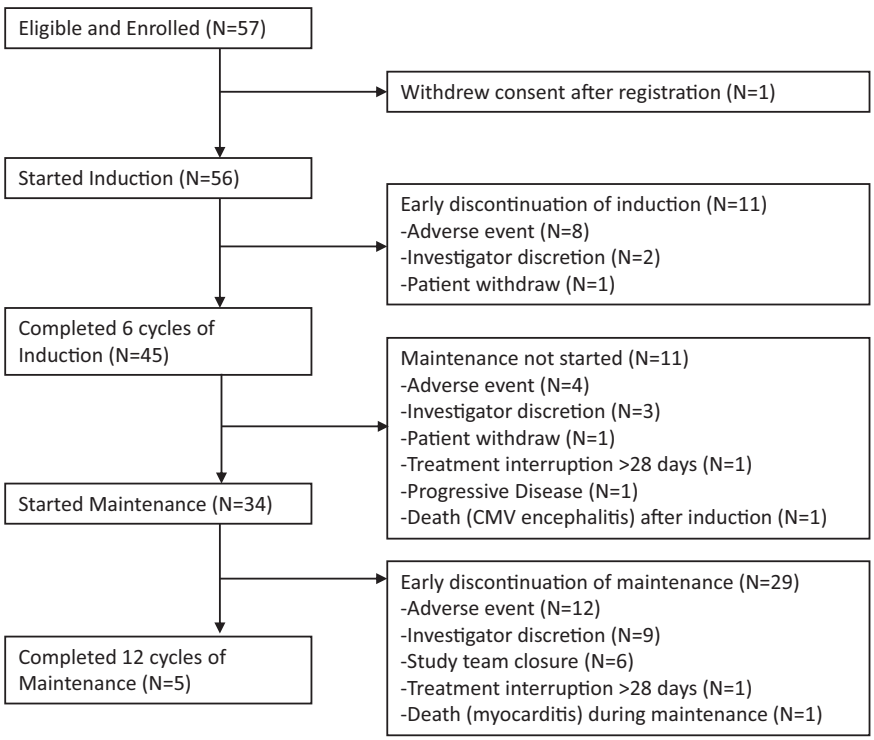

Fig. 2 Subject flow diagram. Flow of all subjects that signed consent through the course of study including reasons for stopping protocol treatment early.

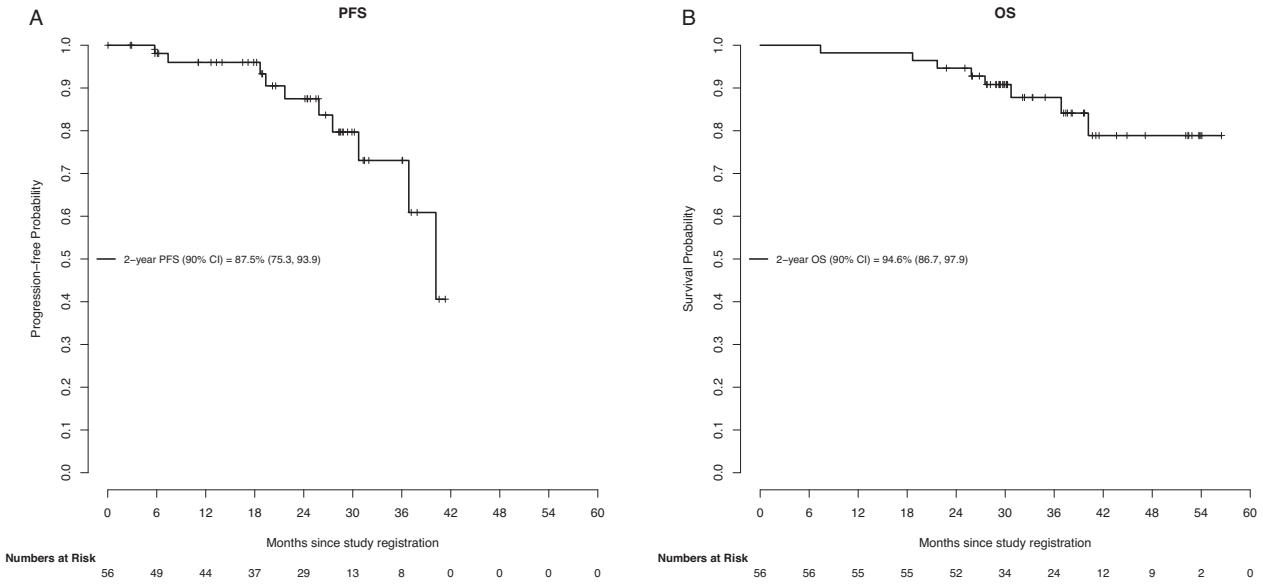

Fig. 3 Survival curves. Progression free (**A**) and Overall Survival (**B**) for all patients treated on protocol ($N = 56$); Median (Q1,Q3) follow up of 34.9 months (29.3mo, 43.6mo); 2 year PFS (90% CI) was 87.5% (75.3%, 93.9%) and 2 year OS (90% CI) was 94.6% (86.7%, 97.9%).

study was modified to monitor for CMV and mandate PJP prophylaxis and anti-viral prophylaxis per institutional standards. No additional CMV infections were identified following the amendment. Another subject developed a Grade 3 PJP event during cycle 3 of maintenance obinutuzumab while on PJP prophylaxis (Bactrim) for 6 months. One subject developed a Grade 4 BK virus nephropathy after cycle 6 of maintenance obinutuzumab, which resulted in end stage renal disease and chronic dialysis. Finally, a Grade 5 myocarditis event, suspected, but not proven to be viral related, occurred in a participant after 8 cycles of maintenance obinutuzumab and 18 months of maintenance venetoclax. After the Grade 5 myocarditis event occurred, all subjects had finished induction and only 7 remained on maintenance. After discussion with the study team, it was decided to discontinue maintenance therapy for all study participants (see Fig. 2).

Immunohistochemistry analysis

Formalin fixed paraffin embedded (FFPE) tumor specimens were available for 47 of 56 study participants. IHC data was missing in 3 for BCL-xL and 1 for MCL-1. Thus, the effective sample size for BCL-2, BCL-xL, and MCL-1 analysis was 47, 44, and 46, respectively. As expected, the vast majority of tumor samples showed robust BCL-2 expression by IHC, with 94% having an H-score of ≥80% (median 210%; range 0–297%). BCL-xL was also highly expressed, with 70% of samples having an H-score of ≥80% (median 106.5%; range 0–180%). Meanwhile, MCL-1 staining was more often minimal to absent (median 11.5%; range 0–189%). (see Fig. 4). H-score correlations were weak between the three proteins. Spearman's correlation between BCL-2 and BCL-xL was -0.20; between BCL-2 and MCL-1 was -0.19; and between BCL-xL and MCL-1 was 0.40.

Correlations with clinical outcomes (CR rate, median PFS, and 2 year OS) were assessed for five different H-scores, including those of the individual antiapoptotic proteins (BCL-2, BCL-xL, and MCL-1) as well as the summed H-score for the non-BCL-2 proteins (BCL-xL and MCL-1) and the summed H-score for all antiapoptotic proteins combined (BCL-xL, MCL-1, and BCL-2) (see supplement Table 2). There was no correlation seen between CR rate for the 5 different assessments, possibly due to the high overall CR rate observed in this study. Further, as described above, BCL-2 and BCL-xL were both expressed at high levels in the vast majority of tumors, thereby limiting the variability between samples. Finally, our immunohistochemical analysis employed a single antibody to assess BCL-2 expression, and there remains the potential for false negative staining due to the impact of somatic hypermutation on the *BCL2* locus and resultant loss of antibody recognition [16].

Cut-offs for high and low H-scores were non-linear for BCL-xL, MCL-1 and the sum of all antiapoptotic proteins. Associations with median PFS were seen for the H-scores of MCL-1 and the sum of all antiapoptotic proteins, utilizing the optimal (non-linear) cut-offs. For both values, higher H-scores were associated with longer median PFS (see supplemental Table 2). Associations with 2-year OS were observed for the sum of all antiapoptotic proteins H-score using both the median cutoff and the optimal cut-off. In both instances, higher H-scores were associated with improved 2-year OS (see supplemental Table 2).

DISCUSSION

VEN-OB is a highly effective treatment for high-risk FL, achieving a PET negative, bone marrow biopsy negative CR rate of 73.2% which met our primary objective in this phase II study. At the time of study design, the GALLIUM data [17, 18] was not available, thus our historical controls included the control arm of EA4208 (bendamustine and rituximab in frontline FL) [11] and the GADOLIN study (bendamustine obinutuzumab in relapsed FL) [12]. The final analysis of the continuous Venetoclax plus bendamustine and rituximab arm of CONTRALTO in relapsed disease had a PET negative CR rate of 75% [5]. Responses seemed durable with a 2-year PFS of 87.9%. The current study showed a similar CR rate and 2-year PFS rate. However, in both our study and CONTRALTO, the induction treatment was poorly tolerated. GI toxicities, including nausea, vomiting and diarrhea were common, though typically low grade. Cytopenias were also common with up to one third of subjects experiencing thrombocytopenia or neutropenia. Neutropenia occurred despite mandated granulocyte colony stimulating factor prophylaxis. Grade ≥ 3 TRAE occurred in 83.9%, which is numerically higher than that seen in the bendamustine and obinutuzumab arm of GALLIUM at 69% [17] and only slightly less than that seen with continuous VEN in CONTRALTO at 94% [5]. Thus, intermittent dosing of VEN with bendamustine and obinutuzumab did not seem to meaningfully improve tolerability when compared to continuous dosing.

GALLIUM, which assessed chemoimmunotherapy with rituximab vs. obinutuzumab in frontline FL, showed an overall PET-CR

Table 2. Incidence of adverse events during induction or maintenance occurring in ≥ 10% of subjects.

	Induction ($N = 56$)		Maintenance ($N = 34$)	
Event (n)	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Non-Hematologic				
Nausea	46 (82.1%)	3 (5.4%)	1 (2.9%)	1 (2.9%)
Fatigue	34 (60.7%)	3 (5.4%)	4 (11.1%)	0 (0%)
Vomiting	26 (46.4%)	2 (3.6%)	1 (2.9%)	1 (2.9%)
Diarrhea	24 (42.9%)	2 (3.6%)	5 (14.7%)	1 (2.9%)
Headache	16 (28.6%)	0 (0%)	0 (0%)	0 (0%)
Decreased Appetite	15 (26.8%)	1 (1.8%)	0 (0%)	0 (0%)
Infusion related reaction	11 (19.6%)	3 (5.4%)	0 (0%)	0 (0%)
Hyperuricemia	10 (17.9%)	3 (5.4%)	0 (0%)	0 (0%)
AST/ALT increase	10 (17.9%)	0 (0%)	0 (0%)	0 (0%)
Constipation	10 (17.9%)	0 (0%)	1 (2.9%)	0 (0%)
Upper respiratory infection	9 (16.1%)	0 (0%)	9 (26.5%)	0 (0%)
Tumor Lysis Syndrome[a]	8 (14.3%)	8 (14.3%)	0 (0%)	0 (0%)
Abdominal Pain	8 (14.3%)	1 (1.8%)	0 (0%)	0 (0%)
Alkaline Phosphatase increase	7 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Dysgeusia	7 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	7 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Pyrexia	7 (12.5%)	0 (0%)	0 (0%)	0 (0%)
COVID-19 infection	1 (1.8%)	0 (0%)	3 (8.8%)	3 (8.8%)
Pneumonia	1 (1.8%)	1 (1.8%)	4 (11.1%)	3 (8.8%)
Sinusitis	1 (1.8%)	0 (0%)	5 (14.7%)	0 (0%)
Atypical infection[b]	2 (3.6%)	2 (3.6%)	4 (11.1%)	4 (11.1%)
Hematologic				
Thrombocytopenia	23 (41.1%)	8 (14.3%)	6 (17.6%)	1 (2.9%)
Neutropenia	21 (37.5%)	9 (16.1%)	7 (20.5%)	5 (14.7%)
Anemia	12 (21.4%)	1 (1.8%)	3 (8.8%)	0 (0%)
Lymphocyte Count Decreased	17 (30.4%)	16 (28.6%)	7 (20.5%)	4 (11.8%)
Overall Adverse Events Gr ≥ 3		47 (83.9%)		19 (55.9%)
Serious Adverse Events[c]	32 (57.1%)		16 (47.1%)	

[a]TLS was closely monitored in C1: 8/21 participants developed [laboratory] TLS when VEN was administered in C1; no clinical TLS was seen; 0/35 when VEN began in C2, although reporting criteria were also revised.
[b]Atypical infections during induction include: fungal infection ($n = 1$), CMV encephalitis ($n = 1$), during maintenance include: Pneumocystis pneumonia ($n = 1$), polyomavirus nephropathy ($n = 1$), bronchopulomonary aspergillosis ($n = 1$), and myocarditis ($n = 1$).
[c]SAEs during induction in >1 subject: Tumor lysis syndrome ($n = 8$, see text), Nausea/Vomitting ($n = 4$), pneumonia ($n = 3$), Viral infection ($n = 3$, including Gr5 CMV, see text), Back pain/myalgia ($n = 3$), neutropenia ($n = 2$), chest pain ($n = 2$). SAEs during maintenance in >1 subject: pneumonia ($n = 4$), COVID-19 ($n = 3$).

rate for the obinutuzumab group of 78.8% [19]. Three-year PFS was reported at 80% [17]. With a CR rate of 73.2% and a 2-year PFS rate of 87.9% in the current study, the addition of intermittent dosing of VEN does not seem to have improved the efficacy of obinutuzumab containing chemoimmunotherapy.

Laboratory TLS occurred when VEN was given with bendamustine and obinutuzumab during cycle 1; no clinical TLS was seen. However, we do not know the incidence of TLS with bendamustine and obinutuzumab alone and attribution to VEN alone is uncertain. Given the risk of TLS with VEN, we monitored closely for TLS during cycle 1, though careful TLS monitoring has not previously been performed with bendamustine and obinutuzumab to our knowledge. After amendment, we did not monitor for TLS during cycle 1 (bendamustine and obinutuzumab alone) but we did not see TLS during cycle 2 when VEN was added, likely reflecting cytoreduction and TLS risk mitigation during cycle 1.

Unfortunately, a high rate of atypical infections, previously rarely seen in FL, occurred after induction and during maintenance treatment, including PJP pneumonia, CMV encephalitis, BK virus nephropathy, and suspected viral myocarditis. These infections are rare but when seen, occur in individuals with severe immunosuppression, particularly lymphopenias. Details of lymphocyte counts, serum immunoglobulins, and T-cell subsets are not available. It is well described that bendamustine causes significant immunosuppression [5, 17, 18]. We can only postulate that VEN-OB caused marked immunosuppression, more than typically seen with bendamustine and obinutuzumab. It should also be noted that this study was enrolled, and induction therapy completed during the height of the COVID-19 pandemic. Given that information on the type of immunosuppression was not collected on this study, it is difficult to postulate how the various aspects of treatment (type of CD20 antibody, use of VEN, use of maintenance therapy, etc.) could be modified to decrease the rate of opportunistic infections.

It is possible that alterations to the regimen may improve tolerability. The dose of VEN at 800 mg was shown to be the maximum tolerated dose as a single agent in a phase I study in most non-Hodgkin lymphoma [4] (not mantle cell lymphoma) [20]. We utilized this dose in combination with bendamustine and obinutuzumab. While it is possible that lower doses may be better tolerated in combination, the potential impact on efficacy is unclear since the 400 mg dose was not as active in the phase I study [4]. Further, we

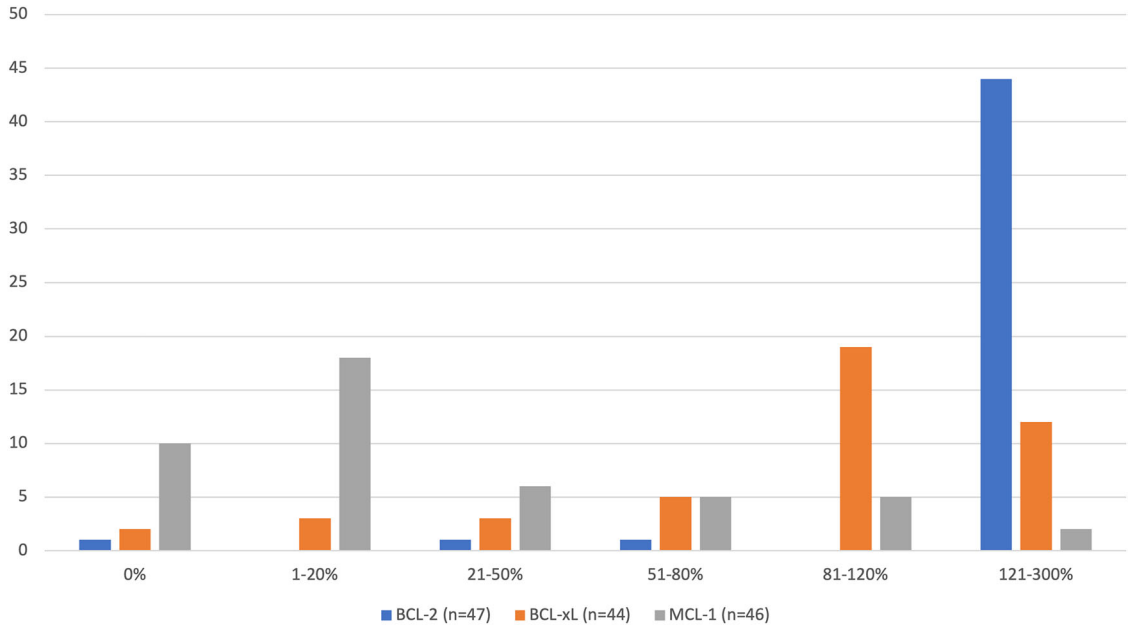

Fig. 4 H-Score distribution for all anti-apoptotic proteins. Immunohistochemistry derived H-Score for antiapoptotic proteins including BCL-2 ($n = 47$), BCL-xL ($n = 44$) and MCL-1 ($n = 46$) on pre-treatment formalin fixed, paraffin embedded diagnostic samples. There was robust expression of BCL-2 and high expression of BCL-xL. Minimal to no expression of MCL-1 was seen.

administered 6 cycles of chemoimmunotherapy per the convention on clinical studies, though a lower number of cycles would certainly decrease toxicity. Bendamustine was also administered as 90 mg/m^2 IV on day 1 and 2, yet typical clinical practices often use lower doses (70 or 50 mg/m^2) for older patients or those with complex medical comorbidities. Finally, the choice of obinutuzumab over rituximab may contribute to the toxicities seen. In GALLIUM, there was an improvement in efficacy for obinutuzumab compared with rituximab, but there was also a suggestion that more toxicity was seen, including late toxicity. Some of these issues may be addressed in another ongoing study, PrE0405, which evaluated VEN with bendamustine and rituximab in untreated mantle cell lymphoma. After initial ramp up during cycle 1, VEN was administered at 400 mg for 10 days with each cycle and bendamustine was allowed to be dose-reduced due to age in cycle 1.

Finally, exploratory IHC analysis showed fairly consistent, high-level expression of BCL-2 and BCL-xL, as measured by H-score, in our untreated FL cohort. Meanwhile, MCL-1 expression was comparatively limited. While the role of BCL-2 overexpression in FL pathogenesis is well established, the significance of other antiapoptotic BCL-2 family proteins has been less thoroughly explored. Correlation between measures of anti-apoptotic proteins and clinical outcomes was not seen, though is limited by low sample size and low number of clinical events on our study. To our knowledge, similar analyses have not been previously reported in front-line FL trials.

Altogether, VEN-OB achieved its primary endpoint of a high CR rate of 73.2% with an estimated 2-year PFS of 87.9%. Despite achieving its main efficacy objective, when evaluating based on CONTRALTO [5], intermittent dosing of VEN did not result in improved tolerability. Further, when comparing to GALLIUM [19], the addition of VEN did not improve the CR rate or PFS. While we acknowledge that these were two different trials and comparing them to each other and our own study is fraught with error, they were in the same patient population and use alterations of the treatment used on PrE0403. Due to an unacceptable occurrence of atypical infections and high incidence of grade ≥3 TRAE, further development of VEN-OB is not recommended in FL without additional significant modification.

DATA AVAILABILITY

The data that support the findings of this study are not openly available to protect the confidentiality of participants. Upon reasonable request, data are available from the corresponding author. The data set is stored in controlled access data storage at PrECOG. Results are uploaded on www.clincialtrials.gov.

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AUTHOR CONTRIBUTIONS

CAP: Enrolled patients on study, oversaw study conduct, analyzed data, interpreted results, wrote manuscript. OAJ: Protocol statistical design, analyzed data, conducted statistical analysis. NWJ: Enrolled patients on study, edited manuscript. GSN: Enrolled patients on study, edited manuscript. CF: Enrolled patients on study, edited manuscript. JBC: Enrolled patients on study, edited manuscript. AE: Enrolled patients on study, edited manuscript. LJR: Enrolled patients on study, edited manuscript. JWC: Edited manuscript, analyzed data and interpreted results with IHC data analysis. NR: Designed and wrote protocol, oversaw study conduct, enrolled patients on study, edited manuscript. BSK: Designed and wrote protocol, oversaw study conduct, Enrolled patients on study, analyzed data, interpreted results, edited manuscript.

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