

## ORIGINAL ARTICLE

# Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: a phase Ib dose-finding study

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**Background:** Venetoclax is a selective, potent inhibitor of the anti-apoptotic B-cell leukemia/lymphoma-2 protein approved for treatment of chronic lymphocytic leukemia. We conducted a dose-finding study of venetoclax in combination with bendamustine–rituximab (BR) in patients with relapsed/refractory non-Hodgkin's lymphoma (NHL).

**Patients and methods:** BR was given for six cycles at standard doses. Intermittent and continuous oral venetoclax administration was explored at 50–1200 mg daily doses. Co-primary objectives included safety, pharmacokinetics (PKs), maximum-tolerated dose (MTD), and recommended phase II dose (RP2D); secondary objective was preliminary efficacy.

**Results:** Sixty patients were enrolled: 32 with follicular lymphoma, 22 with diffuse large B-cell lymphoma, and 6 with marginal zone lymphoma. Nausea (70%), neutropenia (68%), diarrhea (55%), and thrombocytopenia (52%) were the most frequent adverse events (AEs). Most common grade 3/4 AEs were neutropenia (60%) and lymphopenia (38%). Serious AEs were reported in 24 patients; the most frequent were febrile neutropenia and disease progression (8% each). Five patients died from either disease progression ( $n = 4$ ) or respiratory failure ( $n = 1$ ). MTD was not reached; RP2D for venetoclax-BR combination was established as 800 mg daily continuously. Venetoclax PK exposure with and without BR was comparable. For all patients, overall response rate was 65%. Median duration of overall response, overall survival, and progression-free survival was 38.3 months [95% confidence interval (CI) 10.4–NR], not yet reached, and 10.7 months (95% CI 4.3–21.0), respectively.

**Conclusions:** This study established the safety profile of venetoclax in combination with BR, and results demonstrated tolerability and preliminary efficacy of the combination. Additional follow-up is needed to better determine the future role of BR plus venetoclax in the treatment of relapsed/refractory B-cell NHL.

**Trial registered:** Clinicaltrials.gov, NCT01594229.

**Key words:** venetoclax, bendamustine–rituximab, relapsed/refractory NHL, phase Ib

## Introduction

The B-cell leukemia/lymphoma-2 (BCL-2) protein family members are key regulators of the apoptotic pathway [1]. The anti-apoptotic proteins of the BCL-2 family promote cell survival by

preventing activation of the pro-apoptotic proteins BAX/BAK, which are responsible for the initiation of the mitochondrial apoptosis pathway [2, 3]. Overexpression of BCL-2 family members commonly occurs in hematologic malignancies, including non-Hodgkin's lymphoma (NHL), and is a hallmark of indolent

NHL subtypes [4, 5], as well as being associated with tumor initiation and disease progression [6–8]. BCL-2 overexpression has also been linked to increased incidence of resistance to commonly used chemo-immunotherapies, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen [9, 10].

Venetoclax is a highly selective, potent, orally bioavailable BCL-2 inhibitor. Preclinical data demonstrated that venetoclax monotherapy has broad cell-killing activity against a panel of NHL cell lines including follicular lymphoma (FL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) [8]. In a phase I single-agent study, venetoclax was generally well tolerated and demonstrated promising antitumor activity in patients with relapsed/refractory NHL; overall response rate (ORR) was 44%, 13% of patients experienced complete response (CR) [11]. Given the heterogeneity of clinical responses across the different subtypes of NHL, combining venetoclax with other agents was considered, particularly for FL and DLBCL. Furthermore, as venetoclax does not inhibit BCL-X<sub>L</sub> and MCL-1 [12], 2 major anti-apoptotic BCL-2 proteins that are believed to contribute to drug resistance, a combinatorial approach using agents that eliminate cancer cells through apoptosis, such as rituximab and chemotherapy, may provide further benefit.

A commonly used treatment regimen in patients with relapsed/refractory NHL is combined bendamustine and rituximab (BR). An ORR of up to 90%, CRs of 41%–60%, and median progression-free survival (PFS) of 23–24 months have been observed in the indolent subtypes [MCL, FL, small lymphocytic lymphoma, Waldenström macroglobulinemia, marginal zone lymphoma (MZL)] [13, 14], compared with ORRs of 46%–63%, CRs of 15%–37%, and median PFS of 3.6–6.7 months for patients with DLBCL [15, 16]. However, many tumors ultimately become resistant to these agents.

In preclinical studies, venetoclax demonstrated synergy when combined with BR; data from NHL xenograft models harboring t(14; 18) translocations demonstrated that the combination resulted in 100% complete tumor regressions [8]. Here, we report the results of a phase Ib trial of a combination of venetoclax with BR in patients with relapsed/refractory NHL.

## Methods

### Study design

This phase Ib open-label, multicenter, dose-escalation study enrolled patients with relapsed/refractory NHL at seven of the eight sites activated within different regions of the USA between June 2012 and October 2015. The data cut-off was February 2017.

Co-primary objectives were safety, pharmacokinetic (PK) profile, maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of venetoclax administered in combination with BR in patients with relapsed/refractory NHL. The secondary objective was preliminary efficacy; examining correlative biomarkers was an exploratory objective.

To determine an RP2D that best meets the safety/tolerability and efficacy objectives, 3 arms (A, B, and C) corresponded to 3 different venetoclax dosing schedules: 3, 7, or 28 consecutive days of each 28-day cycle (up to 6 cycles of treatment), respectively. Patients were treated with oral venetoclax ranging from 50 to 1200 mg following the respective dosing schedule, according to a standard 3 + 3 design [17]. Intravenous (i.v.)

rituximab was administered at 375 mg/m<sup>2</sup> once per cycle and i.v. bendamustine at 90 mg/m<sup>2</sup> twice per cycle. Dose modification was allowed at investigator discretion based on toxicity. Additional details are available in the [supplementary data](#), available at *Annals of Oncology* online. To mitigate tumor lysis syndrome (TLS) risk, TLS prophylaxis was initiated at least 72 h before the first dose of venetoclax and during treatment in cycle 1.

### Patient eligibility

Eligible patients were ≥18 years of age with histologically confirmed relapsed/refractory NHL, as defined by a B-cell neoplasm in the World Health Organization classification scheme, or relapsed DLBCL that has progressed after salvage therapy and first-line therapy with R-CHOP or equivalent. Full eligibility criteria are available in the [supplementary data](#), available at *Annals of Oncology* online. The study was approved by the institutional review board at each study center and was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, and applicable regulations. Patients provided written informed consent before study participation.

### PK assessment

For venetoclax PK parameters, blood samples were collected from all patients at predetermined time points during phase I of the study. Further details are in the [supplementary data](#), available at *Annals of Oncology* online.

### Exploratory biomarkers

Formalin-fixed, paraffin-embedded tumor samples were evaluated using immunohistochemistry (IHC) for BCL-2 (clone 124) and MYC (clone Y69) from Ventana Medical Systems (Tucson, AZ). Classification of DLBCL tumor samples into activated B-cell (ABC) or germinal center B-cell subtypes was determined using the Lymph2Cx assay at NanoString Technologies (Seattle, WA) [18]. Further details are in the [supplementary data](#), available at *Annals of Oncology* online.

### Statistical analysis

Patients who received at least 1 dose of venetoclax were included in all analyses. Descriptive statistics were used for baseline demographic variables. Treatment-emergent AEs (TEAEs) were graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). For PK assessments, noncompartmental methods were used to determine maximum observed plasma concentration ( $C_{max}$ ), time to  $C_{max}$  (peak time,  $T_{max}$ ), and area under the plasma concentration–time curve from time 0 to 24-h dose interval ( $AUC_{24}$ ).

Responses were assessed by computed tomography scan on day 1 of cycles 3, 5, 7, 11, 14, 17, 23, and then every 6 cycles thereafter, according to the revised 2007 International Working Group criteria [19]. Efficacy end points included PFS, ORR, time to tumor progression, overall survival (OS), and duration of response (DOR). The distribution of DOR, PFS, and OS was estimated using Kaplan-Meier methodology.

## Results

### Patient characteristics and study drug exposure

A total of 60 patients were enrolled; 32 (53%) had FL, 22 (37%) had DLBCL, and 6 (10%) had MZL. Key demographics and clinical characteristics are summarized in Table 1. Median time on study was 7.4 months (range 0.1–55.1 months) and median duration of exposure was 5.5 months (range 0.1–51.8 months; [supplementary Figure S2](#), available at *Annals of Oncology* online).

Table 1. Patient demographics and clinical characteristics

Characteristics	Total N = 60
Age, median (range), years	62 (29–90)
Male, n (%)	40 (67)
Histology, n (%)	
Follicular lymphoma	32 (53)
Diffuse large B-cell lymphoma	22 (37)
Marginal zone B-cell lymphoma	6 (10)
Prior therapies, n, median (range)	3 (1–8)
Rituximab or R-based chemotherapy, n (%)	60 (100)
Bendamustine or BR, n (%)	15 (25)
Refractory to prior therapy, n (%)	32 (52)
Bulky nodes, n (%)	
>5 cm	33 (55)
>10 cm	6 (10)

Over half of the patients (31/60) completed 6 cycles of therapy; 26 patients continued venetoclax monotherapy maintenance on their cohort dose (median time on monotherapy: 14.5 months; range 0.3–48.8 months) and 12, as of 15 February 2017, are still active on treatment (supplementary Table S1, available at *Annals of Oncology* online). The status of the remaining 29 patients who discontinued before 6 cycles of therapy is presented in supplementary Table S1, available at *Annals of Oncology* online. Thirty-five patients (58%) had venetoclax dose interruptions and 15 patients (25%) had dose reductions due to TEAEs, most frequently neutropenia ( $n=16$  and  $n=10$ , respectively). Forty-eight patients (80%) discontinued venetoclax ( $n=34$ ,  $\leq 6$  cycles;  $n=14$ ,  $>6$  cycles); the reasons for discontinuation are listed in supplementary Table S2, available at *Annals of Oncology* online. Among patients with AEs leading to venetoclax dose discontinuation, 14 patients discontinued due to TEAEs [neutropenia and malignant neoplasm progression were the most common ( $n=4$  each)] and 2 patients due to non-TEAEs (onset date  $>30$  days after last dose of venetoclax).

### Safety profile

TEAEs were reported in 98% ( $n=59$ ) of patients; Table 2 summarizes all-grade, grade 3/4 and serious TEAEs. Grade 3/4 TEAEs were reported in 83% ( $n=50$ ) of patients, with neutropenia (60%), lymphopenia (38%), and decreased white blood cell count (22%) the most frequently reported. Serious TEAEs were reported in 24 patients; the most frequent were febrile neutropenia and malignant neoplasm progression (8% each). TEAEs were similar across all cohorts except in arm C 1200 mg, 28/28-day cohort, where the incidence of gastrointestinal AEs was increased. TEAEs leading to death occurred in five patients, all in arm C, due to disease progression ( $n=2$  in 200 mg cohort;  $n=1$  in 800 mg cohort;  $n=1$  in 1200 mg cohort) or respiratory failure ( $n=1$  in 400 mg cohort). Within 30 days of the last dose, 4 deaths occurred: 3 due to disease progression and 1 due to non-disease progression (respiratory failure).

A total of 6 DLTs were reported: 1 in arm B [neutropenia (400 mg cohort)], 5 in arm C [ $n=1$ , thrombocytopenia (200 mg cohort);  $n=1$ , febrile neutropenia and diarrhea (200 mg cohort);

$n=1$ , Stevens–Johnson syndrome (400 mg cohort);  $n=1$ , thrombocytopenia and subdural hematoma (800 mg cohort);  $n=1$ , white blood cell count decrease (1200 mg cohort)].

Considering the DLTs reported, the MTD was not reached after a dose evaluation up to 1200 mg daily. Based on composite safety and efficacy data [11, 20], the RP2D for venetoclax in combination with BR was declared as 800 mg daily (continuous dosing).

### Pharmacokinetics

PK parameters  $C_{max}$ ,  $T_{max}$ , and  $AUC_{24}$  are presented in Table 3. Peak venetoclax concentrations were achieved 5–8 h postdose. At steady state, venetoclax exposure when co-administered with bendamustine was approximately dose proportional. Venetoclax exposure when given with and without bendamustine was comparable, suggesting that bendamustine did not affect venetoclax PKs (supplementary Figures S3 and S4, available at *Annals of Oncology* online).

### Preliminary efficacy

Response rates for the overall study population, and by histologic subtype and by arm are presented in Table 4. The ORRs (CR +CR with incomplete bone marrow [CRi] +nodular partial response [nPR] +PR) for all patients was 65% (95% CI 51.6–76.9); 18 (30%) patients achieved CR, and 21 (35%) achieved PR (there were no reports of CRi or nPR). Considering the data by histologic subtype, ORRs of 75% (95% CI 56.6–88.5), 100% [95% CI: not reached (NR)], and 41% (95% CI 20.7–63.6) were observed in FL, MZL, and DLBCL patients, respectively. The ORRs were similar across each arm, with 2 (25%), 3 (23%), and 13 (33%) patients achieving CR in arms A, B, and C, respectively. Best responses observed per patient are summarized in supplementary Figure S5, available at *Annals of Oncology* online.

Overall, the median DOR for all treated patients was 38.3 months (95% CI 10.4–NR), and median PFS was 10.7 months (95% CI 4.3–21.0); median OS has not yet been reached; data for all patients and by histologic subtype are presented in supplementary Figure S6, available at *Annals of Oncology* online.

### Exploratory: correlative biomarkers

Baseline tissue was available for exploratory biomarker analysis from 21 patients. Of these, 15 (71%) had high expression of BCL-2, the highest levels seen in the indolent NHL subtypes FL (11/14; 79%) and MZL (2/2; 100%) (supplementary Table S3, available at *Annals of Oncology* online). Objective responses and PFS were highest in patients with high BCL-2 expression status ( $\geq 2+$ ), with an ORR of 80% and median PFS of 21 months (supplementary Table S3, available at *Annals of Oncology* online). Patients with low BCL-2 expression status (1+) had an ORR of 50% and median PFS of 3.1 months (supplementary Table S4, available at *Annals of Oncology* online). Of patients with high BCL-2 expression, higher ORRs were achieved in patients with FL (9/11; 82%) and MZL (2/2; 100%) compared with DLBCL (1/2; 50%) (supplementary Table S5, available at *Annals of Oncology* online).

Table 2. Treatment-emergent adverse events

All-grade TEAEs ( $\geq 20\%$ total patients), n (%)	Arm A (3/28-day VEN [+BR]) n = 8	Arm B (7/28-day VEN [+BR]) n = 13	Arm C (28-day VEN [+BR]) n = 39	Total N = 60
<b>Any TEAE</b>	8 (100)	12 (92)	39 (100)	59 (98)
Nausea	7 (88)	8 (61)	27 (69)	42 (70)
Neutropenia	5 (63)	10 (77)	26 (67)	41 (68)
Diarrhea	4 (50)	7 (54)	22 (56)	33 (55)
Thrombocytopenia	2 (25)	6 (46)	23 (59)	31 (52)
Vomiting	5 (63)	4 (31)	19 (49)	28 (47)
Lymphocyte count decrease	0	6 (46)	17 (44)	23 (38)
Fatigue	4 (50)	4 (31)	20 (51)	28 (47)
Constipation	0	6 (46)	18 (46)	24 (40)
Anemia	3 (38)	7 (54)	13 (33)	23 (38)
Hyperglycemia	0	6 (46)	14 (36)	20 (33)
Hypokalemia	1 (13)	4 (31)	13 (33)	18 (30)
Cough	3 (38)	5 (39)	9 (23)	17 (28)
Hypocalcemia	0	6 (46)	10 (26)	16 (27)
Leukopenia	2 (25)	4 (31)	9 (23)	15 (25)
White blood cell count decrease	0	3 (23)	12 (31)	15 (25)
Headache	2 (25)	4 (31)	9 (23)	15 (25)
Pyrexia	1 (13)	3 (23)	10 (26)	14 (23)
Upper respiratory tract infection	2 (25)	3 (23)	9 (23)	14 (23)
Appetite decrease	3 (38)	1 (7)	8 (21)	12 (20)
<b>Grade 3/4 TEAEs (<math>\geq 5\%</math> total patients), n (%)</b>				
<b>Any grade 3/4 TEAE</b>	4 (50)	12 (92)	34 (87)	50 (83)
Neutropenia	3 (38)	10 (77)	23 (59)	36 (60)
Lymphocyte count decrease	0	6 (46)	17 (44)	23 (38)
White blood cell count decrease	0	3 (23)	10 (26)	13 (22)
Leukopenia	1 (13)	4 (31)	7 (18)	12 (20)
Thrombocytopenia	2 (25)	1 (8)	14 (36)	17 (28)
Anemia	2 (25)	2 (15)	6 (15)	10 (17)
Febrile neutropenia	1 (13)	1 (8)	3 (8)	5 (8)
CD4 lymphocytes decrease	0	0	4 (10)	4 (7)
Dyspnea	0	2 (15)	1 (3)	3 (5)
Fatigue	0	1 (8)	2 (5)	3 (5)
Hypokalemia	0	1 (8)	2 (5)	3 (5)
Hypophosphatemia	0	1 (8)	2 (5)	3 (5)
Lymphopenia	0	1 (8)	2 (5)	3 (5)
Nausea	0	0	3 (8)	3 (5)
<b>Serious TEAEs (<math>&gt;2\%</math> total patients), n (%)</b>				
<b>Any serious TEAE</b>	3 (38)	7 (54)	14 (36)	24 (40)
Febrile neutropenia	1 (13)	1 (8)	3 (8)	5 (8)
Malignant neoplasm progression	0	0	5 (13)	5 (8)
Diarrhea	0	1 (8)	1 (3)	2 (3)
Dyspnea	0	1 (8)	1 (3)	2 (3)
Malignant melanoma	0	1 (8)	1 (3)	2 (3)
Nausea	0	0	2 (5)	2 (3)
Respiratory failure	0	0	2 (5)	2 (3)
Syncope	0	2 (15)	0	2 (3)
Vomiting	0	0	2 (5)	2 (3)

## Discussion

This dose-finding study represents the first trial assessing the safety of venetoclax and BR combination in patients with relapsed/refractory NHL. The results demonstrate that the combination has a tolerable safety profile up to 1200 mg venetoclax (daily, continuously). The commonly reported TEAEs were

nausea (70%), neutropenia (68%), and diarrhea (55%). With 6 reported DLTs, the MTD was not reached after exploring a dose up to 1200 mg daily; however, the RP2D was established as 800 mg daily continuously dosed. The RP2D determination considered the composite safety and efficacy data from the current study and from the NHL cohort of patients treated in the M12-

Table 3. Mean  $\pm$  standard deviation PK parameters of venetoclax with and without bendamustine

Cycle/day	Arm	Dose, mg	N	Venetoclax PK parameters				
				$T_{max}$ h <sup>a</sup>	$C_{max}$ $\mu$ g/ml	AUC <sub>24h</sub> $\mu$ g h/ml	Dose-normalized $C_{max}$ (ng./ml)/mg	Dose-normalized AUC <sub>24h</sub> (ng. h/ml)/mg
Cycle 2 day 1 (w/o bendamustine)	A	50	4	5 (4–6)	0.43 $\pm$ 0.39	4.46 $\pm$ 4.60	8.62 $\pm$ 7.86	89.2 $\pm$ 92.1
	A	100	4	7 (6–8)	0.70 $\pm$ 0.12	7.94 $\pm$ 4.05	7.02 $\pm$ 1.25	79.4 $\pm$ 40.5
	B	100	4	6 (4–8)	0.39 $\pm$ 0.29	4.32 $\pm$ 1.70	3.91 $\pm$ 2.88	43.2 $\pm$ 17.0
	B	200	3	8 (6–8)	0.82 $\pm$ 0.80	11.0 $\pm$ 10.0	4.08 $\pm$ 3.99	54.9 $\pm$ 49.8
	B	400	4	6.6 (6–7.5)	1.32 $\pm$ 0.90	18.2 $\pm$ 11.7	3.30 $\pm$ 2.26	45.4 $\pm$ 29.4
	<b>All doses</b>	–	–	–	–	–	<b>5.45<math>\pm</math>4.38</b>	<b>62.8<math>\pm</math>50.3</b>
Cycle 1 day 2 (w/bendamustine)	A	50	4	6 (6–6)	0.29 $\pm$ 0.01	3.54 $\pm$ 0.15	5.86 $\pm$ 0.27	70.7 $\pm$ 3.03
	A	100	4	6 (6–8)	0.66 $\pm$ 0.08	7.40 $\pm$ 1.90	6.59 $\pm$ 0.76	74.0 $\pm$ 19.0
	B	100	4	8 (6–8)	0.31 $\pm$ 0.13	4.06 $\pm$ 1.65	3.08 $\pm$ 1.25	40.6 $\pm$ 16.5
	B	200	4	8 (4–8)	0.52 $\pm$ 0.43	7.54 $\pm$ 5.81	2.62 $\pm$ 2.17	37.7 $\pm$ 29.1
	B	400	5	8 (4–8)	1.10 $\pm$ 0.48	12.4 $\pm$ 8.07	2.74 $\pm$ 1.21	31.0 $\pm$ 20.2
	<b>All doses</b>	–	–	–	–	–	<b>4.11<math>\pm</math>2.07</b>	<b>49.9<math>\pm</math>25.4</b>
Cycle 2 day 2 (w/o bendamustine)	C	100	2	6 (6–6)	0.63 (0.60–0.66) <sup>b</sup>	8.60 (7.46–9.74) <sup>b</sup>	6.33 (6.0–6.66) <sup>b</sup>	86.0 (74.6–86.0) <sup>b</sup>
	C	200	1	4	0.55	ND	2.77	ND
	C	400	7	6 (4–29)	1.87 $\pm$ 1.00	29.0 $\pm$ 16.5	4.68 $\pm$ 2.49	72.6 $\pm$ 41.2
	C	600	7	8 (0–8)	1.83 $\pm$ 1.01	28.8 $\pm$ 16.7	3.04 $\pm$ 1.68	48.0 $\pm$ 27.9
	C	800	3	8 (0–8)	3.23 $\pm$ 0.46	46.3 (39.5–53.0) <sup>b</sup>	4.03 $\pm$ 0.58	57.9 (49.4–66.3) <sup>b</sup>
	C	1200	7	6 (0–8)	5.26 $\pm$ 4.42	90.1 $\pm$ 76.5	4.38 $\pm$ 3.68	75.1 $\pm$ 63.7
	<b>All doses</b>	–	–	–	–	–	<b>4.16<math>\pm</math>2.47</b>	<b>65.7<math>\pm</math>42.8</b>

Arm A: venetoclax daily $\times$ 3 days per a 28-day cycle (3/28-day dosing).

Arm B: venetoclax daily $\times$ 7 days per a 28-day cycle (7/28-day dosing).

Arm C: venetoclax daily $\times$ 28 days per a 28-day cycle (28/28-day dosing).

<sup>a</sup> $T_{max}$  presented as median (range).

<sup>b</sup>Presented as mean (individual values).

ND, not determined.

Table 4. Exploratory antitumor activity

Response by subtype, n (%)	DLBCL n = 22	FL n = 32	MZL n = 6	Total N = 60
<b>Objective response (CR+PR)</b>	<b>9 (41)</b>	<b>24 (75)</b>	<b>6 (100)</b>	<b>39 (65)</b>
CR	3 (14)	12 (38)	3 (50)	18 (30)
Partial response	6 (27)	12 (38)	3 (50)	21 (35)
Stable disease	4 (18)	2 (6)	0	6 (10)
Progressive disease	9 (41)	3 (9)	0	12 (20)
Discontinued without assessment	0	3 (9)	0	3 (5)
Response by schedule, n (%)	Arm A (3/28-day VEN [+BR]) n=8	Arm B (7/28-day VEN [+BR]) n=13	Arm C (28-day VEN [+BR]) n=39	Total N=60
<b>Objective response (CR+PR)</b>	<b>5 (63)</b>	<b>10 (77)</b>	<b>24 (62)</b>	<b>39 (65)</b>
CR	2 (25)	3 (23)	13 (33)	18 (30)
Partial response	3 (38)	7 (54)	11 (28)	21 (35)
Stable disease	2 (25)	0	4 (10)	6 (10)
Progressive disease	1 (13)	2 (15)	9 (23)	12 (20)
Discontinued without assessment	0	1 (8)	2 (5)	3 (5)

175, a first-in-human dose-finding study of venetoclax monotherapy [11], as well as unpublished exposure/response data suggesting that doses above 800 mg daily were not associated with significant benefit among patients with NHL [20].

Venetoclax exposure when given in combination with bendamustine was comparable with that observed with venetoclax monotherapy, suggesting that bendamustine did not affect venetoclax PKs.

Early and durable responses were observed across all dose cohorts in this heavily pretreated population, with responses observed for each of the disease subtypes. Across the entire study population, the ORR was 65% and the CR rate was 30%, which compares favorably with rates reported previously for venetoclax monotherapy in patients with relapsed/refractory NHL [11]. In our study, higher ORRs were observed for the indolent FL and MZL subtypes of NHL, compared with the aggressive DLBCL form [75% (24/32) versus 100% (6/6) versus 41% (9/22), respectively]. However, notwithstanding the lower ORR seen with DLBCL, when compared with the response data seen in FL and DLBCL in the single-agent venetoclax study [11] the current data suggest that the combination produced higher ORRs in both FL and DLBCL subtypes. The median PFS of 10.7 months observed for the entire study population also compares favorably with a median PFS of 6 months reported previously [11].

A possible factor in the observed heterogeneity in response between the different NHL subtypes is the different patterns of BCL-2 expression. Over the entire study population, it is notable that those with high BCL-2 expression, regardless of histologic subtype, had improved response and longer PFS than those with low levels of BCL-2. Therefore, while these initial data indicate a correlation between response and BCL-2 expression, the low patient numbers for whom BCL-2 IHC was available makes interpretation of the data difficult. In conclusion, the development of BCL-2 expression as a valid biomarker in NHL patients warrants further investigation.

A multinational randomized study (#NCT02187861; CONTRALTO/BO29337), which completed accrual in March 2016, is assessing the safety and efficacy of venetoclax with rituximab, as well as venetoclax in combination with BR compared with BR alone, in patients with relapsed/refractory FL. Interim data concur with the ORRs and safety reported herein for patients with FL [20].

In summary, this study has established the safety profile of venetoclax in combination with BR, and demonstrated tolerability and efficacy. Additional follow-up is needed to better determine the future role of BR plus venetoclax in the treatment of relapsed/refractory B-cell NHL.

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## Disclosure

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