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ORIGINAL ARTICLE

Safety and efficacy of parsaclisib in combination with obinutuzumab and bendamustine in patients with relapsed or refractory follicular lymphoma (CITADEL-102): A phase 1 study

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Abstract

Parsaclisib is a potent and highly selective PI3Kδ inhibitor that has shown clinical benefit with monotherapy in a phase 2 study in relapsed or refractory (R/R) follicular lymphoma (FL). CITADEL-102 (NCT03039114), a phase 1, multicenter study, assessed the efficacy of parsaclisib in combination with obinutuzumab and bendamustine in patients with R/R FL. Patients were ≥18 years of age with histologically confirmed and documented CD20-positive FL, and R/R to previous rituximab-containing treatment regimens. Part one (safety run-in) determined the maximum tolerated dose of parsaclisib in combination with standard dosage regimens of obinutuzumab and bendamustine. Part two (dose expansion) was an open-label, single-group design evaluating safety, tolerability (primary endpoint), and efficacy (secondary endpoint) of parsaclisib combination therapy. Twenty-six patients were enrolled in CITADEL-102 and all patients received parsaclisib 20 mg once daily for 8 weeks, followed by 20 mg once weekly thereafter, in combination with obinutuzumab and bendamustine. One patient in safety run-in experienced a dose-limiting toxicity of grade 4 QT interval prolongation that was considered related to parsaclisib. Eight patients (30.8%) discontinued treatment due to treatment-emergent adverse events (TEAEs) of colitis (2 [7.7%]), alanine aminotransferase and aspartate aminotransferase increase (both in one patient [3.8%]), neutropenia, thrombocytopenia, QT prolongation, tonsil cancer, and maculopapular rash (each 1 [3.8%]). The most common reported TEAEs were pyrexia (53.8%), neutropenia (50.0%), and diarrhea (46.2%). Twenty-three patients (88.5%) experienced grade 3 or 4 TEAEs; the most common were neutropenia (34.6%), febrile neutropenia (23.1%), and thrombocytopenia (19.2%). Seventeen patients (65.4%) had a complete response and 3

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patients (11.5%) had a partial response, for an objective response rate of 76.9%. Overall, results from CITADEL-102 suggest that the combination of parsaclisib with obinutuzumab and bendamustine did not result in unexpected safety events, with little evidence of synergistic toxicity, and demonstrated preliminary efficacy in patients with R/R FL who progressed following prior rituximab-containing regimens.

KEYWORDS
bendamustine hydrochloride, follicular, lymphoma, obinutuzumab, parsaclisib, phosphatidylinositol 3-kinase

1 | INTRODUCTION

Follicular lymphoma (FL), a common indolent non-Hodgkin's lymphoma (NHL), accounts for 20%–25% of new NHL cases in Western countries.[1] Patients with FL have a 10-year overall survival (OS) rate of approximately 80%.[1,2] Advanced-stage FL is considered incurable and patients require several lines of therapy due to relapses.[3,4] Anti-CD20-based chemoimmunotherapy regimens approved for first-line systemic treatment of patients with advanced FL include anti-CD20 antibodies rituximab or obinutuzumab in combination with bendamustine, with cyclophosphamide, doxorubicin, vincristine, and prednisolone, or with cyclophosphamide, vincristine, and prednisolone.[5,6] Many patients with advanced FL who respond to these regimens relapse, and each subsequent relapse is associated with shorter durations of response to following treatments.[7] Although a clear standard of treatment has not been established, combination of obinutuzumab and bendamustine followed by obinutuzumab maintenance therapy demonstrated an overall response rate of 79% (17% complete response [CR], 62% partial response [PR]) in the GADOLIN study,[8] and is approved for patients with FL who relapse or are refractory (R/R) to rituximab-containing regimens.[9,10]

Aberrant activation of the phosphoinositide 3-kinase (PI3K) pathway is associated with increased proliferation and survival of malignant B cells.[11–13] PI3K inhibitors have demonstrated clinically meaningful efficacy as monotherapy for treatment of R/R FL, although there have been concerns over safety and tolerability.[13–15] Parsaclisib is a potent oral and highly selective PI3Kδ inhibitor, structurally designed to optimize selectivity and potency, and avoid hepatotoxicity associated with early-generation PI3K inhibitors.[16,17] The phase 1/2 study CITADEL-101 explored daily and weekly dosing regimens with parsaclisib 20 mg, and determined that switching to a weekly dose could mitigate some expected late-onset, class-related side effects including diarrhea and colitis[18]; this regimen was therefore considered appropriate for combination study with anti-CD20 therapy.

In a phase 2 study (CITADEL-203), parsaclisib monotherapy (20 mg administered daily for 8 weeks, followed by 20 mg weekly dosing or 2.5 mg daily dosing) demonstrated rapid and durable responses in patients with R/R FL who had received ≥2 prior systemic therapies.[19] Here, we report results from a phase 1 study of parsaclisib in combination with obinutuzumab and bendamustine in patients with R/R FL who had received prior rituximab-containing regimens, to evaluate the safety profile and preliminary efficacy of the addition of parsaclisib to the obinutuzumab plus bendamustine regimen.

2 | MATERIALS AND METHODS

2.1 | Study design

CITADEL-102 (NCT03039114) was a phase 1, open-label, multicenter, two-part study designed to assess the safety, tolerability, and efficacy of parsaclisib in combination with obinutuzumab and bendamustine in patients with R/R FL previously treated with rituximab (Supplemental Figure 1). The study was conducted in accordance with Good Clinical Practice, principles of the Declaration of Helsinki, and all applicable local regulations. The protocol and amendments were reviewed and approved by a qualified institutional review board/independent ethics committee before enrollment of participants at each site, and informed consent was obtained from each patient before enrollment.

Part one (safety run-in) used a 3 + 3 design to determine the maximum tolerated dose (MTD) of parsaclisib in combination with obinutuzumab and bendamustine. Patients received parsaclisib 20 mg once daily (QD) orally for 8 weeks, then 20 mg once weekly (QW) thereafter; obinutuzumab 1000 mg intravenously on days 1, 8, and 15 of cycle one, then day one of cycles 2–6; and bendamustine 90 mg/m^2 intravenously on days one and two of cycles 1–6. The MTD was deemed to be exceeded and parsaclisib dose de-escalated to 10 mg if dose-limiting toxicities (DLTs; Supplemental Table 1) occurred in ≥2 of the first three or six total evaluable patients in cycle one.

Part two (dose expansion) was an open-label, single-group design evaluating safety, tolerability, and efficacy of parsaclisib in combination with obinutuzumab and bendamustine at the MTD. Patients without progressive disease (PD) after six cycles, in Parts one and two, could continue maintenance therapy with parsaclisib (QW at the MTD) and obinutuzumab (1000 mg on day one of every second cycle) for a further 24 cycles or until disease progression. Patients with active treatment and no evidence of PD at study completion could continue parsaclisib monotherapy.

2.2 | Patients

Patients were ≥18 years of age with histologically confirmed and documented CD20-positive R/R FL to any previous rituximab-containing regimen, had a maximum of four previous anticancer treatment regimens, at least one measurable lesion (>1.5 cm) in at least one dimension by computed tomography or magnetic resonance imaging, and Eastern Cooperative Oncology Group (ECOG) status 0–2.

Key exclusion criteria included clinical evidence of transformation to a more aggressive subtype of lymphoma or grade 3B FL, history of central nervous system lymphoma, allogeneic stem cell transplantation within the last 6 months, prior treatment with a selective PI3Kδ inhibitor or pan-PI3K inhibitor, previous treatment with bendamustine within 12 months of start of study treatment, prior treatment with obinutuzumab, and rituximab treatment within 4 weeks of study initiation.

2.3 | Study endpoints and assessments

The primary study endpoint was safety and tolerability of parsaclisib in combination with obinutuzumab and bendamustine in R/R FL. Safety was assessed by monitoring vital signs, physical examinations, 12-lead electrocardiograms, chemistry and hematology laboratory evaluations, and adverse events (AEs). Adverse events were summarized according to Medical Dictionary for Regulatory Activities v23.1 preferred terms and severity graded using Common Terminology Criteria for Adverse Events v4.03.

Secondary endpoints were objective response rate (ORR, percentage of patients with a CR/complete metabolic response [CMR] and PR/partial metabolic response [PMR]), and CR rate/CMR rate (CRR/CMRR), as determined by investigator assessment based on the Lugano Classification criteria for lymphoma.[20] Additional secondary endpoints were duration of response (DOR), progression-free survival (PFS), and OS. Disease status was assessed by positron emission tomography and computed tomography every 12 weeks for the first 12 cycles, every 16 weeks until the end of cycle 28, and then every 24 weeks until disease progression. Bone marrow biopsy was required at baseline, and to confirm CR (if bone marrow lymphoma involvement was determined at baseline) or as clinically indicated.

Exploratory endpoints included evaluation of potential biomarkers in blood plasma associated with response, treatment resistance, and safety. Plasma samples were collected on cycle 1 day one (baseline predose), cycle 2 day one, cycle 4 day one, then day one of every fourth cycle up to 52 weeks, and end of treatment. Plasma proteins were analyzed using the Olink Normalized Protein eXpression Target 96 platform (Olink, Waltham, MA), and included markers and analytes associated with B-cell activation, inflammation, immune status, and metabolism. A linear mixed model was applied to proteomic data to identify differentially expressed proteins (DEPs) relative to baseline (cycle 1 day one) following treatment at cycle 2 day one, cycle 4 day one, and cycle 8 day one.

2.4 | Statistical analysis

The anticipated total study sample size was 30–45 patients. A sample size of 6–18 patients was planned for Part one, based on six patients per dose level, providing an approximate 80% chance of observing ≤1 DLT with a true event rate of 15%. Sample size was to be expanded to approximately 30 patients in Part two and included patients receiving parsaclisib at the MTD in Part one to give an exact 90% confidence interval for ORR of 64.3%–90.9% with an observed response rate of 80%. The full analysis set (used to summarize demographics, baseline characteristics, patient disposition, and for efficacy analyses) and safety population (used to summarize safety) included all patients who received at least one dose of study medication (parsaclisib, obinutuzumab, or bendamustine).

All statistical analyses were exploratory. Safety data were summarized with descriptive statistics. Objective response rate and CRR as reported by the investigator were summarized, with 95% CIs calculated based on the exact method for binomial distributions. Kaplan-Meier estimates of median DOR, PFS, and OS were determined with 95% CIs using the generalization of Brookmeyer and Crowley's method with a log-log transformation.[21,22] Subgroup post hoc analyses assessed ORR, DOR, PFS, and OS based on R/R status, and disease progression within 2 years (POD24). Absolute fold change >1.5 and false discovery rate <0.05 defined DEP for translational analyses.

3 | RESULTS

3.1 | Patient characteristics and disposition

Twenty-six patients were enrolled in CITADEL-102 at 15 sites in the United States and Europe. Criteria for parsaclisib dose de-escalation in Part one were not met; therefore, all 26 patients received parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW with obinutuzumab and bendamustine and were analyzed in one treatment group. Table 1 summarizes baseline patient demographics and disease characteristics. The median (range) age of patients was 65.0 (44–80) years, all patients were white and mostly male (16 [61.5%]), and had an ECOG status of 0 (14 [53.8%]) or 1 (11 [42.3%]). Fourteen patients (53.8%) were refractory to their last therapy at baseline.

Twenty-one patients discontinued treatment due to the following reasons: AEs (8 [30.8%]), PD (6 [23.1%]), physician decision (3 [11.5%]; these 3 patients proceeded to hematopoietic stem-cell transplantation), withdrawal by participant (3 [11.5%]), or death (1 [3.8%]) (Supplemental Figure 2). An additional 5 patients (19.2%) discontinued this study and continued receiving parsaclisib treatment in a rollover study INCB50465-801 (NCT04509700). Median (range) duration of parsaclisib treatment was 10.6 (0.4–32.8) months, and median (range) obinutuzumab and bendamustine exposure were 11 (1–33) and 6 (1–6) cycles, respectively.

TABLE 1 Baseline patient demographics and disease characteristics.

Characteristic	Parsaclisib + obinutuzumab and bendamustine (*N* = 26)
Age, median (range), years	65.0 (44–80)
Male, *n* (%)	16 (61.5)
Race, *n* (%)	
White/Caucasian	26 (100.0)
Ethnicity, *n* (%)	
Not Hispanic or Latino	23 (88.5)
Hispanic or Latino	1 (3.8)
Unknown	2 (7.7)
ECOG PS, *n* (%)	
0	14 (53.8)
1	11 (42.3)
Missing	1 (3.8)
Time since initial diagnosis, median (range), years[a]	3.3 (0.5–18.4)
Ann Arbor staging, *n* (%)	
Stage I	0 (0.0)
Stage II	4 (15.4)
Stage III	5 (19.2)
Stage IV	17 (65.4)
FLIPI risk category[b]	
Low risk (0 or 1)	8 (30.8)
Intermediate risk (2)	10 (38.5)
Missing	8 (30.8)
POD24, *n* (%)	
Yes (POD<24)	16 (61.5)
No (POD≥24)	8 (30.8)
Unknown	2 (7.7)
Prior systemic therapy regimens, median (range)	1 (1–5)[c]
Relapsed/refractory to last therapy, *n* (%)	
Relapsed	9 (34.6)
Refractory	14 (53.8)
Unknown	3 (11.5)
Selected prior therapies, *n* (%)	
Rituximab	26 (100.0)
Cyclophosphamide	23 (88.5)
Doxorubicin	19 (73.1)
Prednisone	16 (61.5)
Bendamustine	6 (23.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma Prognostic Index; POD24, relapse/progression within 24 months of diagnosis.

[a]Time since initial diagnosis (years) = (Day 1 date – date of diagnosis +1)/365.25.

[b]Only "low" and "intermediate" FLIPI risk categories were collected.

[c]One patient had a prior experimental immunotherapy that was inadvertently not counted toward the maximum number of prior anticancer regimens.

3.2 | Safety

Of the six evaluable patients in Part one, one patient experienced a DLT; therefore, the criteria for parsaclisib dose de-escalation were not met. The patient was an 80-year-old female with stage 3 FL, who had a serious grade 4 QT interval prolongation with hypokalemia and hypomagnesemia beginning on day 13 of the initial parsaclisib QD dosing phase. This resolved on day 18 with conservative treatment and the event was considered parsaclisib-related.

Treatment-emergent adverse events (TEAEs) were experienced by all 26 patients; most common were pyrexia (14 [53.8%]), neutropenia (13 [50.0%]), and diarrhea (12 [46.2%]). Grade 3 or 4 TEAEs were reported in 23 patients (88.5%), with neutropenia (9 [34.6%]), febrile neutropenia (6 [23.1%]), and thrombocytopenia (5 [19.2%]) being the most common (Table 2). Fifteen patients (57.7%) experienced serious TEAEs; the most common were febrile neutropenia (6 [23.1%]), increased alanine aminotransferase (ALT) or increased aspartate aminotransferase (AST) (each 2 [7.7%]) (Table 3). One patient (3.8%) had a fatal TEAE of pneumonia related to COVID-19 that occurred during the QW treatment period and was not considered treatment-related.

Adverse events of special interest (AESIs, based on preferred terms) included diarrhea (12 [46.2%]), rash (8 [30.8%]), febrile neutropenia (6 [23.1%]), pneumonia (2 [7.7%]), colitis (1 [3.8%]), and herpes simplex (1 [3.8%]). One patient (3.8%) had a positive cytomegalovirus (CMV) test and CMV infection (both grade 2), three patients (11.5%) had a positive CMV test (grade 1), and one patient (3.8%) had grade 3 CMV colitis. No cases of pneumonitis were reported. Adverse events of special interest of grade 3 severity were febrile neutropenia (6 [23.1%]) and diarrhea (2 [7.7%]); no patient experienced grade 4 AESI.

Treatment-related adverse events considered parsaclisib-related by the investigator occurred in 23 patients (88.5%), the most common were neutropenia (11 [42.3%]) and thrombocytopenia (8 [30.8%]) (Supplemental Table 2). Sixteen patients (61.5%) experienced parsaclisib-related AEs of grade ≥3 with the most common being neutropenia (7 [26.9%]), increased ALT and increased AST (each 3 [11.5%]). Seven patients (26.9%) experienced serious AEs related to parsaclisib, the most common were increased ALT and increased AST (each 2 [7.7%]) (Table 3). Obinutuzumab-related AEs occurred in 15 patients (57.7%); the most common were neutropenia and thrombocytopenia (each 6 [23.1%]). Eight patients (30.8%) experienced obinutuzumab-related AEs of grade ≥3 (Supplemental Table 2). Bendamustine-related AEs were reported in 21 patients (80.8%); the most common were neutropenia (8 [30.8%]) and thrombocytopenia (7 [26.9%]). Ten patients (38.5%) experienced bendamustine-related AEs of grade ≥3 (Supplemental Table 2).

TABLE 2 Summary of any grade treatment-emergent adverse events (TEAEs) occurring in 5 or more patients and corresponding grade 3 or 4 TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

	Parsaclisib + obinutuzumab and bendamustine (*N* = 26)	
Preferred term, *n* (%)	**Any grade**	**Grade 3 or 4**
Pyrexia	14 (53.8)	1 (3.8)
Neutropenia	13 (50.0)	9 (34.6)
Diarrhea	12 (46.2)	2 (7.7)
Nausea	10 (38.5)	0 (0)
Thrombocytopenia	10 (38.5)	5 (19.2)
Cough	8 (30.8)	0 (0)
Fatigue	8 (30.8)	0 (0)
Rash	8 (30.8)	0 (0)
Anemia	6 (23.1)	0 (0)
Febrile neutropenia	6 (23.1)	6 (23.1)
Vomiting	6 (23.1)	1 (3.8)
ALT increased	5 (19.2)	3 (11.5)
AST increased	5 (19.2)	3 (11.5)
Constipation	5 (19.2)	0 (0)
Dizziness	5 (19.2)	0 (0)
Dyspnea	5 (19.2)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

TABLE 3 Summary of SAEs occurring in at least 1 patient attributed by the investigator to be related to parsaclisib by Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

	Parsaclisib + obinutuzumab and bendamustine (*N* = 26)	
Preferred term, *n* (%)	**Any SAE**	**Parsaclisib-related SAE**
Febrile neutropenia	6 (23.1)	1 (3.8)
ALT increased	2 (7.7)	2 (7.7)
AST increased	2 (7.7)	2 (7.7)
Bacteremia	1 (3.8)	1 (3.8)
Blood bilirubin increased	1 (3.8)	1 (3.8)
CMV colitis	1 (3.8)	1 (3.8)
Colitis	1 (3.8)	1 (3.8)
ECG QT prolongation	1 (3.8)	1 (3.8)
Malaise	1 (3.8)	1 (3.8)
Pancreatitis	1 (3.8)	1 (3.8)
Pyrexia	1 (3.8)	1 (3.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Nine TEAEs led to parsaclisib discontinuation and occurred in eight patients (30.8%; colitis [in two patients; 1 being CMV-related], ALT and AST increase [both in one patient], neutropenia, thrombocytopenia, electrocardiogram QT prolongation, tonsil cancer, and maculopapular rash). Several TEAEs led to obinutuzumab (4 [15.4%]) and bendamustine (2 [7.7%]) discontinuation (Supplemental Table 3). Treatment-emergent adverse events led to parsaclisib dose interruption in 21 patients (80.8%; most commonly neutropenia and thrombocytopenia, each 5 [19.2%]) and dose reduction in six patients (23.1%; most commonly neutropenia, 3 [11.5%]).

Hematology laboratory parameters that most commonly worsened were decreased leukocytes and decreased lymphocytes (each 21 [80.8%]), neutrophils and platelets (each 18 [69.2%]), and decreased hemoglobin (17 [65.4%]); worst post-baseline values were grade 3 for decreased lymphocytes (12 [46.2%]), decreased leukocytes (9 [34.6%]), platelets (5 [19.2%]), and neutrophils (4 [15.4%]), and grade 4 for neutrophils (9 [34.6%]), decreased lymphocytes (8 [30.8%]), decreased leukocytes (2 [7.7%]), and platelets (1 [3.8%]) (Supplemental Table 4). Most shift changes from baseline in CTCAE-grade chemistry laboratory parameters were to grade 1 or 2 (Supplemental Table 4). No patients met criteria for potential drug-induced liver injury.

3.3 | Efficacy

Objective responses were reported in 20 patients for an ORR of 76.9% (95% CI: 56.4–91.0); 17 patients (65.4%) had CR/CMR and three patients (11.5%) had PR/PMR as best overall response (Table 4). Nineteen patients (95.0%) had best percent reduction of >50% in target lesions size (Figure 1). Post hoc analyses of ORR and CRR based on POD24 and R/R status were similar to the overall study population; however, the number of patients in the subgroups is small, limiting interpretation of results (Table 4).

Median DOR was not reached (NR) for all patients (95% CI: 12.2–not evaluable [NE]; Figure 2A) or in patients achieving CR/CMR (95% CI: 18.3–NE; Figure 2B); median DOR was 6.0 months for patients achieving PR/PMR (95% CI: NE–NE; Figure 2B). Median DOR was NR for patients with POD <24 or POD ≥24 (95% CIs: 6.0–NE and 21.4–NE, respectively), and with R/R disease (95% CIs: 11.0–NE and 6.0–NE, respectively). Estimated 12- and 24-month DOR rates for all patients were 86% (95% CI: 55–96) and 60% (95% CI: 28–82), respectively.

Median PFS (95% CI: 15.2–NE) was NR (Figure 2C); estimated 12- and 24-month PFS rates were 85% (95% CI: 60–95) and 63% (95% CI: 35–82), respectively. Median PFS for patients with POD <24 and ≥24 months were 21.1 months (95% CI: 8.9–NE) and NR (95% CI: 24.1–NE), respectively, and for patients with R/R disease were NR (95% CI: 13.7–NE) and 21.1 months (95% CI: 8.9–NE), respectively.

Median OS was NR for all patients (95% CI: NE–NE) (Figure 2D). Estimated 12- and 24-month OS rates were 88% (95% CI: 63–96) and 83% (95% CI: 60–93), respectively. Median OS was NR for patients with POD <24 or POD ≥24 (95% CIs: 22.4–NE and 7.4–NE, respectively), and patients with R/R disease (95% CIs: 7.4–NE and 22.4–NE, respectively). Five patients (19.2%) died during survival follow-up due to either disease progression (n = 3), COVID-19-related pneumonia, or unknown reasons (each n = 1). Median (range) follow-up time was 22.8 (3.3–32.9) months from first dose to end of study (n = 26), and 20.6 (9.8–29.7) months from first response to end of study (n = 20).

3.4 | Translational biomarker analysis

Patient plasma samples were collected at cycle 1 day one (n = 26), cycle 2 day one (n = 22), cycle 4 day one (n = 16), and cycle 8 day one

TABLE 4 Summary of best overall and objective response in all patients, and by POD24, relapsed, and refractory status.

	Parsaclisib + obinutuzumab and bendamustine				
Variable	All patients (N = 26)	POD <24 (n = 16)	POD ≥24 (n = 8)	Relapsed (n = 9)	Refractory (n = 14)
Best overall response, n (%)					
CR/CMR	17 (65.4)	9 (56.3)	6 (75.0)	6 (66.7)	8 (57.1)
PR/PMR	3 (11.5)	3 (18.8)	0	0	3 (21.4)
SD/NMR	1 (3.8)	1 (6.3)	0	0	1 (7.1)
PD/PMD	2 (7.7)	2 (12.5)	0	0	2 (14.3)
NA[a]	3 (11.5)	1 (6.3)	2 (25.0)	3 (33.3)	0
ORR[b], % (95% CI)	76.9 (56.4–91.0)	75.0 (47.6–92.7)	75.0 (34.9–96.8)	66.7 (29.9–92.5)	78.6 (49.2–95.3)
CRR/CMRR[c], % (95% CI)	65.4 (44.3–82.8)	56.3 (29.9–80.2)	75.0 (34.9–96.8)	66.7 (29.9–92.5)	57.1 (28.9–82.3)

Abbreviations: CI, confidence interval; CMR(R), complete metabolic response (rate); CR(R), complete response (rate); NA, not assessed; NMR, no metabolic response; ORR, objective response rate; PD, progressive disease; PMD, progressive metabolic disease; PMR, partial metabolic response; POD24, progression of disease within 2 years; PR, partial response; SD, stable disease.

[a]No post-baseline response data available.

[b]Patients who have best overall response of CR/CMR or PR/PMR.

[c]Patients who have best overall response of CR/CMR.

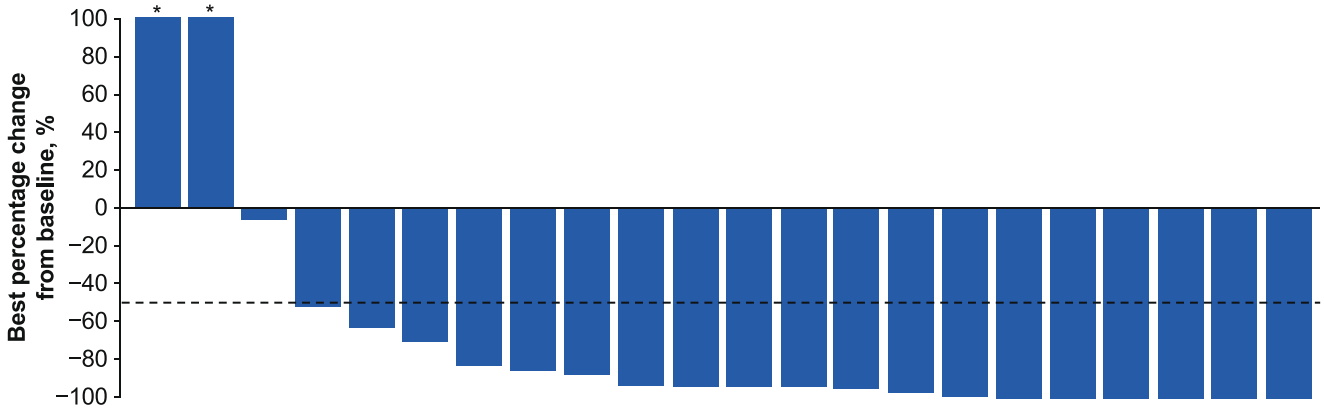

FIGURE 1 Best percentage change in sum of target lesions. *Indicates that the patient had best percentage change >100%. This plot includes patients who had baseline and ≥1 post-baseline valid measurement of target lesions (n = 22).

(n = 14). A set of DEP were identified, with significant fold-changes generally maintained across multiple time points (from cycle 2 day one, cycle 4 day one, and cycle 8 day one) (Supplemental Figure 3). Changes were observed in various proteins previously described as parsaclisib-responsive[23] including B-cell markers, cytokines involved in B-cell trafficking, and proteins elevated in B-cell lymphomas (CXCL13/BCA1, TNFRSF9, FCRL2, CD79B, and TNFRSF13B).

4 | DISCUSSION

In this open-label, phase 1, dose-finding, and cohort-expansion study evaluating safety and efficacy of parsaclisib in combination with obinutuzumab and bendamustine in patients with R/R FL following prior rituximab-containing regimens, criteria for parsaclisib dose de-escalation were not met. All patients experienced at least one TEAE, and most were managed with dose delays or reductions. Most common grade ≥3 TEAEs were neutropenia (35%), febrile neutropenia (23%), and thrombocytopenia (19%); no grade ≥3 anemia was observed.

In the phase 3 GADOLIN study, evaluating obinutuzumab plus bendamustine compared with bendamustine monotherapy in patients with indolent rituximab-refractory NHL (≥80% had FL), 98% of patients receiving combination therapy experienced at least one AE. Most common grade ≥3 AEs reported with obinutuzumab plus bendamustine in GADOLIN were neutropenia (one-third of patients), thrombocytopenia, and anemia; grade ≥3 febrile neutropenia was relatively uncommon.[8] Our study demonstrated little evidence of apparent synergistic toxicity between parsaclisib in combination with obinutuzumab and bendamustine—except for grade ≥3 febrile neutropenia that was more common in our study than the combination of obinutuzumab and bendamustine in patients with rituximab-refractory NHL,[8] or parsaclisib monotherapy in patients with R/R FL.[24]

Early-generation PI3K inhibitors are associated with class-specific AEs including infections; neutropenia; and immune-related, delayed-onset AEs such as diarrhea, colitis, transaminitis, pneumonitis, and dermatologic toxicities.[13,25,26] Some toxicities may be the result of not having established optimal doses or dosing schedules.[26] A modified dosing regimen in the phase 1/2 CITADEL-101 study, in which parsaclisib 20 mg was given daily for 9 weeks and weekly thereafter, was better tolerated than continuous 20 mg daily dosing due to the absence of late-onset TEAEs that lead to discontinuation.[18] Thus, an 8-week period of continuous parsaclisib daily dosing followed by an alternative dosing schedule, such as weekly dosing as assessed in this study, may minimize potential late-onset TEAEs. With respect to PI3K inhibitor class-specific, late-onset TEAEs observed in our study, the incidence of grade ≥3 diarrhea was low (8%) and there was no high-grade rash; no patients had pneumonitis, two patients had colitis (1 being CMV-related), and worsening in transaminases was limited.

In CITADEL-102, 77% of patients achieved an objective response, which was similar to 75.4% (95% CI: 66.9–82.6) reported in the phase 2 CITADEL-203 study of parsaclisib monotherapy in R/R FL patients.[19] In the current study, CRR/CMRR was 65%, whereas in CITADEL-203, CRR was 18.3% (95% CI: 11.9–26.1).[19] In the phase 3 GADOLIN study, 79% (151/192) of patients with indolent NHL (80% of whom had R/R FL) achieved an overall response (CR or PR) following treatment with obinutuzumab plus bendamustine, and 17% (32/192) had CR.[8] Although small patient numbers and study differences make comparisons inconclusive, the observed CRR in CITADEL-102 appears favorable to rates observed following either parsaclisib monotherapy, or obinutuzumab plus bendamustine combination therapy. Post hoc analyses by POD24 and R/R status found ORRs and CRRs similar to the overall patient population in CITADEL-102, however, these analyzes are limited by small subgroup samples sizes.

Two PI3K inhibitors (idelalisib and duvelisib) have been approved by the European Medicines Agency for treatment of R/R FL,[27,28] and four (idelalisib, copanlisib, duvelisib, and umbralisib) received accelerated approval from the US Food and Drug Administration (FDA) for treatment of patients with R/R FL based on single-arm trials.[26] However, FDA approval of umbralisib has since been withdrawn and the R/R FL indication removed for idelalisib and duvelisib in the

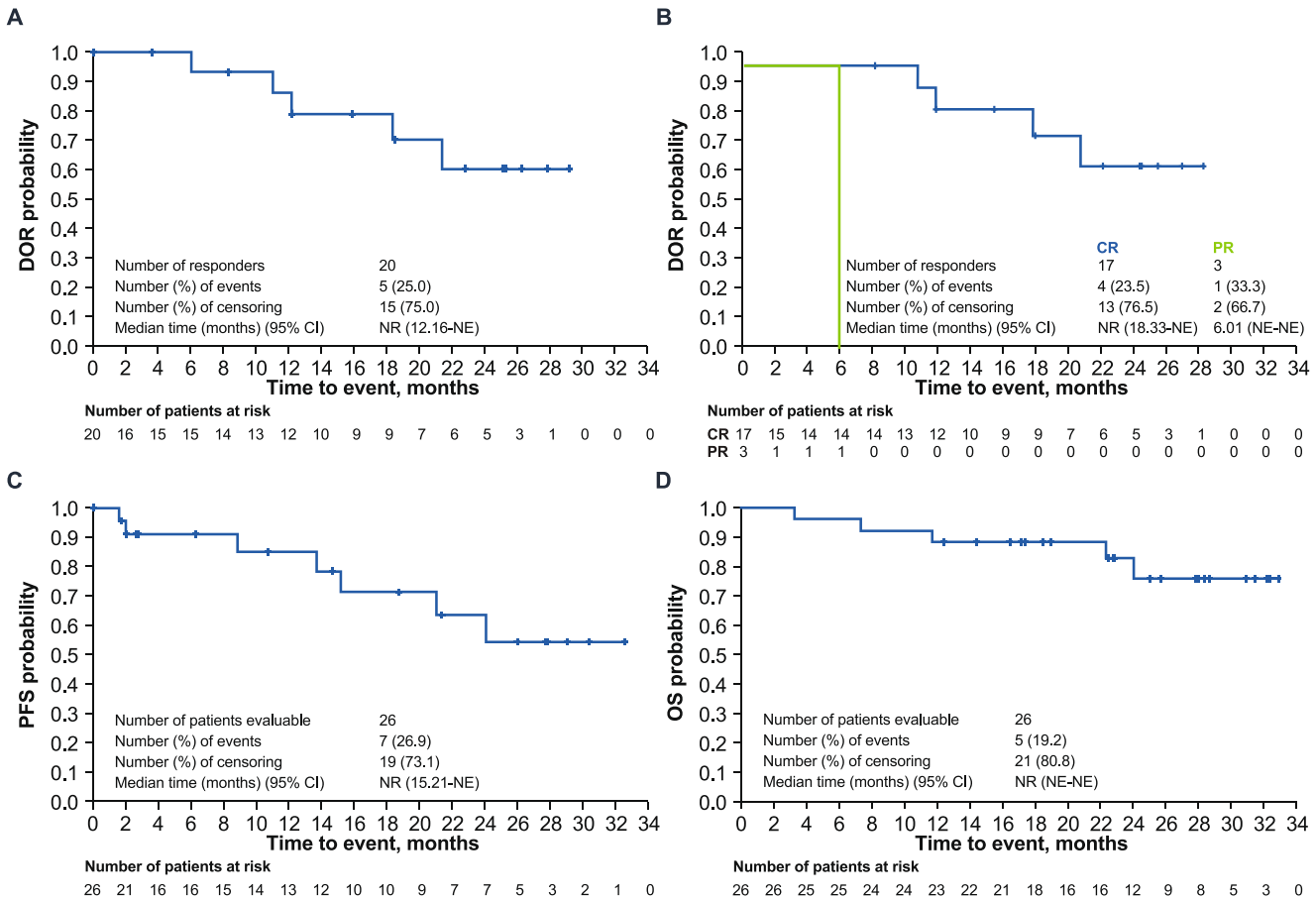

FIGURE 2 Kaplan-Meier estimates of (A) duration of response for all patients (median follow-up 18.5 months), (B) duration of response for patients with CR or PR, (C) progression-free survival (median follow-up 18.8 months), and (D) overall survival (median follow-up 25.8 months). CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

United States.[29–32] Withdrawals were due to issues with confirmatory studies and concerns that PI3K inhibitors may be associated with reduced OS due to increased toxicity.[26,33]

5 | CONCLUSION

In CITADEL-102, parsaclisib administered orally in combination with obinutuzumab and bendamustine did not result in unexpected safety events, with little evidence of synergistic toxicity, and demonstrated preliminary efficacy, including a CR/CMR rate of 65%, in patients with R/R FL who progressed following prior rituximab-containing regimens. Further studies are required to establish the role of PI3K inhibitors in the management of patients with R/R FL.

AUTHOR CONTRIBUTIONS

Mehdi Hamadani, Morton Coleman, Ralph Boccia, Juraj Duras, Martin Hutchings, Pier Luigi Zinzani, Raul Cordoba, Mariana Bastos Oreiro, and Juan-Manuel Sancho acquired the data. Vanessa Williams, Huiqing Liu, Michael Stouffs, and Peter Langmuir analyzed the data. All authors contributed to interpretation of data, drafting and/or critical review of the manuscript, and provided approval of the final version to be published.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g., US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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