Supplementary Material

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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SUPPLEMENTAL TABLE 1 Definition of DLTs

A DLT is defined as any AE that is new in onset or worsening in severity that meets any of the following criteria:
Nonhematologic: • Grade ≥3 nonhematologic toxicity, excluding nausea, vomiting, diarrhea • Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/antidiarrheal therapy lasting >48 hours • Any toxicity considered a DLT in the opinion of the investigator and medical monitor
Hematologic: • Grade 4 neutropenia lasting ≥7 days • Febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single temperature of >38.3 °C [101 °F] or a sustained temperature of ≥38 °C [100.4 °F] for more than 1 hour) • Grade 3 thrombocytopenia associated with clinically significant bleeding (in the opinion of the investigator, or resulting in the need for a red blood cell transfusion) • Grade 4 thrombocytopenia lasting >7 days • Grade 4 anemia
General: • Any specific AE that results in a dose delay or reduction in more than one-third of patients

AE, adverse event; ANC, absolute neutrophil count; DLT, dose-limiting toxicity.

SUPPLEMENTAL TABLE 2 Summary of any grade TRAEs (occurring in at least ≥10% of patients, with corresponding grade 3 or 4 TRAEs), and all grade 3 or 4 TRAEs (occurring in at least ≥5% of patients, with corresponding any grade TRAEs) by MedDRA preferred term

	Parsaclisib + obinutuzumab and bendamustine (*N* = 26)	
	Any grade	**Grade 3 or 4**
Parsaclisib TRAEs, *n* (%)	23 (88.5)	16 (61.5)
Neutropenia	11 (42.3)	7 (26.9)
Thrombocytopenia	8 (30.8)	2 (7.7)
Diarrhea	7 (26.9)	1 (3.8)
Fatigue	7 (26.9)	0 (0)
Rash	7 (26.9)	0 (0)
Nausea	6 (23.1)	0 (0)
ALT increased	4 (15.4)	3 (11.5)
AST increased	4 (15.4)	3 (11.5)
CMV test positive	4 (15.4)	0 (0)
Decreased appetite	4 (15.4)	0 (0)
Anemia	3 (11.5)	0 (0)
Maculopapular rash	3 (11.5)	1 (3.8)
Pyrexia	3 (11.5)	1 (3.8)
Vomiting	3 (11.5)	0 (0)
Neutrophil count decreased	2 (7.7)	2 (7.7)
Obinutuzumab TRAEs, *n* (%)	15 (57.7)	8 (30.8)
Neutropenia	6 (23.1)	5 (19.2)
Thrombocytopenia	6 (23.1)	2 (7.7)
Fatigue	3 (11.5)	0 (0)
Pyrexia	3 (11.5)	1 (3.8)
Bendamustine TRAEs, *n* (%)	21 (80.8)	10 (38.5)
Neutropenia	8 (30.8)	6 (23.1)

Thrombocytopenia	7 (26.9)	4 (15.4)
Nausea	5 (19.2)	0 (0)
Fatigue	4 (15.4)	0 (0)
Febrile neutropenia	4 (15.4)	4 (15.4)
Pyrexia	4 (15.4)	1 (3.8)
Anemia	3 (11.5)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event.

SUPPLEMENTAL TABLE 3 Summary of TEAEs leading to discontinuation of study drugs

Preferred term, *n* (%)	**Parsaclisib + obinutuzumab and bendamustine (*N* = 26)**
Parsaclisib discontinuation[†]	8 (30.8)
ALT increased	1 (3.8)
AST increased	1 (3.8)
CMV colitis	1 (3.8)
Colitis	1 (3.8)
ECG QT prolonged	1 (3.8)
Maculopapular rash	1 (3.8)
Neutropenia	1 (3.8)
Thrombocytopenia	1 (3.8)
Tonsil cancer	1 (3.8)
Obinutuzumab discontinuation[‡]	4 (15.4)
ALT increased	1 (3.8)
AST increased	1 (3.8)
CMV colitis	1 (3.8)
Neutropenia	1 (3.8)
Tonsil cancer	1 (3.8)
Bendamustine discontinuation[§]	2 (7.7)
ALT increased	1 (3.8)
AST increased	1 (3.8)
CMV colitis	1 (3.8)

[†]Nine TEAEs leading to parsaclisib discontinuation occurred in 8 patients (ALT and AST increased [both in 1 patient], CMV colitis, colitis, ECG QT prolonged, maculopapular rash, neutropenia, thrombocytopenia, tonsil cancer).
[‡]Five TEAEs leading to obinutuzumab discontinuation occurred in 4 patients (ALT and AST increased [both in 1 patient], CMV colitis, neutropenia, tonsil cancer).
[§]Three TEAEs leading to bendamustine discontinuation occurred in 2 patients (ALT and AST increased [both in 1 patient], CMV colitis).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; ECG, electrocardiogram; TRAE, treatment-related adverse event.

SUPPLEMENTAL TABLE 4 Treatment-emergent worsening of CTCAE-graded hematology and chemistry laboratory parameters[†]

	Parsaclisib + obinutuzumab and bendamustine (*N* = 26)			
Hematology laboratory parameter, *n* (%)	**Any grade**	**Grade 3**	**Grade 4**	**Missing[‡]**
Leukocytes (GI/L) – low direction	21 (80.8)	9 (34.6)	2 (7.7)	0 (0)
Lymphocytes (GI/L) – low direction	21 (80.8)	12 (46.2)	8 (30.8)	2 (7.7)
Neutrophils (GI/L)	18 (69.2)	4 (15.4)	9 (34.6)	1 (3.8)
Platelets (GI/L)	18 (69.2)	5 (19.2)	1 (3.8)	0 (0)
Hemoglobin (g/L) – low direction	17 (65.4)	0 (0)	NA	0 (0)
Leukocytes (GI/L) – high direction	4 (15.4)	0 (0)	NA	0 (0)
Hemoglobin (g/L) – high direction	1 (3.8)	0 (0)	NA	0 (0)
Lymphocytes (GI/L) – high direction	0 (0)	0 (0)	NA	2 (7.7)
Chemistry laboratory abnormalities, *n* (%)	**Any grade**	**Grade 3**	**Grade 4**	**Missing[‡]**
Potassium (mmol/L) – low direction	10 (38.5)	1 (3.8)	0 (0)	0 (0)
Calcium (mmol/L) – low direction	9 (34.6)	0 (0)	0 (0)	0 (0)
Cholesterol (mmol/L)	9 (34.6)	0 (0)	0 (0)	1 (3.8)
Creatinine (μmol/L) – ULN	9 (34.6)	0 (0)	0 (0)	0 (0)
Alkaline phosphatase (U/L)	8 (30.8)	0 (0)	0 (0)	1 (3.8)
AST (U/L)	7 (26.9)	3 (11.5)	0 (0)	0 (0)
ALT (U/I)	7 (26.9)	2 (7.7)	1 (3.8)	0 (0)

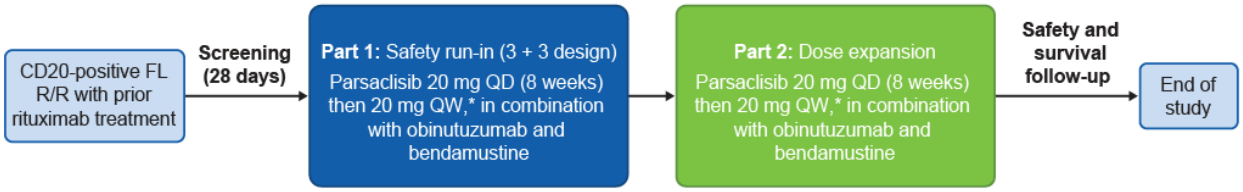
Phosphate (mmol/L) – low	7 (26.9)	2 (7.7)	0 (0)	0 (0)
Bilirubin (µmol/L)	7 (26.9)	1 (3.8)	0 (0)	0 (0)
Albumin (g/L)	7 (26.9)	0 (0)	NA	1 (3.8)
Glucose (mmol/L) – high direction	5 (19.2)	0 (0)	0 (0)	2 (7.7)
Sodium (mmol/L) – low direction	5 (19.2)	0 (0)	0 (0)	0 (0)
Sodium (mmol/L) – high direction	4 (15.4)	0 (0)	0 (0)	0 (0)
Potassium (mmol/L) – high direction	3 (11.5)	0 (0)	0 (0)	0 (0)
Calcium (mmol/L) – high direction	1 (3.8)	0 (0)	0 (0)	0 (0)
Glucose (mmol/L) – low direction	1 (3.8)	0 (0)	0 (0)	0 (0)

[†]If baseline grade was missing, any postbaseline abnormality (Grade 1–4) was considered worsening from baseline.

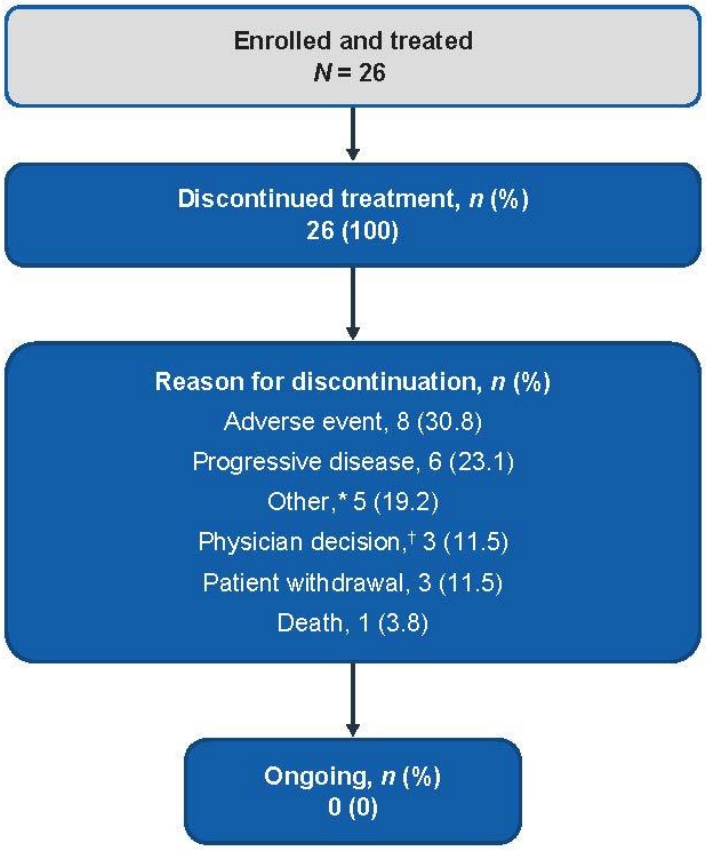
[‡]Patients that had no post-baseline value.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; ULN, upper limit of normal.

SUPPLEMENTAL FIGURE 1 Study design. *A lower dose of parsaclisib could be given if the MTD was exceeded; all 26 patients enrolled in the study received parsaclisib at the dose level of 20 mg QD for 8 weeks followed by 20 mg QW. FL, follicular lymphoma; MTD, maximum tolerated dose; QD, once daily; QW, once weekly; R/R, relapsed/refractory.



SUPPLEMENTAL FIGURE 2 Summary of patient disposition. *All patients whose primary reason for treatment discontinuation was recorded as 'other' continued to receive parsaclisib treatment in a rollover study (NCT04509700). †All patients whose primary reason for treatment discontinuation was recorded as 'physician decision' were moved onto stem cell transplantation.



SUPPLEMENTAL FIGURE 3 Plasma biomarkers differentially expressed from baseline for patients with paired samples. Data represent plasma proteins having significant fold-changes from baseline (FCH>1.5; FDR<0.05) in patients with paired samples. Samples are grouped by day of visit and best overall response. C, cycle; D, day; CR, complete response; FCH, absolute fold change; FDR, false discovery rate; NA, not available; PD progressive disease; PR, partial response.