SUPPLEMENTAL DATA

A phase 2 study of parsaclisib, a PI3Kδ inhibitor, in relapsed and refractory marginal zone lymphoma (CITADEL-204)

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Supplemental Table 1. Schedule of study assessments

	Screening	Treatment				Follow-up		
						Safety	Disease	Survival
Procedure	**Day −28 to −1**	**Day 1***	**Every 4 weeks through week 48 (± 3 days)**	**Every 12 weeks from week 48 (±1 week)**	**EOT**	**EOT + 30–35 days**		**Every 12 weeks (±1 week)**
Informed consent	X							
Contact IWRS	X	X	X	X	X			
Inclusion, exclusion criteria	X	X						
Demography, medical history	X							
HR-QOL FACT-Lym†		X	Every 8 weeks through week 24 (±1 week), then every 12 weeks through week 96, and then every 24 weeks thereafter until PD			X	X‡	
Prior/concomitant medications	X	X	X	X	X	X		
AE assessment§	X	X	X	X	X	X		
Comprehensive physical examination	X‖				X			
Disease-specific physical examination		X	X	X		X		
Vital signs	X	X	X	X	X	X		
12-lead ECG	X	X	X¶	X	X	X		
ECOG PS score	X	X	X	X	X	X		
CT/MRI scan	X		Every 8 weeks through week 24 (±1 week), then every 12 weeks through week 96, and then every 24 weeks thereafter until PD				X‡	
Bone marrow examination	X**		X††				X††	
PJP prophylaxis		X‡‡						
Study drug dispensing		X	X	X				
Study drug compliance		X	X	X	X			
Study drug administration		X	X	X				
Disease follow-up							X‡	
Survival follow-up								X§§

AE, adverse event; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HR-QOL, health-related quality of life; ICF, informed consent form; IWRS, interactive web-response system; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PD, progressive disease; PJP, *Pneumocystis jiroveci* pneumonia; PK, pharmacokinetics. *All procedures are to be performed before administration of study treatment on day 1. †Questionnaire to be administered before any procedures performed at each clinic visit. ‡Only for patients who discontinued study treatment for a reason other than disease progression. Radiologic imaging and assessment of HR-QOL will continue to be performed as per assessment schedule (every 8, 12, or 24 weeks as appropriate with disease progression). §AEs will be monitored from the time the patient signs the ICF until ≥30 days after the last dose of study treatment. Serious AEs occurring >30 days after the last dose of study treatment should be reported to the sponsor or its designee if the investigator suspects a causal relationship to the study treatment. Once detected, AEs should be followed until resolved or judged to be permanent. ‖Height required at screening only. ¶Timed triplicate ECGs will be obtained during the day 1 visit (pre-dose) and week 4 visit (pre-dose and 1.5 hours [±15 minutes] after receiving study treatment). **Required at baseline unless (1) the patient underwent a bone marrow examination as part of standard of care within 60 days of first dose of study treatment or (2) after the last treatment for NHL and the results showed lymphoma involvement in the bone marrow. ††If disease is present in bone marrow at baseline, a bone marrow biopsy will be required to confirm CR or may be performed as clinically indicated. For patients with splenic marginal zone lymphoma without measurable disease (ie, only have histologically confirmed bone marrow infiltration), a bone marrow biopsy/examination must be performed when the number of lymphocytes in the blood normalize. ‡‡PJP prophylaxis should be given while patients are receiving study treatment and continue for at least 2–6 months after the last dose of study treatment. §§May be conducted by clinic visit, telephone, or email.

Supplemental Table 2. Baseline demographics and clinical characteristics (cohort 1)

Characteristic	Weekly dosing group (N = 4)	Daily dosing group (N = 6)	All treated patients (N = 10)
Age, median (range), years	73.5 (71–76)	72.5 (65–78)	73.5 (65–78)
≥65 years, n (%)	4 (100.0)	6 (100.0)	10 (100.0)
Male, n (%)	2 (50.0)	2 (33.3)	4 (40.0)
Race, n (%)			
White	3 (75.0)	5 (83.3)	8 (80.0)
Other*	1 (25.0)	1 (16.7)	2 (20.0)
ECOG PS score, n (%)			
0	0	3 (50.0)	3 (30.0)
1	4 (100.0)	3 (50.0)	7 (70.0)
2	0	0	0
MZL disease subtype, n (%)			
Nodal	3 (75.0)	4 (66.7)	7 (70.0)
Extranodal	0	2 (33.3)	2 (20.0)
Splenic	1 (25.0)	0	1 (10.0)
Ann arbor staging, n (%)			
I	0	0	0
Ii	1 (25.0)	0	1 (10.0)
Iii	0	0	0
Iv	3 (75.0)	6 (100.0)	9 (90.0)
Time since diagnosis, median (range), years	11.3 (5.1–18.2)	5.4 (0.6–10.6)	7.9 (0.6–18.2)
Number of prior treatments, median (range)	5.0 (3–8)	3.0 (1–5)	3.0 (1–8)
Prior therapies, n (%)			
Anti-CD20 mAb	4 (100.0)	5 (83.3)	9 (90.0)
Surgery/surgical procedures	1 (25.0)	1 (16.7)	2 (20.0)
Radiation	1 (25.0)	2 (33.3)	3 (30.0)
HSCT	0	0	0
Status to most recent prior therapy, n (%)			
Relapsed	0	0	0
Refractory	4 (100.0)	5 (83.3)	9 (90.0)
Unknown	0	1 (16.7)	1 (10.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; mAb, monoclonal antibody; MZL, marginal zone lymphoma.

*Includes one Other enrolled in the weekly dosing group and one Black patient enrolled in the daily dosing group.

Supplemental Table 3. Patient disposition and exposure as of Jan 15, 2021 cut-off (cohort 2)

	Weekly dosing group (n = 28)	Daily dosing group (n = 72)	All treated patients (N = 100)
Patients discontinued from treatment, n (%)	15 (53.6)	50 (69.4)	65 (65.0)
Primary reasons for discontinuing, n (%)			
Progressive disease	10 (35.7)	18 (25.0)	28 (28.0)
Adverse event	2 (7.1)	27 (37.5)	29 (29.0)
Withdrawal/physician decision	2 (7.1)	3 (4.2)	5 (5.0)
Protocol deviation	1 (3.6)	1 (1.4)	2 (2.0)
Death	0	1 (1.4)	1 (1.0)
Patients with ongoing treatment, n (%)	13 (46.4)	22 (30.6)	35 (35.0)
Median (range) duration of treatment,* months	19.9 (1.4–30.0)	11.6 (0.4–30.9)	13.4 (0.4–30.9)
Median (range) duration of follow-up,† months	26.6 (21.7–34.8)	21.0 (11.9–37.0)	22.8 (11.9–37.0)

*Duration of treatment (months): (date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment. †Duration of follow-up (months): (cut-off date [Jan 15, 2021] – first dose date + 1) / 30.4375.

Supplemental Table 4. Best overall response, and ORR and CRR among patients receiving parsaclisib (cohort 1)

Response	Weekly dosing group (N = 2)	Daily dosing group (N = 6)	Crossover group (N = 2)	All treated patients (N = 10)
Best overall response, n (%)				
Complete response	0	0	0	0
Partial response	0	2 (33.3)	2 (100.0)	4 (40.0)
Stable disease	2 (100.0)	3 (50.0)	0	5 (50.0)
Progressive disease	0	0	0	0
Not evaluable/assessed	0	1 (16.7)	0	1 (10.0)
ORR, % (95% CI)	0.0 (0.0–84.2)	33.3 (4.3–77.7)	100.0 (15.8–100)	40.0 (12.2–73.8)
CRR, % (95% CI)	0.0 (0.0–84.2)	0.0 (0.0–45.9)	0.0 (0.0–84.2)	0.0 (0.0–30.8)

CI, confidence interval; CRR, complete response rate; ORR, objective response rate.

Supplemental Table 5. Selected new or worsening laboratory abnormalities occurring in patients receiving parsaclisib (cohort 2)

	Weekly dosing group (N = 28)			Daily dosing group (n = 72)			All treated patients (N = 100)		
Preferred term, n (%)	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**
Neutrophils decreased	18 (64.3)	3 (10.7)	1 (3.6)	35 (48.6)	7 (9.7)	3 (4.2)	53 (53.0)	10 (10.0)	4 (4.0)
Hemoglobin decreased	8 (28.6)	0	NA	24 (33.3)	5 (6.9)	NA	32 (32.0)	5 (5.0)	NA
Platelets decreased	6 (21.4)	2 (7.1)	0	14 (19.4)	3 (4.2)	0	20 (20.0)	5 (5.0)	0
ALT increased	6 (21.4)	0	0	21 (29.2)	3 (4.2)	2 (2.8)	27 (27.0)	3 (3.0)	2 (2.0)
AST increased	7 (25.0)	0	0	15 (20.8)	2 (2.8)	1 (1.4)	22 (22.0)	2 (2.0)	1 (1.0)
Bilirubin increased	6 (21.4)	0	0	9 (12.5)	0	0	15 (15.0)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, Common Terminology Criteria for Adverse Events grade not applicable to the parameter.

Supplemental Table 6. Most common any-grade TEAEs (occurring in ≥20% of patients in the total population) and grade ≥3 TEAEs among patients receiving parsaclisib (cohort 1)

	Daily dosing group (N = 6)		All treated patients (N = 10)	
Preferred term (MedDRA), n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any TEAE	5 (83.3)	4 (66.7)	9 (90.0)	6 (60.0)
Abdominal pain	1 (16.7)	0	3 (30.0)	0
Diarrhea	2 (33.3)	1 (16.7)	3 (30.0)	1 (10.0)
Cough	2 (33.3)	0	2 (20.0)	0
Dyspnea	1 (16.7)	0	2 (20.0)	0
Fatigue	1 (16.7)	0	2 (20.0)	0
Hypercalcemia	2 (33.3)	1 (16.7)	2 (20.0)	1 (10.0)
Nasopharyngitis	1 (16.7)	0	2 (20.0)	0
Pulmonary embolism	0	0	2 (20.0)	1 (10.0)
Rash	1 (16.7)	0	2 (20.0)	0

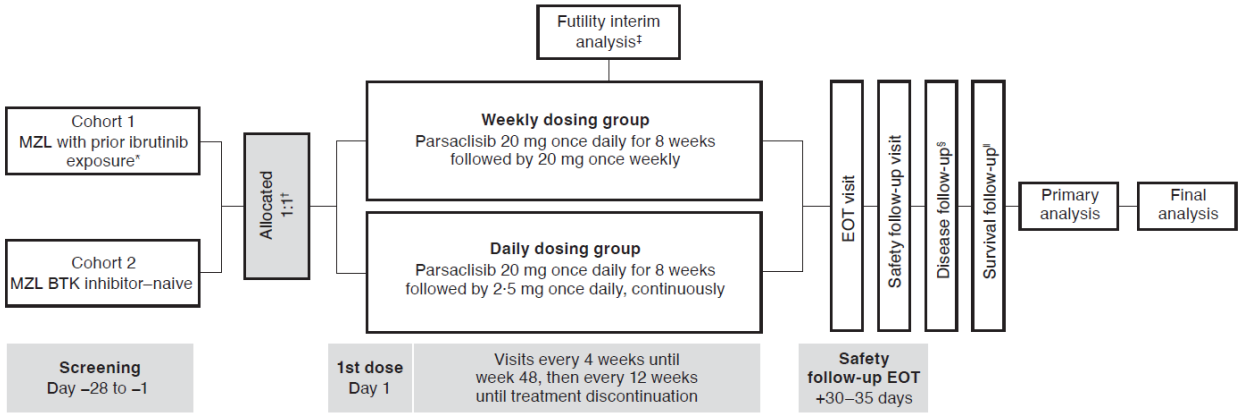
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Supplemental Table 7. Differentially expressed analytes at week 4 of parsaclisib treatment compared with baseline (cohort 2)

Analyte name	Reduction from baseline* (N = 75) (%, 95% CI)
TNFRSF9	−73.2 (−77.9 to −67.4)
CXCL13	−66.9 (−71.9 to −60.95)
TNFRSF13B	−65.3 (−71.3 to −57.9)
FCRL2	−60.3 (−66.5 to −53.0)
LTA	−57.5 (−63.7 to −50.2)
CCL19	−57.45 (−64.0 to −49.7)
TNFRSF4	−56.8 (−62.35 to −50.4)
IL10†	−56.2 (−63.8 to −47.1)
IL10†	−54.4 (−61.95 to −45.45)
CCL17	−52.9 (−61.0 to −43.1)
IL2RA	−47.4 (−54.0 to −39.9)
IL12B	−45.8 (−52.6 to −37.9)
FCER2	−45.6 (−60.05 to −25.9)
CD160	−44.2 (−48.7 to −39.45)
XCL1	−38.15 (−43.4 to −32.4)
MMP9	−36.5 (−45.25 to −26.3)
LAIR2	−35.2 (−40.7 to −29.15)

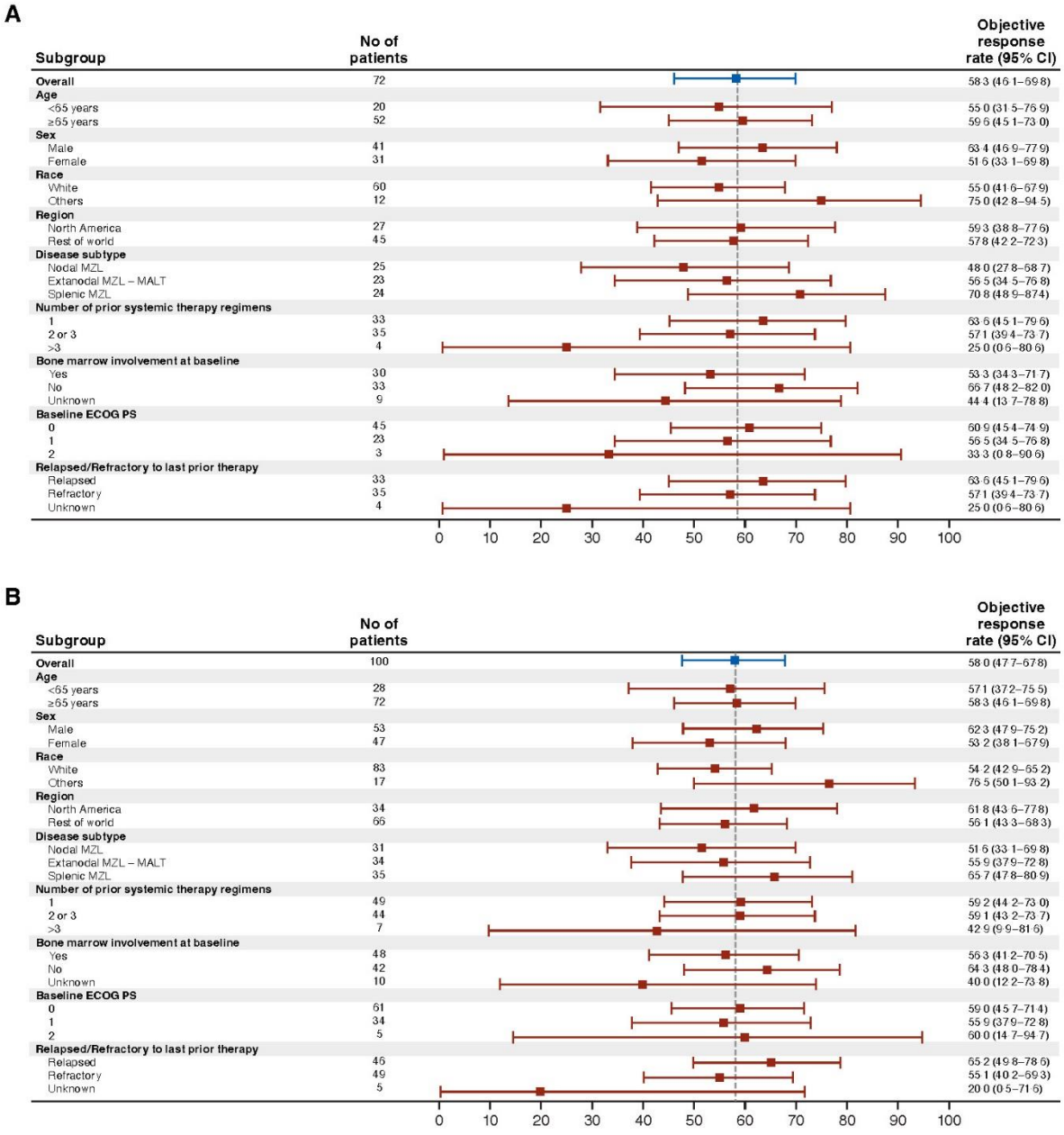
Differentially expressed analytes in common with INCB 50465-101.
*Genomic mean of percentage from baseline. †This analyte was tested twice with similar results.

Supplemental Figure 1. CITADEL-204 study design



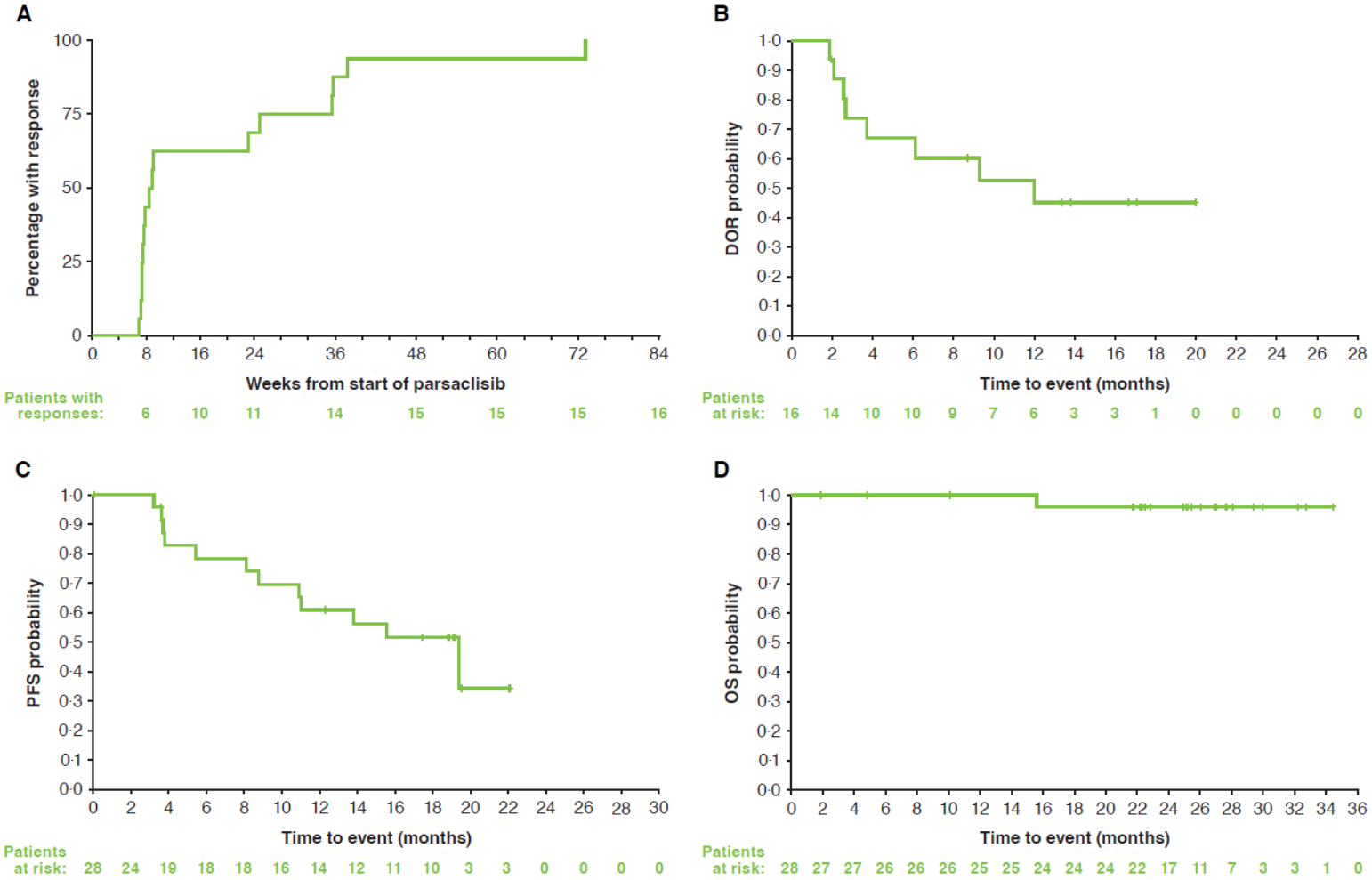
BTK, Bruton tyrosine kinase; EOT, end of treatment; MZL, marginal zone lymphoma.
*Per Protocol Amendment 3, cohort 1 was closed to further enrollment. †The first 60 patients in cohort 2 and all eligible patients in cohort 1 were allocated in a 1:1 ratio to the weekly dosing group and the daily dosing group. An additional 30 patients were planned to be enrolled in the selected dosing group (daily dosing group). ‡A futility analysis was performed for cohort 2 when the first 30 patients were treated and evaluated for response. §Patients who discontinued study treatment for a reason other than disease progression continued with disease assessments by radiologic imaging every 8, 12, or 24 weeks as appropriate until disease progression. ‖Every 12 weeks by clinical visit, telephone, or email.

Supplemental Figure 2. Forest plot of objective response rate by subgroup in (A) the daily dosing group and (B) all treated patients (cohort 2)

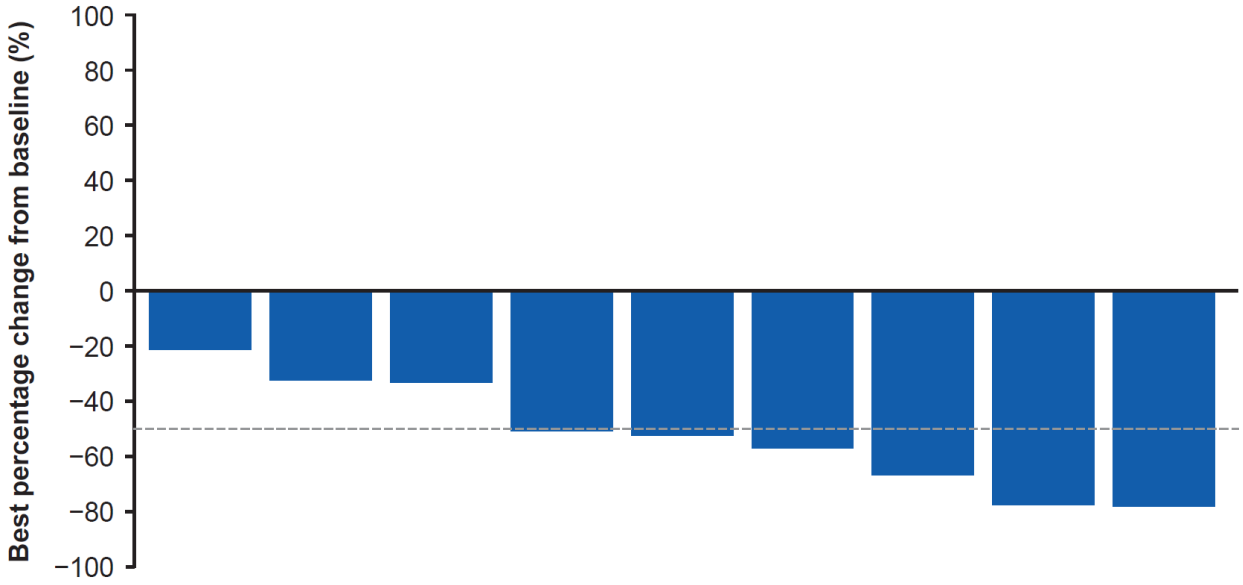


CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.

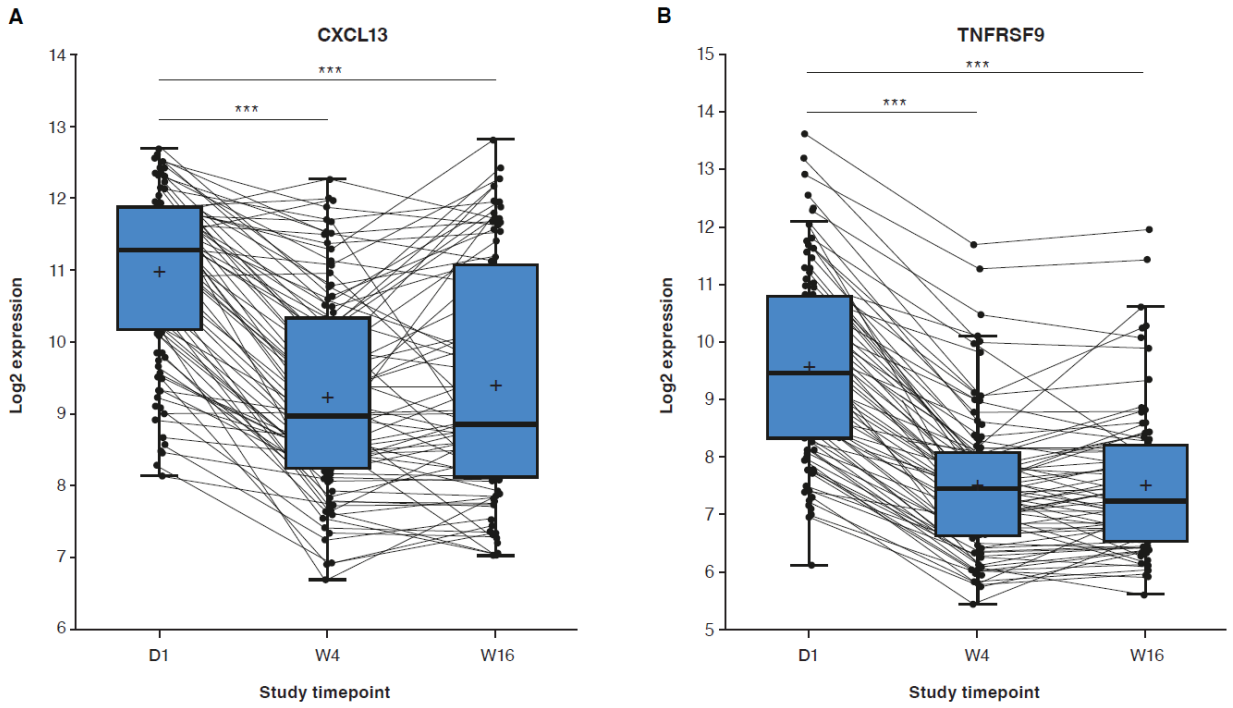
Supplemental Figure 3. (A) Cumulative time to response curves, and (B) Kaplan-Meier estimates of duration of response (DOR), (C) progression-free survival (PFS), and (D) overall survival (OS) in the weekly dosing group (cohort 2). All response assessments were by independent review committee



Supplemental Figure 4. Best percentage change from baseline in target lesion size in all patients with measurable disease at baseline (weekly and daily dosing groups) by independent review committee (cohort 1)



Supplemental Figure 5. Expression of serum CXCL13 and TNFRSF9 at baseline and at weeks 4 and 16 after treatment with parsaclisib (cohort 2)



Data represent serum protein expression (Log_2) values of CXCL13/BCA1 and TNFRSF9 for individual patients at baseline (D1), week 4 (W4), and week 16 (W16). Boxes denote the first and third quartiles for expression among patients on the recommended dose, with bold lines indicating the medians. ***Denotes the false discovery rate p-values of <0.0001 using a generalized linear model.