

## Supplemental Appendix

### A phase 2 study of piasalisib, a PI3K $\delta$ inhibitor, in relapsed and refractory mantle cell lymphoma (CITADEL-205)

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## Supplemental Tables

**Table S1: Schedule of study assessments**

Procedure	Screening	Treatment			EOT	Follow-up		
		Day –28 to –1	Day 1 <sup>a</sup>	Every 4 weeks through week 48 (±3 days)		Every 12 weeks from week 48 (±1 week)	Safety	Disease
	EOT + 30–35 days							Every 12 weeks (±1 week)
Informed consent	X							
Contact interactive web response system	X	X	X	X	X			
Inclusion, exclusion criteria	X	X						
Demography, medical history	X							
HR-QOL FACT-Lym <sup>b</sup>		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 <sup>c</sup>	
Prior/concomitant medications	X	X	X	X	X	X		
AE assessment <sup>d</sup>	X	X	X	X	X	X		
Comprehensive physical exam	X <sup>e</sup>				X			
Disease-specific physical exam		X	X	X		X		
Vital signs	X	X	X	X	X	X		
12-lead ECG	X	X <sup>f</sup>	X <sup>f</sup>	X	X	X		
ECOG status	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 <sup>c</sup>	
Bone marrow exam	X <sup>g</sup>		X <sup>h</sup>				X <sup>h</sup>	
PJP prophylaxis		X <sup>i</sup>						
Study drug dispensing		X	X	X				
Study drug compliance		X	X	X	X			
Study drug administration		X	X	X				
Disease follow-up							X <sup>c</sup>	
Survival follow-up								X <sup>j</sup>

<sup>a</sup>All procedures are to be performed before administration of study treatment on day 1.

<sup>b</sup>Questionnaire to be administered before any procedures performed at each clinic visit.

<sup>c</sup>Only for patients who discontinued study treatment for a reason other than disease progression; radiologic imaging and assessment of HRQOL will continue to be performed as per assessment schedule (every 8, 12, or 24 weeks as appropriate with disease progression).

<sup>d</sup>Adverse events will be monitored from the time the patient signs the informed consent form until at least 30 days after the last dose of study treatment. Serious AEs occurring more than 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.

<sup>e</sup>Height required at screening only.

<sup>f</sup>Timed triplicate ECGs will be obtained during the day 1 visit (predose) and week 4 visit (predose and 1.5 hours [±15 min] after receiving study treatment).

<sup>g</sup>Required at baseline.

<sup>h</sup>If disease is present in bone marrow at baseline, a bone marrow biopsy will be required to confirm complete response or may be performed as clinically indicated.

<sup>i</sup>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.

<sup>j</sup>May be conducted by clinic visit, telephone, or email.

**Table S2: Baseline demographics and clinical characteristics (BTKi-experienced cohort)**

Characteristic	Weekly dosing group* (n=12)	Daily dosing group (n=41)	All treated patients (n=53)
Age, median (range), years	72.5 (53–82)	71.0 (48–89)	71.0 (48–89)
≥65 years, n (%)	8 (66.7)	29 (70.7)	37 (69.8)
Male, n (%)	11 (91.7)	30 (73.2)	41 (77.4)
Race, n (%)			
White/Caucasian	11 (91.7)	37 (90.2)	48 (90.6)
Black/African American	0	0	0
Asian	0	0	0
Other	1 (8.3)	1 (2.4)	2 (3.8)
Missing	0	3 (7.3)	3 (5.7)
ECOG performance status, n (%)			
0	5 (41.7)	21 (51.2)	26 (49.1)
1	5 (41.7)	16 (39.0)	21 (39.6)
2	2 (16.7)	4 (9.8)	6 (11.3)
MIPI risk category, n (%)			
Low (0–3)	1 (8.3)	9 (22.0)	10 (18.9)
Intermediate (4–5)	4 (33.3)	10 (24.4)	14 (26.4)
High (6–11)	7 (58.3)	22 (53.7)	29 (54.7)
Ann arbor staging, n (%)			
I	0	3 (7.3)	3 (5.7)
II	0	7 (17.1)	7 (13.2)
III	2 (16.7)	5 (12.2)	7 (13.2)
IV	10 (83.3)	26 (63.4)	36 (67.9)
Time since diagnosis, median (range), years	6.6 (1.6–19.4)	4.3 (0.4–13.6)	4.7 (0.4–19.4)
Number of prior systemic regimens, median (range)	3.0 (2–3)	2.0 (1–3)	3.0 (1–3)
Prior therapies, n (%)			
Anti-CD20 mAb	11 (91.7)	39 (95.1)	50 (94.3)
Nitrogen mustard analogue	10 (83.3)	39 (95.1)	49 (92.5)
Carmustine	0	1 (2.4)	1 (1.9)
Platinum compound	1 (8.3)	10 (24.4)	11 (20.8)
Status to most recent prior therapy, n (%)			
Relapsed	6 (50.0)	18 (43.9)	24 (45.3)
Refractory	5 (41.7)	18 (43.9)	23 (43.5)
Unknown	1 (8.3)	5 (12.2)	6 (11.3)

ECOG=Eastern Cooperative Oncology Group. MIPI=Mantle Cell Lymphoma International Prognostic Index.

\*Includes 1 patient that switched from 20 mg QW to 2.5 mg QD parsaclisib.

**Table S3: Patient disposition and exposure (BTKi-naïve cohort)**

	<b>Weekly dosing group<sup>‡</sup> (n=31)</b>	<b>Daily dosing group (n=77)</b>	<b>All treated patients (N=108)</b>
Patients discontinued from treatment, n (%)	22 (71.0)	56 (72.7)	78 (72.2)
Primary reasons for discontinuing, n (%)			
Progressive disease	19 (61.3)	30 (39.0)	49 (45.4)
Adverse event	2 (6.5)	23 (29.9)	25 (23.1)
Withdrawal/physician decision	1 (3.2)	2 (2.6)	3 (1.9)
Death	0	1 (1.3)	1 (0.9)
Patients with ongoing treatment, n (%)	9 (29.0)	21 (27.3)	30 (27.8)
Median (range) duration of treatment,* months	11.0 (0.1–30.0)	7.9 (1.7–27.4)	8.3 (0.1–30.0)
Median (range) duration of follow-up, <sup>†</sup> months	26.1 (21.7–31.2)	18.2 (11.6–35.9)	22.9 (11.6–35.9)

\*Duration of treatment (months)=(date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment.

<sup>†</sup>Duration of follow-up (months)=(cutoff date [January 15, 2021] – first dose date + 1) / 30.4375.

<sup>‡</sup>Includes 10 patients that switched from 20 mg QW to 2.5 mg QD parsacalisib.

**Table S4: Patient disposition and exposure (BTKi-experienced cohort)**

	<b>Weekly dosing group*</b> <b>(n=12)</b>	<b>Daily dosing group</b> <b>(n=41)</b>	<b>All treated patients</b> <b>(N=53)</b>
Patients discontinued from treatment, n (%)	12 (100.0)	38 (92.7)	50 (94.3)
Primary reasons for discontinuing, n (%)			
Progressive disease	10 (83.3)	31 (75.6)	41 (77.4)
Adverse event	1 (8.3)	5 (12.2)	6 (11.3)
Death	1 (8.3)	1 (2.4)	2 (3.8)
Withdrawal/physician decision	0	1 (2.4)	1 (1.9)
Patients with ongoing treatment, n (%)	0	3 (7.3)	3 (5.7)
Median (range) duration of treatment, † months	1.0 (0.3–12.0)	3.7 (0.1–22.7)	2.8 (0.1–22.7)
Median (range) duration of follow-up, ‡ months	25.9 (21.4–34.9)	17.1 (8.4–37.8)	20.1 (8.4–37.8)

\*Includes 1 patient that switched from 20 mg QW to 2.5 mg QD piasalisib.

†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)=(cutoff date [January 15, 2021] – first dose date + 1) / 30.4375.

**Table S5: Best overall response, and objective response and complete response rate among patients receiving parsaclisib (BTKi-experienced cohort)**

<b>Response</b>	<b>Weekly dosing group* (n=12)</b>	<b>Daily dosing group (n=41)</b>	<b>All treated patients (N=53)</b>
Best overall response, n (%)			
Complete response	0	1 (2.4)	1 (1.9)
Partial response	1 (8.3)	14 (34.1)	15 (28.3)
Stable disease	3 (25.0)	7 (17.1)	10 (18.9)
Progressive disease	1 (8.3)	12 (29.3)	13 (24.5)
Not estimable/assessed	1 (8.3)	0	1 (1.9)
ORR, % (95% CI)	8.3 (0.2–38.5)	36.6 (22.1–53.1)	30.2 (18.3–44.3)
CRR, % (95% CI)	0 (0.0–26.5)	2.4 (0.1–12.9)	1.9 (0.0–10.1)

CI=confidence interval. CRR=complete response rate. ORR=objective response rate.

\*Includes 1 patient that switched from 20 mg QW to 2.5 mg QD parsaclisib.

**Table S6: TEAEs of special interest (BTKi-naive cohort)**

Preferred term (MedDRA), N (%)	Daily dosing group (N=77)		All treated patients (N=108)	
	Any	Grade ≥3	Any	Grade ≥3
Colitis	7 (9.1)	4 (5.2)	7 (6.5)	4 (3.7)
Cytomegalovirus infection	2 (2.6)	1 (1.3)	3 (2.8)	1 (0.9)
Dermatitis exfoliative	0	0	1 (0.9)	1 (0.9)
Diarrhoea	31 (40.3)	14 (18.2)	37 (34.3)	15 (13.9)
Febrile neutropenia	1 (1.3)	1 (1.3)	1 (0.9)	1 (0.9)
Herpes simplex	1 (1.3)	0	1 (0.9)	0
<i>Pneumocystis jirovecii pneumonia</i>	1 (1.3)	0	1 (0.9)	0
Pneumonia	2 (2.6)	2 (2.6)	2 (1.9)	2 (1.9)
Pneumonitis	1 (1.3)	0	2 (1.9)	0
Rash	11 (14.3)	3 (3.9)	12 (11.1)	3 (2.8)
Varicella zoster virus infection	1 (1.3)	0	2 (1.9)	0

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



**Table S7: Most common any grade and grade  $\geq 3$  TEAEs among patients receiving parsacalisib (occurring in  $\geq 10\%$  of patients in the total population at any grade) (BTKi-experienced cohort)**

Preferred term (MedDRA), n (%)	Daily dosing group (n=41)		All treated patients (N=53)	
	Any grade	Grade $\geq 3$	Any grade	Grade $\geq 3$
Any TEAE	36 (87.8)	22 (53.7)	46 (86.8)	28 (52.8)
Diarrhoea	12 (29.3)	3 (7.3)	14 (26.4)	4 (7.5)
Anaemia	8 (19.5)	4 (9.8)	11 (20.8)	6 (11.3)
Neutropenia	7 (17.1)	5 (12.2)	9 (17.0)	7 (13.2)
Asthenia	8 (19.5)	0	8 (15.1)	0
Pyrexia	6 (14.6)	0	7 (13.2)	0
Cough	5 (12.2)	1 (2.4)	6 (11.3)	1 (1.9)
Decreased appetite	4 (9.8)	0	6 (11.3)	0
Dyspnoea	5 (12.2)	0	6 (11.3)	0
Weight decreased	4 (9.8)	0	6 (11.3)	0

Forty-six out of the 53 (86.8%) patients in the BTKi-experienced cohort had at least one TEAE, and 25 (47.2%) had TEAEs that were considered related to parsacalisib by the investigator. Grade  $\geq 3$  TEAEs occurred in 28 (52.8%) of patients and serious TEAEs in 22 (41.5%) patients. Four patients experienced fatal TEAEs; neutropenia, pneumonia, and septic shock which were considered treatment-related by the investigator in one patient; respiratory tract infection and general physical health deterioration in one patient; neutropenia and dehydration in one patient, and intestinal perforation in one patient, none of which was considered treatment-related by the investigator. TEAEs leading to discontinuation of parsacalisib occurred in six (11.3%) of patients in the BTKi-experienced cohort. MedDRA=Medical Dictionary for Regulatory Activities. TEAE=treatment-emergent adverse event.

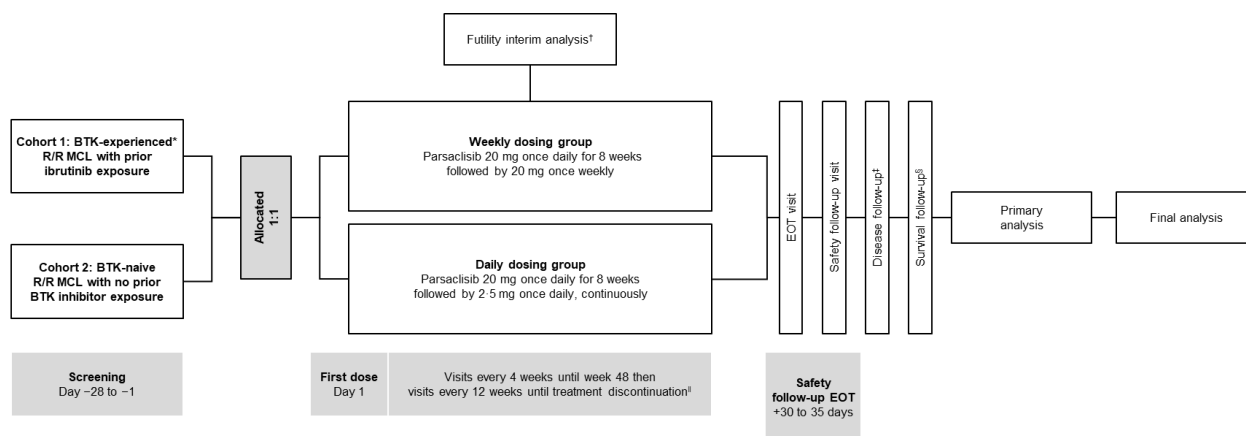
**Table S8: Parsaclisib-responsive plasma proteins showing a change from baseline to week 8 in patients with MCL with CR/PR as best overall response**

Gene symbol	Percent change from baseline to week 8 (95% CI)
<i>TNFRSF9</i>	–85% (–82, –88)
<i>FCRL2</i>	–82% (–78, –85)
<i>CXCL13/BCA1</i>	–75% (–69, –79)
<i>TNFRSF4</i>	–65% (–57, –71)
<i>FCER2</i>	–63% (–55, –70)
<i>MMP9</i>	–56% (–49, –63)
<i>TNFB/LTA</i>	–56% (–50, –61)
<i>CCL19</i>	–55% (–47, –63)
<i>IL2-RA</i>	–52% (–43, –59)
<i>IL12B</i>	–48% (–39, –56)
<i>CD160</i>	–43% (–37, –48)
<i>XCL1</i>	–43% (–38, –51)
<i>LAIR2</i>	–39% (–33, –46)

CI=confidence interval; CR=complete response; MCL=mantle cell lymphoma; PR=partial response.

## Supplemental Figures

**Figure S1: CITADEL-205 study design**



\*The BTKi-experienced cohort was closed to further enrolment.

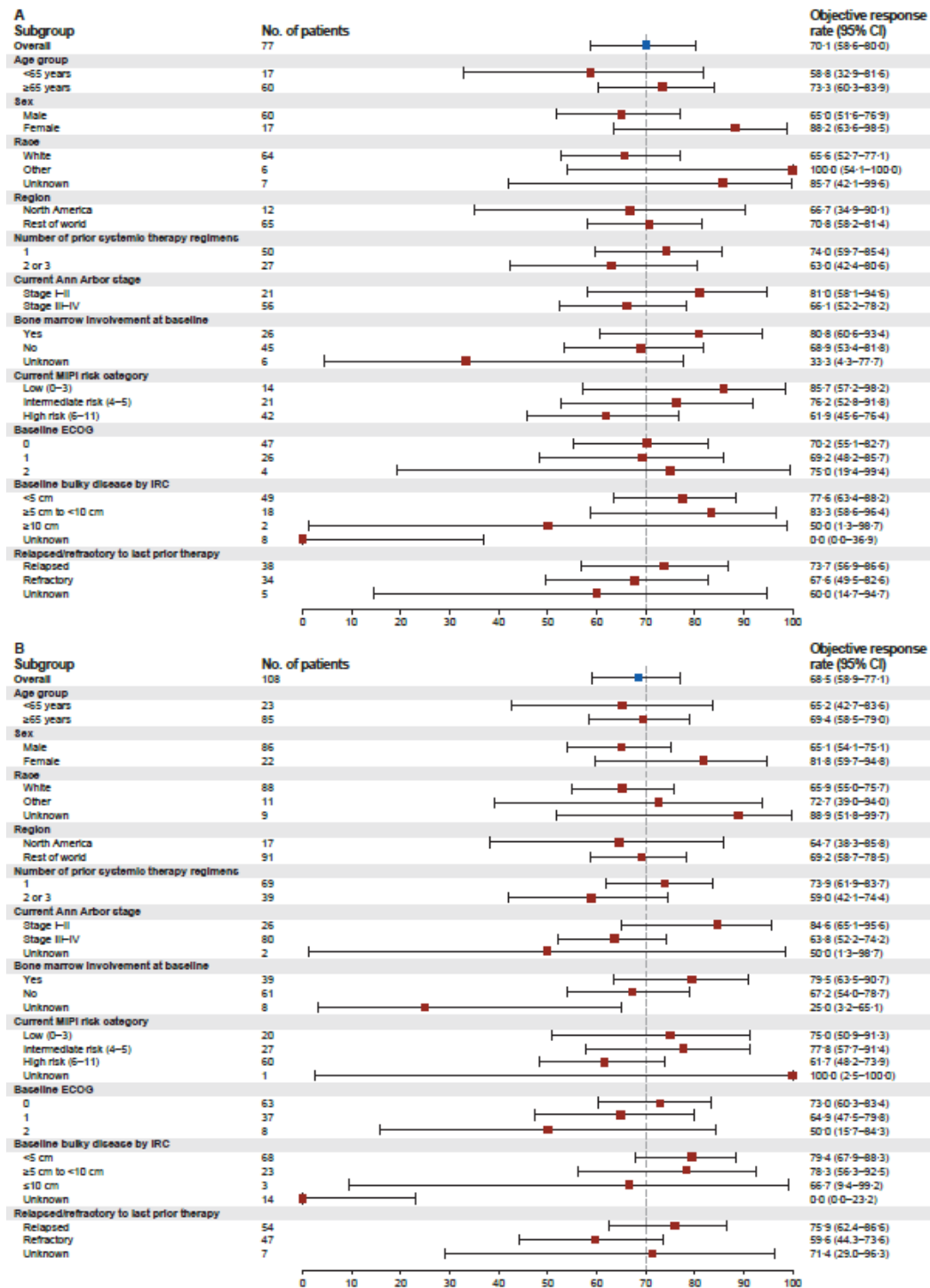
†Futility analysis was performed for each of the cohorts when the first 30 patients were evaluated for a response.

‡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.

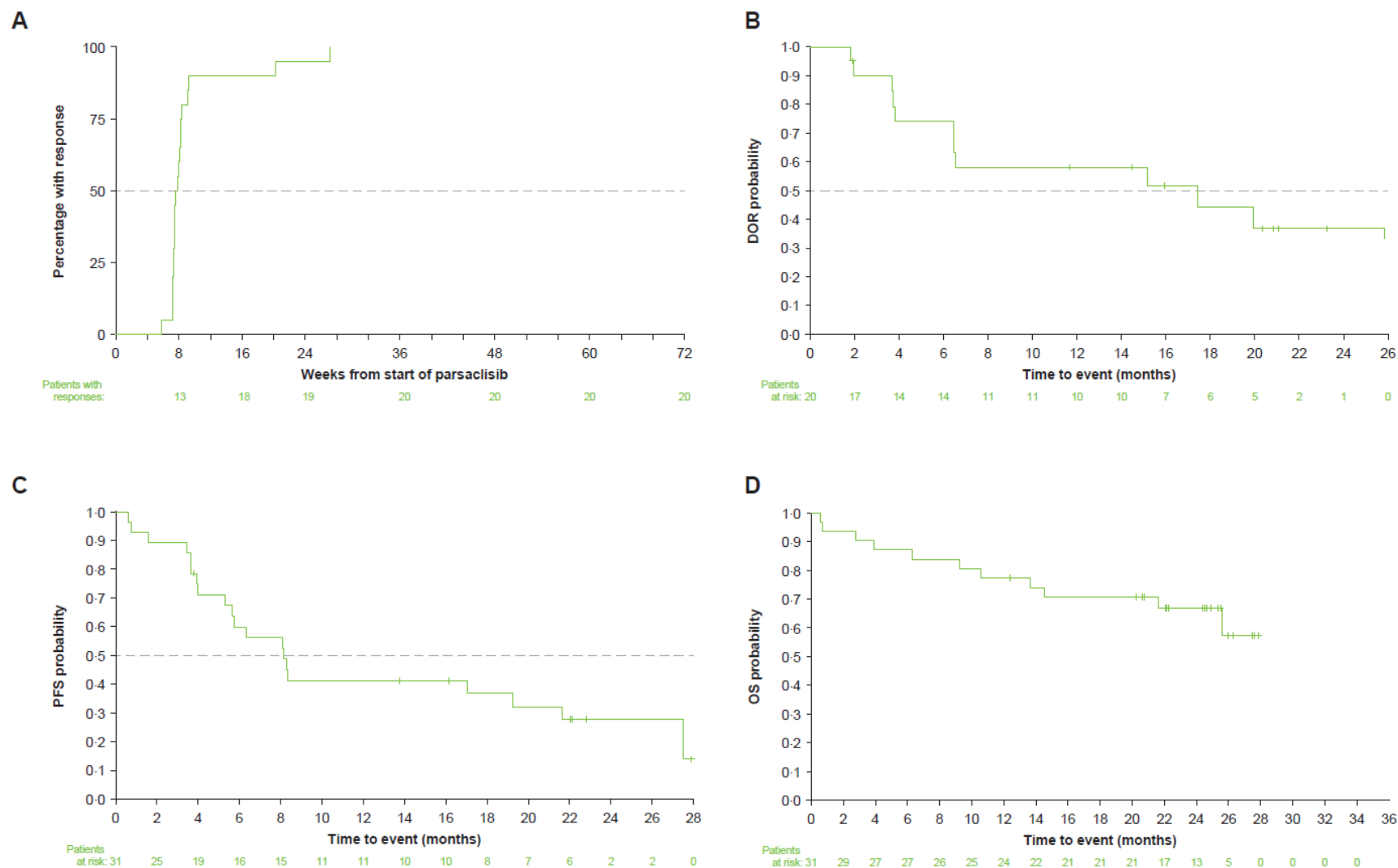
§Every 12 weeks by clinical visit, telephone, or email.

BTK=Bruton's tyrosine kinase. MCL=mantel cell lymphoma. R/R=relapsed/refractory.

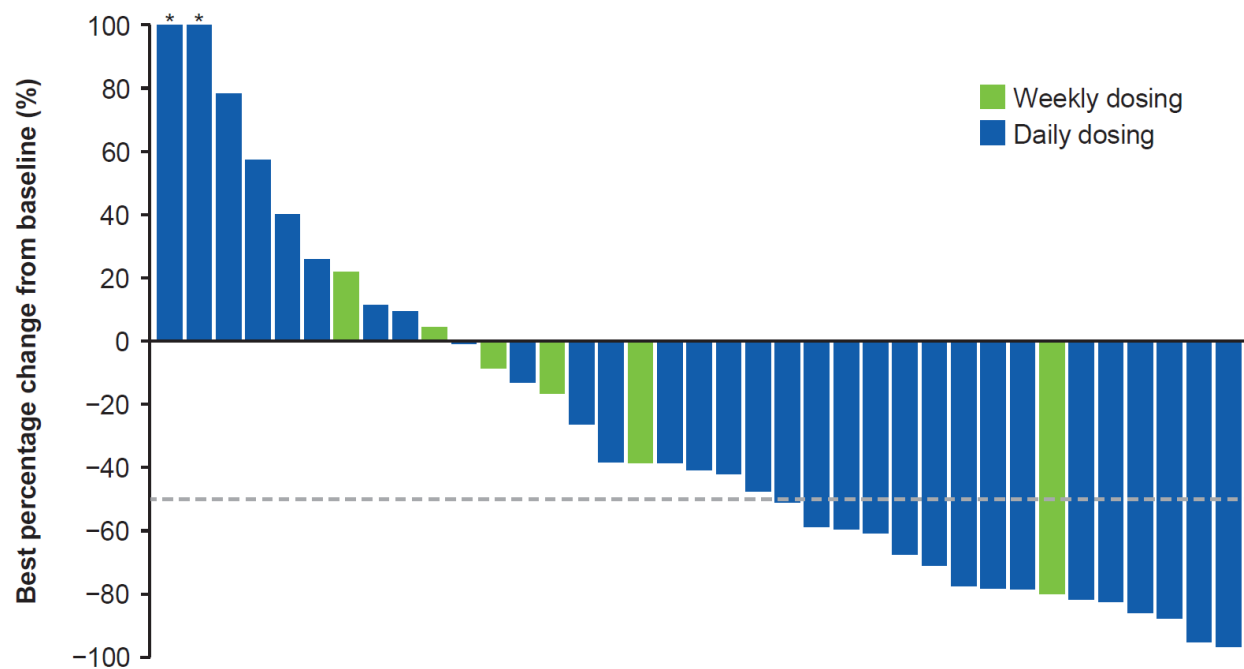
**Figure S2: Forest plot of objective response rate by subgroup in the daily dosing group (A) and all treated patients (B) (BTKi-naïve cohort)**



**Figure S3: Cumulative time to response curves (A), and Kaplan-Meier estimates of duration of response (DOR; B) and progression-free survival (PFS; C) by independent review committee, and overall survival (OS; D) in the weekly dosing group (BTKi-naïve cohort)**

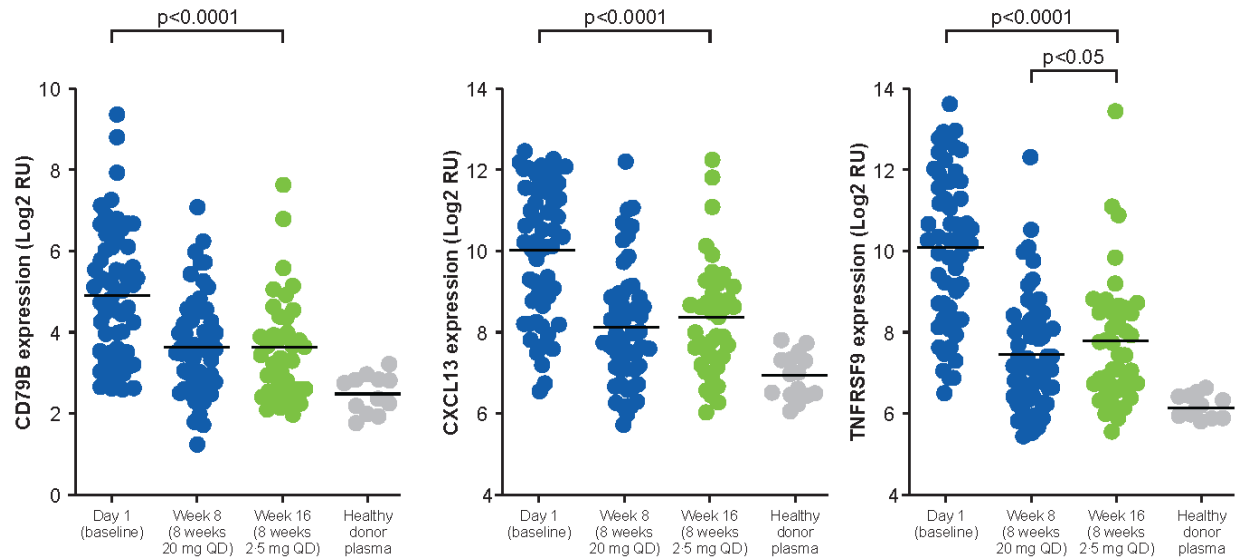


**Figure S4: Best percentage change from baseline in target lesion size by independent review committee (BTKi-experienced cohort)**



\* Patients with best percent change >100%.

**Figure S5: Dose effects on plasma expression of parsaclisib-response proteins CD79B, CXCL13, and TNFRSF9**



Data represent plasma protein expression of CD79B, CXCL13/BCA1, and TNFRSF9 for individual patient samples, including clinical responders (CR/PR as best overall response) on the recommended dose or healthy donor plasma controls. Samples are grouped as day 1 (baseline), week 8 (8 weeks 20 mg QD), or week 16 (8 weeks 2.5 mg QD). Lines indicate the median. P-values determined using Paired *t*-test. CR=complete response; PR=partial response; RU=relative units.