

Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Marginal Zone Lymphoma: Primary Analysis From a Phase 2 Study (CITADEL-204)

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Background

- MZL comprises approximately 8–12% of all NHL¹
 - Clinically heterogeneous with 3 main subtypes (extranodal, nodal, and splenic)²
- First-line treatment for MZL typically includes anti-CD20–based regimens¹; although response rates to first-line regimens are high,³ most patients with MZL will eventually experience serial relapses requiring multiple lines of therapy
- In the United States, anti-CD20 plus lenalidomide is approved for R/R MZL, as well as single-agent ibrutinib (BTK inhibitor), zanubrutinib (BTK inhibitor), and umbralisib (PI3K δ and CK1-epsilon inhibitor), for patients with MZL who received ≥ 1 prior anti-CD20–based therapy^{4–7}
 - No treatments are approved in Europe for R/R MZL
- CITADEL-204 (NCT03144674) evaluated the efficacy and safety of parsaclisib, a potent and highly selective next-generation PI3K δ inhibitor, in patients with R/R MZL with or without prior exposure to a BTK inhibitor (ie, ibrutinib)
 - The primary efficacy and safety analyses (January 15, 2021 data cutoff) for the BTK inhibitor–naive cohort are presented

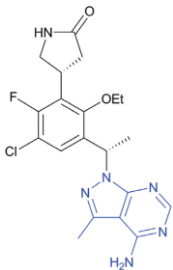
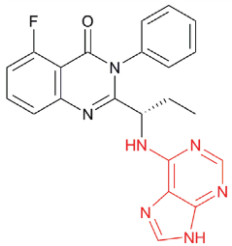
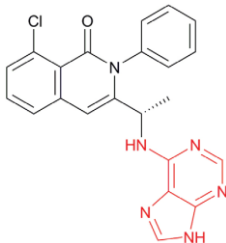
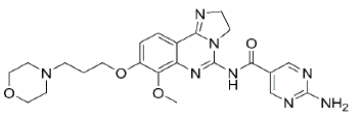
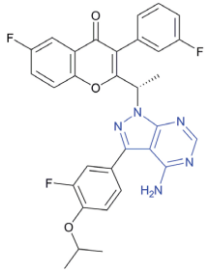
BTK, Bruton's tyrosine kinase; CK, casein kinase; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PI3K, phosphatidylinositol 3-kinase; R/R, relapsed/refractory.

1. Delinger NM, et al. *Cancer Manag Res*. 2018;10:615–624. 2. Rosand CB, et al. *Future Oncol*. 2018;14:1213–1222. 3. Lumish M, et al. *J Hematol Oncol*. 2021;14:5. 4. REVLIMID® (lenalidomide) [prescribing information]. Summit, NJ: Celgene Corporation; 2019. 5. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2020.

6. BRUKINSA® (zanubrutinib) [prescribing information]. San Mateo, CA: BeiGene USA; 2021. 7. UKONIQ™ (umbralisib). Edison, NJ: TG Therapeutics, Inc.; 2021.

Comparative Potency and Isoform Selectivity* of PI3K Inhibitors

- Parsaclisib was structurally designed to optimize both selectivity and potency, and to avoid the hepatotoxicity associated with the early-generation PI3K inhibitors
- Parsaclisib has more than 10,000-fold greater selectivity for the PI3K δ isoform than the α , β , and γ isoforms

	Parsaclisib ¹	Idelalisib ²	Duvelisib ³	Copanlisib ⁴	Umbralisib ^{5,6}
Structure					
PI3K δ IC ₅₀ , nM	1	2.5	2.5	0.7	22.2
Fold selectivity					
PI3K α	>20,000	>300	1602	1	>1500
PI3K β	>20,000	>200	85	5	>1500
PI3K γ	19,000	>35	27	10	225

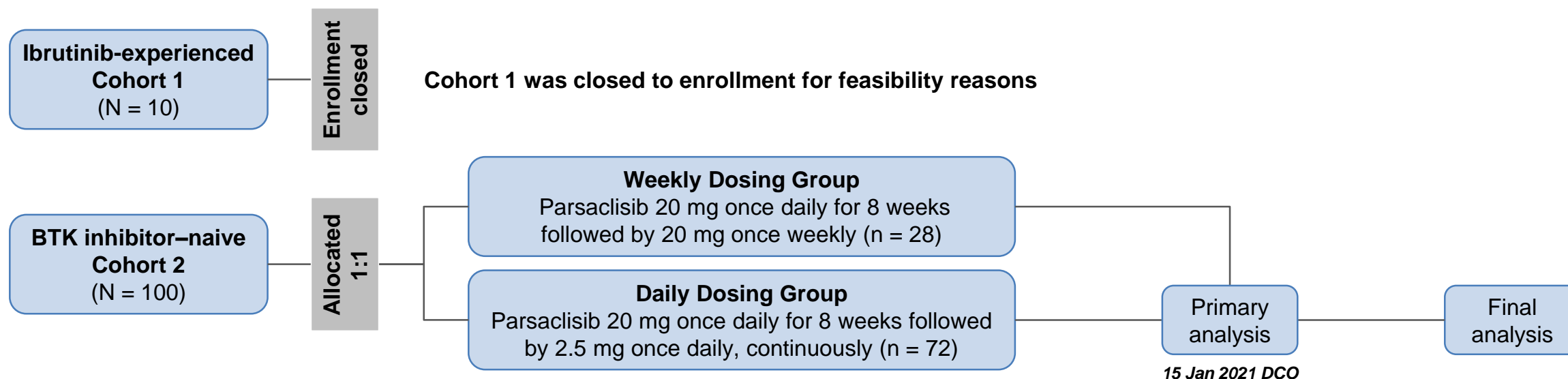
*Based on biochemical enzymatic assay.
IC₅₀, half maximal inhibitory concentration.

1. Shin N, et al. *J Pharmacol Exp Ther*. 2020;374:211–222. 2. Phillips T, et al. Presented at the 58th ASH Annual Meeting & Exposition; December 3–6, 2016; San Diego, CA. Abstract 4195. 3. Winkler DG, et al. *Chem Biol*. 2013;20:1364–1374. 4. Liu N, et al. *Mol Cancer Ther*. 2013;12:2319–2330. 5. Fowler NH, et al. *J Clin Oncol*. 2021;39:1609–1618. 6. Lampson BL, et al. *Exp Opin Investig Drugs*. 2017;26:1267–1279.

CITADEL-204 Study Design

Key inclusion criteria

- ≥ 18 years of age and histologically confirmed R/R MZL (nodal, extranodal, and splenic)
- Received ≥ 1 prior systemic therapy, including ≥ 1 anti-CD20 antibody (as monotherapy or chemoimmunotherapy combination)
- ECOG performance status ≤ 2
- No prior BTK (BTKi-naive cohort) or PI3K inhibitor (both cohorts)
- No recent HSCT (allogeneic ≤ 6 months, autologous ≤ 3 months)



- Following an interim analysis, enrollment continued in the Daily Dosing Group and was closed in the Weekly Dosing Group
- Parsaclisib daily dosing (20 mg daily for 8 weeks followed by 2.5 mg daily) is the recommended dose
- Data are presented for the Daily Dosing Group and for All Treated Patients, which includes patients that switched from 20-mg once-weekly to 2.5-mg once-daily dosing

Study Endpoints and Assessments

Primary endpoint

- ORR

Secondary endpoints

- CRR
- DOR
- PFS
- OS
- Best percentage change in disease burden from baseline
- Safety and tolerability of parsaclisib

Assessments

- Response assessed by CT/MRI using the Lugano criteria¹
- Radiology-based endpoints determined by IRC
- Adverse events assessed using CTCAE v4.03

CRR, complete response rate; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; IRC, independent review committee; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059–3068.

Patient Disposition and Exposure (January 15, 2021 Data Cutoff)

	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Patients discontinued from treatment	65 (65)	50 (69)
Primary reasons for discontinuing parsaclisib		
Progressive disease	28 (28)	18 (25)
Adverse event	29 (29)	27 (37.5)
Withdrawal/physician decision	5 (5)	3 (4)
Protocol deviation*	2 (2)	1 (1)
Death	1 (1)	1 (1)
Patients with ongoing parsaclisib treatment, n (%)	35 (35)	22 (31)
Median (range) duration of treatment, [†] months	13.4 (0.4–30.9)	11.6 (0.4–30.9)
Median (range) duration of follow-up, [‡] months	22.8 (11.9–37.0)	21.0 (11.9–37.0)

*One patient (in Daily Dosing Group) with mantle cell lymphoma; 1 patient with prior PI3K inhibitor therapy.

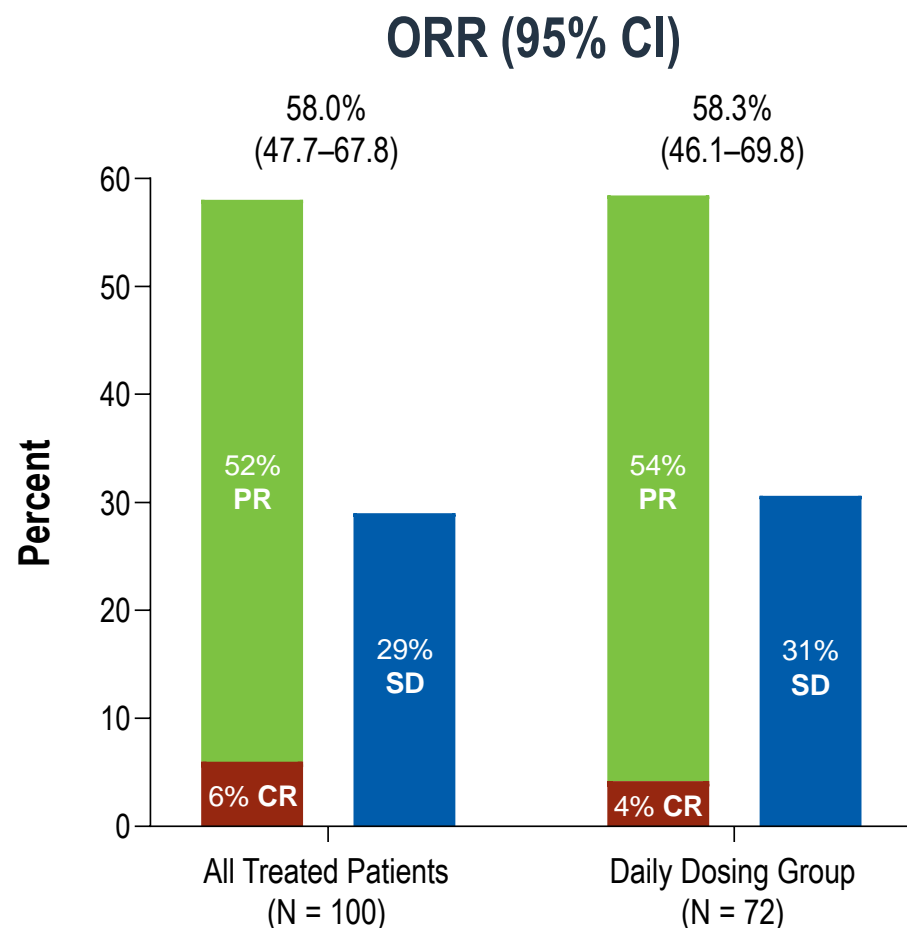
[†]Duration of treatment (months) = (date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment.

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

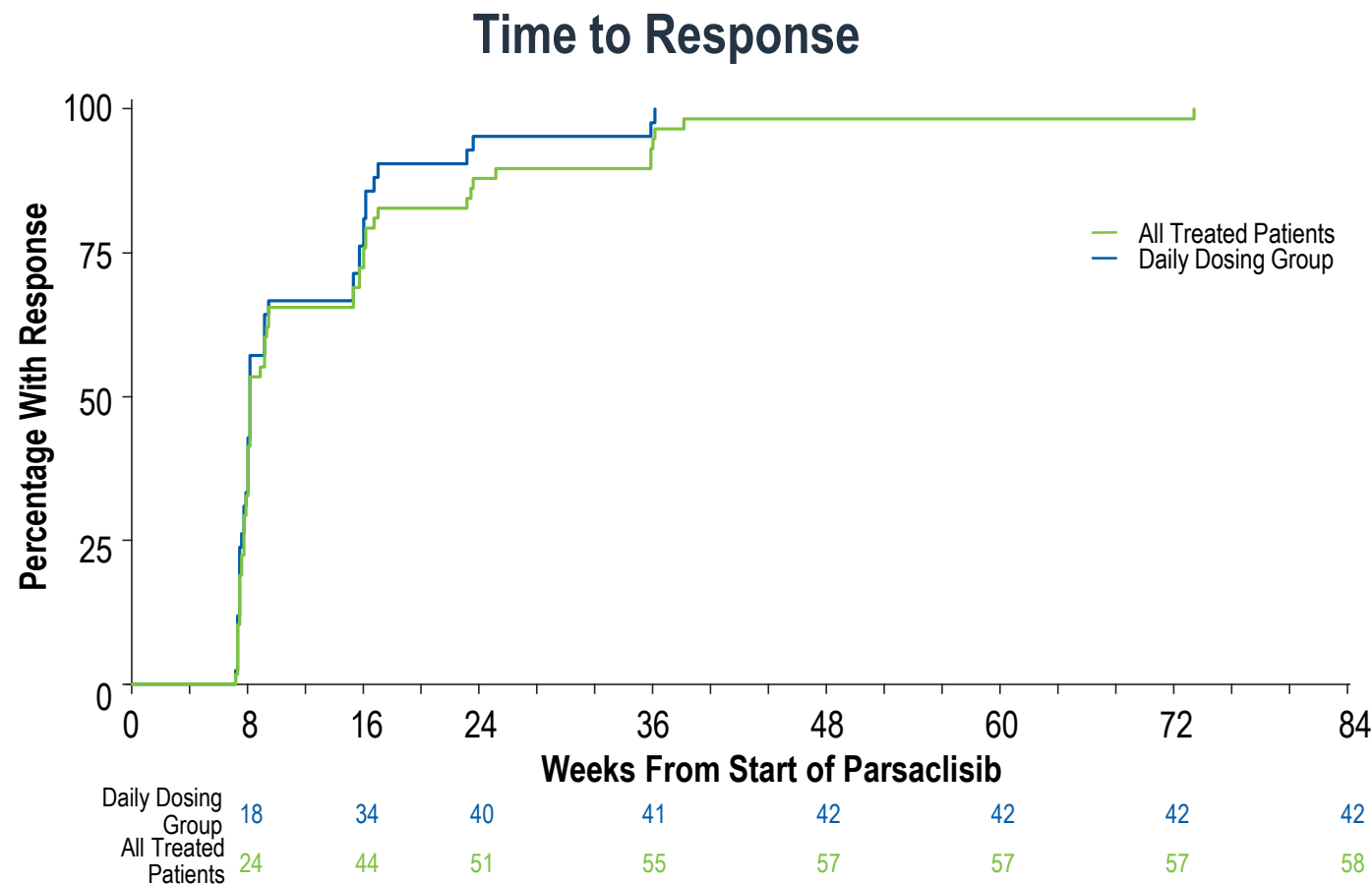
Baseline Characteristics

Characteristic	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Age, median (range), years	71.0 (35–95)	72.0 (35–95)
≥65 years, %	72	72
Male, %	53	57
Time since MZL diagnosis, median (range), years	4.6 (0.1–20.1)	4.4 (0.1–19.8)
MZL subtypes, %		
Nodal	31	35
Extranodal	34	32
Splenic	35	33
ECOG performance status ≤1, %	95	96
Prior therapies		
Median (range) number of prior systemic therapy regimens	2 (1–8)	2 (1–5)
Anti-CD20 monoclonal antibodies, %	100	100
Chemotherapy, %	72	74
Surgery/surgical procedures, %	19	15
Radiation, %	11	10
Prior HSCT, %	4	4
Relapse or refractory to most recent systemic therapy, %		
Relapsed	46	46
Refractory	49	49
Unknown	5	6

Objective Responses by IRC



- ORR by investigator assessment: 72.0% in All Treated Patients, 69.4% in Daily Dosing Group



- 65.5% of all responders had their first response occur at the first disease assessment (8 weeks)

Objective Response Rate by Subtype and Prior Response by IRC

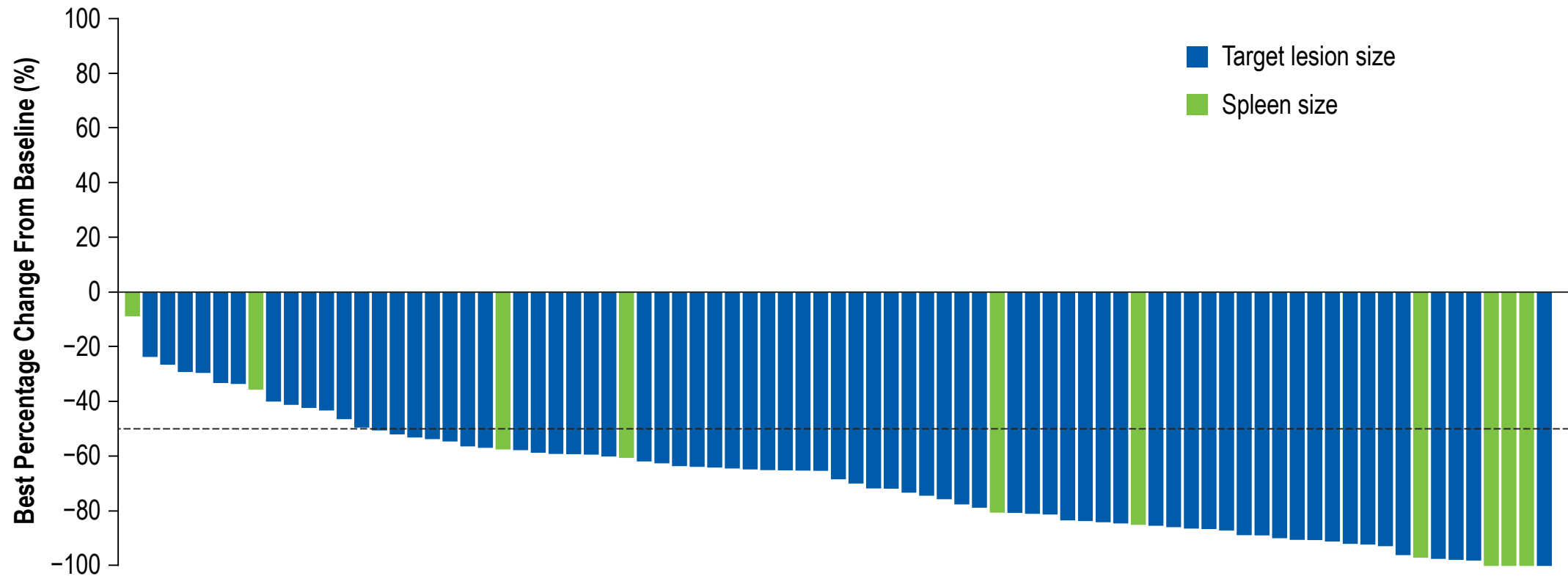
	All Treated Patients (N = 100)				
	Nodal MZL (N = 31)	Extranodal MZL (N = 34)	Splenic MZL (N = 35)	Refractory to Prior Therapy [†] (N = 49)	Relapsed on Prior Therapy [†] (N = 46)
Objective response rate, % 95% CI	51.6 33.1–69.8	55.9 37.9–72.8	65.7 47.8–80.9	55.1 40.2–69.3	65.2 49.8–78.6
Best objective response, n (%)					
Complete response	2 (6.5)	3 (8.8)	1 (2.9)	2 (4.1)	4 (8.7)
Partial response	14 (45.2)	16 (47.1)	22 (62.9)	25 (51.0)	26 (56.5)
Stable disease	10 (32.3)	11 (32.4)	8 (22.9)	17 (34.7)	9 (19.6)
Progressive disease	1 (3.2)	1 (2.9)	0	1 (2.0)	1 (2.2)
Not evaluable/Not assessed*	4 (12.9)	3 (8.8)	4 (11.4)	4 (8.2)	6 (13.0)

*Patients with “Not assessed” had no postbaseline response data available by data cutoff.

[†]Five patients had unknown refractory/relapse status to the most recent prior therapy.

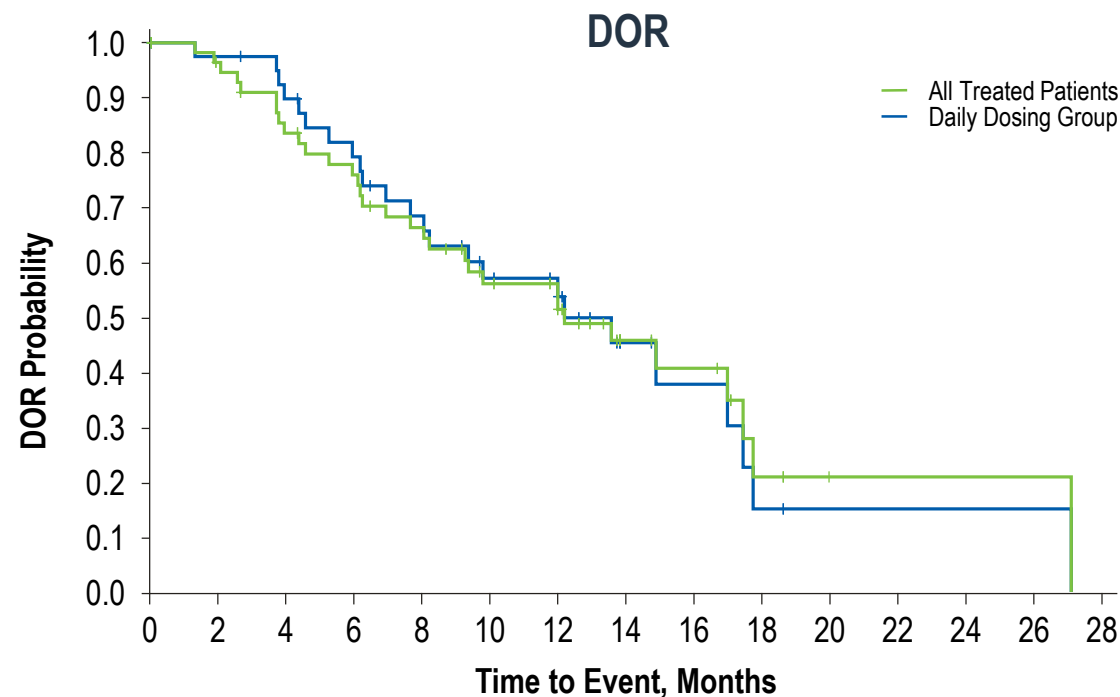
Change From Baseline in Target Lesion or Spleen Size by IRC*

- 100% (81/81) of evaluable patients had regression at target lesions or spleen, 83% (67/81) of whom had >50% reduction in best percentage change from baseline



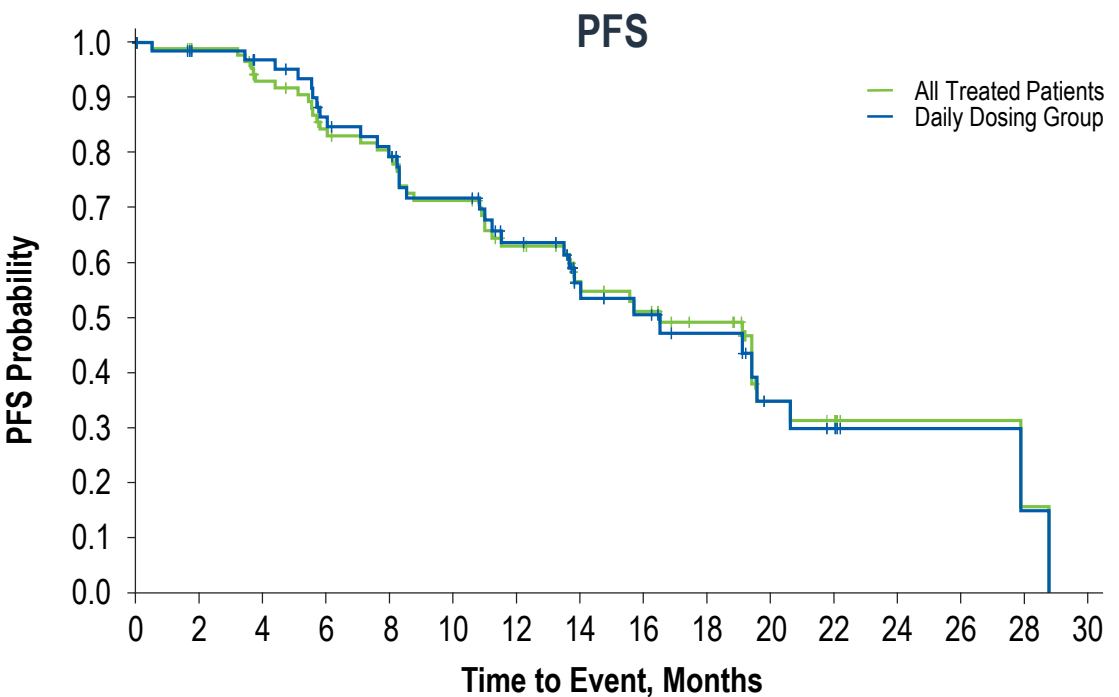
*For patients with measurable lesions at baseline, target lesion size as measured by sum of product of diameters of all target lesions was used to assess disease burden. For splenic MZL patients who have splenomegaly only at baseline, the spleen size as measured by the enlarged portion of the splenic length (ie, splenic length in excess of the 13-cm normal threshold) was used to assess disease burden. Plot includes patients who had baseline and ≥ 1 postbaseline valid measurements for disease burden; no patient had best overall response of not evaluable.

DOR and PFS by IRC



Daily Dosing Group	42	39	35	30	25	19	15	7	5	2	1	1	1	1	0
All Treated Patients	58	53	45	40	34	26	21	10	8	3	1	1	1	1	0

	All Treated Patients (58 Responders)	Daily Dosing Group (42 Responders)
Median DOR (95% CI), months	12.2 (8.1–17.5)	12.2 (8.1–17.5)



Daily Dosing Group	72	61	57	49	44	38	30	20	17	13	7	5	2	2	1	0
All Treated Patients	100	85	76	67	62	54	44	32	28	23	10	8	2	2	1	0

	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Median PFS (95% CI), months	16.5 (13.5–19.6)	16.5 (11.5–20.6)

TEAEs Occurring in >10% of All Treated Patients

Event, %*	All Treated Patients (N = 100)		Daily Dosing Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	96	63	97	72
Diarrhea	47	12	53	15
Cough	23	1	26	1
Rash	18	2	18	3
Anemia	15	6	17	8
Nausea	15	0	17	0
Pruritus	15	0	14	0
Pyrexia	15	1	15	1

Event, %	All Treated Patients (N = 100)		Daily Dosing Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	14	1	15	1
Constipation	13	0	15	0
Decreased appetite	13	0	15	0
Headache	13	0	14	0
Neutropenia	13	9	14	11
Upper respiratory tract infection	13	2	18	3
Abdominal pain	12	3	15	4
Arthralgia	12	2	11	3

*Pneumonia was reported as a grade ≥3 TEAE in 9% and 10% of patients among All Treated Patients and in the Daily Dosing Group; colitis was reported as a grade ≥3 TEAE in 7% and 10% of patients among All Treated Patients and in the Daily Dosing Group, respectively.
TEAE, treatment-emergent adverse event.

Serious TEAEs and Deaths Due to AEs

Serious TEAEs Occurring in >2 Patients Overall*

Event, %	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Any serious TEAE	47	56
Pneumonia	9	10
Colitis	6	8
Febrile neutropenia	5	6
Diarrhea	4	6
Atrial fibrillation	3	4

Deaths

- Two deaths occurred due to adverse events attributed by the investigator to be related to parsaclisib
 - Patient with febrile neutropenia who subsequently died of sepsis/respiratory distress
 - Patient with sepsis

*Rash was reported as a serious TEAE in 3% of patients and pneumonitis was reported as a serious TEAE in 1% of patients, all in the Daily Dosing Group.

Dose Modifications and High-Grade Diarrhea/Colitis Events

Dose Modifications Due to TEAEs (Any Grade)

Modification, %	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Interruption	56	60
Reduction	16	17
Discontinuation	29	37.5

In the Daily Dosing Group:

- Most frequently occurring TEAEs leading to dose interruption were diarrhea (15%) and neutropenia (6%)
- Most frequently occurring TEAEs leading to dose reduction were diarrhea (7%), and colitis and maculopapular rash (3% each)
- Most common TEAEs leading to treatment discontinuation were diarrhea (12.5%) and colitis (7%)

Time to High-Grade Onset and Improvement of Diarrhea or Colitis Events

Time to Onset or Improvement*	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Diarrhea		
Number of patients with grade ≥3 events, %	12	15
Onset of grade ≥3 events, median (range), months	5.6 (0.6–15.1)	5.1 (0.6–15.1)
Improvement to grade ≤2, median (95% CI), days	11.0 (3.0–24.0)	12.0 (3.0–24.0)
Colitis		
Number of patients with grade ≥3 events, %	7	10
Onset of grade ≥3 events, median (range), months	5.6 (1.0–15.4)	5.6 (1.0–15.4)
Improvement to grade ≤2, median (95% CI), days	21.0 (3.0–33.0)	21.0 (3.0–33.0)

*Analyses were for the longest duration of grade ≥3 events using Kaplan-Meier method, and the longest grade ≥3 events that improved in these patients.

Worsening Laboratory Parameters

Event, %	All Treated Patients (N = 100)			Daily Dosing Group (N = 72)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic						
Neutrophils decreased*	53	10	4	49	10	4
Hemoglobin decreased	32	5	NA	33	7	NA
Platelets decreased	20	5	0	19	4	0
Aminotransferase†						
ALT elevation	27	3	2	29	4	3
AST elevation	22	2	1	21	3	1

*Two patients discontinued treatment due to febrile neutropenia/neutropenia (both in Daily Dosing Group).

†One patient discontinued treatment due to aminotransferase elevations (in Daily Dosing Group), and 1 patient discontinued treatment due to transaminases increased (in Daily Dosing Group).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable.

Summary

- BTK-naive patients with R/R MZL demonstrated rapid and durable clinical response after treatment with parsaclisib, a potent, highly selective, next-generation PI3K δ inhibitor
 - 58.3% ORR, 12.2 months DOR, and 16.5 months PFS were observed in the Daily Dosing Group, the recommended dose for parsaclisib
 - Comparable ORRs were observed in patients with nodal, extranodal, and splenic MZL
- Parsaclisib had a manageable safety profile and was generally well tolerated
- Results of parsaclisib treatment in patients with follicular lymphoma (CITADEL-203; Abstract #813) and mantle cell lymphoma (CITADEL-205; Abstract #382) are also presented at this meeting

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