

# Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Mantle Cell Lymphoma Not Previously Treated With a BTK Inhibitor: Primary Analysis From a Phase 2 Study (CITADEL-205)

VIDEO

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# Background

VIDEO

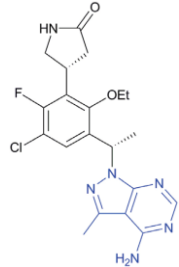
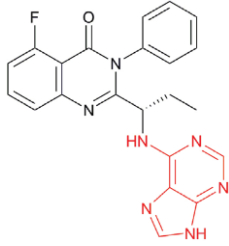
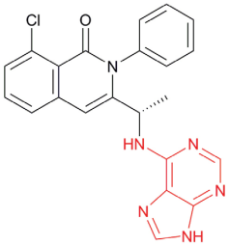
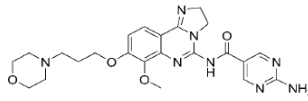
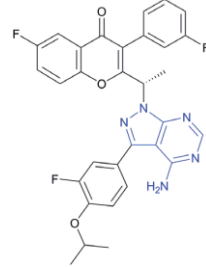
- Mantle cell lymphoma (MCL) is an aggressive type of non-Hodgkin lymphoma (NHL) and accounts for 6% of all NHL cases in Western countries<sup>1</sup>
- First-line treatment options are not curative and most patients experience relapse<sup>2,3</sup>
- Targeted therapies, including Bruton's tyrosine kinase (BTK) inhibitors, are used as second- and later-lines<sup>4,5</sup>
  - Treatment intolerance and failure are common, and survival outcomes for patients with relapsed or refractory (R/R) MCL are poor,<sup>4,5</sup> highlighting the need for novel therapies
- CITADEL-205 (NCT03235544) evaluated the efficacy and safety of piasclisib, a potent and highly selective next-generation PI3K $\delta$  inhibitor, in patients with R/R MCL previously treated with or without a BTK inhibitor (ie, ibrutinib)
  - The primary efficacy and safety analyses (January 15, 2021 data cutoff) for the cohort of BTK inhibitor-naïve patients are presented

; PI3K, phosphoinositide 3-kinase.

1. Thandra KC, et al. *Med Sci*. 2021;9:5. 2. Wu H, et al. *Front Oncol*. 2020;10:588314. 3. Kumar A, et al. *Blood Cancer J*. 2019;9:50. 4. Epperla N, et al. *Hematol Oncol*. 2017;35:528–535. 5. Jain P, et al. *Br J Haematol*. 2018;182:404–411.

# 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 $\delta$  isoform than the  $\alpha$ ,  $\beta$ , and  $\gamma$  isoforms

	Parsaclisib <sup>1</sup>	Idelalisib <sup>2</sup>	Duvelisib <sup>3</sup>	Copanlisib <sup>4</sup>	Umbralisib <sup>5,6</sup>
Structure					
PI3K $\delta$ IC <sub>50</sub> , nM	1	2.5	2.5	0.7	22.2
Fold selectivity					
PI3K $\alpha$	>20,000	>300	1602	1	>1500
PI3K $\beta$	>20,000	>200	85	5	>1500
PI3K $\gamma$	19,000	>35	27	10	225

\*Based on biochemical enzymatic assay.  
IC<sub>50</sub>, half maximal inhibitory concentration.

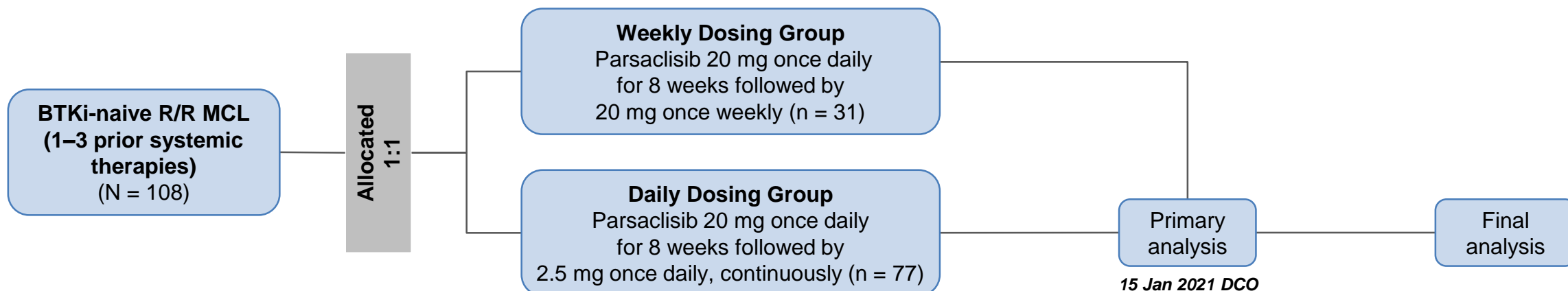
1. Shin N, et al. *J Pharmacol Exp Ther*. 2020;374:211–222. 2. Phillips T, et al. Presented at the 58th ASH Annual Meeting & Exposition; December 3–6, 2016; San Diego, CA. Abstract 4195. 3. Winkler DG, et al. *Chem Biol*. 2013;20:1364–1374. 4. Liu N, et al. *Mol Cancer Ther*. 2013;12:2319–2330. 5. Fowler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

# CITADEL-205 Study Design

## (Cohort 2: BTK Inhibitor–Naive)

### Key inclusion criteria

- ≥18 years of age with pathologically confirmed R/R MCL
- Received 1–3 prior systemic regimens
- No prior PI3K or BTK inhibitors
- ECOG performance status ≤2
- Documented cyclin D1 overexpression or t(11;14) translocation



- 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

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## Primary endpoint

- ORR

## Secondary endpoints

- CRR
- DOR
- PFS
- OS
- Best percentage change in target lesion size from baseline
- Safety and tolerability of parsaclisib

## Assessments

- Response assessed by CT/MRI using the Lugano criteria<sup>1</sup>
- 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 = 108)	Daily Dosing Group (N = 77)
Patients discontinued from treatment, n (%)	78 (72)	56 (73)
Primary reasons for discontinuing parsaclisib		
Progressive disease	49 (45)	30 (39)
Adverse event	25 (23)	23 (30)
Withdrawal/physician decision	3 (3)	2 (3)
Death	1 (1)	1 (1)
Patients with ongoing parsaclisib treatment, n (%)	30 (28)	21 (27)
Median (range) duration of treatment,* months	8.3 (0.1–30.0)	7.9 (1.7–27.4)
Median (range) duration of follow-up,† months	22.9 (11.6–35.9)	18.2 (11.6–35.9)

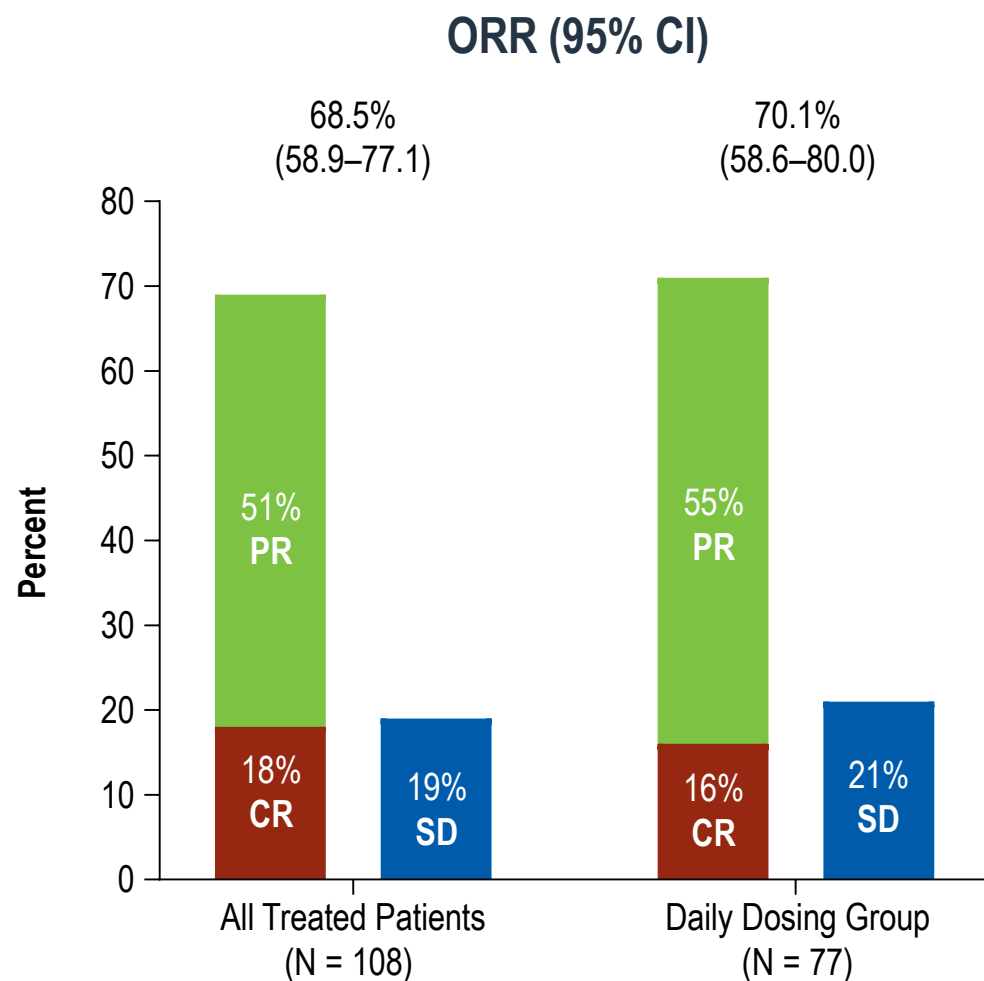
\*Duration of treatment (months) = (date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment.

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

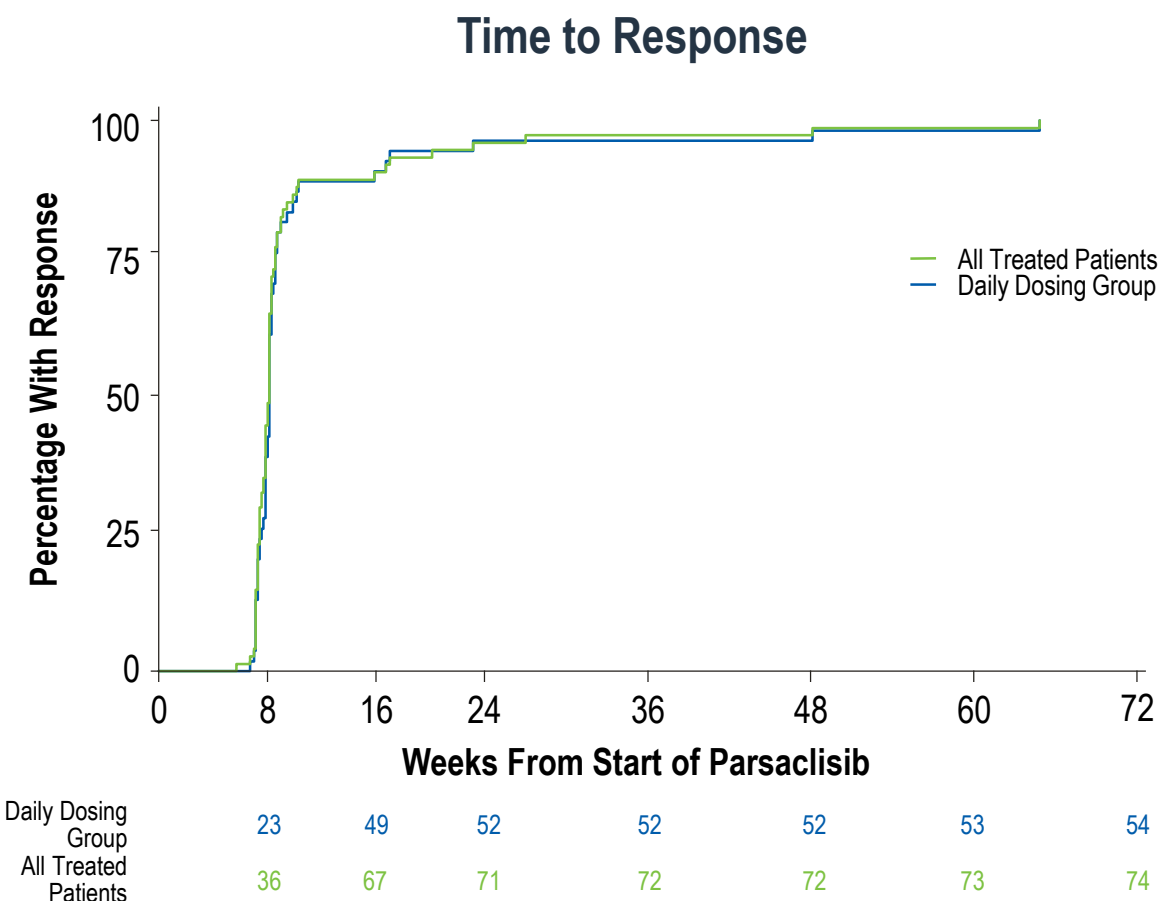
# Baseline Characteristics

Characteristic	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Age, median (range), years	72.0 (43–90)	72.0 (51–90)
≥65 years, %	79	78
Men, %	80	78
Time since MCL diagnosis, median (range), years	3.6 (0.1–20.9)	3.5 (0.1–16.9)
Current Ann Arbor staging, %		
Stage I–II	24	27
Stage III–IV	74	73
Missing	2	0
ECOG performance status ≤1, %	93	95
High-risk MIPI score, %	56	54.5
Prior therapies		
Median (range) prior systemic therapy regimens	1 (1–3)	1 (1–3)
Surgery/surgical procedures, %	5	3
Radiation, %	8	8
HSCT, %	31.5	36
Relapse or refractory to most recent systemic therapy, %		
Relapsed	50	49
Refractory	43.5	44
Unknown	6.5	6.5

# Objective Responses by IRC



- ORR by investigator assessment: 79.6% in All Treated Patients, 81.8% in Daily Dosing Group

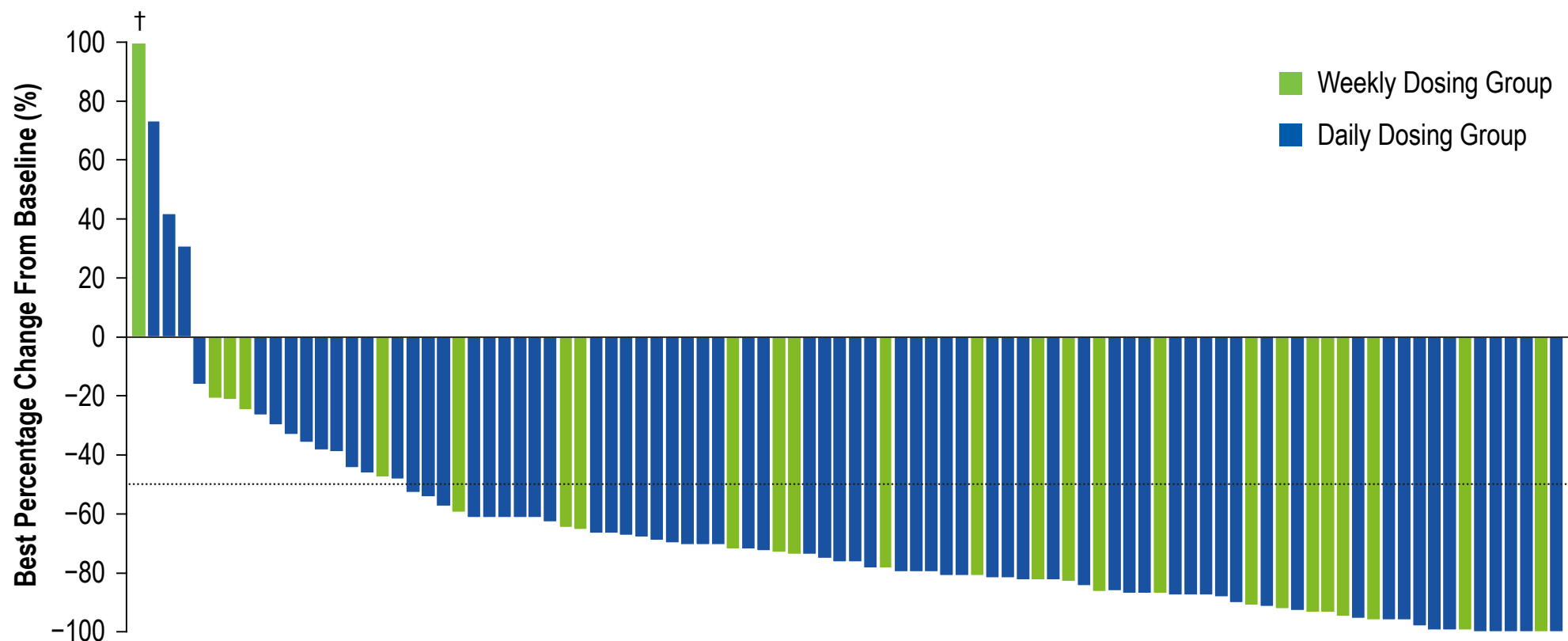


- 89% of all responders had their first response occur at the first disease assessment (8 weeks)



# Change From Baseline in Target Lesion Size by IRC\*

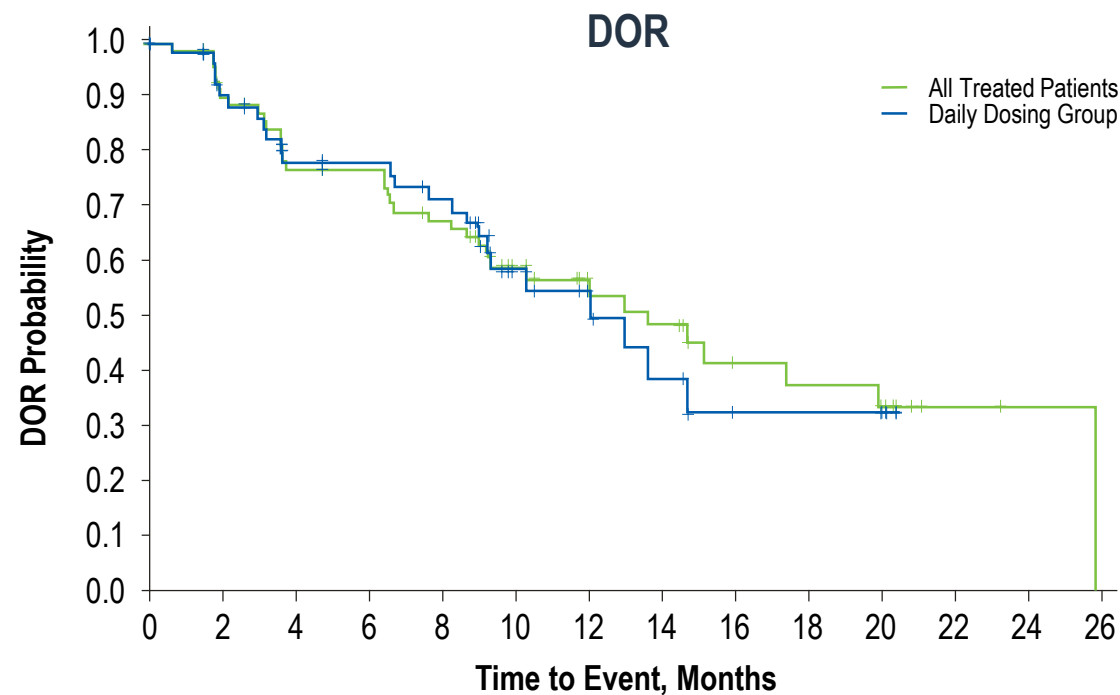
- 96% (90/94) of evaluable patients had regression at target lesions, 84% (76/90) of whom had >50% reduction in best percentage change from baseline



\*Includes patients with measurable lesions at baseline and  $\geq 1$  postbaseline valid measurements of target lesions to assess disease burden.

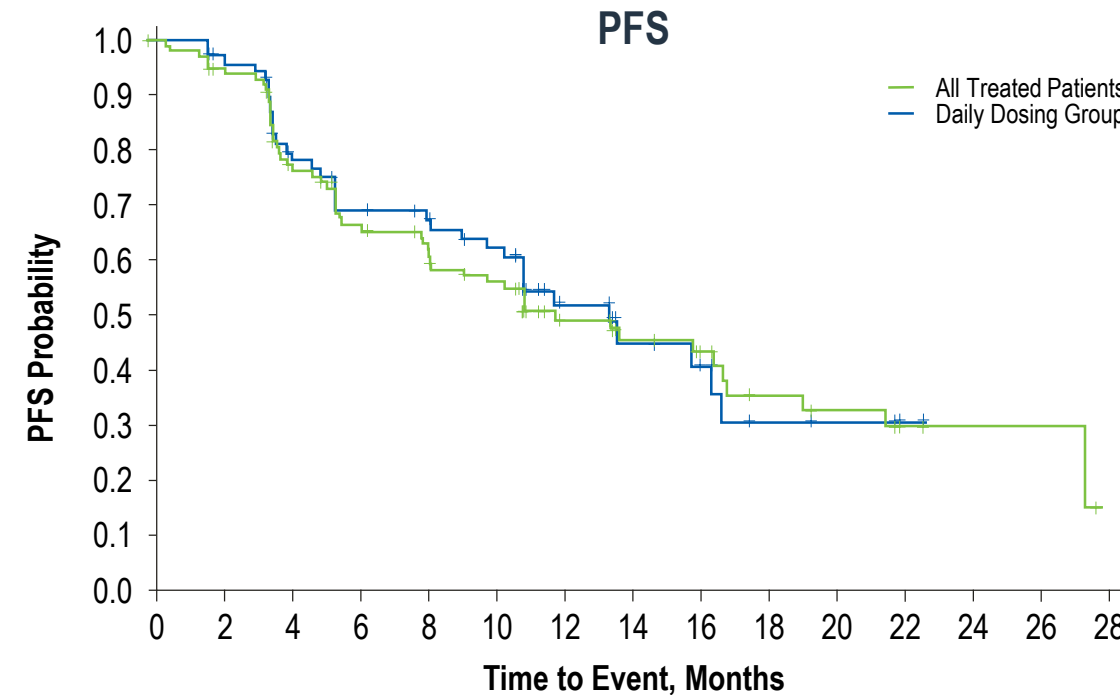
†Indicates patient with best percentage change >100%.

# DOR and PFS by IRC



Daily Dosing Group	54	46	37	36	32	16	11	7	3	3	3	0		
All Treated Patients	74	63	51	50	43	27	21	17	10	9	8	2	1	0

	All Treated Patients (74 Responders)	Daily Dosing Group (54 Responders)
Median DOR (95% CI), months	13.7 (9.0–19.9)	12.1 (9.0–NE)

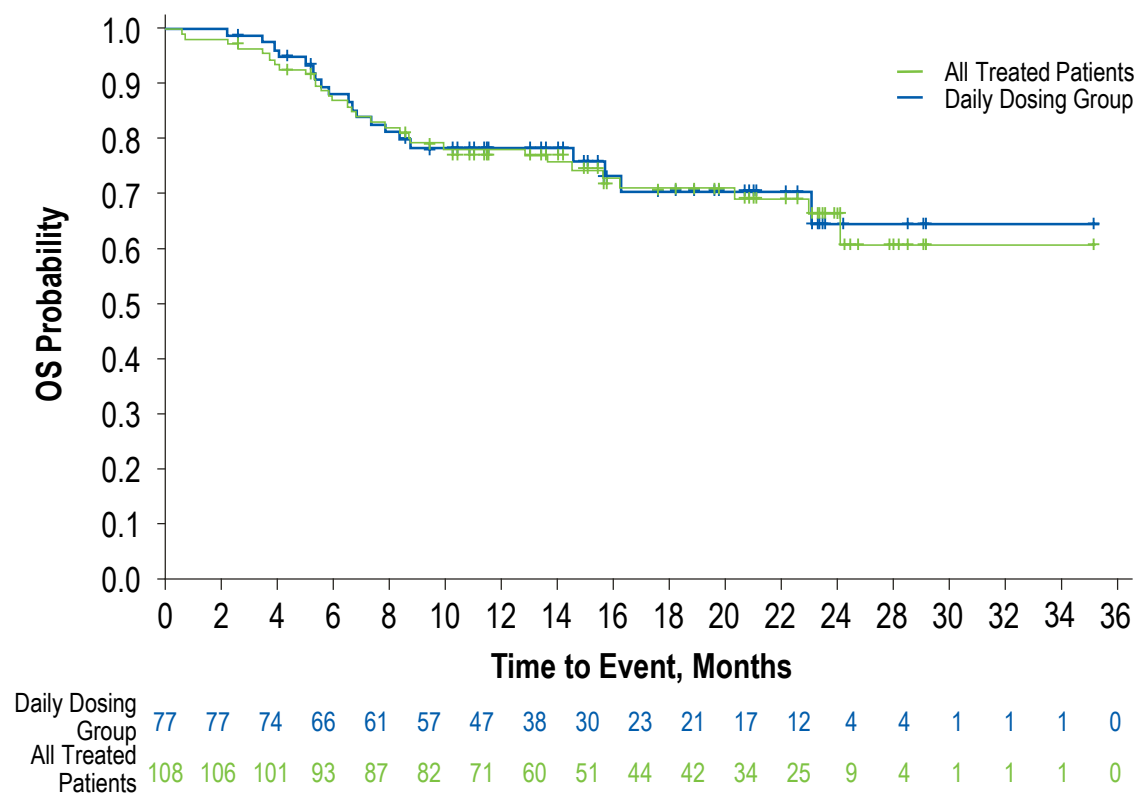


Daily Dosing Group	77	70	55	44	42	37	20	12	11	5	4	3	0		
All Treated Patients	108	95	74	60	57	48	31	22	21	13	11	9	2	2	0

	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Median PFS (95% CI), months	12.0 (8.3–16.9)	13.6 (10.0–16.9)

NE, not estimable.

# OS Estimates by IRC



Kaplan-Meier Estimate of OS

	All Treated Patients (31 Deaths)	Daily Dosing Group (20 Deaths)
Median OS (95% CI), months	NR (25.6–NE)	NR (24.4–NE)

Estimated Survival Rates

	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Survival Rate (95% CI)		
Month 6	0.9 (0.8–0.9)	0.9 (0.8–0.95)
Month 12	0.8 (0.7–0.85)	0.8 (0.7–0.9)

NR, not reached.

# TEAEs Occurring in $\geq 10\%$ of All Treated Patients

Event, %	All Treated Patients (N = 108)		Daily Dosing Group (N = 77)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
Any TEAE	91	62	90	64
Diarrhea	34	14	40	18
Pyrexia	18	2	17	1
Constipation	13	1	14	0
Asthenia	11	2	13	1
Neutropenia	11	8	12	9
Rash	11	3	14	4
Cough	10	0	12	0
Nausea	10	2	9	3

TEAE, treatment-emergent adverse event.

# Serious TEAEs and Deaths Due to AEs

## Serious TEAEs Occurring in $\geq 2$ Patients Overall

Event, %	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Any serious TEAE	43	45.5
Diarrhea	9	13
Colitis	5	6.5
Hypokalemia	3	3
Pyrexia	3	3
Pulmonary embolism	2	1
Rash	2	3

## Deaths

- One death occurred due to TEAEs attributed by the investigator to be related to parsaclisib
  - Patient with leukocytosis, acute myelomonocytic leukemia, and acute kidney injury

# Dose Modifications and High-Grade Diarrhea/Colitis Events

## Dose Modifications Due to TEAEs (Any Grade)

Modification, %	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Interruption	47	51
Reduction	8	9
Discontinuation	25	30

### In the Daily Dosing Group:

- Most frequently occurring TEAEs leading to dose interruption were diarrhea (14%) and neutropenia (9%)
- Most frequently occurring TEAE leading to dose reduction was rash (3%)
- Most frequently occurring TEAEs leading to dose discontinuation were diarrhea (16%) and colitis (6.5%)

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

Time to Onset or Improvement*	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
<b>Diarrhea</b>		
Number of patients with grade $\geq 3$ events, %	14	18
Onset of grade $\geq 3$ events, median (range), months	4.3 (1.0–11.0)	5.1 (1.5–11.0)
Improvement to grade $\leq 2$ , median (95% CI), days	11.0 (5.0–25.0)	10.5 (5.0–25.0)
<b>Colitis</b>		
Number of patients with grade $\geq 3$ events, %	4	5
Onset of grade $\geq 3$ events, median (range), months	3.1 (2.6–3.8)	3.1 (2.6–3.8)
Improvement to grade $\leq 2$ , median (95% CI), days	20.0 (9.0–NE)	20.0 (9.0–NE)

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

# Worsening Laboratory Parameters

Event, %	All Treated Patients (N = 108)			Daily Dosing Group (N = 77)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic						
Neutrophils decreased	54	6	5	61	6.5	5
Platelets decreased	33	5	4	32.5	4	3
Hemoglobin decreased	31.5	3	NA	32.5	4	NA
Aminotransferase						
ALT elevation	31	5	0	31	3	0
AST elevation	26	3	0	25	3	0

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

# Summary

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- Parsaclisib, a potent, highly selective, next-generation PI3K $\delta$  inhibitor, has demonstrated excellent activity in BTKi-naive R/R MCL
    - 70.1% ORR, 12.1 months median DOR, and 13.6 months median PFS were observed in the Daily Dosing Group, the recommended dose for parsaclisib
  - Parsaclisib showed an acceptable safety profile that was generally well tolerated
  - Parsaclisib represents a potentially new treatment option for BTKi-naive R/R MCL and a first-in-class PI3K $\delta$  inhibitor for MCL
- Results of the primary efficacy and safety analysis of parsaclisib treatment in patients with follicular lymphoma (CITADEL-203; Abstract #813) and marginal zone lymphoma (CITADEL-204; Abstract #44) are also presented at this meeting



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# Disclosures

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