

# Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Follicular Lymphoma: Primary Analysis From a Phase 2 Study (CITADEL-203)

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# Background

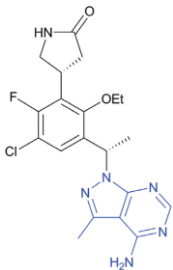
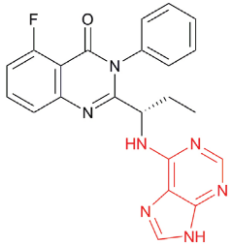
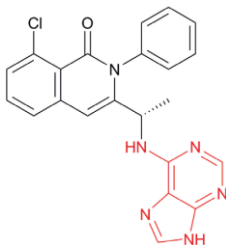
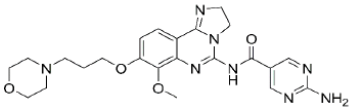
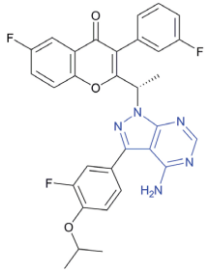
- Follicular lymphoma (FL) is the second most common indolent non-Hodgkin lymphoma (NHL)<sup>1</sup>
- Although response rates to first-line therapy are high for FL, the disease is considered incurable and patients frequently experience relapses<sup>2,3</sup>
- In the United States, lenalidomide in combination with anti-CD20 agents is approved for relapsed/refractory (R/R) FL.<sup>4</sup> Also approved for patients with R/R FL who have received  $\geq 2$  prior therapies are idelalisib,<sup>5</sup> copanlisib,<sup>6</sup> and duvelisib<sup>7</sup> (PI3K inhibitors), CAR T-cell therapy,<sup>8,9</sup> and tazemetostat (EZH2 inhibitor) for patients with *EZH2* mutations who have received  $\geq 2$  prior therapies or have no satisfactory alternative treatment options<sup>10</sup>
  - Umbralisib (PI3K $\delta$  and CK1-epsilon inhibitor) was recently approved for patients with FL who have received  $\geq 3$  prior lines of systemic therapy<sup>11</sup>
- CITADEL-203 (NCT03126019) evaluated the efficacy and safety of parsaclisib, a potent and highly selective next-generation PI3K $\delta$  inhibitor, in patients with R/R FL
  - The primary efficacy and safety analyses (January 15, 2021 data cutoff) are presented

BTK, Bruton's tyrosine kinase; CK, casein kinase; PI3K, phosphatidylinositol 3-kinase.

1. Hübel K, et al. *HemaSphere*. 2020;4:e317. 2. Batlevi CL, et al. *Blood Cancer J*. 2020;10:74. 3. Rivas-Delgado A, et al. *Br J Hematol*. 2019;184:753–759. 4. REVLIMID® (lenalidomide) [prescribing information]. Summit, NJ: Celgene Corporation; 2019. 5. ZYDELIG® (idelalisib) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2020. 6. ALIQOPA® (copanlisib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021. 7. COPIKTRA® (duvelisib) [prescribing information]. Needham, MA: Verastem, Inc.; 2019. 8. BREYANZI® (lisocabtagene maraleucel) [prescribing information]. Bothell, WA: Juno Therapeutics Inc.; 2021. 9. YESCARTA® (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma, Inc.; 2021. 10. TAZVERIK (tazemetostat) [prescribing information]. Cambridge, MA: Epizyme, Inc.; 2020. 11. UKONIQ™ (umbralisib) [prescribing information]. 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 $\delta$  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

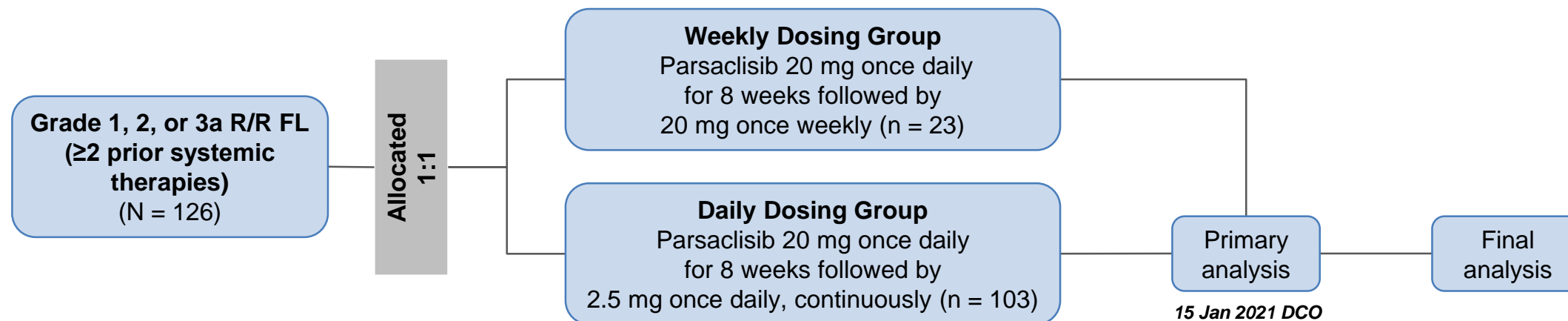
\*Based on biochemical enzymatic assay.  
IC<sub>50</sub>, half maximal inhibitory concentration.

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-203 Study Design

## Key inclusion criteria

- Age  $\geq 18$  years and histologically confirmed R/R FL (grades 1, 2, or 3a)
- Received  $\geq 2$  prior systemic therapies
- No prior PI3K or BTK inhibitors
- ECOG performance status  $\leq 2$
- Ineligible for hematopoietic stem cell therapy



- 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 = 126)	Daily Dosing Group (N = 103)
Patients discontinued from treatment	87 (69)	68 (66)
Primary reasons for discontinuing parsaclisib		
Progressive disease	46 (36.5)	33 (32)
Adverse event	27 (21)	23 (22)
Withdrawal/physician decision	13 (10)	11 (11)
Death	1 (1)	1 (1)
Patients with ongoing parsaclisib treatment, n (%)	39 (31)	35 (34)
Median (range) duration of treatment,* months	8.5 (0.5–27.2)	8.4 (0.8–27.2)
Median (range) duration of follow-up,† months	20.6 (5.7–34.1)	17.6 (5.7–33.1)

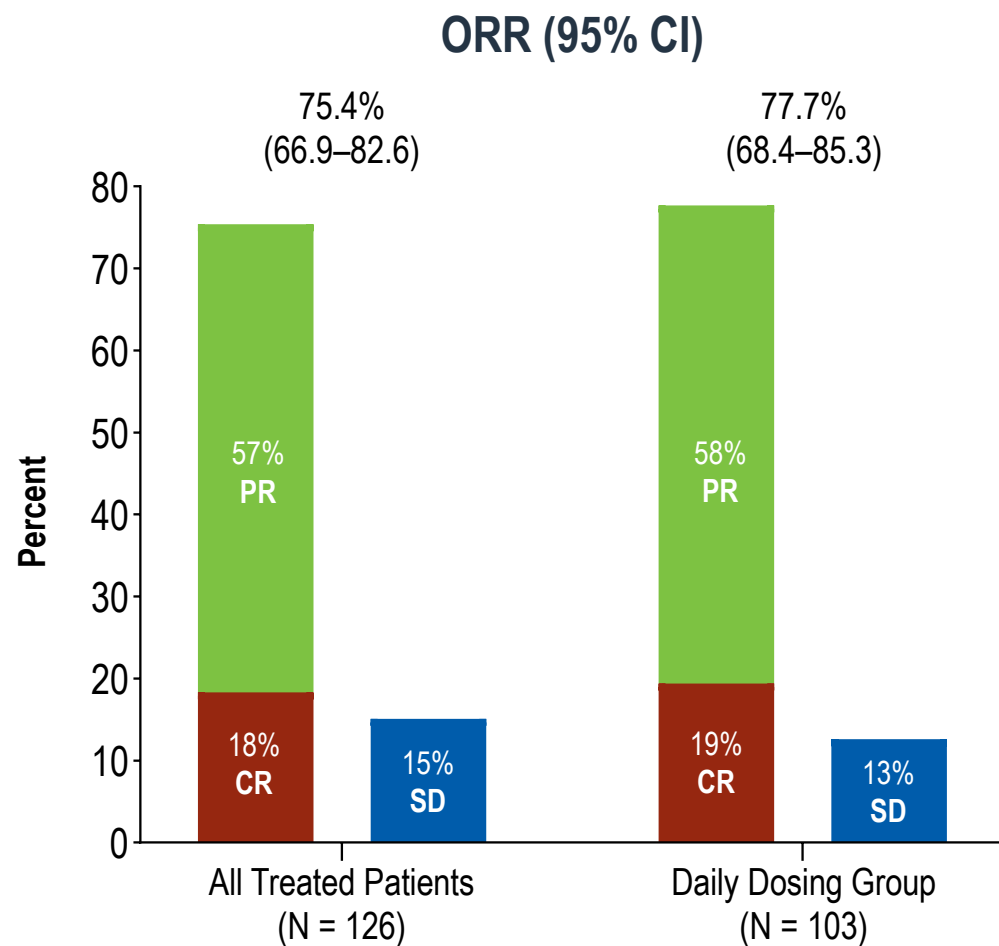
\*Duration of treatment (months) = (date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment.

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

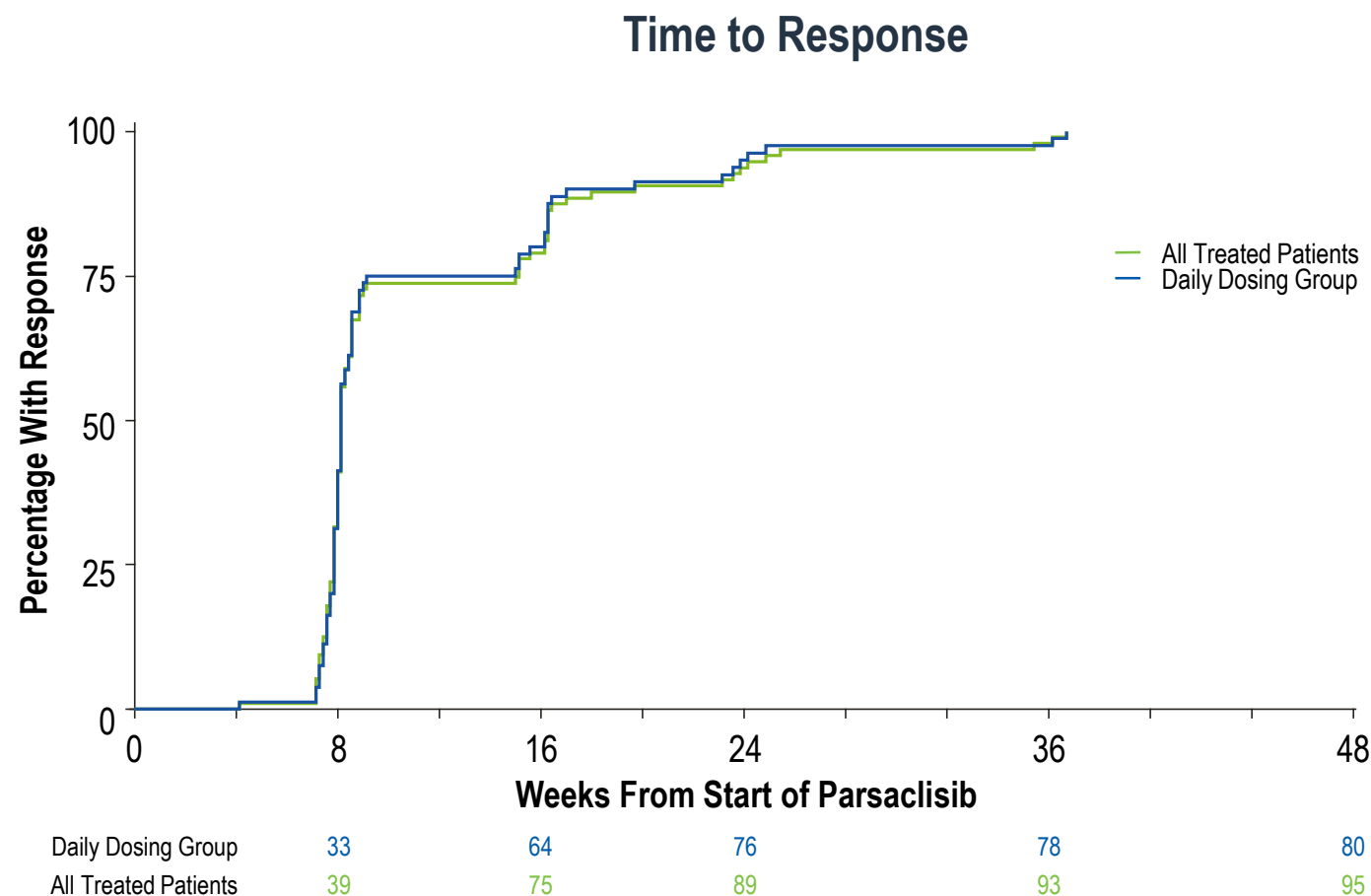
# Baseline Characteristics

Characteristics	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
Age, median (range), years	67.5 (40–88)	69.0 (40–88)
≥65 years, %	60	62
Male, %	56	56
Time since FL diagnosis, median (range), years	6 (0.2–32)	6 (0.2–32)
Current Ann Arbor Staging, %		
Stage I–II	20	20
Stage III–IV	78	77
Missing	2	3
ECOG performance status ≤1, %	94	94
Current FLIPI risk category ≥3, %	45	48.5
Prior therapies		
Median (range) prior systemic therapy regimens	2 (1–8)	2 (1–8)
Anti-CD20, %	99	99
Alkylating agents, %	94	93
Prior HSCT, %	18	16.5
Relapse or refractory to most recent therapy, %		
Relapsed	41	43
Refractory	49	48.5
Unknown/missing	9.5	9

# Objective Responses by IRC



- ORR by investigator assessment: 74.6% in All Treated Patients, 75.7% in Daily Dosing Group

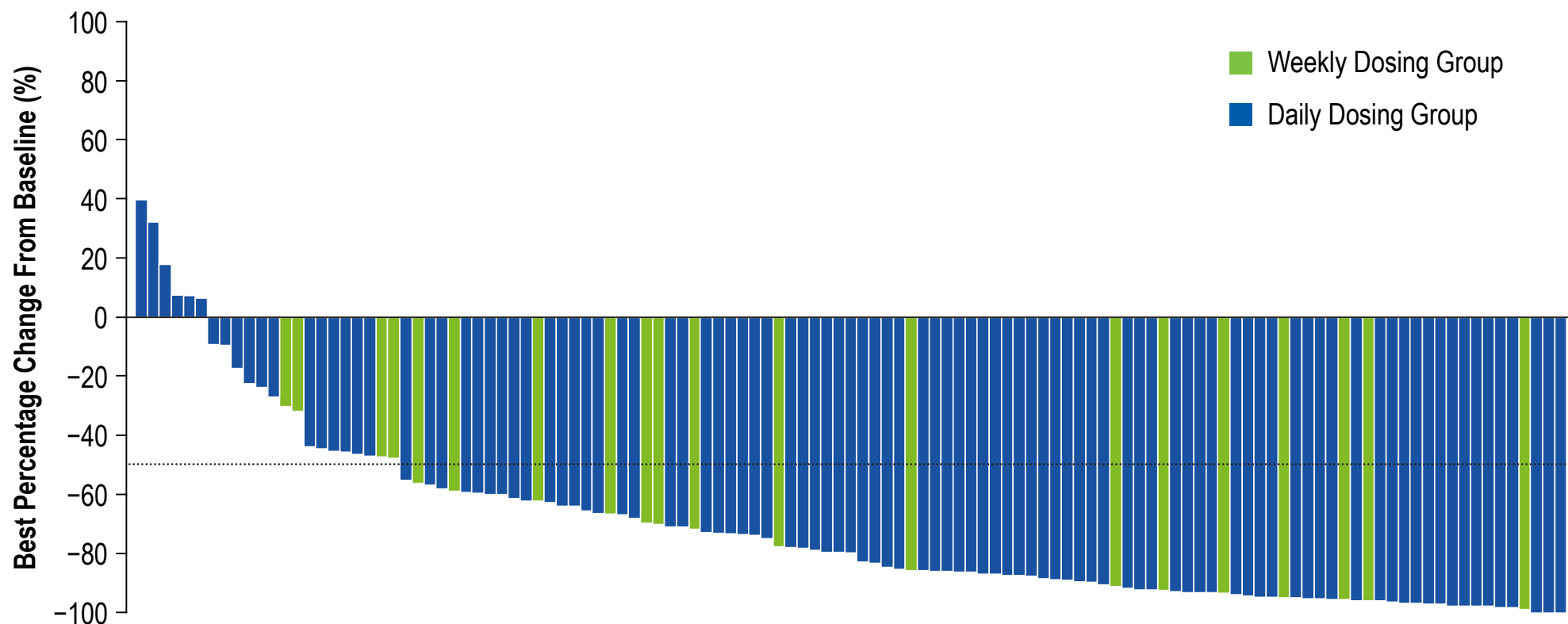


- 74% of all responders had their first response occur at the first disease assessment (8 weeks)



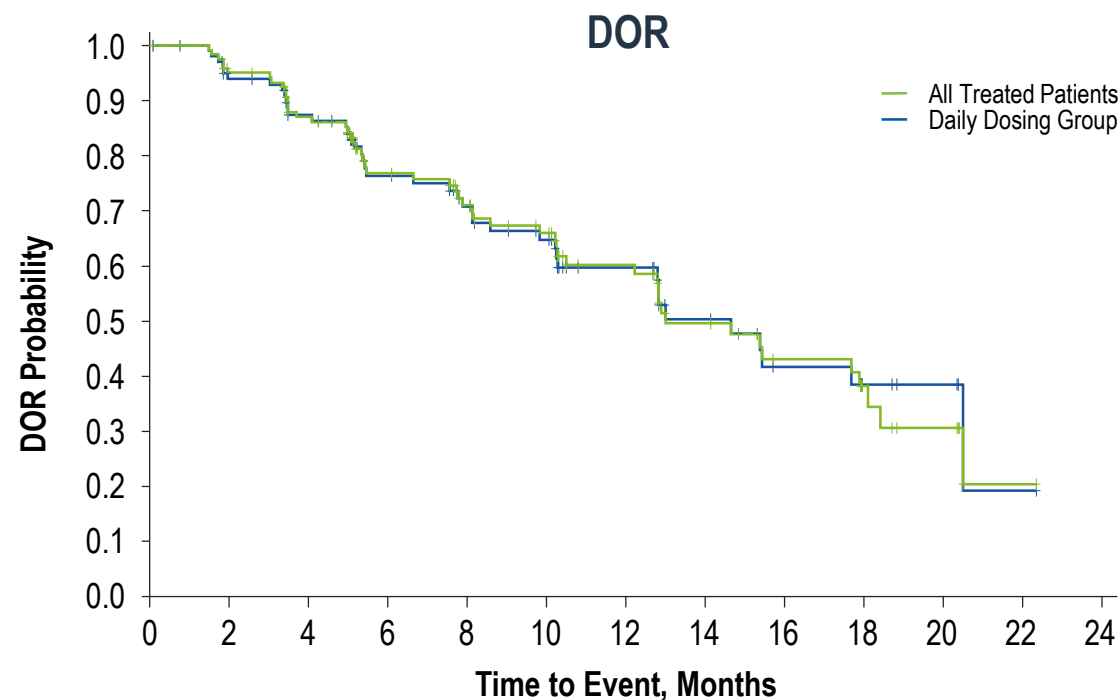
# Change From Baseline in Target Lesion Size by IRC\*

- 95% (113/119) of evaluable patients had regression at target lesions, 86% (97/113) of whom had >50% reduction in best percentage change from baseline



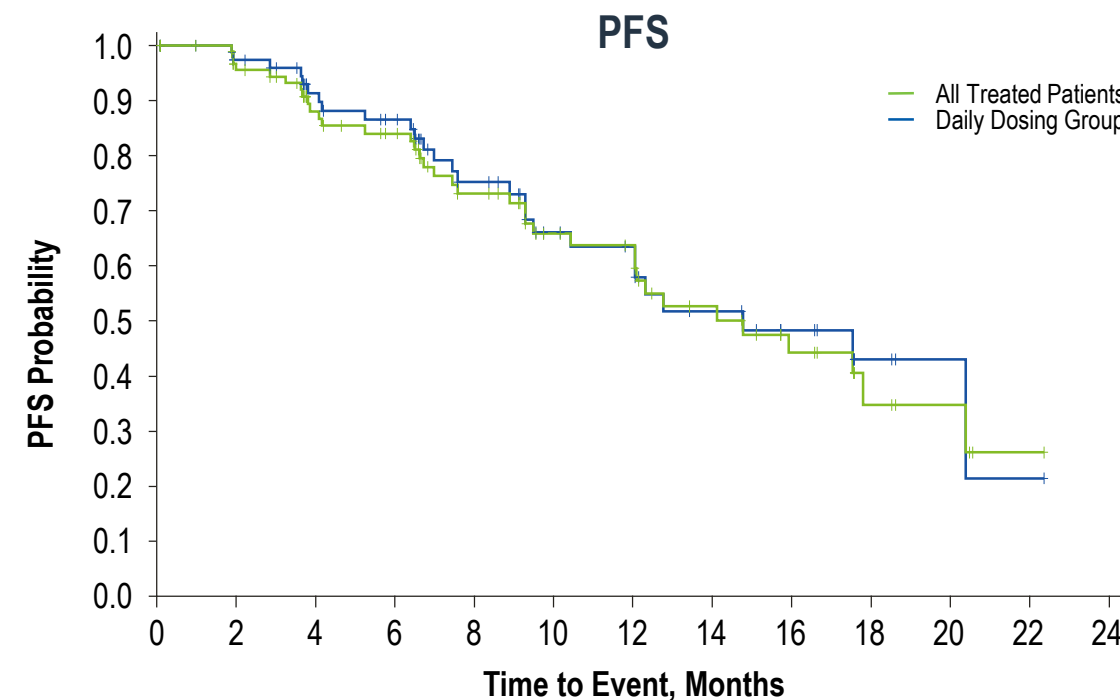
\*Includes patients who had baseline and  $\geq 1$  postbaseline valid measurements of target lesions to assess disease burden.

# DOR and PFS by IRC



Daily Dosing Group	80	70	57	51	37	26	20	16	11	4	2	1	0
All Treated Patients	95	83	66	59	44	33	27	21	14	6	4	1	0

	All Treated Patients (95 Responders)	Daily Dosing Group (80 Responders)
Median DOR (95% CI), months	14.7 (12.0–20.3)	14.7 (10.4–NE)



Daily Dosing Group	103	92	78	58	56	43	29	21	18	13	6	3	1
All Treated Patients	126	113	95	70	68	52	37	27	24	18	8	5	1

	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
Median PFS (95% CI), months	14.0 (11.3–19.6)	15.8 (11.0–NE)

NE, not estimable.

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

Event, %	All Treated Patients (N = 126)		Daily Dosing Group (N = 103)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
Any TEAE	98	59	97	59
Diarrhea	38	12	44	14
Nausea	25	1	24	1
Cough	22	0	24	0
Fatigue	18	1	18	1
Pyrexia	18	2	19	3
Rash	16	3	14	3
Neutropenia	14	10	16	11
Asthenia	13	1	14	1
Arthralgia	10	0	11	0

# Serious TEAEs and Deaths Due to AEs

## Serious TEAEs Occurring in ≥2 Patients Overall

Event, %	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
Any serious TEAE	45	46
Diarrhea	7	9
Colitis	6	8
Pneumonitis	2	2
Acute kidney injury	2	1
Chest pain	2	2
Dehydration	2	1

Event, %	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
Febrile neutropenia	2	2
Pleural effusion	2	2
Pneumonia	2	2
Pyrexia	2	2
Rash	2	2
Respiratory tract infection	2	1
Urinary tract infection	2	2

## Deaths

- Two deaths occurred due to adverse events attributed by the investigator to be related to parsaclisib
  - Patient with Stevens-Johnson syndrome
  - Patient with pneumonia

# Dose Modifications and High-Grade Diarrhea/Colitis Events

Dose Modifications Due to TEAEs (Any Grade)

Modification, %	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
Interruption	47	48
Reduction	17.5	20
Discontinuation	24	25

In the Daily Dosing Group:

- Most frequently occurring TEAEs leading to dose interruption were diarrhea (18%) and neutropenia (7%)
- Most frequently occurring TEAEs leading to dose reduction were diarrhea (12%) and rash (3%)
- Most common TEAEs leading to treatment discontinuation were diarrhea (8%) and colitis (5%)

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

Time to Onset or Improvement*	All Treated Patients (N = 126)	Daily Dosing Group (N = 103)
<b>Diarrhea</b>		
Number of patients with grade ≥3 events, %	12	14
Onset of grade ≥3 events, median (range), months	5.0 (0.2–12.9)	6.0 (0.2–12.9)
Improvement to grade ≤2, median (95% CI), days	18.0 (8.0–28.0)	18.0 (8.0–32.0)
<b>Colitis</b>		
Number of patients with grade ≥3 events, %	6	7
Onset of grade ≥3 events, median (range), months	5.7 (1.9–11.1)	5.7 (1.9–11.1)
Improvement to grade ≤2, median (95% CI), days	14.0 (4.0–16.0)	14.0 (4.0–16.0)

\*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.

# New or Worsening Laboratory Parameters

Event, %	All Treated Patients (N = 126)			Daily Dosing Group (N = 103)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic						
Neutrophils decreased	47	11	4	48	12	4
Hemoglobin decreased	33	3	NA	34	3	NA
Platelets decreased	22	0	0	22	0	0
Aminotransferase						
ALT elevation	30	2	0	30	2	0
AST elevation	28	0	0	29	0	0

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

# Summary

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- Patients with R/R FL had rapid and durable responses after treatment with parsaclisib, a potent, highly selective, next-generation PI3K $\delta$  inhibitor
  - 78% ORR, 14.7 months DOR, and 15.8 months PFS were observed in the Daily Dosing Group, the recommended dose for parsaclisib
- Parsaclisib has a manageable safety profile and was generally well tolerated
  - Significant transaminase elevations were uncommon
  - Diarrhea and colitis events were manageable
- Results of the primary efficacy and safety analysis of parsaclisib in patients with marginal zone lymphoma (CITADEL-204; Abstract #44) and mantle cell lymphoma (CITADEL-205; Abstract #382) are also presented at this meeting

# Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study.

Medical writing assistance was provided by Rachel Shparberg, PhD, of Envision Pharma Group (Philadelphia, PA), and funded by Incyte Corporation.

# Disclosures

**Lynch:** Consultancy – *Morphosys*; Research funding – *Bayer, Cyteir, Genentech, Incyte Corporation, Juno Therapeutics, Rhizen Pharmaceuticals, Takeda, TG Therapeutics*.

This study was sponsored by Incyte Corporation (Wilmington, DE).



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