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Abstract 338

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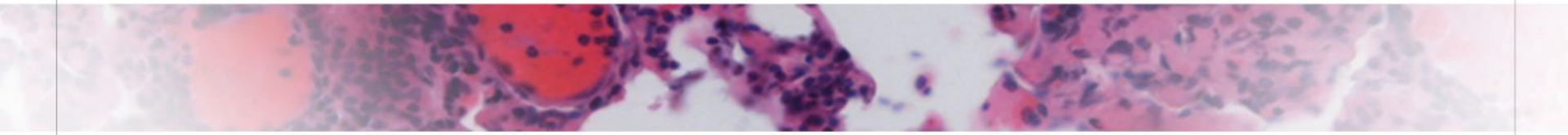

Phase 2 Study Evaluating the Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Marginal Zone Lymphoma (CITADEL-204)

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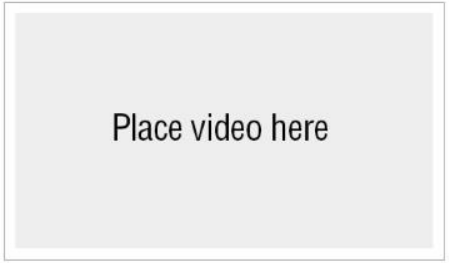
Background



- MZL comprises up ~10% of all NHL[1]
  - Clinically heterogeneous with 3 main subtypes (extranodal, nodal, and splenic)[2]
  - B-cell receptor pathway is a potential driver of MZL[2]
- Single-agent ibrutinib, a BTKi, is approved for MZL with ≥1 prior anti-CD20–based therapy[3]
- Combination therapy with lenalidomide plus rituximab has been approved in the United States for patients with previously treated MZL[4]
- Reported ORR with PI3K inhibitors in MZL ranges from 39–70%[5–8]
- Parsaclisib, a PI3Kδ inhibitor, has shown promising clinical activity in relapsed or refractory B-cell lymphomas, including MZL, in early studies[9]
- CITADEL-204 (NCT03144674) evaluates the efficacy and safety of 2 parsaclisib treatment schedules in patients with relapsed/refractory MZL who are naive to, or were previously treated with, a BTKi
  - Preliminary efficacy and safety data from July 13, 2020 data cutoff are presented

BTKi, Bruton's tyrosine kinase inhibitor; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PI3K, phosphatidylinositol 3-kinase; ORR, objective response rate.

1. Leslie LA, et al. *Expert Rev Hematol.* 2019;12:1011–1022. **2.** Rosand CB, et al. *Future Oncol.* 2018;14:1213–1222. **3.** IMBRUVICA® (ibrutinib). Sunnyvale, CA: Pharmacyclics LLC; 2020. **4.** REVLIMID® (lenalidomide). Summit, NJ: Celgene Corporation; 2019. **5.** Flinn IW, et al. *J Clin Oncol.* 2019;37:912–922. **6.** Gopal AK, et al. *N Engl J Med.* 2014;370:1008–1018. **7.** Fowler N, et al. *J Clin Oncol.* 2019;37(Suppl 15): Abstract 7506. **8.** Dreyling M, et al. *J Clin Oncol.* 2017;35:3898–3905. **9.** Forero-Torres A, et al. *Blood.* 2019;133:1742–1752.

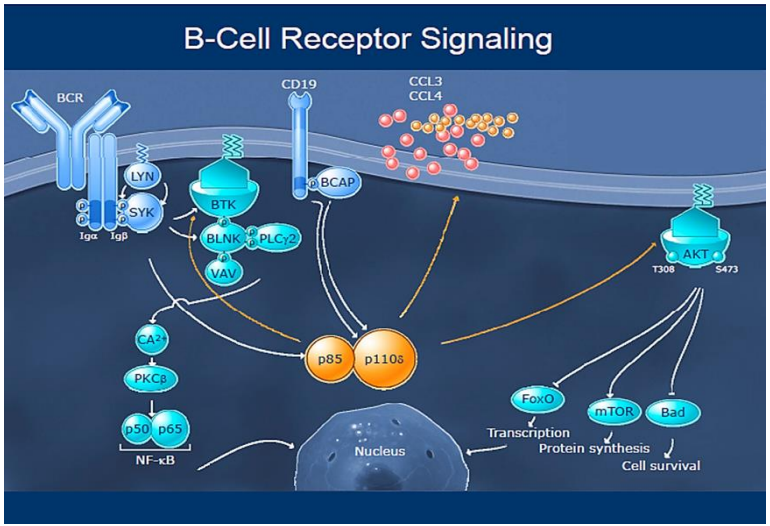
PI3K Structure and Function

- Class IA PI3Ks are heterodimeric lipid kinases composed of a regulatory (p85) and a catalytic subunit (p110)[1–3]
- PI3K is activated by growth factor receptor tyrosine kinases[1–3]

PI3K Catalytic Subunit (p110) Isoforms and Functions

α	Insulin signaling and angiogenesis[4]
β	Platelet function[4]
γ	White blood cell function[5]
δ	Signaling, development, and survival of B cells[6]

- PI3Kδ is required for membrane recruitment and activation of AKT and BTK



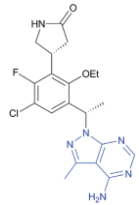
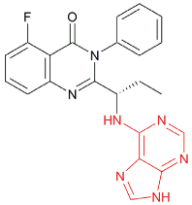
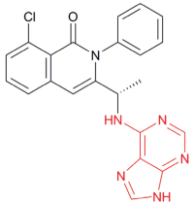
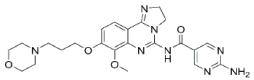
AKT, protein kinase B.

1. Chalhoub N, Baker SJ. *Annu Rev Pathol.* 2009;4:127–150. **2.** Fruman DA, Rommel C. *Nat Rev Drug Discov.* 2014;13:140–156. **3.** Brana I, Siu LL. *BMC Med.* 2012;10:161. **4.** Liu P, et al. *Nat Rev Drug Discov.* 2009;8:627–644. **5.** Hirsch E, et al. *Thromb Haemost.* 2006;95:29–35. **6.** Puri KD, Gold MR. *Front Immunol.* 2012;3:256.

Parsaclisib Is a Potent, Highly Selective, Next-Generation PI3Kδ Inhibitor

- The unique structure of parsaclisib, with a monocyclic core and pyrazolopyrimidine substituent, distinguishes it from other PI3Kδ inhibitors[1]
- Parsaclisib was designed to avoid hepatotoxicity

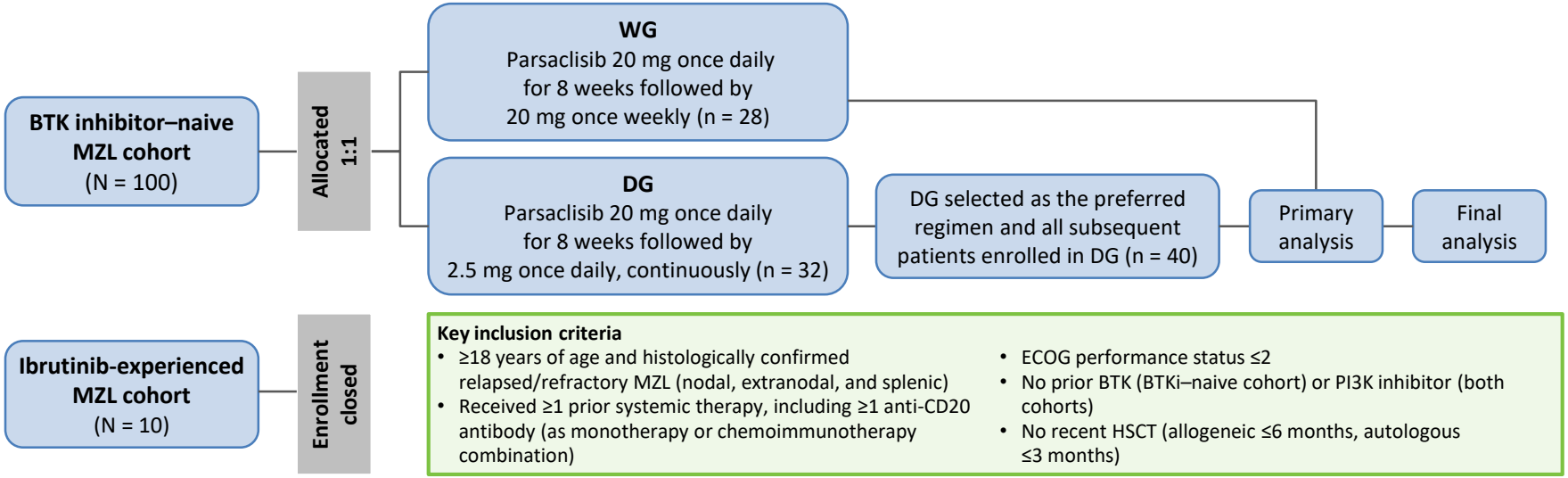
Comparative Potency and Isoform Selectivity*

	Parsaclisib[1]	Idelalisib[2]	Duvelisib[3]	Copanlisib[4]
Structure				
PI3Kδ IC_{50}, nM	1	2.5	2.5	0.7
Fold selectivity				
PI3Kα	>20,000	>300	1602	1
PI3Kβ	>20,000	>200	85	5
PI3Kγ	19,000	>35	27	10

*Biochemical assay.
IC, 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.

CITADEL-204*: Study Design



- During the study, DG was selected as the preferred dosing regimen; 3 of the 28 patients in WG were allowed to switch to DG, after DG was selected in the BTKi–naive cohort
- Data from the BTKi–naive cohort are presented by DG and overall
- Ibrutinib-experienced cohort was terminated due to slower than expected enrollment

*NCT03144674.
DG, Daily Group; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant; WG, Weekly Group.

Study Endpoints and Assessments

Primary endpoint

- Objective response rate (ORR)

Secondary endpoints

- Complete response rate
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Best percentage change in target lesion size from baseline
- Safety and tolerability of parsaclisib
- Radiology-based endpoints determined by IRC

Assessments

- Response assessed by CT/MRI using the Lugano criteria[1]
- Adverse events assessed using CTCAE v4.03
- Primary analysis planned in January 2021

CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; IRC, independent review committee; MRI, magnetic resonance imaging.

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

Baseline Characteristics

Characteristic	All Treated Patients (N = 100)	Daily Group (N = 72)
Age, median (range), years	71.0 (35–95)	72.0 (35–95)
≥65 years, n (%)	72 (72)	52 (72)
Men, n (%)	53 (53)	41 (57)
Time since MZL diagnosis, median (range), years	4.6 (0.1–20.1)	4.4 (0.1–19.8)
MZL subtypes, n (%)		
Nodal / extranodal / splenic	31 (31) / 34 (34) / 35 (35)	25 (35) / 23 (32) / 24 (33)
ECOG performance status ≤1, n (%)	95 (95)	69 (96)
Prior therapies		
Median number of prior systemic therapy regimens	2	2
Chemotherapy, n (%)	72 (72)	53 (74)
Surgery/surgical procedures, n (%)	19 (19)	11 (15)
Radiation, n (%)	11 (11)	7 (10)
Refractory to most recent systemic therapy, n (%)	49 (49)	35 (49)
Prior HSCT, n (%)	4 (4)	3 (4)

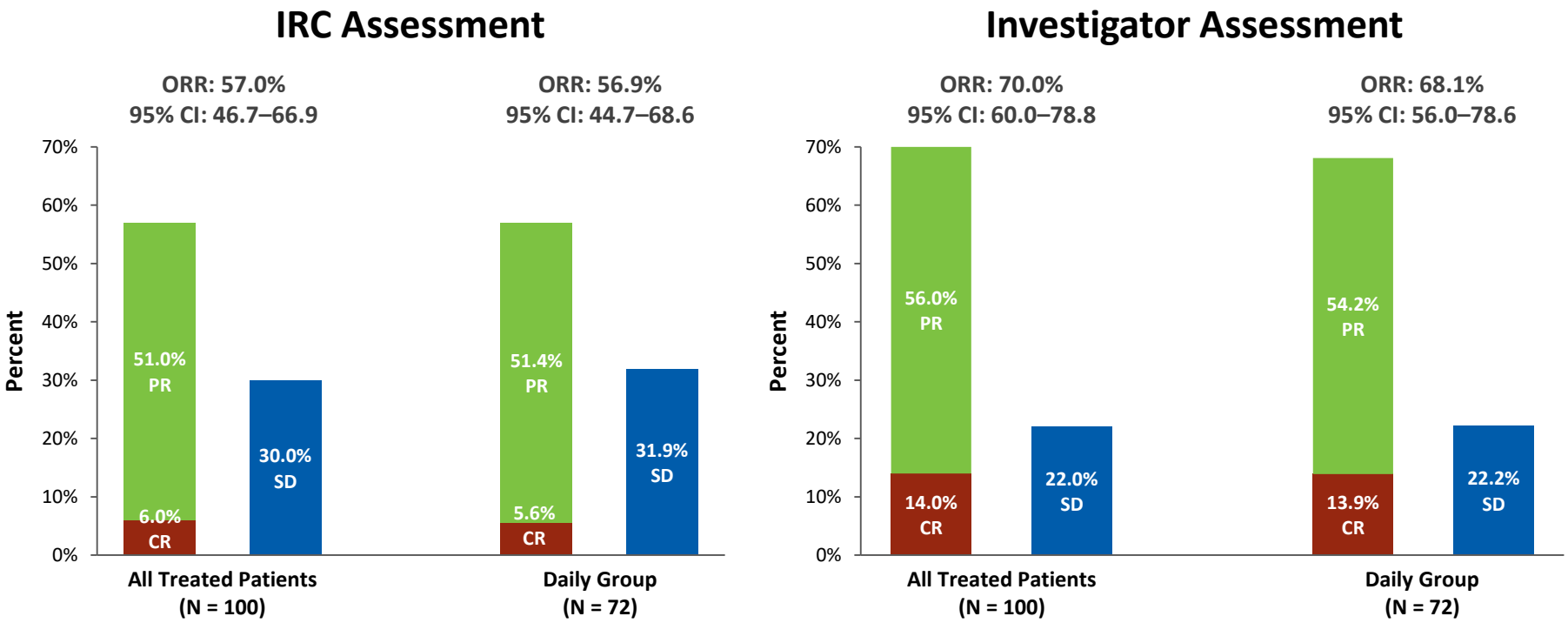
Patient Disposition and Exposure

	All Treated Patients (N = 100)	Daily Group (N = 72)
Median (range) duration on parsaclisib, months	11.4 (0.4–25.1)	9.3 (0.4–25.1)
Median (range) duration of follow-up,* months	16.7 (5.7–30.9)	14.9 (5.8–30.9)
Patients continuing on parsaclisib, n (%)	42 (42)	28 (39)
Primary reasons for discontinuing parsaclisib		
Progressive disease	26 (26)	17 (24)
Adverse event	25 (25)	23 (32)
Withdrawal/Physician decision	5 (5)	3 (4)
Protocol deviation†	2 (2)	1 (1)

*Duration of follow-up days determined as cutoff date (July 13, 2020) – first dose date + 1. †One patient (in Daily Group) with MCL; 1 patient with prior PI3K inhibitor therapy.

MCL, mantel cell lymphoma.

Objective Response Rate



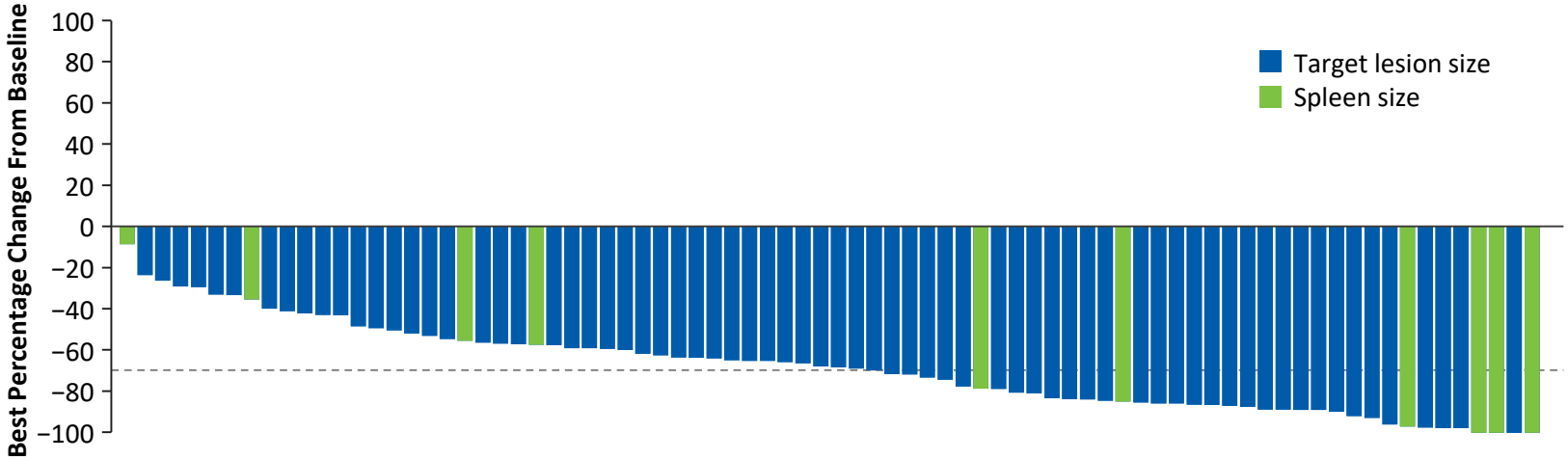
CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Objective Response Rate by Subtype and Prior Response by IRC

	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	62.9 44.9–78.5	51.0 36.3–65.6	67.4 52.0–80.5
Best objective response, n (%)					
Complete response	2 (6.5)	2 (5.9)	2 (5.7)	1 (2.0)	5 (10.9)
Partial response	14 (45.2)	17 (50.0)	20 (57.1)	24 (49.0)	26 (56.5)
Stable disease	10 (32.3)	11 (32.4)	9 (25.7)	19 (38.8)	8 (17.4)
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 not assessed had no post-baseline response data available at 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*

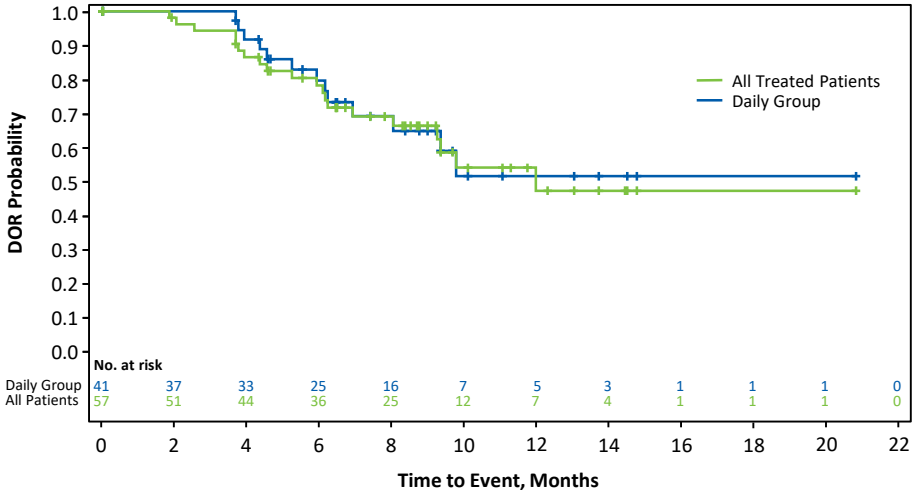


- 67% (38/57) of responders had an objective response (CR or PR) at first assessment
- Median time to first response was 8.1 weeks

*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.

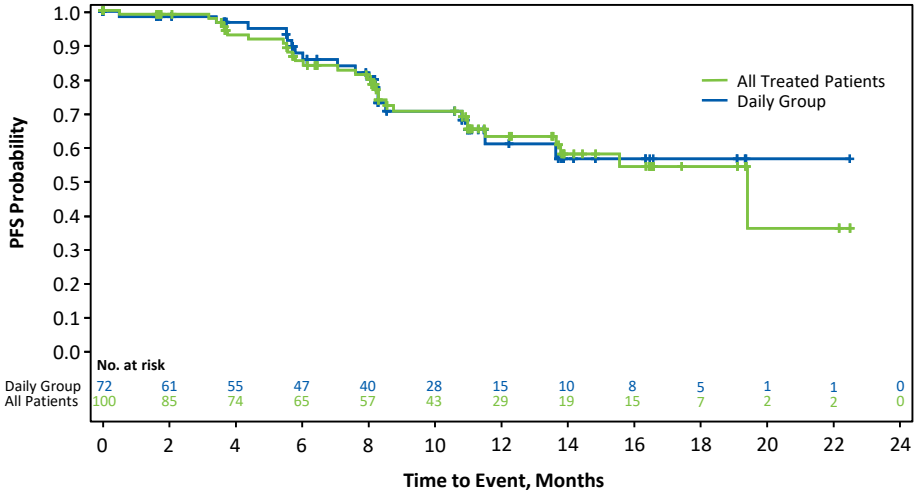
DOR and PFS by IRC

DOR



	All Treated Patients (57 Responders)	Daily Group (41 Responders)
Median DOR (95% CI), months	12.0 (9.3–NE)	NR (8.1–NE)

PFS



	All Treated Patients (N = 100)	Daily Group (N = 72)
Median PFS (95% CI), months	19.4 (13.7–NE)	NR (11.0–NE)

NE, not evaluable; NR, not reached.

TEAEs Occurring in ≥10% of All Treated Patients

Event, n (%)	All Treated Patients (N = 100)		Daily Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	43 (43)	59 (59)	36 (50)	49 (68)
Diarrhea	44 (44)	11 (11)	35 (49)	10 (14)
Cough	22 (22)	1 (1)	18 (25)	1 (1)
Rash	17 (17)	2 (2)	12 (17)	2 (3)
Anemia	14 (14)	5 (5)	11 (15)	5 (5)
Nausea	14 (14)	0	11 (15)	0
Pruritus	14 (14)	0	9 (13)	0
Constipation	13 (13)	0	11 (15)	0
Decreased appetite	13 (13)	0	11 (15)	0

Event, n (%)	All Treated Patients (N = 100)		Daily Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	13 (13)	1 (1)	10 (14)	1 (1)
Neutropenia	13 (13)	9 (9)	10 (14)	8 (11)
Pyrexia	13 (13)	1 (1)	9 (13)	1 (1)
Abdominal pain	12 (12)	3 (3)	11 (15)	3 (4)
Headache	12 (12)	0	10 (14)	0
Arthralgia	11 (11)	1 (1)	7 (10)	1 (1)
Upper respiratory tract infection	11 (11)	2 (2)	11 (15)	2 (3)
Dizziness	10 (10)	0	8 (11)	0

TEAE, treatment-emergent adverse event.

Worsening Laboratory Events

Event, n (%)	All Treated Patients (N = 100)			Daily Group (N = 72)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic						
Neutrophils decreased*	52 (52)	10 (10)	3 (3)	35 (49)	7 (10)	2 (3)
Hemoglobin decreased	29 (29)	4 (4)	NA	22 (31)	4 (6)	NA
Platelets decreased	18 (18)	3 (3)	0	13 (18)	2 (3)	0
Aminotransferase†						
ALT elevation	26 (26)	2 (2)	2 (2)	21 (29)	2 (3)	2 (3)
AST elevation	19 (19)	1 (1)	1 (1)	14 (19)	1 (1)	1 (1)

*Two patients discontinued treatment due to febrile neutropenia/neutropenia (both in Daily Group). †One patient discontinued treatment due to aminotransferase elevations (in Daily Group).

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

Serious TEAEs and Deaths Due to AEs

Serious TEAEs Occurring in ≥2 Patients Overall

Event, n (%)	All Treated Patients* (N = 100)	Daily Group (N = 72)
Any serious TEAE	43 (43)	36 (50)
Pneumonia	7 (7)	6 (8)
Colitis	5 (5)	5 (7)
Diarrhea	5 (5)	5 (7)
Febrile neutropenia	5 (5)	4 (6)
Abdominal pain	3 (3)	3 (4)
Acute kidney injury	3 (3)	3 (4)
Atrial fibrillation	3 (3)	3 (4)
Dehydration	2 (2)	2 (3)
Rash	2 (2)	2 (3)
Sepsis	2 (2)	2 (3)
Upper respiratory tract infection	2 (2)	2 (3)
Lung infection	2 (2)	1 (1)

Deaths

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

*Pneumonitis was reported as a serious TEAE in 1 patient in the Daily Group.

Dose Modifications and High-Grade Diarrhea/ Colitis Events

Dose Modification Due to TEAEs (Any Grade)

Modification, n (%)	All Treated Patients (N = 100)	Daily Group (N = 72)
Interruption	53 (53)	41 (57)
Reduction	14 (14)	10 (14)
Discontinuation	27 (27)*	25 (35)

*Fourteen patients (14%) had diarrhea/colitis events leading to drug discontinuation overall.

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

	All Treated Patients (N = 100)	Daily Group (N = 72)
Onset of grade ≥3 diarrhea/ colitis events, median (range), months	5.3 (0.6–12.0)	5.1 (0.6–12.0)
Improvement to grade ≤2 diarrhea, median (95% CI), days	12.0 (4.0–24.0)	14.5 (3.0–24.0)

Summary

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- Patients with relapsed/refractory MZL had rapid and durable responses after treatment with parsaclisib, a potent, highly selective, next-generation PI3Kδ inhibitor
  - 57% ORR in the Daily Group (median DOR and PFS have not been reached)
  - Comparable efficacy was observed in patients with nodal, extranodal, and splenic MZL
- Parsaclisib has a manageable safety profile and was generally well tolerated
- Parsaclisib represents a potentially new treatment option for relapsed/refractory MZL and a first-in-class PI3Kδ inhibitor for MZL

➢ Results of parsaclisib treatment in patients with follicular lymphoma (CITADEL-203; Abstract 2935) and mantle cell lymphoma (CITADEL-205; Abstracts 1121 and 2044) are also presented at this meeting

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Disclosures

Phillips: Consultant or advisor – *Pharmacyclics and Seattle Genetics*; and Travel reimbursement – *Incyte Corporation*.

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