Results from the Phase 1 Part of the PYNNACLE Study Assessing Rezatapopt in Patients With Advanced Solid Tumors Harboring a *TP53* Y220C Mutation

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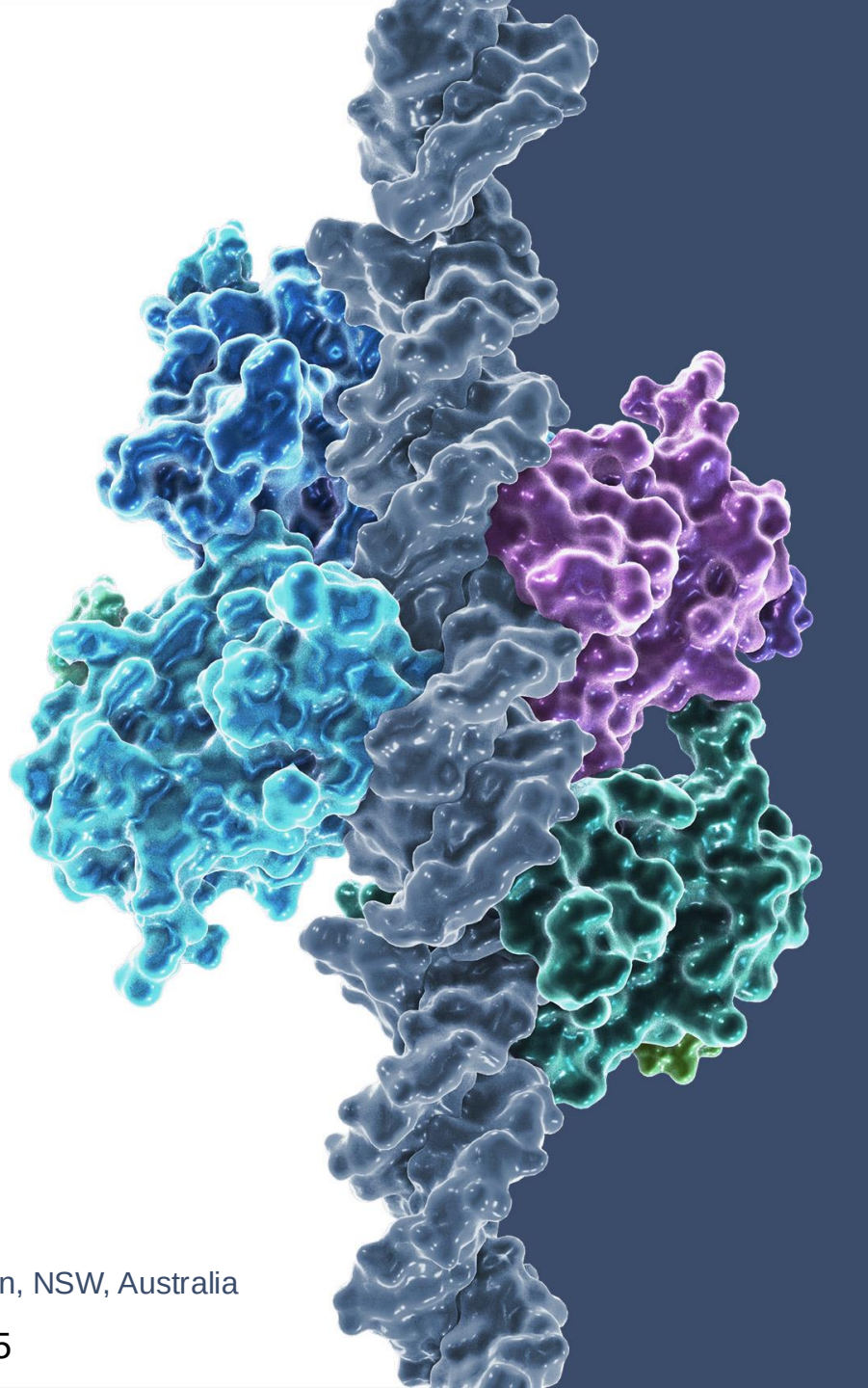

Poster presented at the Australian Precision Oncology Symposium 2025 (APOS), March 7–8, 2025, Kensington, NSW, Australia

Presented by: Amy Body

MA-586-0054 March 2025

Disclaimer

This presentation contains information about rezatapopt (also known as PC14586), an investigational agent that has not been approved by any regulatory agency

This presentation is for informational purposes only

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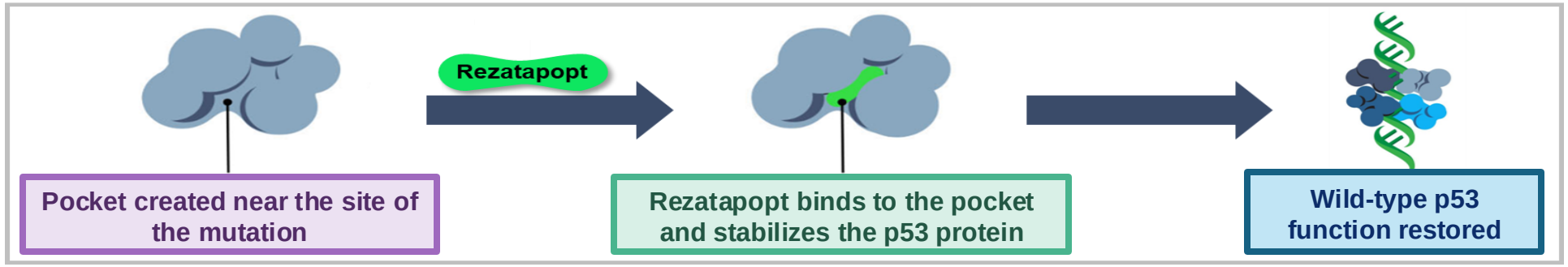
Rezatapopt: Investigational, First-in-Class p53 Reactivator

- *TP53* Y220C is a missense mutation that occurs in ≈1% of solid tumors, including ≈2.9% of ovarian cancers and ≈1% of breast cancers[1,2]
- The tyrosine to cysteine amino acid substitution destabilizes the p53 protein, leading to its inactivation[2]
- Reactivation of the wild-type p53 protein in p53-mutated tumors is an attractive therapeutic approach
- Rezatapopt (also known as PC14586) is an investigational, first-in-class p53 reactivator that selectively binds to the mutated p53 Y220C protein and stabilizes it in the wild-type conformation, thereby restoring p53 activity[2-5]

Rezatapopt Stabilizes p53 Y220C Protein in the Wild-Type Conformation[5]



1. FoundationInsights™. A proprietary database used under license with review and approval from Foundation Medicine®. Available at: https://www.foundationmedicine.com/service/genomic-data-solutions (accessed Jul 2024); 2. Binh V, et al. *ACS Med Chem Lett*. 2025;16:34–39; 3. Schram AM, et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 11–15, 2023, Boston, MA. Oral presentation, late-breaking abstract LB_A25; 4. Dumbrava EE, et al. ASCO Annual Meeting, June 3–7, 2022, Chicago, IL. Oral presentation; 5. PYNNACLE Clinical Study. Available at: https://www.pynnaclestudy.com/PC14586/ (accessed Feb 2025).

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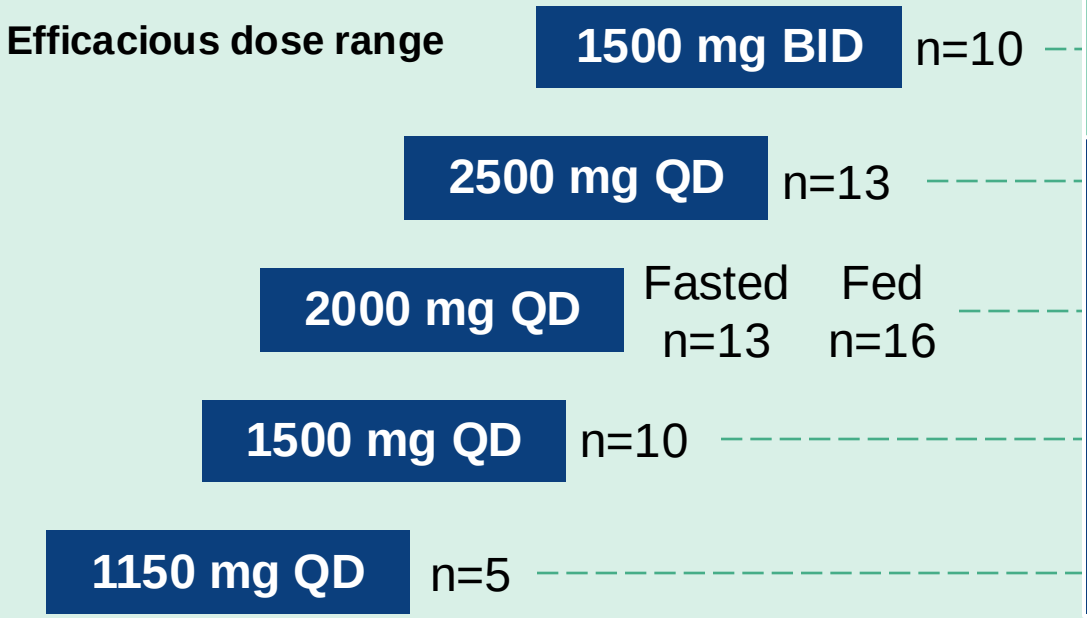
PYNNACLE (NCT04585750): Phase 1/2 Open-Label, Multicenter Clinical Trial

- Assesses rezatapopt in patients with advanced solid tumors harboring a *TP53* Y220C mutation[1,2]
- Phase 1: mTPI design with intrapatient dose escalation
- Rezatapopt administered orally for 21-day continuous cycles to determine the efficacious dose range (1150 mg QD to 1500 mg BID)
- Eligible patients: ≥12 years of age with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation



Enrollment

- 67 patients* (as of Sep 5, 2023)
- 22 patients with ovarian cancer
- 9 patients with breast cancer

- Safety (CTCAE v5.0), preliminary efficacy (RECIST v1.1) investigator assessed
- Results reported: Data cut-off September 5, 2023

*A total of 77 patients were enrolled as of Sep 5, 2023; 67 patients received rezatapopt in the efficacious dose range.
BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; mTPI, modified toxicity probability interval; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. NCT04585750. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT04585750 (accessed Dec 2024); 2. PYNNACLE Clinical Study. Available at: https://www.pynnaclestudy.com/PC14586/ (accessed Dec 2024).

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Patient Demographics and Baseline Characteristics

	Patients treated in the efficacious dose range (1150 mg QD to 1500 mg BID)		
	All patients* (n=67)	Ovarian cancer (n=22)	Breast cancer (n=9)
Median age (min–max), years	63 (32–84)	66 (49-81)	53 (32-65)
Sex, female/male, n (%)	41 (61)/26 (39)	22 (100)/0	9 (100)/0
Race, n (%)			
White	51 (76)	15 (68)	6 (67)
Asian	5 (7)	3 (14)	1 (11)
Black or African American	6 (9)	2 (9)	1 (11)
Other	1 (1)	0	0
Not reported	4 (6)	2 (9)	1 (11)
ECOG PS 0/1, n (%)	22 (33)/45 (67)	6 (27)/16 (73)	3 (33)/6 (67)
Prior systemic therapies, n (%)			
1/2	6 (9)/19 (28)	1 (5)/4 (18)	0/2 (22)
≥3	37 (55)	14 (64)	7 (78)
Median (min–max)	3 (1–9)	4 (1–9)	4 (2–8)
Not reported	5 (6)	3 (14)	0
Germline *TP53* Y220C, n (%)			
Negative/positive	66 (99)/1 (1)	22 (100)/0	9 (100)/0
***KRAS* mutation status, n (%)**			
Wild-type/*KRAS* SNV*	50 (75)/17 (25)	22 (100)/0	9 (100)/0
Measurable disease at baseline, n (%)	64 (95)	20 (91)	8 (89)

Data cut-off September 5, 2023.
*12 pancreas, three colon, one small intestine, one cholangiocarcinoma. BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; SNV, single-nucleotide variant.

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Safety: TRAEs in >5% of Patients (n=67) Receiving Rezatapopt in the Efficacious Dose Range

All TRAEs, n (%)		Max CTCAE			
Preferred term	Overall n=67	1	2	3	4
Any TRAE	**60 (89.6)**	**16 (23.9)**	**27 (40.3)**	**16* (23.9)**	**1† (1.5)**
Nausea	34 (50.7)	22 (32.8)	11 (16.4)	1 (1.5)	–
Vomiting	29 (43.3)	16 (23.9)	12 (17.9)	1 (1.5)	–
Blood creatinine increased	18 (26.9)	10 (14.9)	8 (11.9)	–	–
Diarrhea	13 (19.4)	12 (17.9)	–	1 (1.5)	–
Fatigue	13 (19.4)	8 (11.9)	5 (7.5)	–	–
ALT increased	12 (17.9)	4 (6.0)	5 (7.5)	3 (4.5)	–
AST increased	11 (16.4)	7 (10.4)	2 (3.0)	2 (3.0)	–
Anemia	10 (14.9)	1 (1.5)	6 (9.0)	3 (4.5)	–
Decreased appetite	7 (10.4)	2 (3.0)	4 (6.0)	1 (1.5)	–
Proteinuria	6 (9.0)	1 (1.5)	5 (7.5)	–	–
Rash maculopapular	6 (9.0)	1 (1.5)	3 (4.5)	2 (3.0)	–
Headache	5 (7.5)	4 (6.0)	1 (1.5)	–	–
Lipase increased	5 (7.5)	4 (6.0)	–	1 (1.5)	–
Platelet count decreased	4 (6.0)	1 (1.5)	1 (1.5)	2 (3.0)	–
Amylase increased	4 (6.0)	3 (4.5)	1 (1.5)	–	–
Dehydration	4 (6.0)	–	4 (6.0)	–	–

- Rezatapopt was generally well tolerated
- Across the total population (n=67), TRAEs were mostly grade 1/2
- Administration of rezatapopt with food led to an improvement in gastrointestinal toxicities[1]
- The safety profile in the ovarian and breast cancer subgroups was consistent with that in the overall population

Data cut-off September 5, 2023.
*Includes five additional grade 3 TRAEs: neutrophil count decreased, acute kidney injury, pancreatitis, pneumonitis, and rash erythematous. Note that a patient could have multiple grade 3 events.
†Includes one patient with grade 4 immune thrombocytopenia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; QD, once daily; TRAE, treatment-related adverse event.
1. Kuo HCD, et al. ACCP Annual Meeting, October 12–15, 2024, Phoenix, AR. Poster 044, abstract 1773065.

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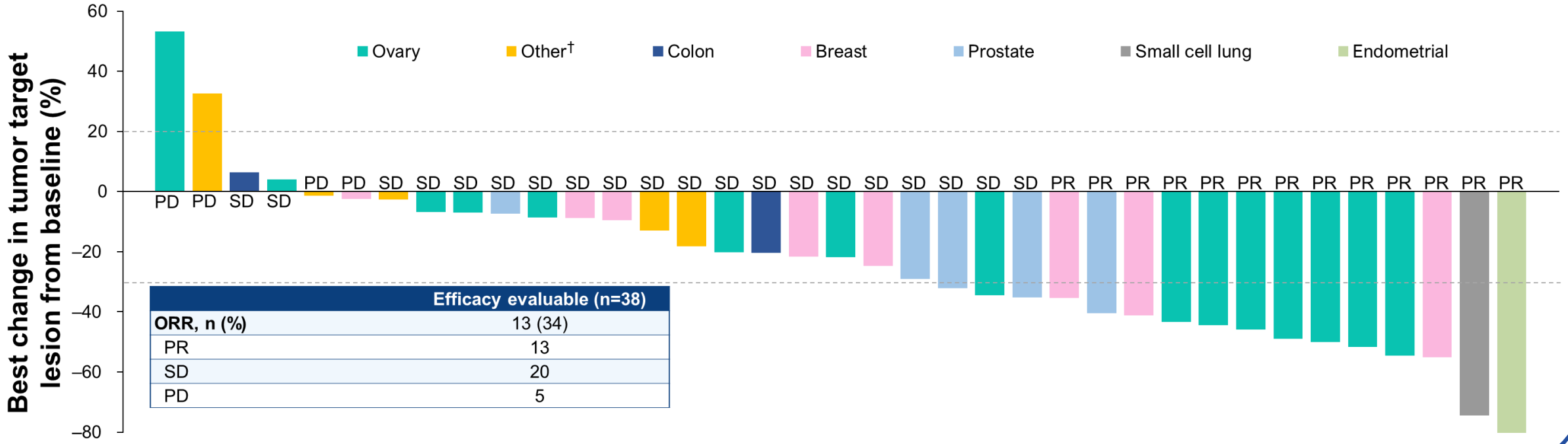
Efficacy:
Target Lesion Reduction Was Observed in Most Patients

Target Lesion Reduction in the *TP53* Y220C/*KRAS* Wild-Type Efficacy-Evaluable Population Receiving Rezatapopt in the Efficacious Dose Range (1150 mg QD to 1500 mg BID) for the Overall Population Across Tumor Types*



	Efficacy evaluable (n=38)
ORR, n (%)	13 (34)
PR	13
SD	20
PD	5

Data cut-off September 5, 2023.
*The efficacy-evaluable population includes patients who have a *TP53* Y220C mutation and were *KRAS* wild type (did not harbor a *KRAS* SNV) with measurable disease at baseline and ≥1 post-baseline tumor assessment receiving rezatapopt in the efficacious dose range. One patient with small cell lung cancer without tumor measurement at first scan is not represented.
†Other tumor types include sarcoma, esophageal cancer, germ cell tumor, pleomorphic rhabdomyosarcoma, and urothelial cancer.
ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SNV, single-nucleotide variant.

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Efficacy:
Responses Seen Across Various Tumor Types

Best Overall Response in the *TP53* Y220C/*KRAS* Wild-Type Efficacy-Evaluable Population*

Patients, n (%)	Rezatapopt RP2D 2000 mg QD (n=16)	Rezatapopt efficacious dose range 1150 mg QD to 1500 mg BID (n=38)
ORR	**6/16 (38)**	**13/38 (34)**
Confirmed PR	6/16 (38)	13/38 (34)
SD	8/16 (50)	20/38 (53)
PD	2/16 (13)	5/38 (13)

Ovarian cancer subgroup	**2/5 (40)**	**7/15 (47)**
Breast cancer subgroup	**2/3 (67)**	**3/8 (38)**
Small cell lung subgroup	0/1 (0)	1/2 (50)
Endometrial subgroup	1/1 (100)	1/1 (100)
Other tumors	1/6 (17)	1/12 (8)

Data cut-off September 5, 2023.
*The efficacy-evaluable population includes patients who have a *TP53* Y220C mutation and were *KRAS* wild type (did not harbor a *KRAS* SNV) with measurable disease at baseline and ≥1 post-baseline tumor assessment receiving rezatapopt in the efficacious dose range.
BID, twice daily; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

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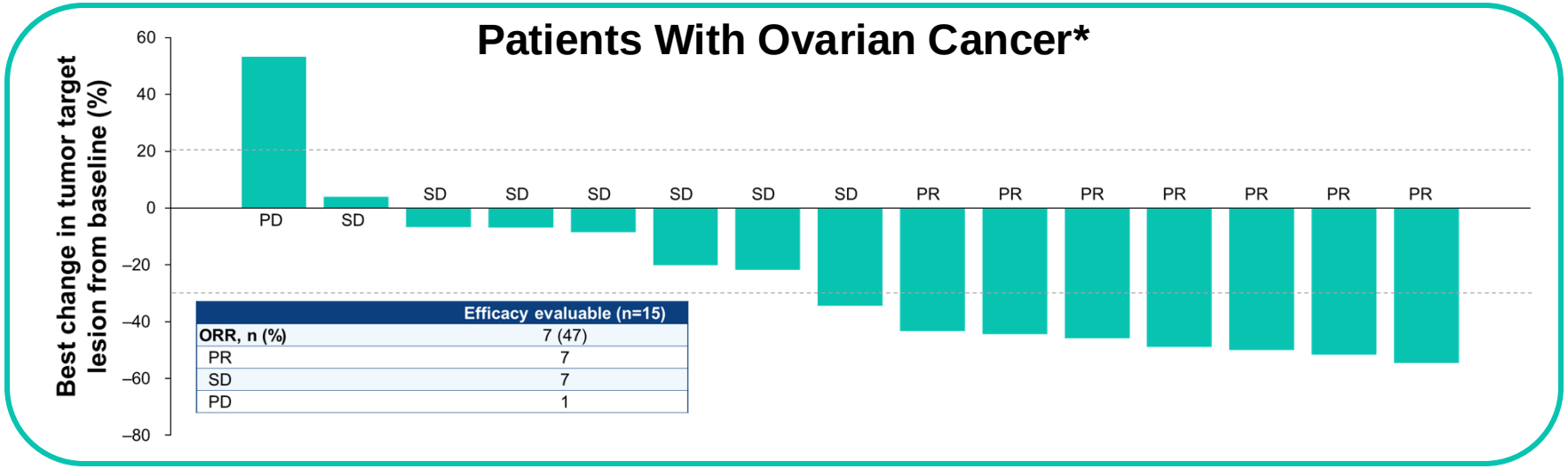
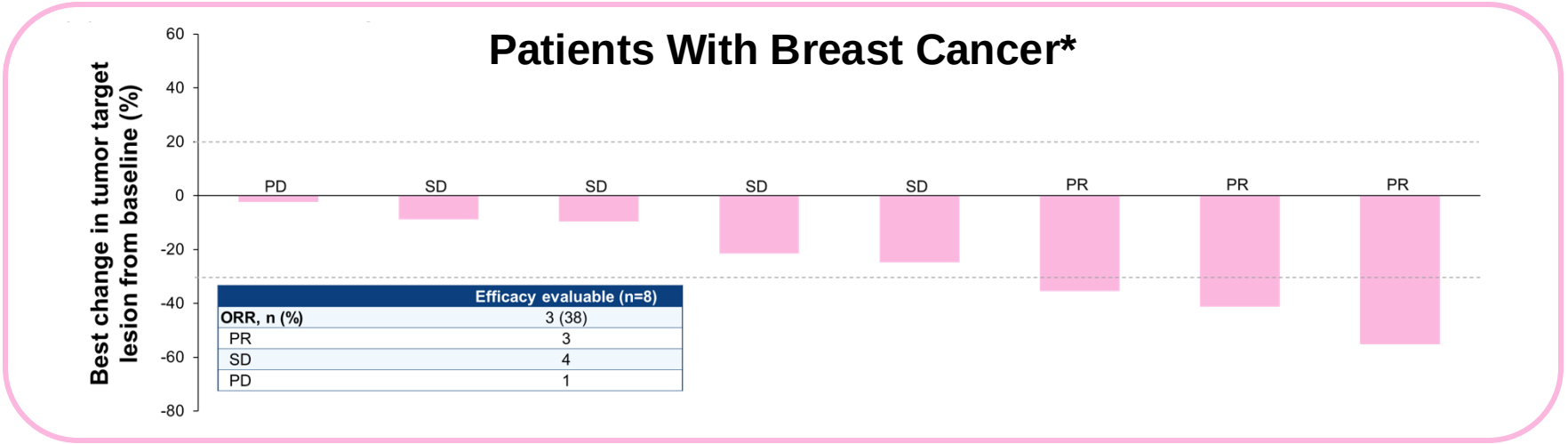
Efficacy: Target Lesion Reduction Was Observed in Most Patients With Ovarian and Breast Cancer





Data cut-off September 5, 2023. *The efficacy-evaluable population includes patients who have a *TP53* Y220C mutation and were *KRAS* wild type (did not harbor a *KRAS* SNV) with measurable disease at baseline and ≥1 post-baseline tumor assessment receiving rezatapopt in the efficacious dose range. ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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PYNNACLE Registrational Phase 2 Study

Assesses efficacy, safety, PK, and QOL of rezatapopt in patients with solid tumors with *TP53* Y220C and *KRAS* wild type[1–3]

PYNNACLE Phase 2 Study Design[1–3]

Phase 2

Basket N = ~114

Rezatapopt 2000 mg QD with food

Cohort 1: Ovarian cancer*	n = ~42
Cohort 2: Lung cancer	n = ~18
Cohort 3: Breast cancer	n = ~18
Cohort 4: Endometrial cancer	n = ~18
Cohort 5: All other solid tumours	n = ~18

Patient population (inclusion criteria)

- Aged ≥18 years (all global sites except Singapore: ≥21 years)
- Adolescents 12–17 years of age (if ≥40 kg, in Australia, South Korea and US only)
- ECOG PS 0 or 1
- Locally advanced or metastatic solid tumours
- Measurable disease at baseline (RECIST v1.1)
- Documented *TP53* Y220C mutation (identified locally) and *KRAS* WT†
- Previously treated with ≥1 line of systemic treatment or ineligible for appropriate SOC

Exclusion criteria

- *KRAS* single nucleotide variant mutations
- Unstable brain metastases
- Primary CNS tumours
- History of leptomeningeal disease or spinal cord compression, organ transplant or gastrointestinal disease that may impact rezatapopt absorption
- Heart conditions (unstable angina, uncontrolled hypertension, heart attack within 6 months prior to screening, heart failure or other clinically significant rhythm abnormalities)
- Uncontrolled Hepatitis B, Hepatitis C or HIV infection

Locations for the PYNNACLE Phase 2 study in Australia: Perth, Adelaide, Melbourne, and Sydney[1,2]

Cohort 5 (all other solid tumors) is fully enrolled; recruitment is ongoing for the other cohorts (ovarian, lung, breast, endometrial)

*Platinum resistant or refractory. †*KRAS* WT defined as the absence of *KRAS* SNV mutations.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; PK, pharmacokinetics; QD, once daily; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; SNV, single-nucleotide variant; WT, wild type

1. NCT04585750. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT04585750 (accessed Dec 2024);
2. PYNNACLE Clinical Study. Available at: https://www.pynnaclestudy.com/ (accessed Feb 2025);
3. Schram AM, et al. ESMO Congress 2024, September 13-17, 2024, Barcelona, Spain. Poster 691 TiP.

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Conclusions

PYNNACLE Phase 1: Rezatapopt demonstrated a favorable safety profile and promising single-agent efficacy across the efficacious dose range in heavily pre-treated patients with locally advanced or metastatic solid tumors, including ovarian and breast cancers

PYNNACLE Phase 2: Ongoing and assessing rezatapopt at the RP2D of 2000 mg QD taken with food in patients with locally advanced or metastatic *TP53* Y220C-mutated and *KRAS* wild-type solid tumors

QD, once daily; RP2D, recommended Phase 2 dose.

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Acknowledgments and disclosures

- We would like to thank all the patients, their families, and caregivers who have participated, and continue to participate, in the clinical trials, and the investigators and research staff

- This study and the clinical trials are sponsored by PMV Pharmaceuticals, Inc.

- Medical writing support was provided by Carolyn Maskin and Danielle Lindley of Nucleus Global, an Inizio company, funded by PMV Pharmaceuticals, Inc.

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