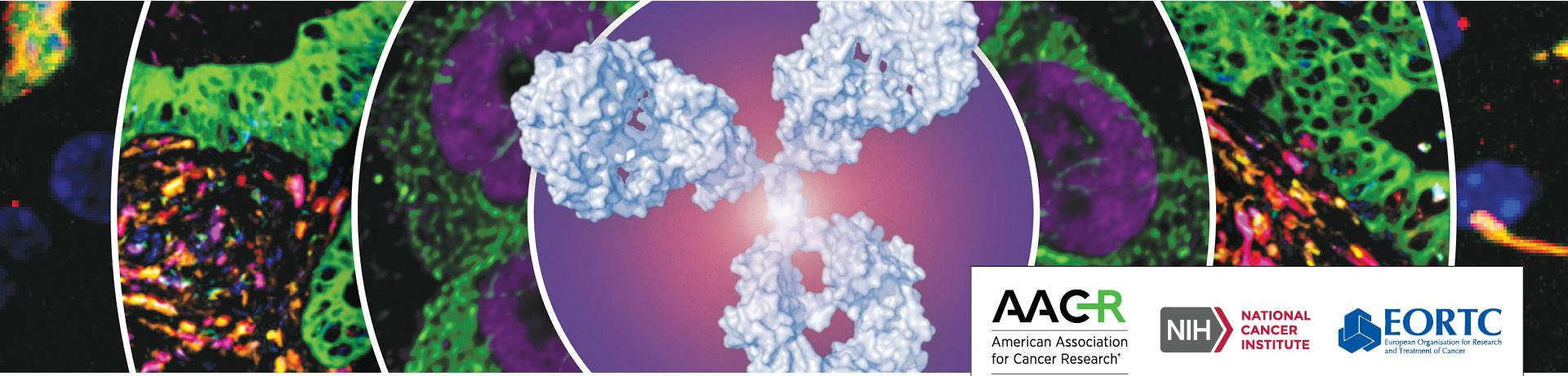

Rezatapopt for locally advanced or metastatic solid tumors with a *TP53* Y220C mutation: Initial analysis of the pivotal PYNNACLE Phase 2 trial

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AACR-NCI-EORTC MOLECULAR TARGETS AND CANCER THERAPEUTICS

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Disclosure information

Alison M. Schram

I have the following relevant financial relationships to disclose:

- Advisory board: Blueprint Medicines, Mersana, Endeavor Biomedicines, Revolution Medicine, Day One Biopharmaceuticals, Transcode Therapeutics, Relay Therapeutics
- Advisory role: Merus, Pfizer, PMV Pharmaceuticals, Inc., Schrodinger, Repare Therapeutics, Relay Therapeutics
- Research funding to institution: ArQule, AstraZeneca, BeiGene, Springworks, Black Diamond, Boehringer Ingelheim, Elevation Oncology, Kura Oncology, Eli Lilly, Merus, Northern Biologics, Pfizer, PMV Pharmaceuticals, Inc., Relay Therapeutics, Repare Therapeutics, Revolution Medicine, Surface Oncology

AMS JF, MJ, AI, ALC, JK, SK, GC, AG, S-AI, GdLL, ARP, AF, PG, MJdML, DRP, DSPT, TJT, MW, and **EED** are principal investigators for the PYNNACLE trial.

KL, AS, DJ, and **MF** are employees of PMV Pharmaceuticals, Inc. and own stock or options in PMV Pharmaceuticals, Inc.

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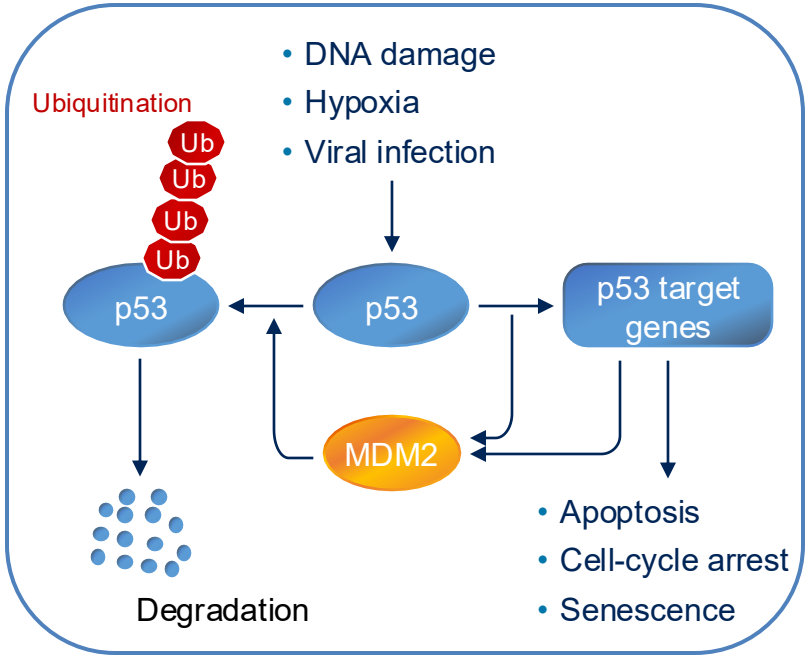
p53 – a key player in the body's defense against cancer

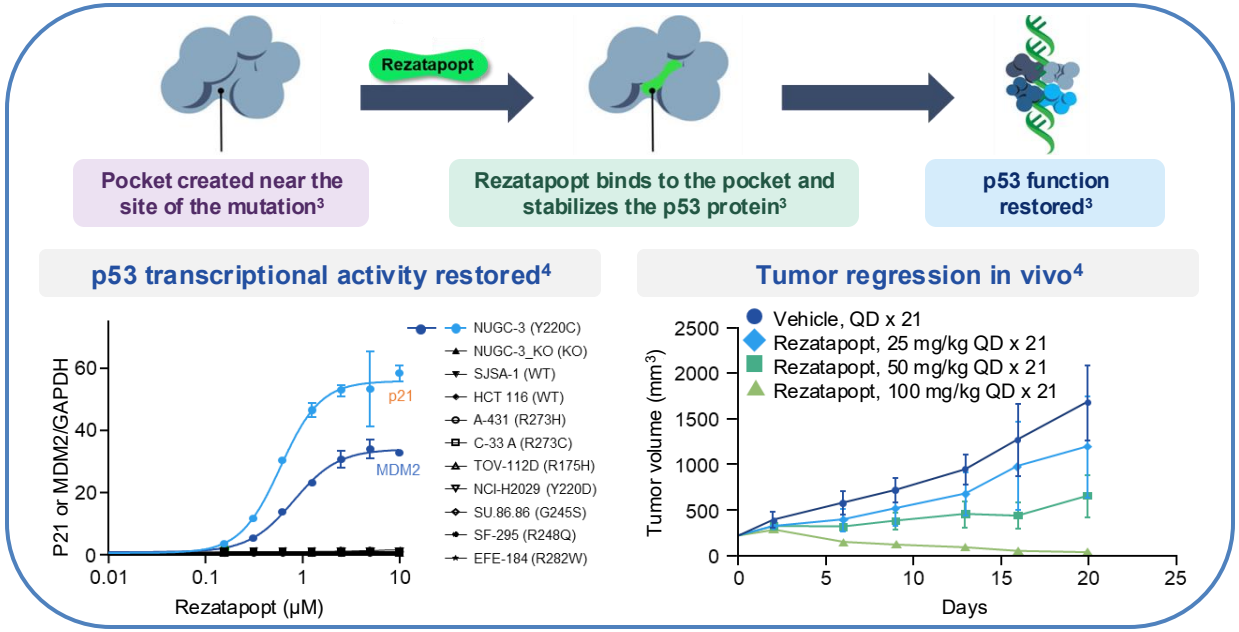
- *TP53* is a tumor suppressor gene that encodes the p53 protein[1,2]
- p53 binds to DNA and plays a key role in cell cycle arrest, DNA repair, and apoptosis[1–3]
- *TP53* mutations result in inactivation of p53, which is a key step in oncogenesis[1–3]
- The *TP53* Y220C mutation occurs in ~1% of solid tumors and in ~3% of ovarian cancers[4–6]
- *TP53* Y220C destabilizes p53, causing loss of tumor suppressor function[4–6]



1. Chillemi G, et al. *Cold Spring Harb Perspect Med*. 2017;7:a028308; 2. Kastenhuber ER, et al. *Cell*. 2017;170:1062–1078; 3. Levine AJ. *Nat Rev Cancer*. 2020;20:471–480; 4. Baugh EH, et al. *Cell Death Differ*. 2018;25:154–160; 5. Vu BT, et al. *ACS Med Chem Lett*. 2024;16:34–39; 6. Puzio-Kuter AM, et al. *Cancer Discov*. 2025;15:1159–1179.

Rezatapopt is a selective p53 Y220C reactivator

- Rezatapopt is an investigational, oral, first-in-class p53 reactivator specific to the *TP53* Y220C mutation[1–3]
- Selectively binds to a pocket created in the mutated p53 Y220C protein, stabilizing it in the wildtype conformation, thereby restoring p53 function[1–3]



KO, knockout; QD, once daily; WT, wildtype. 1. Vu BT, et al. *ACS Med Chem Lett*. 2024;16:34–39; 2. Puzio-Kuter AM, et al. *Cancer Discov*. 2025;15:1159–1179; 3. https://www.pynnaclestudy.com/; 4. Dumble M, et al. *Cancer Res*. 2021;81(13_Suppl):Abstract LB006.

PYNNACLE study design

Pivotal Phase 2, global, multi-cohort clinical trial assessing rezatapopt in locally advanced or metastatic solid tumors with a *TP53* Y220C mutation and *KRAS* wildtype[1,2]

Patient population

- Adults aged ≥18 years[a]
- Adolescents aged 12–17 years[b]
- Locally advanced or metastatic solid tumors, excluding primary CNS tumors
- Documented *TP53* Y220C and *KRAS* wildtype only (no *KRAS* SNV mutations)
- Prior standard therapy or ineligible for appropriate SoC therapy

Basket N=~200

Patient cohorts defined by tumor type

Rezatapopt 2000 mg QD with food

- Cohort 1: Ovarian cancer
- Cohort 2: Lung cancer
- Cohort 3: Breast cancer
- Cohort 4: Endometrial cancer
- Cohort 5: All other solid tumors

Endpoints

Primary: ORR per BICR
- Ovarian cancer cohort
- Across all cohorts

Key secondary:
ORR per investigator, TTR, DoR, DCR, PFS per BICR and investigator, OS, safety

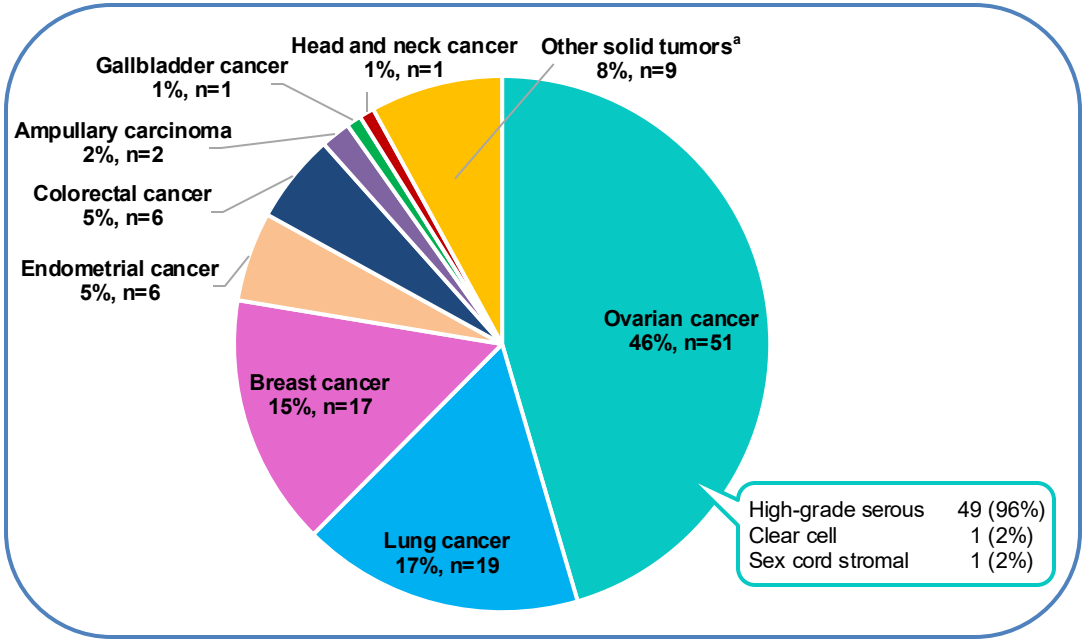
[a] For all global sites except Singapore (must be ≥21 years of age) and South Korea (must be ≥19 years of age). [b] If weighing ≥40 kg (in Australia, South Korea [12–18 years of age], and the USA only).
BICR, blinded independent central review; CNS, central nervous system; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SNV, single nucleotide variant; SoC, standard of care; TTR, time to response.

1. PYNNACLE Study. Available at: https://www.pynnaclestudy.com/. Accessed October 2025; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT04585750. Accessed October 2025.

Patient demographics and disease characteristics

Patients were heavily pretreated across broad spectrum of tumor types

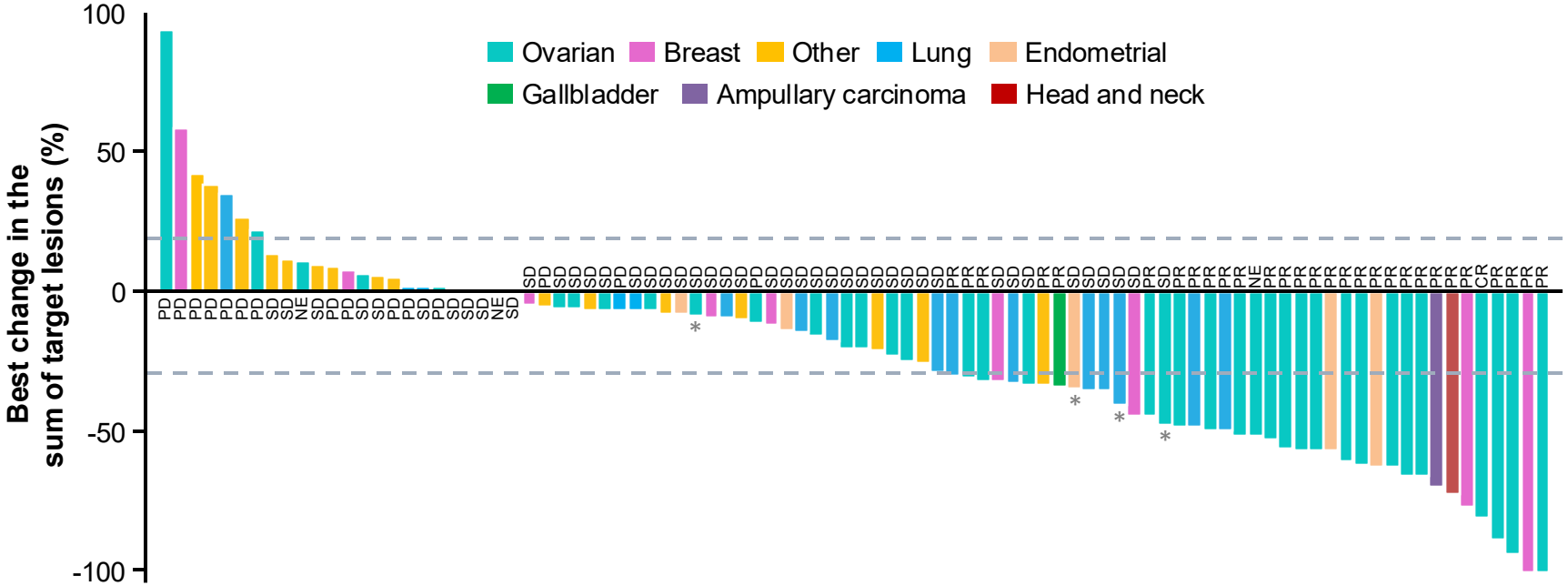
	Overall, N=112
Median age, years (min–max)	65 (37–91)
Sex, female / male, n (%)	82 (73) / 30 (27)
Race, n (%)	n=108
White	81 (75)
Asian	14 (13)
American Indian or Alaska Native	1 (1)
Black or African American	1 (1)
Other	1 (1)
Not reported	10 (9)
ECOG status, n (%)	n=108
0 / 1	47 (44) / 61 (56)
Prior systemic therapies, n (%)	n=107
1	9 (8)
2	29 (27)
≥3	69 (64)
Median (min–max)	3 (1–10)



Data cutoff: Sept 4, 2025. [a] Includes gastric cancer (n=2), sarcoma (n=2), small intestine cancer (n=1), HCC (n=1), pancreatic cancer (n=1), thymic carcinoma (n=1), and esophagus carcinoma (n=1).
ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma.

Tumor shrinkage observed across all cohorts

Reductions in tumor target lesions were observed across the different tumor types (n=92)[a]



Data cutoff: Sept 4, 2025. [a] Including patients (n=92) with a post-baseline tumor assessment. Best overall responses are noted in the figure (* = uPR). At the time of data extraction, an additional uPR was recorded without tumor measurements reported as of yet.
CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

ORR per RECIST v1.1

Based on investigator assessment

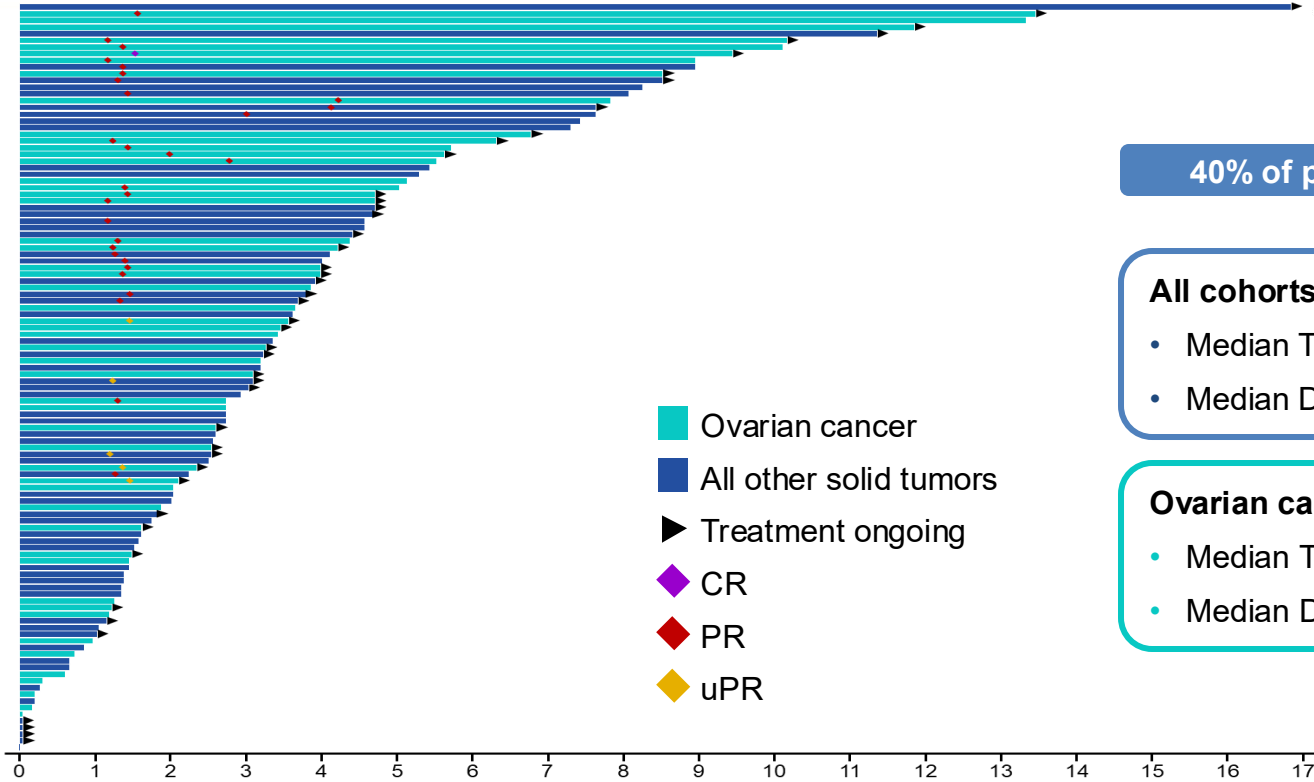
Confirmed responses were seen across tumor types

	Overall n=103[a]	Ovarian n=48
ORR,[b] % (95% CI)	34.0 (24.9–44.0)	45.8 (31.4–60.8)
CR	1	1
PR	29	18
uPR	5[c]	3
SD	39	12
PD	16	4
NE	13	10

	ORR,[b] n (%)
Lung n=19	4 (21.1)
Breast n=12	2 (16.7)
Endometrial n=5	3 (60.0)
Other[d] n=19	4 (21.1)

Data cutoff: Sept 4, 2025. [a] Efficacy-evaluable population includes all enrolled patients with a first post-baseline tumor assessment and patients who discontinued early. [b] ORR is calculated using CR, PR, and uPR. [c] Four uPRs were confirmed and one uPR remains on treatment after the Sept 4, 2025 data cutoff. [d] Includes colorectal (n=6), ampullary carcinoma (n=2), gastric cancer (n=2), sarcoma (n=2), gallbladder cancer (n=1), head and neck cancer (n=1), small intestine cancer (n=1), HCC (n=1), pancreatic cancer (n=1), thymic carcinoma (n=1), and esophagus carcinoma (n=1).
CI, confidence interval; CR, complete response; HCC, hepatocellular carcinoma; NE, non-evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; uPR, unconfirmed partial response.

Rapid and durable responses were observed



40% of patients remain on treatment

All cohorts

- Median TTR: 1.3 months
- Median DoR: 7.6 months

Ovarian cancer cohort

- Median TTR: 1.3 months
- Median DoR: 8.0 months

Data cutoff: Sept 4, 2025. CR, complete response; DoR, duration of response; PR, partial response; TTR, time to response; uPR, unconfirmed partial response.

Treatment Related Adverse Events

All patients (N=112)

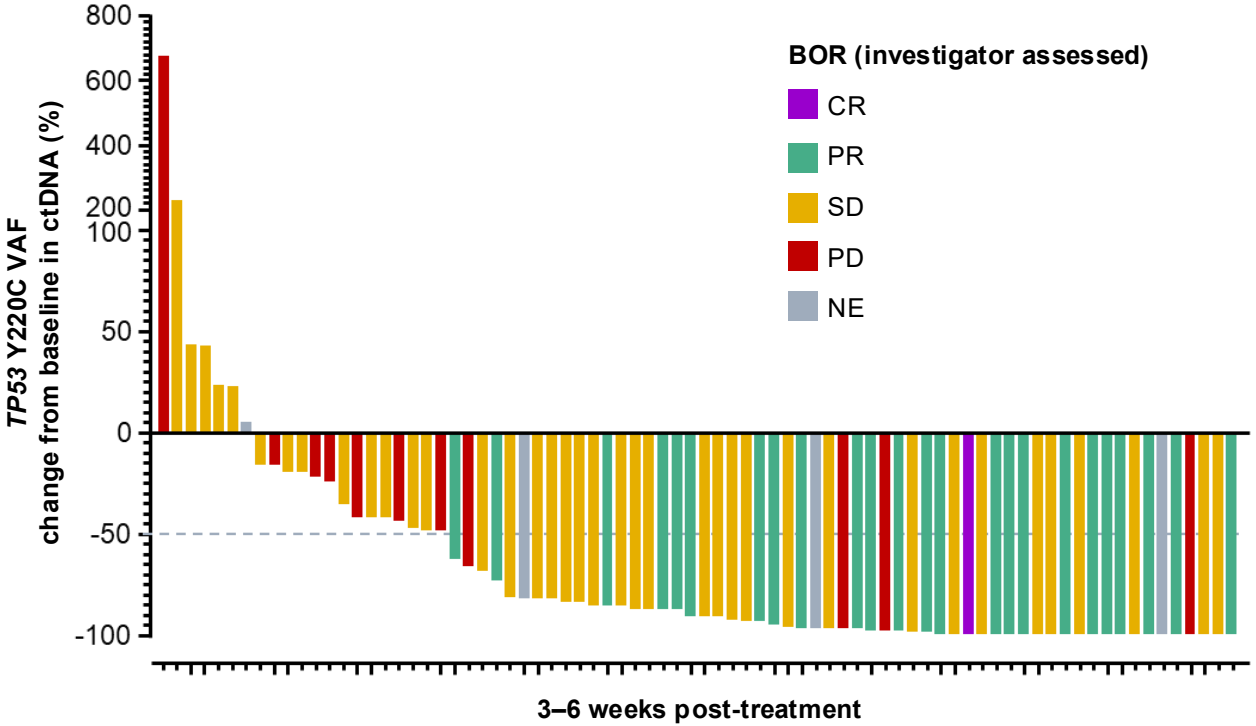
TRAEs in ≥5% of patients

Patients, n (%)	All patients N=112	Max CTCAE toxicity grade[a]			
		1	2	3	4
Nausea	38 (34)	24 (21)	13 (12)	1 (1)	0
Fatigue	26 (23)	11 (10)	13 (12)	2 (2)	0
Blood creatinine increased	22 (20)	5 (4)	16 (14)	1 (1)	0
ALT increased	20 (18)	8 (7)	5 (4)	6 (5)	1 (1)
AST increased	16 (14)	6 (5)	3 (3)	7 (6)	0
Anemia	16 (14)	5 (4)	6 (5)	5 (4)	0
Decreased appetite	14 (13)	11 (10)	3 (3)	0	0
Vomiting	13 (12)	7 (6)	6 (5)	0	0
Diarrhea	10 (9)	8 (7)	1 (1)	1 (1)	0
Platelet count decreased	8 (7)	3 (3)	1 (1)	2 (2)	2 (2)
Pruritus	8 (7)	6 (5)	2 (2)	0	0
Constipation	7 (6)	6 (5)	1 (1)	0	0
Dry mouth	7 (6)	7 (6)	0	0	0
Rash maculo-papular	7 (6)	1 (1)	2 (2)	4 (4)	0
Asthenia	6 (5)	2 (2)	4 (4)	0	0

- TRAEs were mostly Grade 1/2
- Most frequent TRAEs: Nausea, fatigue, blood creatinine increased, ALT increased
- Laboratory abnormalities were manageable / monitorable with most cases being transient and reversible
- Four patients (4%) discontinued treatment due to TRAEs
- Administration of rezatapopt with food decreased incidence of gastrointestinal TRAEs compared with Phase 1[1,2]

Data cutoff: Sept 4, 2025. [a] No Grade 5 TRAEs were observed. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event. 1. Kuo H-CD, et al. Clinical Pharmacology (ACCP) 2024; Poster presentation 044; 2. Schram AM, et al. Annual Meeting on Women's Cancer (SGO). 2024; Oral presentation (abstract LBA 26).

On-target activity supported by decreases in ctDNA *TP53* Y220C VAF



- 78 patients had ctDNA *TP53* Y220C VAF data available at baseline and on treatment (3–6 weeks)
- All patients experiencing a response had a reduction in *TP53* Y220C VAF
- 71 patients (91%) had a reduction in *TP53* Y220C VAF
  - 73% had a reduction of ≥50%

Data cutoff: Sept 4, 2025. BOR, best overall response; CR, complete response; ctDNA, circulating tumor DNA; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; VAF, variant allele frequency.

Platinum-resistant HGSOC with rapid and sustained response

52-year-old female with HGSOC

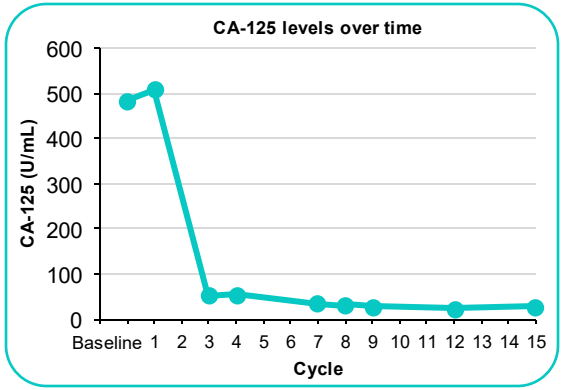
- *BRCA1* mutation, HRD+, high tumor burden, metastases in lung, chest, pelvis, and lymph nodes

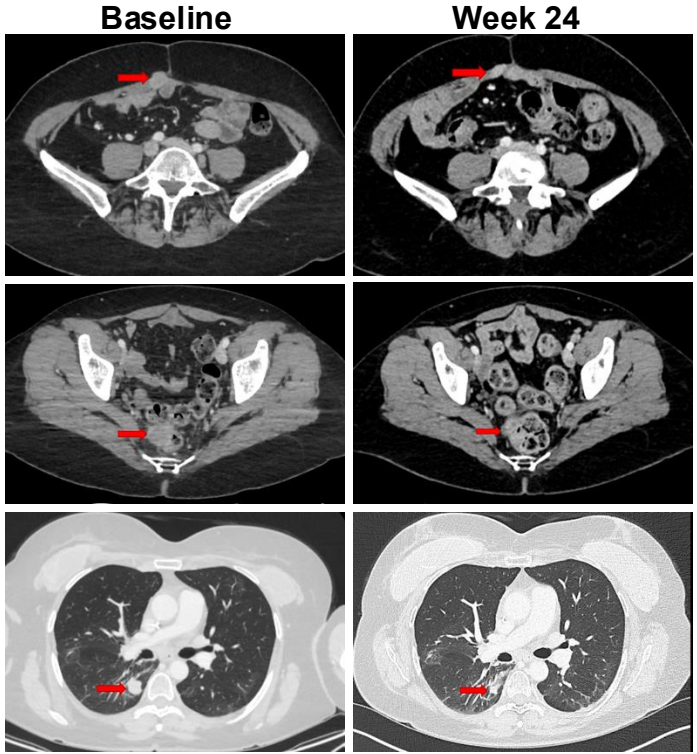
Progressed after multiple lines of prior treatment

- Platinum-based chemotherapy, olaparib, bevacizumab, pembrolizumab, T-cell vaccine, bispecific antibody

Rezatapopt: 2000 mg QD

- PR at 6 weeks: −44% in target lesions; −60% at week 24
- TTR: 1.4 months; DoR: 8.8+ months (ongoing)
- Well-tolerated transient treatment-related grade 1 pruritus and grade 2 nausea
- Treatment ongoing for 10+ months





Courtesy of Dr Italiano and Dr Debien

AE, adverse event; DoR, duration of response; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; PR, partial response; QD, once daily; TRAE, treatment-related adverse event; TTR, time to response.

Conclusions

- In this initial analysis of the pivotal PYNNACLE Phase 2 clinical trial, rezatapopt showed single-agent efficacy and manageable safety
- Clinical efficacy was achieved in heavily pretreated patients across multiple tumor types
- Rezatapopt offers a promising targeted treatment for solid tumors with a *TP53* Y220C mutation

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Acknowledgments

We would like to thank:

- All the patients, their families, and caregivers who have participated, and continue to participate, in this clinical trial
- Investigators and research staff
- PPD, part of Thermo Fisher Scientific
- Resolution Biosciences
- Foundation Medicine

This clinical trial is sponsored by PMV Pharmaceuticals, Inc.

Medical writing was provided by Danielle Lindley and Carolyn Maskin of Nucleus Global, funded by PMV Pharmaceuticals, Inc.

PYNNACLE Phase 2 clinical trial

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