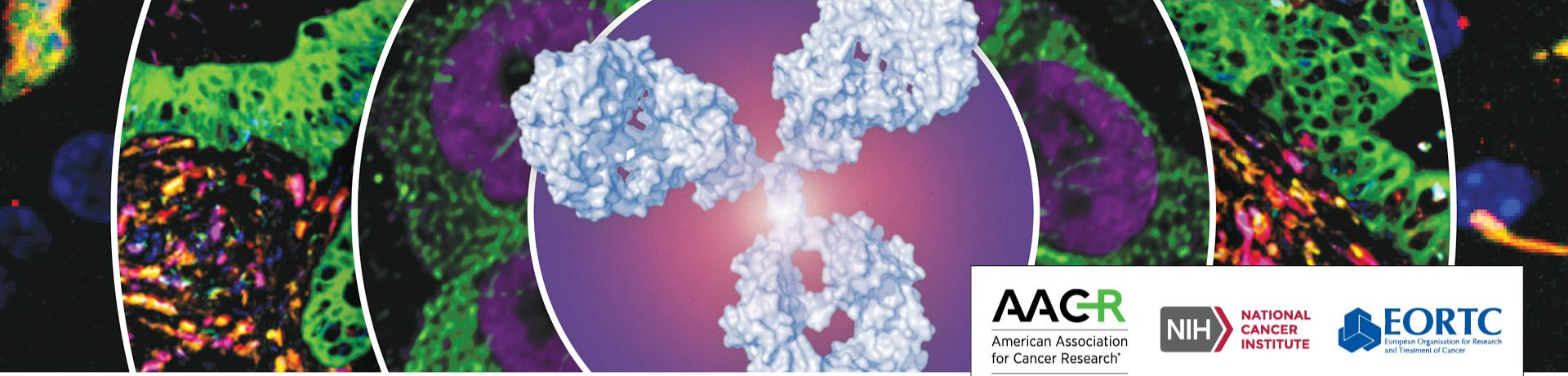

Rezatapopt for locally advanced or metastatic solid tumors with a *TP53* Y220C mutation: Initial analysis of the pivotal PYNNACLE Phase 2 trial

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Disclosure information

Alison M. Schram

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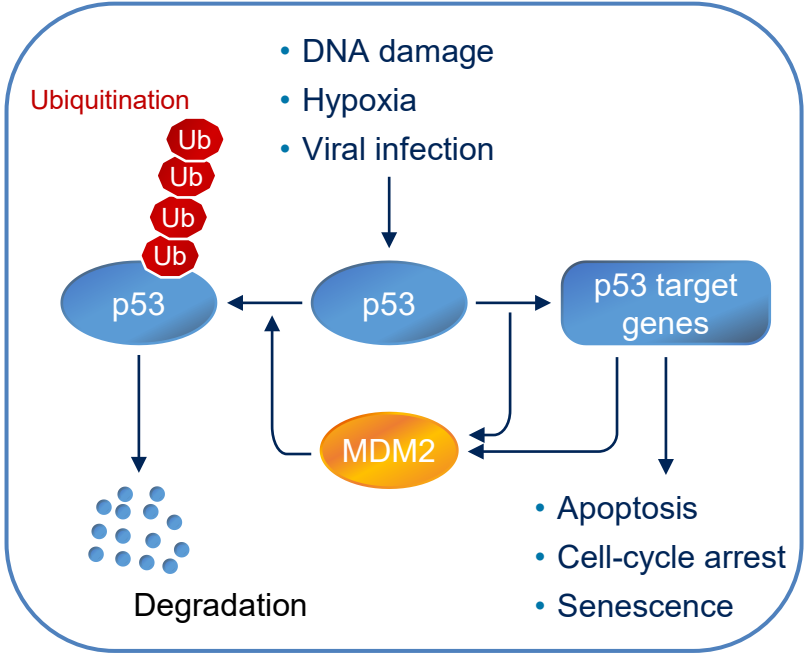
p53 – a key player in the body's defense against cancer

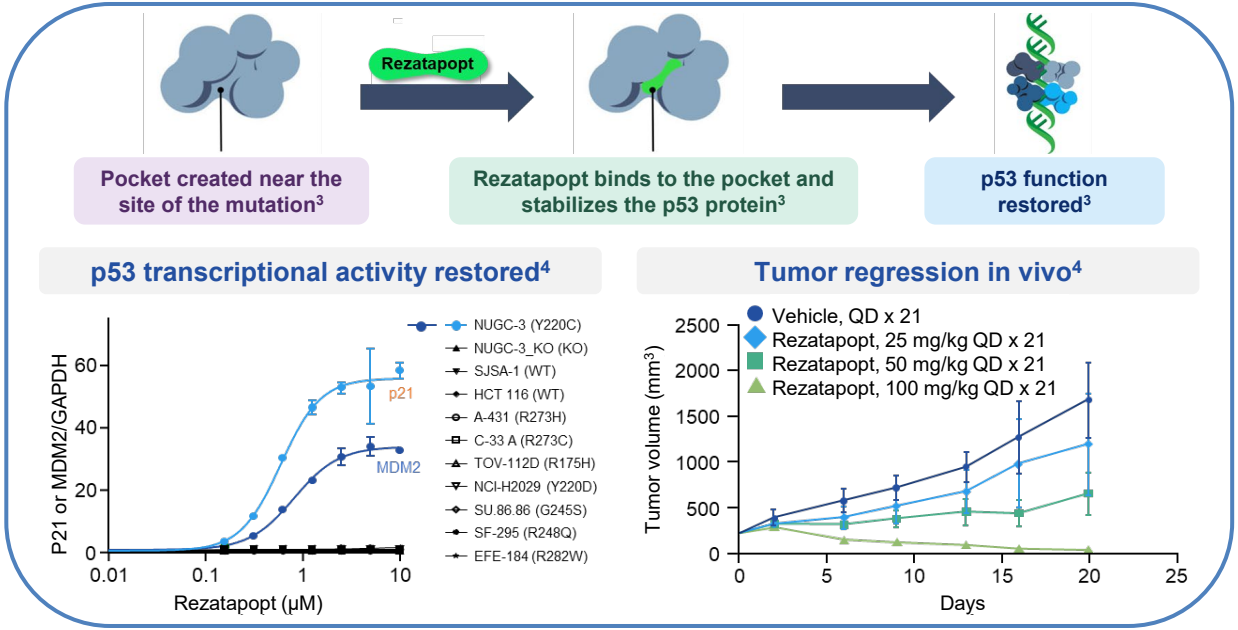
- *TP53* is a tumor suppressor gene that encodes the p53 protein[1,2]
- p53 binds to DNA and plays a key role in cell cycle arrest, DNA repair, and apoptosis[1–3]
- *TP53* mutations result in inactivation of p53, which is a key step in oncogenesis[1–3]
- The *TP53* Y220C mutation occurs in ~1% of solid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

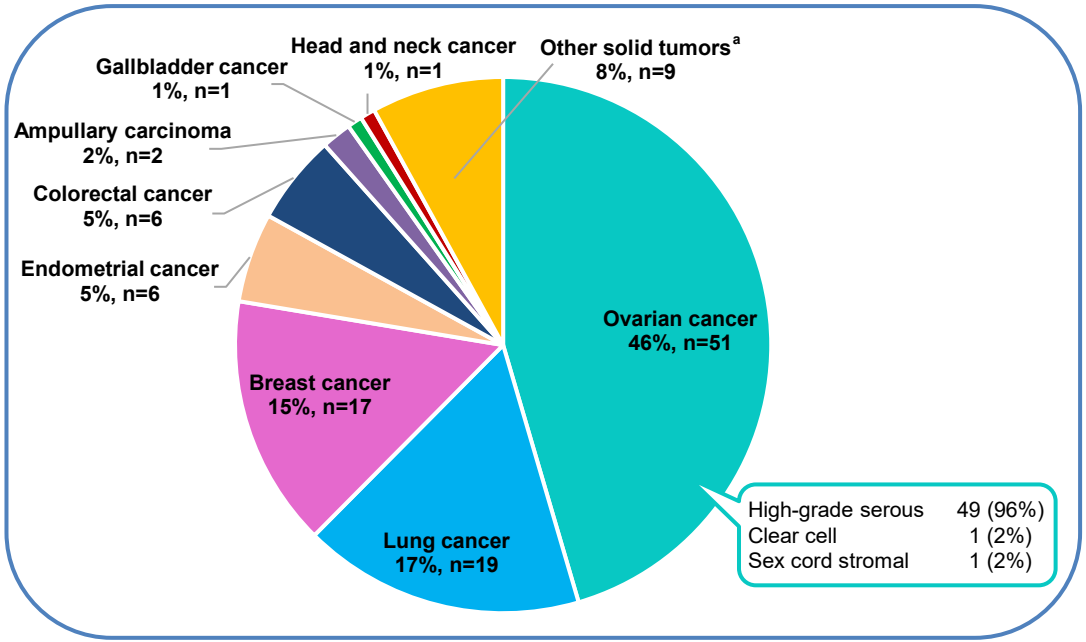
[a] For all global sites except Singapore (must be ≥21 years of age) and South Korea (must be ≥19 years of age). [b] If weighing ≥40 kg (in Australia, South Korea [12–18 years of age], and the USA only).
BICR, blinded independent central review; CNS, central nervous system; DCR, disease control rate; 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

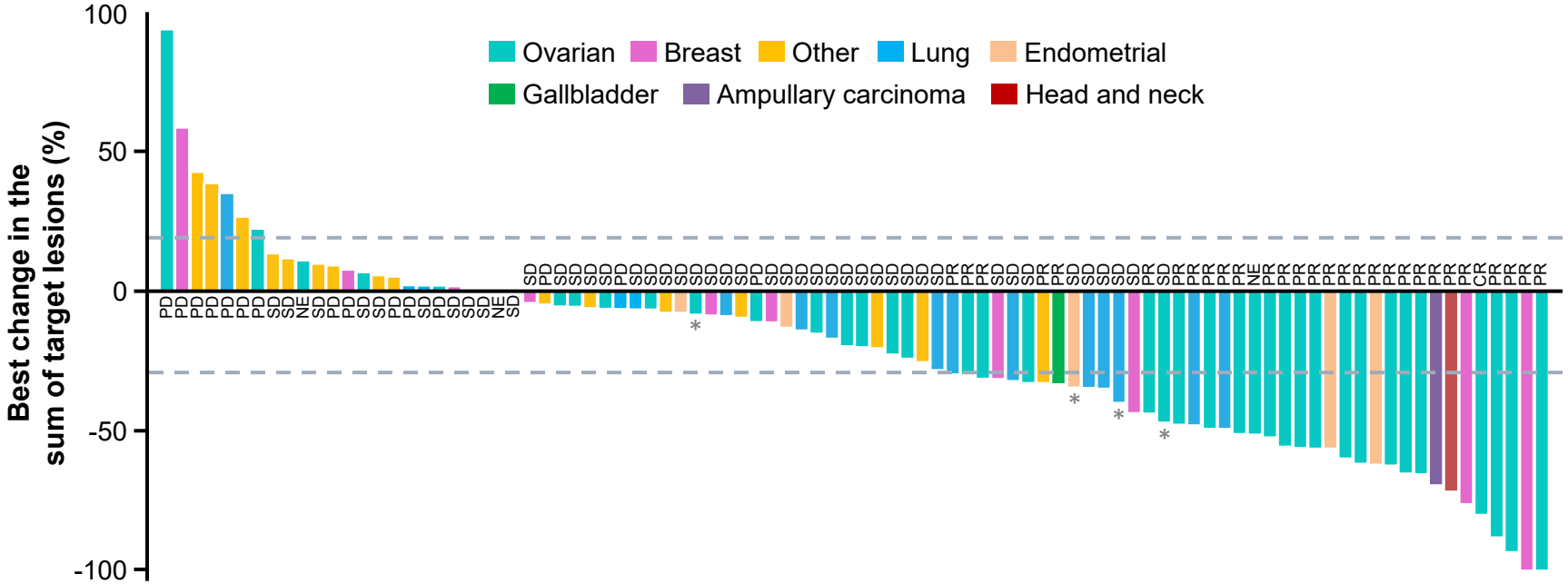
	Overall, N=112
Median age, years (min–max)	65 (37–91)
Sex, female / male, n (%)	82 (73) / 30 (27)
Race, n (%)	n=108
White	81 (75)
Asian	14 (13)
American Indian or Alaska Native	1 (1)
Black or African American	1 (1)
Other	1 (1)
Not reported	10 (9)
ECOG status, n (%)	n=108
0 / 1	47 (44) / 61 (56)
Prior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

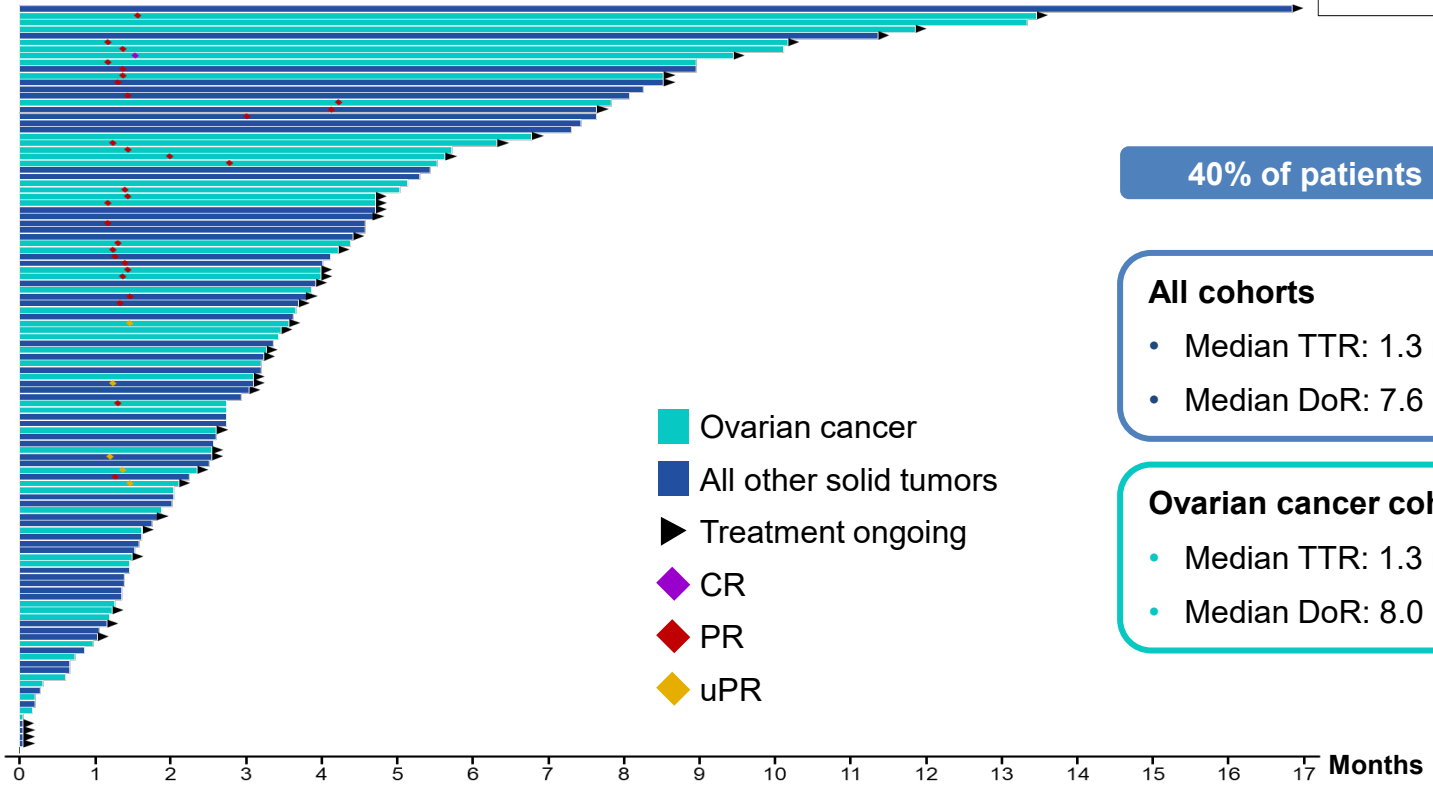
Confirmed responses were seen across tumor types

	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)

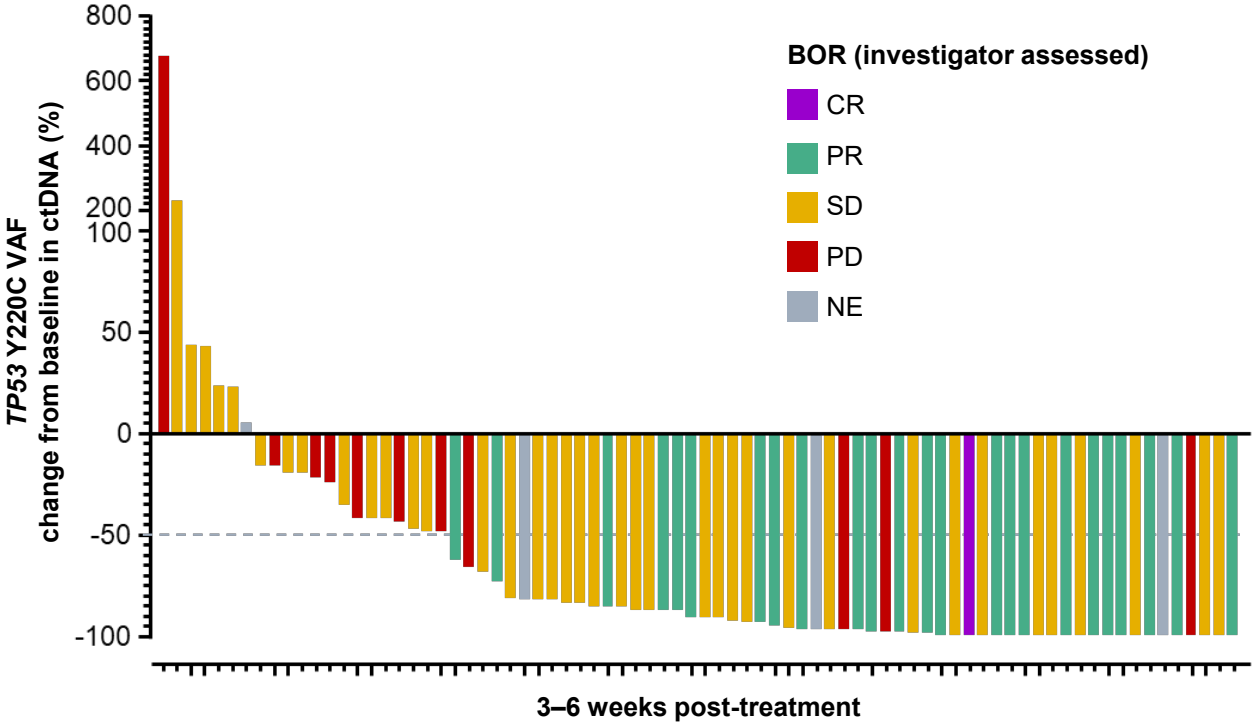
TRAEs in ≥5% of patients

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

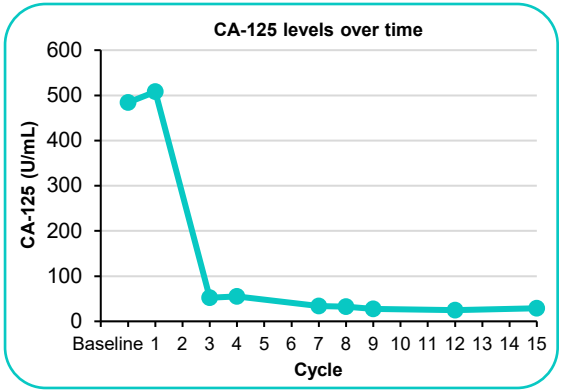
- *BRCA1* mutation, HRD+, high tumor burden, metastases in lung, chest, pelvis, and lymph nodes

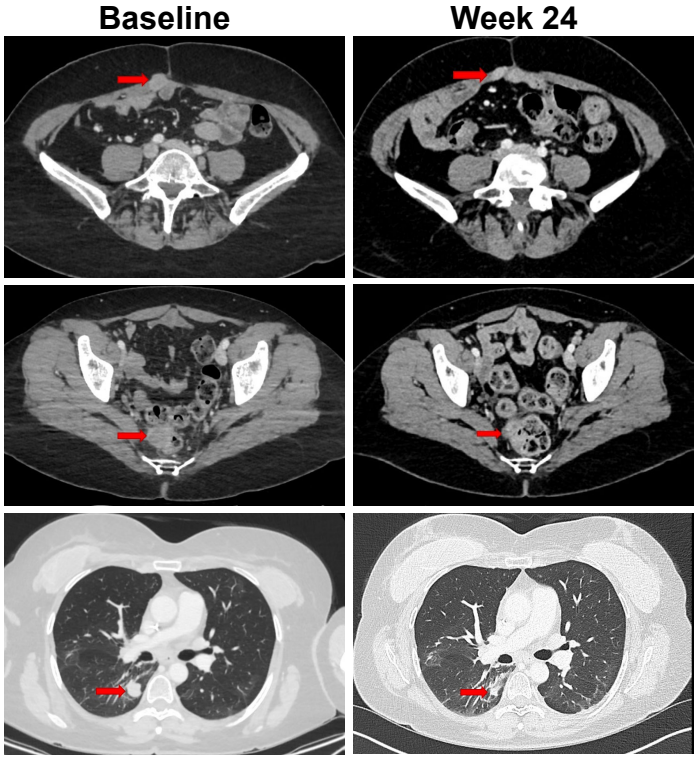
Progressed after multiple lines of prior treatment

- 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

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PYNNACLE Phase 2 clinical trial

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