THE POWER OF SHARED PURPOSE:

Transforming Gynecologic Cancer Care

SGO

ANNUAL MEETING
ON WOMEN'S CANCER

San Diego, CA • 2024

Phase 1 Analysis From the PYNNACLE Phase 1/2 Study of PC14586 in the Subgroup of Patients With Advanced Ovarian Cancer Harboring a *TP53* Y220C Mutation

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Financial Disclosure for:
Dr. Alison M. Schram

I have the following financial relationships with ACCME-defined ineligible companies to report over the past 24 months:

Advisory boards with Relay Therapeutics, Mersana, Merus, PMV Pharma. Consulting role with Blueprint Bio, Flagship Pioneering, Redona Therapeutics. Steering Committee member with Merus, Pfizer. Research to Institution with AstraZeneca, ArQule, BeiGene/SpringWorks, Black Diamond Therapeutics, Elevation Oncology, Kura, Lilly, Merus, Northern Biologics, Pfizer, PMV Pharma, Relay Therapeutics, Repare Therapeutics, Revolution Medicine, and Surface Oncology

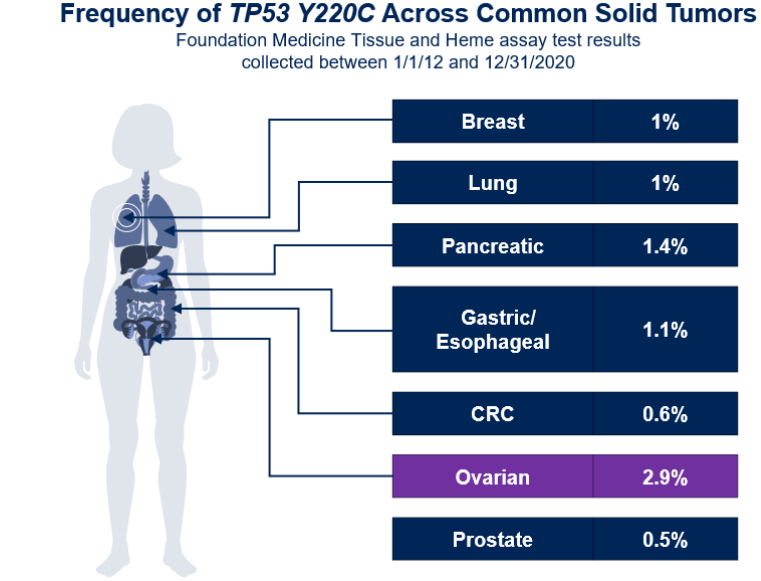
Unlabeled/Investigational Uses

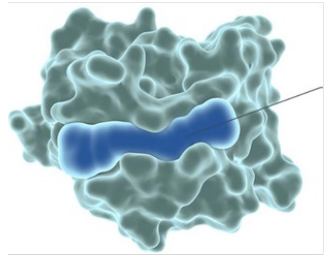
Rezatapopt (also known as PC14586) is an investigational agent being evaluated in the PYNNACLE clinical trial (NCT04585750) in patients with solid tumors harboring a *TP53* Y220C mutation

Rezatapopt is not approved or marketed for use in any country

Targeting p53 Y220C in Ovarian Cancer

- *TP53* mutations occur in 70% of ovarian cancer and >96% of high-grade serous ovarian cancer[1,2]
- *TP53* Y220C, a hotspot mutation, is most prevalent in ovarian cancer (2.9%)[3]
- Rezatapopt (PC14586) is a first-in-class p53 reactivator that selectively binds to the mutated p53 Y220C protein and restores wild-type activity[3]
- The Phase 1 PYNNACLE trial (NCT04585750) showed that rezatapopt has a favorable safety profile and promising efficacy in heavily pre-treated patients across multiple tumor types[4]
- Here, we present the subgroup of patients with ovarian cancer





Rezatapopt selectively binds to the pocket within the mutated p53 Y220C protein and stabilizes it into the p53 wild-type conformation, leading to reactivation of its function

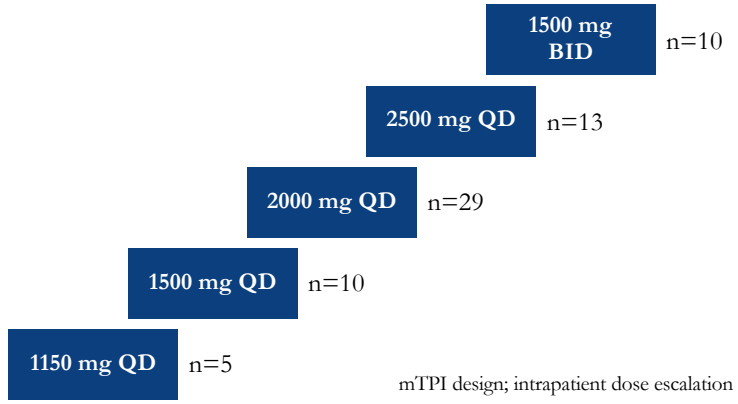
CRC, colorectal cancer.

1. The AACR Project GENIE Consortium. *Cancer Discov.* 2017;7(8):818–831; 2. Oien DB, et al. *Transl Cancer Res.* 2016; 5(Suppl 2):S264–S268; 3. Dumbrava EE. American Society of Clinical Oncology 2022, June 3–7, Chicago, USA; 4. Schram AM, et al. Poster presented at the AACR-NCI-EORTC International conference 2023, October 11–15, Boston, USA.

PYNNACLE Phase 1 Study Design
Efficacious dose range (1150 mg QD to 1500 mg BID)

Patients With Advanced Solid Tumors Harboring a *TP53* Y220C Mutation

Patient population
- ≥12 years of age
- Locally advanced or metastatic solid tumors harboring *TP53* Y220C, identified by local NGS



Enrollment: As of September 5, 2023, 67 patients were enrolled in the efficacious dose range including 22 patients with ovarian cancer

Primary objective	• Determine MTD • Select RP2D • Evaluate safety and tolerability
Secondary objectives	• Pharmacokinetics • Preliminary efficacy (ORR)
Exploratory objectives	• Biomarkers • Pharmacodynamics

- Preliminary efficacy was assessed by imaging per investigator-assessed RECIST v1.1 and serum CA-125 response (defined as >50% decrease at 2 separate timepoints, 4 weeks apart)
- Safety across tumor types was evaluated within the efficacious dose range

BID, twice daily; MTD, maximum tolerated dose; mTPI, modified toxicity probability interval; NGS, next-generation sequencing; ORR, overall response rate; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose.

NCT study identifier: NCT04585750

Patient Demographics and Disease Characteristics

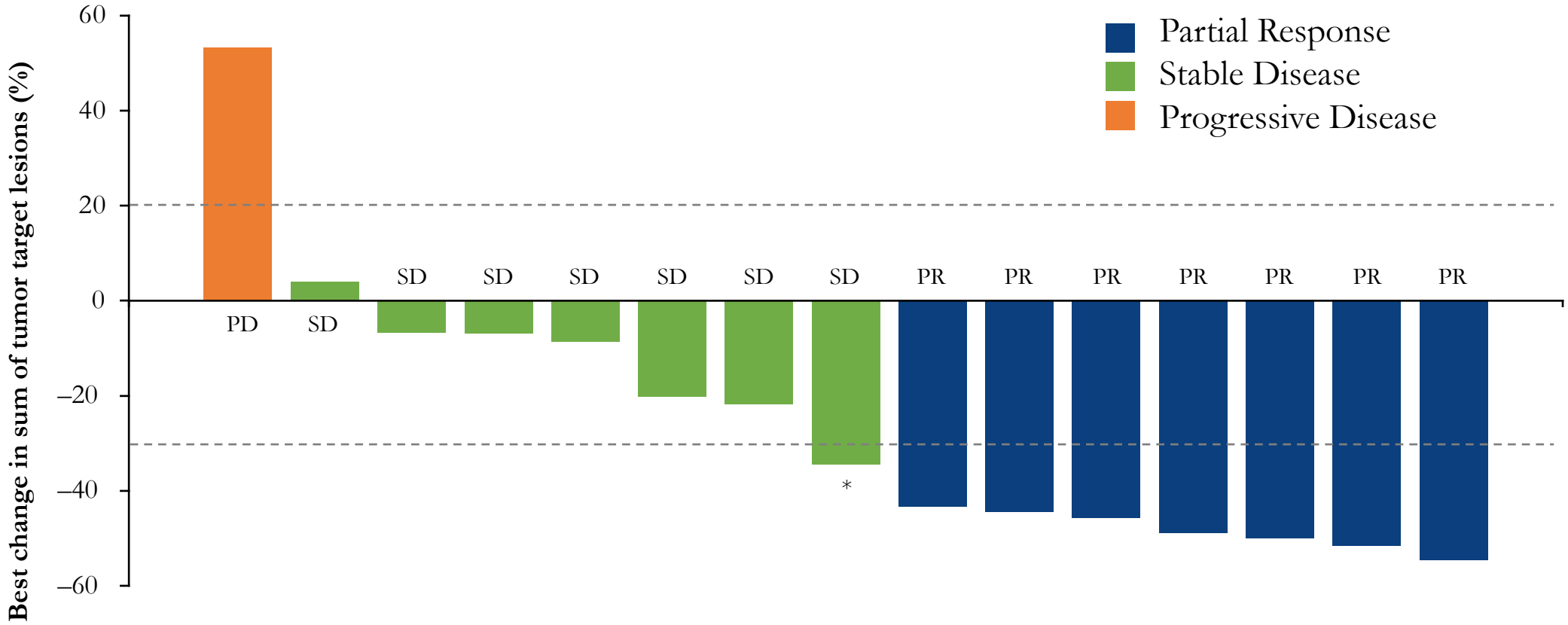
	n=22
Age, years	
Median (min–max)	66 (49–81)
Race, n (%)	
White	15 (68)
Asian	3 (14)
Black or African American	2 (9)
Not reported/unknown	2 (9)
ECOG status, n (%)	
0	6 (27)
1	16 (73)
Prior systemic therapies, n (%)	
1	1 (5)
2	4 (18)
≥3	14 (64)
Not reported	3 (14)
Median (min–max)	4 (1–9)
Platinum status	
Platinum Sensitive	2 (9)
Platinum Resistant*	19 (86)
Platinum Refractory**	1 (5)

	n=22
Histology	
HGSOC	20 (91)
Endometrioid	2 (9)
Measurable disease at baseline, n (%)	
Yes	20 (91)
No	2 (9)
Germline *TP53* Y220C, n (%)	
Negative	22 (100)
Positive	0 (0)
Somatic *BRCA1/2* mutation status, n (%)	
BRCA1	0 (0)
BRCA2	2 (9)
Germline *BRCA1/2* mutation status, n (%)	
No	13 (59)
Unknown	9 (41)
HRD status	
Positive	6 (27)
Negative	11 (50)
Unknown	5 (23)
***KRAS* status, n (%)**	
Wild type†	22 (100)

Data cut-off: September 5, 2023

*Patients with disease progressing within 6 months of platinum-based chemotherapy. **Patients with disease progressing during platinum-based therapy or within 4 weeks after last dose. †Defined as no *KRAS* single-nucleotide variant.
ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency.

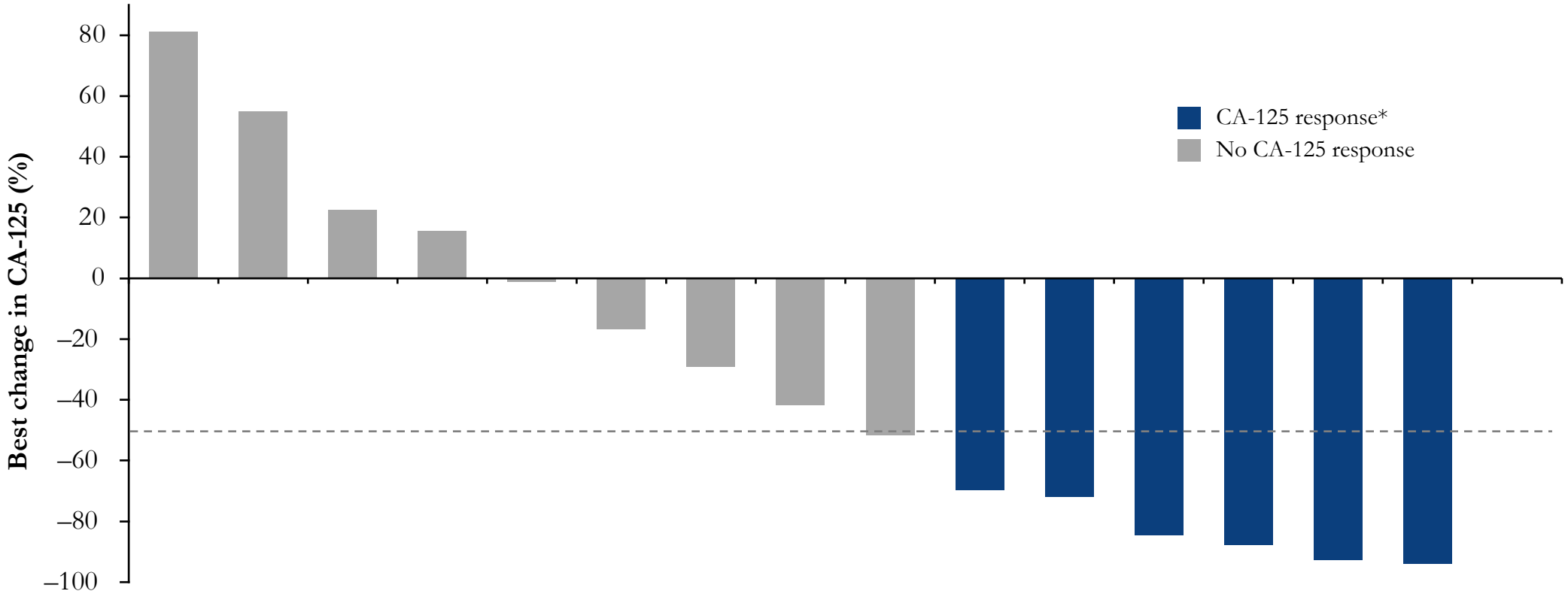
Rezatapopt Activity in Ovarian Cancer



Data cut-off: September 5, 2023

Patients with measurable disease at baseline (n=20). Patients with measurable disease at baseline and NE (n=5). Reasons for NE: patient withdrawal (n=3) and physician decision (n=2). Patients with measurable disease at baseline and at least 1 post baseline tumor assessment (n=15).
*The patient experienced an initial unconfirmed partial response that was not subsequently confirmed.
NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Best Change in CA-125

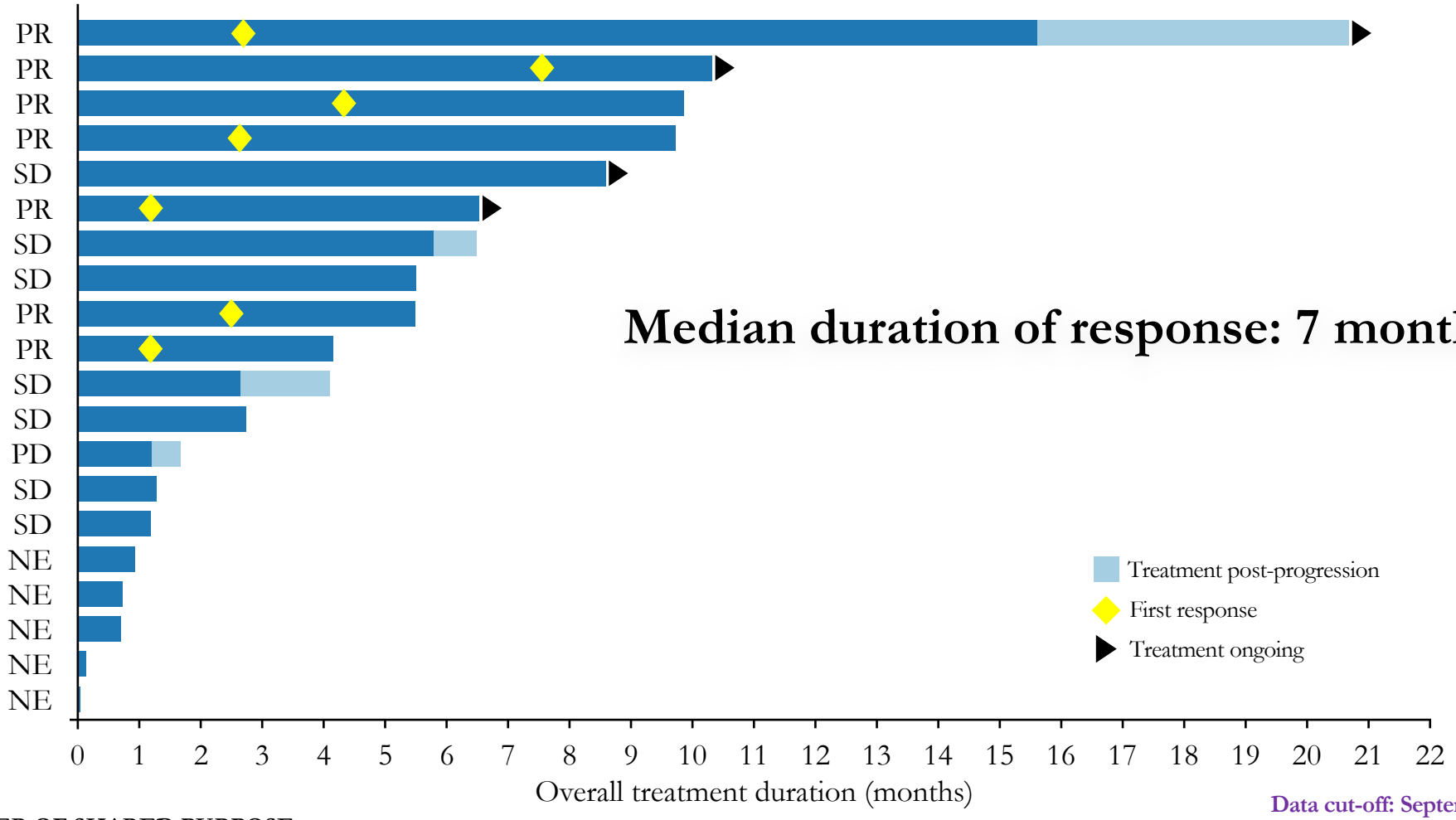


- Of the 15 patients with measurable CA-125 at baseline, five patients with a radiographic PR and one patient with SD achieved a CA-125 response

Data cut-off: September 5, 2023

Includes patients with CA-125 at baseline and at least one post-baseline value (n=15); five patients did not have CA-125 reported.
*Defined as decrease in CA-125 by 50% from baseline at two separate timepoints, 4 weeks apart.
PR, partial response; SD, stable disease.

Time to Response and Duration of Treatment



Data cut-off: September 5, 2023

Includes all patients with measurable disease at baseline and ≥1 post baseline tumor assessment (n=15).
NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Rezatapopt Safety Profile

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 maculo-papular	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)	–	–

- Favorable safety profile
- TRAEs were mostly grade 1/2
- Administration with food led to an improvement in gastrointestinal toxicities
- Low rate (3%) of drug discontinuation due to a TRAE
- The safety profile of the ovarian cancer subset was comparable to the overall patient group

Data cut-off: September 5, 2023

Incidence of the most common TRAEs (≥5%) in the overall cohort (includes patients in the efficacious dose range [1150 mg QD to 1500 mg BID]).
*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.
Data from a poster by Schram AM, et al. presented at AACR-NCI-EORTC International Conference 2023, October 11–15, Boston, USA

Conclusions

- Rezatapopt showed promising efficacy in heavily pre-treated patients with *TP53* Y220C advanced ovarian cancer
- Rezatapopt has a favorable safety profile in the overall population and the ovarian cancer subset
- The pivotal global PYNNACLE Phase 2 clinical trial (NCT04585750) is ongoing and will assess rezatapopt as monotherapy in patients with *TP53* Y220C and *KRAS* wild-type advanced solid tumors

Acknowledgements

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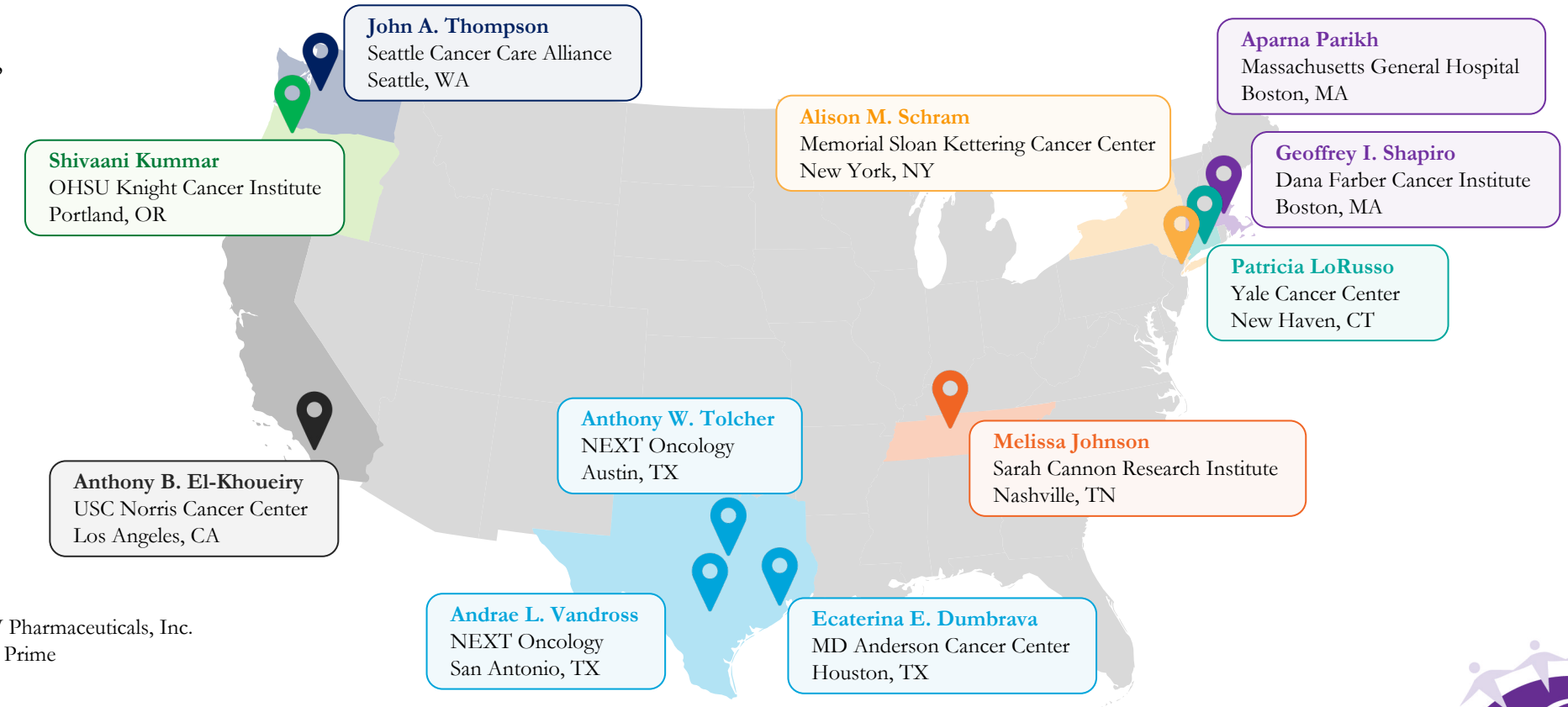
- Investigators and research staff



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