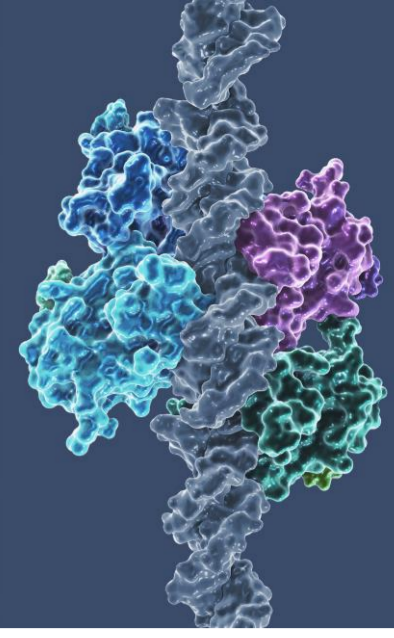


Phase 1 Analysis from the PYNNAACLE Phase 1/2 Study of Rezatapopt in the Subgroup of Patients with Advanced Breast Cancer Harboring a *TP53* Y220C Mutation

Ecaterina E Dumbrava,¹ Shivaani Kummar,² Melissa Johnson,³ Kim LeDuke,⁴ Yajuan G Qin,⁴ Marc Fellous,⁴ Alison M Schram⁵

¹The University of Texas MD Anderson Cancer Center, Houston, USA; ²Knight Cancer Institute, Oregon Health and Science University, Portland, USA; ³Sarah Cannon, Nashville, USA; ⁴PMV Pharmaceuticals, Inc., Princeton, USA; ⁵Memorial Sloan Kettering Cancer Center, New York City, USA

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BACKGROUND

- Globally, breast cancer is the most frequently diagnosed tumor in women and represents up to 36% of all cancer patients¹
- Mutations in the *TP53* gene occur in ~51% of breast cancers and appear to play an early and driving role in breast cancer formation^{2,3}
- TP53* mutations are generally associated with proliferative and aggressive breast tumors, such as large tumor size, axillary lymph node metastasis, high histologic grade, and estrogen receptor negativity³
- There is a high occurrence of *TP53* mutations in patients with TNBC, which typically has poorer outcomes⁴
- Reactivation of wild-type p53 is an attractive therapeutic approach for breast cancers with a *TP53* mutation, particularly for TNBC where treatment options are limited due to a lack of biomarkers and effective targeted therapies⁴
- Rezatapopt (also known as PC14586) is an investigational, first-in-class, p53 reactivator that selectively binds to the mutated p53 Y220C protein and stabilizes the structure in the wild-type conformation, thereby restoring p53 activity⁵
- PYNNAACLE (NCT04585750) is a Phase 1/2 clinical trial of rezatapopt in patients with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation⁶
 - In Phase 1, rezatapopt demonstrated favorable safety and preliminary anti-tumor activity in heavily pre-treated patients (n=67 treated within the efficacious dose range of 1150 mg QD to 1500 mg BID)⁷
 - Administration of rezatapopt with food improved gastrointestinal AEs including nausea and vomiting⁸

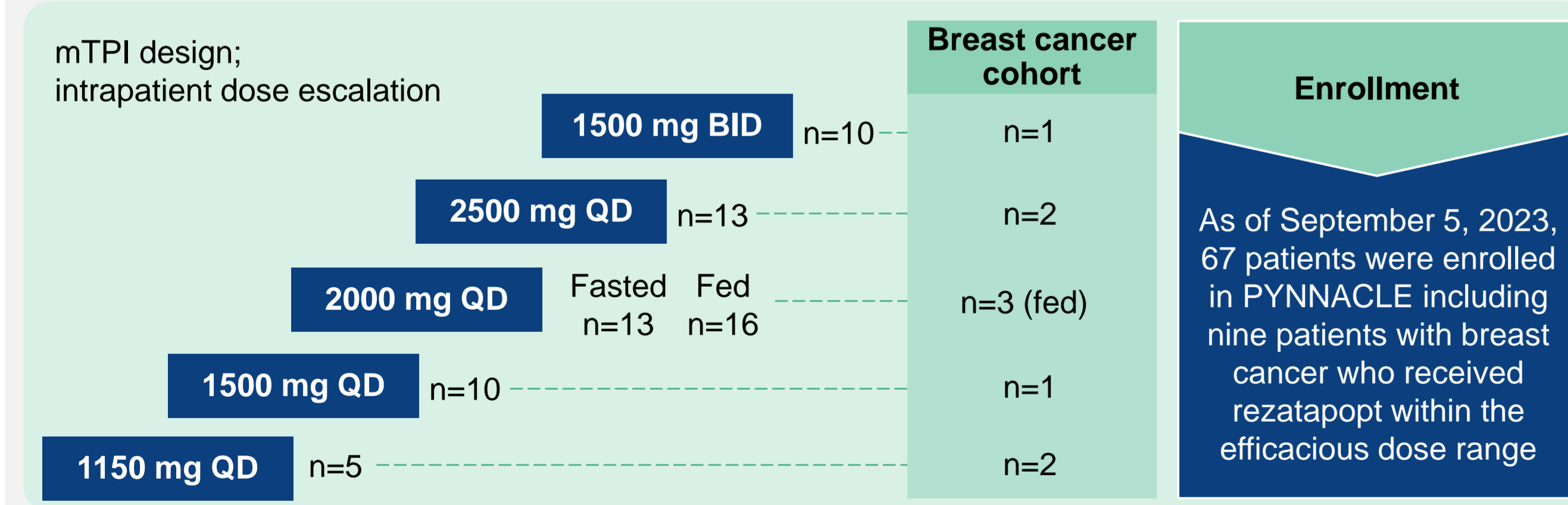
OBJECTIVE

- To assess the safety and efficacy of rezatapopt in the subgroup of patients with locally advanced or metastatic breast cancer harboring a *TP53* Y220C mutation treated with rezatapopt (1150 mg QD to 1500 mg BID) in the Phase 1 part of the PYNNAACLE study

METHODS

- Eligible patients (≥12 years of age) with locally advanced or metastatic solid tumors and a *TP53* Y220C mutation received increasing oral doses of rezatapopt for 21-day continuous cycles (1150 mg QD to 1500 mg BID; **Figure 1**)
- Safety and preliminary efficacy were assessed by the investigator using CTCAE v5.0 and RECIST v1.1, respectively
- Molecular profiling was performed using NGS to determine *TP53* Y220C, *BRCA*, *PIK3CA*, and *KRAS* tumor mutation status
- Results reported here are from a data cutoff of September 5, 2023; information for the patient cases are as of August 2024

Figure 1. PYNNAACLE Phase 1 study design: Open-label, multicenter, advanced cancer study (PMV-586-101, NCT04585750)



RESULTS

- Nine patients with breast cancer (HR+/HER2- n=3; HR+/HER2+ n=1; HER2+/HR- n=1; TNBC n=4) received rezatapopt within the efficacious dose range; the patient population is described in **Table 1**
- The mean (SD) age of patients was 50.4 (12.2) years with an ECOG PS of 0 (n=3) or 1 (n=6)
- Two patients had a somatic *BRCA2* mutation, no patient had a *BRCA1* mutation, two patients had a *PIK3CA* mutation, and all patients were *KRAS* wild type
- The median number of prior lines of systemic therapy was 4 (range 2–9); 78% of patients had received >3 prior lines

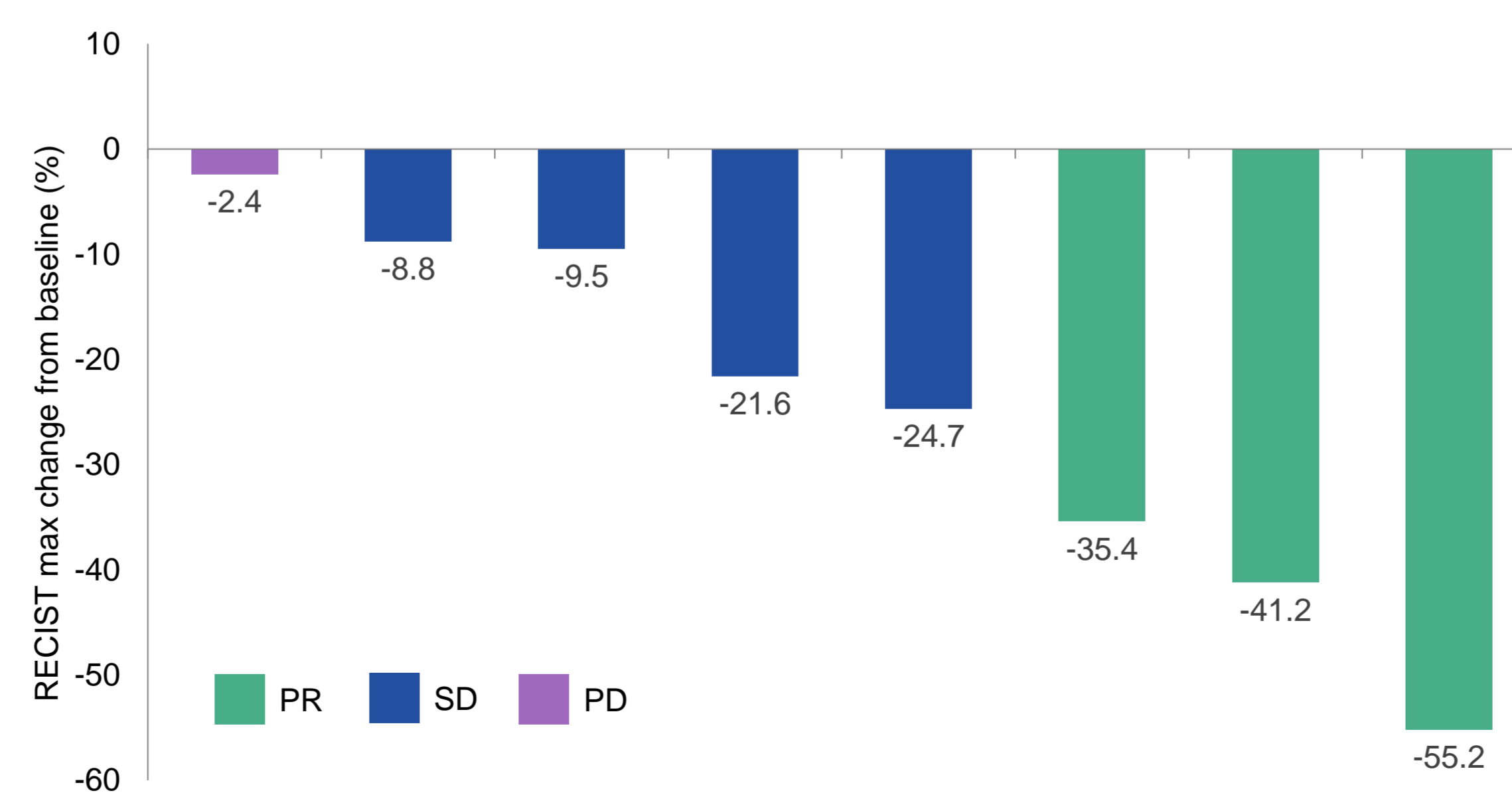
RESULTS

Table 1. Patient population

	1150 mg QD n=2	1500 mg QD n=1	2000 mg QD (fed) n=3	2500 mg QD n=2	1500 mg BID n=1	Total N=9
Mean age, years (SD)	46.0 (19.8)	37.0 (n/a)	56.3 (7.6)	46.0 (11.3)	64.0 (n/a)	50.4 (12.2)
ECOG, n (%)						
0	1 (50.0)	-	1 (33.3)	1 (50.0)	-	3 (33.3)
1	1 (50.0)	1 (100.0)	2 (66.7)	1 (50.0)	1 (100.0)	6 (66.7)
Disease status, n (%)						
Locally advanced	-	-	1 (33.3)	-	-	1 (11.1)
Metastatic	2 (100.0)	1 (100.0)	2 (66.7)	2 (100.0)	1 (100.0)	8 (88.9)
Prior lines of therapy						
Median (range)	3 (2–4)	5	4 (2–8)	4	9	4 (2–9)
Disease markers, n (%)						
HR+	1 (50.0)	1 (100.0)	-	1 (50.0)	1 (100.0)	4 (44.4)
HER2+/HR-	-	-	1 (33.3)	-	-	1 (11.1)
TNBC (PR-, ER-, HER2-)	1 (50.0)	-	1 (33.3)	1 (50.0)	-	4 (44.4)
<i>BRCA1</i> mutation	-	-	-	-	-	-
<i>BRCA2</i> mutation	-	1 (100.0)	1 (33.3)	-	-	2 (22.2)
No <i>BRCA1/2</i> mutations	-	-	1 (33.3)	-	1 (100.0)	2 (22.2)
Measurable disease (%)	2 (100.0)	1 (100.0)	3 (100.0)	1 (50.0)	1 (100.0)	8 (88.9)

- As of the data cutoff (September 5, 2023), there were eight patients with breast cancer who had measurable disease at baseline and ≥1 post-baseline tumor assessment
- Three (37.5%) achieved a confirmed PR, four (50.0%) had SD, and one (12.5%) had PD as best objective response
- All patients had a reduction in target lesions, with a maximum reduction in tumor volume from baseline ranging from -2.4% (patient with PD) to -55.2% (patient with PR) (**Figure 2**)

Figure 2. Maximum change in target lesions from baseline after receiving rezatapopt (1150 mg QD to 2500 mg QD)*



- Among the total population receiving rezatapopt in the efficacious dose range in the Phase 1 PYNNAACLE trial (N=67 patients with solid tumors), 60 patients had a TRAE (89.6%); the majority (71.7%) experienced Grade 1/2 events (**Table 2**)⁷
- In the breast cancer cohort (N=9), the frequency and severity of TRAEs were similar to the overall population
 - Most events were Grade 1/2
 - The most frequently reported TRAEs (in >1 patient) were: nausea (n=5; 56%); vomiting (n=4; 44%); diarrhea (n=3; 33%); fatigue (n=3; 33%); headache (n=2; 22%); AST increased (n=2; 22%)
 - Increased blood creatinine occurred in one patient (11.1%)
- No patient discontinued rezatapopt due to a TRAE

Table 2. TRAEs in patients receiving rezatapopt (1150 mg QD to 2500 mg QD) in the overall population

	Patients, n (%)				
	Total N=67	Max CTCAE Grade			
	Grade 1	Grade 2	Grade 3	Grade 4	
Any TRAE	60 (89.6)	16 (23.9)	27 (40.3)	16 (23.9)	1 (1.5)
TRAEs reported in >15% of patients					
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)	-	-
AST increased	12 (17.9)	4 (6.0)	5 (7.5)	3 (4.5)	-
ALT increased	11 (16.4)	7 (10.4)	2 (3.0)	2 (3.0)	-

Abbreviations

AE, adverse event; ALT/AST, alanine/aspartate aminotransferase; BID, twice daily; BL, baseline; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Score; mTPI, modified toxicity probability interval; n/a, not applicable; NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease; TNBC, triple negative breast cancer; TRAE, treatment-related adverse event; TTR, time to response.

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PYNNAACLE patient case studies

TNBC

Prior treatment

- Neoadjuvant therapy (chemotherapy + pembrolizumab)
- Bilateral mastectomy followed by pembrolizumab maintenance, radiotherapy, and breast reconstruction
- Pegylated liposomal doxorubicin for disease recurrence
- PD in axilla with extensive skin lesions on adjacent breast and arm, limiting mobility

Patient received rezatapopt 2000 mg QD (fed)

- Rapid healing of skin ulcerations, visible reduction in arm swelling, improved mobility of arm & fingers in first week
- PR at 6 weeks (41% reduction in axilla lesion) confirmed at 13 weeks and ongoing
- TTR: 5.6 weeks; DoR: 59.7+ weeks; PFS: 65.3+ weeks (+ = ongoing response)

TNBC

Prior treatment

- Inflammatory breast carcinoma treated with neoadjuvant chemotherapy
- Right mastectomy and axillary lymphadenectomy followed by adjuvant chemotherapy
- Immunotherapy and chemotherapy (pembrolizumab with carboplatin + gemcitabine) with PD; sacituzumab govitecan-hzly with PD
- Received whole-brain radiation for brain metastases

Patient received rezatapopt 2000 mg QD (fed)

- PR confirmed up to 19 weeks (35% reduction from BL)
- TTR: 6.6 weeks; DoR: 12.1 weeks; PFS: 18.6 weeks; OS: 25.6 weeks

HR+/HER2-

Prior treatment

- Breast reconstruction and s/p bilateral mastectomy
- Prior lines of therapy included: fulvestrant + ribociclib; letrozole + alpelisib; capecitabine; weekly paclitaxel
- Hormonal + targeted therapy resulted in unknown response and PD; chemotherapy resulted in PD

Patient received rezatapopt 2500 mg QD

- PR confirmed up to 23 weeks (55% reduction from BL)
- TTR: 5 weeks; DoR: 18.3 weeks; PFS: 23.1 weeks; OS: 28 weeks

CONCLUSIONS

- In this subgroup analysis of the Phase 1 part of the PYNNAACLE trial, rezatapopt demonstrated promising preliminary single-agent efficacy in heavily pre-treated patients with advanced breast cancer harboring a *TP53* Y220C mutation
- Rapid responses to rezatapopt treatment were observed in responders, with some responses seen at the first tumor assessment
- Rezatapopt had a favorable safety profile with improvements in gastrointestinal AEs observed when administered with food
- The PYNNAACLE tumor-agnostic registrational Phase 2 trial, which includes a breast cancer cohort, will assess rezatapopt as monotherapy at the RP2D of 2000 mg QD taken with food in patients with *TP53* Y220C-mutated and *KRAS* wild-type locally advanced or metastatic solid tumors



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