

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

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Poster #: P3-12-27
Abstract #: SESS-2137

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

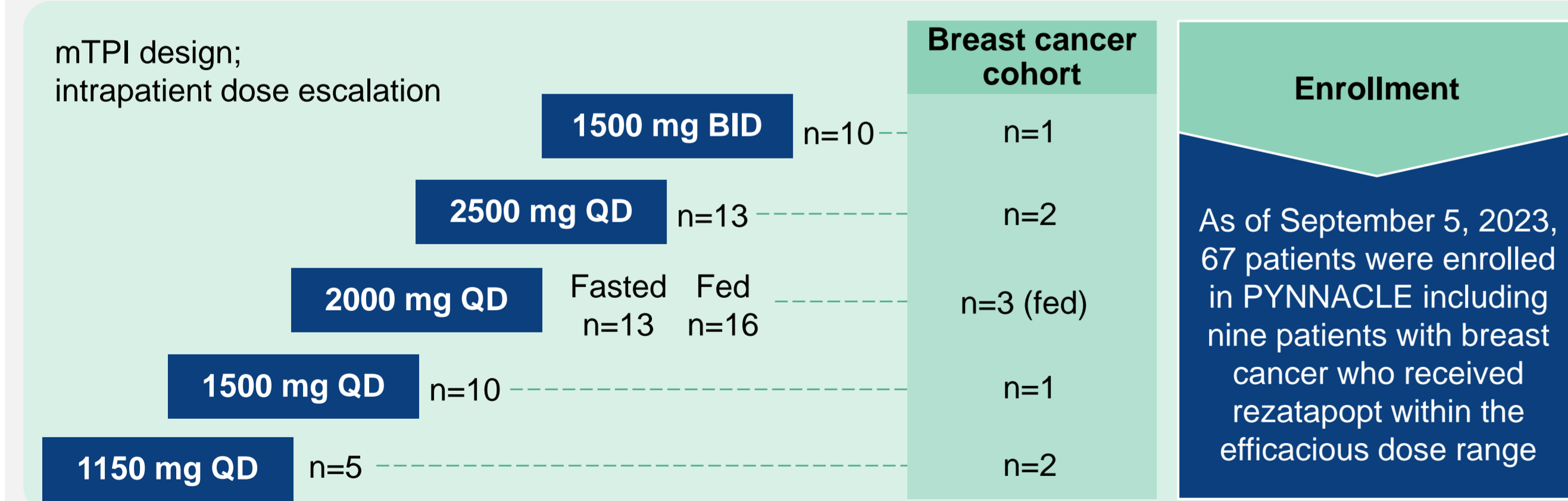
OBJECTIVE

- 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

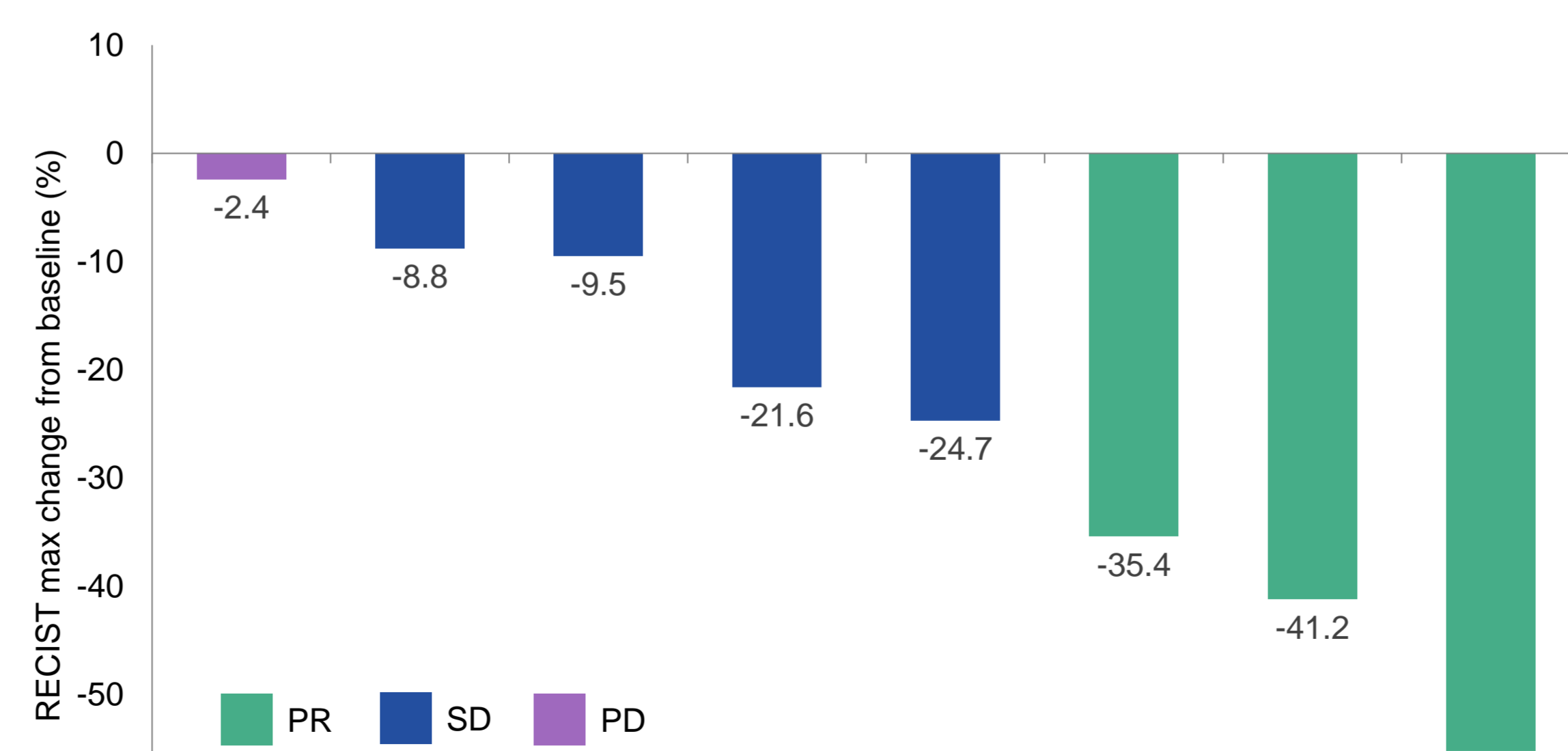
RESULTS

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)*



* Data reported for 8/9 patients with breast cancer, who had measurable disease at baseline and ≥1 post-baseline tumor assessment

- 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.

References

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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 the clinical trials; Investigators and research staff; PPD; and Resolution Biosciences and Foundation Medicine. This study and the clinical trials are sponsored by PMV Pharmaceuticals, Inc. Medical writing was provided by Lucretia Raminath and Danielle Lindley of Nucleus Global, an Inizio company, funded by PMV Pharmaceuticals, Inc.

Disclosures

EED: received research funding/grant from, attended advisory boards for, and provided speaker role for PMV Pharmaceuticals, Inc. SK: local PI, institutional, financial interest, trial funding. MJ: received research funding from PMV Pharmaceuticals, Inc. KLD, YQG, MF: PMV Pharmaceuticals, Inc. employees (with stock options). AMS: attended advisory boards and received research funding from PMV Pharmaceuticals, Inc.

PYNNAACLE patient case studies

Prior treatment

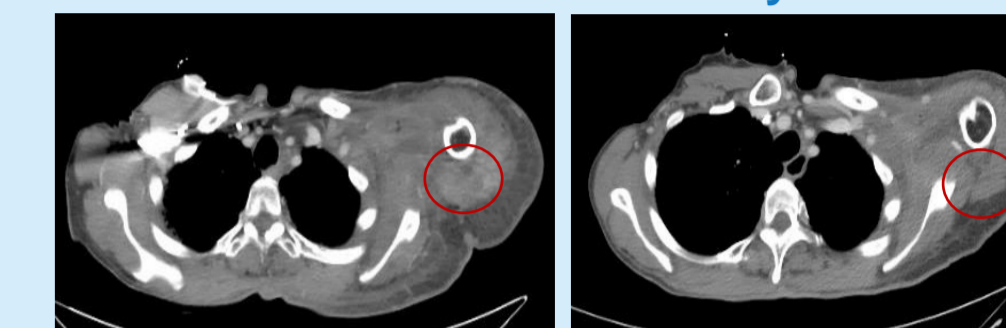
- Neoadjuvant therapy (chemotherapy + pembrolizumab)
- Bilateral mastectomy followed by pembrolizumab maintenance, radiotherapy, and breast reconstruction
- Pegylated liposomal doxorubicin for disease recurrence
- PD in axilla with extensive skin lesions on adjacent breast and arm, limiting mobility

Patient received rezatapopt 2000 mg QD (fed)

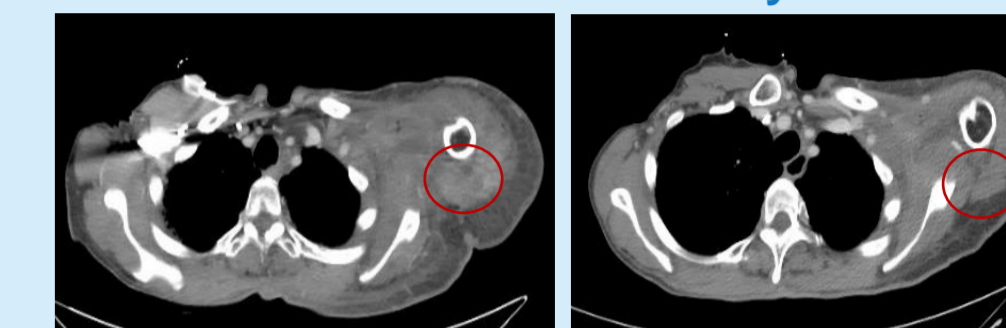
- Rapid healing of skin ulcerations, visible reduction in arm swelling, improved mobility of arm & fingers in first week
- PR at 6 weeks (41% reduction in axilla lesion) confirmed at 13 weeks and ongoing
- TTR: 5.6 weeks; DoR: 59.7+ weeks; PFS: 65.3+ weeks (+ = ongoing response)

TNBC

Baseline



Cycle 3



Prior treatment

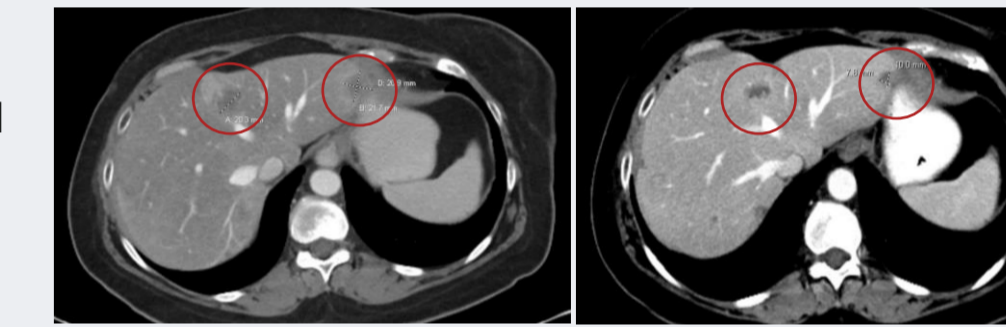
- Inflammatory breast carcinoma treated with neoadjuvant chemotherapy
- Right mastectomy and axillary lymphadenectomy followed by adjuvant chemotherapy
- Immunotherapy and chemotherapy (pembrolizumab with carboplatin + gemcitabine) with PD; sacituzumab govitecan-hzly with PD
- Received whole-brain radiation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

Patient received rezatapopt 2000 mg QD (fed)

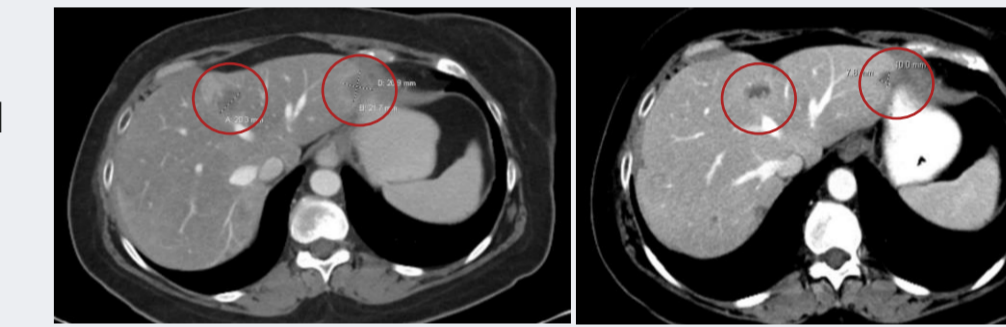
- PR confirmed up to 19 weeks (35% reduction from BL)
- TTR: 6.6 weeks; DoR: 12.1 weeks; PFS: 18.6 weeks; OS: 25.6 weeks

TNBC

Baseline



Cycle 5



Prior treatment

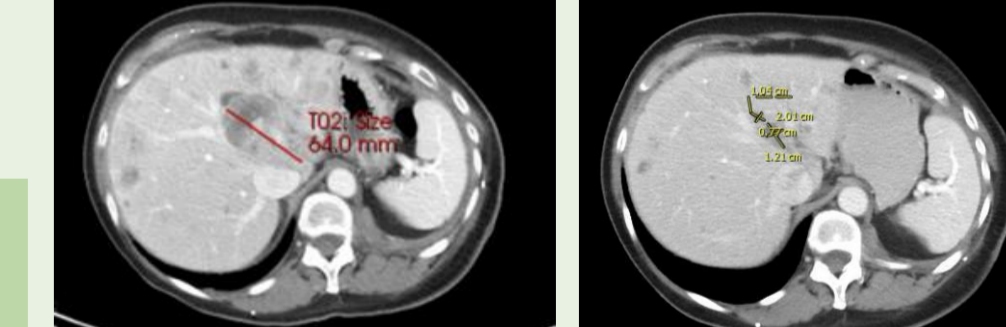
- Breast reconstruction and s/p bilateral mastectomy
- Prior lines of therapy included: fulvestrant + ribociclib; letrozole + alpelisib; capecitabine; weekly paclitaxel
- Hormonal + targeted therapy resulted in unknown response and PD; chemotherapy resulted in PD

Patient received rezatapopt 2500 mg QD

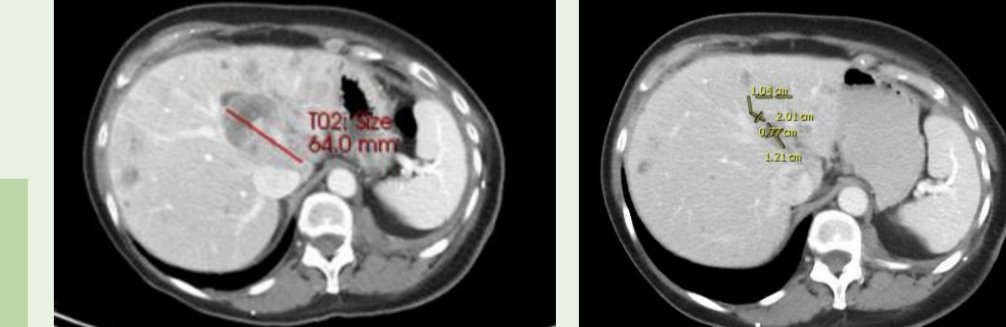
- PR confirmed up to 23 weeks (55% reduction from BL)
- TTR: 5 weeks; DoR: 18.3 weeks; PFS: 23.1 weeks; OS: 28 weeks

HR+/HER2-

Baseline

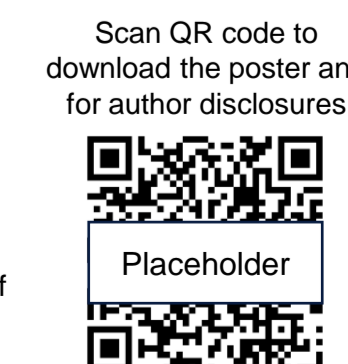


Cycle 7



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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