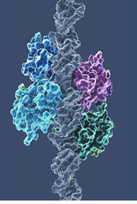
PYNNACLE Phase 2 Study of Rezatapopt in Patients with Advanced Solid Tumours, including Breast Cancers, and a *TP53* Y220C Mutation

Jean-Sebastien Frenel,[1] Paola Zagami,[2] Gilberto De Lima Lopes,[3] Peter Grimison,[4] Melissa Johnson,[5] David Shao Peng Tan,[6,7] Shivaani Kummar,[8] Kim LeDuke,[9] Marc Fellous,[9] Ecaterina E. Dumbrava,[10] Alison M. Schram[11]

[1]Institut de Cancérologie de L'Ouest, Saint-Herblain, France; [2]European Institute of Oncology IRCCS (IEO), Milano, Italy; [3]Sylvester Comprehensive Cancer Center, Miami, FL, USA; [4]Chris O'Brien Lifehouse Hospital, Camperdown, NSW, Australia; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]National University of Singapore (NUS) Centre for Cancer Research (N2CR), Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [7]Department of Haematology-Oncology, National University Cancer Institute, National University Hospital, Singapore; [8]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [9]PMV Pharmaceuticals, Inc., Princeton, NJ, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA

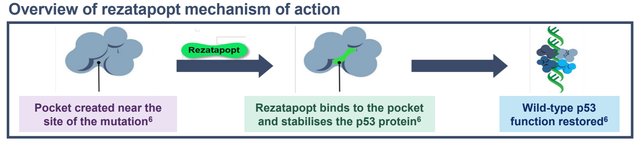
150TiP



BACKGROUND

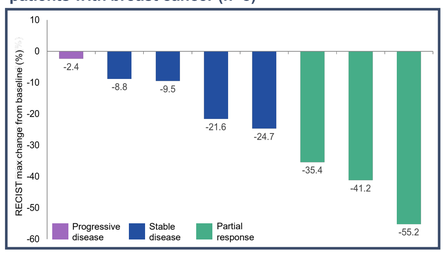
- ***TP53***, encoding the p53 protein, is the most frequently mutated gene across all cancers[1]
  - These mutations destabilise the p53 protein, causing loss of p53 tumour suppressor function and tumour progression[2]
  - *TP53* mutations are found in ~51% of breast cancers[3] and are associated with aggressive and invasive tumour types such as TNBC (occurring in ~60% of cases), which has poorer outcomes[4,5]
- ***TP53* Y220C** is a hot-spot *TP53* missense mutation present in ~1% of all breast cancers[3]
- Reactivation of wild-type p53 in p53-mutated tumours may be an effective therapeutic strategy for breast cancers, particularly for TNBC for which treatment options are limited due to a lack of biomarkers and effective targeted therapies[5]
- **Rezatapopt** (also known as PC14586) is an investigational, first-in-class, selective p53 reactivator specific to the *TP53* Y220C mutation that stabilises the mutated p53 protein in wild-type conformation, restoring p53 transcriptional activity and tumour suppressor functions[6–8]
  - Tyrosine-to-cysteine substitution creates a pocket in the Y220C-mutated protein[6–8]
  - Rezatapopt fits tightly into this pocket via non-covalent hydrogen bonding, enhancing hydrophobic and van der Waals interactions, stabilising the p53 protein in the wild-type conformation[6–8]

Overview of rezatapopt mechanism of action



- **PYNNACLE (NCT04585750): Phase 1/2 clinical study of rezatapopt** in patients with solid tumours harbouring a *TP53* Y220C mutation[6,9]
  - In **PYNNACLE Phase 1**, rezatapopt showed preliminary efficacy in heavily pre-treated patients[10,11]
  - Of 38 evaluable patients receiving rezatapopt in the efficacious dose range (1150 mg QD to 1500 mg BID), **13 had confirmed PRs observed across multiple tumour types, including breast cancer**[10]
  - **Of eight patients with breast cancer, three achieved a PR,** including two with TNBC; rapid responses were observed, with some seen at first post-baseline tumour assessment[11]
  - **Rezatapopt demonstrated a favourable safety profile**, with mostly Grade 1/2 treatment-related AEs, in both the overall population and the breast cancer subset[10,11]
  - In the overall population, the most frequent treatment-related AEs (in >15% of patients) were nausea (50.7%), vomiting (43.3%), blood creatinine increase (26.9%), diarrhoea (19.4%), fatigue (19.4%), AST increase (17.9%) and ALT increase (16.4%)[10,11]

Change in target lesions from baseline in evaluable patients with breast cancer (n=8)



- **Objective:** Describe the study design for the ongoing, pivotal, registrational **PYNNACLE Phase 2 study** assessing rezatapopt 2000 mg QD taken with food in patients with locally advanced or metastatic solid tumours harbouring a *TP53* Y220C mutation and wild-type *KRAS*[6]

OVERVIEW OF THE PYNNACLE STUDY

- The PYNNACLE study aims to assess the efficacy, safety, tolerability, PK and PD of rezatapopt in patients with locally advanced or metastatic solid tumours harbouring a *TP53* Y220C mutation and *KRAS* wild-type[6,9]

Overview of the PYNNACLE study assessing rezatapopt in solid tumours with a *TP53* Y220C mutation[6,9]

Participants
- Aged ≥12 years
- Locally advanced or metastatic solid tumours
- *TP53* Y220C mutation
- Previously treated (or ineligible for SOC)
- ECOG PS 0 or 1

Phase 2
- Aged ≥18 years[a]
- Adolescents aged 12–17 years (if weighing ≥40 kg)[b]
- *KRAS* wild-type[c]

PYNNACLE (PMV-586-101, NCT04585750)

Phase 1
Active, not enrolling

Rezatapopt dose escalation
- Identify MTD and RP2D
- Assess PK, safety and preliminary efficacy

Phase 2
Active, enrolling

Rezatapopt dose expansion at 2000 mg QD with food
- Assess efficacy
- Assess safety, PK and QoL

[a] For all global sites except Singapore (adults ≥21 years); [b] Australia, South Korea and US only; [c] Phase 2 includes patients with *KRAS* wild-type; those with *KRAS* single-nucleotide variant mutations are excluded.

PYNNACLE PHASE 2 TRIAL DESIGN

- **PYNNACLE Phase 2:** Ongoing, global, single-arm, open-label, multicentre, registrational basket trial in patients with solid tumours[6,9]
- **Primary objective** of PYNNACLE Phase 2: Evaluate the efficacy of rezatapopt at the RP2D; **Secondary objectives:** Safety, PK, QoL and other efficacy measures[6,9]
- **Rezatapopt:** Eligible patients receive rezatapopt 2000 mg orally QD with food for continuous 21-day cycles[6,9]
- Patients are followed up until death, loss to follow-up, 2 years after last patient discontinuation or end of study[6,9]

PYNNACLE Phase 2: Patient population[6,9]

Phase 2: Planned cohorts

Basket N = ~114
Rezatapopt 2000 mg QD with food

Cohort 1: Ovarian cancer[a]	n = ~42
Cohort 2: Lung cancer	n = ~18
Cohort 3: Breast cancer	n = ~18
Cohort 4: Endometrial cancer	n = ~18
Cohort 5: All other solid tumours	n = ~18

[a] Platinum resistant or refractory.

Inclusion criteria
- Age ≥18 years for all global sites except Singapore (adults aged ≥21 years)
- Adolescents aged 12–17 years (if weighing ≥40 kg, in Australia, South Korea and US only)
- ECOG PS 0 or 1
- Adequate organ function
- Locally advanced or metastatic solid tumours
- Measurable disease at baseline (RECIST v1.1)
- Documented *TP53* Y220C mutation (identified locally)
- *KRAS* wild-type
- Previously treated with ≥1 line of systemic treatment or ineligible for appropriate SOC

Exclusion criteria
- *KRAS* single-nucleotide variant mutations
- Unstable brain metastases
- Primary CNS tumours
- History of leptomeningeal disease or spinal cord compression, organ transplant or gastrointestinal disease that may impact rezatapopt absorption
- Heart conditions (unstable angina, uncontrolled hypertension, heart attack within 6 months prior to screening, heart failure, QT interval prolongation or other clinically significant rhythm abnormalities)
- Uncontrolled hepatitis B, hepatitis C or HIV infection

PYNNACLE Phase 2: Primary and secondary endpoints[6,9]

PRIMARY OBJECTIVE: Evaluate the efficacy of rezatapopt per BICR (blinded independent central review) assessment

Primary endpoints

ORR
ORR[a]
BICR assessed
RECIST v1.1
Across all cohorts

ORR
ORR[a]
BICR assessed
RECIST v1.1
Ovarian cancer cohort only

Secondary endpoints

ORR
ORR: Investigator assessed; RECIST v1.1
- Across all cohorts and ovarian cancer cohort only

TTR DoR DCR
TTR, DoR, DCR: BICR and investigator assessed; RECIST v1.1
- DCR at 6, 12, 18 and 24 weeks
- Across all cohorts and ovarian cancer cohort only

OS PFS
PFS: BICR and investigator assessed; RECIST v1.1
OS and PFS: Across all cohorts and ovarian cancer cohort only

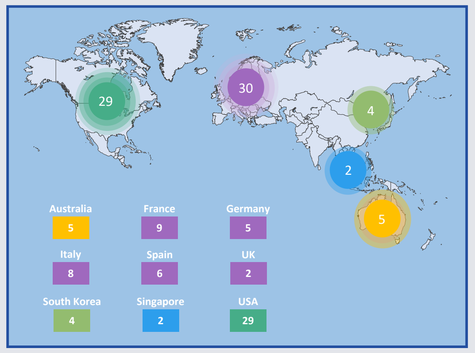
AEs
Safety: AEs, SAEs, laboratory assessments
- AEs graded using CTCAE v5.0[12]

PK
Plasma PK parameters
- May include C_{max}, T_{max}, AUC_{0-t}, AUC_{tau}, C_{trough}

PRO
PROs: EORTC QLQ-C30 for patients aged ≥18 years

[a] ORR will be derived from BICR-assessed BOR based on RECIST v1.1 as assessed in these two populations.

PYNNACLE Phase 2: Planned sites worldwide[9]



References

1. Baugh EH, et al. Cell Death Differ. 2018;25,154–160; 2. Hassin O, et al. Nat Rev Drug Discov. 2023;22:127–144; 3. FoundationInsights™. A proprietary database used under license with review and approval from Foundation Medicine®. Available at: Biopharma Services Overview | Foundation Medicine. Accessed April 2025; 4. Silwal-Pandit L, et al. Cold Spring Harb Perspect Med. 2017;7:a026252; 5. Miki ZI, et al. NPJ Precis Oncol. 2022;6:64; 6. PYNNACLE Study. Available at: https://www.pynnaclestudy.com/. Accessed April 2025; 7. Vu BT, et al. ACS Med Chem Lett. 2025;16:34–39; 8. Dumble ML, et al. AACR Annual Meeting. 2021; Oral presentation, abstract LB006; 9. ClinicalTrials.gov. NCT04585750. Available at: https://clinicaltrials.gov/study/NCT04585750. Accessed April 2025; 10. Schram AM, et al. AACR-NCI-EORTC International Conference. 2023; Oral presentation, abstract LB_A25; 11. Dumbrava EE, et al. SABCS. 2024; Poster presentation, P3-12-27 (abstract SESS-2137); 12. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://dtp.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed April 2025.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-t}, area under the plasma concentration-time curve from before dose to the time of the last quantifiable concentration; AUC_{tau}, area under the plasma concentration-time in one dosing interval; BICR, blinded independent central review; BID, twice daily; BOR, best overall response; C_{max}, maximum plasma concentration; CNS, central nervous system; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; C_{trough}, trough observed concentration; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; HIV, human immunodeficiency virus; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; max, maximum; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcome; QD, once daily; QLQ-C30, Quality of Life Questionnaire; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SOC, standard of care; T_{max}, time to reach maximum plasma concentration; TNBC, triple negative breast cancer; *TP53* Y220C, tumour protein 53 with an amino acid substitution at amino acid position 220 (tyrosine has been replaced by cysteine); TTR, time to response.

Acknowledgements

We would like to thank all the patients, their families and caregivers who have participated, and continue to participate, in the clinical trial; investigators and research staff; PPD, part of Thermo Fisher Scientific; Resolution Bioscience and Foundation Medicine

This study and the clinical trials are sponsored by PMV Pharmaceuticals, Inc. Medical writing was provided by Danielle Lindley of Nucleus Global, funded by PMV Pharmaceuticals, Inc.

Disclosure of conflicts of interest

J-SF, PZ, GDLL, PG: None. **MJ:** Research funding from PMV Pharmaceuticals. **DSPT:** Personal fees for advisory board membership from PMV Pharmaceuticals, institutional funding as local PI from PMV Pharmaceuticals. **SK:** local PI, institutional, financial interest, trial funding from PMV Pharmaceuticals. **KLD, MF:** PMV Pharmaceuticals employees (with stock options). **EED:** Received research funding/grant from, attended advisory boards for and provided a speaker role for PMV Pharmaceuticals. **AMS:** Attended advisory boards and received research funding from PMV Pharmaceuticals.

These disclosures are relevant for this poster; for a more complete list of disclosures of conflicts of interest, please follow the QR code.

Scan QR code to download the poster and for author disclosures

Copies of this poster obtained through the QR, AR and/or text key codes are for personal use only and may not be reproduced without written permission of the authors

MA-568-0064 May 2025

Presented at the European Society for Medical Oncology (ESMO) Breast Cancer Annual Congress 2025; 14–17 May 2025; Munich, Germany

Presented by Jean-Sebastien Frenel (jean-sebastien.frenel@ico.unicancer.fr)