PYNNACLE phase 2 clinical trial of rezatapopt in patients with advanced solid tumors harboring a *TP53* Y220C mutation.

Alison M. Schram, Jean-Sebastien Frenel, Melissa Lynne Johnson, Antoine Italiano, Shivaani Kummar, Andrew L. Coveler, Alexander I. Spira, Amy Body, Elisa Fontana, Elena Garralda, Alastair Greystoke, Michael Millward, Giovanni Scambia, David Shao Peng Tan, Marc Mardoche Fellous, Ecaterina Elena Dumbrava, Gilberto Lopes; Memorial Sloan Kettering Cancer Center, New York, NY; Institut de Cancerologie de L'Ouest, Saint-Herblain, France; Sarah Cannon Research Institute, Nashville, TN; Drug Development Department (DITEP), Gustave Roussy, Villejuif, France; Knight Cancer Institute, Portland, OR; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; NEXT Oncology Virginia, Fairfax, VA; Monash Medical Centre, Monash Health, Clayton, Australia; Sarah Cannon Research Institute UK, London, United Kingdom; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Newcastle Upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; Linear Clinical Research Ltd and School of Medicine, University of Western Australia, Perth, Western Australia, Australia; Fondazione Policlinico Universitario A. Gemelli, IRCCS, Division of Gynecologic Oncology, Catholic university of the Sacred Heart, Rome, Italy; National University Cancer Institute, Singapore, Singapore; PMV Pharma, Cranbury, NJ; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: *TP53*, encoding p53 protein, is one of the most frequently mutated genes across all cancers, with TP53 mutations found in ~59% of all solid tumors. *TP53* mutations result in the loss of p53 tumor suppressor functions leading to tumor development and progression. The *TP53* Y220C mutation, occurring in ~1% of all solid tumors, is a missense mutation that destabilizes the p53 protein. Rezatapopt (also known as PC14586) is an investigational, first-in-class, selective, p53 reactivator specific to the *TP53* Y220C mutation that restores wildtype p53 function. Preliminary findings from Phase 1 part of the PYNNACLE (NCT04585750) Phase 1/2 study, showed that rezatapopt had a favorable safety profile and single-agent efficacy in heavily pre-treated patients with solid tumors harboring a *TP53* Y220C mutation (*Schram A, AACR-NCI-EORTC 2023, LBA25*). Here we describe the study design for the registrational Phase 2 part of the PYNNACLE study. **Methods:** The Phase 2 part of PYNNACLE is an ongoing, global, single-arm, open-label, multicenter basket trial in patients with solid tumors harboring a *TP53* Y220C mutation (Table). Patients must have measurable disease at baseline, ECOG performance status 0 or 1, and adequate organ function; other key inclusion criteria are listed in the table. Patients with *KRAS* single nucleotide variants, primary CNS tumors and unstable brain metastases are excluded. Eligible patients receive rezatapopt 2000mg, orally, once daily, taken with food, for continuous 21-day cycles. Patients are followed until death, lost to follow-up, two years after last patient discontinuation, or end of study. As of March 2024, ≈114 patients are planned to be enrolled. Clinical trial information: NCT04585750. Research Sponsor: PMV Pharmaceuticals, Inc.

PYNNACLE Phase 1/2 basket study (NCT04585750).

Patient population N≈114 (planned)	Key inclusion criteria	Primary endpoints	Secondary endpoints
Cohort 1 **Ovarian cancer (platinum-resistant)** **n≈42** **Cohort 2** **Lung cancer** **n≈18** **Cohort 3** **Breast cancer** **n≈18** **Cohort 4** **Endometrial cancer** **n≈18** **Cohort 5** **Other solid tumors** **n≈18**	· Adults aged ≥18 years (all global sites except ≥21 years in Singapore) · Adolescents aged 12–17 years if weight ≥40 kg (90 lbs; Australia, South Korea and USA only) · Locally advanced or metastatic solid tumors · Documented *TP53* Y220C mutation and *KRAS* wildtype* · Prior standard therapy or ineligible for appropriate standard of care therapy	· ORR per BICR assessment (RECIST v1.1) across all cohorts · ORR per BICR assessment (RECIST v1.1) in ovarian cancer cohort	· ORR per investigator assessment (RECIST v1.1) across all cohorts and the ovarian cancer cohort · Time to response, duration of response, disease control rate · Progression-free survival · Overall survival · Safety · Pharmacokinetics · Quality of life

*Defined as no *KRAS* single nucleotide variant.
BICR, blinded independent central review; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.