The PYNNACLE Phase 2 trial assessing rezatapopt (PC14586), a selective p53 reactivator, in patients with locally advanced or metastatic solid tumors (including ovarian and endometrial cancers) harboring a *TP53* Y220C mutation

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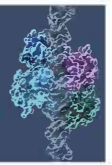

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BACKGROUND

- *TP53*, encoding p53, is the most frequently mutated gene across all cancers[1]
- *TP53* mutations result in loss of p53 tumor suppressor function and tumor progression[2]
- Most *TP53* mutations occur in the central DNA-binding domain, with 10 referred to as 'hot-spot' mutations, accounting for ~30% of *TP53* mutations observed in human cancers[1,3]
- *TP53* mutations are found in ~76% of ovarian cancers and ~53% of endometrial cancers, occurring at a high frequency in more aggressive and invasive tumor types such as high-grade serous ovarian cancer (detected in ~96% of all cases)[4]
- *TP53* Y220C is a key hot-spot *TP53* missense mutation that destabilizes p53 and is present in ~1% of all solid tumors, including ~3% of all ovarian cancers (3.4% of high-grade serous ovarian cancers) and 1.1% of all endometrial cancers[4–6]
- Reactivation of WT p53 in p53-mutated tumors may be an effective therapeutic strategy; however, only a limited number of small molecules targeting mutated p53 have reached clinical trials[2,7]
- Rezatapopt, an investigational agent also known as PC14586, is a first-in-class, selective, p53 reactivator specific to the *TP53* Y220C mutation that restores WT p53 conformation and function by binding to a pocket created by the tyrosine-to-cysteine substitution in the p53 protein[8]
  - Rezatapopt fits tightly into the pocket of the p53 Y220C mutant protein via non-covalent hydrogen bonding, which enhances hydrophobic and van der Waals interactions; this stabilizes the p53 protein in the WT conformation and restores p53 transcriptional activity[8–10]
  - Once p53 tumor suppressor functions are restored, cell-cycle inhibition and apoptosis occur in tumor cells harboring the *TP53* Y220C mutation[11]

- PYNNACLE (NCT04585750) is a Phase 1/2 clinical study investigating rezatapopt in patients with solid tumors harboring a *TP53* Y220C mutation[8]
  - In Phase 1, rezatapopt showed promising single-agent efficacy and a favorable safety profile in heavily pre-treated patients[12]
  - Of the 20 patients with ovarian cancer receiving rezatapopt who had measurable disease at baseline, seven patients achieved a confirmed partial response, with a median duration of response of 7 months[13]
- Here we describe the study design for the ongoing PYNNACLE Phase 2 study assessing rezatapopt 2000 mg QD taken with food in patients with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation and WT *KRAS*

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 tumors harboring a *TP53* Y220C mutation[8,14]

Overview of the PYNNACLE study assessing rezatapopt in solid tumors with a *TP53* Y220C mutation[14]

Participants[8,14]

≥12 years of age with locally advanced or metastatic solid tumors with a *TP53* Y220C mutation

Previously treated (or ineligible for SOC)

ECOG PS 0 or 1

Phase 2:
- ≥18 years of age[a]
- Adolescents 12–17 years of age (if weighing ≥40 kg)[b]
- *KRAS* WT[c]

PYNNACLE (PMV-586-101, NCT04585750)

Phase 1a[14] Active, not enrolling	Phase 1b[8,14] Active, not enrolling	Phase 2[8,14] Active, enrolling
Rezatapopt dose escalation • Identify MTD and RP2D • Assess PK, safety, and preliminary efficacy	Rezatapopt + pembrolizumab dose escalation • Identify appropriate dose in combination with pembrolizumab • Assess PK, safety, and efficacy	**Rezatapopt dose expansion at 2000 mg QD** • Assess efficacy • Assess safety, PK, and QoL

[a] For all global sites except Singapore (adults ≥21 years of age); [b] Australia, South Korea, and USA only; [c] Phase 2 only includes patients that are *KRAS* WT; those with *KRAS* single nucleotide variants are excluded.

PYNNACLE PHASE 2 TRIAL DESIGN[8,14,15]

- PYNNACLE Phase 2: Ongoing, global, pivotal, basket, single-arm, open-label, multicenter trial in solid tumors including ovarian, lung, breast, endometrial, and other cancers
- The primary objective of PYNNACLE Phase 2 is to evaluate the efficacy of rezatapopt at the RP2D; secondary objectives include safety, PK, QoL, and other efficacy measures
- Eligible patients receive rezatapopt 2000 mg orally QD with food for continuous 21-day cycles; patients are followed until lost to follow-up, death, 2 years after last patient discontinuation, or end of study

PYNNACLE Phase 2: Evaluating the efficacy of rezatapopt at the RP2D

Phase 2[8,14,15]

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 tumors	n = ~18

Patient population (inclusion criteria)[8,14,15]

- Aged ≥18 years (all global sites except Singapore: ≥21 years)
- Adolescents 12–17 years of age (if ≥40 kg, in Australia, South Korea, and USA only)
- ECOG PS 0 or 1
- Locally advanced or metastatic solid tumors
- Measurable disease at baseline (RECIST v1.1)
- Documented *TP53* Y220C mutation (identified locally) and *KRAS* WT[b]
- Previously treated with ≥1 line of systemic treatment or ineligible for appropriate SOC

Exclusion criteria[8,14,15]

- *KRAS* single nucleotide variant mutations
- Unstable brain metastases
- Primary CNS tumors
- 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, or other clinically significant rhythm abnormalities)
- Uncontrolled hepatitis B, hepatitis C, or HIV infection

[a] Platinum resistant or refractory; [b] *KRAS* WT defined as the absence of *KRAS* single nucleotide variant mutations.

PYNNACLE Phase 2: Primary and secondary endpoints

PRIMARY OBJECTIVE: Evaluate the efficacy of rezatapopt per BICR assessment

Primary endpoints

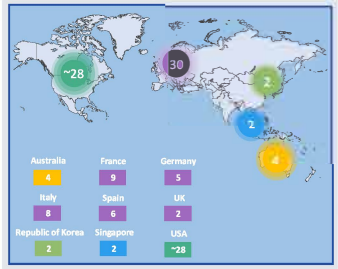
- ORR: **ORR[a]** BICR assessed RECIST v1.1 Across all cohorts
- ORR: **ORR[a]** BICR assessed RECIST v1.1 Ovarian cancer cohort only

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:** Investigator and BICR assessed; RECIST v1.1 **OS & PFS:** Across all cohorts and ovarian cancer cohort only
- AEs: **Safety:** AEs, SAEs, laboratory assessments
  - AEs graded using CTCAE v5.0[16]
- PK: **Plasma PK parameters**
  - May include C_{max}, T_{max}, AUC_{0-t}, AUC_{tau}, C_{trough}
- PRO: **PROs:** EORTC QLQ-C30 for patients ≥18 years of age

[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[14]



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Abbreviations

AE, adverse event; AUC_{0-t}, area under the plasma concentration–time curve from pre-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; BOR, best overall response; C_{max}, maximum plasma concentration; CNS, central nervous system; CTCAE, common terminology criteria for adverse events; C_{trough}, trough observed concentrations; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status Score; EORTC, European Organisation for Research and Treatment of Cancer; HIV, human immunodeficiency virus; KRAS, Kirsten rat sarcoma virus; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; 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 Tumors version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SOC, standard of care; $T_{1/2}$, half-life; T_{max}, time to reach C_{max}; TP53 Y220C, tumor protein 53 with an amino acid substitution at amino acid position 220 (tyrosine has been replaced by cysteine); TTR, time to response; WT, wild type.

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