PYNNACLE Phase 2 Clinical Trial of Rezatapopt in Patients with Advanced Solid Tumors Harboring a TP53 Y220C Mutation

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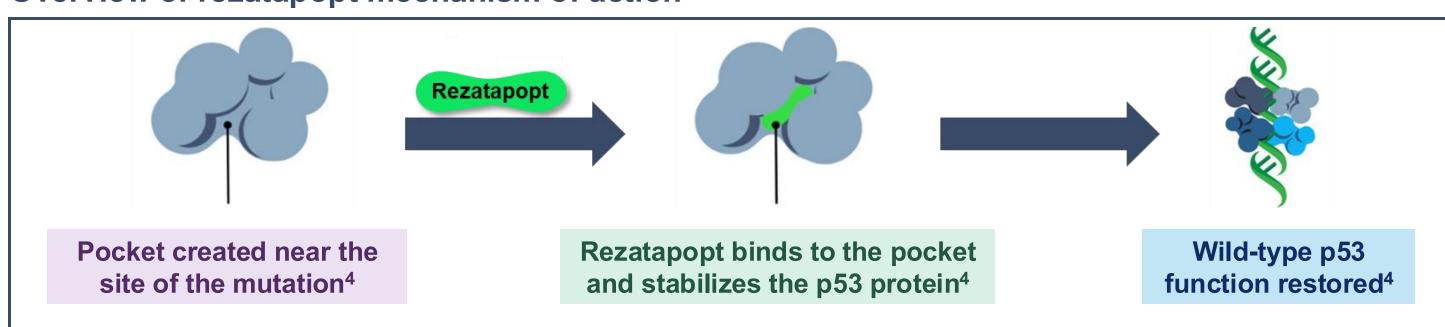
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PYNNACLE

BACKGROUND

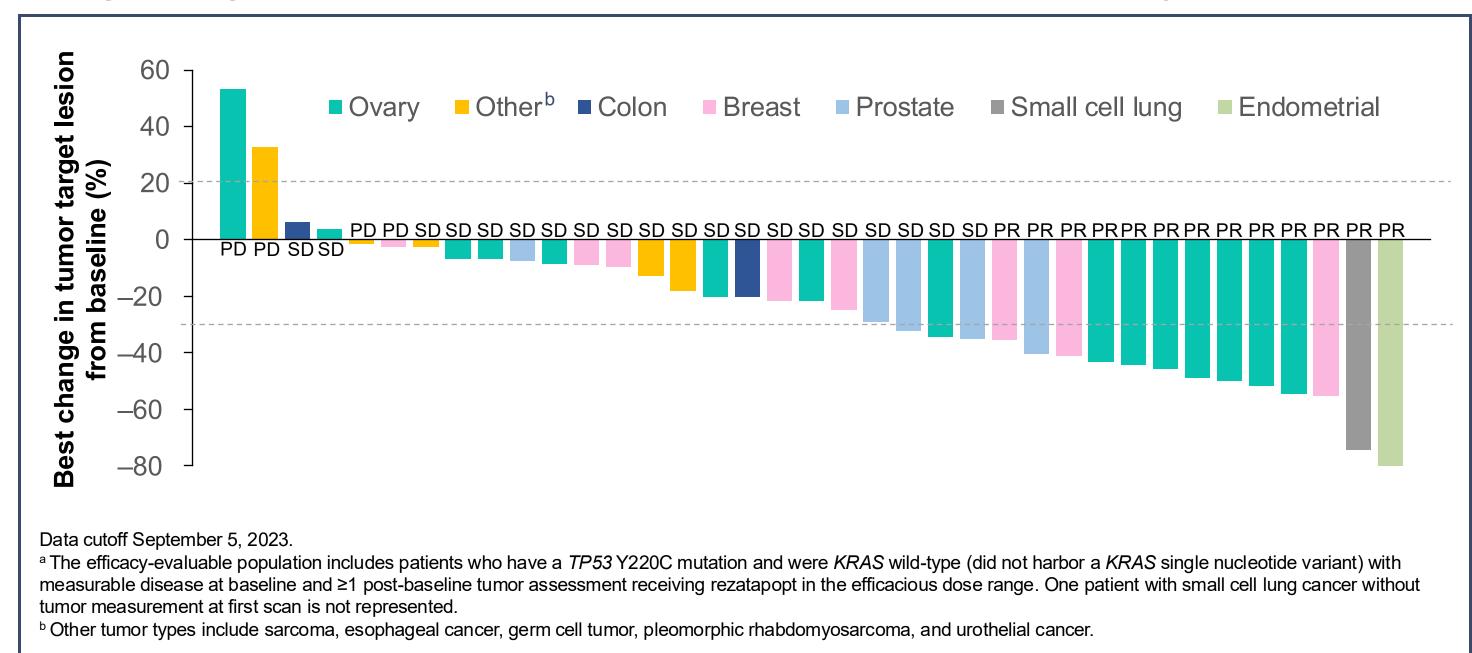
- TP53, encoding the p53 protein, is the most frequently mutated gene across all cancers¹
- TP53 mutations are found in ~59% of all solid tumors²
- o These mutations destabilize the p53 protein, causing loss of p53 tumor suppressor function and tumor progression³
- **TP53 Y220C** is a hot-spot **TP53** missense mutation present in ~1% of all solid tumors²
- **Rezatapopt** (also known as PC14586) is an investigational, first-in-class, selective p53 reactivator specific to the *TP53* Y220C mutation that stabilizes the mutated p53 protein in wild-type conformation, restoring p53 transcriptional activity and tumor suppressor functions^{4–6}
- o Tyrosine-to-cysteine substitution creates a pocket in the Y220C-mutated protein^{4–6}
- Rezatapopt fits tightly into this pocket via non-covalent hydrogen bonding, enhancing hydrophobic and van der Waals interactions, stabilizing the p53 protein in the wild-type conformation^{4–6}

Overview of rezatapopt mechanism of action



- In **PYNNACLE Phase 1** (up to data cutoff: September 5, 2023), rezatapopt showed preliminary efficacy in heavily pre-treated patients⁷
- Thirteen out of 38 (34%) evaluable patients receiving rezatapopt in the efficacious dose range (1150 mg QD to 1500 mg BID) had confirmed PRs⁷
 - PRs were observed across multiple tumor types, including ovarian, breast, small cell lung, and endometrial cancers⁷
- o The median time to response and median duration of response were 1.5 months and 7 months, respectively⁷
- o **Rezatapopt demonstrated a favorable safety profile**, with mostly Grade 1/2 treatment-related AEs⁷
- The most frequent treatment-related AEs (in >15% of patients) were nausea (50.7%), vomiting (43.3%), blood creatinine increase (26.9%), diarrhea (19.4%), fatigue (19.4%), AST increase (16.4%), and ALT increase (17.9%)⁷

Change in target lesions from baseline in evaluable patients across tumor types^a

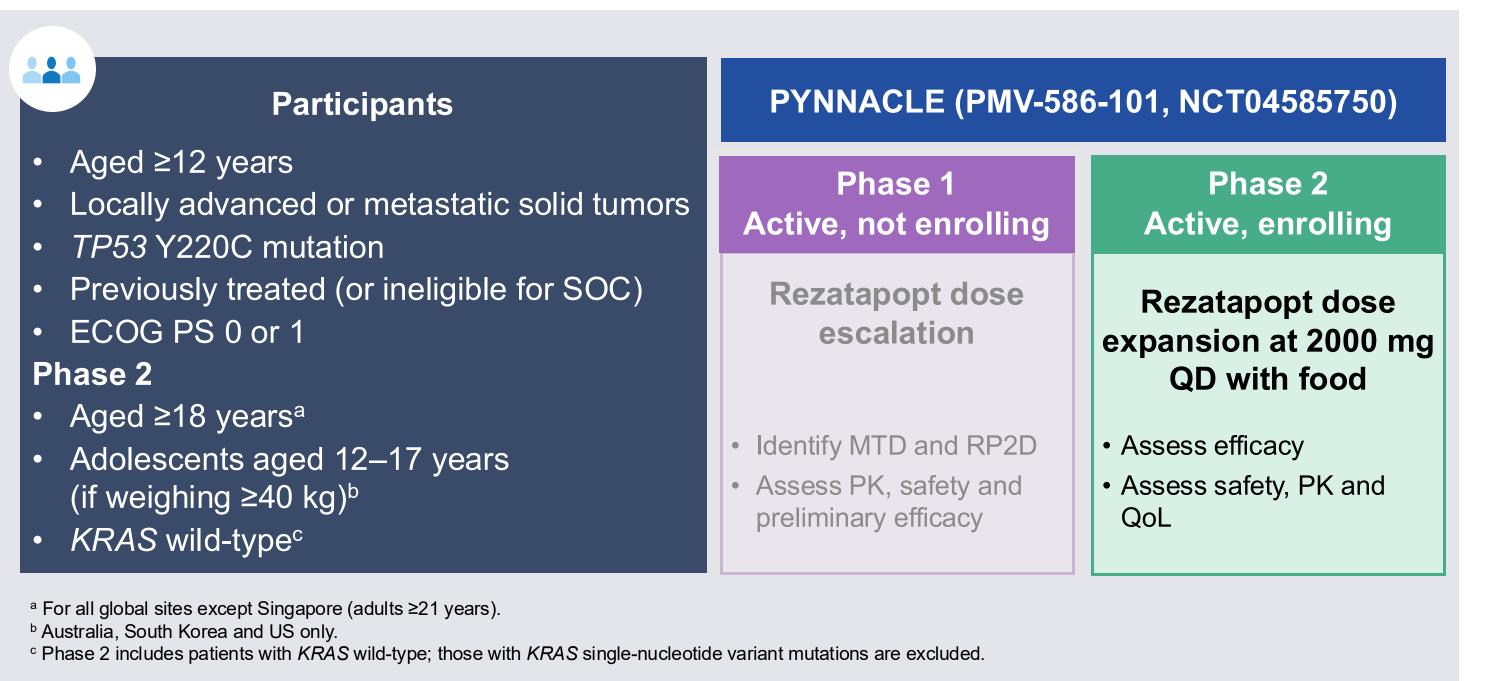


 Here we describe the study design for the ongoing, pivotal, registrational PYNNACLE Phase 2 study assessing rezatapopt 2000 mg QD taken with food in patients with locally advanced or metastatic solid tumors harboring a TP53 Y220C mutation and KRAS wild-type⁴

OVERVIEW OF THE PYNNACLE STUDY

• The PYNNACLE study aims to assess the efficacy, safety, tolerability, PK and pharmacodynamics of rezatapopt in patients with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation and *KRAS* wild-type^{4,8}

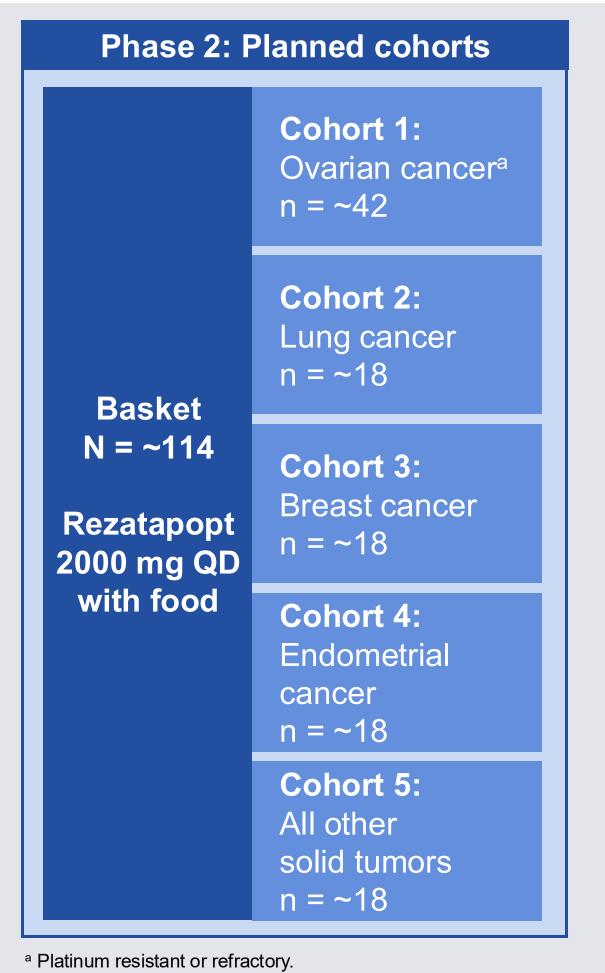
Overview of the PYNNACLE study assessing rezatapopt in solid tumors with a *TP53* Y220C mutation^{4,8}



METHODS

- PYNNACLE Phase 2: Ongoing, global, single-arm, open-label, multicenter, registrational basket trial in patients with solid tumors^{4,7,8}
- **Primary objective**: Evaluate the efficacy of rezatapopt at the RP2D^{4,7,8}
- Secondary objectives: Safety, PK, QoL and other efficacy measures^{4,7,8}
- Rezatapopt: Eligible patients receive rezatapopt 2000 mg orally QD with food for continuous 21-day cycles^{4,7,8}
- Patients are followed up until death, loss to follow-up, 2 years after last patient discontinuation or end of study^{4,7,8}

PYNNACLE Phase 2: Patient population^{4,7,8}



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 tumors
- 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

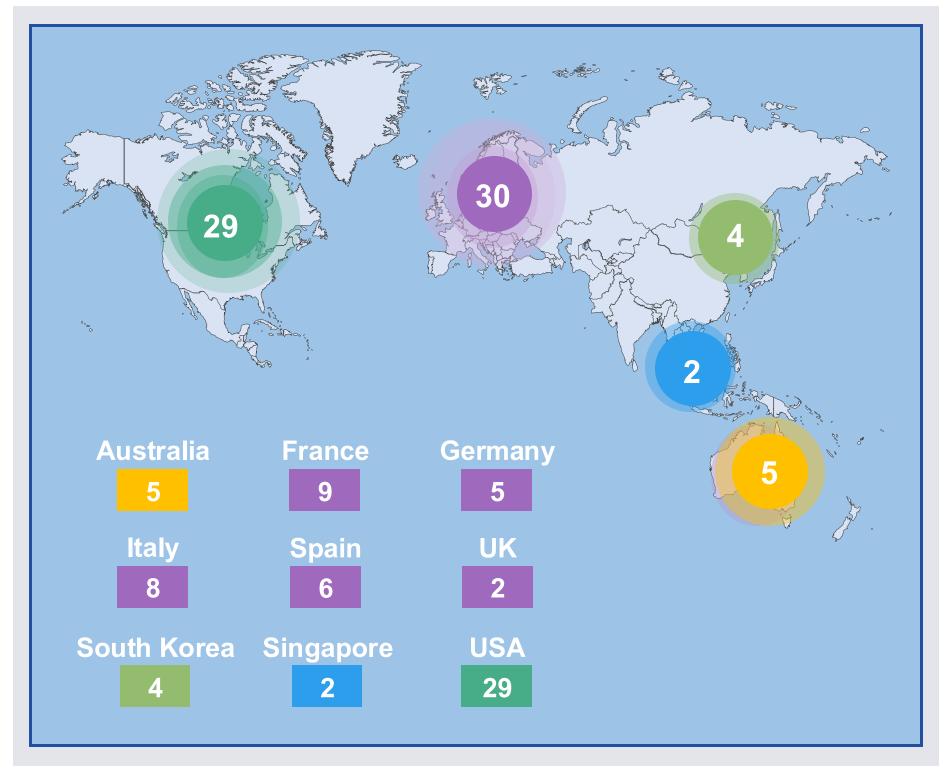
Exclusion criteria

- KRAS single-nucleotide variant mutations
- Unstable brain metastases
- Primary CNS tumors
- History of leptomeningeal disease, 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^{4,7,8}

PRIMARY OBJECTIVE: Evaluate the efficacy of rezatapopt per BICR (blinded independent central review) assessment **Primary endpoints Secondary endpoints ORR:** Investigator assessed; Safety: AEs, SAEs, RECIST v1.1 ORR **AEs** laboratory assessments Across all cohorts and AEs graded using CTCAE v5.09 ovarian cancer cohort only BICR assessed RECIST v1.1 Across all cohorts TTR, DoR, DCR: BICR and investigator assessed; RECIST v1.1 **Plasma PK parameters** May include C_{max}, T_{max}, AUC_{0-t} • DCR at 6, 12, 18 and 24 weeks PK Across all cohorts and ovarian cancer cohort only BICR assessed RECIST v1.1 Ovarian cancer cohort only **PFS:** BICR and investigator assessed; RECIST v1.1 PROs: EORTC QLQ-C30 for **PRO** OS and PFS: Across all cohorts patients aged ≥18 years and ovarian cancer cohort only

PYNNACLE Phase 2: Planned sites worldwide⁸



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

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Abbreviations AF adverse event: Al

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, progressive disease; 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; SD, stable disease; SOC, standard of care; T_{max}, time to reach maximum plasma concentration; *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.

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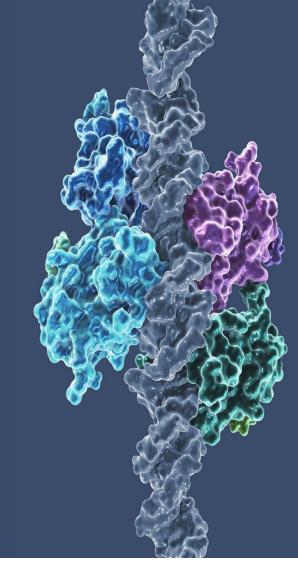
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