PYNNACLE Phase 2 Trial of Rezatapopt (PC14586) in Solid Tumours with a *TP53* Y220C Mutation

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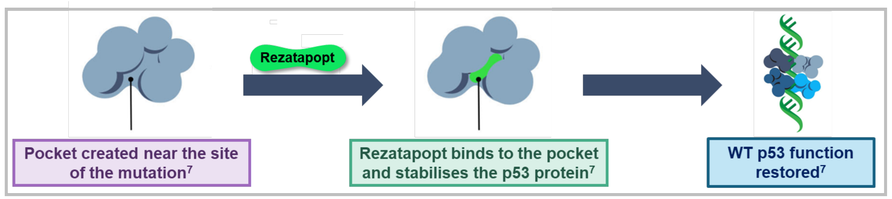
BACKGROUND

- *TP53,* encoding p53, is the most frequently mutated gene across all cancers[1]
- *TP53* mutations result in loss of p53 tumour suppressor function and tumour progression[2]
- Most *TP53* mutations occur in the central DNA-binding domain, with ten referred to as 'hot-spot' mutations, accounting for ~30% of *TP53* mutations observed in human cancer[1,3]
- *TP53* Y220C is a key hot-spot *TP53* missense mutation that destabilises p53 and is present in ~1% of all solid tumours[4,5]
- Reactivation of WT p53 in p53-mutated tumours may be an effective therapeutic strategy; however, only a limited number of small molecules targeting mutated p53 have reached clinical trials[2,6]
- 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[7]
  - Once the mutated p53 Y220C protein is stabilised in its WT conformation, reactivation of p53 transcriptional activity occurs[7,8]
  - p53 tumour suppressor functions are restored, causing cell-cycle inhibition and apoptosis in tumour cells harbouring the *TP53* Y220C mutation[9]



- PYNNACLE (NCT04585750) is a Phase 1/2 clinical study investigating rezatapopt in patients with solid tumours harbouring a *TP53* Y220C mutation[10]
  - In Phase 1, rezatapopt showed single-agent efficacy and a favourable safety profile in heavily pre-treated patients[11]
- Here we describe the study design for the ongoing PYNNACLE Phase 2 study assessing rezatapopt 2000 mg QD with food in patients with locally advanced or metastatic solid tumours harbouring a *TP53* Y220C mutation and *KRAS* WT

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[10,12]

Overview of the PYNNACLE study assessing rezatapopt in solid tumours with a *TP53* Y220C mutation[12]

Participants[10,12]

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

Previously treated (or ineligible for SOC)

ECOG PS 0 or 1

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

PYNNACLE (PMV-586-101, NCT04585750)

Phase 1[10,12]

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

Phase 1b[10,12]

Rezatapopt + pembrolizumab dose escalation
- Identify appropriate dose in combination with pembrolizumab
- Assess PK, safety and efficacy

Phase 2[10,12]

Rezatapopt dose expansion at 2000 mg QD
- 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 only includes patients that are *KRAS* WT; those with *KRAS* single nucleotide variant mutations are excluded.

PYNNACLE PHASE 2 TRIAL DESIGN[12]

- PYNNACLE Phase 2: Ongoing, global, pivotal, basket, single-arm, open-label, multicentre trial in solid tumours 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, PKs, 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[10,12,13]

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

Patient population (inclusion criteria)[10,12,13]
- Aged ≥18 years (all global sites except Singapore: ≥21 years)
- Adolescents 12–17 years of age (if ≥40 kg, in Australia, South Korea and US only)
- ECOG PS 0 or 1
- Locally advanced or metastatic solid tumours
- 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[10,12,13]
- *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 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 (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: Investigator and BICR assessed; RECIST v1.1
OS & PFS: Across all cohorts and ovarian cancer cohort only

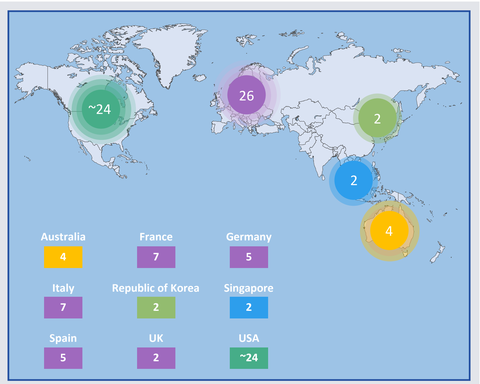
AEs
Safety: AEs, SAEs, laboratory assessments
- AEs graded using CTCAE v5.0[14]

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



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Abbreviations

AE, adverse event; AI, ratio of an exposure measure at steady state to that after the first dose; 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; CLT, total body clearance; 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, tumour 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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