**BACKGROUND**

- **TP53** is a tumor suppressor gene and TP53 mutation resulting in p53 instability is a step in carcinogenesis.
- **TP53** Y220C is a hotspot mutation present in ~1% of all solid tumors, where it destabilizes the p53 protein leading to loss of tumor suppressor function.
- **PC14586** is a first-in-class p53 inhibitor that selectively binds to the mutated p53 Y220C protein and induces reversion of oncogenic p53 (WT) activity.

**METHODS**

- We assessed PC14586 in patients treated in the PYNNACLE Phase 1 across the efficacious dose range (1150 mg once daily [QD] to 1500 mg twice daily [BID]).
- Eligible patients (≥18 years of age) with locally advanced or metastatic solid tumors, ≥1 post-baseline (≥50% and ≥95%) ctDNA NGS testing; PC14586 was administered with food led to improvement in gastrointestinal toxicities.
- Prior systemic therapies, n (%)
- ECOG status, n (%)
- Age, years
- Sex
- Race
- Prior systemic therapies
- KRAS
- TP53
- Germline

**RESULTS**

- **Patient demographics and disease characteristics**
  - Baseline characteristics of patients treated in the efficacious dose range (1150 mg to 1500 mg) QD.
  - Of patients in the efficacious dose range, the median age was 63 (range 43–84 years), 57% were male, and 57% had a baseline assessment.

- **Efficacy**
  - Clinical efficacy was assessed in locally advanced or metastatic cancer patients (at Week 3) of ≥50% and ≥95%, respectively.
  - Among patients with measurable disease (without meaningful disease progression or death) at baseline and at the first scan, the objective response rate (ORR) was 60% (95% CI: 41%–79%) for patients treated at 1150 mg QD and 40% (95% CI: 18%–62%) for patients treated at 1500 mg QD.

- **Safety**
  - Of patients treated with PC14586 therapy, the most frequently reported adverse events were grade 1/2.

- **Exploratory analyses**
  - Of patients with measurable disease at baseline, the median overall survival (OS) was 15.7 months for patients treated at 1150 mg QD and 14.5 months for patients treated at 1500 mg QD.

**CONCLUSIONS**

- **PC14586 demonstrated a favorable safety profile with the efficacious dose range, with improvement in gastrointestinal adverse events when PC14586 is taken with food.**
- **Single agent clinical efficacy was achieved in heavily pre-treated patients across multiple tumor types.**
- **The PYNNACLE randomized Phase 2 trial will assess PC14586 as monotherapy in patients with TP53-mutant malignancies and ARID1A advanced solid tumors.**

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- The authors also thank the investigators, research staff, and patients and families who have participated in this trial.

**References**