Updated Phase 1 results from the PYNNACLE Phase 1/2 study of PC14586, a selective p53 reactivator, in patients with advanced solid tumors harboring a *TP53* Y220C mutation

Alison M. Schram,[1] Geoffrey I. Shapiro,[2] Melissa L. Johnson,[3] Anthony W. Tolcher,[4] John A. Thompson,[5] Anthony B. El-Khoueiry,[6] Andrae L. Vandross,[7] Shivaani Kummar,[8] Aparna R. Parikh,[9] Dale R. Shepard,[10] Ursula Garczarek,[11] Kim LeDuke,[12] Lisa Sheehan,[12] Marc Fellous,[12] Leila Alland,[12] Ecaterina E. Dumbrava[13]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana Farber Cancer Institute, Boston, MA; [3]Sarah Cannon Research Institute, Nashville, TN; [4]NEXT Oncology, San Antonio, TX; [5]Fred Hutchinson Cancer Center, Seattle, WA; [6]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [7]NEXT Oncology, Austin, TX; [8]OHSU Knight Cancer Institute, Portland, OR; [9]Massachusetts General Hospital, Boston, MA; [10]Cleveland Clinic Foundation, Cleveland, OH; [11]Cytel, Inc., Waltham, MA; [12]PMV Pharmaceuticals, Inc., Princeton, NJ; [13]The University of Texas MD Anderson Cancer Center, Houston, TX

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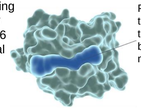
BACKGROUND

- *TP53* is a tumor suppressor gene and *TP53* mutation resulting in p53 inactivation is a key step in oncogenesis.[1–3]
- *TP53* Y220C is a hot-spot mutation present in ~1% of all solid tumors, where it destabilizes the p53 protein leading to its inactivation.[4–6]
- PC14586 is a first-in-class p53 reactivator that selectively binds to the mutated p53 Y220C protein and restores p53 wild-type (WT) activity.[7]
- Initial Phase 1 results from the Phase 1/2 PYNNACLE trial (NCT04585750) evaluating PC14586 in patients with advanced *TP53* Y220C solid tumors showed that PC14586 was well tolerated, with preliminary clinical activity across tumor types.[7]
- Here, we present an updated Phase 1 analysis of safety and efficacy in patients treated across the efficacious dose range.

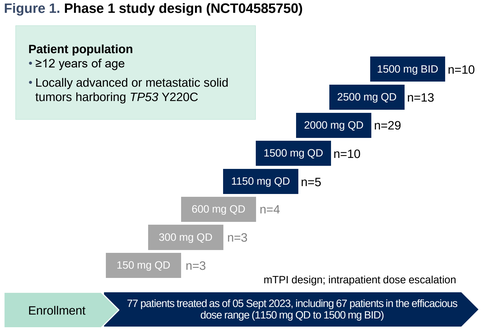


PC14586 is designed to precisely dock into the pocket created by the *TP53* Y220C mutation

METHODS

- We assessed PC14586 in patients treated in the PYNNACLE trial across the efficacious dose range (1150 mg once daily [QD] to 1500 mg twice daily [BID]).
- Eligible patients (≥12 years of age) with locally advanced or metastatic solid tumors with a *TP53* Y220C mutation received increasing oral doses of PC14586 to evaluate safety, pharmacokinetics (PK), biomarkers (circulating tumor DNA [ctDNA]), and preliminary efficacy via Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) (**Figure 1**).
- Molecular profiling was performed on tumors to assess the impact of *KRAS* mutation status on response. *KRAS* mutations were defined as single nucleotide variants (SNVs).
- The *TP53* Y220C / *KRAS* WT efficacy evaluable analysis set included patients with measurable disease (without *KRAS* SNV) at baseline with ≥1 post-baseline tumor assessment within the efficacious dose range.

Figure 1. Phase 1 study design (NCT04585750)



Primary objective
Determine maximum tolerated dose, recommended Phase 2 dose, and evaluate safety and tolerability.

Secondary objectives
PK, preliminary efficacy.

Exploratory objectives
Biomarkers (ctDNA).

Data cut-off: 05 Sept 2023. BID, twice daily; ctDNA, circulating tumor DNA; mTPI, modified toxicity probability interval; PK, pharmacokinetics; QD, once daily.

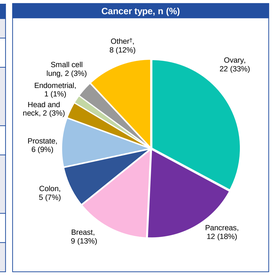
RESULTS

Patient demographics and disease characteristics

- As of 05 Sept 2023, 67 patients were treated in the efficacious dose range (1150 mg QD to 1500 mg BID).
- Of patients in the efficacious dose range, the median age was 63 (range 32–84) years, 61% were female, 76% were white, 67% had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and the median number of prior lines of systemic therapy was 3 (range 1–9) (**Figure 2**).

Figure 2. Patient demographics and disease characteristics

	n=67
Age, years	
Median (min–max)	63 (32–84)
Sex, n (%)	
Female	41 (61)
Male	26 (39)
Race, n (%)	
White	51 (76)
Asian	5 (7)
Black or African American	6 (9)
Other	1 (1)
Not reported/unknown	4 (6)
ECOG status, n (%)	
0	22 (33)
1	45 (67)
Prior systemic therapies, n (%)	
1	6 (9)
2	19 (28)
≥3	37 (55)
Not reported	5 (6)
Median (min–max)	3 (1–9)
Germline *TP53* Y220C, n (%)	
Negative	66 (99)
Positive	1 (1)
***KRAS* mutation status, n (%)**	
Wild-type	50 (75)
KRAS SNV‡	17 (25)



Data cut-off: 05 Sept 2023.†Other tumor types include: sarcoma, cholangiocarcinoma, esophageal cancer, gastro-esophageal cancer, germ cell tumor, pleomorphic rhabdomyosarcoma, small intestine cancer, urothelial cancer. ‡12 pancreas, three colon, one small intestine, and one cholangiocarcinoma.
ECOG, Eastern Cooperative Oncology Group; SNV, single nucleotide variant.

Safety

- Treatment-related adverse events (TRAEs) were mostly grade 1/2.
- Most frequent TRAEs (>20%) were nausea, vomiting, and blood creatinine increased (**Table 1**).
- PC14586 administered with food led to improvement in gastrointestinal toxicities (nausea, vomiting, and diarrhea) (data not shown).
- Low rate (3%) of drug discontinuation due to a TRAE.

Table 1. Incidence of TRAEs in ≥5% of patients (1150 mg QD to 1500 mg BID)

All TRAEs, n (%)		Max CTCAE			
Preferred Term	Overall n=67	1	2	3	4
Any TRAE	**60 (89.6)**	**16 (23.9)**	**27 (40.3)**	**16† (23.9)**	**1‡ (1.5)**
Nausea	34 (50.7)	22 (32.8)	11 (16.4)	1 (1.5)	–
Vomiting	29 (43.3)	16 (23.9)	12 (17.9)	1 (1.5)	–
Blood creatinine increased	18 (26.9)	10 (14.9)	8 (11.9)	–	–
Diarrhea	13 (19.4)	12 (17.9)	–	1 (1.5)	–
Fatigue	13 (19.4)	8 (11.9)	5 (7.5)	–	–
ALT increased	12 (17.9)	4 (6.0)	5 (7.5)	3 (4.5)	–
AST increased	11 (16.4)	7 (10.4)	2 (3.0)	2 (3.0)	–
Anemia	10 (14.9)	1 (1.5)	6 (9.0)	3 (4.5)	–
Decreased appetite	7 (10.4)	2 (3.0)	4 (6.0)	1 (1.5)	–
Proteinuria	6 (9.0)	1 (1.5)	5 (7.5)	–	–
Rash maculo-papular	6 (9.0)	1 (1.5)	3 (4.5)	2 (3.0)	–
Headache	5 (7.5)	4 (6.0)	1 (1.5)	–	–
Lipase increased	5 (7.5)	4 (6.0)	–	1 (1.5)	–
Platelet count decreased	4 (6.0)	1 (1.5)	1 (1.5)	2 (3.0)	–
Amylase increased	4 (6.0)	3 (4.5)	1 (1.5)	–	–
Dehydration	4 (6.0)	–	4 (6.0)	–	–

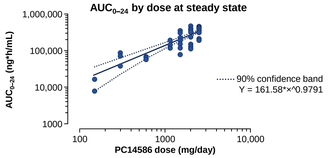
Data cut-off: 05 Sept 2023. †Includes five additional grade 3 TRAEs: neutrophil count decreased, acute kidney injury, pancreatitis, pneumonitis, and rash erythematous. Note that a patient could have multiple grade 3 events. ‡Includes one patient with grade 4 immune thrombocytopenia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; QD, once daily; TRAE, treatment-related adverse event.

Pharmacokinetics

PC14586 demonstrated dose-proportionality and linear PK from 150 mg to 2500 mg QD at steady state (Figure 3).

- The median half-life of PC14586 was 19 hours at steady state (Day 15) across doses.

Figure 3. Day 15 (steady state) exposures of PC14586



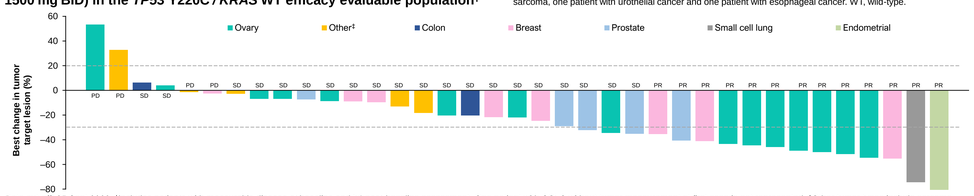
Data cut-off: 05 Sept 2023. AUC, area under the curve; SD, standard deviation.

Efficacy

Clinical efficacy was achieved in heavily pre-treated patients across multiple tumor types with *TP53* Y220C / *KRAS* WT.

- Within the safety population (N=67), 51 patients were efficacy evaluable (measurable disease and ≥1 post-baseline tumor assessment), of whom 13 had tumors that were *TP53* Y220C / *KRAS* SNV mutated and 38 were *TP53* Y220C / *KRAS* WT.
- Tumor target lesion reduction was observed in *TP53* Y220C / *KRAS* WT and *TP53* Y220C / *KRAS* SNV mutated tumors. However, confirmed responses were observed only among patients whose tumors had *TP53* Y220C / *KRAS* WT (**Table 2**).
- **Figure 4** shows the best change in target lesions in the *TP53* Y220C / *KRAS* WT population.

Figure 4. Target lesion reduction across tumor types (1150 mg QD to 1500 mg BID) in the *TP53* Y220C / *KRAS* WT efficacy evaluable population†



Data cut-off: 05 Sept 2023. †Includes patients with measurable disease at baseline and ≥1 post-baseline assessment. One patient with SCLC without tumor measurement at first scan is not represented. ‡Other tumor types include sarcoma, esophageal cancer, germ cell tumor, pleomorphic rhabdomyosarcoma, and urothelial cancer. BID, twice daily; PD, Progressive Disease; PR, Partial Response; QD, once daily; SCLC, small cell lung cancer; SD, Stable Disease; WT, wild-type.

- Of patients whose tumors had *TP53* Y220C / *KRAS* WT, a total of 13 confirmed Partial Responses (PRs) (Overall Response rate [ORR] = 34%) were observed across multiple tumor types, including ovarian, breast, small cell lung, and endometrial cancers (**Table 2**).
  - At 2000 mg QD, the ORR was 38% in patients with *TP53* Y220C and *KRAS* WT tumors.

Table 2. *TP53* Y220C / *KRAS* WT efficacy evaluable population

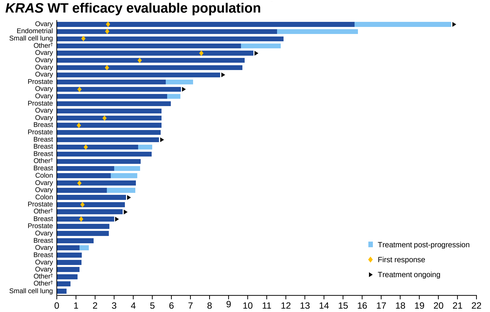
	2000 mg QD N=16	1150 mg QD–1500 mg BID N=38
	ORR, n (%)	ORR, n (%)
Overall	**6 (38)**	**13 (34)**
PRT	6	13
SD	8	20
PD	2	5

	2000 mg QD	1150 mg QD–1500 mg BID
	ORR, n (%)	ORR, n (%)
Ovary	2 (40)	7 (47)
Breast	2 (67)	3 (38)
Small cell lung	0 (0)	1 (50)
Endometrial	1 (100)	1 (100)
Other	1 (17)	1 (8)

Data cut-off: 05 Sept 2023.†All Partial Responses were confirmed. *KRAS* WT efficacy evaluable: All treated patients with measurable disease at baseline, *KRAS* WT defined as no *KRAS* SNVs, and ≥1 post-baseline assessment.
BID, twice daily; ORR, Overall Response Rate; PD, Progressive Disease; PR, Partial Response; QD, once daily; SD, Stable Disease; SNV, single nucleotide variant; WT, wild-type.

- Among all responders, median time to response and median duration of response were 1.5 months and 7 months, respectively (**Figure 5**).

Figure 5. Duration of PC14586 therapy in patients in the *TP53* Y220C / *KRAS* WT efficacy evaluable population

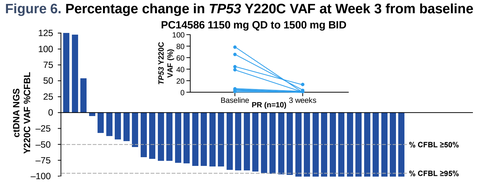


Data cut-off: 05 Sept 2023. Includes all patients with measurable disease at baseline, *TP53* Y220C / *KRAS* WT, and ≥1 post-baseline assessment (n=38). †Other tumor types included one patient with germ cell tumor, two patients with sarcoma, one patient with urothelial cancer and one patient with esophageal cancer. WT, wild-type.

Exploratory analysis

- Among the 51 patients in the efficacy evaluable population, 40 patients had ctDNA *TP53* Y220C variant allele frequency (VAF) results available at baseline and on treatment (at Week 3) (**Figure 6**).
  - 92% (n=37) of patients had a reduction in *TP53* Y220C VAF, suggesting on target activity.
  - 80% (n=32) and 42% (n=17) of patients had a change in *TP53* Y220C VAF from baseline (at Week 3) of ≥50% and ≥95%, respectively.
- In addition, all patients experiencing a RECIST PR had a reduction in *TP53* Y220C VAF.

Figure 6. Percentage change in *TP53* Y220C VAF at Week 3 from baseline

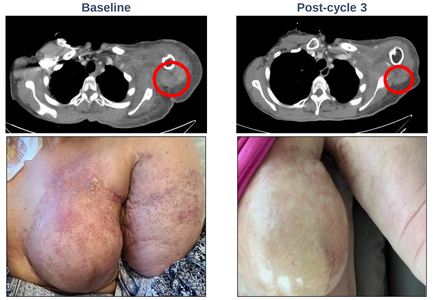


Data cut-off: 05 Sept 2023. CFBL, change from baseline; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PR, Partial Response; QD, once daily; VAF, variant allele frequency.

Patient case

- 51-year-old woman with metastatic triple-negative breast cancer (TNBC).
- Prior treatment course:
  - Neoadjuvant therapy (carboplatin, paclitaxel, and pembrolizumab followed by cyclophosphamide, doxorubicin, and pembrolizumab).
  - Bilateral mastectomy followed by pembrolizumab maintenance, radiotherapy, and breast reconstruction.
  - Pegylated liposomal doxorubicin for disease recurrence.
  - Progressive disease in axilla with extensive skin lesions on adjacent breast and arm, limiting mobility.
- *TP53* Y220C detected by next-generation sequencing.
- PC14586 2000 mg QD was started.
  - Rapid, visible reduction in arm swelling and improved mobility of arm and fingers within the first week.
  - PR at 6 weeks (41% reduction in axilla lesion) confirmed at 12 weeks and ongoing.

Figure 7. Patient images of triple-negative breast cancer at baseline and post-cycle 3



CONCLUSIONS

- PC14586 demonstrated a favorable safety profile in 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.
- Based on the overall data, 2000 mg QD was selected as the RP2D.
- The PYNNACLE registrational Phase 2 trial will assess PC14586 as monotherapy at the RP2D of 2000 mg QD in patients with *TP53* Y220C mutation and *KRAS* WT advanced solid tumors.

References
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Disclosures
AS, GS, AP, MJ, AT, JT, AEK, AV, SK, DS, and **ED** are principal investigators for the PYNNACLE trial. **KL, LS, MF, and LA** are employees of PMV Pharmaceuticals, Inc. and own stock or options in PMV Pharmaceuticals, Inc. **UG** is a consultant for PMV Pharmaceuticals, Inc. Full conflicts of interest can be made available by scanning the QR code.

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