2022 ASCO® ANNUAL MEETING

First-in-Human Study of PC14586, a Small Molecule Structural Corrector of Y220C Mutant p53, in Patients With Advanced Solid Tumors Harboring a *TP53* Y220C Mutation

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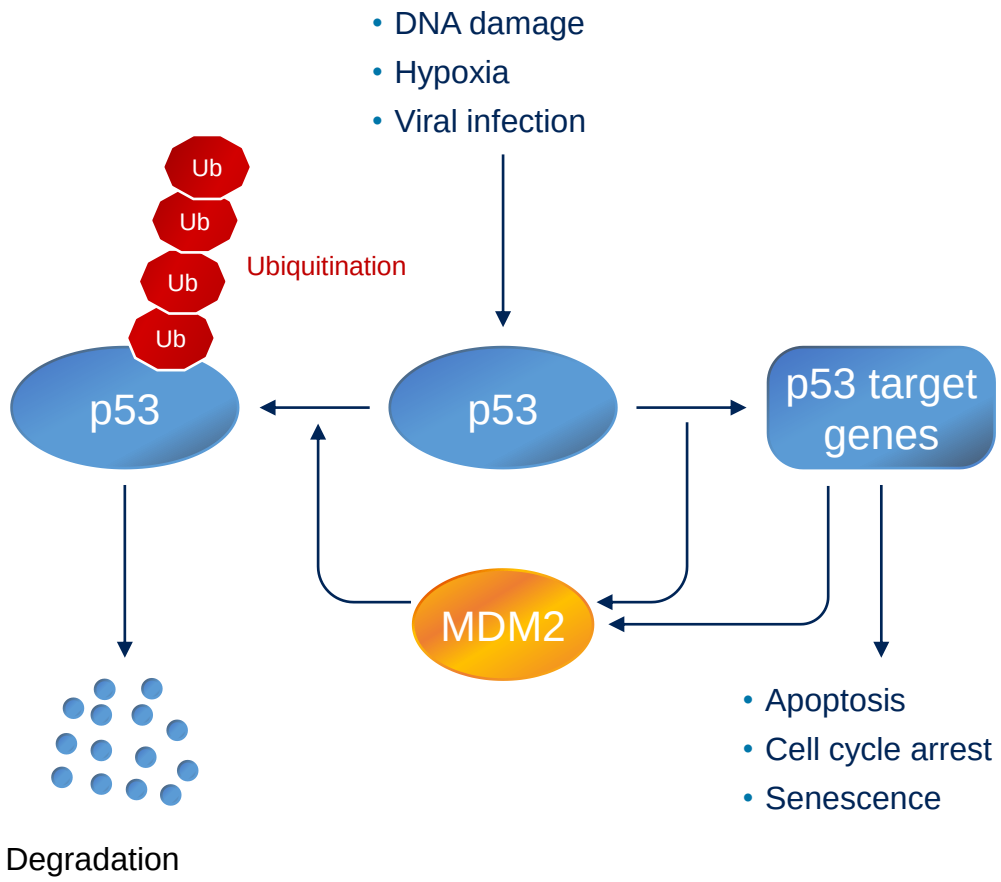
p53 Has a Pivotal Role in the Body's Defense Against Cancer

- *TP53* is a tumor suppressor gene[1–2]
- The p53 protein binds to DNA and has key roles in cell cycle arrest, DNA repair, and apoptosis[1–3]
  - Activated following cellular stress and DNA damage
  - Supports DNA repair before cellular replication
  - Induces apoptosis
- Protein levels are tightly controlled by MDM2[4]
- *TP53* mutation resulting in p53 inactivation is a key step in oncogenesis[3]



DNA, deoxyribonucleic acid; MDM2, mouse double minute 2 homolog.

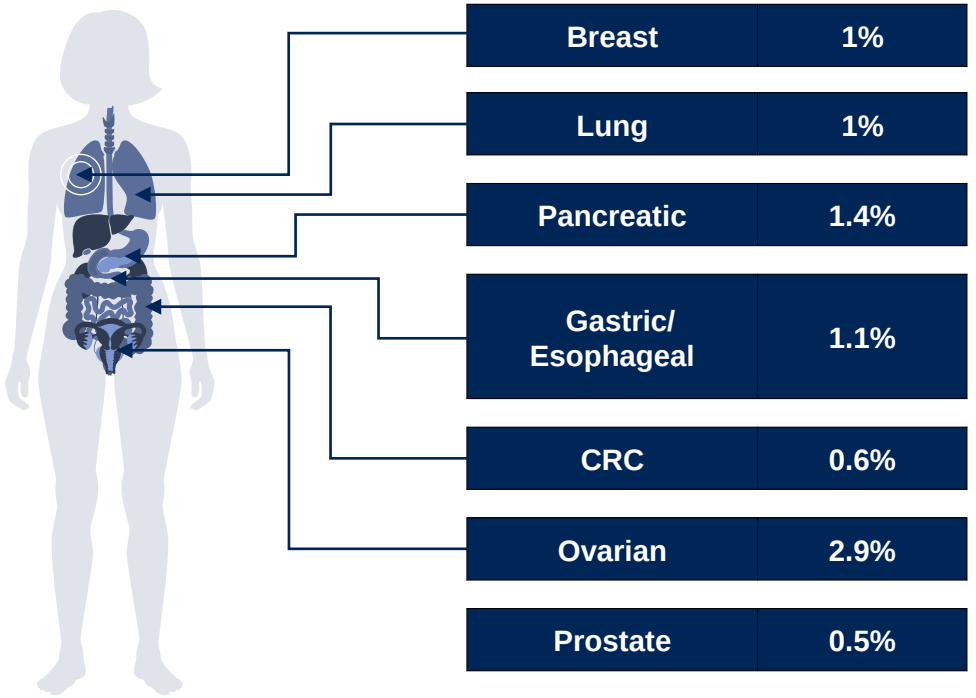
1. Chillemi G, et al. *Cold Spring Harb Perspect Med*. 2017;7:a028308. 2. Kastenhuber ER, et al. *Cell*. 2017;170:1062–1078. 3. Levine AJ. *Nat Rev Cancer*. 2020;20:471–480. 4. Levine AJ. *J Mol Cell Biol*. 2019;11:524–530.

TP53 Y220C Hotspot Mutation is Detected across Solid Tumor Types

- *TP53* mutations are the most common genomic events across all human cancers[1]
- Most *TP53* mutations occur in the central DNA-binding domain and ten of them are referred to as 'hot-spot' mutations, accounting for ~30% of the *TP53* mutations observed in human cancer[1–2]
- p53 Y220C is a key hot-spot *TP53* missense mutation that destabilizes p53[1,3]
- **p53 Y220C is present in ~1% of all solid tumors[4]**

Frequency of *TP53 Y220C* Across Common Solid Tumors

Foundation Medicine Tissue and Heme assay test results collected between 1/1/12 and 12/31/2020



The prevalence of TP53 Y220C across different diseases was analyzed by using the FoundationInsights® web-based software platform to query a pan-solid tumor cohort of ~367,651 US-based, consented-for-research patients in the FoundationCore® Database[4] that received FMI's Commercial Tissue or Heme assays between 1/1/12 and 12/31/2020

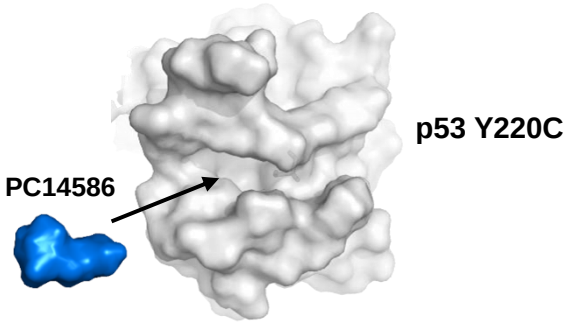
CRC, colorectal cancer; DNA, deoxyribonucleic acid.

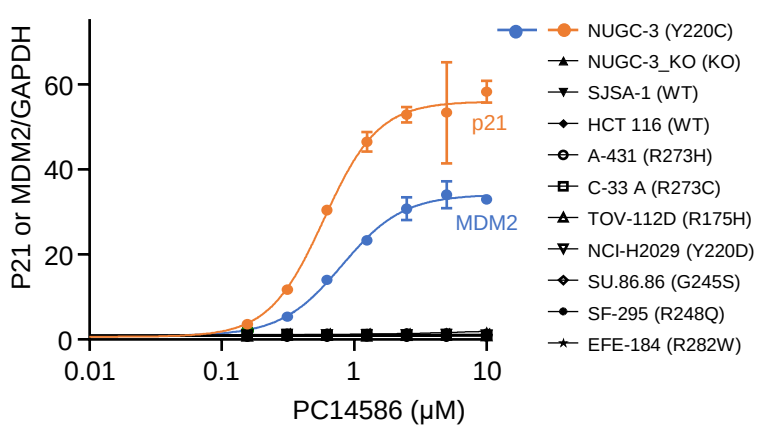
1. Baugh EH, et al. *Cell Death Differ*. 2018;25,154–160.
2. Roszkowska KA, et al. *Int J Mol Sci*. 2020;21:1334.
3. Bouaoun L, et al. *Hum Mutat*. 2016;37:865–876.
4. Westphalen CB, et al. *NPJ Precis Oncol*. 2021;20;5(1):69.

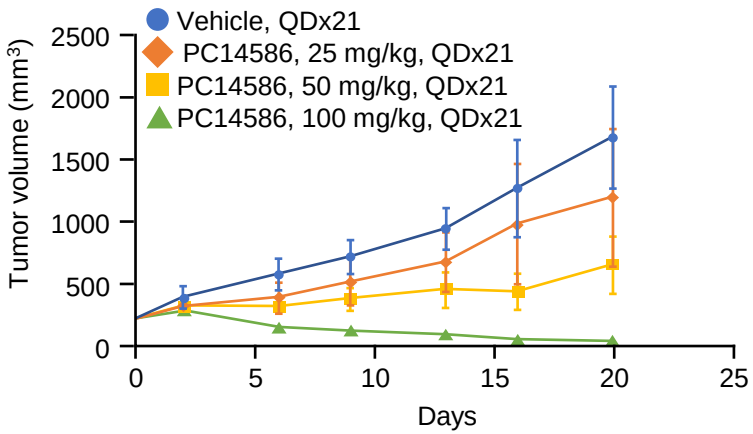
PC14586 is a p53 Y220C-Selective First-in-Class p53 Reactivator

- Orally available small molecule designed to selectively bind to the crevice contained in the p53 Y220C mutant protein[1]
- Stabilizes the p53 Y220C mutant protein in the wild-type p53 conformation, thereby restoring transcription and tumor-suppressor function[1]

Stabilizes p53 Y220C mutant in the WT p53 conformation → **p53 transcriptional activity restored** → **Tumor regression *in vivo***





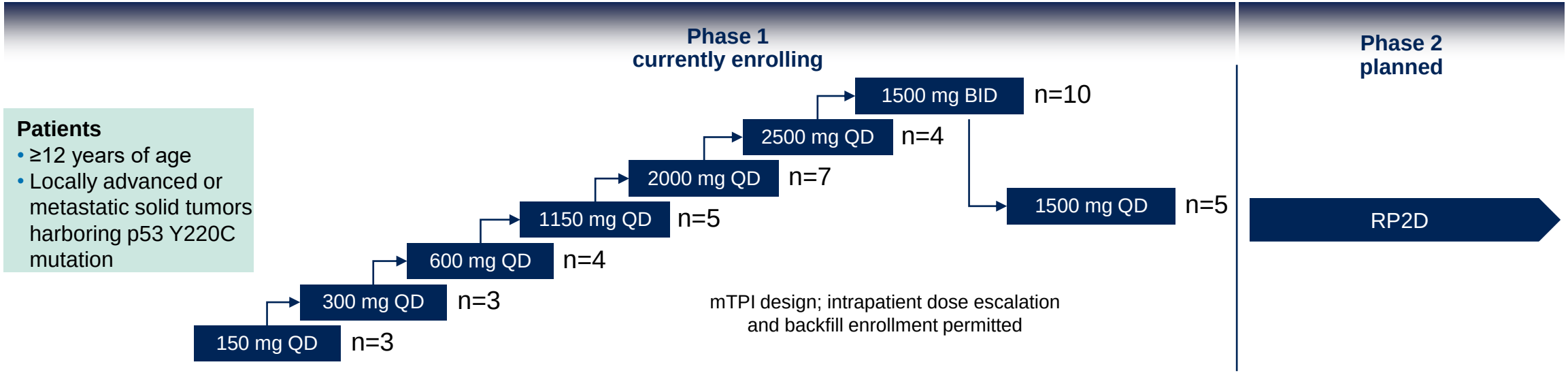


MDM2, mouse double minute 2 homolog; KO, knockout; WT, wild-type.

1. Dumble M, et al. *Cancer Res*. 2021;81(13_Suppl):Abstract LB006.

A Seamless Phase 1/2 Clinical Trial (PYNNACLE trial)

Patients With Advanced Solid Tumors Harboring p53 Y220C Mutation



Enrollment	41 patients as of May 10, 2022	100 patients (estimated)
Primary objective	• Determine MTD, select RP2D, and evaluate safety and tolerability	• ORR based on BICR
Secondary objectives	• PK • Preliminary efficacy	• ORR based on investigator assessment, TTR, DoR, DCR, PFS, OS, safety, quality of life
Exploratory objectives	• Biomarkers (ctDNA, CTC)	• Biomarkers

BICR, blinded independent central review; BID, twice daily; CTC, circulating tumor cells; ctDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; MTD, maximum tolerated dose; mTPI, modified toxicity probability interval design; ORR, objective response rate by RECIST (Response Evaluation Criteria in Solid Tumors) 1.1; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RP2D, recommended Phase 2 dose; TTR, time-to-response.

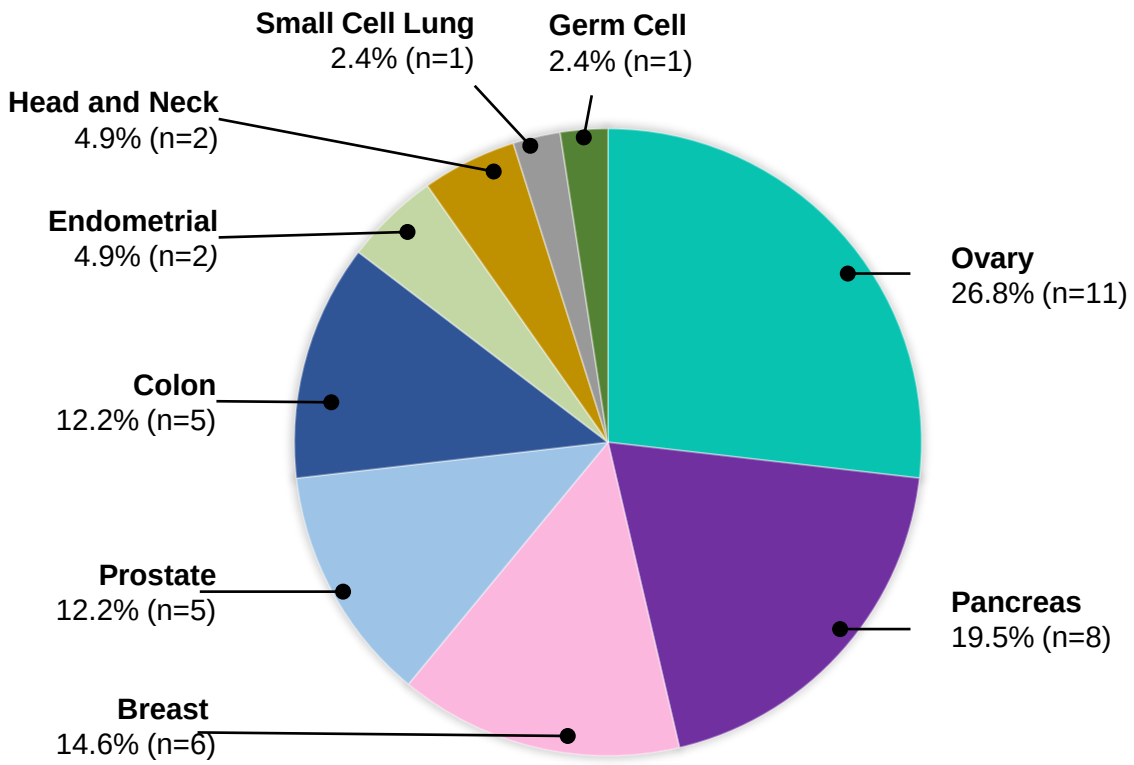
NCT study identifier: NCT04585750.

Patient Demographics and Disease Characteristics

	n=41
Age, years	
Median (min–max)	62 (32–84)
Sex, n (%)	
Female	25 (61)
Male	16 (39)
Race, n (%)	
White	31 (76)
Asian	3 (7)
Black or African American	3 (7)
Other	1 (2)
Not Reported/Unknown	3 (7)
ECOG status, n (%)	
0	18 (44)
1	23 (56)
Prior systemic therapies, n (%)*	
1–2	17 (42.5)
≥3	23 (57.5)
Median (min–max)	3 (1–9)
Germline *TP53 Y220C*, n (%)	
Negative	38 (93)
Positive	2 (5)
Pending	1 (2)

*One patient with unknown prior systemic therapies.

Cancer Type, n (%)



Data cut-off May 10, 2022

Treatment-Emergent Treatment-Related Adverse Events

All Patients (n=41)

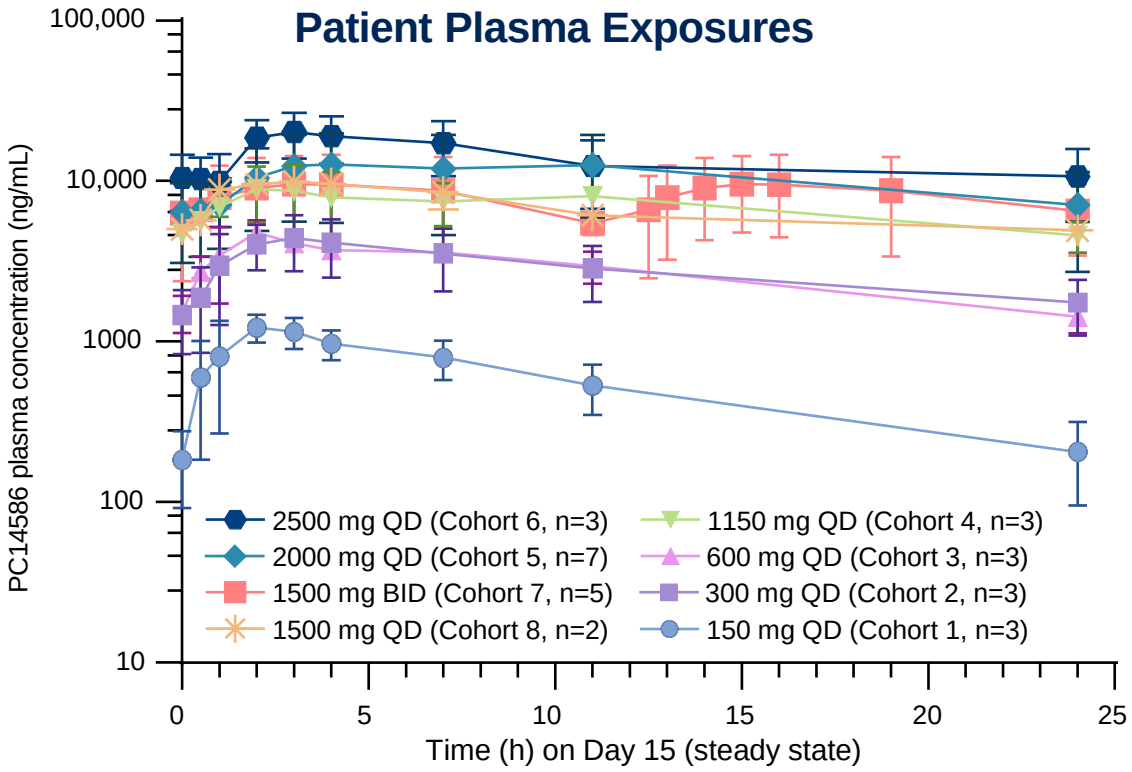
All Treatment-Emergent Treatment-Related AEs (Occurring in ≥3 Patients)		Max CTCAE			
Preferred Term	**Any Grade**	**1**	**2**	**3**	**4**
Any treatment-related AE, n (%)	**33 (80.5)**	**12 (29.3)**	**11 (26.8)**	**9* (22.0)**	**1* (2.4)**
Nausea	18 (43.9)	11 (26.8)	7 (17.1)		
Vomiting	11 (26.8)	6 (14.6)	5 (12.2)		
AST increased	9 (22.0)	7 (17.1)	1 (2.4)	1 (2.4)	
ALT increased	8 (19.5)	2 (4.9)	4 (9.8)	2 (4.9)	
Anemia	7 (17.1)	1 (2.4)	4 (9.8)	2 (4.9)	
Blood creatinine increased	7 (17.1)	3 (7.3)	4 (9.8)		
Fatigue	7 (17.1)	6 (14.6)	1 (2.4)		
Diarrhea	5 (12.2)	5 (12.2)			
Decreased appetite	3 (7.3)	2 (4.9)	1 (2.4)		
Headache	3 (7.3)	3 (7.3)			
Neutrophil count decreased	3 (7.3)	2 (4.9)		1 (2.4)	
Platelet count decreased	3 (7.3)	1 (2.4)	1 (2.4)	1 (2.4)	

- Most frequent treatment-related AEs (>15%) included nausea, vomiting, AST/ALT increase, anemia, blood creatinine increase, and fatigue
- Dose-limiting toxicities reported in 2 patients at 1500 mg BID
  - Grade 3 AST/ALT increase
  - Grade 3 acute kidney injury
- Maximum tolerated dose reached at 1500 mg BID
- RP2D not yet defined

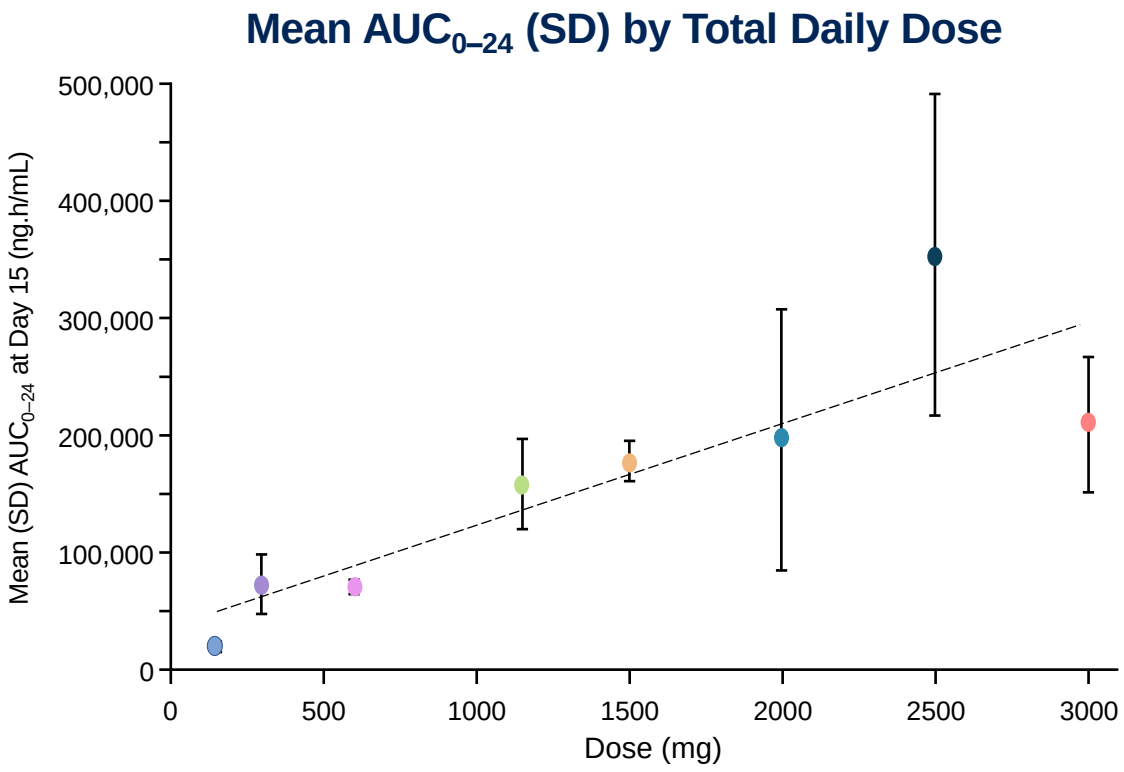
Data cut-off May 10, 2022

*Grade 3 and 4 treatment-related AEs not shown in the table (each in one patient) are Grade 3 acute kidney injury, hypokalemia, and pneumonitis, and Grade 4 immune thrombocytopenia.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; RP2D, recommended Phase 2 dose.

Dose-Proportional Increases in AUC at Steady State



Concentrations from 12–24 h imputed for 1500 mg BID dose group
Median half-life at Day 15 is 19 h



$AUC_{0–12}$ was multiplied by 2 to calculate $AUC_{0–24}$
for 1500 mg BID dose group (3000 mg daily dose)

Data are preliminary with 29 out of 41 patients having Day 15 samples at time of data cut-off. Dose-proportional increases in C_{max} were also observed (not shown).
AUC, area under the curve; BID, twice daily; C_{max}, maximum serum concentration; QD, once daily; SD, standard deviation.

Data cut-off April 26, 2022

Objective Response Rate Per RECIST 1.1

Based on Investigator Assessment

	Dose Cohorts		All
	150 mg QD–600 mg QD	1150 mg QD–1500 mg BID	
Enrolled, n	10	31	41
Patients with measurable disease at baseline, n	8	28	36
Eligible for response evaluation*, n	**8**	**25**	**33**
ORR‡, n (%)	**0 (0)**	**8 (32.0)**	**8 (24.2)**
PR	0	6	6
uPR	0	2	2
SD§	4	11	15
PD	4	3	7
Not evaluable*	0	3	3

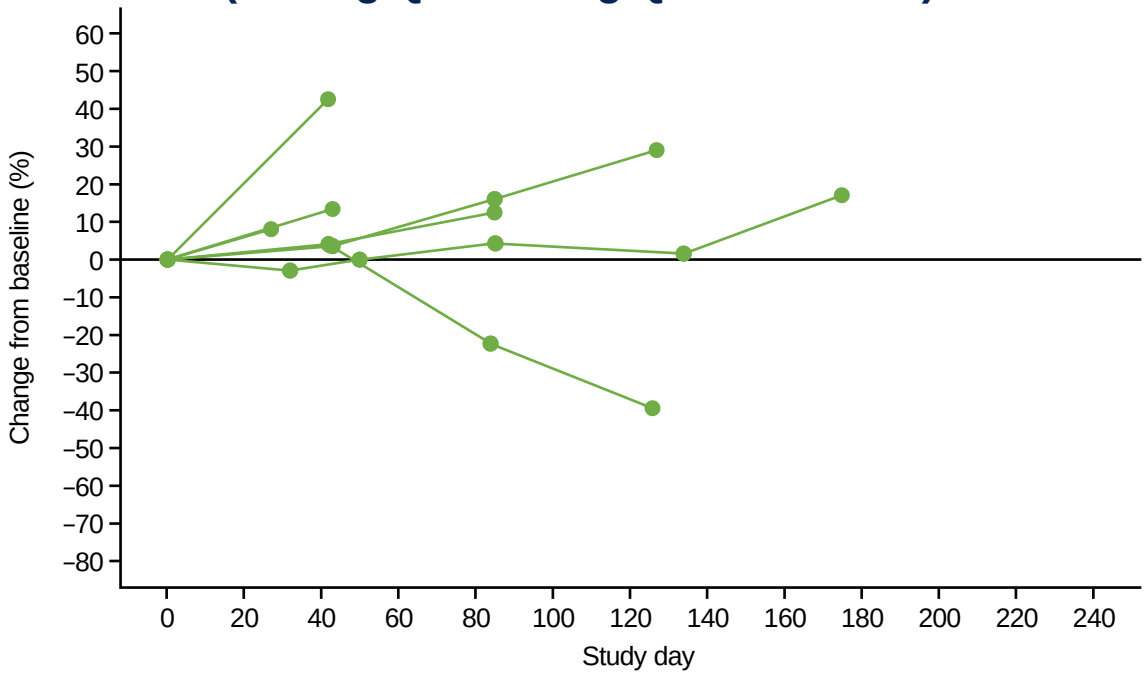
*Patients without a post-baseline assessment are either excluded from “eligible for response evaluation’’ if ongoing, or considered “not evaluable” if discontinued;
‡ORR = PR + uPR; §Includes three initially unconfirmed PR that progressed on the next tumor assessment.

BID, twice daily; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; uPR, unconfirmed PR pending confirmation.

Data cut-off May 10, 2022

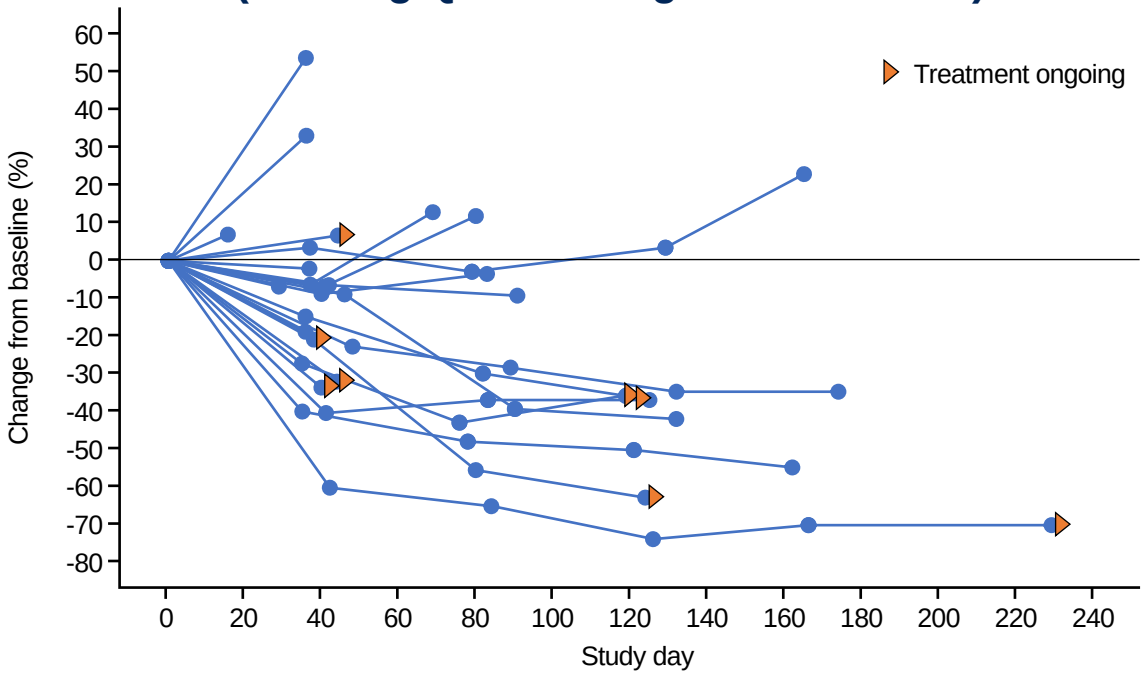
Target Lesion Reduction in Low vs High Dose Cohorts

% Change From Baseline in Tumor Target Lesion (150 mg QD–600 mg QD dose Level)



Dose Cohorts 1 through 3
(150 mg QD to 600 mg QD)

% Change From Baseline in Tumor Target Lesion (1150 mg QD–1500 mg BID dose level)

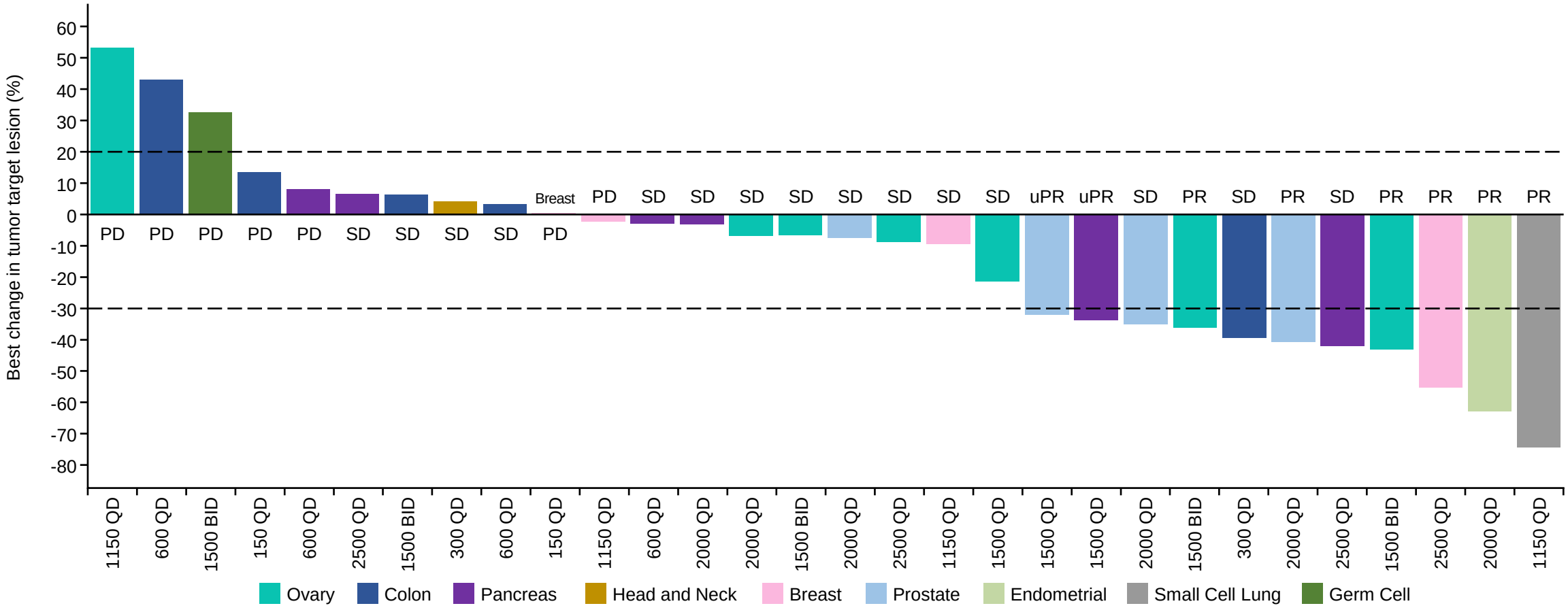


Dose Cohorts 4 through 8
(1150 mg QD to 1500 mg BID)

Patients censored at the time of progression.
BID, twice daily; QD, once daily.

Data cut-off May 10, 2022

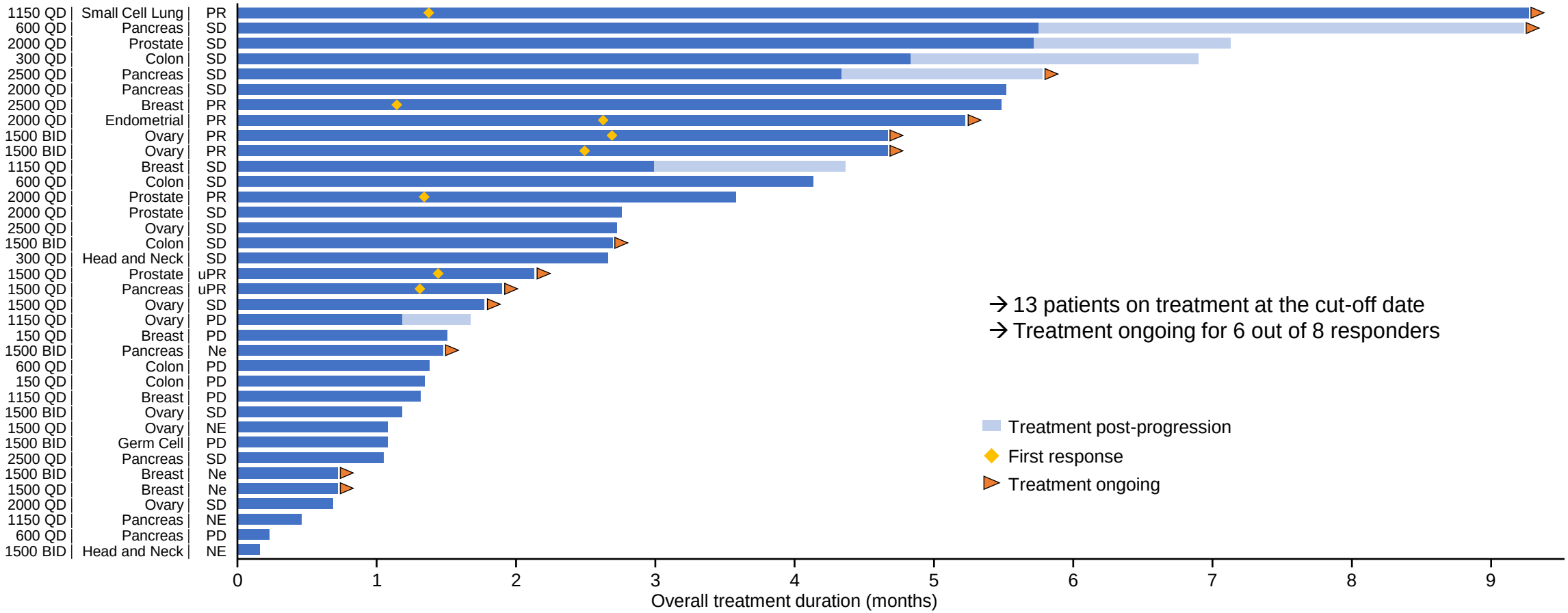
Target Lesion Reduction Across Tumor Types



Includes patients with measurable disease and one post-baseline assessment. All doses are in mg. BID, twice daily; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed PR pending confirmation.

Data cut-off May 10, 2022

Duration of PC14586 Therapy

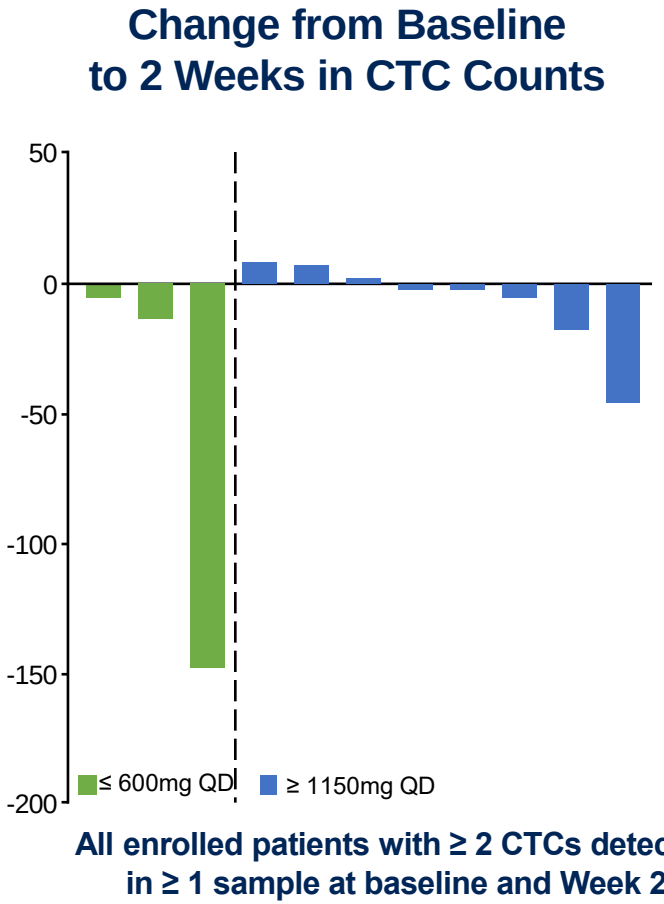


Includes all patients with measurable disease at baseline (n=36). All doses are in mg.

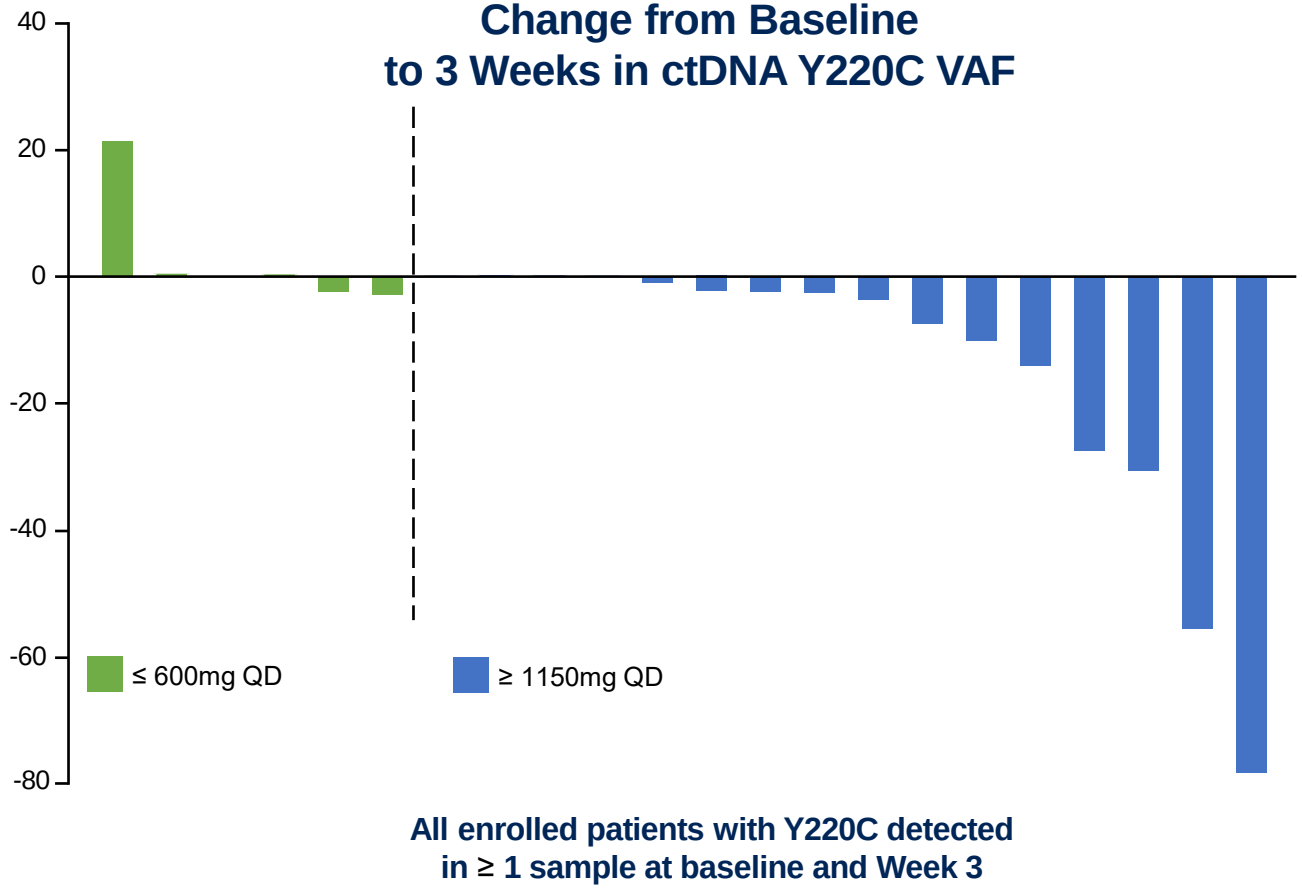
Data cut-off May 10, 2022

BID, twice daily; NE: not evaluable; Ne, not eligible for response assessment; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed PR pending confirmation.

CTC & ctDNA Decreases May Be Early Biomarkers of Anti-Tumor Activity



All enrolled patients with ≥ 2 CTCs detected in ≥ 1 sample at baseline and Week 2



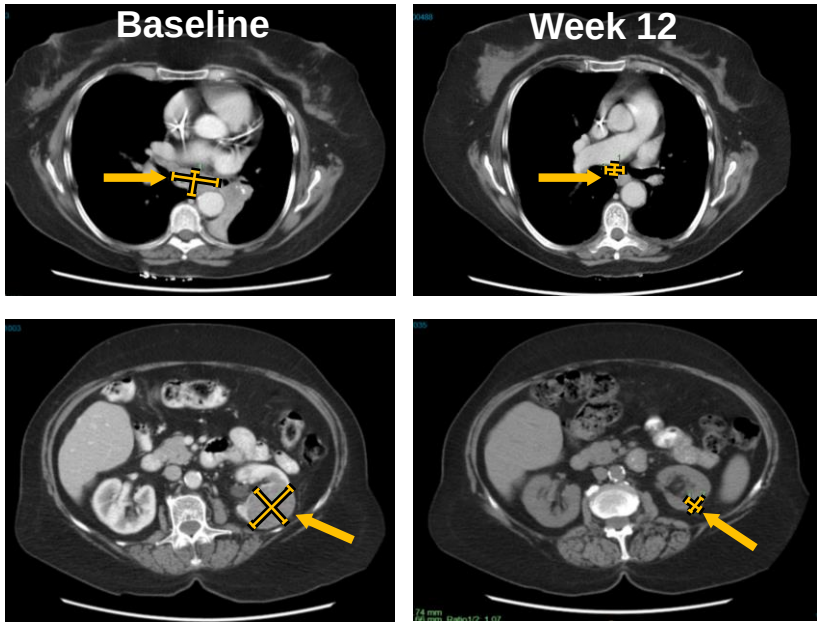
All enrolled patients with Y220C detected in ≥ 1 sample at baseline and Week 3

CTC, circulating tumor cells; ctDNA, circulating DNA, VAF: Variant Allelic Frequency

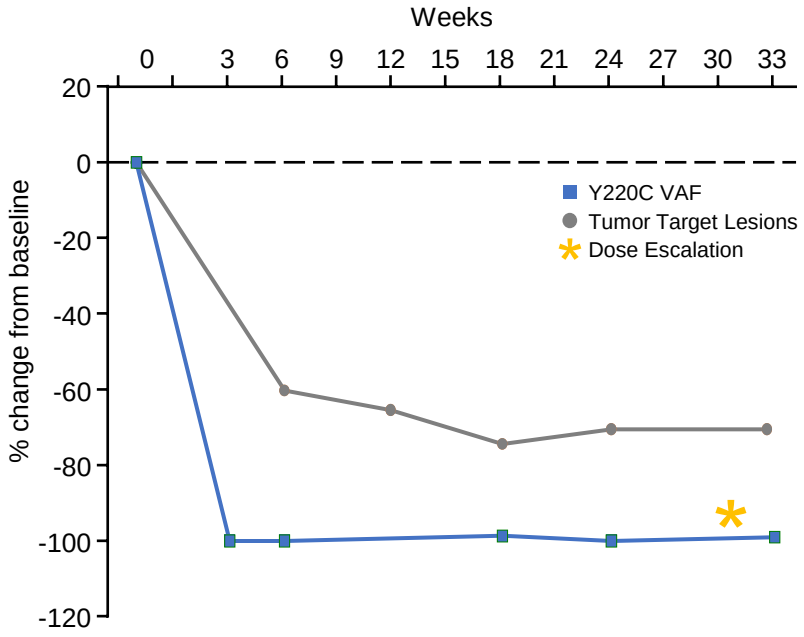
Data cut-off May 10, 2022

SCLC Patient With Rapid and Sustained Partial Response

- 71-year-old woman with ES-SCLC
- Progressed after 2 prior lines of therapy with worsening dyspnea and complete occlusion of the left bronchus with atelectasis
  - Etoposide, carboplatin and atezolizumab (10 months)
  - Topotecan (4 months)
- Prior radiotherapy of brain metastasis
- *TP53 Y220C* detected by NGS
- PC14586 1150mg QD was started
  - PR after 6 weeks with relief of respiratory symptoms
  - Increased to 2000mg QD at week 30
- Well tolerated with transient treatment related Grade 3 neutropenia
- Treatment ongoing for 9+ months



60% reduction in target lesions at Week 6 and at 70% at Week 12



Correlation between radiographic tumor shrinkage and Y220C ctDNA decrease

AE, adverse event; ctDNA, circulating tumor DNA; ES, extensive stage; NGS, next-generation sequencing; PR, partial response; QD, once daily; SCLC, small cell lung carcinoma; VAF, variant allelic frequency.
Images courtesy of Dr Melissa Johnson, Sarah Cannon Research Institute.

Conclusions

- PC14586 has an acceptable safety profile, with MTD reached
- PC14586 exposure is generally dose proportional over a wide dose range and supports once daily dosing
- Preliminary efficacy in patients across solid tumor types harboring *TP53 Y220C* mutation was demonstrated
- Enrollment at dose(s) below the MTD to support RP2D determination is ongoing

Acknowledgments

We would like to thank:

- All the patients, their families and caregivers who have participated, and continue to participate in this clinical trial
- Investigators and research staff
- MedPace, Resolution Biosciences, Foundation Medicine, and Rarecyte

US clinical trial sites

- Dana Farber Cancer Institute, Boston, MA
- NEXT Oncology, Austin, TX
- Massachusetts General Hospital, Boston, MA
- Memorial Sloan Kettering Cancer Center, New York, NY
- Seattle Cancer Care Alliance, Seattle, WA
- USC Norris Cancer Center, Los Angeles, CA
- OHSU Knight Cancer Institute, Portland, OR
- NEXT Oncology, San Antonio, TX
- MD Anderson Cancer Center, Houston, TX
- Sarah Cannon Research Institute, Nashville, TN
- UC San Francisco, San Francisco, CA
- Hoag Cancer Institute, Newport Beach, CA

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