Natural history and prognostic value of the *TP53* Y220C mutation in advanced solid tumors: A real-world study

Marc Fellous[1], *Catherine Green*[1], *Patricia Prince*[2], *John Shen*[2], *Cheryl Cho-Phan*[3], *Spencer Langerman*[3], *Gerald Li*[4], *Ryon Graf*[4], *Ecaterina E Dumbrava*[5], *Alison M Schram*[6]

[1]PMV Pharmaceuticals, Inc., Princeton, NJ, USA; [2]Aetion, New York City, NY, USA; [3]Flatiron Health, New York City, NY, USA; [4]Foundation Medicine, Inc., Boston, MA, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Memorial Sloan Kettering Cancer Center, New York City, NY, USA

BACKGROUND

- *TP53* mutations, the most common genomic alterations in cancer, are associated with poor prognosis across many tumor types[1,2]
- The *TP53* Y220C mutation occurs in ~1% of solid tumors and more frequently in ovarian, pancreatic, gastric, lung, and breast tumors[2,3]
- This mutation creates a pocket on the surface of the p53 protein, destabilizing the protein structure and causing loss of tumor suppressor function[2,3]
- The role of *TP53* mutations in increasing cancer risk and influencing prognosis and clinical outcomes across various solid tumor types is well established;[4,5] the impact of the *TP53* Y220C mutation on survival in patients with solid tumors has not been previously assessed
- This real-world study evaluates the natural history of locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation and the prognostic significance of *TP53* Y220C
  - Here we focus on the endpoints relative to rwOS

OBJECTIVES

- ***Primary***
  - Describe demographic, clinical, and tumor (including genomic) characteristics, as well as the treatment journey, of patients with locally advanced or metastatic *TP53* Y220C-mutated solid tumors
- ***Secondary***
  - Assess rwOS in patients with locally advanced or metastatic *TP53* Y220C-mutated solid tumors
- ***Exploratory***
  - Compare rwOS of patients with *TP53* Y220C-mutated solid tumors vs patients with solid tumors that do not have a *TP53* Y220C mutation (i.e., with other *TP53* mutations or *TP53* wild-type) in patients with solid tumors with no *KRAS* single nucleotide variant (SNV)

METHODS

- Patients with locally advanced or metastatic solid tumors with a *TP53* Y220C mutation were selected (January 1, 2011–September 30, 2023) from the US-based deidentified Flatiron Health-Foundation Medicine Clinicogenomic Database (FH-FMI CGDB)[6,7]
  - Clinical data from the Flatiron Health Research Database[8] are linked to genomic data, derived from FMI's comprehensive genomic profiling tests (FoundationOne®CDx, FoundationOne®), in the FH-FMI CGDB by deterministic matching, providing a deidentified dataset[9–11]
- The study design for the primary, secondary, and exploratory objectives are represented in **Figure 1**

Inclusion criteria for all objectives
- Locally advanced or metastatic disease diagnosis (used as the index date)
- Age ≥18 years
- Tumor tissue tested for *TP53* Y220C and *KRAS* SNV mutations with available results

Exclusion criteria

Primary objective:
- Participation in a clinical trial (assessed any time prior to the index date); also served to exclude any patients who may have received rezatapopt through the PYNNACLE Phase 1/2 trial
- Presence of more than one primary cancer (assessed at any time prior to the index date)
- Death record prior to the index month (assessed at any time prior to the index month)[a]

Exploratory objective:
- Patients with tumors harboring any *KRAS* SNV mutations
- Death record prior to the index month (assessed at any time prior to the index month)[a]

[a] Mortality data were derived from EMR and linked external sources. Patients with a recorded death date preceding their index month were excluded as part of data quality control.

Propensity score matching
- In the exploratory objective, only patients with tumors that do not have *KRAS* SNV (any SNV) mutations were included
- Propensity score matching was carried out between patients with *TP53* Y220C-mutated solid tumors and patients with tumors that do not have a *TP53* Y220C mutation (non-*TP53* Y220C)
  - Each patient with a Y220C-mutated tumor was matched to up to four patients with non-*TP53* Y220C-mutated tumors if possible
  - Non-*TP53* Y220C group: Included patients with tumors harboring other *TP53* mutations or wild-type *TP53*, depending on tumor type
  - Similar trends were seen across breast, endometrial, NSCLC, and prostate cancer subgroups
- Covariates considered in the propensity score matching are shown in **Table 1**

Figure 1. Study design

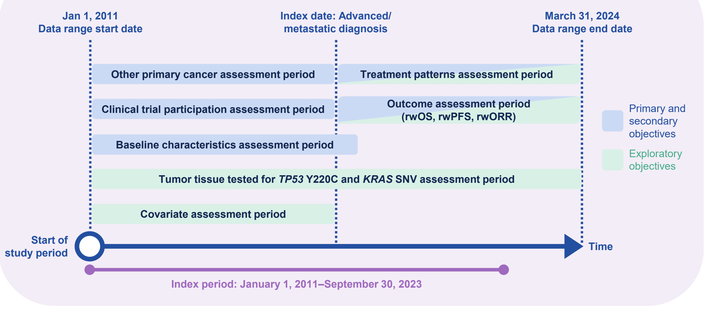


Table 1. Covariates considered for propensity score matching

Covariate	Applicable tumor types
Tumor type[a]	All
Histology[a]	Bladder cancer, breast cancer, endometrial cancer, gastric cancer, NSCLC, ovarian cancer, prostate cancer, renal cell carcinoma
Age	All
Index date (calendar date)	All
Sex	All
De novo locally advanced/ metastatic status	All
Smoking status	Bladder cancer, gastric cancer, head and neck cancer, NSCLC, pancreatic cancer, renal cell carcinoma, SCLC
ECOG performance status	All
Race/ethnicity	All
Socioeconomic status at index	All
***TP53* test timing (before or after index)**	All
HR/HER2 status	Breast cancer
***ALK* rearrangement status**	NSCLC
***EGFR* mutation status**	NSCLC

[a] Exact matching performed.

RESULTS

Primary and secondary objectives

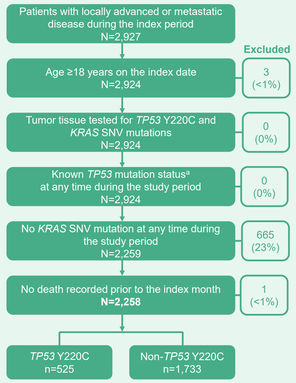
- As of the data cutoff (March 31, 2024), this study included 615 patients with *TP53* Y220C-mutated solid tumors who received at least first-line (n=366), second-line (n=202), or third-line (n=99) therapy
- Mean age was 64 years and 62.1% of the patient population were female (**Table 2**)
- Most (95.8%) were tested for the *TP53* Y220C mutation on or after advanced/metastatic diagnosis (median: 129 days after)
- *KRAS* SNV mutations were mainly observed in pancreatic (59.0%; 79/134) and colorectal cancers (20.1%; 27/134) representing 79.1% of all patients with tumors harboring *KRAS* SNV mutations in this study
  - Lowest frequency of *KRAS* SNV mutations were in patients with ovarian (1%), breast (0%), and prostate cancers (0%)
- In the Y220C cohort, median rwOS was 25.3 months overall
  - For patients with tumors with vs without *KRAS* SNV mutations: 16.0 vs 30.3 months
    - Of note, these populations were not matched and there were differences in tumor type distribution and other confounding factors, which may impact rwOS and explain the difference observed
- Patients with pancreatic cancer had the shortest rwOS (12.7 months) and patients with ovarian cancer had the longest rwOS (56.0 months)

Table 2. Primary and secondary objectives: Baseline characteristics

		KRAS SNV mutation	
	Overall, N=615	Yes, n=134	No, n=481
Mean age, years (SD)	64.43 (11.9)	64.25 (10.4)	64.48 (12.3)
Gender, n (%)			
Female/male	382 (62.1)/ 233 (37.9)	80 (59.7)/ 54 (40.3)	302 (62.8)/ 179 (37.2)
Tumor type[a], n (%)			
Breast	74 (12.0)	0 (0.0)	74 (15.4)
Colorectal	61 (9.9)	27 (20.1)	34 (7.1)
Gastric	37 (6.0)	3 (2.2)	34 (7.1)
NSCLC	125 (20.3)	17 (12.7)	108 (22.5)
Ovarian	100 (16.3)	1 (0.7)	99 (20.6)
Pancreatic	79 (12.8)	79 (59.0)	0 (0.0)
Other solid tumors	36 (5.9)	4 (3.0)	32 (6.7)
Stage at initial diagnosis, n (%)			
Stage 1	39 (6.3)	11 (8.2)	28 (5.8)
Stage 2	61 (9.9)	17 (12.7)	44 (9.1)
Stage 3	152 (24.7)	19 (14.2)	133 (27.7)
Stage 4	297 (48.3)	75 (56.0)	222 (46.2)
Unknown	66 (10.7)	12 (9.0)	54 (11.2)
Breast-specific receptor status, n (%)[b]			
HR+/HER2+	6 (1.0)	0 (0.0)	6 (1.2)
HR–/HER2+	5 (0.8)	0 (0.0)	5 (1.0)
HR+/HER2–	30 (4.9)	0 (0.0)	30 (6.2)
TNBC	24 (3.9)	0 (0.0)	24 (5.0)
NSCLC-specific biomarkers, n (%)			
***ALK* negative/positive**	94 (15.3)/1 (0.2)	14 (10.4)/0 (0.0)	80 (16.6)/1 (0.2)
***EGFR* negative/positive**	85 (13.8)/14 (2.3)	14 (10.4)/0 (0.0)	71 (14.8)/14 (2.9)
ECOG performance status, n (%)			
0	78 (12.7)	24 (17.9)	54 (11.2)
1	59 (9.6)	18 (13.4)	41 (8.5)
≥2	14 (2.3)	4 (3.0)	10 (2.1)
Unknown	464 (75.4)	88 (65.7)	376 (78.2)

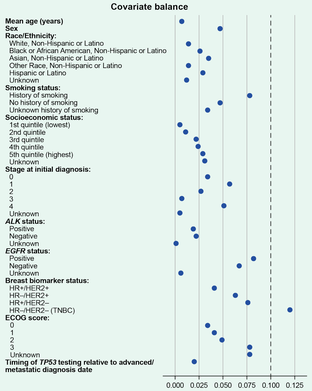
[a] Tumor types reported in ≥5% of patients in the overall population. Other cancer types include bladder, endometrial, head and neck, melanoma, prostate, renal cell carcinoma, and SCLC. [b]Percentage of breast cancer types in the overall breast cancer population: 8.1% HR+/HER2+; 6.8% HR–/HER2+; 40.5% HR+/HER2–; 32.4% TNBC.

Figure 2. Exploratory objective: Patient population



[a] *TP53* Y220C mutation, another non-*TP53* Y220C mutation, or *TP53* wild-type.

Figure 3. Exploratory objective: Baseline characteristics after propensity score matching

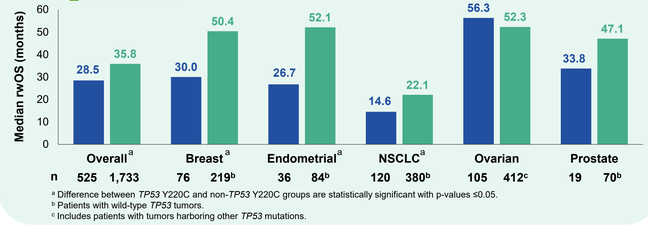


Exploratory objective

- In total, 525 patients had *TP53* Y220C-mutated tumors and 1,733 matched patients with non-*TP53* Y220C-mutated tumors were identified (**Figure 2**)
- Of the 1,733 patients with non-*TP53* Y220C-mutated tumors, 462 (26.7%) had other *TP53* alterations
  - Including 388 (22.4%) with ovarian cancer and 74 (4.3%) with other tumors (SCLC and carcinosarcoma/malignant mixed Müllerian tumor)
  - All remaining 1,271 (73.3%) patients had wild-type *TP53* tumors
- After propensity score matching, baseline characteristics were generally well balanced (absolute standardized difference in a baseline covariate between patients with and without *TP53* Y220C-mutated tumors below 0.10) across patients with *TP53* Y220C-mutated tumors and non-*TP53* Y220C-mutated tumors and across tumor types (**Figure 3**)
  - There was some residual imbalance (absolute standardized difference in a baseline covariate between patients with and without *TP53* Y220C-mutated tumors that reached above 0.10)
    - This suggested some remaining imbalance after matching, though not large enough to warrant other matching methods
- Most patients (>95%) were tested for the *TP53* Y220C mutation on or after advanced/metastatic diagnosis (median *TP53* Y220C: 164.5 days; non-*TP53* Y220C: 150.0 days)
- Median rwOS was shorter in patients with *TP53* Y220C-mutated tumors vs non-*TP53* Y220C-mutated tumors (28.5 vs 35.8 months; hazard ratio 1.14; 95% confidence interval: 1.01–1.29]) (**Figure 4**)
  - Similar trends were seen across breast, endometrial, NSCLC, and prostate cancer subgroups
- The estimated effect of the *TP53* Y220C mutation in the sensitivity analysis was consistent with the primary analysis, though not statistically significant, likely reflecting the association between testing time and survival (i.e., dependent left truncation) among patients with non-*TP53* Y220C-mutated tumors
  - Dependent left truncation was evaluated using conditional Kendall's tau test of quasi-independence (tranSurv package for R)[12]
- The majority of patients with non-*TP53* Y220C ovarian cancer (94.2%) had a different, non-*TP53* Y220C mutation likely inactivating p53; therefore, there was no difference in rwOS observed between the patients with *TP53* Y220C-mutated and non-*TP53* Y220C-mutated ovarian cancer
  - This was an expected observation, given that >96% of patients with HGSOC harbor *TP53* mutations[13]

Limitations
- The sample size was small for certain tumor types, limiting interpretability
- Mutation status (*TP53* Y220C and *KRAS*) was determined from genomic testing at any point during the study period
  - While best practices recommend avoiding inclusion criteria based on future events to prevent selection and immortal time bias, this approach was necessary given that ~50% of patients in the study were de novo metastatic at diagnosis and therefore would not have undergone genomic testing prior to their initial diagnosis
  - To address this, timing of testing was described, and a delayed entry sensitivity analysis for rwOS was conducted, consistent with similar studies[14]

Figure 4. Exploratory objective: rwOS across the tumor cohorts with and without the *TP53* Y220C mutation



[a] Difference between *TP53* Y220C and non-*TP53* Y220C groups are statistically significant with p-values ≤0.05.
[b] Patients with wild-type *TP53* tumors.
[c] Includes patients with tumors harboring other *TP53* mutations.

CONCLUSIONS

- In this real-world study, patients with *TP53* Y220C-mutated solid tumors had poor prognoses and reduced rwOS vs patients with mainly wild-type *TP53* solid tumors
- Such findings highlight a substantial unmet clinical need and contribute to the body of evidence on real-world clinical characteristics, and outcomes associated with *TP53* mutations
- Reactivating p53 offers an attractive therapeutic approach in patients with solid tumors harboring *TP53* mutations, addressing a high unmet medical need where targeted treatments are lacking

Abbreviations: *ALK*, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, estimated glomerular filtration rate; EMR, electronic medical records; HER2, human epidermal growth factor receptor 2; HGSOC, high-grade serous ovarian cancer; HR, hormone receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; PS, propensity-score; rwORR, real-world overall response rate; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; SCLC, small cell lung cancer; SD, standard deviation; SNV, single nucleotide variant; TNBC, triple negative breast cancer.

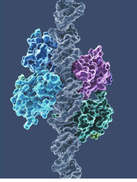
References: 1. Baugh EH, et al. *Cell Death Differ.* 2018;25:154–160; 2. Zhou S, et al. *Front Oncol.* 2023;13:1229696; 3. Puzio-Kuter A, et al. *Cancer Discov.* 2025;15:1159–1179; 4. Gu J, et al. *Mol Clin Oncol.* 2016;5:705–713; 5. Poeta ML, et al. *N Engl J Med.* 2007;357:2552–2561; 6. Estevez M, et al. *Cancers.* 2022;14:3063; 7. Zhang Q, et al. *Value Health.* 2024;27:S274; 8. Flatiron Health. Database Characterization Guide. https://flatiron.com/database-characterization (Accessed October 2025); 9. Singal G, et al. *JAMA.* 2019;321:1391–1399; 10. Milbury CA, et al. *PLoS One.* 2022;17:e0264138; 11. Frampton GM, et al. *Nat Biotechnol.* 2013;31:1023–1031; 12. Martin EC, Betensky RA. *J Am Stat Assoc.* 2005;100:484–492; 13. Backenroth D, et al. *Cancer Epidemiol Biomarkers Prev.* 2022;31:1195–1201; 14. Cole AJ, et al. *Sci Rep.* 2016;6:26191.

Acknowledgments: This study is sponsored by PMV Pharmaceuticals, Inc. Medical writing support was provided by Nucleus Global and funded by PMV Pharmaceuticals, Inc.

Disclosures (related to PMV Pharmaceuticals, Inc. only – for full disclosures please see the QR code): MF, CG: Employees (with stock options). PP, JS, CC-P, SL, GL, RG: None. EED: Received research funding/grant, attended advisory boards, and provided a speaker role. AMS: Provided an advisory role and received research funding.

Scan QR code to download the poster and view full author disclosures

Full author disclosures



Marc Fellous, Catherine Green
- Employee: PMV Pharmaceuticals, Inc. with stock options

Patricia Prince, John Shen
- Employee: Aetion, a Datavant Company, with stock options

Cheryl Cho-Phan, Spencer Langerman
- Employee: Flatiron Health, an independent member of the Roche group
- Stock ownership: Roche

Gerald Li, Ryon Graf
- Employee: Foundation Medicine, Inc. a wholly owned subsidiary of Roche
- Stock ownership: Roche

Ecaterina E Dumbrava
- Research or grant funding: Bayer HealthCare Pharmaceuticals Inc., Immunocore Ltd., Amgen, Aileron Therapeutics, Compugen Ltd., Gilead, BOLT Therapeutics, Aprea Therapeutics, Bellicum Pharmaceuticals, PMV Pharmaceuticals, Inc., Triumvira Immunologics, Seagen, Mereo BioPharma, Sanofi, Rain Oncology, Astex Therapeutics, Sotio, Poseida, Mersana Therapeutics, Genentech, Boehringer Ingelheim, Dragonfly Therapeutics, A2A Pharmaceuticals, Volastra, AstraZeneca, Fate Therapeutics, Pfizer, Jacobio, and ModeX Therapeutics
- Advisory board: BOLT Therapeutics, Mersana Therapeutics, Orum Therapeutics, Summit Therapeutics, Fate Therapeutics, PMV Pharmaceuticals, Inc.
- Speaker: PMV Pharmaceuticals, Inc. and BOLT Therapeutics
- Travel, accommodation, expenses: ASCO, LFSA Association, Rain Oncology, Banner MD Anderson Cancer Center, Triumvira Immunologics, KSMO, and Boehringer Ingelheim

Alison M Schram
- Advisory board: Blueprint Medicines, Mersana, Endeavor Biomedicines, Revolution Medicine, Day One Biopharmaceuticals, Transcode Therapeutics, and Relay Therapeutics
- Advisory role: for Merus, Pfizer, PMV Pharmaceuticals, Inc., Schrodinger, Repare Therapeutics, and Relay Therapeutics
- Research funding to institution: ArQule, AstraZeneca, BeiGene, Springworks, Black Diamond, Boehringer Ingelheim, Elevation Oncology, Kura Oncology, Eli Lilly, Merus, Northern Biologics, Pfizer, PMV Pharmaceuticals, Inc., Relay Therapeutics, Repare Therapeutics, Revolution Medicine, and Surface Oncology