Defining the Clinicogenomic Footprint of PPM1D in Therapy-Related Myeloid Neoplasms

[1] Division of Hematology & Oncology, Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA

Fidel Cai[1], Shining Yang[1], Vincent Merrill[1], Robert Collins[1], Stephen Chung[1], Yazan F. Madanat[1]

SOHO 2026 Annual Meeting

MDS - 1120

INTRODUCTION

- **tMN** are aggressive secondary malignancies after chemotherapy/radiation — worse outcomes than de novo disease.
- Driven by **clonal hematopoiesis (CH)**: genotoxic therapy selects for therapy-resistant mutant clones.
- Retained clones preferentially expand, seeding subsequent myeloid neoplasia.
- *PPM1D* encodes Wip1, a phosphatase attenuating the p53-mediated DNA-damage response.
- Truncating gain-of-function *PPM1D* mutations blunt p53 → clones evade apoptosis and survive therapy.
- Co-mutational partners and clonal trajectory of *PPM1D* in tMN remain incompletely defined.

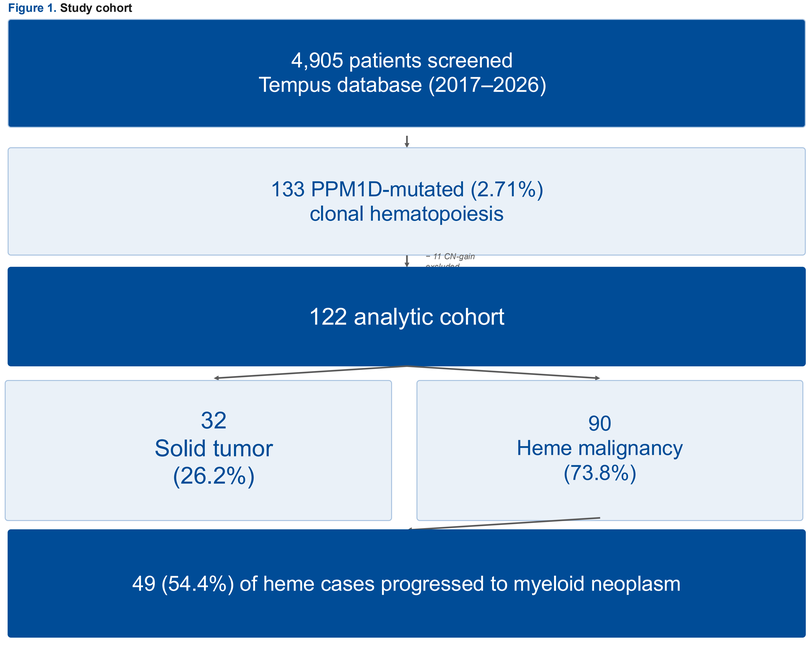
AIM

- Define the clinicogenomic significance of *PPM1D* in tMN.
- Characterize prevalence, antecedent solid-tumor associations, co-mutational landscape, and patterns of clonal evolution.
- Identify features distinguishing *PPM1D*-mutated disease as a biologically distinct subset.

METHOD

- Retrospective analysis of **4,905 patients** (Tempus genomic database, UTSW, 2017–2026).
- Characterized *PPM1D* prevalence, antecedent solid-tumor associations, and co-mutational landscape.
- 133 (2.71%) *PPM1D*-mutated as CH; 11 CN-gain excluded → **122 analytic cohort**.
- Stratified by antecedent tumor, chemotherapy exposure, and *PPM1D* mutation number.
- Mann–Whitney U and Fisher's exact tests (Python, SciPy).

Figure 1. Study cohort



RESULTS

Table 1. Cohort characteristics

Characteristic	Value
Patients screened, n	4,905
PPM1D-mutated (CH), n (%)	133 (2.71)
Analytic cohort, n	122
Solid tumor, n (%)	32 (26.2)
Hematologic malignancy, n (%)	90 (73.8)
Progressed to myeloid neoplasm, n (%)	49 (54.4)
Frameshift / stop-gain variants, %	52.8 / 43.1
Cytotoxic therapy exposure, %	60.7

Table 2. Therapy exposure by antecedent tumor

Exposure	Solid (n=32)	Heme (n=90)
Platinum-based, %	18.8	3.3
Alkylating agent, %	9.4	20.0

Table 3. Significant genomic comparisons

Comparison	Group 1	Group 2	p
Co-occurring mutations, median [95% CI] (chemo-exposed vs unexposed)	3.0 [2–4]	1.0 [0–2]	0.008
≥1 additional somatic mutation, % [95% CI] (chemo-exposed vs unexposed)	83.7 [71.0–91.5]	61.0 [45.7–74.3]	0.018
VAF, median % [95% CI] (≥2 vs single PPM1D mutation)	4.6 [3.7–10.1]	2.9 [2.3–3.8]	0.004

Most frequently co-mutated genes

TP53 · DNMT3A · SF3B1 · RUNX1

Figure 2. Co-mutation burden by chemo exposure

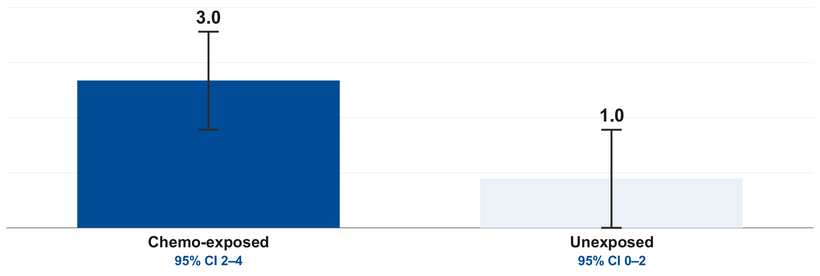


Figure 3. Any additional somatic mutation

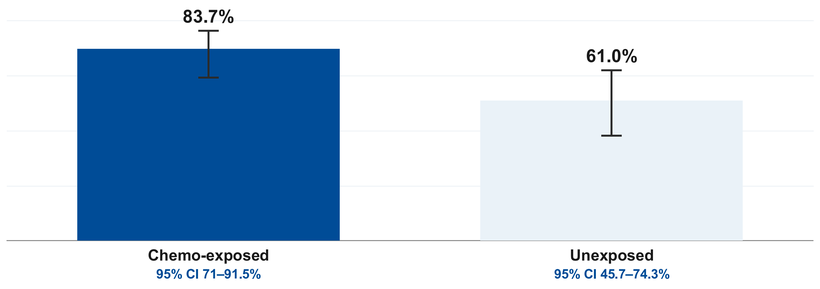


Figure 4. Clonal evolution — VAF

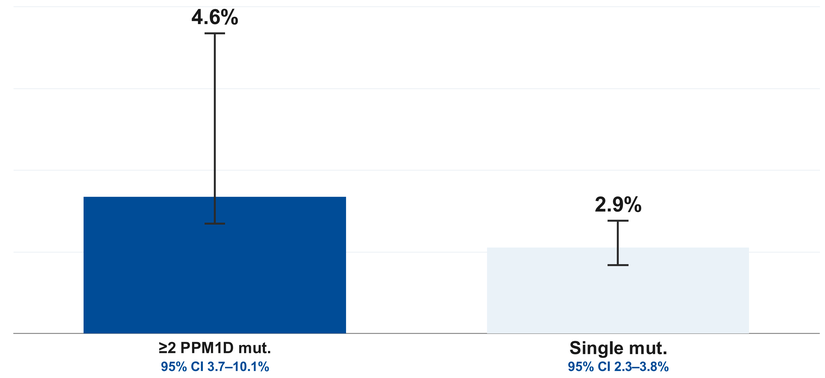
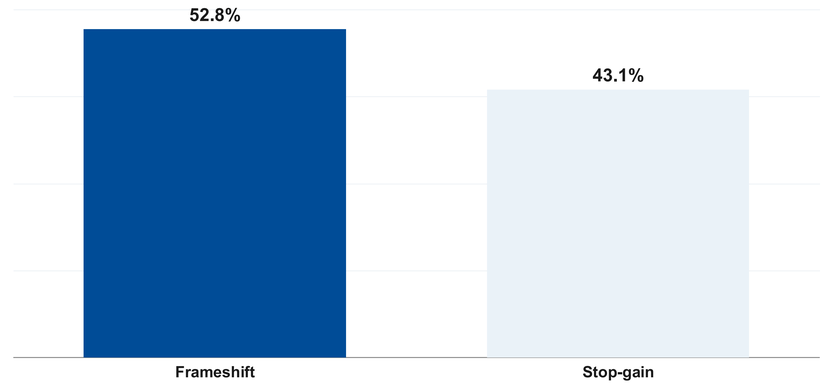


Figure 5. PPM1D variant spectrum



CONCLUSIONS

PPM1D-mutated disease is a rare but biologically distinct subset of tMN, enriched for cooperative genomic alterations with features suggestive of therapy-driven clonal evolution. Chemotherapy-exposed carriers showed a higher co-mutation burden and more often harbored additional mutations, while multiple *PPM1D* mutations tracked with higher VAF — consistent with progressive clonal expansion. As the **largest single-institution real-world genomic cohort** focused on *PPM1D* in tMN, pairing *PPM1D* detection with co-mutational profiling may refine risk stratification and surveillance.

ACKNOWLEDGEMENTS

The authors thank the Harold C. Simmons Comprehensive Cancer Center and the UT Southwestern genomics program.

CONTACT INFORMATION

Fidel Cai · UT Southwestern Medical Center, Dallas, TX

fidel.cai@utsouthwestern.edu

REFERENCES

1. Hsu JI, et al. Cell Stem Cell. 2018.
2. Badar T, et al. Blood Adv. 2026.
3. Fandrei D, et al. Clin Cancer Res. 2025.