Multi-Hit TET2 Inactivation Identifies a High-Risk Subgroup Assigned to Favorable or Intermediate Categories by the HARMONY Framework in NPM1-Mutated AML

Paloma Resende, MD[1]*, Andre Meireles, MD[1], Wysterlanyo Barros, MD[1], Andreza Feitosa Ribeiro, MD, PhD[1], Leonardo Arcuri, MD, PhD[1], Nelson Hamerschlak, MD, PhD[1], Fabio Pires, MD, PhD[1]

[1] *Hematology and Hemotherapy, Einstein Hospital Israelita, São Paulo, Brazil | *paloma.resende@einstein.br | Poster #AML-1483*

BACKGROUND

• NPM1-mutated AML is molecularly heterogeneous and co-occurring mutations as FLT3-ITD, DNMT3A, IDH1/2, and TET2 profoundly modify prognosis.

• The HARMONY classification integrates co-mutation patterns into a validated three-tier framework: Favorable, Intermediate, and Adverse.

• HARMONY does not account for TET2 allelic burden. The prognostic impact of multi-hit TET2 inactivation (≥2 somatic TET2 variants by NGS) beyond the current algorithm is unknown.

OBJECTIVE

To evaluate whether multi-hit TET2 inactivation refines prognostic discrimination beyond the HARMONY classification in NPM1-mutated AML.

METHODS

Training (n=674): Tazi et al., Nat Commun 2022 (UK-NCRI); served as external validation in the original HARMONY study.

Validation (n=307): cBioPortal pooled (Beat AML n=192, TCGA-LAML n=54, IWG 2022 n=61); FLT3-ITD available.

Two refinements proposed:

- Adverse-TET2mh (≥2 somatic TET2 variants by NGS)
- Favorable-RAS (NRAS/PTPN11 in HARMONY-Favorable)

Statistics: C-index, bootstrap (n=1,000), IDI at 24 months, multivariable Cox, subgroup analysis within HARMONY-Adverse.

KEY METRICS

Metric	Train	Valid
C-index HARMONY	0.568	0.557
C-index Refined	0.587	0.584
ΔC-index (bootstrap)	—	+0.027*
IDI (t=24m)	—	+0.010†
TET2mh under-assigned	80.8%	81.0%
HR TET2mh (Cox MV)	1.47‡	—
HR TET2mh in Adverse	2.20§	—

p=0.019 †p=0.033 ‡[1.00–2.16], p=0.050 §[1.16–4.16], p=0.016

RESULTS

TET2 alterations showed a stepwise, allelic burden-dependent prognostic gradient across both cohorts (Figure 1). Median OS: 38.4, 25.5, and 9.2 months for wild-type (n=522), monoallelic (n=79), and multi-hit (n=73) in training (p=0.0003); 19.6, 14.0, and 5.5 months in validation (p=0.017).

80.8%
Training: TET2mh assigned Fav/Int by HARMONY

9.2 mo
Multi-hit median OS (training cohort)

81.0%
Validation: TET2mh assigned Fav/Int by HARMONY

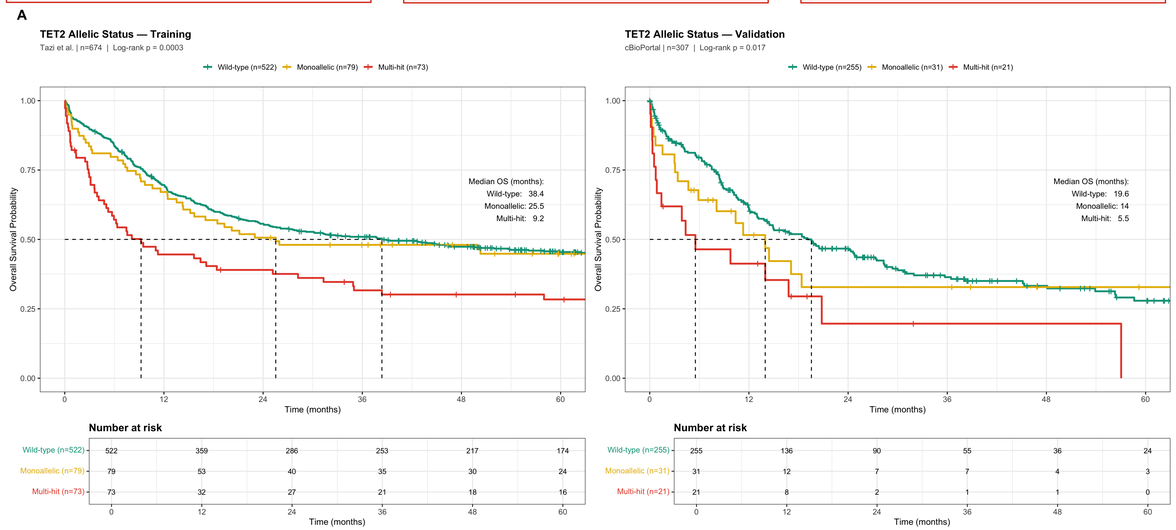

Figure 1. Overall survival by TET2 allelic status. Training (left): median OS 38.4 vs 25.5 vs 9.2 months; p=0.0003. Validation (right): 19.6 vs 14.0 vs 5.5 months; p=0.017.

CONCLUSIONS

- Multi-hit TET2 inactivation identifies a high-risk subgroup consistently assigned to lower-risk categories by HARMONY, with outcomes resembling the Adverse group across two independent cohorts.
- This refinement is detectable using routine NGS panels and warrants prospective validation with VAF-based allelic characterization.

ONGOING WORK

- Web-based prognostic calculator integrating multi-hit TET2 status, WT1, NRAS, KRAS, PTPN11 and other clinical variables into the HARMONY framework – under external validation. ASH 2026 abstract submitted.
- Parallel analysis: evaluating whether TET2 multi-hit patients are significantly older and the independent contribution of age to adverse outcomes beyond allelic burden. ASH 2026 abstract submitted.

• Refined model: C-index 0.584 vs 0.557; ΔC-index +0.027 [95% CI 0.002–0.062], p=0.019; IDI +0.010 [95% CI −0.001 to 0.021], p=0.033 (Figure 2).

• Multivariable Cox: HR 1.47 [1.00–2.16], p=0.050 (marginal). Within HARMONY-Adverse: HR 2.20 [1.16–4.16], p=0.016.

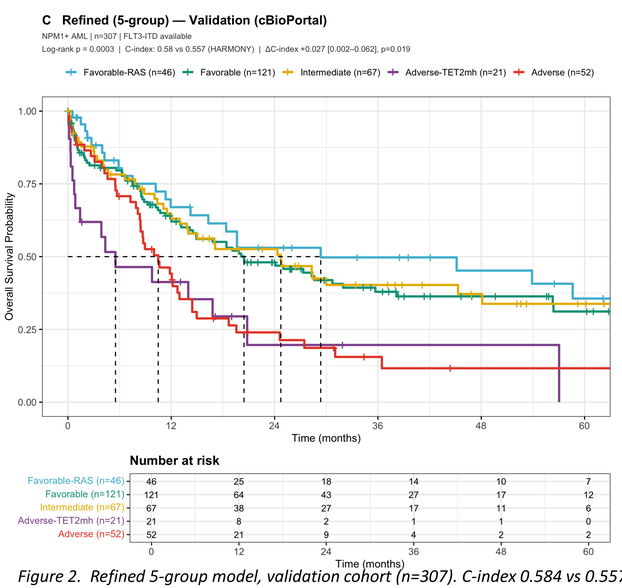

Figure 2. Refined 5-group model, validation cohort (n=307). C-index 0.584 vs 0.557 (HARMONY).

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CONTACT INFORMATION

paloma.resende@einstein.br
+ 55 24992077997