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DEBATES AND DIDACTICS in Hematology and Oncology

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Should NPM1 FLT3-ITD Co-Mutated AML Be Transplanted in First Remission? Yes! (in most cases)

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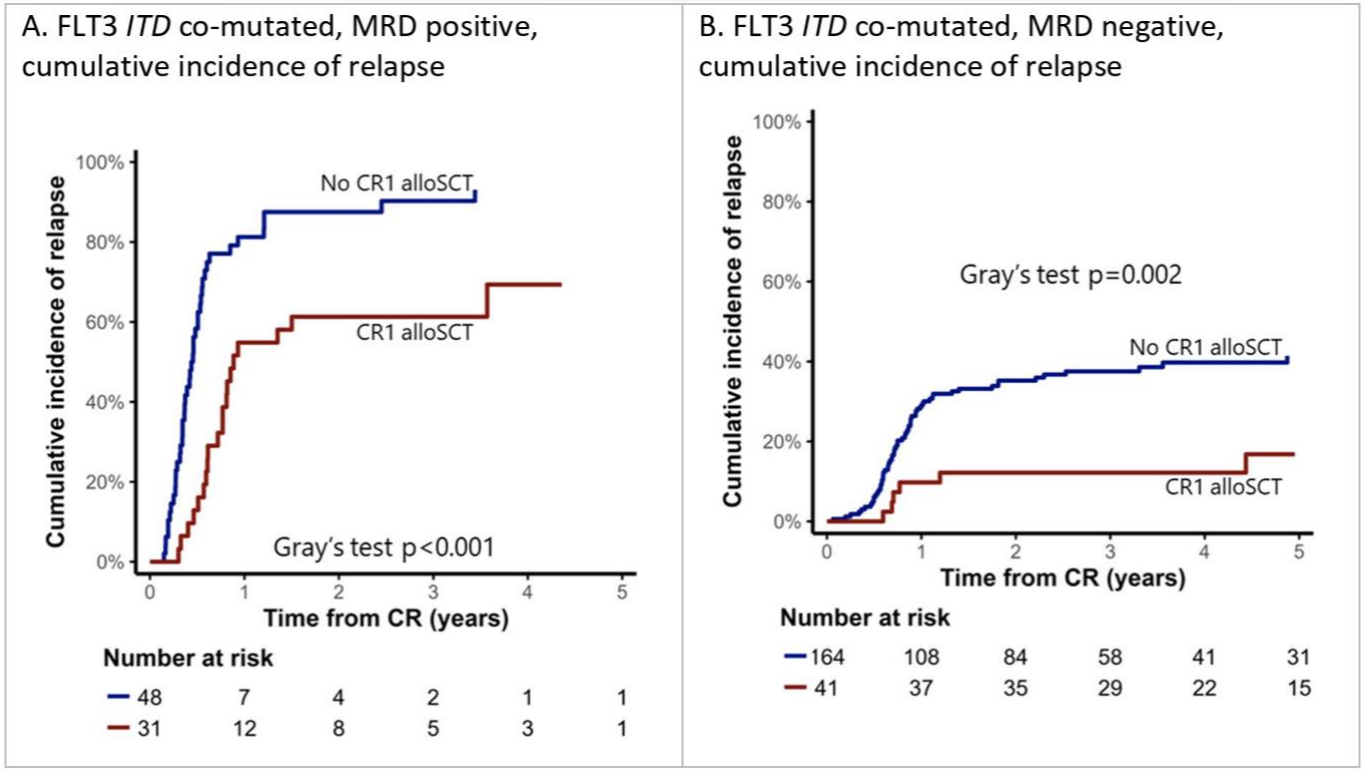
Rapidly evolving treatment landscape

- Nucleophosmin 1 (NPM1) mutations occur in ~30% of cases of acute myeloid leukemia (AML)
- FLT3-ITD co-mutation is common – 39% in NCRI AML17 and AML19 trials
- Guidance regarding role of allogeneic stem cell transplantation (alloHCT) in CR1 in this patient population has significantly changed over the past few years
  - In 2020, EBMT Position Statement noted that alloHCT in CR1 is “controversial” in patients with FLT3-ITD mutation of low allelic ratio <0.5 with concomitant NPM1 mutation and who achieve MRD-negativity
  - AlloHCT in CR1 was recommended for all other patients with AML with FLT3-ITD mutations

Othman et al. *Blood* (2024) 144 (7): 714–728.
Bazarbachi et al. *Haematologica* (2020) 105(6):1507–1516.

AlloHCT reduced cumulative incidence of relapse in both MRD positive and MRD negative patients

- Median age 52 years; only 16% >60 years
- Conducted prior to approval of midostaurin; did not include FLT3 MRD testing



Othman et al. *Blood* (2024) 143 (19): 1931–1936.

FLT3-ITD NGS-MRD refines risk stratification in NPM1 and FLT3 co-mutated AML

- Nearly 40% of MRD-negative (by NPM1 PCR) patients ultimately relapsed in NCRI AML17 and AML19 trials
- Retrospectively performed FLT3 MRD testing for all patients with FLT3-ITD and NPM1 co-mutations and stored samples
  - Limit of detection NPM1 PCR: VAF 0.001%; Limit of detection FLT3 MRD: VAF 0.00005%
- 273 patients included; 28% underwent alloHCT in CR1
- FLT3 MRD prognostic for OS (33% vs 75%) and CIR (70% vs 38%) after second cycle of chemotherapy
- 20% of patients with negative PB NPM1 PCR and detectable FLT3 MRD in bone marrow
  - Inferior outcomes (OS 50% vs 82%; CIR (57% vs 36%)
  - Benefit from alloHCT in CR1 (52% vs 24%, p=0.028%)

Tedjaseputra et al. Blood (2025) 146 (Supplement 1): 345.

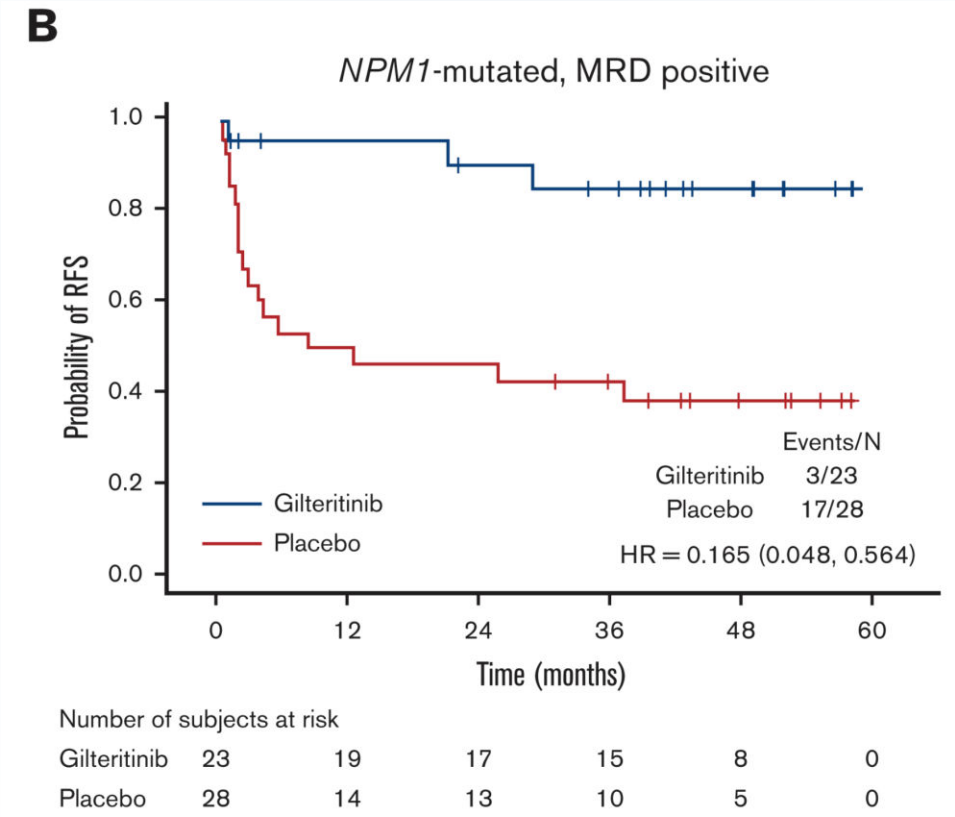
Recent advancements to improve alloHCT outcomes

- Donor selection guidelines
- Novel conditioning regimens
- GVHD prevention and treatment
  - Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq: approved by the FDA on 6/30/26
- Maintenance strategies
  - BMT 1506: RFS was higher for those with detectable FLT3-ITD MRD pre- or post-alloHCT who received gilteritinib

Meyer et al. *Blood* (2026) 147 (11): 1168–1177.
Levis et al. *J Clin Oncol (2024)* 42, 1766-1775.

NPM1 co-mutation associated with the largest magnitude of relapse-free survival benefit from post-alloHCT gilteritinib

- EBMT Guidelines recommend integrating NPM1 MRD assessment with FLT3-ITD MRD status to improve risk stratification



Levis et al. *Blood Adv* (2025) 9 (20): 5123–5133
Sanz et al. *Lancet Oncol.* (2025) ;26(11):e586-e596.

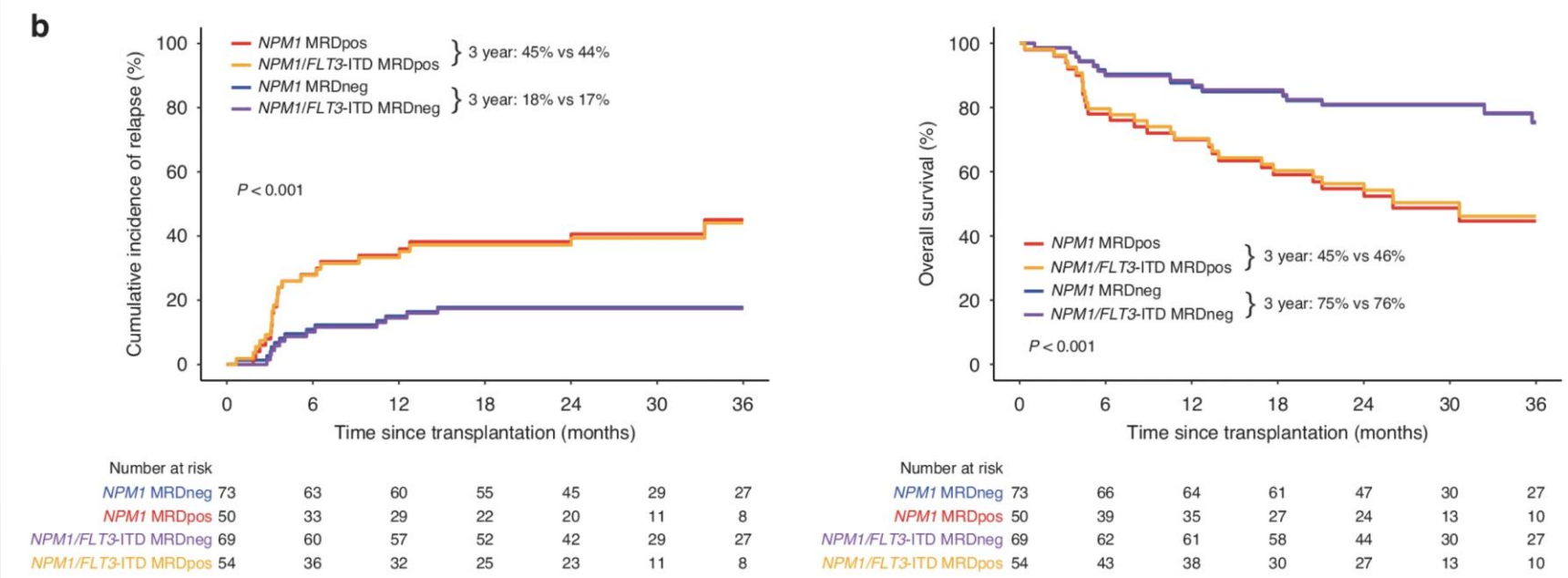
AlloHCT in CR2 is not guaranteed

- In the NCRI AML17 and AML19 trials, only 60% of patients with relapsed AML underwent alloHCT in CR2
- 13.3% CR + CRh with revumenib in patients previously treated with FLT3 inhibitor
- 13% CR + CRh with ziftomenib in patients with FLT3-ITD co-mutation
- Frontline venetoclax-based regimens can be associated with NPM1-wild type relapses, which are enriched with myelodysplasia-related mutations

Arellano et al. *Blood* (2025) 146(9):1065-1077.
Wang et al. J Clin Oncol (2025) 43: 3381-3390.
Jen et al. Am J Hematol (2025) 100(11):2118-2122.

Future directions: Incorporation of NPM1 MRD by NGS

- 123 patients with NPM1 and FLT3-ITD co-mutated AML in CR1 who underwent alloHCT between 2013-2019
- Increased risk of relapse post-alloHCT and worse survival in MRD-positive patients by NGS (0.00005% VAF limit of detection)
- NPM1 and FLT3 MRD NGS assays had similar prognostic value



Al-Ali et al. *Bone Marrow Transplant.* (2026) ; 61(2):222-224.

Conclusions

- AlloHCT in CR1 reduced relapse risk in NCRI AML17 and AML19 trials
  - Recognize limitations of this data set when considering generalizability to modern patient population – included patients treated with intensive induction chemotherapy, utilized NPM1 PCR for MRD assessment, and did not include current standard of care post-alloHCT maintenance therapies
  - Significant proportion of patients were unable to proceed to alloHCT in CR2
- More sensitive (NGS-based) MRD assays will further inform relapse risk discussions and improve identification of patients most likely to benefit from alloHCT in CR1
- Survival continues to improve with post-alloHCT maintenance strategies and reduction in non-relapse mortality through novel graft engineering approaches, GVHD prophylaxis, and advancements in supportive care

Q&A