TRANSPLANTATION IN CR1 FOR NPM1/FLT3 ITD CO-MUTATED AML?

MOSTLY NO!

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MY ARGUMENTS

- AML with NPM^{mut} + FLT3 ITD is clearly a less favorable genotype than other NPM^{mut} AML subtypes, but…
  - MRD testing can predict who <u>needs</u> allo-SCT in CR1
  - We now have multiple effective FLT3 inhibitors that contribute to better up-front outcomes (transplant and non-transplant), as well as more effective salvage in the event of relapse
  - Menin inhibitors have emerged as effective targeted therapies for relapsed AML with NPM^{mut}
- We can select patients for allo-SCT in CR1 based on MRD for both NPM1 and FLT3, and can still get over half of relapsing pts into CR2 to go on to subsequent transplant

CLINICAL TRIALS AND OBSERVATIONS

Postinduction molecular MRD identifies patients with *NPM1* AML who benefit from allogeneic transplant in first remission

Jad Othman,[1-3,*] Nicola Potter,[1,*] Adam Ivey,[4] Jelena Jovanovic,[1] Manohursingh Runglall,[1,2] Sylvie D. Freeman,[5] Amanda Gilkes,[6] Ian Thomas,[7] Sean Johnson,[7] Joanna Canham,[7] Jamie Cavenagh,[8] Panagiotis Kottaridis,[9] Claire Arnold,[10] Hans Beier Ommen,[11] Ulrik Malthe Overgaard,[12] Mike Dennis,[13] Alan Burnett,[14] Charlotte Wilhelm-Benartzi,[7] Richard Dillon,[1,2,*] and Nigel H. Russell[2,*]

- **UK AML 17 and AML 19 studies** included fit patients suitable for intensive induction and consolidation cycles
- Analysis included 737 pts with NPM1^{mut} genotype
  - Focus was on pts achieving CR/CRi after 2 cycles of chemotherapy
  - 286 pts had NPM^{mut} + FLT3 ITD genotype

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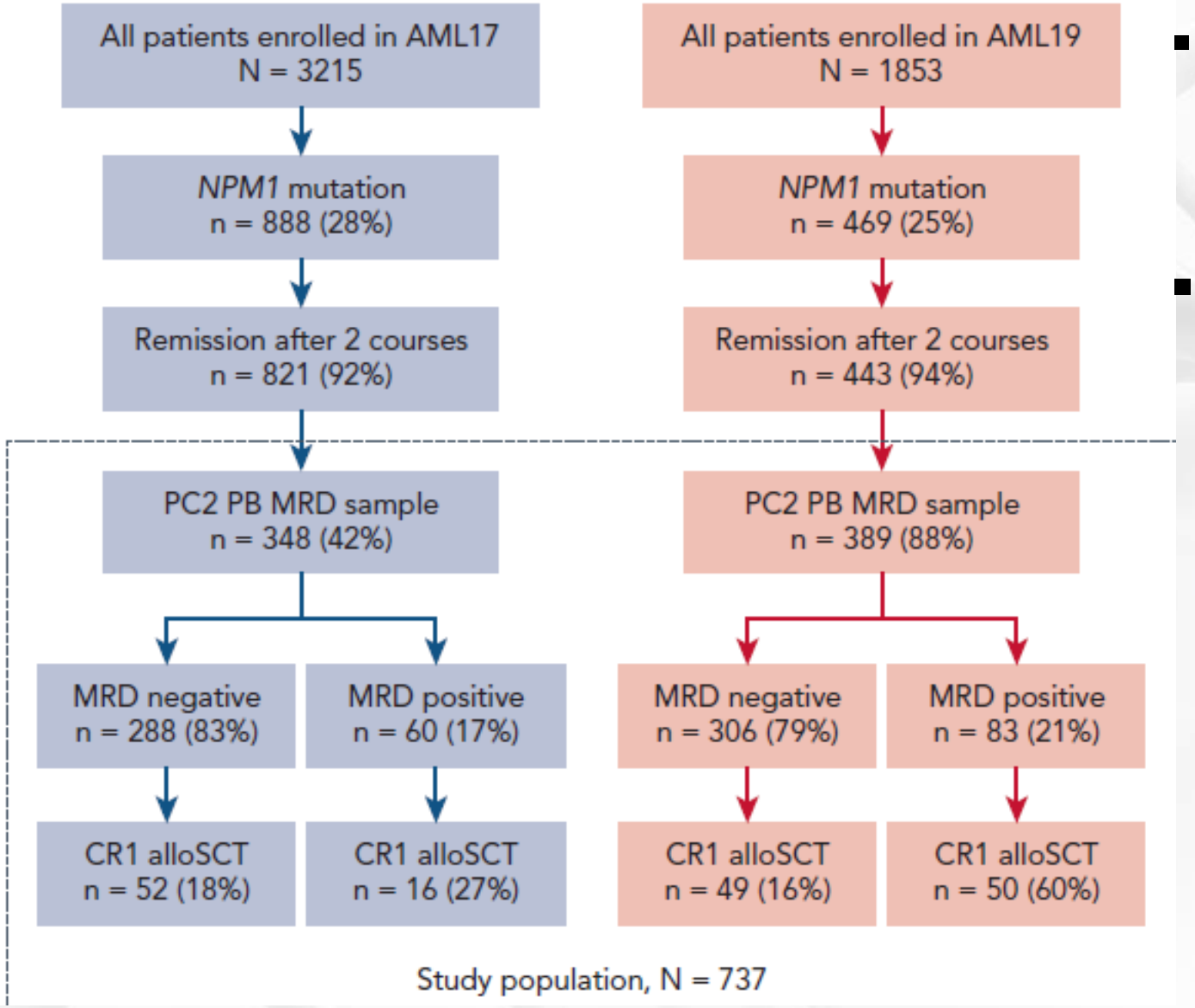
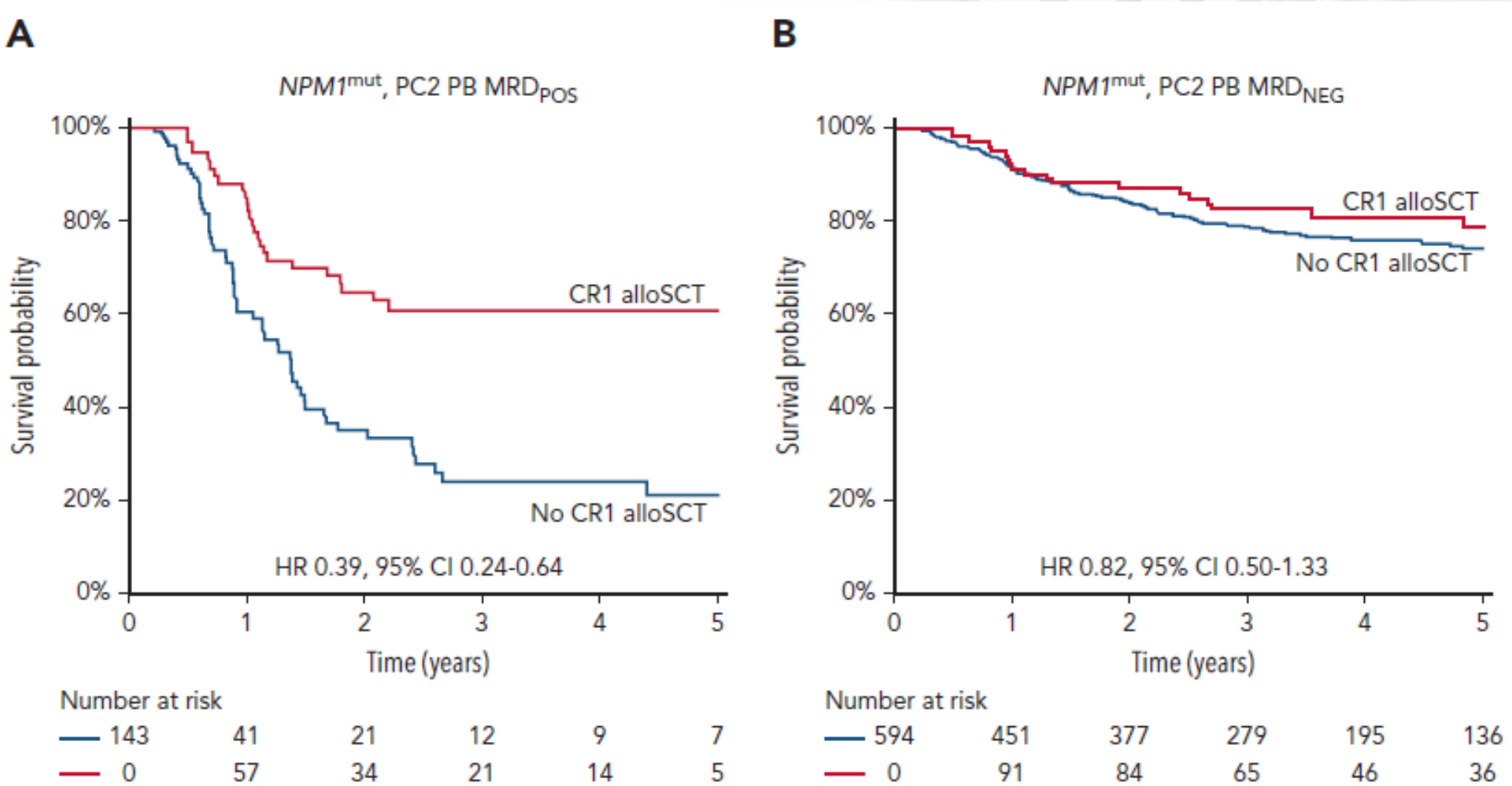


- Randomization +/- lestaurtinib for FLT3 mut pts in AML17—no benefit seen

- MRD monitoring by NPM1 RT PCR (blood) after 2 cycles of chemotherapy
  - Prior to June, 2012 investigators were blinded to MRD data
  - Thereafter, results reported, and in AML19 allo-SCT recommended if MRD+

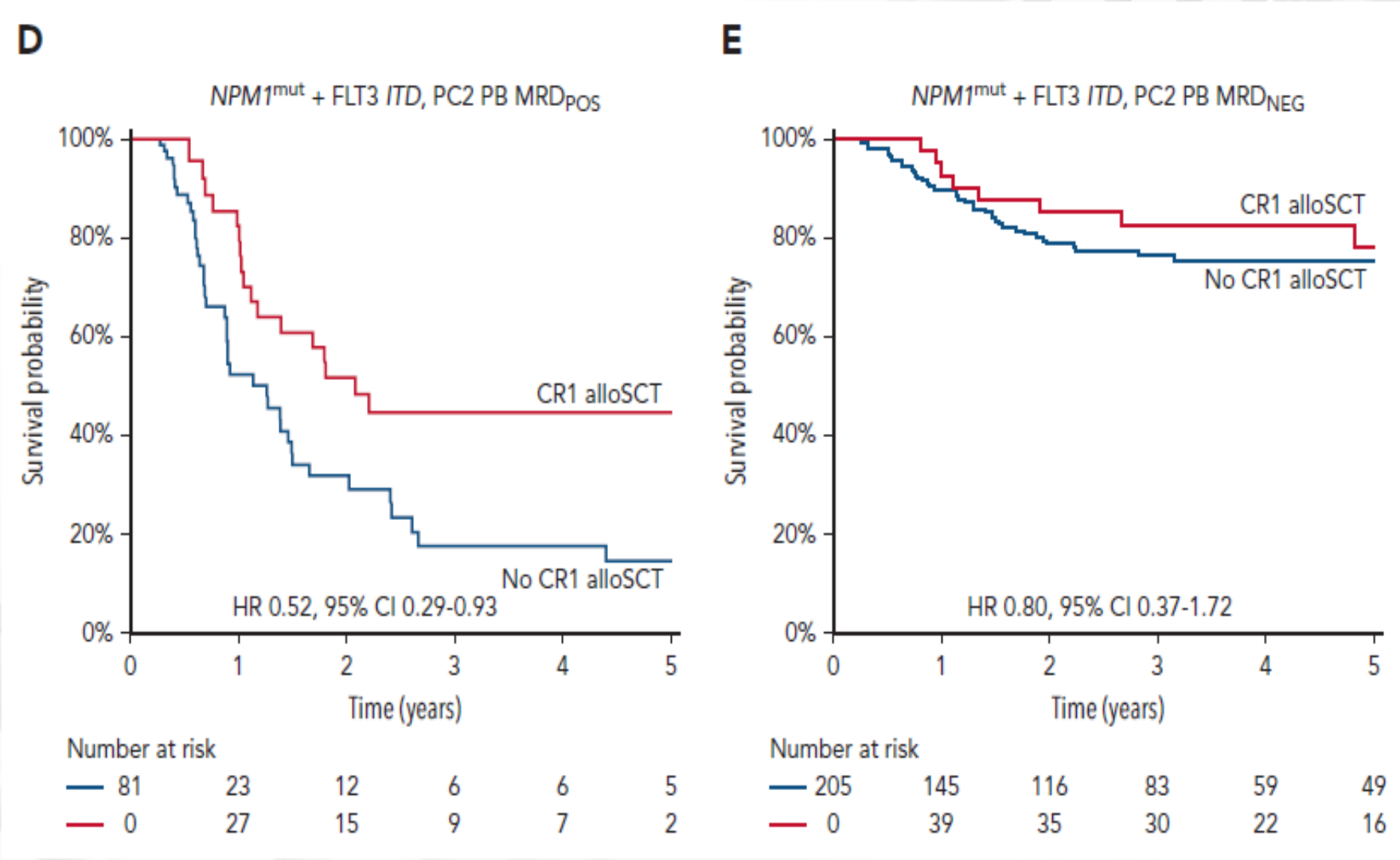
Othman J, et al. Blood, 2024; 143: 1931-36

OVERALL SURVIVAL: ALL NPM^{MUT} PATIENTS



Othman J, et al. Blood, 2024; 143: 1931-36

OVERALL SURVIVAL: NPM^{MUT} + FLT3 ITD PATIENTS



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DIGGING A LITTLE DEEPER…

- Large discrepancy between 3 yr RFS (62%) and OS (82%) in MRD neg pts not receiving allo-SCT in CR1
  - Among MRD neg pts not having allo-SCT in CR1 who relapsed, 103 of 169 pts (61%) went on to allo-SCT
  - 3 yr OS among relapsing pts was 50%

- Why might that be?
  - Lots of effective salvage options
    - HMA/ven has a high rate of CR in NPM^{mut} AML
    - Menin inhibitors can target $NPM1^{mut}$ AML
    - FLT3 inhibitors (quizartinib, gilteritinib) are effective alone and in combination for relapsed FLT3 mut AML

WHAT DOES THIS MEAN?

- Everybody with NPM^{mut} + FLT3 ITD doesn't necessarily need a transplant in CR1
  - ~80% of pts who achieve CR1 will be MRD neg after 2 cycles of therapy and are candidates for completion of consolidation followed by close observation
- What is close observation in MRD neg pts? **[ELN--Cloos, J et al. Blood 2026; 147(11): 1147-67]**
  - MRD (both NPM1 and FLT3) in BM at end of therapy
  - MRD monitoring (both NPM1 and FLT3) in blood (q 4-6 wks) or BM (q 3mos) x 2 yrs
  - **Must have a ready transplant option for a rainy day!**
- Questions/comments
  - What about the impact of other mutations, esp poor risk?
  - What about the very young patient?
  - *What about patients receiving HMA/venetoclax as primary therapy?*
  - **Patients need a voice in the decision given that this is not truly a low risk AML scenario**

QUESTION: WHO WILL YOU TRUST?

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