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ORAL ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

The Impact of *DNMT3A* Mutation on Survival of AML Patients Receiving Allogeneic Hematopoietic Cell Transplantation in First Remission Depends on the Karyotype and Co-Occurring Mutations: On Behalf of the EBMT Acute Leukemia Working Party

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DNMT3A gene mutations are more frequent in cytogenetically normal acute myeloid leukemia (AML) and frequently associated with *NPM1* mutation and internal tandem duplication (ITD) of the *FLT3* gene. However, *DNMT3A* mutation is not included as a distinct prognostic group in the recent European Leukemia Net (ELN) 2022 genetic risk classification of AML. In the context of allogeneic hematopoietic cell transplantation (allo-HCT), the prognostic value of *DNMT3A* is still not well studied. We evaluated, through the European Society for Blood and Marrow Transplantation (EBMT) registry, the impact of *DNMT3A* mutation, according to the karyotype, and *NPM1* and *FLT3*-ITD mutation status, on post-transplant outcomes in AML patients receiving allo-HCT in first complete remission (CR1).

We identified a total of 1374 adult AML patients (51% female, median age 57 years; range 18-78 years) with ELN-2022 intermediate- or poor-risk cytogenetics and available *DNMT3A, FLT3ITD* and *NPM1* mutation status, who underwent their first allo-HCT in CR1 between 2013 and 2021. Of these, 631 (46%) patients had *DNMT3A* mutation. Patients with mutant *DNMT3A* were more likely to be female (57% versus 46%, $p<0.001$), to have normal cytogenetics (75% versus 54%, $p<0.001$), *FLT3*-ITD co-mutation (50% vs 23%, $p<0.001$), *NPM1* co-mutation (60% vs 21%, $p<0.001$), and to receive a myeloablative conditioning and *in vivo* T cell depletion. After a median follow-up of 2.3 years, the 2-year leukemia free survival (LFS) and overall

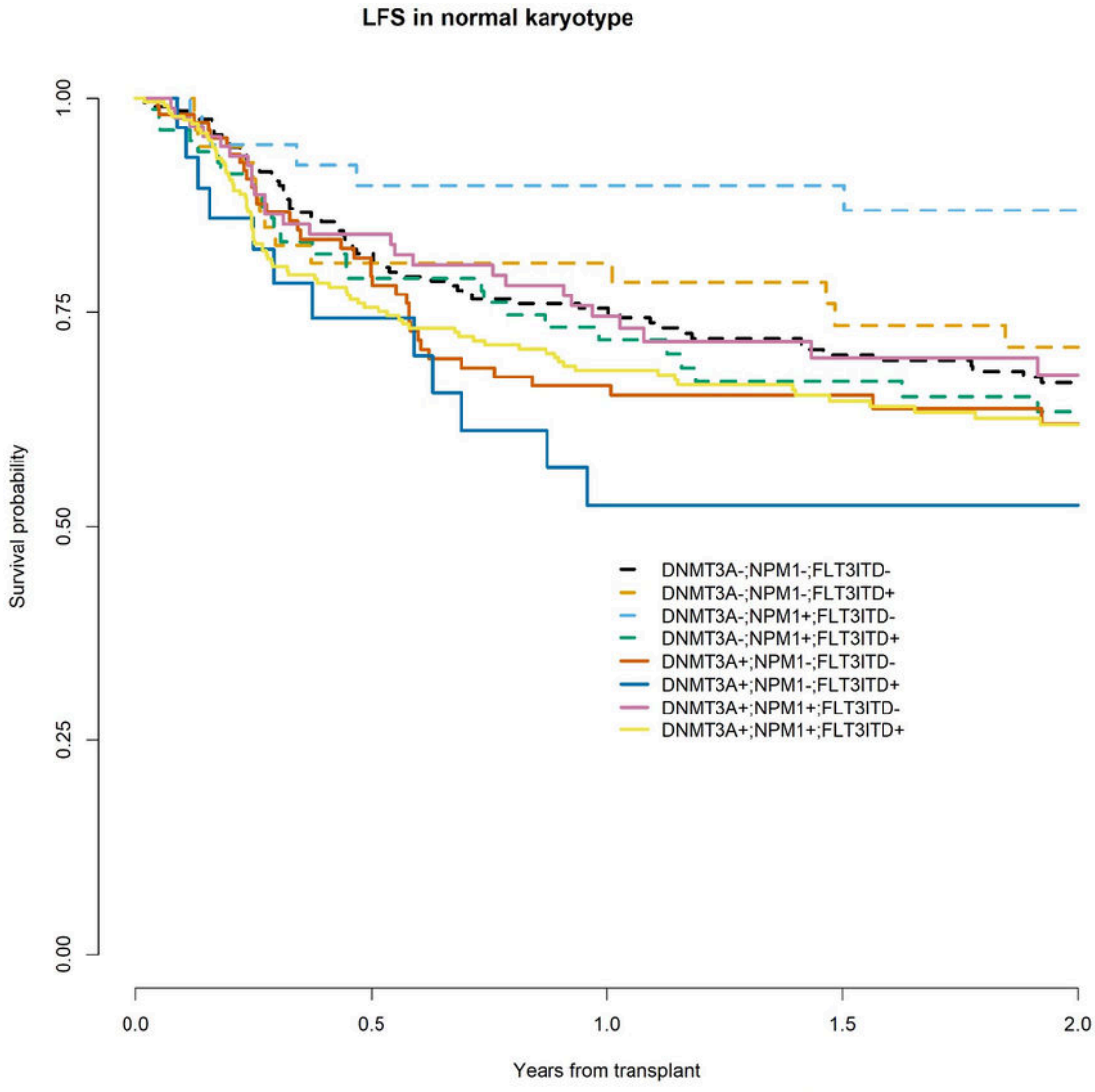
survival (OS) were 62% and 69%, respectively. The subsequent analysis was split according to baseline karyotype (normal or abnormal).

Among 870 patients with normal cytogenetics, 472 (54%) patients had *DNMT3A* mutation. The 2-year relapse incidence (RI), LFS and OS were 24%, 63% and 70% respectively, in patients with *DNMT3A* mutation compared to 18%, 69% and 74% in patients with *wild type DNMT3A*. Among these patients with normal karyotype, multivariable analyses (MVA) were done within the 4 groups of FLT3-ITD and NPM1 mutations. Within the group of 324 patients with both FLT3-ITD and NPM1 positives, 244 were triple-positive (75%), LFS and OS were not significantly different with and without *DNMT3A* mutation (2y LFS: 62% vs 63%, HR: 0.98, p=0.95; 2y OS: 70% vs 73%, HR: 1.17, p=0.58). Conversely, among 146 patients with *NPM1* mutation without *FLT3*-ITD, LFS was significantly lower for 91 patients with DNMT3A mutation (2y LFS: 68% vs 87%, HR: 2.70, p=0.02) but OS was not significantly different (2y OS: 79% vs 87%, HR: 2, p=0.13). On the other hand, among 318 with wild type *NPM1* and without *FLT3*-ITD, LFS and OS were not significantly different for 108 patients with DNMT3A mutation compared to 210 patients with wild type *DNMT3A* (2y LFS: 62% vs 67%, HR: 1, p=0.98; 2y OS: 65% vs 71%, HR: 1.02, p=0.94). Conversely, among 82 patients with *FLT3*-ITD and wild type *NPM1*, 2-year LFS and OS were 53% and 58% respectively, for 29 patients with *DNMT3A* mutation compared to 71% and 76% respectively, for 53 patients with wild type *DNMT3A*. The number of patients didn't allow to perform MVA in this group.

Finally, among 504 patients with abnormal cytogenetics, 159 (31%) patients had *DNMT3A* mutation. On MVA, *DNMT3A* mutation did not significantly affect LFS or OS. Poor-risk cytogenetics was associated with worse LFS, OS and increased RI. Older age negatively affected LFS and OS.

In conclusion, in AML patients allografted in CR1, the impact of *DNMT3A* mutation depends on the karyotype and co-occurring mutations. Our data suggest that *DNMT3A* mutation negatively affects post-transplant survival selectively in patients with normal karyotype and either *NPM1* mutation without *FLT3*-ITD, or patients with normal karyotype, *FLT3*-ITD and wild type *NPM1*. *DNMT3A* mutation shows no impact on post-transplant outcomes in other settings.

Disclosures Huynh: *Medac:* Other: Advisory board; *Astellas:* Other: Advisory board; *Pfizer:* Other: advisory board; *Jazz:* Other: travel fees, advisory board; *Servier:* Other: Advisory board; *Neovii:* Other: Advisory board; *Novartis:* Other: travel fees, advisory board. **Mayer:** *MSD:* Research Funding; *Novartis:* Research Funding. **Esteve:** *Jazz Pharmaceuticals:* Consultancy, Research Funding; *Abbvie:* Consultancy; *Gilead:* Consultancy; *Kronos Bio:* Research Funding; *Pfizer:* Research Funding; *Astellas:* Consultancy. **Ciceri:** *ExCellThera:* Other: Scientific Advisory Board . **Mohty:** *JAZZ PHARMACEUTICALS:* Honoraria, Research Funding.



DNMT3A-;NPM1-;FLT3ITD-:	210	198	161	149	144	138	117	116	109	105	98
DNMT3A-;NPM1-;FLT3ITD+:	53	50	39	39	39	36	33	32	29	29	25
DNMT3A-;NPM1+;FLT3ITD-:	55	52	39	38	38	34	31	31	29	29	27
DNMT3A-;NPM1+;FLT3ITD+:	80	72	58	55	52	49	41	40	39	37	34
DNMT3A+;NPM1-;FLT3ITD-:	108	99	78	67	63	60	48	46	41	40	32
DNMT3A+;NPM1-;FLT3ITD+:	29	24	18	16	14	12	10	10	9	8	8
DNMT3A+;NPM1+;FLT3ITD-:	91	83	71	68	66	57	44	41	37	36	32
DNMT3A+;NPM1+;FLT3ITD+:	244	218	163	152	147	134	112	104	96	90	78

Figure 1

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