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Blood 142 (2023) 2236–2238

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Impact of *KMT2A*-PTD Mutational Subgroups on Outcome of AML Patients after Induction Therapy and Allogeneic Hematopoietic Cell Transplantation

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Introduction
Genetic profiling of acute myeloid leukemia (AML) has increasingly revealed the possibility of adjusted therapeutic options. Recently, updates in genetic risk classifications introduced novel molecular features, but also excluded aberrations like partial tandem duplications in the lysine (K)-specific methyltransferase 2A (*KMT2A*-PTD), formerly associated with adverse prognosis. Furthermore, there is growing evidence that molecular subtypes confer differential prognosis. Therefore, we analyzed a large cohort of AML pts to decipher the prognostic impact of *KMT2A*-PTD mutations (*KMT2A*-PTD ^{mut}) including variants *e9e3*, *e10e3* and *e11e3* and their role in allogeneic hematopoietic cell transplantation (alloHCT).

Methods
Genomic DNA and total RNA of pts enrolled within the SAL registry (NCT03188874) was extracted at diagnosis. Samples were screened for *KMT2A*-PTD ^{mut} using the Mentype AMLplexQS Kit (Biotype, Dresden, Germany). Statistical as-treated analyses included standard statistical methods for categorial and continuous variables. Effects of alloHCT modeled as a time dependent covariate were estimated using Cox regression. Complete remission (CR) and survival rates were defined according to the current European Leukemia Net criteria. Logistic regression was used to evaluate CR rates and Cox regression to estimate hazard ratios (HR). The significance level was set at 0.05. All patients gave written informed consent. The study was conducted in accordance to the Declaration of Helsinki and was approved by the responsible ethics committees.

Results
Among 1409 pts, 206 pts harbored *KMT2A*-PTD ^{mut}, while 1203 pts showed wildtype (WT) alleles. *KMT2A*-PTD ^{mut} status was more often associated with secondary AML ($p = .001$) and less likely with concomitant *NPM1* mutations ($p < .001$).Variants *e9e3* (40.8%) and *e10e3* (36.6%) were more frequently detected than *e11e3* (22.6%).
A total of 136 *KMT2A*-PTD ^{mut} and 859 WT pts received intensive induction therapy (IT). Rates of first complete remission (CR1) did not differ ($p = .14$). However, 5-year RFS was significantly lower in *KMT2A*-PTD ^{mut} pts compared to WT pts (15% vs. 25%), with median RFS of 23 vs. 29 months (HR = 1.4, $p = .008$). Accordingly, median OS was shorter (29 vs. 61 months; HR = 1.6, $p = .002$) and 5-year OS was lower for *KMT2A*-PTD ^{mut} pts compared to the WT counterparts (28% vs. 51%).
In CR1, 81.6% of *KMT2A*-PTD ^{mut} pts proceeded to alloHCT and 18.4% of *KMT2A*-PTD ^{mut} pts received chemotherapy-based consolidation only. Median RFS improved from 15 to 37 months (HR = 0.5, $p = .13$) and chance of 5-year RFS enhanced from 17% to 21% when *KMT2A*-PTD ^{mut} pts underwent alloHCT in CR1 compared to *KMT2A*-PTD ^{mut} pts receiving chemo-consolidation.Median OS increased from 30 to 43 months when being allografted (HR = 0.5, $p = .2$), paralleled by increased rates of 5-year OS (33% chemo-consolidation vs. 47% alloHCT).
Concerning *KMT2A*-PTD variants, there was no difference in likelihood to achieve CR1 between the three variants ($p = .4$). However, a trend towards shorter median OS (*e9e3*: 41 months, *e10e3*:27 months, *e11e3*:27 months) and worse median RFS (*e9e3*: 24 months, *e10e3*:23 months, *e11e3*:23 months) compared to WT pts (median OS: 61 months, median RFS: 29 months) could be revealed. Variant *e10e3* was associated with worst prognosis (OS: HR = 2.1, $p = .006$; RFS: HR = 1.6, $p = .06$) and *e9e3* with best prognosis (OS: HR = 1, $p = .9$; RFS: HR = 1.1, $p = .7$).
e9e3 demonstrated best prognosis for both consolidation strategies. Median OS was not reached until last follow-up. Median RFS was higher in alloHCT pts (15 vs. 38 months, HR = 0.5, $p = .3$). *e10e3* and *e11e3* also had a higher median OS (12 vs. 43 months, HR = 0.3, $p = .3$ and 12 months vs. median survival not reached, HR = 0.2, $p = .3$, respectively) and RFS (11 vs. 41 months, HR = 0.3, $p = .3$ and 11 months vs. median survival not reached, HR = 0.2, $p = .3$, respectively) when allografted.

Conclusions
Based on our retrospective analysis, *KMT2A*-PTD ^{mut} are associated with reduced prognosis and survival in AML patients compared to WT pts. However, poor prognosis was effectively mitigated by alloHCT. Concerning *KMT2A*-PTD variants, we hypothesize alloHCT to be beneficial for improved survival. This effect seemed to be less pronounced for variant *e9e3*and more distinct for variant *e11e3*. Therefore, some *KMT2A*-PTD variants could be potentially implemented in AML risk stratification. However, prospective studies and larger patient numbers are needed.

Disclosures Kunadt: *Jazz Pharmaceuticals:* Honoraria, Other: Travel grants; *Medac GmbH:* Other: Travel grants. **Röllig:** *Astellas:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *Jannsen:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding. **Schliemann:** *Laboratoires Delbert:* Honoraria; *Boehringer Ingelheim:* Research Funding; *AngioBiomed:* Research Funding; *Pfizer:* Honoraria, Other; *Roche:* Honoraria; *Novartis AG:* Honoraria; *Jazz Pharmaceuticals:* Honoraria, Other, Research Funding; *Bristol Myers Squibb:* Honoraria, Other; *AstraZeneca:* Honoraria; *Astellas Pharma Inc.:* Honoraria; *AbbVie Inc.:* Honoraria, Other. **Hilgendorf:** *Novartis:* Consultancy, Honoraria; *Takeda:* Honoraria; *BeiGene:* Honoraria; *Medac:* Honoraria; *AbbVie:* Honoraria; *Amgen:* Honoraria; *Jazz:* Honoraria; *Fondatione Internationale Menarini:* Honoraria; *Janssen:* Honoraria. **Jost:** *Amgen:* Honoraria; *Medac:* Other: travel costs; *JAZZ:* Honoraria; *BMS Celgene:* Honoraria. **Bug:** *Novartis:* Honoraria; *Jazz:* Honoraria, Other: travel grant; *BMS:* Honoraria; *Gilead:* Honoraria, Other: travel grant; *Neovii:* Other: trvel grant; *Pfizer:* Honoraria. **Einsele:** *Sanofi:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *GlaxoSmithKline:* Honoraria, Other: Consulting or

advisory role, Travel support, Research Funding; *Takeda:* Honoraria, Other: Consulting or advisory role, Travel support; *Amgen:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Janssen:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Bristol Myers Squibb/Celgene:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Novartis:* Honoraria, Other: Consulting or advisory role, Travel support. **Hänel:** *Novartis, SOBI, Gilead, Falk Foundation:* Honoraria; *Novartis, BMS/Celgene, Gilead, Pfizer, Incyte, Sanofi/Aventis, Roche, Amgen, SOBI, Janssen:* Consultancy. **Ruhnke:** *BeiGene, Inc.:* Other; *AbbVie Inc.:* Research Funding; *Jazz Pharmaceuticals:* Other; *Neovii Pharmaceuticals:* Other. **Platzbecker:** *Servier:* Consultancy, Honoraria, Research Funding; *Fibrogen:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Consultancy; *Novartis:* Consultancy, Honoraria, Research Funding; *Geron:* Consultancy, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Curis:* Consultancy, Research Funding; *Merck:* Research Funding; *Amgen:* Consultancy, Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Celgene:* Honoraria; *Syros:* Consultancy, Honoraria, Research Funding; *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *Roche:* Research Funding; *BeiGene:* Research Funding; *BMS:* Research Funding. **Baldus:** *Astellas:* Consultancy; *Gilead:* Consultancy; *Jannsen:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *BMS:* Consultancy; *AstraZeneca:* Consultancy; *Amgen:* Consultancy. **Schetelig:** *Eurocept:* Honoraria; *Novartis:* Honoraria; *AstraZeneca:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria. **Stölzel:** *medac:* Speakers Bureau.

https://doi.org/10.1182/blood-2023-187273