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ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Genomic Characterization of Acute Myeloid Leukemia with Aberrations of Chromosome 7: A Multinational Cohort of 523 Patients

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Introduction: Aberrations of chromosome 7 [abn(7)] are found in ≈ 10% of newly diagnosed acute myeloid leukemia (AML) and associate with a dismal prognosis. A large-scale comprehensive exploration of the underlying genetic heterogeneity in AML with abn(7) has yet to be performed and could add essential insights into the outcome of this poorly understood patient group.

Methods: We collected diagnostic samples from 523 adult AML patients (median age 59 years) with abn(7). Whole-exome sequencing (WES) was performed to discover potentially underestimated genetic lesions in 61 paired diagnostic / remission samples. Subsequently, a gene panel including 66 genes and a SNP backbone for copy-number aberration (CNA) detection was designed and applied to the remaining 471 samples. The majority of patients (78%) were diagnosed with *de novo (dn)* AML, whereas 22% had secondary (s) or therapy-related (t) AML. Intensive induction treatment was administered to 80% of

the patients, while 36 % underwent allogenic stem cell transplantation. Apart from 43% of patients with concomitant complex karyotype (abn(7)/CK+), 24% had -7 as a sole abnormality (-7 sole) and 13% del(7q) sole.
Results: A mean of 15.3 single-nucleotide variants (SNVs) and 7.5 CNAs per patient were found by WES. Here, the most frequent recurrent SNVs were identified in *TP53* (29.5%), followed by mutations (mut) in genes involved in epigenetic regulation (*DNMT3A, TET2, ASXL1, IDH2*), transcription factors (*RUNX1*), and genes affecting RAS-signaling (*NF1, KRAS*), Figure 1.
Targeted sequencing revealed 1829 SNVs with a VAF≥ 2% in 64 genes (mean: 3.8 SNVs / patient). 30% of patients harbored at least one mutation in genes located within the commonly deleted region of 7q, most frequently *KMT2C, EZH2 CUX1, SAMD9L, SAMD9, LUC7L2* and *BRAF*. The number of driver gene mutations was higher in CK- than in CK+ patients (4.5 vs. 3.3 SNVs). We found *KRAS* (OR 3.76, CI 1.17-16.87, P= .044) and *RUNX1* (OR 3.61, CI 1.62-8.78, P= .003) mutations to be enriched in -7 sole patients, and *FLT3* mutations to be associated with del(7q) sole status (OR 0.33, CI 0.13-0.82, P= .019). With respect to previously unknown lesions, a high amount of *KMT2C* mutations (16.6%) and recurrent alterations in *FAT1* and *TACC2* were discovered (6.4% each; Fig. 1). For *KMT2C* - located on chr7q36.1 - a total of 98 SNVs with mainly missense (73.5%) and truncating (20.4%) mutations at known cancer hotspots were noted. *KMT2C*mut was associated with *dn*AML and AML with maturation morphology. In the entire cohort, the most common co-occurring chromosomal alterations discovered by high-resolution CNA analysis were deletions in chromosomes 5, 17, and 12. Our approach enabled the identification of small fragment deletions (≤10Mb) affecting the *TP53*, *NF1*, and *ETV6* loci in 5-9% of all cases, which were missed by conventional G-banding. Cancer Cell Fraction and Bradley-Terry models were used to simulate the sequential order of genomic aberrations. While mutations in *TP53* and epigenetic-related genes were early events, -7 and del(7q) were often subclonal and SNVs in *NRAS, KMT2C* very late events in leukemogenesis.
Survival analyses in intensively-treated patients (n= 414) revealed that 61% reached complete remission, 67% relapsed, and median overall survival (OS) was 11.9 months. Abn *TP53* and high WBC count were independently associated with shorter relapse-free survival (RFS). For OS, besides older age and high WBC count, we identified abn *TP53, PTPN11*mut, *TET2*mut,-5, and -18 as poor prognostic factors in multivariate analysis (Table 1). In contrast, *IDH2*mutconferred an independent favorable prognostic effect for RFS and OS. Notably, abn *TP53* outcompeted the prognostic impact of CK+ (Table 1). Compared to *TP53*wt, patients with abn *TP53*/CK+ and abn *TP53*/CK- had a similar poor outcome with median RFS of 6 and 4 months (CK+/CK-, P<.001) and OS of 6.8 and 8.6 months (CK+/CK-, P<.001). In contrast to other genomic studies in myelodysplastic syndrome, we found abn *TP53* to be associated with poor outcome irrespective of the single- or multihit mutation status following definitions of the latest ICC classification (Blood, 2022).
Conclusion: Our results offer novel insights into the genomic landscape and clonal trajectory of AML with abn(7). This work unravels formerly underestimated genetic lesions (*KMT2C*mut) and alterations with high prognostic impact (abn *TP53* and *IDH2*mut) for better future risk stratification.

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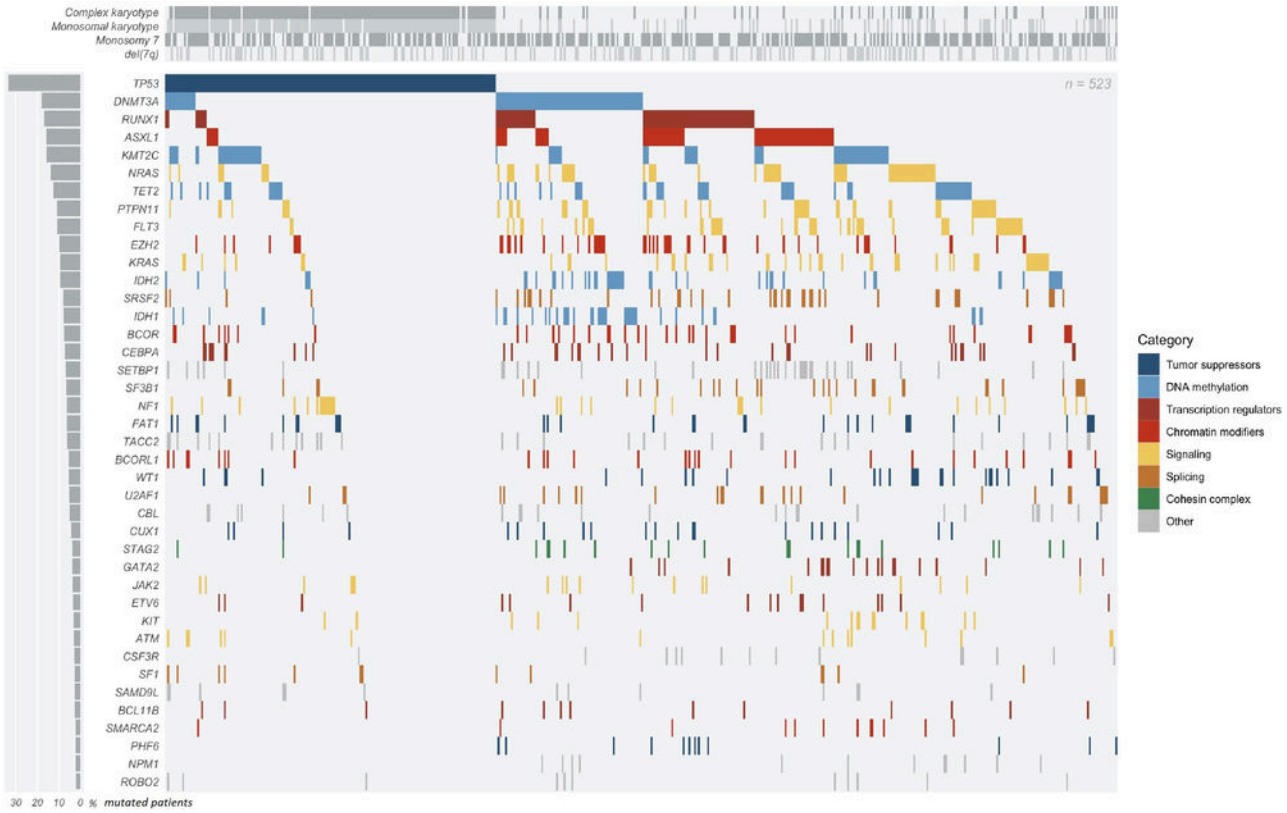

Figure 1: Genomic landscape of SNVs in 523 AML patients with chromosome 7 aberrations detected by WES and targeted DNA sequencing, colored according to the functional gene category. Left panel shows fraction of mutated patients (%).

			Univariate OS			Multivariate OS		
		n	HR	95% CI	p-value	HR	95% CI	p-value
Age	< median (59y)	234	*Reference*			*Reference*		
	≥ median	159	1.29	1.02-1.64	0.033	1.32	1.03-1.69	0.029
WBC	< 10/nl	208	*Reference*			*Reference*		
	≥ 10/nl	185	1.31	1.04-1.65	0.023	1.78	1.39-2.29	<0.001
Complex karyotype	no	225	*Reference*			*Reference*		
	yes	168	2.17	1.72-2.73	<0.001	1.08	0.72-1.62	*0.710*
Monosomy 7	no	140	*Reference*			*Reference*		
	yes	253	1.42	1.11-1.82	0.005	1.46	0.83-2.56	*0.186*
del(7q)	no	277	*Reference*			*Reference*		
	yes	116	0.73	0.56-0.95	0.019	1.02	0.57-1.83	*0.938*
IDH2	wt	356	*Reference*			*Reference*		
	mut	37	0.33	0.19-0.55	<0.001	0.47	0.27-0.81	0.006
PTPN11	wt	347	*Reference*			*Reference*		
	mut	46	1.70	1.21-2.37	0.002	2.11	1.48-3.01	<0.001
TP53	wt	258	*Reference*			*Reference*		
	mut and/or del	135	3.14	2.47-4.01	<0.001	2.50	1.63-3.83	<0.001
Monosomy 5	no	340	*Reference*			*Reference*		
	yes	53	2.76	2.03-3.74	<0.001	1.56	1.09-2.23	0.015
Monosomy 18	no	358	*Reference*			*Reference*		
	yes	35	2.64	1.84-3.80	<0.001	1.65	1.10-2.48	0.016

393 intensively treated patients with available data

0.5 1 2

Table 1: Univariate and multivariate hazard ratios (HR) for overall survival of intensively treated patients. Median age 59 years.

Figure 1

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