POSTER 5: Combined single-cell genotyping and phenotyping reveals underlying TP53 clonai hematopoiesis in adult low-hypodiploid ALL

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Acute lymphoblastic leukemia (ALL) with low-hypodiploid karyotype represents a rare subtype of B-cell precursor ALL with dismal outcome. Previous studies pinpointed the strong association between low-hypodiploid ALL and TP53 mutations, the latter being of germline origin in half of pediatric patients. In adult, the genetic, biological and clinical features oflow-hypodiploid ALL are poorly defined. We performed a comprehensive analysis combining karyotyping, copy-number aberration (CNA) and loss-of-heterozygosity (LOH) data in a total of 591 Philadelphia-negative B-ALL from adult patients enrolled in the GRAALL-2014 (18-59y) and EW ALL-INO (>=:60y) trials, allowing to establish a large cohort of 80 low-hypodiploid cases. Of note, one third had a karyotype failure and halfhad a duplicated genome resembling high hyperdiploidy, underlining the importance ofLOH analysis for proper ALL classification. The proportion oflow-hypodiploidy within adult Ph-negative ALL dramatically increased with age, reaching 31 % in patients aged 55 years and older. Biallelic inactivation of TP53 was observed in most cases (73/75, 97%) and other commonly altered genes were CDKN2A (27%), RBJ (24%), NFJ (23%) and JKZF2 (20%). Analysis ofpost-remission samples revealed the persistence ofTP53 mutation at significant allelic frequencies in 33% of cases. Finally,

using combined single-cell genotyping and phenotyping of diagnosis and remission samples (n=3 each), we demonstrate multi-lineage involvement ofa preleukemic TP53-mutated clone, which can be referred to as age-related clonai hematopoiesis (ARCH). Altogether, our study unveils a link between low-hypodiploid ALL and aging relying on TP53 ARCH, which represents a preleukemic reservoir allowing aneuploidy and giving rise to low-hypodiploid ALL.