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| CLINICAL Utility of Molecular Testing in  aml WITH *KMT2A* REARRANGEMENT  Diagnostic Utility  AML with balanced rearrangements involving the *KMT2A* gene at chromosome 11q23 account for approximately 3% of adult cases1,2 and 16%-18% of paediatric cases3,4. This is a recurrent genetic abnormality that defines AML irrespective of blast count (WHO 5th edition)5.  *KMT2A* rearrangements are also recurrently observed in myeloid neoplasm post cytotoxic therapy (MN-pCT, classified separately), B-ALL, T-ALL and mixed-phenotype acute leukaemia.  *KMT2A* rearrangements typically result in a *KMT2A-*encoded amino-terminus partnering with a carboxy-terminus encoded by the partner gene, and a gene expression profile characterised by overexpression of *HOX* genes.  Over 100 *KMT2A* fusion partners have been identified, with the most common in AML being *MLLT3* from t(9;11)(p22;q23), *MLLT10* from t(10;11)(p12;q23), *ELL* from t(11;19)(q23;p13.1), and *AFDN* from t(6;11)(q27;q23)6.  *KMT2A*-rearranged AML is associated with additional somatic mutations commonly involving the RAS pathway (including *KRAS*, *NRAS* and *PTPN11*) and *FLT3*-TKD2,7-9.  Separate to structural *KMT2A* rearrangements involving chromosomal translocations, cryptic partial tandem duplication of *KMT2A* (*KMT2A*-PTD) has also been described, typically in the setting of trisomy 11 or a normal karyotype10. This is not currently recognised as a distinct AML category.  Prognostic Utility  In the 2022 ELN classification, AML with t(9;11)(p21.3;q23.3)/*KMT2A::MLLT3* carries an intermediate prognosis, while non-*MLLT3* rearrangements [t(v;11q23.3)/*KMT2A*-rearranged] are designated as adverse-risk11.  Although not currently recommended by the 2021 ELN MRD guidelines12, *KMT2A* rearrangements may be amenable to molecular measurable residual disease (MRD) monitoring to provide independent prognostication post therapy for AML13,14, but are complicated by variable breakpoints and multiple fusion partners.  biomarkers of response to therapy  The interaction between KMT2A fusion protein and its critical oncogenic cofactor, menin, can be targeted using small molecule inhibitors of menin, which have demonstrated potent pre-clinical efficacy15 and shown promising activity in early-phase clinical trials16.  *FLT3* mutations are the target of midostaurin17 (*FLT3*-ITD and TKD) (clinical trials included only TKD mutations at Asp835 and Ile836 codons), quizartinib (*FLT3*-ITD only)18 in newly diagnosed AML, and gilteritinib19 in relapsed/refractory AML.  *FLT3* testing should be repeated at relapse/progression as ~20% of patients have a change (gain or loss) in mutation status20.  *IDH1* (Arg132) and *IDH2* (both Arg140 and Arg172) mutations are the target of IDH1 and IDH2 inhibitors, respectively21.  Several mutations have been described in patients with acquired resistance to targeted inhibitors such as *FLT3* Phe691Leu (FLT3 inhibitors)22, second-site IDH1/IDH2 mutations (IDH1/IDH2 inhibitors)23, *BAX* (BCL2 inhibitors)24, and *MEN1* (menin inhibitors)25.  References  **1.** Schoch C, et al. AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. *Blood* 2003; **102**(7): 2395-402. **2.** Papaemmanuil E, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med* 2016; **374**(23): 2209-21. **3.** Raimondi SC, et al. Chromosomal abnormalities in 478 children with acute myeloid leukemia: clinical characteristics and treatment outcome in a cooperative pediatric oncology group study-POG 8821. *Blood* 1999; **94**(11): 3707-16. **4.** Harrison CJ, et al. 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