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| CLINICAL Utility of Molecular Testing in  aml WITH *NPM1* MUTATION  Diagnostic Utility  *NPM1* mutations are the most common genetic abnormality in adult AML, accounting for approximately 30% of cases overall and a higher proportion in cases with a normal karyotype.  AML with *NPM1* mutation is a distinct entity in both the WHO 5th edition1 and International Consensus Classification (ICC)2.  While the diagnosis of AML with *NPM1* mutation can be made irrespective of the blast count according to the WHO 5th edition1, ≥10% blasts is required for the ICC2.  *DNMT3A*, *FLT3*-ITD, *TET2*, *IDH1* and *IDH2* (Arg140)mutations are enriched in AML with *NPM1* mutation3.  Prognostic Utility  AML with *NPM1* mutation is a heterogeneous group with significant gene-gene interactions.  Evaluation of *NPM1* and *FLT3*-ITD status represents a major pillar of the European LeukemiaNet (ELN) genetic-based risk stratification model for AML4. A favourable prognosis is observed with mutated *NPM1* without *FLT3*-ITD.The *FLT3*-ITD allelic ratio is no longer considered in the ELN 2022 risk classification; consequently, AML with *NPM1* mutationand a *FLT3*-ITD is now categorised in the intermediate-risk group, irrespective of the allelic ratio4.  While comutation of *NPM1*/*DNMT3A*/*FLT3*-ITD (triple mutant) has been associated with inferior outcomes in some studies3,5, this profile is considered intermediate risk according to ELN 2022 criteria4.  The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML now defines adverse risk4,6.  A subset of AML with *NPM1* mutation cases have comutation with one or more of the myelodysplasia-related genes (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*). For the time being, the ELN recommends that these should not be used as an adverse prognostic marker if they co-occur with *NPM14.*  *NPM1* mutations are a suitable marker for measurable residual disease (MRD) monitoring7,8. Type A, B and D transcripts comprise approximately 90% of *NPM1* mutations. Other variant types have also been recently described in exon 5 (in-frame), 10 and 11, as well as *NPM1* gene rearrangements9,10.  MRD assessment is an independent prognostic indicator post therapy for AML, and may be a more potent predictor of outcome compared to the baseline clinical and molecular profile7.  biomarkers of response to therapy  *FLT3* mutations are the target of midostaurin16 (*FLT3*-ITD and TKD) (clinical trials included only TKD mutations at Asp835 and Ile836 codons), quizartinib (*FLT3*-ITD only)17 in newly diagnosed AML, and gilteritinib18 in relapsed/refractory AML.  Repeat *FLT3* testing at relapse or disease progression is recommended as approximately 20% of patients have a change (gain or loss) in *FLT3* mutation status11.  *IDH1* and *IDH2* mutations are the target of IDH1 and IDH2 inhibitors, respectively12.  AML with *NPM1* mutationhas a transcriptional signature similar to *KMT2A*-rearranged AML, including *HOX* gene dysregulation, and is potentially targetable by menin inhibitors13.  Several mutations have been described in patients with acquired resistance to targeted inhibitors such as *FLT3* Phe691Leu (FLT3 inhibitors)14, second-site IDH1/IDH2 mutations (IDH1/IDH2 inhibitors)15, *BAX* (BCL2 inhibitors)16, and *MEN1* (menin inhibitors)17.  References  **1.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.fr. **2.** Arber DA, et al. 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