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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 acute myeloid leukaemia (AML), accounting for approximately 30% of cases overall and a higher proportion in cases with a normal karyotype.  Types A, B and D comprise approximately 90% of *NPM1* mutations. Other *NPM1* variant types have also been recently described in exons 5 (in-frame), 10 and 11, as well as *NPM1* gene rearrangements1,2.  AML with *NPM1* mutation is a distinct entity in both the WHO 5th edition3 and International Consensus Classification (ICC)4.  While the diagnosis of AML with *NPM1* mutation can be made with any increase in peripheral blood and/or bone marrow blasts in the appropriate context according to the WHO 5th edition3, ≥10% blasts are required for the ICC4.  *DNMT3A*, *FLT3*-ITD, *TET2*, *IDH1, IDH2* (Arg140), *WT1* and *N/KRAS* gene mutations are enriched in AML with *NPM1* mutation5,6.  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 intensively treated AML7 and for patients receiving less-intensive therapies (ELN 2024 Less-Intensive)8.  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 ratio7.  While comutation of *NPM1* with *DNMT3A* and *FLT3*-ITD (triple mutant) has been associated with inferior outcomes in some studies5,6,9, this profile is considered intermediate risk according to ELN 2022 criteria7.  Non-A/B/D *NPM1* mutations have been associated with increased MRD positivity and relapse from MRD negativity in intensively treated patients6.  The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML now defines ELN 2022 adverse risk7,10.  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 2022 recommends that these should not be used as an adverse prognostic marker if they co-occur with *NPM17.*  In addition to *FLT3*-ITD, concomitant signalling gene mutations (*KRAS*mut, *NRAS*mut) in AML with *NPM1* mutation have been associated with a negative prognostic impact in patients treated with less-intensive therapies8.  *NPM1* mutations are a suitable marker for measurable residual disease (MRD) monitoring11,12.  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 profile11.  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 status13.  *IDH1* and *IDH2* mutations are the target of IDH1 and IDH2 inhibitors, respectively14.  AML with *NPM1* mutationhas a transcriptional signature similar to *KMT2A*-rearranged AML, including *HOX* gene dysregulation, and is potentially targetable by menin inhibitors15.  Several mutations have been described in patients with acquired resistance to targeted inhibitors such as *FLT3* Phe691Leu (FLT3 inhibitors)16, second-site *IDH1*/*IDH2* mutations (IDH1/IDH2 inhibitors)17, *BAX* (BCL2 inhibitors)18, and *MEN1* (menin inhibitors)19.  References  **1.** Martelli MP, et al. Novel NPM1 exon 5 mutations and gene fusions leading to aberrant cytoplasmic nucleophosmin in AML. *Blood* 2021; **138**(25): 2696-701. **2.** Fournier E, et al. Molecular heterogeneity and measurable residual disease of rare NPM1 mutations in acute myeloid leukemia: a nationwide experience from the GBMHM study group. *Leukemia* 2022; **36**(5): 1390-400. **3.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.who.int/637. **4.** Arber DA, et al. 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