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| Clinical Utility of MOLECULAR Testing in  AML with *CEBPA* MUTATION  Diagnostic Utility  Mutations in the transcription factor CCAATT-enhancer binding protein alpha (*CEBPA*) occur in approximately 5%-10% of *de novo* AML, with approximately half of these cases carrying biallelic mutations (*CEBPA*bi)1,2.  *CEBPA* mutation is a defining genetic abnormality in AML according to both the International Concensus Classification (ICC) (AML with in-frame bZIP *CEBPA* mutations when blasts ≥10%)3 and the 5th edition of WHO classification (AML with *CEBPA* mutation when blasts ≥20%)2.  Of note, AML with *CEBPA* mutation as defined by WHO 5th edition includes both biallelic (*CEBPA*bi) as well as single in-frame mutations located in the bZIP domain (*CEBPA*bZIP)2.  *CEBPA*bi is most commonly characterised by the combination of an N-terminal frameshift mutation and a C-terminal in-frame mutation usually affecting the basic leucine zipper (bZIP) domain.  AML with *CEBPA* mutation is frequently associated with a normal karyotype and aberrant CD7 expression on the myeloblasts2.  Genes commonly co-mutated in AML with *CEBPA*mutation include *TET2*, *GATA2*, *WT1*, *FLT3-*ITD, *CSF3R* and *NRAS*4.  AML with germline *CEBPA* mutation is typically characterised by an N-terminal germline *CEBPA* mutation and a C-terminal somatic *CEBPA* mutation, although rare germline C-terminal mutations have been described5,6.  Investigation for the possibility of a germline *CEBPA* mutation is warranted in cases where *CEBPA* mutations are biallelic and/or observed at a germline variant allele frequency.  Prognostic Utility  *CEBPA*bi mutation is associated with favourable outcomes in normal karyotype, *FLT3*-ITD-negative AML7-9.  Patients with *CEBPA*bZIP have recently been shown to have a favourable prognosis similar to those with *CEBPA*bi mutations1,10.  Co-mutations in *CEBPA*bi have been reported to impact outcome such as *TET2* (inferior) and *GATA2* (favourable) however this is not consistent across all studies1,4,10,11.  BIOMARKERS OF RESPONSE TO THERAPY  *FLT3* mutations are the target of midostaurin12 (*FLT3*-ITD and TKD) (clinical trials included only TKD mutations at Asp835 and Ile836 codons), quizartinib (*FLT3*-ITD only)13 in newly diagnosed AML, and gilteritinib14 in relapsed/refractory AML.  *FLT3* testing should be repeated at relapse/progression as ~20% of patients have a change (gain or loss) in mutation status15.  *IDH1* (Arg132) and *IDH2* (both Arg140 and Arg172) mutations are the target of IDH1 and IDH2 inhibitors, respectively16.  Several mutations have been described in patients with acquired resistance to targeted inhibitors such as *FLT3* Phe691Leu (FLT3 inhibitors)17, second-site IDH1/IDH2 mutations (IDH1/IDH2 inhibitors)18, *BAX* (BCL2 inhibitors)19, and *MEN1* (menin inhibitors)20.  References  **1.** Taube F, et al. CEBPA Mutations in 4708 Patients with Acute Myeloid Leukemia - Differential Impact of bZIP and TAD Mutations on Outcome. *Blood* 2021. **2.** 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. **3.** Arber DA, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* 2022; **140**(11): 1200-28. **4.** Wilhelmson AS, Porse BT. CCAAT enhancer binding protein alpha (CEBPA) biallelic acute myeloid leukaemia: cooperating lesions, molecular mechanisms and clinical relevance. *Br J Haematol* 2020; **190**(4): 495-507. **5.** Pabst T, et al. Somatic CEBPA mutations are a frequent second event in families with germline CEBPA mutations and familial acute myeloid leukemia. *J Clin Oncol* 2008; **26**(31): 5088-93. **6.** Pathak A, et al. Whole exome sequencing reveals a C-terminal germline variant in CEBPA-associated acute myeloid leukemia: 45-year follow up of a large family. *Haematologica* 2016; **101**(7): 846-52.  **7.** Green CL, et al. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. *J Clin Oncol* 2010; **28**(16): 2739-47. **8.** Wouters BJ, et al. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. *Blood* 2009; **113**(13): 3088-91. **9.** Fasan A, et al. The role of different genetic subtypes of CEBPA mutated AML. *Leukemia* 2014; **28**(4): 794-803. **10.** Tarlock K, et al. CEBPA-bZip mutations are associated with favorable prognosis in de novo AML: a report from the Children’s Oncology Group. *Blood* 2021; **138**(13): 1137-47. **11.** Grossmann V, et al. CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76.8% of cases with TET2 and GATA2 alterations impacting prognosis. *Br J Haematol* 2013; **161**(5): 649-58. **12.** Stone RM, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med* 2017; **377**(5): 454-64. **13.** Erba HP, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023; **401**(10388): 1571-83. **14.** Perl AE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med* 2019; **381**(18): 1728-40. **15.** Daver N, et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia* 2019; **33**(2): 299-312. **16.** Dohner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129**(4): 424-47. **17.** Smith CC, et al. Molecular profile of FLT3-mutated relapsed/refractory patients with AML in the phase 3 ADMIRAL study of gilteritinib. *Blood Adv* 2022; **6**(7): 2144-55. **18.** Intlekofer AM, et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature* 2018; **559**(7712): 125-9. **19.** Moujalled DM, et al. Acquired mutations in BAX confer resistance to BH3-mimetic therapy in acute myeloid leukemia. *Blood* 2023; **141**(6): 634-44. **20.** Perner F, et al. MEN1 mutations mediate clinical resistance to menin inhibition. *Nature* 2023; **615**(7954): 913-9. |