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| Clinical Utility of MOLECULAR Testing in  AML with *CEBPA* MUTATION  Diagnostic Utility  Mutations in the transcription factor CCAAT-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*bi is most commonly characterised by the combination of an N-terminal frameshift mutation and a C-terminal in-frame (deletion/insertion) mutation within the basic leucine zipper (bZIP) domain3.  Inframe insertion and deletion mutations in the bZIP domain (*CEBPA* bZIPInDel), whether occurring as a single mutation or biallelic, define a distinct subgroup of AML characterised by younger age and specific comutation profile (higher rate of *GATA2* and *WT1* mutations)3.  *CEBPA* mutation is a defining genetic abnormality in AML according to both the International Consensus Classification (ICC) (AML with in-frame bZIP *CEBPA* mutation; blasts ≥10%)4 and the WHO 5th edition (AML with *CEBPA* mutation; blasts ≥20%)2. Of note, the WHO 5th does not specify the type of *CEBPA* bZIP mutation that qualifies patients for this diagnosis.  AML with *CEBPA* mutation is 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*5.  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 described6,7.  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  Patients with *CEBPA* bZIPInDelmutations (either as a single mutation or biallelic) represent a unique subgroup of AML with favourable outcomes. A favourable prognosis is not observed with other mutation types in the bZIP domain including missense, nonsense and frameshift mutations, nor in *CEBPA*bi without a bZIPInDelmutation3.  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 studies1,5,8,9 and likely reflects comutation patterns with *CEBPA* mutation types. *FLT3* and *TET2* mutations have a higher prevalence in *CEBPA* non-bZIPInDel whereas *GATA2* mutations are predominantly found in patients with *CEBPA*  bZIPInDel mutations3.  *CEBPA* bZIPInDel is categorised as favourable risk by the 2022 ELN classification, and as favourable or intermediate risk by the 2024 ELN Less-Intensive depending on the absence or presence of activating signalling gene mutations (*FLT3*-ITDpos, *NRAS*mut, *KRAS*mut), respectively10,11.  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. 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