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| cLINICAL UTILITY OF MOLECULAR TESTING IN  B-lymphoblastic leukaemia/lymphoma  DIAGNOSTIC utility  **Table. WHO 5th edition classification**  The majority of B-lymphoblastic leukaemia/lymphoma (B-ALL) cases can be classified by cytogenetic and/or molecular abnormalities in the WHO 5th edition classification (Table).  *TP53* mutations are common in low hypodiploid B-ALL1. Approximately 50% of *TP53* mutations are germline in paediatric patients with low hypodiploid B-ALL and testing of a germline sample should be considered.  Other recurrently reported genetic abnormalities include *DUX4*, *MEF2D*, *ZNF384, NUTM1* or *MYC* rearrangements, *PAX5* Pro80Arg mutation and alternative *PAX5* alterations. B-ALL with *ZNF384* rearrangement, *DUX4* rearrangement or *PAX5* Pro80Arg may show monocytic differentiation especially following therapy.  The presence of *BCR*::*ABL1* fusion in both myeloid cells and lymphoblasts (detected using fluorescence *in situ* hybridisation) probably represents lymphoid blast phase of chronic myeloid leukaemia, which shows biologically distinct behaviour from *de novo* B-ALL.  *BCR*::*ABL1*-like B-ALL encompass a variety of genetic abnormalities that activate *JAK/STAT*, *ABL*-class or other kinase signalling pathways. *JAK1* and *JAK2* activating mutations (commonly associated with *CRLF2* rearrangement), *JAK2* and *EPOR* rearrangements lead to constitutive activation of the *JAK/STAT* pathway. *ABL*-class alterations include *ABL1, ABL2, CSF1R, PDGFRA, PDGFRB* or *LYN* fusions.  PROGNOSTIC utility  The prognosis of B-ALL is influenced by clinical factors (*e.g.* age, white blood cell count at presentation and disease location), genomic factors and measurable residual disease (MRD) status after therapy.  *TP53* mutations are associated with inferior outcomes in B-ALL1,2.  B-ALL with *DUX4* rearrangementandB-ALL with *ETV6*::*RUNX1* fusionare associated with good prognosis.  B-ALL with *HLF*, *KMT2A, MEF2D* or *MYC* rearrangement and B-ALL with *BCR*::*ABL1*-like features are associated with inferior outcomes.  B-ALL with *BCR*::*ABL1* fusion was previously associated with inferior outcomes however tyrosine kinase inhibitors (TKI) have significantly improved the prognosis.  BIOMARKERS OF RESPONSE TO THERAPY  TKIs in combination with chemotherapy and/or immunotherapy is an established treatment approach in *BCR*::*ABL1* B-ALL and is associated with improved outcomes.  *BCR*::*ABL1* kinase domain mutations associated with TKI resistance may be acquired during TKI therapy but are not typically observed at high level at diagnosis3.  The role of TKIs in *BCR*::*ABL1*-like B-ALL is less clear however this is an area of current investigation and disease may be responsive to targeted inhibitors4.  *FLT3* mutations are observed in approximately 5% of B-ALL5 however the role of targeting these mutations with FLT3 inhibitors is not established.  REFERENCES  **1.** Holmfeldt L, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet* 2013; **45**(3): 242-52. **2.** Chiaretti S, et al. TP53 mutations are frequent in adult acute lymphoblastic leukemia cases negative for recurrent fusion genes and correlate with poor response to induction therapy. *Haematologica* 2013; **98**(5): e59-61. **3.** Short NJ, et al. Ultra-accurate Duplex Sequencing for the assessment of pretreatment ABL1 kinase domain mutations in Ph+ ALL. *Blood Cancer J* 2020; **10**(5): 61. **4.** Roberts KG, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014; **371**(11): 1005-15. **5.** Zhang Y, et al. The mutational spectrum of FLT3 gene in acute lymphoblastic leukemia is different from acute myeloid leukemia. *Cancer Gene Ther* 2020; **27**(1-2): 81-8. |