|  |
| --- |
| cLINICAL UTILITY OF MOLECULAR TESTING IN  B-lymphoblastic leukaemia/lymphoma  DIAGNOSTIC utility  The majority of B-lymphoblastic leukaemia/lymphoma (B-ALL) cases exhibit aneuploidy or a recurrent chromosomal rearrangement detectable by conventional cytogenetics/FISH.  B-ALL without recurrent genetic abnormalities is classified as B-ALL, NOS (“B-other”) and may be classified into additional genomic subtypes defined by distinct gene expression profiles and/or gene rearrangements and gene mutations1. These entities cannot be distinguished by this assay.  *TP53* mutations are common in low hypodiploid B-ALL2. Approximately 50% of *TP53* mutations are germline in paediatric patients with low hypodiploid B-ALL and testing of a germline sample should be considered.  Activating *JAK2* mutations (typically in exon 16) are frequently observed in *BCR*-*ABL1*-like B-ALL with *CRLF2*-rearrangement and their presence should raise the suspicion of this entity.  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 (including the classification of both established and emerging genomic entities) and measurable residual disease (MRD) status after therapy.  *TP53* mutations are associated with inferior outcomes in B-ALL2,3.  *BCR*-*ABL1* and *BCR*-*ABL1*-like B-ALL are both associated with inferior outcomes however tyrosine kinase inhibitors (TKI) have significantly improved the prognosis of *BCR*-*ABL1* B-ALL.  BIOMARKERS OF RESPONSE TO THERAPY  TKIs in combination with chemotherapy 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 diagnosis4.  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 inhibitors5.  *FLT3* mutations are observed in approximately 5% of B-ALL6 however the role of targeting these mutations with FLT3 inhibitors is not established.  REFERENCES  **1.** Paietta E, et al. Molecular classification improves risk assessment in adult BCR-ABL1-negative B-ALL. *Blood* 2021; **138**(11): 948-58. **2.** Holmfeldt L, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet* 2013; **45**(3): 242-52. **3.** 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. **4.** 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. **5.** Roberts KG, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014; **371**(11): 1005-15. **6.** 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. |