|  |
| --- |
| cLINICAL UTILITY OF MOLECULAR TESTING IN  chronic lymphocytic leukaemia/small lymphocytic lymphoma  DIAGNOSTIC utility  In addition to karotypic aberrations, a number of mutations are observed in chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) including *NOTCH1*, *BIRC3*, *SF3B1*, *MYD88*, *XPO1*, *ATM*,MAPK pathway genes (*BRAF*, *NRAS*, *KRAS*, *MAP2K1*)and *TP531,2*.  *SF3B1* mutations are observed frequently in CLL and are less frequently observed in other B cell malignancies3.  *NOTCH1* mutations are more frequently observed in *IGHV*-unmutated CLL/SLL and are enriched in cases with trisomy 124.  *MYD88* mutations are typically confined to *IGHV*-mutated cases in CLL/SLL2.  Richter syndrome (RS) may be clonally related (most common) or unrelated to the underlying CLL/SLL which may have implications for prognosis5.  *CDKN2A* deletion, *TP53* mutation/deletion, *MYC* translocation or amplification and *NOTCH1* mutations are recurrently observed in Richter syndrome (RS)5-7.  B-cell prolymphocytic leukaemia (B-PLL) is characterised by frequent *MYC* aberrations (translocation or gain) and *TP53* deletion and/or mutation. *MYC* aberrations are infrequently observed in CLL/SLL8.  PROGNOSTIC utility  In CLL/SLL, deleted and/or mutated *TP53* predicts for highly inferior outcomes to frontline chemoimmunotherapy9. While targeted agents are superior to chemoimmunotherapy in this population, 17p deletion and *TP53* mutation retain their adverse prognostic impact10,11.  The prognostic impact of low-burden *TP53* mutations (generally considered as VAF <10%) is not consistent across all studies12-16, however low-burden *TP53* mutation pre-treatment has been associated with inferior outcomes and recent data support the incorporation of low-burden *TP53* mutation into clinical decision-making13,14.  Unmutated *IGHV* status in CLL/SLL is associated with inferior outcomes and shorter time to treatment initiation9,17. Note *IGHV* somatic mutation analysis is not performed with this assay.  The prognostic impact of other gene mutations is currently uncertain in the era of targeted therapy.  Approximately one third of patients with CLL/SLL can be grouped into stereotyped B-cell receptor immunoglobulin subsets. Stereotyped subsets #1, #2 and #8 are associated with a more aggressive clinical course. Subset #8 is associated with the highest risk of Richter transformation18.  BIOMARKERS OF RESPONSE TO THERAPY  Acquired resistance to BTK inhibitors in CLL/SLL is associated with recurrent mutations involving *BTK* (most commonly *BTK* Cys481Ser) and *PLCG2* (Arg665Trp, Leu845Phe and Ser707Tyr)19.  Acquired mutations in *BCL2* (Gly101Val, Asp103Tyr and others) are observed in patients with CLL/SLL progressing on venetoclax and confer resistance to venetoclax20.  REFERENCES  **1.** Landau DA, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature* 2015; **526**(7574): 525-30. **2.** Baliakas P, et al. Recurrent mutations refine prognosis in chronic lymphocytic leukemia. *Leukemia* 2015; **29**(2): 329-36. **3.** Quesada V, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. *Nat Genet* 2012; **44**(1): 47-52. **4.** Balatti V, et al. NOTCH1 mutations in CLL associated with trisomy 12. *Blood* 2012; **119**(2): 329-31. **5.** Rossi D, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood* 2011; **117**(12): 3391-401. **6.** Chigrinova E, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood* 2013; **122**(15): 2673-82. **7.** Fabbri G, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med* 2013; **210**(11): 2273-88. **8.** Chapiro E, et al. Genetic characterization of B-cell prolymphocytic leukemia: a prognostic model involving MYC and TP53. *Blood* 2019; **134**(21): 1821-31. **9.** Fischer K, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood* 2016; **127**(2): 208-15. **10.** Tausch E, et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. *Blood* 2020; **135**(26): 2402-12. **11.** Ahn IE, et al. Prediction of Outcome in Patients With Chronic Lymphocytic Leukemia Treated With Ibrutinib: Development and Validation of a Four-Factor Prognostic Model. *Journal of Clinical Oncology* 2021; **39**(6): 576-85. **12.** Rossi D, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. *Blood* 2014; **123**(14): 2139-47. **13.** Malcikova J, et al. Low-burden TP53 mutations in CLL: Clinical impact and clonal evolution within the context of different treatment options. *Blood* 2021. **14.** Nadeu F, et al. Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. *Blood* 2016; **127**(17): 2122-30. **15.** Brieghel C, et al. Deep targeted sequencing of TP53 in chronic lymphocytic leukemia: clinical impact at diagnosis and at time of treatment. *Haematologica* 2019; **104**(4): 789-96. **16.** Blakemore SJ, et al. Clinical significance of TP53, BIRC3, ATM and MAPK-ERK genes in chronic lymphocytic leukaemia: data from the randomised UK LRF CLL4 trial. *Leukemia* 2020; **34**(7): 1760-74. **17.** Stamatopoulos B, et al. Targeted deep sequencing reveals clinically relevant subclonal IgHV rearrangements in chronic lymphocytic leukemia. *Leukemia* 2017; **31**(4): 837-45. **18.** Stamatopoulos K, et al. Antigen receptor stereotypy in chronic lymphocytic leukemia. *Leukemia* 2017; **31**(2): 282-91. **19.** Woyach JA, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med* 2014; **370**(24): 2286-94. **20.** Blombery P, et al. Acquisition of the Recurrent Gly101Val Mutation in BCL2 Confers Resistance to Venetoclax in Patients with Progressive Chronic Lymphocytic Leukemia. *Cancer Discov* 2019; **9**(3): 342-53. |