|  |
| --- |
| cLINICAL UTILITY OF MOLECULAR TESTING IN  chronic myeloid leukaemia  DIAGNOSTIC utility  Chronic myeloid leukaemia (CML) is characterised by the reciprocal translocation t(9;22)(q34.1;q11.2), resulting in the *BCR*::*ABL1* fusion gene.  The p210 BCR::ABL1 fusion protein (p210) is detected in the vast majority of CML cases, encoded by either e13a2 (b2a2) or e14a2 (b3a2) fusion transcripts, or both1.  Rarely, a larger p230 fusion protein (p230) is encoded, characterised by prominent neutrophilic maturation and/or thrombocytosis2.  The p190 fusion protein (p190), resulting from the fusion transcript e1a2, is most frequently associated with Ph-positive ALL, however it occurs as the sole BCR::ABL1 isoform at diagnosis in a minority of CML cases (1%-2%) and has been associated with monocytosis3. The p190 may also be co-expressed at low levels with p2104.  Accelerated phase CML has been omitted by the WHO 5th edition as the outcomes are similar to those presenting in chronic phase in the tyrosine kinase inhibitor (TKI) era 5,6.  Non-*BCR*::*ABL1* mutations in other genes are observed in a proportion of chronic phase CML patients, including *ASXL1*, *TET2*, and *DNMT3A*7-9, but are also observed in clonal haematopoiesis of indeterminate potential (CHIP)10.  In additional to karoytypic abnormalities, mutations may be detected in blast phase CML including *BCR*::*ABL1* kinase domain mutations (45%), *RUNX1* (15%-20%), *ASXL1* (15%-20%), and *IKZF1* (deletion or mutation)7,11,12.  PROGNOSTIC UTILITY  Additional chromosomal abnormalities (ACAs) in Philadelphia chromosome-positive cells at diagnosis are associated with an increased risks of progression to blast phase. These ACAs including 3q26.2 rearrangements, monosomy 7, isochromosome 17q and complex karyotype5.  Monitoring of the *BCR*::*ABL1* transcript is crucial to ensure achievement of on-therapy milestones including 3 (≤10%), 6 (<1%), and 12 months (≤0.1%), as well as assessing eligibility for treatment discontinuation, and to detect loss of major molecular remission during treatment-free remission13.  Emergence of new ACAs or compound mutations in the kinase domain of *BCR*::*ABL1* are associated with increased risk of disease progression5.  BIOMARKERS OF RESPONSE TO THERAPY  The *BCR*::*ABL1* oncoprotein is the target of TKIs14-16.  Acquired point mutations in the kinase domain of *BCR*::*ABL1* are a common cause of resistance to tyrosine kinase inhibitors13,17,18. With superior detection sensitivity, NGS (performed on cDNA) is now recommended over Sanger sequencing for detection of *BCR*::*ABL1* resistance mutations in patients not responding adequately to TKI13.  Specific *ABL1* mutations have differing reported sensitivities to available TKIs and these should be considered when selecting a TKI19.  Ponatinib is an effective TKI for CML with an *ABL1* Thr315Ile (*BCR*::*ABL1*T315I) mutation which confers resistance to both nilotinib and dasatinib20.  Asciminib, a first-in-class allosteic inhibitor specifically targeting the ABL myristoyl pocket (aka STAMP), is effective in CML with kinase domain mutations conferring resistance to TKI, including *ABL1* Thr315Ile. However, resistance to asciminib has been reported due to myristoyl pocket mutations21.  REFERENCES  **1.** Hanfstein B, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. *Haematologica* 2014; **99**(9): 1441-7. **2.** Pane F, et al. Neutrophilic-chronic myeloid leukemia: a distinct disease with a specific molecular marker (BCR/ABL with C3/A2 junction). *Blood* 1996; **88**(7): 2410-4. **3.** Melo JV, et al. P190BCR-ABL chronic myeloid leukaemia: the missing link with chronic myelomonocytic leukaemia? *Leukemia* 1994; **8**(1): 208-11. **4.** van Rhee F, et al. p190 BCR-ABL mRNA is expressed at low levels in p210-positive chronic myeloid and acute lymphoblastic leukemias. *Blood* 1996; **87**(12): 5213-7. **5.** 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. **6.** Geelen IGP, et al. Influence of WHO versus ELN advanced phase chronic myeloid leukemia definitions on overall survival. *Eur J Haematol* 2017; **99**(4): 381-2. **7.** Adnan-Awad S, et al. Mutational landscape of chronic myeloid leukemia: more than a single oncogene leukemia. *Leuk Lymphoma* 2021; **62**(9): 2064-78. **8.** Nteliopoulos G, et al. Somatic variants in epigenetic modifiers can predict failure of response to imatinib but not to second-generation tyrosine kinase inhibitors. *Haematologica* 2019; **104**(12): 2400-9. **9.** Kim T, et al. Spectrum of somatic mutation dynamics in chronic myeloid leukemia following tyrosine kinase inhibitor therapy. *Blood* 2017; **129**(1): 38-47. **10.** Jaiswal S, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; **371**(26): 2488-98. **11.** Adnan Awad S, et al. Mutation accumulation in cancer genes relates to nonoptimal outcome in chronic myeloid leukemia. *Blood Adv* 2020; **4**(3): 546-59. **12.** Grossmann V, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. *Leukemia* 2011; **25**(3): 557-60. **13.** Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* 2020; **34**(4): 966-84. **14.** O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; **348**(11): 994-1004. **15.** Saglio G, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362**(24): 2251-9. **16.** Kantarjian H, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010; **362**(24): 2260-70. **17.** Jabbour E, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. *Leukemia* 2006; **20**(10): 1767-73. **18.** Shah NP, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. *Cancer Cell* 2002; **2**(2): 117-25. **19.** Branford S, et al. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? *Blood* 2009; **114**(27): 5426-35. **20.** Cortes JE, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013; **369**(19): 1783-96. **21.** Yeung DT, et al. Asciminib: a new therapeutic option in chronic-phase CML with treatment failure. *Blood* 2022; **139**(24): 3474-9. |