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| 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 allosteric 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, secondary resistance to asciminib has been reported due to acquired myristoyl pocket mutations21. Additionally, primary resistance has been reported with rare transcript isoforms (e13a3 and e14a3) lacking the *ABL1* exon 222.  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. 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