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| Clinical utility of molecular testing in  acute Promyelocytic leukaemia  Diagnostic Utility  Acute promyelocytic leukaemia (APML or APL) is characterised by the expansion of leukaemic cell block at the promyelocytic stage. Upon clinical suspicion of the disease, rapid confirmation by molecular testing is mandatory.1  A majority of cases with APL harbour the t(15;17)(q24;q21) translocation, resulting in the generation of a chimeric fusion gene involving the *PML* and *RARA* genes. The genomic breakpoints in the *PML* gene are usually located within intron 6, exon 6 or intron 3, fusing invariably to intron 2 of the *RARA* gene, producing the *bcr1, bcr2* and *bcr3* transcript isoforms respectively.2  Less commonly, *RARA* may have a fusion partner other than *PML*. These may include *ZBTB16* (formerly *PLZF), NPM1, NUMA, STAT5B* and at least nine others have been reported to date*.* In addition, gene fusion may uncommonly involve alternative retinoic acid receptor genes (*e.g.* *RARB* or *RARG*).3,4  The detection of *PML::RARA* defines acute promyelocytic leukaemia (APL) with *PML::RARA* fusion regardless of blasts percentage.5 Additionally, “APL with other *RARA* rearrangements” is recognised as a separate acute myeloid leukaemia (AML) entity by the International Consensus Classification (ICC).6  Prognostic Utility  Recurrent comutations detected in APL include *FLT3* (ITD and TKD), *WT1*, *NRAS* and *KRAS*.7,8 The prognostic significance of these are uncertain, particularly in the era of arsenic trioxide (ATO) therapy,9 and their routine detection at diagnosis is not recommended by the European LeukemiaNet (ELN) expert panel.1  Measurable residual disease (MRD) assessment at the end of consolidation therapy is recommended to inform relapse risk by the ELN.1,10 Subsequent molecular monitoring following achievement of MRD negativity is dependent on disease risk. In contrast, there is a lack of clinical value in molecular assessment at the end of induction and this is not routinely recommended.1  BIOMARKERS OF RESPONSE TO THERAPY  APL with gene fusions other than *PML::RARA* may result in resistance to ATRA and/or arsenic trioxide (ATO) therapies. In these cases, chemotherapy based regimens may be required.1  *ZBTB16::RARA* is the most common variant reported and is associarted with poor response to ATRA and ATO.1 *STAT3::RARA, STAT5B::RARA, TBLR1::RARB,* and *CPSF6::RARG* has also been associated with poor response to ATRA and ATO, but evidence for these variant fusions are limited to case reports or small case series.1,3,4,11  *RARA* fusions with *NPM1*, *NUMA*, *FNDC3B*, and *IRF2BP2* have been reported to be sensitive to ATRA.1,3,4,11  In disease relapse, missense mutations in *PML* (typically located in a hotspot cluster Cys212 to Ser220 within the B2 domain associated with ATO resistance12,13) and *RARA* genes (typically the ligand binding domain) have been described.7,8 However, optimal management of relapsed cases harbouring these variants has not yet been defined.1  References  **1.** Sanz MA, et al. 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