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| cLINICAL UTILITY OF MOLECULAR TESTING IN mantle cell lymphoma  DIAGNOSTIC utility  Mantle cell lymphoma (MCL) is characterised by t(11;14)(q13;q32) in the vast majority of cases, leading to increased *CCND1* transcription and cyclin D1 protein overexpression1.  A small subset of MCL cases are cyclin D1 negative, with indistinguishable morphology, immunophenotypes and gene-expression profiles to cyclin D1 positive MCL. The majority (>90%) of these cases have rearrangements of *CCND2* and *CCND3* with immunoglobulin genes (not detected by this assay)1-3.  There are two recognised subtypes of MCL with differing biological and clinical features: Classic MCL (cMCL) expresses the oncogenic transcription factor SOX11, has unmutated/minimally mutated *IGHV* rearrangements and accumulates high numbers of genetic alterations. Leukaemic, non-nodal MCL (nnMCL) typically has hypermutated *IGHV* rearrangements, does not express SOX11, is more genetically stable and is associated with a more indolent course1,4,5.  Recurrently mutated genes in MCL include *ATM*, *TP53*, *CCND1*, *WHSC1*, *KMT2D*, *BIRC3*, *NOTCH1* and *NOTCH2*6-9.  PROGNOSTIC utility  *TP53* mutations in MCL are associated with inferior outcomes including inferior overall survival and progression-free survival8,10. Intensified standard-of-care chemoimmunotherapy regimens in young patients may not overcome the deleterious effects of *TP53* mutations8.  BIOMARKERS OF RESPONSE TO THERAPY  Approximately one third of patients with MCL have primary resistance to ibrutinib. Primary resistance to ibrutinib has been associated with mutations in a number of genes including *CARD11, TRAF2* and *BIRC3*11,12.  Secondary / acquired resistance to Bruton's tyrosine kinase inhibitors (BTKi) can develop due to *BTK* Cys481Ser mutations in the kinase domain of BTK which disrupt the BTKi binding site, however these are less commonly observed in MCL compared to chronic lymphocytic leukaemia13,14.  Alterations in the SWI/SNF chromatic remodelling complex (including *SMARCA4* mutations) have been associated with resistance to treatment with ibrutinib-venetoclax in MCL9,15.  REFERENCES  **1.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Martín-Garcia D, et al. CCND2 and CCND3 hijack immunoglobulin light-chain enhancers in cyclin D1− mantle cell lymphoma. *Blood* 2019; **133**(9): 940-51. **3.** Salaverria I, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. *Blood* 2013; **121**(8): 1394-402. **4.** Ondrejka SL, et al. Indolent mantle cell leukemia: a clinicopathological variant characterized by isolated lymphocytosis, interstitial bone marrow involvement, kappa light chain restriction, and good prognosis. *Haematologica* 2011; **96**(8): 1121-7. **5.** Fernàndez V, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. (1538-7445 (Electronic)). **6.** Bea S, et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. *Proc Natl Acad Sci U S A* 2013; **110**(45): 18250-5. **7.** Yang P, et al. Genomic landscape and prognostic analysis of mantle cell lymphoma. *Cancer Gene Therapy* 2018; **25**(5): 129-40. **8.** Eskelund CW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood* 2017; **130**(17): 1903-10. **9.** Agarwal R, et al. Dynamic molecular monitoring reveals that SWI-SNF mutations mediate resistance to ibrutinib plus venetoclax in mantle cell lymphoma. *Nat Med* 2019; **25**(1): 119-29. **10.** Ferrero S, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. *Haematologica* 2020; **105**(6): 1604-12. **11.** Rahal R, et al. Pharmacological and genomic profiling identifies NF-kappaB-targeted treatment strategies for mantle cell lymphoma. *Nat Med* 2014; **20**(1): 87-92. **12.** Wu C, et al. Genetic heterogeneity in primary and relapsed mantle cell lymphomas: Impact of recurrent CARD11 mutations. *Oncotarget* 2016. **13.** Martin P, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. *Blood* 2016; **127**(12): 1559-63. **14.** Chiron D, et al. Cell-Cycle Reprogramming for PI3K Inhibition Overrides a Relapse-Specific C481S <em>BTK</em> Mutation Revealed by Longitudinal Functional Genomics in Mantle Cell Lymphoma. *Cancer Discovery* 2014; **4**(9): 1022-35. **15.** Zhao S, et al. Efficacy of venetoclax in high risk relapsed mantle cell lymphoma (MCL) - outcomes and mutation profile from venetoclax resistant MCL patients. *American Journal of Hematology* 2020; **95**(6): 623-9. |