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| cLINICAL UTILITY OF MOLECULAR TESTING IN PLASMA CELL MYELOMA  DIAGNOSTIC utility  The majority of cases of plasma cell myeloma (PCM) are either hyperdiploid (manifested by trisomies of several odd-numbered chromosomes) or harbour translocations involving the IGH locus1.  Approximately 40%–50% of newly diagnosed multiple myeloma patients have somatic RAS/MAPK pathway mutations (*KRAS*, *NRAS* and *BRAF*)1,2.  Recurrent mutations are also observed in genes involved in RNA metabolism (*e.g.* *DIS3*, *FAM46C*), DNA repair pathway (*e.g. TP53*, *ATM*)and NF-κB signalling pathway (*e.g.* *TRAF3*, *CYLD*)1,2*.*  *MYD88* Leu265Pro mutations are not observed in PCM. If detected, alternate diagnoses particularly Waldenström macroglobulinaemia/lymphoplasmacytic lymphoma should be considered.  Plasmablastic lymphoma (PBL) is characterised by a high frequency of *MYC* translocations and RAS/MAPK pathway mutations (*KRAS*, *NRAS* and *BRAF*),in addition to mutations in *STAT3* and *TP53*3*.* Unlike PCM, *FAM46C* and *DIS3* mutations are not common in PBL.  PROGNOSTIC utility  Karyotypic events have a stronger impact on prognosis than gene mutations in PCM1.  Biallelic *TP53* inactivation (deletion and mutation) confers a poor prognosis in PCM4,5.  The prognostic significance of monoallelic *TP53* mutation without del(17p) is currently uncertain.  BIOMARKERS OF RESPONSE TO THERAPY  Activating RAS/MAPK pathway mutations represent a potential target of MEK inhibition6.  REFERENCES  **1.** Bolli N, et al. Analysis of the genomic landscape of multiple myeloma highlights novel prognostic markers and disease subgroups. *Leukemia* 2018; **32**(12): 2604-16. **2.** Walker BA, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood* 2018; **132**(6): 587-97. **3.** Frontzek F, et al. Molecular and functional profiling identifies therapeutically targetable vulnerabilities in plasmablastic lymphoma. *Nat Commun* 2021; **12**(1): 5183. **4.** Walker BA, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia* 2019; **33**(1): 159-70. **5.** Corre J, et al. del(17p) without TP53 mutation confers a poor prognosis in intensively treated newly diagnosed patients with multiple myeloma. *Blood* 2021; **137**(9): 1192-5. **6.** Heuck CJ, et al. Inhibiting MEK in MAPK pathway-activated myeloma. *Leukemia* 2016; **30**(4): 976-80. |