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ONCOLOGY: *Plasma Cell Neoplasms*

Biomarkers (Chromosomal)	Specific Alterations	Result Interpretation/ Significance
IGH::CCND1 fusion**	t(11;14) translocation	Standard- risk[$^] ; often associated with non-hyperdiploid karyotype
IGH::CCND3 fusion	t(6;14) translocation	Standard-risk[$]; often associated with non-hyperdiploid karyotype
del 13q / -13**	a minimally deleted region lies between 13q14.11–13q14.3	Standard-risk of progression in SMM[$]. Effect on prognosis is not clear in MM[$]. Negative prognostic factor only when observed on metaphase cytogenetics or associated with other high-risk cytogenetic lesions[$]
Hyperdiplody (a total chromosome number of 48 - 74)	Gain of (three or more) chromosomes 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21	Standard-risk[^A]. A favorable survival outcome if no co-existent high-risk cytogenetic lesions (higher risk of progression to MM in MGUS and SMM)
del17p13 / -17**	Deletion of *TP53* on 17p13 and loss of heterozygosity of *TP53* along with mutation of another allele	High-risk[#$^], a poor prognosis (when present in ≥ 60% of myeloma cells)
IGH::NSD2 fusion**	t(4;14) translocation leading to overexpression of the histone methyltransferase MMSET (WHSC1/NSD2)	High-risk[#$^], a poor prognosis; often associated with non-hyperdiploid karyotype (shorter time of progression in MGUS and SMM)
IGH::MAF fusion**	t(14;16) translocation	High-risk[#$^], poor prognosis; often associated with non-hyperdiploid karyotype
IGH::MAFA fusion	t(8;14) translocation	Rare
IGH::MAFB fusion**	t(14;20) translocation	High-risk[$^], poor prognosis; often associated with non-hyperdiploid karyotype
t(14;unknown)	*IGH* with an unknown fusion partner	Standard-risk
MYC::Various fusion partners	Various fusion partners include *IGH, IGL, IGK, FAM46C, FOXO3*, and *BMP6*, etc.	High-risk associated with high disease burden and an adverse prognostic factor
hypodiploidy and tetraploidy	Hypodiploidy (≤44 chromosomes), and near-tetraploidy (81-103 chromosomes)	Unfavorable outcome[$]
Near-triploidy (58-80)	Heterogeneous group, be cautious of masked doubling of hypodiploidy	If it is doubling of hypodiploidy, poor prognosis; otherwise unclear, may be standard prognosis
Other chromosomal abnormalities	Chromosomal abnormalities without high-risk ones	Standard-risk
t(14;unknown)	*IGH* with an unknown fusion partner	Standard-risk
Complex karyotype	≥3 abnormalities by metaphase chromosome study	High-risk**
Normal		Standard-risk
Double/triple hit Myeloma	Double hit: any 2 high risk genetic abnormalities; Triple hit: ≥3 high risk genetic abnormalities	High risk[^]
Secondary Chromosomal Abnormalities		
1p**	Deletion of 1p, loss of *CDKN2C, FAM46C* genes	High risk of progression in SMM[$], Intermediate-risk MM[$]
1q**	Gain (3 copies) or amplification (≥4 copies); dosage effect of genes like *CKS1B*	High risk of progression in SMM[$], Intermediate-risk in MM[$], High risk[^]
Monosomy 13	Loss of chromosome 13 by metaphase chromosome study	Standard-risk
Monosomy 14	Loss of chromosome 14	Standard-risk

Monosomy 17/17p-	Loss of chromosome 17 or 17p	High-risk, poor prognosis
Biomarkers (Molecular)[B]		
ATM, ATR, TP53, ZNFHX4	Mutations	High-risk, unfavorable prognosis
CCND1	Mutations	Unfavorable prognosis
CYLD	Mutations (loss of function)	Associated with aggressive disease
DIS3	Mutations	Unfavorable prognosis
EGR1	Mutations (missense)	Favorable prognosis
FAM46C *TENT5C*	Loss or mutations	Common secondary genetic event, Unfavorable prognosis
FAT3	Mutations	Promote disease progression
IRF4	Mutations	Favorable prognosis
KRAS, NRAS, BRAF	Mutations	Subclone associated with disease progression
Biomarkers (Molecular)[B] *Continued*		
RB1	Mutations	Unfavorable prognosis
ROBO1	Mutations (truncations)	Unfavorable prognosis
SP140	Mutations (truncations)	May be present in hyperdiploid clone
TRAF3	Mutations (loss of function)	Associated with MM development
Germline Biomarkers		
ULK4, TRAK1, DNMT3A, DNAH11, CDCA7L, DIS3	Pathogenic or likely pathogenic mutations	Predisposition to MM
Emerging Biomarkers		
Gene expression profiling	Gene expression analysis of MM prognostic risk signature	High- or low-risk for disease progression based on gene expression scores
Molecular monitoring minimal residual disease (MRD)	High-sensitivity flow cytometry or next-generation sequencing (NGS)-based assays for MM biomarkers	May provide prognostic stratification and treatment decisions in MM
Liquid biopsy (blood biopsy, cell-free DNA, microRNAs)	Molecular profile of circulatory tumor cells along with the nucleic acids released from the tumor cells in peripheral circulation	May provide the disease biologically relevant information, treatment response, and MRD for determining the occurrence of relapse in MM

**NCCN recommendation; #R-ISS; $IMWG; ^mSMART; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma, SMM: smoldering multiple myeloma; A: Co-existent high risk IgH translocations and del 17p may ameliorate adverse prognosis. The presence of multiple high-risk genetic abnormalities appears to cumulatively increase risk compared with the presence of a single high-risk abnormality. Combinations of ≥3 high-risk abnormalities confer ultra high-risk; B: not a comprehensive gene list.

Samples to Test: Bone marrow (most recent) is preferred if available and adequate; other lesions targeted are acceptable, if collected appropriately.

Sample Types to Test: Fresh bone marrow aspirate for karyotyping, FISH, chromosomal microarray, and molecular tests (CD138 enrichment should preferably be used for FISH/microarray, sequencing-based assay, and gene expression profiling); fixed aspirate smear slides or formalin-fixed, paraffin embedded tissue (FFPE) sections of bone marrow clot section (if adequate) for FISH studies.

Where to Test: Testing should be performed in the laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

References:

1. NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma Version 3.2023 (12/8/2022)
2. Alaggio, Rita, *et al.* "The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms." Leukemia (2022): 1-29. [until official WHO bluebook is out]Kumar SK, Rajkumar SV. The multiple myelomas - current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018 Jul;15(7):409-421. doi: 10.1038/s41571-018-0018-y. PMID: 29686421.
3. Manier S, *et al.* Genomic complexity of multiple myeloma and its clinical implications. Nature reviews clinical oncology **14**, pages100–113 (2017)
4. Palumbo, A. *et al.* Revised international staging system for multiple myeloma: a report from international myeloma working group. J. Clin. Oncol. 33, 2863–2869 (2015).
5. Mikhael, J. R. *et al.* Management of newly diagnosed symptomatic multiple myeloma: updated mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines 2013. Mayo Clin. Proc. 88, 360–376 (2013). Last reviewed Feb 2023
6. Sonneveld P *et. al.*Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016 Jun 16;127(24):2955-62. doi: 10.1182/blood-2016-01-631200. Epub 2016 Mar 21. PMID: 27002115; PMCID: PMC4920674.
7. Chng, W. J. *et al.* IMWG consensus on risk stratification in multiple myeloma. Leukemia 28, 269–277 (2014).

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