

## Molecular In My Pocket™... ONCOLOGY: Plasma Cell Neoplasms

Biomarkers (Chromosomal)	Specific Alterations	Result Interpretation/ Significance
<i>CCND1::IGH</i> fusion**	t(11;14) translocation	Standard- risk <sup>§^</sup> ; often associated with non-hyperdiploid karyotype
<i>CCND3::IGH</i> fusion	t(6;14) translocation	Standard-risk <sup>§</sup> ; often associated with non-hyperdiploid karyotype
del 13q / -13**	13q deletion with a minimally deleted region lies between 13q14.11–13q14.3	Negative prognostic factor only when observed on metaphase cytogenetics or associated with other high-risk cytogenetic lesions <sup>§</sup>
del17p13 / -17**	Deletion of <i>TP53</i> on 17p13 and loss of heterozygosity of <i>TP53</i> along with mutation of another allele	High-risk <sup>§^</sup> , a poor prognosis (when present in ≥ 60% of myeloma cells)
<i>FGFR3::IGH</i> fusion**	t(4;14) translocation leading to overexpression of the histone methyltransferase MMSET ( <i>WHSC1/NSD2</i> )	High-risk <sup>§^</sup> /intermediate risk <sup>^</sup> , a poor prognosis; often associated with non-hyperdiploid karyotype (shorter time of progression in MGUS and SMM)
Hyperdiploidy (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 <sup>^A</sup> . A favorable survival outcome if no co-existent high-risk cytogenetic lesions (higher risk of progression to MM in MGUS and SMM)
<i>MAF::IGH</i> fusion**	t(14;16) translocation	High-risk <sup>§^</sup> , poor prognosis; often associated with non-hyperdiploid karyotype
<i>MAFA::IGH</i> fusion	t(8;14) translocation	Rare
<i>MAFB::IGH</i> fusion**	t(14;20) translocation	High-risk <sup>§^</sup> , poor prognosis; often associated with non-hyperdiploid karyotype
<i>MYC</i> ::Various fusion partners	Various fusion partners include <i>IGH</i> , <i>IGL</i> , <i>IGK</i> , <i>FAM46C</i> , <i>FOXO3</i> , and <i>BMP6</i> , etc.	High-risk associated with high disease burden and an adverse prognostic factor
non-hyperdiploidy (<48 or >75)	Hypodiploid (≤44 chromosomes), pseudodiploid (45–46 chromosomes) and near tetraploid (>75 chromosomes)	Unfavorable outcome <sup>§</sup>
Other chromosomal abnormalities	Chromosomal abnormalities without high-risk ones	Standard-risk
t(14;unknown)	<i>IGH</i> with an unknown fusion partner	Standard-risk
<b>Secondary Chromosomal Abnormalities</b>		
1p**	Deletion of 1p, loss of <i>CDKN2C</i> , <i>FAM46C</i> genes	Negative effect on survival, may be associated with 1q amplification
1q**	Gain or amplification; dosage effect of genes like <i>CKS1B</i>	Intermediate-risk <sup>§^</sup>
Monosomy 13	Loss of chromosome 13	Standard-risk
Monosomy 14	Loss of chromosome 14	Standard-risk
Monosomy 17/17p-	Loss of chromosome 17 or 17p	High-risk, poor prognosis
<b>Biomarkers (Molecular)<sup>B</sup></b>		
<i>ATM</i> , <i>ATR</i> , <i>TP53</i> , <i>ZNFHX4</i>	Mutations	High-risk, unfavorable prognosis
<i>CCND1</i>	Mutations	Unfavorable prognosis
<i>CYLD</i>	Mutations (loss of function)	Associated with aggressive disease
<i>DIS3</i>	Mutations	Unfavorable prognosis
<i>EGR1</i>	Mutations (missense)	Favorable prognosis
<i>FAM46C</i> <i>TENT5C</i>	Loss or mutations	Common secondary genetic event, Unfavorable prognosis
<i>FAT3</i>	Mutations	Promote disease progression
<i>IRF4</i>	Mutations	Favorable prognosis
<i>KRAS</i> , <i>NRAS</i> , <i>BRAF</i>	Mutations	Subclone associated with disease progression

<b>Biomarkers (Molecular)<sup>B</sup> Continued</b>		
<i>RB1</i>	Mutations	Unfavorable prognosis
<i>ROBO1</i>	Mutations (truncations)	Unfavorable prognosis
<i>SP140</i>	Mutations (truncations)	May be present in hyperdiploid clone
<i>TRAF3</i>	Mutations (loss of function)	Associated with MM development
<b>Germline Biomarkers</b>		
<i>ULK4, TRAK1, DNMT3A, DNAH11, CDCA7L, DIS3</i>	Pathogenic or likely pathogenic mutations	Predisposition to MM
<b>Emerging Biomarkers</b>		
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  $\geq 3$  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 5.2022 (3/9/2022)
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).
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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Revised 9/2022