



Review Article

Recent Advances in The Definition of the Molecular Alterations Occurring in Multiple Myeloma

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Abstract. Multiple myeloma (MM) is a disorder of the monoclonal plasma cells and is the second most common hematologic malignancy. MM initiation and progression are dependent upon complex genomic abnormalities. The current pathogenic model of MM includes two types of primary events, represented by chromosome translocations or chromosome number alterations resulting in hyperdiploidy. These primary molecular events are observed both in MM and in monoclonal gammopathy, its premalignant precursor. Subsequent genetic events allow the progression of monoclonal gammopathy to MM and, together with primary events, contribute to the genetic complexity and heterogeneity of MM.

Newer therapies have considerably improved patient outcomes; however, MM remains an incurable disease and most patients experience multiple relapses.

The dramatic progresses achieved in the analysis of the heterogeneous molecular features of different MM patients allowed a comprehensive molecular classification of MM and the definition of an individualized prognostic model to predict an individual MM patient's response to different therapeutic options. Despite these progresses, prognostic models fail to identify a significant proportion of patients destined to early relapse. Treatment strategies are increasingly. Based on disease biology, trials are enriched for high-risk MMs, whose careful definition and categorization requires DNA sequencing studies.

Keywords: Multiple Myeloma; Chromosome Abnormalities; Molecular Events; Mutations.

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Introduction. Multiple myeloma (MM) is a malignant disease of mature B-cell lineage, characterized by the proliferation and accumulation of plasma cells (PCs) in bone marrow with consequent production of a monoclonal antibody. The development of MM is a multistep process through three different tumor stages: (i) an asymptomatic premalignant condition, known as monoclonal gammopathy of undermined significance (MGUS), characterized by the presence in the bone marrow of few abnormal plasma cells and of a

monoclonal (M) protein instead of normal antibodies; (ii) a more advanced condition, called smoldering multiple myeloma (SMM), characterized by a higher serum level of M protein and a higher percentage of abnormal PCs in BM; about 50% of patients with SMM show a progressive increase of monoclonal protein and develop MM.^{1,2}

Genetic Alteration in Multiple Myeloma. Cytogenetic studies have shown that MM can be split into cases with

primary immunoglobulin translocations and cases with hyperdiploidy with trisomies of the odd-number chromosomes: the most frequent translocations are t(11;14), t(4;14), t(14;16), t(14;20) and t(6;14); the most frequent copy number gains and losses are del13q, 1q1, del14q, del6q, del1p and del17p.³ (Table 1 and Table 2)

Table 1. Primary and secondary abnormalities in MM.

Primary cytogenetic Abnormalities	Secondary cytogenetic Abnormalities
-IGH translocations	-1q21 gain/amp
	-1p deletion
-IGH Hyperdiploidy	-17p deletion
	-MYC translocations

Primary Genetic Abnormalities in MM.

Hyperdiploidy. Hyperdiploid MMs are characterized by recurrent chromosome gains, called chromosomal numerical abnormality (CNA). These tumors have 48-75 chromosomes, usually with extra copies of three more specific chromosomes. Hyperdiploid tumors rarely (about 10%) have a primary IgH translocation. The molecular mechanism responsible for development of hyperdiploidy is seemingly related to errors in chromosome segregation during the highly proliferative germinal centre phase of plasma cell ontogeny, as a result of a single catastrophic mitotic event or of multiple aberrant segregation events.⁴

In hyperdiploid MMs gains in chromosomes 19 (95%), 15 (90%) and 9 (90%) are the most frequent events, followed by gains in other chromosomes, such as 5, 11, 3, 7 and 21; del13 is the most common deletion event, observed in 37% of these tumors; the majority of events occurring at lower frequencies in these tumors are deletions; the large majority (>90%) of hyperdiploid tumors had concurrent gains in at least two of the three chromosomes most frequently associated with trisomies.⁵ In the non-hyperdiploid MMs, gain of chromosome 11 (92% of patients) and del 13 (99%) and gain of 1q are the most frequent clonal events, suggesting an important role in the early stages of disease.⁵

A chronological reconstruction of aneuploidies acquisition in hyperdiploid patients showed that: in individual patients pronounced changes in their karyotype were observed over time, including chromosome gains; in 13/18 hyperdiploid patients, cumulative acquisition of copy-number gains was observed, while in the remaining 5 patients trisomies were acquired in one single time window.⁶

The group of hyperdiploid MMs is heterogeneous for the variable association with additional genetic alterations. Hyperdiploid MMs can be subdivided into two subgroups according to the presence or not of concomitant gain(11q25); tumors lacking gain(11q25) characterized by gain(1q).⁷

Barilà and coworkers have defined two subsets of

hyperdiploid MM patients, one characterized by 5 trisomies and defined as T-HRD and the other one by <5 trisomies and defined as N-HRD; T-HRD were characterized by a better outcome than N-HRD patients (mOS 57 vs 32 months).⁸ T-HRD MMs were associated with low rates of FISH alterations compared to N-HRD.⁸

MM patients with hyperdiploidy have a better survival than those without hyperdiploidy when treated with novel anti-myeloma agents.⁹ However, the presence of hyperdiploidy cannot ameliorate the negative prognostic impact of concurrent high-risk cytogenetic abnormalities.⁹ Samur and coworkers, through whole genome sequencing identified a subgroup of MM patients (17% of total), 90% hyperdiploid, with low DNA damage (low genomic scar score with chromosome 9 gain), with frequent *NRAS* mutations, associated with very good outcome (100% overall survival at 69 months).¹⁰

Although it is currently assumed that the two founding events in MM pathogenesis, hyperdiploidy and IgH translocations are mutually exclusive, it was observed that in 4% of newly diagnosed MM patients hyperdiploidy and IgH translocations occur concurrently.¹¹

IgH Translocations. IgH translocations have an important oncogenic effect, placing oncogenes under the control of strong enhancers (Ig heavy chain (IgH) loci). The five most recurrent IgH translocations observed in MM are represented by the: (i) translocation to the long arm of chromosome 11 t(11;14) involving cyclin D1 (*CCND1*), observed in about 16% of cases; translocation to the short arm of chromosome 4 t(4;14) involving *FGFR3/NSD2*, observed in about 15% of cases; translocation to the short arm of chromosome 6 t(6;14) involving Cyclin D3 (*CCND3*), occurring in about 6% of cases; translocation to the long arm of chromosome 16 t(16;14) involving *MAF*, occurring in about 5% of cases; long arm of chromosome 20 t(14;20) involving *MAFB*, occurring in about 2% of cases.¹² (Table 2) When present, these translocations are always clonal events.

T(11;14). Translocations dysregulating cyclin D expression are the most recurrent type of IgH translocations and involve cyclin D1 t(11;14), cyclin D3 t(6;14) and cyclin D2 t(12;14) and lead to increased expression of the corresponding cyclin genes. However, a dysregulated and/or increased expression of cyclin D1, D2 or D3 is a common feature not only of these IgH translocations, but also of other IgH translocations, as well as of hyperdiploid MMs.¹² While cyclin D1 and D3 overexpression is directly related to translocations that dysregulate *CCND1* (11q13) or *CCND3* (6p21), cyclin D2 overexpression is either directly induced by translocations that affect *CCND2* (12p13)^{13,14} or by translocations affecting *MAF* (16q23) or *MAFB* (20q11)

Table 2. Primary, clonal translocation events in MM.

Primary Translocations	IgH translocation partner	Frequency	Association with other genetic abnormalities	Prognosis
t(11;14)	CyclinD1 (CCND1)	15-20%	Increased DIS3 mutations Decreased BRAF mutations Fewer CNAs	Shorter PFS and OS compared to t(11;14)-negative patients Very poor outcome when associated with del(17p)
t(4;14)	FGFR3/NSD2	14-18%	Strongly associated with chromosome 13 abnormalities Enrichment of FGFR3 and PRK2D mutations, gain (1q21), del in 1p, 4q, 11q, 12p, 13q and 14q; KRAS and NRAS mutations less frequent.	t(4;14) is a high-risk genetic abnormality. Early NSD2 breakpoints and association with del(17p) and del(1p) and gain(1q) have poor prognosis.
t(6;14)	CyclinD3 (CCND3)	5-7%	Not explored	Standard-risk
t(14;16)	MAF	4-6%	Strong association with gain(1q); significant association with 17p deletion and with 1p32 deletion.	Patients with early and late NSD2 breakpoints have poorer outcome than those without NSD2 disruption. Cases associated with high-risk abnormalities have poor PFS and OS. Cases without high-risk abnormalities have PFS and OS similar to patients without t(14;16).
t(14;20)	MAFB	2-3%	Not explored	High-risk

transcription factors that target *CCND2*.^{12,15}

Some evidences suggest that t(11;14) could represent an unique MM subset with peculiar biological properties, as evidenced by higher levels of the antiapoptotic protein BCL-2 and frequent expression of the B-cell lineage protein CD20.¹⁶ Characterization of a large cohort of t(11;14)-positive MM patients by NGS showed that these patients have a differentiated genetic architecture, compared to t(11;14)-negative patients, characterized by fewer CNAs associated with increased genomic stability, but increased rates of *DIS3* mutations and decreased rates of *BRAF* mutations.¹⁷ Avet-Loiseau confirmed the presence of a markedly increased frequency of *DIS3* mutations and a decreased frequency of *BRAF* mutations in t(11;14) MM.¹⁸

The prognosis of t(11;14) can be explained by its binary genomics, i.e., cases with very few other lesions and cases with high-risk genetic abnormalities behave differently.¹⁹

Ziccheddu et al. have analyzed 514 newly diagnosed MM and showed that t(11;14) and chr(1q)gain/amps predicted differential expression of the BCL-2 axis and response to Venetoclax.²⁰ The BCL2/BCL2L1 ratio was high in t(11;14) setting, explaining the positive effect of Venetoclax in this subgroup; In contrast, chr(1q)gain/amps display a low BCL2/BCL2L1 ratio and lead to Venetoclax resistance through MCL1 overexpression.²⁰

The oral BCL-2 inhibitor Venetoclax has shown promising efficacy in patients with t(11;14) MM patients, both a single-agent and in combination. Several ongoing trials are exploring Venetoclax in t(11;14) MM patients.²¹⁻²⁵ However, in relapsed/refractory MM patients the phase III placebo-controlled BELLINI trial failed to show superior outcomes from Venetoclax in

combination with bortezomib and dexamethasone compared to placebo plus bortezomib and dexamethasone.²¹ *MCL1* and *BCL2L1* copy number gains and structural rearrangements were linked to Venetoclax resistance in t(11;14) MM.²⁶

T(4;14). T(4;14) is the second most-common translocation, occurring in about 15% of newly diagnosed MMs. This is an example of an IgH translocation resulting in the dysregulation of two different genes with oncogenic potential: *FGFR3* and *MMSET* (named *NSD2*). The t(4;14) was strongly associated with chromosome 13 abnormalities.²⁷

Keats et al. have used a RT-PCR-specific assay to detect hybrid IgH-NSD2 transcript and observed a frequency of about 15% in MM and about 2% in MGUS; the presence of t(4;14) was predictive of poor response to first line chemotherapy and reduced OS.²⁸ The analysis of 67 t(4;14) patients showed in 10% of cases *FGFR3* mutations, in 44% *FGFR3* overexpression without *FGFR3* mutations and in 28% absent *FGFR3* expression; adverse prognosis was restricted only to patients with *FGFR3* mutations.²⁹

Analysis of the genomic landscape of t(4;14) newly diagnosed MM showed enrichment of mutations in *FGFR3* (38%) and *PRK2D* (7%), amplifications of 1q21 and deletions in 1p, 4q, 11q, 12p, 13q and 14q; *KRAS* and *NRAS* mutations are less frequent in t(4;14) than in non-t(4;14) MMs.³⁰

Walker et al. have performed a whole sequencing study and have analyzed the IgH locus breakpoints and identified breakpoints either of the *NSD2* gene or within the coding sequence of this gene.³¹ Only patients with a breakpoint within the *NSD2* gene and downstream the translation start site (identified as late disruptions,

corresponding to 31% of these patients) have a worse overall survival; in contrast, patients with a breakpoint between the transcription and the translation start site (identified as early disruption, corresponding to 23.5% of these patients) and upstream (identified as no disruption, corresponding to 45.5% of these patients) of the *NSD2* gene exhibited progressively longer survival.³²

Geng and coworkers have analyzed the impact of t(4;14) translocation in a group of 606 ND MM patients, including 108 t(4;14) cases.³³ Median OS (56.2 vs 87.3 months) and PFS (25.7 vs 37.6 months) were significantly shorter in patients with t(4;14) than in those without this cytogenetic abnormality.³³ Among the patients with t(4;14), 26.9% had t(4;14) alone, 59.3% had t(4;14) with gain (1q21), 13.9% had t(4;14) with both gain (1q21) and del(17p): patients with t(4;14) alone have an OS comparable to the rest of MM patients, while those with t(4;14) in association with amp (1q21) and del (17p) have a reduced OS.³³ Thus, t(4;14) alone, in the absence of gain (1q21) and del (17p) have a reduced OS, as confirmed by another study.³⁴ In MM, amplification or gain of chromosome 1q (1q⁺) can involve the whole long arm of chromosome 1 or only specific cytobands such as 1q21, 1q22 or 1q23.3. However, it is important to note that, while the survival of double-hit t(4;14) and 1q21⁺ or 1q23⁺ or both is lower than that of t(4;14) alone, the survival of double-hit MM was similar to that displayed by 1q21⁺ or 1q23⁺ alone.³⁴

T(14;16) and t(14;20). The translocations (14;16) and (14;20) are less common (3-5% and 1-2%, respectively) involve the *IGH* locus and the oncogene *c-MAF* and *MAFB*, respectively. *MAF* induces expression of *CCND2* and integrin B7, two events that stimulate MM cell proliferation. Next generation sequencing studies on 5141 newly diagnosed MM have identified 169 (3.3%) t(14;16) cases whose characterization showed a high association with high-risk abnormalities: gain/amplification of 1q was observed in 69% of patients with t(14;16) compared to 29% in those without t(14;16); deletion 1p32 was detected in 20.7% of patients with t(14;16) compared to 8.5% in those without t(14;16); biallelic 1p32 deletion was observed in 4.7% of patients with t(14;16) compared to 1.8% in those without t(14;16); 17p deletion was observed in 22.5% of patients with t(14;16) compared to 8.7% in those without t(14;16); biallelic TP53 inactivation was observed in 8.9% of patients with t(14;16) compared to 3.1% in those without t(14;16); TP53 mutations were detected in 14.2% of cases with t(14;16) compared to 5.5% in those without t(14;16).³² The t(14;16) has not any prognostic impact if isolated (but numbers are very small). In contrast, its interaction with another prognostic lesion can lead to an aggressive disease.³⁵ Clinical data showed that patients with t(14;16) have shorter mPFS (14.3 months) and mOS (61.3 months) compared to those

without t(14;16) who have mPFS of 43.9 months and mOS of 128.8 months; However, the shorter mPFS and mOS observed is due to the association with high-risk abnormalities.³⁵ Cyclin D2 protein was observed in all the cases bearing t(14;16), but in only 24% of those bearing t(4;14) 1q gains.³⁶

In MM patients with t(14;16) and t(14;20) are frequent APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide") family mutational signatures (SBS2 and SBS13); patients with this signature have an increased mutational load and poor outcomes.³⁴ Overexpression of *MAF* and *MAFB* expression results in increased APOBEC3B and APOBEC4 expression, and consequent induction of DNA mutations.³⁷ A recent whole exome sequencing study carried out in 726 MM patients identified APOBEC mutational activity in 57.5% of these patients; however, only 6.6% MM patients were defined as hyper APOBEC, the majority of them (74%) being t(14;16)-positive.³⁸

Secondary Cytogenetic Abnormalities

Subclonal copy number alterations. The most frequent subclonal CNAs observed in MM include gain of the long arm of chromosome 1 (gain 1q), deletion of the long arm of chromosome 13 (del(13q), deletion of the long arm of chromosome 14 (del(14q)), deletion of the short arm of chromosome 17 (del(17p)) and deletion of the short arm of chromosome 1 (del(1p) (**Table 3**).

Gain(1q). Gain 1q occurs in about 40% of patients and is preferentially associated with other cytogenetic abnormalities compared to MMs without gain 1q, involving an higher frequency of t(4;14) and t(14;16), of del(1p), del(17p) and particularly del(13q); furthermore, MMs with gain(1q) have an higher frequency of complex karyotype compared to those without gain(1q).³⁹

The majority of studies have shown a negative impact of gain(1q) on PFS and OS.^{7,36,40}

Several studies have evaluated the outcomes of MM patients with 1q gain who received auto-HSCT. In this context, a study from Mayo Clinic, including 155 MM patients undergoing upfront auto-HSCT, showed a shorter OS in patients with 1q+ compared to patients without this genetic abnormality.⁴¹ In a subgroup of the FORTE trial, involving the comparison of induction therapy followed by auto-HSCT, patients with 1q amplification had shorter mPFS compared to those with 1q gain or no 1q abnormality (21.8 months vs 53 months and not reached, respectively).⁴² Similar results were obtained by D'Agostino et Al.⁴³ and by Fonseca et Al.⁴⁴

It is unclear whether gain(1q) directly is a driver of poor outcomes or is a "passenger" genetic abnormality in the context of a genetically unstable neoplasia.⁴⁵ Thus, a clear pathogenic mechanism related to one or more genes amplified in the 1q region remains unclear,

Table 3. Secondary subclonal copy number abnormalities and secondary translocations in MM.

Genetic Alteration	Affected Genes	Frequency	Association with other genetic abnormalities	Prognosis
Monosomy 13 del(13q)	RB1, DIS3, miR-15-miR-16-1	40-50%	Gain(1q), t(14;16), t(4;14), del(12p), DIS3 and FGFR3 mutations	Negative prognosis of 12 monosomy and of cases associated with high-risk abnormalities
Gain 1q gain(1q)	CKK1B, MCL-1, IL-6R, ILF2, BCL9	40-45%	T(4;14), t(14;16), t(14,20), del(1p), del(13q), del(17p), complex karyotype	Gain 1q is associated with reduced OS. Patients with co-occurring t(4;14), t(14;16), del(17p), del(13q) or with 4 or more 1q copies have reduced PFS and OS.
Deletion 17p del(17p)	TP53	5-12%	TP53 mutations	Negative prognosis Patients with del(17p) and TP53 mutations have a poorer prognosis than those with del(17p) without TP53 mutations
Deletion 1p del(1p)	1p12: FAM46C 1p22.1-1p21.3: MTF2, TMED5, RPL5, EVI5 1p31: MSH4, DAB1 1p32: CDKN2C, FAF1	20-30%	Del 1p12 and del 1p32 are associated with del(17p), t(14;16), gain(1q), TP53 mutations	Del 1p12 and del 1p32 are associated with reduced PFS and OS Biallelic 1p32 inactivation in association with del(17p) and t(4;14) is a very negative prognostic factor
MYC rearrangements (translocations, Ig and non-Ig insertions, terminal tandem duplication, terminal deletions, proximal deletions)	MYC	10-15% (FISH) 20-40% (NGS)	Increased: trisomies Decreased: t(11;14)	Negative outcomes for patients with Ig insertion subtype Improved outcomes for patients with non-Ig insertion subtype

although several candidates have been identified, including CKK1B, MCL-1, IL-6R, ILF2 and BCL9.⁴⁶

Deletion of 13q. Deletion of chromosome 13q is one of the most frequent cytogenetic abnormalities observed in MM, occurring in about 40-50% of these patients.⁴⁷

The presence of chromosome 13q deletions has been suggested to be an adverse prognostic factor in MM patients.⁴⁸ However, the association of del(13q) with poor prognosis has been debated. Thus, Walker et al. have explored 463 newly diagnosed MM patients enrolled in the myeloma XI trial and concluded that the negative impact of del(13q) on PFS could be ascribed to the association with high-risk abnormalities.⁴⁹

Binder et al. reached a different conclusion in that they observed that abnormalities of chromosome 13 were of prognostic significance independently of the co-occurring presence of high-risk alterations.⁵⁰

A possible oncogenic role of chromosome 13 abnormalities dependent on the loss of some specific genes remains undefined. Some possible candidate genes are represented by *RB1* and *DIS3* genes and by the micro-RNAs miR-15a and miR-16-1.^{48,52-54}

Deletion of the short arm of chromosome 1. Del(1p) englobes a heterogeneous group of MM patients characterized by different deletions of the short arm of chromosome 1 and by a heterogeneous prognostic impact.

Four minimally altered regions on chromosome 1p were identified: 1p12, 1p22.1-1p22.3, 1p31 and 1p32.

1p12 is considered as an adverse prognostic factor in MM. In this region maps *FAM46C* gene, a gene of prognostic and pathogenic importance in MM; *FAM46C* acts as a tumor suppressor. The loss of *FAM46C* promotes tumorigenesis by activating the PI3K-AKT pathway, conferring resistance to dexamethasone and lenalidomide treatment, promoting cell survival and cell proliferation.⁵⁵⁻⁵⁷ *FAM46C* is a non-canonical poly(A) polymerase uniquely mutated in up to 20% of MM patients; *FAM46C* selectively stabilizes mRNAs encoding endoplasmic reticulum (ER)-targeted proteins, enhancing the expression of proteins that control ER protein import and processing and stimulating protein secretion.⁵⁸ *FAM46C* expression is markedly induced during normal plasma cell differentiation; *FAM46C* ablation determines a highly significant, MM-specific proliferative advantage, consisting in the restriction of Ig production.⁵⁹

1p22.1-1p21.3 is the region most frequently deleted on 1p, where are mapped the genes *MTF2*, *TMED5*, *RPL5* and *EVI5*. Among these four genes, *EVI5* and *RPL5* seem to be the genes most involved in MM development since the inactivation of both genes induces MM progression.⁶⁰

1p32 contains two genes, *CDKN2C* and *FAF1*, pathogenetically relevant for MM development. Homozygous and hemizygous *CDKN2C* deletions are

associated with a poor prognosis in MM patients and support a role of this gene as a tumor suppressor in MM progression.¹⁵ Most of studies support a negative prognostic impact of del(1p) in MM patients,⁶¹⁻⁶² particularly of biallelic deletion of 1p32, in MM patients.⁶³

Vainshnav et al. performed a retrospective analysis of 453 MM patients undergoing auto-HSCT and observed that patients with del(1p) had inferior PFS (2.43 years vs 3.98 years), TTNT (2.72 years vs 6.17 years) and OS (4.11 years vs 8.38 years) from auto-HSCT compared to those without del(1p).⁶⁴ This trend was confirmed by a retrospective analysis of 3758 MM patients where 844 patients with chromosome 1 abnormalities showed that patients with chromosome 1 abnormalities displayed a significantly shorter PFS and OS.⁶⁵

Deletion 17p. Deletion of 17p13, del(17p) is observed in 5-12% of newly diagnosed MM and its frequency increases with disease progression. The majority of del(17p) involve the entire short arm of chromosome 17, although the deletion may span also few megabases. This high-risk deletion involves the loss of the *TP53* gene. Importantly, *TP53* mutations was initially observed only in MM patients with del(17p).⁶⁶ The analysis of mutation location showed that virtually all mutations occurred in highly conserved domains of the *TP53* molecule involved in DNA-protein interaction.⁶⁶ However, subsequent studies have clearly shown that *TP53* mutations may occur in the absence of del(17p); in fact, Walker et al. in a group of 784 MM patients showed in 5.5% of cases monoallelic *TP53* mutations, in 8% del(17p) in the absence of *TP53* mutations and in 3.80% of cases biallelic *TP53* alterations (del(17p) plus *TP53* mutations); this subgroup (double-hit) of high-risk MM patients including patients with biallelic *TP53* inactivation or *CSK1B* gene amplification; they show also in new diagnosis MM that deletion of 17p alone is not prognostic; in fact when mutation in *TP53* is accounted for, monosomy 17p alone has no prognostic value.⁶⁷ Similar results were reported in a Polish study.⁶⁸

Del(17p) is maintained at relapse in patients bearing this deletion at diagnosis; however, del(17p) may be acquired at relapse.

Chin et al. explored the frequency of *TP53* mutations in del(17p) MM patients during disease progression: del(17p) was observed in 10% of MM patients at diagnosis and 22.3% in patients at relapse; 31% of patients at diagnosis with del(17p) displayed *TP53* mutations.⁶⁹ The longitudinal studies of some patients showed the acquisition of *TP53* mutations at relapse.⁶⁹ Corre et al. explored the response of 121 MM patients with del(17p): 76 of these patients are del(17p)/*TP53*-WT and 45 del(17p)/*TP53*-mutant; in line with Chin observations, and in contrast with the data of Walker, they showed that both these groups of patients displayed

a reduced PFS and OS compared to patients without del(17p); PFS was comparable in the two groups of patients with del(17p), while OS was shorter in patients with both del(17p) and *TP53* mutations than in those with only del(17p) (52.8 months vs 152.2 months, respectively). In conclusion, the study of Corre et al clearly confirms the extremely poor outcome of patients displaying “double hit”, but also that del(17p) alone is still a very high-risk feature, confirming its value as a prognostic indicator for poor outcome.⁷⁰

“Aberrant” biallelic *TP53* inactivations, involve simultaneous copy number loss and aberrant *TP53* splicing, resulting in overexpression of high-risk transcript variants, and lead to biallelic inactivation.⁷¹

The importance of the acquisition chromosome 17 predictive of poor prognosis was confirmed in various studies and methods.⁷²⁻⁷⁵

Cui et al have recently reported the results of 197 MM patients with paired iFISH analysis at both diagnosis and first relapse, showing that: del(17) was observed at diagnosis in 7% of patients and in 18% at first relapse; the subdivision of patients according to del(17p) clone size showed that patients with a minor clone at relapse (10% to 50%) exhibited shorter survival compared to those without del(p17), while no significant difference in survival was observed between patients with minor (10-50%) or major clone size (>50%) at relapse.⁷⁶ According to the change patterns of clonal size, the patients were subdivided into six subgroups: patients who experienced del(17p) loss at relapse (OS 50.3 months); patients who did not have del(17p) at both time points (OS 26.9 months); patients who had newly acquired del(17p) at relapse (OS 20.2 months); patients with a stable clone of del(17p) between the two time points (OS 12.5 months); patients with an increase in clonal size of del(p17) at relapse (OS 12.8 months).⁷⁶ Therapy of myeloma are changing, therefore is important to evaluate the effect of del(17p) in patients treated with the new protocols. Jurgens et al. have retrospectively evaluated the response of 66 newly diagnosed del(17p) MM patients to triplet and quadruplet combination therapies, including bortezomib, lenalidomide, dexamethasone (VRd), carlzomib, lenalidomide, dexamethasone (KRd), +/- daratumumab (DVRd and DKRd). The patients with del(17p) have been subdivided into two subgroups according to the percentage of cells bearing del(17p) either $\leq 20\%$ or $\geq 20\%$. Median PFS was 48.9 months for patients with del(17p) $< 20\%$, 34.3 months for del(17p) $> 20\%$ and not reached for patients with standard-risk MM.⁷⁷ In conclusion, it seems that the acquisition of del (17) at relapse after chemotherapy is a better negative prognosticator than at the onset of the disease.

Concomitant del (1p13) and amplification or gain (1q21). A recent study reported the occurrence of MM patients with concomitant del(1p13.3) with gain(1q21). Thus,

Mohan et al. in a FISH analysis involving 1133 patients reported del(1p13.3) in 19.4% of cases and 1q21 gain (3 copies of 1q) in 26.5% of cases and 1q21 amp in 13.2% of cases; concomitant del(1p13.3) with 1q gain or with 1q amp was observed in 5.7% and 2.5% of patients, respectively.⁷⁸ These double-positive patients displayed enrichment of high-risk features; particularly, the PFS and OS of patients with combined abnormalities was significantly worse compared to del(1p13.3) alone and 1q21 gain or 1q21 amp alone.⁷⁸

MYC rearrangements. A key event in the development of MM is represented by the acquisition of secondary genetic events including *MYC* structural variants. Gene expression studies showed the activation of a *MYC* gene signature in 67% of MM patients but not in MGUS,⁷⁹ and *MYC* rearrangements involving chromosome 8q24 were detected by FISH in 3% of MGUS and 15% of newly diagnosed MM and with comparative genomic hybridization were observed in almost 50% of MM cases.^{80,81}

MYC translocations have been reported in 20-50% of patients with myeloma;⁸² the molecular characterization showed that these translocations were most frequently inter-chromosomal, involving 2-5 chromosomes; in more rare cases, translocations involved inversion of chromosome 8 or intra-chromosomal rearrangements; both inter-chromosomal and intra-chromosomal rearrangements are associated with a significantly higher *MYC* expression *MYC* structural variants were detected in 42% of MM patients, including 57% of hyperdiploid and 25% of MMs with primary IgH translocations.^{82,83}

Patients with *MYC* rearrangements have a shorter OS compared to those without these rearrangements, and further reduced when associated with high-risk cytogenetic abnormalities;⁸⁴ they frequently display elevated β 2-microglobulin, $\geq 50\%$ plasma cells, IgA multiple myeloma and co-occurrence of trisomy.^{82,84}

A lower frequency of *MYC* structural variants (*MYC* SV) was found by FISH (10-15%) compared to NGS (20-40%) and is related to a high false-negative rate of *MYC* break a part FISH probe.^{85,86} Although FISH can identify a lower fraction of *MYC* structural variants (SVs), those identified by this technique are associated with a higher *MYC* gene expression and with a poorer outcome.⁸⁶ *MYC* translocations involve the immunoglobulin (IG) loci (IGH > IGL > IGK) and some non-Ig partners such as FAM46C, FOXO3, and BMP6. Patients with IgL translocations, about 10%, experiment a significantly worse PFS and OS, which was most pronounced for IgL-*MYC* translocations.^{82,86,87}

Conclusions about Chromosomal Alterations. Hyperdiploidy and IgH translocations are considered primary cytogenetic abnormalities and occur at the time of establishment of MGUS (Table 1 and 2) (Figure 1).

In addition, other cytogenetic changes termed secondary cytogenetic abnormalities arise along the disease course of multiple myeloma, including gain(1q), del(1p), del(17p), del(13), and secondary translocations involving *MYC*. Both primary and secondary cytogenetic abnormalities can influence disease course, response to therapy, and prognosis. Importantly, the interpretation and impact of cytogenetic abnormalities in multiple myeloma vary depending on the disease phase in which they are detected.⁸⁸

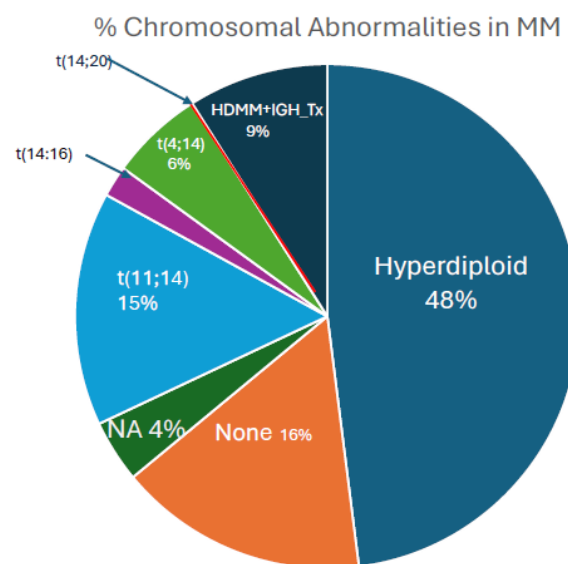


Figure 1. % Chromosomal Abnormalities in MM.

The presence of del(17p), t(4;14), t(14;16), t(14;20), gain 1q, or p53 mutation is considered high-risk multiple myeloma. Presence of any 2 high risk factors is considered double-hit myeloma; 3 or more high risk factors is triple-hit myeloma and are at the base of Myeloma stratification prognosis.⁸⁸

Mutational Landscape of MM

Gene Mutation in newly diagnosed. The mutational events occurring in MM were shown by the Next generation sequencing; they are probably secondary events, associated with tumor progression rather than with tumor initiation. Karyotypic events have a stronger impact on prognosis than mutations, but the mutations can modify the risk attributed to the chromosomal abnormalities. Initial studies have shown that frequently mutated genes involve *KRAS*, *NRAS* and *TP53*; genes involved in MEK/ERK signaling, NF κ B signaling, RAS pathway, cycle progression and RNA processing are mutated in a significant proportion of MM patients.⁸⁹ (Table 4) Subsequent studies based on the analysis of the mutational profile of larger cohorts of MM patients have shown that the 15 most frequently mutated genes in MM are *IRF4*, *KRAS*, *NRAS*, *MAX*, *HIST1H1E*, *RB1*, *EGR1*, *TP53*, *TRAF3*, *FAM46C*, *DIS3*, *BRAF*, *LTB*, *CYLD* and *FGFR3*; the mutational spectrum is dominated by

mutations in the RAS (*KRAS* 21%, *NRAS* 19% and *BRAF* 6.7%) and NF- κ B (*TRAF3* 3.7% mutations and 13% deletions; *CYLD* 2.4% mutations and 17% deletions) pathways; mutations in *CCND1* and DNA repair (*TP53*, *ATM*, *ATR* and *ZNFHX4*) are associated with a negative prognosis, while *IRF4* and *EGR1* mutations are associated with a better prognosis.⁴⁹

Both synonymous and non-synonymous *CCND1* and *IRF4* mutations are predominantly associated with the t(11;14) translocation; *MAF*, *BRAF*, *DIS3* and *ATM* mutations are associated with the t(14;16) translocation; mutations in *FGFR3*, *DIS3* and *PRKD2* are associated with t(4;14) translocation; gain 11q, mutations in *FAM46C* and *MYC* rearrangements are associated with hyperdiploidy.³⁰

Translocations and CNAs had preponderant contribution over gene mutations in defining the genotype and prognosis of each patient.⁸⁹ Other driver abnormalities include chromosomal and segmental chromosome gains and losses, loss of heterozygosity, and APOBEC mutational signature which affect clinical prognosis.⁸⁹ The only mutated gene with a clear prognostic impact on both PFS and OS was *TP53*, while *DNAH11* mutations conferred worse OS only.⁹⁰ The negative prognostic impact of *TP53* was stressed also by others.^{67,70,71}

Maura and coworkers have performed a whole genome sequencing (WGS) study of 67 tumor samples collected at different time points from 30 MM patients identifying 7 bayesian clusters, whose characteristics are shown in **Figure 2**.⁶

Gene Mutations in Refractory/Relapsed MM. A few recent studies have analysed the genetic abnormalities observed in relapsed/refractory multiple myeloma and have compared these alterations to those observed in newly diagnosed MM. A seminal study was performed by the Morgan group using gene expression profiling, high-resolution copy number arrays, and whole-exome sequencing. This study illustrates the mechanistic importance of copy number aberration changes, acquired mutations in known myeloma driver genes and the critical nature of biallelic inactivation events affecting tumor suppressor genes number and their biallelic inactivation, especially *TP53*, was increased in high-risk myeloma, being genomic instability a key feature. All that brings about double-hit events with catastrophic consequences.⁹¹ Other investigations confirmed and amplified these data.⁹²⁻⁹⁹ The importance of inactivation of *TP53* pathway was confirmed,⁹²⁻⁹⁷ resistance to immunomodulatory drugs (IMiDs) and proteasome inhibitors showed an increase of the mutational load and more subclonal mutations than at diagnosis.^{92,94-96} Mutational profiling showed frequent mutations of genes involved in RAS-MAPK pathway (*NRAS*, *KRAS*, *BRAF*, *PTPN11*, *NF1* and *IL6ST*) and in NF- κ B pathway (*CYLD*, *TRAF3*, *TRAF2*, *NFKB1A*, *IRAK1*),⁹³ and *RBI*, *CDKN2A/B*, *BIRC2/3* and *CDKN2C*⁸⁶ (**Figure 3**); other genes preferentially mutated in R/R MM included the sodium bicarbonate transporter *SLC4A7*, the Ras target *MLLT4*, the RNA binding protein *EWSR1*, the MLL complex member *HCFC2*, the COP9 signalosome subunit *COPS3*.⁹⁷ Some novelties were reported by

Table 4. Common gene mutations and their functional pathways in multiple myeloma.

Pathway	Genes mutated	Global frequency of mutations
MEK/ERK signaling	<i>KRAS</i> , <i>NRAS</i> , <i>BRAF</i> , <i>NF1</i> , <i>PTPN11</i> , <i>FGFR3</i>	45-50%
NF κ B activation	<i>TRAF2</i> , <i>TRAF3</i> , <i>CYLD</i> , <i>NFKB2</i> , <i>NFKB1A</i> , <i>BIRC2</i> , <i>BIRC3</i>	20-25%
G1/S cell cycle transition	<i>RBI</i> , <i>CCND1</i> , <i>CDKN2C</i> , <i>CDKN1B</i> , <i>TP53</i>	15-20%
RNA processing	<i>FAM46C</i> , <i>DIS3</i>	15-20%
Epigenetic regulators	<i>DNMT3A</i> , <i>TET2</i> , <i>KDM6A</i>	2-5%

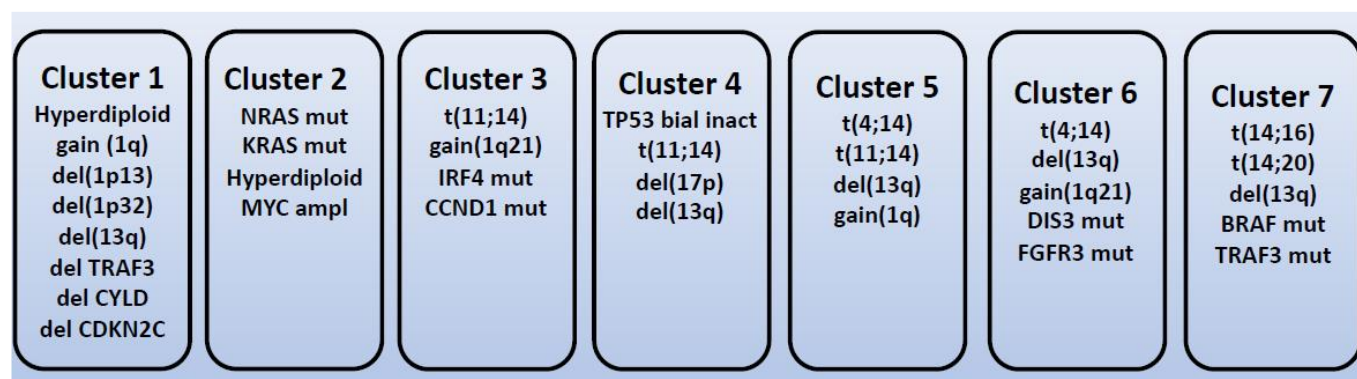


Figure 2. Molecular classification of primary MM samples following Maura et al.⁶

Ansari-Pour and coworkers.⁹⁸ This analysis showed that some genetic abnormalities were enriched in R/R MM, including some gene drivers (*DUOX2*, *EZH2*, *TP53*), biallelic inactivation (*TP53*), some copy number aberrations (1q gain, 17pLOH), and double-hit events (Amp 1q-ISS3, 1q gain-17pLOH).⁹⁸ Similarly, in addition to the genomic events reported in other studies, Braunstein et al. found in MM patients an increase in complex structural variation events, including templated insertions, chromoplexy and chromotripsis: in some patients, chromoplexy and chromotripsis occurred exclusively at relapse; in cases where these events occurred at presentation, their clonal fraction increased at relapse.⁹⁹

Cereblon (CRBN) is the essential binding protein of the widely used immunomodulatory drugs (IMiDs). IMiDs, (thalidomide, lenalidomide, and pomalidomide), form a molecular bridge between cereblon (CRBN) and the transcription factors IKZF1 and IKZF3. Mutation of CRBN was found in many patients resistant to IMiDs,^{86,95,96} on the contrary the *IKZF1* mutation is rare.⁹⁵

Role of Chromotripsis and Other Structural Complex Variations in MM Development. Chromotripsis is a catastrophic mutational process by which numerous clustered chromosomal rearrangements occur in a single event in localised and coupled genomic regions in one or few chromosomes; this event is observed in many cancers.

A comprehensive study of structural variation carried out on 752 newly diagnosed MM patients showed a 24% prevalence of chromotripsis, making MM the hematological cancer with the highest occurrence of chromotripsis.¹⁰⁰ Templated insertions were the second most frequent complex event, involved in super-enhancer hijacking and activation of oncogenes such as *MYC* and *CCND1*.¹⁰⁰ In 31% of MM patients, two or more driver genetic events were caused by a single structural event, thus supporting the view that the complex genomic landscape of MM can be acquired through few molecular events.

Copy number signatures are highly predictive of the presence of chromotripsis and are highly associated.⁹⁴ Exploring a large set of MMs, Maclachlan et al observed six fundamental CNV features: (i) the number of breakpoints per 10 Mb; (ii) absolute CN of segments; (iii) the difference in CN between adjacent segments; (iv) number of breakpoints on chromosome arm; (v) lengths of oscillating CN segment chains; (vi) the size of segments.¹⁰⁶ Chromotripsis can be detected using a logistic regression model with CNV signatures as input, without requiring specific structural variant assessment.¹⁰¹

Yu et al. proposed and designed a deep graph learning

approach to detect chromotripsis in MM samples solely based on CNV data.¹⁰²

In a more recent study, Maclachlan et al. explored 420 MM patients by targeted sequencing and from these data detected 6 key CN features and extraction of CN signatures defined 1 signature containing multiple features consistent with chromotripsis, such as high

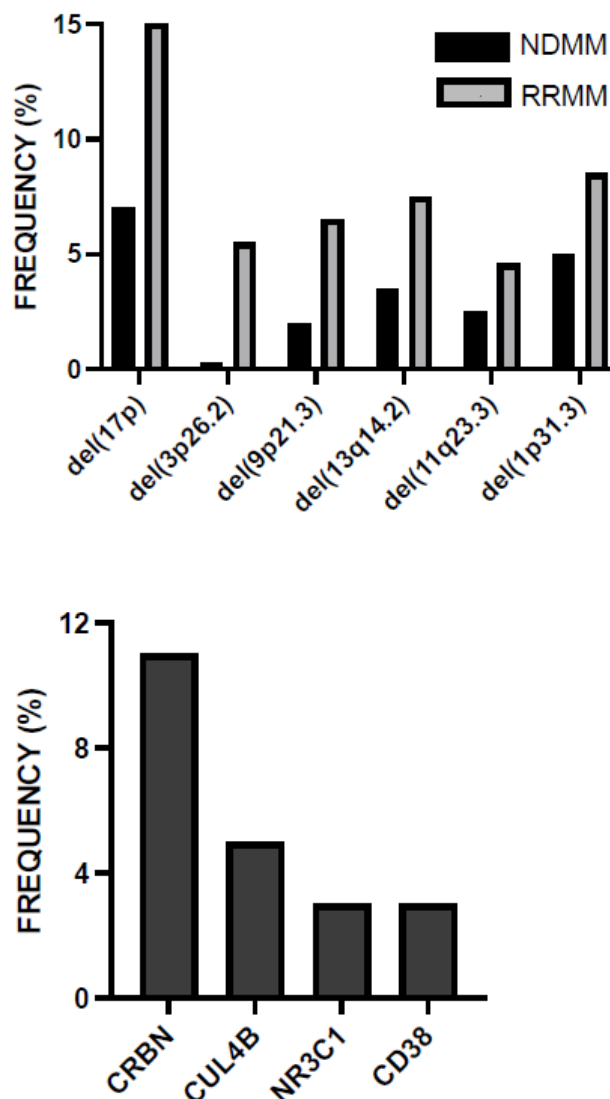


Figure 3. Genetic abnormalities observed in refractory/relapsed MM. *Bottom Panel:* Three gene pathways, RAS-MAPK, NF-kB and DNA Damage Response (DDR) exhibiting frequent gene mutations in R/R MM. *Middle Panel:* Genetic alterations of drug resistance-related genes. *Top Panel:* Focal deletions whose frequency is higher in RRMM compared to NDMM. Del(17p) involves *TP53*, del(3p26.2) *CRBN*, del(9p21.3) *CDKN2A/B*, del(13q14.2) *RBI*, del(13q23.3) *BIRC2/3* and del(1p31.3) *CDKN2C*.

breakpoint count per 10mB, more jumps between adjacent CN segments, longer lengths of oscillating CN segments and a predominance of small CN segments.¹⁰⁴ This signature was predictive of chromotripsis and was predictive of PFS in multivariate analysis when considering age, ISS, t(4;14), TP53 status and gain 1q21.¹⁰³

Table 5. Chromosomal abnormalities and “risk” in myeloma stratification systems.

Cytogenetic defects	R-ISS ¹⁰⁸	R2-ISS ¹⁰⁹	mSMART ¹⁰⁶	MASS ¹¹⁰
Primary abnormalities				
t(4;14)	High	1 point	High	1 point
t(11;14)	--	--	Standard	--
t(14;16)	Hgh	--	High	1 point
t(6;14)	--	--	Standard	--
T(14;20)	--	--	High	1 point
Trisomies	--	--	Standard	--
(hyperdiploidy)		--		
Secondary Abnormalities				
1q gain/amp	--	0.5 points	High	1 point
Del(17p)	High	1 point	High	1 point

All these observations suggest a role played by chromotripsis as a critical pathogenic factor active at early disease phases, associated with negative prognosis.¹⁰⁴

The Rising Role of Genetics in Prognosis Evaluation of MM. The revised ISS (International Staging System) for multiple myeloma defines three stages: stage I (sβ2M <3.5mg/dL; serum albumin ≥3.5 g/dL) stage II (sβ2M <3.5 mg/dL; serum albumin ≤3.5 g/dL; or sβ2M 3.5 to 5.5 mg irrespective of serum albumin); stage III (sβ2M >5.5 mg/L). This system subdivides MM patients into three stages according to clinical parameters and to cytogenetic markers. Particularly, stage I patients must have serum albumin ≥3.5 g/dL, sβ2M <3.5 mg/L, no high-risk cytogenetics and normal serum lactate dehydrogenase (LDH); stage II patients not fitting stage I or III; stage III patients have both of the following: sβ2M >5.5 mg/L, high-risk cytogenetics [t(4;14), t(14;16), or del(17p) or elevated serum LDH].¹⁰⁵

The Mayo Clinic mSMART risk stratification system introduced other parameters in the development of a risk stratification, with the identification, with the identification of: (i) a standard risk, including trisomies, t(11;14) and t(6;14); (ii) a high-risk, including t(4;14), t(14;16), t(14;20), del(17p) and gain (1q); (iii) a double-hit myeloma, including any 2 high-risk factors; (iv) triple-hit myeloma, including any 3 or more high-risk factors.¹⁰⁶

CNAs affecting chromosome 1, such as gain (1q) and del(1p32) were not included in the criteria of the first revision of the ISS, despite their frequency and their negative impact on patients’ outcomes. However, several recent studies support the utility of including gain (1q) in the risk stratification of MM patients. In fact, Weinhold in an analysis carried out on 2,596 MM patients treated with proteasome inhibitors and immunomodulatory agents showed a reduced PFS and OS in patients with

gain (1q) or amp (1q).¹⁰⁷ The inclusion of 1q among the risk stratification criteria allowed to better define the risk of patients with ISS II.¹⁰⁷ Furthermore, stage III patients with multi-hits displayed a very poor outcome.¹⁰⁷ Other studies have shown the consistent heterogeneity of R-ISS stage II MM patients; in this group, the ISS stage and the presence of high-risk chromosome abnormalities are relevant prognostic factors and help to better stratify the risk of these patients.¹⁰⁸

All these considerations have led to the second revision (R2-ISS) of the current R-ISS.¹⁰⁹ A value was assigned to each risk feature according to their impact on OS: ISS-stage III 1.5; ISS-stage II 1; del(17p) 1; high LDH 1; t(4;14) 1; gain/amplification (1q) 0.5 points.¹⁰⁹ Using this scoring system, patients were stratified into four risk groups according to the additive score: low-risk (score =0) mOS not reached, mPFS 68 months; low-intermediate risk (score=0.5-1 points) mOS 109.2 months, mPFS 45.5 months; intermediate-high risk (score=1.5-2.5 points) mOS 68.5 months, mPFS 30 months; high-risk (score= 3.5 points) mOS 37.9 months, mPFS 19.9 months.¹⁰⁹ The 1 q gain is present also in the Mayo additive staging system classifications MASS.¹¹⁰ (Table 5 shows a comparison of different stratification systems).

Alzahrani et al. explored the impact of R2-ISS on outcomes of 1291 MM patients receiving autologous HSCT.¹¹¹ The median PFS was 130.8, 128.5, 94.2 and 61.4 months for patients with R2-ISS stages I, II, III and IV, respectively.¹¹¹ These observations showed that R2-ISS is a reliable prognostic tool for MM patients who received standard anti-myeloma treatment and upfront auto-HSCT.¹¹²

Panopoulou et al in a first study evaluated the prognostic impact of double-hit genetics in MM patients undergoing autologous HSCT: the presence of double-hit genetics negatively impacted the PFS and OS of these patients in comparison with those with no genetic hits.¹¹³

In a second study, the same authors have evaluated the factors that could predict individual patient benefit from lenalidomide maintenance after autologous HSCT in the context of the MyeXI trial.¹¹⁴ 556 MM patients in the MyXI trial were randomized to lenalidomide maintenance or observation after autologous HSCT were genetically profiled for t(4;14), t(14;16), t(14;20), del(1p), gain(1q), and del(17p) and co-occurrence of risk markers was computed. 17% of these patients were double-hit, 32% single-hit and 51% without risk markers; single-hit patients achieved the best benefit from lenalidomide maintenance, with isolated del(1p), del(17p) and t(4;14) exhibiting a 40-fold, 10-fold and 7-fold reduced risk of progression or death, respectively, compared with observation.¹¹⁴

Maura et al have recently proposed a new model predicting with higher accuracy than all comparator prognostic model the individualized risk of newly diagnosed MM patients; integral to model accuracy there were 20 genomic features, 1q21 gain/amp, del 1p, TP53 loss, t(4;14), t(14;16), f(14;20), APOBEC mutational

signatures, copy number signatures reflecting the complex structural variant chromotripsis.¹⁹ This model was based on the analysis of a series of 1,933 patients with available clinical, genomic (mutational profile, copy number alterations, structural variants, gene expression profile), and therapeutic data; according to the results of this extensive analysis, it was proposed a new molecular classification of MM, defining 12 molecular subgroups characterized by a different pattern of molecular alterations (**Figure 4**). In a cohort of 1933 MM patients, the IRMMa model accuracy was significantly higher than all ISS models, with a c-index for OS of 0.726, compared with ISS (0.61), R-ISS (0.572) and R2-ISS (0.625).¹⁹ The IRMMa model allowed to predict individualized patient risks by different treatment strategies in the 12 genomic MM groups and, particularly, to identify patients for whom high-dose melphalan-autologous HSCT is greatly effective versus patients for whom the impact is limited.¹⁹

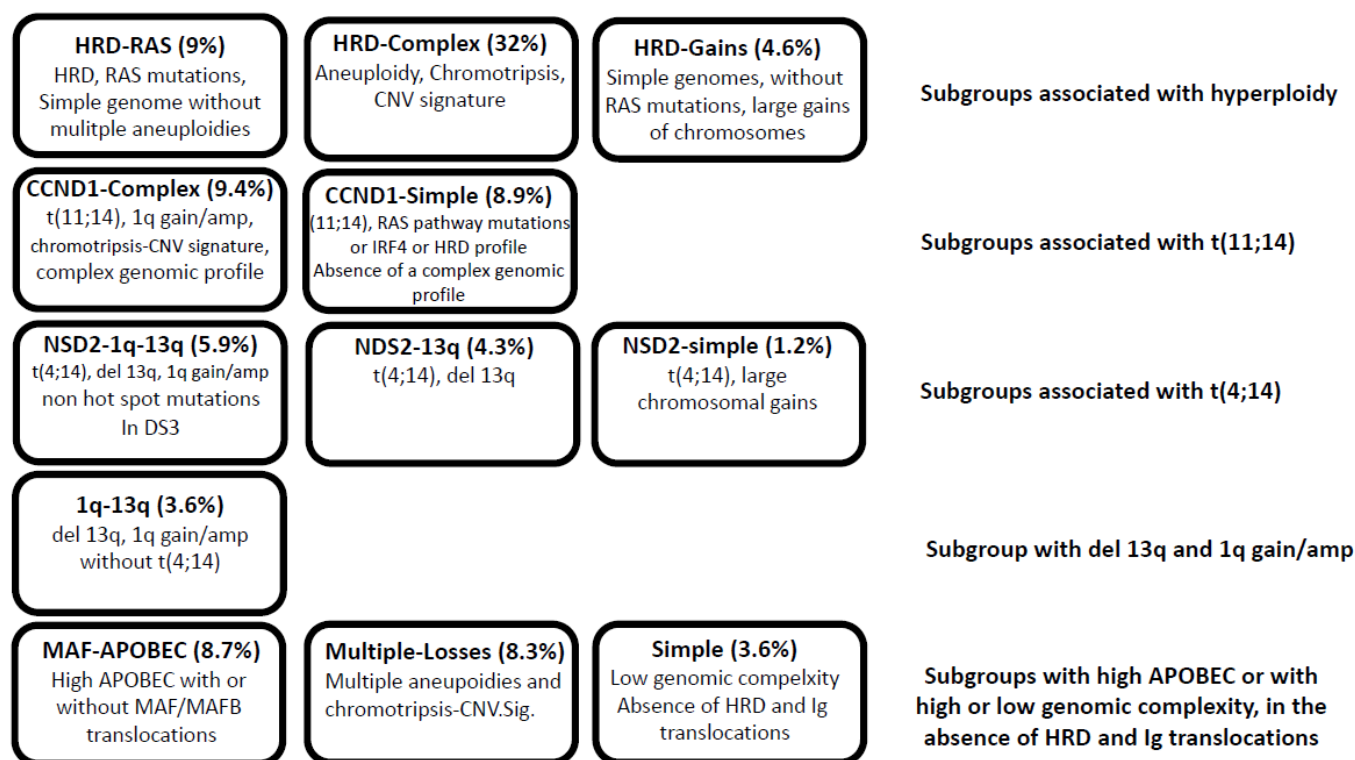


Figure 4. Molecular classification of primary MM according to Maura et al.¹⁹ This classification represents an evolution of the classification reported in Figure 1.

Conclusions and Perspective. Dramatic progresses have been made in the last three decades in the understanding the molecular abnormalities underlying the development of MM. MM development is preceded by a premalignant condition, monoclonal gammopathy. Both these conditions are characterized by the presence of several molecular abnormalities, such as hyperdiploidy, immunoglobulin heavy chain

translocations that dysregulate a cyclin D family gene, a MAF family gene or NSD2 gene. Subsequent genetic events represented by loss of function of tumor suppressor genes and mutations activating RAS, NFkB, MYC and cell cycle pathways allow the progression to a malignant condition.

These remarkable progresses in the molecular understanding of MM have been accompanied by a

concomitant improvement in clinical outcomes of newly diagnosed MM, mainly related to the introduction of novel therapeutic agents. However, a considerable heterogeneity in MM presentation, genetics and therapeutic responses was observed, with a subset of Thus, some patients relapse early (<18 months) and rapidly cycle through therapies. Recent whole-exome, whole-genome and targeted sequencing studies have permitted the identification of several molecular prognostic markers. Particularly, DNA sequencing studies allow a better identification of high-risk MM patients, scarcely responsive to standard treatment and requiring an individualized treatment strategy. The study of these molecular features now allowed a comprehensive molecular classification of MM and the definition of an individualized prognostic model to predict an individual MM patient's response to different therapeutic options. It is noteworthy that more than the single molecular or cytogenetic alteration is the complex of alterations (double or triple-hits) which determines the

prognosis. Therefore, the model proposed by Maura appears the most convincing.

MM genetic diagnostics was traditionally based on fluorescence in situ hybridization (FISH), providing prognostic information based on Ig translocations and main copy number abnormalities (1p, 1q, 17p). However, several prognostically important mutations, focal deletions and biallelic events can be detected only by molecular techniques such as DNA sequencing (NGS). Thus, NGS represents a cost-effective alternative to FISH, to comprehensively detect genomic abnormalities in MM and to identify markers related to prognosis and treatment.

Given the evident limitations of classical interphase FISH analysis in providing a full assessment of the risk status of MM patients related to genomic events, some recent studies have introduced the prospective use of DNA sequencing in clinical trials.

An important question is if the molecular profile could give indication to targeted therapies.^{115,116}

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