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REVIEW

# Cytogenetic Alterations in Multiple Myeloma: Prognostic Significance and the Choice of Frontline Therapy

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**Multiple myeloma tumor cells demonstrate multiple and often complex genetic lesions as evaluated by standard cytogenetic/FISH studies. Over the past decade, specific abnormalities have been associated with standard or high-risk clinical behavior and they have become strong prognostic indicators. Further, as evidenced by recent randomized clinical trials, the choice of front-line therapy (transplant *vs.* no transplant, inclusion of novel drugs such as bortezomib, thalidomide, and lenalidomide) may be able to overcome the adverse effect of high-risk genetic lesions.**

**Keywords:** Cytogenetics, FISH, MGUS, Multiple mieloma, Prognostic factors, Risk groups, Therapy, Thalidomide, Bortezomib



## INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell malignancy that accounts for approximately 10% of all hematologic cancers (1). It is characterized by the accumulation of malignant plasma cells within the bone marrow, the presence of a monoclonal immunoglobulin in the serum and/or urine, lytic bone lesions, frequent anemia, and less often, renal impairment. This disorder shows a variable clinical course, with some patients progressing rapidly, while others have an overall survival greater than 10 years. The natural course of the disease is the result of a multistep process that may progress from monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM), to symptomatic MM and plasma cell leukemia. This process is characterized by a series of genetic events that impact in different signaling pathways changing the biologic characteristics of the myeloma cells and determining proliferative and selective advantages.

Multiple prognostic factors that reflect host factors, tumor biology, tumor burden, and response to treatment have been described in MM (2). Among them, the presence of genetic alterations in plasma cells has been considered to be an important prognostic factor, capable to identify patients with different clinical features and response to therapy (3–5). Although many genetic alterations are amenable to detection by conventional cytogenetics, their detection is hampered by the low proliferative index of plasma cells and, consequently, the limited number of metaphases (6). In addition, some aberrations are cryptic and cannot be detected by standard cytogenetics, thus an apparently normal karyotype is observed in 60–70% of MM patients. However, the introduction of interphase fluorescence *in situ* hybridization (FISH) studies showed genetic alterations in more than 80% of cases.

In the first part of this paper, we review the most common cytogenetic/FISH abnormalities associated with myeloma, the molecular mechanisms involved and their prognostic significance. Later, we review data from recent randomized clinical trials (RCT) to evaluate the relative role of the various treatment regimens proposed in reference to standard and high risk cytogenetic groups.

## CYTOGENETIC AND MOLECULAR ABNORMALITIES IN MULTIPLE MYELOMA

In the last decade, cytogenetic and molecular genetic studies have emerged as relevant prognostic factors, capable to identify patients with different clinical features and response to therapy (5). They may be distinguished initially in primary abnormalities, directly related with the pathogenesis of the disease, and secondary events, associated with progression of the disease. Primary alterations can be subdivided in two cytogenetic categories: hyperdiploid and nonhyperdiploid. The hyperdiploid group (45% of cases) is characterized by the presence of trisomies of the odd-numbered chromosomes and a low frequency of immunoglobulin heavy chain (IGH) translocations involving 14q32 locus. In contrast, the nonhyperdiploid group (40% of cases) (encompassing hypodiploid, pseudodiploid, and near tetraploid MM) is characterized by a high frequency of IGH translocations, indicating that two fundamentally different pathogenic pathways exist for MM development (5). The ploidy categories are stable over time

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**Table 1**. Distribution of Cytogenetic Abnormalities in Patients with Multiple Myeloma

| Group (% of Cases) | Genes | Clinical Characteristics |
|---|---|---|
| Hyperdiploid (45) | | More favorable, IgG-$\kappa$<br>Older patients |
| Nonhyperdiploid (40) | | Aggressive disease, IgA-$\lambda$<br>Younger patients |
| *Cyclin dysregulation* | | |
| t(11;14)(q13;q32) (16) | *CCND1/IGH* | More favorable |
| t(6;14)(p21;q32) (2) | *CCND3/IGH* | |
| t(12;14)(p13;q32) (<1) | *CCND2/IGH* | |
| t(4;14)(p16;q32) (15) | *FGFR3-MMSET/IGH* | Intermediate risk<br>Less frequent bone lesions |
| *MAF rearrangements* | | |
| t(14;16)(q32;q23) (5) | *IGH/c-MAF* | Aggressive disease |
| t(14;20)(q32;q11) (2) | *IGH/MAFB* | |
| t(8;14)(q24.3;q32) (<1) | *MAFA/IGH* | |
| t(6;14)(p25;q32) (2) | *IRF4/IGH* | Poor information |
| Other alterations (15) | | Variable |



and rarely changes at disease progression (7). In a small subset of patients (10%), both IGH translocations and hyperdiploidy can be observed. This association is considered of have an unfavorable outcome (5). In addition, there is a subgroup of cases (15%) that present other type of alterations and variable clinical course.

Overall, hyperdiploidy showed a more favorable clinical evolution, more commonly are elderly individuals, and have a higher incidence of MM bone disease (8). However, this group is heterogeneous, being subdivided by GEP (gene expression profile) in four putative subgroups. Each subgroup was characterized by the overexpression of largely nonoverlapping gene sets associated to different pathways relevant to myeloma biology and with different clinical outcome, such as, cancer testis antigen and mitosis/proliferation-related genes, hepatocyte growth factor (HGF)/interleukin-6 genes, NF-kB/anti-apoptosis genes, and the last one ill-defined and with low expression of HGF (9).

Nonhyperdiploid MM cases are also an heterogeneous group that consists of several molecular subtypes based on the specific partner chromosome involved in the IGH translocation, and mediated primarily by errors during IGH switch recombination process (Table 1). The different subgroups include: *Cyclin D* translocations, t(4;14)(p16.3;q32) and *MAF* translocations.

### *Cyclin D* translocations

Translocation t(11;14)(q13;q32), with the consequent upregulation of *Cyclin D1* (*CCND1*) gene, is the most frequent translocation of this group, occurring in approximately 15–20% of newly diagnosed MM patients (5, 10, 11). The other alterations of this group are: t(6;14)(p21;q32) (2%) and t(12;14)(p13;q32) (<1%), involving *CCND3* and *CCND2* genes, respectively (12, 13). These translocations are associated with nonsecretory or hyposecretory disease, lymphoplasmacytic or small mature plasma cell morphology, lambda light chain usage and CD20 expression (14–18). Translocation t(11;14)(q13;q42) is observed in one half of cases of light chain amyloidosis and can be found in MGUS. This translocation has been associated with a favorable clinical evolution; the disease can be heterogeneous and its global effect on prognosis is considered neutral (5, 11, 19, 20). The International Myeloma Workshop Consensus (21) establishes that t(11;14) does not predict a superior outcome. A recent evaluation of its impact on the outcome of autologous hematopoietic cell transplantation concludes that t(11;14) has a worse outcome than patients with normal karyotype and FISH studies, but better than patients with high risk markers (22).

### t(4;14)(p16.3;q32) translocation

The second most frequent reciprocal translocation in MM patients is t(4;14)(p16.3;q32), which occurs in about 15% of patients (23, 24). This is a cryptic translocation that must be evaluated by FISH or reverse-transcriptase PCR (RT-PCR), and involves two protein coding genes, *MMSET* and *FGFR3,* both mapped at 4p16.3. They are the Wolf-Hirschhom syndrome candidate 1 gene (*WHSC1*) also known as multiple myeloma SET domain (*MMSET*), a protein with homology to histone methyltransferases, and the fibroblast growth factor receptor 3 (*FGFR3*) gene, an oncogenic receptor tyrosine kinase. *MMSET* is expressed in all cases with this translocation; instead *FGFR3* expression is detected in 75% of patients due to the loss of the derivative chromosome 14, in which *FGFR3* is translocated, observed in 25% of cases (24, 25). This loss apparently reflects the presence of clonal evolution during disease progression. Translocation t(4;14)(p16.3;q32) is associated to the use of IgA heavy chain, lambda light chain, and a very high prevalence of chromosome 13 deletion/monosomy (6, 25–28), and identify a subset of MM patients with short survival, even in the context of autologous transplantation (6, 20, 29, 30). This translocation is also observed in cases with MGUS and frequently in patients with SMM (26, 31).

### *MAF* (musculoaponeurotic fibrosarcoma) gene translocations

These translocations are less frequent, being observed in 5–7% of MM patients. They include: t(14;16)(q32;q23) (5%), t(14;20)(q32;q11) (2%) and t(8;14)(q24.3;q32) (<1%), involving *c-MAF*, *MAFB* and *MAFA* genes, respectively. These translocations have been associated with IgA isotype, higher frequency of chromosome 13 deletion and a more aggressive clinical outcome (6). The mechanism of this poor outcome is thought to involve the consequences of MAF upregulation, which include upregulation of cyclin D2, effects on cell interaction and upregulation of apoptosis resistance (32). Particularly, the t(14;16)(q32;q23) juxtapose the *c-MAF* gene (16q13) and IGH locus at 14q32. The breakpoint occurs in the introns of a very large gene named WWOX (WW domain containing oxidoreductase), which spans a fragile site (FRA16D) (33). It is interesting to point out that translocation t(14;20)(q32;q11) involving *MAFB* gene is associated

with short survival in MM patients. The same translocation shows a long-term stable disease in MGUS and SMM patients, suggesting that the translocation alone cannot be responsible for adverse clinical behavior and additional events must be required for disease progression (34). Simultaneously, very scarce information about clinical characteristics of translocation t(8;14)(q24.3;q32) exists.

### Secondary alterations

As previously referred, the presence of secondary genetic events reflects tumor progression. In MM several recurrent secondary alterations have been described, being the most frequent: deletion/monosomy of chromosome 13, deletion of chromosome 17p13, chromosome 1 abnormalities (1p deletions and 1q gains/amplifications), and *C-MYC* translocations (5, 35–37).

### Chromosome 13 alterations

Chromosome 13 alterations are detected in 50% of cases, 85% monosomies, while the remaining 15% are interstitial deletions (38, 39). This alteration was first associated with an unfavorable prognosis and short survival (31, 40, 41), but there is now increasing evidence that its prognostic relevance may be related to its association with high risk *IGH* translocations, particularly t(4;14) (90% of cases), being considered as a marker of nonhyperdiploid MM (5, 6, 40, 41). In addition, Fonseca *et al.* (5) suggest a critical role for chromosome 13 deletion/monosomy as a prerequisite for clonal expansion of myeloma tumors.

### Deletion 17p13

This alteration, in which the tumor suppressor gene *TP53* maps, is considered the most important molecular cytogenetic prognostic factor in MM patients (6, 40, 42). Tumor suppressor protein *TP53* has an important role in promoting apoptosis, senescence, or cell cycle arrest in response to DNA damage, while *TP53* deletion or mutations may either predispose cells to DNA damage or allow cellular survival (43). It is a late event in MM, being reported in about 10% of cases by FISH studies. Its presence predicts for shorter survival, more aggressive disease, higher prevalence of extramedullary disease, hipercalcemia, short duration of response post-high dose therapy, and central nervous system involvement. It is observed in most cases of plasma cell leukemia both primary and secondary, and is very uncommon in MGUS (6, 40, 42, 44–47). FISH studies of clonal evolution indicated that the deletion occurs most commonly in subclones (48).

### Chromosome 1 alterations

Structural aberrations of chromosome 1 are the most frequent additional changes in plasma cell disorders, being found in up to 45% of MM and in almost all PCL patients (49–56). Among them, 1q21 gains/amplifications are highly prevalent in MM and its frequency rises during the course of the disease (52, 56–58). Different studies support that this alteration introduces an increased level of genetic instability in myeloma cells (49, 59) and suggest 1q amplification as a possible subrogate marker of more clonally advanced tumors (60). Significantly short survival was observed in patients with 1q21 gain/amplification compared to those lacking this alteration (56, 61). In addition, higher frequency of 1q21 gain was found in relapsed patients (72% of cases), probably associated to drug resistance (52, 58, 62). One of the key genes mapped on chromosome 1q21 is *CKS1B* (CDC28 protein kinase regulatory subunit 1B) (8, 54), that encodes for a positive cell cycle regulator that activates cyclin-dependent kinases to promote proliferation and cell cycle progression (63, 64). *CKS1B* is essential for the ubiquitination of the inhibitor of the cell cycle *CDKN1B* ($p27^{KIP1}$), which degradation is required for the cellular transition from quiescence cells to the proliferative state (65). Its overexpression was associated with a high rate of proliferation and poor prognosis in MM patients (66–68) and a positive correlation between *CKS1B* expression and 1q21 gain was observed (56, 58, 69). Zhan *et al.* (67) detected high *CKS1B* mRNA and protein levels in aggressive primary MM, which increased during disease progression. A more indolent clinical course was associated to low levels of *CKS1B* expression. In concordance, Stella *et al.* (56) found higher *CKS1B* expression in MM compared to MGUS samples, suggesting a role of this gene in the multiple step process of progression of MGUS to MM. A number of studies have evaluated the association between 1q21 copy gain and *CKS1B* expression with clinical evolution showing 1q21 copy gain as a more significant prognostic factor than *CKS1B* overexpression (56, 58, 61, 70). Patients with 1q21 gain/amplification show a higher prevalence of adverse *IGH@* translocations as well as other secondary alterations like deletions 13q and 17p (58, 62, 63, 71), being suggested that additional genetic abnormalities significantly worsen the poor prognosis of 1q21 gain (63, 71).

Deletions of 1p have been identified in approximately 7–40% of myeloma cases using cytogenetics, FISH, and comparative genomic hybridization (CGH) (4, 72, 73), and a recurrent region of losses at 1p32.3 affecting *CDKN2C* (cyclin-dependent kinase inhibitor 2C) ($p18^{INK4C}$) locus was defined (74, 75). C*DKN2C* gene belongs to the INK4 family of cyclin-dependent kinases (cdk) inhibitors which interacts preferentially with the cdk4/6 preventing G1 progression. Terminal differentiation of B cells into plasma cells is dependent on G1 cell cycle arrest, which is temporally correlated with its increased expression (76). Chromosome 1p deletion has also been associated to adverse clinical outcome in MM patients (53, 66, 73, 77). Association between 1p deletions and 1q21 gains is frequently observed (53, 56). The incidence and prognostic significance of deletions at 1p22 and 1p32 have been recently evaluated in a large cohort of MM showing that even though both deletions were predictive for poor progression free survival and overall survival, deletion 1p32 appears as a major independent prognostic factor (78).

### *MYC* alterations

*MYC* (8q24) rearrangements in MM are often complex involving nonreciprocal alterations, duplications, amplifications that can be mediated by secondary events that do not involve B-cell-specific recombination mechanisms, and sometimes do not involve immunoglobulin loci (79). These

**Table 2**. Cytogenetic Risk Stratification

| |
|---|
| High risk (20% of patients) |
| t(14;16)(q32;q23) (by FISH) |
| t(14;20)(q32;q11) (by FISH) |
| del(17)(p13) (by FISH) |
| Chromosome 1 alterations |
| Complex karyotype |
| Intermediate risk (20% of patients) |
| t(4;14)(p16;q32) (by FISH) |
| del(13)(q14) |
| Standard risk (60% of patients) |
| Hyperdiploid |
| t(11;14)(q13;q32) (by FISH) |
| t(6;14)(p21;q32) (by FISH) |

**Table 3**. Impact of Bortezomib Induction Therapy on Progression Free Survival of Patients Receiving High-Dose Therapy with Autologous Stem Cell Transplantation

| Trial | High-Risk Patients[a] | Standard Risk Patients[b] | *p* value |
|---|---|---|---|
| *GIMEMA (91)* | | | |
| BTD | 58% at 3 years | 63% at 3 years | .713 |
| TD | 19% at 3 years | 61% at 3 years | .001 |
| *PETHEMA/GEM (92)* | | | |
| BTD | 23.5 months | NR | .06 |
| TD | 8.9 months | 29.4 months | .04 |

BTD, bortezomib, thalidomide, dexamethasone; TD, thalidomide, dexamethasone; NR, not reached.
[a]The presence of del(17p13) and/or t(4;14).
[b]The absence of del(17p13) and t(4;14).

alterations occur in 15% of newly diagnosed MM patients (80), but are observed in 45% of cases with advanced disease, and in nearly 90% of human myeloma cell lines, showing a similar prevalence in hyperdiploid and nonhyperdiploid cases (81). Translocations involving MYC and IGH loci are frequently observed as a late event during tumor progression, when the diseases are becoming more proliferative and less stromal dependent. *MYC* activation was also detected in MGUS patients, suggesting it could be an early genetic event in the pathogenesis of MM (82). Experimental studies in a transgenic mouse model support a functional role for *MYC* in the progression of MGUS to MM (83).

### Other alterations

Fifteen percent of patients have other alterations, showing a heterogeneous clinical course. Among them, deletions of the short arm of chromosome 12 occur in about 8% of MM patients and in 24% of cases with plasma cell leukemia (84). The size of the deletion is variable, and it tends to appear in advanced disease, representing a secondary change associated with disease progression. Another point to be considered is the presence of complex karyotypes which are a consequence of the accumulation of sequential genetic changes that appear during tumor clone development and are associated with disease progression (13, 35). Taking into account the clinical outcome, genetic abnormalities in MM can be classified in standard, intermediate and high risk (Table 2).

## CYTOGENETICS AND THERAPY

In order to evaluate the impact of new therapies for patients with specific cytogenetic abnormalities, we identified 8 RCT published in the past 10 years which provided data on outcomes of cytogenetically defined risk subgroups (85–94). While the criteria for high risk groups varied among studies, it generally included del(17q13), t(14;16) and in occasions t(4;14). Our analysis is based on the retrospective evaluation of subgroups of patients from RCT with the known limitations of these types of analyses. Difficulties are further compounded by the fact that high risk groups represent a small fraction of patients in these trials (∼20%). To date, there are no published trials where patients have been prospectively stratified according to their cytogenetic risk profile.

## FRONTLINE THERAPY INCLUDING AUTOLOGOUS STEM CELL TRANSPLANTATION

### Thalidomide

In the MRC IX trial, which randomized 1111 evaluable patients, the incorporation of thalidomide during induction with CTD (cyclophosphamide, thalidomide, and dexamethasone) was compared to CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) followed by a single course of high-dose therapy and autologous stem cell transplantation (HD-ASCT). No significant differences in progression free survival (PFS) or overall survival (OS) were observed. A late, modest OS benefit was noted with CTD in patients with standard risk cytogenetics, but it was not seen in high-risk patients (85).

### Bortezomib

HOVON65 evaluated the incorporation of bortezomib in combination with doxorubicin and dexamethasone (BAD) compared to standard VAD (vincristine, doxorubicin, and dexamethasone) (86). They randomized 827 patients to either induction therapy followed by one or two cycles of HD/ASCT. Patients in the VAD arm received thalidomide maintenance, while patients in BAD received bortezomid maintenance. Overall, the study showed a superior complete remission rate (CR) and PFS for BAD, with a nonsignificant trend for better overall survival (OS) at 6 years: 61% versus 55%.

In patients with del(17p13) BAD resulted in better PFS (26.2 m *vs*. 12 m, $p = .02$) and OS at 3 years (69% *vs*. 17%, $p = .02$) than VAD. Among patients treated with BAD, del(17p13) was no longer a predictor of PFS or OS, while it remained a strong predictor among VAD treated patients ($p = .001$ for PFS and $p = .001$ for OS). Interestingly, among del(17p13) negative patients, there was no difference in outcomes comparing BAD and VAD.

### Thalidomide and bortezomib

Two RCT evaluated induction therapy with bortezomib concomitant with thalidomide/dexamethasone (BTD) compared with thalidomide/dexamethasone (TD) (87, 89) prior to HD/ASCT (Table 3).

In the first trial, patients received BTD or TD before tandem HD-ASCT and followed by consolidation. Overall, a benefit for BTD was reported with PFS at 3 years of 68% *versus* 56% ($p = .005$), but with no significant differences in OS (87). PFS for BTD patients with t(4;14) was 69% compared to 74% in those without the abnormality ($p = .66$). The adverse prognosis of t(4;14) was retained in TD treated patients: PFS 37% *versus* 63% ($p = .013$). Overall, post-transplant consolidation with the same regimen used for induction improved CR rates and PFS. BTD consolidated patients with t(4;14) and/or del(17p13) had a 3 years PFS of 54%, similar to that patients without these abnormalities. TD consolidated patients had a PFS of 19% in the presence of t(4;14) (88).

In the second trial, BTD treated patients achieved, overall, significantly improved CR rates (35% *vs*. 14%) and PFS (56.2 *vs*. 28.2 months) compared to TD treated patients. Among cytogenetically defined high-risk groups which included t(4;14) and del(17p13), BTD treated patients had significantly improved CR rates (38% *vs*. 0%, $p = .01$) PFS at three years (23.5 months compared to 8.9 month in TD treated patients) (89). OS was shorter in high-risk patients regardless of the treatment assigned. In this trial, patients received a single course of HD/ASCT. After transplantation patients underwent a second randomization to maintenance therapy with interferon, thalidomide, or bortezomib plus thalidomide.

## FRONTLINE THERAPY NOT INCLUDING AUTOLOGOUS STEM CELL TRANSPLANTATION

### Thalidomide

In the large MRC IX trial for patients unsuitable for transplantation, 849 patients were randomized to receive CTD or melphalan and prednisone (MP). Overall, CTD patients had higher response rates, but no differences in PFS and OS. Standard risk patients showed a late (after 18 months) OS benefit, which was not observed in high-risk patients (90).

### Bortezomib

The VISTA trial, compared bortezomib plus melphalan/prednisone (BMP) versus MP, overall no significant differences were seen in terms of CR rates, PFS, and OS when high-risk and standard risk patients were compared for the entire population (91).

### Bortezomib and thalidomide

In a comparison of BMP with BTD, the adverse prognosis associated with high-risk cytogenetics was not affected by the treatment arm. However, OS at three years in nonhyperdiploid patients, was 53% with BTD and 72% in BMP treated patients (92). A second randomization assigned patients to maintenance with bortezomib/thalidomide (BT) or bortezomib/prednisone. In high-risk patients, PFS and OS were similar with both maintenance schemas (PFS 28 *vs*. 27 months, OS 55% *vs*. 53% at 4 years). Standard risk patients had a nonsignificant trend of better PFS (47 *vs*. 36 months) and better OS (79% *vs*. 69% at 4 years) with BT (93). Neither maintenance regimen was able to overcome the effect of adverse cytogenetics.

The incorporation of thalidomide to BMP (BMP+T) followed by BT maintenance improved PFS compared to BMP without maintenance (35.3 months *vs*. 24.8 months, $p < .001$). The benefit was shown in standard risk patients (HR 0.62), but BMP+T could not improve the outcomes of high-risk patients (HR 0.98) (94).

### Lenalidomide

While lenalidomide has been shown to improve PFS in patients treated with or without transplantation (95–98), there is limited data available to evaluate its relative impact according to cytogenetic/FISH defined standard and high-risk groups. Subgroup analyses from one of these trials (98) suggest the continuous lenalidomide plus dexamethasone does not improve PFS or OS in high-risk, transplant ineligible patients as compared to melphalan, prednisone, and thalidomide.

## SUMMARY

In the transplant or in the conventional dose therapy settings, patients receiving thalidomide as induction and/or maintenance have a modest OS benefit which is limited to standard risk patients, but is not seen in high-risk patients.

Transplanted patients receiving induction therapy with bortezomib (in combination with doxorubicin or thalidomide), demonstrate a major impact on outcomes of high-risk patients, improving their CR rates, PFS, and OS. In at least two trials, bortezomib was able to completely overcome the adverse effect of high-risk cytogenetics (86, 87). It is not clear, from the data available, if the addition of thalidomide to bortezomib during induction therapy results in any additional benefits.

For patients treated with conventional dose therapy, bortezomib in combination with MP or TD has not been shown to improve the outcomes of high-risk patients (92, 93). Maintenance with BT or BP produced similar results in high-risk patients, with a trend for better PFS and OS with BT in standard risk subgroups (92). Similarly, the four drug combination BMP+T with BT maintenance improved PFS of standard risk patients but not of high-risk patients (94).

Based on the available data, high-risk patients should be treated with bortezomib-based induction therapy followed by HD-ASCT. A recent meta-analysis shows that induction therapy including bortezomib prior to transplantation improves the outcomes in the general trial population compared to nonbortezomib protocols (99). In our analysis, this approach has been shown to improve outcomes of high-risk patients. Standard dose therapy with BMP, BTD, or BMP+T primarily improved the outcomes of standard risk patients, but not for those with adverse cytogenetics.

Genetic abnormalities evaluated by cytogenetics/FISH have a strong prognostic value in MM. They should be included in the evaluation of all patients at the time of diagnosis, as they may be able to help select the most appropriate therapy. Cytogenetic abnormalities are currently included in

a new staging system (100) and they will be essential to stratify patients with different prognosis for specific risk-directed therapies in future RCT.

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## DECLARATION OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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