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REVIEW ARTICLE

# Clinical implications of cytogenetic and molecular aberrations in multiple myeloma

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## Abstract

Multiple myeloma (MM) is an incurable haematological malignancy affecting approximately 7:100,000 people. Monoclonal gammopathy of undetermined significance (MGUS) and 'smouldering' MM precede symptomatic MM. Cytogenetics in MM is the most powerful prognostication tool incorporated into different classifications, including the Revised International Staging System (R-ISS) and the Mayo Clinic Risk Stratification for Multiple Myeloma (mSMART). Methods commonly used to test for cytogenetic aberrations include conventional karyotyping and fluorescence *in situ* hybridisation (FISH), although the difficulty of obtaining metaphases in plasma cells results in low yields.

Therefore, new genomic tools are essential to explore the complex landscape of genetic alterations in MM. These include next generation sequencing, a highly sensitive method to monitor minimal residual disease. The serial evolution of MGUS to MM is accompanied by a range of heterogenous genetic abnormalities, divided into primary (involving mostly chromosome 14 translocations and trisomies) and secondary genetic aberration events (involving mostly 17p, 1p, 13q deletions, 1q gain, or MYC translocations). Based on the primary genetic aberration results, strong prognostic features of MM have been identified with distinct clinical characteristics. High risk aberrations include 17p deletion, t(4;14), t(14;16), t(14;20) and chromosome 1 abnormalities. The incorporation of novel drugs and maintenance strategies in conjunction with autologous stem cell transplantation partially overcome the adverse effect of some of these genetic aberrations. Nonetheless, survival remains worse in this group compared to standard risk patients. Clinical decisions regarding treatment should be based on the cytogenetic results. The establishment of individualised and mutation-targeted therapies are of the greatest importance in future studies.

**Key words:** myeloma, cytogenetics, prognosis, high risk, genomics, aberration

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## Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder which affects approximately seven in every 100,000 people, giving it the second highest incidence among all haematological malignancies in the Western world [1–3]. MM is preceded by a pre-malignant stage called monoclonal gammopathy of undetermined significance (MGUS), which is present in over 3% of the population >50-years-old, and the incidence increases with age [4]. The risk of progression of MGUS to MM is approximately 1% per year depending on prognostic features (e.g. paraprotein concentration, immunoglobulin isotype and free light chain ratio) [5]. While MGUS is a 'benign precursor state' which is devoid of any myeloma defining events (MDE), MM can cause severe symptoms and end-stage organ damage including renal insufficiency (present in 20% of newly diagnosed patients), anaemia (haemoglobin <12 g/dL present in 73% of patients), skeletal lesions (present in approximately 65–75% of patients) or hypercalcemia (calcium level >11 mg/dL present in 13% of patients) [6]. According to the updated International Myeloma Working

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**Table I.** For diagnosis of multiple myeloma, the criterium of clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma should be met, and any one or more of the following myeloma-defining events (SLiM CRAB) should be present

| | |
|---|---|
| **C**alcium | Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal or >2.75 mmol/L (>11 mg/dL) |
| **R**enal Insufficiency | Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2 mg/dL) |
| **A**naemia | Anaemia: haemoglobin value of >2 g/dL below lower limit of normal, or haemoglobin value <10 g/dL |
| **B**ones | Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) |
| **S**ixty | Clonal bone marrow plasma cell percentage ≥60% |
| **L**ight chains | Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L) |
| **M**agnetic resonance | >1 focal lesion on magnetic resonance imaging (MRI) studies (at least 5 mm in size) |

Group (IMWG) criteria, the diagnosis requires ≥10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma plus evidence of one or more MDE included in the SLiM-CRAB acronym (Table I) [7]. However, unlike other haematological malignancies, no specific cytogenetic pathognomonic criterium for MM exists.

The disease is considered incurable, and survival may vary from a few months to over 15 years; this diversity is most strongly driven by the genetic abnormalities present in the plasma cells [8].

In the era of modern drugs including proteasome inhibitors (PIs) (bortezomib/carfilzomib/ixazomib), immunomodulatory drugs (IMIDs) (thalidomide/lenalidomide/pomalidomide), monoclonal antibodies (daratumumab/isatuximab/elotuzumab), and antibody drug conjugates (belantamab mafodotin), median overall survival reaches 6+ years [9].

Several features affect survival: host characteristics, tumour burden and biology (cytogenetics) as well as the response to treatment. Laboratory risk factors for a poorer prognosis have been identified, including serum beta$_2$-microglobulin (β2M), low albumin and/or elevated lactate dehydrogenase. However, genetic changes seem to play the largest role in prognosis in MM [10].

Studying myeloma genetics has been always limited due to low proliferation potential of the plasma cells for standard karyotype analysis. Nonetheless, in recent years the development of genetic tools including microarrays and next-generation sequencing (NGS) has led to substantial progress in understanding the genetics of MM [11].

MM remains a highly heterogenous and complex disease with varied genetic aberrations resulting in multiple subclones. A major clone dominates throughout the disease course, although minor clones may evolve and be responsible for chemoresistance or serve as a reservoir for relapses or progressions [11, 12]. Interestingly, in a recent study by Merz et al., the presence of subclones was prognostic for smouldering MM to transform into MM; however, the risk of progression was not constant and changed due to clonal evolution [13]. Nonetheless, the mechanism and driving factors resulting in the development of how these subclones emerge, how they are selected and what is their prognostic implication, need to be investigated in future studies.

In general, the pathogenesis of MM can be visualised by two steps: the establishment of MGUS and progression from MGUS to MM (Figure 1) [14]. This process is accompanied by different cytogenetic changes (Table II). The evolution of MGUS is thought to be a result of abnormal antigen stimulation and is caused by primary cytogenetic aberration events, so-called 'disease-initiating' aberrations. The primary cytogenetic abnormalities help to classify MGUS and MM into several subtypes and consist mostly of trisomies and translocations involving chromosome 14 [5]. Additionally, primary cytogenetic abnormalities are mostly non-overlapping [15]. The second step occurs rather due to random cytogenetic mutations (called secondary cytogenetic aberration events) resulting in the evolution to symptomatic MM and further MM progression [16]. Secondary cytogenetic aberrations might overlap, and are typically subclonal (Figure 1) [5].

This review provides an overview of the different cytogenetic approaches used to stratify MM patients. We will discuss cytogenetic and molecular aberrations, their frequency, and clinical and prognostic implications.

## Laboratory testing strategy

### Conventional cytogenetics (G-band karyotyping)

Conventional cytogenetics is a well-established and universally available test, and it also provides a whole genome analysis at once. On the other hand, the detection of chromosomal abnormalities using conventional cytogenetics is limited due to low proliferative activity of malignant plasma cells and low number of plasma cells in an often haemodiluted bone marrow aspirate. Chromosomal abnormalities are detected in only 30% of patients without CD138$^+$ cell enrichment [17]. In plasma cell leukemia, cytogenetic aberrations are more common (up to 68% of cases) [18]. Despite this limitation, karyotyping provides essential

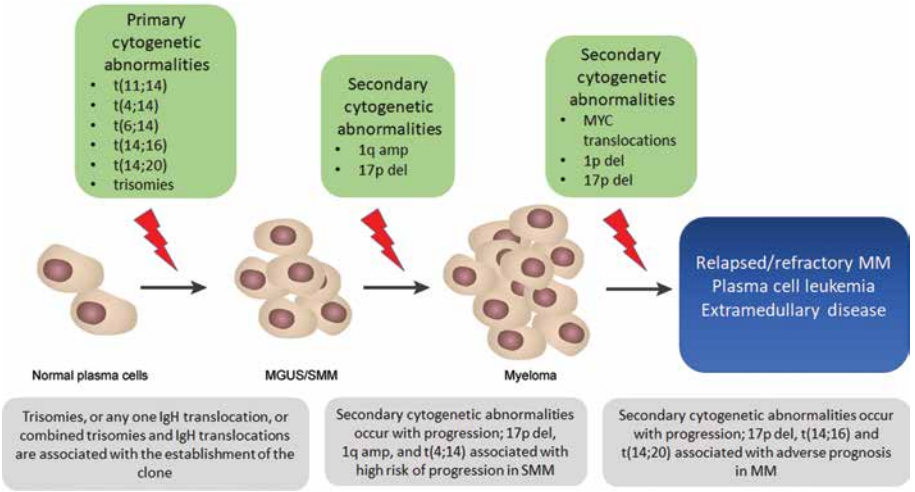


**Figure 1.** Cytogenetic abnormalities in multiple myeloma (MM) (modified from [14]); amp — amplification; del — deletion; IgH — immunoglobulin heavy chain; MGUS — monoclonal gammopathy of undetermined significance; SMM — smoldering multiple myeloma; t — translocation

**Table II.** Genetic abnormalities in multiple myeloma, their frequency and clinical impact

| Cytogenetic abnormalities | | Frequency [%] | Clinical impact, additional characteristics |
|---|---|---|---|
| Primary | t(4;14)(p16;q32) | 10–15 | Adverse, good response to proteasome inhibitors, unfavourable for any immunomodulatory drug |
| | t(6;14)(p21;q32) | 2 | Neutral |
| | t(11;14)(q13;q32) | 15–20 | Neutral, sensitive to venetoclax |
| | t(14;16)(q32;q23) | 2–3 | Adverse |
| | t(14;20)(q32;q12) | 1 | Adverse |
| | Hypodiploidy | 13–20 | Adverse |
| | Hyperdiploidy | 50 | Favourable, good response to lenalidomide in patients with trisomies |
| Secondary | 13q deletion | 45–50 | Adverse |
| | MYC translocation | 15–20 | Neutral or adverse |
| | 1q21 gain | 35–40 | Adverse, might be implicated in bortezomib resistance |
| | 1p32 deletion | 30 | Adverse |
| | 17p deletion | At diagnosis <10, at relapses >30% | Adverse, possible central nervous system involvement, pomalidomide seems to be beneficial |

information on numerical and structural chromosomal changes. Numerical aberrations include hyperdiploidy or non-hyperdiploidy, whereas structural abnormalities include translocations or copy number aberrations (i.e. deletions or gains). Furthermore, conventional karyotyping is an independent prognostic factor even in the era of modern testing modalities [e.g. fluorescence *in situ* hybridisation (FISH), NGS, and gene-expression profiling (GEP)], and should be routinely performed as an initial diagnostic workup especially in situations where a FISH test is unavailable [19, 20].

## FISH analysis

FISH testing is based on the use of fluorescent probes that bind to highly complementary nucleic acid sequence. Using a variety of FISH probes, numerous genetic alterations might be detected, including numerical amplifications or deletions, structural rearrangements and translocations [21]. On conventional cytogenetics, in patients with complex karyotype, some aberrations (e.g. translocations) are cryptic, and FISH enables their detection [22]. Furthermore, a FISH test does not depend on the proliferation rate, and the probes can be applied on nondividing cells, mainly on interphase cells [21]. However, the detection sensitivity is limited by the number of plasma cells in the whole bone marrow, which is especially low in patients after treatment or early in the diagnosis or relapse (when plasma cells range from 1–20%) [23]. Consequently, FISH is run mainly on $CD138^+$ enriched cells, and different techniques are used to target and enrich the monoclonal plasma cells, e.g. immunostaining (cytoplasmic immunoglobulin FISH, cIg-FISH),

**Table III.** Staging strategies in multiple myeloma according to different working groups

| Staging system | Stage | Criteria |
|---|---|---|
| International Staging System (ISS) | Stage I | β2M <3.5 mg/dL and albumin ≥3.5 g/dL |
| | Stage II | Neither I nor III |
| | Stage III | β2M ≥5.5 mg/dL |
| Revised International Staging System (R-ISS) | Stage I | ISS I, standard risk by FISH (no high-risk chromosomal abnormalities) and normal LDH |
| | Stage II | Neither R-ISS I nor III |
| | Stage III | ISS III, either high risk by FISH [del(17p) and/or t(4;14) and/or t(14;16)] or high LDH (> upper limit of normal) |
| Mayo Clinic Risk Stratification for Multiple Myeloma (mSMART) | Standard risk | Trisomies |
| | | t(11;14) |
| | | t(6;14) |
| | High risk | t(4;14) |
| | | t(14:16) |
| | | t(14;20) |
| | | 17p deletion |
| | | 1q gain |
| | | R-ISS stage III |
| | | High plasma cell S-phase (cut-off varies) |
| | | GEP: high risk signature |
| | | **Double-hit:** any two high-risk factors |
| | | **Triple-hit:** any three or more high-risk factors |
| Gene-expression-based signatures | | Presence of alterations detected by: UAMS, Skyline 92–HOVON, IFM |

β2M – beta$_2$ microglobulin; FISH – fluorescence *in situ* hybridisation; GEP – gene expression profiling; LDH – lactate dehydrogenase

selection by magnetic cell sorting (MACS), fluorescence-activated cell sorting (FACS), as well as targeted manual scoring or customised automated image analysis [24].

The European Myeloma Network (EMN) guidelines recommend that at least 100 cells should be scored when analysing FISH [23]. The cut-off value for positivity remains a controversial issue and varies from laboratory to laboratory; there is no uniform criterion. It is related to the testing strategy and the various ways to establish cut-off for different FISH patterns in different laboratories [25, 26]. It is recommended by the EMN to use conservative cut-off levels: 10% for fusion or break-apart probes and 20% for numerical abnormalities [23], although in clinical practice the threshold for a positive test is very often much lower.

## Molecular methods

Although not used in daily clinical practice outside clinical trials, advanced oncogenomic analyses are very important tools to understand the complex genetic landscape, and hence clinical outcomes, of MM patients. Different genomic analysis methods exist to research into the various processes of translating the genomic information. The most comprehensive test, NGS, is a process that allows the determination of the sequence of nucleotides in a section of DNA. This provides a full, integrated spectrum of gene mutations, aneuploidies, segmental copy-number changes and translocations. Utilising NGS has identified several recurrent gene mutations in newly diagnosed MM patients, including the most common mitogen activated protein kinase (MAPK) pathway, NF-κB pathway and TP53 pathway genes [27]. Although NGS is not yet universally available, in the future it will be an important tool in the diagnosis and monitoring of the minimal residual disease (MRD) due to its high sensitivity [28]. Of note, large sequencing studies in MM are being conducted to determine the relevance of different mutations, and preliminary results are promising (CoMMpass, The Myeloma Genome Project) [29, 30]. The GEP analyses the RNA expression of different genes pertinent to different functions [31]. It is an important marker to detect high risk patients (Table III) [32], and it also helps to establish classifiers for prognostication in addition to the International Staging System (ISS) or FISH known high risk factors [33]. Several genes lists have been found to have strong prognostic information, including commercially available GEP70 and SKY92 profiles [32, 34]. A single-nucleotide polymorphism (SNP)-microarray is a technique of the hybridisation of fragmented single-stranded DNA to arrays containing hundreds of thousands of unique nucleotide probe sequences. SNP is the smallest genetic variation that can occur within a DNA sequence. SNP microarray can detect small copy number changes such as gene deletion, chromothripsis, complex copy number changes, and amplification, as well as copy neutral loss of heterozygosity (CN-LOH), which is an important oncogenic event [25]. It also detects aberrations in small populations (subclones) due to clonal evolution [25], of which the most common are complex MYC 8q24 rearrangements or amplifications, 1q gain, 1p and 17p deletions [35, 36].

Using the genomic tools, several molecular classifications have been established in MM. They have been also incorporated into well-known staging systems to more precisely estimate an individual patient's disease risk and clinical outcome. Incorporating the novel molecular methods into clinical use and establishing personalised therapies based on the molecular findings will be of the utmost urgency.

## Cytogenetic abnormalities

### Primary cytogenetic abnormalities

#### Hyperdiploidy

Hyperdiploidy, commonly involving gain of odd-numbered chromosomes (trisomies), is detected in approximately 50% of patients with MM [5, 37]. Trisomies 3 and 5 are known to improve overall survival, but trisomy 21 impairs overall survival [38]. Patients with trisomies have particularly good response to IMIDs [39]. In approximately 10% of patients, trisomies and IgH translocations coexist [37]. The prognostic impact of this coexistence is a matter of controversy. Kumar et al. reported the presence of trisomies in patients with high risk translocations, namely t(4;14), t(14;16), t(14;20), or TP53 deletion, treated with modern drugs (PI and IMiD- based regimens). The adverse impact associated with these prognostic markers was partially ameliorated [37]. In contrast, Pawlyn et al. showed that in high risk cytogenetic patients coexistent hyperdiploidy did not abrogate a poor prognosis, although the patients were treated with older conventional drugs (cyclophosphamide with thalidomide and dexamethasone, or with vincristine) [40]. Hyperdiploidy is often accompanied by other structural chromosome changes (e.g. translocations, deletions or duplications) and a hyperdiploid karyotype with ≥2 of those aberrations should be considered as an independent high risk factor [41].

#### Non-hyperdiploidy

Non-hyperdiploidy is defined as hypodiploid, pseudodiploid, and near-tetraploid karyotypes. Hypodiploidy is defined as having ≤44 chromosomes in a cell, pseudodiploidy as having 45–46 chromosomes in a cell, and near-tetraploid karyotype originates from doubling of the hypodiploid and pseudodiploid karyotypes (>75 chromosomes) [42]. Hypodiploidy was an important independent factor for worse overall survival in multivariate analysis that included Durie and Salmon stage, treatment or bone marrow plasmocytosis [43]. In the non-hyperdiploid population, hypodiploid cases are associated with a higher prevalence of genetic alterations and a worse prognosis [42].

#### IGH translocations

IGH translocations, with a breakpoint on chromosome 14 band q32, are often present in tumours of the lymphoid lineage due to the common physiological DNA rearrangements at the immunoglobulin heavy chain (IGH) *locus* that might have been displayed incorrectly [44]. The aberration in IGH in MM occurs mostly during class switching, and the juxtaposition of an oncogene next to the IGH *locus* results in overexpression of the affected oncogene [45]. In MM, the IGH translocations occur in up to 60% of patients [15, 46]. There are five main translocation partner chromosomes including the t(4;14)(p16;q32) — multiple myeloma set domain (MMSET), t(6;14)(p21;q32) — cyclin D3 gene, t(11;14)(q13;q32) — cyclin D1 gene, t(14;16)(q32;q23) — musculoaponeurotic fibrosarcoma (C-MAF), and t(14;20)(q32;q12) — musculoaponeurotic fibrosarcoma oncology family, protein B (MAFB) [45]. Moreover, the recurrent IGH translocations (mostly with partner chromosomes 11, 4, and 16) are highly associated with nonhyperdiploid karyotype [47].

#### t(4;14)(p16;q32)

Translocation t(4;14), present in 10–15% of newly diagnosed cases, is not detectable by conventional karyotyping [25, 48, 49]. It is associated with poor prognosis and is considered to be a high-risk prognostic factor [48, 49]. Translocation t(4;14) is associated with immature morphology, higher tumour mass, and more frequent chromosome 13 abnormalities [50]. It is also reported to be less frequently associated with bone lesions, which consequently might be associated with delayed diagnosis [51]. Patients with t(4;14) seem to benefit from bortezomib-based therapy and bortezomib maintenance, and lenalidomide maintenance also might provide better survival in this group of patients [52, 53, 54]. It is also recommended to implement autologous stem cell transplantation (ASCT) as soon as possible in this cytogenetic subtype, and tandem ASCT should be considered [5]. Moreover, data from the MM-003 trial shows that pomalidomide plus low-dose dexamethasone is an effective strategy in relapsed/refractory settings in patients with t(4;14) [55].

#### t(11;14)(q13;q32)

The most common IGH translocation, accounting for 15–20% of cases, is t(11;14) [48, 49, 56]. This translocation results in upregulation and overexpression of the cyclin D1 that might be detected by immunohistochemistry [57]. Translocation t(11;14) is more prevalent in plasma cell leukemia patients as well as in light chain amyloidosis patients than in MM patients [58, 59, 60]. Although the prognostic impact is considered to be standard, some studies suggest that the overall survival and response rates are inferior to other standard risk patients [61, 62]. Translocation t(11;14) is more frequent among the African-American population and exerts negative influence on the survival in African-Americans compared to non-African-Americans [63, 64]. It is associated with lymphoplasmacytic morphology and frequently with low serum monoclonal protein or nonsecretory MM, and it is also less likely to coexist with hyperdiploid karyotype [50, 57]. In t(11;14) the expression of CD20 is often present [65]. The Mayo Clinic experts recommend the use of combined bortezomib and lenalidomide regimens followed by early ASCT and lenalidomide maintenance in t(11;14) patients [5]. The t(11;14) is associated with high expression of BCL2 protein and several studies have suggested the efficacy of the use of venetoclax, the BCL2 inhibitor, in t(11;14) positive patients.

### t(14;16)(q32;q23)

The more common MAF translocation, t(14;16), present in 2–5% of newly diagnosed cases, is hardly detectable by conventional karyotyping [25, 49, 56]. Translocation t(14;16) is associated with adverse outcomes, even in the era of novel drugs, something recently confirmed by a large international sample study conducted by our group [49, 66, 67]. Renal failure as a MDE is more frequently observed in patients with t(14;16) than in other cytogenetic subtypes. It is associated with high levels of free light chain in serum, which might partially explain the poorer prognosis in t(14;16) positive group of patients [51, 68]. It has been observed that t(14;16) is associated with negativity in CD56 expression and high proliferative activity, which might predispose toward an adverse outcome [69]. According to the Mayo Clinic experts, the treatment approach should be similar as in t(4;14), and in patients with renal failure it is recommended to combine bortezomib with cyclophosphamide, thalidomide or adriamycin over lenalidomide [5]. Our study suggests that at least a three-drug induction regimen (including IMID and PI) should be used, ASCT should be performed wherever possible [67, 68], and tandem ASCT should be considered [5]. Maintenance should be based on bortezomib [5].

### t(14;20)(q32;q12)

The second MAF translocation, t(14;20), has a low prevalence, 1%, and also exhibits adverse impact on outcomes, comparable to t(14;16) [56, 70, 71]. Translocation t(14;20) is also associated with higher frequency of renal failure due to high levels of free light chains in serum [51, 68]. Treatment based on PI should be used in an induction therapy [68]. Double ASCT should be considered as an upfront treatment strategy in this group of patients [70], and maintenance should include bortezomib [5].

## Secondary cytogenetic abnormalities

### MYC translocation

MYC translocations are secondary events and occur at late stages of tumour progression. They are present in 15–20% of patients [48, 72]. Most MYC translocations involve IGH *locus*, however other genes might be also involved (*IGL, IGK, FAM46C, FOXO3* or *BMP6*) [56]. As a result of the juxtaposition, the expression of c-MYC is increased [73]. The impact of MYC translocation on survival is believed to be negative, although it is still a matter of debate [73, 74]. It has been suggested that the negative impact on outcome of MYC is restricted to hyperdiploid MM and is caused by an interaction between t(MYC) and gain of 1q21 [72].

### 1q gain

1q gain is one of the most common aberrations in MM, present in approximately 30% of patients [75]. It is associated with end-organ damage and a higher tumour burden [75]. It has been shown that 1q gain is associated with the evolution from MGUS to MM, and the copy number of the 1q gain increases with disease progression [76]. Although the prognostic impact is a contentious issue, recent studies suggest that 1q gain has a strong, independent negative impact on survival, even in the era of modern drugs and ASCT [75, 77]. Although neither IMID- and PI-based treatment regimens nor ASCT seem to prolong survival in patients with 1q gain, a recent Mayo Clinic study suggested that PI-based strategies might show a slightly better effect on outcomes [75]. Nonetheless, another study showed that with increasing number of copies of 1q gain, bortezomib resistance also increases [78].

### 1p deletion

1p deletion is present in approximately 20% of patients and has an adverse impact on outcomes [79, 80]. These patients might need more intensive treatment, similar to that for other high-risk MM subtypes [5, 80].

### 13q deletion

13q deletion is present in 45–50% of patients with MM [48]. The 13q deletion often coexists with other cytogenetic abnormalities, and the presence and time of occurrence of 13q deletion depends on the presence of specific concurrent abnormalities [81]. 13q deletion detected by conventional karyotyping appears to predict poor outcomes (present in 10–15% of newly diagnosed patients) [82]. It has been shown that bortezomib might overcome the adverse impact of 13q deletion [83].

### 17p deletion

17p deletion (associated with loss of the *TP53* gene) is present in 10% of newly diagnosed patients, and the incidence increases with disease progression [48, 56]. It is present in the majority of cases of plasma cell leukemia [84]. 17p deletion is considered to be the most detrimental prognostic factor of high-risk disease and a poor outcome [66, 71]. The size of clone carrying the abnormality seems to be significant for the prognosis, although a recent study found contradictory results [85]. The bi-allelic inactivation of TP53 has an additional negative impact on survival [86]. TP53 deletions are associated with more aggressive disease course and complications including plasmocytomas and hypercalcemia [49]. The studies on the influence of different treatment strategies are inconsistent. BMT CTN 0702 trial results showed no survival benefit of either tandem ASCT or intensive treatment that included ASCT with a subsequent four cycles of bortezomib and lenalidomide followed by lenalidomide maintenance in patients with 17p deletion [87]. Moreover, Lakshman et al. showed that a deletion 17p positive patient did not benefit from IMID plus PI-based induction as well as early ASCT [85]. On the other hand, according

to the recent study based on the EMN02/HO95 trial, patients with 17p deletion were benefiting from intensive treatment including tandem ASCT and bortezomib-based induction therapy [88].

Despite all these differences, recommendations suggest using induction therapy based on IMIDs and PI (bortezomib or carfilzomib) and subsequently considering tandem ASCT and prolonged bortezomib maintenance [71, 89]. Of note, pomalidomide seems to be particularly active in 17p deletion [90].

### Specific mutations

In recent years, the genomic landscape of MM has been thoroughly studied, and several recurrent mutations identified, most of them involving genes implicated in the translocation of chromosome 14 or MAPK pathway, critical in cell growth and survival [91]. Some of them are related to the cytogenetic MM subtype, e.g. *FGFR3* or *PRKD2* genes mutations occur mainly in t(4;14) positive patients; *CCND1, KRAS* and *IRF4* genes mutations are detected in t(11;14) positive patients or *TP53* gene mutation is present in 17p deletion positive patients [5]. The *MAPK* genes mutations are represented by *KRAS* and *NRAS*, present in 40% of patients as well as *BRAF* genes mutations present in approximately 4% of patients [92]. Patients with mutations in *NRAS* or *KRAS* have worse survival than those with wild-type *RAS* genes [93]. It has been shown that patients with *NRAS* mutation exhibit reduced sensitivity to bortezomib [94]. For the MAP kinase pathway, several mutation-specific drugs are tested, e.g. vemurafenib in BRAF positive tumours or trametinib in AKT mutation [5].

### Double/triple hit MM

High risk cytogenetic aberrations, especially secondary genetic aberration events, often overlap. For example, in a study by Boyd et al. in a group of patients with adverse IGH translocation [t(4;14), t(14;16) or t(14;20)], almost 72% had additionally 1q gain, and 12.4% had 17p deletion [95]. To address the prognosis of patients with multiple adverse cytogenetic aberrations, the mSMART classification includes the concepts of 'double hit' (when any two high risk factors are present) and 'triple hit' (when any three high risk factors are present) as a high risk stage with poor prognosis (Table III) [7]. A recent study showed the predictive value of double- and triple-hit MM, with double-hit MM having OS of 6 months vs. 32 months for patients with one high risk factor, and 57 months for patients with no high risk factor [96].

## Staging approaches

The most universally accepted staging systems are set out in Table III. The Mayo Clinic recommends both conventional cytogenetic and FISH tests, and FISH is preferred if both are not available. All patients should be stratified and classified into standard- or high-risk groups using the mSMART criteria (Table III) and the FISH set should include detecting at least t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), trisomies, and 17p deletion [71, 97]. The EMN recommends performing FISH after $CD138^+$ plasma cell enrichment, and the analysis should include at least t(4;14) and 17p deletion; analysis of t(14;16), 1q gain and 1p deletion [98]. The National Comprehensive Cancer Network (NCCN) recommends FISH panel on bone marrow which includes 13 deletion, 17p deletion, t(4;14), t(11;14), t(14;16), t(14:20), 1q amplification and 1p deletion as an initial work-up [99]. According to the IMWG, the essential testing should include either cIg-FISH or FISH carried out on the nuclei from purified plasma cells. The minimum panel required for prognostic estimation should include t(4;14), t(14;16) and 17p deletions. A more comprehensive panel should include testing for t(11;14), 13 deletion, ploidy category and chromosome 1 abnormalities [100]. The Polish guidelines for the basic evaluation of cytogenetic prognosis suggest stepwise FISH testing: the first step includes *TP53* gene and *IGH* gene. If the IGH rearrangement is present, gene *FGFR3*/t(4;14) should be verified. If there is no *FGFR3* fusion, further analysis should include *MAF*/t(14;16) gene status. Extended testing should include additionally t(14;16), t(14;20), chromosome 1 status, t(11;14), *MYC* rearrangement, 13 deletion and the 5, 9 and 15 chromosome aberrations. Karyotyping is an optional study according to the Polish experts' recommendations [101].

It should be highlighted that the risk factors described for newly diagnosed patients might be applicable to the relapse or refractory setting. However, in that case, other factors seem to be equally crucial. For example, the resistance to primary treatment (primary refractory patients), or a short response after first line treatment with ASCT have poor prognosis, even if other high risk factors were not detected [102, 103]. Another powerful predictor of outcome in MM is MRD status after induction treatment, and its negativity predicts better survival [104]. Although not routinely monitored, MRD has a growing significance in monitoring the disease in clinical trials. MRD can be monitored by multiparameter flow cytometry or using molecular techniques like polymerase chain reaction (PCR) or NGS on a bone marrow sample. Studies evaluating NGS in MRD have shown that its negativity surpasses the traditional complete remission criterium in predicting better outcomes in MM patients [105, 106], and its sensitivity reaches $10^{-6}$ [107]. Limitations in utilising NGS in MRD monitoring include lack of standardisation, low availability, and frequent haemodilution of the bone marrow sample [98].

## Conclusions

MM is a highly heterogenous, gnomically evolving and ever-changing disease, with no disease-identifying unique

molecular aberration. The coexisting numerous subclones and potential lack of functionality of some mutations make interpretation even more difficult. Nonetheless, based on the cytogenetic and molecular landscape, several different subtypes of MM have been identified with different clinical characteristics and prognosis, and clinical decisions regarding treatment should be made based on the cytogenetic results. The establishment of individualised and cytogenetic subtype- or mutation-targeted treatment strategies are of the utmost importance in future studies.

## Authors' contributions

SGM — wrote manuscript; DHV, AJ — critically revised manuscript.

## Conflict of interest

None.

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None.

## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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