## PERSPECTIVE

# Perspectives on the Risk-Stratified Treatment of Multiple Myeloma

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**Summary:** The multiple myeloma treatment landscape has changed dramatically. This change, paralleled by an increase in scientific knowledge, has resulted in significant improvement in survival. However, heterogeneity remains in clinical outcomes, with a proportion of patients not benefiting from current approaches and continuing to have a poor prognosis. A significant proportion of the variability in outcome can be predicted on the basis of clinical and biochemical parameters and tumor-acquired genetic variants, allowing for risk stratification and a more personalized approach to therapy. This article discusses the principles that can enable the rational and effective development of therapeutic approaches for high-risk multiple myeloma.

## CHALLENGES IN THE MANAGEMENT OF HIGH-RISK MULTIPLE MYELOMA

The number of treatments available for patients with multiple myeloma has increased over the last two decades. These therapies have been incorporated into the current optimum therapeutic approach that uses cassettes of treatment comprising synergistic non–cross-reacting agents given as induction, consolidation, and maintenance phases. The aim of this strategy is to overcome clonal heterogeneity, reducing the malignant clone to minimal levels and thereby maximizing progression-free survival (PFS) and overall survival (OS).

However, there remains considerable heterogeneity in outcome, with some patients having a good prognosis while others fail to respond or relapse quickly and progress rapidly to death. Interestingly, it is the low-risk segment of disease that has seen the most significant improvement in survival. In contrast, poorest outcomes have changed minimally for patients in the high-risk (HR) segment. This is particularly important to address as it imposes a significant burden on both patients and caregivers, negatively impacting quality of life, psychosocial well-being, and survival.

Current expert opinion suggests that a reasonable benchmark for the definition of survival of this segment is a median OS of less than 3 years (1). To improve this, we need to improve our capacity to identify cases at presentation, and move from the current one-size-fits-all therapeutic approach to a personalized risk-stratified approach (2). Taking this

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approach will enable appropriate prognostic information to be discussed with the patient and allow the optimization of therapy for an individual patient, thus leading to better psychologic well-being and improved survival.

A risk-stratified approach is feasible based on the use of clinical and biochemical parameters and tumor-acquired genetic variants. Current multiple myeloma staging systems, however, lack sensitivity and specificity for use in individual patient risk stratification and could be improved and more widely implemented. In this article, we discuss data supporting multiple myeloma risk stratification, current therapeutic approaches for HR disease, and set out the principles for future developments in this area.

## THE BIOLOGY OF HIGH-RISK DISEASE

It is essential to understand the biology of HR disease to design and implement successful therapeutic approaches. HR multiple myeloma (HRMM) is an acquired biological trait that is mediated by more than one biological mechanism and leads to a phenotype of increased proliferation, resistance to apoptosis, and bone marrow–independent cell growth. It is associated with loss of $G_1$–S checkpoint transition as a consequence of deletion of *CDKN2C* or *RB1*. Biallelic inactivation of *TP53* explains resistance to cytotoxic chemotherapy in some cases (3, 4). Associated epigenetic factors include overexpression of PHD finger protein 19 (*PHF19*), which controls a master transcriptional program associated with cell-cycle progression, the integrity of mitosis, and the structural integrity of the multiple myeloma genome (5). This effect is mediated, at least in part, via aberrant control of the PRC2 complex and alterations in H3K27 tri-methylation, and is influenced by EZH2 (6). A number of recent publications have also identified a role for the HR microenvironment, but this remains difficult to quantitate at a cellular level (7–9).

Translocations involving chromosome 14 and expression of cyclin D genes have been used to segment multiple myeloma into 7 biologically distinct segments [the Translocation-Cyclin D (TC) classification; ref. 10]. Three common translocations segments are considered HR, t(4;14), t(14;16), and t(14;20), which have their biology defined by the increased expression of *NSD2*, *MAF*, and *MAFB*, respectively. Interestingly, not all cases within these adverse translocation subgroups have poor outcomes, suggesting that additional driver events are required for HR behavior. If the GEP70 (described below) is used to identify HR cases, 21% of cases are derived from t(4;14), 18% from t(14;16), 42% from a more proliferative (PR) group, and the remaining cases from the other biological segments. Thus, HR behavior is an acquired characteristic reflecting the deregulation of a common set of genes that can occur in any TC segment, but is more likely to occur in the adverse translocation and cyclin D2–expressing segments. Many of the genes forming the GEP70 are situated on 1q (11), an area of recurrent gain and amplification pointing to its importance in HR.

One characteristic feature of HR disease is the presence of focal lesions within the bone marrow. Genetic analysis of these lesions has identified intraclonal heterogeneity that increases at relapse and drives disease progression. This has led to a model of multiple myeloma progression based on Darwinian biology and selective sweeps of better adapted higher risk subclones (12). Small proliferative HR subclones can be selected for by treatment, resulting in the emergence of resistant disease and early relapse, even following deep responses. Moving forward, successful strategies for managing HR disease need to overcome intraclonal heterogeneity, aiming for minimal residual disease (MRD)-negative states and clonal eradication.

## FEATURES OF HIGH-RISK DISEASE

There are a number of clinical, laboratory, and genetic features that can be used to identify patients with HR disease biology (Box 1).

### Clinical Features

The clinical definition of HRMM has evolved over time, with current data supporting the existence of two poor risk strata of patients: HR and ultra-HR (UHR; ref. 13). HR refers to a group of patients with a median OS of 3 to 5 years. These patients have a similar clinical course to standard-risk patients, but have a shorter PFS and OS. In contrast, UHR describes a group of patients with a median OS of 3 years or less with a number of distinct static and dynamic clinical features. These features include a high frequency of extramedullary disease (EMD; ref. 14), primary plasma cell leukemia (PCL; ref. 15), being primary refractory to treatment (16), or initially responding to therapy but then relapsing within 12 to 18 months and progressing rapidly to death (17).

Although, HR/UHR disease is associated with a number of pathologic features, many are difficult to quantify and are, therefore, not suitable as diagnostic criteria; for example, plasmablastic morphology (18). Aggressive subsets of disease often lack detectable bone disease, but this is too variable to be utilized clinically. Other potentially relevant clinical factors include elevated creatinine level (19) and frailty (20); however, these features reflect the capacity of the patient to tolerate treatment rather than defining intrinsic HR biology.

### Laboratory Features

For many years the level of serum albumin and β2-microglobulin ($B_2M$) as part of the International Staging System (ISS) has been the most widely used risk score (21). While the ISS is useful, it is neutral in respect to the biology of the tumor and has low sensitivity and specificity for identifying individual patient risk. This deficit is illustrated when gene expression risk scoring (e.g., GEP70) is applied to the different ISS strata, as cases with HR behavior can be identified in the low-risk ISS strata (11). To improve upon ISS staging, additional genetic tests should be performed to identify patients at the highest risk.

### Genetic Features

The systematic investigation of large trial datasets and application of new methodologies, e.g., next-generation sequencing (NGS), has resulted in refinements to the genetic definition of HR. Initial studies used metaphase cytogenetics and discovered that in many multiple myeloma cases, it was not possible to obtain metaphase spreads for examination.

## BOX 1: THE HIGH-RISK MULTIPLE MYELOMA DISEASE SEGMENT

The challenges of HR disease
- HR disease is seen in up to 30% of NDMM.
- The proportion of patients with HR disease increases with each successive relapse.
- HR disease is a significant cause of mortality in multiple myeloma.
- Current therapy has not significantly improved the outcome of HR.

The biology of HR disease
- HRMM is an acquired biological trait that is characterized by a phenotype of:
  - increased proliferation rate
  - resistance to apoptosis
  - focal growth
  - bone marrow–independent growth
  - more than one type of biology
  - intraclonal heterogeneity
- HR subclones may be selected for by treatment.
- Treatment needs to address intraclonal heterogeneity.

Features of HR disease
- Clinical features
  - extra-medullary disease
  - large focal lesions
  - plasma cell leukemia
  - primary refractoriness to treatment
- Laboratory and genetic features
  - R-ISS
  - cytogenetic features
    - t(4;14)
    - t(14;16)
    - t(14;20)
    - gain(1q)
    - deletion and mutation of TP53
  - HR gene expression profiles
- Functional features
  - Initial response to therapy with relapse within 12–18 months.
- Novel features
  - Microenvironment features identified by single-cell analysis and advanced imaging.

The ability, therefore, to generate abnormal metaphase spreads *per se* is considered a poor prognostic factor (22). The presence of a complex karyotype and detection of monosomy 13 on metaphase analysis are also poor prognostic factors; however, many characteristic myeloma markers initially identified by Southern blot are karyotypically silent [e.g., t(4;14)], leading to CD138-selected interphase FISH (iFISH) being the preferred test.

Purification of CD138$^+$ plasma cells prior to iFISH analysis is critical to ensure robust results. Standard panels now include the identification of t(4;14), t(14;16), t(14;20), gain(1q), and del(17p) as adverse features. Importantly, large studies show that adverse features cosegregate, and that the presence of more than one adverse abnormality can be used to refine risk stratification as part of a simple additive scoring system (23, 24).

The presence of t(4;14), t(14;16), and del(17p) have been incorporated into the ISS along with serum LDH level, to generate the revised ISS (R-ISS; ref. 25). At the time of developing this score, there was only limited access to large data sets that included data on the cut-off value for clonally positive cells carrying del(17p), the role of gain (3 copies) versus amplification of 1q (>3 copies) and the role of 1p loss; and as a consequence, important prognostic factors were not included. This deficiency has been addressed, at least in part, by the development of R2-ISS (26), R-ISS-1q (27) and a cytogenetic risk score that incorporates del(1p) and features relating to individual trisomies 5 and 21 (28). Current consensus is that data on 1q should be included in the definition of HR disease; however, more data are required before 1p can be included.

There are a number of important subtleties associated with iFISH analysis that are often overlooked. These relate to the cut-off value of positive cells used to assign risk. In clinical practice, a positive result can be as low as 2% but this value does not necessarily reflect clinical HR where the percentage can vary between 10% and 60%. A number of trials show that levels greater than 50% are required to firmly assign UHR behavior for del(17p) (29, 30), and it is likely that similar features are also important for 1q gain and amplification (4, 31). Thus, the percentage of cells positive for an iFISH signal needs to be addressed when using it for clinical risk assignment.

### Functional Features

The continuous assessment of a number of markers during therapy can add to the definition of risk (32). Patients developing progressive disease despite effective induction therapy should be considered as UHR. The size of this group is getting smaller with the addition of more effective combination therapy. The other group of patients that are considered UHR are those that obtain a good response and then relapse quickly. Relapse in these UHR cases often occurs between treatment phases; for example, between induction and autologous stem cell transplant (ASCT) especially if there is a delay in harvesting or ASCT, or between ASCT and maintenance during transplant recovery, at a time when the selective pressure on the clone is reduced.

The depth of response, attaining MRD negativity at $10^{-5}$ or $10^{-6}$, and the stability of MRD-negative states over time (e.g., over a year) have prognostic significance (33). This is particularly important in patients with HR genetic features (34–38). Cases with a poor outcome are those who fail to attain MRD negativity; those that become MRD negative but do not sustain it have an intermediate outcome. Importantly, if MRD negativity is sustained and the patient reaches 5 years

follow-up, then long-term survival is a possibility (33, 39, 40). An area of active research is how computer-based artificial intelligence (AI) technologies may be able to estimate prognosis for individual patients based on the clinical, laboratory, genetic, and functional features described above. The results of this type of study may allow a dynamic assessment of risk over time to be made.

## High-Risk at Relapse

Compared to diagnosis, there is an increased frequency of mutation and structural variation associated with an increased prevalence of homozygous alterations involving genes such as *TP53*, *RB1*, and *CDKN2C* (41, 42). Applying the GEP70 prognostic score at relapse shows that the number of cases with adverse risk-status increases with each subsequent relapse (43, 44). In addition, at relapse, further dynamic clinical information is available to aid therapeutic decision making including the duration of first remission and the rate of increase in the biochemical markers of relapse. Using this clinical information brings with it the potential to identify patients in a functional HR state where molecular markers of adverse outcome may be absent, but patients are clearly behaving in a HR fashion (45). Functional HR can be defined as cases relapsing within 18 to 24 months of the start of initial therapy. Although this group contains patients with HR genetic abnormalities, it also includes a significant proportion of patients with standard-risk genetics who would not otherwise have been identified as HR (46–48).

## OPTIMIZING THE IDENTIFICATION OF HIGH-RISK DISEASE

A number of newer technologies are available that either alone or in combination with currently used tests can enhance our ability to detect HR disease.

## Gene Expression Profiling

Expression-based prognostic scores can identify adverse risk behavior with a high degree of specificity. A number of tools have been developed including the GEP70 (11) and EMC92 (49), which identify 10% to 15% of NDMM as being UHR. In 2020, a "genome challenge" confirmed GEP70 as the most predictive measure of adverse outcome (5). The clinical use of approved GEP expression tests [EMC92 as "SKY92" (SkylineDx) and GEP70 as "MyPRS" (Quest diagnostics)], has been limited by reimbursement issues. Studies have suggested that the combination of a GEP signature together with the ISS outperforms other methods for identifying UHR cases (49, 50), and serve as a proof-of-principle that scoring systems that incorporate biological markers of risk are helpful.

## Whole-Exome Sequencing

Mutational analysis by whole-exome sequencing has demonstrated the multiple myeloma mutational load falls at the median of the distribution of mutations in cancer in general (51–53). Some variation in mutational load between cases has been identified, particularly in the t(14;16) subgroup where an APOBEC signature was noted (54), as was an increase in load at the later stages of disease. High mutational load is associated with increased risk, but as this marker is associated

with t(14;16), it is not clear which factor drives the increased risk. Mutations and somatic copy-number abnormalities have been recognized to comprise over 60 driver lesions (55). However, due to interactions between the different variants analyzed, only a limited number were identified as being significant for defining prognosis in multivariate analyses. The most significant genetic contributors were biallelic inactivation of *TP53* and 1q amplification in the context of ISS III, defined as "Double-Hit" multiple myeloma (4). Another study found that deletion of *TP53* alone, without mutation, was also associated with poor outcome, but the patient series was preselected for HR patients with greater than 50% deletion by FISH (30) and other studies vary (56). Datasets of patients with longer follow-up identified biallelic alterations in *DIS3*, and inactivating mutations in *BRAF* as being associated with poor outcome (57). Complex structural arrangements and HR mutational profiles occur commonly in PCL cases even when traditional low-risk features such as t(11;14) or hyperdiploidy are present and may explain, at least in part, the aggressive nature of PCL (58).

## Whole-Genome Sequencing

The application of whole-genome sequencing (WGS) extended the findings of exome-based studies and demonstrated new potential clinically relevant genetic risk markers. Examples include complex structural events, the most prognostically significant of which is chromothripsis (59), an APOBEC mutational signature, and mutational load (60). WGS can also quantify copy number abnormalities and precisely map translocations, making it an excellent tool for ongoing discovery of genetic abnormalities. However, currently it is not appropriate for general clinical use due to a number of challenges including the complexity of analysis, data storage and cost. This situation is rapidly changing with the application of low-depth WGS for quantifying copy-number changes and for detecting MRD.

## Targeted Panels

Newer technologies provide the ability to determine relevant translocation, copy number (common chromosomal myeloma gains/losses), and mutational data in one assay. Therefore, a number of targeted panels have been developed that are useful for risk determination and provide a cost-efficient method for use in the clinic (61–64). These assays include clinically-relevant regions of the genome for mutational analysis, including coding exons of genes that are important for risk stratification, prognosis, or as therapeutic targets. Appropriate panel design can also enable detection of copy-number abnormalities, regions of loss of heterozygosity (LOH), and copy-number neutral LOH. In addition, multiple myeloma–specific translocations can be detected through tiling of the *IGH* and *MYC* loci to detect any chromosomal translocation partner in an unbiased manner. Such panels will enable the 17p locus to be fully assessed (e.g., whether *TP53* is biallelically inactive by combining copy number with mutation of *TP53*), allow the inclusion of frequent mutations, for example, those in the RAS/MAPK pathway, and those associated with risk in univariate analyses. It is, therefore, possible to replace FISH, mutation analysis and karyotyping with a single targeted panel assay.

Tumor purity obtained through CD138+ selection of samples is very important for these assays, as samples contaminated with normal cells lead to a loss of signal. Use of a patient–matched control DNA sample, saliva, or peripheral blood, is also crucial for the analysis. Panel analysis is simple and amenable to automated bioinformatic pipelines. Potential downsides include ensuring all the information required is captured within the initial panel design, and standardization of content and sensitivity across platforms. Over time the sensitivity of methods to detect markers in the peripheral blood based on circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) will increase.

## Imaging Analysis

Focal bone lesions are typical of multiple myeloma, and occur more frequently in HR cases; hence, their presence can help in the assignment of risk status. Functional imaging including PET-CT (65) and MRI (66) quantification of the number, size, and intensity of focal lesions can enhance the definition of risk. In the clinic, functional imaging is currently used to reclassify cases of smoldering multiple myeloma to multiple myeloma that require therapy, proving the utility of the approach. For risk assignment in NDMM, it has been shown that greater than or equal to 3 large focal lesions or the presence of EMD is associated with an adverse prognosis (67). Genetic analysis of material from focal lesions within the same patient has shown the presence of spatial genetic heterogeneity with different lesions having either low or HR features; and if HR is present in the focal lesion, the patient follows a more clinical HR behavior (12).

## Miscellaneous Analytic Approaches

A high plasma cell proliferative index (S-phase>2%) determined by cell-cycle analysis of DNA content by flow cytometry at diagnosis is a poor prognostic factor independent of R-ISS stage and age, but is not widely used (22, 68). The presence of circulating plasma cells is also known to have prognostic significance and the definition of plasma cell leukemia has recently been refined to include patients with at least 5% circulating plasma cells (69). Aging is an important adverse prognostic factor, and defining risk in older age requires the incorporation of additional information. In the elderly, classical molecular HR prognostic factors become less useful as their impact is less penetrant, and performance status and frailty become more important predictors of prognosis (70). The assessment of frailty and its role in guiding therapy decisions is an area of active research. Information on telomere length and chromothripsis offers a novel way of improving the identification of adverse prognosis in patients over the age of 65 years (71). The presence of clonal hematopoiesis does not currently seem to add additional benefit to risk stratification (72). Results from ongoing studies using single-cell techniques are aiming to incorporate signals from the immune environment and microenvironment into current staging systems (73–75).

## THE SIZE OF THE HIGH-RISK PROBLEM

With current treatments it is now possible to achieve median PFS and OS for transplant-eligible (TE) patients of 4 to 6 and 6 to 9+ years, respectively [IFM2009 study (76) VRd+ASCT (PFS median 47 months, OS at 8 years 62%), GRIFFIN study (77) Dara-VRd+ASCT (PFS at 2 years 96%, OS at 2 years >96%) and Cassiopeia study (78) Dara-VTd+ASCT (PFS at 18 months 93%); and for transplant-noneligible patients (TNE) of 2 to 5 and 5 to 7+ years, respectively (FIRST study (79, 80) Rd (PFS median 26 months, OS median 59 months), MAIA study (81) D-Rd (PFS at 5 years 50%, OS at 5 years 66%) and ALCYONE study (82) D-VMP (PFS median 36 months, OS at 3 years 78%); Supplementary Table S1].

Only a few randomized phase III studies have compared the Kaplan–Meier curves for HR and standard-risk subgroups within a given treatment arm. When HR outcomes on the experimental arm are compared with similar patients in the control arm, many studies show improvement in outcomes with the experimental arm. However, there still remains a group of patients with very poor clinical outcomes.

With a few exceptions, most clinical trials of NDMM have been for "all comers" who are either transplant eligible or transplant noneligible. The impact of therapy on subgroups with variably defined HR features has predominantly been analyzed on the basis of *post hoc* analyses using the detection of the t(4;14), t(14;16), del(17p) or gain(1q) adverse features by iFISH. Although these analyses are not always statistically powered to detect a significant difference in outcome, they do provide information on the impact of therapy on this segment.

Depending on the features included in the definition of risk, between 6% and 30% of patients can be considered as HR (Supplementary Table S2). If the ISS is used alone, the number of patients with stage III varies from 15% to 25% [Myeloma XI study (83) 25%, IFM 2009 study (76) 18%, Cassiopea study (78) 15%, Griffin study (77) 13.5%, EMN02 study (84) 20%]. If iFISH alone is used, HR single abnormalities occur at t(4;14) 15%, t(14;16) 3%, del(17p) 8% and gain(1q) 40%. If the R-ISS is used, then the R-ISS III group size is around 10% (EMN02 study 8% but 15% missing data). MyPRS/SKY92 HR cases occur in 10% of patients. "Double-Hit" cases occur in 6% (4).

To estimate how single adverse prognostic factors interact, data from the CoMMpass/MGP study have been analyzed (85). Using NGS and expression data, the hazard ratios for each of the individual risk factors in comparison to a standard risk segment were estimated. These data show that there is significant variability in the impact of individual factors. For combinations of markers, the hazard ratio identified showed a more significant negative impact on outcome than single markers. Interestingly the Double-Hit and GEP70 high were associated with the highest hazard ratio at 3.1 and 3.5, respectively, for OS.

There is little information to accurately estimate the incidence rates of cases of PCL or cases with increased circulating plasma cells. Similarly, the number of cases with EMD at diagnosis is difficult to estimate, but is likely to be low. It is critical to distinguish para-medullary from true EMD, as lesions in the bone naturally extend outward, and if reported as extramedullary can result in falsely high rates of EMD. Numerous small studies have examined therapy in PCL and EMD, but it is difficult to draw definitive conclusions.

## TAILORING CURRENT THERAPEUTIC OPTIONS FOR HIGH-RISK DISEASE

Most treatment recommendations for patients with HR disease utilize data from the "all comer" studies or from single center series (Supplementary Table S1; refs. 37, 86). A meta-analysis has addressed the role of proteasome inhibitor (PI)-based treatment as first-line therapy for patients with t(4;14) and del(17p). This analysis suggested a benefit for the use of PIs in improving the negative prognostic impact of these genetic variants (87). Studies have also shown that immu-nomodulatory drugs (IMiD) are active in the HR segment (88). What is abundantly clear is that combining the mechanism of action of PIs, IMiDs, and steroids as triplet combinations leads to deeper responses than using a doublet in all-risk groups.

The addition of anti-CD38 mAbs to triplet and doublet regimens has demonstrated that immunotherapy can make a significant improvement in response rates, depth of response, PFS, and OS in NDMM, including those with HR disease (89). The preliminary results of ongoing risk-stratified studies further exploring the role of anti-CD38 mAbs are promising including the UAMS TT7 study, the German Multiple Myeloma group (GMMG; ref. 90) CONCEPT, and the UK MUK9B Optimum study (91, 92).

Several large randomized clinical trials, as well as nonrandomized comparisons, suggest tandem ASCT may be beneficial in HR disease (84). However, there remains considerable debate about the value of this approach, despite it being standard in a number of European countries. Alternative conditioning regimens to melphalan have also been shown to be effective in HR disease but are not widely used (93). The mechanistic basis of these associations is unclear and may simply reflect the importance of achieving a deep MRD-negative response.

Randomized studies have reported data on the impact of risk status in the maintenance setting, and have shown the benefit of single-agent IMiDs (lenalidomide) and PI (ixazomib) compared to observation irrespective of risk status [lenalidomide (Myeloma XI; ref. 88) hazard ratio for SR 0.38, HR 0.45, UHR 0.42; ixazomib (Tourmaline (94)) SR 0.65, HR 0.62]. In a lenalidomide meta-analysis, there were differences in the hazard ratios between risk groups (SR 0.48, HR 0.86; ref. 95). A recent study combining carfilzomib and lenalidomide in the maintenance setting showed a benefit for the combination compared with single-agent lenalidomide across risk groups [with the exception of amp(1q)], with hazard ratios in a similar range (FORTE study KR vs. R HRs SR 0.4, HR 0.6, UHR 0.53; ref. 38).

In the HR relapsed setting, many of the above agents in combination as well as newly introduced agents such as selinexor demonstrate activity (96). Immunotherapy approaches are being evaluated in this setting, including anti-BCMA antibody–drug conjugates, T-cell engaging therapies such as bispecific antibodies, and CAR T cells. The ability of these agents to induce MRD-negative responses in relapsed/refractory myeloma (RRMM), including a substantial proportion of HR/UHR cases suggests these agents have significant potential (97). Importantly, the impaired immune response in RRMM suggests these agents will be more effective in NDMM, where the immune system is less impaired. Another potential benefit of immune therapies is immunogenic cell death which has the potential to prime and reprogram T-cell responses, to generate effective antitumor immunity (98, 99). A note of caution, though, is raised from the results of treating relapsed non-Hodgkin lymphoma, where cases with *TP53* loss and *MYC* over expression respond less well to novel immuno-therapies than cases lacking these lesions. It will therefore, be important in multiple myeloma to evaluate outcomes for each individual risk strata, and to potentially determine novel risk factors based on the marrow immune microenvironment.

Although precision medicine offers a potential therapeutic strategy, a targeted approach using patient-specific genetic information is currently limited by a lack of appropriate agents. For example, no therapies are available specifically for t(4;14), t(14;16), or del(17p). Recent studies have shown excellent responses when venetoclax, a BCL2 inhibitor, is used at relapse for t(11;14) patients, even those with HR features (100–102). Studies have also shown RAS pathway inhibitors may be useful, although addressing individual mutations is hampered by the presence of intraclonal heterogeneity where the target is only present in a subclone (103, 104).

## RECOMMENDATIONS FOR IMPROVING OUTCOMES IN HIGH-RISK DISEASE

To improve the outcomes for patients with HR there are a number of important variables that need to be systematically addressed (Box 2).

### Optimizing Clinical Care

The treatment of HR patients in everyday clinical practice should be optimized by using the most appropriate treatment from the current therapeutic armamentarium. Achieving MRD negativity is particularly important for HR cases and is crucial to the achievement of long-term outcomes. The widespread adoption of MRD testing in the clinic including mass spectrometry, flow cytometry, and molecular testing will enable clinicians to optimize the impact of current therapies.

### Improving Diagnostics

Health care systems should accept the concept of risk-stratification in multiple myeloma, approve reimbursement of novel diagnostic tests and allow drug reimbursement to enable a personalized approach to treatment. Testing should be performed on purified bone marrow plasma cells. iFISH panels should include translocations [t(4;14), t(14;16), and t(11;14)]; copy-number analysis of odd number chromosomes (e.g., 5,9,15,19 and 21) for the identification of hyperdiploid cases, as well as an assessment of gain and amplification of 1q, deletion of 1p and 17p together with quantification of the number of clonal cells carrying these markers; and mutational analysis of *TP53*. Moving forward, a move from iFISH to NGS-based diagnostic panels is anticipated. These panels will detect all clinically relevant prognostic variables in a single rapid turn-around test, and may also include other common mutations that can be targeted therapeutically (100–105).

### Implementing High-Risk Clinical Trials

Outstanding questions in relation to the development of risk-stratified trials include the definition and size of the HR group, and the outcome of individual risk strata. Addressing these questions will enable regulatory approval

## BOX 2: RECOMMENDATIONS FOR IMPROVING OUTCOMES FOR HIGH-RISK DISEASE

- Health care systems should:
  - recognize the importance of HRMM.
  - approve reimbursement of novel diagnostic tests.
  - provide appropriate reimbursement policies to enable personalized therapy.
- Clinical and molecular stratification should be performed on all NDMM.
  - Testing should be performed on purified bone marrow plasma cells.
  - Panels should include identification of:
    - adverse translocations
      - t(4;14), t(14;16)
    - other translocations
      - t(11;14)
    - copy number abnormalities
      - the odd number chromosomes to identify hyperdiploidy
      - gain and amplification of 1q
      - deletion of 1p

- deletion of 17p
  - the number of clonal cells carrying these markers
- mutational analysis
  - of TP53
  - cancer clonal fraction with the abnormality
- Moving forward, we should move from iFISH to NGS-based diagnostic panels that:
  - detect all clinically relevant prognostic variables in a single rapid turn-around test.
  - targetable lesions such as RAS and BRAF should be included in the panel design.
- Clinical care should be optimized based on risk status.
  - Appropriate treatments should be chosen from the current therapeutic armamentarium.
  - The achievement of MRD negativity should be an early treatment goal.
  - Whenever possible, patients should enter a clinical trial.

and reimbursement for HR therapies in a group where entry criteria, definitions, diagnostic methods, and reporting are standardized and reproducible (Box 3).

There are two general approaches to evaluating the impact of therapies on HR disease. In the most widely used approach the treatment of HR disease is not the primary focus of study, with the analysis of risk segments being carried out *post hoc*. If HR cases are included in standard-risk trials, the randomization should be stratified to avoid imbalance of the treatment arms, and a planned analysis of the HR patients should be included in the statistical analysis plan.

The second approach specifically sets out to evaluate the outcome of HR patients as part of the study design. A key design feature of such studies is that they can be smaller and have a shorter median follow-up, offering a platform to explore novel therapeutic hypotheses. Furthermore, given that clinical trials have already been carried out in HR segments and their relative resistance to current therapies is known, it is ethically appropriate to test novel therapies in these patients. Such approaches recognize the balance between improvements in outcome on one side, and the potential for a greater level of side effects on the other.

## BOX 3: RECOMMENDATIONS FOR THE DESIGN OF HRMM HIGH-RISK MULTIPLE MYELOMA CLINICAL TRIALS

- Appropriate clinical trial designs include:
  - risk-stratified treatment studies
    - using standard inclusion criteria.
    - with phase II studies that explore highly active regimens.
  - all-comer trials
    - where randomization is stratified based on risk to avoid arm imbalance.
    - with a planned analysis of HR patients included in the statistical analysis plan.
- The methodology used to define risk should be reported including:
  - cytogenetics, iFISH, GEP, DNA panels.
  - the percentage of cells positive or the cancer clonal fraction for specific abnormalities.

- Reporting of trials should be standardized and include:
  - depth of response with
    - PR, VGPR, and CR.
    - MRD negativity.
    - PFS and OS at set time points.
  - proportion of patients reaching predetermined protocol time points.
  - safety data.
- Biological samples
  - should be collected in all studies.
  - aim to further understand the biology of HR.
  - should refine:
    - current risk markers.
    - novel risk makers.
    - novel targets for therapy.
  - Data should be shared with the community.

## Risk-Stratified Trial Design

Data from HR patients treated in previous "all-comer" studies can be used to guide the design of future risk-stratified phase II/III studies, particularly in respect to the quantification of study size and the choice of appropriate control arms for randomized studies. Currently, defining control therapies is difficult because of the very poor outcome in UHR where a standard treatment approach is not yet defined. Previously used regimens in HR studies include combinations of chemotherapy, immunotherapy, and ASCT such as those used in the TT studies, or the SWOG study, which compared VRD versus VRD-elotuzumab (106). The SWOG study, however, found no difference in outcome between the arms. Thus, at this stage, single-arm phase II studies may be an appropriate approach to optimize therapy before moving into randomized phase II or III studies. Such phase II studies should have standardized inclusion criteria to enable a comparison of new clinical trial results with historical datasets. Current phase II studies are exploring both induction and postinduction therapeutic strategies aimed at improving remission depth and duration (e.g., anti-CD38 in combination with PI, IMiD, and transplant, followed by dual therapy maintenance). Importantly, when novel therapies active in RRMM are identified, they should be rapidly evaluated in ND HRMM.

Given the aggressive nature of HRMM and the inherent delays in obtaining genetic data before being able to risk-stratify and start specific therapy, it is acceptable to allow patients to receive up to 2 to 3 prior cycles of standard induction therapy before entry into a risk-stratified study. This approach enables therapy to be initiated and an attempt at early disease control to be made whilst risk assessments are being carried out.

## Clinical Trial Reporting

The size and outcome of the HR group is dependent on the criteria used for its identification. While still the subject of ongoing refinement, there are now an agreed set of cytogenetic, iFISH, mutational, and expression-based markers that can be used to select patients for trials (Box 2). Although it is important to be inclusive of methodologies to enable good clinical trial recruitment, it is imperative to report these methods as part of the trial publication including the diagnostic test used for risk stratification (e.g., cytogenetics, iFISH, GEP, DNA panels), the frequency of each variable, and the number of cells positive for each specific abnormality. This will ensure that trial results can be compared; and as more data becomes available, that risk assignment can be refined. As the variables used to define risk cosegregate, it is essential that the results of all the critical variables are reported to appropriately attribute risk.

A number of other factors are important to collect and report systematically including the percentage and number of circulating plasma cells, the organ involved by EMD and for relapsed cases the previous best response to therapy (if any), and length of first response to therapy. For therapies targeting specific genes/proteins, information on copy number by FISH or inferred from sequencing data at the same gene locus should be collected. For example, for immune strategies targeting B-cell maturation antigen (BCMA) the copy number and mutational status of 16p at the BCMA locus,

*TNFRSF17*, needs to be assessed, as acquired deletions and mutations have already been identified that are associated with treatment resistance (107, 108).

## Clinical End Points

For HRMM, the traditional clinical trial efficacy endpoints of PFS and OS remain appropriate and are often reached after a relatively short median follow-up. However, the reporting of these features needs to standardized to include survival rates at 1 year, 3 years, 5 years, and median values when reached, so that results can be compared between studies (Supplementary Table S1). The reporting of response rates also needs to be standardized as currently studies vary in what type of response is reported (e.g., whether MRD, CR, VGPR, and PR are reported) and the timing when such responses are noted (e.g., postinduction, posttransplant, during maintenance), This is highlighted in Supplementary Table S1, where >VGPR rates vary between 80% and 90%, stringent CR rates between 19% and 30% and MRD negativity rates between 20% and 65% depending on time of reporting. It is important to assess MRD at early time points, using a continuous scale of response depth and sensitivity threshold; although it is not used currently to change therapy, such data will be useful to design and guide statistical considerations for future studies.

Other important endpoints include safety data, the ability to reach each protocol-defined treatment stage, the early relapse rate (e.g., at 3, 6, 9, and 12 months), and time to next treatment.

## Linking Outcome Data to Disease Biology

It is essential to further understand the biology of HR disease if we are to recognize and treat it effectively. Clinical studies should include standardized timing of sample collection and the analysis of the material collected, so that the impact of therapy on the individual segments contributing to HR disease can be determined. With the increasing use of immunotherapy, translational studies should include studies of the HR microenvironment as well as the clonal tumor cells. Such studies will enable the confirmation and refinement of current markers as well as the identification of novel makers. Analysis of datasets from large clinical trials will also ascertain the most appropriate diagnostic technology and a standardized testing policy going forward.

## CONCLUSIONS

Despite recent treatment advances, patients with HRMM continue to have poor clinical outcomes. With the promise of new therapeutic approaches, it is no longer appropriate to just describe this poor outcome; rather, it is critical that therapy be optimized via a clinical trial strategy. The implementation of such an approach will require collaboration between physicians, study groups, pharmaceutical partners, patient groups, trial sponsors and regulatory organizations. This article represents a first step in this process, with the long-term aim to achieve stepwise improvements in outcome comparable to the improvements that have taken place in standard-risk disease.

## Authors' Disclosures

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## Note

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## REFERENCES

1. Usmani SZ, Rodriguez-Otero P, Bhutani M, Mateos MV, Miguel JS. Defining and treating high-risk multiple myeloma. Leukemia 2015; 29:2119–25.
2. Pawlyn C, Davies FE. Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood 2019;133:660–75.
3. Weinhold N, Ashby C, Rasche L, Chavan SS, Stein C, Stephens OW, et al. Clonal selection and double-hit events involving tumor suppressor genes underlie relapse in myeloma. Blood 2016;128:1735–44.
4. Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies F, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia 2019;33:159–70.
5. Mason MJ, Schinke C, Eng CLP, Towfic F, Gruber F, Dervan A, et al. Multiple Myeloma DREAM Challenge reveals epigenetic regulator PHF19 as marker of aggressive disease. Leukemia 2020;34:1866–74.
6. Pawlyn C, Bright MD, Buros AF, Stein CK, Walters Z, Aronson LI, et al. Overexpression of EZH2 in multiple myeloma is associated with poor prognosis and dysregulation of cell cycle control. Blood Cancer J 2017;7:e549.

7. Danziger SA, McConnell M, Gockley J, Young MH, Rosenthal A, Schmitz F, et al. Bone marrow microenvironments that contribute to patient outcomes in newly diagnosed multiple myeloma: a cohort study of patients in the Total Therapy clinical trials. PLoS Med 2020;17:e1003323.

8. Solimando AG, Da Vià MC, Cicco S, Leone P, Di Lernia G, Giannico D, et al. High-risk multiple myeloma: integrated clinical and omics approach dissects the neoplastic clone and the tumor microenvironment. J Clin Med 2019;8:997.

9. Visram A, Dasari S, Anderson E, Kumar S, Kourelis TV. Relapsed multiple myeloma demonstrates distinct patterns of immune microenvironment and malignant cell-mediated immunosuppression. Blood Cancer J 2021;11:45.

10. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. Blood 2005;106:296–303.

11. Shaughnessy JD Jr, Zhan F, Burington BE, Huang Y, Colla S, Hanamura I, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 2007;109:2276–84.

12. Rasche L, Chavan SS, Stephens OW, Patel PH, Tytarenko R, Ashby C, et al. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. Nat Commun 2017;8:268.

13. Shah V, Sherborne AL, Walker BA, Johnson DC, Boyle EM, Ellis S, et al. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. Leukemia 2018;32:102–10.

14. Bhutani M, Foureau DM, Atrash S, Voorhees PM, Usmani SZ. Extramedullary multiple myeloma. Leukemia 2020;34:1–20.

15. Tuazon SA, Holmberg LA, Nadeem O, Richardson PG. A clinical perspective on plasma cell leukemia; current status and future directions. Blood Cancer J 2021;11:23.

16. Majithia N, Vincent Rajkumar S, Lacy MQ, Buadi FK, Dispenzieri A, Gertz MA, et al. Outcomes of primary refractory multiple myeloma and the impact of novel therapies. Am J Hematol 2015;90:981–5.

17. Majithia N, Rajkumar SV, Lacy MQ, Buadi FK, Dispenzieri A, Gertz MA, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia 2016;30:2208–13.

18. Greipp PR, Leong T, Bennett JM, Gaillard JP, Klein B, Stewart JA, et al. Plasmablastic morphology–an independent prognostic factor with clinical and laboratory correlates: Eastern Cooperative Oncology Group (ECOG) myeloma trial E9486 report by the ECOG Myeloma Laboratory Group. Blood 1998;91:2501–7.

19. Rana R, Cockwell P, Drayson M, Cook M, Pratt G, Cairns DA, et al. Renal outcome in patients with newly diagnosed multiple myeloma: results from the UK NCRI Myeloma XI trial. Blood Adv 2020;4:5836–45.

20. Cook G, Larocca A, Facon T, Zweegman S, Engelhardt M. Defining the vulnerable patient with myeloma-a frailty position paper of the European Myeloma Network. Leukemia 2020;34:2285–94.

21. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–20.

22. Mellors PW, Binder M, Ketterling RP, Greipp PT, Baughn LB, Peterson JF, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv 2020;4:2236–44.

23. Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia 2012;26:349–55.

24. Avet-Loiseau H, Attal M, Campion L, Caillot D, Hulin C, Marit G, et al. Long-term analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t(4;14), del(17p), 1q gains] play a major role in defining long-term survival. J Clin Oncol 2012;30:1949–52.

25. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015;33:2863–9.

26. D'Agostino M, Lahuerta J-J, Wester R, Waage A, Bertsch U, Zamagni E, et al. A new risk stratification model (R2-ISS) in newly diagnosed multiple myeloma: analysis of mature data from 7077 patients collected by European Myeloma Network within harmony big data platform. Blood 2020;136:34–7.

27. Weinhold N, Salwender HJ, Cairns DA, Raab MS, Waldron G, Blau IW, et al. Chromosome 1q21 abnormalities refine outcome prediction in patients with multiple myeloma - a meta-analysis of 2,596 trial patients. Haematologica 2021;106:2754–8.

28. Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien ML, Royer B, et al. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol 2019;37:1657–65.

29. Thakurta A, Ortiz M, Blecua P, Towfic F, Corre J, Serbina NV, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. Blood 2019;133:1217–21.

30. Corre J, Perrot A, Caillot D, Belhadj K, Hulin C, Leleu X, et al. del(17p) without TP53 mutation confers a poor prognosis in intensively treated newly diagnosed patients with multiple myeloma. Blood 2021;137:1192–5.

31. Schmidt TM, Fonseca R, Usmani SZ. Chromosome 1q21 abnormalities in multiple myeloma. Blood Cancer J 2021;11:83.

32. Zaccaria GM, Bertamini L, Petrucci MT, Offidani M, Corradini P, Capra A, et al. Development and validation of a simplified score to predict early relapse in newly diagnosed multiple myeloma in a pooled dataset of 2,190 patients. Clin Cancer Res 2021;27:3695–703.

33. Diamond B, Korde N, Lesokhin AM, Smith EL, Shah U, Mailankody S, et al. Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance: a single-arm, single-centre, phase 2 trial. Lancet Haematol 2021;8:e422–e32.

34. Oliva S, Bruinink DHO, Rihova L, D'Agostino M, Pantani L, Capra A, et al. Minimal residual disease assessment by multiparameter flow cytometry in transplant-eligible myeloma in the EMN02/HOVON 95 MM trial. Blood Cancer J 2021;11:106.

35. Perrot A, Lauwers-Cances V, Corre J, Robillard N, Hulin C, Chretien ML, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood 2018;132:2456–64.

36. Gambella M, Omedé P, Spada S, Muccio VE, Gilestro M, Saraci E, et al. Minimal residual disease by flow cytometry and allelic-specific oligonucleotide real-time quantitative polymerase chain reaction in patients with myeloma receiving lenalidomide maintenance: a pooled analysis. Cancer 2019;125:750–60.

37. Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. J Clin Oncol 2020;38:1928–37.

38. Gay F, Mina R, Rota-Scalabrini D, Galli M, Belotti A, Zamagni E, et al. Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance: Efficacy in high-risk patients. J Clin Oncol 2021;39:8002.

39. Kazandjian D, Korde N, Mailankody S, Hill E, Figg WD, Roschewski M, et al. Remission and progression-free survival in patients with newly diagnosed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone: five-year follow-up of a Phase 2 Clinical Trial. JAMA Oncol 2018;4:1781–3.

40. Costa LJ, Chhabra S, Medvedova E, Dholaria BR, Schmidt TM, Godby KN, et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. J Clin Oncol 2021; JCO2101935.

41. Jones JR, Weinhold N, Ashby C, Walker BA, Wardell C, Pawlyn C, et al. Clonal evolution in myeloma: the impact of maintenance lenalidomide and depth of response on the genetics and sub-clonal structure of relapsed disease in uniformly treated newly diagnosed patients. Haematologica 2019;104:1440–50.

42. Croft J, Ellis S, Sherborne AL, Sharp K, Price A, Jenner MW, et al. Copy number evolution and its relationship with patient outcome-

an analysis of 178 matched presentation-relapse tumor pairs from the Myeloma XI trial. Leukemia 2021;35:2043–53.

43. Boyle EM, Rosenthal A, Wang Y, Farmer P, Rutherford M, Ashby C, et al. High-risk transcriptional profiles in multiple myeloma are an acquired feature that can occur in any subtype and more frequently with each subsequent relapse. Br J Haematol 2021;195:283–6.

44. Skerget S, Penaherrera D, Chari A, Jagannath S, Siegel DS, Vij R, et al. Genomic basis of multiple myeloma subtypes from the MMRF CoMMpass Study. medRxiv 2021.

45. Soekojo CY, Chung TH, Furqan MS, Chng WJ. Genomic characterization of functional high-risk multiple myeloma patients. Blood Cancer J 2022;12:24.

46. Bygrave C, Pawlyn C, Davies F, Craig Z, Cairns D, Hockaday A, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. Br J Haematol 2021;193:551–5.

47. Corre J, Montes L, Martin E, Perrot A, Caillot D, Leleu X, et al. Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk. Haematologica 2020;105:e480–3.

48. Gopalakrishnan S, D'Souza A, Scott E, Fraser R, Davila O, Shah N, et al. Revised international staging system is predictive and prognostic for early relapse (<24 months) after autologous transplantation for newly diagnosed multiple myeloma. Biol Blood Marrow Transplant 2019;25:683–8.

49. Kuiper R, van Duin M, van Vliet MH, Broijl A, van der Holt B, El Jarari L, et al. Prediction of high- and low-risk multiple myeloma based on gene expression and the International Staging System. Blood 2015;126:1996–2004.

50. Kuiper R, Zweegman S, van Duin M, van Vliet MH, van Beers EH, Dumee B, et al. Prognostic and predictive performance of R-ISS with SKY92 in older patients with multiple myeloma: the HOVON-87/NMSG-18 trial. Blood Adv 2020;4:6298–309.

51. Walker BA, Boyle EM, Wardell CP, Murison A, Begum DB, Dahir NM, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. J Clin Oncol 2015;33:3911–20.

52. Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P, Lawrence MS, Auclair D, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell 2014;25:91–101.

53. Bolli N, Avet-Loiseau H, Wedge DC, Van Loo P, Alexandrov LB, Martincorena I, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Nat Commun 2014;5:2997.

54. Walker BA, Wardell CP, Murison A, Boyle EM, Begum DB, Dahir NM, et al. APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. Nat Commun 2015;6:6997.

55. Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies FE, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. Blood 2018;132:587–97.

56. Martello M, Poletti A, Borsi E, Solli V, Dozza L, Barbato S, et al. Clonal and subclonal TP53 molecular impairment is associated with prognosis and progression in multiple myeloma. Blood Cancer J 2022;12:15.

57. Boyle EM, Ashby C, Tytarenko RG, Deshpande S, Wang H, Wang Y, et al. BRAF and DIS3 mutations associate with adverse outcome in a long-term follow-up of patients with multiple myeloma. Clin Cancer Res 2020;26:2422–32.

58. Schinke C, Boyle EM, Ashby C, Wang Y, Lyzogubov V, Wardell C, et al. Genomic analysis of primary plasma cell leukemia reveals complex structural alterations and high-risk mutational patterns. Blood Cancer J 2020;10:70.

59. Maura F, Bolli N, Angelopoulos N, Dawson KJ, Leongamornlert D, Martincorena I, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. Nat Commun 2019;10:3835.

60. Hoang PH, Cornish AJ, Dobbins SE, Kaiser M, Houlston RS. Mutational processes contributing to the development of multiple myeloma. Blood Cancer J 2019;9:60.

61. Yellapantula V, Hultcrantz M, Rustad EH, Wasserman E, Londono D, Cimera R, et al. Comprehensive detection of recurring genomic abnormalities: a targeted sequencing approach for multiple myeloma. Blood Cancer J 2019;9:101.

62. Hultcrantz M, Rustad EH, Yellapantula V, Arcila M, Ho C, Syed MH, et al. Baseline VDJ clonotype detection using a targeted sequencing NGS assay: allowing for subsequent MRD assessment. Blood Cancer J 2020;10:76.

63. Kortuem KM, Braggio E, Bruins L, Barrio S, Shi CS, Zhu YX, et al. Panel sequencing for clinically oriented variant screening and copy number detection in 142 untreated multiple myeloma patients. Blood Cancer J 2016;6:e397.

64. Bolli N, Li Y, Sathiaseelan V, Raine K, Jones D, Ganly P, et al. A DNA target-enrichment approach to detect mutations, copy number changes and immunoglobulin translocations in multiple myeloma. Blood Cancer J 2016;6:e467.

65. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweegman S, et al. Role of (18)F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol 2017;18:e206–e17.

66. Hillengass J, Ayyaz S, Kilk K, Weber MA, Hielscher T, Shah R, et al. Changes in magnetic resonance imaging before and after autologous stem cell transplantation correlate with response and survival in multiple myeloma. Haematologica 2012;97:1757–60.

67. Rasche L, Angtuaco EJ, Alpe TL, Gershner GH, McDonald JE, Samant RS, et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. Blood 2018;132:59–66.

68. Greipp PR, Lust JA, O'Fallon WM, Katzmann JA, Witzig TE, Kyle RA. Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood 1993;81:3382–7.

69. Fernández de Larrea C, Kyle R, Rosiñol L, Paiva B, Engelhardt M, Usmani S, et al. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. Blood Cancer J 2021;11:192.

70. Pawlyn C, Cairns D, Kaiser M, Striha A, Jones J, Shah V, et al. The relative importance of factors predicting outcome for myeloma patients at different ages: results from 3894 patients in the Myeloma XI trial. Leukemia 2020;34:604–12.

71. Boyle EM, Williams L, Blaney P, Ashby C, Bauer M, Walker BA, et al. Improving prognostic assignment in older adults with multiple myeloma using acquired genetic features, clonal hemopoiesis and telomere length. Leukemia 2022;36:221–4.

72. Mouhieddine TH, Sperling AS, Redd R, Park J, Leventhal M, Gibson CJ, et al. Clonal hematopoiesis is associated with adverse outcomes in multiple myeloma patients undergoing transplant. Nat Commun 2020;11:2996.

73. Tirier SM, Mallm JP, Steiger S, Poos AM, Awwad MHS, Giesen N, et al. Subclone-specific microenvironmental impact and drug response in refractory multiple myeloma revealed by single-cell transcriptomics. Nat Commun 2021;12:6960.

74. Maura F, Boyle EM, Diamond B, Blaney P, Ghamlouch H, Ziccheddu B, et al. Genomic and immune signatures predict sustained MRD negativity in newly diagnosed multiple myeloma patients treated with daratumumab, carfilzomib, lenalidomide, and dexamethasone (D-KRd). Blood 2021;138:325.

75. Guerrero C, Puig N, Cedena MT, Goicoechea I, Perez C, Garcés JJ, et al. A machine learning model based on tumor and immune biomarkers to predict undetectable MRD and survival outcomes in multiple myeloma. Clin Cancer Res 2022.

76. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med 2017;376:1311–20.

77. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 2020;136:936–45.

78. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019;394:29–38.

79. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906–17.

80. Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood 2018;131:301–10.

81. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 2019;380:2104–15.

82. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518–28.

83. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide before and after autologous stem cell transplantation for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial. Haematologica 2021;106:1957–67.

84. Cavo M, Gay F, Beksac M, Pantani L, Petrucci MT, Dimopoulos MA, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol 2020;7:e456–e68.

85. Siegel A, Boyle EM, Blaney P, Wang Y, Ghamlouch H, Choi J, et al. Unifying the definition of high-risk in multiple myeloma. Blood 2021;138:2714.

86. Nooka AK, Kaufman JL, Muppidi S, Langston A, Heffner LT, Gleason C, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia 2014;28:690–3.

87. Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol 2013;31:3279–87.

88. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2019;20:57–73.

89. Giri S, Grimshaw A, Bal S, Godby K, Kharel P, Djulbegovic B, et al. Evaluation of daratumumab for the treatment of multiple myeloma in patients with high-risk cytogenetic factors: a systematic review and meta-analysis. JAMA Oncol 2020;6:1759–65.

90. Leypoldt LB, Besemer B, Asemissen AM, Hänel M, Blau IW, Görner M, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. Leukemia 2022;36:885–8.

91. Brown S, Sherratt D, Hinsley S, Flanagan L, Roberts S, Walker K, et al. MUKnine OPTIMUM protocol: a screening study to identify high-risk patients with multiple myeloma suitable for novel treatment approaches combined with a phase II study evaluating optimised combination of biological therapy in newly diagnosed high-risk multiple myeloma and plasma cell leukaemia. BMJ Open 2021;11:e046225.

92. Kaiser MF, Hall A, Walker K, Tute RD, Roberts S, Ingleson E, et al. Depth of response and minimal residual disease status in ultra high-risk multiple myeloma and plasma cell leukemia treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Dara-CVRd): Results of the UK optimum/MUKnine trial. J Clin Oncol 2021;39:8001.

93. Saini N, Bashir Q, Milton DR, Tang G, Delgado R, Rondon G, et al. Busulfan and melphalan conditioning is superior to melphalan alone in autologous stem cell transplantation for high-risk MM. Blood Adv 2020;4:4834–7.

94. Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2019;393:253–64.

95. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol 2017;35:3279–89.

96. Richard S, Chari A, Delimpasi S, Simonova M, Spicka I, Pour L, et al. Once weekly selinexor, bortezomib, and dexamethasone (SVd) versus twice weekly bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma: high-risk cytogenetic risk planned subgroup analyses from the Phase 3 Boston Study. Blood 2020;136:35–6.

97. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med 2019;380:1726–37.

98. Spisek R, Charalambous A, Mazumder A, Vesole DH, Jagannath S, Dhodapkar MV. Bortezomib enhances dendritic cell (DC)-mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications. Blood 2007;109:4839–45.

99. Gulla A, Morelli E, Samur MK, Botta C, Hideshima T, Bianchi G, et al. Bortezomib induces anti-multiple myeloma immune response mediated by cGAS/STING pathway activation. Blood Cancer Discov 2021;2:468–83.

100. Kumar S, Kaufman JL, Gasparetto C, Mikhael J, Vij R, Pegourie B, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. Blood 2017;130:2401–9.

101. Moreau P, Chanan-Khan A, Roberts AW, Agarwal AB, Facon T, Kumar S, et al. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. Blood 2017;130:2392–400.

102. Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2020;21:1630–42.

103. Stein CK, Pawlyn C, Chavan S, Rasche L, Weinhold N, Corken A, et al. The varied distribution and impact of RAS codon and other key DNA alterations across the translocation cyclin D subgroups in multiple myeloma. Oncotarget 2017;8:27854–67.

104. Andrulis M, Lehners N, Capper D, Penzel R, Heining C, Huellein J, et al. Targeting the BRAF V600E mutation in multiple myeloma. Cancer Discov 2013;3:862–9.

105. Gooding S, Ansari-Pour N, Towfic F, Ortiz Estévez M, Chamberlain PP, Tsai KT, et al. Multiple cereblon genetic changes are associated with acquired resistance to lenalidomide or pomalidomide in multiple myeloma. Blood 2021;137:232–7.

106. Usmani SZ, Hoering A, Ailawadhi S, Sexton R, Lipe B, Hita SF, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. Lancet Haematol 2021;8:e45–54.

107. Da Vià MC, Dietrich O, Truger M, Arampatzi P, Duell J, Heidemeier A, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. Nat Med 2021;27:616–9.

108. Samur MK, Fulciniti M, Aktas Samur A, Bazarbachi AH, Tai YT, Prabhala R, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. Nat Commun 2021;12:868.