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International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma

Hervé Avet-Loiseau, MD, PhD¹ ; Faith E. Davies, MD² ; Mehmet K. Samur, PhD³ ; Jill Corre, PharmD, PhD¹ ; Mattia D'Agostino, MD^{4,5} ; Martin F. Kaiser, MD^{6,7} ; Marc S. Raab, MD⁸ ; Niels Weinhold, PhD⁸ ; Norma C. Gutierrez, MD, PhD⁹ ; Bruno Paiva, PhD¹⁰ ; Paola Neri, MD¹¹; Katja Weisel, MD¹² ; Francesco Maura, MD¹³ ; Brian A. Walker, PhD¹⁴ ; Mark Bustoros, MD¹⁵ ; A. Keith Stewart, MB, CHB¹⁶ ; Saad Z. Usmani, MD¹⁷ ; Jens Hillengass, MD, PhD¹⁸ ; Wee Joo Chng, MD¹⁹ ; Jonathan J. Keats, PhD²⁰ ; Joaquin Martinez-Lopez, MD²¹ ; Adam S. Sperling, MD, PhD²² ; Cyrille Touzeau, MD²³ ; Fenghuang Zhan, PhD²⁴ ; Noopur S. Raje, MD²⁵ ; Michele Cavo, MD²⁶; Niccolò Bolli, MD, PhD²⁷ ; Irene M. Ghobrial, MD²⁸ ; Madhav V. Dhodapkar, MD²⁹ ; Sundar Jagannath, MD³⁰ ; Andrew Spencer, MD³¹ ; Samir Parekh, MD³² ; Nizar J. Bahlis, MD¹¹ ; Sagar Lonial, MD³³; Pieter Sonneveld, MD, PhD³⁴ ; Leif Bergsagel, MD³⁵ ; Robert Z. Orlowski, MD, PhD³⁶ ; Gareth Morgan, MD²; María Victoria Mateos, MD⁹ ; S. Vincent Rajkumar, MD³⁷; Jesus F. San Miguel, MD³⁸ ; Kenneth C. Anderson, MD³⁹ ; Philippe Moreau, MD²³ ; Shaji Kumar, MD³⁷ ; Felipe Prósper, MD⁴⁰; and Nikhil C. Munshi, MD⁴¹

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ABSTRACT

Despite significant improvements in survival of patients with multiple myeloma (MM), outcomes remain heterogeneous, and a significant proportion of patients experience sub-optimal outcomes. Importantly, traditional prognostic factors based on data from patients treated with older therapies no longer capture prognosis accurately in the contemporary era of novel triplet or quadruplet therapies. Therefore, risk stratification requires refinement in the context of available and investigational treatment options in routine practice and clinical trials, respectively. The current identification of high-risk MM (HRMM) in routine practice is based on the Revised International Staging System, which stratifies patients using a combination of widely available serum biomarkers and chromosomal abnormalities assessed via fluorescence in situ hybridization. In recent years, a substantial body of evidence concerning additional clinical, biological, and molecular/genomic prognostic factors has accumulated, along with new MM risk stratification tools and consensus reports. The International Myeloma Society, along with the International Myeloma Working Group, convened an Expert Panel with the primary aim of revisiting the definition of HRMM and formulating a practical and data-driven consensus definition, based on new evidence from molecular/genomic assays, updated clinical data, and contemporary risk stratification concepts. The Panel proposes the following Consensus Genomic Staging (CGS) of HRMM which relies upon the presence of at least one of these abnormalities: (1) del(17p), with a cutoff of >20% clonal fraction, and/or *TP53* mutation; (2) an IgH translocation including t(4;14), t(14;16), or t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del(1p32) along with 1q+ or biallelic del(1p32); or (4) $\beta 2$ microglobulin ≥ 5.5 mg/L with normal creatinine (<1.2 mg/dL).

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INTRODUCTION

The current therapeutic landscape of multiple myeloma (MM), a plasma cell malignancy with increasing prevalence worldwide, includes multiple drug classes.¹⁻³ Use of triplet/quadruplet regimens combining immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies, along with chimeric antigen receptor T-cell therapy and bispecific antibodies,³ as well as high-dose melphalan therapy with autologous stem-cell transplant, has yielded significant survival improvements.⁴⁻⁷ However, because of the inability to completely eradicate the tumor, long-term disease-free outcome remains less frequent.⁴⁻⁷ The clinical/biological

heterogeneity translates into heterogeneous outcomes for patients with MM, with survival ranging from a few months to over a decade.⁸ There have been efforts to risk stratify patients with MM to facilitate prognostication and develop risk-adapted therapy and to improve outcomes for high-risk patients with the poorest prognosis.

MM risk stratification systems, since the introduction of the Durie-Salmon (DS) system in 1975,⁹ have undergone revisions in tandem with the development of novel therapies. For instance, while the DS system was predictive of clinical outcomes in the era of standard-dose chemotherapy, it became a less precise predictor when high-dose therapies

and novel agents were introduced.¹⁰ The 2005 International Staging System (ISS), which integrated $\beta 2$ microglobulin ($\beta 2M$) and serum albumin, was the first validated risk stratification model developed for patients with newly diagnosed MM (NDMM), but most of the available data did not then reflect wide use of IMiDs and PIs.¹¹ The 2015 Revised ISS (R-ISS) integrated clinical and cytogenetic markers and has become the standard risk-definition approach.¹² Since then, additional evidence on clinical, biological, and molecular/genomic prognostic factors has accumulated, along with new risk stratification tools; consensus reports refining MM risk stratification have also been published.^{8,13-18}

Despite availability of different NDMM risk stratification systems and significant advances in MM therapies, including novel therapies with a potential impact on certain cytogenetic/molecular alterations that improve outcomes for some patients, high-risk patients have not uniformly benefited as much and still experience early disease progression and death.¹⁹⁻²¹ Moreover, 62% of patients with NDMM were characterized as intermediate-risk at diagnosis per R-ISS.¹² Patients within the same risk category experience highly heterogeneous outcomes, despite use of updated MM risk stratification approaches.²² Updated and/or add-on risk stratification approaches in the modern era remain challenging to apply in routine practice because of the heterogeneity of assessments across laboratories, lack of uniformity in high-risk MM (HRMM) criteria and thresholds for specific markers, or issues with access to assessment technologies.^{8,14-16,23}

HRMM remains challenging to identify and manage, and there is a lack of uniformity in HRMM definition across clinical studies and in nonclinical research and routine clinical practice.^{13,24,25} HRMM definitions vary in which markers are tested, testing methods (interphase fluorescence in situ hybridization [iFISH], next-generation sequencing [NGS], gene expression profiling [GEP] signatures), and marker positivity thresholds.^{13,24,25} Technological and analytical advances and decreasing assay costs have enabled inclusion of sequencing/NGS-based assessments in molecular risk stratification and their use in routine practice in hematologic malignancies, including myelodysplastic syndrome (MDS) and AML.²⁶⁻²⁸ Broader sequencing/NGS use and evolving data provide the framework for incorporating sequencing/NGS-based data into revised MM risk stratification algorithms.

To review new molecular/genomic evidence and the role of previous prognostic markers in the current era of triplet-/quadruplet-based MM therapies, the International Myeloma Society (IMS), along with the International Myeloma Working Group (IMWG), convened an Expert Panel to establish a practical and data-driven consensus on HRMM definition. Here, we present the consensus definition of HRMM in the genomics era and provide recommendations on future HRMM explorations, based on the discussions and data presented at the July 2023, IMS "Workshop on Genomics:

Defining High-Risk Disease and Developing Targeted Therapies in MM" (IMS/IMWG Genomics Workshop hereafter).

The Panel's approach was based on the understanding that the revised HRMM definition should not only incorporate data on high-risk features, including chromosomal abnormalities (CAs) and genomic/genetic alterations, but also define assessment method-specific cutoffs for markers. Moreover, identifying a subset, representing around 20% of patients with MM with the poorest prognosis, was considered a reasonable benchmark for HRMM.

METHODS

Format of the IMS/IMWG Genomics Workshop

The IMS/IMWG Genomics Workshop, attended by researchers and clinicians focused on myeloma and representing all major myeloma cooperative groups, was held on July 7-8, 2023, in Barcelona, Spain. The Workshop included a series of presentations on relevant data, both previously published and unpublished/novel analyses, on the prognostic impact of specific risk factors. In addition to inviting meeting participants to engage in robust discussion and debate, an egalitarian approach was adopted throughout, allowing meeting attendees to share data with all attendees via screen-sharing. A list of meeting attendees and summary of the agenda are provided in the Data Supplement (online only).

Patients and Methods

The data sets discussed included previous and novel analyses of data from MM cohorts within the Intergruppo Francophone du Myélome (IFM) cohorts,^{29,30} the HARMONY Project (used in R2-ISS),⁸ the FORTE study (ClinicalTrials.gov identifier: [NCT02203643](#)),³¹ Grupo Español de Mieloma Múltiple (GEM),³² the German-speaking Myeloma Multi-center Group (including HD4, MM5, and HD6 [ClinicalTrials.gov identifier: [NCT02495922](#)] studies),³³⁻³⁵ MYELOMA XI,³⁶ Emory 1000,³⁷⁻³⁹ the Multiple Myeloma Research Foundation (MMRF) Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile (CoMMpass) data set,^{40,41} and Mayo Clinic NDMM cohorts.^{42,43} Data from individual data sets analyzed independently were used to address key questions and develop consensus based on the preponderance of evidence across studies/data sets. Data from different studies/data sets were not pooled for analyses. Descriptions of these data sets and other data shared at the workshop are included in the Data Supplement (Table S1).

RESULTS

Review of Rationale and Evidence Supporting the Revised Consensus Genomic Staging of HRMM

The results of the comprehensive discussions at the IMS/IMWG Genomics Workshop are organized below by session

topics. CAs shown to be associated with poor prognosis in the contemporary era include deletion of the short arm of chromosome 17 (del [17p]); translocations t(4;14), t(14;16), and t(14;20); and chromosome 1 abnormalities, such as gain (three copies of 1q) or amplification (>3 copies of 1q), collectively referred to as 1q+, and deletion of the short arm of chromosome 1 (del[1p32]).^{13,44,45}

Status of del(17p), del(17p) Clonal Fraction, and TP53 Mutation

del(17p), present in up to 10% of patients at diagnosis and enriched in patients with RRMM (reported in 10%–60%),^{8,46–48} is a well-established high-risk feature in the current MM staging criteria, including R-ISS.^{8,12,45,49} Patients with del(17p) at diagnosis usually present with advanced-stage disease and aggressive clinical features, with a median overall survival (OS) of 3 years.⁴⁹ del(17p) at relapse is also associated with poor prognosis^{47,50,51}; for instance, a median progression-free survival (PFS) of 5.4 months and a median OS of 18.1 months were reported in patients with del(17p) MM.⁵⁰

In addition to del(17p), the relative proportion of myeloma cells carrying del(17p) also affects prognosis. The heterogeneity in the cutoffs for defining del(17p) positivity, ranging from >60% positive cells (cancer clonal fraction [CCF] >0.6) to as low as 1% in some phase III studies, and the variations in treatment regimens used, within and across data sets, have contributed to discordance in the prognoses reported for del(17p)-positive patients.^{52,53} Moreover, the tumor suppressor *TP53* is encoded in the minimal deleted region on 17p, and *TP53* dysregulation is involved in the pathogenesis of many cancers, including MM.⁵² While del(17p) would also lead to *TP53* loss, only a third of cases with monoallelic del(17p) harbor mutations in the remaining *TP53* allele⁵² and some evidence suggests that biallelic *TP53* alteration—mostly, via loss because of del(17p) and concomitant mutation of the remaining allele—contributes to worse outcomes.^{54,55}

The Panel reviewed data on the prognostic roles of del(17p) and *TP53* mutations, both as independent factors and as co-occurring features, and considered the practical aspects of iFISH thresholds for del(17p) as a high-risk feature and the impact of clonality to establish a standardized approach for risk prognostication based on del(17p) and/or *TP53* dysregulation.

Although patients with del(17p) with co-occurring high-risk CAs (HRCAs) have the poorest outcomes, accumulating evidence confirms the independent prognostic impact of isolated del(17p) on both OS and PFS.^{8,53} The Panel reviewed data from subgroup analyses of the FORTE trial³¹ (del(17p) status by FISH) and the CoMMpass data set (del(17p) status and *TP53* mutations by sequencing) and analyses conducted by GEM (discussed below), which confirmed the prognostic impact of isolated del(17p). Similarly, in the IFM/DFCI2009

cohort (del(17p) status by FISH and sequencing and *TP53* mutations by sequencing), del(17p) was prognostic for PFS and OS.⁵⁶ Based on the preponderance of evidence for del(17p) as an independent prognosticator of poor outcomes, the consensus recommendation was to include del(17p) as a HRMM feature.

In analyses conducted by GEM, OS and PFS significantly differed in patients with and without del(17p), for del(17p) CCF thresholds $\geq 20\%$ (Data Supplement, Table S2 and Figs 1A and 1B). Analysis of HARMONY data also showed significant differences in OS and PFS, when comparing patients with del(17p) with CCF >50% and 20%–50%, but not with CCF <20% (Data Supplement, Fig S1). The greatest discriminative capacity to predict outcome is seen with del(17p) CCF $\geq 40\%$ to >60% across studies.^{50,53,54} However, the prognostic impact of del(17p) remains high in patients with CCF $\geq 20\%$. Median PFS and median OS with a CCF cutoff of 10% were longer than those with CCF thresholds $\geq 20\%$; the median OS for patients with CCF $\geq 10\%$ was 54.2 months, compared with 37.0–38.1 months for patients with CCF 20%–59% (Data Supplement, Table S2). Therefore, the consensus recommendation for the del(17p) threshold was CCF $\geq 20\%$, by analyses conducted on CD138-positive/purified cells, in the revised HRMM definition.

Patients with del(17p) with concurrent *TP53* dysregulation on the remaining allele via loss or mutation have the poorest outcomes.^{8,53,54,58–61} In Myeloma XI, for instance, inactivation of both *TP53* alleles was independently associated with inferior survival, in terms of both PFS (hazard ratio [HR], 3.1; $P = .00047$) and OS (HR, 5.01; $P = 3.9 \times 10^{-6}$).⁵⁸ The prognostic impact of *TP53* inactivation by mutation and/or deletion is also borne out in data from the CoMMpass cohort and the IFM data set (Figs 1C and 1D, and Data Supplement, Fig S2). While patients with *TP53* mutations have worse prognosis, patients with deletions (eg, del(17p)) also have poor prognosis in terms of OS (Figs 1C and 1D) and PFS (Data Supplement, Fig S2), consistent with other reports.^{60,62,63}

Given the prognostic impact of *TP53* mutations on PFS and OS, the Panel recommended that *TP53* mutation, identified using NGS-based methods on CD138-positive/purified cells, should be included in the HRMM definition.

Translocations t(14;16), t(14;20), and t(4;14)

t(14;16) is prevalent in $2.1\% \pm 0.6\%$ of patients with NDMM and, along with t(14;20), represents the MAF translocation group.¹³ t(14;16) has been associated with poor prognosis although recent data suggest that it may not be an independent prognostic factor.^{59,64} In an IFM real-world cohort, the PFS and OS of patients with t(14;16) were 24.3 and 63.1 months, respectively, compared with 39.2 and 99.4 months, in patients lacking t(14;16); PFS and OS outcomes did not differ between patients with isolated t(14;16) and those lacking high-risk features (Figs 2A and

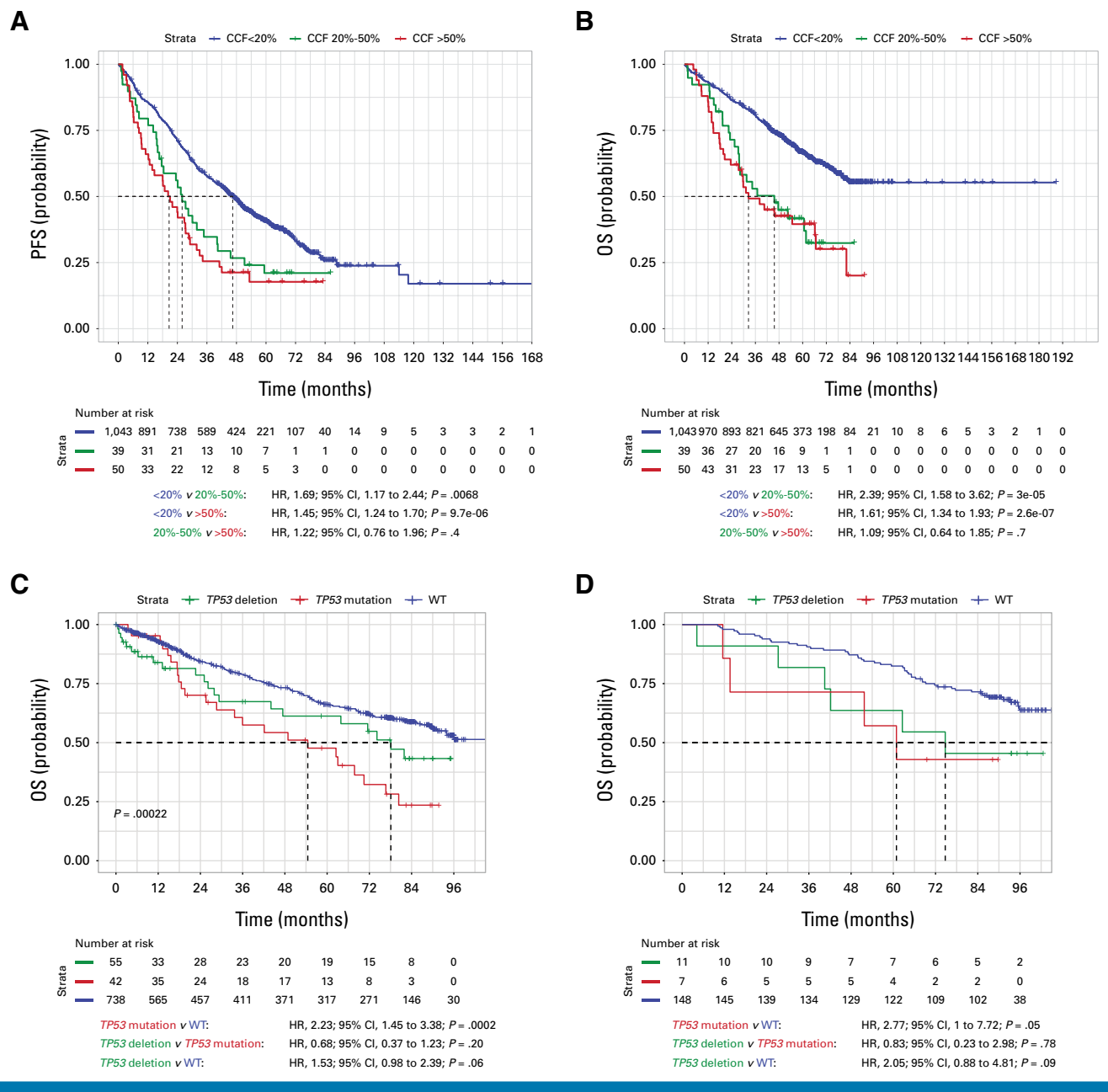


FIG 1. Impact of del(17p) CCF and events involving *TP53* on survival outcomes. Impact of del(17p) CCF on survival outcomes: Shown are (A) PFS and (B) OS analyses in patients from the GEM studies (GEM05mas65, GEM05menores65, GEM2010, and GEM2012), with del(17p) distributed into three groups according to CCF cutoffs: <20% (blue), 20%-50% (green), and >50% (red). The Kaplan-Meier method was used to estimate time-to-event, and significance was determined using a two-sided log-rank test. Pairwise comparison statistics are shown. Impact of events involving *TP53* on survival outcomes in the CoMMpass and IFM cohorts: Shown are OS analyses for patients with *TP53* mutation (red), *TP53* deletion (green), or WT (blue) in the (C) CoMMpass/MMRF and (D) IFM cohorts. For the CoMMpass/MMRF cohort, the analysis was performed using all available data in the MMRF Researcher Gateway⁵⁷ for CoMMpass Interim Analysis 21. The Kaplan-Meier method was used to estimate time-to-event data, and significance was determined using a two-sided log-rank test; pairwise comparison statistics are shown. CCF, cancer clonal fraction; CoMMpass; Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile; HR, hazard ratio; MMRF, Multiple Myeloma Research Foundation; GEM, Grupo Español de Mieloma Múltiple; IFM, Intergroupe Francophone du Myélome; OS, overall survival; PFS, progression-free survival; WT, wild-type.

2B).⁶⁴ t(14;16) is strongly associated with other CAs—69.2%, 22.5%, and 20.7% of patients with t(14;16) also harbor 1q+, del(17p), and del(1p32), respectively⁶⁴—high apolipoprotein B mRNA-editing enzyme, and catalytic

polypeptide-type (APOBEC) mutational signature.^{44,65,66} Patients with t(14;16) without co-occurring 1q+ tend to have other HRCAs, such as del(17p) or *TP53* mutations, confirming the rarity of isolated t(14;16) in NDMM.⁶⁴

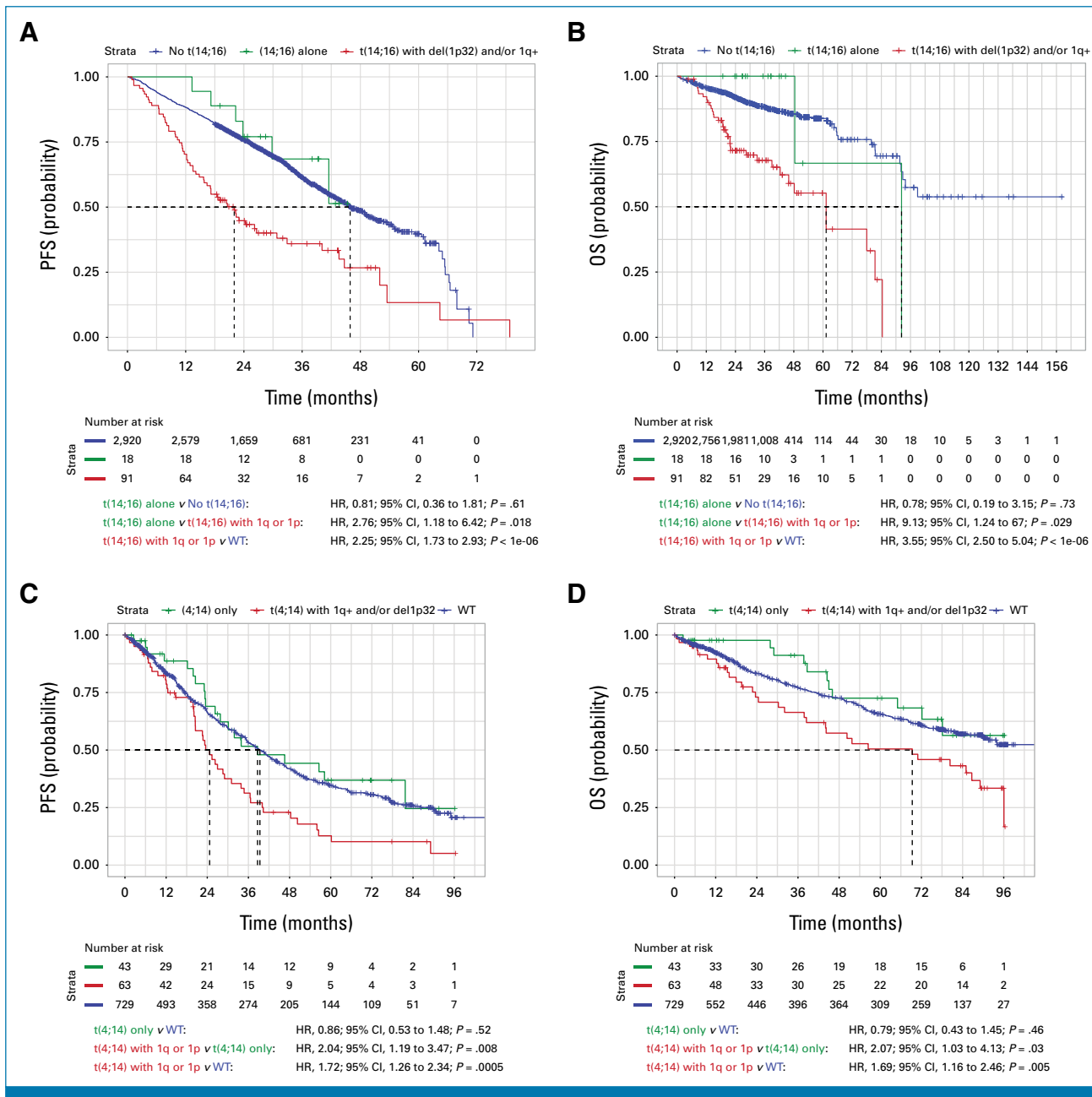


FIG 2. Prognostic impact of translocations in the context of other CAs. Impact of t(14;16) in the context of other CAs: Shown are (A) PFS and (B) OS analyses in patients with NDMM with isolated t(14;16) (t(14;16) without 1q+ and/or del(1p32); green), compared with those with co-occurring gain(1q) and/or del(1p32) (red), and WT (all patients without t(14;16); blue), in the IFM data set. The Kaplan-Meier method was used to estimate time-to-event, and significance was determined using a two-sided log-rank test; pairwise comparison statistics are shown. Impact of t(4;14) in the context of other CAs: Shown are (C) PFS and (D) OS analyses in patients with NDMM with isolated t(4;14), compared with those with co-occurring CAs, in the CoMMpass/MMRF data set. The analysis was performed using all available data in the MMRF Researcher Gateway⁵⁷ for CoMMpass Interim Analysis 21. Kaplan-Meier PFS (left) and OS (right) plots for patients with isolated t(4;14) (t(4;14) without 1q+ and/or del(1p32); green), t(4;14) with co-occurring 1q+ and/or del(1p32) (red), and WT (all patients without t(4;14); blue). The Kaplan-Meier method was used to estimate time-to-event data, and significance was determined using a two-sided log-rank test; pairwise comparison statistics are shown. CAs, chromosomal abnormalities; CoMMpass; Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile; HR, hazard ratio; IFM, Intergroupe Francophone du Myélome; OS, overall survival; MMRF, Multiple Myeloma Research Foundation; PFS, progression-free survival; WT, wild-type.

Moreover, the survival outcomes of patients with t(14;16) without 1q+ are comparable with those of patients without t(14;16) (Figs 2A and 2B).⁶⁴

The t(4;14) translocation events between chromosome 4 (NSD2) and chromosome 14 (IgH locus), prevalent in 10% $\pm$ 1.2% of patients with NDMM, are considered high-risk

features per the R-ISS.¹² However, only 30%–40% of t(4;14)-positive patients are clinically high-risk, with the remaining achieving outcomes comparable with patients with standard or intermediate risk.^{61,67} Therefore, risk stratification in t(4;14)-positive patients may require further refinement based on co-occurring CAs, with 1q+ and del(1p32) contributing significantly to worse prognosis when co-occurring with t(4;14).^{68,69} Data from the CoMMpass study show that t(4;14) events co-occur with 1q+ (55.6%), with few cases co-occurring with del(1p32) (11.3%).

In a recent assessment of patients with t(4;14)-positive NDMM, specific translocation breakpoints (associated with *NSD2* fusion transcripts), as well as del(17p)/amp(1q), were independently associated with OS in patients with high-risk disease (OS <24 months).⁷⁰ While *NSD2* breakpoint-mediated prognosis is not currently considered high-risk and may be addressed in future risk stratification approaches, these data support consideration of t(4;14) as a high-risk feature when co-occurring with 1q+ or del(1p32). The prognostic impact of t(4;14) in the context of co-occurring 1q+ and/or del(1p32), but not in isolation, is also seen in patients with NDMM in the CoMMpass data set (Figs 2C and 2D). In MYELOMA XI, patients with isolated t(4;14), isolated del(1p), or 1q+ had a significantly better prognosis than patients with two risk markers.³⁶ Consistent with this, t(4;14)-positive patients harboring ≥1 additional hits in the GEM studies displayed a significantly worse prognosis.⁷¹

Similarly, t(14;20), prevalent in 2% of patients, has the highest prognostic impact only when considered along with 1q+ or del(1p32). In an NDMM patient similarity network analysis of the CoMMpassSM cohort, outcomes for patients with translocations affecting *NSD2/MMSET* (t(4;14)), *MAF* (t(14;16)), or *MAF-C* (t(14;20)) were worse when co-occurring with 1q changes.⁷² In MYELOMA XI, patients with *MMSET*-/*MAF*-associated translocations accumulated other risk markers—del(17p), 1q+, and/or del(1p)—at relapse.⁷³ Analysis of pooled data from 2,596 patients with NDMM from three phase III trials also confirms poor prognosis of patients with these *MMSET*-/*MAF*-associated translocations when co-occurring with 1q+.¹⁸ The IMS-IMWG consensus recommendation is to consider t(14;16), t(14;20), and t(4;14) as high-risk features only in the context of co-occurring 1q+ or del(1p32).

Role of Chromosome 1 Aberrations: 1q Changes and del(1p32)

In patients with NDMM, 1q+ and del(1p32) are relatively common, occurring in about 35% ± 2.7% and 13.4% ± 1.1%, respectively.^{74,75} Although previous risk stratification systems did not include del(1p32) as a high-risk factor, recent data indicate that del(1p32) has an adverse prognostic impact, second only to del(17p).¹⁵

In an earlier IFM cohort of 1635 patients with NDMM (treated between 2000 and 2012), isolated del(1p32) or 1q+ was associated with intermediate prognosis, whereas co-occurring

del(1p32) and 1q+ conferred a significantly worse prognosis.¹⁵ The Panel reviewed data from an updated analysis of an IFM cohort of 2,551 patients diagnosed more recently (2010–2021).⁷⁵ In this cohort, 1q+ occurred at a higher frequency in patients with del(1p32), compared with those without (55% v 33.8%); the median PFS and OS were 17 and 49 months in patients with del(1p32), compared with 30 and 124 months, respectively, in patients without del(1p32).⁷⁵ After adjustment for age and treatment, the risk of progression and death was 1.3 and 1.9 times higher, respectively, among del(1p32)-positive patients.⁷⁵ Among patients with del(1p32), the 20% with biallelic deletions had a significantly worse prognosis compared with patients with monoallelic del(1p32) (PFS, 9 months v 19 months and OS, 24 months v 60 months for biallelic v monoallelic del(1p32)).⁷⁵ In the MMRF/CoMMpass data set, survival outcomes were worse for patients with biallelic del(1p32) events or with monoallelic del(1p32) co-occurring with 1q+, compared with those with monoallelic del(1p32) alone, with 1q+ alone, or without cytogenetic abnormalities (Fig 3). Biallelic del(1p32) was similarly associated with worse PFS and OS in analyses of whole-genome sequencing data in HD6 (Data Supplement, Fig S3). Overall, evidence suggests that biallelic del(1p32) and monoallelic del(1p32) co-occurring with 1q+ are high-risk features.

Although 1q+ is often considered a poor prognostic marker, it is difficult to use 1q+ in defining high-risk because of its high prevalence (up to 40% of NDMM).⁷⁴ 1q+ occurs at higher frequencies in patients with other adverse clinical or cytogenetic features; however, it is also prevalent in patients with standard-risk MM.⁷⁴ Therefore, restratification of risk in 1q+ NDMM is necessary. In the GEM cohort, no negative impact on survival was found in patients harboring 1q+ as an isolated cytogenetic aberration, suggesting that cosegregation of other cytogenetic abnormalities is critical in deciding the prognostic impact of 1q+.⁷¹ Moreover, outcomes did not differ between patients with gain(1q) versus amp(1q); these findings are consistent with results in the IFM cohort (Data Supplement, Fig S4) although amp(1q) demonstrated a worse prognostic impact than gain(1q) in some studies.^{8,18,36,59,76–79}

Overall, evidence supports 1q+ as a high-risk feature when considered in combination with other risk factors, such as the t(4;14), t(14;16), and t(14;20) translocations or monoallelic del(1p32). Currently, detailed analyses of del(1p32) or 1q CCF and the impact on prognosis are not available; therefore, clonality of del(1p32) or 1q was not considered in the current IMS-IMWG HRRM definition. The consensus recommendation is to consider biallelic del(1p32), as detected by loss of *FAF1* or *CDKN2C*, or monoallelic del(1p32), as detected by loss of *FAF1* or *CDKN2C*, co-occurring with 1q+, as HRMM features.

Role of ISS and Other Clinical Features

Unlike the genomic markers discussed above, which may affect prognosis by promoting aggressive disease biology,

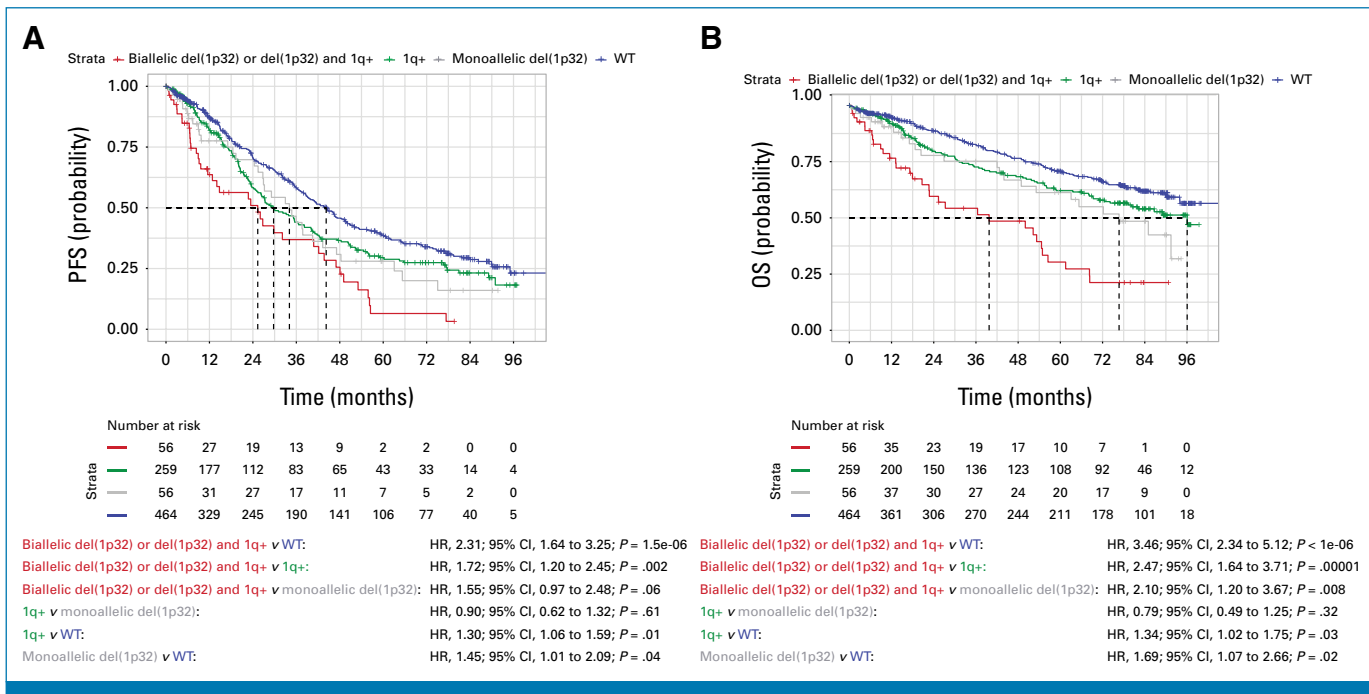


FIG 3. Prognostic impact of monoallelic and biallelic chromosome 1p aberrations. Shown are (A) PFS and (B) OS analyses in patients with NDMM in the CoMMpass/MMRF data set, with monoallelic del(1p32) (without co-occurring 1q+; gray), biallelic del(1p32) events, or co-occurring del(1p32) and 1q+ (red), 1q+ (green), and WT (blue). The analysis was performed using all available data in the MMRF Researcher Gateway⁵⁷ for CoMMpass Interim Analysis 21. The Kaplan-Meier method was used to estimate time-to-event data, and significance was determined using a two-sided log-rank test; pairwise comparison statistics are shown. CoMMpass; Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile; HR, hazard ratio; MMRF, Multiple Myeloma Research Foundation; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; WT, wild-type.

previous staging and risk stratification systems included additional variables that conferred adverse prognosis because of host characteristics (low albumin, renal impairment) and tumor burden ($\beta 2M$, monoclonal protein levels). While the ISS,¹¹ developed nearly 20 years ago, served as a practical, easy-to-use, and expedient tool for routine clinical use for several decades, it does not capture features that track the underlying biology of MM and would not be a relevant system now. Although cytogenetic risk features were added to the ISS to develop the R-ISS, its stages/risk categories are not reported consistently across trials. Moreover, neither ISS nor R-ISS explored the independent prognostic role of del(17p) or t(4;14).^{11,12} Often, ISS stage and CAs are reported separately, even in clinical studies conducted after establishing R-ISS; ISS stage III continues to be prognostic of poor outcomes in modern trials of MM and is subsumed into newer NDMM risk stratification systems.^{8,14,30,80,81}

The R2-ISS attempted to improve upon the ISS and R-ISS and does consider del(17p), t(4;14), and 1q+ in defining HRMM.⁸ However, the R2-ISS used the HARMONY data set, which includes academic clinical studies but not industry-led trials, and does not include studies of mAb-based regimens.⁸ Therefore, the prognostic relevance of individual parameters in previous risk stratification models needs to be reconsidered, along with contemporary evidence on other

relevant markers, to redefine HRMM based on biological features that drive an aggressive clinical course.

The role and value of $\beta 2M$ as an independent high-risk feature are contentious, because of discrepancies regarding its independent prognostic value across data sets. $\beta 2M$ levels in myeloma can be elevated because of renal dysfunction, high tumor burden, or both. Since, from a therapeutic standpoint, overcoming adverse prognosis because of host characteristics (age, renal failure) requires a completely different strategy than overcoming high-risk disease because of biological aggressiveness or high tumor burden, it is important to ascertain the prognostic effect of $\beta 2M$ in the absence of renal failure. In CoMMpass and FORTE data sets, patients with isolated high $\beta 2M$ (≥ 5.5 mg/L) in the absence of renal failure (creatinine < 1.2 mg/dL) had worse survival outcomes, compared with standard-risk patients, with outcomes comparable with genomically defined high-risk patients (Figs 4A-4D). Serum creatinine levels, but not creatinine clearance, were available for both data sets; hence, creatinine > 1.2 mg/dL was considered indicative of renal failure in this analysis. Therefore, the Panel included high $\beta 2M$ (≥ 5.5 mg/L), without renal failure (creatinine < 1.2 mg/dL), in the definition of HRMM. Importantly, $\beta 2M$ and renal function assessments should, under no circumstances, be considered a substitute for detailed genomic profiling for all patients with MM.

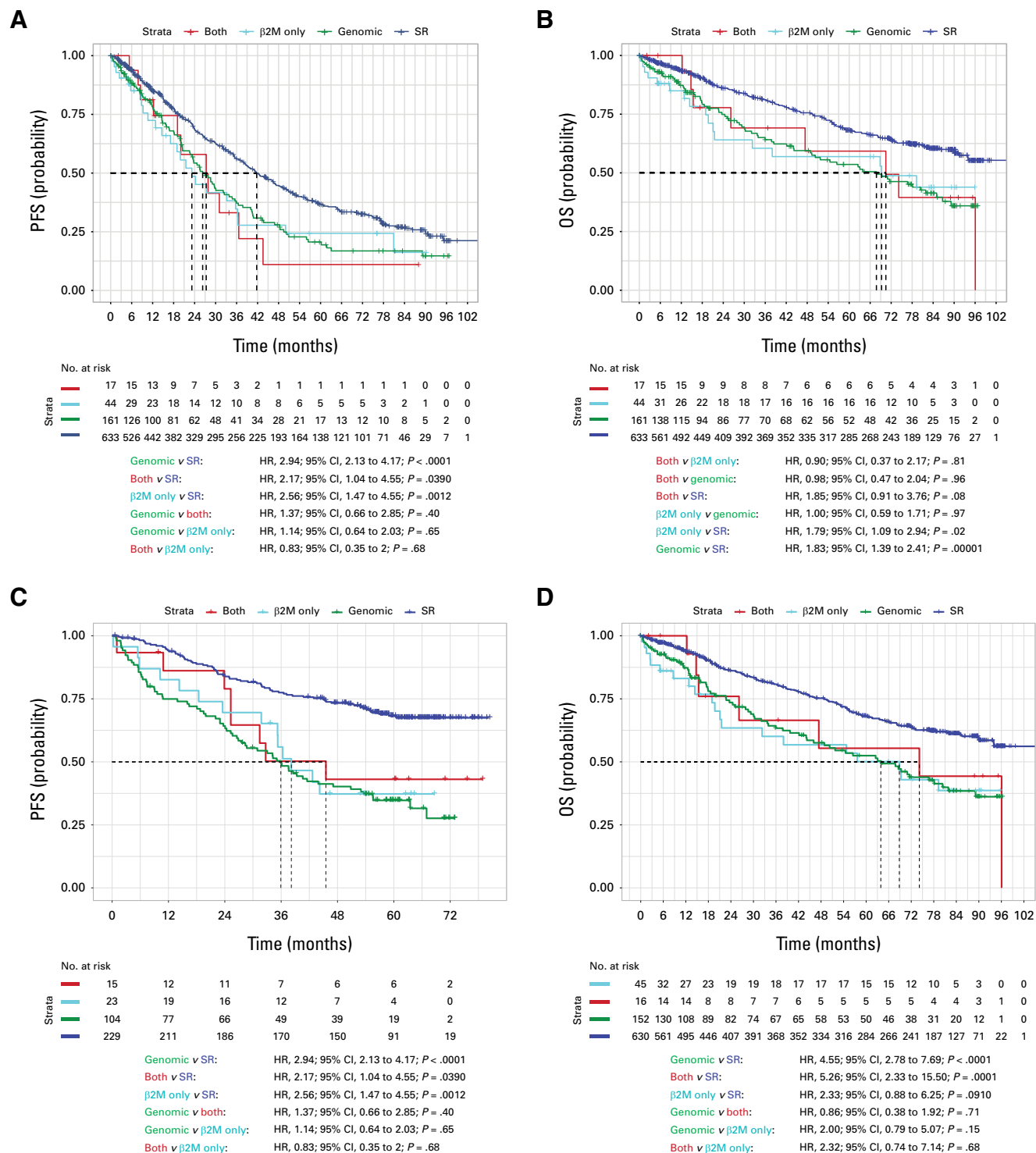


FIG 4. Prognostic impact of high β2M (≥ 5.5 mg/L) without renal failure (creatinine < 1.2 mg/dL). Prognostic impact of high β2M without renal failure in the CoMMpass/MMRF data set: Shown are the (A) PFS and (B) OS analyses of patients from the CoMMpass/MMRF data set with isolated high β2M (≥ 5.5 mg/L) without renal failure (defined as creatinine < 1.2 mg/dL) without genomic high-risk features (β2M only; cyan), high β2M along with genomic high-risk features (both; red), genomic high-risk features without high β2M (genomic; green), and SR (blue). The analysis was performed using all available data in the MMRF Researcher Gateway⁵⁷ for CoMMpass Interim Analysis 21. The Kaplan-Meier method was used to estimate time-to-event, and significance was determined using a two-sided log-rank test; pairwise comparison statistics are shown. Prognostic impact of high β2M without renal failure in the FORTE study: Shown are the (C) PFS and (D) OS analyses of patients from the FORTE study with isolated high β2M (≥ 5.5 mg/L) without renal failure (creatinine < 1.2 mg/dL) without genomic high-risk features (β2M only; cyan), high β2M along with genomic high-risk features (both; red), genomic high-risk features without high β2M (genomic; green), and SR (blue). The Kaplan-Meier method was used to estimate time-to-event data, and significance was determined using a two-sided (continued on following page)

FIG 4. (Continued). log-rank test; pairwise comparison statistics are shown. β 2M, β 2 microglobulin; CoMMpass; Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile; HR, hazard ratio; MMRF, Multiple Myeloma Research Foundation; OS, overall survival; PFS, progression-free survival; SR, standard-risk.

The IMS-IMWG consensus HRMM definition and the supporting rationale are summarized in Table 1 and the Data Supplement (Table S3), respectively. General considerations applicable to the IMS-IMWG consensus HRMM definition are summarized in Table 2. Some previous MM risk stratification systems are compared in the Data Supplement (Table S4).

DISCUSSION

This report outlines the 2024 IMS-IMWG Consensus Genomic Staging (CGS) of HRMM, based on available data on underlying biology and genomic/molecular features. The use of a consistent HRMM definition is an important requisite in our effort to improve outcomes for high-risk patients and allows clinicians to provide patients more realistic prognostic information. Uniform use of this definition in clinical trials will also enable better comparison of outcomes with specific therapies in high-risk patients as they are typically a subgroup embedded in all-comer trials. We hope that this data-driven consensus definition will promote the design and conduct of clinical trials focused on patients with HRMM. Finally, given the heterogeneous outcomes in MM, future myeloma therapy is likely to be risk-adapted, and this consensus definition represents an important step toward using risk-stratified therapeutic approaches in our clinics. We strongly recommend universal use of this IMS-IMWG CGS of HRMM in clinical trials going forward to ensure uniformity of high-risk patient populations across trials.

This first iteration of a genomic/molecular HRMM definition requires sequencing-based analyses. NGS-based technologies have been implemented as the standard of care in hematologic malignancies, including MDS and AML.²⁶⁻²⁸ The Panel recognizes that sequencing-based tools may not be immediately available universally across world regions or practice settings; in such instances, the proposed HRMM definition can still be used in the interim with available elements since mutational data pertain to a very small subset of patients in this system.

The Panel noted that rather than uniform reporting of details for individual cytogenetic abnormalities assessed via FISH in clinical trials, reporting composite risk categories that combine features adds to the challenge of heterogeneity in data collection and analyses. Moreover, CCF cutoff values for defining high-risk are not always reported. The Panel recommended that data pertaining to individual CAs and thresholds for defining high-risk should be above the false-positivity rate for the assay used and that analytical

methods, frequencies, and thresholds for CAs be reported mandatorily for MM studies henceforth.

The current approach does not integrate specific molecular drivers, but rather a set of abnormalities, all of which define a clinical phenotype characterized by short response duration, early development of multidrug resistance, and relatively short survival. It is important to differentiate risk stratification from molecular classification as these concepts guide different therapeutic approaches; while HRMM will require aggressive management, molecular classification will guide the use of molecularly/genomically guided therapies for specific patients. For instance, identification of t(11;14), a molecular classifier, can guide selection of venetoclax in patients with RRMM.⁸²

Rare abnormalities, such as t(14;16), may be under-represented even in larger data sets, making it difficult to estimate their individual contributions to prognosis at present. Therefore, the Panel considered it more prudent to assess their prognostic contributions against the background of co-occurring CAs, such as 1q+ or del(1p32), at this time. Moving forward, the ability of newer therapies to overcome the poor prognostic impact of a single HRCA and the impact of ≥ 2 HRCAs need to be re-evaluated.

The IMS Panel reviewed other prognostic factors that may help refine future HRMM definitions when additional data become available or technologies are more readily accessible/applicable in routine practice. These include GEP signatures—while GEP signatures (eg, SKY92 or UAMS70) remain significant independent prognostic factors and can help identify high-risk patients who cannot be sufficiently categorized based on any of the DNA-based diagnostic tools

TABLE 1. Summary of the International Myeloma Society-International Myeloma Working Group Consensus Genomic Staging of HRMM

Criteria for HRMM
del(17p) ^a and/or <i>TP53</i> mutation ^b
One of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with 1q+ and/or del(1p32)
Monoallelic del(1p32) along with 1q+, or biallelic del(1p32) ^b
High β 2M (≥ 5.5 mg/L) with normal creatinine (< 1.2 mg/dL)

Abbreviations: 1q+, gain (three copies) or amplification (≥ 4 copies) of the long arm of chromosome 1; β 2M, β 2 microglobulin; CCF, cancer clonal fraction; HRMM, high-risk multiple myeloma; NGS, next-generation sequencing.

^aCCF $\geq 20\%$, by analyses conducted on CD138-positive/purified cells.

^bAssessed using an NGS-based method.

TABLE 2. General Considerations for the IMS Consensus HRMM Definition

Feature/Method	Consideration
NGS-based methods	WGS/targeted NGS should now be used for broad molecular profiling, similar to other hematologic malignancies
iFISH	iFISH is not sufficient to fully risk stratify patients with MM If performed, selected/enriched plasma cells, with a $\geq 70\%$ purity, should be used Percentage of cells with abnormalities reported should be corrected based on the purity of the sample Mutations in p53 and a small deletion in 1p require sequencing, and iFISH alone is no longer sufficient to detect these changes
Sample source/analyte	Although data suggest that the molecular profile (CAs, mutations, other genomic alterations) is spatially heterogeneous (ie, different tumor sites can have different molecular profiles or clonal distributions), currently, bone marrow should be used for assessing the molecular profile
Timing of risk assessment and risk status definition	It is important to perform risk assessment at diagnosis and at relapse Risk features should be evaluated at relapse and before participation in a clinical trial The risk status at relapse supplants risk status at diagnosis, unless the patient was deemed high-risk at diagnosis

Abbreviations: CA, chromosomal abnormality; GEP, gene expression profiling; HRMM, high-risk multiple myeloma; iFISH, interphase fluorescence in situ hybridization; IMS, International Myeloma Society; MM, multiple myeloma; NGS, next-generation sequencing; WGS, whole-genome sequencing.

currently available, there are currently limitations to their use in routine practice.^{23,83–85} The Panel supports continued exploration, wherein feasible, of validated GEP signatures with prognostic impact, and revisiting their role in future classification efforts. Similarly, further exploration of circulating tumor (CTC)/plasma cells is warranted to determine the prognostic significance of CTCs independent of CAs/other genomic features. The presence of $\geq 0.01\%$ CTCs was reported as a potential new risk factor when integrated with other risk factors.¹⁶ Extramedullary disease (EMD), both de novo and secondary confirmed EMD, prognosticates poor outcomes at presentation and relapse.^{86–88} The size, number, and metabolic features of focal lesions may also affect prognosis.⁸⁹ Although EMD is not included in this iteration of HRMM, patients with EMD warrant further investigation, and if biopsied and/or feasible, EMD-derived tissue may be assessed for high-risk features. Other potential high-risk features reviewed by the Panel included serum ferritin, alterations affecting specific genes (*BRAF*, *MYC*), alterations in multiple genes/loci queried using targeted sequencing panels and translocation profiling, lactate dehydrogenase, platelet counts, and serum albumin, some of which have been considered/included in previous risk stratification schemes.^{11,12,90–92} The Panel identified potential high-risk prognosticators, including t(11;14) with amp(1q), t(8;14), hyper-APOBEC signature, biallelic inactivation of tumor suppressor genes (besides *TP53*), and chromothripsis, as features requiring further future exploration and validation.^{93,94}

In patients with renal disease, the consensus was to use all other proposed genetic risk features to determine risk. It is possible that within the subset of patients with standard-risk cytogenetics and renal dysfunction, there may be a rare patient with inherently higher $\beta 2M$, further aggravated by

renal dysfunction. However, currently, it is not feasible to identify those very rare cases with renal failure who might have truly increased $\beta 2M$ without the influence of renal dysfunction. Risk determination in these rare cases will require further consideration in the future as more data become available. In addition, as granular data on high tumor burden or M-protein levels are currently not available, these parameters were not considered along with high $\beta 2M$ in the current analysis.

Risk stratification across the disease/treatment continuum is important as high-risk features can be accrued at relapse; therefore, risk re-evaluation based on this genomic definition should be considered beyond the NDMM population, at first relapse or clinical trial enrollment. Current recommendations were mainly driven by OS. The Panel considers the patient's risk at relapse/re-evaluation to be their risk status, unless they were identified as high-risk at diagnosis, in which case the high-risk designation prevails.

The Panel recognizes that the CGS of HRMM may need to be revisited in the future as new data emerge with new treatments and technologies.

In conclusion, to our knowledge, the IMS-IMWG CGS of HRMM is the first consensus definition based on genomic high-risk features in the context of contemporary MM therapies. This definition captured a subset of patients, around 20%, with poor prognosis despite receiving treatment with currently established MM therapies, including triplet and quadruplet combinations and post-transplant maintenance. The Panel recommends the use of this HRMM definition henceforth in all clinical trials and in routine practice.

AFFILIATIONS

¹Unité de Genomique du Myélome, Institut National de la Santé et de la Recherche Médicale, University Cancer Center of Toulouse, Toulouse, France

²Perlmutter Cancer Center, NYU Langone Health, New York, NY

³Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

⁴Division of Hematology, AOU Città della Salute e della Scienza di Torino, Torino, Italy

⁵University of Torino and Department of Molecular Biotechnology and Health Sciences, Torino, Italy

⁶Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom

⁷Department of Haematology, The Royal Marsden Hospital, London, United Kingdom

⁸Department of Medicine V, Heidelberg Myeloma Center, University Hospital and Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany

⁹Departamento de Hematología, Hospital Universitario de Salamanca, (HUSA/IBSAL), Centro de Investigación del Cáncer-IBMCC (CSIC/USAL), CIBERONC, Salamanca, Spain

¹⁰Cancer Center Clínica Universidad de Navarra (CCUN), Centro de Investigación Médica Aplicada (CIMA LAB Diagnostics), IDISNA, CIBERONC, Pamplona, Spain

¹¹Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Canada

¹²Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

¹³Division of Myeloma, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

¹⁴Division of Hematology and Oncology, School of Medicine, Melvin and Bren Simon Comprehensive Cancer Center, Indiana University, Indianapolis, IN

¹⁵Division of Hematology and Medical Oncology, Joan and Sanford I. Weill Department of Medicine, Sandra & Edward Meyer Cancer Center, Weill Cornell Medicine, New York, NY

¹⁶Division of Hematology-Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

¹⁷Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

¹⁸Department of Medicine—Myeloma, Roswell Park Comprehensive Cancer Center, Buffalo, NY

¹⁹Department of Medical Oncology, National University Cancer Institute, and Cancer Science Institute of Singapore, National University of Singapore, Singapore, Singapore

²⁰Integrated Cancer Genomics Division, Translational Genomics Research Institute, Phoenix, AZ

²¹Hospital 12 de Octubre, i+12, School of Medicine Universidad Complutense, CNIO, Madrid, Spain

²²Dana-Farber Cancer Institute, Boston, MA

²³Hematology Department, University Hospital Hôtel-Dieu, Nantes, France

²⁴Department of Internal Medicine, Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR

²⁵Department of Hematology/Oncology, Center for Multiple Myeloma, Harvard Medical School, Massachusetts General Hospital, Boston, MA

²⁶Dipartimento di Scienze Mediche e Chirurgiche, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università di Bologna, Bologna, Italy

²⁷Department of Oncology and Onco-Hematology, University of Milan and Hematology Section Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

²⁸Department of Medical Oncology, Center for Early Detection and Interception of Blood Cancers, Dana-Farber Cancer Institute, Boston, MA

²⁹Emory University School of Medicine, Atlanta, GA

³⁰Icahn School of Medicine at Mount Sinai, New York, NY

³¹Department of Haematology, The Alfred Hospital and Monash University, Melbourne, Australia

³²Department of Medicine, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

³³Winship Cancer Institute, Emory University, Atlanta, GA

³⁴Department of Hematology, EMN/Erasmus MC Cancer Institute, Rotterdam, the Netherlands

³⁵Division of Hematology, Mayo Clinic, Phoenix, AZ

³⁶Departments of Lymphoma/Myeloma and Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

³⁷Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

³⁸Cancer Center Clínica Universidad de Navarra (CCUN), CIMA, CIBERONC, IDISNA, Pamplona, Spain

³⁹Department of Medical Oncology, Jerome Lipper Multiple Myeloma Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

⁴⁰Hematology and Cell Therapy and Program of Hematology-Oncology CIMA, Clínica Universidad de Navarra, IDISNA, CIBERONC, Pamplona, Spain

⁴¹Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

CORRESPONDING AUTHOR

Nikhil C. Munshi, MD; e-mail: nikhil_munshi@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Hervé Avet-Loiseau, Faith E. Davies, Mehmet K. Samur, Mattia D'Agostino, Katja Weisel, Brian A. Walker, Mark Bustoros, A. Keith Stewart, Saad Z. Usmani, Wee Joo Chng, Joaquin Martinez-Lopez, Adam S. Sperling, Irene M. Ghobrial, Nizar J. Bahlis, Sagar Lonial, Pieter Sonneveld, Leif Bergsagel, Robert Z. Orlowski, Gareth Morgan, María Victoria Mateos, S. Vincent Rajkumar, Kenneth C. Anderson, Philippe Moreau, Shaji Kumar, Felipe Prósper, Nikhil C. Munshi

Provision of study materials or patients: Hervé Avet-Loiseau, Martin F. Kaiser, Marc S. Raab, Niels Weinhold, Saad Z. Usmani, Jonathan J. Keats, Joaquin Martinez-Lopez, Madhav V. Dhodapkar, Pieter Sonneveld, Gareth Morgan, María Victoria Mateos

Collection and assembly of data: Faith E. Davies, Mehmet K. Samur, Mattia D'Agostino, Martin F. Kaiser, Marc S. Raab, Niels Weinhold, Norma C. Gutierrez, Brian A. Walker, Mark Bustoros, Saad Z. Usmani, Jonathan J. Keats, Joaquin Martinez-Lopez, Irene M. Ghobrial, Pieter Sonneveld, Leif Bergsagel, Robert Z. Orlowski, Gareth Morgan, María Victoria Mateos, Kenneth C. Anderson, Shaji Kumar, Felipe Prósper, Nikhil C. Munshi

Data analysis and interpretation: Hervé Avet-Loiseau, Faith E. Davies, Mehmet K. Samur, Jill Corre, Mattia D'Agostino, Martin F. Kaiser, Marc S. Raab, Norma C. Gutierrez, Bruno Paiva, Paola Neri, Katja Weisel, Francesco Maura, Brian A. Walker, Mark Bustoros, A. Keith Stewart, Saad Z. Usmani, Jens Hillengass, Jonathan J. Keats, Joaquin Martinez-Lopez, Cyrille Touzeau, Fenghuang Zhan, Noopur S. Raje, Michele Cavo,

Niccolò Bolli, Madhav V. Dhodapkar, Sundar Jagannath, Andrew Spencer, Samir Parekh, Nizar J. Bahlis, Sagar Lonial, Pieter Sonneveld, Leif Bergsagel, Robert Z. Orlowski, Gareth Morgan, María Victoria Mateos, Jesus F. San Miguel, Kenneth C. Anderson, Philippe Moreau, Shaji Kumar, Nikhil C. Munshi

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma

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Faith E. Davies

Employment: University of Arkansas for Medical Sciences, NYU Langone Medical Center

Honoraria: Takeda, Bristol Myers Squibb, AbbVie, Janssen Oncology, GlaxoSmithKline, Sanofi, Pfizer, Regeneron

Consulting or Advisory Role: Takeda, Bristol Myers Squibb, Janssen Oncology, Sanofi, GlaxoSmithKline, AbbVie, Pfizer, Regeneron

Mehmet K. Samur

Consulting or Advisory Role: AbbVie, K36, NCGM

Jill Corre

Honoraria: Amgen, Celgene, Janssen, Sanofi, Takeda, Bristol Myers Squibb/Celgene, Pfizer, AbbVie

Consulting or Advisory Role: Celgene, Sanofi

Travel, Accommodations, Expenses: Sanofi, Janssen

Mattia D'Agostino

Honoraria: Sanofi, GlaxoSmithKline, Janssen

Consulting or Advisory Role: Sanofi, GlaxoSmithKline, Bristol Myers Squibb/Celgene, Adaptive Biotechnologies

Research Funding: Janssen (Inst)

Martin F. Kaiser

Honoraria: Janssen Oncology, Sanofi

Consulting or Advisory Role: Janssen Oncology, Bristol Myers Squibb, AbbVie, GlaxoSmithKline, Pfizer, Regeneron, Poolbeg, Sanofi, Roche

Research Funding: Celgene (Inst)

Marc S. Raab

Honoraria: AbbVie, Bristol Myers Squibb/Celgene, Janssen, Sanofi

Consulting or Advisory Role: Bristol Myers Squibb/Celgene (Inst), Amgen (Inst), GlaxoSmithKline (Inst), Janssen (Inst), Sanofi (Inst), Pfizer (Inst)

Research Funding: Bristol Myers Squibb/Celgene (Inst), Janssen (Inst), Sanofi (Inst)

Travel, Accommodations, Expenses: AbbVie, Bristol Myers Squibb/Celgene, Amgen, Janssen, Sanofi, Pfizer

Niels Weinhold

Honoraria: GlaxoSmithKline

Consulting or Advisory Role: Sanofi

Research Funding: Celgene/Bristol Myers Squibb

Norma C. Gutierrez

Honoraria: Amgen, Sanofi, Johnson & Johnson/Janssen

Travel, Accommodations, Expenses: AbbVie, Kite, a Gilead company

Bruno Paiva

Honoraria: Sanofi, Roche/Genentech, Adaptive Biotechnologies, GlaxoSmithKline, Bristol Myers Squibb/Celgene, Johnson & Johnson/Janssen, Becton Dickinson, The Binding Site

Consulting or Advisory Role: Sanofi, Bristol Myers Squibb/Celgene, Johnson & Johnson/Janssen, Roche/Genentech

Research Funding: Sanofi (Inst), Roche/Genentech (Inst),

GlaxoSmithKline (Inst), BeiGene (Inst), Bristol Myers Squibb/Celgene

Travel, Accommodations, Expenses: Bristol Myers Squibb/Celgene

Paola Neri

Honoraria: BMS, Sanofi, Janssen, Pfizer, Amgen

Consulting or Advisory Role: BMS, Sanofi, Janssen, Pfizer

Katja Weisel

Honoraria: Amgen, Bristol Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Karyopharm Therapeutics, Takeda, Sanofi, AbbVie, Novartis, Pfizer, Celgene, Janssen (Inst), Oncopeptides, Roche, Stemline Therapeutics, AstraZeneca, BeiGene

Consulting or Advisory Role: Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Karyopharm Therapeutics, Sanofi,

Takeda, Oncopeptides, Roche, Menarini, Regeneron, AbbVie, BeiGene

Research Funding: Amgen (Inst), Celgene (Inst), Sanofi (Inst), Janssen-Cilag (Inst), Bristol Myers Squibb/Celgene (Inst), GlaxoSmithKline (Inst), AbbVie (Inst)

Travel, Accommodations, Expenses: Amgen, Celgene, Bristol Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Takeda, Menarini

Francesco Maura

Honoraria: Sanofi, Medidata

Brian A. Walker

Honoraria: MMRF, International Myeloma Society

Consulting or Advisory Role: AbbVie, Multiple Myeloma Research Foundation

Speakers' Bureau: Sanofi

Research Funding: Genentech, Bristol Myers Squibb/Celgene

Mark Bustoros

Honoraria: Takeda, DAVA Oncology, Janssen Oncology, Bristol Myers Squibb/Celgene, Karyopharm Therapeutics, Menarini Silicon Biosystems, Sanofi

Consulting or Advisory Role: Takeda, Janssen Oncology, Bristol Myers Squibb/Celgene

Travel, Accommodations, Expenses: Takeda, DAVA Oncology, Bristol Myers Squibb (Mexico)

A. Keith Stewart**Leadership:** Genomics England**Stock and Other Ownership Interests:** Tempus AI**Consulting or Advisory Role:** Janssen, Sanofi, GlaxoSmithKline, Skyline Diagnostics, Pfizer**Research Funding:** Janssen, Regeneron**Patents, Royalties, Other Intellectual Property:** Patents on PIKFYVE inhibitors**Other Relationship:** PIKSci INC**Saad Z. Usmani****Consulting or Advisory Role:** Janssen Oncology, GlaxoSmithKline, AbbVie, Genentech, Bristol Myers Squibb/Celgene, Regeneron, Oricell Therapeutics, AstraZeneca**Research Funding:** Janssen Oncology, Bristol Myers Squibb, GlaxoSmithKline, Gracell Therapeutics, Gilead Sciences, K36 Therapeutics**Jens Hillengass****Employment:** Roswell Park Cancer Institute**Honoraria:** Janssen Biotech, BeiGene, Targeted Oncology, IntegrityCE, Cancer Network**Consulting or Advisory Role:** Janssen Biotech, Regeneron, Sebia, Prothena, Angitia, Regeneron**Research Funding:** Celgene (Inst), GlaxoSmithKline (Inst), Bristol Myers Squibb/Celgene (Inst)**Wee Joo Chng****Honoraria:** Johnson and Johnson, Amgen, Celgene, Takeda, AbbVie**Research Funding:** Janssen (Inst), Celgene (Inst), Amgen (Inst)**Joaquin Martinez-Lopez****Stock and Other Ownership Interests:** Altum sequencing**Speakers' Bureau:** Novartis, Janssen-Cilag, Celgene, BMS, Incyte**Research Funding:** BMS**Adam S. Sperling****Consulting or Advisory Role:** Novartis**Cyrille Touzeau****Honoraria:** AbbVie, Amgen, Takeda, Janssen, Sanofi, Bristol Myers Squibb/Celgene, Pfizer**Consulting or Advisory Role:** Amgen, AbbVie, Takeda, Janssen, Pfizer, Bristol Myers Squibb/Celgene**Research Funding:** Sanofi (Inst)**Travel, Accommodations, Expenses:** Johnson & Johnson/Janssen, Pfizer, Sanofi**Noopur S. Raje****Consulting or Advisory Role:** Amgen, Celgene, Takeda, Bristol Myers Squibb, Merck, Janssen Oncology, Immuneel Therapeutics, Caribou Biosciences, Pfizer**Research Funding:** Bluebird Bio (Inst), Pfizer (Inst)**Michele Cavo****Honoraria:** Janssen, Sanofi, GlaxoSmithKline, Takeda, Amgen, AbbVie, Adaptive Biotechnologies, Celgene/Bristol Myers Squibb, Karyopharm Therapeutics, Menarini Group**Consulting or Advisory Role:** Amgen, AbbVie, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm Therapeutics, Menarini Stemline, Sanofi, and Karyopharm Therapeutics**Speakers' Bureau:** Janssen, Celgene/Bristol Myers Squibb**Niccolò Bolli****Honoraria:** Janssen, GlaxoSmithKline, Pfizer, Jazz Pharmaceuticals, Amgen, Sanofi, Menarini, Oncopeptides**Consulting or Advisory Role:** Pfizer, Takeda, Janssen**Research Funding:** Janssen**Travel, Accommodations, Expenses:** Janssen**Irene M. Ghobrial****Employment:** Disc Medicine (I)**Leadership:** Disc Medicine (I)**Stock and Other Ownership Interests:** Predicta Biosciences, Disc Medicine (I)**Honoraria:** Bristol Myers Squibb, Takeda, Amgen, Janssen, Adaptive Biotechnologies, Sanofi, Vor Biopharma, Menarini Silicon Biosystems, Regeneron, Curio Science**Consulting or Advisory Role:** Bristol Myers Squibb, Novartis, Amgen, Takeda, Sanofi, GlaxoSmithKline, Adaptive Biotechnologies, Janssen, Pfizer, 10× Genomics, AbbVie, The Binding Site, Menarini Silicon Biosystems, Regeneron, Aptitude Health, Standard Biotech**Travel, Accommodations, Expenses:** Bristol Myers Squibb, Novartis, Onyx, Millennium, Celgene, Takeda, Janssen Oncology**Madhav V. Dhodapkar****Consulting or Advisory Role:** Roche/Genentech, Lava Therapeutics, Janssen Oncology, Sanofi**Sundar Jagannath****Consulting or Advisory Role:** Bristol Myers Squibb, Janssen, Legend Biotech, Takeda, Sanofi, Regeneron, Caribou Biosciences, Poseida, Genmab, GlaxoSmithKline**Travel, Accommodations, Expenses:** Bristol Myers Squibb, Janssen Biotech, Regeneron, International Myeloma Society, Poseida**Andrew Spencer****Honoraria:** Janssen-Cilag, Pfizer, BMS, Antengene, Thermofisher Scientific Biomarkers, Genentech/Roche**Consulting or Advisory Role:** Janssen-Cilag, GlaxoSmithKline, Haemalogix, Pfizer, Antengene, Rheumagen, Celltrion**Speakers' Bureau:** Janssen-Cilag, Thermofisher Scientific Biomarkers, Pfizer**Research Funding:** Janssen-Cilag, BMS, Sanofi, Antengene**Samir Parekh****Employment:** Mount Sinai Health System**Consulting or Advisory Role:** Regeneron, Genentech/Roche, GRAIL, Poseida Therapeutics**Research Funding:** Celgene/BMS Corporation, Caribou Biosciences, GRAIL, imCORE, Poseida Therapeutics**Nizar J. Bahlis****Honoraria:** Celgene, Janssen, AbbVie, Amgen, Sanofi, Takeda, Karyopharm Therapeutics, GlaxoSmithKline, Genentech/Roche**Consulting or Advisory Role:** Janssen, Celgene, Amgen, Sanofi, Takeda, Pfizer, Karyopharm Therapeutics**Research Funding:** Janssen (Inst), Celgene (Inst), Pfizer (Inst)

Sagar Lonial**Stock and Other Ownership Interests:** TG Therapeutics**Consulting or Advisory Role:** Celgene, Bristol Myers Squibb, Janssen Oncology, Novartis, GlaxoSmithKline, Amgen, AbbVie, Takeda, Merck, Sanofi, Pfizer, Regeneron**Research Funding:** Celgene, Bristol Myers Squibb, Takeda, Janssen Oncology, Novartis**Other Relationship:** TG Therapeutics**Pieter Sonneveld****Leadership:** European Myeloma Network**Consulting or Advisory Role:** Celgene, Janssen, Amgen, Karyopharm Therapeutics, CARsgen Therapeutics**Research Funding:** Janssen (Inst), Amgen (Inst), Skyline Diagnostics (Inst), BMS (Inst)**Leif Bergsagel****Consulting or Advisory Role:** CellCentric, AbbVie, Omeros, Pfizer**Research Funding:** Pfizer (I), Celgene, Sanofi**Patents, Royalties, Other Intellectual Property:** Mouse model of multiple myeloma**Open Payments Link:** <https://openpaymentsdata.cms.gov/physician/59882>**Robert Z. Orlowski****Stock and Other Ownership Interests:** Asyria Therapeutics, Inc**Consulting or Advisory Role:** Bristol Myers Squibb, Janssen, Sanofi, Takeda, Regeneron, GlaxoSmithKline, BioTheryX, Meridian Therapeutics, Monte Rosa Therapeutics, IASO Biotherapeutics, Lytixa Therapeutics**Research Funding:** Heidelberg Pharma (Inst), Asyria Therapeutics, Inc (Inst), CARsgen Therapeutics (Inst), Sanofi/Aventis (Inst), Exelixis (Inst), Takeda (Inst), Janssen Biotech (Inst), Celgene/Bristol Myers Squibb (Inst)**Patents, Royalties, Other Intellectual Property:** Asyria Therapeutics, Inc**Gareth Morgan****Honoraria:** BMS, Janssen, Genentech, Sanofi, Takeda**Consulting or Advisory Role:** Takeda, GlaxoSmithKline**Travel, Accommodations, Expenses:** BMS, Janssen**María Victoria Mateos**This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.**Honoraria:** Janssen-Cilag, Celgene, Amgen, GlaxoSmithKline, AbbVie/Genentech, Sanofi, Pfizer**Consulting or Advisory Role:** Takeda, Janssen-Cilag, Celgene, Amgen, AbbVie, GlaxoSmithKline, Pfizer, Regeneron, Roche/Genentech, Stemline Therapeutics, Kite, a Gilead company**S. Vincent Rajkumar****Honoraria:** Research to Practice, Medscape**Patents, Royalties, Other Intellectual Property:** Authorship Royalties from Up To Date**Jesus F. San Miguel****Consulting or Advisory Role:** Amgen (Inst), Celgene (Inst), Takeda (Inst), Bristol Myers Squibb (Inst), MSD (Inst), Novartis (Inst), Sanofi (Inst), Janssen (Inst), Roche (Inst), AbbVie (Inst), GlaxoSmithKline (Inst), Karyopharm Therapeutics (Inst), Secura Bio (Inst), Regeneron (Inst), Haemalogix (Inst), Pfizer (Inst), Kite, a Gilead company (Inst), Dr. Reddy's (Inst)**Kenneth C. Anderson****Leadership:** C4 Therapeutics, Starton Therapeutics, Window Therapeutics, Dynamic Cell Therapies, Predicta Biosciences**Stock and Other Ownership Interests:** C4 Therapeutics, OncoPep, Raqia, NextRNA, STARTON Therapeutics, Window Therapeutics, Predicta Biosciences**Consulting or Advisory Role:** Janssen Oncology, Pfizer, AstraZeneca, Genentech/Roche**Patents, Royalties, Other Intellectual Property:** C4 Therapeutics, OncoPep**Philippe Moreau**This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.**Honoraria:** Celgene, Janssen-Cilag, Amgen, GlaxoSmithKline, AbbVie, Sanofi, Pfizer**Consulting or Advisory Role:** Celgene, Janssen, Amgen, GlaxoSmithKline, Sanofi, AbbVie, Pfizer**Shaji Kumar****Consulting or Advisory Role:** Takeda (Inst), Janssen Oncology (Inst), Genentech/Roche (Inst), AbbVie (Inst), Bristol Myers Squibb/Celgene (Inst), Pfizer (Inst), Regeneron (Inst), Sanofi (Inst), K36 (Inst)**Research Funding:** Takeda (Inst), AbbVie (Inst), Novartis (Inst), Sanofi (Inst), Janssen Oncology (Inst), MedImmune (Inst), Roche/Genentech (Inst), CARsgen Therapeutics (Inst), Allogene Therapeutics (Inst), GlaxoSmithKline (Inst), Regeneron (Inst), Bristol Myers Squibb/Celgene (Inst)**Travel, Accommodations, Expenses:** AbbVie, Pfizer, Janssen, BeiGene**Felipe Prósper****Consulting or Advisory Role:** Oryzon Genomics, Mission Bio**Travel, Accommodations, Expenses:** Johnson and Johnson**Nikhil C. Munshi****Stock and Other Ownership Interests:** OncoPep, C4 Therapeutics, Raqia**Consulting or Advisory Role:** Janssen, OncoPep, AbbVie, Adaptive Biotechnologies, BeiGene, Karyopharm Therapeutics, Bristol Myers Squibb, Bristol Myers Squibb/Celgene, Legend Biotech, Novartis, Sebia, Pfizer, GlaxoSmithKline, Genentech, Recordati**Patents, Royalties, Other Intellectual Property:** OncoPep

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