Navigating High-Risk and Ultrahigh-Risk Multiple Myeloma: Challenges and Emerging Strategies

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DOI https://doi.org/10.1200/EDBK_433520

Accepted March 29, 2024
Published May 21, 2024

Am Soc Clin Oncol Educ Book 44:e433520

OVERVIEW

Despite significant improvement in the outcomes of patients with newly diagnosed multiple myeloma (NDMM) with novel therapies, there is still an underserved high-risk (HR) population that experiences early disease progression and death. With the median survival crossing 10 years, we defined ultrahigh-risk (uHR)MM as MM leading to death within 24-36 months of diagnosis and HRMM as MM leading to death within 36-60 months. Several features have emerged as markers of uHRMM: the co-occurrence of two or more high-risk cytogenetic abnormalities, extramedullary disease, plasma cell leukemia and a high-risk gene expression profiling signature. The heterogeneous risk definition across trials, the few trials available designed for HR patients, and the small HR subgroups in all-comers trials make it difficult to generate recommendations with high levels of evidence. Nevertheless, regardless of treatment administered, several studies consistently showed that achieving and maintaining measurable residual disease negativity is now considered the main factor able to mitigate the adverse prognosis related to baseline features. For fit patients with HR transplant-eligible (TE) NDMM, quadruplet induction/consolidation treatment with anti-CD38 monoclonal antibodies, immunomodulatory agents, proteasome inhibitors and dexamethasone, and autologous stem-cell transplant and maintenance with, if available, at least a doublet combination could be considered the option of choice. For non-TE NDMM, considering the recent data generated and carefully reviewing those upcoming, quadruplet treatment consisting of anti-CD38 monoclonal antibodies, immunomodulatory agents, proteasome inhibitors, and dexamethasone should also be considered. Future trials integrating BCMA-directed novel generation immunotherapies hold great potential for further advancing the treatment landscape in all NDMM patients with HR disease.

HOW DO WE DEFINE HIGH-RISK AND ULTRAHIGH-RISK MULTIPLE MYELOMA?

Therapeutic advances have led to unprecedented survival outcomes in multiple myeloma (MM), and young newly diagnosed patients now experience median overall survival (OS) exceeding 10 years.[1] However, novel therapies have disproportionately benefited standard-risk patients, and an underserved high-risk population continues to experience early disease progression and death.[2] Herein, we will define ultrahigh-risk (uHR)MM as MM leading to death within 24-36 months of diagnosis and high-risk (HR)MM as MM leading to death within 36-60 months.[3] Although large clinical databases, sophisticated genomic interrogation, and collaborative efforts have identified myriad prognostic factors, succinct, practical, and clinically meaningful definitions for HR and uHRMM remain elusive. Existing risk models classify patients into large heterogenous categories that lack granularity at the individual level, produce discordant results, and fail to identify many patients destined for early relapse (ER). Since the concept of uHRMM was introduced over a decade ago, several defining features have emerged: the co-occurrence of two or more high-risk cytogenetic abnormalities (HRCAs, multihit MM), extramedullary disease (EMD), plasma cell leukemia (PCL), and a high-risk gene expression profiling (GEP) signature. As the definition of uHRMM coalesces around these features, the boundaries of HRMM have shifted to fill the space created between uHR and standard-risk disease. We review the established and emerging features of HR and uHRMM and discuss future challenges in the era of immunotherapy.

Current Definitions

Numerous validated risk stratification systems exist but are limited by interclassification discordance, poor specificity, and indifference to multihit MM, Table 1. For instance, using the revised international staging system (R-ISS), 73% of del(17p) and 52% of biallelic *TP53* patients are classified as intermediate-risk.[16] Similarly, the International Myeloma Working Group (IMWG) consensus defines 20% of newly diagnosed (ND)MM as HR with a median OS of 2 years,[6]

PRACTICAL APPLICATIONS

- Multihit myeloma (the co-occurrence of two or more high-risk cytogenetic abnormalities), extramedullary disease, plasma cell leukemia, and a high-risk gene expression profiling signature have emerged as defining features of ultrahigh-risk multiple myeloma (uHRMM).
- Future risk models which use whole-genome sequencing, immune function assays, and computer models to integrate clinical, genetic, and treatment information hold promise to improve the detection of functional high-risk patients at diagnosis.
- Up-front treatment for newly diagnosed transplant-eligible multiple myeloma includes quadruplet pre-transplant induction and post-transplant consolidation with anti-CD38 monoclonal antibodies plus proteasome inhibitor and immunomodulatory agents, followed by continuous treatment.
- Achievement of measurable residual disease negativity is the main factor able to mitigate the adverse prognosis related to baseline features.
- For transplant-noneligible patients, first-line quadruplet treatments are expected to provide the best treatment outcome; however, they have to be even more carefully balanced between efficacy and potential toxicity.

whereas the R-ISS, second-revision(R2-)ISS, and SKY92 classify 10%, 9%, and 20% as HR with the median OS of 3.6, 2.8, and 2 years.[4,5,9,10] Lastly, many biological HR patients are misclassified; for example, 5%-10% of low-risk R-ISS patients relapse within 12 months and experience OS under 3 years.[4]

PCL and EMD

Plasma cell independence from the bone marrow microenvironment represents a major evolutionary step in disease biology, and accordingly, it defines the disease entities of PCL and EMD. The revised IMWG definition of PCL requires ≥5% circulating plasma cells (CTCs). However, the spectrum of risk exists below this threshold. It has been recognized with sensitive flow cytometric assays, ranging from low risk with no detectable CTCs to HR with many CTCs.[17] The presence of 2%-5% CTCs mimics the outcomes of pPCL, independent of HRCAs, lactate dehydrogenase (LDH), and ISS stage, and similarly, in the FORTE trial, ≥0.07% CTCs were identified as an optimal cutoff predictive of shorter progression-free survival (PFS) and OS.[18,19] Conversely, the absence of CTCs defines an ultralow-risk group; patients with transplant-eligible (TE) newly diagnosed MM (NDMM) without CTCs experience a 7-year PFS of 90% and OS of 97%.[20] How to integrate CTC detection into other risk stratification models remains to be determined, but CTC assessment at diagnosis is informative and practical.

Extraosseous EMD arises in visceral and soft tissues from the hematogenous spread of MM; it affects 2%-4.5% of NDMM and is associated with HRCAs, resistance to therapy, and a worse prognosis at any point in the disease course.[21-23] In a Mayo Clinic series, the median PFS was 1 year and the OS was 3.6 years for de novo EMD.[24] With improving survival, the burden of EMD with relapse has increased, the median time to the development of secondary EMD is 2 years, and EMD frequency increases sharply after ≥3 lines of therapy.[25] Few therapies effectively treat EMD, and standard immunomodulatory-PI-based regimens and immunotherapies have modest efficacy. For example, idecabtagene vicleucel and ciltacabtagene autoleucel achieved the median PFS of only 4.9 and 8.1 months, respectively, for EMD, albeit in the relapsed refractory patients.[26,27]

Genetics and Multihit MM

Translocations involving the immunoglobulin heavy chain locus on 14q32 and trisomies occur in 45% and 55% of MM, respectively; these primary cytogenetic abnormalities are established at the monoclonal gammopathy of undetermined significance stage to produce a dominant clone and are universally present within the MM cells of an individual. Secondary cytogenetic abnormalities, such as 1q gain and deletion 17p, are subsequently acquired to produce a diverse subclonal disease. Important HRCAs are summarized in Table 2.

As the low proliferation of MM cells impedes karyotyping, cytogenetic abnormalities are generally detected using interphase fluorescence in situ hybridization (FISH).[28] However, historical variations in plasma cell enrichment methods, probe selection, and cutoff values produced substantial differences in the prognostic significance attributed to HRCAs. The co-occurrence of HRCAs has been recognized in recent years, explaining some of the observed past heterogeneity.[29-33]

Multihit MM affects 14%-30% of NDMM; a meta-analysis of over 5,000 trial patients showed that multihit status produces significantly worse OS and PFS compared with single-hit; OS hazard ratio 2.97 (95% CI, 2.37 to 3.71) versus 1.87 (95% CI, 1.60 to 2.19) and PFS hazard ratio 2.18 (95% CI, 1.92 to 2.47) versus 1.63 (95% CI, 1.43 to 1.86).[33] The OPTIMUM trial provides key insights into uHRMM treated with modern intensive therapy; herein, uHRMM was defined as ≥2 HRCAs, SKY92 high-risk signature, or PCL.[34] Patients received an intensive treatment program, including daratumumab, low-dose cyclophosphamide, lenalidomide, bortezomib, and dexamethasone (Dara-CRVd) before and after autologous stem-cell transplantation (ASCT). Despite this transplant-quintuplet approach, a high proportion of uHR patients

TABLE 1. Existing Risk Stratification Models in Multiple Myeloma, Their Definition of High-Risk Disease, Survival Estimates, Strengths, and Weaknesses

Model	Laboratory Features	Genetic Features	High-Risk Definition	High-Risk (%)	Median PFS/OS	Strengths	Weaknesses
R-ISS[4]	B2M, Alb, LDH	Del(17p) t(4;14) t(14;16)	ISS III and LDH >ULN OR HRCAs	10	29/43 months	Robust and widely available Generally accepted standard	Large intermediate group Some HRCAs not included
R2-ISS[5]	B2M, Alb ISS II = 1 ISS III = 1.5 LDH >ULN = 1	Del(17p) = 1 t(4;14) = 1 Gain/amp(1q) = 0.5	Score 3-5	9-10	15/34 months	Weighted score Better discriminates the large group of intermediate-risk seen with the R-ISS	Awaiting further validation in relapsed and real-world settings
IMWG[6]	B2M, Alb	Del(17p) t(4;14) Gain/amp(1q)	ISS II-III AND Del(17p) OR t(4;14)	20	NA/24 months	Easy to use	Several HRCAs not included
mSMART[7,8]	B2M, Alb, LDH	Del(17p), *TP53* inactivation t(4;14) t(14;16) t(14;20) Gain/amp(1q) High-risk GEP	R-ISS III High-risk GEP HRCAs High PC S-phase	>25	NA/NA	Encompasses most acknowledged risk factors	Broad definition
Cytogenetic prognostic index[9]	None	Del(17p) = 1.2 t(4;14) = 0.4 del(1p32) = 0.8 gain(1q) = 0.5 Trisomy 5 = −0.3 Trisomy 21 = 0.3	Prognostic index score >1	11-18	NA/26-34 months	Includes positive and negative prognostic factors with weighted score	No cytogenetic abnormality identified in 20%-25% of patients
SKY92[10]	None	High-risk signature on the basis of 92-genes	NA	20	NA/24 months	Adverse prognostic impact independent of HRCAs, extensive validation	Not routinely available
Myeloma genome project[11,12]	B2M, Alb	*TP53* inactivation Amp(1q)	ISS III and Amp(1q) OR biallelic *TP53*	6	15/21 months	Specific definition uHRMM population	Excluded patients ≥75 years *TP53* sequencing not routine
The Mayo Additive Staging System[13]	B2M, Alb ISS III = 1 LDH >ULN = 1	Del(17p) = 1 t(4;14) = 1 t(14;16) = 1 t(14;20) = 1 Gain/amp(1q) = 1	Score ≥2	31	29/54 months	Incorporates FISH abnormalities not included in R-ISS and adverse risk of co-occurring HRCAs	Large proportion of high-risk patients (31%)
Individualized risk in NDMM[14]	Age, B2M, Alb, LDH treatment	Many gain/amp(1q), del1p, *TP53* inactivation, NSD2 translocations, APOBEC signature, CN signatures	Individualized	NA	Individualized	Integrates a large number of genomic and clinical features and adjusting to treatment strategies	Cannot provide estimates for newer treatments (ie, anti-CD38 Abs) or incorporate MRD
Myeloma Prognostic Score System[15]	LDH, B2M, Alb, platelet count	Del(17p) t(4;14) t(14;16) Gain/amp(1q)	MPSS score 4-7	21.3	20/35-50 months	Weighted model which incorporates co-occurrence of HRCAs	Smaller sample size for development

Abbreviations: Abs, antibodies; Alb, albumin; amp, amplification; B2M, beta-2-microglobulin; CN, copy number; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; HRCA, high-risk cytogenetic abnormality; IMWG, International Myeloma Working Group; ISS, international staging system; LDH, lactate dehydrogenase; MPSS, myeloma prognostic score system; MRD, measurable residual disease; NA, not available; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PC, plasma cell; PFS, progression-free survival; R-ISS, Revised International Staging System; uHRMM, ultrahigh-risk multiple myeloma; ULN, upper limit of normal.

TABLE 2. Adverse Primary and Secondary Cytogenetic Abnormalities in Newly Diagnosed Multiple Myeloma

Abnormality	Genes Involved	Freq, %	Clinical Features	Second HRCAs
Primary abnormalities				
t(14;20)	*MAFb*	<3	Like t(14;16) Limited data because of rarity	Any second HRCA = 60% Del(17p) = 8% T(4;14) = 19% T(14;16) = 15%
t(14;16)	*MAF*	3-5	Innate PI resistance High *APOBEC* mutational burden High SFLCs and risk of renal failure 14% of pPCL	Gain/Amp(1q) = 69% Del(17p) = 22% *TP53*mut = 14% Del(1p) = 21%
t(4;14)	*MMSET*	10-15	Fewer lytic bone lesions Bortezomib sensitivity	Gain/Amp(1q) = 71% Del(17p) = 11%
Secondary abnormalities				
Del(17p)	*TP53*	10	Common with disease progression Advanced ISS, high LDH Clonal cancer fraction relevant	Biallelic loss = 4%
Del(1p)	*FAM46C, CDKN2C*	5-19	Advanced ISS Different FISH probes used	Biallelic loss = 3.4% Gain/Amp(1q) = 6%
Gain(1q) Amp(1q)	*CKS1B, MCL-1, IL-6R, PBX-1, SLAMF7, FcRH5, ANP32E, BCL9, PDZK1*	30 10	Increased genomic instability—*jumping 1q* Possible dosage effect: amp(1q)>>gain(1q)	

Abbreviations: Amp, amplification; FISH, fluorescence in situ hybridization; HRCA, high-risk cytogenetic abnormality; ISS, International Staging System; LDH, lactate dehydrogenase; mut, mutation; PC, plasma cell; PI, proteasome inhibitor; pPCL, primary plasma cell leukemia; SFLC, serum-free light chains.

experienced ER (<18 months), 71% of triple-hit (5 of 7), 24% of SKY92 high-risk (20 of 82), and 14% of double-hit (7 of 50) patients. Del(17p) was the only individual HRCA associated with ER, with 50% of del(17p) patients relapsing within 18 months.[34] Next-generation sequencing (NGS) techniques can assess copynumber abnormalities, recurrent mutations, and translocation events. Although a compendium of genomic abnormalities has been identified through NGS, it is rarely performed at diagnosis because the prognostic yield of many mutations is modest next to chromosomal changes.[14] A notable exception is biallelic *TP53* inactivation, which occurs in 4% of NDMM. After deletion (60%), mutation (40%) is the most common cause of *TP53* inactivation, but it is not detected by FISH, and hence, a substantial proportion of these patients are missed on routine assessment.[11]

Gene Expression Profiling

Several GEP assays, which measure the expression of genes critical to plasma cell biology, have been developed, but their widespread application has stalled because of a lack of standardization, and none are currently US Food and Drug Administration–approved. SKY92 was developed from the HOVON/GMMG-HD4 trial, and it categorizes 20% of NDMM as high-risk and has extensive trial and real-world validation.[35,36] SKY92 appears to identify a previously unrecognized high-risk group that lacks HRCA, and in the Myeloma XI trial, SKY92 recategorized 12% of patients without any HRCAs as high-risk and predicted PFS and OS regardless of the induction regimen.[37]

Functional High-Risk

Regardless of baseline risk, response to therapy remains the key determinant of outcome and many ostensibly low-risk patients are either refractory to or relapse early after first-line therapy, a testament to the disease biology that remains invisible to current assessment. Recent studies using highly effective induction therapies, including monoclonal antibodies, estimate that 7% of patients have primary refractory MM with a median OS of 4 years.[38] Similarly, ER within 12-18 months of first-line therapy affects 9%-15% of patients with MM and represents another functional high-risk (FHR) group with a median OS of 1-2 years.[39,40]

Approximately 30% of patients destined for ER lack HRCAs or traditional risk factors (ie, ISS ≥2, high BMPC%).[41,42] In these individuals, high-risk biology may result from treatment-induced selection of a highly resistant MM clone or inadequate baseline assessment. Standard evaluation, which examines a set number of biologic features, sampled from a single location at one time point, overlooks key disease features, and many known prognostic variables such as CTCs, functional imaging, and GEP are not routinely tested. In addition, the dynamic integration of genetic, biologic, and response variables exceeds human mental capacity and requires the adoption of computer learning

models. Addressing these shortcomings is fundamental to the early identification of FHR individuals who are difficult to salvage and readily cycle through treatments.

Proposed Definitions

As treatments are increasingly focused on disease biology and trials are designed specifically for high-risk subgroups, there is a need for a succinct and specific definition of uHRMM. While a revised IMWG definition is awaited, we believe that the following features are consistent with uHRMM:

- Biallelic *TP53* inactivation
- ≥2 HRCAs: del(17p), *TP53* mutation, t(4;14), t(14;16), t(14;20), gain(1q), amp(1q), del(1p32)
- High-risk GEP signature
- EMD
- ≥2% circulating PCs
- Primary refractory disease or ER (<12-months) after first-line therapy.

Owing to the emergence of uHRMM, the definition of HRMM loses precision as it captures the spectrum of diseases that exists between uHR and standard risk diseases, Figure 1, and it includes the features listed below:

- Single-hit del(17p) or *TP53* mutation
- Isolated del(1p), gain(1q), t(4;14), t(14;16), t(14;20)
- Low burden circulating PCs, ≥0.07%
- High-risk according to ISS, R-ISS, R2-ISS, mSMART, etc but not satisfying criteria for uHRMM.

INDUCTION STRATEGIES FOR NEWLY DIAGNOSED HIGH-RISK MULTIPLE MYELOMA

The expected survival of ND fit transplant-eligible (TE) patients receiving a triplet induction including a PI and an immunomodulatory drug (IMID) is now more than 10 years.[43,44] More recently, quadruplet combinations adding anti-CD38 monoclonal antibodies (MoABs) to standard triplet significantly improved the PFS: with the combination of daratumumab plus bortezomib-lenalidomide-dexamethasone (Dara-VRd) followed by ASCT, 84% of patients are currently progression-free at 4 years.[45] Despite the improvement in PFS in the overall population, and an intensive treatment approach, the outcome for uHRMM patients is still suboptimal, even for what concern younger patients with no virtual limit on treatment choice based on patient's fitness.

The heterogeneous HR definition across trials, the few trials available designed for HR patients, and the small HR subgroups in all-comers trials make it difficult to generate recommendations with high levels of evidence. Nevertheless, regardless of treatment administered, several studies consistently showed that achieving and maintaining over time high-quality responses (namely, measurable residual disease [MRD] negativity[46-48]) is the only way to obtain a

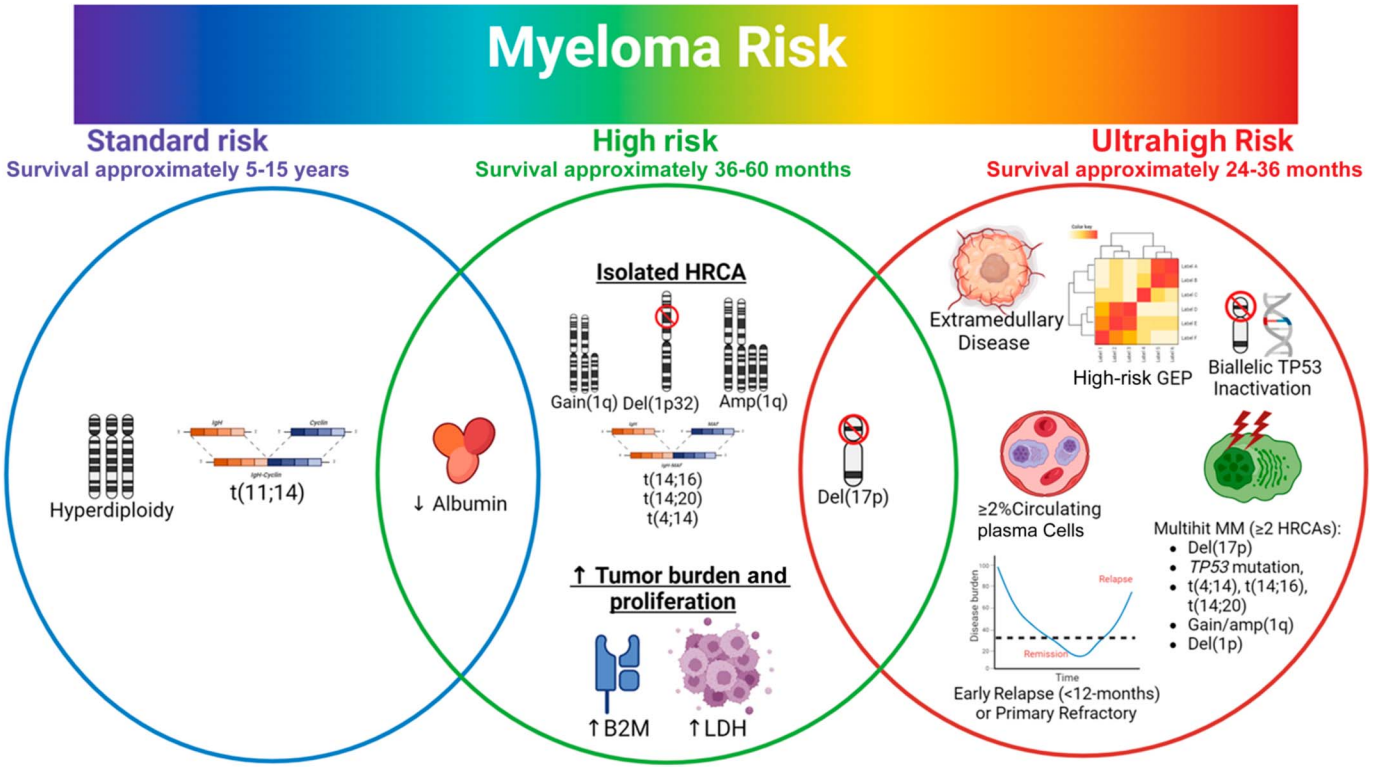

FIG 1. The spectrum of myeloma risk and conceptual thresholds for high-risk and ultrahigh-risk myelomas. amp, amplification; B2M, beta-2-microglobulin; GEP, gene expression profiling; HRCA, high-risk cytogenetic abnormality; LDH, lactate dehydrogenase; MM, multiple myeloma.

durable disease control in HR patients. MRD is now considered the main factor able to mitigate the adverse prognosis related to baseline features. Strategies aiming at achieving and maintaining MRD negativity in HR and uHR patients are therefore warranted. It is well known that each log of reduction of MRD is associated with improved outcome. International recommendations state that MRD assays used in MM trials must have a limit of detection of $<10^{-5}$ and, when possible, MRD $<10^{-6}$ should also be reported.[49] Recent data from the ISKIA trial showed that in the context of highly effective regimens and in the context of HR disease, the 10^{-6} cutoff might be more informative.[50]

Induction and Consolidation Regimens

A three-drug induction therapy including a PI, an IMID, and dexamethasone for four to six cycles was the mainstay of treatment in most countries. The VRd[51,52] is still included as one of the suggested induction regimens in the majority of guidelines.[7,53,54] First-line treatment with the second-generation PI carfilzomib in combination with lenalidomide and dexamethasone (KRd) was explored in many phase I and II trials[55-59]: the high rate of complete responses and MRD negativity achieved in NDMM, including HR patients,[31] support its further evaluation. So far, the phase III ENDURANCE trial is the only randomized study that compared KRd versus VRd in NDMM without intention for immediate ASCT; this study failed to show advantage of KRd versus VRd but excluded patients with HR disease.[60] The ongoing phase III randomized COBRA study (ClinicalTrials.gov identifier: NCT03729804), enrolling a similar population of NDMM without intention for immediate ASCT, but including HR patients, is comparing extended *KRd* (24 cycles) versus VRd for eight cycles followed by lenalidomide maintenance; results of this trial may shed light on the optimal PI overall and in specific risk groups. A retrospective, single-center, nonrandomized study provided initial evidence of a higher efficacy of KRd induction compared with VRd in patients with NDMM with HRCA (median PFS for KRd 70.9 months *v* 41 months with VRD, $P = .016$).[61]

Many large, randomized trials enrolling patients with TE NDMM clearly and consistently demonstrated that the addition of an anti-CD38 MoAbs (Daratumumab or Isatuximab) to PI plus IMID backbones, as pretransplant induction and post-transplant consolidation, increased MRD negativity and improved PFS compared with standard triplets. Toxicities were manageable and consisted mainly of a slight increase in hematologic AEs and infections. Subgroup analyses of these trials provide evidence on the impact of quadruplets in HR disease setting (Table 3).

MRD and available PFS results in patients with HR and multihit MM are summarized in Table 3. Specific data on the impact of induction alone in HR are often lacking. Most of the trials report MRD rate after consolidation or overall. The 10^{-5} MRD negativity after consolidation ranges between 44% and 68% in HR patients; data from these trials, even if encouraging, must be interpreted with caution as HR cytogenetic patients consisted only of 15%-21% of the enrolled patients. In multihit patients (8%-20% in different trials), 10^{-5} MRD rates ranges between 60% and 79%. Most of the data show that indeed adding the anti-CD38 MoAbs to standard of cares improved MRD rate and PFS and support the use of quadruplet also in patients with HR and multihit MM, as achieving MRD negativity is probably the first step toward prolonged remission.

In the past 2 years, results from three clinical trials selectively designed for patients with HR TE NDMM have been reported. The variability on the definition of high-risk subgroups is also reflected in the inclusion criteria of these three trials, which are not uniform. Nevertheless, all these studies included anti-CD38 MoABs plus IMIDs and PIs as pretransplant induction and post-transplant consolidation. Table 4 summarizes main inclusion criteria, treatment schema, and results of these studies.

Role of High-Dose Melphalan and ASCT

Randomized comparisons of triplet induction followed or not by ASCT[55,72-74] showed a PFS advantage in patients receiving up-front ASCT, with inconsistent OS data. Subgroup analyses of the DETERMINATION trial showed that the PFS benefit for up-front transplant after VRD induction is even more evident in HR patients (median 55.5 months *v* 17.1 of months, hazard ratio, 1.99 [95% CI, 1.21 to 3.26]) than in standard-risk (median 82.3 *v* 53.2, hazard ratio, 1.38 [95% CI, 1.07 to 1.79]).[73]

Randomized comparison of double- versus single-transplant up front after 3-drug induction also suggested a possible benefit of double transplant in patients with high-risk disease.[74,75]

No data are available on randomized comparisons of up-front versus delayed ASCT in the context of quadruplet induction/consolidation regimens. Subgroup analysis of GRIFFIN (Dara-VRd) and MASTER (Dara-KRd) study showed that in patients with one HRCA, quadruplet induction and up-front transplant induced a PFS that is similar to the one of standard-risk patients.[63] On the other hand, the outcome of uHR patients is still suboptimal. Whether these patients may benefit from a double ASCT is an open question.

To our knowledge, the phase II IFM 2018 trial for HR patients is the only trial exploring the role of double ASCT in the context of quadruplet induction/consolidation with Dara-KRd.[69] Fifty patients were enrolled in the trial, and 36 received double ASCT; thus, because of the low number of patients, it is difficult to draw any conclusion on the specific role of second ASCT in deepening the response. After the second transplant, in intention-to-treat analysis, 64% of the patients were MRD-negative at 10^{-5}.

TABLE 3. Overview of Subgroup Analyses From Large All-Comer Trials Exploring Anti-CD38 Monoclonal Antibodies Quadruplets in Transplant-Eligible Newly Diagnosed Multiple Myeloma

Trial	Median Follow-up	High-Risk Group	High-Risk Group Definition	Induction Treatment	No. of High-Risk Patients	MRD 10-5 Definition	MRD Rates in High-Risk Patients	PFS Definition	PFS
CASSIOPEIA[62]	18.8 months	High risk cytogenetics	del17p and/or t(4;14)	DVTd	82/543 (15%)	MRD after consolidation 10^{-5}	60%	Median PFS	Not reached (hazard ratio, 0.67 [95% CI, 0.35 to 1.30] *v* VTd)
				VTd	86/542 (16%)		44%		Not reached
GRIFFIN[63-65]	49.6 months	High risk cytogenetics	del17p and/or t(4;14), and/or t(14;16)	DVRd	16/98 (16%)	MRD negativity at 10^{-5} at the end of the study	44%	Median PFS	Not reached (hazard ratio, 0.54 [95% CI, 0.15 to 1.88] *v* VRd)
				VRd	14/97 (14%)		29%		36.1 months
		≥2 HRCA	At least two among del17p, t(4;14), t(14;16), t(14;20), or gain/amp(1q21) (≥3 copies of chromosome 1q21)	DVRd	10/97 (10%)		60%		33.9 months (hazard ratio, 1.65 [95% CI, 0.30 to 9.18] *v* VRd)
				VRd	8/97 (8%)		13%		Not reached
PERSEUS[45]	47.5 months	High risk cytogenetics	del17p and/or t(4;14), and/or t(14;16)	DVRd	76/355 (21%)	MRD negativity at 10^{-5} at any time	68%	Median PFS	Not reached (hazard ratio, 0.59 [95% CI, 0.36 to 0.99] *v* VRd)
				VRd	78/354 (22%)		47%		44.1 months
GMMGHD7[66]	125 days until end of induction	High risk cytogenetics	del17p and/or t(4;14), and/or t(14;16)	IsaVRd	58/331 (18%)	MRD negativity at 10^{-5} after induction	59%	NA	NA
				VRd	66/329 (20%)		44%		NA
		≥2 HRCA	At least 2 among del17p, t(4;14), t(14;16), or gain/amp(1q21) (≥3 copies of chromosome 1q21)	IsaVRd	48/331 (15%)		56%		NA
				VRd	34/329 (10%)		44%		NA
MASTER[67]	42.2 months	≥2 HRCA	At least 2 among del17p, t(4;14), t(14;16), t(14;20), or gain/amp(1q21) (≥3 copies of chromosome 1q21)	DKRd	24/123 (20%)	MRD negativity at 10^{e-5} at any time by NGS	79%	3-year PFS rate	50%
ISKIA[50]	21 months	≥2 HRCA	At least 2 among del17p, t(4;14), t(14;16), or gain/amp(1q21) (≥3 copies of chromosome 1q21)	IsaKRd	13/151 (9%)	MRD negativity at 10^{-5} after consolidation	77%	NA	NA
				KRd	15/151 (10%)		53%		NA

Abbreviations: amp, amplification; D, daratumumab; d, dexamethasone; HRCA, high-risk cytogenetic abnormality; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; NA, not available; NGS, next-generation sequencing; PFS, progression-free survival; R, lenalidomide; T, thalidomide; V, bortezomib.

TABLE 4. Dedicated Trials on High-Risk Patients With Transplant-Eligible Newly Diagnosed Multiple Myeloma

Trial	Median Follow-up	High-Risk Group	High-Risk Group Definition	Treatment	No. of High-Risk Patients	MRD 10-5 Definition	MRD Rates in High-Risk Patients	PFS Definition	PFS
GMMG CONCEPT[68]	44 months	Whole population	ISS II or III combined with ≥1 of the following: del17p, t(4;14), t(14;16), or >3 1q21 copies (amplification 1q21)	Isa-KRd induction ×6, HDM/ASCT, Isa-KRd consolidation ×4, Isa-KR maintenance ×26	99 (100%)	MRD negativity at 10^{-5} at any time	82%	3-year PFS rate	69%
IFM 2018-04[69]	33 months	Whole population	del17p and/or t(4;14), and/or t(14;16)	Dara-KRd induction ×6, HDM/ASCT, Dara-KRd consolidation ×, II HDM/ASCT, Dara-R maintenance ×2 years	50 (100%)	MRD negativity at 10^{-5} before maintenance	64%	30-month PFS rate	80%
OPTIMUM (MUK) NINE[70]	41.2 months	Whole population	≥2 HRCA among t(4;14), t(14;16)/t(14;20), gain(1q), del(1p), del(17p) or high risk SKY92 GEP signature or PCL (>20% circulating plasmablasts)	Dara-CVRd induction ×6, HDM/ASCT, Dara-VRd consolidation ×6, Dara-VR consolidation ×12, Dara-R maintenance until progression	107 (100%)	MRD negativity at 10^{-5} post-ASCT	64%	30-month PFS rate	77%
KPd maintenance in HRMM[71]	25.8 months	Whole population	del17p and/or t(4;14), and/or t(14;16) and/or PCL (>20% circulating plasma cells)	SoC treatment including up-front HDM/ASCT, followed by KPd maintenance for at least 3 years	29 (100%)	MRD negativity at 10^{-5} at any time, data available on 15 patients only	80%	3-year PFS rate	63%

Abbreviations: ASCT, autologous stem-cell transplantation; C, cyclophosphamide; d, dexamethasone; Dara, daratumumab; GEP, gene expression profiling; HDM, high dose melphalan; Isa, isatuximab; HRCA, high-risk cytogenetic abnormalities; HRMM, high-risk multiple myeloma; ISS, International Staging System; K, carfilzomib; MRD, minimal residual disease; P, pomalidomide; PCL, plasma cell leukemia; PFS, progression-free survival; R, lenalidomide; SOC, standard of care; V, bortezomib.

Beyond baseline risk, an option could be to rely on the MRD evaluation to decide on further intensification with 1 or 2 ASCT. In the phase III MIDAS trial (ClinicalTrials.gov identifier: NCT04934475), after six cycles of induction with isatuximab-KRd, patients who are MRD-negative are randomly assigned to ASCT versus no ASCT; patients who are MRD-positive are instead randomly assigned to double versus single ASCT. Results of the trial may shed light on the role of single/double ASCT according to dynamic risk evaluation in the context of quadruplet induction/consolidation.

Continuous Treatment Approach

The standard treatment for NDMM after ASCT and consolidation for patients with TE NDMM is continuous maintenance treatment, regardless of patient risk. The approved regimen throughout different countries is single-agent lenalidomide. There is conflicting evidence on the benefit of single-agent lenalidomide in patients with HR and uHRMM.[76-78]

Recent data from randomized trials showed a PFS advantage for the doublet carfilzomib-lenalidomide versus single-agent lenalidomide overall and in HR.[55,79]

Data from GRIFFIN and PERSEUS studies showed improved PFS with a strategy exploring daratumumab not only in addition to VRd induction/consolidation but also in addition to lenalidomide maintenance.[45,64] Data on the specific role of lenalidomide + anti-CD38 MoABs in the context of maintenance only are not yet available.

In patients with high-risk disease, it could be rationale to apply a long-lasting combination strategy to maintain the disease under control and prevent emergence of resistant clones. Indeed, particularly in the context of HR, even patients who reached MRD negativity may not sustain it over time with suboptimal therapy.

In the MASTER study, treatment interruption in MRD-negative multihit patients led to a higher rate of MRD resurgence and of progression compared with HR and standard-risk groups.[67] In the FORTE study during continuous treatment with KR, the risk of MRD resurgence was lower compared with R alone,[80,81] but after preplanned discontinuation of carfilzomib after 2 years of maintenance, the risk of MRD resurgence became superimposable compared with lenalidomide alone, highlighting the role of continuous combination treatment.

In the recent clinical trials designed for patients with high-risk TE NDMM, a continuous treatment approach with at least a doublet have been explored. In the GMMG CONCEPT trial, after six cycles of isatuximab-KRd induction, ASCT, four cycles of isatuximab-KRd consolidation patients received 26 cycles of isatuximab-KR maintenance. This treatment led to a 10^{-5} MRD negativity rate of 82%, and 69% of the patients were alive and progression-free at 3 years.[68]

In the IFM 2018-04 trial, after six cycles of daratumumab-KRd induction, first ASCT, four cycles of daratumumab-KRd consolidation, and second ASCT, patients received 2 years of daratumumab lenalidomide maintenance. 80% of the patients were alive and progression-free at 30 months.[69]

In the OPTIMUM trial, after DaraCVRd induction, ASCT, and Dara-VRd consolidation, patients received Dara-VR for 12 cycles and Dara-R maintenance until progression. Seventy-seven percent of the patients were alive and progression-free at 30 months.[70]

A three-drug maintenance with carfilzomib-pomalidomide-dexamethasone after standard-of-care induction and up-front ASCT was explored in a phase II study producing a 3-year PFS rate of 63%.[71]

In all trials, treatment was manageable in the population of fit patients with TE NDMM enrolled. Results of these high-risk trials are summarized in Table 4.

NOVEL TREATMENT APPROACHES AND CARING FOR OLDER ADULTS WITH HIGH-RISK MULTIPLE MYELOMA

Despite a paradigm shift in the treatment landscape of MM, with the introduction of novel agents leading to significantly prolonged survival,[82] transplant-noneligible (TNE) patients with HR MM still represent a challenging subset with limited data available, limited treatment options, and poorer outcomes compared with younger TE patients, even with HR disease.[83] Reasons include higher frailty with more comorbidities and therefore less intense treatments or more severe side effects from intense treatments resulting in treatment cessations and disease recurrence or even in toxicity-related death.

Until recently, risk-adapted treatments in frontline and/or relapsed and refractory (r/r) MM were not established, and outcomes of HR patients are mainly available from subgroup analyses of phase III clinical trials where approximately 15% of patients are considered as HR. If in TE patients, most recently, a small number of risk-adapted clinical trials including exclusively HR patients or enriched for those were conducted,[67,68,70,84] in TNE patients, data for risk-adapted strategies remain scarce. Specifically, for older patients with HR disease, it should be noted that many are not included into clinical trials because of frailty, lacking inclusion criteria, or the need of emergency treatment. Taking this into account, interpretation of the available data is even more challenging than for younger patients and might not fully reflect clinical reality.

General Considerations

Current standard regimens for TNE patients according to guidelines are mostly triplet combinations, such as daratumumab, lenalidomide, dexamethasone (DRd), or VRd as treatment extension from doublet to triplet regimens

consistently led to improvement in PFS and OS.[85,86] Subgroup analyses for HR patients are often lacking significance despite numerical improvement in PFS and are overall to interpret with caution because of low absolute numbers. In addition, despite the overall beneficial outcome with triplet versus doublet regimens, the negative impact of HR disease is in general not overcome by the addition of the third drug. In one of the leading trials in frontline treatment of TNE patients, the large phase III MAIA trial investigating DRd versus Rd, addition of daratumumab improved median PFS in both standard-risk and HR patients with a median (m)PFS of 63.8 and 34.4 months for DRd compared with Rd in standard-risk versus 45.3 and 29.6 months for HR patients, respectively.[87] A significant OS benefit was only shown for standard but not for HR patients.[88] The SWOG 0777 trial investigating VRd versus Rd in patients not intended for high-dose treatment documented significant superiority in PFS for the total patient population (mPFS 43 months [VRd] *v* 30 months [Rd]); however, it confirmed a significantly inferior outcome for HR patients: 44 HR patients had a mPFS of 38 (VRd) versus 16 months (Rd), respectively, lacking statistical significance.[86,89]

The consequent introduction of anti-CD38 MoAb in frontline treatment of both TE and TNE patients was one of the major milestones of the past decade. For HR patients, a recent meta-analysis evaluating three randomized phase III trials (ALCYONE, CASSIOPEIA, MAIA) where daratumumab was added to the backbone regimen documented improvement in PFS with a pooled hazard ratio of 0.67.[90] Again, in contrast to the effect of adding daratumumab in standard-risk patients, the benefit for HR patients was not statistically significant. One explanation might be the limited number of patients, with HR patients constituting only 15.9% of patients in the ALCYONE trial, 14.3% in MAIA, and 15.5% in CASSIOPEIA. Another explanation could be that the effect of the strategy targeting CD38 might be more effective in standard-risk compared with HR patients.

But how could prognosis of HR TNE patients be further improved? Is there room for optimizing the individual chosen drugs to better target HR disease and/or are extended combinations key in a population where a marked amount of patients is considered frail?

Recently, data are pointing toward a potential beneficial role for isatuximab, another anti–CD38-moAb approved for treatment in several combinations in r/rMM, in the subgroup of HR patients with 1q21 gain (three copies) and/or 1q21 amplification (four or more copies), a HR criterion with a growing impact during recent years and often co-occurring with other HR features.[5,91,92] In two large phase III trials introducing the addition of isatuximab to standard-of-care regimens (IKEMA, ICARIA-MM), the negative impact of gain/amp(1q21) was overcome when these patients were compared with standard-risk patients.[93] In ICARIA-MM, investigating isatuximab, pomalidomide, and dexamethasone (Isa-Pd) versus pomalidomide and dexamethasone (Pd) in patients with r/rMM, the mPFS for patients in the Isa-Pd group with 1q21+ was 9.5 months versus 11.6 months for those without, comparing favorably with a mPFS of 3.8 months for those with 1q21+ versus 9.8 months for patients without 1q21+ in the Pd group.[94] Similar findings were reported in the IKEMA trial adding isatuximab to carfilzomib and dexamethasone (Isa-Kd *v* Kd).[94,95] Whether this positive signal of isatuximab in patients with 1q21 abnormalities is due to the unique epitope binding on CD38 has to be further elucidated in preclinical and clinical investigations. Second, emerging data show that second-generation PI carfilzomib leads to beneficial outcomes especially in HR patients. First data were generated from trials conducted in the r/rMM setting.[96] However, more recent findings underscore the role of carfilzomib in improving outcome for HR patients also in the frontline setting; however, it is mainly restricted to the TE population.[31] Whether the positive effect of carfilzomib on HR disease is due to the feasibility of extended application because of the much lower rates of significant peripheral neuropathy or due to effects relying on the distinct irreversible proteasome inhibition or the epoxyketone structure is yet to be elucidated. The use of carfilzomib in the elderly population was often restrained because of concerns regarding potential cardiac toxicity. However, recent data show that carfilzomib can be safely used in the elderly and even frail patient cohort without a significant increase in severe cardiac events.[97-100]

Introducing Quadruplet Regimens With Tolerability

Unlike for TE patients for whom a quadruplet treatment comprising an anti–CD38-moAb, an IMiD, a PI, and dexamethasone has become undisputed standard in first-line therapy, large phase III trials with quadruplet regimens in frontline TNE NDMM are still lacking. It is anticipated that the phase III IMROZ trial (ClinicalTrials.gov identifier: NCT03319667) investigating the addition of isatuximab to the standard VRd backbone in frontline treatment of TNE patients will be presented at this year's ASCO convention, after a press release announced superiority of the Isa-VRd regimen compared with VRd.[101] However, in view of the fact that HR patients in particular require more intensive treatment approaches to effectively control aggressive disease, quadruplets should be foremost investigated in this setting.

The CONCEPT trial (ClinicalTrials.gov identifier: NCT03104842) as a dedicated HR trial investigating Isa-KRd in NDMM was pivotal in also including TNE patients without an upper age limit at a time when Rd was still standard of care.[68] The CONCEPT trial was conceptually designed as a single-arm phase II trial with two arms conducted independently in parallel, one for TE and one for TNE patients. In the TNE arm, the six-cycle induction treatment with Isa-KRd was followed by two additional treatment cycles. All patients received four cycles of Isa-KRd consolidation and a triplet maintenance with Isa-KR over a full 2-year period. Twenty-six patients were included in TNE Arm B of the

CONCEPT study with a median age of 74 years, with the oldest patient being 87 years at trial inclusion. All patients had HR cytogenetic abnormalities (del(17p), t(4;14), t(14;16), amp(1q21)) in the context of ISS2 and/or ISS3 disease. Main HRCA in TNE patients was amp(1q21) in 14 patients (53.8%) followed by del(17p) in 11 (42.3%); seven patients (26.9%) showed ≥2 HRCA. Isa-KRd treatment was able to induce deep and durable responses as demonstrated by an MRD negativity rate of 69.2% with 46.2% of ≥1-year-sustained MRD-negative remissions and an mPFS that was not yet reached after 35 months of follow-up.[68] Treatment in the TNE population was feasible, and main higher-grade (3-4) nonhematologic toxicities were infections in 28% and cardiac events in 20% of patients; however, none of those led to treatment discontinuation. The SWOG-1211 trial (ClinicalTrials.gov identifier: NCT01668719) investigating addition of the anti-SLAMF7-moAb elotuzumab to RVd was also designed for HR TNE patients. Of 100 included patients, 27 and 21 patients were 65 years and younger in the Elo-RVd and RVd arm, respectively. The trial could not demonstrate an advantage of adding elotuzumab with an mPFS of 33.64 months (RVd) and 31.47 months (Elo-RVd); outcome of the patient population older than 65 years was not separately reported.[84] Hence, recent treatment approaches have focused on anti–CD38-moAb (Table 5). At the 2023 ASH convention, a study pointed toward higher rates of treatment-related adverse events and deaths because of infections with the use of anti–CD38-moAb-based quadruplets in TNE patients considered frail, but, on the other hand, it highlighted again the high effectiveness and good tolerability in fit TNE patients.[103] Hence, quadruplets should not be withheld from the elderly in general, but every effort should be made with optimized supportive treatment and tailored management to deliver these effective regimens to HR TNE patients.

Despite the acknowledgment of the HR population in treatment recommendations and guidelines for TE patients, distinct recommendations for this difficult-to-treat patient group in the TNE setting are missing. The National Comprehensive Cancer Network guidelines do not add specific recommendations for the treatment of aggressive or HR disease in TNE patients.[104] The 2023 updated mSMART (Stratification for Myeloma and Risk-Adapted Therapy) guidelines differ between HR and standard risk; however, despite the recommendation for optimized quadruplet regimens in the HR TE situation, specific treatment recommendations between standard-risk and HR TNE patients are missing.[8]

Identifying and Treating Patients With High-Risk MM: Future Directions

The first step to improve the treatment of patients with high-risk MM is to reliably and uniformly identify them. Despite advances, an unacceptable number of patients are misclassified by current assessments and physicians need to carefully weigh the cost of comprehensive frontline testing against the price of not recognizing high-risk diseases. Developments in sequencing, immunology, and integrative computer models hold promise for future prognostication. NGS examines the entire genome, captures mutational events, and is free of the error introduced by cytogenetic calls. As access increases, it is likely to become the preferred standard of genetic analysis.[105] With the introduction of highly active immunotherapies, future risk assessments may incorporate immune profiling to assess host responsiveness and disease sensitivity. Such assays may assess T-cell exhaustion, target antigen expression, and immune system normalization post-treatment, all of which have been associated with MM outcomes.[106-108] Finally, as genomic, clinical, and immune profiling data expand, machine learning and bioinformatic systems will be essential for computing and distilling meaning from these data.[109] The survival of present-day MM patients defies even the most optimistic historical expectations. Nonetheless, a HR subset of patients has been left in the past. To address this, patients and doctors need to establish a consensus on the minimum necessary diagnostic testing and a definition to distill the ever-growing number of prognostic factors into meaningful clinical decisions.

Regarding treatment of young patients with TE NDMM, quadruplet induction/consolidation treatment, ASCT up front followed by maintenance with, if available, at least a doublet combination could be considered the option of choice in HR disease.

Standard of care for frontline treatment of HRMM will continue to evolve as we learn more from long-term follow-up of quadruplet therapies.

Beyond baseline risk, strategies on the basis of MRD are being explored in clinical trials as MRD is so far the main dynamic prognostic factor able to mitigate the adverse prognosis of baseline features.

The deepness of MRD needed (10^{-6} *v* 10^{-5}) and the optimal duration of MRD negativity as a marker of extended survival and as a dynamic factor helping in the therapeutic choices are still a matter of debate.

To further improve the outcomes of these patients, new immunotherapies (eg, chimeric antigen receptor [CAR] T cells and bispecific antibodies) might play a role. In the KarMMa-2 study, patients having a suboptimal response after ASCT (<Very Good Partial Response) received idecabtagene vicleucel infusion as further consolidation, leading to a CR rate of 77% and a 3-year PFS rate of 77%.[110]

Inclusion of immunotherapies up front is being explored in large phase III trials. The Cartitude-6 trial is comparing ciltacabtagene autoleucel versus ASCT in TE NDMM (ClinicalTrials.gov identifier: NCT05257083), whereas the MajesTEC-4 trial is exploring the role of teclistamab alone or in combination with lenalidomide versus lenalidomide alone as maintenance treatment (ClinicalTrials.gov identifier: NCT05243797). Subgroups analyses of HR patients enrolled

TABLE 5. Overview of Dedicated HR Trials and Subgroup Analyses From Large All-Comer Phase III Trials in TNE NDMM

Trial	Phase and Design	Study Population	Treatment	HR Definition, No. (%)	Primary End Point	Outcome Overall	Outcome HR Subgroup	Other Key Findings
ALCYONE[102] NCT02195479	III Two-arm, randomized	NDMM, TNE N = 706	Bortezomib, melphalan, prednisone with or without daratumumab	del17p, t(4;14), or t(14;16) n = 98 (15.9)	PFS	hazard ratio for PFS: 0.50 (95% CI, 0.38 to 0.65)	hazard ratio for PFS in HR: 0.78 (95% CI, 0.43 to 1.43)	hazard ratio for PFS in SR: 0.39 (0.28 to 0.55), n = 518
GMMG-CONCEPT[68] NCT03104842	II, single-arm (two treatment arms according to TE/TNE)	HR NDMM TE and TNE N = 153	Isatuximab, carfilzomib, lenalidomide, dexamethasone	ISS 2 or ISS 3 in combination with ≥1 HRCA: del(17p), t(4;14), t(14;16), amp(1q21) n = 26	MRD negativity (10^{-5}) at end of consolidation	69.2% with 46.2% of ≥1-year-sustained MRD-negative remissions	69.2% with 46.2% of ≥1-year-sustained MRD-negative remissions	mPFS not reached (mFU: 35 months); 1-year PFS rate: 75.1% (95% CI, 59.7 to 94.5) 2-year PFS rate: 62.6% (95% CI, 46.0 to 85.3)
IMROZ[101] NCT03319667	III Two-arm, randomized	NDMM, TNE N = 706	VRd with or without daratumumab	NA	PFS	Isa-VRd with statistically significant improvement in PFS Details NA	NA	NA
MAIA[85,87,88] NCT02252172	III Two-arm, randomized	NDMM, TNE N = 737	Rd with or without daratumumab	del17p, t(4;14), or t(14;16) n = 92 (14.3%)	PFS	hazard ratio for PFS: 0.56 (95% CI, 0.43 to 0.73)	hazard ratio for PFS in HR: 0.85 (95% CI, 0.44 to 1.65)	hazard ratio for PFS in SR: 0.49 (95% CI, 0.36 to 0.67), n = 550
SWOG-0777[86,89] NCT00644228	III Two-arm, randomized	NDMM, without intent for immediate ASCT N = 525	Rd with or without bortezomib	del17p, t(4;14), or t(14;16) n = 44 (8.4%)	PFS	mPFS 43 months (VRd) *v* 30 months (Rd)	mPFS 38 (VRd) *v* 16 months (Rd)	
SWOG-1211[84] NCT01668719	III Two-arm, randomized	HR NDMM, TNE N = 100	VRd with or without elotuzumab	Gene expression profiling high risk, t(14;16), t(14;20), del(17p) or amp1q21, primary plasma cell leukemia, and elevated serum LDH	PFS	mPFS 33.64 months (RVd) *v* 31.47 months (Elo-RVd); stratified hazard ratio was 0.968 (80% Wald CI, 0.697 to 1.344)	mPFS 33.64 months (RVd) *v* 31.47 months (Elo-RVd), stratified hazard ratio was 0.968 (80% Wald CI, 0.697 to 1.344)	

Abbreviations: amp: amplification; ASCT, autologous stem-cell transplantation; Elo-RVd, elotuzumab, lenalidomide, bortezomib, dexamethasone; HR, high risk; HRCA, high-risk cytogenetic aberration; Isa, isatuximab; ISS, International Staging System; LDH, lactate dehydrogenase; mFU, median follow-up; mPFS, median progression-free survival; MRD, minimal residual disease; NA, not available; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; Rd, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib, dexamethasone; SR, standard risk; TE, transplant-eligible; TNE, transplant-noneligible; VRd, lenalidomide, bortezomib, and dexamethasone.

in these trials may inform us on the role of new immunotherapies up front in the management of HR disease.

Regarding TNE patients, novel treatment approaches, including quadruplet regimens, offer promising therapeutic options for patients with HR MM. Considering the recent data generated and carefully reviewing those upcoming, to our view also quadruplet treatment consisting of PI, IMiD, and anti–CD38-moAb combinations in TNE patients should be considered.

Looking ahead, future trials integrating BCMA-directed novel generation immunotherapies hold great potential for further advancing the treatment landscape in TNE patients with HR MM.

The phase I DREAMM-9 trial (ClinicalTrials.gov identifier: NCT04091126) evaluated the efficacy and safety of a quadruplet regimen comprising belantamab mafodotin in combination with RVd in TNE patients with NDMM . Preliminary data from this trial demonstrated encouraging response rates and manageable toxicity profiles, supporting the integration of BCMA-directed treatments into first-line regimens in this patient population.[111]

Upcoming trials integrating CAR T-cell therapies and bispecific antibodies hold promise for further improving outcomes in TNE patients with HR MM. With the phase III CARTITUDE-5 trial (ClinicalTrials.gov identifier: NCT04923893), TNE patients with NDMM are randomly assigned after VRd induction either to receive ciltacabtagene autoleucel followed by observation or to continue Rd maintenance.[112] Similarly, bispecific antibodies are being integrated into current treatment regimens to enhance immune-mediated cytotoxicity against MM cells: teclistamab in combination with daratumumab (cohort A) or lenalidomide (cohort B) is investigated in TNE patients in the phase II IFM2021-01 trial (ClinicalTrials.gov identifier: NCT05572229).[113] Whether these approaches will be able to overcome the negative impact of HR disease and are feasible in the elderly population remains to be seen.

While we largely focused on the treatment of patients with high-risk chromosomal abnormalities, dedicated trials in patients with other types of high-risk disease like PCL[114] and EMD[115] are beginning to emerge as well. In RRMM with EMD, promising data come from a combination of two bispecific antibodies targeting BCMA and GPRC5D, respectively,[116] supporting the evaluation of this combination in this setting.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc.

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Research Funding: Takeda (Inst), Abbvie (Inst), Novartis, 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)
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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

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No other potential conflicts of interest were reported.

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