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## Approach to the Older Adult With Multiple Myeloma

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### Abstract

Multiple myeloma (MM) is a disease of aging adults, and numerous therapeutic options are available for this growing demographic. MM treatment of older adults continues to evolve and includes novel combinations, new generations of targeted agents, immunotherapy, and increasing use of autologous stem cell transplantation (ASCT). Understanding age-related factors, independent of chronologic age itself, is an increasingly recognized factor in MM survivorship, especially in understudied populations, such as octogenarians. Octogenarians have inferior survival that cannot be explained by cytogenetic profiles alone. Incorporating assessments of geriatric factors can provide guidance on how to intensify or de-escalate therapeutic options. Functional status, using objective testing, is superior to traditional metrics of performance status and should be implemented to optimize the risk-benefit ratio of ASCT. ASCT is feasible and cost-effective, and chronologic age should not exclude ASCT eligibility. Upfront ASCT remains the standard of care, in the context of a sequential approach that includes pre-transplantation induction and post-transplantation maintenance. High-risk MM is classically defined by disease characteristics, yet shifting frameworks suggest that the high-risk designation could refer to any patient subgroup who is at risk for poorer outcomes—beyond disease-focused outcomes to patient-focused outcomes. Defining the optimal treatment of subgroups of older patients with high-risk disease on the basis of chromosomal abnormalities is unexplored. Here, we review tools to assess individual health status, explore vulnerability in octogenarians with MM, address ASCT decision-making, and examine high-risk MM to understand factors that contribute to survival disparities for older adults with MM.

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## INTRODUCTION

Multiple myeloma (MM) is a disease of older adults, and approximately 30,000 new occurrences will be diagnosed this year.<sup>1</sup> The median age of patients with myeloma is 70 years. Therapy for MM continues to evolve and includes novel combination therapy, new generations of targeted agents, immunotherapy, and increasing use of autologous stem cell transplantation (ASCT).<sup>2</sup> As a result of these advances, survival for MM has improved for most demographics, yet improvements in survival for older adults with myeloma have been modest and require ongoing investigation. Understanding the needs of the aging myeloma demographic requires research in real-world myeloma populations with diverse health status, variable functional trajectories, and pre-existing comorbidities. Prescriptive clinical trial designs often lead to highly selected MM populations, which results in queries about how to implement and optimize therapy for patients with MM who have age-related conditions that predated and may be exacerbated by a myeloma diagnosis. Numerous MM treatment combinations are available for older adults and are stratified for the individual according to the ability to tolerate ASCT and by disease risk stratification.<sup>3</sup> Randomized trials have demonstrated the survival advantages of ASCT, yet less than 20% of all patients older than age 65 are undergoing ASCT.<sup>4</sup> When comparing trends in the modern era, patients with MM who are younger than age 65 have improved 10-year relative survival rates (9.6% vs. 35%;  $p < .001$ ); patients age 75 or older do not share the same survival advantages (7.8% vs. 9.3%;  $p = .3$ ).<sup>5</sup> MM deaths overall are highest in patients age 75 or older, and early mortality is most common in those age 70 or older.<sup>6,7</sup> Optimizing quality of life, improving early mortality, and increasing access to ASCT for MM are active areas of investigation.<sup>8-10</sup> Here, we examine evidence to support geriatric assessments, explore MM in octogenarians, address ASCT decision-making, and explore high-risk MM to understand factors that are attributable to survival disparities for older adults with MM.

## GERIATRIC ASSESSMENT IN MM

Bridging the disciplines of geriatric oncology with MM is an important first step in the field of aging research. Understanding age-related factors, independent of chronologic age itself, is imperative in rendering a myeloma disease trajectory. Age influences all facets of myeloma disease course, including diagnosis, outcomes, and survivorship. The study of aging and life span, and the influence of myeloma development, parallels studies in geriatrics. Geriatrics is the study of health and disease in later life,<sup>11</sup> wherein a comprehensive geriatric assessment (GA), although variably defined, is an interdisciplinary approach to identify, intervene, and create a longitudinal care plan to improve clinical outcomes for frail older adults.<sup>12,13</sup> The term frailty “is used more frequently than it is defined” but is accepted to be a complex syndrome of physiologic decline that signifies increased vulnerability.<sup>14,15</sup> As such, many myeloma providers have recognized the need to incorporate assessments of geriatric factors, given numerous treatment options and divergent intensities of therapeutic options. In the myeloma setting, implementing geriatric screening tools or collating assessments of geriatric domains (e.g., functional status, psychological status, cognition, socioeconomic factors, comorbidities, nutritional status, and sensory loss) have served as a diagnostic index in predicting vulnerability to adverse outcomes (Table 1). An understanding of the specific geriatric tools and domain assessments helps characterize

how to best care for older adults. We aim to outline geriatric screening tools, GAs, and evidence to support use in older adults with MM.

Oncologists routinely assess patient vulnerability, often subjectively, to determine the likelihood of treatment tolerance, estimate treatment benefit, and predict risk of adverse complications and/or mortality. GA tools are shown to accurately assess risk of morbidity and mortality in cancer populations independent of performance status and age.<sup>27–29</sup> Myeloma-specific studies evaluating geriatric variables are an important advance when caring and managing treatment decisions for older adults. The International Myeloma Working Group (IMWG) used a simplified GA tool based on age, comorbidities, activities of daily living (ADL), and instrumental activities of daily living (IADL) for newly diagnosed older adults enrolled into nontransplantation frontline clinical trials.<sup>16</sup> The IMWG tool classified patients as fit, intermediate fit, and frail; scores were predictive of death, progression, treatment discontinuation, and nonhematologic toxicities. The IMWG frailty score profiles were independent of treatment, cytogenetics, or stage in the MM population.<sup>16</sup> The Freiburg Comorbidity Index, also known as the Initial Myeloma Comorbidity Index (I-MCI), is an assessment tool based on Karnofsky performance status, lung disease, and renal disease by estimated glomerular filtration rate.<sup>17</sup> The Freiburg Comorbidity Index is predictive of survival independent of MM stage, therapy, and age ( $p < .0015$ ).<sup>26</sup> The Revised Myeloma Comorbidity Index (R-MCI) expanded to include age, frailty, and cytogenetics; in the Engelhardt study, frailty was identified in 74 (13%) of 552 patients and the hazard ratio (HR) for overall survival among frail patients was 9.57 (CI, 6.52–14.03).<sup>18</sup> The Geriatric Assessment in Hematology (GAH) scoring system focuses on eight geriatric dimensions (polypharmacy, gait speed, mood, ADL, health status, nutrition, mental status, comorbidities) and is brief (approximately 10–12 minutes); with this tool, increasing deficits have been associated with survival in adults older than age 65 who were newly diagnosed with hematologic malignancy.<sup>19,20</sup> Recently, Murillo et al<sup>25</sup> compared the IMWG frailty score with the Fried model<sup>30</sup> and reported that frailty defined by the Fried model was significantly associated with risk of death (prefrail HR, 2.88 [95% CI, 0.80–10.41]; frail HR, 4.91 [95% CI, 1.29–18.61]; global  $p = .04$ ). In contrast to the Fried model, there was no statistically significant association with risk of death by frailty category using the IMWG model.<sup>25</sup> These results reflect either an older demographic or a more real-world analysis of patients with myeloma. Efforts to streamline GA tools for ASCT decision-making are ongoing and require further investigation; GA instruments may predict the likelihood of receiving a transplantation,<sup>22</sup> and geriatric deficits are associated with increased length of hospital admission and event-free survival.<sup>23</sup> Others have explored large MM data sets, creating a frailty index using geriatric domains (mental health, physical function, comorbidities, ADL, general health) whereby a 10% increase in the frailty index was associated with a 16% increased risk for death (adjusted HR, 1.159; 95% CI, 1.080–1.244;  $p < .001$ ).<sup>24</sup>

Personalizing therapy on the basis of patient fitness or frailty may improve patient outcomes in older adults, but requires prospective clinical trials. Each of these assessments, whether through a survey, risk assessment profile, or clinical visit, is intended to screen and evaluate for frailty. Frailty is a state of patient vulnerability and is highly relevant for the older adult MM population. Essential for this discussion is recognizing that frailty is dynamic and that

one-time screening for frailty is unlikely to result in meaningful benefit as the state of frailty may improve or decline, and therefore alter treatment decisions.

## OCTOGENARIANS WITH MM

Because of the increasing lifespan, 434 million people in the world will be older than age 80 in 2050.<sup>31</sup> The availability of MM treatment options that are not only effective but also feasible in octogenarians will lead to more rigorous screening for MM. This age-related impact was recently described in Europe and is expected to occur also in middle-income countries.<sup>32</sup> Therefore, the incidence and prevalence of octogenarians with MM will continue to expand, so exploring treatment modalities in this demographic is increasingly relevant.

The IMWG frailty index was created to identify vulnerable patients with MM; the index reflects worse PFS and OS as well as increased incidences of grades 3 to 4 nonhematologic toxicities and discontinuation rates in frail patients. According to this index, patients older than age 80 are, by definition, frail.<sup>16</sup> Although chronologic aging is accompanied by age-related physiologic changes, there is a pronounced heterogeneity in physiologic and functional age.<sup>33</sup> Therefore, it is questionable whether age of 80 years alone should be a definition of frailty in patients with MM. Patients defined as frail by the IMWG frailty index have had higher rates of functional impairments and loss of muscle mass than nonfrail patients, suggesting that the index indeed reflects biologic frailty.<sup>34</sup> However in this study, although more frail than fit patients have died 3 years after the initiation of treatment (43% vs. 16%), 57% of frail patients survived, emphasizing the benefit of treatment among even patients deemed vulnerable.<sup>16</sup> Therefore, there is an unmet need to identify patients older than age 80 who are expected to benefit from treatment before deciding to abstain from MM treatment and provide supportive care only.

An important consideration for weighing treatment decisions in octogenarians is life expectancy based on age in concert with general health status, because they relate to the expected survival benefit with a given MM treatment. Also, the risk of developing treatment-related mortality, but especially morbidity, must be considered. In octogenarians, morbidity not only may affect the quality of life but also might have a negative impact on independent ADLs and the ability to maintain independence. Therefore, the preferences and values of patients in life before the MM diagnosis are important to discuss in the shared decision-making model before treatment decision are made.<sup>35</sup> For the prediction of general life expectancy, there are several tools available in which not only age but also functional and physiologic characteristics are taken into account; these were recently reviewed by Yourman et al.<sup>36,37</sup>

Whether OS will be improved by MM treatment is difficult to answer, because data on the efficacy of treatment in octogenarians are scarce. Actually, there are no separate analyses of patients older than age 80 in recent clinical trials. Data on the eldest patients with MM are limited to subanalyses of patients older than age 75. In the FIRST trial comparing lenalidomide/dexamethasone continuously (Rd) versus 18 cycles of Rd (Rd18) versus melphalan/prednisone/thalidomide (MPT), patients older than age 75 also benefited from Rd

versus MPT; however, the PFS and OS decreased for this older group relative to patients age 75 years or younger (PFS, 20.3 vs. 28.1 months; OS, 52.3 vs. 60.9 months).<sup>38</sup> In the VISTA trial comparing bortezomib/melphalan/prednisone (VMP) with melphalan/prednisone, a benefit of VMP was also found in older adults; however, again, the benefit was less pronounced in the eldest (OS, 43.3 months in patients age 75 or older vs. not reached in patients younger than age 75), data on PFS were not reported.<sup>39</sup> In the recent ALCYONE trial, no difference in PFS was found between patients younger than age 75 and those age 75 or older in either the VMP or daratumumab/VMP arm.<sup>40</sup> In addition, two studies were specifically developed for patients age 75 or older to investigate two- or three-drug regimens with bortezomib or dose-adjusted VMP. Both studies supported dose adjustments. However, even with dose adjustment, the outcome was still inferior compared (in a non-head-to-head manner) with younger non-transplantation eligible patients; the median PFS was only approximately 15 months in the older patients versus 20–25 months in all patients who were not eligible for transplantation (in general, age 65 and older).<sup>34,41</sup>

We performed a subanalysis based on age in three HOVON trials for non-transplantation eligible patients. In the HOVON 87 trial, melphalan/prednisone was combined with either thalidomide or lenalidomide. Both immunomodulatory drugs (IMiDs) were given until progression occurred or after nine induction cycles.<sup>42</sup> Of the population, 65 (10%) of 636 patients were older than age 80. The median PFS was similar independent of age (22 months in age 80 or older vs. 22 and 21 months in patients age 75–79 and age 75 or younger, respectively). In contrast, the median OS was worse in patients age 80 and older (41 vs. 55 and 56 months for the two younger age groups, respectively). In the HOVON 126, non-transplantation eligible patients were treated with nine induction cycles of ixazomib/thalidomide/dexamethasone followed by a random assignment to maintenance with placebo or ixazomib.<sup>43</sup> Of the population, 11 (8%) of 143 patients were older than age 80. PFS was not significantly different in those age 80 or older (median PFS, 10 months vs. 15 and 14 months in ages 75–79 and age 75 or younger, respectively). OS at 2 years was worse (63% vs. 75% and 90% for the younger groups, respectively). The HOVON 123 was a study specifically designed for patients age 75 or older, and 101 (42%) of 238 patients were age 80 or older. The median PFS was 17 months, irrespective of age, and the OS was 29 months among octogenarians.<sup>34</sup> Moreover, the GIMEMA and PETHEMA studies revealed results similar to the HOVON studies (personal communication, A. Larocca, February 2019; and M. V. Mateos, February 2019; respectively): Comparable PFS but inferior OS was observed in patients age 80 and older compared with the age groups of 75–79 and 75 or younger (GIMEMA MM-03–05 plus EMN 01 trial: median PFS, 24, 19, and 27 months, respectively; median OS, 39, 52, and not reached, respectively; GEM2005MAS65: median PFS, 22, 16, and 29 months, respectively; median OS, 35, 35, and 53 months, respectively).

The inferior OS in patients age 80 or older cannot be explained by a higher prevalence of adverse cytogenetic profile, which was even less pronounced in older adults because of a lower incidence of translocation (4;14). Only International Staging System (ISS) stage was higher in patients age 80 or older in all above-described subanalyses of the HOVON and GIMEMA studies. Life expectancy is shorter for octogenarians, but other relevant factors among individuals being treated for MM could include higher levels of toxicity induced during first-line treatment and more comorbidities that preclude subsequent treatment at

relapse. Indeed, Brinthen and colleagues<sup>44</sup> found that the risk of death was higher in patients who experienced severe infections, cardiac events, or gastrointestinal events and in those who required drug discontinuation because of adverse events.<sup>44</sup> They also found a higher incidence of toxic deaths among octogenarians compared with patients younger than age 80 (12% vs. 4%).<sup>45</sup> A subanalysis showed a slightly higher incidence of grades 3 and 4 toxicity in patients age 80 or older (21% vs. 17% in the whole patient population; personal communication, A. Larocca, February 2019). Similarly, in the HOVON studies, we found an approximately 80%–90% rate of grades 3 and 4 toxicity in patients age 80 or older versus a rate of approximately 65%–85% in patients younger than age 80. The reason for such limited differences in toxicity is probably caused by a selection bias in clinical studies. This is supported by the fact that the World Health Organization performance status and number of comorbidities were rather comparable across age groups in the GIMEMA, PETHEMA, and HOVON trials.

The demographics of hospital or population-based registries have been found to be different as well. In a Greek hospital based octogenarian population (n = 110), both disease characteristics and patient characteristics differed from what is generally observed in a clinical trial population: 61% had ISS stage 3 disease, 13% had high lactate dehydrogenase levels, 36% had an estimated glomerular filtration rate less than 30 mL/min/1.73m<sup>2</sup>, 66% had a World Health Organization performance status of 3 or 4, and 46% had a Charlson comorbidity index of 2 or greater. The median PFS was 7 months, and the OS was 21 months compared with 69 months for patients younger than age 80. Moreover, there was a high early death rate (< 2 months) of 21%.<sup>46</sup> From the Dutch population-based registry, comparable data were found; the OS was 27 months for patients age 80–84 and was 8 months for patients age 85 or older, with accordingly high early death rates (< 3 months) of 17% and 26%, respectively (personal communication, A. Dinmohamed, February 2019). That such patients are less often eligible for studies has been observed in the MM Connect database,<sup>47</sup> which showed that, in general, 40% of patients with MM were not eligible for participation in trials independent of octogenarian status. Those patients had worse renal function, higher ISS stages, and worse survival compared with patients who were eligible. As such, integrating a personalized approach for the aging demographic, which is at risk for high mortality and morbidity from the disease and from treatment, is imperative for the MM population.

## TRANSPLANTATION IN OLDER ADULT PATIENTS WITH MM

High-dose chemotherapy followed by ASCT is currently considered a standard procedure for younger patients with newly diagnosed multiple myeloma (NDMM). Four randomized trials compared upfront ASCT with a non-ASCT, novel, agent-based approach in younger patients (< 65 years). Incorporating high-dose melphalan followed by ASCT in a novel, agent-based, frontline strategy significantly improved PFS and OS, although the OS benefit was inconsistent across the trials.<sup>48–53</sup>

Historically, the age cutoff adopted to determine ASCT eligibility in clinical trials was 65 years. This age limit prevents a notable proportion of patients with MM from undergoing ASCT, because more than two-thirds of patients with NDMM are age 65 or older. In clinical

practice, however, this limit has been extended to the age of 70–75.<sup>54–56</sup> In Europe, the European Society for Medical Oncology guidelines recommended ASCT in patients up to the age of 70<sup>57</sup>; conversely, in the United States, the NCCN guidelines did not set an age cutoff for ASCT eligibility.<sup>58</sup>

Recent population-based studies reported an increasing use of ASCT in older adult patients with MM.<sup>5,56</sup> In a study evaluating age-related trends in the use of ASCT in 31 European countries (1991–2010), the highest increase in the rates of ASCT occurred in patients older than age 65, representing 3% of all ASCTs between 1991 and 1995 and 18% between 2006 and 2010.<sup>56</sup> Similarly, in a study in the United States and Canada, the use of ASCT in patients older than age 65 increased from 8% (1995–1999) to 24% (2005–2010).<sup>5</sup>

Table 2 summarizes prospective and retrospective trials that evaluated the efficacy and safety of ASCT in older adult patients. Unfortunately, most of the studies are retrospective or registry based, and only two randomized trials, conducted before the introduction of lenalidomide and bortezomib, compared ASCT with a nontransplantation approach, with conflicting results.<sup>59,60</sup>

Subsequent trials, however, showed that ASCT in older patients with MM was a feasible and effective procedure, with a low treatment-related mortality (TRM). In 2001, Badros et al<sup>75</sup> initially reported a high TRM (16%) in patients older than age 70 receiving 200 mg/m<sup>2</sup> of melphalan (MEL) as a conditioning regimen before ASCT. More recently, however, the TRM has been significantly lowered (< 5%) through the adoption of reduced MEL doses (140 mg/m<sup>2</sup>) and the improvement of patient selection and supportive care.<sup>75</sup> As reported in some studies, older patients (> 65 years) were at higher risk of prolonged hospitalization<sup>68</sup> and post-ASCT complications (especially nonhematologic toxicities) than younger patients.<sup>69</sup> This, however, did not translate into a higher TRM compared with younger patients, probably because of upfront dose reductions applied in most of the studies.<sup>65,66,68,69</sup> A prospective, phase II study showed that bortezomib induction followed by tandem MEL (100 mg/m<sup>2</sup>), ASCT, lenalidomide/prednisone consolidation, and lenalidomide maintenance was highly effective and feasible in patients age 75 or younger. However, tandem transplant followed by consolidation and maintenance in patients older than age 70 experienced a significantly higher rate of TRM (19%) compared to younger patients (age < 70, 5%).<sup>61</sup>

These data clearly showed that we need a careful assessment to identify patients for ASCT. All older adult patients should be evaluated for frailty with the IMWG frailty score or similar tool, as outlined in Table 1.<sup>16,70,76</sup> In fit patients, performance status and organ function should be considered to better define the risk-benefit ratio of transplantation (Fig. 1). In the absence of prospective trials that clearly identify the optimal dose of MEL with ASCT, we cannot make definite recommendations on the dose of MEL in older adult patients. However, it seems reasonable to reduce the dose to 100–140 mg/m<sup>2</sup> in the presence of the following: age older than 70, renal impairment, R-MCI of 4–6, or performance status less than 90% not related to MM. Novel combinations of therapy for patients with NDMM are numerous and are often adjusted on the basis of individual tolerance (Table 3).

Using the Surveillance, Epidemiology, and End Results-Medicare database, Shah et al<sup>87</sup> compared the survival of and cost associated with 270 patients age 65 or older who received ASCT versus those of patients who did not. The mean overall cost of care for a patient who underwent transplantation was \$299,554 versus \$199,973 for a patient who did not, which was an increase of \$99,581. Similarly, the mean survival was 4.94 years with ASCT compared with 3.57 years without ASCT, which meant a gain of 1.37 years with ASCT. The resultant incremental cost-effectiveness ratio was \$72,852 per life-year gained. Given the commonly accepted threshold of \$100,000 per life-year gained, ASCT for patients with MM who are older than 65 is cost-effective.<sup>88</sup>

The greater efficacy of the new combinations, including second-generation proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, may still challenge the role of upfront ASCT, especially in older patients with MM.<sup>81,86,89</sup> Two recent randomized trials showed that the addition of daratumumab to standard regimens, such as VMP or Rd, significantly halved the risk of death or progression (HR, 0.43, and HR, 0.56, respectively), inducing minimal residual disease negativity (the strongest predictor for prolonged OS) in one-fourth of patients.<sup>81,86</sup> Similarly, preliminary results from a phase I/II study showed that carfilzomib combined with lenalidomide and dexamethasone provided a high rate of deep and durable responses (minimal residual disease negativity rate, 60%) with good tolerability. Impressively, after a median follow-up time of 30.5 months, four patients had experienced progression and none had died.<sup>90,91</sup> Although comparisons among different settings are usually inappropriate, the preliminary results (especially in terms of response rate and PFS) achieved by older adults in these recent trials remarkably challenged those obtained by younger patients who underwent ASCT: the PFS with daratumumab/lenalidomide/dexamethasone (71% at 30 months)<sup>86</sup> compared favorably with that of standard induction with bortezomib/lenalidomide/dexamethasone followed by ASCT.<sup>57</sup>

In conclusion, upfront ASCT still remains the standard of care in the context of a sequential approach that includes pre-transplantation induction and post-transplantation consolidation/maintenance with novel drugs in eligible patients. In older patients with MM, ASCT is feasible and cost-effective, showing that age per se should not be used as an exclusion criterion for ASCT. A thorough identification of potential ASCT-eligible patients and a careful evaluation of their fitness are essential to define the eligibility criteria for ASCT and the appropriate dose of MEL. Future clinical trials comparing ASCT-based versus non-ASCT-based approaches will help clarify whether newer regimens that combine immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies will eventually supersede ASCT in the treatment of older fit patients.

## MANAGING HIGH-RISK MYELOMA IN OLDER PATIENTS

### Defining High Risk

Within the myeloma literature, the term “high risk” is generally used in reference to disease biology, whereby intrinsic features of the malignant plasma cells make responses to therapy shorter, yielding shorter PFS and OS. However, viewed more broadly, high risk could refer to any patient subgroup who is at risk for poorer outcomes, even beyond disease-focused outcomes to include patient-focused outcomes (Fig. 2). In addition to disease factors, aging-



associated vulnerabilities, including functional impairments and comorbidities, are associated with poorer outcomes as well.<sup>16,92</sup> As outlined earlier, several scales have been developed, highlighting the impact of aging-associated deficits on outcomes.

The chromosomal abnormalities grouped to define a high-risk subgroup of MM currently refer in general to translocation (4;14), translocation (14;16), and deletion (17p), though the definition of high risk can vary by study. The prevalence of individual chromosomal abnormalities differs across the age spectrum. In a cohort of more than 1,800 older patients with myeloma, translocation (4;14) is actually less common in the oldest subgroup—present in 8.3% of patients older than age 75—compared with the group younger than age 65 (14.3%). The prevalence of deletion (17p) was consistent, at 6% across the age groups. The prevalence of translocation (14;16) was not presented in this study.<sup>93</sup> The translocation (4;14) and deletion (17p) abnormalities were associated with poorer OS (HR 1.89; 95% CI, 1.28–2.80,  $p < .001$ ; and 2.14; 95% CI, 1.39–3.28;  $p < .001$ , respectively). Numerous studies have confirmed the prognostic impact of high-risk chromosomal abnormalities in older adults with myeloma.<sup>42,82,94–96</sup>

Regarding disease-focused stratification system, the revised-ISS (R-ISS) incorporates serum albumin,  $\beta$ 2-microglobulin, and lactate dehydrogenase levels along with high-risk chromosomal abnormalities.<sup>92,96</sup> Although disease-related factors like the R-ISS stage and chromosomal abnormalities can influence outcomes in older adults with myeloma, so too can patient-related factors. In an analysis of 490 older patients treated on two clinical trials, investigators examined factors associated with disease-related death within 2 years of diagnosis, which occurred in 13.8% of patients.<sup>97</sup> After deaths as a result of other factors were excluded, on multivariable analysis, four factors were associated with increased risk of early death as a result of disease progression: elevated serum lactate dehydrogenase (odds ratio, 3.8; 95% CI, 1.9–7.9), high-risk chromosomal abnormalities of translocation (4;14), translocation (14;16), and/or deletion (17p) (odds ratio, 2.6; 95% CI, 1.4–5.0), ISS stage III (odds ratio, 2.1; 95% CI, 1.2–3.9), and age older than 75 (odds ratio, 1.9; 95% CI, 1.0–3.5). As discussed earlier, age in this setting likely serves as a surrogate for aging-associated deficits. The R-MCI includes both aging-associated domains and chromosomal abnormalities, highlighting that neither exist in isolation.<sup>18</sup> An analysis of more than 3,800 patients with myeloma showed that chromosomal abnormalities actually had a decreasing impact on outcomes across the age spectrum, whereas performance status remained of similar relevance across age subgroups.<sup>98</sup>

It is also relevant to consider what outcomes the individual at high risk is at risk for. Traditional approaches have focused on inferior PFS and OS.<sup>99</sup> The IMWG frailty model examined toxicity and treatment discontinuation as outcomes affected by frailty.<sup>16</sup> However, the outcomes of greatest importance to older adults may not be disease specific. Seminal work by Fried et al<sup>100</sup> completed nearly 2 decades ago showed that older adults prioritized maintaining independence in function and preservation of cognition instead of longer survival. This work was recently confirmed in a study of older adults with malignancies, in which 58% prioritized maintaining the independence instead of survival, and 80% prioritized maintaining cognition instead of survival.<sup>101</sup> A recent latent-class analysis of preferences in patients with myeloma (half of whom were older than age 65) showed that a

subgroup prioritized avoiding peripheral neuropathy, by nearly two-fold, instead of longer PFS.<sup>102</sup> It is of particular interest that, by definition, grade 2 and grade 3 neuropathy cause dependence in IADL and ADL, respectively. To date, myeloma studies have largely focused on survival-oriented outcomes, and these results indicate that research on functional outcomes is greatly needed.

### Treatment Based on Chromosomal Abnormalities

Defining the optimal treatment of subgroups of older patients with high-risk disease on the basis of chromosomal abnormalities has been challenging because of the relative rarity of each abnormality. To date, no published clinical trial for older adults has exclusively been designed for patients with high-risk disease. Clinicians must extrapolate from subgroup analyses and observations applied from younger cohorts to determine the optimal therapy for an older patient with high-risk disease on the basis of myeloma biology.

Interest in carfilzomib as a drug of choice for patients with high-risk disease has been piqued by the efficacy of carfilzomib in these patients. The strongest evidence for this is in the relapsed setting, in studies that enrolled patients across the age spectrum rather than confined the research to older or transplantation-ineligible patients. Carfilzomib with dexamethasone was superior to bortezomib and dexamethasone in patients with high-risk relapsed/refractory myeloma (PFS: HR 0.65; 95% CI, 0.45–0.92;  $p = .0075$ ).<sup>103</sup> In the randomized trial of carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone, the triplet improved PFS compared with the doublet in patients with high-risk relapsed/refractory myeloma (HR 0.70; 95% CI, 0.43–1.16).<sup>104</sup> However, a randomized trial of carfilzomib, melphalan, prednisone (KMP) versus VMP for initial therapy in older adults with myeloma demonstrated similar PFS times (22.3 months with KMP vs. 22.1 months with VMP).<sup>105</sup> The overall response rate favored KMP (84.3% with KMP vs. 78.8% with VMP; odds ratio, 1.41; 95% CI, 1.09–1.97); although the rates of grade 3 or greater adverse events were similar (74.7% with KMP vs. 76.2% with VMP), renal failure, cardiac toxicity, dyspnea, and hypertension were more frequent in the KMP group. Subgroup analysis by risk group has not been reported, but the lack of PFS benefit in the overall study makes a benefit in the high-risk subset less likely. The reason for the difference in PFS outcomes between this study and those mentioned earlier with regard to the role of carfilzomib needs more clarification, so the role for carfilzomib in the initial treatment of older adults with high-risk myeloma remains to be defined.

As detailed in a recent review by Avet-Loiseau and Facon,<sup>98</sup> no study focused on older adults has demonstrated a sustained, consistent survival benefit in patients with high-risk myeloma. Outcomes in the high-risk subgroups from selected studies of initial therapy in older adults with high-risk myeloma are presented in Table 4. Overall, the longest PFS in a high-risk subgroup was reported in S0777 with the combination of bortezomib, lenalidomide, and dexamethasone; notably, however, this study was in a substantially younger population than the other relevant studies.<sup>50</sup> Lenalidomide, bortezomib, dexamethasone (RVD)-lite is a regimen modified to improve the tolerability of this triplet in older adults, and it has an excellent response rate (86%) and a low rates of discontinuation of therapy-associated toxicity (4%).<sup>85</sup> However, the number of individuals with high-risk

disease in the phase II study was too small to draw conclusions about the subgroup (personal communication, February 2019). An IMWG consensus panel analyzed the available evidence and concluded that patients with high-risk myeloma should be treated with a combination of a proteasome inhibitor and lenalidomide or pomalidomide along with dexamethasone. Similarly, when they focused on studies designed for older adults with myeloma, Avet-Loiseau and Facon<sup>98</sup> concluded that older adults with high-risk cytogenetics would benefit from regimens that combine novel agents.

### Treatment of Myeloma in a Vulnerable Patient

In the patient-centered view of high risk, focused on aging-associated vulnerabilities rather than on myeloma biology, adverse outcomes for which the patient may be at risk include early death, toxicity of therapy, functional decline, and other outcomes of interest in older adults. In a pooled analysis of more than 1,100 older patients enrolled in clinical trials and treated with novel agents, early death rates were lower than historical comparisons, but deaths as a result of toxicity were still nearly as likely as deaths as a result of disease progression (4.1% vs. 4.4%).<sup>45</sup> Of toxicity-related deaths during first-line of therapy, 28% were caused by cardiac complications; 26%, infections; and 15%, vascular complications. On multivariable analysis, age and ISS stage were associated with increased risk of toxic death. Whether modifying treatment according to frailty improves outcomes is not yet known. In solid tumor oncology, there are well-validated measures to estimate the risk of toxicity of systemic therapy in older adults, and predictors include falls, hearing impairment, IADL dependence, nutritional compromise, and cognitive impairment.<sup>106–108</sup> This approach will be tested in the MRC XIV Fitness Trial, wherein 740 patients will be randomly assigned to standard treatment with lenalidomide, ixazomib, and dexamethasone or to treatment dosing adapted to their level of frailty (NCT03720041).

Associations between chronologic age and adverse outcomes imply that age serves as a surrogate for aging-associated vulnerabilities. Efforts are underway to define which specific geriatric impairments increase an individual's risk for treatment toxicity. In the myeloma literature, efforts are ongoing, and several recommended approaches to modifying treatment according to frailty scores, comorbidities and functional impairments have been published.<sup>76,109</sup> In conclusion, personalized decisions based on disease-related characteristics in conjunction with age-related factors will continue to affect survivorship for older adults with MM. Scarce data exist about octogenarians with MM, but investigations demonstrate similar PFS but inferior OS compared with younger patients. ASCT use in older adults is the standard of care, is feasible, and is cost-effective. Future clinical trials focusing on older adults with high-risk myeloma is an unmet need. Whether modifying treatment according to frailty improves outcomes is not yet known, but it is clearly worth exploring.

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**PRACTICAL APPLICATIONS**

- Evaluate metrics of frailty using geriatric variables and assessment tools for older adults with multiple myeloma, including octogenarians with multiple myeloma.
- Explore autologous stem cell transplantation use, risks, and benefits in older adults with multiple myeloma.
- Identify high-risk populations and review novel combinations of therapy with adjustment based on individual tolerance.

IMWG Frailty score		
<p><b>FIT</b> Age ≤75 years, ADL &gt;4, IADL &gt;5, and CCI ≤1</p>		
<p><b>ASCT eligibility:</b> cardiac function (LVEF &gt;40%) liver function (bilirubin &lt;1.5 ULN, AST/ALT &lt;2.5 ULN) pulmonary function (DLCO/FEV1 &gt;40-80%)</p>		
<b>ASCT</b>		<b>No ASCT</b>
<p>MEL200 mg/m<sup>2</sup> if:</p> <ul style="list-style-type: none"> <li>- age ≤70 years</li> <li>- no renal impairment</li> <li>- rMCI 1-3</li> <li>- performance status ≥90% (not related to MM)</li> </ul>	<p>MEL100-140 mg/m<sup>2</sup> if:</p> <ul style="list-style-type: none"> <li>- age &gt;70 years</li> <li>- and/or renal impairment</li> <li>- and/or rMCI 4-6</li> <li>- and/or performance status &lt;90% (not related to MM)</li> </ul>	<p>Dara-VMP Dara-Rd VRd VCd VMP* Rd*</p>
		<p><b>Reduced-intensity regimens</b></p> <p>Weekly VMP Weekly VCd Vd Rd Rd-R vrd lite<sup>°</sup></p>
		<p><b>Dose-adjusted regimens</b></p> <p>rd<sup>°</sup> vd<sup>°</sup></p>
		<p><b>Palliation and supportive care</b></p>
		
		

**FIGURE 1. Newly Diagnosed Patients With MM: Approach to Treatment**

Abbreviations: ADL, activities of daily living; ALT, alanine aminotransferase; ASCT, autologous stem cell transplantation; AST, aspartate aminotransferase; CCI, Charlson comorbidity index; Dara, daratumumab; DLCO, diffusion capacity of carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; IADL, instrumental ADLs; IMWG, International Myeloma Working Group; LVEF, left ventricular ejection fraction; MEL, melphalan (with dosages in mg/m<sup>2</sup>); MM, multiple myeloma; Rd, lenalidomide and dexamethasone; Rd-R, lenalidomide and dexamethasone followed by lenalidomide maintenance; rMCI, revised myeloma comorbidity index; ULN, upper limit of normal; VCd, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd/vrd, bortezomib, lenalidomide, and dexamethasone. (\*) If daratumumab-based combinations or VRd are unavailable. (°) The lowercase letter indicates a reduced dose.

Domain	Predictors	Outcomes	Treatment Modification
Disease-focused	ISS	Response rates	Combination regimens
	Chromosomal abnormalities	Progression-free survival	
	Gene-expression profiling	Overall survival	Dose-intensification
Aging-focused	Comorbidities	Toxicity	Modified dosing
	Functional impairment	Independence	Start-low; Go-slow approach
	Frailty	Quality of life	

**FIGURE 2. Reconsidering High-Risk Myeloma: A Conceptual Framework for Older Adults**  
 Abbreviation: ISS, international staging system.

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**TABLE 1.**

Geriatric Variable Assessment in MM Populations

Study	Geriatric Domains	Population	Status	Endpoints
IMWG frailty score 2015 <sup>16</sup>	Age	NDMM age 65 years	Fit	OS
	ADL/IADL	Median age, 74 years (range, 70–78 years)	Intermediate fit	PFS
	Comorbidities	Nontransplantation Clinical trial population (n = 869)	Frail	Drug discontinuation Toxicity
Freiburg Comorbidity Index (F-MCI) 2013 <sup>17</sup>	KPS	Chart audit	Fit	OS
	Lung disease*	Symptomatic MM	Intermediate fit	
	Renal disease	Median age, 62 years (range, 27–90 years) Transplantation and nontransplantation (n = 466)	Frail	
R-MCI 2017 <sup>18</sup>	Age	NDMM	Fit	OS
	KPS	Median age, 63 years (range, 21–93 years)	Intermediate fit	PFS
	Lung disease*	Transplantation and nontransplantation (n = 801)	Frail	
GAH 2015 <sup>19,20</sup>	Renal disease			
	Frailty**			
	Cytogenetics			
	Comorbidities			
	Medications	Patients with MM	Score 1	OS
	Gait speed	GAH original cohort	Score 2–6	
	Mood	Median age, 76 years (range, 71–81 years; validation cohort; n = 60 MM/164 total)	Score > 6	
	ADL			
	Health status			
	Nutrition			
Mental status				
Comorbidities				
Edmonton frailty, Schutz et al 2017 <sup>21</sup>	Cognitive impairment	Chart audit age > 65 years	Fit	OS
	Depression	NDMM	Vulnerable	
	Medications	Median age, 77 years (range, 65–98 years; n = 150)	Frail	

Study	Geriatric Domains	Population	Status	Endpoints				
Wildes et al, GA 2018 <sup>22</sup>	Urinary incontinence	NDMM Median age, 71 years (SD, ±5.1 years) Transplantation and nontransplantation (n = 40)	NA	Transplantation recipient status				
	Functional impairment							
	Gait disturbance/falls							
	Low weight							
	Prior hospitalization							
	Age							
	IADL							
	Cognition							
	Mental health inventory							
	TUG							
Rosko et al, GA 2018 <sup>23</sup>	Medications	Transplantation MM	NA	Length of stay Hospitalization EFS Change in deficits				
	Comorbidities							
	Nutrition							
	KPS							
	Self-report function							
	Fatigue							
	Hand grip							
	Gait disturbance							
	Anxiety/depression							
	Social support							
Frailty index 2018 <sup>24</sup>	Cognition	SEER-Medicare database age > 66 years NDMM Median age, 74 years (range, 66–110; n = 30b)	Cumulative deficits frailty index	OS				
	ADL							
	Comorbidities							
	Physical function							
	General health							
	Mental health							
	Murillo et al <sup>25</sup>				IMWG frailty	Patients with MM age > 75 years	Fit/intermediate fit/frail	OS
					IMWG vs. Fried Model <sup>26</sup>	Median age, 79 years (n = 107)	Robust/pre-frail/frail	

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Abbreviations: ADL, activities of daily living; EFS, event-free survival; FEV<sub>1</sub>, forced expiratory volume; FVC, forced vital capacity; GA, geriatric assessment; GAH, geriatric assessment in hematology; IADL, instrumental ADL; I-MCI, Initial-Myeloma Comorbidity Index; IMWG, International Myeloma Working Group; KPS, Karnofsky performance status; MM, multiple myeloma; NA, not applicable; NDMM, newly diagnosed MM; OS, overall survival; PFS, progression-free survival; R-MCI, Revised Myeloma Comorbidity Index; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; TLC, total lung capacity; TUG, Timed up and Go.

\* Lung disease: dyspnea, FEV<sub>1</sub>/FVC, FEV<sub>1</sub>, TLC, respiratory insufficiency.

\*\* Frailty: weakness, poor endurance, low physical activity, slow gait speed.



**TABLE 2.**  
Prospective and Retrospective Studies of ASCT for Older Adult Patients With MM

First Author	No. of Patients	Patient Population (age in years)	Median (range) Age (years)	Conditioning Regimen	ASCT	TRM (%)	ORR/C R (%)	PFS	OS	Comments
<b>Prospective studies</b>										
Palumbo et al 2004 <sup>59</sup>	95	65–70	NA	MEL100	Double	7 (early deaths)	68/NA	Median EFS: 28 months	3-year: 77%	
Facon et al 2007 <sup>60</sup>	126	65–75	70 (39% / total population)	MEL100	Double	9	65/18	Median: 19.4 months	Median: 38.3 months	
Gay et al 2013 <sup>61</sup>	102	75	67 (46–74)	MEL100	Double	< 70 years: 5 70–75 years: 19	95/53	5-year: 48%	5-year: 68%	
Garderet et al 2016 <sup>62</sup>	56	65	67.4 (64–74)	MEL200 (64% of patients) MEL140 (36% of patients)	Single	0	94/40	2-year: 76%	2-year: 88%	Patients in the MEL200 group were slightly younger (68.7 vs. 66.5 years) and had fewer comorbidities (HCT-CI, 0: 79% vs. 50%)
Straka et al 2016 <sup>63</sup>	434	60–70	65 (60–72)	MEL140	Double	First-line ASCT: 1.4 Second-line ASCT: 0	87/12–17	Median: 20–21.4 months	Median: 53.4–55.9 months	> 65 years: TRM, 1.1% (first ASCT) and 0% (second ASCT); 60–64 years and 65–70 years: no difference in PFS/OS
Nadiminti et al 2018 <sup>64</sup>	37	65	68 (65–75)	MEL200	Single	2.7	99/47	3-year: 82%	3-year: 90%	
<b>Retrospective studies</b>										
Bashir et al 2012 <sup>65</sup>	84	70	72 (70–80)	MEL200: 65% of patients MEL140: 25% of patients MEL100: 10% of patients	NA	All patients: 3 < 75 years: 2 75 years: 6	85/18	5-year: 27%	5-year: 67%	No difference in grade 3–4 toxicities in patients < 75 and 75 years
Merz et al 2014 <sup>66</sup>	202	60	65	MEL200	Single: 100% Double: 8%	60–64 years: 2.4 65–69 years: 1 70–75 years: 0	nCR + CR:	Median: 60–64 years: 38 months 60–64 years: 27 months 65–69 years: 23 months	Median: 60–64 years: NR 65–69 years: NR	

First Author	No. of Patients	Patient Population (age in years)	Median (range) Age (years)	Conditioning Regimen	ASCT	TRM (%)	ORR/C R (%)	PFS	OS	Comments
Ozaki et al 2014 <sup>67</sup>	38	65	65–68	MEL200/140	NA	0	70–75 years: 31	70–75 years: 23 months	70–75 years: NR	
Sanchez et al 2017 <sup>68</sup>	2209	< 65: 74.7% 65: 25.3%	NA	NA	NA	< 65 years: 2.3 65 years: 1.2	NA	Median: 26.8–35.2 months	NA	Patients > 65 years had longer in-hospital stay and higher risk of transplantation-related mortality.
Stettler et al 2017 <sup>69</sup>	61	65	NA	MEL200: 65–70 years MEL140: > 70 years	NA	65–70 years: 0 > 70 years: 0	CR: NA 65–70 years: 45 > 70 years: 58	2-year: NA 65–70 years: 80% > 70 years: 53%	2-year: NA 65–70 years: 96% > 70 years: 100%.	Patients > 70 years had longer hospitalization time (26 vs. 20 days) than patients 65–70 years
Belotti et al 2018 <sup>70</sup>	72	65–75	NA	MEL200: 68% of patients < MEL200: 32% of patients	Single: 70% Double: 30%	0	NA	Median: 35.6 months 65–69 years: 51.5 months; 70 years: 27.7 months	NA	
Chilardi et al 2018 <sup>71</sup>	388	> 65	67.5 (65–77)	MEL200: 75.3% MEL70-MEL180: 24.7%	Single: 88.7% Double: 11.3%	1.5	NA	Median: NA 70 years: 27.2 months; > 70 years: 21.5 months (p = NS)	Median: NA 70 years: 82.8 months > 70 years: 56.2 months (p = .02).	
Marini et al 2019 <sup>72</sup>	29	> 65	67 (66–70)	MEL200: 38% MEL140: 62%	NA	NA	51	Median: NA MEL200: 62 months; MEL100/140: 45 months	NA	
Mizuno et al 2018 <sup>73</sup>	287	65	66 (65–76)	MEL200/140/100: < 65 years: 95%/4%/1% of patient	Single	< 65 years: 0.4 65 years: 1.2	NA	NA	5-year: NA < 65 years: 63%	

First Author	No. of Patients	Patient Population (age in years)	Median (range) Age (years)	Conditioning Regimen	ASCT	TRM (%)	ORR/C R (%)	PFS	OS	Comments
Saini et al 2018 <sup>4</sup>	9	80	81 (80-83)	MEL140 65 years: 76%/18%/6% of patients	Single	0	100/45	Median: 31.5 months	NR; 2-year 64% 75%	

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; EFS, event-free survival; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; MEL, melphalan; NA, not applicable; nCR, near-complete response; NR, not reported; NS, nonsignificant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TRM, treatment-related mortality.

**TABLE 3.**

Novel Combinations for the Treatment of Older, Newly Diagnosed Adult Patients With Multiple Myeloma

Treatment	Schedule
VMP <sup>77</sup>	Nine 6-week cycles: V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4); and days 1, 8, 22, 29 (cycles 5–9) M: 9 mg/m <sup>2</sup> days 1–4 P: 60 mg/m <sup>2</sup> days 1–4
VMP weekly <sup>78,79</sup>	Nine 5-week cycles: V: intravenously 1.3 mg/m <sup>2</sup> days 1, 8, 15, 22 M: 9 mg/m <sup>2</sup> orally days 1–4 P: 60 mg/m <sup>2</sup> orally days 1–4
VCd <sup>80</sup>	Four 4-week cycles: V: 1.3 mg/m <sup>2</sup> intravenously days 1, 4, 8, 11 C: 300 mg/m <sup>2</sup> orally days 1, 8, 15, 22 d: 40 mg orally days 1–4, 9–12, and 17–20
Dara-VMP <sup>40,81</sup>	Nine 6-week cycles: Dara 16 mg/kg days 1, 8, 15, 22, 29, 36 of cycle 1 and days 1, 22 of cycles 2–9, then every 4 weeks thereafter V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 and days 1, 8, 22, 29 of cycles 2–9 M: 9 mg/m <sup>2</sup> days 1–4 P: 60 mg/m <sup>2</sup> days 1–4
Rd <sup>82,83</sup>	4-week cycles, until PD: R: 25mg/day days 1–21 d: 40 mg days 1,8,15,22 Induction: nine 4-week cycles:
Rd-R <sup>84</sup>	R: 25 mg/day days 1–21 d: 20 mg days 1, 8, 15, 22 Maintenance, until PD: R: 10 mg/day for 21 days until PD
VRd <sup>50,51</sup>	Induction: eight 3-week cycles:

Treatment	Schedule
	V: 1.3 mg/m <sup>2</sup> intravenously (push) days 1, 4, 8, 11
	R: 25 mg/day days 1–14
	d: 20 mg/day days 1, 2, 4, 5, 8, 9, 11, 12
	Maintenance: 4-week cycles until PD:
	R: 25 mg/day days 1–21
	d: days 1, 8, 15, 22
Vrd lite <sup>85</sup>	Induction: 5-week cycle:
	v: 1.3 mg/m <sup>2</sup> days 1, 8, 15, 22
	r: 15 mg days 1–21
	d: 20 mg days 1, 2, 8, 9, 15, 16, 22, 23 for patients age < 75 years; days 1, 8, 15, 22 for patients age > 75 years
	Consolidation: 6-week cycles:
	v: 1.3 mg/m <sup>2</sup> days 1,15
	r: 15 mg days 1–21
	Until PD:
Dara-Rd <sup>86</sup>	Dara: 16 mg/kg (intravenously) every week for cycles 1 and 2, every other week for cycles 3–6, every 4 weeks thereafter
	R: 25 mg (oral) daily days 1–21
	d: 40 mg (oral) days 1, 8, 15, 22

Abbreviations: C, cyclophosphamide; d, dexamethasone; Dara, daratumumab; M, melphalan; P, prednisone; PD, progressive disease; R, lenalidomide; V, bortezomib.

Outcomes in High-Risk Subgroups: Results From Selected Recent Trials for Transplantation-Ineligible Patients With Myeloma

TABLE 4.

Study or First Author	Proportion of Entire Study Population Age 65 Years or Older (%)	Treatment Arm	Median Progression-Free Survival in High-Risk Subgroup (months)	Median Overall Survival in High-Risk Subgroup (months)
Mateos et al <sup>40</sup>	91.5	VMP-dara	18.0	Not reported
		VMP	18.1	Not reported
SWOG S0777 <sup>50</sup>	43	RVD	38	Not reported
		Rd	16	Not reported
FIRST trial <sup>79,83</sup>	94.3	Rd continuous	8.4	29.3
		Rd-18	17.5	24.3
		MPT	14.6	35.5
VISTA trial <sup>39,77</sup>	96.6	VMP	Not reported	40.0
Zweegman et al <sup>42</sup>	33–34 (age 75)	MPR-R with +(1q21)	19	50
		MPR-R with del (17p)	15	35
		MPR-R with t(4; 14)	14	Not reached
		MPR-R with +(1q21)	17	30
		MPT-T with (17p)	15	41
		MPT-T with t(4; 14)	12	23

Abbreviations: D, dexamethasone; dara, daratumumab; M, melphalan; P, prednisone; R, lenalidomide, T, thalidomide; V, bortezomib.