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Abstract

Introduction. In the majority of cases, Multiple Myeloma is a disease occurring in elderly patients. In the last decades, a major improvement in myeloma patients' outcome has been achieved with the introduction of several new drugs. However, this positive outcome was less likely to occur in elderly patients.

Areas covered. An overall increase of myeloma cases in elderly patients is expected in the next years. This patient population is highly heterogeneous in terms of physiological functions and ability to resist stressing conditions such as myeloma and its treatment. While physicians cannot prevent the stress arising from the disease itself, the intensity of therapeutic approaches can be tuned according to patients' predicted tolerance. In this review, we focus on the assessment of patients' fitness and on available significant data on treatment efficacy and tolerability in elderly patients.

Expert commentary. Fit elderly patients should undergo full-dose therapy to maximize the depth of response, while intermediate and frail patients benefit from reduced-dose regimens in order to avoid toxicity and preserve quality of life. Ongoing trials will provide further evidence to individualize treatment on the basis of geriatric assessment and disease characteristics.

Keywords: Multiple Myeloma (MM), novel agents, frailty, geriatric assessment, tailored therapy

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1. Introduction

Multiple myeloma (MM) is a hematologic neoplasia arising from malignant plasma cells whose main characteristics are monoclonal protein production in blood and/or urine and organ dysfunction, including renal impairment, hypercalcemia, anemia and/or bone lytic lesions (CRAB) [1]. Median age at diagnosis is 69 years, and more than 60% of newly diagnosed MM (NDMM) patients have at least 65 years of age [2].

The world population is rapidly aging. According to World Health Organization (WHO) estimates, in 2015 617 million people worldwide are aged 65 or older [3]. However, these numbers are constantly rising in the last years and by 2050 the number of older people is predicted to dramatically increase, reaching 1.6 billion persons, representing more than 15% of the projected total world population. Thus, in the near future, physicians will deal with a significantly increased number of elderly patients affected by MM.

Elderly patients are highly heterogeneous and persons equal in age can show many differences in terms of physical and cognitive conditions [4]. After the introduction of novel agents, such as proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), the prognoses of NDMM patients have significantly improved, although this survival advantage was seen predominantly in younger rather than in older patients [5,6]. This lack of outcome improvement in elderly patients can be at least partially explained by an increased likelihood of treatment-related toxicity [7]. Indeed, MM and its treatment are significant stressors for elderly individuals, and while disease-related stress at diagnosis is not preventable, the intensity of treatment could be tailored by physicians according to patient frailty [8].

The concept of frailty is best explained as a cumulative decline in physiological functions leading to a diminished adaptability to unfavorable conditions, which in the MM field correspond to all the consequences of a treatment cycle. The exact role of novel agents in frail patients is partially known, since this patient population, often affected by a high comorbidity burden, is frequently excluded by clinical trials. Nowadays, MM treatment is mainly tailored on transplant eligibility and, in transplant-

ineligible patients, by the physician's perception of patient frailty. However, tools taking into account objective data in addition to age are needed to identify frail patients in a reliable manner, with the actual objective to tune treatment intensity, in cancer, 3 evidence-based models have been proposed so far to identify frailty [9]: the phenotype model, the cumulative deficit model, and the comprehensive geriatric assessment (CGA). The phenotype model takes into account only physical characteristics such as weight loss, slow gait speed and poor hand-grip strength, while the cumulative deficit model takes into account the sum of individual deficits due to different single diseases. CGA is an interdisciplinary assessment of a multiplicity of factors, such as fatigue, cognition, mobility and nutrition, all of them analyzed by using validated tools. CGA is widely adopted in the treatment of geriatric patients and has been introduced in geriatric oncology as well [10,11]. Though CGA is the most complete tool, it is also complex and time-consuming. In the next section, we describe the geriatric assessment tools that have been introduced so far in the MM field.

1.1. Geriatric assessment in multiple myeloma

In MM patients 3 frailty scores based on solid data have been proposed so far (figure 1).

In 2015 the International Myeloma Working Group (IMWG) analyzed the results from three multicenter trials (EMN01-NCT01093136; 26866138MMY2069-NCT01190787; IST- CAR-506-NCT01346787) enrolling transplant-ineligible NDMM patients, during which a baseline geriatric assessment (GA) was prospectively collected [8]. Three tools were used for the GA, namely Katz's Activity of Daily Living (ADL), Lawton's Instrumental Activity of Daily Living (IADL) and Charlson Comorbidity Index (CCI). ADL and IADL assessed the independence status of patients [12], while CCI assessed the amount and severity of comorbidities [13]. 869 patients were included in a multivariate analysis adjusted for International Staging System, cytogenetic risk and type of therapy. Age (75-80 years HR 1.13, >80 years HR 2.4), ADL ≤4 (HR 1.58), IADL ≤5 (HR 1.81), and CCI ≥2 (HR 1.58) were independent variables impacting on overall survival (OS). According to these results, an additive frailty score based on the relative weight of each of these parameters was created

(HR between 1 and 2 = 1 point, HR >2 = 2 points) stratifying patients into three distinctive groups with different OS: fit (score = 0, 39% of patients, 3-year OS 84%), intermediate (score = 1, 31% of patients, 3-year OS 76%, HR 1.61 compared to fit patients, P=0.042), and frail (score ≥2, 30% of patients, 3-year OS 57%, HR 3.57 compared to fit patients, P<0.001). Of note, although all patients with >80 years of age were classified as frail, only 19% of total frail patients were assigned to this group only because of age. Grade ≥3 non-hematologic adverse events (AEs) were more frequent in frail compared to fit patients (30% vs. 18%, HR 1.57, P=0.008); the same difference was observed in terms of treatment discontinuation (31% vs. 16% at 12 months, HR 2.21, P<0.001). Higher treatment discontinuation rates led to a significantly worse progression-free survival (PFS) in frail compared to fit patients (3-year PFS 33% vs. 48%, HR 1.68, P<0.001).

The IMWG frailty score was developed in the context of clinical trials in which a consistent part of frail patients was excluded. Therefore, this score was validated in a German cohort of 125 consecutive NDMM patients, included in the study independently from transplant eligibility [14]. This cohort was more similar to a 'real-world' cohort and, as expected, fewer fit (18% vs. 39%), and more frail patients (48% vs. 30%) were analyzed, compared to the IMWG study. The 3-year OS rates were 91%, 77% and 47% respectively for fit, intermediate and frail patients, thus validating IMWG data. In this study, the use of CCI alone and of other frailty tools – such as the Kaplan-Feinstein Index (KFI), the Hematopoietic Cell Transplant-Co-morbidity Index (HCT-CI) and the revised myeloma comorbidity index (R-MCI) – also allowed the stratification of patients in a fit and frail population with a different outcome, whilst IMWG-frailty score and R-MCI performed best.

The R-MCI score, in particular, was prospectively developed in 801 consecutive NDMM patients in a single German center [15]. Median age was 63 years, 28% of patients were 66-75 years old, 13% were older than 75 years. Approximately one half of the population received autologous stem-cell transplantation (ASCT) that was recommended in fit patients up to the age of 70 years. The R-MCI was developed in a training set of patients (2/3 of the total population) and then tested in a validation set population (1/3 of the total population). Multivariate analysis identified renal, lung, Karnofski

performance status impairment, frailty and age as significant risk factors impacting overall survival. R-MCI was generated by combining the weighted impact of the aforementioned risk factors, thus identifying fit (R-MCI <3, 31% of patients, median OS 10 years), intermediate (R-MCI 4-6, 56%, median OS 4.4 years) and frail patients (R-MCI >6, 13%, median OS 1 year). R-MCI remained significant in subgroup of patients undergoing ASCT or not, treated or not with novel agents, ≤ and > 65 years (P<0.0001).

The IMWG-frailty index was tested in the prospective FIRST trial, which evaluated lenalidomide-based first-line treatment in elderly transplant ineligible MM patients [16]. However, since ADL and IADL were not prospectively obtained at diagnosis, they were estimated using the EQ-5D questionnaire on quality of life. This proxy IMWG-frailty score confirmed a better outcome of fit compared to frail patients both in terms of median PFS (28 vs. 20 months, HR 0.67) and OS (median not reached [n.r.] vs. 45 months, HR 0.42).

Another simple risk score developed at the Mayo clinic was based on the prognostic value of N-terminal natriuretic peptide type B (NT-proBNP), a widely available laboratory marker that measures ventricular dysfunction and is cleared by the kidney, two fundamental organ systems determining fitness [17]. A multivariate analysis in 351 NDMM patients identified NT-proBNP ≥300, age ≥70 and ECOG performance status ≥ 2 as independent factors impacting survival. Four patient groups were identified by assigning 1 point to each of these factors. The OS had a median value of 18, 28, 58 and n.r. for patients with 3, 2, 1 and 0 points respectively (P<0.0001).

Other imaging-based markers of frailty in NDMM – such as low subcutaneous adipose tissue detected through computed tomography – could be additional factors impacting patients' survival [18].

In 2017, the Spanish Group evaluated the Geriatric Assessment in Hematology (GAH) scale in a retrospective, multicenter, observational study enrolling 108 patients diagnosed with myelodysplastic syndrome, acute myeloblastic leukemia, multiple myeloma, or chronic lymphocytic leukemia. This tool is a brief questionnaire that takes into account 8 dimensions of geriatric assessment (number of drugs, gait speed, mood, ADL, subjective health status, nutrition, mental status, and comorbidity).

The sum of the GAH scale score, ranging from 0 to 66, is integrated by a factor derived from the treatment intensity (34 points for intensive therapy or 0 for attenuated) leading to a maximum score of 100 points. The score allows to stratify patients into 3 categories: low probability to develop toxicity (points 0-19), high likelihood to develop toxicity with intensive therapy (points 19-47), high probability to develop toxicity regardless of treatment intensity (points >47). The GAH scale is potentially useful for election of individual treatment regimens. Further studies need to be performed to confirm these findings [19].

2. First-line treatment in elderly MM patients

MM patients are defined as "elderly" when they are aged >65 years. Traditionally, patients ≤65 years old and in good health are candidate to novel-agents-based induction treatment, followed by high-dose therapy (HDT) with melphalan at 200 mg/m^2 (HDM) rescued by ASCT; whereas patients >65 years old are considered transplant ineligible. However, in modern clinical practice, the cut-off age for transplant ineligibility is not so strict as before. Indeed, the treatment strategy is based on comorbidity, disability, and/or frailty status, as well as chronological age.

Table 3 summarizes performance status, proportion of elderly patients, efficacy and toxicities of the main clinical trials described below.

2.1. Transplant eligibility, efficacy and safety

In recent years, the introduction of GA in NDMM patients has allowed clinicians to identify categories of elderly patients able to tolerate HDT-ASCT in order to achieve deep and durable responses [20]. The R-MCI or the HCT-CI are risk-assessment scores that have been studied also in the context of transplant-eligible NDMM patients and thus are the most appropriate to evaluate

transplant eligibility [15,21]. In the majority of clinical trials evaluating ASCT in the elderly, patients are aged 65-75 years, while severe comorbidities and organ dysfunctions are exclusion criteria.

A French study on 56 NDMM patients aged ≥65 years evaluated the safety and efficacy of bortezomib-based induction followed by HDM-ASCT. The conditioning regimen was either with melphalan 140 mg/m^2 (36%) or melphalan 200 mg/m^2 (64%) at physician's discretion, and tandem ASCT was allowed (6%). The overall response rate (ORR) 3 months after ASCT was 94%, and estimated PFS rate at 2 years was 76%, with a better trend for the group receiving melphalan 200 mg/m^2. Transplant-related mortality at 100 days was 0% in this highly selected elderly population (80% of patients with ≤1 comorbidity prior to transplantation). The most frequent non-hematologic toxicities observed were infections (36% of patients) and oral mucositis (36%), with no significantly increased toxicity in the group receiving melphalan 200 mg/m^2 [22].

Another study enrolled 102 NDMM patients aged 65-75 years receiving bortezomib-doxorubicin-dexamethasone (PAD) induction followed by melphalan 100 mg/m^2-ASCT and lenalidomide maintenance (R-maint). The ORR was 94% after ASCT (with 75% ≥VGPR) and 95% after R-maint (with 82% ≥VGPR), while median PFS was 48 months. The most frequent non-hematologic grade 3-4 toxicities were infections (33%), peripheral neuropathy (18%), gastrointestinal (18%), dermatologic (10%) and thromboembolism (7%). As expected, the subgroup of patients aged ≥70 years had greater rates of infections (26% vs. 20%) and transplant-related toxicity (19% vs. 5%) during ASCT [23]. These results compared well in terms of efficacy with similar studies on younger patients. As an example PAD induction followed by ASCT and bortezomib maintenance in patients aging ≤ 65 years (HOVON-65/GMMG-HD4 trial) produced a median PFS of 34 months [24]. In a meta-analysis of 3 randomized clinical trials exploring the role of R-maint after ASCT (2 studies enrolling patients ≤ 65 years, 1 study ≤ 71 years) median PFS in R-maint arm was 52.8 months [25].

ASCT is effective and well tolerated in the elderly fit patient, and even if the current trend in clinical trials is to use reduced doses of melphalan as conditioning regimen (100 or 140 mg/m^2), full-dose melphalan (200 mg/m^2) proved to be feasible in highly selected patients. The tendency to treat a

patient older than 65 years with HDM-ASCT is increasingly frequent, as reported in a recent study that analyzed 53675 MM patients who underwent HDM-ASCT between 1991 and 2010. The study showed that ASCT is more frequently performed in older patients, improving survival especially in the elderly. Early deaths after ASCT decreased to very low levels in all age groups. These advances are mainly due to improvements in supportive care and to a more accurate selection of patients [20].

2.2. Treatment in transplant-ineligible patients

Transplant-ineligible patients are treated with different approaches according to age and patient status. Fit patients, aged 65-75 years, are suitable for full-dose, novel agent-based chemotherapy. Intermediate (frail patients >75 years, or younger ones with comorbidities) should undergo reduced-intensity chemotherapy regimens, possibly including novel agents.

The choice of treatment should consider benefit/risk ratio, patient clinical status and quality of life [26].

Historically, standard frontline treatment for elderly, transplant-ineligible patients was the alkylating agent melphalan in combination with prednisone (MP). This regimen was well-tolerated and quite effective. Nowadays, the availability of novel agents – (including IMiDs, PIs, and monoclonal antibodies (MoAbs) – has allowed the development of new regimens, characterized by higher efficacy and acceptable toxicity profile, as compared with MP [27] (Table 1).

2.2.1. Thalidomide-based regimens

A meta-analysis of six randomized clinical trials, comparing thalidomide (T) associated to MP (MPT) vs. MP alone, showed a significant increase in ORR (59% vs. 37%) and a prolongation of PFS (20 vs. 15 months, P=0.0001) and overall survival (OS, 39 vs. 33 months, P=0.004) in patients treated with MPT [28]. The most frequent grade 3-4 non-hematologic toxicities described in MPT patients were peripheral neuropathy (6%-23%), thromboembolism (3%-12%), infections (10%-13%), cardiac

complications (2%-7%), and gastrointestinal events (5%). Thalidomide discontinuation because of unacceptable AEs was reported in 33%-45% of patients [29].

Alternatively, T might be added to cyclophosphamide (Cy) and dexamethasone (D). CyTD showed an ORR (64%) similar to MPT. CyTD, as compared with MP, was less myelosuppressive, whereas a higher incidence of sensory and motor neuropathy, thromboembolic events, constipation, infections, and rash was reported [30].

2.2.2. Bortezomib-based regimens

The addition of bortezomib (V) to MP as initial standard therapy in patients unsuitable for ASCT was studied in the VISTA trial. VMP showed a higher ORR, as compared to MP (71% vs. 35%, P <0.001) [31]. After a median follow-up of 60 months, OS was longer in VMP group (56 months vs. 43 months, P <0.001) [32]. However, VMP lowered quality of life (QoL) and increased toxicity. Fortunately, by the end-of-treatment visit, QoL returned comparable between VMP and MP [33]. Neutropenia (40%) was the main adverse event associated with VMP, followed by thrombocytopenia (37%), peripheral neuropathy (14%), infections (10%), and gastrointestinal events (7%).

VMP was better tolerated in comparison with VTP, without significant differences in terms of efficacy [34].

The association of bortezomib, melphalan, prednisone and thalidomide (VMPT) represented a more intensive combination. Despite better results in terms of efficacy, this regimen was too toxic in the elderly setting, especially for severe neutropenia, cardiac complication, and thromboembolic events [35].

Different treatment schedules and routes of bortezomib administration were examined with the aim of reducing toxicity. Once-weekly bortezomib was associated with a significant reduction in the development of peripheral neuropathy, as well as of any other hematologic or non-hematologic adverse event, without affecting efficacy. Indeed, because of lower discontinuation rates, the delivered cumulative dose of bortezomib was similar in patients treated with once- and twice-weekly

schedules [36,37]. Subcutaneous bortezomib injection was reported to be not inferior to endovenous administration, with a significant reduction in toxicity [38].

2.2.3. Lenalidomide-based regimens

The FIRST trial randomly assigned 1623 elderly, NDMM patients to receive continuous lenalidomide-dexamethasone (Rd-cont) vs. 18 cycles of MPT vs. 18 cycles of lenalidomide-dexamethasone (Rd-fix). The results showed the significant superiority of Rd-cont in terms of ORR, PFS, and reduction of death risk, as compared to MPT. The proportion of patients with ≥1 AE of grade (G) ≥ 3 was 85% in the Rd-cont, 89% in the MPT, and 80% in the Rd-fix groups. G≥3 neutropenia was much higher in the MPT group (46%), whereas G≥3 infections were more frequent in the Rd-cont (29%). The incidence of thromboembolic events was also higher in the Rd-cont group (8%). Instead, G≥3 peripheral neuropathy was 9 times more frequent in MPT (9%) than in lenalidomide-based regimens (1%) [39].

Recently, the addition of intravenous bortezomib to Rd (VRd) was compared to Rd alone in the phase III SWOG S0777 trial, in which patients were enrolled without an immediate intent to undergo ASCT [40]. This trial enrolled also young patients and median age was 63 years. A PFS (median 43 vs. 30 months, P=0.0018) and OS (median 75 vs. 64 months, P=0.025) benefit was noted in the VRd vs Rd arm. The outcome of patients older than 75 years (median PFS of 39 months vs. 20 months and median OS of 63 months vs. 31 months in the VRd vs Rd arms) was consistent with the outcome of the overall population, although only OS improvement reached statistical significance. Nonetheless, the discontinuation rate due to toxicity was higher in VRd (23%) vs Rd (10%) groups. Results for the SWOG S0777 trial as a potentially useful regimen for elderly patients should be taken with caution due to several limitations both in the design as well as in the results of the study: the assessment of response was suboptimal since not all levels of response were confirmed; different dosing schedules were used for VRd (eight 21-day cycles) vs Rd (six 28-day cycles); bortezomib was administered IV and on a twice weekly basis, but such approach led to a higher incidence of severe neuropathy and

early discontinuation and is no longer considered standard; age was not a stratification factor, which led to an imbalance between the treatment groups and complicated assessment of outcomes by age; patients with severe renal impairment and/or compromised bone marrow function were excluded, preventing the generalization of these results to those patient populations.

2.2.4. Daratumumab in combination with bortezomib, melphalan and prednisone

Daratumumab (Dara) is a human IgG/K monoclonal antibody that targets CD38, an antigen highly expressed in multiple myeloma cells. Dara showed the ability to induce complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and potent anti-tumor activity in mouse xenograft tumor models. Other mechanisms of action included antibody-dependent cellular phagocytosis (ADCP) and activation of caspase-dependent cell death pathway [41]. On the basis of promising results in terms of safety and efficacy, Dara was combined to VMP (Dara-VMP) in ≥65 years old NDMM patients and compared to standard VMP. The ORR was 91% in the Dara group vs. 74% in the control group (P<0.001). The median PFS was not reached in the Dara-VMP cohort, while it was 18 months in the standard VMP arm (P<0.001). The safety profile was similar, but the Dara-VMP group was affected by a higher G≥3 infections rate (23% vs. 15%), and by a 5% of G≥3 infusion-related reactions [42].

2.3. Role of maintenance in the elderly

Maintaining the response of the first-line therapy is an important goal. In MM, both interferon (IFN) and glucocorticosteroids were examined as maintenance treatment without obtaining great success. The development of novel agents-based regimens provided the opportunity to study the efficacy and safety of these new drugs also in the maintenance setting [43]. In the context of elderly patients, the role of T was explored in two trials. One study was conducted by the Central European Myeloma Study Group (CEMSG) and compared T plus IFN (T-IFN) vs. IFN alone. It showed a significant PFS benefit for the T-IFN group (28 vs. 13 months, P=0.007). Peripheral neuropathy, constipation, skin

and renal toxicities were significantly higher in the T-IFN arm [44]. The second study compared T vs. no maintenance in patients previously treated with both intensive and conventional chemotherapy. The trial confirmed the prolongation of PFS in both groups, reporting a median PFS of 11 vs. 9 months (P = .014) in favor of T maintenance in the non-intensive pathway [45].

VT as maintenance therapy was evaluated by Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA). The trial randomized 511 patients to either nine 6-week cycles of VMPT induction therapy followed by VT maintenance or to nine 6-week cycles of VMP induction treatment. The protocol was amended because of excessive toxicity. The biweekly schedule of bortezomib was reduced to a once-weekly administration to enhance tolerance. Both the VMPT and the VMP regimens were changed to nine 5-week cycles. Albeit the evaluation of the benefit of maintenance treatment in this trial is difficult because different induction treatments had been used in the 2 arms, patients in the VMPT-VT group achieved a higher rate of complete response, longer PFS and time to next treatment (TTNT). Despite the VT association, no significant increase in neurotoxicity was described [35,46]. In the Spanish Programa Español de Tratamientos en Hematología (PETHEMA) trial, after an induction based on VTP or VMP regimens, 178 patients were randomized to either VT or bortezomib and prednisone (VP) maintenance therapy. Both treatments were given for up to 3 years. Bortezomib maintenance was administered at day 1, 4, 8, and 11 every 3 months. The VT group received thalidomide at a dose of 50 mg/day, and the VP cohort received prednisone at a dose of 50 mg/m^2 every other day. Maintenance therapy improved response rates, without significant differences between the two arms. G≥3 peripheral neuropathy was reported in 3% of patients in the VP group, and 9% in the VT group [47].

The phase III NCRI Myeloma XI study recruited 1970 patients (among which 723 were transplant-ineligible) to compare lenalidomide at 10 mg (R-10), at days 1-21 of a 28-day cycle vs. observation. R-10, irrespective of induction therapy, prolonged PFS (26 vs. 11 months, P<0.0001). The benefit of R-10 was described also in high-risk patients, defined as carriers of at least one of the following cytogenetic alterations: t(4;14), t(14;16), t(14;20), gain(1q) and/or del(17p) [48]. Melphalan,

prednisone, lenalidomide (MPR), followed by R maintenance (MPR-R), was compared to MPR and to MP in another phase III trial. The study showed a significant prolongation of PFS in the R maintenance cohort (31 vs. 14 vs. 13 months, P<0.001), with the higher benefit observed in patients aged 65-75 years [49].

2.4. Dose and therapy tailoring upon frailty

Before addressing the topic of dose tailoring according to patients' frailty, it is necessary to mention that current recommendations about this matter are based on expert opinion, single center experiences, or deduced by the analysis of results of clinical trials designed for other purposes. Furthermore, for many new drugs – such as ixazomib, elotuzumab, or daratumumab – there are no data available to support treatment adjustment upon frailty. Therefore, there is an urgent need to design focused trials that may offer evidence sufficiently strong to elaborate supported guidelines. Data presented in the preceding paragraphs show that many therapeutic options are potentially available for patients ≥65 years old. For this very reason, defining the patient status is a key strategy for the selection of the appropriate treatment and the maximization of the benefit/risk ratio. Very fit patients aged 65-70 years might be eligible for HDT-ASCT. Independently of chronological age, patients with comorbidities and/or frail, should be treated with less intensive therapies [26].

In fit patients, the primary goal of treatment remains the maximization of efficacy. Therefore, the association of novel agents to standard chemotherapy as backbone may be considered the best option to reach the higher response, with an acceptable toxicity profile. Fit patients may benefit from triple regimens combining a novel agent, such as bortezomib or thalidomide or lenalidomide, with conventional chemotherapy, such as melphalan or cyclophosphamide or prednisone. Full-dose Rd is another possible treatment in this patient population.

Intermediate and frail patients should be considered at high risk for unacceptable toxicity. Therefore, the main goal of treatment should focus on tolerability in order to keep the patient on treatment as long as possible.

The choice of the most appropriate treatment for intermediate and/or frail patients should take into account multiple factors: cardiovascular history, renal function, history of diabetes, presence of peripheral neuropathy, psychosocial status, preferences of patient and caregivers [50].

Doublet rather than triplet combinations may be preferred since more intensive treatments are characterized by a very high risk of intolerance. The phase IIIB UPFRONT trial compared three frontline bortezomib-based regimens in transplantation-ineligible patients. VTD or VMP did not offer any advantage in terms of ORR, PFS and OS against bortezomib and dexamethasone (Vd) [51].

This effect was evident also in another trial enrolling a large number of frail patients (25%) and comparing lenalidomide-based triplets (MPR, CPR) vs. the doublet Rd. No benefit was noted in the triplet arms compared to Rd in terms of PFS and OS [52].

Vd is probably the best choice in case of aggressive disease, and/or renal dysfunction occurring in a patient able to attend numerous hospital visits to undergo therapy.

In case of non-aggressive disease with normal renal function or with pre-existing peripheral neuropathy, Rd might be the most appropriate regimen. Indeed, it is an all oral regimen, and this is a key feature to avoid the inconveniences of hospitalization [50].

About 50% of elderly patients experience G≥3 AEs during the early cycles of treatment with a novel agent. This leads to treatment discontinuation or lowering of dose rates. Therefore, it is very important to apply strategies to avoid severe AEs. According to risk status, therapy should be started at reduced dose and, in case of good tolerance, a dose escalation might be considered (Table 2).

Furthermore, the use of antimicrobial drugs and thromboembolic risk-based prophylaxis, as well as the application of growth factors and erythropoiesis-stimulating agents, should be considered to avoid infections, cardiovascular complications, and myelosuppression.

If a G≥3 AE occurs during treatment, therapy should be stopped until resolution of the toxicity, usually before the start of the following cycle, when treatment can be restarted at a lower dose.

Supportive measures should be applied to control pain, to prevent bone disease, and to slow the global deterioration that accompanies the disease, especially in relation to the cardiovascular, renal, pulmonary, and hepatic functions [27].

In patients with severe impairment of cognitive function or social dependency, the goal of treatment should be the control of disease symptoms. In these cases, low-dose corticosteroids, melphalan or cyclophosphamide might be the best choice, given their low toxicity profile, ease of administration, versatility, and evidence of some anti-myeloma effect.

Continuous treatment should not be precluded to intermediate and/or frail patients, especially the ones who respond slowly and tolerate well the therapies. R is one of the drugs which can be used in the maintenance setting because of its oral administration, relatively low toxicity profile, and good efficacy. Furthermore, the first oral proteasome inhibitor, ixazomib (Ixa), has been showing promising results in continuous treatment, and might represent an additional weapon against the disease [50,53].

Elderly patients with relapsed or refractory multiple myeloma should be treated following almost the same criteria leading to the choice of therapy at diagnosis. Retreatment with the same first-line regimen could be an option if a response lasted ≥12 months (≥6 months in frail relapsed patients) without relevant toxicity. For short-term responses, an alternative regimen should be proposed, provided that no increase of cumulative toxicity across the lines of treatment occurs [27].

3. Treatment in relapsed and/or refractory elderly MM patients

In the past few years, treatment options for relapsed/refractory multiple myeloma (RRMM) have grown consistently, thanks to the approval of new PIs, IMIDs and MoAbs to be used alone and in combination therapy. This broader scenario is going to improve prognosis in RRMM patients, but at the same time is bringing up new questions about how to choose the best treatment at relapse. The answer is even more difficult to find in the heterogeneous elderly patient setting [54].

3.1. Treatment in patients not refractory to PIs and IMIDs

In the phase III ASPIRE study, 792 RRMM patients were randomized to carfilzomib, lenalidomide and dexamethasone (KRd) vs. Rd alone. The KRd regimen showed a better PFS compared to Rd (26 vs. 17 months). This benefit was observed also in the subgroup of patients aged ≥70 years (24 vs. 16 months) and in the small cohort aged ≥75 years (30 vs 16 months). Among patients aged ≥70 years, G≥3 AEs rate was similar in the two arms, but the KRd group experienced a higher rate of G≥3 cardiovascular toxicity (14 % vs. 3%), thrombocytopenia (20% vs. 15%) and neutropenia (37% vs 23%). As expected, the frequency of cardiovascular events was higher in patients aged ≥70 years receiving K vs. younger ones (14% vs. 5%), leading to a higher rate of K discontinuation due to cardiac toxicity in the elderly (7% vs. 1%). However, treatment discontinuation rates among the elderly patients were similar in the two arms (34% vs. 35%), suggesting that KRd is a triplet with an acceptable toxicity profile also for the older patients [55,56].

Ixazomib is an oral analogue of bortezomib, showing promising efficacy and safety profile [57]. The completely oral combination Ixa-Rd was compared to Rd alone in 722 RRMM patients enrolled in the phase III TOURMALINE-MM1 study.

A better PFS was observed in the Ixa group compared to the control group (21 vs. 15 months), and this advantage was also observed in the patients aged ≥75 years (18 vs. 13 months). G≥3 toxicities were similar between the two arms (74% vs. 69%), with the exception of thrombocytopenia, which was more frequent in the Ixa cohort (19% vs 9%). Treatment discontinuation rates due to side effects were also similar in the two arms (17% vs 14%) [58].

3.2. Treatment in patients not refractory to PIs

929 RRMM patients were enrolled in the phase 3 ENDEAVOR trial comparing Vd vs. carfilzomib-dexamethasone (Kd). A significantly longer PFS was observed in the Kd arm (19 vs. 9 months). This advantage was also observed in patients 65 to 74 years old (15 vs. 9 months) and in ≥75 years old ones (19 vs. 9 months). G≥3 cardiovascular events and hypertension were more frequently observed

in the Kd group irrespective of patients' age. Remarkably, Kd showed a significantly lower incidence of peripheral neuropathy, which represents the main reason for discontinuation in the Vd cohort. Treatment discontinuation rates due to AEs were similar in the two treatment arms for younger patients (21% vs. 22%). In patients aged ≥75 years, the discontinuation rate for AEs was higher in the Vd cohort (26% vs. 35%) [59,60].

The conventional Vd regimen was compared also to the triplet Dara-Vd in the phase III CASTOR trial recruiting 498 RRMM patients. Dara-Vd proved to be significantly superior in terms of PFS both in the overall population (median not reached vs. 7 months, HR 0.39) and in the elderly patients (n.r. vs. 7 months, HR 0.35). In the Dara-Vd arm a higher rate of G≥3 AEs was observed (76% vs. 62%), mainly regarding hematologic toxicities such as thrombocytopenia (45% vs. 33%) and neutropenia (13% vs. 4%).

Treatment discontinuation rates were similar in the two groups (7% vs. 9%). Dara infusion-related reactions were generally mild and occurred only during the first infusion in 98% of cases. 9% of patients experienced a G3 reaction, with no G4 reactions observed [61].

3.3. Treatment in patients not refractory to IMIDs

In the phase III POLLUX trial Dara-Rd was compared to Rd in 569 RRMM patients. A better PFS was observed in the Dara-Rd arm (n.r. vs. 18 months, HR 0.37) also for patients aged ≥75 years (n.r. vs. 11 months, HR 0.11). A slightly higher G≥3 AEs rate, mainly regarding neutropenia (52% vs. 37%) and infections (28% vs. 23%), was observed in the Dara cohort. Treatment discontinuation rates were similar in the two arms (7% vs. 8%). Only 5% had a G3 Dara infusion-related reaction [62].

Rd was also tested in combination with elotuzumab (Elo) in the phase III ELOQUENT trial enrolling 646 RRMM patients. Elo-Rd was superior in PFS (19 vs. 15 months), and the benefit was also observed in patients aged ≥65 years (HR 0.65).

In the 3-year extended follow-up, the PFS advantage remained also consistent in the elderly patient subgroups (HR 0.72 and 0.59 in ≥65 and ≥75 years old patients, respectively). G≥3 AEs rates were

similar in both treatment arms except from G≥3 lymphocytopenia, which occurred more frequently in the Elo-Rd cohort (77% vs 49%). Only 1% of patients experienced G3 Elo infusion-related reactions, mostly limited to the first infusion [63,64].

3.4. Treatment in heavily pretreated patients

Relapsed/refractory disease in heavily pretreated, elderly patients is an even more demanding challenge. The combination of Pomalidomide with dexamethasone or Dara as a single agent showed to be valid options in elderly patients [65,66].

4. Expert commentary

MM is a hematologic malignancy predominantly occurring in the elderly. Indeed, the median age at diagnosis is about 70 years, and nearly 35% of patients are ≥75 years old.

The development of novel agents, such as PIs (bortezomib, carfilzomib, ixazomib) or IMiDs (thalidomide, lenalidomide, pomalidomide) or MoAbs (daratumumab and elotuzumab), is considerably improving the prognosis for patients. An estimate of the 5-year relative survival of patients with multiple myeloma in the United States from 1990-1992 to 2002-2004 reported a significant survival increase from 29% to 35%. However, while patients aged <59 years benefited a more substantial improvement, the increases were much less pronounced in patients aged 60-69 years (5-year relative survival from 31% to 36%), and no improvement was seen in patients aged >70 years (5-year relative survival from 27% to 29%) [67].

Several factors might be involved in the influence of age on patient prognosis. Aging is associated with a gradual, progressive decrease in physiologic reserve. The reduction in muscle mass, the body fat increase, and the intracellular water levels reduction lead to changes in body composition. More importantly, aging is associated with clinically significant reductions in renal, cardiovascular, pulmonary, gastric and hepatic function, as well as changes in blood flow and bone marrow status. All of these changes may affect the metabolism of drugs, altering clinical efficacy and potentially

increasing toxicity. Reduced tolerability and reduced dose intensity lead to the poorer outcomes observed in elderly patients with cancer [27]. Furthermore, elderly patients are underrepresented in clinical trials [68].

Based on these considerations, the choice of treatment should take into account the patient characteristics, not merely in terms of age, but also in terms of comorbidity, disability, and frailty. Easy-to-calculate prognostic scores are available (for example: http://www.myelomafrailtyscorecalculator.net/) and offer an objective, reproducible, rapid tool to associate a patient to a risk of toxicity and survival probability. On the basis of the score, the patient is classified as fit, intermediate or frail and, consequently, a more appropriate treatment may be chosen. The treatment of fit patients should aim to maximize efficacy because their organism is still able to take full advantage of the benefic effects of intensive, or combinations regimens against disease. Intermediate or frail patients are at higher risk of developing unacceptable toxicities because their organism cannot properly metabolize intensive or full-dose multi-drugs regimens. For this reason, less intensive combinations of the best drugs, appropriately tailored to each patient, should be chosen, and dose reductions should be applied if necessary. Supportive therapy, careful clinical monitoring, and patient education remain fundamental to improve QoL, thus increasing chances to prolong treatment and, as a consequence, to improve survival.

5. Five-year view

Determining treatment intensity in elderly MM patients is not an easy task and in the near future the wider therapeutic armamentarium available to clinicians will make it harder. However, in the authors' opinion, the addition of MoAbs to the current standard of care in transplant-ineligible NDMM patients will consistently improve patients' outcome without adding significant toxicity even in the frail population. Indeed, many trials investigating the addition of Dara or Elo to the current first-line treatments in transplant-ineligible patients are ongoing [69]. The ALCYONE trial (Dara--VMP vs. VMP) did not show a reduced efficacy in patients aged ≥75 years with ECOG ≥1, thus suggesting

that MoAbs-based quadruplets are feasible, at least in intermediate and/or fit patients. Results from the MAIA (NCT02252172, Dara-Rd vs. Rd) and ELOQUENT-1 (NCT01335399, Elo--Rd vs. Rd) phase III trials are going to determine the impact of adding these MoAbs to first-line Rd treatment in transplant-ineligible patients.

In the context of maintenance therapy, the results of the TOURMALINE-MM4 trial investigating the oral PI Ixa (NCT02312258, Ixa vs. placebo after induction therapy) in transplant-ineligible patients will be of great interest.

The use of GA tools is becoming more frequent in tertiary centers treating MM patients, although results from clinical trials specifically designed to enroll patients according to GA are lacking.

An Italian phase III trial enrolling intermediate fit patients according to GA is exploring continuous Rd vs. Rd for 9 cycles followed by reduced-dose R maintenance until progression (NCT02215980).

Trials investigating the role of ASCT in elderly fit patients are ongoing (NCT01090089) and dose-adjusted therapeutic schemes in transplant-ineligible and frail patients are being investigated as well [70].

The results from these trials will help clinicians to reduce the gap between clinical trial patients and real-world patients, in order to approach the selection of treatment options in a more evidence-based manner.

Unfortunately, the role of GA in RRMM patients is largely unknown and future work has to be done in order to understand how to tailor treatment in this patient population on the basis of frailty status.

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[* **: *Reference annotations are below*]

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Key issues

- Multiple myeloma is a disease predominantly occurring in the elderly and, in the near future, physicians will deal with a significantly increased number of elderly MM patients.
- Elderly patients are highly heterogeneous and nowadays we have evidence-based tools to identify and measure frailty [9].
- Many multiple myeloma-specific frailty scores have been proposed so far. IMWG, R-MCI and the Mayo clinic frailty scores are the most widely used and have been developed on solid data.
- A reduced-dose melphalan-based conditioning followed by ASCT is feasible and effective in highly selected elderly fit patients.
- Bortezomib-melphalan-prednisone, bortezomib-lenalidomide-dexamethasone, and lenalidomide-dexamethasone are currently the standard of care in elderly fit patients.
- Intermediate and frail patients benefit from reduced-dose regimens in order to maximize benefit/risk ratio and quality of life.
- Monoclonal antibodies are currently changing the treatment landscape by improving efficacy without significantly increasing toxicity and in the near future they could be administered in combination with the current standard treatments.
- Trials specifically designed to enroll patients according to geriatric assessment and a better definition of frailty in relapsed and/or refractory patients are needed to approach the selection of treatment in a more evidence-based manner.

Table 1. Outcomes from key randomized phase III clinical trials in elderly patients with newly diagnosed multiple myeloma

Regimen	Median age, y	Schedule	ORR, %	Median PFS, m	Discontinuation rate, %	Any G≥3 AE, %
MPT [28]	69-78	Variable	59	20	16-45	non-hematologic: 40-50
VMP VISTA [31,71]	71	• **V**: 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 for first four 6-wk cycles; days 1, 8, 15, and 22 for subsequent five 6-wk cycles • **M**: 9 mg/m^2 on days 1-4 for five 6-wk cycles • **P**: 60 mg/m^2 on days 1-4 for five 6-wk cycles	71	20	34	81
VMPT-VT [35,46]	71	• **V**: 1.3 mg/m^2 on days 1, 8, 15, and 22 for nine 5-wk cycles and on days 1, 15 until relapse • **M**: 9 mg/m^2 on days 1-4 for nine 5-wk cycles • **P**: 60 mg/m^2 on days 1-4 for nine 5-wk cycles • **T**: 50 mg daily until relapse	89	35	23	non-hematologic: 46
FIRST [39]	73	• **R**: 25 mg on days 1 to 21 of each 28-day cycle • **D**: 40 mg was on days 1, 8, 15, and 22	75	25	20	85
ALCYONE [69]	71	• **Dara**: 16 mg/kg once weekly in cycle 1, every 3 weeks in cycles 2-9, and every 4 weeks thereafter • **V**: 1.3 mg/m^2 twice weekly on weeks 1, 2, 4, and 5 of cycle 1 and once weekly on weeks 1, 2, 4, and 5 of cycles 2-9 M. 9 mg/m^2 on days 1-4 of each 6-weeks cycle • **P**: 60 mg/m2 on days 1-4 of each cycle	91	n.r.	due to AEs: 5%	n.a.

y: years, m: months, ORR: overall response rate, PFS: progression-free survival, G: grade, AE: adverse event, M: melphalan, P: prednisone, T: thalidomide, V: bortezomib, R: lenalidomide, D: dexamethasone, Dara: daratumumab, n.r.: not reached, n.a.: not available.

Table 2. Dose reductions on the basis of risk status in elderly frail patients [1,72]

Age >75 years Frailty status Comorbidities (≥1): cardiac, renal, pulmonary, hepatic dysfunction	0	≥1	≥1 plus any G≥3 non-hematologic AE
IMWG-frailty index	0	1	≥2
R-MCI	1-3	4-6	7-9
Agent	**Level 0**	**Level -1**	**Level -2**
Prednisone	60 mg/m^2 d 1-4 or 50 mg qad	30 mg/m^2 d 1-4 or 25 mg qad	15 mg/m^2 d 1-4 or 12.5 mg qad
Dexamethasone	40 mg/d d 1,8,15,22 / 4 weeks	20 mg/d d 1,8,15,22 / 4 weeks	10 mg/d d 1,8,15,22 / 4 weeks
Melphalan	0.25 mg/kg or 9 mg/m^2 d 1-4 every 4-6 weeks	0.18 mg/kg or 7.5 mg/m^2 d 1-4 every 4-6 weeks	0.13 mg/kg or 5 mg/m^2 d 1-4 every 4-6 weeks
Cyclophosphamide	100 mg/d d 1-21 / 4 weeks or 300 mg/m^2/d d 1,8,15 / 4 weeks	50 mg/d d 1-21 / 4 weeks or 150 mg/m^2/d d 1,8,15 / 4 weeks	50 mg qod d 1-21 / 4 weeks or 75 mg/m^2/d d 1,8,15 / 4 weeks
Bortezomib	1.3 mg/m^2 twice weekly d 1,4,8,11 / 3 weeks	1.3 mg/m^2 once weekly d 1,4,8,11 / 5 weeks	1.0 mg/m^2 once weekly d 1,4,8,11 / 5 weeks
Carfilzomib, dexamethasone	56 mg/m^2 d 1,2,8,9,15,16 / 4 weeks	45 mg/m^2 d 1,2,8,9,15,16 / 4 weeks	36 or 27 mg/m^2 d 1,2,8,9,15,16 / 4 weeks
Carfilzomib, lenalidomide, dexamethasone	27 mg/m^2 d 1,2,8,9,15,16 / 4 weeks	20 mg/m^2 d 1,2,8,9,15,16 / 4 weeks	15 mg/m^2 d 1,2,8,9,15,16 / 4 weeks
Thalidomide	100 mg/d	50 mg/d	50 mg qad
Lenalidomide	25 mg/d d 1-21 / 4 weeks	15 mg/d d 1-21 / 4 weeks	10 mg/d d 1-21 / 4 weeks
Pomalidomide	4 mg/d d 1-21 / 4 weeks	3 mg/d d 1-21 / 4 weeks	2 or 1 mg/d d 1-21 / 4 weeks

G: grade, AE: adverse event, IMWG: International Myeloma Working Group, R-MCI: revised myeloma comorbidity index, d: day, qd: everyday, qad: every other day.

Table 3. Performance status, proportion of elderly patients, efficacy outcomes and key toxicities in the main clinical trials described in the paper

	REGIMEN (N)	FITNESS/FRAILTY EVALUATION	FRAIL PATIENTS ENROLLED N (%)	ELDERLY PATIENTS ENROLLED N (%)	EFFICACY OUTCOMES	KEY TOXICITIES (G≥3)* N (%)
NDMM	V-based induction + ASCT + V- or R-based consolidation [22] (N=56)	Sorror	Sorror ≥3 7 (14%)	≥70y 13 (23%)	2-y PFS 76% 2-y OS 88%	n.a.
	V-based induction + ASCT + R consolidation/maintenance [23]	n.a.	n.a.	≥70y 26 (26%)	5-y PFS 43% 5-y OS 63%	<u>Hematologic</u> Neutropenia 92 (90%) Thrombocytopenia 93 (91%)

	(N=102)					Anemia 16 (16%) Non-hematologic Infection 34 (33%) PNP 18 (18%) Gastrointestinal 18 (18%) Dermatological 10 (10%)
	MPT vs. MP [28] (N=1685)	WHO	WHO ≥3 4-30%	median age of single studies range 69-79y	Median PFS 20 vs. 15 m Median OS 39 vs. 33 m	n.a.
	CTD vs. MP [30] (N=1970)	n.a.	n.a.	>80y 70 (8%)	Median PFS 13 vs. 12 m Median OS 33 vs. 31 m	Hematologic Cytopenia 47 (11%) vs. 64 (15%) Non-hemtologic[2] Infection 55 (13%) vs. 31 (7%)
	VMP vs. MP [31,32] (N=682)	Karnofsky	Karnofsky <70% 233 (34%)	≥75y 208 (30%)	Median PFS 22 vs. 15 m Median OS 56 vs. 43 m	Hematologic Neutropenia 136 (40%) vs. 128 (38%) Thrombocytopenia 126 (37%) vs. 102 (30%) Anemia 62 (18%) vs. 92 (27%) Non-hematologic PNP 44 (13%) vs. 0 Gastrointestinal 55 (16%) vs. 5 (1%) Infection 33 (10%) vs. 23 (6%)
	VMP vs. VTP [34] (N=260)	ECOG	ECOG ≥3 excluded	≥75y 88 (34%)	Median PFS 31 m (no significant difference between arms) Median OS n.a.	Hematologic Neutropenia 51 (39%) vs. 29 (22%) Thrombocytopenia 35 (27%) vs. 16 (12%) Anemia 15 (12%) vs. 10 (8%) Non-hematologic PNP 9 (7%) vs. 12 (9%)

					3-y OS 70% (no significant difference between arms)	Gastrointestinal 9 (7%) vs. 2 (2%) Infections 9 (7%) vs. 1 (1%)
	VMPT-VT vs. VMP [35] (N=511)	Karnofsky	Karnofsky <60% excluded	≥75y 137 (27%)	Median PFS n.r. vs. 27 m Median OS n.a. 3-y OS 89% vs. 87%	<u>Hematologic</u> Neutropenia 95 (38%) vs. 71 (28%) Thrombocytopenia 54 (22%) vs. 50 (20%) Anemia 25 (10%) vs. 25 (10%) <u>Non-hematologic</u> Cardiologic events 26 (19%) vs. 14 (5%) PNP 20 (8%) vs. 13 (5%) Infections 32 (13%) vs. 23 (9%)
	Rd vs. MPT [39] (N=1623)	ECOG	ECOG ≥3 6 (<1%)	≥75y 567 (35%)	Median PFS 25 vs. 21 m Median OS n.a. 4-y OS 59% vs. 51%	<u>Hematologic</u> Neutropenia 148 (28%) vs. 243 (45%) Thrombocytopenia 44 (8%) vs. 60 (11%) Anemia 97 (18%) vs. 102 (19%) <u>Non-hematologic</u> Infection 154 (29%) vs. 93 (17%) Cardiac disorder 63 (12%) vs. 46 (9%) TEE 42 (8%) vs. 29 (5%)
	VRd vs. Rd [40] (N=525)	ECOG	ECOG 2-3 64 (14%)	≥65y 202 (43%)	Median PFS 43 vs. 30 m Median OS 75 vs. 64 m	<u>Hematologic</u> Cytopenia 114 (47%) vs. 104 (46%) <u>Non-hematologic</u> Infection 35 (15%) vs. 31 (14%) Neurological 80 (33%) vs. 25 (11%) Gastrointestinal 53 (22%) vs. 17 (7%)
	Daratumumab-VMP vs. VMP [42]	ECOG	ECOG 2 174 (25%)	≥75y 211 (30%)	Median PFS n.r. vs. 18 m	<u>Hematologic</u>

	(N=706)				Median OS n.r.	Neutropenia 138 (40%) vs. 137 (39%) Thrombocytopenia 119 (34%) vs. 133 (38%) Anemia 55 (16%) vs. 70 (20%) <u>Non-hematologic</u> Infection 80 (23%) vs. 52 (15%)
	MPR/CPR vs. Rd [52] (N=662)	IMWG-FI	FRAIL 168 (25%)	≥75y 249 (38%)	Median PFS 22 vs. 21 m Median OS n.r. 4-y OS 67% vs 58%	<u>Hematologic</u> Neutropenia 136 (64%) vs. 63 (29%) vs. 52 (25%) Thrombocytopenia 37 (18%) vs. 19 (9%) vs. 15 (7%) Anemia 32 (15%) vs. 14 (6%) vs. 9 (4%) <u>Non-hematologic</u> Infection 23 (11%) vs. 16 (7%) vs. 20 (9%)
RRMM	KRd vs. Rd [55,56] (N=792)	ECOG	ECOG 2 75 (9.5%)	≥70y 218 (28%)	Median PFS 26 vs. 18 m Median OS n.r. 2-y OS 73% vs. 65%	<u>Hematologic</u> Neutropenia 116 (29%) vs. 103 (26%) Thrombocytopenia 65 (16%) vs. 48 (12%) Anemia 70 (18%) vs. 103 (26%) <u>Non-hematologic</u> Pneumonia 49 (12%) vs. 41 (10%) Cardiovascular 45 (11%) vs. 22 (5%)
	Ixazomib-Rd vs. Rd [58] (N=722)	ECOG	ECOG 2 42 (6%)	≥75y 108 (15%)	Median PFS 21 vs. 15 m Median OS n.r.	<u>Hematologic</u> Neutropenia 81 (22%) vs. 58 (16%) Thrombocytopenia 69 (19%) vs. 32 (9%) Anemia 34 (9%) vs. 48 (13%) <u>Non-hematologic</u> Dhiarrea 23 (6%) vs. 9 (3%) TEE 11 (3%) vs. 12 (3%)
	Kd vs. Vd [59,60] (N=929)	ECOG	ECOG 2 62 (7%)	≥75y 143 (15%)	Median PFS 19 vs. 9 m	<u>Hematologic</u>

					Median OS n.r.	Thrombocytopenia 39 (8%) vs. 43 (9%) Anemia 67 (14%) vs. 45 (10%) <u>Non-hematologic</u> Hypertension 41 (9%) vs. 12 (3%) PNP 1 (<1%) vs. 24 (5%)
	Daratumumab-Vd vs. Vd [61] (N=498)	n.a.	n.a.	≥75y 58 (6%)	Median PFS n.r. vs. 7 m Median OS n.r.	<u>Hematologic</u> Neutropenia 31 (13%) vs. 10 (4%) Thrombocytopenia 36 (13%) vs. 38 (14%) Anemia 35 (12%) vs. 55 (20%) <u>Non-hematologic</u> Pneumonia 20 (8%) vs. 23 (10%) PNP 11 (5%) vs. 16 (7%)
	Daratumumab-Rd vs. Rd [62] (N=569)	ECOG	ECOG 1-2 280 (49%)	≥75y 64 (11%)	Median PFS n.r. vs. 18 m Median OS n.r. 1-y OS 92% vs. 87%	<u>Hematologic</u> Neutropenia 147 (52%) vs. 104 (37%) Thrombocytopenia 110 (45%) vs. 78 (33%) Anemia 35 (14%) vs. 38 (16%) <u>Non-hematologic</u> Diarrhea 15 (5%) vs. 9 (3%)

Abbreviations: N: number of patients, V: bortezomib, ASCT: autologous stem cell transplantation, R: lenalidomide, PFS: progression-free survival, OS: overall survival, PNP: peripheral neuropathy, M: melphalan, P: prednisone, T: thalidomide, C: cyclophosphamide, K: carfilzomib, TEE: thromboembolic event, n.a.: not available, n.r.: not reached, m: months, y: years.

*Key toxicities reported if occurred in >10% of patients or when considered clinically significant.

Figure title and legend

Figure 1. Definition of frailty status and treatment goals in elderly NDMM patients.

[See the Figure 1.tiff file]

Abbreviations:
ADL: Activity of Daily Living; IADL: Instrumental Activity of Daily Living; CCI: Charlson Comorbidity Index; KPS: Karnofsky Performance Status; ASCT: Autologous Stem Cell Transplantation; R-MCI: Revised Myeloma Comorbidity Index; VMP: bortezomib-melphalan-prednisone; VRD: bortezomib-lenalidomide-dexamethasone; Rd: lenalidomide-dexamethasone; Vd: bortezomib-dexamethasone.

Figure 1

IMWG-frailty index: *CCI ≥2 = 1, IADL ≤5 = 1, ADL ≤ 4 = 1, Age 76-80 = 1, >80 = 2*

R-MCI: Age 60-69 = 1, ≥70 = 2, KPS 80-90% = 2, ≤ *70% = 3,* Renal disease (egfr < 60) = 1, Lung disease moderate/severe = 1, Frailty moderate or severe = 1, unfavorable cytogenetics = 1

Mayo frailty index: Age ≥70 = 1, ECOG PS ≥ 2 = 1, NT-ProBNP ≥ 300 ng/L = 1

FIT 0 IMWG-frailty index 0-3 R-MCI 0 Mayo frailty index	**INTERMEDIATE** 1 IMWG-frailty index 4-6 R-MCI 1-2 Mayo frailty index	**FRAIL** 2 IMWG-frailty index 7-9 R-MCI 3 Mayo frailty index
		
GOAL = high efficacy	**GOAL =** balance efficacy and safety	**GOAL =** low toxicity
TREATMENT	**TREATMENT**	**TREATMENT**
ASCT TRIPLETS (VMP, VRd) DOUBLETS (Rd)	LOW-DOSE TRIPLETS DOUBLETS (Vd, Rd)	LOW-DOSE DOUBLETS (Vd, Rd) PALLIATION + SUPPORTIVE CARE