Practical management of multiple myeloma: Update 2020

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On behalf of the BHS Myeloma Subgroup

SUMMARY

With the introduction of immunomodulatory drugs, proteasome inhibitors and anti-CD38 monoclonal antibodies, major improvements have been achieved in the treatment and outcome of multiple myeloma (MM). Different treatment combinations are now in use and other therapies are being developed. This rapidly changing therapeutic landscape urges for an update on practical guidelines. Based on an extensive review of the recent literature, we propose recommendations on myeloma management, to be used by haematologists as a reference for daily practice.

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INTRODUCTION

The landscape of treatment in multiple myeloma (MM) is rapidly changing. Based on an extensive review of the recent literature, we propose an update of our recommendations on myeloma care, to be used by Belgian haematologists as a reference for daily practice.[1] Levels of evidence and grades of recommendations are based on previously published methods.[2] We recommend participation in clinical trials to gain knowledge in the fast evolving field of MM treatment.

DIAGNOSIS

Recommendation 1 - Diagnosis of MM requires the fulfilment of the 2014 IMWG criteria (IV, C).[3]

The diagnosis of MM requires the presence of >10% clonal plasma cells (PC) in the bone marrow (BM) or in a bone or extramedullary lesion biopsy. The majority of patients diagnosed with active MM present with symptoms related to organ damage, referred as CRAB-SLiM criteria (*Table 1*).[3]

Recommendation 2 - Investigations to be performed at diagnosis are listed in Table 2 *(IV, C). Cytogenetic analysis should follow the IMWG recommendations reported in* Table 3 *(IV, C).*[4]

STAGING

Recommendation 3 - All patients should undergo risk stratification using the International staging system (ISS)(I, A) and cytogenetics (FISH)(II, B), even if risk-adapted therapy is not available at the moment in most cases.

The ISS is based on β2-microglobulin that remains the most relevant biological prognostic parameter.[6] The revised ISS (R-ISS) includes also serum LDH and bone marrow FISH evaluation done on sorted plasma cells, since cytogenetics remains the most prominent prognostic factor (*Table 4*).[7] The most relevant high-risk features are the t(4;14), del(17p), del(1p) and gains (1q).[8-10] The presence of a double-hit MM defined as the presence of two or more high-risk factors is also associated with a very poor prognosis.[11] Apart from elevated serum LDH, other factors associated

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TABLE 1. CRAB-SLiM criteria.
Adapted from Rajkumar, Lancet Oncol 2014.[3]

C	Hypercalcemia	serum calcium >0.25 mmol/l (>1 mg/dl) higher than upper limit of normal or >2.75 mmol/l (>11 mg/dl)
R	Renal dysfunction	serum creatinine >177 mmol/l (>2 mg/dl) with no other etiology or creatinine clearance < 40 ml/min
A	Anaemia	haemoglobin value >20 g/l below the lowest limit of normal or a haemoglobin value <10g/dl
B	Bone lesions	one or more osteolytic lesions on skeletal x-rays, CT or PET-CT. If BM < 10% clonal PC, more than one bone lesion is required to distinguish from solitary plasmocytoma with minimal BM involvement
S		≥60% clonal BM PC
Li		serum FLC ratio involved/uninvolved ≥100
M		more than 1 focal lesion (≥5 mm each) detected on MRI studies

Abbreviations: BM, bone marrow; FLC, free light chain; M-protein, monoclonal protein; PC, plasma cell; MRI, magnetic resonance imaging.

with aggressive disease include the presence of circulating PC or extramedullary disease. Patient-specific factors include age, comorbidities; functional status and frailty that have been clearly associated with survival.[12,13] Geriatric assessments to be performed at diagnosis are reported in *Appendices 1 & 2*. However, their implication in routine assessment can be cumbersome. More simple scores based on age, Charlson comorbidity index (CCI) and ECOG performance status (PS) can be easily performed, providing the same information.[14]

GOAL OF THERAPY

Recommendation 4 - The goal of therapy is to achieve the best possible response.

Complete response (CR) is the most important surrogate marker of overall survival (OS). In addition, minimal resi-

TABLE 2. Investigations required at diagnosis.

Biological tests	serum blood count, urea, creatinine, calcium, phosphorus proteins, electrophoresis of serum/urine, quantification of immunoglobulins immunofixation on serum/urine, characterization of heavy/light chains M-protein quantification in serum/urine (24h urine concentrate) measurement of FLC in oligo- or non-secretory and light chain MM albumin, beta-2-microglobulin CRP, LDH
Bone marrow aspirate	bone marrow aspirate and trephine biopsy, flow cytometry FISH analysis or another equivalent molecular genetic technique on selected or identified plasma cells
Radiology (at choice)	WBLDCT or standard skeletal survey if WBLDCT not available x-rays of symptomatic areas spine MRI plus x-rays of the skull, humeri, femora and ribs or WBMRI PET-CT

Abbreviations: FISH, fluorescence in situ *hybridisation; FLC, free-light chain; MM, multiple myeloma; PET-CT, positron emission tomography computed tomography; WBLDCT, whole-body low-dose computed tomography; WBMRI, whole body MRI.*

TABLE 3. International Myeloma Working Group consensus panel on interphase FISH. Adapted from Sonneveld, Blood 2016 and Rack, Leukemia 2019.[4,5]

	IMWG consensus panel on FISH	IMWG extended panel (clinical trials)
Parameters	del(17p) t(4;14) gain(1q) and possibly t(14;16)	+ t(11;14), t(14;20), del(1p), del(13q) and ploidy status

Abbreviations: IMWG, International Myeloma Working group.

dual disease (MRD) negativity is associated with better long-term outcome.[15,16] However, in the elderly, increased progression-free survival (PFS) is a worthwhile objective if quality of life (QoL) is maintained and can delay the onset of disease side effects.

INDICATION FOR THERAPY

Recommendation 5 - Treatment should be considered in all patients with a diagnosis of symptomatic MM as defined by the IMWG 2014 criteria (IV, C). Treatment choice depends on whether or not the patient is eligible for autologous stem cell transplantation (ASCT) based on age, performance status and comorbidities.

Recommendation 6 - In asymptomatic MM, treatment can only be recommended in the context of a clinical trial. Patients should be monitored for symptoms and followed every three to six months according to their risk of progression (IV, C).

Treatment of asymptomatic MM (smoldering MM, SMM) is not recommended at the moment, although the upfront use of Rd showed a prolonged PFS and OS in a trial that mainly concerned high-risk SMM that should nowadays be reclassified as active disease.[17,18] Nevertheless, a more recent trial confirmed a significant prolongation of the time to symptomatic MM, the benefit being more pronounced in the high-risk subgroup.[19]

Other very promising studies aim either to control and delay progression with prolonged administration of IMiDs or monoclonal antibodies (MoAbs), or cure the disease using aggressive approaches such as carfilzomib-lenalidomide-dexamethasone (KRd) induction followed by ASCT.[20-22]

The risk of progression of SMM can be evaluated by the '3x20' risk score, that refers to a BM plasmocytosis >20%, level of M-protein >20g/l and serum FLC ratio >20, and stratifies patients in low-, intermediate- and high-risk groups with a median PFS of 110, 68 and 29 months, respectively.[23]

Recommendation 7 – Solitary plasmocytoma should be treated with radiation therapy.

Solitary plasmocytoma is usually managed with radiation therapy for a 40-50 Gy administered in fractionated doses.[24] Careful follow-up is mandatory since two thirds of patients evolve to MM at ten years, particularly in case of persistence of M-spike after radiotherapy.[25]

TABLE 4. Revised ISS risk stratification for MM. Adapted from Palumbo, JCO 2015.[7]

MM Patients	Stage I - standard-risk 20%	Stage II - intermediate-risk 60%	Stage 3 - high-risk 20%
Parameters	ISS I and standard risk cytogenetics by iFISH and normal LDH	Not R-ISS I or III	ISS III and either HR cytogenetics by iFISH or elevated LDH
Median PFS	66 months	42 months	29 months
5-y OS	82%	62%	40%
Median OS	not reached	83 months	43 months

Abbreviations: iFISH, interphase FISH; HR cytogenetics, high-risk cytogenetics defined by the presence of del(17p) and/or t(4;14) and/or t(14;16); MM, multiple myeloma; PFS, progression-free survival; OS, overall survival.

TABLE 5. Frontline induction regimens in transplant-eligible patients.

Front-line regimens	Schedule	n	ORR	≥VGPR	mPFS	mOS
VTD vs. VCD Moreau, Blood 2016[26]	Bortezomib 1.3 mg/m^3, days 1,4,8,11 Dexamethasone 40 mg orally, days 1-4, 9-12 Repeated every 4 weeks Thalidomide 100 mg orally, days 1-28 Cyclophosphamide 500 mg/m^3 orally, days 1,8,15	368	92 vs. 83%	66 vs. 56%	NA	NA
vTD Moreau, Blood 2011[34]	Bortezomib 1 mg/m^2 sq, days 1,4,8,11 Thalidomide 100 mg, J1-21 Dexamethasone 40 mg orally, days 1-4,9-11 on cycles 1-2, days 1-4 on cycles 3-4 Repeated every 3 weeks	199	89%	51%	26m	NA
VRD vs VRD-ASCT Attal, NEJM 2017[27]	Bortezomib 1.3 mg/m^2 sq, days 1,4,8,11 Lenalidomide 25 mg orally, days 1-14 Dexamethasone 20 mg orally, days 1,2,4,5,8,9,11,12 Repeated every 3 weeks	700	97 vs. 98%	77 vs. 88%	36 vs. 50m	NR for both 82 vs. 81% at 4y
VRD vs. Rd Durie, Lancet 2017[28]	Bortezomib 1.3 mg/m^2 sq, days 1,4,8,11 Lenalidomide 25 mg orally, days 1-14 Dexamethasone 20 mg orally, days 1,2,4,5,8,9,11,12 Repeated every 3 week	471	82 vs. 72%	43 vs. 32%	43 vs. 31m	75 vs. 64m
PAD vs. VAD Sonneveld, J Clin Oncol 2012[35]	Bortezomib 1.3 mg/m^2 sq, days 1,8,15,22 Adriamycine, 9 mg/m^2, days 1-4 Dexamethasone 40 mg orally, days 1-4,9-12,17-20 Repeated every 4 weeks	827	78 vs. 54%	42 vs. 14%	35 vs. 28m mFU of 41m HR 0.75	NR for both at 66 m 61 vs. 55% at 5y (NS)
CASSIOPEIA Dara-VTD vs. VTD Moreau, Lancet 2019[32]	Daratumumab 16mg/kg IV weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Bortezomib 1.3 mg/m^2 sq, days 1,8,15,22 Thalidomide 100mg orally, days 1-28 Dexamethasone 40 mg orally, days 1,2,8,9,15,16,22,23 on cycles 1,2, days 1,2 on cycles 3,4, 20 mg orally, days 8,9,15,16 on cycles 3,4 Repeated every 4 weeks	1085	92.6 vs. 89.9%	83 vs. 78%	NR vs. NR HR 0.47	NA
GRIFFIN Dara-VRD vs. VRD Voorhees, Blood 2019[33]	Daratumumab 16mg/kg IV, days 1,8,15, cycles 1-4, days 1,15, cycles 5-6 Lenalidomide 25 mg orally, days 1-14 Bortezomib 1.3 mg/m^2 sq, days 1,4,8,11 Dexamethasone 40 mg orally, days 1,8,15,22 Repeated every 4 weeks	207	99 vs. 92%	91 vs. 73%	NA	NA
KRD12 vs. KRD4/ASCT/ KRD4 vs. KCD4/ASCT/ KCD4 Gay, J Clin Oncol 2019[30]	Carfilzomib 36 mg/m^2 IV, days 1,2,8,9,15,16 Dexamethasone 20 mg orally, days 1,2,8,9,15,16,22,23 Lenalidomide 25 mg orally, days 1-21 or Cyclophophamide 300 mg/m^2, days 1,8,15 Repeated every 4 weeks	474	83 months	87% vs. 89% vs. 76%	NA	NA MRD negativity (10^{-5}) 54% vs. 58% vs. 42% Persistent MRD at 1y 78% vs. 90% vs. NRp

Abbreviations: A, doxorubicin; ASCT, autologous stem cell transplantation; C, cyclophosphamide; D, dexamethasone; Dara, daratumumab; K, carfilzomib; KCD4, carfilzomib-cyclophosphamide-dexamethasone 4 cycles; KRD4, carfilzomib-lenalidomide-dexamethasone 4 cycles; KRD12, carfilzomib-lenalidomide-dexamethasone 12 cycles m, months; M, melphalan; P, prednisone; NA, not available; NR, not reached; NRp, not reported; NS, not significant; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression-free survival; PR, partial response; R, lenalidomide; t, low-dose thalidomide; T, thalidomide; v, low dose bortezomib; V, bortezomib; VGPR, very good partial response; y, years.

TREATMENT OF NEWLY DIAGNOSED MM ELIGIBLE FOR TRANSPLANT

Recommendation 8 – In transplant-eligible MM patients, induction followed by high-dose melphalan (HDM) and ASCT remains the standard of care in patients in good clinical condition. Based on response rates, depth of response and PFS, 3-drug induction including at least bortezomib and dexamethasone is considered the standard of care before ASCT (I, A).

VTD is superior to **VCD** but at the cost of more peripheral polyneuropathies.[26] **VRD** results in significantly higher response rates, response duration and PFS, compared to previous studies using VTD.[27-29] There is no phase III trial comparing head-to-head these two induction regimens. VRD is not reimbursed in Belgium in this setting.

Other highly effective combinations such as **KRD**, even in association with MoAbs, are currently being evaluated in phase III trials with promising results, particularly regarding the achievement of MRD negativity.[30,31] Addition of **daratumumab** to VTD significantly improves the rates of stringent complete response (sCR), MRD negativity and eighteen month PFS.[32] Similar results are awaited with the daratumumab-VRD combination.[33]

Carfilzomib and daratumumab are not reimbursed in first-line therapy in Belgium.

Current induction regimens are listed in *Table 5*.

Recommendation 9 – Four cycles are recommended before stem cell collection. There is no data identifying the ideal depth of responses required prior to proceed to ASCT.

Since post-transplant depth of response is more important than pre-transplant response, ASCT should be performed independently of depth of response, except in patients with progressive disease.[36]

*Recommendation 10 – **Upfront ASCT** remains the cornerstone in the management of newly diagnosed (ND) MM, since it increases response rates, depth of response, MRD negativity and PFS, when used after a triplet induction. However, in the absence of OS benefit, delayed ASCT can be an option in selected patients.*

In the IFM 2009 trial, VRD induction plus ASCT opposed to VRD alone resulted in significant improvement in PFS (50 vs. 36 months, HR 0.65), CR rate (59% vs. 48%), MRD negativity (79% vs. 65%) and median time to progression (TTP)(50 vs. 36 months), but with no effect on OS, taking into account that transplantation could not be done in one-third of the patients due to age, comorbidities or progression.[27]

In the EMN02-HOVON95 trial, upfront ASCT (single or double) compared to VMP after VCD induction was associated with a decreased risk of progression and death and improved three year PFS, regardless of initial adverse prognostic factors.[37]

The role of upfront ASCT is further challenged by the addition of MoAbs such as daratumumab to triplet induction regimens, or the use of second generation PI such as carfilzomib.[30,32] It is also likely that the MRD status achieved after induction will have an impact on ASCT decisions in the future.

*Recommendation 11 – **Tandem ASCT** can be beneficial for patients with high-risk cytogenetic features or those with a suboptimal response to first transplant.*

In the EMN02/H095 trial, tandem ASCT improved the depth of response by 25%, with more than 50% patients achieving at least CR. It was also associated with an advantage over single transplant in terms of PFS and OS, particularly in high-risk disease (3-year PFS, 69% vs. 44%). Double transplant emerged as an independent prognostic factor predicting PFS.[37]

On the opposite, tandem ASCT failed to show any PFS or OS advantage over single transplant in the StaMINA trial, in the context of lenalidomide maintenance. Of note, this study had several limitations such as various induction regimens given for various durations, doublets induction, and more than 30% of patients randomised to tandem ASCT did not receive the second transplant.[38]

*Recommendation 12 – The **role of consolidation** is still unclear. It remains a reasonable practice in patients who failed to achieve at least CR after transplantation.*

Bortezomib-based consolidation is associated with increased CR, molecular CR and prolonged PFS in patients achieving a good response after transplantation, but has no impact on OS.[39,40]

More recently, two trials have evaluated the role of VRD in consolidation after ASCT.

In the EMN02-HO95 trial, two cycles of VRD were superior to no consolidation, except in high-risk diseases.[37]

On the opposite, the StaMINA trial failed to identify any PFS benefit using either a second transplant or three cycles of VRD consolidation.[38] Both studies were different in terms of design, and the lack of PFS benefit may be influenced by the follow-up as well as the maintenance given to all patients.

*Recommendation 13 – **Maintenance with lenalidomide** after ASCT is considered a standard of care since it has been proven to improve OS. The optimal duration of maintenance is still a matter of debate. Overall, an average duration of two years with a 3-week on, 1-week off treatment has become widely adopted. It exposes patients to an increased incidence, albeit modest, of second primary malignancies (SMP). The benefit of maintenance with lenalidomide is less clear in high-risk diseases.*

Daily lenalidomide given in monotherapy at the dosage of

TABLE 6. Selected maintenance regimens used after ASCT.

Maintenance	Schedule	mPFS	OS
Lenalidomide McCarthy, J Clin Oncol 2017[41]	Lenalidomide 10 mg, days 1-21 until progression	52.8 vs. 23.5m HR 0.48	mOS, NR vs. 86m after mFU of 79.5m HR 0.75
MM XI R maintenance vs. placebo Jackson, Lancet Oncol 2019[42]	Lenalidomide 10 mg, days 1-21/28 until progression	39 vs. 20m after mFU of 31m HR 0.46	3y-OS, 78.6% vs. 75.8% HR 0.87
HOVON T after VAD-ASCT vs. V after PAD-ASCT Sonneveld, J Clin Oncol 2012[35]	Thalidomide 50mg/d or Bortezomib 1.3mg/m^2 qw, for 2 years	28 vs. 35m CR/nCR, 34% vs. 49%	5y-OS, 55% vs. 61%
Ixazomib vs. placebo Dimopoulos, Lancet 2019[43]	Ixazomib 4mg, days 1,8,15 28-day cycles, for 2 years	26.5 vs. 21.3m after mFU of 31m HR 0.72	

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; d, day; HR, hazard ratio; m, months; mFU, median follow-up; mPFS, median progression-free survival; NA, not available; nCR, near complete response; NR, not reached; OS, overall survival; PAD, bortezomib, adriamycin, dexamethasone; PFS, progression-free survival; R, lenalidomide; T, thalidomide; V, bortezomib; VAD, vincristine, adriamycin, dexamethasone.

10-15 mg significantly improves PFS, regardless of age, disease stage, induction regimen (exposure to lenalidomide in induction) and depth of response after transplant. It also significantly improved OS, with a 25% reduction in the risk of death, increasing the median survival by approximately 2.5 years, except in high-risk diseases where conflicting data have been published.[41,42]

The OS benefit of lenalidomide maintenance largely outweighs the risk of developing a SPM.[41] Patients should be informed and monitored accordingly.

*Recommendation 14 – **Maintenance with bortezomib** should be preferred in high-risk patients, but is not approved by EMA or national health systems.*

Bortezomib given every other week for two years after a tandem ASCT was the first to demonstrate a survival advantage compared to thalidomide, particularly when used in induction, in patients with del(17p).[35] **Ixazomib**, an oral PI given once weekly for two years, improves PFS by 39% and reduces the risk of progression/death by 28%, when compared to placebo, but is not approved in this indication. Additional trials incorporating pomalidomide, carfilzomib and MoAbs are currently ongoing.[43]

Selected maintenance regimens used in this setting are listed in *Table 6*.

*Recommendation 15 – Consolidation with **allogeneic transplantation** is still considered investigational for MM. Because of the risk of severe treatment-related mortality (TRM) and graft-versus-host disease (GvHD), it should only be performed in young patients with (ultra)-high-risk disease in good response, preferably within clinical trials (IV, C).*

TREATMENT OF NEWLY DIAGNOSED MM INELIGIBLE FOR TRANSPLANT

Recommendation 16 – Before starting therapy, elderly patients should be assessed for risk factors defined as age ≥75y, presence of comorbidities, frailty or disability. Geriatric scales may be helpful in identifying frail patients. In the presence of ≥1 risk factor, treatment dose reductions are mandatory.

Geriatric scores should be assessed in order to identify frail patients (*Table 5*) as these scores can predict outcomes and help us to adapt therapy (*Appendices 3 & 4*).[12-14]

*Recommendation 17 – Outside clinical trials, patients not eligible for ASCT should receive either **VMP, Rd** or **VRd** as standard front-line therapy. Based on the FIRST trial, **MPT** is no more considered as a standard of care.*

There is no evidence of the superiority of VMP over Rd in the absence of randomised clinical trials.[44,45] In contrast, compared to Rd, VRd is associated by better ORR, PFS, and OS,[28] and has become a new standard of care.

Recommended treatment duration is eight cycles for VRd, followed by lenalidomide maintenance, nine cycles for VMP and up to progression for Rd, particularly in patients achieving VGPR or better (II,A), but can be shorter because of therapy-related toxicities.

TABLE 7. Common induction regimens for myeloma transplant-ineligible patients.

Front-line regimens	Schedule	n	ORR	≥VGPR	mPFS	mOS
VMP vs. MP San Miguel, NEJM 2008[44]; San Miguel, JCO 2013[58]	Melphalan 9mg/m² orally, days 1-4 Prednisone 60mg/m² orally, days 1-4 Bortezomib 1.3mg/m² IV, days 1,4,8,11,22,25,29,32 (cycles 1-4), 1,8,22,29 (cycles 5-9) 42-day cycles	668	71 vs. 35%	41 vs. 8%	24 vs. 18m	56.4 vs. 43m after mFU of 60.1m HR 0.7
VMP once weekly vs. twice weekly Bringhen, Blood 2010[59]	Melphalan 9mg/m² orally, days 1-4 Prednisone 60mg/m² orally, days 1-4 Bortezomib 1.3mg/m², days 1,8,15,22 (cycles 1-9)	511	NA	NA	33.1 vs. 31.7m after mFU of 23.2m HR 1.95	3y-OS, 88% vs. 89% HR 1.22
Rdcont vs. Rd18 vs. MPT Benboubker, NEJM 2014[45]; Facon, Blood 2018[60]	Lenalidomide 25mg orally, days 1-21 Dexamethasone 40mg, days 1,8,15,22 Repeated every 4 weeks Melphalan 0.25mg/kg, days 1-4, Prednisone 2mg/kg, days 1-4, Thalidomide 200mg/day, 42-day cycles	1623	75 vs. 73 vs. 62%	44 vs. 43 vs. 28%	26 vs. 21 vs. 21m	59.1 vs. 62.3 vs. 49.1m after mFU of 67m HR 0.69
D-VMP Mateos, NEJM 2018[54]; Mateos, Blood 2019[55]	Daratumumab 16mg/kg IV weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Melphalan 9mg/m² orally, days 1-4 Prednisone 60mg/m² orally, days 1-4 Bortezomib 1.3mg/m² IV, days 1,4,8,11,22,25,29,32 (cycles 1-4), 1,8,22,29 (cycles 5-9)	706	90.9 vs. 73.9%	≥CR, 42.6 vs. 24.4% MRD (10^{-5}) 22.3 vs. 6.2%	36.4 vs. 19.3m after mFU of 40.m	36m-OS, 78% vs. 68% mOS NR in both groups
D-Rd Facon, NEJM 2019[57]	Daratumumab 16mg/kg IV weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Lenalidomide 25mg orally, days 1-21 Dexamethasone 40mg, days 1,8,15,22 (20mg over 75) Repeated every 4 weeks	737	92.9 vs. 81.3%	79.3 vs. 53.1% ≥CR 48 vs. 25% MRD (10^{-5}) 24.2 vs. 7.3%	30m PFS, NR vs. 31.9m	NR in both
VRD vs. Rd Durie, Lancet 2017[28]	Bortezomib 1.3mg/m² sq, days 1,4,8,11 Lenalidomide 25mg orally, days 1-14 Dexamethasone 20mg orally, days 1,2,4,5,8,9,11,12 Repeated every 3 week	471	82 vs. 72%	43 vs. 32%	43 vs. 31m	75 vs.64m
VRd lite O'Donnell, Br J Haematol 2018[46]	Bortezomib 1.3mg/m² sq, days 1,8,15,22 Lenalidomlide 15mg orally, days 1-21 Dexamethasone 20mg orally, days 1,2,8,9,15,16,22,23	50	86%	66%	35.1m	NR After mFU of 30m

Abbreviations: B, bendamustine; C, cyclophosphamide; CR, complete response; d, low-dose dexamethasone; D, high-dose dexamethasone; HR, hazard ratio; m, months; M, melphalan; mPFS, median progression-free survival; mOS, median overall survival; ORR, Overall response rate; OS, overall survival; P, prednisone; PFS, progression-free survival; PR, partial response; R, lenalidomide; Ref, references; T, thalidomide; V, bortezomib; VGPR, very good partial response.

Bortezomib-based regimens may be preferred in patients with high-risk cytogenetics, renal impairment and increased risk for VTE or contra-indications to anticoagulants. Rd may be preferred in patients with pre-existing PN.

VRd is effective in all age subgroups, including patients over 75, but should be preferred for fit elderly patients.[28] **VRd lite** is a highly effective alternative for less fit patients that balances adequately efficacy and toxicity.[46]

Bortezomib-related neurotoxicity can be reduced by weekly dosing as well as by subcutaneous administration, with no impact on OS.[47,48] Bortezomib requires antiviral prophylaxis against herpes zoster. Rd is better tolerated when administered with low dose dexamethasone (20 mg per week in patients over 75).[49,50] Dexamethasone can even be stopped after nine cycles in intermediate-fit patients, without any impact on ORR, PFS or OS.[51] Rd requires prophylactic anticoagulation and dose reduction in case of renal dysfunction.

Regarding the VMP regimen, there is no advantage to replace bortezomib by carfilzomib (**KMP**).[52] In contrast, melphalan can be replace by cyclophosphamide (**VCD**) with high response rates, prolonged PFS and good tolerability.[53]

The combination of daratumumab to VMP (**Dara-VMP**, ALCYONE trial) is associated with a very high ORR and a 50% reduction of the risk of progression/death, a benefit consistent across all subgroups including patients ≥75, ISS stage 3, renal impairment and high-risk cytogenetics, without additional toxicities except for increased infectious events.[54] It is also associated with OS prolongation.[55] In unfit elderly MM patients; other combinations such as Daratumumab-Ixazomib-Dexamethasone are under investigation with the purpose to limit toxicity.[56]

The Rd regimen serves as backbone for triplet combinations with PI or other agents. The addition of daratumumab to Rd (**Dara-Rd**, MAIA trial) results in a 93% ORR, nearly doubling the ≥CR rate compared to Rd, and inducing a 3-fold higher MRD negativity (24% vs. 7%) that translates in a 44% reduction of the risk of progression/death, at the cost of more grade 3-4 neutropenia and pneumonia.[57]

Other combinations using PI (KRd, IRd) or MoAbs (Dara-VRD, isatuximab-VRD (IMROZ), sqDara-VRD (CEPHEUS), Elotuzumab-Rd) are also under investigation. Preliminary results failed to demonstrate any superiority of elotuzumab or ixazomib combined with Rd, compared to Rd (unpublished data).

Common induction regimens used in transplant-ineligible patients are listed in *Table 7.*

Recommendation 18 – Continuous therapy with Rd is recommended until progression.

Continuous Rd has been associated with an improvement in PFS when compared to Rd given for a fixed duration of eighteen months, a benefit even more prominent in patients achieving at least VGPR, at the cost of more toxicities, particularly in the very old and frail population.[45,60] Duration of therapy should take into account patient preferences, toxicities, QoL and costs.

Future studies will evaluate the role of less toxic agents such as MoAbs as well as the role of MRD testing for selecting patients that are more susceptible to benefit from continuous therapy.

RELAPSE, DEFINITION AND INDICATION OF RETREATMENT

Recommendation 19 – Diagnosis of progression or relapse requires the fulfilment of the 2014 IMWG criteria (IV, C).

Progressive disease is defined by an increase of at least 25% in the serum M-protein (with a minimum value of 0.5g/dl), or ≥200 mg in light chain excretion in a 24-hour urine collection, or an increase ≥100 mg/l in the difference of involved/uninvolved light chain in a patient without a measurable serum or urine M-protein.[61]

Work-up should at least include imaging, in order to identify new lytic lesions or extramedullary disease. Bone marrow evaluation is not mandatory, but should be performed in case of oligo- or non-secretory MM or unexplained cytopenias. Cytogenetics by FISH allows to identify abnormalities seen at progression such as del17p and 1q amplification, that predict a more aggressive disease.[62] Identification of t(11;14) might be of interest since this abnormality has been reported to be sensitive to venetoclax.[10]

Recommendation 20 – Biochemical (asymptomatic) relapses that require close observation should be differentiate from clinical (symptomatic, CRAB features) relapses that require immediate treatment.

EARLY RELAPSES

Recommendation 21 – Treatment choice at relapse will be based on various factors including the timing and aggressiveness of relapse, response and tolerance to prior therapies, age and PS, drug availability and patients preferences. Participating in clinical trials should always be proposed.

*Recommendation 22 – **Salvage ASCT** should be considered in patients who never had one as part of their front-line therapy and in those who enjoyed a prolonged remission after a first ASCT.*

This refers to a remission of at least 36 months when maintenance was part of initial therapy.[63]

*Recommendation 23 – Recommended strategy ideally requires a **switch of drugs** regarding those used in front-line, from PI-based to IMiD-based regimens, or vice-versa. Triplet combinations appear to be superior to doublets, in terms of prolonging PFS. Doublets are not recommended for high-risk patients.*

TABLE 8. Common regimens used in first relapses.

	Schedule	n	ORR	≥VGPR	mPFS	mOS
LEN-based						
POLLUX Dara-RD vs. Rd Dimopoulos, NEJM 2016[64]; Dimopoulos, Haematologica 2018[68]	Daratumumab 16mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Lenalidomide 25mg orally, days 1-21 Dexamethasone 40mg, days 1,8,15,22 28-day cycles	569	92.9 vs. 76.4%	75.8 vs. 44.2%	NR vs. 17.5m after mFU of 25.4m HR 0.41	
ASPIRE KRd vs. Rd Steward, NEJM 2015[69]; Siegel, JCO 2018[65]	Carfilzomib 20mg/m^2 (days 1 -2 of cycle 1) and 27 mg/m^2 (subsequent doses) IV days 1,2,8,9,15,16 Lenalidomide 25 mg orally, days 1-21 Dexamethasone 40 mg orally days 1,8,15,22 28-day cycles	792	87.1 vs. 66.7%	69.9 vs. 40.4%	26.3 vs. 17.6m HR 0.69	48.3 vs. 40.4m after mFU of +/-67m HR 0.79 (p, 0.04)
TOURMALINE IRd vs. Rd Moreau, NEJM 2016[70]	Ixazomib 4mg orally, days 1,8,15 Lenalidomide 25mg orally, days 1-21 Dexamethasone 40mg orally, days 1,8,15,22 28-day cycles	722	78 vs. 72%	80.3 vs. 72.7%	20.6 vs. 14.7m after mFU 14.7m HR 0.74	
ELOQUENT-2 Elo-Rd Lonial, NEJM 2015[71]	Elotuzumab 10mg/kg IV weekly x 8 weeks, then every 2 weeks Lenalidomide 25 mg orally, days 1-21 Dexamethasone 40 mg orally, days 1,8,15,22 28-day cycles	646	79 vs. 66%	33 vs. 28%	19.7 m vs. 14.9m after mFU of 32.4m HR 0.73	
PI-based						
CASTOR Dara-Vd Palumbo, NEJM 2016[72]; Spencer, Haematologica 2018[73]	Daratumumab 16mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly, until progression Bortezomib 1.3 mg/m^2 sq, days 1,8,15,22, cycles 1-8 Dexamethasone 40mg, days 1,8,15,22 28-day cycles	498	82.9 vs. 63.2%	59.2 vs. 29.1%	16.7 vs. 7.1m after mFU of 19.4m HR 0.31	NA
PANORAMA Pano-Vd vs. Vd San Miguel, Lancet Oncol 2014[74]; San Miguel, Lancet Haematol 2016[75]	Panobinostat 20mg orally, 3 times a week, x 2 weeks Bortezomib 1.3mg/m^2 sq, days 1,8,15 Dexamethasone 20 mg orally days 1,2,4,5,8,9,11,12 12 cycles eight 3-week cycles, then four 6-week cycles	768	60.7 vs. 54.6%	≥CR, 27.6 vs. 15.7% (NS)	11.99 vs. 8.08m after mFU of ±6.5m HR 0.63	no difference in OS 40.3 vs. 35.8 m HR 0.94
OPTIMISMM PVd vs. Pd Richardson, Lancet 2019[66]	Bortezomib 1.3mg/m^2 d1,4,8,11 (cycles 1-8), d1,8 (cycles 9+) Pomalidomide 4 mg days 1-21 Dexamethasone 20mg days 1,2,4,5,8,9,11,12 (10 mg if age > 75)	712	82.2 vs. 50%	52.7 vs. 18.3%	11.2 vs. 7.1m after mFU of 15.9m HR 0.61 In len- refractory, 9.53 vs. 5.59m HR 0.64	No difference in OS, 31%

Abbreviations: CR, complete response; d, low-dose dexamethasone; D, high-dose dexamethasone; DRd, daratumumab-lenalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; Elo, elotuzumab; HR, hazard ratio; I, ixazomib; K, carfilzomib; m, months; mFU, median follow-up; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, overall response rate; OS, overall survival; P, pomalidomide; Pano, panobinostat; PFS, progression-free survival; PI, proteasome-inhibitors; R, lenalidomide; V, bortezomib; VGPR, very good partial response.

TABLE 9. Common regimens used in later relapses.

	Schedule	Nb of prior lines of therapy	n	ORR	mPFS	mOS
Pomalidomide-based						
PCd vs. Pd Baz, Blood 2016[77]	Pomalidomide 4mg, d1-21, Cyclophosphamide 400mg, d1,8,15 Dexamethasone 40mg weekly (20mg if >75) 28-day cycles	≥2 LEN refractory	80	64.7 vs. 38.9%	9.5 vs. 4.4m	16.8m vs. NR (NS)
OPTIMISMM **PVd vs. Pd** Richardson, Lancet 2019[66]	Bortezomib 1.3mg/m^2, d1,4,8,11 (cycles 1-8), d1,8 (cycles 9+) Pomalidomide 4mg, days 1-21 Dexamethasone 20mg, days 1,2,4,5,8,9,11,12 (10 mg if > 75)	1-3 LEN-exposed (100%)/ refractory (70%)	559	52.7 vs. 18.3%	11.2 vs. 7.1m after mFU HR 0.61	NA
Elo-Pd Dimopoulos, NEJM 2018[78]	Elotuzumab 10mg/kg IV, d1,8,15,22 (cycle 1), d1,15 (cycles 2+) Pomalidomide 4mg orally, d1-21 Dexamethasone 40mg orally, weekly (20mg if >75) 28-day cycles	3 (range 2-8)	117	53 vs. 26%	10.3 vs. 4.7m after mFU of 9.1m HR 0.54	NA
ICARIA-MM **Isa-Pd vs. Pd** Attal, Lancet 2019[79]	Isatuximab 10mg/kg IV, days 1,8,15,22 (cycle 1), days 1,15 (cycles 2+) Pomalidomide 4mg orally, days 1-21 Dexamethasone 40mg, days 1,8,15,22 (20mg > 75) 28-day cycles	≥2 LEN- and PI-refractory	307	60.4 vs. 35.3% ≥VGPR, 31.8 vs. 8.5%	11.53 vs. 6.47m after mFU of 11.6m HR 0.6	NR vs. NR 72 vs. 63% after mFU of 11.6m HR 0.69
Dara-Pd Chari, Blood 2017[80]	Daratumumab 16mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Pomalidomide 4mg orally, days 1-21 Dexamethasone 40mg, days 1,8,15,22 28-day cycles	Median of 4 ≥3 in >75%	103	60%	8.8m after mFU of 13.1m	17.5m
Daratumumab monotherapy						
GEN501/SIRIUS Usmani, Blood 2016[82]	Daratumumab 16mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly	5	148	31%	4m in responders, 15m vs. 3m	20.1m in responders, NE vs. 18.5m
Carfilzomib-based						
ENDEAVOR Kd vs. Vd Dimopoulos, Lancet Oncol 2016[83]; Dimopoulos, Lancet Oncol 2017[84]	Carfilzomib 20mg/m^2 (days 1 -2 of cycle 1) and 56mg/m^2 (subsequent doses) IV, days 1,2,8,9,15,16 Dexamethasone 20 mg orally, days 1,2,8,9,15,16,22,23 28-day cycles	1-3	929	77 vs. 63%	18.7 vs. 9.4m after mFU of ±11m (Vd) HR 0.53	47.6 vs. 40m after mFU of ±37m (Vd) HR 0.791

ARROW Moreau, Lancet Oncol 2018[85]	Carfilzomib 20mg/m^2, days 1-2, (cycle 1) and 70 mg/m^2 (subsequent doses) IV, days 1,2,8,9,15,16 Dexamethasone 40mg, days 1,8,15 (all cycles) and 22 (cycles 1-9) 28-day cycles	2-3	578	62.9% vs. 40.8%	11.2m vs. 7.6 m	NE
CANDOR **Dara-Kd vs. Kd** Usmani, Blood 2019[82]	Daratumumab 8mg/kg IV, days 1,2, cycle 1, then 16mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Carfilzomib 20mg/m^2, days 1-2, cycle 1) and 56 mg/m^2 (subsequent doses) IV, days 1,2,8,9,15,16 Dexamethasone 40mg, days 1,8,15,22 28-day cycles	1-3	466	84.3 vs. 74.7% ≥CR, 28.5 vs. 10.4%	NR vs. 15.8m after mFU of 16.9m	NR after mFU of 17m

Abbreviations: C, cyclophosphamide; d, dexamethasone; D, daratumumab; DPd, daratumumab-pomalidomide-dexamethasone; HR, hazard ratio; I, ixazomib; Isa, isatuximab; m, months; mFU, median follow-up; mPFS, median progression-free survival; mOS, median overall survival; NE, not evaluable; NR, not reached; NS, not significant; ORR, overall response rate; OS, overall survival; P, pomalidomide; Pano, panobinostat; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

The best triplet and sequence of administration remain unclear in this setting, since there have been no head-to-head trials comparing the newer agents. Dara-Rd provides the longest PFS, with a higher rate of CR and MRD negativity, while KRd is associated with an OS benefit.[64,65]

Triplets administration should be recommended in fit and/or high-risk patients, and should be continued until progression. There are not enough data to recommend stopping therapy based on response such as achievement of a negative MRD status.

Results of the common regimens used in first relapses are reported in *Table 8*.

Recommendation 24 – With lenalidomide increasingly used in the frontline setting and for longer periods of time, ***patients refractory to lenalidomide*** *represent an* ***unmet need*** *population with significantly lower median PFS.*

PVd offers a significant PFS benefit in patients already exposed/refractory to lenalidomide (100% and 70%, respectively). The benefit is even more important in patients with only one prior line of therapy.[66] Similarly, **KPd** is effective in patients already exposed/refractory to bortezomib and lenalidomide.[67] Final results from trials combining Kd or Pd with anti-CD38 or anti-SLAMF7 MoAbs are eagerly awaited.

Pomalidomide is reimbursed after two lines of therapy, PVd has been be reimbursed as from May 1, 2020. KPd is not reimbursed at the moment.

LATER RELAPSES

Recommendation 25 – In later relapses, there is no standard of care. Benefits and potential risks should be balanced to minimise excess toxicities. Enrolling patients in clinical trials remains of first importance, if available. The main therapeutic options rely on pomalidomide and daratumumab.

Pomalidomide given in association with dexamethasone provides a 30% ORR, with a four-month mPFS and twelve month mOS.[76] Outcomes are significantly improved when pomalidomide is combined with either cyclophosphamide, bortezomib, elotuzumab or isatuximab, and other associations (Dara-PD, KPd, and IPd) are being investigated with very promising results.[66,77-80]

Daratumumab monotherapy induces rapid, deep, and durable responses, with a clinical benefit that extended to patients with stable disease or better.[81] Combination with Kd is also effective, including for lenalidomide exposed/refractory patients, with a 37% reduction in the risk of progression or death.[82]

Results of main trials reported in later relapses are listed in *Table 9*.

TABLE 10. Expected landscape of MM in the very near future.

First line – transplant eligible MM VTD, Dara-VTD VCD (VRD), Dara-VRD, Isa-VRD KRd maintenance with R	**First line – transplant non eligible MM** VMP, D-VMP Rd, Dara-Rd VRd, Dara-VRD, Isa-VRD
First relapse – bortezomib-based regimens Doublets : Vd, Kd Triplets : Dara-Vd, (Dara-Kd) VCD, Elo-VD, PVd, (KPd)	**First relapse – lenalidomide-based regimens** Doublets : Rd Triplets : Dara-Rd, KRd, IRd, Elo-Rd
Second relapse and beyond Pomalidomide-based : Pd, PVd, PCd, Elo-Pd, Dara-Pd, Ixa-Pd, KPd, Isa-Pd Others : Pano-VD, Sel-D, Sel-Pd, Dara-Kd, Dara monotherapy Chemotherapy : DTC-PACE, PAD Clinical trials Immunotherapy : immunoconjugates – CAR-T cell therapy – BiTEs Others : venetoclax – melflufen - CELMoD	

*Recommendation 26 – In **triple-class refractory patients**, prognostic is poor. Inclusion in clinical trials should be proposed, in order to provide access to new drugs or immunotherapies.*

Conventional chemotherapy can elicit partial but transient response in around 50% patients, but is better proposed as a bridge to another therapy.

Venetoclax, a selective oral BCL-2 inhibitor, is particularly active in association with bortezomib and dexamethasone, with an ORR over 90% in patients bearing the t(11;14) chromosomal abnormality and not refractory to bortezomib.[86] There are concerns about infections related to the drug.[87]

Selinexor, a selective inhibitor of nuclear export protein, is also particularly efficient in penta-refractory MM patients or in combination with a PI like bortezomib, with a 80% ORR in patients not refractory to PI. Results are more modest in combination with dexamethasone, with a 26% ORR, mDOR of 4 months and mPFS of 3.4 months.[88] Selinexor is now studied in combination with various drugs including IMiDs, PIs and MoAbs (STOMP protocols).

Melflufen, a lipophilic peptide-conjugated alkylator, is a promising new compound with selective cytotoxicity to MM cells and strong anti-angiogenic properties, able to overcome drug resistance. Tested in refractory late-stage MM, it exhibits encouraging results with 32% ORR and manageable toxicities, particularly in association with IMiDs or PI.[89,90]

Iberdomide is a potent Cereblon E3 ligase modulator with anti-tumour and immunostimulatory activities in IMiD-refractory MM with favourable efficacy in heavily pre-treated patients when given with dexamethasone.[91,92]

Immunotherapy with B cell maturation antigen (BCMA) as a target opens a new therapeutic era, where antibody-drug conjugates, T-cell bispecific engagers (BiTEs) and CAR T cells are investigated with promising results.[90,93-99]

PLASMA CELL LEUKAEMIA

Recommendation 27 – In transplant eligible patients, upfront therapy should include a 3-drug bortezomib-based regimen (VCD, VTD, KRd, PAD, VRD or VDT-PACE) followed by HDM and ASCT, consolidation with 2-4 cycles (VTD or RVD), and maintenance with bortezomib until progression. Consolidation with allo-SCT can be considered in young patients, in the setting of a clinical trial.

Upfront therapy should include a triplet regimen with novel agents (VRd or KRd). The IFM proposed to alternate PAD and VCD for four cycles.[100] In patients with high disease burden or non-responsive to initial therapy, VTD-PACE or VRD-PACE should be considered, since doxorubicin and cyclophosphamide are particularly active in lymphoproliferative diseases. ASCT upfront, if possible

INTERNATIONAL PROPOSITIONS REGARDING THE COVID-19 PANDEMIC Adapted from Malard, Lancet Oncol 2020.[104]	
IMM patients might be at higher risk of severe COVID-19 with regards to older age, comorbidities and immunosuppressive treatments.	
1	Advice patients of their vulnerability to COVID-19 with regards to the weakness of their immune system
2	Consider oral regimens rather treatments that require IV/sq administration deliver oral treatment for 2 months at a time
3	Reduce the dosage of dexamethasone to 20 mg weekly, or to 10 mg weekly in patients >70, consider stopping it in some cases
4	Consider using a reduced frequency of IV drugs in patients harbouring an excellent response (i.e. weekly carfilzomib, monthly daratumumab - starting cycle 3)
5	For patients starting VRD in the non-transplant setting, consider to initiate therapy with Rd, and adding bortezomib later on; in high-risk diseases, consider home sq administration For patients on VRD, consider to change to Rd if appropriate, or, if high-risk, continue with bortezomib home sq administration
6	For patients eligible for ASCT, postpone front-line ASCT by adding 2 additional cycles of induction In patients with active/high-risk disease, do not postpone therapy
7	In patients with immunoparesis associated with severe infections, continue immunoglobulins infusions; consider home sq administration
8	In regards to clinical trials, avoid including new patients In patients already participating in a study, use telemedicine for follow-up, in order to avoid unnecessary visits to the hospital

in tandem, is recommended to achieve a deeper response and likely longer disease control. Consolidation should be proposed in patients not achieving CR, followed by maintenance with either bortezomib or lenalidomide.[101] Allo-SCT should only be proposed on a case-to-case basis. Attention has been drawn to venetoclax that induces deep responses in refractory pPCL with t(11;14).[102]

Recommendation 28 – In transplant ineligible patients, treatment should be based on bortezomib (MPV or RVD regimens) followed by maintenance.

In elderly or frail patients, induction with VCD or PAD can be used as a milder alternative, given for up to 8-10 cycles, followed by indefinite maintenance therapy to keep the disease under control.[101]

RENAL FAILURE

Recommendation 29 – Renal failure requires prompt rehydration and treatment of precipitating events (IV, C). High-dose dexamethasone should be started immediately (IV, C). Bortezomib is safely used without dose modification, even in patients under dialysis (IV, C). Triplet combinations should be preferred (IV, C). Lenalidomide requires appropriate dose reductions (IV, C). Physical methods to remove FLC from the blood should be performed within clinical trials (IV, C). ASCT can be proposed for patients with GFR <30ml/min, including patients on dialysis, using melphalan 100-140mg/m^2 (II, B).

SUPPORTIVE CARE

Recommendation 30 - Supportive care should follow the Belgian guidelines published in 2018.[103]

CONCLUSIONS

The treatment landscape of MM is evolving rapidly. Changes in the front-line setting will inevitably affect the therapy proposed at relapse (*Table 10*). Long-term therapy with Rd at diagnosis or introduction of daratumumab up-front will undoubtedly influence the therapeutic efficacy of Rd-based triplets proposed at relapse.

APPENDIX 1. IMWG geriatric scores based on ADL and IADL components and Charlson comorbidity index. Adapted from Palumbo, Blood Rev 2013.[105]

Activities of daily living (ADL)	Instrumental activities of daily living (IADL)
Bathing Dressing Toileting Transferring Continence Feeding	Ability to use the telephone Shopping Food preparation Housekeeping Laundry Transportation Responsibility for own medications Ability to handle finances
Ability to perform the activity independently: unable = 0, able = 1.	

MM Patients	Charlson comorbidity index
1	Myocardial infarction, congestive heart failure, peripheral vascular disease Dementia, cerebrovascular disease Chronic lung disease Connective tissue disorder Ulcer, chronic liver disease
2	Hemiplegia Moderate/severe kidney disease Diabetes, diabetes with complications Tumour, leukaemia, lymphoma
3	Moderate/severe liver diseases
6	Malignant tumour, metastasis AIDS

Fit	Intermediate-fit	Frail
Age ≤ 75 and all the following : dependence in ≤ 1 ADL dependence in ≤2 IADLs Charlson comorbidity index score 0-1	Does not meet criteria for Fit or Frail categories	Age ≥ 80 or any 2 of the following : age 76-80 dependence in ≥ 2 ADLs dependence in ≥ 3 IADLs Charlson comorbidity index score ≥ 2
Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.		

APPENDIX 2. ECOG-based frailty score predicting outcomes in transplant ineligible MM patients. Adapted from Facon, Leukemia 2020.[14]

Category		Score	Sum of score	
Age	≤75 76-80 >80	0 1 2		
CCI	≤1 >1	0 1	≥2 0-1	Frail Non frail
ECOG PS	0 1 ≥2	0 1 2		

Abbreviations: CCI, Charlson comorbidity index; ECOG, eastern cooperation oncology group; PS, performance status.

APPENDIX 3. Therapy doses adaptation regarding risk factors in elderly patients. Adapted from Palumbo, Blood Rev 2013.[105]

	Risk factors	point(s)
Age	≥75 years	1
co-morbidities	cardiac, pulmonary, hepatic, renal, marrow dysfunction	1
Frailty	weakness, poor endurance, weight loss, low physical activity, slow gait speed	1
Disability		1

Risk factors	dose level adaptation
0	**0**
≥1	**-1**
≥1 and previous grade 3-4 non-hematologic toxicity	**-2**

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APPENDIX 4. Suggested dose adjustment in elderly.
Adapted from Palumbo, Blood Rev 2013.[105]

Drug	Schedule	Initial/standard dose *Dose level 0*	Reduced dose *Dose level -1*	Further reduction if needed *Dose level -2*
Dexamethasone	days 1,8,15,22, every 4 weeks	40mg	20mg	10mg
Prednisone	3x/week	50mg	25mg	12,5mg
Melphalan	days 1-4, every 4-6 weeks	0.25mg/kg	0.18mg/kg	0.13mg/kg
Cyclophosphamide	days 1-21	100mg	50mg	50mg qod
Thalidomide	Continued	100mg	50mg	50mg qod
Lenalidomide in RD/Rd	days 1-21 every 4 weeks	25mg	15mg	10mg
Bortezomib	days 1,4,8,11 every 3 weeks days 1,8,15,22 every 5 weeks	1.3mg/m² twice weekly	 1.3mg/m² once weekly	1mg/m² once weekly

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