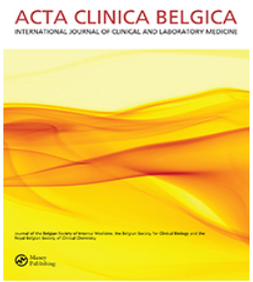

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REVIEW

Recommendations on the management of multiple myeloma in 2020

Marie-Christiane Vekemans, Chantal Doyen, Jo Caers, Kalung Wu, Alain Kentos, Philippe Mineur, Lucienne Michaux, Michel Delforge and Nathalie Meuleman

ABSTRACT
With the introduction of immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, major improvements have been achieved in the treatment of multiple myeloma (MM), with a significant impact on the outcome of this disease. Different treatment combinations are now in use and other therapies are being developed. Based on an extensive review of the recent literature, we propose practical recommendations on myeloma management, to be used by hematologists as a reference for daily practice.

KEYWORDS
Multiple myeloma; upfront therapy; relapse; novel agents; transplantation; immunotherapy; covid-19

1. 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 [1], to be used by Belgian hematologists as a reference for daily practice. 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.

2. Diagnosis

Recommendation 1 – Diagnosis of MM requires the fulfillment of the 2014 IMWG criteria (IV,C).

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 symptomatic (active) MM present with symptoms related to organ damage, referred to as the CRAB-SLiM criteria [3] (Table 1).

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) [4,5].

3. 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 serum β2-microglobulin, the most relevant biological prognostic parameter [6]. The revised ISS (R-ISS) includes also serum LDH and bone marrow FISH analysis done on sorted PC, since cytogenetics remains the most prominent prognostic factor (Table 4)[7]. High-risk features encompass t(4;14), del(17p), del(1p) and gains (1q) [8–10]. Double-hit MM defined by the presence of 2 or more high-risk factors, is also associated with a very poor outcome (Walker, Leukemia 2019) [11].

Apart from elevated serum LDH, other factors associated with aggressive disease include the presence of circulating PC or extramedullary disease (EMD). 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 and 2. 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 [14,15].

4. 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). However, the true value of CR relies in the minimal residual disease (MRD) status. MRD negativity is associated with better long-term outcome [16–18]. Of note, in the elderly, increased progression-free survival (PFS) is a worthwhile objective if the quality of life (QoL) is maintained and can delay the onset of disease complications.

5. Indication for therapy

*Recommendation 5 – Treatment should be considered in all patients with a diagnosis of **symptomatic MM** as*

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Supplemental data for this article can be accessed here.

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 creatinin >177 mmol/l (>2 mg/dl) with no other etiology or creatinine clearance < 40 ml/min
A	Anemia	hemoglobin value >2 g/dl below the lowest limit of normal or a hemoglobin value <10 g/dl
B	Bone lesions	one or more osteolytic lesions on skeletal x-rays, WBLDCT or PET-CT. If BM < 10% clonal PC, more than one bone lesion is required to distinguish MM 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; MM, multiple myeloma; PC, plasma cell; PET, positron emitting tomography; MRI, magnetic resonance imaging; WBLDCT, whole-body low-dose computed tomography

Table 2. Investigations required at diagnosis.

Biological tests	serum blood count, urea, creatinin, 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 (24 h 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* hybridization; FLC, free-light chain; MM, multiple myeloma; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; WBLDCT, whole-body low-dose computed tomography

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.

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, PS, 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 3 to 6 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 (lenalidomide-dexamethasone) showed a prolonged PFS and OS [19,20]. In fact, this trial mainly concerned high-risk SMM that should nowadays be reclassified as active MM. However, in a more recent trial, time to symptomatic MM was prolonged, particularly in high-risk SMM [21].

Other very promising studies aim either to control and delay progression with prolonged administration of immunomodulatory drugs (IMiDs) or monoclonal antibodies (MoAbs), or to cure the disease using aggressive approaches such as carfilzomib-lenalidomide-dexamethasone (KRd) induction followed by ASCT [22–24].

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 >20 g/l and serum FLC ratio >20, and stratifies patients in low-, intermediate- or high-risk groups with a median PFS of 110, 68 or 29 months, respectively [25].

Table 4. Revised ISS risk stratification for MM (adapted from Palumbo, JCO 2015) [7].

	Stage I – standard risk	**Stage II–intermediate risk**	**Stage 3 – high risk**
MM Patients	20%	60%	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; ISS, international staging system; 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

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

Solitary plasmocytoma is usually managed with radiation therapy with 40–50 Gy administered in fractionated doses [26]. Careful follow-up is mandatory since two-thirds of patients progress to MM at 10 years, particularly in case of persistence of M-spike after radiotherapy [27].

6. Treatment of newly diagnosed MM not eligible for transplant

Recommendation 8 – Before starting therapy, elderly patients should be assessed for risk factors defined as age over 75, presence of comorbidities, frailty, or disability.

Frailty, defined as a complex syndrome of physiologic decline associated with increased vulnerability, is recognized as an adverse risk factor even more discriminative than age or cytogenetics. In this perspective, it is highly recommended to perform, in collaboration with geriatric specialists, a comprehensive geriatric assessment (GA) that can predict both survival and toxicities in elderly MM patients.

The complexity of carrying for older patients arises in part from the heterogeneity of aging. GA tools have been shown to accurately assess the risk of morbidity and mortality in cancer patients independent of age and PS. In MM, geriatric scales, even complex, are helpful to identify frail patients [12,13], predict drug toxicities [28], and adapt therapy [13]. Because their implication in routine can be cumbersome, simpler scores based on age, the Charlson comorbidity index (CCI) and the ECOG PS have been developed, that provide similar informations [14,15] (Appendices 3,4).

*Recommendation 9 – Outside clinical trials, patients not eligible for ASCT should receive either **VMP** (bortezomib-melphalan-prednisone), **Rd** or **VRd** (bortezomib-lenalidomide-dexamethasone) as standard front-line therapy. Based on the FIRST trial, **MPT** (melphalan-thalidomide-dexamethasone) is no more considered as a standard of care.*

There is no evidence of the superiority of VMP over Rd in the absence of randomized clinical trials [29,30]. In contrast, compared to Rd, VRd is associated by better overall response rates (ORR), PFS and overall survival (OS) [31], 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, but can be shorter because of therapy-related toxicities.

VRd is effective in all age subgroups, including patients over 75, but should be preferred for fit elderly patients [31]. **VRd lite** is a highly effective alternative for less fit patients that balances adequately efficacy and toxicity [32].

Bortezomib-based regimens may be preferred in patients with high-risk cytogenetics, renal impairment and increased risk for VTE or contra-indications to anticoagulants, but requires antiviral prophylaxis against herpes zoster and monitoring for drug-related polyneuropathy (PN). This neurotoxicity can be reduced by weekly dosing as well as by subcutaneous administration, without impact on OS [33,34]. Rd may be preferred in patients with pre-existing PN, but requires prophylactic anticoagulation and dose reduction in case of renal dysfunction. It is better tolerated when given with low-dose dexamethasone (20 mg per week in patients over 75) [35,36]. Dexamethasone can even be stopped after nine cycles in intermediate-fit patients, without any impact on ORR, PFS, or OS [37].

Regarding the VMP regimen, there is no advantage to replace bortezomib by carfilzomib (**KMP**) [38]. In contrast, melphalan can be replaced by cyclophosphamide (**VCD**) with high response rates, prolonged PFS, and good tolerability [39].

The combination of daratumumab to VMP (**Dara-VMP**, ALCYONE trial) provides very high ORR and a 50% reduction of the risk of progression/death, a benefit consistent across all subgroups including patients over 75, ISS 3, renal impairment and high-risk cytogenetics [40], without additional toxicities except for increased infectious events. It is also associated with OS prolongation [41]. In unfit elderly MM patients, other combinations such as **Dara-Ixazomib**-dexamethasone (Dara-Ixa-d) are under investigation with the purpose to limit toxicity [42].

The Rd regimen serves as backbone for triplet combinations with proteasome-inhibitors (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 threefold 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 [43].

Other combinations using PI (KRd, Ixa-Rd) or MoAbs (Dara-VRD, isatuximab-VRD (IMROZ), sqDara-VRD (CEPHEUS), elotuzumab-Rd) are also under investigation. Preliminary results fail 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 5.

Recommendation 10 – Continuous therapy with Rd is recommended until progression.

Continuous Rd is associated with an improvement in PFS when compared to Rd given for a fixed duration of 18 months, a benefit even more prominent in patients achieving at least very good partial response (VGPR) [44], at the cost of more toxicities, particularly in the very old and frail population [30]. Duration of therapy should take into account patient preferences, toxicities, QoL and costs.

Table 5. Common induction regimens for myeloma transplant-ineligible patients.

Front-line regimens	Schedule	n	ORR	≥VGPR	mPFS	mOS
VISTA **VMP vs. MP** San Miguel, NEJM 2008; San Miguel, JCO 2013 [29,116]	Melphalan 9 mg/m^2 orally days 1–4 Prednisone 60 mg/m^2 days orally 1–4 Bortezomib 1.3 mg/m^2 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. 18 m	56.4 vs. 43 m after mFU of 60.1 m HR 0.7
VMP once weekly vs. twice weekly Bringhen, Blood 2010 [117]	Melphalan 9 mg/m^2 orally days 1–4 Prednisone 60 mg/m^2 days orally 1–4 Bortezomib 1.3 mg/m^2 days 1,8,15,22 (cycles 1–9)	511	NA	NA	33.1 vs. 31.7 m after mFU of 23.2 m HR 1.95	3y-OS, 88% vs. 89% HR 1.22
FIRST **Rdcont vs. Rd18 vs. MPT** Benboubker, NEJM 2014; Facon, Blood 2018 [30,44]	Lenalidomide 25 mg orally days 1–21 Dexamethasone 40 mg, days 1,8,15,22 Repeted every 4 weeks Melphalan 0.25 mg/kg, days 1–4, Prednisone 2 mg/kg, days 1–4, Thalidomide 200 mg/day, 42-day cycles	1623	75 vs. 73 vs. 62%	44 vs. 43 vs. 28%	26 vs. 21 vs. 21 m	59.1 vs. 62.3 vs. 49.1 m after mFU of 67 m HR 0.69
ALCYONE **Dara-VMP** Mateos, NEJM 2018; Mateos, Blood 2019 [40,41]	Daratumumab 16 mg/kg IV weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Melphalan 9 mg/m^2 orally days 1–4 Prednisone 60 mg/m^2 days orally 1–4 Bortezomib 1.3 mg/m^2 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. 19.3 m after mFU of 40.m	36 m-OS, 78% vs. 68% mOS NR in both groups
MAIA **Dara-Rd** Facon, NEJM 2019 [43]	Daratumumab 16 mg/kg IV weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Lenalidomide 25 mg orally days 1–21 Dexamethasone 40 mg, days 1,8,15,22 (20 mg 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%	30 m PFS, NR vs. 31.9 m	NR in both
VRd vs. Rd Durie, Lancet 2017 [31]	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. 31 m	75 vs.64 m
VRd lite O'Donnell, Br J Haematol 2018 [32]	Bortezomib 1.3 mg/m^2 sq days 1,8,15,22 Lenalidomlide 15 mg orally days 1–21 Dexamethasone 20 mg orally days 1,2,8,9,15,16,22,23	50	86%	66%	35.1 m	NR After mFU of 30 m

Abbreviations: B, bendamustine; C, cyclophosphamide; CR, complete response; d, low-dose dexamethasone; D, high-dose dexamethasone; dara, daratumumab; HR, hazard ratio; m, months; M, melphalan; mFU, median follow-up; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, Overall response rate; OS, overall survival; P, prednisone; PFS, progression-free survival; PR, partial response; R, lenalidomide; Rdcont, Rd continuous; Rd18, Rd for 18 months; Ref, references; T, thalidomide; V, bortezomib; VGPR, very good partial response.

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.

7. Treatment of newly diagnosed MM eligible for transplant

Recommendation 11 – In transplant-eligible MM, 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 (bortezomib-thalidomide-dexamethasone) is superior to **VCD** but at the cost of more peripheral polyneuropathies [45]. Substitution of thalidomide by lenalidomide (**VRD)** results in significantly higher response rates, response duration and PFS [31,46,47] compared to previous studies using VTD. There is no phase 3 trial comparing head-to-head VTD and VRD. Replacement of bortezomib by carfilzomib (**KRD**) is highly effective with up to 89% ORR, particularly regarding the achievement of MRD negativity (up to 58%) [48].

Similarly, addition of **daratumumab** to VTD (**Dara-VTD**, CASSIOPEIA trial) significantly improves the rates of stringent complete response (sCR), MRD negativity, and 18-month PFS [49]. Similar results are awaited with the **dara-VRD** (GRIFFIN trial) [50] or dara-KRD combinations [51].

VRD, carfilzomib, and daratumumab are not reimbursed in first-line therapy in Belgium.

Current induction regimens are listed in Table 6.

Recommendation 12 – Four cycles are recommended before stem cell collection (SCC). 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 [52].

Recommendation 13 – Sufficient SCC (at least for more than one ASCT) should be considered upfront, since later SCC can be hampered after prolonged drug exposure such as melphalan or IMiDs.

Successful engraftment can be achieved with 2×10^6 CD34+ peripheral hematopoietic stem cells/kg, but the optimal target is usually 5×10^6 CD34+/kg per transplant.

Mobilization is achieved using filgrastim (10 µg/kg/day for 4–6 consecutive days, apheresis on days 5–6) or cyclophosphamide (2–4 g/m^2).

Prolonged exposure to lenalidomide may impair SCC. In this case, apheresis should not be performed beyond 4 cycles and may require the use of cyclophosphamide or plerixafor [53].

Recommendation 14 – Conditioning with melphalan 200 mg/m^2 (MEL200) remains the standard regimen used prior to ASCT.

Dose reductions (140 mg/m^2) are recommended in case of renal impairment (estimated GFR <60 ml/min) [54]. There is no benefit to add total body irradiation (TBI) or any other agent such as bortezomib [55].

*Recommendation 15 – **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.*

In the IFM 2009 trial, **VRD** induction plus ASCT opposed to VRD alone results in significant improvement in PFS (50 vs. 36 months, HR 0.65), CR rate (59% vs. 48%), MRD negati
vity (79% vs. 65%) and median time to progression (mTTP) (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 [46].

In the EMN02-HO95 trial, upfront ASCT (single or double) compared to VMP after VCD induction was associated with a decreased risk of progression/death and improved 3-year PFS, regardless of initial adverse prognostic factors [56].

The role of upfront ASCT is further challenged by the addition of MoAbs such as daratumumab to triplet induction regimens [49,50], or the use of second-generation PI such as carfilzomib [48,51]. It is likely that the MRD status achieved after induction will have an impact on ASCT decisions in the future.

*Recommendation 16 – **Tandem ASCT** can be beneficial for patients with high-risk cytogenetic features or those with a suboptimal response to first transplant.*

In the EMN02/HO95 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 [56].

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 including doublets, given for various durations, and more than 30% of patients randomized to tandem ASCT did not receive the second transplant [57].

*Recommendation 17 – The **role of consolidation** is still unclear. The optimal regimen, number of cycles and subgroups that will benefit from consolidation as well as its efficacy when followed by optimal maintenance in the era of novel agents are questions that should be answered. It remains a reasonable practice in patients who failed to achieve at least CR after transplantation.*

Table 6. Frontline induction regimens in transplant-eligible patients.

Front-line regimens	Schedule	n	ORR	≥VGPR	mPFS	mOS
VTD vs. VCD Moreau, Blood 2016 [45]	Bortezomib 1.3 mg/m^2 sq days 1,4,8,11 Dexamethasone 40 mg orally days 1–4, 9–12 Repeated every 3 weeks Thalidomide 100 mg orally, days 1–21 or Cyclophosphamide 500 mg/m^2 orally, days 1,8,15	368	92 vs. 83%	66 vs. 56%	NA	NA
vTD Moreau, Blood 2011 [118]	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%	26 m	NA
VRD vs VRD-ASCT Attal, NEJM 2017 [46]	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. 50 m	NR for both 82 vs. 81% at 4y
VRD vs. Rd Durie, Lancet 2017 [31]	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. 31 m	75 vs. 64 m
PAD vs. VAD Sonneveld, J Clin Oncol 2012 [62]	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. 28 m mFU of 41 m HR 0.75	NR for both at 66 m 61 vs. 55% at 5y (NS)
CASSIOPEIA **Dara-VTD vs. VTD** Moreau, Lancet 2019 [49]	Daratumumab 16 mg/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 100 mg orally, days 1–28 Dexamethasone 40 mg orally days 1,8,15,22 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 [50]	Daratumumab 16 mg/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
FORTE **KRD12 vs. KRD4/ASCT/KRD4 vs. KCD4/ASCT/KCD4** Gay, J Clin Oncol 2019 [48]	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		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; HR, hazard ratio; 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, thalidomide; v, low-dose bortezomib; V, bortezomib; VGPR, very good partial response; y, years.

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 [58,59].

More recently, two trials 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 [56]. On the opposite, the StaMINA trial failed to identify any PFS benefit using either a second transplant or three cycles of VRD consolidation [57]. 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. Attempts to guide consolidation decisions based on the MRD status obtained after ASCT are ongoing [51].

Recommendation 18 – ***Maintenance with lenalidomide*** *after ASCT is considered a standard of care since it improves OS. In addition, it can favor the conversion to MRD negativity. Its benefit in high-risk diseases is less clear, and the optimal duration of maintenance is still a matter of debate. Overall, an average duration of 2 years with a 3-week on, 1-week off treatment has become widely adopted. It exposes patients to an increase incidence, albeit modest, of second primary malignancies (SMP).*

Daily **lenalidomide** given in monotherapy at the dosage of 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 OS by approximately 2.5 years, except in high-risk diseases where conflicting data have been published [60,61].

The OS benefit of lenalidomide maintenance largely outweighs the risk of developing an SPM [60]. Patients should be informed and monitored accordingly.

Recommendation 19 – ***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 2 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) [62]. **Ixazomib**, an oral PI given once weekly for 2 years, improves PFS by 39% and reduces the risk of progression/death by 28%, when compared to placebo [63], but is not approved in this indication. Additional trials incorporating pomalidomide, carfilzomib, and MoAbs are currently ongoing.

Selected maintenance regimens used in this setting are listed in Table 7.

Recommendation 20 – Consolidation with ***allogeneic transplantation*** *is still considered investigational for MM. Because of the risk of severe treatment-related mortality and graft-versus-host disease, it should only be performed in young patients with (ultra)-high-risk disease in good response [64], preferably within clinical trials if available (IV,C).*

8. Relapse, definition and indication of retreatment

Recommendation 21 – Diagnosis of progression or relapse requires the fulfillment 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 0.5 g/dl), or ≥200 mg in light-chain excretion in a 24-h 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 [65].

Work-up should at least include imaging in order to identify new lytic lesions or EMD. BM 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 del(17p) and 1q amplification, that predict a more aggressive disease [66]. Identification of t(11;14) might be of interest since this abnormality has been reported to be sensitive to venetoclax.

Recommendation 22 – Biochemical (asymptomatic) relapses that require close observation should be differentiate from clinical (symptomatic, with CRAB features) relapses that require immediate treatment.

9. Early relapses

Recommendation 23 – 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 24 – ***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 [67]. It is, however, important to balance the risk, albeit modest, and side effects of ASCT with the excellent PFS obtained so far with new combinations.

Recommendation 25 – 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 diseases.*

The best triplet and sequence of administration remains 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

Table 7. Selected maintenance regimens used after ASCT.

Maintenance	Schedule	mPFS	OS
Lenalidomide McCarthy, JCO 2017 [60]	Lenalidomide 10 mg, days 1–21 until progression	52.8 vs. 23.5 m HR 0.48	mOS, NR vs. 86 m after mFU of 79.5 m HR 0.75
MM XI R maintenance vs. placebo Jackson, Lancet Oncol 2019 [61]	Lenalidomide 10 mg, days 1–21/28 until progression	39 vs. 20 m after mFU of 31 m HR 0.46	3y-OS, 78.6% vs. 75.8% HR 0.87
HOVON T after VAD-ASCT vs. V after PAD-ASCT Sonneveld, JCO 2012 [62]	Thalidomide 50 mg/d or Bortezomib 1.3 mg/m^2 qw, for 2 years	28 vs. 35 m CR/nCR, 34% vs. 49%	5y-OS, 55% vs. 61%
TOURMALINE-MM3 Ixazomib vs. placebo Dimopoulos, Lancet 2019 [63]	Ixazomib 4 mg, days 1,8,15 28-day cycles, for 2 years	26.5 vs. 21.3 m after mFU of 31 m 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.

CR and MRD negativity [68], while KRd is associated with an OS benefit [69].

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 to stop therapy based on response such as achievement of a negative MRD status.

Common regimens used in first relapses are reported in Table 8.

Recommendation 26 – 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.*

Resistance to lenalidomide is not dose-dependent. Patients with a longer duration of prior lenalidomide therapy (>12 months)(possible inherent IMiD sensitivity), and longer IMiD-free interval (≥18 months)(potential re-emergence of IMID-sensitive clones), have longer PFS and OS, irrespective of prior lines of therapy [70].

In this context, **PVd** (pomalidomide-bortezomib-dexamethasone) offers a significant PFS benefit in patients already exposed (100%)/refractory (70%) to lenalidomide (Table 8). The benefit is even more important in patients exposed to only one prior line of therapy [71]. Similarly, **KPd** (carfilzomib-pomalidomide-dexamethasone) is effective in patients already exposed/refractory to bortezomib and lenalidomide [72]. 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 1 May 2020. KPd or other combinations are not reimbursed at the moment.

10. Later relapses

Recommendation 27 – In later relapse, there is no standard of care. Benefits and potential risks should be balanced to minimize excess toxicities. Enrolling patients in clinical trials remain of first importance, if available. The main therapeutic options rely on pomalidomide and daratumumab.

Pomalidomide given in association with dexamethasone provides only a 30% ORR, with a 4-month mPFS and 12-month mOS [73]. Outcomes are significantly improved when pomalidomide is combined with cyclophosphamide [74], bortezomib [71], elotuzumab [75], or isatuximab [76], and other associations (Dara-Pd, KPd, Ixa-Pd) are being investigated with very promising results [77].

Daratumumab monotherapy induces rapid, deep, and durable responses, with a clinical benefit that extends to patients with stable disease or better [78]. Combination with Kd is also effective, including for lenalidomide exposed/refractory patients, with a 37% reduction in the risk of progression/death [79].

Main trials reported in later relapses are listed in Table 9.

Recommendation 28 – In ***triple-class refractory MM patients****, prognostic is poor. Inclusion in clinical trials should be proposed, in order to provide access to new drugs or immunotherapies.*

In **penta-refractory** patients, mOS is less than 6 months [80]. When progressing under a CD-38 MoAb-based regimen, prognosis is unfavorable even if patients they might still be responsive to a PI or an IMiD, opening the way to other combinations.

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

Venetoclax is a selective oral BCL-2 inhibitor, is particularly active in association with bortezomib and dexamethasone, with an ORR over 90% in patients bearing translocations t(11;14) and not refractory to bortezomib [81]. There are concerns about infections related to the drug [82].

Selinexor is a selective inhibitor of nuclear export protein, is also particularly efficient in penta-refractory MM patients or in combination with a PI like bortezomib,

Table 8. Common regimens used in first relapses.

	Schedule	N	ORR	≥VGPR	mPFS	mOS
LEN-based						
POLLUX **Dara-Rd vs. Rd** Dimopoulos, NEJM 2016; Dimopoulos, Haematologica 2018 [68,119]	Daratumumab 16 mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Lenalidomide 25 mg orally, days 1–21 Dexamethasone 40 mg, days 1,8,15,22 28-day cycles	569	92.9 vs. 76.4%	75.8 vs. 44.2%	NR vs. 17.5 m after mFU of 25.4 m HR 0.41	
ASPIRE **KRd vs. Rd** Steward, NEJM 2015; Siegel, JCO 2018 [69,120]	Carfilzomib 20 mg/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. 17.6 m HR 0.69	48.3 vs. 40.4 m after mFU of ±67 m HR 0.79 (p, 0.04)
TOURMALINE **Ixa-Rd vs. Rd** Moreau, NEJM 2016 [121]	Ixazomib 4 mg orally, days 1,8,15 Lenalidomide 25 mg orally, days 1–21 Dexamethasone 40 mg orally, days 1,8,15,22 28-day cycles	722	78 vs. 72%	80.3 vs. 72.7%	20.6 vs. 14.7 m after mFU 14.7 m HR 0.74	
ELOQUENT-2 **Elo-Rd vs. Rd** Lonial, NEJM 2015 [122]	Elotuzumab 10 mg/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. 14.9 m after mFU of 32.4 m HR 0.73	
PI-based						
CASTOR **Dara-Vd vs. Vd** Palumbo, NEJM 2016; Spencer, Haematologica 2018 [123,124]	Daratumumab 16 mg/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, cyles 1–8 Dexamethasone 40 mg, days 1,8,15,22 28-day cycles	498	82.9 vs. 63.2%	59.2 vs. 29.1%	16.7 vs. 7.1 m after mFU of 19.4 m HR 0.31	NA
PANORAMA **Pano-Vd vs. Vd** San Miguel, Lancet Oncol 2014; San Miguel, Lancet Haematol 2016 [125,126]	Panobinostat 20 mg orally, 3 times a week, x 2 weeks Bortezomib 1.3 mg/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. 8.08 m after mFU of ±6.5 m HR 0.63	no difference in OS 40.3 vs. 35.8 m HR 0.94
OPTIMISMM **PVd vs. Pd** Richardson, Lancet 2019 [71]	Bortezomib 1.3 mg/m^2 d1,4,8,11 (cycles 1–8), d1,8 (cycles 9+) Pomalidomide 4 mg days 1–21 Dexamethasone 20 mg 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. 7.1 m after mFU of 15.9 m HR 0.61 In len-refractory, 9.53 vs. 5.59 m HR 0.64	No difference in OS, 31%

Abbreviations: CR, complete response; d, low-dose dexamethasone; D, high-dose dexamethasone; Dara-Rd, daratumumab-lenalidomide-dexamethasone; Dara-Vd, daratumumab-bortezomib-dexamethasone; Elo, elotuzumab; HR, hazard ratio; Ixa, 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 [74]	Pomalidomide 4 mg, d1-21, Cyclophosphamide 400 mg, d1,8,15 Dexamethasone 40 mg weekly (20 mg if >75) 28-day cycles	≥2 LEN refractory	80	64.7 vs. 38.9%	9.5 vs. 4.4 m	16.8 m vs. NR (NS)
OPTIMISMM **PVd vs. Pd** Richardson, Lancet 2019 [71]	Bortezomib 1.3 mg/m^2 d1,4,8,11 (cycles 1–8), d1,8 (cycles 9+) Pomalidomide 4 mg days 1–21 Dexamethasone 20 mg days 1,2,4,5,8,9,11,12 (10 mg if > 75)	1–3 100% LEN-exposed, 70% LEN-refractory	559	52.7 vs. 18.3%	11.2 vs. 7.1 m after after mFU HR 0.61	NA
ELOQUENT-3 **Elo-Pd** Dimopoulos, NEJM 2018 [75]	Elotuzumab 10 mg/kg IV d1,8,15,22 (cycle 1), d1,15 (cycles 2+) Pomalidomide 4 mg, orally, d1-21 Dexamethasone 40 mg orally, weekly (20 mg if >75) 28-day cycles	3 (range 2–8) 100% LEN or BORT-exposed, refractory to last line	117	53 vs. 26%	10.3 vs. 4.7 m after mFU of 9.1 m HR 0.54	NA
ICARIA-MM **Isa-Pd vs. Pd** Attal, Lancet 2019 [76]	Isatuximab 10 mg/kg IV days 1,8,15,22 (cycle 1), days 1,15 (cycles 2+) Pomalidomide 4 mg orally days 1–21 Dexamethasone 40 mg days 1,8,15,22 (20 mg > 75) 28-day cycles	≥2 LEN- and PI-refractory	307	60.4 vs. 35.3% ≥VGPR, 31.8 vs. 8.5%	11.53 vs. 6.47 m after mFU of 11.6 m HR 0.6	NR vs. NR 72 vs. 63% after mFU of 11.6 m HR 0.69
EQUULEUS **Dara-Pd** Chari, Blood 2017 [77]	Daratumumab 16 mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Pomalidomide 4 mg orally, days 1–21 Dexamethasone 40 mg, days 1,8,15,22 28-day cycles	Median of 4 ≥3 in >75%	103	60%	8.8 m after mFU of 13.1 m	17.5 m
MoAb-based						
GEN501/SIRIUS **Dara monotherapy** Usmani, Blood 2016 [78]	Daratumumab 16 mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly	5	148	31%	4 m in responders, 15 m vs. 3 m	20.1 m in responders, NE vs. 18.5 m
CANDOR **Dara-Kd vs. Kd** Usmani, Blood 2019 [79]	Daratumumab 8 mg/kg IV, days 1,2, cycle 1, then 16 mg/kg IV, weekly x 8 weeks, then every 2 weeks for 4 months, then monthly Carfilzomib 20 mg/m^2, days 1–2, cycle 1) and 56 mg/m^2 (subsequent doses) IV days 1,2,8,9,15,16 Dexamethasone 40 mg, days 1,8,15,22 28-day cycles	1–3 90% BORT-exposed, 42% LEN-exposed, 33% LEN-refractory	466	84.3 vs. 74.7% ≥CR, 28.5 vs. 10.4%	NR vs. 15.8 m after mFU of 16.9 m	NR after mFU of 17 m
IKEMA **Isa-Kd vs. Kd** Moreau, EHA 2020 [127]	Isatuximab 10 mg/kg IV days 1,8,15,22 (cycle 1), days 1,15 (cycles 2+) Carfilzomib 20 mg/m^2 days 1, 2 (cycle 1), 56 mg/m^2 thereafter, twide weekly for 3 of 4 weeks, Dexamethasone 20 mg twice weekly (10 mg > 75) 28-day cycles	1–3 90% BORT-exposed, 78% LEN-exposed	302	86.6 vs. 82.9% ≥VGPR, 72.6 vs. 56.1% CR, 39.7 vs. 27.6% MRD neg, 29.6 vs. 13%	NR vs. 19.15 m HR 0.531 after mFU of 20.7 m	NA
Carfilzomib-based						
ENDEAVOR **Kd vs. Vd** Dimopoulos, Lancet Oncol 2016; Dimopoulos, Lancet Oncol 2017 [128,129]	Carfilzomib 20 mg/m^2 (days 1 − 2 of cycle 1) and 56 mg/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. 9.4 m after mFU of ±11 m (Vd) HR 0.53	47.6 vs. 40 m after mFU of ±37 m (Vd) HR 0.791
ARROW **Kd once-weekly vs. twice-weekly** Moreau, Lancet Oncol 2018 [130]	Carfilzomib 20 mg/m^2, days 1–2, (cycle 1) and 70 mg/m^2 (subsequent doses) IV days 1,2,8,9,15,16 Dexamethasone 40 mg, days 1,8,15 (all cycles) and 22 (cycles 1–9) 28-day cycles	2–3	578	62.9% vs. 40.8%	11.2 m vs. 7.6 m	NE

Abbreviations: BORT, bortezomib; C, cyclophosphamide; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; HR, hazard ratio; Ixa, ixazomib; Isa, isatuximab; LEN, lenalidomide; 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; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

with a 84% ORR in PI-non refractory and 43% in PI-refractory patients [83]. Results are more modest in combination with dexamethasone, with a 26% ORR, an mDOR of 4 months and an mPFS of 3.4 months [84]. Selinexor is now studied in combination with various drugs including IMiDs, PIs, and MoAbs in the STOMP protocols.

Melflufen is a lipophilic peptide-conjugated alkylator, 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 [85], particularly in association with IMiDs or PI [86].

Iberdomide is a potent cereblon-E3-ligase modulator with anti-tumor and immunostimulatory activities in IMiD-refractory MM [87] with favorable efficacy in heavily pre-treated patients when given with dexamethasone [88].

Immunotherapy with B cell maturation antigen (BCMA) as a target opens a new therapeutic era, where antibody-drug conjugates [89,90], T-cell bispecific engagers (BiTEs) [91], and CAR T cells [92–95] are investigated with promising results.

11. Plasma cell leukemia and extramedullary disease

Recommendation 29 – Diagnosis of plasma cell leukemia (PCL) requires the fulfillment of the 2013 IMWG criteria [96]. *Initial work-up should include peripheral blood analysis for detecting circulating PC, and PET-CT for identifying EMD.*

PCL is clinically, biologically, and cytogenetically distinct from MM, with a younger age at diagnosis, an aggressive clinical presentation with a higher association to EMD. Of note, MM patients carry the same adverse prognosis as PCL in the presence of >5% circulating PC [97]. PCL is frequently associated with complex karyotypes and hypodiploïdy, as well as t(11;14), add(1q) and del(17p) [95]. Survival is affected by factors that include age <60, platelets count <100,000/µl, PC >20,000/µl [98].

Recommendation 30 – There are no precise guidelines in the PCL setting. Clinical trials should always be recommended, if available.

Recommendation 31 – In transplant eligible patients, upfront therapy should include a 3-drug bortezomib-based regimen or a schema used in aggressive lymphomas, followed by HDM and ASCT, consolidation with 2–4 bortezomib-based cycles or second ASCT, and maintenance with bortezomib until progression (IB). Consolidation with allo-SCT can be considered in young patients (IB), in the setting of a clinical trial, if available.

Upfront therapy should include a triplet regimen with at least a PI and an IMiD (VTD/VRd, KRd, or PAD). The IFM proposed to alternate PAD and VCD for four cycles [99]. In patients with high disease burden or non-responsive to initial therapy, VTD/VRD-PACE or hyperCVAD-VD should be considered, since doxorubicin and cyclophosphamide are particularly active in lymphoproliferative diseases. ASCT upfront, in tandem if possible, is recommended to achieve a deeper response and longer disease control. Consolidation should be proposed in patients not achieving CR, followed by maintenance with either bortezomib or lenalidomide [100,101]. Allo-SCT should only be considered on a case-to-case basis. Attention has been drawn to venetoclax that induces deep responses in refractory primary PCL with t(11;14) [102].

Recommendation 32 – In transplant ineligible patients, treatment should be based on bortezomib (VMP or VRD regimens) followed by maintenance.

In elderly or frail patients, induction with VCD or VRD 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].

Recommendation 33 – Extramedullary disease is considered as high-risk disease and should be treated accordingly.

EMD is defined by the presence of PC outside the BM. It can be found in up to 30% of MM patients across the overall disease course, and is associated with adverse prognostic factors and poor prognosis. Spread to soft tissues is associated with worse outcomes compared to involvement of bones [103].

12. Response assessment

Recommendation 34 – Responses to therapy should be assessed using the IMWG response criteria.

Response assessment includes evaluation of the level of M-protein by serum and urine protein electrophoresis every month while on therapy, and every 3–4 months when off-therapy. The FLC assay is needed to monitor patients who lack a measurable M-protein, particularly in oligo- or non-secretory and light-chain MM, provided the FLC ratio is abnormal and the involved FLC level is ≥100 mg/l. It is also required to define the stringent CR criteria [65].

MRD negativity has been associated with improved outcomes [16–18]. It is defined as the absence of detectable disease either by next-generation sequencing (NGS) or next generation flow (NGF) [65] and imaging (Pet-CT) [104]. It is now regularly assessed in clinical trials and represents the future treatment goal in MM [104]. Efforts are made to determine the optimal timing, frequency and level of sensitivity of MRD testing, as well as its impact on treatment decisions. However, at the moment, it is not used routinely.

13. Supportive care

Recommendation 35 – Supportive care should follow international guidelines.

Recommendation 36 – ***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 such as VCD or VTD should be preferred (IV,C). Lenalidomide requires appropriate dose reductions (IV,C). The place of physical methods to remove FLC from the blood is still controversial. ASCT can be proposed for patients with GFR <30 ml/min, including patients on dialysis, using melphalan 100–140 mg/m^2 (II,B).

*Recommendation 37 – **Bone disease** concerns up to 80% of MM patients, and should be treated with biphosphonates in all symptomatic MM regardless the presence of lytic lesions. Because of the risk of osteonecrosis of the jaw (ONJ), dental evaluation should be carried out before starting therapy.*

Both **zoledronic acid** (ZA) and **pamidronate** are effective with respect to skeletal-related events (SRE) prevention, but ZA has been associated with a prolonged OS [105]. Dose should be adjusted in patients with moderate renal dysfunction (creatinine clearance 30–60 ml/min) [106]. **Denosumab** is an antibody targeting RANK ligand that has the advantage of being administered subcutaneously while not being cleared by the kidneys. Compared to ZA, denosumab provides a lower rate of SRE and a prolonged PFS, but without OS benefit [107].

There is no consensus regarding the duration of bisphosphonate therapy. However, given the risk of ONJ, it should not be administered longer than 2 years [106,108]. Dental evaluation should be carried out before starting therapy and invasive dental procedures should be avoided thereafter.

*Recommendation 38 – MM patients have an increased risk of **thromboembolic event**, a risk that is significantly enhanced by the use of specific therapeutic agents. Risk of thrombosis should be assessed before starting therapy.*

Apart from personal risk factors (age, obesity, inherited thrombophilia, familial history of thrombosis, surgery, immobilization, presence of catheter), MM patients presented an increased risk of thrombosis that is significantly enhanced by the use of high-dose dexamethasone, anthracyclines, growth factors (EPO), IMiDs and carfilzomib [109].

Patients due to initiate an IMiD-based therapy should be started on aspirine 100 mg daily in the absence of risk factors, or low-molecular-weight-heparin (LMWH) in higher risk situations, for at least 4–6 months or as long as the risk of thrombosis remains high [106]. LMWH requires dosage adaptation in patients with renal impairment. New oral anticoagulants (NOAC) are effective, safe, and patient-friendly [110,111]. Thalidomide or lenalidomide monotherapy does not require thromboprophylaxis.

*Recommendation 39 – MM patients have an increased risk **of infectious complications**, particularly at start of therapy when the disease is active, in elderly frail patients.*

Infections represent the second cause of mortality in MM patients. Performance status, serum β2-microglobulin, LDH, and hemoglobin levels have been recognized as prognostic factors of the occurrence of ≥ grade 3 infections [112].

Antibiotic prophylaxis remains controversial, but may be beneficial within the first 2–3 months in patients under lenalidomide or pomalidomide, or in those at high-risk (previous severe infections, neutropenia) [106,113]. **Prophylactic acyclovir/valacyclovir** is recommended in patients receiving PI or MoAbs, as well as **vaccination** against streptococcus pneumonia and influenza [106]. **Prophylactic immunoglobulins** are not routinely recommended, except in patients with severe, recurrent bacterial infections [106].

Recommendation 40 – Due to older age, comorbidities, and use of immunosuppressive therapies, MM patients might be at higher risk of severe COVID-19.

SARS-CoV2 is a novel coronavirus responsible for a pandemic disease called COVID-19. Transmission mainly occurs through contact with respiratory droplets from infected patients. Symptoms, usually occurring around 2 to 14 days after viral exposure, are non-specific, including fever, cough, chest pain, shortness of breath, conjunctivitis, anosmia and ageusia, less frequently, nausea, and diarrhea. Treatment is mainly supportive [114].

International propositions are summarized in Table 10.

14. Conclusions

The treatment landscape of MM is rapidly evolving. Changes in the front-line setting will inevitably impact treatments proposed at relapse (Table 11). Long-term therapy with Rd at diagnosis and introduction of

Table 10. International propositions regarding the COVID-19 pandemic.

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 stem cell collection and 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 studied, use telemedicine for follow-up, in order to avoid unnecessary visits to the hospital

Table 11. Expected landscape of MM in the near future.

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

MoAbs up-front will also undoubtedly influence the therapeutic efficacy of Rd-based triplets proposed at relapse [115].

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