SPECIAL ARTICLE

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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INCIDENCE AND EPIDEMIOLOGY

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100 000/year. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.[1]

DIAGNOSIS AND STAGING

In 2017, ESMO published clinical practice guidelines for the diagnosis, staging and definitions of progressive disease, relapse and refractoriness to therapy, which have not changed and are summarised in Supplementary Tables S1-S3, available at https://doi.org/10.1016/j.annonc.2020.11.014.[2]

The recommendations for the tests that are required for the diagnosis, determination of prognosis and follow-up of MM are described in Table 1.

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Response criteria to anti-myeloma therapy

One of the most significant improvements in the response criteria is the introduction of minimal residual disease (MRD) both in the bone marrow (BM) [using either next-generation sequencing or next-generation flow cytometry (NGF)] and outside the BM [using positron emission tomography-computed tomography (PET-CT); imaging MRD].[3] MRD negativity in the BM in patients who have achieved conventional complete response (CR) consistently correlates with prolonged progression-free survival (PFS) and overall survival (OS) in both newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM) patients.[4,5]

MRD negativity in the BM, defined as the absence of tumour plasma cells within 1 000 000 BM cells ($<10^{-6}$) shows the best results for the prediction of both PFS and OS compared with higher cut-off values (i.e. 10^{-5}).[4] Outside the BM, PET-CT is able to recognise hypermetabolic areas in approximately 15%-20% of patients with MRD negativity in the BM and is considered the best method for imaging MRD to date.[6]

MRD has been found to be a surrogate endpoint for PFS in patients receiving first-line treatment.[7] Therefore, MRD may be used as an endpoint to accelerate drug development. The use of MRD to drive treatment decisions is under investigation, e.g. whether maintenance/continuous therapy in MRD-negative patients can be stopped or whether treatment needs to be changed in MRD-positive patients, especially in high-risk MM. The results of several phase III trials in the field will clarify the role of MRD in making decisions about therapy in MM.

Table 1. Recommendations on examinations at diagnosis, response assessment, during follow-up and at relapse of MM

	Tool	Diagnosis	At response	At follow-up	At relapse
Blood	Blood count and blood smear	Obligatory	Obligatory	Obligatory	Obligatory
	Serum electrophoresis and IF	Obligatory	Obligatory (IF for CR confirmation)	Obligatory (IF for CR patients)	Obligatory
	Serum-free light chain	Obligatory	Obligatory to confirm sCR	Obligatory	Obligatory
	Serum immunoglobulin levels	Obligatory	Obligatory	Obligatory	Obligatory
	Renal and liver function tests	Obligatory	Obligatory	Obligatory	Obligatory
	Calcium	Obligatory	Obligatory	Obligatory	Obligatory
	Lactate dehydrogenase	Obligatory	Obligatory	Obligatory	Obligatory
	Albumin, β2m	Obligatory	Not required	Optional	Obligatory
	Flow cytometry	Optional	Not required	Not required	Optional
Urine	Urine sample from 24 h urine collection to check for proteinuria and light-chain proteinuria	Obligatory	Obligatory	Obligatory	Obligatory
	Urine electrophoresis and IF electrophoresis	Obligatory	Obligatory (IF for CR confirmation)	Obligatory (IF for CR patients)	Obligatory
Bone marrow	BM cytology and biopsy to confirm plasmacytosis and monoclonality	Obligatory	Obligatory to confirm CR or for non-secretory MM	Not required	Optional (obligatory for non-secretory disease)
	NGF or NGS to detect clonal plasma cells	Obligatory	Obligatory to confirm MRD negativity in CR or sCR patients	Every 12 months in CR and/or MRD-negative patients[a]	Optional
	Cytogenetics: karyotype and FISH for detection of del17p, t(4;14), t(14;16), ampl 1q/ gain 1q, t(11;14)	Obligatory	Not required	Not required	Obligatory for del17p, ampl 1q/ gain 1q and t(11;14)
	Advanced techniques: GEP, NGS	For clinical trials use only	For clinical trials use only	For clinical trials use only	For clinical trials use only
Imaging	WBLD-CT	Obligatory	Not required	When symptomatic (or CT of the symptomatic area)	Obligatory
	PET-CT	Optional (it may be carried out instead of WBLD-CT if available)	Obligatory to confirm imaging MRD	Every 12 months in bone marrow MRD-negative patients[b]	Optional
	Whole-body MRI	Obligatory in WBLD-CT-negative cases and if PET-CT is not carried out	Not required	When symptomatic	Optional

ASCT, autologous stem cell transplantation; β2m, beta-2 microglobulin; BM, bone marrow; CR, complete response; CT, computed tomography; FISH, fluorescent *in situ* hybridisation; GEP, gene expression profiling; IF, immunofixation; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGF, next-generation flow cytometry; NGS, next-generation sequencing; PET, positron emission tomography; PFS, progression-free survival; sCR, stringent complete response; WBLD-CT, whole-body low-dose computed tomography.

[a] Sustained MRD negativity is supported by IMWG guidelines,[3] although it is not fully reimbursed in several countries. In a recent 'Real-World' study, MRD assessments were carried out in 139 patients before starting lenalidomide maintenance after ASCT and/or at the achievement of CR, while additional assessments were subsequently carried out on an annual basis until sustained MRD negativity was confirmed. In total, 34.3% of patients who were MRD-positive after induction treatment achieved MRD-negative status during maintenance and ultimately had improved PFS. Sequential MRD assessments identified patients with progressively decreasing MRD levels who also had better PFS outcomes, compared with patients not showing a decreasing pattern of MRD.[90]
[b] Recommended based on panel consensus in order to confirm extramedullary MRD negativity in patients who are MRD-negative in the bone marrow.

Adapted with permission from Caers et al.[85]

FRONT-LINE THERAPY

Smouldering MM

Patients with standard- or intermediate-risk smouldering MM (SMM; see Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.11.014) do not need immediate therapy. Myeloma treatment should be initiated according to the International Myeloma Working Group (IMWG) recommendations.[8] Regarding high-risk SMM, which is recently defined by the '20-20-20' rule (Supplementary Table S4,

available at https://doi.org/10.1016/j.annonc.2020.11.014),[9] two randomised, phase III studies have shown that lenalidomide plays a significant role in prolonging PFS. In the first study, 119 patients with high-risk SMM (before the introduction of the new criteria for the definition of myeloma)[8] were randomly assigned either to receive treatment with the combination of lenalidomide plus dexamethasone (Rd) for 9 cycles followed by lenalidomide maintenance or to observation. At a median follow-up of 75 months, Rd improved both PFS [median PFS (mPFS) not reached versus

23 months; P < 0.0001] and OS compared with observation [hazard ratio (HR) 0.43; P = 0.024].[10,11] However, this study was conducted several years ago and enrolled a number of patients who are considered as having MM according to the revised definition. In the second study,[12] 182 patients with intermediate- or high-risk SMM were randomly assigned either to receive lenalidomide monotherapy or to observation. At a median follow-up of 35 months, PFS was longer with lenalidomide (HR 0.28; P = 0.002); this result was driven mainly by the high-risk SMM group.[12] This study has not reported OS advantage for the lenalidomide arm to date. Several phase II studies using daratumumab (Dara) monotherapy,[13] isatuximab (Isa) monotherapy or other Rd-based regimens [with elotuzumab (EloRd), or with ixazomib] have shown encouraging results.

All the above data suggest that high-risk SMM patients should be encouraged to participate in randomised phase III trials to reveal the best treatment that offers OS advantage. To date, no treatment has been approved for SMM.

Newly diagnosed patients who are eligible for high-dose therapy and autologous transplantation

For fit NDMM patients, aged <70 years, without comorbidities, induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) and lenalidomide maintenance is the recommended treatment. Two recent phase III trials comparing the use or not of upfront ASCT, after triplet novel agent-based induction, showed that PFS was improved in the upfront ASCT arm.[14-16] The first study was conducted by the French Myeloma Study Group and included 700 patients who were randomised to receive induction therapy with 3 cycles of bortezomib, lenalidomide and dexamethasone (VRd) and then consolidation therapy with either 5 additional cycles of VRd or high-dose melphalan (HDM) plus ASCT followed by 2 additional cycles of VRd. Patients in both groups received maintenance therapy with lenalidomide for 1 year. After a median follow-up of 44 months in the VRd-alone group and 43 months in the ASCT group, the mPFS was longer in the ASCT group (50 versus 36 months; P < 0.001). This benefit was observed across all patient subgroups, including advanced Revised International Staging System (R-ISS) and high-risk cytogenetics. OS at 4 years was not different between the ASCT and the non-ASCT groups.[15]

The second study was conducted by the European Myeloma Network (EMN)—EMN02/HO95 trial—and included 1503 patients who received an induction therapy with 3-4 cycles of bortezomib, cyclophosphamide and dexamethasone (VCD) followed by the first randomisation between bortezomib, melphalan and prednisone (VMP) versus ASCT. A second randomisation to consolidation therapy (2 cycles of VRd) versus no consolidation was carried out after intensification therapy, to be followed by lenalidomide maintenance until progression or toxicity in both arms. With a median follow-up from the first randomisation of 60.3 months, the mPFS was improved with ASCT compared with VMP (56.7 versus 41.9 months; P = 0.0001).[16]

Induction regimen. A three-drug combination, including at least bortezomib and dexamethasone, has been the standard of care.[2,17] Bortezomib, thalidomide, dexamethasone (VTD) induction showed better response rates over VCD at the expense of a higher rate of peripheral neuropathy.[18] VCD and bortezomib, doxorubicin and dexamethasone (PAd) were equally effective in terms of response but VCD was less toxic.[19] In single-arm studies, VRd produced high very good partial response (VGPR), CR and MRD negativity rates, as well as prolonged PFS.[4,15,20-22] However, there is no direct comparison between VTD with VRd induction before ASCT. There is only an integrated analysis of three randomised trials, presented in abstract form, which showed that VRd produces higher VGPR and MRD negativity rates compared with VTD.[23]

The introduction of monoclonal antibodies (mAbs), and especially of Dara, in the front-line setting has changed the treatment landscape in MM. In the phase III CASSIOPEIA trial, 4 cycles of induction with VTD (n = 542) were compared with 4 cycles of VTD plus Dara (DaraVTD) (n = 543); patients then received a single ASCT followed by consolidation and maintenance.[24] PFS at 18 months showed the superiority of DaraVTD over VTD (93% versus 85%, P < 0.0001).[25] The combination of Dara with VRd (DaraVRd) had better results. In the randomised phase II GRIFFIN study, 207 patients were randomly assigned to receive VRd ± Dara induction (4 cycles), ASCT, VRd ± Dara consolidation (2 cycles) and lenalidomide ± Dara maintenance (26 cycles). The 24-month PFS rates were 95.8% for DaraVRd and 89.8% for VRd.[21]

The substitution of bortezomib with the second-generation proteasome inhibitor (PI) carfilzomib (K) resulted in high sustained MRD negativity rate in carfilzomib, lenalidomide and dexamethasone (KRd) compared with VRd, especially in patients with advanced R-ISS.[26] There is no direct comparison between VRd and KRd in NDMM patients who are eligible for ASCT; however, in the ENDURANCE trial (see Elderly patients' section), which included <30% of patients who received an ASCT, there was no PFS difference between the two regimens.

Based on the above data, VRd is likely to offer the best risk-benefit profile to date among triplet combinations [II, B]. The four-drug combination DaraVTD is more efficacious than VTD [I, A] but comparisons are lacking versus DaraVRd or VRd [these regimens have not been approved by the European Medicines Agency (EMA)]. The EMA approval of DaraVTD makes it a new standard of care for induction before ASCT. Novel studies that are ongoing compare DaraVRd versus VRd, DaraVCD versus VTD, or combinations with novel mAbs such as IsaVRd, IsaKRd or EloVRd will reveal the best induction regimen in the future.

Conditioning regimen before ASCT. HDM (200 mg/m^2) remains the standard conditioning regimen before ASCT for NDMM patients. The addition of busulfan to melphalan has not shown OS benefit over HDM.[27,28] The addition of bortezomib to HDM did not improve the efficacy of the conditioning regimen and had higher toxicity.[29]

Consolidation therapy. The EMN02/HO95 study showed that at a median follow-up of 42 months, consolidation therapy with 2 cycles of VRd improved mPFS compared with no consolidation (58.9 versus 45.5 months; *P* = 0.014).[16] It must be noted that induction treatment in this study included 4 cycles of VCD and not VRd or DaraVTD.

The use of a second planned ASCT as consolidation has also been tested in clinical trials. In the EMN02/HO95 study, in centres with a policy of double ASCT, patients were assigned to receive VMP, single ASCT (ASCT-1) or two planned ASCTs (administered 2-3 months apart; ASCT-2) to prospectively compare ASCT-1 with ASCT-2. Patients who received ASCT-2 had a prolonged PFS compared with those who received ASCT-1: the 3-year PFS probability was 53.5% for ASCT-2 versus 44.9% for ASCT-1 group (*P* = 0.036), which represented a 26% reduced risk of progression or death in the ASCT-2 group. Importantly, ASCT-2 significantly improved the outcome of patients with high-risk cytogenetics (mPFS: 46 and 26.7 months for ASCT-2 and ASCT-1, respectively; HR 0.59; *P* = 0.062).[14] In the same study, OS from the first randomisation was significantly prolonged with ASCT-2 compared with ASCT-1 (3-year rate: 89% versus 82%; HR 0.52; *P* = 0.011); this benefit was also reported in patients with R-ISS II + III (HR 0.48; *P* = 0.013) and with high-risk cytogenetics (HR 0.52; *P* = 0.042).[14]

The phase III StaMINA study randomised 758 patients who received induction therapy for up to 12 cycles, followed by one ASCT versus tandem ASCT versus ASCT-1 followed by 4 subsequent cycles of VRd; all treatment groups received lenalidomide maintenance until disease progression.[30] The 6-year PFS in high-risk patients was 43.6% and 26% for tandem ASCT and ASCT-1, respectively (*P* = 0.03).[31]

Finally, a study which compared tandem ASCTs with ASCT-1 followed by allogeneic SCT (allo-SCT) has recently reported the 10-year median follow-up results. In both standard-risk (*n* = 625) and high-risk patients (*n* = 85), there was no PFS or OS difference.[32]

Maintenance therapy. Treatment with lenalidomide maintenance after ASCT offers PFS and OS benefits over placebo as reported in two large randomised trials.[33,34] A meta-analysis including more than 1200 patients, with a median follow-up of 79.5 months, showed that lenalidomide maintenance offers more than 2 years of PFS benefit (52.8 versus 23.5 months) and 2.5 years of OS benefit over placebo. In this study, there was no benefit in patients with ISS-III disease or high-risk cytogenetics.[35] However, the Medical Research Council (MRC) myeloma-XI trial, in which 1137 patients were assigned to lenalidomide maintenance and 834 patients to observation, showed that, in high-risk patients, the 3-year OS was 75% in the lenalidomide group compared with 64% in the observation group, and in ultra-high-risk patients it was 63% versus 43.5%, respectively.[36] These results should be taken with caution as the study was not powered to show differences in the two sub-populations and all patients who entered the maintenance phase were immunomodulatory drug (IMiD)-exposed and -sensitive. Furthermore the definition of high-risk patients

was different in the meta-analysis and in the MRC-XI trial; in the meta-analysis, high-risk cytogenetics included only t(4;14) and del17p patients while in the MRC-XI trial patients were classified into three cytogenetic risk groups: standard risk (no adverse cytogenetic abnormalities), high risk (one adverse cytogenetic abnormality) or ultra-high risk (two or more adverse cytogenetic abnormalities) [adverse cytogenetic abnormalities were defined as gain(1q), t(4;14), t(14;16), t(14;20), or del(17p)].[35,36] The EMA has approved lenalidomide for maintenance therapy post-ASCT for all MM patients until progression.

Bortezomib maintenance showed PFS benefit compared with thalidomide maintenance in a randomised study, but the induction treatment was not the same between the two treatment groups [PAd versus vincristine, doxorubicin and dexamethasone (VAD), respectively].[37] A recent double-blind, placebo-controlled, phase III trial (TOURMALINE-MM3) compared the oral PI ixazomib with placebo in 656 patients who received induction therapy plus HDM + ASCT. There was a 28% reduction in the risk of progression or death with ixazomib (mPFS: 26.5 versus 21.3 months, respectively; *P* = 0.0023). In the high-risk population, ixazomib also offered similar PFS advantage over placebo (HR 0.62, 95% CI 0.38-1.02).[38] Bortezomib and ixazomib have not yet been approved by the EMA for maintenance after ASCT.

Elderly patients or patients with NDMM who are 'not' eligible to receive HDT and autologous transplantation

Before 2019, VMP and Rd were the standards of care for NDMM patients who were not eligible for an ASCT in Europe.[39,40] A phase III trial comparing VRd with Rd in 525 NDMM patients (43% were younger than 65 years of age) was recently updated and showed the superiority of VRd regarding PFS (mPFS: 41 versus 29 months; *P* = 0.003) and OS [median OS (mOS) not reached versus 69 months; *P* = 0.0114].[41] Based on these results, the EMA approved VRd in April 2019 for use in NDMM patients who are not eligible for ASCT. The substitution of bortezomib with K in the Rd combination seems not to offer better results. The ENDURANCE trial, which compared KRd versus VRd in NDMM patients without an immediate intent for ASCT, failed to show superiority of KRd regarding PFS in the study population (*n* = 1087), which included a low number of patients with high-risk cytogenetics.[42]

The addition of Dara to VMP and Rd has created two new standards of care. DaraVMP and DaraRd were approved by the EMA in October 2019, based on the results of two large phase III studies. In the ALCYONE study, 706 patients with NDMM who were ineligible for ASCT were randomised to receive 9 cycles of VMP either alone or with Dara (DaraVMP); then Dara was given until disease progression.[43] At a median follow-up of 40 months, the mPFS was 36.4 versus 19.3 months for the DaraVMP and VMP arms, respectively, while the 36-month rate of OS was 78% and 68% for the two groups (HR 0.60; *P* = 0.0003).[44] In the
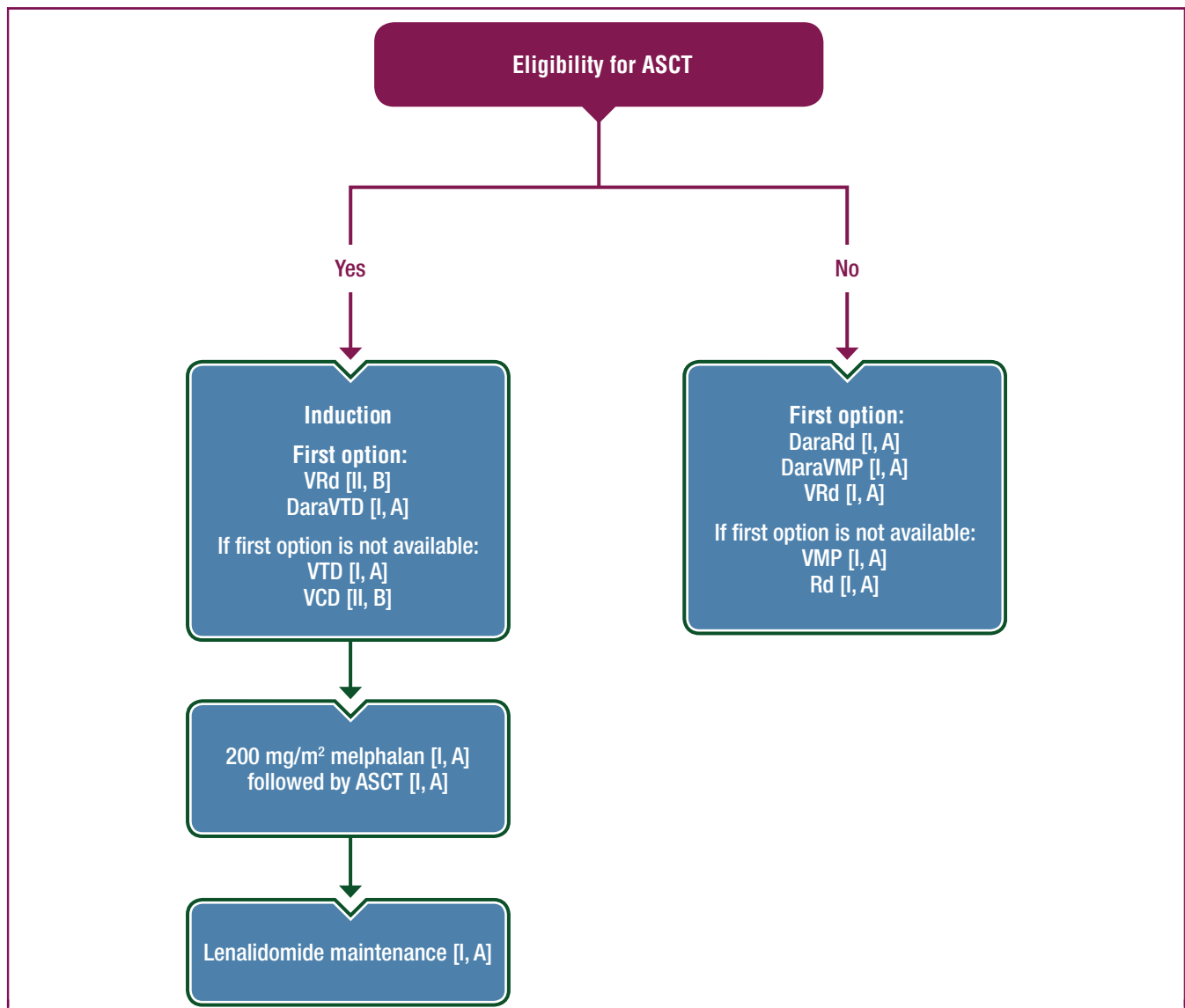
Figure 1. Recommendations for MM front-line therapy.
ASCT, autologous stem cell transplantation; DaraRd, daratumumab/lenalidomide/dexamethasone; DaraVMP, daratumumab/bortezomib/melphalan/prednisone; DaraVTD, daratumumab/bortezomib/thalidomide/dexamethasone; MM, multiple myeloma; Rd, lenalidomide/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

MAIA study, 737 NDMM patients who were ineligible for ASCT were randomised to receive either DaraRd or Rd until disease progression. At a median follow-up of 28 months, the estimated PFS at 30 months was 70.6% in the DaraRd group and 55.6% in the Rd group (HR 0.56; $P < 0.001$).[45]

Other approved regimens in this setting include bendamustine plus prednisone[46] and melphalan, prednisone and lenalidomide (MPR),[47] but they are not routinely used and cannot be considered as standards of care.

It is important to realise that one-third of patients are older than 75 years at diagnosis and at least 30% are frail. Please refer to Management of frail elderly patients in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.11.014, for consensus panel recommendations for the management of these patients.

Although maintenance is not standard for patients who are not eligible for ASCT (almost all approved regimens are

used continuously until progression or unacceptable toxicity), ixazomib maintenance was tested in a phase III study which included 706 patients who received 6-12 months of standard induction before being randomised to receive either ixazomib or placebo. Ixazomib maintenance offered a PFS benefit over placebo (17.4 versus 9.4 months, HR 0.65, $P = 0.00003$).[48] Figure 1 depicts the first-line options for the treatment of NDMM patients.

Recommendations

- 'Watch-and-wait' remains the recommended approach for SMM [II, B]. High-risk patients are encouraged to participate in randomised phase III studies that are powered for OS advantage of the experimental treatment modality.

- For patients <70 years without comorbidities, induction therapy followed by HDM and ASCT is the recommended treatment [I, A].
- Regarding induction therapy pre-ASCT, VRd is likely to offer the best risk-benefit profile to date among triplets based on bortezomib [II, B]; however, VRd lacks direct comparisons with VTD or DaraVTD and is not licensed by the EMA. The four-drug combination DaraVTD is more efficacious than VTD [I, A] and is the new standard of care. If this is not available, VTD [I, A] or VCD [II, B] may be used. DaraVRd and IsaVRd are under clinical investigation and may be standards of care in the near future. Induction with 4-6 cycles is the recommended approach.
- HDM (200 mg/m^2) is the standard conditioning regimen before ASCT [I, A].
- Consolidation therapy post-ASCT has not been established to date as standard therapy; 2 cycles of VRd consolidation has to be considered in patients who receive VCD induction [II, B], while a tandem ASCT is recommended for patients with genetically defined high-risk disease [II, B] or in all patients who received VCD induction [II, B]. Allo-SCT following ASCT does not offer OS benefit even in high-risk disease compared with tandem ASCT.
- Maintenance with lenalidomide is considered the standard of care for all MM patients post-ASCT [I, A]; bortezomib may be considered for patients with high-risk disease [II, B]. Ixazomib maintenance offers PFS benefit over placebo [I, A], but has not been approved by the EMA or the US Food and Drug Administration (FDA).
- For patients who are not eligible for ASCT, there are three new standards of care: VRd, DaraVMP and DaraRd [I, A]. When DaraRd and DaraVMP are not available, VRd is the preferred option in fit patients; Rd and VMP may be considered for patients who cannot receive the previous regimens [I, A].

TREATMENT OF RELAPSED/REFRACTORY PATIENTS

Patients who have received one prior line of therapy

Salvage ASCT may be an option for patients who have received front-line induction with bortezomib-based triplet combination followed by an ASCT. Two prospective studies of salvage ASCT have been published so far. The first included a bortezomib-based re-induction and a randomisation between salvage ASCT or cyclophosphamide, which is suboptimal for relapsed patients. Salvage ASCT significantly extended mPFS (19 versus 11 months; $P < 0.001$) and OS (67 versus 52 months; $P = 0.0169$).[49] The second included patients with first to third relapse who were randomised to a transplant arm ($n = 139$) consisting of 3 Rd re-induction cycles, ASCT and lenalidomide maintenance (10 mg/day) or to a control arm ($n = 138$) of continuous Rd. Although there was no difference regarding PFS and OS between the two arms, almost 30% of the patients in the transplant arm did not receive the assigned ASCT mainly

due to early disease progression. Multivariate landmark analyses from the time of ASCT showed superior PFS and OS ($P = 0.0087$ and $P = 0.0057$ respectively) in patients who received ASCT.[50] The American and European Associations for Bone and Marrow Transplantation have reported that HDT and ASCT should be considered appropriate treatment of any patient relapsing after primary therapy that includes an ASCT with initial remission duration of >18 months.[51] However, this recommendation was made before the broad use of lenalidomide as maintenance therapy post-ASCT. Although there is no evidence for the role of salvage ASCT in patients who received lenalidomide maintenance, the panel suggests that second-line ASCT is a logical approach for patients who relapse after primary therapy that includes an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months. The use of re-induction is a matter of debate as there is no prospective study on this issue. Retrospective studies suggest that the use of re-induction does not offer survival benefit in salvage ASCT.[52]

In patients in whom a salvage ASCT is not considered, the second-line therapy should include an Rd-based regimen, i.e. KRd, DaraRd, ixazomib/lenalidomide/dexamethasone (IRd) or EloRd for patients who received a bortezomib-based therapy upfront without lenalidomide or Dara (i.e. VCD, VTD, VMP); all these combinations were found to be superior to Rd, in terms of PFS, in pivotal phase III studies.[53-56] Based on both HR and absolute values of mPFS, DaraRd provides the longest PFS for patients with RRMM who have received 1-3 prior lines of therapy and have a standard-risk cytogenetic profile. KRd and EloRd have also shown OS benefit over Rd: mOS 48.3 versus 40.4 months for KRd versus Rd (HR 0.79; $P = 0.0045$),[57] and 48.3 versus 39.6 months for EloRd versus Rd,[58] respectively. DaraRd is likely to have OS benefit over Rd, but mature data have not been presented, while IRd has no OS benefit over Rd. For relapsed patients with high-risk cytogenetics, although different cut-off values are used for the definition of del17p positivity, all above triplets have shown better results compared with Rd; however, the combination of a PI with Rd, i.e. KRd or IRd, along with DaraRd seem to offer the best benefit to date.

Elderly patients who received Rd upfront without Dara[59] or patients who received lenalidomide maintenance after ASCT and are progressing (lenalidomide-refractory patients), according to previous guidelines, could receive either K plus dexamethasone (Kd) or Dara and bortezomib plus dexamethasone (DaraVd) (patients treated with Kd or DaraVd had significantly improved PFS compared with Vd).[60,61] Three phase III studies suggest that the combination of pomalidomide with bortezomib and dexamethasone (PomVd) and the combinations of Dara or Isa with K and dexamethasone (DaraKd or IsaKd) are new options for this setting.[60-62] In the first study, PomVd ($n = 278$) was compared with Vd ($n = 270$) in RRMM patients who had received 1-3 prior lines of therapy that included lenalidomide. More than 70% of the patients were refractory to lenalidomide. After a median follow-up of 16 months,

PomVd improved mPFS in the study population (11.2 versus 7.1 months; HR 0.61; $P < 0.0001$) as well as in patients refractory to lenalidomide (9.5 versus 5.6 months; $P = 0.0008$) and in patients refractory to lenalidomide who received only 1 prior line of treatment (17.8 versus 9.5 months; $P = 0.03$).[62] PomVd was approved by the EMA in May 2019.

In the second study (CANDOR), DaraKd was compared with Kd in RRMM patients who had received 1 prior line of therapy. This study showed that the mPFS was not reached for the DaraKd group and it was 15.8 months for the Kd group (HR 0.63; $P = 0.0014$). DaraKd resulted in a better PFS benefit both among lenalidomide-exposed (HR 0.52) and lenalidomide-refractory patients (HR 0.45).[63]

Finally, in the third study, which was reported at the European Hematology Association (EHA) 2020 meeting, only 302 patients with RRMM and 1-3 prior lines of therapy were randomised to receive either IsaKd ($n = 179$) or Kd ($n = 123$). At a median follow-up of 20.7 months, mPFS was not reached for IsaKd whereas it was 19.1 months for Kd (HR 0.53; $P = 0.0007$).[64]

Thus, PomVd, DaraKd and IsaKd are recommended therapies for patients who were previously exposed or are refractory to lenalidomide, while DaraKd or IsaKd can also be given in patients who are refractory to bortezomib.

The approval of Dara-based regimens (DaraVTD, DaraVMP and DaraRd) and of VRd, as first-line therapy for myeloma patients, makes the treatment of second and subsequent lines of therapy very challenging. Although there is some evidence that Dara retreatment can be efficacious in some patients,[65,66] there are no data for Dara retreatment at second line.

Venetoclax is a selective Bcl-2 inhibitor that promotes MM cell apoptosis. The phase III BELLINI trial evaluated the combination of venetoclax with Vd (VenVd) compared with Vd among RRMM patients, who had received 1-3 prior lines of therapy and were PI-sensitive. A significant PFS benefit was reported with VenVd among patients with t(11;14) (HR 0.10; $P = 0.003$) and those with high BCL2 expression (HR 0.26; $P < 0.001$) but no OS difference was shown in this population. On the contrary, Vd was superior to VenVd in terms of OS among patients without t(11;14) and low BCL2 (HR 3.13; $P = 0.019$).[67] Therefore, VenVd is an option only for patients with t(11;14) or high BCL2 levels who have failed lenalidomide and are sensitive to PI. VenVd is awaiting EMA approval.

Selinexor is an oral, selective inhibitor of XPO1-mediated nuclear export, leading to the reactivation of tumour-suppressor proteins. Selinexor in combination with Vd (SVd) was compared with Vd in a phase III study with 402 patients with RRMM who received 1-3 prior lines of therapy. SVd significantly prolonged mPFS compared with Vd (13.9 versus 9.4 months, HR 0.70, $P = 0.0066$), suggesting that SVd might be another option in patients who were treated with lenalidomide-based regimens upfront.[68] SVd is awaiting EMA approval.

In Figure 2, the possible options for second-line therapy, taking into consideration the previous line and the

refractoriness to specific agents, are described. For Dara-previously exposed or -refractory patients, the recommendations are based on panel opinion as there is no evidence for the efficacy of the approved second-line regimens in these patients to date.

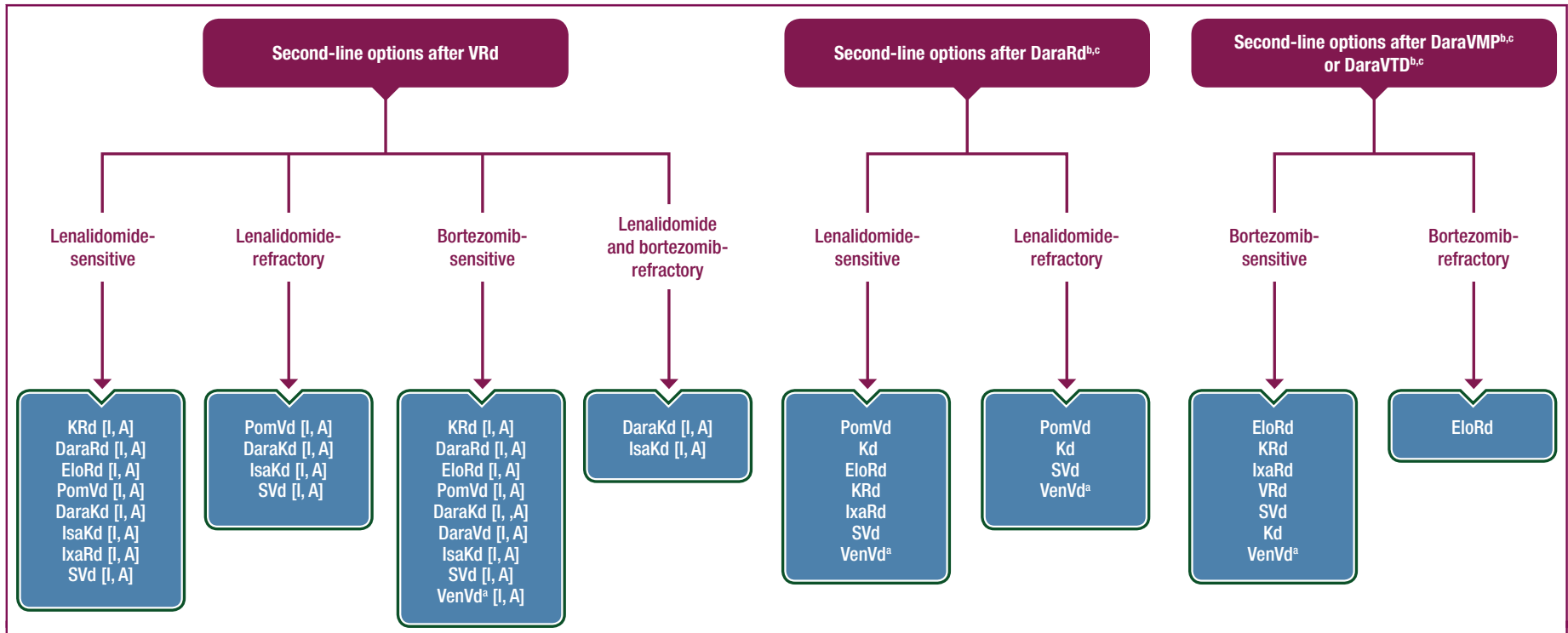## Patients who have received two or more prior lines of therapy

Treatment of RRMM patients who received two or more prior lines of therapy is becoming challenging.[69] A recent study revealed that patients who are refractory to two PIs, two IMiDs and a CD38 mAb have an mOS of 5.6 months only.[70] For patients who have been exposed or are refractory to both bortezomib and lenalidomide, who have not received an mAb, DaraKd or IsaKd are suitable options. The combinations of Elo or Isa with pomalidomide and dexamethasone (EloPd and IsaPd, respectively) are suitable options for patients who have failed ≥2 lines of previous therapies, including lenalidomide and a PI, based on the results of two studies. The first was a phase II study, in which patients were randomly assigned to receive either EloPd ($n = 60$) or Pd ($n = 57$). After a follow-up period of 9 months, the mPFS was 10.3 months in the EloPd group and 4.7 in the Pd group (HR 0.54; $P = 0.008$).[71] The second was a phase III study, in which patients were randomised to receive either IsaPd ($n = 154$) or Pd ($n = 153$). At a median follow-up of 11.6 months, mPFS was 11.5 months in the IsaPd group versus 6.5 months in the Pd group (HR 0.596; $P = 0.001$).[72] EloPd and IsaPd were recently approved by the EMA in this setting.

The combination of Dara with pomalidomide and dexamethasone (DaraPd) has been approved by the FDA for patients who have failed ≥2 lines of previous therapies, including lenalidomide and a PI. This was based on a phase II non-randomised study where DaraPd was given in 103 patients with RRMM. At a median follow-up of 13 months, the mPFS was 8.8 months and the mOS was 17.5 months.[73] DaraPd has not yet been approved by the EMA, as the results of the phase III APOLLO study (DaraPd versus Pd) are pending.

Patients with t(11;14), who are refractory to lenalidomide and are PI-sensitive may be treated with VenVd, when this regimen is licensed, as previously discussed.

For triple-class refractory patients, selinexor-dexamethasone (Sd) or belantamab mafodotin monotherapy may be suitable options. In a phase II study with 122 RRMM patients (median number of 7 prior lines of therapy), oral selinexor was given with dexamethasone twice weekly. An mPFS of 3.7 months and an mOS of 8.6 months were reported. Fatigue, nausea and decreased appetite were common and were typically grade 1 or 2 events; grade 3 events were noted in up to 25% of patients and no grade 4 events were reported.[74]

Belantamab mafodotin is an antibody-drug conjugate targeting B-cell maturation antigen (BCMA). In a phase II study, 196 patients with triple-class refractory MM received

Second-line options after VRd

Second-line options after DaraRd[b,c]

Second-line options after DaraVMP[b,c] or DaraVTD[b,c]

Lenalidomide-sensitive

Lenalidomide-refractory

Bortezomib-sensitive

Lenalidomide and bortezomib-refractory

Lenalidomide-sensitive

Lenalidomide-refractory

Bortezomib-sensitive

Bortezomib-refractory

KRd [I, A]
DaraRd [I, A]
EloRd [I, A]
PomVd [I, A]
DaraKd [I, A]
IsaKd [I, A]
IxaRd [I, A]
SVd [I, A]

PomVd [I, A]
DaraKd [I, A]
IsaKd [I, A]
SVd [I, A]

KRd [I, A]
DaraRd [I, A]
EloRd [I, A]
PomVd [I, A]
DaraKd [I, ,A]
DaraVd [I, A]
IsaKd [I, A]
SVd [I, A]
VenVd[a] [I, A]

DaraKd [I, A]
IsaKd [I, A]

PomVd
Kd
EloRd
KRd
IxaRd
SVd
VenVd[a]

PomVd
Kd
SVd
VenVd[a]

EloRd
KRd
IxaRd
VRd
SVd
Kd
VenVd[a]

EloRd

Figure 2. Second-line options for MM patients who received VRd and Dara-based front-line therapies.

The three different flow-charts shown in this figure depict three different scenarios—depending on the first-line treatment given (from left to right):
● second-line options after VRd first-line treatment
● second-line options after DaraRd first-line treatment and
● second-line options after DaraVMP or DaraVTD first-line treatment.

Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; MM, multiple myeloma; PomVd, pomalidomide/bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone; S, selinexor; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednislone; VRd, bortezomib/lenalidomide/dexamethasone; Ven, venetoclax; VTD, bortezomib/thalidomide/dexamethasone.

[a] Patients with t(11;14).

[b] Patients who progress while on monthly Dara are considered as Dara-refractory.

[c] All recommendations for patients who receive front-line therapy with Dara-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients refractory or exposed to Dara.
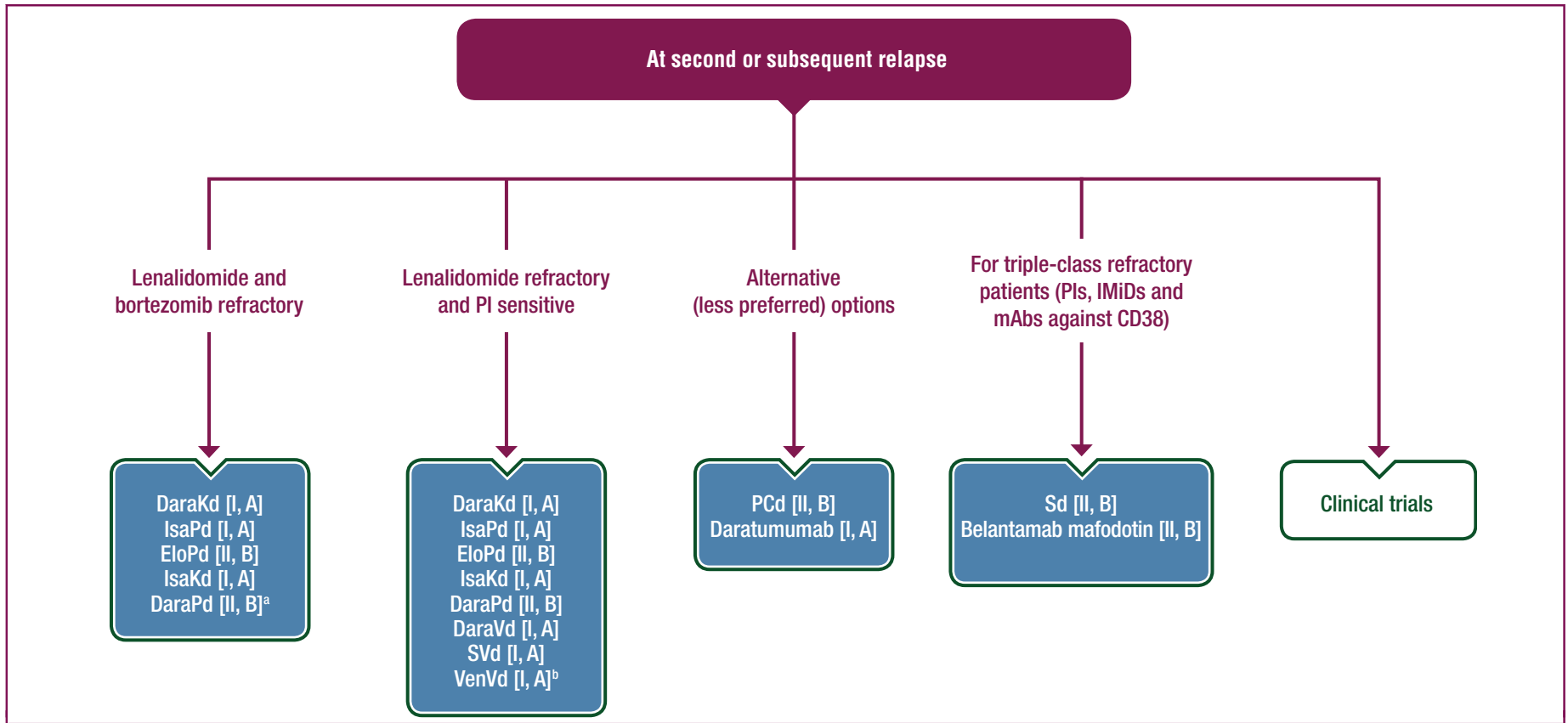
Figure 3. Recommendations for MM patients who receive a third or subsequent line of therapy.

Dara, daratumumab; Elo, elotuzumab; IMiD, immunomodulatory drug; Isa, isatuximab; Kd, carfilzomib/dexamethasone; mAb, monoclonal antibody; MM, multiple myeloma; PCd, pomalidomide/cyclophosphamide/dexamethasone; Pd, pomalidomide/dexamethasone; PI, proteasome inhibitor; S, selinexor; Sd, selinexor/dexamethasone; Vd, bortezomib/dexamethasone; Ven, venetoclax.
[a] Only phase IB data are published for DaraPd. Publication of phase III data are expected in 2021.
[b] For patients with t(11;14) or high *BCL2* levels.

two different doses of belantamab mafodotin (2.5 and 3.4 mg/kg). The mPFS was 2.9 and 4.9 months for the two doses, respectively. The most common grade 3-4 adverse events included keratopathy (27% and 21% of patients for the two doses, respectively), thrombocytopaenia and anaemia.[75] Melflufen may also be beneficial in Dara and pomalidomide-refractory patients but the results of the phase III trial have not yet been reported.[76]

Figure 3 summarises the recommendations for RRMM patients who receive third or subsequent lines of therapy.

Immunotherapy strategies targeting BCMA or other antigens on the surface of myeloma cells, including bispecific T-cell engagers (BiTEs) and chimeric antigen receptor T (CAR-T) cells, are under clinical investigation in RRMM patients. Results for the first published study with a CAR-T cell product in myeloma patients showed that infusion of bb2121 in 33 consecutive patients with multi-refractory disease resulted in an objective response rate of 85%, including 15 patients (45%) with CR; all were MRD-negative. The mPFS was 11.8 months. CAR-T cell expansion was associated with better responses and CAR-T cells persisted up to 1 year after the infusion. A total of 25 patients (76%) had cytokine release syndrome, while neurological toxic effects occurred in 14 patients (42%).[77] Several studies using other CAR-T cell products or T-cell engagers (TCEs) were reported in the American Society of Clinical Oncology (ASCO) and EHA 2020 meetings and had similar results, suggesting that these immunotherapy techniques may increase survival of myeloma patients (see Supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.11.014, section on novel immunotherapies for myeloma).

Recommendations

Patients who receive second-line therapy

- Second-line ASCT is an option for patients who received primary therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months (panel consensus).
- Patients who had received a bortezomib-based therapy upfront without lenalidomide or Dara should receive an Rd-based regimen, i.e. KRd, DaraRd, IRd or EloRd [I, A]. DaraRd provides the best PFS for these patients, while only KRd and EloRd showed an OS benefit over Rd to date.
- Patients who are refractory to lenalidomide upfront could receive either PomVD, DaraKd, IsaKd or DaraVd [I, A]. PomVd is the approved indication with best results, in terms of PFS, as second-line therapy in lenalidomide-refractory patients. DaraKd has given the best reported PFS to date in lenalidomide-refractory patients, but DaraKd is awaiting EMA approval. Similarly, IsaKd and SVd, which are also suitable for this setting [I, A], have not yet been approved by the EMA.
- VenVd is a suitable option for patients with t(11;14) who have failed lenalidomide and are sensitive to PIs [I, A], if available.

Patients at third and subsequent lines of treatment

- For patients who have been exposed or are refractory to both bortezomib and lenalidomide, DaraKd [I, A], IsaPd [I, A], IsaKd [I, A] and EloPd [II, B] are recommended.
- Patients with t(11;14), who are refractory to lenalidomide and are PI-sensitive may be treated with VenVd [I, A], if available.
- For triple-class refractory patients, Sd or belantamab mafodotin monotherapy is recommended [II, B], if available. Results of phase III studies of melflufen, TCEs and CAR-Ts in triple-class refractory patients are awaited.

MANAGEMENT OF PLASMA CELL LEUKAEMIA

Primary plasma cell leukaemia (PPCL) is a rare and aggressive variant of MM, operationally defined by the presence of 20% and/or an absolute number $>2 \times 10^9$/l of clonal plasma cells in the peripheral blood without a previous history of MM.[78] The cut-off value of circulating plasma cells for the definition of PCL may be reduced to 5% in the near future, as the survival of these patients is similar to those with 20% of circulating plasma cells.[74] PPCL should be distinguished from secondary PCL, which generally constitutes the leukaemic evolution of a pre-existing, end-stage RRMM, and from extramedullary myeloma. Diagnostic work-up and staging procedures in PPCL are similar to those applied in MM. However, they have to be implemented by peripheral blood analysis for measuring circulating PC count and PET-CT for detecting possible extramedullary lesions.[79]

The outcome of patients with PCL remains poor and the mOS is around 1 year.[78,79] There are no precise guidelines for the treatment of PPCL due to the lack of phase III trials in this setting. Only two prospective phase II studies have been published so far for PPCL.[80,81] Overall, treatment should be immediate and possibly oriented toward bortezomib and/or lenalidomide-based multiphase approaches in combination with chemotherapy agents, with short treatment-free intervals. It should ideally include induction, double ASCT, consolidation and maintenance [II, B]. KRd may be another option for these patients[82] but more data are needed before a recommendation can be made for PCL patients.

Allo-SCT should be considered in selected cases [III, C]. In a recent study, 71 patients (median age 56 years) with PPCL underwent an allo-SCT and the 4-year outcomes were: non-relapse mortality 12%, PFS 19% and OS 31%.[83] Thus, in patients younger than 50 years of age with a suitable donor, a myeloablative allo-SCT can be considered. Otherwise, a tandem transplant with an ASCT followed by a reduced-intensity conditioning allo-SCT if a related or an unrelated donor is available can be considered [IV, C].

Patients not eligible for transplant procedures should preferably receive continuous treatment [III, C]. In relapsed/refractory PPCL, a switch to drugs not used at diagnosis should be considered, favouring combinations of lenalidomide or pomalidomide plus dexamethasone with K or mAbs

(Dara or Elo) (expert consensus). See Supplementary Table S6, available at https://doi.org/10. 1016/j.annonc.2020.11.014, for summary recommendations.

MANAGEMENT OF SOLITARY PLASMACYTOMA

Solitary plasmacytoma is an infrequent form of plasma cell neoplasm that presents as a single mass of monoclonal plasma cells, with either extramedullary or intraosseous location.[84,85] Clonal PCs are typically absent in the BM aspirate by conventional morphology or immunohisto-chemistry and there are no other MM features (hyper-calcaemia, anaemia or renal disease attributable to MM).[8] In some patients, a BM aspiration can detect a low monoclonal plasma cell infiltration, which indicates a high risk of early progression to an overt myeloma disease.[84,85] Furthermore, in a study following the use of high sensitivity flow cytometry, half of the patients showed occult BM infiltration and half of these cases progressed at 2 years.[86] Thus, detection of clonal PC using sensitive techniques in the BM is suggested [II, B] and systemic treatment of myeloma should be considered in these patients [III, B]. Before treatment initiation, whole-body magnetic resonance imaging (MRI) and PET-CT should be carried out to exclude the presence of multiple plasmacytomas, commending systemic treatment instead of radiotherapy (RT) [I, A].[6,87] Local high-dose RT is the preferred treatment of choice [II, A], but about two-thirds of patients develop MM at 10 years' follow-up.[88] With current staging techniques, i.e. NGF and PET-CT, the incidence of solitary plasmacytoma is expected to decrease and the cure rate to increase. See Supplementary Table S6, available at https://doi.org/10. 1016/j.annonc.2020.11.014, for summary recommendations.

SUPPORTIVE CARE

Recommendations for the management of myeloma complications, i.e. bone disease, anaemia, BM failure, infections, vaccination strategies and renal impairment, are described in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.11.014, in the section on Supportive Care.

FOLLOW-UP AND LONG-TERM IMPLICATIONS

Table 1 includes all tests that have to be carried out during follow-up of myeloma patients. Full blood count, serum and urine electrophoresis and serum-free light chain (sFLC) determination, creatinine and calcium tests should be carried out monthly or at least every 3 months. sFLC should be used to detect light chain escape. In cases of relapsed patients with no positivity for del17p or add1q at diagnosis, FISH analysis for del17p and add1q should be carried out to reveal high-risk relapse. In case of bone pain, whole-body low-dose CT (WBLD-CT), MRI or PET-CT should be carried out to detect new bone lesions.[85]

MM has for a long time been considered as an incurable disease. Recent trials incorporating novel agents and ASCT report a statistical cure fraction of more than 15%.[1,22] The addition of quadruplet combinations including mAbs as part of front-line therapies and novel immunotherapy strategies seems to further increase this apparent cure rate.

PERSONALISED MEDICINE

The presence of t(11;14) in RRMM patients should be investigated to decide for venetoclax-based regimens, when available in Europe. Otherwise, no prognostic factor or staging system, including R-ISS or gene-expression profiling, is used routinely to define a risk-adapted strategy. In myeloma, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. An interdisciplinary panel of clinical experts on MM, members of ESMO, EHA and EMN, selected the relevant literature. Levels of evidence and grades of recommendations were assigned according to the adapted Infectious Diseases Society of America-United States Public Health Service Grading System (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc. 2020.11.014).[89] Statements without grading were considered justified standard clinical practice by the experts.

DISCLOSURE

MAD reported consultancy and honoraria from Janssen, Celgene, Takeda, Amgen and Bristol Myers Squibb; PM reported honoraria from Celgene, Janssen, Takeda, Amgen and Abbvie; ET reported honoraria from Bristol Myers Squibb, Janssen, Celgene, Takeda, Genesis Pharma, Amgen, Sanofi and Novartis; research funding from Janssen, Amgen, Takeda, Sanofi and Genesis Pharma; MVM reported honoraria from lectures and boards from Janssen, Celgene, Amgen, Takeda, Abbvie, GlaxoSmithKline, Adaptive, Roche and Seattle Genetics; SZ reported participation in advisory boards for Takeda, Celgene, Janssen, Sanofi and Oncopeptides and research funding from Celgene, Janssen and Takeda; GC reported being a member of speaker bureau for Takeda, Bristol Myers Squibb, Celgene, Amgen, Sanofi and Janssen and has received research grants from Bristol Myers Squibb, Celgene

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