nature reviews clinical oncology

https://doi.org/10.1038/s41571-025-01041-x

Evidence-based guidelines

Check for updates

EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma

A list of authors and their affiliations appears at the end of the paper

Abstract

Since the publication in 2021 of the European Hematology Association (EHA) Clinical Practice Guidelines for the treatment of patients with smouldering multiple myeloma (SMM) and multiple myeloma (MM), developed in collaboration with the European Society for Medical Oncology, a novel international staging system (R2-ISS) has been developed, several prognostic factors are entering clinical practice (such as minimal residual disease, circulating plasma cells and monoclonal protein assessed by mass spectrometry) and, at the time of writing, 14 novel regimens have been approved by the EMA and/or the FDA for the treatment of patients with MM. A multidisciplinary group of experts from the EHA and European Myeloma Network, based in various institutions mostly located in Europe, have updated the previous guidelines and produced algorithms for everyday clinical practice that incorporate levels of evidence and grades of recommendation based on the aforementioned new data.
In these Evidence-Based Guidelines, we provide key treatment recommendations for both patients with newly diagnosed MM and those with relapsed and/or refractory MM, including guidance for the use of established drugs as well as contemporary immunotherapies. Novel approaches for the management of patients with SMM focus on those who might require early intervention. Finally, we provide recommendations for myeloma-related complications and adverse events, such as bone disease, renal impairment and infections, as well as for those associated with T cell-mobilizing therapies, such as cytokine-release syndrome and immune effector cell-associated neurotoxicity syndrome.

Sections

e-mail: eterpos@med.uoa.gr

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for 1–2% of all cancers and 10–15% of all haematological malignancies[1]. In Europe, MM is the second most common haematological cancer, with an estimated incidence 4.5–6.0 cancers/100,000 persons per year[1,2]. MM is diagnosed most commonly in individuals with a median age of 65–70 years[1,2]. MM accounted for almost 22% of all haematological cancer-related deaths in the USA in 2023 (ref. 3). Over the past 20 years, survival outcomes in patients with MM have improved substantially: among those involved in clinical trials, almost 60% of patients eligible for autologous haematopoietic stem cell transplantation (ASCT) remained alive 10 years after the procedure[4]. However, data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that the 5-year overall survival (OS) in all patients with MM was 61.1% in 2024 (ref. 5), and that only 10–15% of them will reach the expected survival of the matched general population[6]. Most patients with MM eventually have disease relapse that becomes refractory to current treatments[7].

Smouldering MM (SMM) is an asymptomatic condition that occurs at the time between monoclonal gammopathy of undetermined significance (MGUS) and MM along the spectrum of clonal plasma cell proliferative disorders. SMM is not a biological intermediate stage between MGUS and MM, but rather represents a heterogeneous clinically defined condition in which some patients (approximately two-thirds) have MGUS (a premalignancy), and some (approximately one-third) have MM (a malignancy)[8]. The International Myeloma Working Group (IMWG) has defined SMM as a clonal plasma cell disorder with ≥10% clonal bone marrow plasma cells and/or a serum levels of paraprotein of ≥3 g/dl (or urine levels of paraprotein of ≥500 mg/24 h in the absence of a serum monoclonal protein (M protein) spike) with no hypercalcaemia, renal failure, anaemia or bone disease, or pathological features of light chain amyloidosis[9]. The prevalence of SMM in the overall population is 0.53% in individuals aged ≥40 years[10].

In 2021, the European Hematology Association (EHA) and European Society for Medical Oncology co-developed clinical practice guidelines for the management of patients with MM[11,12]. Since then, several novel regimens have been approved by the EMA and the FDA for use in patients with newly diagnosed MM (NDMM) disease and/or in those with relapsed and/or refractory MM (RRMM). In addition, novel methods have been developed to improve prognostication, define high-risk disease and evaluate minimal residual disease (MRD). In these Evidence-Based Guidelines, we provide up-to-date recommendations for the management of patients with MM, taking into consideration the novel data in the field, and we propose practical algorithms for the treatment of these patients based on the current levels of evidence. Although the guidelines have been mainly developed by European experts and regional variations apply, their intended scope is global.

Methods

The EHA and the European Myeloma Network (EMN) convened an interdisciplinary panel of experts in MM from various institutions and countries in Europe, who reviewed all the relevant literature, including randomized clinical trials, guidelines, meta-analyses, systematic reviews, observational studies, case series and case reports related to the diagnosis and management of MM. The literature search was performed using PubMed and Institute for Scientific Information databases, and records from 1 January 2021 until 31 May 2025 were retrieved. Levels of evidence and grades of recommendation, adapted from the US Public Health Service Grading System, were used for the development of these recommendations (Supplementary Table 1). The initial draft guidelines were discussed at the 20th EHA Annual Meeting (Madrid, Spain, 13–16 June 2024) and the manuscript subsequently underwent three rounds of revision by the panel members. When the evidence for a specific recommendation was not clear, panel consensus was reached during revision rounds. For panel consensus all authors had to agree on the final recommendation; these recommendations are clearly indicated as such. All panel members agreed on the described recommendations. These guidelines were approved by the EHA and the EMN boards in their respective meetings.

Regarding the section discussing therapy for MM, all regimens that are approved by the EMA and/or the FDA or have been investigated in registrational trials are included in both the main text and Figs. 1–3. Regimens that have shown benefit in phase III trials but are not likely to result in regulatory approval because they have not been tested in registrational studies are discussed but not included in the recommendations.

Diagnosis and staging

The diagnostic criteria for MM and SMM defined in the EHA guidelines from 2021 remain unchanged[11,12]. Diagnosis should be performed using recommended tests (Table 1).

The Second Revision of the International Staging System (R2-ISS), which was presented by the EMN in 2022 (ref. 13), is being increasingly used. This staging system is based on four prognostic markers, combining serum biomarkers and chromosomal abnormalities. In the seminal study describing R2-ISS, patients were stratified into four risk groups according to the total additive score: low (19.2% of patients), low–intermediate (30.8%), intermediate–high (41.2%) and

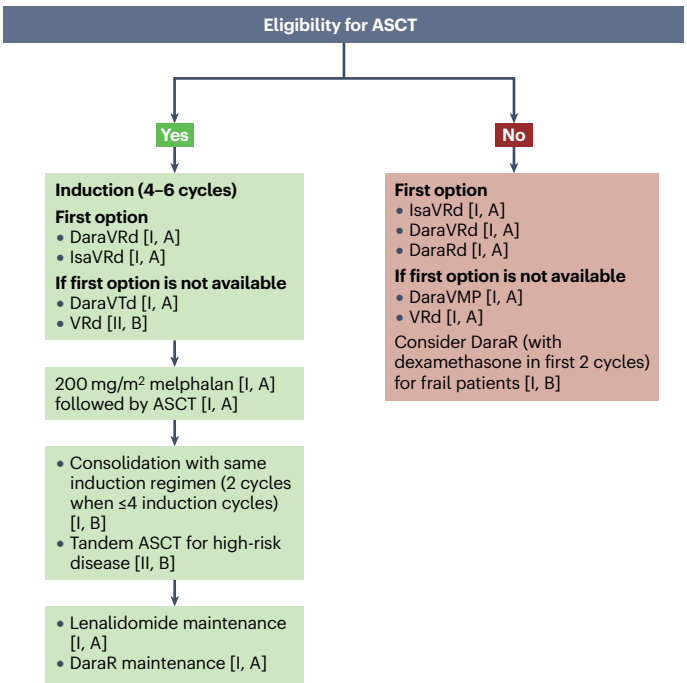

Fig. 1 | Recommendations for the treatment of patients with newly diagnosed multiple myeloma. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). ASCT, autologous stem cell transplantation; d, dexamethasone; Dara, daratumumab; Isa, isatuximab; M, melphalan; P, pomalidomide; R, lenalidomide; T, thalidomide; V, bortezomib.

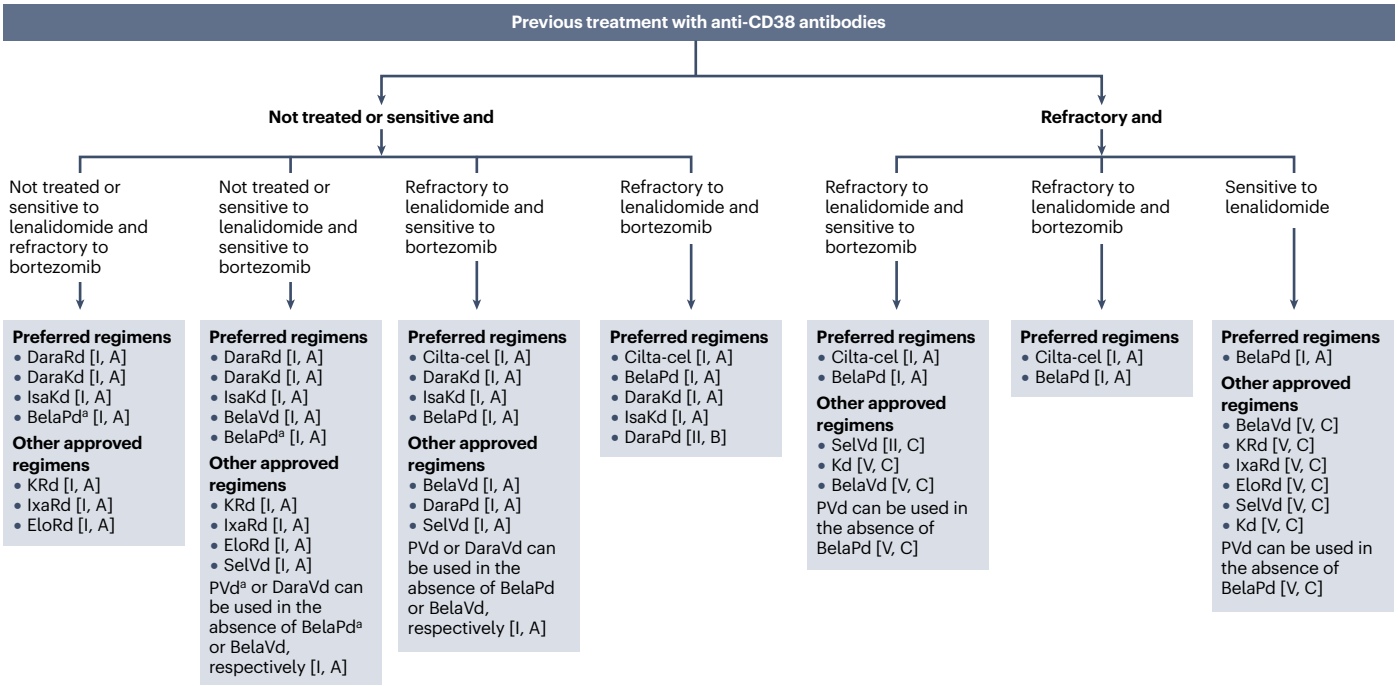

Fig. 2 | Recommendations for the treatment of patients with relapsed and/or refractory multiple myeloma at second line. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). [a]Only in patients exposed to lenalidomide. Bela, belantamab mafodotin; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; P, pomalidomide; R, lenalidomide; Sel, selinexor.

high (8.8%). The risk groups had different median OS (not reached, 109.2 months, 68.5 months and 37.9 months, respectively) and median progression-free survival (PFS) (68 months, 45.5 months, 30.2 months and 19.9 months) using standard-of-care (SOC) therapies[13]. A new proposed definition of high-risk myeloma (discussed in the New prognostic criteria section) (Box 1) could soon affect the current staging systems (R-ISS[14] and R2-ISS[13]).

New prognostic criteria

The International Myeloma Society (IMS) and the IMWG have updated their consensus definition of high-risk MM[15] (Box 1). These disease features need to be assessed with recommended tests (Table 1) and will influence disease staging and prognostication in the near future.

Several techniques that could soon change the routine management of patients with MM include the assessment of circulating plasma cells (CPCs), the evaluation of M protein using mass spectrometry (MS), and gene expression profiling. Several groups have reported on the prognostic value of CPCs[16–18], albeit without agreement on a universal cut-off percentage in blood. An EMN committee is currently establishing the definition of a CPC cut-off percentage to be used in routine clinical practice. The combination of CPC assessment with ISS might further improve disease staging[19]. CPC values determined using next-generation flow cytometry (NGF) might also be used for a more accurate diagnosis of plasma cell leukaemia[20,21], which is currently defined as ≥5% of CPCs in peripheral blood smears[22].

Quantitative immunoprecipitation (QIP) MS is more sensitive than immunofixation electrophoresis for detecting M protein in patients with MM, both at baseline and during treatment, and has greater predictive value[23,24]. Clonotypic peptide MS might be even more sensitive than QIP MS, although clinical data remain sparse[25]. The combination of QIP MS with CPC assessment has prognostic value and might be suitable for response assessment and MRD evaluation in peripheral blood[26]. This approach will be tested in clinical trials, with results eagerly awaited because they might lead to the substitution of bone marrow sampling with less-invasive techniques when performing response assessment in the future.

Finally, gene expression profiling has independent prognostic value, especially in patients with NDMM[27–29]. Nevertheless, this tool is not widely available in routine clinical settings.

Assessment of response to therapy

The 2016 definitions from the IMWG for response, progressive disease, relapse and refractoriness to therapy have not changed[30] (Supplementary Box 1). These criteria introduced the use of MRD assessment both in the bone marrow (using either next-generation sequencing (NGS) or NGF) and outside the bone marrow (using PET–CT; also referred to as imaging MRD). Bone marrow MRD negativity is a strong predictor of a favourable prognosis and correlates with improved PFS and OS in both patients with NDMM and those with RRMM[31,32]. On the basis of these and other data discussed on 12 April 2024 (refs. 33,34), the FDA Oncologic Drugs Advisory Committee recommended the use of MRD negativity as an end point in clinical trials involving patients with MM and provided considerations regarding timing of assessment, patient populations and trial design for future studies that intend to use MRD to support Accelerated Approval of a new product or supplementary indication. This decision resulted in the implementation of MRD negativity as a

primary end point in registrational trials with the aim of minimizing the time to approval of novel drugs.

In their 2016 criteria[30], the IMWG define bone marrow MRD negativity as the absence of malignant plasma cells within 100,000 nucleated bone marrow cells (that is, the sensitivity threshold is $<10^{-5}$). However, novel data suggest that lower cut-off values (such as 10^{-6}) provide better prognostication than the standard definition, although this sensitivity is harder to achieve[35]. In these guidelines, we use the cut-off value of 10^{-5} when we refer to MRD negativity; if the cut-off value of MRD negativity is different in a given study, we clarify this in the text. Outside the bone marrow, PET–CT can help to identify hypermetabolic areas in ~15–20% of patients with bone marrow MRD negativity, and is considered one of the best methods currently available for imaging MRD[36]. Diffusion-weighted imaging (DWI) is a form of MRI based on measuring the random Brownian motion of water molecules within a voxel of tissue. A meta-analysis found that DWI MRI is significantly more sensitive than PET–CT in depicting abnormal areas in the bone marrow of patients with MM[37]. Furthermore, DWI MRI is effective for predicting sustained imaging MRD negativity[38], although prospective data from large-cohort randomized trials comparing the two functional imaging techniques for the definition of imaging MRD negativity are not available at present. Novel immuno-PET approaches are under development. For example, CD38-targeted immuno-PET enabled the detection of >100 myeloma foci in a patient with biochemical progression but with a negative [^{18}F]fluorodeoxyglucose PET–CT scan[39]. These techniques are not widely available, and they have not been compared to functional MRI or even to PET–CT in clinical studies; however, their value might be demonstrated in the future.

Sustained MRD negativity for ≥12 months strongly correlates with PFS and OS in patients with NDMM[40]. The use of MRD to drive treatment decisions is under investigation. Such decisions include whether to stop maintenance or continuous therapy in patients with MRD negativity (MRD-negative patients) or whether treatment needs to be changed in MRD-positive patients (especially those with high-risk MM). Data from the past few years support the discontinuation of post-ASCT maintenance therapy with the immunomodulatory drug lenalidomide (abbreviated as 'R' in combinations) after 3 years of sustained MRD negativity[41,42], mainly in patients with standard-risk MM, although this finding needs to be confirmed in randomized clinical trials.

Over the past few years, experts have debated the use of urine specimens collected over a 24-h period for the evaluation of response according to the IMWG criteria. Serum free light chain evaluation has been shown to outperform immunofixation of urine samples collected over a 24-h period regarding prognosis. A study[43] involving transplant-eligible patients with NDMM showed that response classifications changed in only 4% of them when using 'urine-free' criteria based on serum free light chain measurement versus standard IMWG criteria[43,44].

The IMS and IMWG have revised response criteria and, as a result, the publication of new criteria is planned later this year. Examinations for response assessment, during follow-up and at relapse of MM should be performed as recommended (Table 1).

Recommendations

- Both PET–CT and DWI MRI are considered complementary to bone marrow MRD for the evaluation of MRD negativity [panel consensus; V, B].
- Urine-based tests are not obligatory for the assessment of response or during follow-up, but should be performed at diagnosis and at the time of each relapse to exclude other pathologies (such as light chain amyloidosis or free light chain deposition disease) [III, C].

Smouldering multiple myeloma

Various classification models have been developed to assess the risk to progression to MM in patients with SMM. One such model is the IMWG

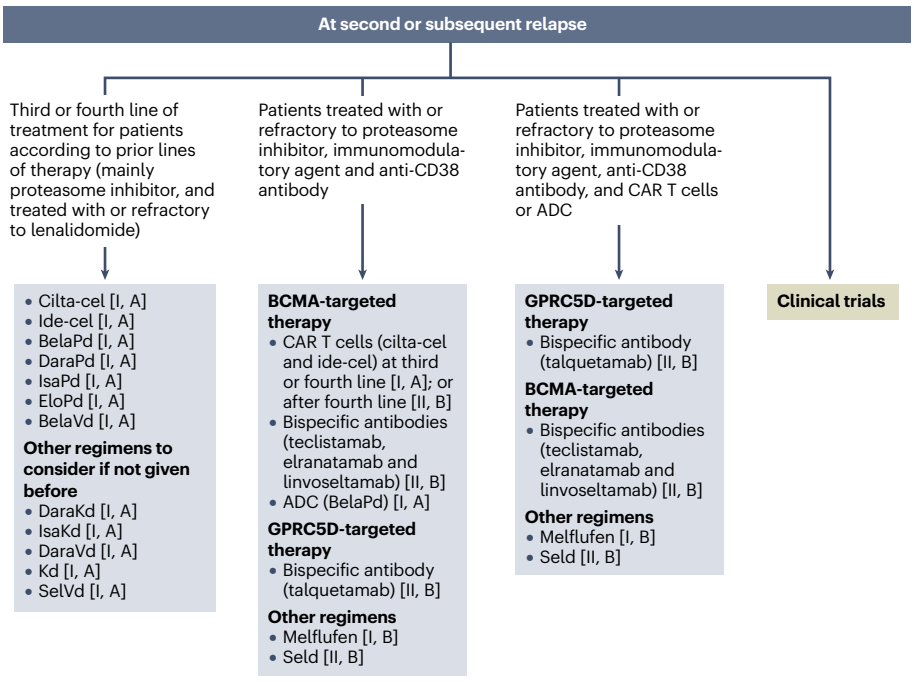

Fig. 3 | Recommendations for the treatment of patients with relapsed and/or refractory multiple myeloma at third line and beyond. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). ADC, antibody–drug conjugate; Bela, belantamab mafodotin; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; ide-cel, idecabtagene vicleucel; Isa, isatuximab; K, carfilzomib; P, prednisone; Sel, Selinexor; V, bortezomib.

20-2-20 model, which is used to classify patients as having a low, intermediate or high risk of progression. This model is commonly referred to as the three-factor model because it combines three risk factors: serum M protein, ratio of involved to uninvolved serum free light chains, and bone marrow plasma cell infiltration[45]. The addition of cytogenetic abnormalities to this tool yielded the four-factor model, which enables classification into four risk groups[45]. In a retrospective study, the high-risk subgroup accounted for 29% and 9% of patients using the three-factor model and four-factor model, respectively, and these patients had a 2-year progression rate of 44% and 63%, respectively[45].

Currently, a 'watch and wait' approach is the standard management strategy recommended in all patients with SMM[11,12,46]. However, two independent phase III trials have shown that patients with high-risk SMM (based on the standard definition at the time of trial initiation) who received lenalidomide plus dexamethasone (abbreviated as 'd' in combinations) or lenalidomide alone had longer PFS durations (and OS in the case of Rd) than those in the observation group[47,48]. Unfortunately, these pivotal studies were not registrational and thus neither approach is approved for the treatment of SMM by the EMA or FDA. These trials, however, have led to the initiation of several further trials involving patients with high-risk SMM, which had two strategies as their main objective: delaying progression to MM and cure.

Delaying progression to MM

Trials testing this approach have used the anti-CD38 antibody daratumumab (abbreviated as 'Dara' in combinations) as monotherapy. In the phase II CENTAURUS trial, 123 patients with intermediate-risk or high-risk SMM were randomly assigned (1:1:1) to receive intravenous daratumumab with a dose scheduling of long, intermediate or short intensity. At a median follow-up duration of 85 months, the median PFS was not reached, 84.4 months and 74.1 months with schedules of long, intermediate and short intensity, respectively[49,50].

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

Tool	Diagnosis	At response	At follow-up	At relapse
Blood tests				
Blood count and blood smear	Obl	Obl	Obl	Obl
Serum electrophoresis and immunofixation	Obl	Obl	Obl	Obl
Serum free light chain	Obl	Obl to confirm sCR	Obl	Obl
Serum immunoglobulin levels	Obl	Obl	Obl	Obl
Renal and liver function tests	Obl	Obl	Obl	Obl
Calcium	Obl	Obl	Obl	Obl
Lactate dehydrogenase	Obl	Obl	Obl	Obl
Albumin, β_2 microglobulin	Obl	NR	Opt	Obl
Flow cytometry	Opt	NR	NR	Opt
Urine tests				
Urine sample from 24-h urine collection to check for proteinuria and serum free light chain proteinuria	Obl	NR	NR	Obl
Urine electrophoresis and immunofixation	Obl	Obl	NR	Obl
Bone marrow assessments				
Bone marrow cytology and biopsy to confirm plasmacytosis and monoclonality	Obl	Obl to confirm CR or for non-secretory MM	NR	Opt (obl for non-secretory MM)
NGF or NGS to detect clonal plasma cells	Obl	Obl to confirm MRD negativity in patients with CR or sCR	Every 12 months in MRD-negative patients	Opt
Cytogenetics: karyotype and FISH for detection of del17p, t(4;14), t(14;16), t (14;20), 1q gain or amplification, del1p32 and t(11;14), and NGS for *TP53* mutations	Obl	NR	NR	Obl in patients with del17p, del1p32, 1q gain or amplification and *TP53* mutations
Advanced techniques: GEP, NGS	Only in clinical trials	Only in clinical trials	Only in clinical trials	Only in clinical trials
Imaging				
PET–CT or DWI MRI	Obl	Obl to confirm imaging MRD	Every 12 months in MRD-negative patients	Obl (also for detection of paramedullary or extramedullary disease)
WBLD CT	Obl (if PET–CT or DWI MRI NA)	NR	When symptomatic (or CT of the symptomatic area)	Obl (if PET–CT or DWI MRI NA)

CR, complete response; DWI, diffusion-weighted imaging; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; MM, multiple myeloma; MRD, minimal residual disease; NA, not available; NGF, next-generation flow cytometry; NGS, next-generation sequencing; NR, not required; Obl, obligatory; Opt, optional; sCR, stringent complete response; WBLD, whole-body low-dose.

In the phase III AQUILA trial, 390 patients with high-risk SMM were randomly assigned (1:1) to either receive subcutaneous daratumumab for 3 years or undergo active monitoring. The definition of high-risk SMM in this study included serum M protein levels ≥30 g/l, predominance of IgA in serum (commonly referred to as IgA SMM), immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes, a ratio of involved to uninvolved serum free light chains of 8:100, or a percentage of bone marrow clonal plasma cells of ≥50% to <60%. The primary end point was PFS. At 5 years, PFS was 63.1% versus 40.8% in the daratumumab and active-monitoring groups (HR 0.49, 95% CI 0.36–0.67; $P < 0.001$), and OS was 93.0% versus 86.9% (HR 0.52, 95% CI 0.27–0.98)[51]. Although the definition of high-risk SMM in this study differed from that in the three-factor and four-factor models, daratumumab improved PFS and OS compared to active monitoring in all patient subgroups, and the greatest benefit was observed in patients with high-risk SMM according to the IMWG three-factor model[51]. PFS in the next following line of treatment was also superior in patients receiving daratumumab, indicating that early intervention did not seem to negatively affect response to subsequent treatment. We note, however, that only 18% of patients in the active-monitoring group received a daratumumab-based combination for the treatment of progressive disease.

Curative-intent treatment

Thus far, three phase II trials have tested curative-intent treatment approaches for SMM. Results from the CESAR trial[52], the largest of these studies, were published in 2024. A total of 90 patients with high-risk SMM and who were eligible for ASCT received induction therapy with six cycles of the proteasome inhibitor carfilzomib (abbreviated as 'K' in combinations) plus Rd followed by high-dose (HD) melphalan (abbreviated as 'M' in combinations), followed by ASCT, two consolidation cycles of KRd, and Rd maintenance for 2 years. The primary end point was MRD-negativity rate assessed by NGF after ASCT. After a median follow-up of 70 months, 62% of patients were MRD-negative (31% for at least 4 years) and OS was 92%[52]. In a previous phase II trial[53], 54 patients with high-risk SMM received eight 4-week cycles of KRd followed by 24 28-day cycles of lenalidomide maintenance, without ASCT. At 8 years, PFS was 91.2% and no MM-related deaths had occurred. Finally, in the phase II ASCENT trial 87 patients with high-risk SMM (defined according to the three-factor IMWG model or the IMWG scoring system) received the quadruplet regimen DaraKRd as induction and consolidation for 12 cycles and then DaraR as maintenance for another 12 cycles. The rate of bone marrow MRD negativity was 84% and PFS at 3 years was 89.9%[54].

Recommendations

- Patients with low-risk or intermediate-risk SMM should be evaluated every 6 months or every 3–6 months, respectively, to assess their risk of progression to MM [I, B]; risk assessment should be performed using the IMWG classification models.
- Although approval by regulatory agencies is pending at the time of writing, daratumumab monotherapy for 3 years can be considered in patients with high-risk SMM [I, A].

Newly diagnosed multiple myeloma

Patients eligible for ASCT

The 2021 EHA guidelines[11,12] supported the treatment of transplant-eligible patients with NDMM with induction regimens such as the proteasome inhibitor bortezomib (abbreviated as 'V' in combinations) plus Rd or daratumumab in combination with bortezomib, the immunomodulatory drug thalidomide (abbreviated as 'T' in combinations) and dexamethasone, followed by one or two cycles of HDM, ASCT and lenalidomide maintenance. In 2024, results from the phase III PERSEUS trial[55] provided evidence supporting the use of new SOC regimens for induction, consolidation (both with DaraVRd) and maintenance (DaraR) in these patients. A total of 709 patients were randomly assigned (1:1) to receive subcutaneous daratumumab combined with VRd induction and consolidation therapy followed by DaraR maintenance therapy (DaraVRd group) or VRd induction and consolidation followed by lenalidomide maintenance (VRd group). Patients in the DaraVRd group with sustained MRD negativity for 12 months received maintenance with DaraR for up to 2 years followed by lenalidomide alone until disease progression or unacceptable toxicity; all other patients in this group received DaraR until disease progression or unacceptable toxicity. The primary end point was PFS. At a median follow-up of 47.5 months, the estimated 4-year PFS was 84.3% versus 67.7% in the DaraVRd and VRd groups (HR 0.42, 95% CI 0.30–0.59; $P < 0.001$), respectively[55].

The subsequent publication of results from the phase III AURIGA trial[56] further reinforced the value of DaraR maintenance. Patients with NDMM who had a very good partial response (vgPR) or better, were MRD-positive and had not previously received anti-CD38 antibodies after ASCT were randomly assigned to receive either DaraR ($n = 99$) or lenalidomide alone ($n = 101$) for up to 36 cycles. The primary end point, MRD negativity rate at 12 months from the start of maintenance therapy, was higher in the DaraR group (50.5% versus 18.8%; OR 4.51, 95% CI 2.37–8.57; $P < 0.0001$). At a median follow-up of 32 months, DaraR also improved PFS (82.7% versus 66.4% with lenalidomide alone at 30 months)[56].

In the phase III GMMG-HD7 trial[57], transplant-eligible patients with NDMM were randomly assigned to receive VRd ($n = 329$) or VRd plus the anti-CD38 antibody isatuximab (abbreviated as 'Isa' in combinations; $n = 331$) as induction therapy followed by single or tandem ASCT and by a second randomization to receive either IsaR or lenalidomide alone as maintenance. In updated results from this study, the MRD negativity rate after ASCT was higher with IsaVRd (66% versus 48% with VRd). IsaVRd induction was associated with prolonged PFS regardless of maintenance therapy (HR 0.70, 95% CI 0.52–0.95; $P = 0.018$).

Long-term follow-up results from the phase III CASSIOPEIA trial[58] confirmed DaraVTd as a SOC induction and consolidation regimen,

Box 1 | Summary of the IMS–IMWG 2024 consensus definition of high-risk MM

- del(17p)[a] and/or *TP53* mutation[b]
- t(4;14), t(14;16) or t(14;20), co-occurring with +1q[c] and/or del(1p32)
- Monoallelic del(1p32) along with 1q gain, or biallelic del(1p32)
- High β_2 microglobulin (>5.5 mg/dl) with normal creatinine (<1.2 mg/dl)

IMS, International Myeloma Society; IMWG, International Myeloma Working Group; MM, multiple myeloma. [a]Cancer clonal fraction ≥20%, by analyses conducted on CD138-positive/purified cells. [b]Assessed using a next-generation sequencing-based method. [c]+1q refers to gain (three copies) or amplification (four or more copies) of the long arm of chromosome 1. See ref. 15.

and supported daratumumab monotherapy maintenance as a subsequent option in transplant-eligible patients with NDMM. In this trial, 1,085 patients were first randomly allocated (1:1) to receive DaraVTd versus VTd for induction and consolidation. Those with a partial response or better were then randomly assigned (1:1) to daratumumab maintenance versus observation. At a median follow-up of 80.1 months and 70.6 months from the first and second randomizations, respectively, PFS from the second randomization was significantly longer with daratumumab maintenance (median not reached versus 45.8 months with observation; HR 0.49, 95% CI 0.40–0.59; $P < 0.0001$). Therefore, CASSIOPEIA showed that the inclusion of daratumumab in induction, consolidation and maintenance regimens results in superior PFS outcomes[58]. However, the maintenance phase compared daratumumab monotherapy with observation only, an approach considered suboptimal.

The substitution of bortezomib with carfilzomib in quadruplet regimens has resulted in excellent MRD negativity rates, especially in patients with high-risk disease[59–62]. For example, in the phase III Iskia trial[63], 302 patients were randomly assigned (1:1) to receive four cycles of either IsaKRd or KRd followed by HDM plus ASCT and another four cycles of IsaKRd or KRd, respectively, as consolidation. The MRD negativity rate after consolidation, the primary end point, was 77% with IsaKRd versus 67% with KRd (OR 1.67; $P = 0.049$); the respective rates at the cut-off of 10^{-6} were 67% versus 48% (OR 2.29; $P < 0.001$). The 10^{-6} MRD negativity rates with IsaKRd were 72% in patients with high-risk MM and 67% in patients with standard-risk disease[63]. In the phase III MIDAS trial[62], 791 transplant-eligible patients with NDMM received six 28-day induction cycles of IsaKRd before ASCT. The objective response rate (ORR) was 95%, with 91% of patients having a vgPR or better after induction. The MRD negativity rate was 63% (47% at the 10^{-6} threshold)[62]. Unfortunately, these very effective regimens (IsaKRd and DaraKRd) are not expected to be licensed by the FDA or EMA because they have not been tested in registrational trials.

In transplant-eligible patients with NDMM, collection of haematopoietic stem cells should be performed after three or four induction cycles because this approach is associated with a low incidence of ASCT failure[62,64]. For example, in the MIDAS trial, stem cell collection after three induction cycles with IsaKRd enabled at least one ASCT in almost 97% of patients and 94% had enough cells for tandem ASCT[62].

Regarding maintenance treatment, randomized trials have shown a PFS advantage with bortezomib monotherapy over thalidomide, specifically in patients with high-risk disease[65], and with monotherapy with the proteasome inhibitor ixazomib (abbreviated as 'Ixa' in combinations) versus observation[66,67]. However, the addition of ixazomib to Rd maintenance did not improve PFS[68]. Although some patients derive benefit from these proteasome inhibitors, they are not approved by the EMA or FDA for maintenance because these trials were not registrational.

Finally, allogeneic haematopoietic stem cell transplantation (alloSCT) seems to be of very limited value in patients with MM. A phase III trial[69] revealed that non-myeloablative alloSCT after ASCT is not more effective than tandem ASCT in patients with standard-risk MM[69,70], whereas a phase II trial[71] demonstrated that alloSCT does not prolong PFS compared with ASCT in patients aged <60 years. AlloSCT might provide a limited PFS and OS benefit in a specific subset of patients with high-risk MM[70]; however, this benefit has not been confirmed in the setting of quadruplet induction, consolidation after ASCT or DaraR maintenance.

Patients not eligible for ASCT

DaraRd[72], DaraVM plus prednisone[73] and VRd[74] are the SOC regimens previously recommended by the EHA[11,12] for the treatment of transplant-ineligible patients with NDMM. Since then, results from trials testing two other quadruplet regimens in this population have been published. In the open-label phase III IMROZ trial[75], 446 patients aged <80 years were randomly assigned (3:2) to receive IsaVRd versus VRd as induction followed by IsaRd and Rd, respectively, as maintenance therapy. At a median follow-up of 59.7 months, the estimated 5-year PFS was 63.2% in the IsaVRd group versus 45.2% in the VRd group (HR 0.60, 98.5% CI 0.41–0.88; $P < 0.001$). The incidence of adverse events (AEs) during treatment and that of AEs leading to discontinuation were similar in the two groups; however, grade 5 AEs were twice as common in the IsaVRd group (11% versus 5.5%)[75].

The value of IsaVRd is further supported by results from the phase III BENEFIT trial[76], conducted by the Intergroupe Francophone du Myeloma (IFM). In this trial, 270 transplant-ineligible patients with NDMM aged 65–79 years were randomly assigned (1:1) to receive IsaVRd versus IsaRd. The MRD negativity rate at 18 months from randomization, the primary end point, was higher with IsaVRd (53% versus 26%; OR 3.16, 95% CI 1.89–5.28; $P < 0.0001$). Despite the superiority of IsaVRd in terms of MRD negativity rate, at a median follow-up of 23.5 months PFS was comparable in both arms. Peripheral neuropathy of grade ≥2 occurred in 27% of patients in the IsaVRd arm versus 10% in the IsaRd arm (bortezomib was administered on a weekly schedule in this study)[76].

In the phase III CEPHEUS trial[77], the addition of daratumumab to VRd improved MRD negativity rates compared with VRd alone in transplant-ineligible patients with NDMM or in whom ASCT had been deferred; those with a high IMWG frailty score (FS) of <2 were excluded. A total of 395 patients were randomly allocated (1:1) to receive DaraVRd or VRd for eight cycles followed by DaraRd or Rd, respectively, until disease progression or unacceptable toxicity. Overall MRD negativity rate at 10^{-5}, the primary end point, was 60.9% in the DaraVRd group versus 39.4% in the VRd group (OR 2.37, 95% CI 1.58–3.55; $P < 0.0001$). At a median follow-up of 58.7 months, the median PFS duration was not reached in the DaraVRd group versus 52.6 months in the VRd group (HR 0.57, 95% CI 0.41–0.79; $P = 0.0005$); 54-month PFS was 68.1% versus 49.5%. The incidence of grade 5 AEs was 16.7% versus 10.7%[77]. Owing to the high incidence of grade ≥2 peripheral neuropathy in both arms (38.6% versus 44.1%), a dose-adaptation schedule of bortezomib (that is, weekly versus biweekly schedule in CEPHEUS) should be taken into consideration.

Finally, the final analysis of the phase III ALCYONE trial[78] showed that, after a median follow-up of 86.7 months, the DaraVMP combination provided a median OS of 83 months versus 53.6 months with VMP (HR 0.65, 95% CI 0.53–0.80; $P < 0.0001$). The most common grade 3–4 AEs were neutropenia (40% versus 39%), thrombocytopenia (35% versus 38%) and anaemia (18% versus 20%).

Patients with frailty

Frailty is a functional term that refers to a decline in physiological function, leading to dependency, vulnerability to stressors and a high risk of poor health-related conditions (such as metabolic disorders, infections or cancer), resulting in an increased morbidity and mortality[79]. At least two-thirds of patients with MM have frailty to some extent, and in a large-cohort population study, at least 40% of patients had severe frailty[80–82]. However, patients with frailty might not always have access to the evolving range of treatments and precision medicine approaches

that are improving outcomes in most patients with MM of a younger age and/or more favourable performance status, therefore presenting a substantial and growing unmet clinical need[83]. Identifying patients at risk of frailty is key to improving overall patient outcomes. For this purpose, the IMWG FS was developed as an MM-adapted geriatric assessment clinical scoring system that includes not only functional but also clinical assessments and is regarded as the gold standard in the field[84]. The IMWG FS is used to classify patients with MM into three categories on the basis of frailty, although it has never been tested in patients aged <55 years. A high FS (≥2) can predict poor treatment tolerability, inferior response to treatment, and poor survival and quality-of-life outcomes, not only in clinical trials but also in real-world populations[85–87]. Other scoring systems have been developed and tested in trials and real-world cohorts[82,88,89]. Despite evidence demonstrating the prognostic potential of these clinically based scoring systems, limited data are available to confirm their predictive value, thus limiting their adoption in clinical practice to guide treatment decisions. The phase III FiTNEss trial has shown a benefit in both event-free survival and OS when the all-oral combination IxaRd was administered in a schedule modified upfront on the basis of IMWG FS versus standard delivery[90]. Nevertheless, publication of the full data is still awaited and, therefore, no recommendations on the use of IMWG FS for therapy administration can be made at present.

DaraRd is currently considered the SOC regimen for the treatment of patients with NDMM and an IMWG FS of ≥2 because the trials testing quadruplet regimens previously described included patients up to the age of 80 years. In the phase III MAIA trial[91], DaraRd was superior to Rd in terms of both PFS and OS in the subgroup of patients with an IMWG FS of ≥2 (ref. 91). The phase III IFM2017-03 trial[92], with results published in 2024, tested a dexamethasone-sparing strategy in older patients and/or those with an IMWG FS of ≥2. This approach involves treatment with DaraR and only two cycles of dexamethasone. A total of 295 transplant-ineligible patients with NDMM and the aforementioned disease characteristics were randomly assigned (2:1) to receive DaraR versus Rd; the median PFS duration was 53.4 months versus 22.5 months (HR 0.51, 95% CI 0.37–0.71; $P < 0.0001$) and the median OS duration was not reached versus 47.2 months (HR 0.46, 95% CI 0.31–0.69; $P = 0.0001$). Although the median duration of treatment was longer in the DaraR group (31.6 months versus 14.3 months with Rd), the occurrence of grade ≥3 infections was similar (19% versus 21%)[92]. Therefore, DaraR can also be considered as a recommended option in patients with an IMWG FS of ≥2.

Finally, the single-arm phase II REST trial[93], with results published in 2025, tested IsaVRd (with weekly bortezomib and dexamethasone only in the first two cycles) in 51 transplant-ineligible patients with NDMM and an average age of 77 years. The MRD-negative complete response (CR) rate was 38% in the overall cohort and 31% in those aged >80 years. Although REST is a phase II trial, it provides the rationale for a safe and efficacious delivery of a quadruplet regimen to patients who might not be able to tolerate the IMROZ or CEPHEUS regimens[93].

Recommendations

- In patients aged <70 years without comorbidities, induction therapy followed by HDM and ASCT is recommended [I, A].
- Regarding induction therapy before ASCT, DaraVRd and IsaVRd provide the best risk–benefit profile to date among quadruplets and are recommended as the new SOC regimens [I, A], despite not being approved yet by the EMA. DaraVTd is another valid option in this setting [I, A], although it has not been compared directly with DaraVRd. If the above regimens are not available, VRd can be used [II, B]. For all induction regimens, four to six cycles are recommended (Fig. 1).
- Collection of haematopoietic stem cells should be performed after three or four induction cycles [I, A].
- HDM (200 mg/m^2) is the recommended SOC conditioning regimen before ASCT [I, A].
- To date, consolidation therapy after ASCT has not been established as a SOC approach. In patients who have received only four cycles of DaraVRd induction, two cycles of DaraVRd consolidation should be considered [I, B].
- Tandem ASCT might be suitable in patients with genetically defined high-risk disease [II, B] or in all patients who have received induction with bortezomib, dexamethasone and cyclophosphamide (abbreviated as 'C' in combinations) [I, A].
- Lenalidomide was considered the SOC maintenance treatment after ASCT in all patients with MM [I, A]. On the basis of PFS results from the PERSEUS trial[55], the addition of daratumumab to lenalidomide is the new SOC [I, A].
- Patients who are not eligible for ASCT but have an IMWG FS of <2 and are <80 years old can receive two new SOC regimens: IsaVRd and DaraVRd [I, A], although at the time of writing, DaraVRd is pending approval by the EMA. DaraRd is a valuable option in all transplant-ineligible patients, especially those with an IMWG FS of ≥1 [I, A]. A dexamethasone-sparing strategy (DaraR) should be considered in patients with an IMWG FS of ≥2 [I, B]. If none of the above-mentioned options is available, DaraVMP or VRd can be used [I, A].

Relapsed and/or refractory multiple myeloma

Patients who have received one prior line of treatment

Second-line treatment regimens are selected on the basis of the efficacy and toxicity of, and refractoriness to, the regimens received previously as well as patients' comorbidities. Patients who have not received lenalidomide or have disease sensitive to this drug should receive regimens that have been recommended in the 2021 EHA guidelines[11,12], or novel regimens supported by the data described here.

Belantamab mafodotin (abbreviated as 'Bela' in combinations) is an antibody–drug conjugate (ADC) that comprises an afucosylated humanized anti-BCMA IgG1 antibody linked to the microtubule disrupting agent monomethyl auristatin F. This ADC has been recommended for approval by the Committee for Medicinal Products for Human Use (CMHP) of the EMA in combination with Vd or pomalidomide (abbreviated as 'P' in combinations) plus dexamethasone for the treatment of patients with RRMM who have received one to three prior lines of therapy; FDA approval is awaited at the time of writing. In the phase III DREAMM-7 trial[94,95], 494 patients were randomly assigned (1:1) to receive BelaVd versus DaraVd. At a median follow-up of 39.4 months, median PFS was 36.6 months with BelaVd versus 13.4 months with DaraVd (HR 0.41, 95% CI 0.31–0.53; $P < 0.001$)[94]. OS at 36 months was superior with BelaVd (74% versus 60%; HR 0.58, 95% CI 0.43–0.79; $P < 0.001$)[95]. Ocular toxicities were more common with BelaVd (79% versus 29% with DaraVd); such AEs were managed with dose modifications, and of those (85%) involving worsening visual acuity, the majority (87%) resolved[94]. Of note, 33% and 0% of patients in the BelaVd group had lenalidomide-refractory and daratumumab-refractory disease, respectively[94,95]. In summary, BelaVd is a new SOC for the treatment of patients who have received one to three prior lines of therapy, although formal approval by relevant authorities is pending at the time of writing.

Based on the first-line therapy received, many patients in the second-line setting are expected to have lenalidomide but would be refractory to lenalidomide. Two trials with results published after the latest (2021) update of the EHA guidelines[11,12] have focused on this population. In the phase III CARTITUDE-4 trial[96,97], 419 patients with lenalidomide-refractory MM who had received one to three prior lines of therapy were randomly allocated (1:1) to receive the BCMA-targeted chimeric antigen receptor (CAR) T cell product ciltacabtagene autoleucel (cilta-cel) versus SOC (PVd or DaraPd). At a median follow-up of 33.6 months, the median PFS was not reached with cilta-cel versus 11.8 months with SOC (HR 0.29, 95% CI 0.22–0.39; $P < 0.001$). At 30 months, PFS was 59.4% versus 25.7%, and OS was also superior with cilta-cel: 76.4% versus 63.8% (HR 0.55, 95% CI 0.39–0.79; $P < 0.001$)[97]. A greater percentage of patients in the cilta-cel group had MRD-negative disease: 62% versus 18.5%. Among the 176 patients who received cilta-cel, 76% had cytokine-release syndrome (CRS), which was of grade 3–4 in 1%; 5% had immune effector cell-associated neurotoxicity syndrome (ICANS), all of grade 1–2; and 13% had non-ICANS neurological AEs, of grade 3 in <2%[96,97]. One criticism of this trial is that DaraKd or IsaKd, which had provided the best outcomes in patients with lenalidomide-refractory disease up to the time of study design, were not included in the SOC arm. On the basis of the above data, cilta-cel was approved by the EMA for the treatment of patients with lenalidomide-refractory RRMM who have received at least one prior line of therapy including an immunomodulatory drug and a proteasome inhibitor and have disease progression on their last line of therapy.

In the phase III DREAMM-8 trial[98,99], 302 patients with RRMM who had received at least one line of therapy with lenalidomide were randomly allocated (1:1) to receive BelaPd versus PVd. At a median follow-up of 21.8 months, the estimated 12-month PFS was 71% versus 51% (HR 0.52, 95% CI 0.37–0.73; $P < 0.001$). In patients with lenalidomide-refractory disease (78% of the cohort), the median PFS was 25 months with BelaPd versus 8.6 months with PVd (HR 0.31, 95% CI 0.19–0.48). Ocular AEs occurred in 89% of patients who received BelaPd (grade 3–4 in 43%) and 30% of those who received PVd (grade 3–4 in 2%). The median dose intensity of belantamab mafodotin was 1.9 mg/kg given every 8–12 weeks, despite the scheduled dose of 2.5 mg/kg every 4 weeks for the first cycle and 1.9 mg/kg every 4 weeks from the second cycle and after. Ocular AEs led to treatment discontinuation in 9% of the patients in the BelaPd arm[98,99]. Approval of BelaPd by regulatory authorities is pending at the time of writing.

The combination of selinexor (abbreviated as 'Sel' in combinations) with Vd was approved by the EMA and FDA in June 2022 for the treatment of patients with RRMM who have received one to three prior lines of therapy on the basis of results from the phase III BOSTON trial[100], which compared the SelVd regimen with Vd[100–102]. Results at a median follow-up duration of 28 months were published in 2024 (ref. 101). The median PFS was longer with the addition of selinexor in all patient subgroups ($P < 0.05$). Patients with lenalidomide-refractory disease had longer OS with SelVd (26.7 months versus 18.6 months with Vd (HR 0.53, 95% CI 0.30–0.95; $P = 0.015$)). The most frequent grade 3–4 AEs were thrombocytopenia (39% versus 17%), fatigue (13% versus 1%), anaemia (16% versus 10%) and pneumonia (11% versus 11%). Other SelVd-associated AEs included gastrointestinal toxicities, such as nausea, vomiting or diarrhoea, which needed dose modification of selinexor and prophylaxis with at least two antiemetics[100–102].

The treatment of patients with MM refractory to both lenalidomide and daratumumab is very challenging. CARTITUDE-4 (refs. 96,97) and DREAMM-8 (refs. 98,99) are the only phase III trials that have included such patients, but the percentage was low in both trials (<25%). On the basis of the data currently available from clinical trials, cilta-cel and BelaPd are the preferred options in these patients, and KPd might be an alternative option. In the phase II SELECT trial[103], 52 patients received KPd at first or second relapse, of whom 75% had disease refractory to both lenalidomide and daratumumab. Carfilzomib was given once weekly, at a dose of 56 mg/m^2. Median PFS was 11.1 months and median OS was 18.8 months[103]. In another phase II trial[104], 111 patients with disease progression or relapse in the previous phase III EMN02 trial in transplant-eligible patients with NDMM[105] received second-line therapy with KPd. Among these patients, 77% had received bortezomib and lenalidomide, but none had received daratumumab. After the completion of eight cycles of KPd, patients were randomly allocated to receive continuous treatment with either pomalidomide alone ($n = 44$) or Pd ($n = 42$). At a median follow-up of 40 months, median PFS was 26 months[104]. KPd is a widely available regimen but, owing to the lack of registrational trials, it is not approved by the EMA or FDA for the treatment of patients with RRMM.

Recommendations

- In patients who have received a bortezomib-based regimen upfront without lenalidomide or an anti-CD38 antibody, and have bortezomib-refractory disease, the preferred regimens are DaraRd, DaraKd and IsaKd [I, A]. Other approved regimens include KRd, IxaRd and elotuzumab (abbreviated as 'Elo' in combinations) plus Rd [I, A]. In patients who have received lenalidomide, BelaPd can also be used [I, A] (Fig. 2).
- Patients who have received a bortezomib-based regimen upfront without lenalidomide or an anti-CD38 antibody and have bortezomib-sensitive disease should preferably receive DaraRd, DaraKd, IsaKd or BelaVd [I, A]. Other approved regimens include KRd, IxaRd, EloRd, SelVd and Kd [I, A]. In patients who have received lenalidomide, BelaPd is also an efficacious option [I, A]. DaraVd or PVd can also be used if BelaVd or BelaPd, respectively, is unavailable [panel consensus; I, A].
- Patients eligible for treatment with CAR T cells with disease refractory to first-line lenalidomide and who have not received or have disease sensitive to anti-CD38 antibodies should receive cilta-cel, if available [I, A]. Other options in patients with lenalidomide-refractory disease include DaraKd, IsaKd, BelaPd, BelaVd, DaraPd and SelVd [I, A]; combinations of anti-CD38 antibodies with Kd or BelaPd provide the best outcomes in patients with lenalidomide-refractory MM, and are preferred. PVd or DaraVd can be used if BelaPd or BelaVd, respectively, are unavailable [panel consensus; I, A].
- Patients with disease both refractory to lenalidomide and bortezomib, and who have not received or have disease sensitive to anti-CD38 antibodies should receive cilta-cel, BelaPd, DaraKd or IsaKd [I, A], or DaraPd [II, B].
- In patients with disease refractory to both lenalidomide and daratumumab, cilta-cel and BelaPd are the preferred options [I, A] because they are the only regimens that have been tested in patients who have received both lenalidomide and daratumumab previously, in the early relapse setting. SelVd [II, C], BelaVd [V, C] and Kd [V, C] can be used in this setting (only in patients with bortezomib-sensitive disease) if other options are not available; however, limited or no evidence supports this recommendation because almost no patients with daratumumab-refractory disease

have been involved in the registrational studies of these regimens [panel consensus].
- In patients with limited access to novel regimens, second-line ASCT can be an option in those who received primary therapy including an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months [panel consensus; III, C].

Patients who have received two or more prior lines of treatment

The treatment of patients with MM who have received two or more prior lines of therapy is becoming challenging because by the third line most of them have been exposed to triple-class regimens (that is, containing a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody) or have triple-class refractory disease, and some might also have been exposed to BCMA-targeted immunotherapies. Therefore, depending on exposure and refractoriness to prior therapies, some of the combinations already discussed might be suitable third-line treatments. These regimens are mainly based on pomalidomide (Fig. 3). Since the publication of the 2021 EHA guidelines[11,12], the DaraPd combination has been approved by the EMA and the FDA. These decisions were based on the results of the phase III APOLLO trial[106,107], in which 304 patients were randomly assigned (1:1) to receive either DaraPd or Pd. This study also included patients who had received one prior line of therapy, only if they had lenalidomide-refractory disease. At a median follow-up of 39.6 months, median PFS was 12.4 months in the DaraPd arm versus 6.9 months with Pd (HR 0.63, 95% CI 0.47–0.85; $P = 0.002$), although median OS was only numerically improved: 34.4 months versus 23.7 months (HR 0.82, 95% CI 0.61–1.11; $P = 0.2$)[106,107].

An important question when treating these patients is whether re-administration of anti-CD38 antibodies is of any value; real-world data from a population of 183 patients show a median PFS of <6 months in this setting[108]. Retreatment with these agents just after anti-CD38 refractoriness might provide very poor results: another study showed that MM cells derived from patients who had stopped receiving daratumumab for >1 year had greater sensitivity to anti-CD38 antibodies than those from patients with exposure <1 year before; however, cells from patients who had not received daratumumab were the most sensitive[109]. Therefore, if retreatment with anti-CD38 antibodies is the only option in patients with RRMM, these agents might need to be given only after a treatment-free interval of ≥1 year, although this approach needs to be tested in clinical studies.

The choice of proteasome inhibitor to be combined with daratumumab is another important consideration. The best results have been observed with DaraKd[110]. The substitution of bortezomib or carfilzomib for ixazomib in combination with daratumumab does not result in improved outcomes[111]. EloPd might also be considered in patients with disease refractory to anti-CD38 antibodies. Real-world data indicate that the latter regimen is widely used in this setting[112], although a phase II trial testing EloPd in the post-daratumumab setting showed limited efficacy, with a median PFS of 3.7 months[113].

In patients who have been exposed to triple-class regimens (including those with triple-class refractory RRMM), several immunotherapies have been approved by the EMA and/or FDA since 2021, including two CAR T cell products and four bispecific T cell engagers. Cilta-cel was approved in 2021 for the treatment of patients who have received three or more lines of therapy, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and have disease progression on the last line. This approval was supported by the results from the pivotal phase I/II CARTITUDE-1 trial[114,115], which involved 113 patients who had received a median of six prior lines of therapy (range three to 18) including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody. Of these patients, 29 and 68 received a cilta-cel infusion at the recommended phase II dose (0.75×10^6 CAR-positive viable T cells per kilogram) in the phase I or II part, respectively. At a median follow-up of 27.7 months, the ORR was 97.9%, and 82.5% of patients had a stringent CR. The 27-month PFS and OS rates were 54.9% and 70.4%, respectively. The duration of response (DOR), PFS and/or OS were shorter in patients with high-risk disease, high tumour burden or plasmacytoma. Grade 3–4 haematological AEs included neutropenia (in 95% of patients), anaemia (68%), leukopenia (61%), thrombocytopenia (60%) and lymphopenia (50%). CRS occurred in almost all patients and was of grade 3–4 in 4%; the median time to onset and median duration were 7 days and 4 days, respectively. CRS resolved in all except one patient, who had both grade 5 CRS and haemophagocytic lymphohistiocytosis. ICANS and other CAR T cell-related neurotoxicities occurred in 21% of patients and were of grade 3–4 in 9%[114,115].

Idecabtagene vicleucel (ide-cel) is the second CAR T cell product approved by the EMA and FDA for the treatment of patients with MM. The initial EMA and FDA approvals were for patients who had received three or more lines or four or more lines of therapy, respectively, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and who had disease progression on their last line of treatment. This approval was based on the results of the phase II KarMMa trial[116], in which 128 patients who had received three or more lines of therapy, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, were treated with ide-cel. At a median follow-up duration of 13.3 months, the ORR was 73%, with a CR in 33% of patients. MRD negativity was confirmed in 26% of patients. The median PFS was 8.8 months. Common AEs of any grade included neutropenia (in 91% of patients), CRS (84%, which was of grade ≥3 in 5%), anaemia (70%), thrombocytopenia (63%) and neurotoxicity (18%, which was of grade 3 in 5%; no grade ≥4 neurotoxicities occurred)[116].

The initial approvals of ide-cel were expanded in 2024 to include patients who have received two or more prior lines, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and who had disease progression on their last line of therapy. These decisions were based on the results of the phase III KarMMa-3 trial[117,118] in which 386 patients with RRMM who had received two to four prior lines of therapy (with the characteristics previously described) were randomly assigned (2:1) to receive either ide-cel (at a dose range of 150×10^6 to 450×10^6 CAR-positive T cells) or one of five SOC regimens (DaraPd, DaraVd, IxaRd, Kd or EloPd). A total of 66% and 95% of the patients had triple-class refractory and daratumumab-refractory disease, respectively. At a median follow-up of 31 months, the median PFS was 13.8 months in the ide-cel group versus 4.4 months with SOC (HR 0.49, 95% CI 0.38–0.63; $P < 0.001$). The ORR was 71% versus 42%, with a CR in 39% versus 5% of patients ($P < 0.001$). Median OS at interim analysis was similar in the two arms: 41.4 months versus 37.9 months (HR 1.01, 95% CI 0.73–1.40). Given that the trial allowed crossover, sensitivity analysis adjusting for crossover was performed and showed a median OS of 41.4 months versus 23.4 months (HR 0.72, 95% CI 0.49–1.01). Among the 225 patients who received ide-cel, 88% had any-grade CRS (5% of grade ≥3) and 15% had any-grade investigator-identified neurotoxicity (3% of grade ≥3)[117,118].

Four bispecific T cell engagers have been approved for the treatment of patients with RRMM: teclistamab, elranatamab and linvoseltamab, which target BCMA, and talquetamab, which targets

GPRC5D. The EMA and FDA approvals are for patients who have previously received three or more lines or four or more lines of therapy, respectively, and in all approvals these criteria include an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and disease progression on the last line of therapy. These approvals were all based only on the results from single-arm phase II trials. Teclistamab was evaluated in the registrational phase I/II MajesTEC-1 trial[119,120], in which 165 patients received a weekly subcutaneous injection of this agent at 1.5 mg/kg after two step-up doses of 0.06 mg/kg and 0.3 mg/kg. These patients had received a median of five previous lines of therapy and 77.6% had triple-class refractory disease. At a median follow-up of 30.4 months, ORR, the primary end point, was 63.0%, and 46.1% of patients had a CR or better. Among patients evaluable for MRD, 85.7% were MRD-negative. The median DOR was 24 months and not reached in patients with a CR, and median PFS was 11.4 months. Common AEs of any grade or grade 3–4 included CRS (in 72.1% and 0.6% of patients, respectively, with no grade 4 events reported), neutropenia (in 71.5% and 65.5%), anaemia (in 55.2% and 37.6%), thrombocytopenia (in 41.8% and 23%), infections (78.8% and 55.2%) and neurotoxicity (14.5%, including ICANS in 3.0%, all of grade 1–2)[119,120].

Elranatamab was evaluated in the phase II MagnetisMM-3 trial[121,122], in which patients received a weekly subcutaneous injection of this agent at 76 mg after two step-up priming doses (12 mg and 32 mg); after six cycles, responders received elranatamab once every 2 weeks. The currently available results are from patients who had not received any prior BCMA-targeted therapy (n = 123). The ORR, the primary end point, was 61.0%, and 37.4% of patients had a CR or better. At a median follow-up of 33.9 months, median DOR was not reached, median PFS was 17.2 months and median OS was 24.6 months. Common AEs of any grade or grade 3–4 included infections (in 69.9% and 39.8% of patients, respectively), CRS (57.7% and 0%), anaemia (48.8% and 37.4%) and neutropenia (48.8% and 48.8%). With biweekly dosing, the occurrence of grade 3–4 AEs decreased from 58.6% to 46.6%[121,122].

In the phase II LINKER-MM1 trial[123], 117 patients received linvoseltamab once weekly through week 14 and then once every 2 weeks. At a median follow-up of 14.3 months, the ORR (primary end point) was 71%, with 50% patients having a CR or better. The median DOR in patients receiving a 200 mg dose (n = 83) was 29.4 months. The most common AEs in those receiving the 200 mg dose included CRS (of any grade in 46% of patients and grade 3 in <1%), neutropenia (of any grade in 43% of patients and grade 3–4 in 42%) and anaemia (of any grade in 39% of patients and grade 3 in 31%). ICANS of any grade occurred in 8% of patients and was of grade 3 in 3%, and infections of any grade occurred in 74% and were of grade 4 in 3%; infection frequency and severity declined over time[123].

In the phase II MonumenTAL-1 trial[124,125], patients who had received a median of five prior lines of therapy received a subcutaneous dose of either 0.8 mg/kg every 2 weeks or 0.4 mg/kg weekly (recommended dose from the phase I part of the study) of talquetamab. At a median follow-up of 23.4 months, the ORR was 69.5% and 74.1% at the dose of 0.8 mg/kg every 2 weeks and 0.4 mg/kg weekly, respectively; median PFS was 11.2 months and 7.4 months, and 24-month OS was 67.1% and 60.6%. This study also included 51 patients who had previously received T cell-mobilizing therapies such as bispecific T cell engagers (35.3% of this subgroup), CAR T cells (70.6%) or both (6%). At a median follow-up of 20.5 months, the ORR was similar in these patients and in those who had not received T cell-mobilizing therapies (ORR 66.7%, with a CR or better in 42.4%). Median DOR was not assessed in this subgroup and 24-month OS was 57.3%. The most common grade 3–4 AEs in the 0.4 mg/kg once a week group, the 0.8 mg/kg every 2 weeks group, and the previous T cell-mobilizing therapy group were neutropenia (in 31%, 21% and 47% of patients, respectively), anaemia (31%, 26% and 27%) and lymphopenia (26%, 26% and 17%). Fatal AEs occurred in five patients, seven patients and no patients in each group, respectively; none was related to treatment[124,125].

In August 2022, the EMA approved the alkylating peptide–drug conjugate melphalan flufenamide (melflufen) in combination with dexamethasone for the treatment of patients with RRMM who have received three or more prior lines of therapy, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody, and had disease progression on or after their last therapy. This approval, based on the results of the phase II HORIZON[126] and the phase III OCEAN[127] trials, included the specification that melflufen is suitable in patients who have not undergone ASCT, or in those who have, but with a time to progression of ≥3 years since ASCT. In OCEAN, 495 patients were randomly assigned (1:1) to receive melflufen–dexamethasone versus Pd; ~50% had not undergone ASCT. Median PFS was 6.8 months versus 4.9 months (HR 0.79, 95% CI 0.64–0.98; P = 0.03). The most common grade 3–4 AEs in the melflufen group were thrombocytopenia (63%), neutropenia (54%) and anaemia (43%)[127].

Treatment sequencing of immunotherapies, such as CAR T cells, ADCs and bispecific T cell engagers, presents challenges. Data from phase II trials or real-world cohort studies suggest that the efficacy of CAR T cells is compromised if they are administered after progression on BCMA-targeted ADCs or bispecific T cell engagers[128]. Median PFS with ide-cel was <4 months in patients who had previously received an ADC[129]. Median PFS with cilta-cel was 9.5 months and only 5.3 months in those who had previously received an ADC and bispecific T cell engager, respectively[130]. By contrast, bispecific T cell engagers seem effective after CAR T cells, especially if the target is switched (from BCMA-targeted agents to GPRC5D-targeted T cell engagers), although PFS is inferior[131–133]. In an analysis of patients with disease relapse after treatment with ide-cel (n = 130) or cilta-cel (n = 9) who went on to receive different regimens, the ORR with teclistamab (n = 37) and talquetamab (n = 28) were 64% and 79%, respectively, with a CR in 32% and 39% of patients[131]. By contrast, in patients who received salvage therapy with a triple-class regimen after CAR T cell therapy, the ORR was only 30% and no CRs were reported (P < 0.001)[131]. DOR and OS were also significantly better with bispecific T cell engagers[131]. In a pooled analysis of trials testing elranatamab in patients who had previously received BCMA-targeted ADCs or CAR T cells, the median PFS was 4.8 months[132]. Finally, another analysis showed median PFS durations of 4.4 months and 7.3 months in patients who had received teclistamab after BCMA-targeted CAR T cells or ADCs, respectively[133]. In summary, additional data are needed to define the optimal sequencing of immunotherapies in patients with RRMM.

Recommendations

- In the third or fourth line of treatment, patients can receive treatments that they have not been previously exposed to, including cilta-cel, ide-cel, BelaPd, DaraPd, IsaPd, EloPd, BelaVd [I, A] or other regimens (Fig. 3).
- Retreatment with an anti-CD38 antibody after disease progression on this therapeutic class is not recommended. If such a retreatment strategy is the only option, it should be started only after an anti-CD38 antibody-free interval of ≥1 year [panel consensus; IV, C].
- Patients with triple-class refractory MM can receive cilta-cel or ide-cel in the third or fourth lines of treatment [I, A] or in the fifth

line and beyond [II, B], teclistamab [II, B], elranatamab [II, B], linvoseltamab [II, B], talquetamab [II, B] or BelaPd [I, A]. These patients can also receive melflufen if they had not previously undergone ASCT or if the time to disease progression after ASCT is ≥3 years [I, B]. Seld is another option in these patients [II, B].

- In patients with triple-class refractory MM that is also refractory to either CAR T cells or an ADC, options include talquetamab, teclistamab, elranatamab and linvoseltamab [II, B], as well as melflufen and Seld if no other option is available [panel consensus; V, C].
- Sequencing of the immunotherapies in patients with RRMM presents challenges; further prospective studies will provide more insights into this important issue. Currently available data suggest that CAR T cell therapies might need to be given to eligible patients before BCMA-targeted ADCs or bispecific T cell engagers [panel consensus; III, B]. Bispecific T cell engagers can be effective immediately after disease progression on CAR T cells, and talquetamab is possibly the agent with better outcomes in this setting [panel consensus; V, C].

Supportive care

Common complications and adverse events in patients with MM

Bone disease. Osteolytic bone disease is the most common complication in patients with MM that leads to deterioration of quality of life and patient outcomes[134]. Several organizations and medical societies (ASCO, IMWG and EMN) have published recommendations addressing this devastating complication and its management in patients with MM[135–137]. A phase III trial[138] has compared the antiresorptive agents denosumab and zoledronic acid in 1,718 patients receiving treatment for NDMM and with at least one bone lesion. The time to first skeletal-related event was similar in both groups (~17 months). Denosumab showed a superior renal safety profile along with an advantage in PFS (46.1 months versus 35.4 months with zoledronic acid (HR 0.82, 95% CI 0.68–0.99; $P = 0.036$))[138,139]. However, in this study, patients who had severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2) were excluded because zoledronic acid is cleared through the kidneys and is not recommended in these patients. A study from the IMWG with results published in 2024 (ref. 140) showed that denosumab is efficacious in patients with severe renal impairment, but caution is needed owing to the higher incidence of hypocalcaemia found in this trial.

In the IMWG recommendations for the management of MM-related bone disease[135] the time of zoledronic acid administration is 12 months in patients with a vgPR or more with treatments for MM. This recommendation was based on a subgroup analysis of the phase III MRC-IX trial[141] involving 1,111 transplant-eligible patients with MM. In patients with a vgPR or less, zoledronic acid was superior to clodronate in reducing skeletal-related events ($P = 0.048$), whereas in those with a CR, both agents were equivalent. The treatment duration of zoledronic acid was also the aim of the phase II Magnolia trial, also with results presented in 2024 (ref. 142), in which 193 patients receiving treatment for NDMM were randomly assigned to receive zoledronic acid for 2 years versus 4 years. Those treated for 4 years had a statistically significant lower risk of progressive bone disease (HR 0.40, 95% CI 0.18–0.87; $P = 0.0021$). No differences in the occurrence of osteonecrosis of the jaw or other AEs were reported[142].

Anaemia and bone marrow failure. Anaemia is a common problem in patients with MM. Although this complication has a complex aetiology, it is mainly caused by the mechanisms underlying anaemia in chronic disease, which is characterized among others, by impairment of iron metabolism and consequently iron-restricted erythropoiesis, resulting from the upregulation of the iron distributing regulator hepcidin. Erythropoiesis-stimulating agents have been the SOC for anaemia since the early 1990s, and result in high response rates and improved quality of life[143,144].

Infections. Infections are the main cause of death in patients with myeloma. T cell immune dysfunction and changes in the B cell compartment with consequent hypogammaglobulinaemia increase the risk of developing bacterial and viral infections including COVID-19 (ref. 145). Recommendations from IMWG and EMN have also been reported for the management of infections in myeloma patients[146–148]. In the phase III TEAMM trial[149], addition of prophylactic levofloxacin to active treatment for NDMM during the first 12 weeks reduced the occurrence of first febrile episode or death from any cause (19% versus 27% with placebo (HR 0.66, 95% CI 0.51–0.86; $P < 0.002$)) without increasing the occurrence of infections acquired in health-care settings (8% versus 9%), which are typically resistant to antibiotics.

Renal impairment. Renal impairment is a common complication in patients with MM (present in up to 20% of patients at diagnosis). The IMWG has also provided recommendations for this complication[150]. Lenalidomide is typically given at reduced doses according to renal function because it is cleared through the kidneys. However, a phase I/II trial[151] demonstrated that lenalidomide can be given at the full dose of 25 mg daily to patients without severe renal impairment (creatinine clearance >30 ml/min) and at a dose of ≥15 mg daily to those with creatinine clearance <30 ml/min, even when on dialysis[151]. These doses are also being used in the phase II/III REMNANT trial (NCT04513639) testing the value of MRD negativity in guiding treatment decisions, confirming the safety of these doses. Daratumumab can be given to patients with renal impairment, resulting in high rates of renal responses, without any modification as suggested by several studies[152–154]. Very limited evidence on the effects of CAR T cells or ADCs on renal impairment is currently available[155], whereas teclistamab has shown some efficacy in patients with renal impairment, including those on dialysis[156,157].

Common adverse events from novel therapeutic agents in patients with MM

Ocular toxicities. Ocular AEs, in particular changes in best corrected visual acuity from baseline and keratopathy, are the most common AEs observed in patients receiving belantamab mafodotin and the main reason for dose holds and delays. Dose modifications (such as 1.9 mg/kg or 1.4 mg/kg) and extended administration schedules (every 8 or 12 weeks), especially in patients with a response to treatment, enable management of ocular AEs without negatively affecting treatment efficacy[158]. The publication of novel guidelines on the management and prevention of belantamab mafodotin-related ocular AEs is expected later this year; these include ophthalmology visits before each belantamab mafodotin infusion for the first four cycles to decide about administration of the next dose, and decision-making from the treating physician using the anamnestic tool afterwards. The treating physician decision is based on the vision-related anamnestic tool, which is a questionnaire based on symptoms and daily activities of patients. In a small, randomized phase II study in NDMM with the combination of BelaRd in intermediate-fit patients and those with frailty, no significant differences were found between the ophthalmologist's evaluation and

the haematologist's evaluation in the decision to continue or delay therapy with belantamab mafodotin[159]. More importantly, no drug administration defined by the haematologist's ocular assessment was interrupted by the ophthalmologist owing to grade 3 ocular AEs.

Cytokine-release syndrome. CRS is a systemic inflammatory response mediated by the activation of T lymphocytes, observed mainly after treatment with BCMA-targeted CAR T cells or bispecific T cell engagers[158,160]. In patients with MM receiving novel immunotherapies, such as bispecific antibodies and CAR T cells, CRS is usually of grade 1–2.

In patients receiving bispecific T cell engagers, systemic CRS is mainly observed after initial exposure to bispecific antibodies comprising an anti-CD3 antibody, but can occur even during subsequent step-up doses[158]. In those receiving CAR T cells, CRS usually occurs within the first week after infusion (median 1 day and 7 days with ide-cel and cilta-cel, respectively) and peaks within 1–2 weeks after infusion. CRS usually begins with fever and constitutional symptoms (such as rigor, malaise and anorexia)[160]; other features include fatigue, chills, headache, and more severe toxicities such as hypotension, hypoxia, tachycardia, vascular leak, circulatory collapse and organ toxicity. The administration of the anti-IL-6 antibody tocilizumab and corticosteroids together with immunotherapies in patients with higher CRS grading has been shown to reduce the risk of severe CRS[161].

Immune effector cell-associated neurotoxicity syndrome and other neurotoxicities. ICANS is a pathological process affecting the CNS following administration of immune effector-based therapies that results from the activation or deployment of endogenous or infused T cells and/or other immune effector cells. In patients with MM, ICANS is very rare with bispecific antibodies and usually of grade 1–2 with CAR T cell therapies.

ICANS is the second most common toxicity associated with CAR T cell therapy, with an incidence of around 15% for mild ICANS and of 5% for severe ICANS[162]. Symptoms often begin with word-finding difficulties, confusion, dysphasia, expressive aphasia, and impairment of fine motor and cognitive skills, and can include somnolence, headache, disorientation, seizures and cerebral oedema[163,164]. Some patients can develop non-ICANS neurotoxicities such as cranial nerve palsy and/or late neurological complications such as Parkinson disease-like movement disorders[165]. The exact biological mechanisms underlying these neurotoxicities are not fully understood but, similar to CRS, the production of pro-inflammatory cytokines by CAR T cells and the activation of bystander immune cells (such as macrophages) in the tumour microenvironment are thought to be responsible for the pathogenesis[166]. Furthermore, these neurotoxicities also seem to be related to off-target expression of BCMA in basal ganglia and the frontal cortex[165].

Given that ICANS is often associated with CRS, the prevention of CRS is of great importance, although a few patients can develop ICANS without prior or concomitant CRS[149]. Tocilizumab is much less effective in ICANS than in CRS because it doesn't cross the blood–brain barrier[167] and, thus, it is not recommended for the management of ICANS. In fact, given that tocilizumab might worsen ICANS by increasing IL-6 levels, it should be given only in the co-presence of CRS. Agitated patients with grade 1 ICANS might experience symptom improvement with haloperidol or lorazepam[161]. Those with grade 2 ICANS, especially if it is refractory to anti-IL-6 antibodies, should receive dexamethasone (10 mg every 6 h) or methylprednisone (1 mg/kg every 12 h) and, if the response is inadequate, the dexamethasone dose should be increased to 20 mg every 6 h. The IL-1R antagonist anakinra can be considered as it has been shown to reduce ICANS[168]. In patients with grade ≥3 ICANS, transfer to the intensive care unit should be considered[161].

Recommendations

- All patients with MM with osteolytic disease at diagnosis should receive antiresorptive agents, such as zoledronic acid or denosumab [I, A], in addition to myeloma-directed therapy (Box 2).
- Patients without bone disease (assessed by conventional radiography) should also receive antiresorptive agents, although their advantage is not clear in those with no bone involvement on whole-body low-dose CT or PET–CT [II, B].
- In patients with a CR or vgPR to anti-MM therapy, the optimal duration of treatment with antiresorptive agents remains to be determined but should be at least 12 months and up to 48 months, and then at the physician's discretion on the basis of AEs such as osteonecrosis of the jaw or renal impairment [III, B]. In patients with osteonecrosis of the jaw, bisphosphonates or denosumab should be discontinued and can be re-administered if this AE resolves [V, C]. In patients with less than a vgPR, monthly use of these agents is recommended for at least 4 years [I, A].
- In patients with SMM, zoledronic acid or denosumab are not recommended in the absence of osteoporosis; in those with MGUS or SMM as well as osteoporosis, antiresorptive agents must be used following guidelines for the management of osteoporosis [III, C]. Patients with SMM who are receiving myeloma-directed therapy including dexamethasone should receive antiresorptive agents, following recommendations for MM [panel consensus; V, C].
- In patients with severe renal impairment aminobisphosphonates are not recommended because they are cleared through the kidneys. Denosumab is a reasonable option but caution is needed owing to a high risk of hypocalcaemia [III, C].
- Denosumab should be given continuously every 4 weeks. The discontinuation of this agent is challenging because of the lack of data from patients with MM; until these data are available, discontinuation of denosumab must be followed by a dose of zoledronic acid (6–9 months after the last dose of denosumab) to prevent any 'rebound' phenomenon [III, B].
- Vitamin D and calcium supplementation is mandatory when administering either bisphosphonates or denosumab [I, A].
- Low-dose radiotherapy (up to 30 Gy) can be used as palliative treatment for uncontrolled bone pain, impending pathological fracture or impending spinal cord compression [II, A]. Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain [II, B]. Surgery is recommended for long-bone fractures, bony compression of the spinal cord or vertebral column instability [II, A].
- Recombinant human erythropoietin and darbepoetin alfa can be used for the treatment of myeloma-associated anaemia (haemoglobin levels <10 g/dl) if other causes of anaemia have been excluded. The target is to maintain haemoglobin levels <12 g/dl to avoid thromboembolic complications and hypertension [II, B].
- Treatment with granulocyte colony-stimulating factor might be required to treat chemotherapy-induced severe neutropenia [II, B].
- Infectious episodes require immediate therapy with broad-spectrum antibiotics [I, A]. Therefore, levofloxacin-based prophylaxis for infections during the first 3 months of therapy is

Box 2 | Summary of recommendations for the management of common complications in patients with multiple myeloma

Bone disease

- Antiresorptive agents should be given in addition to myeloma-directed therapy in all patients with MM and osteolytic disease at diagnosis [I, A].
- Denosumab is a reasonable option in patients with severe renal impairment, in whom aminobisphosphonates are not recommended; caution is needed owing to a high risk of hypocalcaemia [III, C].
- Zoledronic acid should be given monthly in patients with suboptimal response (PR or less) and at least for 4 years [I, A].
- In patients who have a CR or vgPR, 12–48 months of therapy with zoledronic acid seems adequate. At relapse, zoledronic acid should be reinitiated [III, B].
- Denosumab should be given every 4 weeks continuously. Discontinuation of denosumab is challenging owing to the lack of data on how to stop denosumab in patients with MM; until these data are available, discontinuation of denosumab must be followed by a dose of zoledronic acid (6–9 months after the last dose of denosumab) to prevent any 'rebound' phenomenon [III, B].
- Vitamin D and calcium supplementation is mandatory when administering either bisphosphonates or denosumab [I, A].
- Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathological fracture, or for impending spinal cord compression [II, A].
- Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain [II, B].
- Surgery is recommended for long-bone fractures, bony compression of the spinal cord, or vertebral column instability [II, A].

Anaemia

- Recombinant human erythropoietin and darbepoetin alfa for the treatment of myeloma-associated anaemia if other causes of anaemia have been excluded [II, B].
- G-CSF might be required to treat chemotherapy-induced severe neutropenia [II, B].

Infections

- Immediate therapy with broad-spectrum antibiotics [I, A].
- Prophylactic antibiotics (such as levofloxacin) for the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in those at high risk of infections [I, A].
- Sulfamethoxazole and trimethoprim are recommended for the prevention of *Pneumocystis jirovecii* infection [I, A].
- Acyclovir or valacyclovir for herpes zoster prophylaxis is recommended in patients receiving proteasome inhibitors, anti-CD38 antibodies and BCMA-targeted therapies [II, A].
- Vaccination for influenza, varicella zoster (inactivated vaccine), SARS-CoV-2 and pneumococcal infections [II, A] as well as for respiratory syncytial virus [III, C].
- Intravenous IgG prophylaxis is not routinely recommended although it is highly recommended in patients receiving either bispecific T cell engagers or CAR T cells [III, C]; it should be used in patients with low IgG levels (<400–500 mg) and in those with at least two severe infections requiring hospitalization during the previous year [II, B].

Impaired renal function

- Bortezomib-based regimens remain the cornerstone of the management of MM-related renal impairment [I, A].
- High-dose dexamethasone at least for the first month of therapy [II, B].
- Patients eligible for ASCT can receive DaraVTd or DaraVCd [II, B]. If reversal of renal impairment is observed, thalidomide or cyclophosphamide might be substituted by lenalidomide [panel consensus; V, B]. In patients who are ineligible for ASCT, DaraVCd or VMP can also be administered [II, B] but no data on this regimen in patients undergoing dialysis are available.
- Pomalidomide, carfilzomib, ixazomib, daratumumab and isatuximab need no dose modifications in patients with renal impairment [II, B].
- CAR T cells can be given in patients with mild to moderate renal impairment [II, B].
- Teclistamab can be given to patients with MM-related renal impairment, even including those undergoing dialysis [III, C].

ASCT, autologous stem cell transplantation; C, cyclophosphamide; CAR, chimeric antigen receptor; CR, complete response; d, dexamethasone; Dara, daratumumab; G-CSF, granulocyte colony-stimulating factor; M, melphalan; P, pomalidomide; PR, partial response; T, thalidomide; vgPR, very good partial response. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1).

useful, especially in patients receiving lenalidomide orpomalidomide, or in those at high risk of infections (for example, previous serious infections or neutropenia) [I, A].

- Sulfamethoxazole–trimethoprim is recommended for the prevention of *Pneumocystis jirovecii* infection [I, A], especially in patients receiving BCMA-targeted immunotherapies and/or with severe lymphopenia.
- Vaccinations against influenza, varicella zoster, SARS-CoV-2 and pneumococcal infections are recommended [II, A]. Vaccination against respiratory syncytial virus can be considered in patients with a history of frequent infections [III, C].
- Acyclovir or valacyclovir are recommended for prophylaxis of herpes zoster virus infections in patients receiving proteasome inhibitor-based, anti-CD38 antibody-based and BCMA-targeted therapies [II, B]. Intravenous IgG-based prophylaxis is not routinely recommended and should only be used in patients with low IgG levels (<400–500 mg), in those with at least two severe infections needing hospitalization during the previous year [II, B] and/or in those who receive BCMA-targeted bispecific T cell engagers owing to a high risk of infections [III, C].
- Bortezomib-based regimens with the addition of daratumumab is the cornerstone of the management of MM-related renal

impairment [I, A]. HDM should be administered at least for the first month of therapy [II, B]. The combination of DaraVTd or DaraVCd should be the frontline treatment of choice [II, B]. If reversal of renal impairment is observed, thalidomide or cyclophosphamide can be substituted by lenalidomide [panel consensus; V, B]. This recommendation is based on the evidence of efficacy with daratumumab in patients with severe renal impairment [II, B]. Patients who are ineligible for ASCT can receive DaraVCd or VMP, although no data are available on the role of these regimens in patients undergoing dialysis [II, B].

- Thalidomide is effective and safe in patients with MM and renal impairment and can be given without dose modifications [II, B].

Box 3 | Summary of recommendations for the management of toxicities derived from novel therapies in patients with multiple myeloma

Ocular toxicities

- Ophthalmology evaluation is recommended before each belantamab mafodotin infusion for the first four cycles [I, A].
- The treating physician can decide for the next dose administration or delay based on the vision-related anamnestic tool [II, B].
- Dose delays, dose reductions and prolonged intervals (every 8 to 12 weeks) between belantamab mafodotin administration lead to the recovery of ocular AEs without affecting the efficacy of the drug [I, A].

CRS

Grade 1

- Supportive care including analgesics and antipyretics [I, A].
- If fever persists, check for infections [I, A].
- Consider tocilizumab for persistent (>3 days) and refractory fever [I, A].

Grade 2

- Intravenous fluid bolus [I, A].
- Tocilizumab early if fever of ≥39°C persists, if hypotension persists despite the use of initial fluid bolus or after initiation of oxygen supplementation [II, B].
- If hypotension persists after a second fluid bolus and tocilizumab, transfer to the intensive care unit [I, A].
- Add dexamethasone if hypotension persists after anti-IL-6 antibodies, high risk of severe CRS, worsening hypoxia or clinical concern [panel consensus, IV, C].

Grade 3

- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Add dexamethasone if no response within 24 h, increasing dose if refractory [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- Consider etanercept as clinically appropriate [panel consensus; III, C].

Grade 4

- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Administer high-dose methylprednisolone [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- If CRS remains unresponsive consider alternative agents such as etanercept [panel consensus; III, C].

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade 1

- Observation.
- Withhold oral food, medicine and fluid intake and switch to intravenous intake.
- Haloperidol or lorazepam if patient is agitated [II, B].
- Consider early dexamethasone in high-risk patients [II, B].
- Start non-sedating AEDs if not already being administered [panel consensus; III, C].
- MRI of brain, lumbar puncture, funduscopic examination and/or EEG [I, A].

Grade 2

- Dexamethasone [II, B].
- If no improvement after 48 h, increase dexamethasone dose or administer alternative agents such as anakinra or tocilizumab in the concomitant presence of CRS [II, B].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].

Grade 3

- Dexamethasone [II, B].
- If no improvement after 24 h, increase dexamethasone dose [II, B], or administer high-dose methylprednisolone and/or alternative agents such as anakinra [panel consensus; IV, C].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].
- Acetazolamide if increased CSF pressure [panel consensus; IV, C].

Grade 4

- Dexamethasone [II, B].
- If refractory, administer high-dose methylprednisolone [panel consensus; IV, C].
- If ICANs remains refractory, consider alternative therapies including lymphodepletion with cyclophosphamide or other drugs [panel consensus; IV, C].
- Consider mechanical ventilation, EEG and CT or MRI [II, B].
- Drain CSF if increased CSF pressure [panel consensus; V, C].

AE, adverse event; AED, anti-epileptic drug; CRS, cytokine-release syndrome; CSF, cerebrospinal fluid; EEG, electroencephalography; ICANS, immune effector cell-associated neurotoxicity syndrome. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). See ref. 161.

Lenalidomide is also effective and safe in patients with mild to moderate renal impairment and should be administered with dose adjustments according to creatinine clearance [II, B]. HDM–ASCT is feasible in patients with MM and renal impairment; the dose of melphalan should be restricted to 100–140 mg/m^2 [III, C]. Pomalidomide can be administered at standard doses in patients with severe renal impairment, even those on dialysis [II, B]. Carfilzomib is another option in patients with RRMM and renal impairment and it needs no dose modifications in those with creatinine clearance >15 ml/min, with similar outcomes in patients with and without renal impairment [II, B]. Ixazomib can be safely administered in combination with lenalidomide and dexamethasone in patients with RRMM and creatinine clearance ≥30 ml/min [II, B]. Daratumumab can be also given to patients with severe renal impairment [II, B]. Finally, teclistamab is another option in patients with MM and renal impairment (even on dialysis) [III, C].

- Ophthalmology evaluation is recommended before each belantamab mafodotin infusion for the first four cycles [I, A] (Box 3). The treating physician might be able to decide for the next dose administration or delay based on the vision-related anamnestic tool [II, B]. Dose delays, dose reductions and prolonged interval (every 8 to 12 weeks) between belantamab mafodotin administration lead to the recovery of ocular AEs without affecting the efficacy of the drug [I, A].
- For grade 1 CRS, we recommend supportive care including analgesics and antipyretics. If fever persists (>3 days) and infections are excluded, consider tocilizumab [I, A].
- For grade 2 CRS, give an intravenous fluid bolus of 500–1,000 ml to maintain a systolic blood pressure of >90 mmHg; administer tocilizumab (8 mg/kg infused over 1 h) early if fever of ≥39°C persists, or if hypotension persists after administration of the initial fluid bolus or initiation of oxygen supplementation [II, B]. If hypotension persists after administration of a second fluid bolus and tocilizumab, transfer to the intensive care unit for consideration of low-dose vasopressor therapy. Add dexamethasone (10 mg intravenously every 6 h) if hypotension persists, especially after anti-IL-6 therapy [panel consensus; IV, C].
- For grade 3 CRS, consider intensive care, administer tocilizumab and add dexamethasone if there is no response within 24 h and increase the dose if refractory (to 20 mg intravenously every 6 h); add anakinra (2 mg/kg daily for 3–5 days) if the CRS is unresponsive; consider etanercept as clinically appropriate [panel consensus; III, C].
- For grade 4 CRS, the patient should be in the intensive care unit and receive tocilizumab and high-dose methylprednisolone (1 g/day); add anakinra if the CRS is unresponsive or even alternative agents such as etanercept [panel consensus; III, C].
- For grade 1 ICANS, observe the patient, withhold oral food, medicine and fluid intake, and switch to intravenous intake; haloperidol or lorazepam if the patient is agitated; consider early dexamethasone in patients with high-risk disease [II, B]. Start non-sedating antiepileptic drugs if not already being administered [panel consensus; III, C]. MRI of brain, lumbar puncture, funduscopic examination and/or electroencephalography should be performed [I, A].
- For grade 2 ICANS, give dexamethasone (10 mg every 12 h) and if no improvement is observed after 48 h, increase dexamethasone dose (20 mg every 6 h) or administer alternative agents such as anakinra or tocilizumab in the concomitant presence of CRS [II, B].
- For grade 3 ICANS, start dexamethasone (10 mg every 6 h) and if no improvement is observed after 24 h, consider high-dose dexamethasone (20 mg every 6 h), high-dose methylprednisolone (1–2 g/day) and/or alternative agents such as anakinra [panel consensus; IV, C]. Consider acetazolamide if cerebrospinal fluid (CSF) pressure is increased [panel consensus; IV, C].
- For grade 4 ICANS, give dexamethasone (20 mg every 6 h). If ICANS is dexamethasone-refractory, consider high-dose methylprednisolone (2 mg/kg every 12 h). If still refractory, consider alternative therapies including lymphodepletion with cyclophosphamide or other drugs [panel consensus; IV, C]. If CSF pressure >20 mmHg, drain CSF to < 20 mmHg via an Ommaya device [panel consensus, V, C].

Conclusions

The experts in this panel reviewed all the new data available from January 2021 until May 2025. During this period of time, 14 new drugs or drug combinations were approved by the EMA and/or FDA. In these guidelines, the panel provides useful recommendations for the diagnosis, follow-up and treatment of patients with MM in different clinical scenarios, such as disease refractory to both anti-CD38 antibodies and lenalidomide, or with four-class refractoriness, to name a few. The experts also agree that the high efficacy of novel therapeutic agents creates the need for new response criteria that will lead to therapeutic decisions, such as when to stop maintenance or when to change therapy to achieve the best results in patients.

As the cure in a proportion of patients with MM is on the horizon, the panel experts acknowledge the existing global variation in access to drugs and monitoring tools. For example, some non-approved but extremely efficacious drug combinations have greater availability in the USA than in Europe, Canada, Australia or other regions because they are recommended by the NCCN Guidelines[169]. Furthermore, a major issue with CAR T cell products is the lack of availability in the majority of European countries.

Finally, as described in the Methods section, in these guidelines we only recommend regimens approved by the EMA or FDA, or those tested in phase III registrational trials. We discuss but cannot recommend all other regimens that have shown benefit but have not been tested in registrational trials (such as Rd for high-risk SMM, IsaKRd or DaraKRd as induction and consolidation therapy in transplant-eligible patients with NDMM, or KPd in those with RRMM). Furthermore, the expert panel members were mainly based in Europe and formulated these recommendations for application in routine clinical practice in Europe. Nevertheless, we believe that these guidelines are a useful resource for clinicians treating patients with MM in other regions.

Published online: 7 July 2025

References

1. Malard, F. et al. Multiple myeloma. *Nat. Rev. Dis. Prim.* **10**, 45 (2024).
2. Sun, et al. Global landscape and trends in lifetime risks of haematologic malignancies in 185 countries: population-based estimates from GLOBOCAN 2022. *eClinicalMedicine* **83**, 103193 (2025).
3. Siegel, R. L., Miller, K. D., Wagle, N. S. & Jemal, A. Cancer statistics, 2023. *CA Cancer J. Clin.* **73**, 17–48 (2023).
4. Sonneveld, P. et al. Consolidation treatment with VRD followed by maintenance with lenalidomide in multiple myeloma improves overall survival: long-term follow-up of the EMN02/HOVON95 randomized phase 3 trial. *Blood* **144**, 674–674 (2024).
5. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: myeloma. *NIH* https://seer.cancer.gov/statfacts/html/mulmy.html (2024).
6. Engelhardt, M., Kortum, K. M., Goldschmidt, H. & Merz, M. Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible. *Haematologica* **109**, 2420–2435 (2024).

7. Martinez-Lopez, J. et al. Real-world treatment patterns, healthcare resource use and disease burden in patients with multiple myeloma in Europe. *Future Oncol.* **19**, 2103–2121 (2023).
8. Rajkumar, S. V., Kumar, S., Lonial, S. & Mateos, M. V. Smoldering multiple myeloma current treatment algorithms. *Blood Cancer J.* **12**, 129 (2022).
9. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br. J. Haematol.* **121**, 749–757 (2003).
10. Thorsteinsdóttir, S. et al. Prevalence of smoldering multiple myeloma based on nationwide screening. *Nat. Med.* **29**, 467–472 (2023).
11. Dimopoulos, M. A. et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **32**, 309–322 (2021).
12. Dimopoulos, M. A. et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Hemasphere* **5**, e528 (2021).
13. D'Agostino, M. et al. Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY project. *J. Clin. Oncol.* **40**, 3406–3418 (2022).
14. Palumbo, A. et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J. Clin. Oncol.* **33**, 2863–2869 (2015).
15. Avet-Loiseau, H. et al. International Myeloma Society/International Myeloma Working Group consensus recommendations on the definition of high-risk multiple myeloma. *J. Clin. Oncol.*, https://doi.org/10.1200/JCO-24-01893 (2025).
16. Bertamini, L. et al. High levels of circulating tumor plasma cells as a key hallmark of aggressive disease in transplant-eligible patients with newly diagnosed multiple myeloma. *J. Clin. Oncol.* **40**, 3120–3131 (2022).
17. Garces, J. J. et al. Circulating tumor cells for the staging of patients with newly diagnosed transplant-eligible multiple myeloma. *J. Clin. Oncol.* **40**, 3151–3161 (2022).
18. Kostopoulos, I. V. et al. Circulating plasma cells in newly diagnosed multiple myeloma: prognostic and more. *J. Clin. Oncol.* **41**, 708–710 (2023).
19. Kostopoulos, I. V. et al. Low circulating tumor cell levels correlate with favorable outcomes and distinct biological features in multiple myeloma. *Am. J. Hematol.* **99**, 1887–1896 (2024).
20. Jelinek, T. et al. More than 2% of circulating tumor plasma cells defines plasma cell leukemia-like multiple myeloma. *J. Clin. Oncol.* **41**, 1383–1392 (2023).
21. Musto, P. et al. European Myeloma Network Group review and consensus statement on primary plasma cell leukemia. *Ann. Oncol.* **36**, 361–374 (2025).
22. Fernandez de Larrea, C. et al. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. *Blood Cancer J.* **11**, 192 (2021).
23. Puig, N. et al. Mass spectrometry vs immunofixation for treatment monitoring in multiple myeloma. *Blood Adv.* **6**, 3234–3239 (2022).
24. Giles, H. V. et al. Progression free survival of myeloma patients who become IFE-negative correlates with the detection of residual monoclonal free light chain (FLC) by mass spectrometry. *Blood Cancer J.* **14**, 50 (2024).
25. Noori, S. et al. Dynamic monitoring of myeloma minimal residual disease with targeted mass spectrometry. *Blood Cancer J.* **13**, 30 (2023).
26. Puig, N. et al. Measurable residual disease by mass spectrometry and next-generation flow to assess treatment response in myeloma. *Blood* **144**, 2432–2438 (2024).
27. Shah, V. et al. Predicting ultrahigh risk multiple myeloma by molecular profiling: an analysis of newly diagnosed transplant eligible myeloma XI trial patients. *Leukemia* **34**, 3091–3096 (2020).
28. Skerget, S. et al. Comprehensive molecular profiling of multiple myeloma identifies refined copy number and expression subtypes. *Nat. Genet.* **56**, 1878–1889 (2024).
29. Bhutani, M. et al. Investigation of a gene signature to predict response to immunomodulatory derivatives for patients with multiple myeloma: an exploratory, retrospective study using microarray datasets from prospective clinical trials. *Lancet Haematol.* **4**, e443–e451 (2017).
30. Kumar, S. et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* **17**, e328–e346 (2016).
31. Paiva, B. et al. Impact of treatment effect on MRD and PFS: an aggregate data analysis from randomized clinical trials in multiple myeloma. *Blood Adv.* **8**, 219–223 (2024).
32. Ntanasis-Stathopoulos, I. et al. Evaluating minimal residual disease negativity as a surrogate endpoint for treatment efficacy in multiple myeloma: a meta-analysis of randomized controlled trials. *Am. J. Hematol.* **100**, 427–438 (2025).
33. Landgren, O. et al. EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical end point for multiple myeloma. *Blood* **144**, 359–367 (2024).
34. Landgren, O. & Devlin, S. M. Minimal residual disease as an early endpoint for accelerated drug approval in myeloma: a roadmap. *Blood Cancer Discov.* **6**, 13–22 (2025).
35. Martinez-Lopez, J. et al. Measurable residual disease (MRD) dynamics in multiple myeloma and the influence of clonal diversity analyzed by artificial intelligence. *Blood Cancer J.* **14**, 131 (2024).
36. Cavo, M. et al. Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. *Lancet Oncol.* **18**, e206–e217 (2017).
37. Rama, S. et al. Comparative performance of whole-body MRI and FDG PET/CT in evaluation of multiple myeloma treatment response: systematic review and meta-analysis. *AJR Am. J. Roentgenol.* **218**, 602–613 (2022).
38. Belotti, A. et al. Predictive role of sustained imaging MRD negativity assessed by diffusion-weighted whole-body MRI in multiple myeloma. *Am. J. Hematol.* **98**, E230–E232 (2023).
39. Ulaner, G. A., Lewis, J. & Landgren, O. CD38-targeted ^{89}Zr-DFO-daratumumab PET of myeloma: immuno-PET impacting clinical care. *J. Nucl. Med.* **66**, 482 (2025).
40. Pasquini, M. C. et al. Minimal residual disease status in multiple myeloma 1 year after autologous hematopoietic cell transplantation and lenalidomide maintenance are associated with long-term overall survival. *J. Clin. Oncol.* **42**, 2757–2768 (2024).
41. Derman, B. A. et al. Discontinuation of maintenance therapy in multiple myeloma guided by multimodal measurable residual disease negativity (MRD2STOP). *Blood Cancer J.* **14**, 170 (2024).
42. Terpos, E. et al. Sustained MRD negativity for three years can guide discontinuation of lenalidomide maintenance after ASCT in multiple myeloma: results from a prospective cohort study. *Blood* https://doi.org/10.1182/blood-2024-209826 (2024).
43. Radocha, J. et al. Urine immunofixation negativity is not necessary for complete response in intact immunoglobulin multiple myeloma: retrospective real-world confirmation. *Int. J. Lab. Hematol.* **43**, e244–e247 (2021).
44. Natsuhara, K. H. et al. Significance of the pee-value: relevance of 24-hour urine studies for patients with myeloma. *Leuk. Lymphoma* **64**, 1186–1193 (2023).
45. Mateos, M. V. et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J.* **10**, 102 (2020).
46. Schmidt, T. & Callander, N. Diagnosis and management of monoclonal gammopathy and smoldering multiple myeloma. *J. Natl Compr. Canc Netw.* **18**, 1720–1729 (2020).
47. Mateos, M. V. et al. Lenalidomide-dexamethasone versus observation in high-risk smoldering myeloma after 12 years of median follow-up time: a randomized, open-label study. *Eur. J. Cancer* **174**, 243–250 (2022).
48. Lonial, S. et al. Randomized trial of lenalidomide versus observation in smoldering multiple myeloma. *J. Clin. Oncol.* **38**, 1126–1137 (2020).
49. Landgren, C. O. et al. Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS). *Leukemia* **34**, 1840–1852 (2020).
50. Landgren, O. et al. Efficacy and safety of daratumumab in intermediate/high-risk smoldering multiple myeloma: final analysis of CENTAURUS. *Blood* **145**, 1658–1669 (2025).
51. Dimopoulos, M. A. et al. Daratumumab or active monitoring for high-risk smoldering multiple myeloma. *New Engl. J. Med.* **392**, 1777–1788 (2025).
52. Mateos, M. V. et al. Curative strategy for high-risk smoldering myeloma: carfilzomib, lenalidomide, and dexamethasone (KRd) followed by transplant, KRd consolidation, and Rd maintenance. *J. Clin. Oncol.* **42**, 3247–3256 (2024).
53. Kazandjian, D. et al. Carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance for prevention of symptomatic multiple myeloma in patients with high-risk smoldering myeloma: a phase 2 nonrandomized controlled trial. *JAMA Oncol.* **7**, 1678–1685 (2021).
54. Kumar, S. K. et al. Fixed duration therapy with daratumumab, carfilzomib, lenalidomide and dexamethasone for high risk smoldering multiple myeloma – results of the ascent trial [abstract]. *Blood* **140**, 1830–1832 (2022).
55. Sonneveld, P. et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **390**, 301–313 (2024).
56. Badros, A. et al. Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: the AURIGA study. *Blood* **145**, 300–310 (2025).
57. Mai, E. K. et al. Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy for transplant-eligible newly diagnosed multiple myeloma: final part 1 analysis of the GMMG-HD7 trial. *J. Clin. Oncol.* **43**, 1279–1288 (2025).
58. Moreau, P. et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. *Lancet Oncol.* **25**, 1003–1014 (2024).
59. Touzeau, C. et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with tandem transplant for high-risk newly diagnosed myeloma. *Blood* **143**, 2029–2036 (2024).
60. Costa, L. J. et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. *J. Clin. Oncol.* **40**, 2901–2912 (2022).
61. Leypoldt, L. B. et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone for the treatment of high-risk newly diagnosed multiple myeloma. *J. Clin. Oncol.* **42**, 26–37 (2024).
62. Perrot, A. et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone induction in newly diagnosed myeloma: analysis of the MIDAS trial. *Blood* https://doi.org/10.1182/blood.2024026230 (2025).
63. Gay, F. et al. Results of the phase III randomized Iskia trial: isatuximab-carfilzomib-lenalidomide-dexamethasone vs carfilzomib-lenalidomide-dexamethasone as pre-transplant induction and post-transplant consolidation in newly diagnosed multiple myeloma patients [abstract]. *Blood* **142**, 4 (2023).
64. Kauer, J. et al. Stem cell collection after lenalidomide, bortezomib and dexamethasone plus elotuzumab or isatuximab in newly diagnosed multiple myeloma patients: a single centre experience from the GMMG-HD6 and -HD7 trials. *BMC Cancer* **23**, 1132 (2023).
65. Mai, E. K. et al. Bortezomib before and after high-dose therapy in transplant-eligible patients with newly diagnosed multiple myeloma: long-term overall survival after more than 10 years of follow-up from the phase III HOVON-65/GMMG-HD4 trial. *Hemasphere* **8**, e70052 (2024).

66. Cook, G. et al. Ixazomib as consolidation and maintenance versus observation in patients with relapsed multiple myeloma eligible for salvage autologous stem-cell transplantation (Myeloma XII [ACCoRD]): interim analysis of a multicentre, open-label, randomised, phase 3 trial. *Lancet Haematol.* **11**, e816–e829 (2024).
67. Dimopoulos, M. A. et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* **393**, 253–264 (2019).
68. Rosinol, L. et al. Lenalidomide and dexamethasone maintenance with or without ixazomib, tailored by residual disease status in myeloma. *Blood* **142**, 1518–1528 (2023).
69. Krishnan, A. et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol.* **12**, 1195–1203 (2011).
70. Knop, S. et al. Allogeneic transplantation in multiple myeloma: long-term follow-up and cytogenetic subgroup analysis. *Leukemia* **33**, 2710–2719 (2019).
71. Kroger, N. et al. Autologous-allogeneic versus autologous tandem stem cell transplantation and maintenance therapy with thalidomide for multiple myeloma patients under 60 years of age: a prospective, phase II study. *Haematologica* **109**, 1469–1479 (2024).
72. Facon et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N. Engl. J. Med.* **380**, 2104–2115 (2019).
73. Mateos, M. V. et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N. Engl. J. Med.* **378**, 518–528 (2018).
74. Durie et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* **389**, 519–527 (2017).
75. Facon, T. et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **391**, 1597–1609 (2024).
76. Leleu, X. et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. *Nat. Med.* **30**, 2235–2241 (2024).
77. Usmani, S. Z. et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS study. *Nat. Med.* **31**, 1195–1202 (2025).
78. Mateos, M. V. et al. Bortezomib, melphalan, and prednisone with or without daratumumab in transplant-ineligible patients with newly diagnosed multiple myeloma (ALCYONE): final analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol.* **26**, 596–608 (2025).
79. Fried, L. P. et al. From bedside to bench: research agenda for frailty. *Sci. Aging Knowl. Env.* **2005**, pe24 (2005).
80. Cook, G., Larocca, A., Facon, T., Zweegman, S. & Engelhardt, M. Defining the vulnerable patient with myeloma – a frailty position paper of the European Myeloma Network. *Leukemia* **34**, 2285–2294 (2020).
81. Collard, R. M. et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *J. Am. Geriatr. Soc.* **60**, 1487–1492 (2012).
82. Engelhardt, M. et al. A concise revised myeloma comorbidity index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. *Haematologica* **102**, 910–921 (2017).
83. Cook, G., Pawlyn, C., Cairns, D. A. & Jackson, G. H. Defining FiTNEss for treatment for multiple myeloma. *Lancet Healthy Longev.* **3**, e729–e730 (2022).
84. Palumbo, A. et al. Geriatric assessment predicts survival and toxicities in elderlymyeloma patients: an International Myeloma Working Group report. *Blood* **125**, 2068–2074 (2015).
85. Haider, I. et al. Prevalence of geriatric impairments and frailty categorization among real-world patients with multiple myeloma: a prospective cohort study (MFRAIL). *Leuk. Lymphoma* **65**, 1167–1174 (2024).
86. Gahagan, A. et al. Evaluating concordance between International Myeloma Working Group (IMWG) frailty score and simplified frailty scale among older adults with multiple myeloma. *J. Geriatr. Oncol.* **15**, 102051 (2024).
87. Sim, S. et al. The importance of frailty assessment in multiple myeloma: a position statement from the Myeloma Scientific Advisory Group to Myeloma Australia. *Intern. Med. J.* **53**, 819–824 (2023).
88. Facon, T. et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia* **34**, 224–233 (2020).
89. Cook, G. et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance risk profile): a development and validation study. *Lancet Haematol.* **6**, e154–e166 (2019).
90. Cook, G. et al. IMWG frailty score-adjusted therapy delivery reduces the early mortality risk in newly diagnosed TNE multiple myeloma: results of the UK Myeloma ResearchAlliance (UK-MRA) myeloma XIV fitness trial [abstract]. *Blood* **144**, 673 (2024).
91. Facon, T. et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. *Leukemia* **36**, 1066–1077 (2022).
92. Manier, S. et al. The IFM2017-03 phase 3 trial: a dexamethasone sparing-regimen with daratumumab and lenalidomide for frail patients with newly-diagnosed multiple myeloma [abstract]. *Blood* **144**, 774–775 (2024).
93. Askeland, F. B. et al. Isatuximab, bortezomib, lenalidomide, and limited dexamethasone in patients with transplant-ineligible multiple myeloma (REST): a multicentre, single-arm, phase 2 trial. *Lancet Haematol.* **12**, e120–e127 (2025).
94. Hungria, V. et al. Belantamab mafodotin, bortezomib, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **391**, 393–407 (2024).
95. Hungria, V. et al. Belantamab mafodotin, bortezomib, and dexamethasone vs daratumumab, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma: overall survival analysis and updated efficacy outcomes of the phase 3 dreamm-7 trial [abstract]. *Blood* **144**, 772 (2024).
96. San-Miguel, J. et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N. Engl. J. Med.* **389**, 335–347 (2023).
97. Popat, R. et al. Ciltacabtagene autoleucel (Cilta-cel) vs standard of care (SoC) in patients with lenalidomide (Len)-refractory multiple myeloma (MM) after 1-3 lines of therapy: minimal residual disease (MRD) negativity in the phase 3 Cartitude-4 trial [abstract]. *Blood* **144**, 1032 (2024).
98. Dimopoulos, M. A. et al. Belantamab mafodotin, pomalidomide, and dexamethasone in multiple myeloma. *N. Engl. J. Med.* **391**, 408–421 (2024).
99. Trudel, S. et al. Results from the randomized phase 3 DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in relapsed/refractory multiple myeloma (RRMM) [abstract]. *J. Clin. Oncol.* **42**, LBA105 (2024).
100. Grosicki, S. et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet* **396**, 1563–1573 (2020).
101. Mateos, M. V. et al. Impact of prior treatment on selinexor, bortezomib, dexamethasone outcomes in patients with relapsed/refractory multiple myeloma: extended follow-up subgroup analysis of the BOSTON trial. *Eur. J. Haematol.* **113**, 242–252 (2024).
102. Gavriatopoulou, M. et al. Integrated safety profile of selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. *Leukemia* **34**, 2430–2440 (2020).
103. Perrot, A. et al. An open-label phase 2 study treating patients with first or second relapse of multiple myeloma with carfilzomib, pomalidomide, and dexamethasone (KPd): SELECT study. *Leuk. Lymphoma* **65**, 833–842 (2024).
104. Sonneveld, P. et al. Carfilzomib, pomalidomide, and dexamethasone as second-line therapy for lenalidomide-refractory multiple myeloma. *Hemasphere* **6**, e786 (2022).
105. Cavo, M. et al. Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Hematol.* **7**, e456–e468 (2020).
106. Dimopoulos, M. A. et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol.* **22**, 801–812 (2021).
107. Dimopoulos, M. A. et al. Subcutaneous daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma (APOLLO): extended follow up of an open-label, randomised, multicentre, phase 3 trial. *Lancet Haematol.* **10**, e813–e824 (2023).
108. Kastritis, E. et al. Management and outcomes of anti-CD38 refractory patients: the impact of retreatment and of subsequent therapies. *Hemasphere* **7**, e975 (2023).
109. Perez de Acha, O. et al. CD38 antibody re-treatment in daratumumab-refractory multiple myeloma after time on other therapies. *Blood Adv.* **7**, 6430–6440 (2023).
110. Usmani, S. Z. et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. *Blood Adv.* **7**, 3739–3748 (2023).
111. Terpos, E. et al. Efficacy and safety of daratumumab with ixazomib and dexamethasone in lenalidomide-exposed patients after one prior line of therapy: final results of the phase 2 study DARIA. *Am. J. Hematol.* **99**, 396–407 (2024).
112. Martino, E. A. et al. Outcomes and prognostic indicators in daratumumab-refractory multiple myeloma: a multicenter real-world study of elotuzumab, pomalidomide, and dexamethasone in 247 patients. *ESMO Open.* **10**, 104084 (2025).
113. Parrondo, R. D. et al. Phase II trial of elotuzumab with pomalidomide and dexamethasone for daratumumab-refractory multiple myeloma. *Blood Cancer J.* **14**, 152 (2024).
114. Berdeja, J. G. et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet* **398**, 314–324 (2021).
115. Martin, T. et al. Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. *J. Clin. Oncol.* **41**, 1265–1274 (2023).
116. Munshi, N. C. et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N. Engl. J. Med.* **384**, 705–716 (2021).
117. Rodriguez-Otero, P. et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N. Engl. J. Med.* **388**, 1002–1014 (2023).
118. Ailawadhi, S. et al. Ide-cel vs standard regimens in triple-class-exposed relapsed and refractory multiple myeloma: updated KarMMa-3 analyses. *Blood* **144**, 2389–2401 (2024).
119. Moreau, P. et al. Teclistamab in relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **387**, 495–505 (2022).
120. Garfall, A. L. et al. Long-term follow-up from the phase 1/2 MajesTEC-1 trial of teclistamab in patients with relapsed/refractory multiple myeloma [abstract]. *J. Clin. Oncol.* **42**, 7540 (2024).
121. Lesokhin, A. M. et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat. Med.* **29**, 2259–2267 (2023).

122. Prince, H. M. et al. MagnetisMM-3: long-term update and efficacy and safety of less frequent dosing of elranatamab in patients with relapsed or refractory multiple myeloma [abstract]. *Blood* **144**, 4738 (2024).
123. Bumma, N. et al. Linvoseltamab for treatment of relapsed/refractory multiple myeloma. *J. Clin. Oncol.* **42**, 2702–2712 (2024).
124. Chari, A. et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N. Engl. J. Med.* **387**, 2232–2244 (2022).
125. Chari, A. et al. Safety and activity of talquetamab in patients with relapsed or refractory multiple myeloma (MonumenTAL-1): a multicentre, open-label, phase 1–2 study. *Lancet Haematol.* **12**, e269–e281 (2025).
126. Richardson, P. G. et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. *J. Clin. Oncol.* **39**, 757–767 (2021).
127. Schjesvold, F. H. et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study. *Lancet Haematol.* **9**, e98–e110 (2022).
128. Costa, L. J. et al. International Myeloma Working Group Immunotherapy Committee recommendation on sequencing immunotherapy for treatment of multiple myeloma. *Leukemia* **39**, 543–554 (2025).
129. Ferreri, C. J. et al. Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy. *Blood Cancer J.* **13**, 117 (2023).
130. Cohen, A. D. et al. Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to other BCMA-targeting agents. *Blood* **141**, 219–230 (2023).
131. Merz, M. et al. Bispecific antibodies targeting BCMA or GPRC5D are highly effective in relapsed myeloma after CAR T-cell therapy. *Blood Cancer J.* **14**, 214 (2024).
132. Nooka, A. K. et al. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma (RRMM) and prior B-cell maturation antigen (BCMA)-directed therapies: a pooled analysis from MagnetisMM studies [abstract]. *J. Clin. Oncol.* **41**, 8008 (2023).
133. Touzeau, C. et al. Efficacy and safety of teclistamab in patients with relapsed/refractory multiple myeloma after BCMA-targeting therapies. *Blood* **144**, 2375–2388 (2024).
134. Terpos, E., Ntanasis-Stathopoulos, I. & Dimopoulos, M. A. Myeloma bone disease: from biology findings to treatment approaches. *Blood* **133**, 1534–1539 (2019).
135. Terpos, E. et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. *Lancet Oncol.* **22**, e119–e130 (2021).
136. Terpos, E. et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica* **100**, 1254–1266 (2015).
137. Anderson, K. et al. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* **36**, 812–818 (2018).
138. Raje, N. et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* **19**, 370–381 (2018).
139. Terpos, E. et al. Denosumab compared with zoledronic acid on PFS in multiple myeloma: exploratory results of an international phase 3 study. *Blood Adv.* **5**, 725–736 (2021).
140. Terpos, E. et al. Evaluation of the safety and efficacy of denosumab in patients with multiple myeloma and severe renal impairment; results from an IMWG Bone Subcommittee study [abstract]. *Blood* **144**, 3343–3344 (2024).
141. Larocca, A. et al. The impact of response on bone-directed therapy in patients with multiple myeloma. *Blood* **122**, 2974–2977 (2013).
142. Lund, T. et al. In multiple myeloma, monthly treatment with zoledronic acid beyond two years offers sustained protection against progressive bone disease. *Blood Cancer J.* **14**, 65 (2024).
143. Katodritou, E. et al. Update on the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia of multiple myeloma and lymphoma. *Cancer Treat. Rev.* **35**, 738–743 (2009).
144. Terpos, E. et al. Management of complications in multiple myeloma. *Semin. Hematol.* **46**, 176–189 (2009).
145. Blimark, C. et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica* **100**, 107–113 (2015).
146. Raje, N. S. et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. *Lancet Haematol.* **9**, e143–e161 (2022).
147. Ludwig, H. et al. Recommendations for vaccination in multiple myeloma: a consensus of the European Myeloma Network. *Leukemia* **35**, 31–44 (2021).
148. Raje, N. et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. *Blood Cancer J.* **13**, 116 (2023).
149. Drayson, M. T. et al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet Oncol.* **20**, 1760–1772 (2019).
150. Dimopoulos, M. A. et al. Management of multiple myeloma-related renal impairment: recommendations from the International Myeloma Working Group. *Lancet Oncol.* **24**, e293–e311 (2023).
151. Mikhael, J. et al. Lenalidomide and dexamethasone in patients with relapsed multiple myeloma and impaired renal function: PrE1003, a PrECOG study. *Blood Cancer J.* **8**, 86 (2018).
152. Dimopoulos, M. A. et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. *Ann. Oncol.* **25**, 195–200 (2014).
153. Cejalvo, M. J. et al. Single-agent daratumumab in patients with relapsed and refractory multiple myeloma requiring dialysis: results of a Spanish retrospective, multicentre study. *Br. J. Haematol.* **190**, e289–e292 (2020).
154. Kastritis, E. et al. Prospective phase 2 trial of daratumumab with dexamethasone in patients with relapsed/refractory multiple myeloma and severe renal impairment or on dialysis: the DARE study. *Am. J. Hematol.* **98**, E226–E229 (2023).
155. Wasch, R. et al. Safe and successful CAR T-cell therapy targeting BCMA in a multiple myeloma patient requiring hemodialysis. *Ann. Hematol.* **102**, 1269–1270 (2023).
156. Joiner, L., Bal, S., Godby, K. N. & Costa, L. J. Teclistamab in patients with multiple myeloma and impaired renal function. *Am. J. Hematol.* **98**, E322–E324 (2023).
157. Lebreton, P. et al. Teclistamab for relapsed refractory multiple myeloma patients on dialysis. *Br. J. Haematol.* **205**, 2077–2079 (2024).
158. Lonial, S. et al. Management of belantamab mafodotin-associated corneal events in patients with relapsed or refractory multiple myeloma (RRMM). *Blood Cancer J.* **11**, 103 (2021).
159. Terpos, E. et al. Belantamab mafodotin plus lenalidomide/dexamethasone in newly diagnosed intermediate-fit and frail multiple myeloma patients: long-term efficacy and safety from the phase 1/2 BELARD clinical trial [abstract]. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2025.43.16_suppl.7512 (2025).
160. Li, J. et al. CD3 bispecific antibody-induced cytokine release is dispensable for cytotoxic T cell activity. *Sci. Transl. Med.* **11**, eaax8861 (2019).
161. Ludwig, H. et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. *Lancet Oncol.* **24**, e255–e269 (2023).
162. Han, M. W. et al. Incidence of immune effector cell-associated neurotoxicity among patients treated with CAR T-cell therapy for hematologic malignancies: systematic review and meta-analysis. *Front. Neurol.* **15**, 1392831 (2024).
163. Brudno, J. N. & Kochenderfer, J. N. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. *Blood Rev.* **34**, 45–55 (2019).
164. Santomasso, B. D. et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov.* **8**, 958–971 (2018).
165. Van Oekelen, O. et al. Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. *Nat. Med.* **27**, 2099–2103 (2021).
166. Morris, E. C., Neelapu, S. S., Giavridis, T. & Sadelain, M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat. Rev. Immunol.* **22**, 85–96 (2022).
167. Costa, B. A. et al. Prognostic impact of corticosteroid and tocilizumab use following chimeric antigen receptor T-cell therapy for multiple myeloma. *Blood Cancer J.* **14**, 84 (2024).
168. Jatiani, S. S. et al. Myeloma CAR-T CRS management with IL-1R antagonist anakinra. *Clin. Lymphoma Myeloma Leuk.* **20**, 632–636.e1 (2020).
169. Kumar, S. K. et al. NCCN guidelines insights: multiple myeloma, version 1.2025. *J. Natl Compr. Canc Netw.* **23**, 132–140 (2025).
170. Gross, P. A. et al. Purpose of quality standards for infectious diseases. *Clin. Infect. Dis.* **18**, 421 (1994).

Author contributions

M.A.D. and E.T. researched data for the article. M.A.D., E.T., M.Bo., P.M., M-V.M., S.Z., F.S., E.Z., M.M., H.L., H.E., J.S.-M. and P.S. contributed substantially to discussion of the content. E.T. and G.C. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

M.A.D. has received honoraria as a consultant, or member of the advisory board or speaker's bureau for Amgen, AstraZeneca, Beigene, BMS, GSK, Janssen, Menarini, Regeneron, Sanofi, Swixx and Takeda. E.T. has been a member of the advisory board for Amgen, AstraZeneca, BMS, EUSA Pharma, GSK, Johnson & Johnson, Menarini, Pfizer, Sanofi and Takeda; has received honoraria from Amgen, Antengene, AstraZeneca, BMS, EUSA Pharma, Forus, GSK, Johnson & Johnson, Menarini, Novartis, Pfizer, Sanofi, Swixx and Takeda; research funding from Amgen, GSK, Johnson & Johnson, Sanofi and Takeda; and travel expenses from Takeda. M.Bo. has received honoraria from AbbVie, Amgen, BMS, Celgene, Janssen, Novartis and Sanofi; has been a member of the advisory board for GSK and Janssen; and has received research funding from Amgen, BMS, Celgene, Janssen, Mundipharma, Novartis and Sanofi. P.M. has received honoraria as a member of the advisory board for Abbvie, Amgen, BMS, Johnson & Johnson, Pfizer, Sanofi and Takeda. M.-V.M. has received honoraria as a member of the advisory board for Abbvie, Amgen, BMS, GSK, Johnson & Johnson, Kite, Menarini, Oncopeptides, Pfizer, Roche and Sanofi. S.Z. has received research support from Janssen and Takeda; and has been a member of the advisory board for BMS, Janssen, Sanofi and Oncopeptides, for which she received no personal funding. G.C. has received research funding from BMS, Johnson & Johnson and Takeda, BMS; acted as a paid consultant for AstraZeneca, Johnson & Johnson, Menarini and Pfizer; and acted as a member of the speaker's bureau for Johnson & Johnson, Menarini and Pfizer. M.E. has been a member of the advisory board for BMS, GSK, Janssen, Menarini, Oncopeptides, Pfizer, Sanofi; and received honoraria from Abbvie, BMS, GSK, Janssen, Menarini, Oncopeptides, Pfizer and Sanofi. M.D. has received honoraria as a member of the advisory board or speaker's bureau for AbbVie, Amgen, BMS, GSK, Johnson & Johnson, Menarini, Pfizer, Roche and Sanofi; and works for an institution that receives grants from Johnson & Johnson. R.H. has been a consultant or member of the advisory board for Abbvie, Amgen, BMS, Celgene, Janssen, Novartis, PharmaMar and Takeda; has received honoraria from Amgen, BMS, Celgene, Janssen, PharmaMar and Takeda; and has received research funding from Amgen, BMS, Celgene, Janssen, Novartis and Takeda. F.S. has

been a consultant for AbbVie, BMS, Celgene, GSK, Johnson & Johnson, Oncopeptides, Sanofi and Takeda; has received honoraria from AbbVie, Amgen, BMS, Celgene, Daiichi–Sankyo, GSK, Johnson & Johnson, Novartis, Oncopeptides, Sanofi, Schain, SkylineDx, Skylite and Takeda; and has received research funding from Celgene, GSK, Johnson & Johnson, Oncopeptides, Sanofi and Targovax. F.G. has been a member of the advisory board for Abbvie, Amgen, AstraZeneca, BMS, Celgene, GSK, Janssen, Kite, Pfizer, Regeneron, Roche Pharma, Sanofi and Takeda; and has received honoraria from Abbvie, BMS, Celgene, Janssen, Menarini, Pfizer, Regeneron, Roche, Sanofi and Takeda. S.M. has been a consultant for Abbvie, Adaptive Biotechnology, Amgen, BMS, Celgene, GSK, Janssen, Kite, Novartis, Pfizer, Regeneron, Roche, Sanofi and Takeda. K.C.W. has had an advisory role or provided expert testimony for Abbvie, Adaptive, Amgen, AstraZeneca, Beigene, BMS, Celgene, GSK, Janssen, Karyopharm, Menarini, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi and Takeda; has received honoraria from Abbvie, Adaptive, Amgen, AstraZeneca, Beigene, BMS, Celgene, GSK, Janssen, Karyopharm, Menarini, Novartis, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi and Takeda; and has received research funding from Abbvie, Amgen, BMS, Celgene, GSK, Janssen and Sanofi. M.K. has had an advisory role or provided expert testimony for Abbvie, Adaptive, BMS, Celgene, GSK, Janssen, Pfizer, Regeneron, Roche, Sanofi and Takeda; and works for an institution that has received research support from BMS, Celgene and Janssen. N.W.C.J.v.d.D. has received research support from Amgen, BMS, Celgene, Cellectis, Janssen and Novartis; and has been a member of the advisory board for AbbVie, Adaptive, Amgen, Bayer, BMS, Celgene, Janssen, Kite, Merck, Novartis, Pfizer, Roche, Sanofi, Servier and Takeda; all these roles have been paid to his institution. E.Z. has received honoraria as a member of the advisory board for Amgen, BMS, GSK, Janssen, Menarini, Pfizer, Oncopeptides and Sanofi. P.R.-O. has received honoraria as a member of the advisory board participation or as a consultant for Abbvie, AstraZeneca, BMS, GSK, H3Biomedicine, Johnson & Johnson, Pfizer, Regeneron, Roche and Sanofi; has been a member of the speaker's bureau for Abbvie, BMS, GSK, Johnson & Johnson, Pfizer and Sanofi; and has received travel grants from Pfizer. A.P. has received honoraria as a member of the advisory board for Abbvie, Amgen, BMS, GSK, Johnson & Johnson, Menarini, Pfizer and Sanofi. C.D. has received honoraria for advisory roles for Amgen, BMS, GSK, Janssen, Pfizer and Sanofi. J.B. has had an advisory role or provided expert testimony for Amgen, Amicus, Galenika, Johnson & Johnson, Pfizer and Takeda; and has received honoraria from Amgen, Amicus, Galenika, Hemofarm, Johnson & Johnson, Pfizer and Takeda. D.D. has received honoraria from Amgen, BMS, GSK, Janssen, Pfizer and Sanofi; and research funding from Amgen, Celgene and Janssen. C.T. has received honoraria from Abbvie, Amgen, BMS, GSK, Janssen, Pfizer and Sanofi; and research support from Abbvie, GSK, Sanofi and Takeda. M.Be. has been a member of the advisory board for BMS, GSK, Janssen, Menarini, Pfizer, Sanofi and Takeda; a member of the speaker's bureau for BMS, GSK, Menarini, Pfizer, Sanofi and Takeda; and has received research support from Janssen. M.S.R. has had an advisory role for Abbvie, BMS, GSK, Janssen, Karyopharm, Menarini, Oncopeptides, Pfizer and Sanofi; has received honoraria from Abbvie, BMS, GSK, Janssen, Karyopharm, Menarini, Novartis, Oncopeptides, Pfizer and Sanofi; and has received research funding from BMS, Celgene, Janssen and Sanofi. M.C. has been a consultant or had an advisory role for AbbVie, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Menarini and Sanofi; and has received honoraria from Amgen, AbbVie, BMS, Celgene, GSK, Karyopharm, Janssen, Menarini and Sanofi. M.M. has been a consultant or had an advisory role for Janssen, Jazz and Sanofi; has received grants or research support from Janssen and Sanofi; has been a member of the speaker's bureau for Janssen, Jazz and Sanofi; and has received honoraria from Amgen, Janssen, Novartis, Pfizer, Sanofi and Takeda. A.S. has been a consultant for BMS, Celltrion, Haemalogix, Janssen and Rheumagen; a member of the speaker's bureau for BMS, Janssen, Pfizer, Sanofi and Thermofisher; a member of the advisory board for Antengene, BMS, Roche, Haemalogix, Janssen, Pfizer and Sanofi; received honoraria from AbbVie, Antengene, BMS, Roche, Haemalogix, Janssen, Pfizer, Sanofi and Thermofisher; and received research funding from AbbVie, Antengene, Haemalogix and Janssen. H.L. has been a consultant or a member of the speaker's bureau for Amgen, BMS, Celgene, Janssen, Pfizer, Sanofi and Takeda; and received research funding from Amgen and Sanofi. H.E. has been a consultant or had advisory roles for Amgen, BMS, Celgene, GSK, Janssen, Novartis, Sanofi and Takeda; has received research funding from Amgen, BMS, Celgene, GSK, Janssen and Sanofi; and honoraria and travel support from Amgen, BMS, Celgene, GSK, Janssen, Novartis, Sanofi and Takeda. J.S.-M. has been a consultant for Abbvie, Amgen, BMS, Celgene, Roche, GSK, HaemaLogiX, Janssen, KaryoPharm, Merck, Novartis, Pfizer, Regeneron, Sanofi, SecuraBio and Takeda. P.S. has been a consultant or had advisory roles for BMS, Celgene, GSK, Janssen and Sanofi; has received research funding from Amgen, BMS, Celgene, Janssen, Karyopharm and Sanofi; and honoraria from BMS, Celgene, GSK, Janssen and Sanofi. E.L. declares no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41571-025-01041-x.

Peer review information *Nature Reviews Clinical Oncology* thanks R. Fonseca, K. Kim and O. Landgren for their contribution to the peer review of this work.

Meletios A. Dimopoulos[1,36], Evangelos Terpos[1,36] ✉, Mario Boccadoro[2], Philippe Moreau[3], María-Victoria Mateos[4], Sonja Zweegman[5], Gordon Cook[6,7], Monika Engelhardt[8], Michel Delforge[9], Roman Hajek[10,11], Fredrik Schjesvold[12], Francesca Gay[13], Salomon Manier[14,15], Katja C. Weisel[16], Martin Kaiser[17,18], Niels W. C. J. van de Donk[5], Elena Zamagni[19,20], Paula Rodriguez-Otero[21], Aurore Perrot[22], Christoph Driessen[23], Jelena Bila[24], Edward Laane[25], Dominik Dytfeld[26], Cyrille Touzeau[3], Meral Beksac[27], Marc S. Raab[28], Michele Cavo[20], Mohamad Mohty[29,30], Andrew Spencer[31,32], Heinz Ludwig[33], Hermann Einsele[34], Jesus San-Miguel[21] & Pieter Sonneveld[35]

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece. [2]Department of Biotechnology and Health Science, University of Torino, Turin, Italy. [3]Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France. [4]University Hospital of Salamanca, IBSAL, Cancer Research Center, Salamanca, Spain. [5]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands. [6]Leeds Institute of Clinical Trial Research, University of Leeds, Leeds, UK. [7]Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK. [8]Department of Hematology and Oncology, Interdisciplinary Cancer Center and Comprehensive Cancer Center Freiburg, University of Freiburg, Faculty of Freiburg, Freiburg, Germany. [9]Department of Hematology, University Hospital Leuven, Leuven, Belgium. [10]Department of Hemato-Oncology, University Hospital Ostrava, Ostrava, Czech Republic. [11]Faculty of Medicine, University Hospital Ostrava, Ostrava, Czech Republic. [12]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway. [13]University Division of Hematology, AOU Città della Salute e della Scienza di Torino, Turin, Italy. [14]Department of Hematology, Lille University Hospital, Lille, France. [15]INSERM UMR-S1277 and CNRS UMR9020, Lille, France. [16]Department of Oncology, Hematology and BMT, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [17]Department of Haematology, The Royal Marsden Hospital, London, UK. [18]Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK. [19]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy. [20]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy. [21]Clinica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain. [22]Université de Toulouse, Centre Hospitalo-Universitaire, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France. [23]Department of Medical Oncology and Hematology, HOCH Health Ostchweiz, St. Gallen, Switzerland. [24]Clinic of Hematology, University Clinical Center of Serbia, Medical Faculty, University of Belgrade, Belgrade, Serbia. [25]Hematology-Oncology Clinic, Tartu University, Tartu, Estonia. [26]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznań, Poland. [27]Ankara Liv Hospital, Istinye University, Ankara, Turkey.

[28]Heidelberg Myeloma Center, Department of Internal Medicine V, Heidelberg University Hospital and Faculty, Heidelberg, Germany. [29]Centre de Recherche Saint-Antoine INSERM UMRs938, Sorbonne Université, Paris, France. [30]Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France. [31]Department of Malignant Hematology and Stem Cell Transplantation, The Alfred Hospital, Melbourne, Victoria, Australia. [32]Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia. [33]Wilhelminen Cancer Research Institute, First Department of Medicine, Center for Oncology, Hematology, and Palliative Care, Clinic Ottakring, Vienna, Austria. [34]Department of Internal Medicine II, University Hospital Wurzburg, Wurzburg, Germany. [35]Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, Netherlands. [36]These authors contributed equally: Meletios A. Dimopoulos, Evangelos Terpos.