swiss medical weekly

Review article: Biomedical intelligence | Published 23 October 2025 | doi:https://doi.org/10.57187/s.4252
Cite this as: Swiss Med Wkly. 2025;155:4252

Updated recommendations for diagnosis and treatment of multiple myeloma in Switzerland

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Summary

Multiple myeloma is a malignant disease characterised by the clonal proliferation of plasma cells. Since the last update of the Swiss recommendations for the diagnosis and treatment of multiple myeloma in 2019, the therapeutic landscape has evolved significantly, with the development of new monoclonal antibodies, novel combination therapies, and the introduction of T-cell-redirecting treatments such as bispecific antibodies and CAR T-cell therapy. This article summarises the current diagnostic procedures and therapeutic recommendations in Switzerland.

Introduction

Since the last update of the recommendations for the diagnosis and treatment of multiple myeloma in Switzerland in 2019 [1], therapies have advanced significantly. Key developments include the use of highly active monoclonal antibodies in first-line treatments and the introduction of immunotherapeutic strategies, such as bispecific antibodies (bsAbs) and chimeric antigen receptor (CAR) T-cell therapies, particularly at relapse or progression. This update provides an overview of current diagnostic tests and highlights innovations in multiple myeloma treatment.

Biology

Multiple myeloma is part of a broader group of plasma cell disorders, including monoclonal gammopathy of undetermined significance (MGUS), smouldering myeloma (SM), and other rarer conditions, such as solitary plasmacytoma, monoclonal gammopathy of clinical significance (MGCS), POEMS syndrome, and light chain (AL) amyloidosis. These disorders are characterised by the accumulation of clonal plasma cells, primarily in the bone marrow, leading to the overproduction of dysfunctional immunoglobulins. The malignant transformation of plasma cells involves genetic changes, mostly early translocations of the immunoglobulin heavy chain locus (IgH) on chromosome 14 or hyperdiploidy, followed by secondary mutations in genes such as *KRAS, NRAS, BRAF*, or *TP53* [2].

Diagnosis

The diagnosis of multiple myeloma is based on clinical findings, laboratory tests (especially the detection of monoclonal protein in the urine or blood), imaging techniques, and bone marrow examination. The diagnostic criteria have not changed since the last update in 2019. Multiple myeloma diagnosis requires ≥10% clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma plus the presence of one or more myeloma-defining events or biomarkers of malignancy – the so-called SLiM-CRAB criteria. The SLiM-CRAB criteria are as follows: ≥60% clonal plasma cells in the bone marrow (S); an involved-to-uninvolved serum free light chain (FLC) ratio of ≥100, provided the involved free light chain level is ≥100 mg/l (Li); >1 focal lesion of ≥5 mm on MRI studies (M); and the presence of hypercalcaemia (C), renal insufficiency (R), anaemia (A), and ≥1 osteolytic lesions on skeletal radiography, CT, or FDG-PET/CT (B). Treatment is indi-

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cated when multiple myeloma is confirmed by the presence of at least one SLiM-CRAB criterion.

Imaging

Imaging techniques are essential for the diagnosis, staging, and monitoring of disease progression in multiple myeloma. Whole-body low-dose computed tomography (WBLD-CT) remains the preferred diagnostic method for detecting osteolytic lesions in plasma cell disorders with high sensitivity [3]. Magnetic resonance imaging (MRI) is highly sensitive for detecting bone marrow infiltration by myeloma cells. A whole-body MRI in patients showing ≥10% clonal bone marrow plasma cell infiltration in the absence of other myeloma-defining criteria is mandatory to rule out active myeloma. MRI is the preferred diagnostic tool for evaluating spinal or soft tissue compression and is particularly useful in special cases, such as during pregnancy.

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is increasingly used in clinical studies for staging and response assessment. If available, FDG-PET/CT can be used in clinical practice, as it has a similar sensitivity to MRI in detecting bone lesions [4] and is particularly effective at identifying active extramedullary myeloma lesions. It may also play a key role in response assessment and minimal residual disease (MRD) evaluation in the future. However, as of 2024, FDG-PET/CT is not yet recommended for routine use in Switzerland.

Genetic testing

Genetic testing of multiple myeloma cells provides prognostic insights into newly diagnosed multiple myeloma. Common methods include cytogenetics and fluorescence in situ hybridisation (FISH) to detect chromosomal abnormalities. Additional methods, such as array-comparative genomic hybridisation (aCGH) and next-generation sequencing, can identify deletions, amplifications, and point mutations. As of 2024, the recommendations in Switzerland [1] have not changed. Swiss recommendations advise that fluorescence in situ hybridisation should be performed at diagnosis to identify high-risk translocations, including t(4;14), del17p, t(14;16), t(14;20), 1q gain, and 1p deletion [5]. Additionally, the presence of the t(11;14) translocation should be determined, as it has predictive potential for the use of BCL-2 inhibitors such as venetoclax [6]. Next-generation sequencing is recommended only in advanced stages when standard treatment options are exhausted and targeted treatment approaches, such as *BRAF* inhibition, are considered.

Supportive care

Because prolonged survival and repeated therapies lead to severe immunosuppression, effective treatments for multiple myeloma require adequate supportive measures. The following section discusses the most important prophylactic approaches.

Antimicrobial prophylaxis

Patients with multiple myeloma are highly immunosuppressed because of the disease itself and repeated anti-myeloma therapies, with the highest risk of infection occurring within the first three months after starting treatment. For most three- and four-drug combination therapies and T-cell-engaging therapies, antibiotic prophylaxis with trimethoprim/sulfamethoxazole should be considered to prevent *Pneumocystis jirovecii* pneumonia, especially when using higher doses of corticosteroids [7]. Additional prophylactic use of levofloxacin can help reduce severe infections and mortality during the first three months of therapy [8]; however, the potential development of antibiotic resistance should be considered. Antiviral prophylaxis is recommended for most combination therapies, especially those involving proteasome inhibitors and monoclonal and bispecific antibodies (bsAbs), to prevent herpes infections/reactivation (e.g. herpes simplex and varicella zoster virus), with valacyclovir commonly used in Switzerland.

Vaccinations are crucial in reducing infection risk, particularly in immunocompromised patients. Early immunisation, preferably before the initiation of therapy when clinically feasible, is strongly recommended. According to the Swiss vaccination guidelines by the Bundesamt für Gesundheit (BAG) and the Eidgenössische Kommission für Impffragen (EKIF), patients with multiple myeloma should receive vaccinations against pneumococcal disease, varicella zoster virus, seasonal influenza, and COVID-19 [9]. However, the effectiveness of vaccination during ongoing therapy and in patients with hypogammaglobinaemia remains uncertain.

All patients with multiple myeloma should be screened for immunoglobulin deficiency at diagnosis and throughout the course of the disease. In IgG-secreting myeloma, diagnosing secondary immunoglobulin deficiency can be challenging. Therefore, assessing the polyclonal immunoglobulin component (by subtracting the M spike from the total IgG level) or analysing immunoglobulin subclasses may be beneficial. With advanced disease, especially after several multiple myeloma treatment lines, the risk of developing secondary hypogammaglobinaemia increases. Generally, in patients with hypogammaglobinaemia (IgG <4 g/l), intravenous immunoglobulin substitution should only be initiated if recurrent severe infections occur [10]. However, when using T-cell-engaging therapies in heavily pretreated patients with multiple myeloma, the risk of hypogammaglobinaemia and lethal infections is very high. It has been shown that severe infections can be reduced by primary prophylactic administration of intravenous immunoglobulin [11]. Thus, continuous monitoring of total IgG levels, and their substitution if their count drops below 4 g/l, is recommended in patients treated with T-cell-engaging therapies.

Thrombosis prophylaxis

The recommendations for thrombosis prophylaxis remain unchanged from the previous update. Patients with active multiple myeloma are at increased risk of venous thromboembolism due to both the disease and its treatments, particularly when high-dose steroids, immunomodulators, and chemotherapy (doxorubicin or multi-agent chemotherapy)

are used [12]. Various scores are available to assess the risk of thromboembolism, such as SAVED [13] and IMPEDE [14]. Most patients can be effectively managed with low-dose aspirin. Those at higher risk for venous thromboembolism may require low-molecular-weight heparin or direct oral anticoagulants. However, the latter are off-label, and insurance approval is required.

Osteoprotection

Patients with multiple myeloma are prone to bone loss and skeletal events due to bone marrow infiltration by plasma cells, osteolytic bone changes, and high-dose steroid therapy. Zoledronic acid, a bisphosphonate, is recommended for all patients with newly diagnosed multiple myeloma, regardless of whether osteolytic lesions are present. Zoledronic acid should be administered monthly for at least 12 months, with extended intervals recommended after achieving a very good partial response [15]. A dental examination is required before initiating zoledronic acid because of the increased risk of osteonecrosis of the jaw. Additionally, renal function should be regularly monitored, with dose adjustments made accordingly.

Denosumab, a nuclear factor-kappa B ligand (RANKL) inhibitor, is equally effective in preventing skeletal events in patients with multiple myeloma [16] and does not cause kidney damage, although it is associated with an increased risk of hypocalcaemia. Abrupt discontinuation of RANKL inhibitors can lead to a rebound phenomenon; therefore, a single dose of zoledronic acid should be administered within six months of the last dose of denosumab. However, denosumab is not approved for multiple myeloma treatment in Switzerland and requires cost approval.

Treatment options for patients with multiple myeloma

The therapeutic landscape for multiple myeloma has evolved substantially in recent years, both in initial and later-line therapies. Various agents can be used alone or in combination. The active substance classes include chemotherapy, proteasome inhibitors, immunomodulators, monoclonal antibodies, CAR T cells, and bispecific antibodies. Additional active substances, not yet approved/reimbursed in Switzerland, include BCL-2 and XPO1 inhibitors, the antibody-drug conjugate belantamab mafodotin, as well as Cereblon E3 Ligase Modulatory Drugs (CelMods), which are likely to be incorporated into clinical practice in the near future. Table 1 provides an overview of the active substances used in multiple myeloma treatment.

At the time of diagnosis, patients are typically classified as either young and fit (transplant-eligible) or not eligible for transplant (transplant non-eligible). Eligibility for high-dose chemotherapy is not standardised but is generally based on age (under 70 years), the absence of significant comorbidities (e.g. heart dysfunction), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. All patients under 70 years should be evaluated for transplant eligibility, though biological fitness is more important than chronological age. Additionally, the patient's fitness should be regularly reassessed during treatment to ensure that those with disease-related impairments are not overlooked. However, kidney impairment *per se* is not a contraindication for high-dose chemotherapy.

First-line treatment for transplant-eligible patients

Standard induction therapy typically includes at least a triplet regimen. In Switzerland, the VRd regimen [17] – combining an immunomodulator, a proteasome inhibitor, and dexamethasone – has been widely used in recent years. However, recent advancements have introduced quadruplet regimens that add an anti-CD38 antibody (daratumumab or isatuximab). These regimens result in improved progression-free survival (PFS) and higher rates of sustained MRD-negative complete remission (CR) compared to three-drug regimens [18–22], albeit with slightly increased toxicity (e.g. neutropenia and infections) and higher costs.

Two pivotal trials, the Phase II GRIFFIN and Phase III PERSEUS trials, have demonstrated improved outcomes with the addition of daratumumab to the VRd backbone, with significant differences in their administration. The PERSEUS regimen administers lenalidomide on days 1–21 over a 4-week cycle, contrasting with the GRIFFIN regimen, which administers the drug from days 1–14 over a 3-week cycle. In both trials, bortezomib follows, as in the VRd regimen, the originally published and approved biweekly schedule on days 1, 4, 8, and 11. Moreover, daratumumab is administered subcutaneously in the PERSEUS trial, a method favoured in daily clinical practice for its convenience. The PERSEUS protocol employs a significantly higher dose of dexamethasone – a total calculated dose of 1920 mg over six cycles compared to 720 mg in the GRIFFIN trial. Because of concerns regarding the high steroid dosage, most clinicians prefer lower dexametha-

Table 1:
Overview of active substances that can be used in the treatment of multiple myeloma. The non-approved/reimbursed drugs for multiple myeloma (so far) are marked with *.

Cytotoxic agents	Adriblastin*
	Bendamustin*
	Carboplatin*, cisplatin*
	Cyclophosphamide*
	Etoposide*
	Melphalan
Proteasome inhibitors	Bortezomib
	Carfilzomib
	Ixazomib
Immunomodulatory drugs	Thalidomide*
	Lenalidomide
	Pomalidomide
	Iberdomide*
	Mezigdomide*
Monoclonal antibodies	Daratumumab
	Isatuximab
	Elotuzumab
CAR T	Idecabtagene-vicleucel
	Ciltacabtagene-autoleucel
Bispecific antibodies	Teclistamab
	Elranatamab
	Talquetamab
	Cevostamab*
Others	Selinexor*
	Venetoclax*
	Belantamab mafodotin*
	Panobinostat*

sone doses, suggesting potential dexamethasone modifications according to the GRIFFIN study.

In summary, the three-drug VRd regimen remains a reasonable first-line option for patients with standard-risk disease. However, due to prolonged progression-free survival and doubling of MRD-negative complete remission rates with the addition of an anti-CD38 antibody, a quadruplet regimen is highly recommended for patients with standard-risk disease. Because progression-free survival and minimal residual disease benefits are observed across all cytogenetic risk subgroups, including patients with revised high-risk disease and those with gain(1q21) or amp(1q21), a four-drug regimen is also strongly recommended for this high-risk patient population. A daratumumab-containing quadruplet-based induction regimen has been approved by the FDA; however, neither daratumumab nor isatuximab is approved for this indication in Switzerland yet.

In all the landmark studies, bortezomib was administered twice a week. This dosing schedule can lead to a quicker therapeutic response but is also associated with a higher incidence of peripheral neuropathy. When a rapid response is critical, initiating treatment with biweekly dosing may help achieve faster reductions in paraprotein levels. However, weekly dosing has become more common from the start of treatment because it is convenient for patients and has a more favourable side effect profile.

Stem cell mobilisation and collection

Following 4–6 cycles of induction therapy, high-dose chemotherapy with melphalan followed by autologous stem cell transplant (HD-Mel-ASCT) remains the recommended consolidation therapy for patients with newly diagnosed transplant-eligible multiple myeloma [18, 23–25]. Mobilisation of peripheral blood stem cells is crucial and can be achieved using granulocyte-colony stimulating factor (G-CSF) alone or in combination with other agents, such as plerixafor or cyclophosphamide. In Switzerland, mobilisation chemotherapy with vinorelbine and G-CSF is commonly used [26, 27], though alternatives such as gemcitabine may be considered in cases of pre-existing polyneuropathy [28, 29]. The target number of CD34+ cells during the stem cell collection depends on the patient's condition and treatment plan. In general, the goal is to collect at least 4.0 x 10^6 per kg body weight CD34+ cells (i.e. enough stem cells for two transplants), and this can typically be achieved using G-CSF and plerixafor. Induction regimens containing anti-CD38 antibodies decrease CD34+ cell yield [30]. Therefore, when using an anti-CD38 antibody-containing regimen in induction, early stem cell collection (e.g. after three cycles) is recommended.

ASCT consolidation

With each advancement in induction therapy, the value of HD-Mel-ASCT as consolidation therapy has been challenged. Nevertheless, randomised trials have continued to show a benefit for the transplant arm. HD-Mel-ASCT resulted in a significant benefit in progression-free survival in the IFM2009 [31] and DETERMINATION [17] trials, which used VRd induction and consolidation followed by lenalidomide maintenance. However, HD-Mel-ASCT was not linked to an overall survival (OS) benefit. Recent pivotal first-line clinical trials incorporated HD-Mel-ASCT in their standard and experimental arms [18, 32, 33]. Trials challenging the role of HD-Mel-ASCT in the context of quadruplet induction, or comparing it with the early application of CAR T-cell therapy, are currently recruiting.

As of today, and awaiting the readout of the above-mentioned and other ongoing trials, HD-Mel-ASCT after triplet or quadruplet induction is still considered the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma in Switzerland.

Role of tandem transplant

Tandem HD-Mel-ASCT has been incorporated into first-line treatment for patients with high-risk disease based on data from the EMN02/HOVON95 Phase III trial, which showed a progression-free survival and overall survival benefit in the whole study population, mainly driven by patients with high-risk disease, especially those with del17p [34]. This strategy has been challenged by the results of the Phase III BMT CTN 0702 trial using primarily a VRd-based induction regimen for up to 12 months, followed by randomisation to tandem HD-Mel-ASCT, single HD-Mel-ASCT combined with VRd consolidation, or HD-Mel-ASCT with a lenalidomide consolidation. No significant difference was observed in progression-free survival between the three consolidation arms in the primary intention-to-treat analysis [35]. However, a post hoc per-protocol analysis – conducted because a substantial proportion of patients did not receive the assigned second transplant – showed a progression-free survival benefit for a second HD-Mel-ASCT, which was again mainly driven by patients with high-risk disease [36]. It should be noted that in patients receiving modern quadruplet induction therapy, the value of tandem transplantation is even less clear.

In summary, tandem-HD-Mel-ASCT is not mandatory but can be considered for patients with high-risk or ultra-high-risk disease on an individualised, case-by-case basis. Key factors that should be considered include cytogenetic risk, suboptimal response to induction therapy, deepening of response after the first HD-Mel-ASCT course, excellent patient fitness, and good tolerability of the initial HD-Mel-ASCT course. However, the definition of high-risk multiple myeloma is evolving, and an international consensus is awaited to clarify which patients should be classified as functionally high-risk in the context of current highly active multiple myeloma treatments.

Maintenance therapy

Lenalidomide remains the standard-of-care maintenance therapy and is typically recommended until disease progression or unacceptable toxicity occurs [17, 37].

Both the GRIFFIN and PERSEUS trials have incorporated daratumumab alongside lenalidomide for maintenance over at least two years. In the PERSEUS study, patients in the daratumumab-containing treatment arm who achieved sustained MRD negativity for at least one year were allowed to discontinue daratumumab after at least 24 months of maintenance treatment, whereas the drug was continued until disease progression in patients who did not achieve sustained MRD negativity.

Recently, long-term follow-up of the CASSIOPEIA trial demonstrated a progression-free survival benefit for daratumumab in the maintenance setting, even in patients who had received daratumumab (dara) during induction (Dara-VTd + daratumumab vs Dara-VTd + observation) [38]. The Phase 3 AURIGA trial showed a deepening of remission and a significant prolongation of progression-free survival with the addition of daratumumab during maintenance [39]. Thus, considering the maturing data from the PERSEUS trial showing relevant deepening of response under daratumumab-containing maintenance [40], the incorporation of an anti-CD38 antibody as part of maintenance is currently being studied further in prospective trials (e.g. the GMMG-HD7 (NCT0361773) and S1803 DRAMMATIC (NCT04071457) trials).

Particularly for patients with high-risk disease, attempts have been made to incorporate a proteasome inhibitor in maintenance treatment based on the class-inherent favourable impact on certain high-risk cytogenetic features. Bortezomib has a role as a single agent, especially in high-risk patients, based on the HOVON65/GMMG-HD4 trial [41]. Lenalidomide as monotherapy has shown benefit in patients with high-risk disease in the UK Myeloma XI trial, depending on the type and co-occurrence of high-risk cytogenetic markers [42]. No prospective randomised trial data are currently available regarding the additional value of bortezomib to the lenalidomide backbone. However, retrospective data on a risk-adapted intensified maintenance approach after VRd induction and HD-Mel-ASCT showed a higher-than-expected progression-free survival of 40.3 months for a subgroup of patients with high-risk disease treated with combined immunomodulator and proteasome inhibitor maintenance, predominantly with VRd, comparing favourably with historic controls [43].

For the second-generation proteasome inhibitor carfilzomib, data from the FORTE trial showed a progression-free survival benefit for carfilzomib + lenalidomide vs lenalidomide alone [44]. Likewise, an unplanned interim analysis of the ATLAS trial showed a progression-free survival benefit after 33.8 months of follow-up for intensified maintenance treatment with carfilzomib, lenalidomide, and dexamethasone versus lenalidomide alone [45]. The progression-free survival benefit was significantly longer in both trials for the whole study population, whereas it did not reach statistical significance when focusing on the high-risk group, mainly due to the small sample size.

In summary, lenalidomide maintenance treatment remains the approved standard-of-care maintenance treatment, and a proteasome inhibitor can be used in high-risk situations. However, proteasome inhibitor maintenance therapy has not been approved in Switzerland. The role of anti-CD38 antibodies in maintenance therapy, including optimal duration, remains uncertain, and the results of ongoing studies are awaited. Since sustained MRD-negative complete remission is a strong predictor of improved outcomes, MRD-informed treatment decisions may provide a strategy for ending maintenance in certain subsets of patients with multiple myeloma patients in the future.

Treatment of non-transplant-eligible patients

Frailty assessment

All non-transplant-eligible patients should undergo a frailty assessment at diagnosis and before each line of therapy to tailor treatment strategies, minimise the risk of toxicities, and reduce the likelihood of early treatment discontinuation. Several scoring systems have been proposed for assessing frailty in non-transplant-eligible patients; the most commonly used tool is the International Myeloma Working Group (IMWG) frailty score, which predicts the risk of toxicity and mortality following first-line treatment. An online calculator for this score is available at http://www.myelomafrailtyscorecalculator.net. A simplified version, known as the simplified IMWG frailty score, incorporates age, the Charlson comorbidity index, and ECOG status to provide an easier assessment. Additionally, cognitive function (e.g. the Mini-Cog test), physical function (e.g. the Up and Go test), and nutritional status should be assessed to facilitate early interventions aimed at improving overall health, such as home support, physical therapy, and nutritional counselling.

First-line therapy in newly diagnosed non-transplant-eligible patients

For upfront therapy in non-transplant-eligible patients, the most effective regimen should be used, as approximately 60% of these patients may not receive subsequent lines of therapy. Additionally, the first-line treatment offers the best opportunity to achieve durable disease control and improve survival [46]. Currently, first-line therapy is continued until disease progression or intolerable toxicity. However, particularly in older patients, in whom maintaining quality of life is a key treatment goal, treatment should be individualised. This may include de-escalating treatment through dose reduction, omitting certain agents, extending intervals, implementing treatment breaks, or even discontinuing therapy when appropriate.

Several Phase III clinical trials have evaluated drug combinations for newly diagnosed non-transplant-eligible patients. The most relevant regimens for the Swiss landscape are discussed below.

The most commonly used first-line regimen for non-transplant-eligible patients is the triple combination of daratumumab, lenalidomide, and dexamethasone (Dara-Rd), based on the Phase III MAIA study [47]. This study compared Dara-Rd with Rd alone, demonstrating improved progression-free survival at 30 months (70.6% vs 55.6%) and a higher complete response (CR) rate (47.6% vs 24.9%). After a median follow-up of 89.3 months, an overall survival benefit was shown for Dara-Rd (90.3 months compared to 64.1 months) [48]. Regarding toxicity, the triple combination is associated with increased rates of pneumonia and neutropenia [47]. The combination Dara-Rd is administered until progression and is approved in Switzerland.

The results of the SWOG-S0777 trial led to the approval of the VRd combination [49] . This randomised Phase III trial compared VRd with Rd and demonstrated a survival advantage for VRd (median overall survival not reached vs 69 months). Unlike the MAIA trial, the overall survival

benefit was not statistically significant in the subgroup of patients aged ≥65 years [50]. For patients classified as frail, a dose-reduced regimen known as VRd-lite is available, providing a feasible alternative [51].

In cases of lenalidomide intolerance, the combination of daratumumab with bortezomib, melphalan, and prednisone (Dara-VMP) is another effective regimen. The Phase III ALCYONE study demonstrated a progression-free survival benefit for Dara-VMP at 18 months (71.6% vs 50.2%) and a significant overall survival difference after 74.4 months of follow-up (82.7 months vs 53.6 months) [52]. Notably, patients given Dara-VMP received continuous maintenance with daratumumab, whereas those in the VMP arm had time-limited therapy.

Post hoc frailty sub-analyses of the MAIA and ALCYONE trials showed that patients classified as frail experienced higher toxicity rates and shorter survival compared to non-frail patients. However, the addition of daratumumab improved quality of life and led to similar or lower discontinuation rates compared to the control groups [53]. As a result, triplet regimens, particularly those including an anti-CD38 antibody, are recommended over doublets, even for patients with frailty.

Recent data from the Phase III IMROZ, BENEFIT, and CEPHEUS trials indicate that quadruplet combinations (Isa-VRd or Dara-VRd) are feasible and more effective than triplet combinations in non-transplant-eligible patients. In the IMROZ trial, which compared Isa-VRd to VRd, the estimated progression-free survival at 60 months was 63.2% in the Isa-VRd group versus 45.2% in the VRd group [54]. Similarly, the BENEFIT trial showed that adding weekly bortezomib to the Isa-Rd combination significantly improved 18-month MRD negativity rates (53% vs 26%) [55]. The CEPHEUS trial, which compared Dara-VRd to VRd, demonstrated a higher MRD-negativity rate for the quadruplet regimen (60.9% vs 39.4%) after a median follow-up of 58.7 months. Additionally, the estimated 54-month progression-free survival, a secondary endpoint, was significantly improved with the addition of the anti-CD38 antibody, consistent with findings from isatuximab studies (86.1% vs 49.5%) [56].

Ongoing trials are still evaluating quadruplet regimens in non-transplant-eligible patients, and these combinations will become part of first-line therapies in both transplant-eligible and non-transplant-eligible patients. However, clinical trials for newly diagnosed non-transplant-eligible patients often enrol fitter individuals than those typically seen in real-world settings. Additionally, quadruplet regimens are more toxic, especially in older or frailer patients. As a result, it is not yet clear which non-transplant-eligible patients should be treated with the quadruplet regimen. Consequently, recommendations for patients classified as frail are largely based on expert opinions and extrapolations. Several approaches have been suggested to tailor first-line therapy according to the IMWG Frailty Score at diagnosis (Table 2). Dose adaptations for patients classified as intermediate-fit and frail are recommended to minimise early discontinuation and mortality, with the possibility of dose escalation if treatment is well tolerated or if patient fitness improves.

Use of steroids in older patients

Most multiple myeloma clinical trials recommend reducing corticosteroid dosing by half (20 mg instead of 40 mg per week) for older patients. However, this population remains particularly vulnerable to complications from steroids, including infections, diabetes mellitus, agitation/delirium, and osteopenia. Recent studies suggest that shortening dexamethasone exposure in patients with frailty maintains similar efficacy while offering a better safety profile [57]. For patients classified as intermediate-fit and frail, early discontinuation of dexamethasone may be a good strategy. This approach is currently under investigation in the French IFM 2017-03 trial, which has shown promising preliminary results [58].

Relapsed/refractory multiple myeloma (rrMM)

Relapse criteria

Relapsed multiple myeloma refers to disease progression following an initial response to previous therapy. Biochemical relapse typically occurs before clinical progression. The definition of progressive disease remains unchanged [59]. Refractoriness to a drug is defined as disease progression observed during or within 60 days of stopping systemic anti-myeloma treatment [59].

According to the 2021 International Myeloma Working Group (IMWG) recommendations, initiating the next line of treatment before the development of new myeloma-related organ dysfunction, specifically before any CRAB criteria are met, is advised. However, this does not mandate

Table 2:
Expert consensus recommendations for dose adaption for non-transplant-eligible patients.

IMWG Frailty score		**Fit patients**	**Intermediate-fit patients**	**Patients with frailty**
Score		**Score 0**	**Score 1**	**Score ≥2**
Aim		**Reduction of multiple myeloma clone**	**Balance efficacy and safety**	**Quality of life**
First-line treatment		Dara-Rd or Isa-VRd*	Dara-Rd	Dara-Rd
		VRd	VRd-lite	VRd-lite
		Dara-VMP	Dara-VMP	Rd
				Dara monotherapy*
Dose reduction	Bortezomib	1.3 mg/m^2 weekly	1 mg/m^2 weekly	1 mg/m^2 weekly
	Lenalidomide	25 mg	15 mg	10 mg
	Dexamethasone	20 mg weekly	20 mg weekly	8–10 mg weekly

Dara: daratumumab; d: dexamethasone; R: lenalidomide; V: bortezomib; IMWG: International Myeloma Working Group.

* indicates that the therapy (combination) is not approved/reimbursed in Switzerland.

immediate changes to therapy in cases of biochemical relapse only. The initiation of re-treatment is recommended in cases of either clinical relapse or relevant biochemical relapse, as defined in Table 3, according to the recommendations of an International Myeloma Workshop Consensus Panel [59].

Before starting a new therapy, a re-evaluation of the bone marrow is recommended, particularly in patients initially diagnosed with standard-risk disease, to identify any new high-risk cytogenetic features. If not assessed at initial diagnosis, predictive molecular markers such as the t(11;14) translocation should be tested at relapse, as venetoclax may be a potential therapeutic option.

Treatment strategies at first relapse

The selection of the next line of treatment depends mainly on prior drug exposure and refractoriness. Key considerations include the duration and effectiveness of previous therapy, the kinetics of the first relapse, patient-specific factors such as side effects (e.g. polyneuropathy), comorbidities, and patient preferences. The general rule for second-line treatment is to use the most potent available regimen and select drug classes not previously used. Triple-drug regimens are superior to doublets, and the new T-cell-engaging therapies outperform even triplet regimens in the relapsed/refractory setting. Treatment decisions are influenced by the patient's risk classification, which may differ between those with high-risk aggressive disease and those with standard-risk disease. Achieving MRD-negativity strongly correlates with better outcomes in both previously untreated patients and those with relapsed/refractory multiple myeloma [60]. Due to the current trend of intensive induction therapy using quadruplet regimens in frontline therapy, most patients will be exposed to three drug classes and be single- or double-class refractory at first relapse. This will influence future treatment strategies.

Almost all transplant-eligible patients will have received maintenance therapy with lenalidomide after HD-Mel-ASCT. As a result, lenalidomide refractoriness is very common at first relapse. In the future, an increasing number of patients may also be double-refractory to lenalidomide and anti-CD38 antibodies. The decision algorithm shown in Figure 1 is mainly based on lenalidomide and anti-CD38 refractoriness.

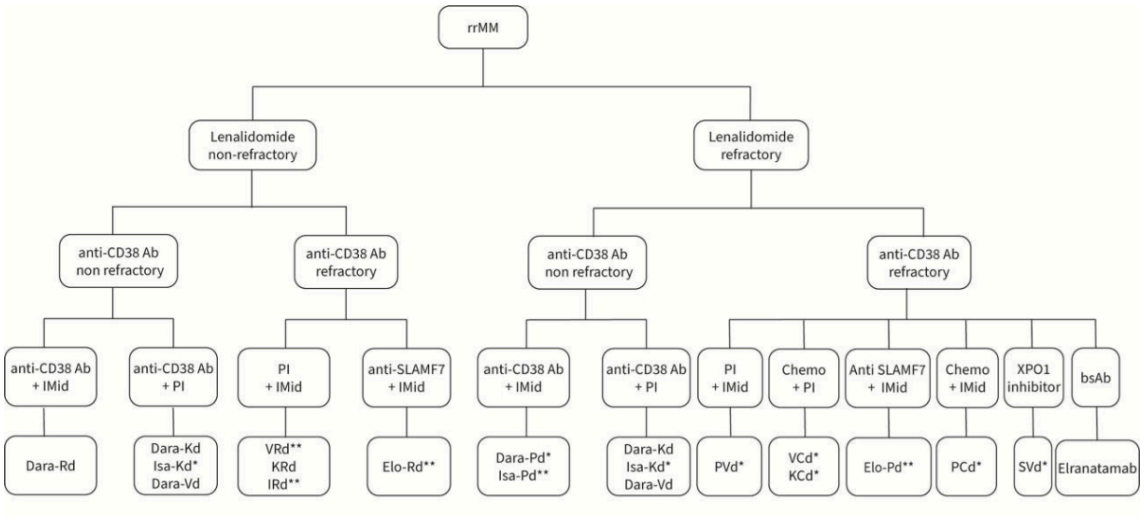
Table 3:
Suggested criteria to initiate or modify multiple myeloma therapy. Relevant biochemical relapse and clinical relapse are distinguished. Relevant biochemical relapse is sufficient to warrant a change in therapy (no clinical criteria are required). The clinical relapse criteria only apply if they can be attributed to the myeloma.

Clinical relapse/direct indicators of end-organ damage	New soft tissue plasmacytoma or bone lesion
	Definite increase in the size of existing plasmacytomas or bone lesions*
	Hypercalcaemia >2.875 mmol/l
	Decrease in haemoglobin of more than 20 g/l or to less than 100 g/l
	Rise in serum creatinine by ≥177 mmol/l
	Hyperviscosity
Relevant paraprotein relapse	Doubling of serum M-protein (2 measurements ≤2 months)
	Absolute serum M-Protein ≥10 g/l
	Increase in urine M-protein ≥500 mg/24 hours
	Increase of involved FLC level ≥200 mg/l with an abnormal FLC ratio (2 measurements ≤2 months)

M-protein: monoclonal protein; FLC: free light chain.

* Defined as an increase of >50% and at least 1 cm, as measured serially by the sum of the products of the cross-diameters of the measurable lesion, adapted from [59].

Figure 1: Treatment options after first relapse. The primary decision criterion is based on lenalidomide or anti-CD38 refractoriness. * Not approved in Switzerland. ** Approved in Switzerland, but not for use in second-line therapy. Ab: antibody; bsAB: bispecific antibody; C: cyclophosphamide; Dara: daratumumab; d: dexamethasone; Elo: elotuzumab; IMiD: immunomodulatory agent; Isa: isatuximab. I: ixazomib; K: carfilzomib; PI: proteasome inhibitor; P: pomalidomide; R: lenalidomide; rrMM: relapsed/refractory multiple myeloma; S: Selinexor; SLAMF7: Signalling Lymphocyte Activation Molecule F7; V: bortezomib; XPO1: exportin 1.



Anti-CD38-sensitive disease

For patients who are refractory to lenalidomide but sensitive to anti-CD38 antibodies, an anti-CD38 antibody should be included in second-line treatment. In the now rare cases in which the disease is sensitive to both lenalidomide and anti-CD38 antibodies, the preferred option is Dara-Rd, which achieves an mPFS of 55 months [61]. For patients with lenalidomide-refractory disease, various combinations of anti-CD38 antibodies with proteasome inhibitors (such as Dara-Vd, Dara-Kd, or Isa-Kd) and the second-generation immunomodulator pomalidomide (Dara-Pd or Isa-Pd) are approved.

In the CASTOR study, the Dara-Vd regimen (daratumumab, bortezomib, and dexamethasone) was compared to Vd alone. In the experimental arm, daratumumab maintenance was continued until disease progression after eight cycles of Dara-Vd, unlike in the control arm, in which no maintenance was administered. The addition of the anti-CD38 antibody led to a significant overall survival benefit with longer follow-up (49.6 months vs 38.5 months) [62], although the progression-free survival observed with Dara-Vd in this population is relatively short [63].

The effects of the second-generation proteasome inhibitor carfilzomib combined with an anti-CD38 antibody were examined in the CANDOR (daratumumab) [64] and IKEMA (isatuximab) [65] studies. These regimens demonstrated significant progression-free survival benefits of 28.6 and 35.7 months, respectively. Administering carfilzomib weekly instead of biweekly improves convenience for patients while maintaining or even enhancing its effectiveness [66]. However, patients must be selected carefully because of the potential cardiac toxicities of carfilzomib, and it is important to note that Isa-Kd, unlike Dara-Kd, has not yet been approved.

The combination of pomalidomide with anti-CD38 antibodies was evaluated in the APOLLO (daratumumab) [67] and ICARIA (isatuximab) [68] trials. These regimens are generally well tolerated and are viable options for patients with lenalidomide-refractory disease, although the progression-free survival of 18 months is lower than that of the carfilzomib-containing regimens in cross-trial comparisons, likely due to a higher percentage of patients with lenalidomide-refractory disease accrued in the later trials compared to the anti-CD38-containing regimens.

Lenalidomide-sensitive, anti-CD38-refractory disease

For patients who are sensitive to lenalidomide but refractory to anti-CD38 antibodies, the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) is an approved option. The Phase III ASPIRE trial demonstrated an mPFS of 26.3 months with this regimen [69].

Double-refractory disease to lenalidomide and anti-CD38 antibody

In patients refractory to both lenalidomide and anti-CD38 antibodies, several triple combinations – including pomalidomide with the Signalling Lymphocyte Activation Molecule F7 (SLAMF7) antibody elotuzumab or first- or second-generation proteasome inhibitors (bortezomib or carfilzomib) – have been tested.

The Phase III ELOQUENT-3 trial demonstrated a benefit of adding elotuzumab to pomalidomide and dexamethasone (EPd) [70]. This combination is preferably used after an interval from prior anti-CD38 antibody therapy to restore NK cell activity and is approved after at least two lines of therapy, including lenalidomide and at least one proteasome inhibitor.

In the Phase III OPTIMISMM trial, pomalidomide combined with bortezomib and dexamethasone (PVd) was compared to bortezomib and dexamethasone alone. Treatment with PVd resulted in a significant improvement in progression-free survival (11.2 vs 7.1 months) [71].

In patients who have not received HD-Mel-ASCT as frontline therapy or who have achieved a very long remission after HD-Mel-ASCT, HD-Mel-ASCT may be an option, although supporting data are limited and somewhat contradictory [72, 73].

T-cell-engaging therapies

Despite significant advancements in treatment options, multiple myeloma remains an incurable disease, with most patients experiencing relapses. The need for novel therapeutic approaches has led to the development of T-cell-engaging therapies, which harness the patient's immune system to target and eliminate malignant plasma cells.

Among the most promising T-cell-engaging strategies are CAR T-cell therapy and bispecific antibodies. CAR T-cell therapy involves the genetic modification of a patient's T cells to express a CAR, which recognises specific antigens on multiple myeloma cells, such as BCMA. Once reinfused, these CAR T cells bind to their target antigen, leading to T-cell activation and proliferation and the subsequent destruction of malignant cells.

Bispecific antibodies are engineered to simultaneously bind to a T-cell receptor, typically CD3, and a tumour-specific antigen, such as BCMA or GPRC5D, on multiple myeloma cells. This dual binding brings T cells into close proximity to cancer cells, facilitating their activation and targeted killing. Unlike CAR T-cell therapy, which requires *ex vivo* manipulation, bispecific antibodies can be administered directly to the patient, offering a more readily accessible therapeutic option. Both CAR T-cell therapy and bispecific antibodies have shown remarkable efficacy in clinical trials, particularly in patients with relapsed/refractory multiple myeloma in whom other treatment options have been exhausted. However, these therapies are not without challenges; cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infectious complications are the most common adverse effects.

BCMA-directed bispecific antibodies

The two BCMA-directed bispecific antibodies, elranatamab (MagnestiMM-3) [74] and teclistamab (MajesTEC-1) [75], are approved based on early Phase II data, with an overall response rate (ORR) of around 60%. Both agents have the same target antigen (BCMA), route of administration, and safety profiles, and they show similar efficacy. However, dosing protocols and patient demographics vary in their registration trials. Notably, MagnetisMM-3 included a higher proportion of patients with triple-refrac-

tory (97%) and penta-refractory (42%) disease, achieving a mPFS of 17.2 months [74], compared to 11.4 months for teclistamab in the MajesTEC-1 study [75]. In Switzerland, teclistamab is approved and reimbursed for triple-class-exposed relapsed/refractory multiple myeloma after at least three lines of prior therapy, whereas elranatamab has approval and reimbursement for triple-class relapsed/refractory multiple myeloma irrespective of the number of prior lines of therapy.

Cytokine release syndrome is common, with most patients receiving elranatamab or teclistamab experiencing grade 1-2 cytokine release syndrome. Inpatient step-up dosing is recommended for both, with elranatamab requiring inpatient monitoring during the first two dose levels and teclistamab during the first three, which may affect treatment logistics due to hospital bed availability constraints.

Infection is a major complication, occurring in approximately 60–70% of patients treated with BCMA-directed bispecific antibodies, with 40% experiencing severe (grade 3 or 4) infections. This is attributed to prolonged B-cell immunodeficiency, hypogammaglobinaemia, neutropenia, and cumulative immune system damage from prior therapies.

Besides intravenous immunoglobulin substitution, prolonging the dosing interval of bispecific antibodies is an important strategy to manage infection risk. The MajesTEC-1 study allowed responding patients to switch from weekly to fortnightly dosing. Most patients who switched (68.7%) continued with responses of two or more years. Notably, spacing out the dosing reduced the rate of grade ≥3 infections (15.6% vs 33.3%) [75].

GPRC5D-directed bispecific antibody talquetamab

Talquetamab is approved in Switzerland and is a valuable therapeutic option for patients with triple-class-exposed relapsed/refractory multiple myeloma after three lines of therapy, possibly capable of bypassing resistance mechanisms developed against BCMA-directed therapies. Talquetamab showed a 71% overall response rate in patients previously treated with CAR T-cell therapy or antibody-drug conjugates [76]. While talquetamab is associated with lower infection rates compared to BCMA-directed bispecific antibodies in cross-trial comparisons, a consistent pattern of dermatological and oral adverse events, including skin and nail disorders, xerostomia, dysgeusia, and significant weight loss, has been reported [76]. Because of its distinct antigen target, talquetamab is occasionally used in clinical practice as a bridging therapy before BCMA-directed CAR T-cell therapy, though randomised data are lacking. In light of the potentially burdensome side effects, we generally recommend the use of talquetamab after BCMA-directed therapy in patients who are not intended to undergo subsequent BCMA-directed CAR T-cell treatment.

CAR T-cell therapy

Currently, two BCMA-directed CAR T-cell products are approved in Switzerland: idecabtagene vicleucel (ide-cel) since 2021 and ciltacabtagene autoleucel (cilta-cel) since 2022. Ide-cel is approved for third- and fourth-line treatment based on the KarMMa-3 study [77], whereas cilta-cel is approved for fourth-line treatment based on the CARTITUDE-1 study [78] and as third-line therapy in patients with lenalidomide-refractory triple-class-exposed disease, based on the data from the CARTITUDE-4 study (s. below) [79].

Indirect comparisons between these two products must be made cautiously because of differences in patient populations and study design. However, the data suggest that cilta-cel offers a higher overall response rate, improved progression-free survival, and better overall survival, with similar rates of cytokine release syndrome but with a later onset. In addition, a significant safety difference for patients treated with cilta-cel is the occurrence of late-onset neurotoxicity, particularly movement and neurocognitive treatment-emergent adverse events, which have been reduced following preventive measures. Recommended strategies include reducing tumour burden using bridging therapy, aggressive treatment of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, and extended monitoring beyond day 100.

The Phase III CARTITUDE-4 trial compared cilta-cel to conventional triplets (Dara-Pd or PVd) in patients with lenalidomide-refractory multiple myeloma who had received only one to three prior lines of therapy [79]. After a median follow-up of 15.9 months, cilta-cel showed superior response and progression-free survival at 12 months (75.9% vs 48.6%), and in an updated analysis, it even showed an improved 34-month overall survival (76.4% vs 63.8%) [80], leading to expanded approval for use in relapsed/refractory multiple myeloma.

Sequencing of bispecific antibodies and CAR T-cell therapies

Determining the optimal sequence of bispecific antibodies and CAR T cells is an ongoing challenge. Preliminary data suggest that using CAR T-cell therapy first and reserving bispecific antibodies for later lines of therapy may be more effective, as response rates decline more when CAR T cells are administered after bispecific antibodies rather than vice versa. For example, in cohort C of the CARTITUDE-2 study, only 60% of patients previously treated with bispecific antibodies responded to cilta-cel [81], compared to 97% in the initial cohort [78]. In contrast, in a pooled analysis of the MagnetisMM studies, elranatamab following CAR T-cell therapy showed an overall response rate of 52.8% [82], compared to 61% in the MagnetisMM-3 study [74]. Real-world data indicate similar response rates for ide-cel following bispecific antibodies compared to no prior bispecific antibodies treatment (86% and 88%, respectively), although the patient numbers in this study were low [83]. Future studies analysing the sequencing of bispecific antibodies and CAR T-cell therapies targeting different antigens will provide further insights into the optimal sequencing of these T-cell-activating therapies.

In summary, T-cell-engaging therapies are highly effective new therapeutic options for relapsed/refractory multiple myeloma. However, although generally well-tolerated, specific side effects such as cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and long-lasting immunosuppression must be considered.

Other active agents: venetoclax, selinexor, and belantamab mafodotin

Venetoclax, a BCL-2 inhibitor, was evaluated in combination with bortezomib and dexamethasone (VenVd) or daratumumab and dexamethasone and resulted in a high overall response rate. However, venetoclax combination regimens should be used exclusively in multiple myeloma patients harbouring the t(11;14) translocation [6, 84].

Selinexor is a selective inhibitor of nuclear export factor 1 (XPO1). In the single-arm STORM trial, selinexor combined with dexamethasone showed moderate anti-myeloma activity in a heavily pretreated patient population (median of seven previous lines of therapy), achieving a partial response rate of 26% and an mPFS of 4.4 months [85]. In the randomised BOSTON trial, adding selinexor to bortezomib and dexamethasone resulted in a significant progression-free survival benefit compared to bortezomib and dexamethasone alone (13.9 months vs 9.5 months) [86]. Selinexor is an effective treatment option in specific situations; however, particular attention should be given to gastrointestinal toxicities, especially nausea and vomiting. Selinexor was recently approved after four lines of therapy.

Belantamab mafodotin is the first and currently the only antibody-drug conjugate for multiple myeloma treatment. It consists of a humanised monoclonal IgG1 antibody against BCMA, conjugated to the microtubule inhibitor monomethyl auristatin F [87]. Disappointing results from the DREAMM-3 study, in which single-agent belantamab mafodotin failed to show superior activity over pomalidomide plus dexamethasone (Pd) [88], dampened enthusiasm for the drug and led to US and Swiss market withdrawal. However, two recently published Phase III trials have renewed interest in the drug. In the DREAMM-7 trial, patients with relapsed multiple myeloma, after receiving at least one line of therapy, experienced significantly better mPFS and overall survival with belantamab mafodotin combined with bortezomib and dexamethasone (BVd) compared to Dara-Vd (36.6 months vs 13.4 months) [89]. In the DREAMM-8 study, belantamab mafodotin combined with Pd (BPd) was superior to bortezomib plus Pd, with a 12-month estimated progression-free survival of 71% versus 51% in lenalidomide-exposed patients with at least one prior line of therapy [90]. While ocular toxicity remains a common issue, dose modifications, treatment interval prolongation, and supportive care measures may help mitigate this limitation. Belantamab mafodotin is currently not approved in Switzerland, but an EAP is available. The different treatment options after second line are summarised in figure 2. Due to the lack of data, the optimal sequencing of the available drugs is unknown.

Take-home messages

Overview

- Although multiple myeloma remains incurable for most patients, survival rates have significantly improved in recent years. Achieving optimal disease control typically requires long-term, continuous treatment with appropriate sequencing of effective drugs.

First-line treatment options

- For transplant-eligible patients, the quadruple combination Dara-VRd is considered the preferred first-line regimen.
- In fit, non-transplant-eligible patients, Dara-Rd or Isa-VRd (if available / approved) is the preferred option.

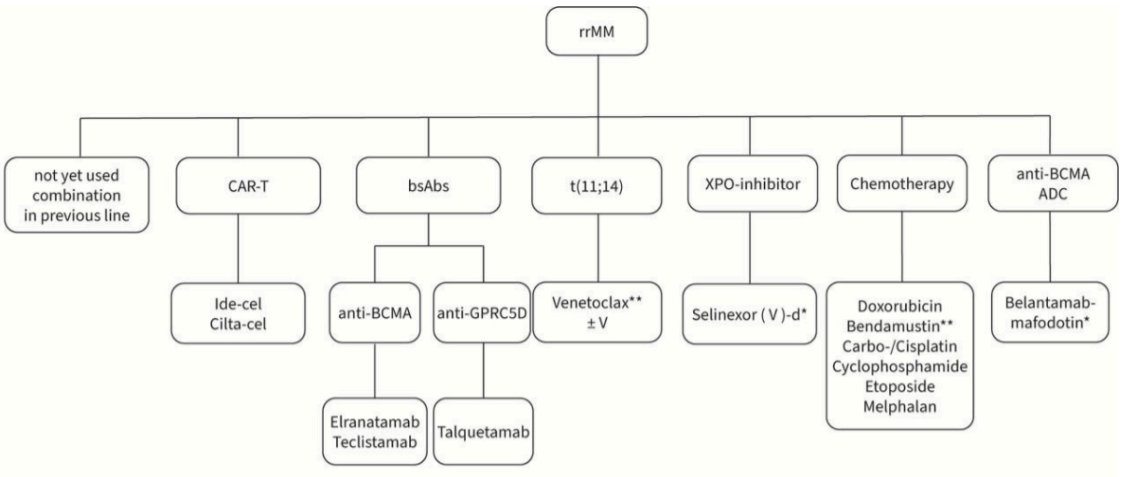
High-dose chemotherapy and stem cell transplantation

- HD-Mel-ASCT can still be considered standard of care for transplant-eligible patients in the first-line setting, as it can achieve deeper responses and prolonged progression-free survival.
- Tandem HD-Mel-ASCT should be considered only in patients with high-risk and ultra-high-risk disease.

Maintenance therapy

- Lenalidomide maintenance until progression or intolerance is the standard of care for most patients following

Figure 2: Treatment options after second line. * Not approved or reimbursed in Switzerland. ** Off-label indication. ADC: antibody-drug conjugate; BCMA: B-cell maturation antigen; bsAbs: bispecific antibodies; CAR-T: chimeric antigen receptor T-cell therapy; cilta-cel: ciltacabtagene autoleucel; d: dexamethasone; GPRC5D: G protein-coupled receptor class C group 5 member D; ide-cel: idecabtagene vicleucel; rrMM: relapsed/refractory multiple myeloma; t(11;14): translocation 11;14; V: bortezomib; XPO1: exportin 1.



HD-Mel-ASCT. Preliminary data suggest that maintenance with an additional anti-CD38 antibody may further prolong progression-free survival.

Second-line and later treatments

– Numerous new treatment options are available for second-line or later lines of therapy. The choice of the optimal regimen should consider prior treatments, toxicity profiles, comorbidities, and patient preferences.

– Key decision criteria include assessing refractoriness to lenalidomide and/or anti-CD38 antibodies.

T-cell-engaging therapies

– T-cell-engaging therapies, including CAR T cells and bispecific antibodies, have revolutionised the treatment landscape for multiple myeloma.

Financial disclosure
The authors did not receive any financial support for the preparation of this manuscript.

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. – M. Bertschinger received consulting fees from AbbVie, support for attending meetings and/or travel from Beigene, Pfizer, Sanofi, and AbbVie and fees for participation on a data safety monitoring board or an advisory board from Stemline, Janssen, Eli Lilly, and Novartis. – H.W. Auner received fees for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BMS, Pfizer, and Menarini Stemline, payment for expert testimony from Takeda and support for attending meetings and/or travel from Amgen and BMS. – C. de Ramon Ortiz received support for attending meetings and/or travel from Amgen and Janssen and insitutional fees for Advisory Boards from Janssen, Sanofi and Pfizer. – C. Driessen received consulting fees from BMS, Amgen, Johnson & Johnson and fees for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Johnson & Johnson paid to his institution. – S. Gerull received fees for participation on advisory boards from Sanofi and Janssen. – B. Jeker received fees for participation on advisory boards from Janssen and Amgen, paid to her institution, and support for attending meetings from Janssen. – E. Lerch received consulting fees from captoo, support for attending meetings and/or travel from Janssen and for participation on a data safety monitoring board or an advisory board from Amgen, BMS, and Janssen. – R. Muller received consulting fees from BMS, Johnson & Johnson, GSK and AbbVie, fees for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Astellas, payment for expert testimony from Johnson & Johnson, support for attending meetings from Amgen and Johnson & Johnson and for participation on a data safety monitoring board or advisory board from Sanofi, BMS, Johnson & Johnson, Amgen, Stemline, GSK, AbbVie, and Pfizer. – A. Schmidt received consulting fees from Takeda, Janssen, Celgene, Sobi, Roche, Sanofi, Amgen, Beigene, Novartis, Incyte, Eli Lilly, and Bayer. – C. Taverna received support for attending meetings and/or travel from Amgen and Gilead. – T. Zander received consulting fees from Pfizer, Janssen-Cilag, and Bristol-Myers Squibb. – U. Mey received fees for participation on a data safety monitoring board or advisory board from Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Janssen-Cilag, Novartis, Pfizer, Roche, Takeda, and Sanofi. – C. Renner received consulting fees from AbbVie, Roche, Gilead, Janssen, Beigene, Sanofi and MBS/Celgene, lecture honoraria from Amgen, AbbVie, Gilead and Roche, payment for expert testimony from Janssen and Sanofi, support for attending meetings and/or travel from Sanofi and Abbvie and fees for participation on a data safety monitoring board or an advisory board from Abbvie, Roche, Gilead, Janssen, Beigene, Sanofi and BMS/Celgene, all paid to his institution.

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