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Treatment of relapsed and refractory multiple myeloma

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ABSTRACT

The approach to the patient with relapsed or relapsed/refractory multiple myeloma (RRMM) requires a careful evaluation of the results of previous treatments, the toxicities associated with them and an assessment of prognostic factors. Since the majority of patients will have received prior therapy with drug combinations including a proteasome inhibitor and/or an immunomodulatory drug (IMiD), it is the physician's task to choose the right moment for the start of therapy and define with the patient which goals need to be achieved. The choice of regimen is usually based on prior responsiveness, drugs already received, prior adverse effects, the condition of the patient and expected effectiveness and tolerability. Many double and triple drug combinations are available. In addition, promising new drugs like pomalidomide, carfilzomib and monoclonal antibodies are, or will be, available shortly, while other options can be tried in clinical studies. Finally, supportive care and palliative options need to be considered in some patients. It is becoming increasingly more important to consider the therapeutic options for the whole duration of the disease rather than take a step by step approach, and to develop a systematic approach for each individual patient.

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Introduction

Multiple myeloma (MM) is a hematologic disorder which is characterized by a proliferation of malignant, monoclonal plasma cells in the bone marrow (BM) and/or extramedullary sites.[1] Symptomatic MM is characterized by typical manifestations of organ damage named CRAB, such as lytic bone lesions, hypercalcemia, anemia and renal impairment.[1] Recently the criteria for MM were redefined by the International Myeloma Working Group (IMWG), which are summarized in Table 1.[2] Progress in the first progression-free survival (PFS) and overall survival (OS) has been achieved through the introduction of high-dose therapy (HDT) with autologous stem cell transplantation (ASCT), and by the introduction of thalidomide, bortezomib and lenalidomide.[3] Despite the recent progress in OS rates, MM remains an incurable disease and the majority of patients will relapse and will require treatment.

Definitions of relapsed and relapsed/refractory risease

The IMWG published definitions of relapsed MM as well as treatment indications in 2006, 2009 and 2011.[4-6] Relapsed MM is regarded as a recurrence of the disease after prior response, and has been defined based on objective laboratory and radiological criteria: ≥ 25 % increase of the serum or urine monoclonal protein (M-protein) or ≥ 25 % difference between involved and uninvolved serum free light chains from its nadir, respectively, or the development of new plasmacytomas or hypercalciemia. In patients with non-secretory disease, relapse is defined as an increase of the bone marrow plasma cells. In general, an indication for relapse treatment has been defined as either the appearance or reappearance of one or more CRAB criteria or a rapid and consistent biochemical relapse. Relapsed/refractory MM (RRMM) is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy.[7]

Indications for relapse treatment

The aim of relapse treatment is to relieve disease symptoms and/or to prevent the development of CRAB symptoms. Second and later remissions tend to be shorter because of more aggressive tumor behavior at each relapse due to the selection of resistant clones and the development of refractory disease.[8] In the case of relapse presenting with new or worse CRAB symptoms, immediate treatment is mandatory. A biochemical relapse or progression may require immediate treatment, or in the case of indolent disease, careful monthly monitoring of M-protein levels until significant progression.[9] The indications for starting treatment at clinical and /or biochemical relapse were recently defined in a consensus paper by the IMWG.[10] These are summarized in Table 2. In brief, the treatment of biochemical relapse is indicated if any of the following is present: a doubling of the serum M-protein, an increase of serum M-protein by ≥ 10 g/L, an increase of urine M-protein by ≥ 500 mg/24h or an increase of involved serum free light chains (FLC) level by ≥ 200 mg/L (plus abnormal ratio) by 2 measurements, 2 months apart. In the presence of high-risk factors, such as aggressive disease at diagnosis, a short treatment-free interval with a suboptimal response to the previous treatment line, imminent risk for organ dysfunction such as previous light chain-induced renal impairment, aggressive bone lesions or unfavorable cytogenetics t(4;14) or del17p, treatment should be initiated at the stage of biochemical relapse before serious symptomatic disease develops.[11]

Treatment considerations at relapse

When the indication for treatment has been made, various factors may be considered in order to make the optimal treatment choice. First, a risk estimation has to be made since the clinical course of the disease varies widely between patients. Twenty percent of patients have high-risk disease, which is associated with unfavorable cytogenetics del17p, t(4;14), add 1q, t(14;16), a high-risk gene expression profile, ISS3 and high serum lactodehydrogenase at diagnosis, or plasmacel leukemia or a rapid progression/relapse.[12,13] These patients require immediate treatment with combination regimens. Intermediate-risk (60 %) and low-risk (20 %) patients may benefit from less intensive regimens or even monotherapy, respectively. Patient-related factors such as age and performance status may limit the number and type of treatment options. It is important to consider the previous line(s) of therapy, the disease responses and prior adverse events (Figure 1). The choices are also influenced by age, frailty status and the expectations of the patients and their families. The physical and emotional impact of hospitalization or frequent hospital visits should be considered. In many relapse trials the occurrence of any grade treatment-related adverse events is approximately 50% and serious adverse events (SAE) 20%. Treatment-related AEs are therefore a frequent cause of premature discontinuation, which will influence the outcome. It is important that the patient completes the planned treatment in order to achieve control of the disease.[14] Quality of life is an important goal, which reflects the patient's ability to continue their activities.[15,16] In Table 3 these factors are listed. As of 2015 the EMA has approved for the treatment of relapsed MM i) lenalidomide in combination with dexamethasone; ii) bortezomib alone or in combination with pegylated liposomal doxorubicin. Treatment with carfilzomib combined with lenalidomide and dexamethasone was also recently approved, while approval is expected for therapy with panobinostat combined with bortezomib and dexamethasone. For RRMM pomalidomide combined with dexamethasone has been approved. However, many other drugs are used that were not formally approved for this indication, such as thalidomide and bendamustine.

Prognostic factors at relapse and impact of response

Results of prior treatment. The majority of patients with NDMM receive a triple-drug induction regimen that contains at least one novel agent plus dexamethasone and a third agent. The European Medicine Agency (EMA) has approved bortezomib and thalidomide for first-line treatment in transplant eligible and non-transplant eligible patients. Continuous lenalidomide plus dexamethasone has recently received approval by the EMA for use in non-transplant eligible NDMM patients based on the MM-020

Table 1. Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering myeloma.

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events: • Myeloma defining events:
• Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
• Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
• Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 mol/L (>2 mg/dL)
• Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
• Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
• Any one or more of the following biomarkers of malignancy:
• Clonal bone marrow plasma cell percentage* ≥60%
• Involved:uninvolved serum free light chain ratio§ ≥100
• >1 focal lesions on MRI studies¶
Definition of smouldering multiple myeloma
Both criteria must be met:
• Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
• Absence of myeloma defining events or amyloidosis

*PET-CT: 18F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing / -light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.*

Table 2. Indications for treatment at relapse.

Indications for treatment at relapse
Clinical relapse
• Development of new soft-tissue plasmacytomas or bone lesions
• Definite increase (≥50%) in size of existing plasmacytomas or bone lesions
• Hypercalcemia (≥11.5 mg/dL; 2.875 mmol/L)
• Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L), or to < 10g/dL because of myeloma
• Rise in serum creatinine by ≥2 mg/dL or more (≥177 mmol/L), due to myeloma
• Hyperviscosity requiring therapeutic intervention
Significant biochemical relapse in patients without clinical relapse
• Doubling of the M-component in two consecutive measurements separated by 2 months with the reference value of 5 g/L, or
• In two consecutive measurements any of the following increases: o the absolute levels of serum M protein by ≥10 g/L, or o an increase of urine M protein by ≥500 mg per 24 hours, or o an increase of involved FLC level by ≥20 mg/dL (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

trial.[17] Consequently, more patients will receive lenalidomide in first-line treatment, and this will reduce or change the number of options in relapsed MM. The IMWG has conducted a survey of the risk of progression in patients relapsing after prior therapy with IMiDs and bortezomib, showing that that the median OS and event-free survival (EFS) rates were 9 months and 5 months, respectively.[18] In two individual studies single-agent bortezomib or bortezomib plus pegylated liposomal doxorubicin and dexamethasone were evaluated. A lower response rate was observed in thalidomide-exposed compared to thalidomide-naïve patients with bortezomib monotherapy as salvage treatment.[19] When bortezomib was combined with pegylated liposomal doxorubicin and dexamethasone this difference was not observed.[20] In an analysis of the MM-009 and MM-010 trials comparing lenalidomide plus dexamethasone with dexamethasone in relapsed MM, thalidomide-naïve patients had a significantly better overall response rate (ORR) than patients who had received thalidomide. Also, time to progression (TTP, 13 *vs*. 8 months) and PFS (13 *vs*. 8 months) were superior in thalidomide-naïve patients, while OS was not different.[21] In other trials a similar difference was observed between thalidomide-naïve *versus* thalidomide exposed patients who received subsequent treatment with VRD (bortezomib, lenalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone) or VTD (bortezomib, thalidomide, dexamethasone).[22-24] In a recent update of the VISTA trial, patients who had been treated upfront with VMP (bortezomib, melphalan, prednisone) had a similar or better outcome following relapse treatment with bortezomib-based or IMiD-based regimens as compared to MP (melphalan, prednisone) treated patients.[25] Other studies of the impact of upfront bortezomib treatment on the outcome of relapse treatment with lenalidomide plus dexamethasone showed less favorable results.[26-28] Bortezomib retreatment has been investigated in a recent prospective Italian trial, where 40% of patients achieved a response with a TTP of 8 months and there was a better outcome in patients who achieved a complete response (CR) following prior bortezomib (see below).[29]

Achievement of response. In first relapse clinically relevant responses can be achieved in 40 – 50% of patients. An important question is whether the depth of response affects long-term outcome in relapsed MM (for review see Lonial *et al.*[30]) In the APEX trial the achievement of CR with bortezomib was associated with a longer time to next treatment compared with VGPR or PR (24 *vs*. 13 *vs*. 6 months).[31] In the MM-009 and MM-010 trials using lenalidomide plus dexamethasone TTP and OS were significantly longer in patients who achieved VGPR or better compared with PR (TTP: 27 *vs.* 12 months; OS: not reached *vs*. 44 months).[32] At subsequent relapses and in RRMM virtually no impact of CR/VGPR on OS or TTP is observed as was demonstrated in the MM-003 trial with pomalidomide plus low-dose dexamethasone.[33] These data indicate that in first relapse CR may be a relevant treatment goal which can be actively pursued in patients. In second relapse and beyond the goal of treatment is to prevent organ impairment and to control the disease.

Cytogenetics. In contrast to newly diagnosed MM the impact of unfavorable cytogenetics on the outcome of relapse treatment has not been well documented, due to the lack of consistent data in large clinical trials. In addition, there is a selection bias of patients able to participate in trials with experimental agents and the number of patients in Phase 2 trials is too small to allow subanalyses. Therefore, the results of cytogenetic subgroups should be considered with caution. In a trial in relapsed MM patients treated with bortezomib, gain of 1(q21) was associated with a worse PFS (7 *vs.* 2 months) and OS (24 *vs*. 5 months), while del17p, del(1p21) and del13q had no impact.[34] In a trial with escalated dose bortezomib plus RD followed by lenalidomide maintenance in patients in first relapse no impact of unfavorable cytogenetics on PFS or OS was observed.[35] In a prospective trial comparing VRD *vs*. lenalidomide plus dexamethasone (RD) in relapsed MM, the presence of +1(q21) was associated with shorter OS in the RD group, while the impact of t(4;14) and del13q was less clear. In this trial del17p had a poor outcome in both groups.[24] In a study by the Intergroupe Francophone du Myelome (IFM), t(4;14) had a negative

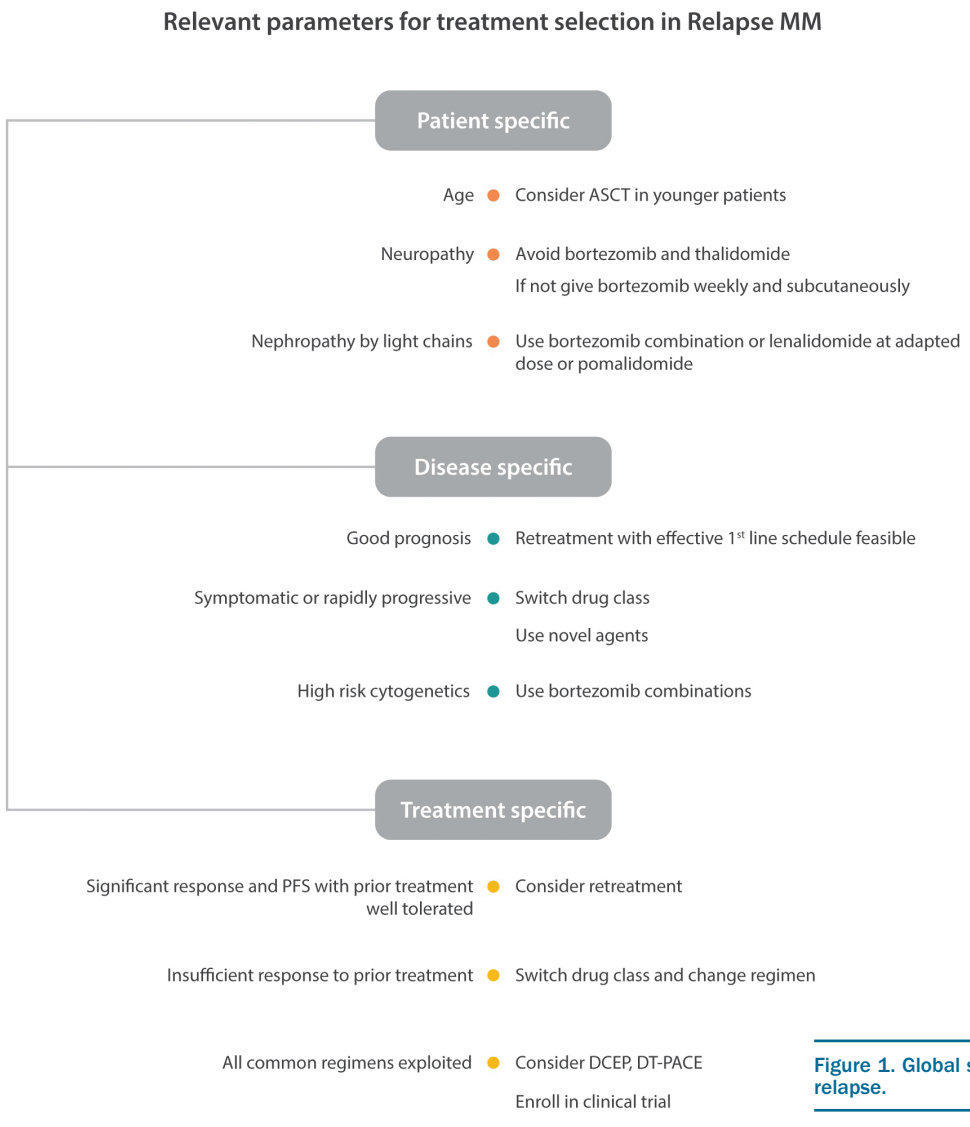

Figure 1. Global strategy for treatment strategy at relapse.

impact on OS in relapsed MM patients treated with lenalidomide plus dexamethasone.[26] More recently, in a trial with single-agent carfilzomib, relapsed MM patients with del17p or t(4;14) or t(14;16) had a worse OS than patients without these karyotypes (19 *vs*. 9 months).[36] In contrast, the Aspire trial using carfilzomib plus lenalidomide and dexamethasone showed no difference in PFS and TTP across subgroups with high-risk *versus* standard-risk cytogenetics.[37] Finally, a subgroup analysis of the MM-003 trial showed a benefit of response and PFS (3 months *vs*. 1 month) in patients with t(4;14) or del17p who received pomalidomide plus LD dexamethasone compared to dexamethasone alone.[38] From these few studies one may conclude that at present there is no convincing evidence that patients with relapsed MM who have high-risk cytogenetics should be excluded from relapse treatment.

Treatment options at relapsed MM

New regimens which include the novel agents thalidomide, bortezomib and lenalidomide as single-agents or in combination with dexamethasone have shown significant activity in patients with relapsed MM and are generally well tolerated.[39-44] These agents have set the stage for the development of next-generation immunomodulatory drugs (IMiDs) and proteasome inhibitors, i.e. pomalidomide and carfilzomib in relapsed and/or refractory disease.[33,37] In general, doublet or triplet regimens are preferred above single agents for optimal effect. Recently the IMWG published recommendations for global myeloma care including treatment options at relapse.[45] Figure 1 gives a general strategy for treatment selection, which will be discussed below. In Figure 2 the European Myeloma Network guideline for myeloma care shows specific treatment choices, which are endorsed by the authors.[11,14] The reader is also referred to recently published ESMO guidelines, other publications[11,14,46,47] and to published overviews.[48,49]

Retreatment

Retreatment with an agent used previously is considered feasible, provided the treatment produced a clinically meaningful response of adequate duration and acceptable toxicity. In general, the minimal depth of the initial

response should be partial response, while the minimal duration should be at least 6 months. Trials and retrospective analyses have shown that retreatment with bortezomib is feasible and effective and does not incur cumulative toxicity.[50-52] Lenalidomide retreatment is also feasible and may induce responses in up to 44 % of relapsed patients, and is better than retreatment with thalidomide.[51,53] Tolerability is another important consideration, and factors like neuropathy, myelosuppression and thrombosis may influence the choice of therapy. For some patients a change to a less intensive schedule or dose may make the treatment better tolerated. For bortezomib changing to a weekly and subcutaneous schedule will reduce toxicity.[54] If an effective alternative treatment is available at relapse, switching drug class is preferable, while previously used agents may then be considered in later lines.[29,50] Patients may even become sensitive to (escalated dosages of) drugs to which they were previously refractory, based on the appearance of different tumor clones during subsequent stages of the disease.[55]

Thalidomide

Thalidomide monotherapy has long been considered a valuable treatment option for patients with relapsed MM. However, there are no randomized phase III clinical trials supporting the use of thalidomide in this indication. In a systematic review of 42 clinical studies of thalidomide monotherapy in 1629 intent-to-treat patients, thalidomide was associated with a partial response or better in 29% of patients (CR 1.6%) and led to a median OS of 14 months.[56] These results were validated by a meta-analysis limited to trials of ≥50 patients, which reported a similar ORR of 28% (CR 2% and PR 26%).[57] Median doses were in the range of 200–800 mg/day, indicating the lack of standards regarding the optimal dose of thalidomide treatment. A later phase III comparison of low-dose (100 mg) and high-dose (400 mg) thalidomide showed similar activity, with improved safety associated with low-dose thalidomide indicating that 100 mg should be the preferred dose.[58] Retreatment with thalidomide was associated with a 30% ORR. Combining thalidomide with dexamethasone improves its efficacy in relapsed MM and phase II studies have reported an ORR of 41–56%.[59,60] The efficacy is further improved when thalidomide is used in triple or even quadruple combinations, including thalidomide with dexamethasone and bortezomib (VTD), dexamethasone and cyclophosphamide (CTD), bortezomib plus melphalan and prednisone (VMPT) or dexamethasone (VMDT), lenalidomide, melphalan and prednisone (RMPT), or VTD with pegylated liposomal doxorubicin.[23,61-66] These regimens have been associated with an ORR of 63–90% with CR being reported in 2–35% of patients.

Conclusion. Thalidomide combined with dexamethasone is still an option for relapsed patients especially if they are thalidomide-naïve, for whom an oral treatment schedule is needed and who are not eligible for bortezomib or lenalidomide-based treatment. However, the use of thalidomide has diminished because its continuous use is hampered by poor tolerability, the risk of thrombotic events and/or peripheral neuropathy as well as the availability of effective alternative treatments.

Bortezomib

Bortezomib is an effective drug for patients with relapsed MM. It can be safely and effectively administered to patients with renal impairment.[67] The drug is now routinely administered subcutaneously and may be used in a weekly schedule in elderly patients. Its main toxicities include peripheral neuropathy which may preclude further treatment[68], gastrointestinal symptoms and transient thrombocytopenia. The phase III APEX trial reported that bortezomib, as compared with dexamethasone, improves outcomes in patients with RRMM.[69] Patients treated with bortezomib had higher ORRs (38% *vs.* 18%; CR 6% *vs.* <1%; $P<0.001$ for each), longer TTP (6.2 months *vs.* 3.5 months; $P<0.001$), and better 1-year OS (80% *vs.* 66%; $P=0.003$) than those treated with dexamethasone. An updated analysis, based on a median follow-up period of 22 months for surviving patients, confirmed a survival benefit of 6 months for bortezomib compared with dexamethasone (median OS 29.8 months *vs.* 23.7 months) despite a 62% crossover of patients from the dexamethasone group to the bortezomib group.[70] Retreatment with bortezomib has clinical value if the patients were responsive previously, and if the response lasted more than 6 months.[29] Bortezomib is effective in combination with other agents and studies have reported improved ORR and good tolerability in combination with dexamethasone and/or pegylated liposomal doxorubicin.[20,71-74] Bortezomib is also effective as part of quadruple drug salvage regimens (ORR 56–88%; CR 6–46%;(VGPR or better 34–55%), and favorable response rates have been reported of bortezomib with CTD (VCTD), VMPT, and bortezomib with doxorubicin, dexamethasone, and lenalidomide (DVD-R).[62,75,76] Bortezomib also appears to enhance the effects of lenalidomide, and combinations of these two agents are currently under clinical evaluation.

Conclusion: Bortezomib combined with dexamethasone is an effective treatment for RRMM. Its efficacy is increased when combined with thalidomide, cyclophos-

Table 3. Patient- and treatment-related factors in the selection of treatment at relapse MM.

Patient- and treatment-related factors in the selection of treatment at relapse MM
Patient-related Factors
Age and Frailty
WHO Performance Status
Comorbidities
Transplant eligibility
Residual or late effects of prior therapies
Pre-existing (peripheral) neuropathy and/or thrombotic events
Disease-related Factors
Type and risk status of initial disease
Response and response duration following prior therapies
Presence of refractory disease
Aggressiveness of current relapse
Treatment-related factors
Response and/or refractoriness to prior therapies
Previous use of IMiDs and proteasome inhibitor
Previous use of alkylators
Prior HDT with ASCT
Single, dual or triple drug combination
Type and severity of adverse events related to prior therapies
Bone marrow reserve
Expected efficacy & toxicity of proposed therapy
Availability, cost and management requirements
Expectations of the patient

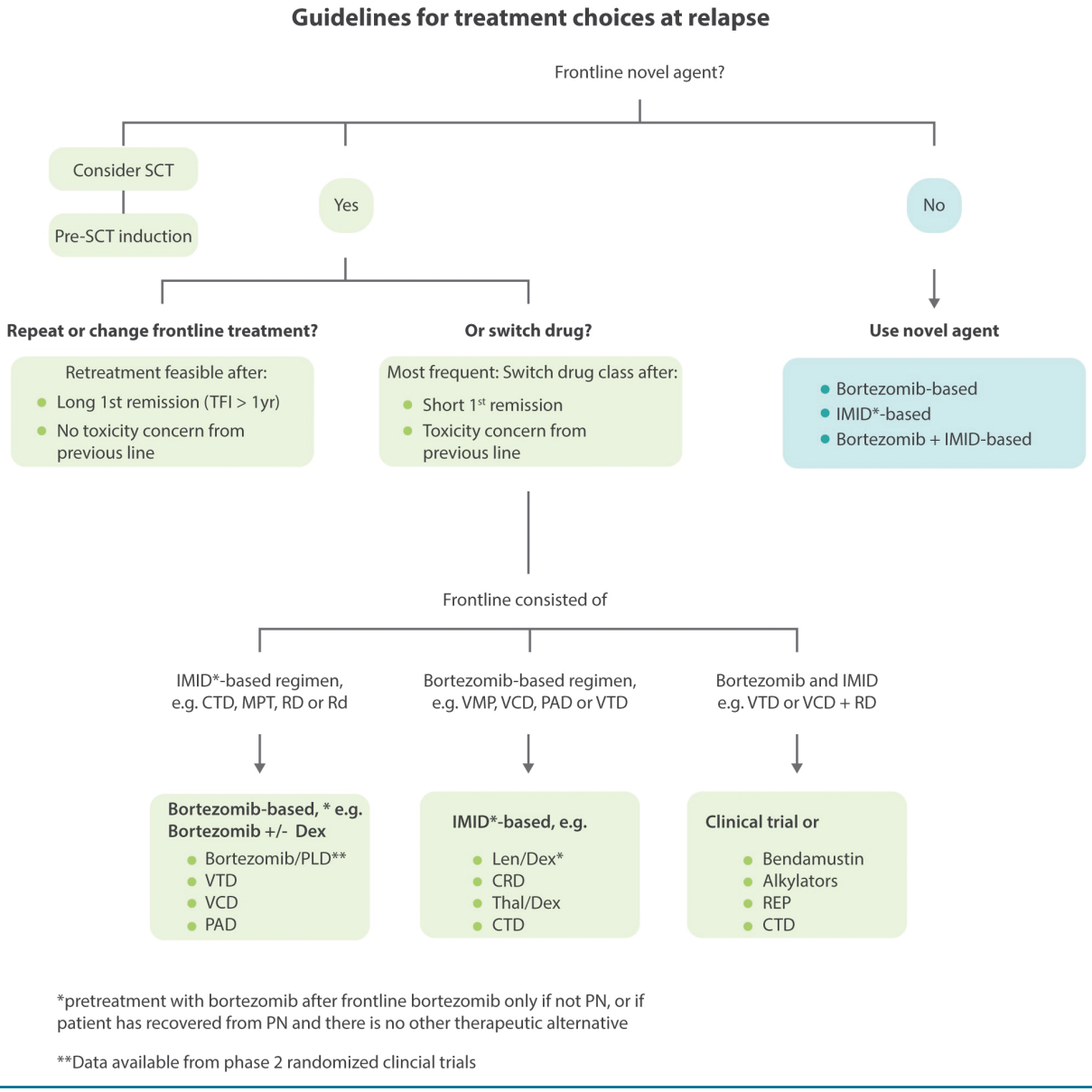

Figure 2. Guideline for treatment choices in patients with relapsed and/or refractory multiple myeloma developed by the European Myeloma Network.

phamide or an anthracyclin. Patients should be carefully monitored for neuropathy, in case the dose and schedule need to be reduced.

Lenalidomide

Lenalidomide as a single agent is active and well tolerated in patients with relapsed MM, and adding dexamethasone to lenalidomide has been shown to further improve response rates by up to 30%.[77] In the MM-009 and MM-010 trials patients were treated with lenalidomide plus dexamethasone until disease progression or unacceptable toxicity was observed.[78,79] In the MM-010 trial lenalidomide plus dexamethasone significantly improved ORR (60.2% *vs.* 24.0%), TTP (11.3 months *vs.* 4.7 months), and OS (not reached *vs.* 20.6 months; HR = 0.66) compared with dexamethasone alone. An analysis of pooled data from the MM-009 and MM-010 trials after a follow-up of 48 months confirmed the improved outcomes with lenalidomide plus dexamethasone, which significantly improved ORR (60.6% *vs.* 21.9%), duration of response (15.8 *vs.* 7 months), and median TTP (13.4 *vs.* 4.6 months). OS was also significantly longer in patients treated with lenalidomide plus dexamethasone compared with dexamethasone alone (38 *vs.* 31.6 months).[80] A later analysis suggested that to achieve a maximum PFS benefit, patients should be treated for at least 12 months with full-dose lenalidomide plus dexamethasone, followed by lower-dose continued therapy.[81] Because of the good tolerability of lenalidomide, high clinical activity and its oral formulation various combination regimens have been evaluated. Among these, the addition of cyclophosphamide to lenalidomide and dexamethasone for continuous treatment has clinical value in patients with suboptimal response.[82] As lenalidomide

appears to enhance the anti-myeloma effects of bortezomib, these two agents have been evaluated as combination therapy in patients with relapsed MM.[83] Retreatment with lenalidomide has shown a significant ORR. The combination lenalidomide, bortezomib and dexamethasone (RVD) is an active and well-tolerated regimen in patients with relapsed MM and can overcome drug resistance in patients previously treated with lenalidomide, bortezomib, thalidomide, or ASCT. With a follow-up of >2 years, MR or better was achieved by 78% of patients, including PR or better in 64% and CR or near CR in 25% of patients; the median PFS was 9.5 months and the median OS was 26 months. A four-agent combination regimen (RMPT) followed by maintenance with lenalidomide was effective and well tolerated in patients with relapsed MM with a 1-year PFS and OS of 51% and 72%, respectively.[84] The European Myeloma Network has defined a consensus statement for the use of lenalidomide.[85]

Conclusion. Lenalidomide combined with dexamethasone is currently the most efficient option for relapsed MM and may be combined with bortezomib, cyclophosphamide or other agents.

It is necessary to give the full-dose with dexamethasone during reinduction and continue with a lower-dose until progression.

Pomalidomide

Recently, pomalidomide alone or combined with dexamethasone was approved by the EMA, based on the results of the MM-003 trial for use in patients who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression. Dosing variations in early clinical trials defined the dose of pomalidomide at 4 mg on days 1-21 in a 28-day schedule.[86] Pomalidomide has demonstrated an ORR of 33% and a median response duration of 8 months in heavily pretreated patients.[87] In the extended Phase 2 part of the MM-002 trial, PFS and OS were 4 and 16 months, respectively.[88] The pivotal trial demonstrating the superiority of pomalidomide with dexamethasone was MM-003, which showed a better PFS (4 *vs*. 1.9 months) and OS (12 *vs.* 8 months) in spite of crossover from the dexamethasone arm for those patients who did not respond.[33] Recently an expert panel consensus statement was published on the optimal use of pomalidomide in RRMM.[89]
Conclusion. Pomalidomide is the only agent with demonstrated clinical activity in end-stage disease in patients who have received bortezomib and lenalidomide. It should be given until progression, preferably combined with dexamethasone.

Corticosteroids and conventional agents

Dexamethasone is added to most other therapies at a weekly dose of 20-40 mg. Its toxicities, i.e. osteoporosis and infections, limit prolonged use of the drug. However, in patients who have exhausted other options weekly dexamethasone or continuous low-dose (20 mg) prednisolone may be considered. Cyclophosphamide is an alkylating agent that is usually well tolerated and can be given orally or intravenously. It is often combined with bortezomib in the VCD or CyBorD schedules or with lenalidomide, but it can also be taken alone in a 300 mg/m^2 weekly regimen. Standard-dose intermittent oral melphalan may also be a valuable option for economic reasons or when patients have no other treatment options. High-dose chemotherapy such as DCEP and DT-PACE can be given in RRMM, although responses are usually short.[90]

Bendamustine

This is a bi-functional alkylating agent that was approved for the treatment of chronic lymphocytic leukemia, indolent B-cell non-Hodgkin lymphoma and NDMM in patients who cannot tolerate thalidomide or bortezomib because of neuropathy. Bendamustine is currently undergoing clinical evaluation as an anti-myeloma treatment. Early studies have reported promising efficacy and good tolerability with a regimen of bendamustine in combination with thalidomide, in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone in patients with relapsed MM.[91-93]

High-Dose Therapy (HDT) with autologous stem cell transplantation (ASCT) or Allogeneic SCT

In transplant eligible patients with relapse or progression, HDT followed by ASCT may be considered. In patients who did not receive HDT before, it is the treatment of choice if stem cells can be obtained.[94] In general, HDT plus ASCT is valuable if patients had responded to a previous HDT and have achieved at least 2 years of PFS. This has also become an option in patients of a more advanced age.[95] As shown recently in a randomized trial by the NCRI a second high-dose melphalan plus ASCT is a better option than weekly cyclophosphamide in patients who received ASCT at least 18 months before, resulting in a longer time to progression (19 *vs.* 11 months).[96] Two international trials by IFM with an American consortium and by the European Myeloma Network are currently investigating the benefit of HDT in newly diagnosed MM versus first relapse.

Allogeneic transplantation is an experimental option for use in clinical trials in patients with high-risk disease and unfavorable karyotypes.[97] The European Group for Blood and Marrow Transplantation published a long follow-up of NDMM and relapsed MM patients treated with autologous/reduced-intensity allogeneic SCT *vs.* autologous SCT, showing a superior OS with the former combination (47% *vs*. 31% at 96 months).[98] The same group more specifically analyzed the results of reduced-intensity allogeneic SCT in relapsed MM.[99] At the present time, most investigators currently regard allogeneic SCT as an option for younger, fit patients with high-risk disease in first relapse.

Novel agents under clinical development

In addition to approved novel agents, ongoing trials show promising activity of various agents of different drug classes. While these drugs are not available as yet, they are considered experimental in Europe. Because of their interest for patients wishing to participate in clinical trials they will be briefly discussed. An extensive, recent summary of this topic was published by the IMWG group.[100]

Carfilzomib when combined with lenalidomide and dexamethasone has recently demonstrated significant clinical activity in the ASPIRE trial, leading to an unprecedented PFS of 26 months *versus* 17 months in the control group.[37] The combination was well tolerated and there was a clinical benefit in the quality of life. In the ENDEAV-

OUR study, carfilzomib plus dexamethasone was superior to bortezomib plus dexamethasone in relapsed MM, including patients who were treated with but not refractory to bortezomib.[101] The EMA evaluated the drug in 2015 and full access to the market is expected in 2016. Another trial comparing single agent carfilzomib with dexamethasone (FOCUS) was not positive because of good results in the control arm, where > 90 % received cyclophosphamide/dexamethasone. This also suggests that carfilzomib must be combined with other agents.

HDAC inhibitors. Panobinostat and vorinostat are epigenetic drugs that can be combined with other agents.[102,103] Vorinostat combined with bortezomib and dexamethasone showed a PFS advantage of only 1 month compared with bortezomib and dexamethasone. Panobinostat had a significant advantage when combined with bortezomib and dexamethasone over those drugs with placebo, however, at the cost of gastrointestinal symptoms and fatigue. The EMA and FDA have the drug combination under consideration.

Antibodies. Amongst novel agents the monoclonal antibodies elotuzumab and daratumumab carry a high promise for the treatment of relapsed MM. Elotuzumab is a monoclonal antibody which targets SLAMF-7, which is present on the surface of plasma cells. While it has little single-agent activity in RRMM, elotuzumab combined with lenalidomide and low-dose dexamethasone showed more than 80 % ORR without significant toxicity.[104] In Phase 2 studies the lower-dose of 10 mg/kg was associated with a longer PFS than the dose of 20 mg/kg (33 *versus* 19 months).[105] The results of the Phase 3 trial ELOQUENT-2 confirm the effect of elotuzumab in relapsed MM.[106]

Daratumumab is an antibody that targets CD38 and kills plasma cells through ADCC and CDC mediated mechanisms.[107] In a study in patients of whom 75 % were refractory to bortezomib and lenalidomide, single agent daratumumab resulted in an ORR of 36% at the 16mg/kg dose, while 65% of responding patients were progression-free at 12 months.[108] Based on preclinical studies lenalidomide has been identified as a synergistic partner for daratumumab.[109] Clinical trials have been initiated using various combinations of daratumumab with other drugs. SAR650984 is another anti-CD38 antibody which is currently being investigated in clinical trials.

Conclusions. Monoclonal antibodies are a novel class of agents which specifically target plasma cells, have strong clinical activity in particular when combined with other agents, and show limited toxicity. It is expected that antibodies will have an important place in the future treatment of relapsed MM.

Supportive care

Patients with relapsed MM are vulnerable due to the presence of disease, prior exposure to chemotherapy, myelosuppression, prolonged exposure to corticosteroids and organ impairment. Frequent infections and bone disease are common and should be adequately prevented and treated. Intravenous zoledronate or pamidronate should be started or restarted at relapse, with calcium and vitamin D supplements. Low-dose local radiotherapy (20-40 Gy) may be administered to local bone lesions in case of pain or imminent fractures. Infections should be managed proactively, especially those of encapsulated pathogens. Prophylactic vaccination is recommended for influenza A and B, pneumococci and hemophilus influenza. Anemia may be treated with erythropoietin (40.000 U weekly) or darbopoietin (500 mcg q 3 weeks) or transfusion. Patients with increased risk for venous thrombolic events and those who will be treated with thalidomide or lenalidomide should receive prophylaxis with aspirin (1 risk factor) or LMWH (≥2 risk factors). Treatment for polyneuropathy and pain should be administered according to published guidelines.[110] For detailed guidelines the reader is referred to the IMWG consensus.[45]

Conclusions and future directions

Treatment with thalidomide, lenalidomide, and bortezomib has improved responses in patients with relapsed MM. Continuous or repeated therapy with lenalidomide and bortezomib is well tolerated and leads to durable clinical responses, resulting in improved PFS and OS. The majority of adverse events associated with these novel agents are hematologic and can be managed using dose modifications and/or growth factor support; however, patients on long-term thalidomide or bortezomib should be regularly monitored for the development of peripheral neuropathy. Long-term treatment with novel agents could result in the emergence of drug-resistant MM clones, especially in patients with adverse FISH cytogenetics. Therefore, well-designed phase III studies with long-term follow-up are required to confirm the clinical benefits and safety of the continuous treatment approaches in MM patients. Approaches for patients relapsing on long-term treatment are yet to be defined. Continuous therapy from first relapse to disease progression has the potential to maintain the suppression of residual disease, prolong the time to subsequent relapse and extend OS rates. In effect, this treatment strategy may generate prolonged control of the disease. If this can be achieved in RRMM patients, it will represent a paradigm shift, allowing MM to be managed as a chronic illness.

References

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548.
3. Rajkumar SV. Treatment of multiple myeloma. Nat Rev Clin Oncol. 2011;8(8):479-491.
4. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473.
5. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3-9.
6. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.
7. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. Leukemia. 2008;22(2):231-239.
8. Magrangeas F, Avet-Loiseau H, Gouraud W, et al. Minor clone provides a reservoir for relapse in multiple myeloma. Leukemia. 2013;27(2):473-481.
9. Fernández de Larrea C, Jiménez R, Rosiñol L, et al. Pattern of relapse and progression

after autologous SCT as upfront treatment for multiple myeloma. Bone Marrow Transplant. 2014. 49(2):223-227.
10. Palumbo A, Rajkumar SV , San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014;32(6):587-600.
11. Ludwig H, Sonneveld P, Davies F, et al., European perspective on multiple myeloma treatment strategies in 2014. Oncologist. 2014;19(8):829-844.
12. Moreau P, Cavo M, Sonneveld P, et al., Combination of international scoring system 3, high lactate dehydrogenase, and t(4;14) and/or del(17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. J Clin Oncol. 2014;32(20):2173-2180.
13. Mikhael JR, Dingli D, Roy V, et al., Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360-376.
14. Ludwig H, Sonneveld P. Disease control in patients with relapsed and/or refractory multiple myeloma: what is the optimal duration of therapy?. Leuk Res. 2012;36 Suppl 1:S27-34.
15. Sonneveld P, Verelst SG, Lewis P, et al. Review of health-related quality of life data in multiple myeloma patients treated with novel agents. Leukemia. 2013;27(10):1959-1969.
16. Dimopoulos MA, Palumbo A, Hajek R,et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged >/= 65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. Leuk Lymphoma. 2014;55(7):1489-1497.
17. Benboubker L, Dimopoulos MA ,Dispenzieri A, et al., Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.
18. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26(1):149-157.
19. Vogl DT, Stadtmauer EA, Richardson PG, et al. Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed/refractory multiple myeloma. Br J Haematol. 2009;147(4):531-534.
20. Sonneveld P, Hajek R, Nagler A, et al. Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy. Cancer. 2008; 112(7):1529-1537.
21. Wang M, Dimopoulos MA , Chen C, et al. Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma regardless of prior thalidomide exposure. Blood. 2008;112(12):4445-4451.
22. Kropff M, Bisping G, Schuck E, et al. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Br J Haematol. 2007;138(3):330-337.
23. Pineda-Roman M, Zangari M, van Rhee F, et al. VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. Leukemia. 2008;22(7): 1419-1427.
24. Dimopoulos MA, Kastritis E, Christoulas D, et al. Treatment of patients with relapsed/refractory multiple myeloma with lenalidomide and dexamethasone with or without bortezomib: prospective evaluation of the impact of cytogenetic abnormalities and of previous therapies. Leukemia. 2010;24(10):1769-1778.
25. Mateos MV, Richardson PG, Schlag R, et al., Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28(13):2259-2266.
26. Avet-Loiseau H, Soulier J, Fermand JP, et al. Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone. Leukemia. 2010;24(3):623-628.
27. Reece D, Song KW, Tu T, et al. Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. Blood. 2009;114 (3):522-525.
28. Klein U, Neben K, Hielscher T, et al., Lenalidomide in combination with dexamethasone: effective regimen in patients with relapsed or refractory multiple myeloma complicated by renal impairment. Ann Hematol. 2011;90(4):429-439.
29. Petrucci MT, Giraldo P, Corradini P, et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol. 2013;160(5):649-659.
30. Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. Leukemia. 2014;28 (2):258-268.
31. Niesvizky R, Richardson PG, Rajkumar SV, et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. Br J Haematol. 2008;143(1):46-53.
32. Harousseau JL, Dimopoulos MA, Wang M, et al. Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. Haematologica. 2010;95(10):1738-1744.
33. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-1066.
34. Chang H, Trieu Y, Qi X, Jiang NN, Xu W, Reece D. Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: Adverse effect of 1q21 gains. Leuk Res. 2011;35(1):95-98.
35. Jakubowiak AJ, Siegel DS, Martin T, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. Leukemia. 2013;27(12):2351-2356.
36. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med. 2015;372(2):142-152.
37. Glasmacher A, von Lilienfeld-Toal M. The current status of thalidomide in the management of multiple myeloma. Acta Haematol. 2005;114 Suppl 1:3-7.
38. Richardson PG, Boral AL, Anderson KC. Bortezomib in multiple myeloma (vol 352, pg 2487, 2005). N Engl J Med. 2005; 353(12):1297-1298.
39. Richardson PG, Barlogie B, Berenson J, et al., A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348(26):2609-2617.
40. Richardson P, Jagannath S, Schlossman R, et al. Thalidomide for relapsed multiple myeloma after high dose therapy and stem cell transplantation: Results of an open-label, multicenter phase two study of efficacy, toxicity and correlation with biological activity. Blood. 2002;100(11):813a-813a.
41. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357(21):2123-2132.
42. Weber DM, Chen C, Niesvizky R, et al., Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357(21):2133-2142.
43. Ludwig H, Miguel JS, Dimopoulos MA, et al., International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014;28(5):981-992.
44. van de Donk NW, Lokhorst HM, Dimopoulos M, et al. Treatment of relapsed and refractory multiple myeloma in the era of novel agents. Cancer Treat Rev. 2011;37(4):266-283.
45. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013. 24 Suppl 6:vi133-37.
46. Gentili S, Lonial S. Relapsed and refractory multiple myeloma: new therapeutic strategies. Hematol Oncol Clin North Am. 2014;28(5):861-890.
47. Engelhardt M, Terpos E, Kleber M, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. Haematologica. 2014;99(2):232-242.
48. Knopf KB, Duh MS, Lafeuille MH, et al. Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk. 2014;14(5):380-388.
49. Mohty B, El-Cheikh J, Yakoub-Agha I, et al. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and 'retreatment' approaches in the era of novel agents. Leukemia. 2012;26(1):73-85.
50. Taverna C, Voegeli J, Trojan A, et al. Effective response with bortezomib retreatment in relapsed multiple myeloma--a multicentre retrospective survey in Switzerland. Swiss Med Wkly. 2012; 142:w13562.
51. Madan S, Lacy MQ, Dispenzieri A, et al. Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma. Blood. 2011;118(7): 1763-1765.
52. Moreau P, Coiteux V, Hulin C, et al. Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma.

Haematologica. 2008;93(12):1908-1911.
53. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. Blood. 2012;120(5): 1067-1076.
54. Glasmacher A, Hahn C, Hoffmann F, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006;132(5):584-593.
55. Prince HM, Schenkel B, Mileshkin L. An analysis of clinical trials assessing the efficacy and safety of single-agent thalidomide in patients with relapsed or refractory multiple myeloma. Leuk Lymphoma. 2007;48 (1):46-55.
56. Yakoub-Agha I, Mary JY, Hulin C, et al. Low-dose vs. high-dose thalidomide for advanced multiple myeloma: a prospective trial from the Intergroupe Francophone du Myelome. Eur J Haematol. 2012;88(3):249-259.
57. Dimopoulos MA, Zervas K, Kouvatseas G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001;12(7):991-995.
58. Palumbo A, Bertola A, Falco P, et al. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Hematol J. 2004;5(4):318-324.
59. Kyriakou C, Thomson K, D'Sa S, et al. Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma. Br J Haematol. 2005;129(6):763-770.
60. Palumbo A, Ambrosini MT, Benevolo G, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood. 2007;109(7):2767-2772.
61. Terpos E, Kastritis E, Roussou M, et al. The combination of bortezomib, melphalan, dexamethasone and intermittent thalidomide is an effective regimen for relapsed/refractory myeloma and is associated with improvement of abnormal bone metabolism and angiogenesis. Leukemia. 2008;22(12):2247-2256.
62. Offidani M, Bringhen S, Corvatta L, et al. Thalidomide-dexamethasone plus pegylated liposomal doxorubicin vs. thalidomide-dexamethasone: a case-matched study in advanced multiple myeloma. Eur J Haematol. 2007;78(4):297-302.
63. Palumbo A, Larocca A, Genuardi M, et al. Melphalan, prednisone, thalidomide and defibrotide in relapsed/refractory multiple myeloma: results of a multicenter phase I/II trial. Haematologica. 2010;95(7):1144-1149.
64. Garderet L, Iacobelli S, Moreau P, et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2012;30(20):2475-2482.
65. Scheid C, Sonnveld P, Schmidt-Wolf IG, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. Haematologica. 2014;99(1):148-154.
66. Delforge M, Bladé J, Dimopoulos MA, et al. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. Lancet Oncol. 2010;11(11):1086-1095.
67. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-2498.
68. Richardson PG, Sonneveld P, Schuster MW, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood. 2007;110(10):3557-3560.
69. Jagannath S, Barlogie B, Berenson JR, et al. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. Br J Haematol. 2008;143(4):537-540.
70. Mikhael JR, Belch AR, Prince HM, et al. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program. Br J Haematol. 2009;144(2):169-175.
71. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25(25):3892-3901.
72. Dimopoulos MA, Orlowski RZ, Facon T, et al. Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma. Haematologica. 2015;100 (1):100-106.
73. Kim YK, Sohn SK, Lee JH, et al. Clinical efficacy of a bortezomib, cyclophosphamide, thalidomide, and dexamethasone (Vel-CTD) regimen in patients with relapsed or refractory multiple myeloma: a phase II study. Ann Hematol. 2010;89(5): 475-482.
74. Berenson JR, Yellin O, Kazamel T, et al. A phase 2 study of pegylated liposomal doxorubicin, bortezomib, dexamethasone and lenalidomide for patients with relapsed/refractory multiple myeloma. Leukemia. 2012;26(7):1675-1680.
75. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2006;108(10):3458-3464.
76. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357(21):2123-2132.
77. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357(21):2133-2142.
78. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia. 2009;23(11): 2147-2152.
79. Dimopoulos MA, Hussein M, Swern AS, Weber D. Impact of lenalidomide dose on progression-free survival in patients with relapsed or refractory multiple myeloma. Leukemia. 2011;25(10):1620-1626.
80. van de Donk NW, Wittebol S, Minnema MC, et al. Lenalidomide (Revlimid) combined with continuous oral cyclophosphamide (endoxan) and prednisone (REP) is effective in lenalidomide/dexamethasone-refractory myeloma. Br J Haematol. 2010;148 (2):335-337.
81. Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. Blood. 2014;123(10):1461-1469.
82. Palumbo A, Larocca A, Falco P, et al. Lenalidomide, melphalan, prednisone and thalidomide (RMPT) for relapsed/refractory multiple myeloma. Leukemia. 2010;24(5): 1037-1042.
83. Dimopoulos MA, Palumbo A, Attal M, et al. Optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement. Leukemia. 2011;25 (5):749-760.
84. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. Blood. 2013;121(11): 1968-1975.
85. Richardson PG, Siegel D, Baz R, et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood. 2013;121(11):1961-1967.
86. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123 (12):1826-1832.
87. Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia. 2014;28(8):1573-1585.
88. Gerrie AS, Mikhael JR, Cheng L, et al. D(T)PACE as salvage therapy for aggressive or refractory multiple myeloma. Br J Haematol. 2013;161(6):802-810.
89. Ramasamy K, Hazel B, Mahmood S, et al. Bendamustine in combination with thalidomide and dexamethasone is an effective therapy for myeloma patients with end stage renal disease. Br J Haematol. 2011;155(5):632-634.
90. Rodon P, Hulin C, Pegourie B, et al. Phase 2 study of bendamustine, bortezomib and dexamethasone as second-line treatment for elderly patients with multiple myeloma: the Intergroupe Francophone du Myelome 2009-01 trial. Haematologica. 2015;100 (2):e56-59.
91. Lentzsch S, O'Sullivan A, Kennedy RC, et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with relapsed or refractory multiple myeloma is feasible and highly effective: results of phase 1/2 open-label, dose escalation study. Blood. 2012;119(20):4608-4613.
92. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92(9): 3131-3136.
93. Auner HW, Szydlo R, Hoek J, et al. Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: increased use and improved outcomes in elderly patients in recent years. Bone Marrow Transplant. 2015;50(2):209-215.
94. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell trans-

plantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(8):874-885.
95. Lokhorst H, Einsele H, Vesole D, et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. J Clin Oncol. 2010;28(29):4521-4530.
96. Gahrton G, Iacobelli S, Björkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055-5063.
97. Auner HW, Szydlo R, van Biezen A, et al. Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48(11):1395-1400.
98. Ocio EM, Richardson PG, Rajkumar SV, et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). Leukemia. 2014;28(3):525-542.
99. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. Lancet Oncol. 2013;14(11):1129-1140.
100. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-1206.
101. Lonial S, Vij R, Harousseau JL, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. J Clin Oncol. 2012;30(16):1953-1959.
102. Richardson PG, Jagannath S, Moreau P, et al. A Phase 2 Study of Elotuzumab (Elo) in Combination with Lenalidomide and Low-Dose Dexamethasone (Ld) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (R/R MM): Updated Results. Blood. 2012;120(21):202 abstr.
103. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015;373(7):621-631.
104. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-1848.
105. Nijhof IS, Groen RW, Lokhorst HM, et al. Upregulation of CD38 expression on multiple myeloma cells by all-trans retinoic acid improves the efficacy of daratumumab. Leukemia. 2015;29(10):2039-2049.
106. Nijhof IS, Lammerts van Bueren JJ, et al. Daratumumab-mediated lysis of primary multiple myeloma cells is enhanced in combination with the human anti-KIR antibody IPH2102 and lenalidomide. Haematologica. 2015;100(2):263-268.
107. Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia. 2012;26(4):595-608.