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How to treat patients with relapsed/refractory multiple myeloma: evidence-based information and opinions.

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Abstract

Relapsed/refractory multiple myeloma (rrMM) remains a difficult condition to treat, despite the availability of new drugs. In this review, we searched for evidence to guide physician in the choice of salvage therapy in certain subgroups of patients. We tried to provide evidence-based information and to suggest possible approaches based on data on prior therapies, prior remission duration, toxicity of prior treatments, patient's comorbidities and disease characteristics at relapse. Unfortunately, little evidence is available, there are no large and/or randomized trials nor direct comparisons of drugs or combinations for rrMM patients to draw any definite conclusion. Almost all the studies presented here suggest that depth of response is a key factor also for patients with rrMM. Which one between combinations and sequential therapies is the best approach remains controversial. Several studies favor the former approach in early relapse, since it leads to a higher complete response rate, regardless of prior therapies. However, in both strategies, achieving maximal response should always remain a main goal. Consolidation/maintenance therapy is beneficial both in combination or sequential therapies also in rrMM. Second generation new-drugs, such as pomalidomide, carfilzomib, bendamustine and histone-deacetylase inhibitors, will probably expand the rescue possibilities also in this setting.

Introduction

Novel agents, namely the immunomodulatory drugs Thalidomide and Lenalidomide, and the proteasome inhibitor Bortezomib, were tested in different clinical trials and led to good results in patients with multiple myeloma (MM). In particular, benefits with novel agents were also seen in relapsed/refractory multiple myeloma (rrMM)[1].

Besides the approved regimens, new combinations containing novel drugs with/without conventional chemotherapies and/or steroids have been studied for the treatment of rrMM. To date, no comparative studies are available to help physicians choose the best treatment for rrMM patients. Treatment choice for rrMM is based on prior therapy, remission duration and toxicity of treatment, patient's comorbidities and disease characteristics at relapse. Direct evidence and more precise guidelines are needed.

This review reports on the latest data and evidence about treatment of rrMM.

Is quality of response a critical end-point?

In newly diagnosed multiple myeloma (MM) patients, a complete response (CR) is a surrogate marker of long-term outcome. After the introduction of novel drugs, CR has become a more achievable aim, also for rrMM patients. However, the role of CR in these patients needs to be validated. Table 1 summarizes the studies addressing this issue. A retrospective study investigated the relationship between response rate and outcome in more than 300 patients with rrMM treated

with thalidomide $\pm$ dexamethasone. In this study, the achievement of CR and very good partial response (VGPR) was associated with a significantly longer progression-free survival (PFS) and overall survival (OS) compared with partial response (PR) and stable disease (SD)[2]. In another retrospective analysis on rrMM patients treated with the combination of Doxil, Vincristine, low-dose dexamethasone and Thalidomide (DVd-T) found that patients achieving CR/VGPR had a significantly better PFS and OS compared with those achieving PR/SD[3].

In the randomized phase III APEX trial, a post-hoc analysis including patients treated with bortezomib as single agent showed a relation between CR and both better treatment free interval (TFI) and better time to alternative therapy (TTAT), although time-to-progression (TTP) and OS were similar[4]. These results were consistent with those reported in a retrospective analysis on 70 patients treated with bortezomib $\pm$ dexamethasone[5]. Patients obtaining CR/VGPR had a considerably better TTP, TTAT, TFI compared with those achieving PR. In another study, the combination of bortezomib with doxorubicin and dexamethasone led to a significant higher event-free survival (EFS) in patients obtaining CR/VGPR if compared with PR[6]. In a recent observational study, 769 patients were treated with bortezomib-based therapy. After at least 4 courses of therapy, CR rate was 12% and near CR (nCR) 16%[7]. These patients had a significantly improved survival compared with those who did not achieved CR and nCR. Another trial assessed the role of the 4-drug combination Thalidomide-Doxil-Dexamethasone-Bortezomib (ThaDD-V)[8]. Patients who achieved CR had a significantly longer PFS compared with those achieving a lower response. In this study, patients attaining a stringent CR (sCR) had a better outcome than those achieving CR only. This demonstrates the importance of a deeper response also in rrMM.

A post-hoc analysis pooled data from two trials comparing patients treated with lenalidomide and high-dose dexamethasone[9]. In this analysis, patients achieving CR/VGPR had a significantly better TTP and OS compared with those achieving PR. This benefit was independent of when CR/VGPR was achieved and it was confirmed by a landmark analysis at 12-months. However, the

two groups of patients were not well balanced. Patients who achieved CR/VGPR had a shorter disease history and received less prior treatments, particularly with thalidomide. No adjustment for these important factors was made in this study, and this is a major limitation.

These studies suggest that rrMM patients who achieve deeper response have a better outcome, at least in terms of PFS. These data should be considered with caution, since they derive from retrospective studies. Well-designed prospective studies are warranted to establish the relationship between response and outcome in rrMM.

Choosing treatment for patients with suboptimal response to induction regimen

Overall response rate (ORR/ at least PR) after first-line therapy with novel agents accounts for 57-100%[10-12]. MM patients considered “truly” refractory to induction therapy,i.e. those who fail to reach at least PR after three cycles of induction with novel agent-containing therapy, as defined in recent guidelines provided by an international panel of experts [13], may need salvage treatment

In the non-transplant setting, the role of therapy aiming to improve depth of response should be investigated. No benefit with this approach was seen in elderly patients failing to reach at least PR, since these patients may have difficulties in prolonging treatment. Better quality of response was associated with improved long-term outcomes with VMP treatment, regardless of whether best response, in particular CR, was achieved early or late (even after 24 weeks of treatment). This was particularly evident in older patients and in those with high serum β 2-microglobulin levels or higher tumor burden (ISS stage II or III)[14]. Prolonging lenalidomide-based treatment was linked to an improvement in quality of response[15]. These data suggest that initial treatment should be continued beyond first response, if tolerated, in order to achieve higher quality response. Ongoing or future prospective trials addressing this issue will validate this approach. This should be always considered an individualized approach and should be based on patient’s characteristics such as age, performance status, presence of comorbidities, type of previous therapy, quality of response achieved, tolerance to therapy, side-effects of drugs. Some important aspects should be considered,

such as risk of disease, possible worsening of quality of life due to prolonged treatment, poor outcome after relapse/refractory to novel agents, and drug resistance at relapse. These factors may reduce the spectrum of new therapeutic options that can be used. However, stabilization of a symptom-free condition despite evidence of persistent disease should remain a major goal in unfit elderly patients, while, in the other patients, treatment should aim at achievement of the best possible response.

In the transplant setting, not achieving at least PR after induction therapy with old agents did not affect PFS or OS, and a response was achieved after transplantation [16,17]. However, different outcomes were reported according to the depth of response achieved. Conversely, a recent retrospective analysis of 286 patients showed that failure to respond to immunomodulatory-based (IMiD, thalidomide or lenalidomide) induction treatment leads to significantly shorter post-transplant PFS and OS[18]. This study also suggested that the mechanisms underlying resistance to IMiD therapies are similar to those with high-dose melphalan. This observation raises the question of whether patients not responding to induction regimens including novel agents should be immediately treated with alternative therapies before transplant.

So far, induction therapy has aimed to achieve the deepest and fastest response before transplantation. No data are currently available on possible consolidation after induction and before transplantation for patients achieving “suboptimal” response to induction. New studies are ongoing to further improve the results obtained after induction treatments, by reducing doses (thus increasing tolerability), adding a fourth drug to the regimen used, or combining the two most potent agents (bortezomib and lenalidomide)[19-21]. Besides risk-adapted therapies, in the near future, response-adapted strategies may have a fundamental role to choose treatment and to further improve outcome.

How many drugs in rrMM?

Three- and 4-drug combinations improve CR rate and outcome of newly diagnosed MM[22]. Is it the same also for rrMM?

The CR rate with approved single- or 2-agent therapies for rrMM such as bortezomib[23] lenalidomide[24], bortezomib-doxil[25] and lenalidomide-dexamethasone[26,27] ranges from 2 to 15%, TTP from 5 to 11 months. Many 3- or 4-drug combinations have been recently studied in phase I-II studies in patients with rrMM. CR rates and PFS of the main regimens used in rrMM are reported in the Fig. 1. Data show that a more intense approach leads to higher CR rate and subsequently to better outcome. Three- or 4-drug combinations containing thalidomide, bortezomib, dexamethasone and anthracyclines showed the best results in rrMM, CR rates approximately doubled and PFS improved if compared with single- or 2-agent regimens. Toxicity is not always strictly associated with the number of drugs used. As showed in Table 2, the incidence of neutropenia, infections and DVT with regimens including 3 or 4 drugs were comparable with those reported with 2-drug combinations. However, thrombocytopenia and neuropathy are more common when 3- or 4-drug combinations including bortezomib are used. In order to improve outcome by reducing toxicity, some studies demonstrated that reducing bortezomib schedule from twice- to once-weekly administration significantly decreases bortezomib-induced peripheral neuropathy [28-30]. These more complex regimens are beneficial also in rrMM, provided that patients have not particular contraindications, such as neuropathy, and if they are able to tolerate potential toxicities associated with such combinations, for instance thrombocytopenia and neuropathy. Replacing thalidomide with lenalidomide and reducing bortezomib dose-intensity may improve outcome and decrease non-hematological toxicity.

How long should rrMM therapy last?

In newly diagnosed MM, prolonged or continuous therapy (i.e. consolidation-maintenance) is associated with higher quality of response and translates into better outcome[28,31-35]. Treatment

duration is a burning question also in rrMM. Whether induction therapy should be limited to 6-9 courses and repeated if necessary, or if it should be prolonged or continued until progression remains an open issue.

Limited therapy with 3- or 4-drug combinations (i.e. lenalidomide-adriamycin-dexamethasone [RAD] or bortezomib-melphalan-prednisone-thalidomide [VMPT])[36,37] do not improve the results obtained with 2-drug regimens such as lenalidomide-dexamethasone (LD)[38] or bortezomib-dexamethasone (VD)[39] whereas consolidation plus maintenance (i.e. bortezomib-adriamycin-dexamethasone [PAD] followed by thalidomide-dexamethasone consolidation (TD) and thalidomide maintenance, or thalidomide-dexamethasone-doxil-bortezomib [ThaDD-V] followed by VD/TD consolidation and thalidomide maintenance)[8,40] after induction with regimens containing bortezomib triples CR rate and improves PFS.

Four-drug combinations such as dexamethasone-bortezomib-doxorubicin-lenalidomide (DVR)[41] or lenalidomide-melphalan-prednisone-thalidomide (RMPT)[42] followed by maintenance with lenalidomide do not seem to improve outcome compared with continuous LD.

Some studies investigated re-treatment with bortezomib after an adequate rest period. Patients enrolled in VISTA trial, who relapsed after VMP and were re-treated with bortezomib, had a CR rate similar to patients treated with lenalidomide- or thalidomide-based salvage therapy[30]. Ongoing prospective study (RETREIVE study) demonstrated that re-treatment with bortezomib is feasible and safe but the benefits of this strategy needs to be confirmed[43].

A recent sub-analysis pooled MM-09 and MM010 studies[9]. Patients achieving PR after induction with LD had 50% probability of obtaining CR/VGPR with further treatment and this response upgrade translated into a better outcome. However, in this study, 60% of patients tolerated and continued therapy after induction, and only 30% remained in the landmark analysis at 12 months. Long-term treatment with LD is feasible and well-tolerated although severe hematologic toxicity, infections and thrombosis are a considerable drawback. Further investigation will define clinical

and biological characteristics of patients who are more likely to benefit from long-term therapy. To date, no specific study has assessed which is the patient population that benefits more from this approach. In particular, the role of prolonged treatment remains controversial in elderly patients for whom long-term therapy may be detrimental. Therefore, a close evaluation of the risk/benefit ratio is warranted.

What is the impact of prior therapy?

Most young and elderly patients with newly diagnosed MM are currently treated with combinations containing at least one new drug. Identifying the best approach at relapse is difficult, especially considering that all patients have already been exposed to thalidomide, lenalidomide and bortezomib. Moreover, few data about the impact of prior therapies on quality of response and outcome in patients with rrMM are available. Before the introduction of novel agents, duration of response progressively shortened with subsequent regimens[44]. Similarly, patients who relapsed or became refractory to novel agents show a poor outcome in terms of both PFS and OS[45].

As shown in Fig. 2, in two studies, the number of previous therapy did not significantly impact on response rate in relapsed/refractory MM patients receiving either bortezomib[23] or lenalidomide monotherapy[24]. Patients included in these two studies were not matched for number of prior therapies (2 or fewer prior treatment regimens versus 3 or more in patients treated with lenalidomide; one prior line of therapy versus more than one in those receiving bortezomib). In patients heavily pre-treated, bortezomib led to a response rate similar to patients who received lenalidomide alone (at least PR 34% vs 26%). Considering the toxicities associated with lenalidomide/bortezomib and the possible presence of comorbidities, these agents could be used alone in elderly or frail heavily pretreated rrMM patients for whom preserving quality of life is essential.

A subset analysis of MM-009/MM-010 trials assessing LD, reported a higher ORR rate (67% vs 57%) and significantly longer PFS (14 months vs 9.5 months; $p=0.047$) and OS (median not

reached *vs* 30.8 months; $p=0.028$) in patients receiving only one prior therapy[46]. These results are consistent with those obtained in a retrospective analysis on patients receiving LD where a higher number of prior regimens was associated with lower ORR[47]. However, this trend was not confirmed in studies including patients treated with 3- or 4-drug combinations. ORR obtained in patients receiving bortezomib-lenalidomide-dexamethasone (VRD)[48] and PAD[6] was not affected by the number of prior therapies. Of note, responses with PAD as second-line treatment (at least PR=80%; CR=13.5%) were similar to PAD as fourth-line treatment (at least PR=64%; CR=12%), and no significant difference in term of 1-yr EFS was detected between patients receiving PAD as second-line or beyond[6]. On the contrary, VMPT regimen is more effective at early-stage disease, leading to a CR rate of 36% compared with 0% in patients heavily pretreated. This also translated into a significantly higher PFS (1-yr 100% *vs* 27%; $p=0.009$)[37]. Similar results were obtained with ThaDD-V combination[8]. No definite data are available to explain how prior therapies may impact on outcome of the 3- and 4-drug combinations described above. However, in patients who received one prior therapy, VMPT and ThaDD-V induce CR rates similar to those obtained in newly diagnosed MM. Conversely, CR rate after PAD regimen is unexpectedly low in these patients, and is comparable to results obtained with lenalidomide plus dexamethasone (Fig. 2). It is not clear if such results depend on the different study population, the limited number of patients enrolled, or any other reason. Of note, these more intense approaches are associated with grade 3-4 neutropenia, infection and peripheral neuropathy, hence they may be more suitable for younger patients or compliant patients at early relapse phase.

As for the type of previous therapies, mainly data on thalidomide and its impact on salvage therapy are available. Thalidomide was introduced before bortezomib and lenalidomide, and it has in fact been used more extensively. Data about previous therapy with thalidomide, summarized in Fig. 3 and Fig. 4, are quite conflicting. Patients receiving bortezomib alone[49] showed worse response and outcome if they had received prior thalidomide; on the contrary, no differences in terms of

ORR and TTP were found in patients previously treated or not with thalidomide and receiving bortezomib plus pegylated liposomal doxorubicin[50]. Pooled data from MM-009/MM-010 trials showed that ORR and TTP were significantly lower in patients with prior thalidomide exposure, suggesting the possibility of a cross-resistance between thalidomide and lenalidomide. However, in this study, patients previously treated with thalidomide had a significant higher number of prior lines of therapy and a longer time from diagnosis[51]. These results are partly in contrast with those from a French retrospective analysis on patients treated with LD[47]. In this study, response rate and PFS were not affected by prior thalidomide, although progression on thalidomide negatively affected both PFS and OS. This may suggest the negative impact of thalidomide maintenance therapy[47,52]. Nevertheless, a recent retrospective study, including a wide cohort of heavily pretreated patients, demonstrated that lenalidomide is effective in patients both thalidomide-resistant or sensitive to a previous thalidomide-therapy.[53] Although only retrospective analyses are currently available, prior thalidomide seems to not affect salvage therapy with lenalidomide.

More complex regimens, such as the combinations bortezomib-dexamethasone-cyclophosphamide (BCD)[54], bortezomib-thalidomide-dexamethasone (VTD)[55], bortezomib-lenalidomide-dexamethasone (VRD)[48] showed a significant higher efficacy in patients who did not receive prior treatment with thalidomide or who are not resistant to it (Fig 4).

The impact of previous therapy with bortezomib is controversial. As reported in Fig. 5, two studies[26,47] with LD showed conflicting results: in one study previous bortezomib did not affect ORR, while in the other one ORR, PFS and OS were significantly better in patients who had not been previously treated with bortezomib. However, the two patient populations did not match for median number of previous regimens (2 vs 4, respectively). In the MM-016 study, multivariate analysis in patients treated with LD showed that prior bortezomib is an adverse risk factor affecting PFS and OS[56]. In contrast with VRD regimen[48], ORR of patients who received PAD regimen was not affected by prior bortezomib exposure, showing the efficacy of bortezomib in consecutive

lines of therapies[6]. This was also confirmed in another study using ThaDD-V combination[8]. The recent update analysis of the VISTA trial shows that bortezomib administered as first-line treatment does not negatively affect response to lenalidomide-, thalidomide- or bortezomib-based regimens at relapse[30]. Data on the impact of previous bortezomib on subsequent salvage therapies are limited and conflicting, and they mainly derive from retrospective studies including small number of patients. Therefore, no definitive conclusion can be drawn [6,8,48].

With regard to salvage treatment following LD, bortezomib-based regimens[57] in heavily pretreated patients led to at least PR rate 43% and prolonged. Another study on patients previously treated with lenalidomide, bortezomib in combination with lenalidomide and dexamethasone showed encouraging results (at least PR = 57%; CR = 15%)[58]. Lenalidomide, cyclophosphamide and prednisone (REP) may be another alternative option in this setting. In one trial, REP induced a response rate of 50% (CR = 14.3%) in patients refractory to LD[59]. On the contrary, thalidomide-based therapies do not exert a substantial activity in patients who received prior treatment with lenalidomide, although only results from very small study are available[60].

A prior stem cell transplantation does not seem affect response and outcome in patients receiving new-drug combinations[48,49,61]. In patients who relapsed after single or tandem autologous stem cell transplantation (ASCT), a recent Italian study reported a significant higher response rate in patients receiving ASCT as second-line compared with those treated with thalidomide/bortezomib based-regimens (85% vs 49%; p=0.0004). However, no differences in terms of PFS or OS were detected between two groups of patients [62].

What is the impact of cytogenetics in rrMM?

The prognostic value of chromosomal abnormalities such as del(13), t(4;14) or del(17p) has not been well defined in rrMM patients treated with new drugs since no prospective, randomized trials have been performed yet. In most retrospective analyses of phase II/III studies including patients

receiving single-agent or new drug combinations, del(13) by FISH was not associated with a significant lower ORR and a shorter TTP/PFS[47,56,63,65]. Jagannath and colleagues evaluated the impact of del(13) identified by either FISH or metaphase cytogenetics on response and outcome in patients receiving bortezomib in SUMMIT and APEX trials. This study found no adverse prognostic impact of del(13) also by conventional cytogenetics, but the number of patients included was considerably small [64]. However, in a Korean study assessing a four-drug combination (bortezomib, cyclophosphamide, thalidomide, dexamethasone) reported a PFS significantly shorter in patients with del(13) by FISH compared with those with normal karyotypes[66] (Fig. 6 and Fig. 7). In a small Canadian study[65], bortezomib seems to be effective in patients with t(4;14) abnormality, while results from studies using LD combination are conflicting[47,56]. Neither bortezomib- or lenalidomide-based combination proved to overcome poor prognosis associated with 17p deletion[36,56,65]. However, no definitive conclusion can be drawn from these small retrospective trials. Moreover, other prognostic factors could be somewhat more relevant than cytogenetics in advanced disease.

An overview of new drugs of second generation

Recent early phase I and II clinical trials using new proteasome inhibitors, third-generation IMiDs and alkylating agents have produced encouraging results in terms of both efficacy and toxicity.

Novel proteasome inhibitors, such as carfilzomib (CFZ; PR-171)[67] salinosporamide (NPI-0052)[68] and CEP18770[69], will soon become part of clinical therapy. Preliminary clinical data on CFZ have been reported, while less information is available on NPI-0052 or CEP18770. CFZ is a new proteasome inhibitor that binds its target selectively and irreversibly[67,70]. Preclinical studies showed that CFZ was more potent in its ability to induce caspase-8 and caspase-9 than BTZ and could overcome bortezomib-resistance in cell lines and primary plasma cell models[67]. After phase I studies targeting B-cell-derived malignancies [71,72], several phase I/II studies investigated

the role of CFZ in patients with rrMM. In PX-171-003 study, 266 patients received CFZ 20 mg/m² on days 1, 2, 8, 9, 15, 16 of a 28-day cycle and, after first cycle, CFZ dose was escalated to 27 mg/m². Patients had received a median of 5 prior lines of therapy (range 1-20) including bortezomib (99.6%), thalidomide (74%), lenalidomide (94%) and stem cell transplantation (65%). Sixty-five percent of patients were refractory to bortezomib. At least PR was reported in 24% of patients, with a median duration of response of 7.4 months. Main grade 3-4 side effects were thrombocytopenia (22%), anemia (20%) and pneumonia (8%) whereas severe peripheral neuropathy was documented in less than 1% of patients [73]. A recent safety analysis evaluating pooled data from more than 600 patients enrolled in 4 trials confirmed that CFZ rarely induced $\geq$ grade 3 peripheral neuropathy [74] and, due to excellent tolerability it can be administered for prolonged periods [75]. Recent studies have reported encouraging preliminary safety and efficacy results with CFZ in patients with renal impairment (RI)[76,77] and with cytogenetic abnormalities [78]. A phase Ib dose-escalation study, evaluated CFZ in association with lenalidomide and low-dose of dexamethasone (CRd) in 40 heavily pre-treated rrMM patients. ORR for the 29 evaluable patients was 59% and median duration of response (DOR) has not been reached (median follow-up 5.2 months). No dose-limiting toxicities (DLTs) or deaths attributed to therapy have been observed. The most common $\geq$ grade 3 adverse events were hematological (thrombocytopenia [n=6], anemia [n=4], and neutropenia [n=6]), and all were reversible. No treatment-related neuropathy, or thrombotic events $\geq$ grade 3 were observed [79]. Based on these data, a Phase III international trial of CRd vs lenalidomide plus low-dose dexamethasone (Rd) in relapsed MM was started in 2010.

Pomalidomide (POM, CC4047) is another IMiD recently introduced[80,81]. In vitro studies showed that POM is more potent than the other IMiDs[82-84]. In a phase I study, POM was given at 4 dose levels (2, 3, 4, 5 mg) on days 1–21 of 28-day cycle, and 32 patients were included. Median number of prior regimens was 7 (range 2–18). MTD has not yet been reached. Eight of 21 (38%) patients treated with POM alone achieved a response (1 CR, 2 PR, 5 MR); mean TTP was 8.3 weeks (range

2–36). In 5 of 13 patients (38%), responses improved after dexamethasone was added (2 PR, 2 MR, 1 SD). Neutropenia and thrombocytopenia were the most common grade 3/4 toxicities, with no dose-dependent increase[85]. In the first phase II trial, 60 patients with rrMM received POM 2 mg daily orally, on days 1 through 28 of a 28-day cycle and dexamethasone 40 mg daily on days 1, 8, 15, 22 of each cycle. Thirty-eight patients achieved objective responses (63%) including 5% of CR and 28% of VGPR. Response rates achieved in lenalidomide- (40%)[86,87], thalidomide- (37%) and bortezomib-refractory patients (60%)[86] were also promising, and so was long-term response found in an extended follow-up of phase I study[88].

The alkylating agent bendamustine is structurally similar to both alkylating agents and purine analogs, and is not cross-resistant with alkylating agents and other drugs in vitro[89]. Bendamustine showed strong activity in MM patients, also in untreated patients[90,91]. Recently, a phase I study investigated the role of bendamustine in combination with lenalidomide and dexamethasone in patients with rrMM[92]. Seven out of 9 evaluable patients (67%) achieved a response, including 1 VGPR and 5 PRs. The MTD of bendamustine and lenalidomide has not been identified at this point. Grade 3/4 adverse events included neutropenia (2 patients), thrombocytopenia (1), anemia (1), hyperglycemia (1), and prolonged QT interval (1).

Several other agents targeting novel molecular mechanisms are in late-stage clinical testing (Table 3). Unfortunately, to date none of these trials has yet reported significant single-agent activity, since some of these agents may result in a more cytostatic than cytotoxic effect. Some of these compounds have also been used in combination with bortezomib or lenalidomide in phase Ib/II trials; however, it is difficult to identify the benefit of these agents when they are used in combination with active agents[93]. Numerous other investigational agents are being considered for early-phase clinical testing. Therapeutic options for MM will continue to increase, and this will substantially improve outcomes.

Expert opinion

To date, there is no strong evidence to guide physicians in the treatment choice for rrMM, and mainly post-hoc analyses are available. Randomized studies are awaited in this context.

First-line therapy choice plays an important role. All compliant patients should receive combination therapy followed by intensification and maintenance with the aim to obtain maximal tumor burden reduction. Valid options are currently available.

The studies described in this review suggest that depth of response is a key factor also in rrMM patients. Indeed, patients attaining a deeper response, in particular CR, have a prolonged PFS.

In patients with suboptimal response to induction, type of therapy represents another crucial point. The data presented here also suggest that in the non-transplant setting, therapy should be prolonged, if tolerated, beyond first response, with the aim of achieving deeper response. However, caution is necessary, and patients' characteristics, such as age, performance status, comorbidities, type of previous therapy, response and tolerance to previous treatments should be taken into account. In younger patients, data are controversial, and the role of prolonged treatment in patients failing to achieve the deepest and fastest response before transplantation remains an open issue. Before the introduction of novel drugs, young patients with suboptimal response to induction benefited most from early transplantation. However, in the era of new drugs, new data have questioned whether transplantation should be preformed early or if second-line treatment should be preferred to improve response before high-dose therapy.

Data reported in published studies showed that more intense treatment regimens including 3 of 4 drugs proved to be beneficial in rrMM. Of course, the toxicity profile of these regimens should be carefully considered. To decrease toxicity and eventually treatment discontinuation, replacing thalidomide by lenalidomide, and reducing bortezomib schedule from twice- to once-weekly administration seem to be effective actions.

As for the type of previous treatment, in patients who received prior treatment with thalidomide, bortezomib alone, as well as BCD, VTD, and VRD, led to negative results, while conflicting results were reported with LD. One study also suggested cross-resistance between thalidomide and

lenalidomide. Prior treatment with bortezomib appeared to negatively impact on outcome in patients receiving VRD, while it did not affect patients treated with PAD combination. Similarly to prior treatment with thalidomide, results with LD are conflicting in patients previously treated with bortezomib. Prior treatment with lenalidomide positively impacted on patients treated with VRD, but no substantial advantage was seen in patients who received thalidomide-based regimens. However, in our opinion, young and compliant patients in first or, at most, second relapse, who have not received multi-drug combination therapies, or who have shown an optimal outcome with them, should receive a combination therapy containing bortezomib, one IMiD, dexamethasone, and possibly one chemotherapeutic agent. This approach aims to obtain a CR, as well as long-term remission duration. On the contrary, younger patient non-compliant with or having a suboptimal outcome after multi-drug combination therapies, elderly patients, and those in third or subsequent relapse, should receive sequential therapy based on the type, side effects and effectiveness of prior therapies. Patient comorbidities, aggressiveness of disease and patients' preference should be considered as well, since there is no evidence to support a specific treatment choice in certain subgroups. The achievement of maximal response should always remain a main goal. Thalidomide with or without steroids may be more suitable in advanced stage of disease. If side effects and complications occur, palliative and supportive therapies to maintain quality of life are a reasonable option.

Consolidation and/or maintenance therapy seems to be of benefit both in combination or sequential therapies also in rrMM. Caution is necessary when using long-term thalidomide since a prolonged exposure to thalidomide may cause peripheral neuropathy, thus limiting the choice of subsequent therapies. On the contrary, lenalidomide seems to be the best candidate for long-term treatment given its safety profile and effectiveness.

To date, there is not sufficient evidence to base therapy choice for rrMM on cytogenetics.

Second generation new-drugs, such as pomalidomide, carfilzomib, bendamustine and histone-deacetylase inhibitors, showed promising preliminary results. They will probably enter the clinical

practice soon, thus expanding the treatment spectrum of multi-drug combinations, and eventually increasing the rescue possibility.

Ongoing and future studies will increase the treatment options available to rrMM patients and improve outcome

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References

1. Kumar SK, Rajkumar SV, Dispenzieri A et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111: 2516–2120.
2. Corso A, Zappasodi P, Barbarano L et al. Long-term outcome in relapsed and refractory multiple myeloma treated with thalidomide. Balancing efficacy and side-effects. *Leuk Res* 2009; 33: e 145-e 149.
3. Hussein MA, Baz R, Srkalovic G et al. Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. *Mayo Clin Proc* 2006; 81: 889-895.
4. 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: 46-53.
5. Corso A, Varettoni M, Mangiacavalli S et al. Bortezomib plus dexamethasone is highly effective in relapsed and refractory myeloma patients but responses are short-lived. *Eur J Haematol* 2009; 83: 449-454.
6. Palumbo A, Gay F, Bringhen S et al. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. *Ann Oncol* 2008; 19: 1160-1165.
7. Delforge M, De Samblanx H, Demuynck H et al. International observational study on bortezomib (VELCADE) in relapsed multiple myeloma: preliminary efficacy and quality of life

- (QoL) results from the belgian population. *Blood* (ASH Annual Meeting Abstract) 2009; 114: abstract 4523.
8. Offidani M, Polloni C, Corvatta L et al. Thalidomide, Dexamethasone, Doxil and Velcade (ThaDD-V) induction therapy followed by consolidation/maintenance is very effective in early relapsed/refractory MM. *Blood* (ASH Annual Meeting Abstract) 2010
9. Harousseau JL, Dimopoulos MA, Wang M et al. The quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. *Haematologica* 2010; 95: 1738-1744.
10. Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. *Leukemia* 2009; 23: 449-456.
11. Palumbo A, Gay F. How to treat elderly patients with multiple myeloma : combination of therapy or sequencing. *Hematology Am Soc Hematol Educ Program* 2009: 566-577.
12. Mehta J, Cavo M, Singhal S. How I treat elderly patients with myeloma. *Blood* 2010; 116: 2215-2223.
13. Patriarca F, Petrucci MT, Bringhen S et al. Considerations in the treatment of multiple myeloma: a consensus statement from Italian experts. *Eur J Haematol* 2009; 82: 93-105.
14. Harousseau JL, Palumbo A, Richardson PG et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with non-intensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. *Blood* 2010, prepublished online July 13. DOI 10.1182/blood-2010-03-275800.
15. Niesvizky R, Jayabalan DS, Christos PJ et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naïve symptomatic multiple myeloma. *Blood* 2008; 111: 1101-1109.
16. Kumar S, Dingli D, Dispenzieri A et al. Impact of additional cytoreduction following autologous SCT in multiple myeloma. *Bone Marrow Transplant* 2008; 42: 259-264.

17. Lahuerta JJ, Mateos MV, Martinez-Lopez J et al. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. *J Clin Oncol* 2008; 26: 5775-5782.
18. Gertz MA, Kumar S, Lacy MQ et al. Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction. *Blood* 2010; 115: 2348-2353.
19. Moreau P, Facon T, Attal M et al. Comparison of reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as induction treatment prior to ASCT in de novo multiple myeloma (MM): results of IFM2007-02 study. *J Clin Oncol* 2010; 28 (suppl): abstract 8014.
20. Ludwig H, Viterbo L, Greil R et al. Phase II study of bortezomib, thalidomide and dexamethasone $\pm$ cyclophosphamide as induction therapy in previously untreated multiple myeloma (MM): safety and activity including evaluation of MRD. *Haematologica* 2010; 95 (suppl. 2): abstract 0371.
21. Richardson PG, Weller E, Lonial S et al. Lenalidomide, bortezomib and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010;116: 679-686.
22. Kumar S, Fkinn IW, Hari PI et al. Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide for newly diagnosed multiple myeloma: encouraging results from the multi-center, randomized, phase 2 EVOLUTION Study. *Blood (ASH Annual Meeting Abstract)* 2009; 114: abstract 127.
23. Richardson PG, Sonneveld P, Schuster M et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; 352: 2487-2498.
24. Richardson P, Jagannath S, Hussein M et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood* 2009; 114: 772-778.

25. Orlowski RZ, Nagler A, Sonneveld P et al. Randomized phase III trial 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: 3892-3901.
26. Weber DM, Chen C, Niesvizky R et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; 357: 2133-2142.
27. Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; 357: 2123-2132.
28. Mateos MV, Oriol A, Martinez-Lopez J et al. Bortezomib, melphalan and prednisone versus bortezomib. Thalidomide and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010; 11: 934-941.
29. Bringhen S, Larocca A, Rossi D et al. Efficacy and safety of once weekly bortezomib in multiple myeloma patients. *Blood* 2010; 116: 4745-4753.
30. Mateos M-V, 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: 2259-2266.
31. McCarthy PL, Owzar K, Anderson KC et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. *J Clin Oncol* 2010; 28 (suppl.); abstract 8017.
32. Attal M, Cristini C, Marit G et al. Lenalidomide maintenance after transplantation for myeloma. *J Clin Oncol* 2010; 28 (suppl.); abstract 8018.
33. Ladetto M, Pagliano G, Ferrero S et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol* 2010; 28:2077-2084.

34. Palumbo A, Bringhen S, Rossi D et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol* 2010; 28(34): 5101-5109.
35. Palumbo A, Gay F, Falco P et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *J Clin Oncol* 2010; 28: 800-807.
36. Knop S, Gerecke C, Liebisch P et al. Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myeloma). *Blood* 2009; 113: 4137-4143.
37. Palumbo A, Ambrosini MT, Benevolo G et al. Bortezomib, melphalan, prednisone and thalidomide for relapsed multiple myeloma. *Blood* 2007; 109: 2767-2772.
38. 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* 2010; 23: 2147-2152.
39. Harrison SJ, Quach H, Dean J et al. Bortezomib and dexamethasone from cycle 1 as treatment and maintenance for multiple myeloma relapse (The BoMeR trial): impact on response and time to progression. *J Clin Oncol* 28 (suppl.); abstract 8151.
40. Sook Lee S, Suh C, Kim BS et al. Bortezomib, doxorubicin, and dexamethasone combination therapy followed by thalidomide and dexamethasone consolidation as a salvage treatment for relapsed or refractory multiple myeloma: analysis of efficacy and safety. *Ann Hematol* 2010; 89: 905-912.
41. Baz R, Walker E, Karam MA et al. Lenalidomide and pegylated liposomal doxorubicin-based chemotherapy for relapsed or refractory multiple myeloma: safety and efficacy. *Ann Oncol* 2006; 17: 1766-1771.

42. Palumbo A, Larocca A, Falco P et al. Lenalidomide, melphalan, prednisone and thalidomide (RMPT) for relapsed/refractory multiple myeloma. *Leukemia* 2010; 24: 1037-1042.
43. Petrucci MT, Blau IW, Corradini P et al. Efficacy and safety of retreatment with bortezomib in patients with multiple myeloma: interim results from RETRIEVE, a prospective international phase 2 study. *Blood (ASH Annual Meeting Abstract)* 2009; 114: abstract 3866.
44. Kumar SK, Therneau TM, Gertz MA et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004; 79: 867-874.
45. Kumar SK, Crowley J, Klein SK et al. Treatment patterns and outcome among patients with multiple myeloma relapsing and or refractory to bortezomib and immunomodulatory drugs: a multicenter International Myeloma Working Group study. *J Clin Oncol* 2010; 28 (suppl.); abstract 8125.
46. Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. *Eur J Haematol* 2009; 82: 426-432.
47. Avet-Loiseau H, Soulier J, Fermand J-P 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: 623-628.
48. 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: 1769-1778.
49. 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: 531-534.

50. 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: 1529-1537.
51. 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: 4445-4451.
52. Barlogie B, Tricot G, Anaissie E et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; 354: 1021-1030.
53. Guglielmelli T, Bringhen S, Roderh S et al. Previous thalidomide therapy may not affect lenalidomide response and outcome in relapsed or refractory multiple myeloma patients. *Eur J Cancer* 2011. DOI: 10.1016/j.ejca.2010.12.026.
54. 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: 330-337.
55. 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: 1419-1427.
56. Reece D, Song KW, Fu 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: 522-525.
57. Reece DE, Trieu Y, Chen C et al. Sequencing novel agents in relapsed/refractory multiple myeloma: use of bortezomib-based therapy after lenalidomide + dexamethasone. *Blood (ASH Annual Meeting Abstract)* 2009; 114: abstract 1853.
58. Richardson P, Jagannath S, Jakubowiak A et al. Lenalidomide, bortezomib, and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma (MM): encouraging response

- rates and tolerability with correlation of outcome and adverse cytogenetics in a phase II study. Blood (ASH Annual Meeting Abstract) 2008; 112: abstract 1742.
59. van de Donk NWCJ, Wittebol S, Minnema MC et al. Lenalidomide (Revlimid) combined with continuous oral cyclophosphamide (endoxan) and prednisone (REO) is effective in lenalidomide/dexamethasone-refractory myeloma. Br J Haematol 2009; 148: 332-340.
 60. Young T, Chu C-M, Xu W et al. Activity with thalidomide-based therapy following lenalidomide plus dexamethasone in patients with relapsed/refractory multiple myeloma. Blood (ASH Annual Meeting Abstract) 2009; 114: abstract 3855.
 61. Chanan-Khan AA, Yu Z, Weber D et al. Lenalidomide (L) in combination with dexamethasone (D) significantly improves time to progression (TTP) in non-stem cell transplant patients with relapsed or refractory /rel/ref) multiple myeloma (MM): analysis from MM-09 and MM-010 randomized phase III clinical trials. Blood (ASH Annual Meeting Abstract) 2006; 108: abstract 3554.
 62. Crippa C, Ferrari S, Drera M et al. Outcome of autologous stem cells transplantation (ASCT) in comparison with new drugs-based regimens as salvage treatment after first line therapy with single or tandem ASCT in multiple myeloma patients. Haematologica 2010; 95 (suppl 2): abstract 0378.
 63. Sagaster V, Ludwig H, Kaufmann H et al. Bortezomib in relapsed multiple myeloma: response rates and duration of response are independent of a chromosome 13q-deletion. Leukemia 2007; 21: 164-168.
 64. Jagannath S, Richardson PG, Sonneveld P et al. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. Leukemia 2007; 21: 151-157.
 65. Chang H, Trieu Y, Qi X et al. Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: adverse effect of 1q21 gains. Leuk res 2010; May25. DOI: 10.1016/j.leukres.2010.05.002.

66. Kim y-k, Sohn S-K, Lee J-H 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: 475-482.
67. Kuhn DJ, Chen Q, Voorhees PM et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood* 2007;110: 3281–3290.
68. Chauhan D, Hideshima T, Anderson KC. A novel proteasome inhibitor NPI-0052 as an anticancer therapy. *Br J Cancer* 2006; 95:961–965.
69. Piva R, Ruggeri B, Williams M et al. CEP-18770: a novel, orally active proteasome inhibitor with tumor-selective pharmacologic profile competitive with bortezomib. *Blood* 2008; 111: 2765-2775.
70. Bennett MK, Kirk CJ. Development of proteasome inhibitors in oncology and autoimmune diseases. *Curr Opin Drug Discov Devel* 2008; 11: 616–625.
71. Alsina M, Trudel S, Vallone M et al. Phase 1 single agent antitumor activity of twice weekly consecutive day dosing of the proteasome inhibitor carfilzomib (PR-171) in hematologic malignancies. *Blood (ASH Annual Meeting Abstract)* 2007; 110: abstract 411.
72. Orłowski RZ, Stewart K, Vallone M et al. Safety and antitumor efficacy of the proteasome inhibitor carfilzomib (PR-171) dosed for five consecutive days in hematologic malignancies: phase 1 results. *Blood (ASH Annual Meeting Abstract)* 2007; 110: abstract 409.
73. Siegel DS, Martin T, Wang M et al. Results of PX-171-003-A1, an open-label, single arm, phase 2 (Ph 2) study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma. *Blood (ASH Annual Meeting Abstract)* 2010; 116: abstract 985.
74. Singhal SB, Siegel DS, Martin T et al. Pooled safety analysis from phase 1 and 2 studies of carfilzomib (CFZ) in patients with relapsed and/or refractory multiple myeloma (MM). *Blood (ASH Annual Meeting Abstract)* 2010; 116: abstract 1954.

75. Jagannath S, Vij R, Kaufman JL et al. Long-term treatment and tolerability of the novel proteasome inhibitor carfilzomib (CFZ) in patients with relapsed and/or refractory multiple myeloma. *Blood (ASH Annual Meeting Abstract)* 2010; 116: abstract 1953.
76. Badros AZ, Vij R, Martin T et al. Phase I study of carfilzomib in patients (Pts) with relapsed and refractory multiple myeloma (MM) and varying degrees of renal insufficiency. *Blood (ASH Annual Meeting Abstract)* 2009; 114: abstract 3877.
77. Niesvizky R, Vij R, Martin T et al. Phase II study of carfilzomib in patients with relapsed or refractory multiple myeloma and varying degrees of renal insufficiency. *Haematologica* 2010; 95 (suppl.2): abstract 0392
78. Jakubowiak A, Wang L, Orlowski RZ et al. Influence of Cytogenetics in Patients with Relapsed and Refractory Multiple Myeloma (MM) Treated with Carfilzomib (CFZ). *Blood (ASH Annual Meeting Abstract)* 2009; 114: abstract 1827.
79. Wang M, Bensinger W, Orlowski R et al. PX-171-006, a phase IB dose-escalation study of carfilzomib + lenalidomide + low-dose dexamethasone in relapsed and/or refractory multiple myeloma. *Haematologica* 2010; 95 (suppl.2): abstract 0388.
80. Streetly MJ, Gyertson K, Daniel Y et al. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol*. 2008;141: 41–51.
81. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol* 2004; 22: 3269–3276.
82. Galustian C, Meyer B, Labarthe MC et al. The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol Immunother* 2009; 58: 1033–1045.
83. Verhelle D, Corral LG, Wong K et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res* 2007; 67: 746–755.

84. Shalapour S, Zelmer A, Pfau M et al. The thalidomide analogue, CC-4047, induces apoptosis signaling and growth arrest in childhood acute lymphoblastic leukemia cells in vitro and in vivo. *Clin Cancer Res* 2006; 12: 5526–5532.
85. Richardson P, Siegel D, Baz R et al. A Phase 1/2 Multi-Center, Randomized, Open Label Dose Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of Pomalidomide Alone or in Combination with Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib. *Blood* (ASH Annual Meeting Abstract) 2009; 114: abstract 301.
86. Lacy MQ, Hayman SR, Gertz MA et al. Pomalidomide (CC4047) plus low-dose dexamethasone (Pom/dex) is highly effective therapy in relapsed multiple myeloma. *Blood* (ASH Annual Meeting Abstract) 2008; 112: abstract 866.
87. Lacy MQ, Hayman SR, Gertz MA et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 2010; 24: 1934-1939.
88. Streetly M, Stewart O, Gyertson K et al. Pomalidomide Monotherapy for Relapsed Myeloma Is Associated with Excellent Responses and Prolonged Progression Free and Overall Survival. *Blood* (ASH Annual Meeting Abstract) 2009; 114: abstract 3878.
89. Diehl V, Cheson BD. Bendamustine in the treatment of hematologic malignancies. Introduction. *Semin Oncol* 2002; 29:1–3.
90. Pönisch W, Rozanski M, Goldschmidt H et al. Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. *Br J Haematol* 2008; 143: 191–200.
91. Pönisch W, Mitrou PS, Merkle K et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and

- prednisone--a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). *J Cancer Res Clin Oncol* 2006;132:205–212.
92. Lentzsch S, O’Sullivan A, Lalo S et al. A Phase I Study of Bendamustine Combined with Lenalidomide and Dexamethasone in Patients with Refractory or Relapsed Multiple Myeloma. *Blood* (ASH Annual Meeting Abstract) 2009; 114: abstract 1856.
93. Stewart AK. Novel therapies for relapsed myeloma. *Hematology Am Soc Hematol Educ Program* 2009: 578-86.
94. Ciolli S, Leoni F, Casini C et al. The addition of liposomal doxorubicin to bortezomib, thalidomide and dexamethasone significantly improve clinical outcome of advanced multiple myeloma. *Br J Haematol* 2008; 141: 814-819.