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Novel agents in Waldenström macroglobulinemia

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Abstract

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow with lymphoplasmacytic cells and the detection of an IgM monoclonal gammopathy in the serum. WM is considered an incurable disease, with a median overall survival of 87 months. The success of targeted therapy in multiple myeloma has led to the development and investigation of more than 30 new compounds in this disease and in other plasma cell dyscrasias, including WM, both in the preclinical settings and as part of clinical trials. Among therapeutic options, first-line therapies have been based on single-agent or combination regimens with alkylator agents, nucleoside analogues and the monoclonal antibody anti-CD20. Based on the understanding of the complex interaction between WM tumor cells and the bone marrow microenvironment, and the signaling pathways that are deregulated in WM pathogenesis, a number of novel therapeutic agents are now available and have demonstrated significant efficacy in WM. The range of the overall response rate for these novel agents is between 25 and 96%. Ongoing and planned future clinical trials include those using protein kinase C inhibitors such as enzastaurin, new proteasome inhibitors such as carfilzomib, histone deacetylase inhibitors such as LBH589, humanized CD20 antibodies such as ofatumumab and additional alkylating agents such as bendamustine. These agents, when compared with traditional chemotherapeutic agents, may lead in the future to higher responses, longer remissions and better quality of life for patients with WM. This article will mainly focus on those novel agents that have entered clinical trials for the treatment of WM.

Keywords

novel agents; targeted therapies; Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow with lymphoplasmacytic cells and the demonstration of an IgM monoclonal gammopathy [1–4]. WM is classified, according to the Revised European American Lymphoma and WHO systems, as a lymphoplasmacytic lymphoma [3,4]. The overall incidence of WM varies between two and five new cases per million people per year, which includes 1500 new cases diagnosed each year in the USA [5–7]. The incidence rates are higher in Caucasians compared with African-Americans, and when looking at the age-adjusted rates for men and women within the USA, men have a higher incidence, with 3.4 per million compared with 1.7 per million, respectively [5–7]. The most recognized risk factor for developing WM is the presence of IgM-monoclonal gammopathy of undetermined

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significance (IgM-MGUS) in the serum, which confers a 46-fold higher relative risk than the general population [8]. There is also a higher risk among individuals who have a first-degree relative with a B-cell neoplasm, which is approximately 18.7% of patients in various studies [9,10]. WM remains an incurable disease with a median overall survival (OS) of 87 months and a median disease-specific survival of 11.2 years [7]. Factors associated with poor prognosis include advanced age, high β 2-microglobulin, cytopenias, low albumin, serum IgM monoclonal protein and organomegaly [7–11]. Patients with low-risk disease had a 5-year survival of 87%, while patients with high-risk disease had a 5-year survival of only 36%. This is now accepted as the uniform prognostic staging system for WM [7].

After almost 40 years, the paradigm for the treatment of monoclonal gammopathies has dramatically changed; for example, therapeutic options in multiple myeloma (MM) have evolved from the introduction of melphalan and prednisone in the 1960s, high-dose chemotherapy and stem cell transplantation in the late 1980s and 1990s, to the rapid introduction of small novel molecules within the last 7 years. Similar advances have been reached in the treatment of WM based on the understanding of the complex interaction of WM cells with the bone marrow microenvironment and the signaling pathways that are dysregulated in this process. A number of novel therapeutic agents are now available and are playing a key role in the preclinical settings and/or as part of clinical trials for the treatment of WM [12]. Novel agents include immunomodulatory drugs, proteasome inhibitors, phosphoinositide 3-kinase (PI3K)/Akt and mTOR inhibitors.

Timing & choice of treatment

The treatment of patients with WM depends on the presence of symptoms or the signs of disease progression. Patients with asymptomatic disease should not be treated independent of the monoclonal protein level. Some of the clinical signs or symptoms that indicate time to initiate therapy include:

- Recurrent fever, night sweats, weight loss and fatigue;
- Hyperviscosity;
- Lymphadenopathy, which is either symptomatic or bulky (≥ 5 cm in maximum diameter);
- Symptomatic hepatomegaly and/or splenomegaly;
- Symptomatic organomegaly and/or organ or tissue infiltration;
- Peripheral neuropathy due to WM;
- Symptomatic cryoglobulinemia;
- Cold agglutinin anemia;
- Immune hemolytic anemia and/or thrombocytopenia;
- Nephropathy related to WM;
- Amyloidosis related to WM;
- Platelet count $< 100 \times 10^9/l$;
- Hemoglobin level < 10 g/dl [13].

Standard therapeutic options

Current therapies used in the upfront or relapsed settings include alkylator agents (e.g., chlorambucil or cyclophosphamide), nucleoside analogues (e.g., cladribine or fludarabine)

and the monoclonal antibody rituximab (Table 1) [14–16]. The overall response rates (ORRs) in the upfront setting varies between 30 and 70%; this includes complete response (CR), partial response (PR) and minimal response (MR), with CR rates <10%, and median durations of response averaging 2–3 years [14,17]. In the salvage setting, the ORR is between 30–40%, with a median response duration ≤ 1 year [14,18]. The use of fludarabine or alkylating agents in combination therapy will stimulate high responses, however, with elderly patients the consequence involves significant toxicities [19,20]. A total of 337 WM patients were enrolled in a Phase III clinical trial comparing chlorambucil versus fludarabine. The authors reported a PR plus CR rate of 40 versus 51%, respectively, and a progression-free survival (PFS) of 36.4 versus 27.1 months, respectively. No statistically significant differences in OS was reported [21].

Rituximab is one of the most commonly used treatment options in WM, especially in the USA, and standard treatment yielded response rates of 35–48% (four weekly infusions of 375 mg/m² or extended treatment involving four weekly rituximab treatments repeated at 3 months) [15,21–23]. Another important note involving rituximab treatment is the initial increase in the IgM level; this is termed as the ‘IgM flare’ and is seen in approximately 54% of patients [24,25]. Although these levels may remain elevated for 3–4 months, they do not indicate treatment failure. Alemtuzumab has also been tested in 28 patients with WM, five were untreated and 23 were treated. All of the treated patients had prior rituximab treatment. The ORR was 76% with 32% PRs. In addition, the combinations of rituximab, cyclophosphamide, doxorubicin, oncovin and prednisone (R-CHOP) or rituximab, cyclophosphamide, vincristine (oncovin) and prednisone (R-CVP) or rituximab, cyclophosphamide and prednisone (R-CP) have shown high responses with >80% ORR in patients with WM in small prospective or retrospective reviews [26–28]. The combination of bendamustine and rituximab (BR) has recently been compared with R-CHOP in a large cohort of newly diagnosed untreated low-grade lymphomas that includes 42 patients with WM [29,30]. The ORR in 40 evaluable patients was 96% for BR versus 94% for R-CHOP. BR was associated with lower incidences of grade 3 and 4 cytopenias, infectious complications and alopecia.

Novel therapeutic agents

Novel therapeutic agents that have demonstrated efficacy in WM include bortezomib, thalidomide, perifosine, enzastaurin, everolimus and histone-deacetylases inhibitors. This efficacy has been shown in single agent-based clinical trials (Table 2) as well as in combinatory studies (Table 3).

Bortezomib—Bortezomib has been widely tested in clinical trials in WM patients [29–38]. The use of bortezomib as a single agent in WM has been tested in two Phase II clinical trials in relapsed WM. In one of these, the agent was used in the standard dose of 1.3 mg/m² twice a week on days 1, 4, 8 and 11. To determine the effectiveness in the general WM patient population, Chen *et al.* administered bortezomib to 27 WM patients, 44% of whom were previously untreated and 56% were previously treated with bortezomib [35]. The ORR was 78% and major responses (PR or better) were seen in 44% of patients; there were no CRs observed in these studies. Sensory neuropathy was the primary toxicity with 20 out of 27 (74%) patients affected.

A recent study using the combination of bortezomib, rituximab and dexamethasone was tested in newly diagnosed patients with WM and exhibited an exciting ORR of 96%, including 83% achieving PR [36]. However, neuropathy was again a major toxicity with this regimen. Therefore, treatment of bortezomib in current clinical trials has been reduced to once a week at 1.6 mg/m² in an attempt to reduce the occurrence of peripheral neuropathy.

A Phase II study aimed to evaluate weekly bortezomib in combination with rituximab in patients with relapsed/refractory WM has recently been conducted [37]. All patients received bortezomib intravenously weekly at 1.6 mg/m² on days 1, 8, and 15 every 28 days × six cycles, and rituximab 375 mg/m² on days 1, 8, 15 and 22 on cycles one and four. A total of 37 patients (26 men and 11 women; median age: 62 years; range: 42–73 years) were treated. All of them had symptomatic disease and required therapy. The median number of lines of previous treatment was three (range: 1–5 lines), including previous bortezomib and previous rituximab in some of those patients. The median IgM baseline level was 3540 mg/dl (range: 700–10,800 mg/dl). The median follow up is 10 months (range: 1–24 months). At least MR or better was observed in 81% (95% CI: 65–92%) with two patients (5%) in CR/near CR, 17 (46%) in PR, and 11 (30%) in MR. The median time to progression was 16.4 months (95% CI: 11.4–21.1%). Death occurred in one patient due to viral pneumonia. The most common grade 3 and 4 therapy-related adverse events included reversible neutropenia (in 16%), anemia (in 11%) and thrombocytopenia (in 14%). Grade 3 peripheral neuropathy occurred in only two patients (5%). The median event-free survival is 12 months (95% CI: 11–20%), with estimated 12 month and 18 month event-free survival of 49% (95% CI: 31–67%) and 38% (95% CI: 20–56%), respectively. The median OS has not been reached [37]. No significant peripheral neuropathy has been observed to date with this regimen. Studies using this combination in newly diagnosed patients are ongoing.

A Phase II trial of weekly bortezomib in combination with rituximab has been conducted in untreated patients with WM [38]. This study aimed to determine the activity and safety of weekly bortezomib and rituximab in WM. Only patients who had symptomatic WM and were not previously treated were enrolled in this study. All patients received bortezomib intravenously weekly at 1.6 mg/m² on days 1, 8, 15 and 28 × six cycles, and rituximab 375 mg/m² weekly on cycles one and four. Dexamethasone was not added. A total of 26 patients were treated. At least MR or better was observed, assessed using serum protein electrophoresis, in 24 out of 26 cases (92%) with two patients (8%) in CR/near CR, 15 (54%) in PR and 7 (27%) in MR. Two patients (8%) had stable disease. By using IgM by nephelometry, all 26 patients (100%) had at least a minor response, with two (8%) CR, 15 (58%) in PR and nine (35%) with minor response. The median time of follow up is 11.2 months (range: 3–18.6). To date, six (23%) patients have developed progressive disease (PD) or required a new therapy. A single patient has died due to disease progression. The median PFS and OS have not been reached. The most common grade 3 and 4 therapy-related adverse events included anemia (in three patients), lymphopenia (in two patients), neutropenia, leukopenia, thrombocytopenia, pneumonia, fatigue, allergic reaction and nausea and vomiting (in one patient) for each. A total of five patients developed grade 2 peripheral neuropathy, including four who did not have neuropathy at baseline. This required dose reduction in cycles four and five and these neuropathies resolved to grade 1 or less with follow up. One case developed grade 1 herpes zoster reactivation in cycle one. The combination of weekly bortezomib and rituximab exhibited significant activity and minimal neurological toxicity in patients with untreated WM.

Immunomodulatory drugs—The combination of thalidomide and rituximab has been tested in WM, using thalidomide 200 mg daily for the first 2 weeks followed by 400 mg daily for a total of 1 year. A total of 23 patients were evaluable for this study and had an ORR of 78% with 65% PRs. Dose reductions of thalidomide occurred in all patients and led to discontinuation of therapy in 11 patients [39]. Lenalidomide 25 mg/day in combination with rituximab has been tested in 16 patients. Of these, 12 were evaluable for response, with an ORR of 67% including four PRs. Acute decreases in hematocrit were observed during the first 2 weeks of lenalidomide therapy in 13 out of 16 (81%) patients with a median hematocrit decrease of 4.4% (1.7–7.2%), resulting in four patient hospitalizations [40].

Perifosine—Perifosine is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkylphospholipids [41]. It has shown activity in Phase II trials in MM. Our previous studies have shown that the activity of the survival protein Akt is upregulated in B cells from patients with WM compared with normal B cells, and that downregulation of Akt leads to significant inhibition of proliferation and induction of apoptosis in WM cells *in vitro*. *In vivo* studies of perifosine have shown significant cytotoxicity and inhibition of tumor growth in a xenograft mousemodel [42]. Moreover, perifosine was shown to induce synergistic cytotoxicity with rituximab and bortezomib, as well as with other conventional agents, including fludarabine and cyclophosphamide [42]. Based on this preclinical activity, a Phase II clinical trial using Perifosine was conducted, involving 37 patients (27 men and ten women; median age: 65 years; range: 44–82 years) [43]. Of these patients, 49% were relapsed and 30% were relapsed and refractory to previous therapy. The median number of lines of previous treatment was two (range: one–five lines). Previous therapy included rituximab, nucleoside analogues (e.g., fludarabine and 2-CDA), combination chemotherapy (e.g., R-CHOP and R-CVP), chlorambucil and bortezomib. Of the patients, 11% achieved a PR, with a MR observed in 24% of the patients. Stable disease occurred in 54% of the patients, PFS was 12.6 months.

Perifosine was generally well tolerated with minimal grade 3 and 4 toxicities [43]. The clinical findings were also corroborated by translational studies that demonstrated a significant reduction of pGSK3 at protein level, as shown by immunoistochemistry on bone marrow slides of patients at the end of treatment, together with an inhibition of NFκB family genes at gene expression level in primary tumor cells at the end of treatment [43].

Enzastaurin—Enzastaurin is an oral serine/threonine kinase inhibitor that targets the protein kinase C and PI3K/AKT pathways. Enzastaurin has demonstrated activity in preclinical models of MM and WM [44,45], and clinical studies suggest encouraging activity and a well-tolerated safety profile in a variety of hematologic cancers. A multicenter Phase II trial is ongoing to determine whether further study of single-agent enzastaurin is warranted in patients with previously treated WM or MM [46]. The primary objective is to assess the response rate, secondary objectives include assessment of time to progression, safety, biomarkers and the impact of adding dexamethasone to enzastaurin in patients with PD. Eligible patients with WM and one–five prior therapies were enrolled and treated with oral enzastaurin twice daily in 28-day cycles. A total of 29 patients with WM were enrolled. The median age was 65.6 years (range: 51.7–82.3 years) and 93% of patients had an Eastern Cooperative Oncology Group performance status of 0–1. Patients had a median of two prior systemic therapies and 26 patients (89.7%) had prior rituximab. Patients completed a median of four cycles. Six patients received ≥six cycles of enzastaurin treatment. A total of 20 patients remain on study. There were no drug-related discontinuations. One patient had a PR and seven patients had a MR, for a response rate (CR plus PR plus MR) of 27.6%. IgM decreased by ≥25% in 11 patients. Three (10.3%) patients had a PD. One patient had a drugrelated grade 3 wound complication; there were no other drug-related grade ≥3 toxicities. Although the results are preliminary, enzastaurin appears to have activity and is well tolerated in patients with previously treated WM. The WM cohort was expanded to allow up to 50 patients to be treated on study.

Everolimus (RAD001)—Based on the preclinical data showing increased activity of the PI3K/mTOR pathway in WM, rapamycin (a mTOR inhibitor) has been studied *in vitro* in WM. It has shown significant cytotoxicity in WM cells lines, specifically when combined with bortezomib [47].

A Phase II trial of single-agent everolimus initiated patients with WM with relapsed or relapsed/refractory disease [48]. This study was conducted in a collaborative effort between

the Dana-Farber Cancer Institute and Mayo Clinic College of Medicine. Eligible patients had measurable disease (IgM monoclonal protein >1000 mg/dl, with >10% marrow involvement or nodal masses >2 cm), a platelet count >75,000 $\times$ 10⁶/l, a neutrophil count >1000 $\times$ 10⁶/l, and a creatinine and bilirubin <2 $\times$ laboratory upper limit of normal. Patients received everolimus 10 mg orally daily and were evaluated monthly. Tumor response was assessed after cycles two and six and then every three cycles until progression. A total of 50 patients were treated. The median age was 63 years (range: 43–85 years). The ORR (CR plus PR plus MR) was 70% (95% CI: 55–82%), with a PR of 42% and 28 MR. The median duration of response and median PFS has not been reached. The estimated PFS at 6 and 12 months is 75% (95% CI: 64–89%) and 62% (95% CI: 48–80%), respectively. Grade 3 or higher related toxicities were observed in 56% of patients. The most common were hematological toxicities with cytopenias.

Everolimus represents, a potentially very effective drug in WM: it has high single-agent activity with an ORR of 70% and manageable toxicity in patients with relapsed WM, and offers a potential new therapeutic strategy for this patient group.

Panobinostat (LBH589)—Preclinical studies have demonstrated that primary WM cells exhibit a higher level of histone-deacetylases (HDACs), thus providing the rational for testing HDAC inhibitors in this disease. Specifically, *in vitro* studies have confirmed the antitumor activity of panobinostat (LBH589) in primary tumor cells and cell lines [49]. Subsequently, a study has been conducted in order to determine the safety and activity of panobinostat in patients with relapsed or relapsed/refractory WM [50]. A total of 27 patients have been enrolled. The median number of cycles on therapy is four (range: 1–12) and four of the patients came off due to toxicity. MR or better has been achieved in 60% of patients (PR: 24%; MR: 36%). In addition, 36% of the patients achieved stable disease and 4% showed progression. Grade 3 and 4 toxicities include anemia (in 15%), grade 4 leukopenia (in 3%), neutropenia (in 26%) and thrombocytopenia (in 52%). These findings indicate that panobinostat is an active therapeutic agent in patients with WM, with an ORR of 60% in patients with relapsed or refractory WM [50]. Future Phase II–III trials will be required to better define efficacy of HDAC inhibition in WM patients.

Monoclonal antibody-based therapies—It has been demonstrated that CD52 is widely expressed on WM cells, as well as on bone marrow-derived mast cells [51], thus providing the preclinical rational for testing anti-CD52 monoclonal antibodies in WM patients. Alemtuzumab (anti-CD52 antibody) has been tested in 27 previously treated WM patients; and an ORR of 76% was observed, with 32% of the patients achieving a major response. With a median follow-up exceeding 9 months, 58% of the patients were free of progression. Hematologic-related side effects and cytomegalovirus reactivation were observed [52].

Preclinical efficacy of new small molecules & epigenetic-based therapies in WM

Preclinical studies have demonstrated anti-WM activity in the new proteasome inhibitors, NPI-0052 and PR-047, and the PI3K/Akt/mTOR inhibitor, NVPBEZ235 [53,54], either *in vitro* or *in vivo*. This has provided the rational for testing these compounds in WM. It has been recently demonstrated that primary WM cells present a specific microRNA signature. Among the deregulated microRNAs in WM cells, as compared with the related normal cellular counterpart, WM tumor cells are characterized by an upregulation of microRNA155. This provides *in vitro* and *in vivo* preclinical evidences for testing antimicroRNA155-based therapy in this disease [55].

Conclusion

In summary, the last decade has marked a new era in the treatment of monoclonal gammopathies. Indeed, a new paradigm shift has evolved utilizing novel therapeutic agents targeting the malignant clone and its bone marrow microenvironment. The combination of novel agents with chemotherapeutic drugs and/or glucocorticoids has demonstrated high response rates with CR rates, comparable to those achieved in the stem cell transplant setting. This has been supported by *in vitro* and *in vivo* evidence, showing the antitumor activity of those novel agents in WM, as well as in other B-cell malignancies (Figure 1).

Response rates have improved significantly with less long-term toxicities with these novel combinations. Nevertheless, to date there are no US FDA approved therapeutic agents for this rare disease. Further efforts are needed to perform large multicenter clinical trials that will allow the approval of these novel agents, which will pave the way for further drug development and better responses in patients with WM.

The future holds many more challenges for the treatment of WM, including the combination of agents, which achieve higher response rates, more resilient durations of response, less toxicity and prolonged survival for patients, as well as making WM an increasingly chronic and treatable disease.

Future perspective

Over the last 5 years, significant advances have occurred in the understanding of the underlying pathogenesis of WM. This has led to the development of novel therapeutic agents and better targeted agents for patients with this disease. Over the next 5–10 years, we expect several major advances in WM, including genome sequencing studies that can help identify specific mutations in subgroups of patients with WM, advances in understanding the role of epigenetic modifications that occur in WM and how to target these changes through the use of regulators of miRNA, demethylating agents and histone deacetylase inhibitors. Finally, a better understanding of the role of the bone marrow microenvironment and the niches regulating the growth and dissemination of the tumor clone will significantly advance the development of therapeutic agents that do not only target the tumor clone, but also its supportive bone marrow milieu.

Executive summary

Epidemiology

- The overall incidence of Waldenström macroglobulinemia (WM) varies between 2 and 5 new cases per million people per year, which includes 1500 new cases diagnosed each year in the USA. The incidence rates are higher in Caucasians compared with African–Americans and when looking at the age-adjusted rates for men and women within the USA, men have a higher incidence, with 3.4 per million compared to 1.7 per million.

Clinical presentation

- The most common clinical presentations are related to cytopenias, specifically anemia.
- Patients may also present with symptoms of hyperviscosity related to elevated IgM levels including headache, blurring of vision and epistaxis.

- Hepatosplenomegaly and lymphadenopathy occur in 20% of the patients and some patients may present with B symptoms, including night sweats, fever and weight loss.
- Other features include neuropathy, cryoglobulinemia, skin rash (Shnitzler's syndrome), cold-agglutinin hemolytic anemia and amyloidosis.

Prognosis factors

- Factors associated with poor prognosis include advanced age, high b2-microglobulin, cytopenias, low albumin, serum IgM monoclonal protein and organomegaly.

Timing & choice of treatment

- The treatment of patients with WM depends on the presence of symptoms or the signs of disease progression. Patients with asymptomatic disease should not be treated independent of the monoclonal protein level. Standard therapeutic options include:
 - Current therapies used in the upfront or relapsed setting include alkylator agents, nucleoside analogues, bortezomib and the monoclonal antibody rituximab. The overall response rates in the upfront setting vary from 30 to 90% and median durations of response averaging 2–3 years;
 - Rituximab is one of the most commonly used treatment options in WM, especially in the USA, and standard treatment yields response rates of 35–48%;
 - Novel therapeutic agents such as bortezomib, thalidomide, lenalidomide, perifosine, enzastaurin and everolimus have been tested in WM. The combination of bortezomib and rituximab, with or without dexamethasone, has yielded high response rates, over 80–90% in most studies performed to date;
 - Newer targeted agents such as proteasome inhibitors (e.g., carfilzomib and Onyx 0912), immunomodulators (e.g., pomalidomide), mTOR inhibitors (e.g., TORC1/2 inhibitors such as INK128 and PI3K/mTOR inhibitors such as BEZ235), new monoclonal antibodies (e.g., ofatumumab), along with other therapeutic agents, are currently being tested in clinical trials in WM. Future use of these agents alone or in combinations should help improve responses and decrease toxicity related to therapy in patients with WM.

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Figure 1.
Mechanisms of action of novel agents.
CTL: Cytotoxic T lymphocytes; NK: Natural killer.

Table 1

Response summary for single agent-based clinical trials.

Study (year)	Regimen/phase study	Number of patients enrolled	ORR% (PR or better)	ORR% (MR or better)	MR	PR	CR	PD	Ref.
Treon <i>et al.</i> (2005)	Rituximab/II	29	48.3	65.5	17.2	43.8	0	13.8	[15]
Dimopoulos <i>et al.</i> (1993)	Fludarabine/II	28	36	NR	NR	6	3	NR	[16]
Weber <i>et al.</i> (2003)	Cladribine/II	16	94	NR	NR	NR	19	NR	[17]
Dimopoulos <i>et al.</i> (2002)	Rituximab/II	17	35	NR	NR	NR	0	NR	[22]

CR: Complete response; MR: Minimal response; NR: Not reported; ORR: Overall response rate; PD: Progressive disease; PR: Partial response.

Table 2

Response summary for single novel agents-based clinical trials.

Study (year)	Regimen/phase study	Number of patients enrolled	ORR% (PR or better)	ORR% (MR or better)	MR	PR	nCR	CR	Ref.
Dimopoulos <i>et al.</i> (2005)	Bortezomib/II	10	60	80	20	60	0	0	[31]
Treon <i>et al.</i> (2007)	Bortezomib/II	26	48	85	37	48	NR	0	[34]
Ghobrial <i>et al.</i> (2010)	Perifosine/II	37	11	36	24	11	0	0	[43]
Dimopoulos <i>et al.</i> (2002)	Everolimus/II	50	42	70	28	42	0	0	[22]

CR: Complete response; MR: Minimal response; nCR: Near complete response; NR: Not reported; ORR: Overall response rate; PD: Progressive disease; PR: Partial response.

Table 3

Response summary for combinatory studies.

Study (year)	Regimen/phase study	Number of patients enrolled	ORRs (%)						Ref.		
			Overall PR or better (%)	Overall MR or better (%)	SD	MR	PR	>75% decrease in m-spoke	VGPR (>90% decrease)	nCR	CR PD
Treon <i>et al.</i> (2008)	Thalidomide/rituximab/II	25	68	72	NR	8	60	NR	NR	NR	4 NR [39]
Treon <i>et al.</i> (2009)	Lenalidomide/rituximab/II	16	25	50	NR	25	25	NR	NR	NR	0 NR [40]
Treon <i>et al.</i> (2009)	Bortezomib/rituximab/dex/II	23	83	96	NR	13	48	NR	13	9	13 NR [36]
Ghobrial <i>et al.</i> (2010)	Bortezomib/rituximab/II	37	51	81	11	30	46	NR	NR	3	3 3 [38]

CR: Complete response; dex: Dexamethasone; MR: Minimal response; nCR: Near complete response; NR: Not reported; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; VGPR: Very good partial response.