

REVIEW

Review of clinical trials conducted in Waldenstrom macroglobulinemia and recommendations for reporting clinical trial responses in these patients

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Abstract

Many novel therapeutic agents are being tested in clinical trials for Waldenstrom macroglobulinemia (WM). However, given the paucity of large clinical trials in WM, the establishment of a standard treatment regimen that can be used for comparison of response has become challenging. We therefore performed a review of published clinical trials in WM. Systematic searches of the PubMed and Medline databases, including The Cochrane Library, were performed for the search terms: clinical trials, Waldenstrom, macroglobulinemia, and lymphoplasmacytic lymphoma. Studies of transplant in WM are beyond the scope of this review and were excluded. A total of 44 clinical trials were found in this search (38 full articles, six abstracts). Of these, 11 were performed in patients with untreated WM, 14 in patients with relapsed or refractory WM, 17 in both upfront and relapsed or refractory WM, and two studies did not provide this information. Based on this review, we recommend new response criteria and definitions of time to event analysis to be used in future clinical trials of WM. This review of the published literature would serve as a reference for comparison of response and survival analysis in current clinical trials.

Keywords: *Lymphoma and Hodgkin disease, prognostication, chemotherapeutic approaches*

Introduction

Waldenstrom macroglobulinemia (WM) is a distinct low-grade B-cell lymphoma characterized by infiltration of the bone marrow (BM) with lymphoplasmacytic cells, as well as detection of an immunoglobulin M (IgM) monoclonal gammopathy in the serum [1–4]. It was first described by Dr. Jan Gosta Waldenstrom in 1944, when he identified two patients who developed oronasal bleeding, lymphadenopathy, anemia and thrombocytopenia, elevated erythrocyte sedimentation rate, high serum viscosity, normal bone radiographs, and bone marrow showing predominantly lymphoid cells [5,6]. The overall incidence of WM is about three per million persons per year, with 1500 new cases diagnosed per year in the USA [7,8]. WM is currently classified by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) systems as a lymphoplasmacytic lymphoma [9]. WM cells

express pan-B-cell markers including CD19, CD20, and CD22, but lack CD10, CD23, CD38, FMC7, and cytoplasmic Ig [9,10]. CD5 and CD23 are expressed in 5–20% and 35% of cases, respectively [11].

WM is a heterogeneous disease, and patients can present with a broad spectrum of symptoms and signs [12–14]. The most common clinical presentations are related to cytopenias, specifically anemia related to replacement of the bone marrow with tumor cells [4]. Fatigue is a very common presentation of WM that is multifactorial, due, at least in part, to the underlying degree of cytopenias. Patients may also present with symptoms of hyperviscosity related to elevated IgM levels, including headache, blurring of vision, and epistaxis [4,15]. Hepatosplenomegaly and lymphadenopathy occur in 20% of patients, and some patients may present with B-symptoms including night sweats, fever, and weight loss [15]. Other presentation features include neuropathy,

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cryoglobulinemia, skin rash (Shnitzer's syndrome) [16], cold-agglutinin hemolytic anemia, and amyloidosis [2,17]. Since patients with WM have a wide range of overall survival, it is important to define prognostic factors [18].

Patients should receive therapy only if they have symptoms or signs related to WM or specific laboratory abnormalities, and not based only on the serum monoclonal protein level [19]. The most common reason for the initiation of therapy is anemia. Other causes include hyperviscosity symptoms, cytopenias, evidence of disease transformation, and significant neuropathy, adenopathy, or hepatosplenomegaly [3,19,20].

There is no standard of therapy for the treatment of WM [19]. In addition, to date there are no Food and Drug Administration (FDA)-approved therapeutic agents for the specific treatment of WM [19]. Most treatment options were originally derived from other lymphoproliferative diseases, including multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) [3]. The fourth International Workshop on WM updated the treatment recommendations for frontline and salvage therapy of WM [21]. The panel emphasized that many factors should be considered in making the decision: the age of the patient, the presence of cytopenias, and the rate of disease progression. The recommendations for upfront therapy included alkylating agents, nucleoside analogs, and the monoclonal antibody rituximab [19,21]. For patients with relapsed disease, the use of alternative first-line agents, re-use of a first-line agent, use of combination myelotoxic chemotherapy, and use of thalidomide as a single agent or in combination therapy were recommended [19,21]. High-dose chemotherapy with autologous stem cell rescue in primary refractory or relapsed disease should be considered for eligible patients. However, allogeneic and 'non-myeloablative allogeneic' transplants should be cautiously approached, given the associated high mortality and/or morbidity risks, and should be undertaken only in the context of a clinical trial [19,21].

Many novel therapeutic agents are being tested in clinical trials for WM. However, given the paucity of large clinical trials in WM, especially phase 3 clinical trials, the establishment of a standard treatment regimen that can be used for comparison of the response obtained with these clinical trials has become challenging. We therefore analyzed all clinical trials performed in WM and examined responses and corresponding survival data presented in these studies. This review of the published literature would serve as a reference for comparison of response and survival analysis in current clinical trials.

Methods

For this review, systematic searches of the PubMed and Medline databases, including The Cochrane Library, were performed for the search terms: clinical trials, Waldenstrom, macroglobulinemia, and lymphoplasmacytic lymphoma. Studies of transplant in WM are beyond the scope of this review and were excluded.

Results

A total of 44 clinical trials were found in this search (38 full articles, six abstracts). Of these, 11 were performed in patients with untreated WM, 14 in patients with relapsed or refractory WM, 17 in both upfront and relapsed or refractory WM, and two studies did not provide this information.

Single agents tested in WM included alkylating agents such as chlorambucil, nucleoside analogs such as fludarabine and cladribine, and monoclonal anti-CD20 antibody rituximab, described in Tables I and II and Figure 1. There were two large clinical trials using chlorambucil in WM: one was a phase 3 and one a retrospective review of 167 patients [22,23]. The phase 3 study randomized 46 patients to continuous or intermittent chlorambucil and demonstrated an overall response rate (partial response [PR] or better) of 75% in patients who received continuous chlorambucil [22]. Improvement of hemoglobin by >2 g/dL was also included as a response criterion in this study, which led to an increase in the objective response to 79% for patients receiving continuous chlorambucil [22]. Nucleoside analogs such as cladribine and fludarabine were then tested as single agents in WM and had an average response rate (PR or better) of 36% (range, 30–46) [24–28]. This was then followed by use of the monoclonal antibody rituximab in several clinical trials. The largest trial was an Eastern Cooperative Oncology Group (ECOG) study conducted by Gertz *et al.* that included 69 patients with WM (34 upfront and 35 relapsed or refractory to therapy) [29,30]. However, studies using rituximab in patients who were previously treated included patients who were rituximab-naïve, in most cases. The median overall response rate (PR or better) in these single-agent studies was 40% (range, 32–49) [30–32]. No complete remissions were reported. The ECOG study used weekly rituximab $\times 4$ doses, while the extended rituximab regimen used by Treon *et al.* and Dimopoulos *et al.* included rituximab weekly $\times 4$, repeated weeks 1–4 and then 12–16 [30–32].

Table II describes the time to event analysis reported in these studies. As shown, many of the studies did not report time to progression, event-free

Table I. Response summary for single agents.

| Study author | Regimen | Phase | No. of patients | Patient population | | Response rate (%) | | | | | | |
|-----------------------------|-------------------------------------|-------|-----------------|--------------------|-----|----------------------|----------|----------------|----------------|------|----------------------------|-------------------|
| | | | | Upfront | R/R | ORR, PR or better | ORR, MR+ | MR | PR | >75% | CR | PD |
| Kyle [22] | Chlorambucil cont. vs. intermittent | 3 | 46 | 46 | | 75 vs. 64 (total 70) | NR | NR | 73 vs. 64 | NR | 2 (in cont.) | NR |
| Facon* [23] | Chlorambucil | 2 | 128 | 128 | | 31 | 75.5 | 44.5 | 26 | 5 | NR | NR |
| Weber* [27] | Cladribine | 2 | 16 | 16 | | 94 | NR | NR | NR | 75 | 19 | NR |
| Dimopoulos [51] | Cladribine | 2 | 26 | 26 | | 85 | NR | NR | 73 | NR | 11 | NR |
| Dimopoulos [52] | Cladribine | 2 | 46 | | 46 | 43 | NR | NR | 41 | NR | 2 | NR |
| Dimopoulos [24] | Fludarabine | 2 | 28 | 2 | 26 | 36 | NR | NR | 6 | 27 | 3 | NR |
| Leblond [25] | Fludarabine | 2 | 71 | | 71 | 30 | NR | NR | 30 | NR | 0 | NR |
| Dhodapkar [26] SWOGS9003 | Fludarabine | 2 | 183 | 118 | 64 | 36 | NR | NR | 19 | 14 | 2% (upfront only, unconf.) | NR |
| Gertz [29,30] | Rituximab | 2 | 69 | 34 | 35 | 32 | 55 | U: 17, R/R: 31 | U: 35, R/R: 20 | NR | 0 | U: 17.6, R/R: 5.7 |
| Treon [32] | Rituximab | 2 | 29 | 12 | 17 | 48.3 | 65.5 | 17.2 | 43.8 | NR | 0 | 13.8 |
| Dimopoulos [31] | Rituximab | 2 | 17 | 17 | | 35 | NR | NR | 35 | NR | 0 | NR |
| Dimopoulos [53] | Rituximab | 2 | 27 | 15 | 12 | 44 | 69 | 25 | 44 | NR | NR | 19 |

*Retrospective analysis. Cont., continuous; R/R, relapsed/refractory; ORR, overall response rate; PR, partial response; MR, minor response; CR, complete response; PD, progressive disease; NR, not reported.

survival, or duration of response. The duration of response observed with chlorambucil was 26 months for continuous dosing, but 46 months for an intermittent dosing schedule [22]. The median overall survival of these patients was 60 months. The longest follow-up of a clinical trial in WM was the updated follow of the Southwest Oncology Group Study 9003 (SWOGS9003), where the estimated 5-year progression-free survival was 41% in patients who received fludarabine as a single agent [26]. In addition, 20% of patients had a 10-year event-free survival. The median time to progression with rituximab was 31 months in the ECOG study conducted by Gertz *et al.*, but only 14 months (range, 13–17) in the studies reported by Treon *et al.* and Dimopoulos *et al.* [30–32].

The use of novel agents alone has recently been studied in patients with WM (Tables III and IV). Unlike standard therapeutic studies, these clinical trials mainly enrolled patients with relapsed, or relapsed and refractory disease, indicating that this patient population is different and cannot be directly compared to the patients treated with cytotoxic agents or single-agent rituximab. These studies included the use of bortezomib, thalidomide, perifosine, and everolimus [33–37]. The studies using

bortezomib as a single agent showed an average response rate of 48% (range, 30–60) [33–35]. Perifosine single-agent showed a PR rate of 11% [37], while everolimus in a similar patient population showed a PR rate of 42% [36].

Table IV summarizes the results of event analysis of novel single agents. The median time to progression with bortezomib was short, with a median of 6.6 months in the Waldenström Macroglobulinemia Clinical Trials Group (WM-CTG) study, reported by Treon *et al.* [35]. The progression-free survival was 16.3 months in the study conducted by Chen *et al.* [34]. The median progression-free survival with perifosine was 10.7 months [37], while with everolimus the median PFS was not reached, but the estimated PFS at 6 months was 75%, and at 12 months was 62% [36].

Table V summarizes the combinations of two or three agents, including combinations of alkylating agents, nucleoside analogs, and rituximab, as well as the addition of high-dose steroids in many of these regimens. Combinations of therapeutic agents induced higher response rates and longer remissions. These included combinations of alkylating agents such as cyclophosphamide, or melphalan and nucleoside analogs such as fludarabine or cladribine,

Table II. Event analysis summary for single agents.

| Study author | Regimen | Phase | No. of patients | Progression-free survival | Time to progression | Overall survival | Event-free survival | Duration of response |
|-----------------------------|-------------------------------------|-------|-----------------|-----------------------------------|--|--|---|---|
| Kyle [22] | Chlorambucil cont. vs. intermittent | 3 | 46 | NR | NR | 64 months | NR | Cont. chlor: 26 months; inter. chlor: 46 months |
| Facon* [23] | Chlorambucil | 2 | 128 | NR | NR | 60 months | NR | NR |
| Weber* [27] | Cladribine | 2 | 16 | NR | NR | 73 months | NR | 23 months |
| Dimopoulos [51] | Cladribine | 2 | 26 | NR | Median follow-up of 13 months, 19% patients relapsed | Median follow-up of 13 months, 19% patients died | NR | NR |
| Dimopoulos [52] | Cladribine | 2 | 46 | 12 months for responding patients | NR | 28 months | NR | NR |
| Dimopoulos [24] | Fludarabine | 2 | 28 | NR | NR | 32 months overall; median not reached for resp. patients; 12 months for patients ref. to fludarabine | NR | 38 months |
| Leblond [25] | Fludarabine | 2 | 71 | NR | Time to TXT failure: 32 months | 23 months overall; 34 months for TXTed patients still alive | NR | NR |
| Dhodapkar [26] SWOGS9003 | Fludarabine | 2 | 183 | 60 months est. 41% | NR | 80 months (U & R/R patients) | 3.0 years (U & R/R patients); 10-year EFS was 20% | NR |
| Gertz [29,30] | Rituximab | 2 | 69 | 23.1 months overall | 31 months overall | At 60 months was 66% | NR | 27 months overall |
| Treon [32] | Rituximab | 2 | 29 | 23.1 months | U: 17 months, R/R: 14 months | NR | NR | PR: 18+ months; MR: 20+ months |
| Dimopoulos [31] | Rituximab | 2 | 17 | NR | 13 months | With FUP 16-40 months, only 1 patient died | NR | NR |
| Dimopoulos [53] | Rituximab | 2 | 27 | NR | 16 months for all patients (only 8.3 months for patients w/SD) | NR | NR | NR |

*Retrospective analysis. NR, not reported; resp., responding; ref., refractory; TXT, treatment; est., estimated; U, upfront; R/R, relapsed/refractory; FUP, follow-up; PR, partial response; MR, minor response; SD, stable disease.

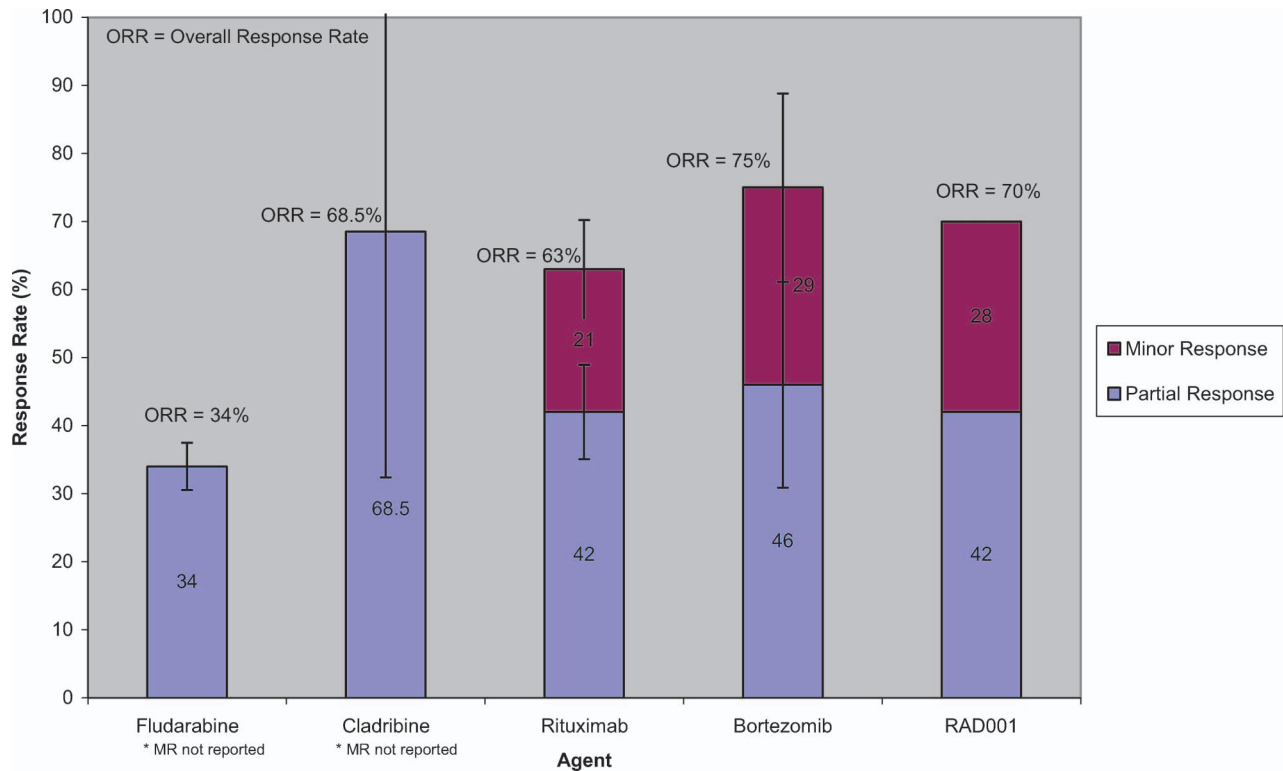


Figure 1. Response to single-agent therapy in WM. In this figure, the response rate including minor response and partial response is presented in a bar graph for all therapeutic agents that were used as single agents in clinical trials in WM. The x-axis represents the agents used and the y-axis represents the response rate (%) in these trials. Each bar represents the average response for all clinical trials using this therapeutic agent. The error bars represent the standard deviation for the response observed in these trials.

Table III. Summary of response for novel single agents.

| Study author | Regimen | Phase | No. of patients | Patient population | | Response rate (%) | | | | | |
|-----------------|-------------|-------|-----------------|--------------------|-----|--|--|----|--|-----|----|
| | | | | Upfront | R/R | ORR, PR+ | ORR, MR+ | MR | PR | nCR | CR |
| Dimopoulos [33] | Bortezomib | 2 | 10 | | 10 | 60 | 80 | 20 | 60 | 0 | 0 |
| Chen [34] | Bortezomib | 2 | 27 | 12 | 15 | 26 (if organ resp. incl.); 48 (by IgM alone) | 59 (if organ resp. incl.); 78 (by IgM alone) | 33 | 26 (if organ resp. incl.); 44 (by IgM alone) | 4 | 0 |
| Treon [35] | Bortezomib | 2 | 26 | | 26 | 48 | 85 | 37 | 48 | NR | 0 |
| Dimopoulos [54] | Thalidomide | 2 | 20 | 10 | 10 | 25 | 25 | 0 | 25 | 0 | 0 |
| Rossi [55] | Atacicept | 1 | 4 | | 4 | 0 | 25 | 25 | 0 | 0 | 0 |
| O'Connor [55] | PR-171 | 1 | 29 (1 with WM) | | 29 | | | 3 | | | |
| Ghobrial [37] | Perifosine | 2 | 37 | | 37 | 11 | 36 | 24 | 11 | 0 | 0 |
| Ghobrial [36] | Everolimus | 2 | 50 | | 50 | 42 | 70 | 28 | 42 | 0 | 0 |

WM, Waldenström macroglobulinemia; R/R, relapsed/refractory; ORR, overall response rate; PR, partial response; IgM, immunoglobulin M; MR, minor response; nCR, near complete response; CR, complete response; resp., response; incl., included; NR, not reported.

with or without rituximab. Some of these studies included small numbers of patients (fewer than 20 patients), but others included larger numbers, such as 92 patients in one randomized study of fludarabine

versus cyclophosphamide–doxorubicin–prednisone (CAP) conducted by Leblond *et al.* [38]. The median response rate to these combinations was 78% (range, 11–100). Table VI summarizes the time to event

Table IV. Summary of event analysis data for novel single agents.

| Study author | Regimen | Phase | No. of patients | Progression-free survival | Time to progression | Overall survival | Event-free survival | Duration of response |
|-----------------|-------------|-------|-----------------|---|--------------------------------|------------------|---------------------|--|
| Dimopoulos [33] | Bortezomib | 2 | 10 | NR | Median 11+ months | NR | NR | NR |
| Chen [34] | Bortezomib | 2 | 27 | 16.3 months | NR | NR | NR | For PR: 10 months (1.4–14.9 months); for SD: 14.3 months (1.2–28.5 months) |
| Treon [35] | Bortezomib | 2 | 26 | NR | 6.6 months (2.9–21.4+ months) | NR | NR | NR |
| Dimopoulos [54] | Thalidomide | 2 | 20 | NR | 5 months | NR | NR | 11 months |
| Rossi [55] | Atacept | 1 | 4 | NR | NR | NR | NR | NR |
| O'Connor [55] | PR-171 | 1 | 29 (1 with WM) | NR | NR | NR | NR | NR |
| Ghobrial [37] | Perifosine | 2 | 37 | Median 10.7 (7.2–not reached) | Median 12.6 (10.2–22.7 months) | 26 months | 8.3 months (6.7–10) | Median 5.6 months |
| Ghobrial [36] | Everolimus | 2 | 50 | Estimated PFS at 6 months is 75%; at 12 months is 62% | Not reached | Not reached | NR | Not reached |

WM, Waldenstrom macroglobulinemia; NR, not reported; PR, partial response; SD, stable disease.

analysis of these trials. The durations of response were longer, and the progression-free survival and overall survival were not reached when these studies were reported.

Studies using novel therapeutic agents in combination with rituximab are presented in Tables VII and VIII, and include those using thalidomide or lenalidomide with rituximab, or, more recently, bortezomib in combination with rituximab. These studies were able to show a median overall response, with a PR or better, of 51% (25–83%) [39–42]. Complete remissions were reported in the thalidomide and rituximab combination [41], as well as the bortezomib/rituximab combination. The highest response rate was observed in the upfront bortezomib/dexamethasone and rituximab study, showing 13% complete remission [39]. Time to progression was reported with thalidomide and rituximab, showing an overall time to progression of 38.7 months [41]. The combination of bortezomib and rituximab in relapsed or refractory WM showed a median progression-free survival of 15.6 months and duration of response of 19.5 months [42].

Finally, several studies have been reported in abstract form, as shown in Tables IX and X. Alemtuzumab used as a single agent had an overall response rate (PR or better) of 32% [43]. The combination of bortezomib and rituximab used in the upfront setting showed a >PR rate of 65%, with 4% complete remissions [44].

Discussion

The implementation of new agents in clinical trials, used in various combinations, has improved responses and prolonged survival in many hematological malignancies. WM is a rare hematological malignancy, and therefore large randomized studies have not been conducted to date. Indeed, there is no standard of care in WM, and different centers treat patients with different combinations, depending on risk stratifications, age, and other factors.

Given that new therapeutic agents are being tested in WM, we sought to perform a review of all clinical trials conducted to date in WM in order to attain a clear understanding of responses and survival data obtained in these trials. These studies can be used as the standard to which new agents can be compared. In addition, these studies can help define future combinations.

As shown in this review, many studies have been conducted in small numbers of patients, and many included different patient populations, such as untreated or relapsed and refractory patients. We recommend that studies include a uniform group of patients with well-defined disease characteristics, such as a defined number of prior lines of therapy, certain age groups, and possibly well-defined risk factors. Although it may be difficult to perform risk stratifications in WM trials, given the paucity of patients entering these trials, it would be critical to

Table V. Summary of response for agents in combination.

| Study author | Regimen | No. of patients | Patient population | | Response rate (%) | | | | | | | | |
|-----------------|---|-----------------|--------------------|-----------|-------------------|------------------------|-----|-----------------------|-----|---------------------------|-----------------------|----------------------|----------------------|
| | | | Upfront | R/R Phase | ORR, PR+ | ORR, MR+ | SD | MR | PR | > 75% decrease in M-spike | VGPR (> 90% decrease) | CR | PD |
| Tam [56] | Fludarabine/CTX | 9 | 2 | 7 | 2 | 100 | 100 | NR | NR | NR | NR | 0 | 0 |
| Leblond [57] | Fludarabine/CTX | 49 | 14 | 35 | 2 | 77.6 | NR | 18.4 | NR | 77.6 | 18.4 | 0 | 4.1 |
| Dimopoulos [58] | Fludarabine/CTX | 11 | 2 | 9 | 2 | 55 | NR | NR | NR | 55 | NR | 0 | NR |
| Weber* [27] | Gladribine/CTX | 37 | 37 | 92 | 2 | 84 | NR | NR | NR | NR | 79 | 5 | NR |
| Leblond [38] | Fludarabine vs. CAP | 92 | | | 3 | 30 vs. 11 | NR | NR | NR | 30 vs. 11 | NR | 0 | NR |
| Treon [48] | Fludarabine/rituximab | 43 | 27 | 16 | 2 | 82 | 95 | NR | 9.3 | 48.8 | NR | 4.6 | NR |
| Tam [59] | Fludarabine/CTX/rituximab | 10 | 4 | 6 | 2 | U: 75, R/R: 40 | NR | NR | NR | U: 75, R/R: 40 | 0 | U: 25, R/R: 0 | NR |
| Weber* [27] | Gladribine/CTX/rituximab | 17 | 17 | | 2 | 94 | NR | NR | NR | NR | 76 | 18 | NR |
| Weber* [27] | Gladribine/prednisone | 20 | 20 | | 2 | 60 | NR | NR | NR | NR | 55 | 5 | NR |
| Hensel [60] | Pentostatin/CTX ± rituximab | 17 | 9 | 8 | 2 | 64.7 | NR | 35.3 | NR | 52.9 | NR | 11.7 | 0 |
| Petrucchi [61] | Melphalan/CTX/chlorambucil/prednisolone | 31 | 31 | | 2 | 74 | NR | 19 | NR | 48 | NR | 26 | 6 |
| Case [62] | Carmustine/CTX/VCR/melphalan/prednisone (M2 protocol) | 33 | 26 | 7 | 2 | 82 | NR | NR | NR | 63 | NR | 18 | NR |
| Annibaldi [63] | Melphalan/CTX/prednisone | 71 | 72 | | 2 | 77.4 | NR | 9.8 | NR | 64.7 | 12.7 | NR | NR |
| Dimopoulos [64] | Dexamethasone/CTX/rituximab | 72 | 72 | | 2 | 74 | 83 | 8 | 9 | 67 | NR | 7 | 8 |
| Treon [65] | CHOP/rituximab | 13 | 3 | 10 | 2 | 84.5 | 92 | NR | 7.5 | 61.5 | NR | 23 | NR |
| Buske [66] | CHOP vs. R-CHOP | 48 | 48 | | 3 | R-CHOP = 91, CHOP = 60 | NR | R-CHOP = 9, CHOP = 32 | NR | R-CHOP = 83, CHOP = 56 | NR | R-CHOP = 9, CHOP = 4 | R-CHOP = 0, CHOP = 8 |

*Retrospective analysis.

CTX, cyclophosphamide; CAP, cyclophosphamide, doxorubicin, prednisone; VCR, vincristine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, oncovin, prednisone; R/R, relapsed/refractory; ORR, overall response rate; PR, partial response; MR, minor response; SD, stable disease; VGPR, very good partial response; CR, complete response; PD, progressive disease; NR, not reported.

Table VI. Summary of event analysis data for agents in combination.

| Study author | Regimen | PFS | TTP | OS | EFS | DOR | Time to treatment failure | Time to best response |
|-----------------|---|---|--------------------|---|-----------|----------------------------------|--|-----------------------|
| Tam [56] | Fludarabine/CTX | NR | NR | At 60 months, estimated 55% ($\pm 8\%$) | NR | 13.1 months | NR | NR |
| Leblond [57] | Fludarabine/CTX | NR | NR | Not reached | 27 months | NR | 27 months | NR |
| Dimopoulos [58] | Fludarabine/CTX | NR | 24 months | At 24 months, estimated 70% | NR | NR | NR | 4 months |
| Weber* [27] | Cladribine/CTX | NR | NR | Not reached | NR | 36 months | NR | NR |
| Leblond [38] | Fludarabine vs. CAP | NR | NR | 41 months (F) vs. 45 months (CAP) | NR | 19 months (F) vs. 3 months (CAP) | NR | NR |
| Treon [48] | Fludarabine/rituximab | NR | Median 51.2 months | NR | NR | NR | NR | 19.2 months |
| Tam [59] | Fludarabine/CTX/rituximab | At 36 months, estimated 48% | NR | At 36 months, estimated 72% | NR | NR | NR | NR |
| Weber* [27] | Cladribine/CTX/rituximab | NR | NR | Not reached | NR | Not reached | NR | NR |
| Weber* [27] | Cladribine/prednisone | NR | NR | 41 months | NR | 9 months | NR | NR |
| Hensel [60] | Pentostatin/CTX \pm rituximab | NR | Not reached | NR | NR | NR | NR | 4 months |
| Petrucci [61] | Melphalan/CTX/chlorambucil/prednisolone | NR | NR | NR | 66 months | Not reached | NR | NR |
| Case [62] | Carmustine/CTX/VCR/melphalan/prednisone (M2 protocol) | NR | NR | At 120 months, estimated 54% | NR | CR = 43 months, PR = 39 months | NR | NR |
| Annibali [63] | Melphalan/CTX/prednisone | 55 months | NR | 66 months | 47 months | 64 months | NR | NR |
| Dimopoulos [64] | Dexamethasone/CTX/rituximab | 2-year PFS rate of 67% (80% for responders) | NR | 2-year OS rate of 81% | NR | NR | NR | 4.1 months |
| Treon [65] | CHOP/rituximab | NR | NR | NR | NR | NR | NR | NR |
| Buske [66] | CHOP vs R-CHOP | NR | NR | Not reached for either arm | NR | NR | R-CHOP, median = 63 months; CHOP, median = 22 months | NR |

*Retrospective analysis. CTX, cyclophosphamide; CAP, cyclophosphamide, doxorubicin, prednisone; VCR, vincristine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, oncovin, prednisone; PFS, progression-free survival; NR, not reported; TTP, time to progression; OS, overall survival; EFS, event-free survival; DOR, duration of response; PR, partial response; CR, complete response

analyze all of the patients entering these clinical trials for their risk factors based on the International Staging System – Waldenström Macroglobulinemia (ISS-WM) [18] (Supplementary Table I), so that future comparisons can be performed between these patients.

In addition, many of these studies did not include uniform response criteria, and comparisons were

therefore difficult in some of these cases. We chose to include the data of partial response or better as the overall response rate, because minimal responses were not included in some of the studies. However, we recommend that future studies include minimal responses based on the recent study conducted by Gertz *et al.* [29], indicating that progression-free survival is similar in patients who achieve partial

Table VII. Response summary for combinations using novel agents.

| Study author | Regimen | No. of patients | Patient population | | | Response rate (%) | | | | | | | | | |
|-----------------|--|-----------------|--------------------|-----|-------|-------------------|----------|----|----|----|---------------------------|----------------------|-----|----|----|
| | | | Upfront | R/R | Phase | ORR, PR+ | ORR, MR+ | SD | MR | PR | > 75% decrease in M-spike | VGPR (>90% decrease) | nCR | CR | PD |
| Dimopoulos [54] | Thalidomide/dexamethasone/clarithromycin | 12 | 12 | 2 | 2 | 25 | 42 | 25 | 17 | 25 | NR | NR | 0 | 0 | 50 |
| Treon [67] | Thalidomide/rituximab | 25 | 20 | 5 | 2 | 68 | 72 | NR | 8 | 60 | NR | NR | NR | 4 | NR |
| Treon [40] | Lenalidomide/rituximab | 16 | 12 | 4 | 2 | 25 | 50 | NR | 25 | 25 | NR | NR | NR | 0 | NR |
| Treon [39] | Bortezomib/rituximab/dexamethasone | 23 | 23 | 2 | 2 | 83 | 96 | NR | 13 | 48 | NR | 13 | 9 | 13 | NR |
| Ghobrial [42] | Bortezomib/rituximab | 37 | 37 | 2 | 2 | 51 | 81 | 11 | 30 | 46 | NR | NR | 3 | 3 | 3 |

R/R, relapsed/refractory; ORR, overall response rate; PR, partial response; MR, minor response; SD, stable disease; VGPR, very good partial response; nCR, near complete response; CR, complete response; PD, progressive disease; NR, not reported.

response or minimal response. In addition, some studies included major responses with > 75% reduction in monoclonal protein, while others showed very good partial remissions (90% reduction) and near complete remissions (immunofixation positive). Some of these definitions are not currently present in the uniform response criteria of WM that were defined by Weber *et al.* and Kimby *et al.* [45,46]. We recommend that these response criteria be revised to be more inclusive of these definitions, so that all future clinical trials use the same response criteria. In addition, some of the studies used the monoclonal protein response as the only response criterion, while others included organ and lymph node responses. For example, the response rate reported by Chen *et al.* was up to 44% partial response if monoclonal protein response was used, but only 26% if organ and lymph node response was included [34]. The current consensus recommendations include organ and lymph node measurements when partial responses are assessed. Therefore, we recommend that all future studies adhere to strict response criteria when reporting clinical trials. Table XI summarizes our recommendations of response criteria to be included in future clinical trials. Studies may include the response rate by monoclonal protein alone; however, they should also report responses obtained using the strict criteria of response.

Finally, many current studies are showing high responses by monoclonal protein, with minimal responses obtained in the bone marrow. We recommend that complete remissions and near complete remissions be confirmed by bone marrow biopsies. Partial responses cannot be confirmed by 50% reductions in tumor cells from bone marrow biopsies, since involvement in the bone marrow is variable. Some other markers of response, such as hematological response or lymph node and organ response, will indicate that these responses are durable, and do not just represent reductions in secretion of the IgM protein. Indeed, one of the best predictors of whether a response is not merely a change in IgM protein level is the duration of response obtained. Therefore, all studies should report the duration of response, and whether the study allowed the continuation of therapy until progression or was stopped at a certain time point of therapy (a specified number of cycles). Moreover, some studies reported response by monoclonal protein using serum protein electrophoresis, while others reported response using the IgM level by nephelometry. When we compared the results of both measurements in the same trials, we found minimal differences between these response rates. However, for better comparison of studies, we recommend that all studies report the measurement using serum

Table VIII. Summary of time to event analysis for combinations using novel agents.

| Study author | Regimen | PFS | TTP | OS | EFS | DOR | Time to treatment failure | Time to best response |
|-----------------|--|----------------|---|----------------|-----|----------------|---------------------------|-----------------------|
| Dimopoulos [54] | Thalidomide/ dexamethasone/ clarithromycin | NR | NR | NR | NR | NR | NR | NR |
| Treon [67] | Thalidomide/rituximab | NR | 34.8 months; 38.7 months for responders | NR | NR | NR | NR | 18.9 months |
| Treon [40] | Lenalidomide/rituximab | NR | 17.1 months; 18.9 months for responders | NR | NR | NR | NR | 11.8 months |
| Treon [39] | Bortezomib/rituximab/ dexamethasone | NR | Not reached | NR | NR | NR | NR | > 15 months |
| Ghobrial [42] | Bortezomib/rituximab | 15.6 months | Median 16.4 months | Not reached | | 19.5 months | 17.6 months | 6 months |

PFS, progression-free survival; TTP, time to progression; OS, overall survival; EFS, event-free survival; DOR, duration of response; NR, not reported.

Table IX. Summary of response for abstracts.

| Study author | Regimen | Phase | No. of patients | Patient population | | Response rate (%) | | | | | | |
|----------------|--------------------------------|-------|-----------------|--------------------|-----|-------------------|----------|----|----|---------------------------|----|----|
| | | | | Upfront | R/R | ORR, PR+ | ORR, MR+ | MR | PR | > 75% decrease in M-spike | CR | PD |
| Hunter [43] | Alemtuzumab | 2 | 28 | | 23 | 32 | 76 | 44 | 32 | NR | 0 | |
| Gertz [68] | Genasense | 1 | | | | | | | | | | |
| Patterson [69] | Sildenafil | 2 | 30 | 18 | 12 | NR | 17 | NR | NR | NR | NR | NR |
| Treon [70] | Imatinib mesylate (Gleevec) | 2 | 28 | | 28 | 7 | | 26 | 7 | 0 | 0 | |
| Ghobrial [71] | Enzastaurin | 2 | 29 | | 29 | | 27 | 24 | 3 | 0 | 0 | |
| Ghobrial [44] | Bortezomib/ rituximab | 2 | 26 | 26 | | 65 | 88 | 23 | 58 | NR | 4 | 0 |

R/R, relapsed/refractory; ORR, overall response rate; PR, partial response; MR, minor response; CR, complete response; PD, progressive disease; NR, not reported.

Table X. Summary of time to event analysis data for abstracts.

| Study author | Agent(s) | PFS | TTP | OS | EFS | DOR |
|----------------|--------------------------------|----------------|------------------------------------|-------------|-----|---|
| Hunter [43] | Alemtuzumab | NR | NR | NR | NR | Median FUP 8.5+ months, 11/19 responders remain free of progression |
| Gertz [68] | Genasense | | | | | |
| Patterson [69] | Sildenafil | | NR | NR | NR | NR |
| Treon [70] | Imatinib mesylate (Gleevec) | NR | Median 8.4 months (2–15 months) | NR | NR | NR |
| Ghobrial [71] | Enzastaurin | NR | NR | NR | NR | NR |
| Ghobrial [44] | Bortezomib/ rituximab | Not reached | NR | Not reached | NR | NR |

PFS, progression-free survival; NR, not reported; TTP, time to progression; OS, overall survival; EFS, event-free survival; DOR, duration of response; FUP, follow-up.

protein electrophoresis. IgM measurements can be used in specific cases where quantification of the M-spike cannot be obtained accurately (e.g. migrating in the beta region).

Confirmation of response in WM has been adopted from the response criteria of multiple myeloma. We believe that the WM confirmation of response should be updated, as it has been for

multiple myeloma [47], where response is confirmed at any time point and not at 6 weeks.

Survival data are not well documented in many studies reported for WM. Based on some of these studies, it appears that the depth of response correlates with progression-free survival for complete remissions and very good partial remissions [48]. There also appears to be a longer time to progression for patients who achieve minor or partial response rates as well, indicating that response, even if minor, is beneficial in these patients [29]. We recommend that all studies should include overall survival, progression-free survival, time to progression, and event-free survival. The specific definitions of these responses are shown in Table XII, and are similar to those recommended in multiple myeloma [47].

Progression in WM does not always indicate that the patient requires the initiation of a new therapy.

Given that patients may present with a 25% increase in their monoclonal protein, but do not have symptomatic disease that requires therapy, we therefore believe that all clinical trials should report the time to progression, as well as time to next therapy, since these two parameters may not be identical in an indolent disease such as WM.

Current studies are evaluating the role of other markers of response, such as serum free light chain, and the role of better imaging modalities [49]. Serum free light chain assays have been used in multiple myeloma, and have demonstrated a significant benefit in improving the measurement of response in this disease [50]. These assays may help improve our current measurements of the tumor burden in WM, as well.

In summary, we recommend that the uniform response criteria for WM be updated to include all

Table XI. Recommended response criteria.

| | |
|------------------------------------|--|
| Complete remission (CR) | Disappearance of monoclonal protein by immunofixation; no histologic evidence of bone marrow involvement, resolution of any adenopathy/organomegaly (confirmed by CT scan), or signs or symptoms attributable to WM. Reconfirmation of CR status is required with a second immunofixation at any time point |
| Near CR (nCR) | As above except that immunofixation is still positive |
| Very good partial remission (VGPR) | At least 90% reduction of serum monoclonal protein using serum protein electrophoresis (SPEP) |
| Partial response (PR) | At least 50% reduction of serum monoclonal concentration on protein electrophoresis and at least a decrease in adenopathy/organomegaly on physical examination or CT scan. No new symptoms or signs of disease |
| Minimal response (MR) | At least 25% but less than 50% reduction of serum monoclonal protein. No new symptoms or signs of active disease |
| Stable disease | Less than 25% reduction and less than 25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM |
| Progressive disease | At least 25% increase in serum monoclonal IgM protein electrophoresis confirmed by a second measurement at any time, as well as an absolute increase of the M-spike by 0.5 g/dL, or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly or symptoms of disease) or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis attributable to WM |
| Refractory to therapy | Progression of disease while on therapy, or progression within 60 days of most recent therapy |

CT, computed tomography; WM, Waldenstrom macroglobulinemia; IgM, immunoglobulin M.

Table XII. Definitions of time to event end points.

| | |
|---------------------------------|--|
| Time to progression (TTP) | Duration from start of treatment to disease progression, with deaths due to causes other than progression censored |
| Progression-free survival (PFS) | Duration from start of treatment to disease progression or death (regardless of cause of death), whichever comes first |
| Event-free survival (EFS) | The definition for EFS depends on how 'event' is defined. In many studies, the definition of EFS used is the same as PFS. EFS may include additional 'events' that are considered to be of importance besides death and progression, including serious drug toxicity |
| Disease-free survival (DFS) | Duration from the start of CR to the time of relapse from CR. DFS applies only to patients in complete response |
| Duration of response (DOR) | Duration from first observation of a response to the time of disease progression, with deaths due to causes other than progression censored. Duration of CR and PR and MR should each be reported |
| Time to next therapy (TTNT) | Duration from the end of treatment to the initiation of next therapy, censored at date last known alive without initiation of next therapy |

CR, complete response; PR, partial response; MR, minor response.

response categories, specifically near complete response and very good partial response. Furthermore, we believe that uniform survival analysis data should also be included in all clinical trials. With the advances of novel combinations and better therapeutic agents, we hope to be able to better compare responses and survival improvements with these newer agents, compared to standard therapies used in WM.

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