Treatment recommendations for patients with Waldenström's Macroglobulinemia (WM) and related disorders: consensus from the Eight International Workshop on WM

Véronique Leblond[1], Efstathios Kastritis[2], Ranjana Advani[3], Stephen.M Ansell[4], Christian Buske[5], Jorge J. Castillo[6], Ramón García-Sanz[7], Morie Gertz[8], Eva Kimby[9], Charalampia Kyriakou[10], Giampaolo Merlini[11], Monique C Minnema[12], Pierre Morel[13], EnricaMorra[14], Mathias Rummel[15], AshutoshWechalekar[16], Steven P. Treon[6] and Meletios Dimopoulos[2]

[1] AP-HP Hôpital Pitié Salpêtrière, UPMC univ Paris 6 GRC-11, GRECHY, Paris France

[2]Department of clinical Therapeutics, National &Kapodistrian University of Athens School of Medicine Greece

[3]Stanford Cancer Institute, Stanford, CA, USA

[4]Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

[5]CCU-Ulm, Institute Of Experimental Cancer Research, University Hospital Ulm,Germany

[6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

[7]Servicio de Hematología, Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain

[8] Mayo Clinic, Rochester, MN

[9]Karolinska Institute, Department of Medicine, Hematology Center, Stockholm, Sweden

[10]RFH & NPH Hospitals United Kingdom

[11]Amyloidosis Research and Treatment Center, Foundation IRC Policlinico San Matteo, Department of Molecular Medicine, University of Pavia, Italy

[12]Department of Hematology Cancer Center UMC Utrecht, Utrecht, The Netherlands

[13]Service d'Hématologie Clinique, Centre Hospitalier Schaffner, Lens, France

[14]Department of Hematology, NiguardaCa' Granda Hospital, Milano, Italy

[15]Med. Klinik IV, Hospital of the Justus-Liebig-University Giessen, Germany

[16] University College London (Royal Free Campus) United Kingdom

Correspondence : Véronique Leblond AP-HP, UPMC univ Paris 6 GRC-11, GRECHY Hôpital Pitié Salpêtrière 47 boulevard de l'Hôpital 75013 Paris France Veronique.leblond2@aphp.fr

Running title: Treatment recommendations for WM

Treatment recommendations

IWWM-8 task force on treatment recommendations

Abstract

Waldenström's macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder for which clearly defined criteria for the diagnosis, initiation of therapy and treatment strategy have been proposed as part of the consensus panels of the International Workshops on WM (IWWM). At the last IWWM in London 2014 the IWWM-8 task force for the treatment recommendations, based on recently published and ongoing clinical trials, answered specific questions for updating the IWWM-7 recommendations on the impact of new mutations (MYD88, CXCR4) on treatment decisions, the indications of new BCR and proteasome inhibitors and the best options to test in future clinical trials. Moreover the identification of the common somatic mutation in MYD88 has offered the opportunity for a more targeted approach. Therapeutic strategy in WM should be based on individual patient and disease characteristics. The immunochemotherapy combinations with rituximab (R) and cyclophosphamide/dexamethasone (DRC), or bendamustine (BR) or bortezomib/ dexamethasone (BDR) have provided durable responses and are still indicated for most patients but the approval of the BTK-inhibitor ibrutinib in the US and in Europe in this setting will modify treatment options in both treatment–naïve and relapsing patients. Other BCR-inhibitors, second-generation proteasome inhibitors (carfilzomib) and mTOR inhibitors are promising and may expand future treatment options. In most patients with WM active enrollment of patients in clinical trials is highly encouraged.

Introduction

Waldenström'smacroglobulinemia (WM) is, according to WHO classification, a lymphoplasmacyticlymphoma, in which the bone marrow is infiltrated by IgM-producing clonal lymphoplasmacytic cells (1).The Second International Workshop on WM (IWWM-2) proposed criteria for the clinical pathological diagnosis and for initiation of therapy in WM patients(2,3). IWWM consensus panels have provided treatment recommendations, which were last updated in 2008 (IWWM-4) and in 2012 (4-7). As part of its last consensus deliberations (IWWM-8, London August 2014), the panel considered the results from phase II

studies of several chemo-immunotherapy regimens, novel drugs (alone or with rituximab) and of novel targeted agents (everolimus, carfilzomib, ibrutinib) and examined these data and updated its recommendations, which are presented herein.

The use of anti-CD20 monoclonal antibodies is a standard of care in WM patients in first line and in relapse. The combination of anti-CD20 monoclonal antibody with chemotherapy or with bortezomib remains a recommended therapy in most patients with WM. Most of the published series are small phase II trials using rituximab in combination with alkylating agents (cyclophosphamide, bendamustine), with purine analogues (fludarabine) with or without alkylating agents, and with proteasome inhibitors (bortezomib). The studies with new anti-CD20 monoclonal antibodies (ofatumumab, obinutuzumab) or with other new monoclonal antibodies are scarce. The choice of immuno-chemotherapy depends on the patient comorbidities, short and long-term toxicities, necessity for rapid control of the disease, and the need of hematopoietic stem cell collection. Despite considerable heterogeneity in biology and clinical course, many mature B-cell malignancies are highly sensitive to kinase inhibitors that disrupt BCR signalling. Thus, targeted therapy through inhibition of BCR signalling is emerging as a new treatment paradigm also for patients with WM. Chemotherapy-free combinations with new target agents such as BCR inhibitors are promising.

I. Treatment indications

Not all patients with a diagnosis of WM do need immediate therapy. Criteria for the initiation of therapy (proposed in the IWWM-2 consensus panel and confirmed in IWWM-8) are IgM related complications and/or cytopenias, B symptoms and bulky disease. For patients who do not fulfill the criteria, and in whom only laboratory evidence may indicate a possible development of progressive disease (such as a minor decrease in hemoglobin level with asymptomatic anemia or mild increases in IgM) or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient, close observation is recommended (3).

Plasmapheresis should always and immediately be used for patients with severe hyperviscosity. Furthermore this is an important tool to prevent flare in patients with high IgM level pre-rituximab administration. Plasmapheresis alone is not an effective treatment of the disease and must be followed by a rapidly acting cytoreductive treatment targeting the tumor cells. (7). To omit rituximab for the first one - two cycles of chemotherapy is an alternative to induce tumor debulking and reduce the risk of IgM flare.

II. Monoclonal antibodies as a single agent

Treatment strategies and modalities have changed at the beginning of the 21st century with the use of the anti-CD20 monoclonal antibody rituximab. Rituximab is widely used in WM patients and since 2000, also new monoclonal antibodies, targeting CD20 or other antigens, have been investigated. The combination of anti-CD20 monoclonal antibody with chemotherapy is still the standard of care and rituximab-based regimens remain the commended primary therapy for most patients with WM (7-11).

II.1- Rituximab

Rituximab is a chimeric monoclonal antibody, which targets the CD20 antigen, expressed on B cells, including WM cells. Since the beginning of 2000's, rituximab is widely used in B lymphoproliferative diseases. Two schedules of administration were studied in monotherapy for WM: the standard one, in which one weekly infusion of 375 mg/m2 is administrated for 4 weeks, and the extensive one, in which responsive patients received 4 more infusions mostly between the 12th and the 16th week after initiation of therapy. In the standard schedule, overall response rates (ORR) varied between 27 and 60%, with 27-35% of major response (≥ partial response), with a median time to response of 3 months and duration of response (DOR) of 8 months, both in previously treated and untreated patients (12,13). Even for patients with minor response, an improvement of hemoglobin and platelet counts, and a reduction of lymphadenopathy and splenomegaly was observed. Extensive therapy allowed an ORR between 35 and 48%, with a DOR longer than 29 months (14,15). Rituximab is well tolerated; however, about 50% of patients will experience a transient increase of the IgM level, named IgM-flare. No predicting factors for the development of IgM-flare, like baseline IgM level, plasma viscosity level, bone marrow infiltration, or previous therapy, have been identified. The IgM-flare-up effect is seen mostly during the first months of treatment and can persist until the 4th month. This phenomenon is associated with a higher risk of treatment failure, but physicians should be cautious not to interpret this phenomenon hastily as lack of response or even progression, because decrease of IgM level can occur slowly. In patients with baseline serum IgM level or serum viscosity higher than 50g/L or 3.5cp respectively, IgM-flare-up can

induce hyperviscosity related complications. Such patients at risk should undergo prophylactic plasmapheresis, or avoid rituximab during the first one or two courses of chemotherapy until IgM levels decline to a safer level (16). Late-onset neutropenia (LON) has also been described with rituximab, mostly when combined with chemotherapy (17). The underlying mechanism of LON is not understood, but a cellular immune mechanism or antibody-mediated complement cytotoxicity have been proposed (18). An association between a specific polymorphism in the immunoglobulin G Fc receptor (FCγRIIIaV158 F) and LON was also described (19). Predisposing factors of LON in hematologic B-cell malignancies after rituximab therapy are previous autologous stem cell transplantation, advanced disease, purine analogues exposure, and previous intensive chemotherapy, eventually associated with radiotherapy (17).

Because of the lower chance to respond if the IgM level is high, the long time to response and the risk of an IgM-flare, rituximab single agent therapy is now mostly only used for WM patients with immunological disorders secondary to the WM, such as anti-MAG neuropathy or in patients with low IgM level and cytopenias not eligible for combination immuno-chemotherapy as frail patients.

II.2. Ofatumumab

Ofatumumab is a humanized CD20-directed monoclonal antibody that targets a CD20-region at a different epitope than that of rituximab. One phase II trial studied ofatumumab as a monotherapy in 37 treatment naïve or previously treated patients. Ofatumumab was given at two dose levels and for two blocks of weekly consecutive infusions: 59% of the patients achieved at least a minimal response after both cycles (38% a PR), with somewhat higher responses at higher doses (47% versus 68%), in therapy-naïve (6/9, 67%) and rituximab-naïve (9/12, 75%) patients than in rituximab-exposed patients (13/25, 52%). But patients experienced an IgM flare requiring plasmapheresis also with this anti-CD20 monoclonal antibody (20). In patients with intolerance to rituximab, ofatumumab is another therapeutic option (21).

III. Combinations with rituximab

Because rituximab is an active and a non-myelosuppressive agent, its combination with various chemotherapeutic agents has been extensively explored in WM. The combination of anti-CD20 monoclonal antibody and chemotherapy is considered standard of care in patients in first line treatment. The choice of chemotherapy depends on the comorbidities, how fast control of the disease is required and the phenotype of the disease.

III.1 Rituximab + alkylators

The combination of dexamethasone, rituximab and cyclophosphamide (DRC) has been tested in a phase II trial in 72 untreated WM patients. A high response rate (83%) was observed, with 7% and 67% complete and partial responses, respectively. The 2-year PFS was 67% in all cohort and 80% in responders. Median time to response was however long with 4.1 months, suggesting that this combination is not appropriate if a rapid control of disease is necessary. Toxicities were mild, with only 9% of grade 3-4 neutropenia (24). This study was recently updated with a follow up longer than 7years for all patients. Time to treatment failure and time to next treatment were 35 and 51 months, respectively. The majority of relapsing patients were still sensitive to rituximab-based therapies and long-term toxicity profile was favorable with only one case of MDS and two cases of transformation to DLBCL (one after exposure to multiple lines of therapy). The causes of death were followed prospectively in this study: among 35 patients (49%) who died, 20 (57%) were related and 15 (43%) were unrelated to WM. WM-related death at 8 years was 32% and WM-unrelated was 21%. The 8-year OS per the ISSWM was 100%, 55% and 27% for low, intermediate or high risk disease respectively(p=0.005) (22, 23).

This update indicates that DRC is an active and safe treatment choice in first line for WM with a manageable toxicity, even in frail patients and is widely used in first line in this setting

III.2. Rituximab + purine analogues

Most data on fludarabine–based regimens has been discussed in the previous recommendation papers in 2009 and 2014 (6, 7). Rituximab, fludarabine and cyclophosphamide is one of the most effective and fast acting regimen in relapsed patients with the longest PFS (median: 70 months), at least in a historical comparison with other salvage regimens (24).

Fludarabine-based combinations should be considered in fit patients with relapsed/refractory WM. In young patients who are ASCT eligible, stem cells should be collected before fludarabine administration.

III.4. Rituximab + bendamustine

Rituximab + bendamustine (BR) was compared to RCHOP in a phase 3 open-label trial. A total of 546 patients were enrolled in this study for indolent NHL patients, including 41 patients with WM (22 treated with BR and 19 with R-CHOP). Patients on the BR arm received 6 cycles of bendamustine at 90 mg/m2 on days 1, 2 and rituximab at 375 mg/m2 on day 1 every 4 weeks. A similar ORR (95%) but with a longer PFS was reported for the RB arm (median 69.5 months, versus 28.1 months in the RCHOP arm), with a better tolerance of chemotherapy (lower rates of grade 3-4 neutropenia, infectious complications and peripheral neuropathies, and no alopecia) (25).

In the salvage setting, the outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone, or with a CD20-directed antibody was reported by Treon et al. An overall response rate of 83% and a median progression free survival of 13 months were reported in this study. Overall, therapy was well tolerated though prolonged myelosuppression occurred in patients who had received prior nucleoside analogue therapy [26]. Tedeschi reported an Italian retrospective study in 72 patients with relapsed/refractory disease. Two doses of bendamustine were used: 45 patients (63%) received 90 mg/m2 and 22 (31%) were treated with 70 mg/m2on day 1 and 2 (4 patients received 50 mg/m2 due to comorbidities). Overall and major response rates were 80% and 75%. Major toxicity was grade 3/4 neutropenia occurring in 13% of courses. There was no significant association between baseline features or patients' characteristics and response achievement. Median progression-free survival was not reached after a median follow-up of 19 months (range 3-54). Among responders the median time to 50% reduction in serum monoclonal protein was 3 months (range 1 – 6). No IgM flare was recorded in any of the patients. Sixty-six percent of patients completed the planned 6 courses. Ten patients discontinued due to toxicity (infection in 4 and myelosuppression in 6). A better quality of response (CR plus VGPR) was observed in patients with an IgM level <3000 mg/dL and in those treated with the higher dosage of B (90 mg/m^2). Most of the patients received prophylactic growth factors, and grade 3-4 neutropenia

developed in 13% of courses, in 36% of patients. None of the patients developed aggressive lymphoma or secondary myelodysplastic syndrome/acute myeloid leukemia, but in 3 cases, a solid cancer was observed (27).

BR combination seems to be as effective in treatment-naïve and as in pretreated WM patients. Treatment is well tolerated even in elderly patients with limited episodes of myelosuppression and infections when compared to purine analogues-based regimens. This combination could be an option even in frail patients or in patients with renal impairment

III.5. Rituximab +Bortezomib

Treon studied rituximab, bortezomib and dexamethasone in combination in 23 untreated patients, with administration of intravenous bortezomib at 1.3 mg/m^2 and dexamethasone 40 mg twice a week at day 1, 4, 8, 11, and rituximab 375 mg/m^2 at day 11, for 4 cycles as induction treatment, and 4 more cycles at 3 months as maintenance treatment. ORR and major response rate were 96% and 83% respectively, with a median time to response of 1.4 months, and a late improvement of response after treatment discontinuation with a median time to best response of 15 months. Sixty percent of patients discontinued treatment after 4 cycles because of the development of peripheral neuropathy. The median PFS was 52 months (28). Treatment with bortezomib was then reduced to once a week at 1.6 mg/m^2 in an attempt to reduce the occurrence of peripheral neuropathy, resulting in Grade 2 – 39%; Grade 3 – 30%. This schedule of rituximab + bortezomib was studied in first line by Ghobrial in 26 patients, with bortezomib 1.6 mg/m^2 administrated intravenously at day 1, 8 and 15 during 6 cycles, in a 28-day cycle, and rituximab 375 mg/m^2 at each cycle during 4 cycles. Eighty-eight percent of patients obtained a response, including 65% of major response (58% ≥PR, 8% CRs/nCRs). The 1-year event free survival was 79%. Response was obtained on? both IgM serum level and tumor mass. Neurologic complications were limited, and no grade 3-4 peripheral neuropathy was reported. Grade 3-4 neutropenia was noted in 12% of patients (29). Likewise in relapse/refractory patients, ORR was 81% with 51% of major responses and a median PFS of 15.6 months. Sixteen percent of patients developed a grade 3 neutropenia and a grade 3 neuropathy occurred in only 5% of patients (30). Dimopoulos reported the efficacy and toxicity of bortezomib, rituximab and dexamethasone (BDR) in 59 treatment-naïve patients. In order

to avoid “IgM flare” the first induction cycle consisted of bortezomib (i.v.1.3 mg/m2 days 1, 4, 8 & 11), followed by four cycles of weekly bortezomib (i.v.1.6 mg/m2 for 4 weeks) with rituximab and dexamethasone in cycles 2 and 5. Peripheral neuropathy was observed in 46% of the patients (grade≥3 in 7%) but only 5 (8%) discontinued bortezomib due to neuropathy. After a minimum follow-up of 32 months, median progression-free survival was 42 months, 3-year duration of response for patients with PR was 70%, and 3- year survival was 81% (31). In contrast to BCR-inhibitors, bortezomib is also effective in vitro on tumor cells with CXCR4 mutation (32).

In the last 2014 recommendation on bortezomib the panel wrote “Neurotoxicity is the major concern with bortezomib because underlying IgM-related neuropathy or neuropathies due to age-related co-morbidities (such as diabetes) are common. Weekly dosing and subcutaneous administration may reduce rates and severity of neuropathy and is explored in a clinical trial (NCT01592981). Bortezomib is not stem cell toxic and long-term follow-up in myeloma patients does not suggest a risk for secondary malignancies. Prophylaxis against herpes zoster is strongly recommended. Primary therapy with bortezomib is recommended for patients with high levels of IgM, with symptoms of or at risk of developing hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutinemia, amyloidosis and renal impairment(7).

The panel agrees that bortezomib is less neurotoxic given once weekly and by subcutaneous route but, in case of urgent reduction of the IgM level, bortezomib could be started at a dose of twice a week for one or two cycles and then be changed to once weekly dosing.

III.6 Rituximab+ Carfilzomib

Carfilzomib, a second-generation proteasome inhibitor, is associated with a low risk of neurotoxicity in multiple myeloma (MM) patients and was recently evaluated in combination with rituximab and dexamethasone (CaRD), mainly in untreated WM patients (33). The schedule of carfilzomib was attenuated (days 1, 2 & 8, 9) compared to myeloma dosing, and maintenance therapy (days 1, 2 only) was given every 8 weeks for 8 cycles. Overall response rate was 87% (≥VGPR in 35%), and no grade≥3 neuropathy was observed. With a median follow-up of 15.4 months, 20/31 (65%) patients remain progression-free.

CaRD therefore could represent an emerging neuropathy-sparing option for proteasome-inhibitor based therapy for WM. Cardiac toxicity has been reported in 2% of MM patients and could be an issue especially in elderly WM patients with pre-existing cardiac conditions (34).Other open issues include the optimal dose of carfilzomib (27 mg/m2 vs. higher doses, and the schedule of administration, if once per week dosing schedule as developed in MM)

IV. Maintenance

One retrospective study used rituximab as maintenance therapy in 86 patients responsive to combination therapy with rituximab. Maintenance treatment with rituximab seemed to extend PFS and OS, without major secondary effects (35). However this result need to be confirmed in prospective randomized studies, and the use of rituximab in maintenance therapy is still discussed. A randomized prospective study is ongoing in Germany (MAINTAIN study, NCT00877214), analyzing the impact of 2-years rituximab maintenance after an induction with rituximab + bendamustine in untreated patients.

The panel agrees that robust data must be available before recommending anti-CD20 monoclonal antibodies maintenance in this setting

V. Stem cell transplantation (SCT) for patients with WM

SCT (stem cell transplantation) remains an option for salvage therapy in WM, particularly among younger patients who have had multiple relapses or with primary refractory disease. In an European Bone Marrow Transplant Registry study including 615 autologous stem cell transplantation (ASCT) in WM patients, the 5-year disease –free survival (DFS) and overall survival (OS) were 46% and 65%, respectively, for patients with predominately multi-relapsed or refractory disease who received ASCT (36) The non-relapse mortality at 1 year was low (7%). With a median follow-up of surviving patients of 53 months, the 5-year OS was 65%, DFS was 46%, incidence of relapse (IR) was 47% and NRM was 7%. IR was significantly lower in patients receiving ASCT in first response (CR1, VGPR1, PR1) compared to transplantation in subsequent complete or partial responses or with refractory disease *(39% vs 53%; p=0.001)*, translating into a significant DFS (50% vs 40%, p= 0.004) and OS benefit (71% vs 63%; p= 0.033) for the patients transplanted early. As single-hit, ASCT can induce long term response with relatively low toxicity and economic burden, and it may serve as benchmark for the upcoming novel targeted therapeutics entering the WM / LPL treatment arena. The outcome of

previously treated WM patients who received myeloablative and reduced-intensity allogeneic transplantation was also reported by the European Bone Marrow Transplant Registry (37). The ORR was 76%, and the 5-year PFS and overall survival rates were 56% and 62%, respectively. Among patients who received reduced-intensity allogeneic transplantation, similar PFS and overall survival rates were observed (49% and 64%). Non-relapse mortality at 3 years was high, 33% and 23% for myeloablative and reduced-intensity allogeneic transplantation, respectively. SCT should be discussed in very selected cases currently uneasy not easy? to identify, taking the numerous available treatment options into account and should be preferably considered in the context of clinical trials.

VI. New compounds

VI.1 Lenalidomide

In a phase I/II study lenalidomide monotherapy was used at low dose (starting at 15 mg) (trial RV-WM-0426) in seventeen previously treated patients (38). At the highest dose tested, 20 mg, dose limiting toxicities occurred thus the dose of lenalidomide chosen for further testing was 15 mg/day for 21 days out of 28. Seven out of 14 (50%) patients completed one year of single agent lenalidomide treatment at 15mg/ day. In an intent-to-treat analysis (n= 17) single agent lenalidomide provided an overall response (MR and better) of 29%. Interestingly, all responses were obtained from cycle 9 to 12, which implies a potential immunological effect of lenalidomide in WM, on top of the direct antitumor and stromal inhibition mechanisms of action. A flare effect (transient initial increase of the M spike) was observed in 3 patients. With a median follow-up of 36 months, median TTP was 16 months (95%CI 5.5-26) and the 5-year OS was 91%. The most frequent AEs≥ grade 3 at 15mg were 14% anemia and 43% neutropenia; no grade 3 thrombocytopenia was reported. The combination of rituximab and lenalidomide 25 mg daily for 3 weeks followed by 1 week rest was studied by Treon, in 16 patients (12 in first line). ORR was 50%, and only 1 case of neuropathy was noted. However, 88% of patients had reduction of their hematocrite, in spite of lenalidomide dose reduction to 5 mg. Thus, lenalidomide with rituximab was associated with significant hematologic toxicity (39).

Based on the current data and the potential toxicity observed with lenalidomide, this drug should only be considered in the context of a clinical trial, until further data are available.

VI. 2 mTOR Inhibitor

Ghobrial reported the long–term results of a phase II trial with everolimus in 60 relapsed/refractory patients (40). The response rate was 50% of PR and 23% of MR. The median time to response was 2months and the median PFS was 21 months. Toxicity was hematologic with 27% and 20% of grade3-4 anemia and thrombocytopenia. Pulmonary toxicity was also reported.

VI.3 New monoclonal antibodies

VI.3.1 Anti-BLyS monoclonal antibody

The B-lymphocyte stimulator (BLyS) protein is a cytokine belonging to the tumor necrosis factor (TNF) family, implicated in B-cell survival and maturation, and is over expressed in WM. One phase II study used the anti-BLyS monoclonal antibody, belimumab, in 12 patients with WM. No objective response was reported but 10 patients had stable disease. Belimumab has not been studied in combination therapy yet (41).

VI.3.2 Ublituximab

Ublituximab is a novel chimeric anti-CD20 monoclonal antibody that has a high affinity for NK FcγRIIIa receptors. Preclinical studies showed that ublituximab is more efficient than rituximab in inducing NK cell degranulation and antibody-dependent cellular cytotoxicity (42). A Phase I/II trial with single agent ublituximab in patients with rituximab relapsed/refractory NHL, including WM patients is currently ongoing (NCT 01647971).

The panel agrees that scarce data are available in patients treated with new monoclonal anti-CD20 or other target directed antibodies. Phase II studies are needed in combination with chemotherapy, proteasome inhibitors or BCR inhibitors to evaluate their activity in different disease settings as well as their safety.

VI.4 B-Cell Receptor (BCR) pathway inhibitors

Ibrutinib is a BTK inhibitor effective in high-risk CLL and in mantle cell lymphoma patients. There is a strong rationale to use this drug in WM patients regarding the interaction of BTK and MYD88 pathway. The mutation in MYD88 enhances the proliferation of WM cells, by activating NF kappa B pathway via BTK and BCR activation. Treon recently reported the results

of a prospective study of ibrutinib in 63 symptomatic patients with WM who had received at least one previous treatment (43). The median time to at least a minor response was 4 weeks. The overall response rate was 91%, and the major response rate was 73%. The estimated 2-year progression-free and overall survival rates among all patients were 69% and 95%, respectively. Treatment-related toxic effects of grade 2 or higher included neutropenia (in 22% of the patients) and thrombocytopenia (in 14%), which were more common in heavily pretreated patients; post procedural bleeding (in 3%); epistaxis associated with the use of fish-oil supplements (in 3%); and atrial fibrillation associated with a history of arrhythmia (5%). The results of therapy with ibrutinib as a single agent are impressive. However, the experience is still limited and the side effects and drug interactions of this drug must be stressed, especially in the elderly population. The off target effect of ibrutinib on platelet aggregation with bleeding complications has been described in CLL trials (44). The use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Moreover acquired von Willebrand disease associated with a high IgM level and can be responsible for bleeding (45). The panel recommends to test the von Willebrand activity in patients with high IgM level or with bleeding before starting ibrutinib and to perform plasmapheresis for improving the von Willebrand factor level at the beginning of ibrutinib administration. The efficacy of the drug on IgM levels is rapid (4 weeks to reach a minor response) allowing stopping plasmapheresis. In case of surgery, ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. Another off- target effect is through the inhibition of cardiac PI3K-AKt pathway with a risk of atrial fibrillation (46). In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered. In patients who develop atrial fibrillation on therapy with ibrutinib a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are no suitable, tightly controlled treatment with anticoagulants should be considered. Ibrutinib produces a mild decrease in QT interval (mean 7.5 ms). Underlying mechanism and safety relevance of this finding is not known. Clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QT duration. Randomized studies are ongoing comparing the efficacy of R+ placebo versus R+ ibrutinib in relapsing and in treatment-naïve patients (NCT02165397).

Novel BTK inhibitors are in clinical development and may offer additional choices if they have a different toxicity profile (CC-292 (AVL-292), and ONO-4059, ACP-196)

Ibrutinib is definitively an option in symptomatic WM patients. This drug was approved in first line and in relapsing patients by the FDA in the US in February 2015 and by the EMA in July 2015. However, the optimal time point of therapy with ibrutinib (in first line, relapse or later) and the optimal combination (with rituximab or other anti-CD20, with PI inhibitors such as bortezomib or carfilzomib) is still under investigation. The costs of ibrutinib monotherapy (and potential combinations) against the benefit in terms of PFS or OS must be weighed.

The MYD88 mutation is observed in almost all patients with WM and results in tonic MYD88-IRAK signaling, which activates the NF-κB and MAPK pathways supporting growth and survival of WM cells. Of note MYD88 wild type patients had a lower rate and quality of response to ibrutinib than MY88 mutated patients (47). The efficacy of this drug may be also depend on CXCR4 mutation, with a lower response rate in mutated patients asking the question whether treatment should be stratified according to the CXCR4 mutational status. CXCR4 mutations are observed in 30% of the patients and are associated with a significant but lower response rate to BCR-inhibitors in vitro and in vivo (35,43). The interaction of the chemokine CXCL12 with CXCR4 regulates homing of tumor cells in bone marrow in WM. The role of the CXCR4/CXCL12 axis in WM was already pointed out by Ngo et al. in WM CXCL12/CXCR4 axis interacts with VLA-4 in regulating adhesion of tumor cells to BM stromal cells (48). The distribution and the clinical influence of the CXCL12 (−801GA) polymorphism was shown by Poulain et al., documenting that CXCL12 (−801GG) WM patients show a shorter median survival after initiation of first line therapy than remaining patients (49). The CXCR4 mutation is more difficult to test than MYd88 mutation and requires routinely Sanger sequencing with sufficient tumor cells for analysis.

The panel recommends testing MYD88 and CXCR4 mutations in clinical trials for their impact on the quality of the response but more data are needed for tailoring treatment options to MYD88 and CXCR4 results

Idelalisib is a BCR inhibitor, which targets PI3Kinase delta and was approved for treatment in relapsed CLL and follicular lymphoma. Few data are available in WM. Gopal reported the efficacy of rituximab and idelalisib combination in ten WM patients with 80% overall response rate and a median PFS of 22 months. Trials are ongoing in this setting in naïve-treated and relapsing patients in combination with anti-CD20 antibodies. Grade 3-4 adverse effects of idelalisib are diarrhea (19%) neutropenia (28%) pneumonia (16%) and elevated ALT/AST (12%) (50)

The panel agrees there are more data needed before recommending this combination in relapsing/refractory patients with WM

VII. The future options

Which clinical trials should be prioritized in the front line setting for symptomatic WM patients?

Many options are available in first line: immunochemotherapy with anti-CD20 monoclonal antibodies or the combination of anti-CD20 MoAbs with proteasome inhibitors. The aim of the first line treatments is to reach a high response rate but?with a prolonged PFS. The panel agrees there is need to perform clinical trials with chemo-free combinations with new compounds alone or in combination with anti-CD20 antibodies. Ibrutinib is approved in front-line setting and front line trials with BCR inhibitors are needed for assessing the efficacy and tolerability of this drug in treatment-naïve patients alone and in particular in combinations.

Which clinical trials should be prioritized in the salvage setting for symptomatic WM patients?

The panel agrees with the interest of BCR- inhibitors and new compounds in patients in relapse setting. Combination with proteasome inhibitors would be of interest for overcoming resistance, interfering with the two key pathways that are affected by MYD88. A randomized trial comparing the efficacy of BCR inhibitors to that of BCR-inhibitors+ proteasome inhibitors

could answer this question. Obinutuzumab with its shown efficacy in CLL and also now in follicular lymphoma will be of interest as a combination partner in WM.

VII. Conclusion

Treatment goals may differ significantly for different patients (Tables 1 and 2). Many patients do not succumb to WM but to other causes as previously shown in retrospective and prospective studies. Thus, the goal of therapy is different in patients who are young and in whom we could consider intensified combinations with curative intent or long maintained deep remissions. New agents have real promise and we have to utilize them in combination for an abbreviated course of treatment to achieve the best response rate and duration of response and in parallel limiting costs. The combinations can include monoclonal antibodies, new compounds and also chemotherapy in a curative strategy.

In elderly patients, who comprises the majority of WM patients, toxicity of the regimen (both short term and long term) must be considered first, especially in those who do not require immediate response with intensive regimens because e.g. lack of bulky disease or IgM – related complications. Since many patients, especially elderly ones, will benefit from low toxicity regimens with adequate tumor control, such therapeutic approaches should be considered as primary choices. The cost and effectiveness of such regimens must be weighed against that of other new therapies.

In the salvage setting, especially for patients with disease refractory to standard chemo-immunotherapy, there is a need for development of novel therapies and approaches. Such approaches may include new monoclonal antibodies, BTK-inhibitors or PI3kdelta-inhibitors, BCL2-inhibitors, immune-checkpoint modifiers, etc. (51). Recently, impressive results has been seen in other indolent B – cell lymphomas, using PD1 inhibitors in combination with rituximab, following the concept to exploit the maximum of ADCC of rituximab by inhibiting co-inhibitory molecules on effector cells (52). Combination strategies that aim to overcome drug resistance (for example PI inhibitors with BTK inhibitors) may be explored in clinical trials.

Collectively, immunochemotherapy is still the backbone of treatment for the majority of patients today. Rituximab in combination with chemotherapy is among the most effective treatment in WM and is uniformly recommended in national and international guidelines for first line and salvage treatment in this disease. Rituximab single agent offers the possibility to

elderly patients with co-morbidities to control their disease, although to a lesser extent than rituximab/chemotherapy and also with a prolonged time to first response. All this shows that immunotherapy will stay one of the key therapeutic principles in patients with WM in the future. Despite this, the emergence of drugs such as ibrutinib most likely heralds a new era of treatment in WM and novel signal transduction inhibitors will surely enrich our arsenal to fight WM in the future.

Table 1: Modifications of the recommendations for initial therapy according to clinical conditions of patients with WM.

Clinical condition	Recommendation 2015/2016 [IWWM 8]	Recommendation 2012 [IWWM 7](7)	Recommendation 2009 [IWWM 4] (6)
Cytopenias	DRC Bendamustine-Rituximab Bortezomib/Rituximab Ibrutinib	DRC, Bendamustine-Rituximab, Bortezomib-Rituximab	DRC Thalidomide+Rituximab
High M-protein, auto transplant candidate	Bendamustine-Rituximab, Bortezomib-Rituximab Ibrutinib	Bendamustine -Rituximab, Bortezomib-Rituximab	R-CHOP, DRC
High M-protein, non-autotransplant candidate	Bendamustine-Rituximab, Bortezomib-Rituximab Ibrutinib	Bendamustine-Rituximab, Bortezomib-Rituximab	Nucleoside analogs + rituximab; nucleoside analogs + rituximab + cyclophosphamide
Comorbidities and cytopenias	Rituximab Ibrutinib		Rituximab
Older age, slow progression, candidate for oral therapy	Ibrutinib Oral fludarabine	Oral fludarabine	Cladribine
IgM-related Peripheral Neuropathy	Rituximab DRC Ibrutinib Rituximab+Fludarabine		

Table 2: Recommendations for initial therapy of patients with WM, based on the individual patient characteristics

	Primary choice(s)	Alternative (s)
Patients with WM related cytopenias or organomegaly	DRC Bendamustine/rituximab Ibrutinib	Bortezomib/rituximab
Patients with symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia	Bortezomib followed by bortezomib/rituximab Bendamustine / rituximab Ibrutinib	Fludarabine/rituximab+/-cyclophosphamide
Patients with paraprotein related neuropathy	Rituximab alone DRC Ibrutinib	Fludarabine/R Bendamustine / rituximab Carfilzomib, dexa, rituximab
Elderly patients with poor PS	DRC Oral fludarabine Ibrutinib	Rituximab monotherapy Chlorambucil
Elderly patients not eligible for systemic IV therapy	Oral fludarabine Ibrutinib	Chlorambucil
Young patients eligible for ASCT	DRC Bortezomib/rituximab Ibrutinib	Bendamustine/rituximab R-CHOP

References

1. Swerdlow SH. vol. 2. Geneva: World Health Organization; 2008. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues,
2. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom'smacroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom'sMacroglobulinemia. SeminOncol. 2003;30(2):110–115.
3. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom'smacroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom'sMacroglobulinemia. SeminOncol. 2003;30(2):116–120.
4. Gertz MA, Anagnostopoulos A, Anderson K, et al. Treatment recommendations in Waldenstrom'smacroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom'sMacroglobulinemia. SeminOncol. 2003;30(2):121–126.
5. Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom'smacroglobulinemia. Blood. 2006;107(9):3442–3446. [
6. Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the Fourth International Workshop on Waldenstrom'sMacroglobulinemia. J Clin Oncol. 2009;27(1):120–126.
7. Dimopoulos MA, KastritisE, Owen RG, , Kyle RA,, Landgren 0,Morra E et al. , Treatment recommendations for patients with Waldenström'sMacroglobulinemia (WM) and related disorders: consensus from the Seventh International Workshop on WM. Blood2014:124(9):1404-11.
8. Buske C, Leblond V. How to manage Waldenstrom'smacroglobulinemia.Leukemia. 2013 4:762-72
9. Buske C, Leblond V, Dimopoulos M, Kimby E, Jäger U, Dreyling M; ESMO Guidelines Working Group. Waldenstrom'smacroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.AnnOncol. 2013 Suppl 6:vi155-9.
10. Buske C, Seymour J. Immunochemotherapy in Waldenströmmacroglobulinemia - still the backbone of treatment. Leuk Lymphoma. 2015 Jun 9:1-6. [Epub ahead of print]
11. Treon SP: How I treat Waldenstrom'smacroglobulinemia. Blood. 2015 May 22. pii: blood-2015-01-553974. [Epub ahead of print]
12. Treon SP, Agus DB, Link B, Rodrigues G, Molina A, Lacy MQ, et al. CD20-Directed Antibody-Mediated Immunotherapy induces responses and facilitates hematologic recovery in patients withWaldenstrom'sMacroglobulinemia. J Immunother.2001;24: 272–79

13. Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, and Greipp PR. Multicenter phase 2 trial of rituximab for Waldenströmmacroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). Leuk.Lymphoma. 2004; 45: 2047–2055
14. Dimopoulos MA, Zervas C, Zomas A, Kiamouris C, Viniou NA, Grigoraki V et al. Treatment of Waldenström'smacroglobulinemiawith rituximab. J ClinOncol. 2002; 20 : 2327–33
15. Treon SP, Emmanouilides C, Kimby E, Kelliher A, Preffer F, Branagan AR, et al. Extended rituximab therapy in Waldenström'smacroglobulinemia. Ann Oncol. 2005; 16: 132–38
16. Ghobrial IM, Fonseca R, Greipp PR, Blood E, Rue M, VesoleDH,et al. Initial immunoglobulin M "flare" after rituximab therapy in patients diagnosed with Waldenstrommacroglobulinemia: an Eastern Cooperative Oncology Group Study. Cancer 2004; 101: 2593–2598
17. Wolach O, Bairey O, and Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine(Baltimore) 2010; 89: 308–318
18. Wolach O, Shpilberg O, and Lahav M. Neutropenia after rituximab treatment: new insights on a late complication. Curr.Opin.Hematol.2012; 19: 32–38
19. Li SC, Chen YC, Evens AM, Lee CC, Liao HF, Yu CC, Tung YT, et al. Rituximab-induced late-onset neutropenia in newly diagnosed B-cell lymphoma correlates with Fc receptor FcγRIIIa 158(V/F) polymorphism. Am. J. Hematol.2010; 85:810–812
20. Furman RR, Eradat H, Switzky J. A Phase II Trial of Ofatumumab in Subjects with Waldenstrom'sMacroglobulinemia. Blood. 2011: 118: Abstract 3701
21. Kanan S, Meid K, Treon SP, Castillo JJ. Clinical characteristic of Rituximab intolerance in patients with Waldenstrom'smacroglobulinemia. Blood 2014, 124: abstract 2610
22. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J. Clin. Oncol.2007; 25 : 3344–49
23. Kastritis E Blood. 2015 Sep 10;126(11):1392-4
24. Tedeschi A, Ricci F, Goldaniga MC, Benevolo G, Varettoni M, Motta M, et al. Fludarabine, cyclophosphamide, and rituximab in salvage therapy of Waldenström'smacroglobulinemia.Clin Lymphoma Myeloma Leuk. 2013 ; 2:208-10
25. Rummel MJ, Niederle N, MaschmeyerG,Banat GA, vonGrünhagen U, LosemC, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet.2013; 381:1203–1210
26. Treon SP, Hanzis C, Tripsas C, Ioakimidis L, Patterson CJ, Manning RJ, Sheehy P.Bendamustine therapy in patients with relapsed or refractory Waldenström'smacroglobulinemia.Clin Lymphoma Myeloma Leuk. 2011 ;1:133-5
27. Tedeschi A, Picardi P, Ferrero S, Benevolo G, Margiotta Casaluci G, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström macroglobulinemia.Leuk Lymphoma. 2015 Mar 14:1-6.
28. Treon SP, Ioakimidis L, SoumeraiJD,Patterson CJ, Sheehy P, Nelson M, et al. Primary therapy of Waldenströmmacroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J. Clin. Oncol. 2009; 27: 3830–35

29. Ghobrial IM, Xie W, PadmanabhanS,BadrosA,Rourke M, Leduc R ,et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with WaldenströmMacroglobulinemia. Am. J. Hematol. 2010; 85: 670–74
30. Ghobrial IM, Hong F, Padmanabhan S, Badros A, Rourke M, Leduc R, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrommacroglobulinemia. J. Clin. Oncol. 2010; 28: 1422–28
31. Dimopoulos MA, García-Sanz R, Gavriatopoulou M, Morel P, Kyrtsonis MC, Michalis E, et al. Primary therapy of Waldenstrommacroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN) Blood. 2013 122:3276-82
32. Hunter ZR, Liu X, Xu L, Yang G, Chen J,et al. The WHIM-like CXCR4 (S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom'sMacroglobulinemia.Leukemia2015 29:169-76.
33. Treon SP, Tripsas CK, Meid K, Kanan S, Sheehy P, Chuma S, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström'smacroglobulinemia.Blood 2014 ;124: 503-10.
34. Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies.Haematologica 2013; 98: 1753-1761
35. Treon SP, Hanzis C, Manning RJ,Ioakimidis L, Patterson CJ, Hunter ZR, et al. Maintenance rituximab is associated with improved clinical outcome in rituximab naïve patients with WaldenstromMacroglobulinaemia who respond to a rituximab-containing regimen. Br. J. Haematol2011; 154: 357–62
36. Kyriakou C, Boumendi A, Finel H, Vernant JP, Cornelissen JJ, Thieblemont C et al. Autologous Stem Cell Transplantation (ASCT) for the Treatment of Patients with Waldenstrom’sMacroglobulinemia / Lymphoplasmacytic Lymphoma (WM/LPL). a Risk Factor Analysis By the European Society for Blood and Marrow Transplantation (EBMT) Lymphoma Working Party. Blood 2014; 124: 678
37. Kyriakou C, Canals C, Cornelissen JJ, Socie G, Willemze R, Ifrah N, et al.Allogeneic stem-cell transplantation in patients with Waldenstrom macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010 28: 4926-4934.
38. Fouquet G, GuidezS, Petillon MO,, Louni C , Ohuba B, Dib M et al. Lenalidomide Is safe and active in Waldenstrom Macroglobulinemia. Am J Hematol 2015 in press
39. Treon SP, Soumerai JD, Branagan AR, Hunter ZR, Patterson CJ, IoakimidisL,et al. Lenalidomide and rituximab in Waldenstrom’smacroglobulinemia. Clin. Cancer Res. 2009; 15: 355–60

40. Ghobrial IM, Witzig TE, Gertz M, LaPlant B, Hayman S, Camoriano J et al. Long-term results of the phase II trial of the oral m-TOR inhibitor everolimus(RAD 001) in relapsed or refractory WaldenstromMacroglobulinemia. Am J Hematol 2014 89: 237-242.
41. Bishton M, Spencer A, Dickinson M, and Ritchie D. A Single-Arm, Phase II Study of the Anti-Blys Monoclonal Antibody Belimumab in Symptomatic WaldenstromMacroglobulinemia.Clin Lymphoma Myeloma Leuk.2013;13: 575-78

42. Le Garff-Tavernier M, Herbi L, de Romeuf C, Azar N, Roos-Weil D, Bonnemye P, et al The optimized anti-CD20 monoclonal antibody ublituximab bypasses natural killer phenotypic features in Waldenström macroglobulinemia.Haematologica. 2015; 100: 147-51.
43. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R et al. Ibrutinib in previously treated Waldenstrom macroglobulinemia. N Engl J Med 2015; 372:1430-40.
44. Levade M, David E, Garcia C, Laurent PA, Cadot S, Michallet AS et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014; 124: 3991-5.
45. Hivert B, Caron C, Petit S, Charpy C, Fankam-Siaka C, Lecocq Set al. Clinical and prognostic implications of low or high level of von Willebrand factor in patients with Waldenstrom macroglobulinemia. Blood 2012; 120:3214-21.
46. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ[3], Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124:3829-30
47. MYD88 Mutations and Response to Ibrutinib in Waldenström's Macroglobulinemia. Treon SP, Xu L, Hunter Z. N Engl J Med. 2015; 373:584-6
48. Ngo HT, Leleu X, Lee J, Jia X, Melhem M, Runnels J et al. SDF-1/CXCR4 and VLA-4 interaction regulates homing in Waldenstrom macroglobulinemia.Blood. 2008; 112:150-8.
49. Poulain S, Ertault M, Leleu X, Coiteux V, Fernandes J, Stalnikiewicz L et al. SDF1/CXCL12 (-801GA) polymorphism is a prognostic factor after treatment initiation in Waldenstrom macroglobulinemia.Leuk Res. 33: 1204-7.
50. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. NEngl J Med. 2014; 370: 1008-18. Jan 22
51. Tam CS: ABT-199 (GDC-0199) achieves deep and durable responses in patients with heavily pretreated Waldenström Macroglobulinemia (WM**):** Preliminary results from an ongoing phase I study. Proc 8[th.] International Workshop on Waldenström Macroglobulinemia London Aug 14-16 2014 (Abstr W3)
52. Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol. 2014; 15:69-77.