# To the editor:

## Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenström macroglobulinemia: final analysis of a phase 2 study

Reports of long-term outcomes of therapies in Waldenström macroglobulinemia (WM) are particularly important given the protracted course of the disease. In a large phase 2 study in 72 patients, using contemporary criteria for diagnosis and initiation of therapy,[1,2] primary therapy with dexamethasone, rituximab, and cyclophosphamide (DRC) was active with limited toxicity.[3] DRC is one of the most commonly used regimens for symptomatic WM and is evaluated, with or without bortezomib, in the randomized European Consortium for Waldenström Macroglobulinemia (ECWM-1) study (NCT01788020). Herein we present outcomes after a minimum follow-up of 7 years (median 8, range 7 to 10 years), and this is one of the few studies in WM with long-term data. Patients were enrolled between November 2002 and April 2006. Inclusion required the presence of $CD20^+$ lymphoplasmacytoid lymphoma involving the bone marrow, positive serum immunofixation for monoclonal IgM, and at least 1 of the consensus criteria for initiation of treatment.[2] DRC consisted of six 21-day courses of dexamethasone 20 mg IV, followed by rituximab IV 375 mg/$m^2$ and oral cyclophosphamide 100 mg/$m^2$ twice daily (days 1 to 5). Patients without progressive disease were followed without treatment. Response was evaluated on an intention-to-treat basis per standard criteria.[4] The cause of death was assessed prospectively by the treating physicians as either "WM-related" (ie, resulting from progressive disease, transformation to myelodysplastic syndrome [MDS] or diffuse large B-cell lymphoma [DLBCL], infections, or treatment-related complications), or "unrelated" (ie, died while WM was in remission, off treatment, resulting from causes such as stroke, myocardial infarction, or a second cancer, and without evidence of disease progression or relapse during this period). The characteristics of the patients, toxicity, and response have been published.[3] On intent-to-treat, 83%

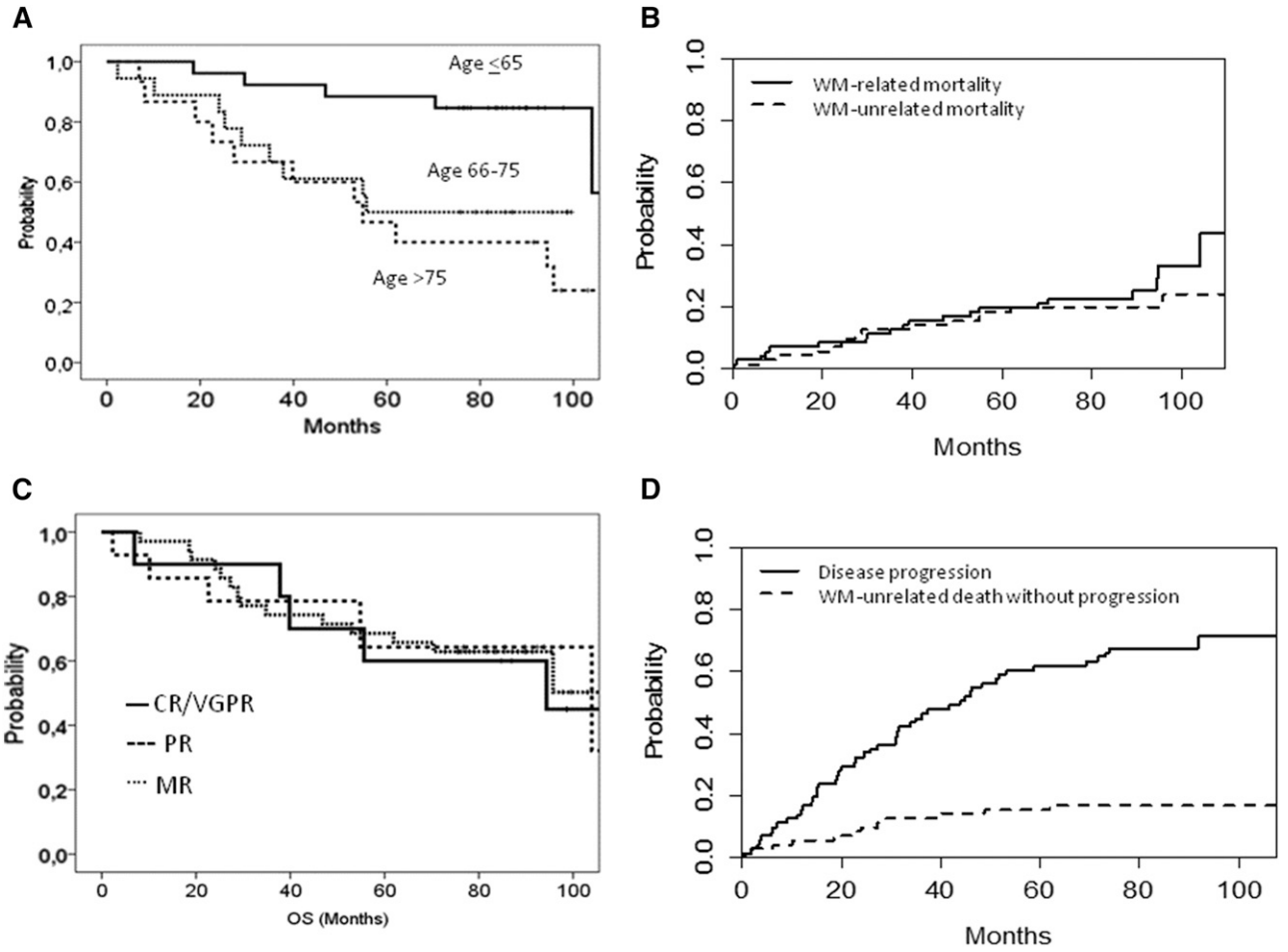


**Figure 1. Time to event curves for patients in the phase 2 DRC study.** (A) Overall survival (OS) according to age (≤65, 66 to 75, and 75 years). (B) WM-related and unrelated mortality. (C) OS per response category (including very good partial response [VGPR] category as per the revised response criteria published by Owen et al[1]). (D) Progression, and unrelated mortality without progression. CR, complete response; MR, minor response.

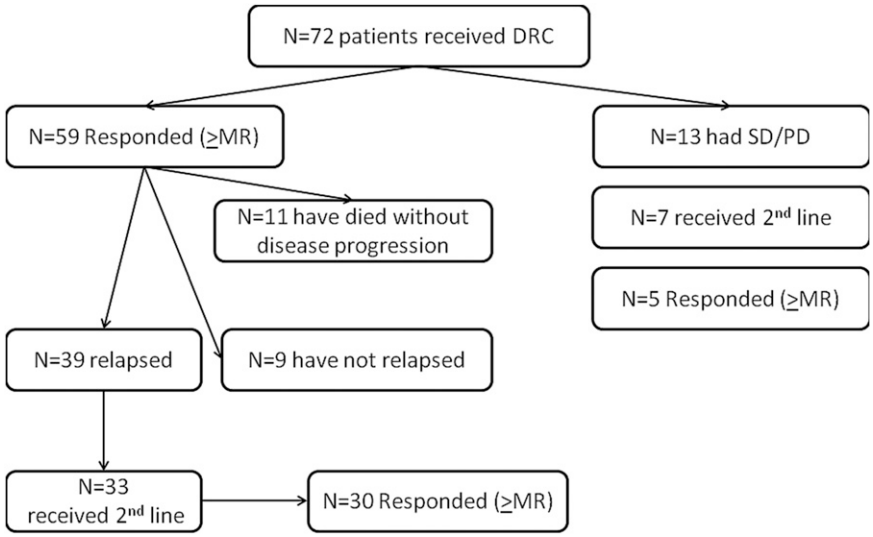


**Figure 2. Outcomes of patients who participated in the phase 2 study of the combination of DRC in previously untreated patients with symptomatic WM.** PD, progressive disease; SD, stable disease.

achieved a response (complete remission: 7%, partial remission: 67%, minor remission: 9%); 9% had stable and 8% experienced progressive disease. Median progression-free survival (PFS) was 35 months (95% confidence interval, 22 to 48 months); disease progression at 3 years was 45%, and unrelated death, without disease progression, was 12% (Figure 1). In comparison, median PFS after single-agent rituximab was 23 months.[5] Other rituximab-containing regimens (such as bortezomib, dexamethasone, rituximab) were also associated with a median PFS of around 3 years; however, these included an additional toxicity profile and shorter follow-up.[6] Bendamustine with rituximab was superior to *R*-CHOP (PFS 69 vs 28 months with less toxicity),[7] however the numbers at each group were small and the follow-up was short.

Forty patients (56%) received second-line therapy (Figure 2). Median time to next treatment was 51 months. Among patients who received second-line treatment, 28 (70%) were retreated with a rituximab-based regimen with high response rates (82% achieved at least a minor response); 12 patients (30%) were treated with alkylating agents, fludarabine, or bortezomib (67% achieved at least a minor response). Thus in patients who have achieved a relatively long-lasting response with initial rituximab-based therapy, a similar regimen may be considered as a reasonable option at relapse.

Thirty-five patients (49%) have died: 20 (57%) were WM-related, and in 15 (43%) death was unrelated to WM (related to solid tumors in 8, [lung in 4, bladder in 1, melanoma in 1, gastric in 1, and pancreatic in 1], heart disease in 4, stroke in 2, and pancreatitis in 1). Secondary MDS and transformation to DLBCL occur in ~3% and ~10% of WM patients, respectively.[8-10] However, only 1 developed MDS after he had received fludarabine, and 2 patients (2.7%) developed DLBCL (1 after exposure only to DRC and the other after multiple treatments, including nucleosides). The rate of nonhematologic tumors was higher than MDS/DLBCL; whether the incidence of solid tumors is higher than expected for this elderly population and if these are related to WM or therapy requires further investigation. Median OS is 95 months (95% confidence interval, 87-103) and 8-year OS is 47%. Accounting for unrelated deaths as a competing event, WM-related death at 8 years was 32% and WM-unrelated was 21%. The 8-year and estimated 10-year OS related to WM was 64% and 53%, respectively. Thus we prospectively documented that unrelated mortality has significant impact on the survival of WM patients. The 8-year OS per the international prognostic scoring system for WM was 100%, 55%, and 27% for low, intermediate, or high-risk disease, respectively ($P = .005$).

In conclusion, PFS after DRC is about 3 years, whereas retreatment is feasible. The OS after primary DRC was about 8 years, affected by the risk status; however, second nonhematologic cancers were observed and about one-fifth of patients died of unrelated causes.

**Efstathios Kastritis**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

**Maria Gavriatopoulou**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

**Marie-Christine Kyrtsonis**
*First Department of of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece*

**Maria Roussou**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

**Evdoxia Hadjiharissi**
*Theageneion Cancer Center, Thessaloniki, Greece*

**Argyris Symeonidis**
*Department of Hematology, University of Patras School of Medicine, Patras, Greece*

**Panagiotis Repoussis**
*Metaxa Cancer Center, Piraeus, Greece*

**Evridiki Michalis**
*Department of Hematology, G. Genimatas Hospital, Athens, Greece*

**Sosana Delimpasi**
*Department of Hematology and Bone Marrow Transplant, Evangelismos Hospital, Athens, Greece*

**Konstantinos Tsatalas**
*School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece*

**Panagiotis Tsirigotis**
*Second Department of Internal Medicine, National and Kapodistrian University of Athens, Haidari, Greece*

**Amalia Vassou**
*Department of Hematology, University of Ioannina School of Medicine, Ioannina, Greece*

**Elina Vervessou**
*Henry Dunant Hospital, Athens, Greece*

**Eirini Katodritou**
*Theageneion Cancer Center, Thessaloniki, Greece*

**Dimitra Gika**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

**Evangelos Terpos**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

**Meletios A. Dimopoulos**
*Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

The online version of this article contains a data supplement.

**Contribution:** E. Kastritis and M.A.D. collected and analyzed data, wrote the manuscript, and performed statistical analysis; and M.G., M.-C.K., M.R., E.H., A.S., P.R., E.M., S.D., K.T., P.T., A.V., E.V., E. Katodritou, D.G., and E.T. treated patients, collected and analyzed data, and critically reviewed the manuscript.

**Conflict-of-interest disclosure:** M.A.D. received honoraria from Celgene, Janssen, and Onyx. E.T. received honoraria from Celgene and Onyx. The remaining authors declare no competing financial interests.

**Correspondence:** Meletios A. Dimopoulos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, 80 Vas. Sofias Av, Athens, Greece, 11528; e-mail: mdimop@med.uoa.gr.

## References

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol.* 2003;30(2):110-115.
2. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol.* 2003;30(2):116-120.
3. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol.* 2007;25(22):3344-3349.
4. Weber D, Treon SP, Emmanouilides C, et al. Uniform response criteria in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol.* 2003;30(2):127-131.
5. Gertz MA, Abonour R, Heffner LT, Greipp PR, Uno H, Rajkumar SV. Clinical value of minor responses after 4 doses of rituximab in Waldenström macroglobulinaemia: a follow-up of the Eastern Cooperative Oncology Group E3A98 trial. *Br J Haematol.* 2009;147(5):677-680.
6. Dimopoulos MA, García-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (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(19):3276-3282.
7. Rummel MJ, Niederle N, Maschmeyer G, et al; Study group indolent Lymphomas (StiL). 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(9873):1203-1210.
8. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. *J Clin Oncol.* 2013;31(3):301-307.
9. Leleu X, Soumerai J, Roccaro A, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström macroglobulinemia treated with nucleoside analogs. *J Clin Oncol.* 2009;27(2):250-255.
10. Leblond V, Lévy V, Maloisel F, et al; French Cooperative Group on Chronic Lymphocytic Leukemia and Macroglobulinemia. Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood.* 2001;98(9): 2640-2644.

DOI 10.1182/blood-2015-05-647420





# To the editor:

## Preclinical activity of the repurposed drug auranofin in classical Hodgkin lymphoma

The treatment of classical Hodgkin lymphoma (cHL) patients with refractory/relapsed disease remains a clinical challenge.[1] To find a new therapeutic option for cHL, we investigated the preclinical activity of the repurposed drug auranofin (AF).[2] AF is an anti-inflammatory drug used for rheumatoid arthritis and is now considered a potential anti-cancer drug. AF, approved by the US Food and Drug Administration for clinical trials in chronic lymphocytic leukemia and in ovarian and lung cancer, seems to have application also in bacterial and parasitic infections as well as in HIV/AIDS.[3]

With the goal of repurposing AF for refractory cHL, we demonstrated its antitumoral activity in in vitro and in vivo tumor models. AF inhibited proliferation (Figure 1A) and clonogenic growth (supplemental Figure 1A, available on the *Blood* Web site) of L-1236, L-428, KM-H2, HDLM-2, and L-540 cHL-derived cell lines with IC50 ranging from 0.7 to 1.5 μM (supplemental Table 1). AF was also active in L-540 gemcitabine-resistant and HDLM-2 brentuximab-resistant cells (Figure 1A; supplemental Table 1). AF induced cytotoxic effects by promoting apoptotic stimuli: it decreased the mitochondrial membrane potential (Figure 1B) and induced cyt-c release (Figure 1B), upregulated BAX (Figure 1C) and downregulated the antiapoptotic Bcl-2 (Figure 1C) and Bcl-xL (Figure 1C) molecules, and induced caspase 3 activation (supplemental Figure 1B) and DNA fragmentation (supplemental Figure 1C). AF reduced TrxR activity (Figure 1D) and induced the accumulation of ROS (Figure 1E), which was inhibited by the ROS scavenger N-acetyl-cysteine (NAC) (Figure 1E). NAC reverted apoptotic effects by AF (supplemental Figure 1D).

AF not only could exert a direct cytotoxic activity but also could counteract the survival signals from the microenvironment dependent on: (1) inflammatory cells[4] expressing CD40L or CD30L; (2) collagen secreted by stromal cells and capable of activating DDR1; and (3) Jagged1 expressed by endothelial, smooth muscle, and epithelioid cells.[5] In fact, AF inhibited nuclear factor κB (Figure 1F),