STIMULUS REPORT

blood advances

Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia

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Key Points

- Daratumumab was associated with an overall response of 23% and a median PFS of 2 months in previously treated patients with WM.
- The 2 patients who attained a partial response to daratumumab exhibited higher baseline CD38 median fluorescent intensity in plasma cells.

Introduction

Waldenström macroglobulinemia (WM) is characterized by the accumulation of malignant immunoglobulin M–secreting lymphocytes in the bone marrow and other organs. CD38 is a bona fide marker of plasmacytic differentiation and is expressed in a subset of WM cells.[1] Daratumumab is an anti-CD38 monoclonal antibody, which has shown durable responses and survival benefit in patients with multiple myeloma and systemic light chain amyloidosis.[2-7] In vitro data suggest that exposure to daratumumab attenuates the expression of important mediators of WM cell survival, such as Bruton tyrosine kinase (BTK), phospholipase C gamma 2, extracellular signal-regulated kinase 1/2, and protein kinase B, and delays tumor growth in a WM murine xenograft model.[8] Given prior preclinical data in WM cells and evidence of clinical safety and efficacy in myeloma and amyloidosis, daratumumab emerged as a rational treatment option for WM patients. We designed a multicenter, prospective phase 2 study aimed at evaluating the efficacy of daratumumab monotherapy in previously treated patients with WM.

Methods

All patients provided written informed consent before participation on the study. Eligibility criteria included meeting clinicopathologic criteria for WM,[9] needing treatment according to consensus guidelines,[10] and prior receipt of 1 or more treatment regimens. Other criteria for participation included platelet count $\geq 50 \times 10^3/\mu L$, absolute neutrophil count $\geq 1 \times 10^3/\mu L$, serum creatinine level ≤ 2 mg/dL, total bilirubin level ≤ 1.5 m/dL, serum liver aminotransferase levels ≤ 2.5 times the upper limit of normal, and Eastern Cooperative Oncology Group performance status ≤ 2. Patients with infection with HIV, hepatitis B, hepatitis C, and central nervous system involvement by WM were excluded. Daratumumab was administered IV at a dose of 16 mg/kg once weekly for 8 doses (cycles 1 and 2), then once every 2 weeks for 8 doses (cycles 3-6), and then once every 4 weeks for 12 doses (cycles 7-18), for a total of 28 doses of daratumumab over 18 months. Premedications included acetaminophen, diphenhydramine, famotidine, montelukast, and steroids. Herpes zoster prophylaxis was mandatory throughout therapy. The primary objective was to determine overall response rate (ORR) using criteria from the Sixth International Workshop on WM.[11] Secondary objectives included determination of major response, progression-free survival (PFS), and drug safety. Bone marrow aspirations and biopsies and computed tomography scans (if extramedullary disease present at baseline) were repeated after completing cycles 6 and 18. Allele-specific polymerase chain reaction assays were used to detect *MYD88 L265P*. *CXCR4* mutational status was determined by Sanger sequencing and allele-specific polymerase chain reaction. Sample size was estimated based on an α of 0.05 and a β of 0.20, assuming a null ORR $\leq 40\%$ and an alternative ORR $\geq 70\%$ based on other monotherapies used in

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previously treated patients with WM.[12-14] PFS was defined as the time between the initiation of therapy and the date of disease progression, death, or last follow-up. The Kaplan-Meier method was used for time-to-event analyses. $P < .05$ was considered significant. Statistical analyses were performed using STATA 15 (Statacorp, College Station, TX).

Results and discussion

Between July 2018 and May 2019, 13 patients with previously treated WM were enrolled in the study. Baseline characteristics of the participants are shown in Table 1. Indications for treatment initiation were constitutional symptoms (n = 6), peripheral neuropathy (n = 6), anemia (n = 5), hyperviscosity (n = 2), and extramedullary disease (n = 1). At best response, 2 patients attained partial response (PR), 1 attained minor response, and 3 had stable disease (SD), and 7 experienced progressive disease, for an ORR of 23%, major response rate of 15%, and clinical benefit of 54%. The median number of cycles of daratumumab received was 2 (range, 0-18), and only 2 patients completed the planned 18 cycles of therapy, both of which had only 1 prior line of therapy; 1 patient attained PR and 1 attained SD at the end of cycle 18. Daratumumab was stopped prematurely in 11 patients because of disease progression (n = 9) and lack of response (n = 2). Median PFS was 2 months (95% confidence interval, 1-4 months; Figure 1Ai). Grade 4 adverse events included neutropenia and thrombocytopenia (n = 1 each). Grade 3 adverse events included febrile neutropenia, bacteremia, infusion reaction, increased alanine aminotransferase, and lymphopenia (n = 1 each). Grade 2 adverse events included upper respiratory infections (n = 5), infusion reactions (n = 4), lymphopenia (n = 2), and muscle cramps, headache, increased aspartate aminotransferase, confusion, and fatigue (n = 1 each). One patient died within 20 days of study enrollment because of rapid disease progression. This patient had progressed on ibrutinib, which was stopped 48 hours before starting daratumumab. Given the suboptimal depth and durability of response to daratumumab monotherapy seen in the first 13 patients, the study was terminated because of futility.

We proceeded to investigate the CD38 expression, reported as median fluorescence intensity (MFI), in primary B cells and plasma cells from study participants. Baseline CD38 expression was higher in plasma cells than in B cells (MFI, 18 048 and 2574, respectively; $P < .001$). Baseline CD38 MFI in plasma cells of participants who attained and did not attain PR were 25 511 and 14 000, respectively ($P = .10$; Figure 1Aii). Baseline CD38 MFI in B cells did not associate with response to daratumumab. We then evaluated the effect of daratumumab on CD38 expression by immunohistochemistry and flow cytometry in primary WM cells from the 2 patients who completed all cycles of study treatment. We also evaluated the concurrent expression of CD138, another universal plasma cell marker, by immunohistochemistry and flow cytometry. As shown in Figure 1B, CD38 expression by flow cytometry decreased at a higher proportion than CD138 expression after cycle 6 compared with baseline. In both cases, there were too few plasma cells for assessment of CD38 or CD138 by flow cytometry after cycle 18. Immunohistochemical evaluation showed decreasing expression of CD38 in plasma cells from baseline to only scattered cells at end of treatment, as shown in Figure 1C. However, CD138 expression in plasma cells persisted. By flow cytometry and immunohistochemistry, CD38 expression in B cells was reduced on daratumumab therapy, but CD20 expression persisted (data not shown). Our findings suggest that response to daratumumab might be impacted by baseline CD38 expression in plasma cells, as previously described in myeloma.[15] Although daratumumab might have induced plasma cell killing, there was possible CD38 antigen masking. Also, daratumumab did not seem to have impacted B-cell survival. All of these might in part explain the lack of meaningful clinical responses to daratumumab in WM.

Table 1. Baseline characteristics of 13 patients with WM treated with daratumumab

Characteristic	n (%) or median (range)
Age at WM diagnosis, y	60 (42-77)
Age at daratumumab initiation, y	69 (53-81)
Time from WM to daratumumab, y	5.8 (2.3-27.4)
Male sex	10 (77)
Serum immunoglobulin M level, mg/dL	2031 (920-4566)
Hemoglobin level, g/dL	12.4 (7.6-15)
Platelet count, $\times 10^3/\mu L$	176 (79-335)
Serum β-2-microglobulin level, mg/L	3.9 (1.8-15.6)
Bone marrow involvement, %	30 (5-80)
Lymphadenopathy ≥1.5 cm	7 (54)
Splenomegaly ≥15 cm	3 (23)
MYD88 L265P mutation	11/12 (92)
CXCR4 mutations	4/10 (40)
Prior lines of therapy	3 (1-9)
Prior anti-CD20 therapy	13 (100)
Prior chemotherapy	10 (77)
Prior proteasome inhibitors	7 (54)
Prior BTK inhibitors	4 (31)
Refractory to previous line of therapy	4 (31)
IPSSWM	
Low risk	2 (15)
Intermediate risk	8 (62)
High risk	3 (23)

IPSSWM, International Prognostic Scoring System for WM.

We conclude that daratumumab monotherapy induced lower than expected responses in WM, despite being effective in myeloma and light chain amyloidosis.[6,16] However, our study suggests daratumumab might have some activity in WM, and it is possible that the future of daratumumab in the treatment of WM would rely on combinations with other agents. Preclinical data have suggested a synergistic effect on CD38 blockade and BTK inhibition in WM cells,[8] and a prospective study combining ibrutinib and daratumumab is ongoing (#NCT03679624). However, given the high rates of durable responses to ibrutinib monotherapy in WM patients,[14,17] the benefit of adding daratumumab could be difficult to elucidate. Another potential strategy in WM would be to induce CD38 upregulation, as it is also being pursued in myeloma.[18,19] Finally, evaluating daratumumab in combination with B-cell targeting agents, such as anti-CD20 monoclonal antibodies, would be of clinical interest.

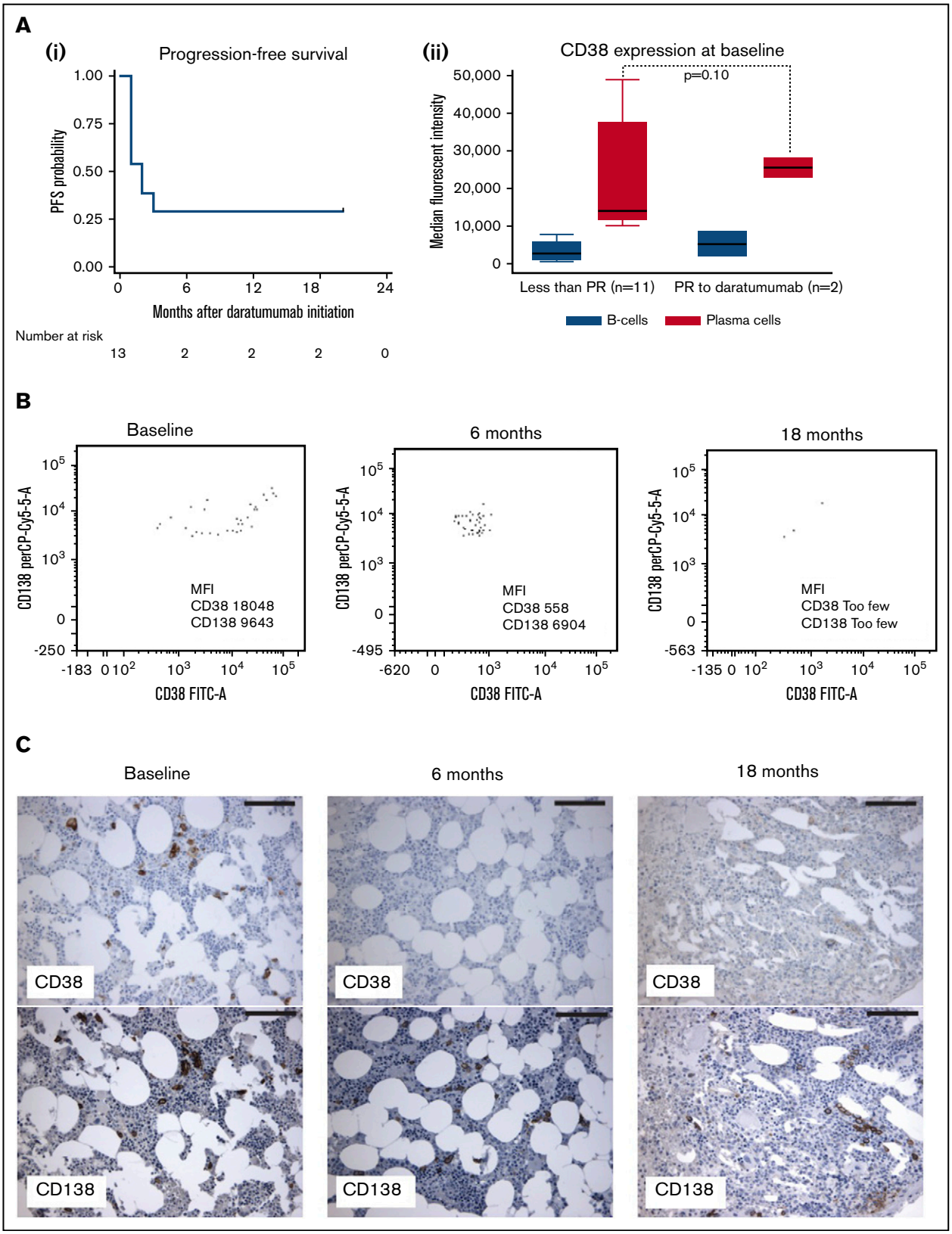

Figure 1. PFS, and CD38 and CD138 expression by flow cytometry and immunohistochemistry in patients with Waldenström macroglobulinemia treated with daratumumab. (Ai) PFS of 13 patients with WM treated with daratumumab. (Aii) Baseline CD38 expression in B cells and plasma cells (box and whisker plots represent median and 95% confidence intervals) in WM patients who attained less than PR and who attained PR. Representative CD38 and CD138 expression by flow cytometry (B) and immunohistochemistry (C) in a patient with WM treated with daratumumab.

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Authorship

Contribution: J.J.C. and S.P.T. designed the study and performed data analysis; J.J.C., E.N.L., S.M.A., M.L.P., and C.A.F. took care of participants and collected study data; K.M. and C.L. coordinated the study, collected study data, and provided regulatory oversight; C.B.H., T.S., E.A.M., R.C., and J.R.F. performed pathologic evaluation of samples; G.Y. and Z.H. performed MYD88 and CXCR4 genotyping; J.J.C. wrote the first draft of the manuscript; and all authors approved the final version of the manuscript.

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