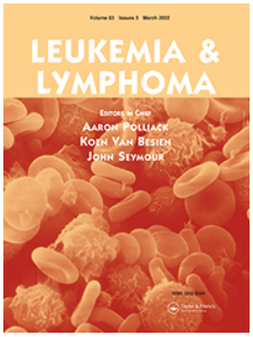

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LETTER TO THE EDITOR

Plamotamab (XmAb®13676) for Ibrutinib- refractory CXCR4-mutated extramedullary Waldenström macroglobulinemia

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Waldenström macroglobulinemia (WM) is an indolent, IgM-producing lymphoproliferative disorder that represents 1–2% of all non-Hodgkin lymphomas (NHL) [1]. High-risk patients, as defined by the international prognostic scoring system for WM (IPSSWM), have an overall survival (OS) of less than 3 years [2]. The phase III iNNOVATE study led to the FDA approval of the front-line combination of ibrutnib plus rituximab for WM patients [3]. However, in two retrospective studies of WM patients who progressed following ibrutinib treatment, the median OS ranged from 32 to 41 months [4–5]. Patients with certain C-X-C chemokine receptor type 4 (CXCR4) mutations are reported to have lower ORR and PFS when treated with ibrutinib [6]. Novel therapeutic regimens are urgently needed for patients with CXCR4 mutations and who have ibrutinib-refractory disease.

Bispecific antibodies (bsAb) are antibodies containing two different antigen-binding sites in one molecule; a tumor epitope and a T-cell antigen, commonly CD3. Plamotamab (XmAb®13676) is a humanized bsAb that binds both CD3 and the tumor antigen CD20 in order to recruit cytotoxic T cells to kill CD20+ tumor cells. XmAb13676 showed potent *in-vitro*, dose-dependent killing accompanied by strong activation and proliferation of both CD4+ and CD8+ lymphocytes when combined with various CD20-expressing lymphoma cell lines [7].

Herein we describe a case of a 54-year-old female patient with relapsed, ibrutinib refractory, CXCR4 mutated, extramedullary WM (EMWM) treated with XmAb®13676 who achieved a minor hematologic response (MR) and near-complete resolution of EM tumors after 4 cycles of therapy but ultimately relapsed after 7.5 cycles due to the emergence of CD20-negative WM.

Response criteria from the VIth International WM Workshop was used [8] .Hematoxylin and eosin (H&E) and Immunohistochemistry (IHC) stained slides were reviewed and interpreted by two hematopathologists. IHC was performed on paraffin-embedded tissue with antibodies including CD20 (Cell Marque, clone L26), CD79a (Leica, clone JCB117), PAX5 (DAKO, clone DAK PAX5), CD8 (Leica, clone 4B11), Ki-67 (DAKO, clone MIB-1), PD-L1(DAKO, clone 28-8), (FOXP3 (Abcam, clone 236 A/E7), and CD25 (Cell Marque, clone 4C9).

Molecular study for MYD88 gene mutation were performed on amplification of DNA by using allele-specific polymerase chain reaction with allele-specific primer that distinguishes the presence of the MYD88 L265P mutation. For CXCR4 gene mutation study, the C-terminus end of CXCR4 was amplified from extracted genomic DNA by PCR; subsequent bridged nucleic acid (BNA) clamping -enhanced and regular Sanger sequencing and capillary electrophoresis analysis were performed.

A 54-year-old woman was diagnosed with WM in March of 2015 after work-up for cytopenias revealed 90% infiltration of the bone marrow by lymphoplasmacytic cells (Figure 1(A)). The patient's ECOG performance status was 0 and her IPSSWM was 4 (high risk). Between 2015 and 2019, the patient received rituximab, bortezomib and dexamethasone, ibrutinib 420 mg daily and bendamustine plus rituximab (BR). The deepest response achieved with each treatment was a partial response. Within 5 months of completion of BR, the patient noticed the development of hard, mobile, non-tender masses on her left anterolateral thigh and right inner thigh. A PET-CT was obtained which revealed several FDG-avid soft tissue tumors in the right inner thigh (Figure 1(B)) and in the left anteromedial thigh (Figure 1(C)). A biopsy was obtained from a right inner thigh mass (red arrow, Figure 1(B)) and it revealed diffuse infiltration by a CD20, PAX5, and MYD88L265P mutation + lymphocyte population (Figure 2(A,B)), consistent with WM. A CXCR4 1013 C > G (S338X) nonsense mutation was detected. The soft tissue tumor showed a dense (90%) CD8+ T cell infiltrate (Figure 2(C)) and a Ki67 proliferation index of 30% (Figure 2(D)).

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A. Diagnostic Laboratory Studies

	Diagnosis 4/2015	Extramedullary Relapse: 1/2020	After 2 cycles of XmAb®13676: 4/2020
HGB	7.8 g/dL	10.4 g/dL	10.0 g/dL
PLT	22 x 10^9/L	150 x10^9/L	109 x10^9/L
WBC/ANC	2.0/1.0x 10^9/L	1.8/1.33 x10^9/L	2.2/1.60 x10^9/L
Cr	0.78 mg/dL	1.11 mg/dL	1.13 mg/dL
LDH	566 U/L	130 U/L	228
B_2-microglobulin	3.93 mcg/mL	N/A	6.35 mcg/mL
M-spike (serum)	3.8 g/dL	0.4 g/dL	0.3g/dL
IFE (serum)	IgM kappa	IgM kappa	IgM kappa
IgG	304 mg/dL	274 mg/dL	163 mg/dL
IgA	20 mg/dL	14 mg/dL	7 mg/dL
IgM	7190 mg/dL	665 mg/dL	362 mg/dL
Bone marrow biopsy	90% lymphoplasmacytic lymphoma cells; CD20+, CD5-, CD10-,CD11c-MYD88L265P positive Cytogenetics: del 6q and trisomy 4	Focal marrow infiltration by lymphoplasmacytic lymphoma cells.	No morphologic evidence of lymphoplasmacytic lymphoma. MYD88L265P not detected,

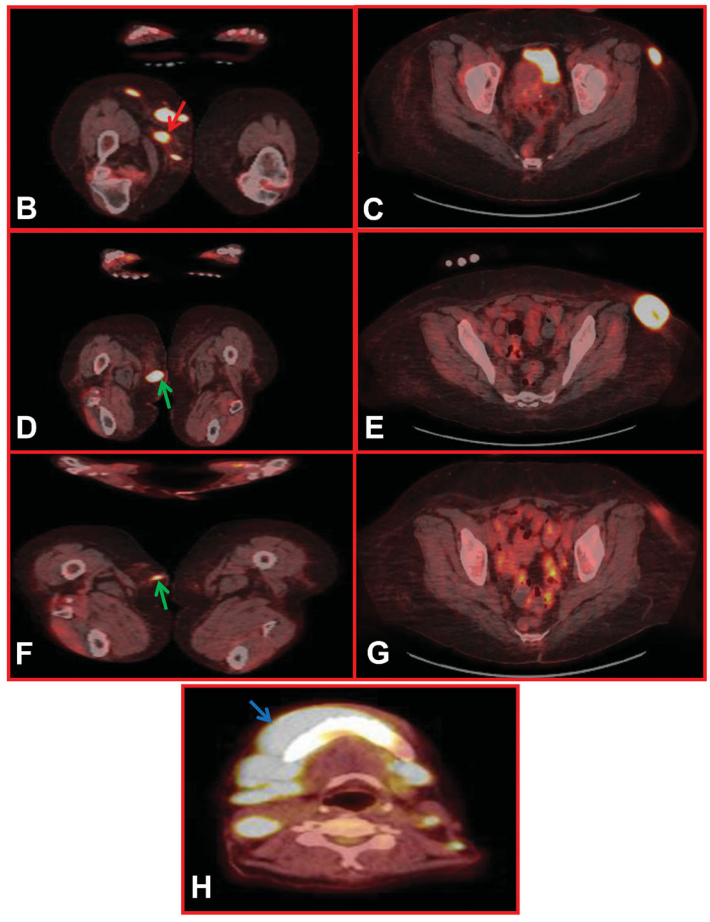

Figure 1. (A) Diagnostic Laboratory Studies. (B) PET-CT images of right inner thigh soft tissue tumors prior to initiation of XmAb®13676. (C) PET-CT images of left anterolateral thigh soft tissue tumor prior to initiation of XmAb®13676. (D) PET-CT images of right inner thigh soft tissue tumors after two cycles of XmAb®13676. (E) PET-CT images of left anterolateral thigh soft tissue tumor after two cycles of XmAb®13676.(F) PET-CT images of right inner thigh soft tissue tumors after four cycles of XmAb®13676. (G) PET-CT images of left anterolateral thigh soft tissue tumor after four cycles of XmAb®13676. (H) PET-CT images of mandibular mass developing after 7.5 cycles of XmAb®13676.

The patient was subsequently enrolled in *NCT02924402* and went on to receive plamotamab at 45 μg/kg on days 1, 8, 15 and 22 of a 28-day cycle. She was supposed to go up to 80 mcg/kg beginning at C1D8 but did not due to safety. On day 1, cycle 1, she developed a grade 2 cytokine release syndrome (CRS) characterized by rigors, fever of 101 °F, and hypotension that was not responsive to fluid resuscitation. Her peak IL-6 level measured on day 1, cycle 1 was 2412 pg/mL (24-h after the start of the infusion). She received 1 mg/kg of solumedrol and tocilizumab 8 mg/kg and achieved hemodynamic stability. The patient received an additional 7 infusions of XmAb®13676 to complete 2 cycles of treatment with one additional episode of CRS (Grade 2 on day 10 of cycle 1). On day 8 of cycle 1, at 1-h post-infusion of plamotamab, the IL-6 level was 1288 pg/mL, while at Day 10 of cycle 1, when CRS occurred, the IL-6 level was 534 pg/mL.

Re-staging studies after 2 cycles revealed disappearance of 4 out of the 5 right inner thigh masses, with one of them growing in size (Figure 1(D), green arrow) as well as growth of the left anterolateral thigh tumor (Figure 1(E)). Bone marrow biopsy showed no evidence of WM involvement with negative MYD88 mutation testing (Figure 1(A)). Serum IgM level decreased by 45%. A biopsy of the left anterolateral thigh tumor showed diffuse involvement by small, CD20+ lymphocytes (Figure 2(E,F)) a scattered CD8 positive T cell population (40%) and a Ki67 proliferation index of 80% (Figure 2(G,H)). The patient was deemed to have stable disease and went on to receive an additional two cycles of plamotamab. A re-staging PET-CT showed a decrease in size of the right inner thigh mass (Figure 1(F), green arrow) and near resolution of the left anterolateral thigh tumor (Figure 1(G)). Immunohistochemical stains for PD-L1 and for regulatory T-cells (CD4, CD25 and FOXP3) were performed on the right inner thigh tumor as well as the left anterolateral thigh tumor and were all negative (stains not shown).

The patient went on to receive an additional 3.5 cycles of plamotamab. Prior to cycle 7 day 15, the patient noted a rapidly enlarging, hard, fixed mass over her right mandible. A PET-CT revealed evidence of progressive disease

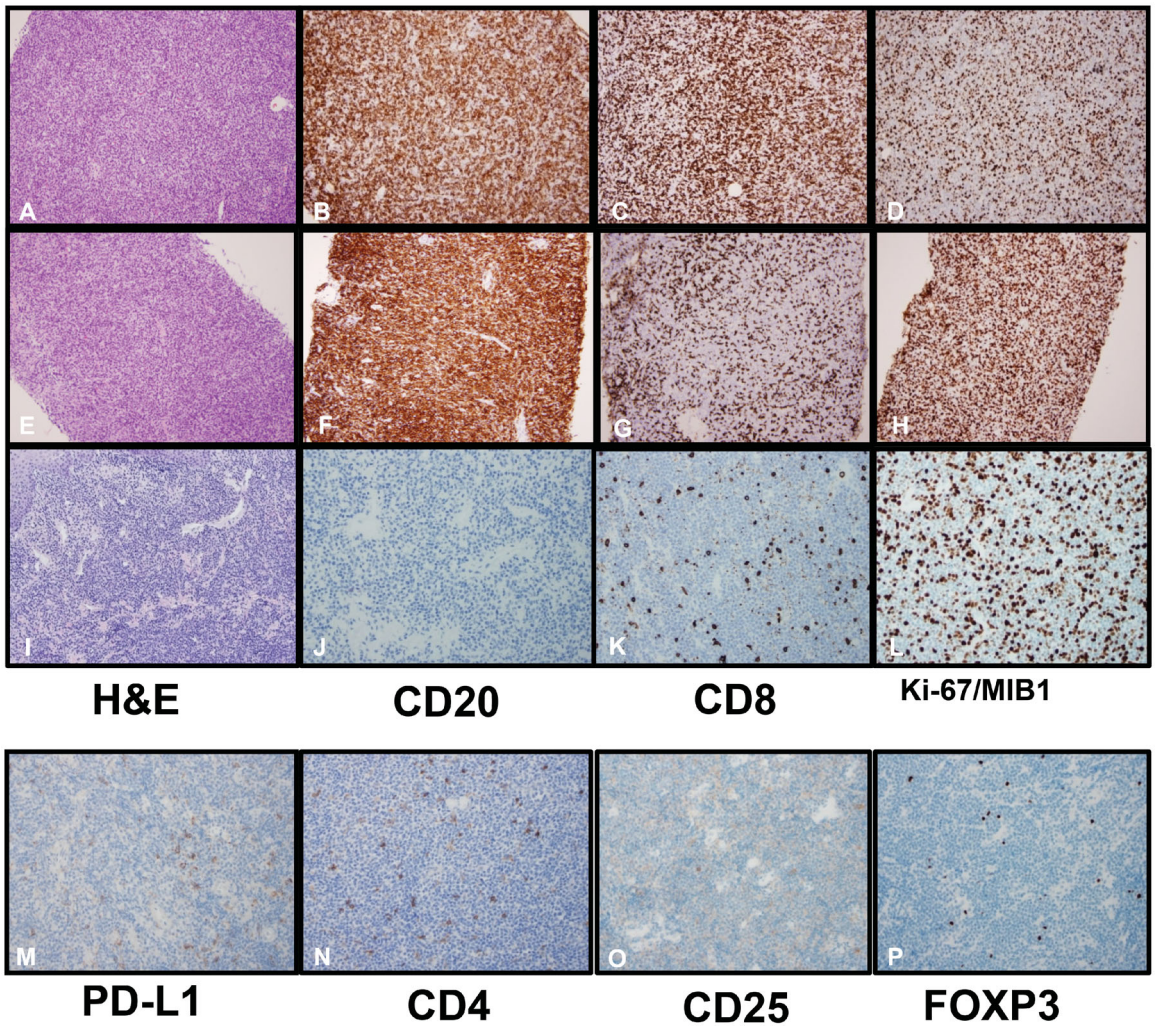

Figure 2. (A) 100× Hematoxylin and eosin (H&E) stain of right inner thigh tumor. (B) 100× CD20 stain of right inner thigh lesion. (C) 100× CD8 stain of right inner thigh tumor. (D) 100× Ki67/MIB1 stain of right inner thigh tumor. Figures A–D are prior to initiation of XmAb®13676. (E) 100× H&E stain of left anterolateral thigh tumor. (F) 100× CD20 stain of left anterolateral thigh tumor. (G) 100× CD8 stain of left anterolateral thigh tumor. (H) 100× Ki67/MIB1 stain of left anterolateral thigh tumor. Figures E–H are after two cycles of XmAb®13676. (I) 200× H&E staining of right mandibular mass. (J) 200× CD20 stain of right mandibular mass. (K) 200× CD8 staining of right mandibular mass. (L) 200× Ki-67/MIB1 of right mandibular mass. (M) 200× PD-L1 stain of right mandibular mass. (N) 200× CD4 stain of right mandibular mass. (O) 200× CD25 stain of right mandibular mass. (P) 200× FOXP3 stain of right mandibular mass. Figures I–P are after 7.5 cycles of XmAb®13676.

with development of mandibular, neck nodal, paraspinal, and osseous involvement of WM. A biopsy of the right mandibular mass (Figure 2(H), blue arrow) revealed a diffuse, sheet-like proliferation composed predominantly of lymphocytes with focal plasmacytic differentiation (Figure 2(I)). The neoplastic lymphocytes were positive for PAX-5 and CD79a and negative for CD20 (Figure 2(J)). The tumor contained a sparse (10%) CD8+ T-cell infiltrate (Figure 2(K)) and a Ki67 proliferation index of 30% (Figure 2(L)). PD-L1 (28-8) staining on tumor infiltrating T-cells was negative (Figure 2(M)) as was staining for regulatory T-cells (CD4, CD25 and FOXP3) in the right mandibular mass (Figures N-P).

To our knowledge, this is the first reported case of an anti-CD20 bsAb showing efficacy in an ibrutinib-refractory WM patient with a CXCR4 mutation. CXCR4 mutations are reported in approximately 30% of WM cases with the S338 hotspot being the most common somatic mutation [9,10]. Patients having nonsense CXCR4 mutations have lower ORR to ibrutinib compared to frameshift mutations and wild type (55%, 79% and 85%, respectively; $p =<$ 0·001) as well as lower PFS; 43 months vs. not reached for patients with frameshift mutations and wildtype CXCR4 mutations ($p = 0.01$) [7]. Furthermore, CXCR4 mutations have been associated with the presence of deletion 6q and trisomy 4, both of which confer an adverse prognosis [11]. Proteasome inhibitors seem to overcome the detrimental effects of CXCR4 mutations on therapeutic outcomes, however our patient developed progressive disease following treatment with bortezomib [10]. The CXCR4 1013 C > G nonsense mutation has been implicated in the development of EMWM [12]. The

prognosis of patients who develop EMWM at relapse appears to be similar to patients without EMWM (median OS of 79% at 10 years) [13] and thus there is a rationale to continue to develop novel therapies for these patients to reduce disease burden and improve quality of life.

As shown in Figure 2(C), the patient's right inner thigh EMWM tumor that completely disappeared after 2 cycles of XmAb®13676 had a dense CD8+ T cell infiltrate whereas the left anterolateral thigh EMWM tumor that grew in size after 2 cycles of XmAb®13676 had a scattered CD8+ T cell infiltrate (Figure 2(G)). However, the left anterolateral thigh EMWM tumor eventually regressed after an additional 2 cycles of XmAb®13676 (Figure 1(G)). It is therefore plausible that the density of CD8+ T cells in the tumor microenvironment (TME) predicts time to response when treated with a bsAb, although the validity of this theory in NHL remains unknown at this time. Furthermore, it has been reported in the literature that resistance to bsAb antibody therapy has been associated with T-cell exhaustion *via* up regulation of PD-L1 on cancers cells or other immune cells in the TME, antigen escape characterized by downregulation of the target tumor antigen, and development of an immunosuppressive TME with upregulation of T regulatory cells [14]. Our patient developed progressive disease due to down regulation of CD20 on WM cells (Figures 2(J,M–P)).

In summary, plamotamab appears to show preliminary efficacy in CXCR4 mutated ibrutinib-refractory EMWM. Further evaluation of plamotamab in WM patients is warranted.

Ethics approval statement

The clinical trial referenced in this report was registered at www.clinicaltrials.gov as # NCT02924402 and was approved by the institutional review board and scientific committee at Mayo Clinic Cancer Center. Informed consent was obtained from the patient before trial enrollment per the Declaration of Helsinki.

Disclosure statement

R.D.P., V.A., V.R., D.M.M., L.J. and A.A.C.K have no conflicts of interest to declare.

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D.L., C.J. and R.C. are employed by Xencor, Inc. and have equity in the company.

The remaining authors declare no competing financial interests.

Author contributions

Contribution: R.D.P., D.M.M., L.J., and S.A. designed the research, performed the research, analyzed data, and wrote the manuscript; A.A.C.K, V.R., V.A., performed the research, designed the research and analyzed data; D.L, and C.J. designed and are conducting the clinical study on behalf of Xencor. R.C. developed the and implemented the biomarker plan for the study; and all authors provided feedback and approved the manuscript.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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