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Waldenström macroglobulinemia (WM) is a rare indolent B lymphoma with an annual incidence of 3-4 cases per million.[1] The disease is characterized by bone marrow (BM) infiltration by malignant cells with lymphoplasmacytic differentiation, a detectable serum monoclonal IgM immunoglobulin (mIgM), and the recurrent MYD88 L265P somatic mutation in the majority of cases (>90 %).[2] Time-limited rituximab-based chemoimmunotherapy, such as bendamustine/rituximab, and continuous therapy with covalent Bruton tyrosine kinase inhibitors (BTKi) (ibrutinib, zanubrutinib) are key treatment options in the management of WM.[3] While current therapies provide high overall response rates with durable control, complete remissions (CR) with eradication of clonal cells remain difficult to achieve, and the disease is still considered incurable.[3] Relapsed disease, particularly after BTK inhibitor failure, is a therapeutic challenge and is associated with an adverse prognosis.[4]

Bispecific antibodies (bsAbs) redirect T cells toward malignant cells by simultaneous binding of a tumor-associated antigen and CD3 on T cells. They are highly active agents in relapsed or refractory multiple myeloma (targeting BCMA, GPRC5D) and B-cell lymphomas (CD20).[5] Recent data suggest that anti-BCMA bsAbs effectively eliminate both tumor and normal plasma cells (PCs) as well as B cells.[6] Thus, we hypothesized that teclistamab, a BCMA targeted bsAb, might be a novel and effective treatment approach in WM. Here we present, to our knowledge, the first case report of a relapsed/refractory WM patient successfully treated with an anti-BCMA bsAb. This case report was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient, and all samples were processed according to standard operating procedures approved by the Institutional Ethics Committee under approval number 413/2012.

A 56-year-old non-Hispanic White male with otherwise unremarkable medical history was diagnosed with symptomatic WM in 2014, preceded by IgM kappa monoclonal gammopathy of undetermined significance (MGUS) by 9 years. At diagnosis, BM infiltration was 70% by lymphoplasmacytic lymphoma. Next-generation sequencing (NGS) on CD19-sorted BM cells identified MYD88 L265P and a CXCR4 C-terminal truncating frameshift mutation (p.T318Nfs*26). Disease was low risk by International Prognostic Scoring System for WM (IPSSWM) and intermediate risk according to the modified staging system (MSS-WM). In 2023, WM progression was accompanied by the

development of hepatosplenomegaly. The diagnosis was subsequently reconfirmed by BM evaluation in 2018, 2023, and 2025.

Prior to teclistamab, the patient had received seven lines of therapy: rituximab, cyclophosphamide, dexamethasone (2014); achieving stable disease (SD), rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (2014); achieving partial remission (PR), bendamustine, rituximab (2018; PR); bortezomib, dexamethasone, rituximab (2023; SD followed by extramedullary progressive disease (PD); ibrutinib (2023-2024; 6 months, SD); zanubrutinib (2024-2025; 12 months); achieving a minimal response (MR) followed by extramedullary progressive disease (PD); venetoclax (2025; ramp-up to 800mg/day, 5 months) achieving SD as the best response followed by PD. Two stem cell collections yielded suboptimal CD34+ counts (2.6×10^6 and 1.8×10^6 cells/kg) and the products were not released due to failed quality-control parameters. Mobilization failure was attributed to extensive prior cytotoxic therapy and late collection.

By October 2025, venetoclax was considered ineffective because of worsening edema, ascites, hepatosplenomegaly and absent hematologic response. The liver and spleen measured 23.2 cm and 16.8 cm in the midclavicular line, respectively. Liver or spleen biopsy was not performed. Concomitant AL amyloidosis was not demonstrated on abdominal fat pad biopsy. BM aspirate analyzed by flow cytometry, performed according to EuroFlow protocols, demonstrated 0.15% PCs (100% clonal) with CD19+ CD38+ CD45+ CD138+ cytKappa+ immunophenotype and 0.1% B-lymphocytes (100% clonal) with a CD5-, CD11c-, CD19+, CD20+, CD22+, CD25low, CD27+, CD38low, CD79b+, CD81+, CD305-, sIgM+, cytKAPPA+ immunophenotype. The trephine biopsy was not performed. Fluorescence in situ hybridization was negative for del(17p), and TP53 mutation was not detected by NGS. Spectral cytometry was also performed for detailed lymphoid cell and PC phenotyping with use of anti-BCMA/PE conjugate,[7] detecting 0.1% PCs, 90% of which were BCMA-positive. No considerable BCMA expression was detected on mature B cells.

Teclistamab monotherapy was initiated in December 2025 after off-label reimbursement approval based on highly refractory symptomatic WM, absence of standard alternatives, and the biological rationale for BCMA targeting. At treatment initiation, laboratory workup showed anemia (Hb 112 g/L; 135–175), elevated β2-microglobulin (6.67 mg/L; 0.8–2.34), IgM 25 g/L (0.4–2.3), m-IgM 13.5 g/L, FLC kappa 357 mg/L (3.3–19.4), and FLC ratio 87, with suppressed IgG 4.4 g/L (7–16) and IgA <0.22 g/L (0.88–4.1); albumin, LDH, and CRP were within normal range, and soluble BCMA was

102.9 µg/L. Teclistamab was administered subcutaneously according to the standard step-up schedule: 0.06 mg/kg, 0.3 mg/kg, then 1.5 mg/kg weekly. Per local institutional protocol, tocilizumab 8 mg/kg was given before the first step-up dose to reduce the risk and severity of cytokine release syndrome (CRS). No CRS or neurotoxicity occurred. Grade 3 neutropenia developed on day 8 and resolved after one dose of granulocyte colony-stimulating factor. From day 12, the patient developed renal impairment (peak creatinine 164µmol/L; 60–105, GFR 0,66ml/s; 1–2.35) of unclear etiology despite comprehensive workup, without oliguria, proteinuria, hematuria, obstruction, infection, thrombotic microangiopathy, or metabolic disturbance. Renal function stabilized after cycle 2 and normalized by cycle 4 without intervention. Immunoglobulin replacement, Pneumocystis prophylaxis, and varicella-zoster prophylaxis were administered. No infectious complications occurred during follow-up to date.

For response assessment, 11th International Workshop on Waldenstrom's macroglobulinemia response criteria were used. A rapid hematologic response was observed: PR after cycle 1, very good partial response after cycle 2, and CR after cycle 4, maintained through cycle 5, with early normalization of free light chains (FLC) (Figure 1, Figure 2C). Flow cytometry of the BM aspirate after the third cycle showed complete eradication of clonal PCs and clonal B cells (Figure 2A). A radiologic response was also documented, with partial regression of hepatomegaly and resolution of splenomegaly; liver and spleen diameters decreased to 19.0 cm and 11.5 cm, respectively (Figure 2B). The patient also experienced rapid clinical improvement during cycle 1, with disappearance of lower-extremity edema and subsequent regression of ascites. At 5 months, the hematologic CR and clinical benefit were ongoing, with a CR duration of 4 weeks at manuscript submission. Teclistamab is planned for 12 months, with interval extension to every 2 weeks from month 6 and every 4 weeks from month 9 if disease control and tolerability persist.

Malignant cells in WM most likely originate from an IgM+ memory B cell with partial plasma-cell differentiation into a lymphoplasmacytic/plasma-cell clone that secretes IgM.[8] Flow cytometry studies in WM have clearly demonstrated the co-existence of clonal B-cells and an identical light-chain-isotype clonal PC population with an immunophenotypic profile resembling normal PCs rather than myeloma PCs.[9] This biological overlap supports the investigation of B-cell and plasma-cell–associated targets as potential therapeutic strategies in WM. Daratumumab monotherapy produced

suboptimal activity in WM, with an overall response rate of 23% and median progression-free survival of 2 months, underscoring the need for alternative targets and strategies.[10] Direct data on BCMA expression in WM are limited; however, broader analyses suggest BCMA expression in subsets of non-Hodgkin lymphomas, including WM, generally at lower levels than in multiple myeloma.[11] Elsawa et al. found BCMA expression by flow cytometry in 8/12 (67%) WM patients, with mostly low and occasional intermediate expression.[12]

There are conflicting reports on BCMA expression on precursor, naïve, and memory B cells.[13] Despite limited expression of BCMA on B-cells by flow cytometry, anti-BCMA bsAbs are able to effectively target and eliminate all B-cell subsets from the small pre-B stage onward. Single-cell RNA sequencing demonstrated low but detectable BCMA mRNA expression across mature B cells and B-cell precursors, including immature B cells and both small and large pre-B cells, with the highest expression observed in the small pre-B subset.[6]

BsAbs are among the most active agents currently available for relapsed or refractory multiple myeloma and B-cell lymphomas, producing high response rates even in heavily pretreated patients.[5] Off-label use of teclistamab has recently been reported in three patients with refractory BCMA-positive plasmablastic lymphoma.[14] Evidence of bsABs activity in WM is very limited. A 2022 case report described plamotamab, a CD20×CD3 bsAb, in ibrutinib-refractory, CXCR4-mutated extramedullary WM, inducing minor hematologic response and near-complete extramedullary disease resolution before relapse with CD20-negative disease.[15] A phase II trial of epcoritamab (CD20×CD3) in previously treated WM (NCT06510491) is currently recruiting; however, no preliminary results have been reported to date. Etentamig (ABBV-383), a BCMA×CD3 bsAB, is being evaluated in phase I/II trial for RRWM (NCT07420959), led by Mayo Clinic.

In this heavily pretreated relapsed/refractory WM patient, teclistamab monotherapy led to a rapid and deep hematologic response (CR) with complete eradication of clonal PCs and B cells in the BM. The patient had received multiple prior lines of therapy – including standard chemoimmunotherapy, a proteasome inhibitor, first and second generation BTKi, and venetoclax administered over several years, none of which induced a major response. In contrast, teclistamab proved to be highly effective and very well tolerated with no serious adverse events. Although limited to a single-patient observation, this case provides initial clinical evidence supporting BCMA-directed bsAbs

as a promising therapeutic approach in WM by targeting both malignant plasma-cell and B-cells.

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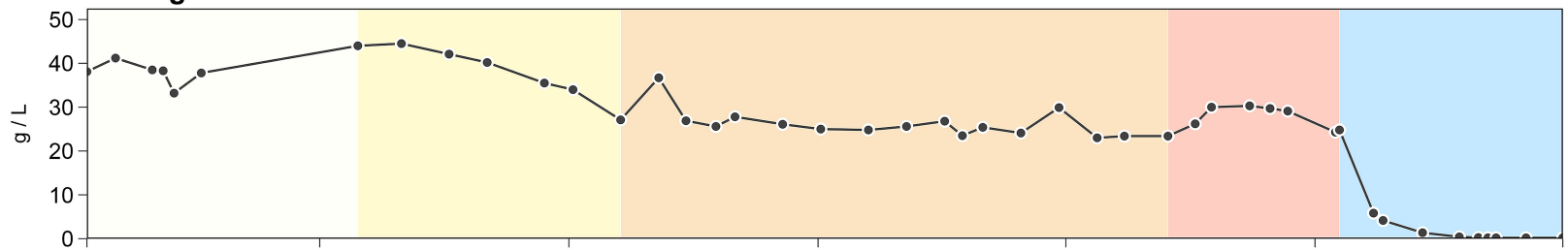
FIGURE 1. Longitudinal monitoring of serum total IgM, involved free light chain kappa concentrations during treatment course. Borte-Dexa-Ritu: bortezomib-dexamethasone-rituximab; CT: computed tomography; HSM: hepatosplenomegaly; TCP: thrombocytopenia.

FIGURE 2. Multimodal Assessment of Response to Teclistamab Therapy (A) Flow cytometry of the bone marrow aspirate before teclistamab administration and after 3 months of therapy, showing complete eradication of both - clonal PCs and B cells. **(B)** Computed tomography demonstrating hepatosplenomegaly before teclistamab initiation and partial regression of hepatomegaly and normalization of spleen size at month 4 of therapy. **(C)** Serum protein electrophoresis and immunofixation at baseline and at month 4 of therapy.

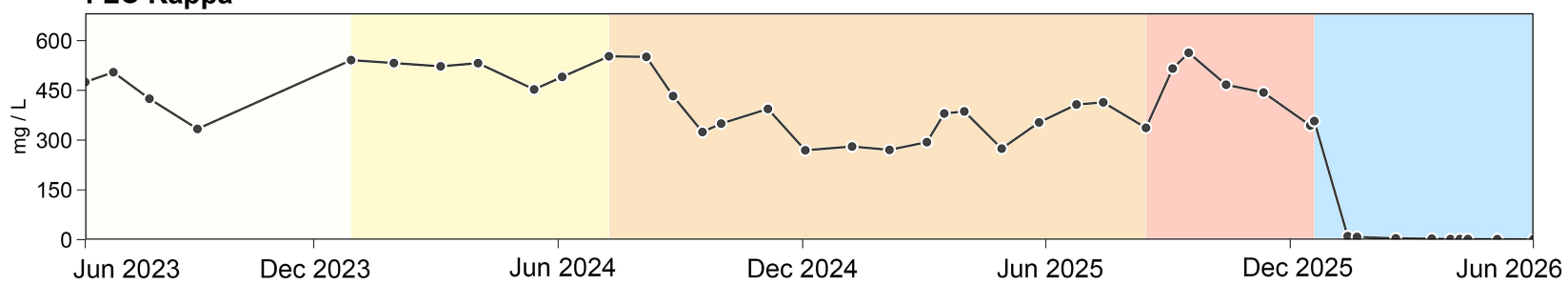
Regimen

Borte−Dexa−Ritu	Ibrutinib	Zanubrutinib	Venetoclax	Teclistamab

Total IgM



FLC Kappa



Indication for Treatment

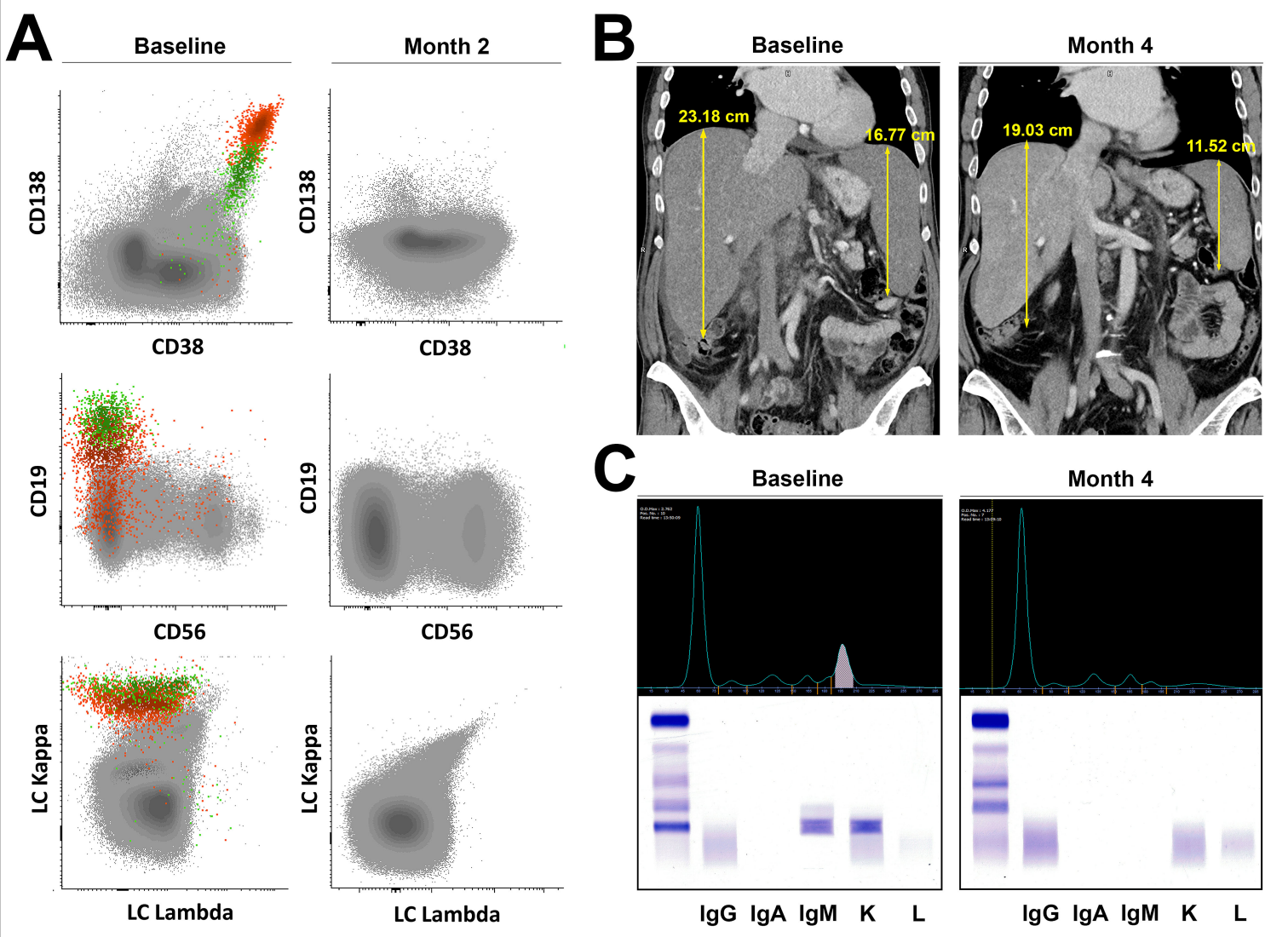
Anemia (Hg <100g/L), weight loss	Anemia (Hg <100g/L), new HSM	Progressive HSM	HSM, TCP	HSM, asictes, edema

Hematological Response

Stable disease	Stable disease	Minimal response	Stable disease	Complete response

Extramedullary Response (by CT)

Progressive disease, HSM	No response	Progressive disease, HSM	Progressive disease	Partial response


A
Baseline
Month 2
CD138
CD38
CD19
CD56
LC Kappa
LC Lambda
B
Baseline
Month 4
23.18 cm
16.77 cm
19.03 cm
11.52 cm
C
Baseline
Month 4
IgG IgA IgM K L
IgG IgA IgM K L