

ARI-0001 (varnimcabtagene autoleucel) in Relapsed/Refractory Waldenström Macroglobulinemia

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BACKGROUND

Waldenström macroglobulinemia (WM) remains incurable, and patients relapsing after chemoimmunotherapy and Bruton's tyrosine kinase (BTK) inhibitors have limited therapeutic options. Clinical experience with CD19-directed chimeric antigen receptor (CAR) T-cell therapy in WM is limited. Varnimcabtagene autoleucel (var-cel, ARI-0001) is a CD19-directed CAR-T developed and manufactured in Hospital Clínic de Barcelona which has previously demonstrated efficacy in B-cell malignancies (Ortiz-Maldonado, *Mol Ther.* 2021). We report the first clinical experience with this construct in patients with relapsed/refractory (R/R) WM.

METHODS

We conducted a single-center observational study of patients with R/R WM treated with var-cel through a compassionate-use program. Eligible patients had received ≥ 2 prior therapies, including BTK inhibitors and chemoimmunotherapy. Following fludarabine/cyclophosphamide lymphodepletion, 5×10^6 CAR T cells/kg were administered in three escalating fractions (0.5, 1.5 and 3×10^6 CAR T cells/kg) separated by at least 24 hours.

Response was assessed according to International Workshop on WM (IWWM) criteria. *MYD88* L265P was assessed using droplet digital PCR (ddPCR) on whole bone marrow (BM) samples (limit-of-detection of 0.025%). Minimal residual disease (MRD) was assessed by multiparametric flow cytometry (sensitivity 10^{-5}). Next generation sequencing was performed using an amplicon-based panel covering 60 genes including *MYD88*, *CXCR4*, *TP53* and other B-cell lymphoma drivers.

RESULTS

Four patients underwent leukapheresis; three received lymphodepletion and var-cel administration. One patient did not receive treatment due to progressive disease-related death. Baseline characteristics of infused patients are shown in Table 1.

Patient 1 achieved a partial response with undetectable MRD at 3 and 6 months.

Serum IgM decreased from 10.5 g/L pre-infusion to 4.58 g/L and 3.72 g/L at 3 and 6 months, respectively. Although *MYD88* remained detectable by ddPCR after CAR-T therapy, it decreased

from 0.56% pre-treatment to 0.09% post-treatment. Despite sustained CAR-T persistence, clonal plasma cells persisted at month 3 (Figure 1).

Patient 2 achieved a complete nodal response by month 3, along with undetectable MRD and *MYD88*. Baseline IgM was normal (Figure 2). Serum immunofixation became negative by month 3. At last follow-up (7 and 5 months, respectively), both patients maintained responses with persistent B-cell aplasia (Figures 1-2).

Patient 1 developed grade 2 CRS on day 6, which resolved quickly after a single dose of tocilizumab and dexamethasone. No other CRS or any-grade ICANS were observed. Regarding infections, patient 1 developed influenza A and norovirus infection, without requiring hospitalization. No relevant adverse events occurred in patient 2.

A third patient recently received var-cel and was not evaluable at submission.

Correlative single-cell analyses of paired pre- and post-treatment samples will be presented at the meeting.

CONCLUSION

Var-cel induces rapid and deep responses with a manageable safety profile in R/R WM. The achievement of MRD negativity, reduction or clearance of *MYD88*-mutated clones, along with persistent B-cell aplasia demonstrates biological activity of this approach. These findings support further clinical investigation of var-cel in R/R WM. The persistence of clonal plasma cells despite sustained CAR-T persistence in one patient highlights the potential value of using strategies targeting both the B-cell and plasma cell compartments, including dual-target CAR-T approaches.

Table 1. Baseline characteristics of the infused cohort.

	Patient 1	Patient 2	Patient 3
Age	62	73	66
Sex	Male	Male	Male
Clinical presentation	Hyperviscosity	Lymphadenopathy, B Symptoms	Anemia, thrombocytopenia
Prior therapies	3	2	4
BM infiltration (morphology; flow cytometry)	20%; 2.2%	4%; 2.5%	90%; 27%
MYD88 L265P	Mutated	Mutated (VAF = 34.1%)	Mutated (VAF = 11.4%)
CXCR4	Wild-type	Wild-type	Mutated (S341Ffs*3; VAF = 27%)
TP53	Wild-type	Wild-type	Mutated (R248G; VAF = 24.5%)
Serum IgM levels	10.5 g/L	1.2 g/L	14 g/L

Figure 1. Kinetic response of patient 1 after ARI-0001. Left panel: B-cell aplasia and CAR-T expansion kinetics assessed by qPCR monitoring of the CAR-T transgene. Right panel: Longitudinal changes in serum IgM, bone marrow clonal B cells and plasma cells, and *MYD88* L265P quantified by ddPCR.

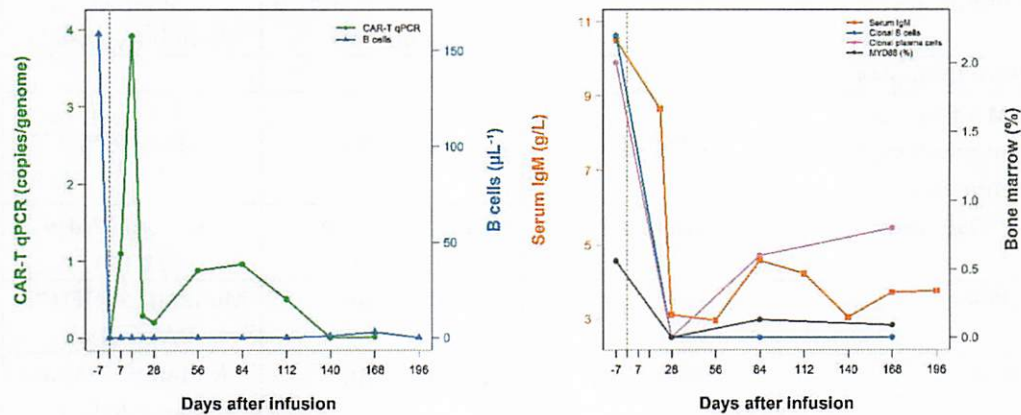
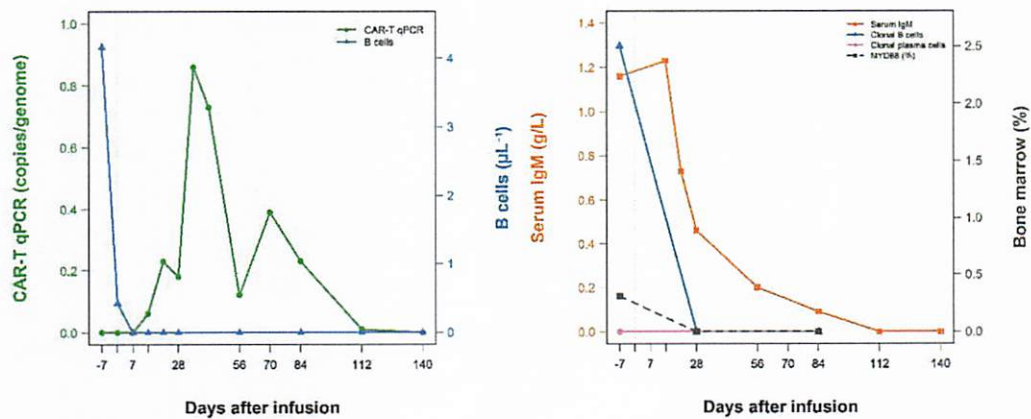


Figure 2. Kinetic response of patient 2 after ARI-0001. Left panel: B-cell aplasia and CAR-T expansion kinetics assessed by qPCR monitoring of the CAR-T transgene. Right panel: Longitudinal changes in serum IgM, bone marrow clonal B cells and plasma cells, and *MYD88* L265P quantified by ddPCR.



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