

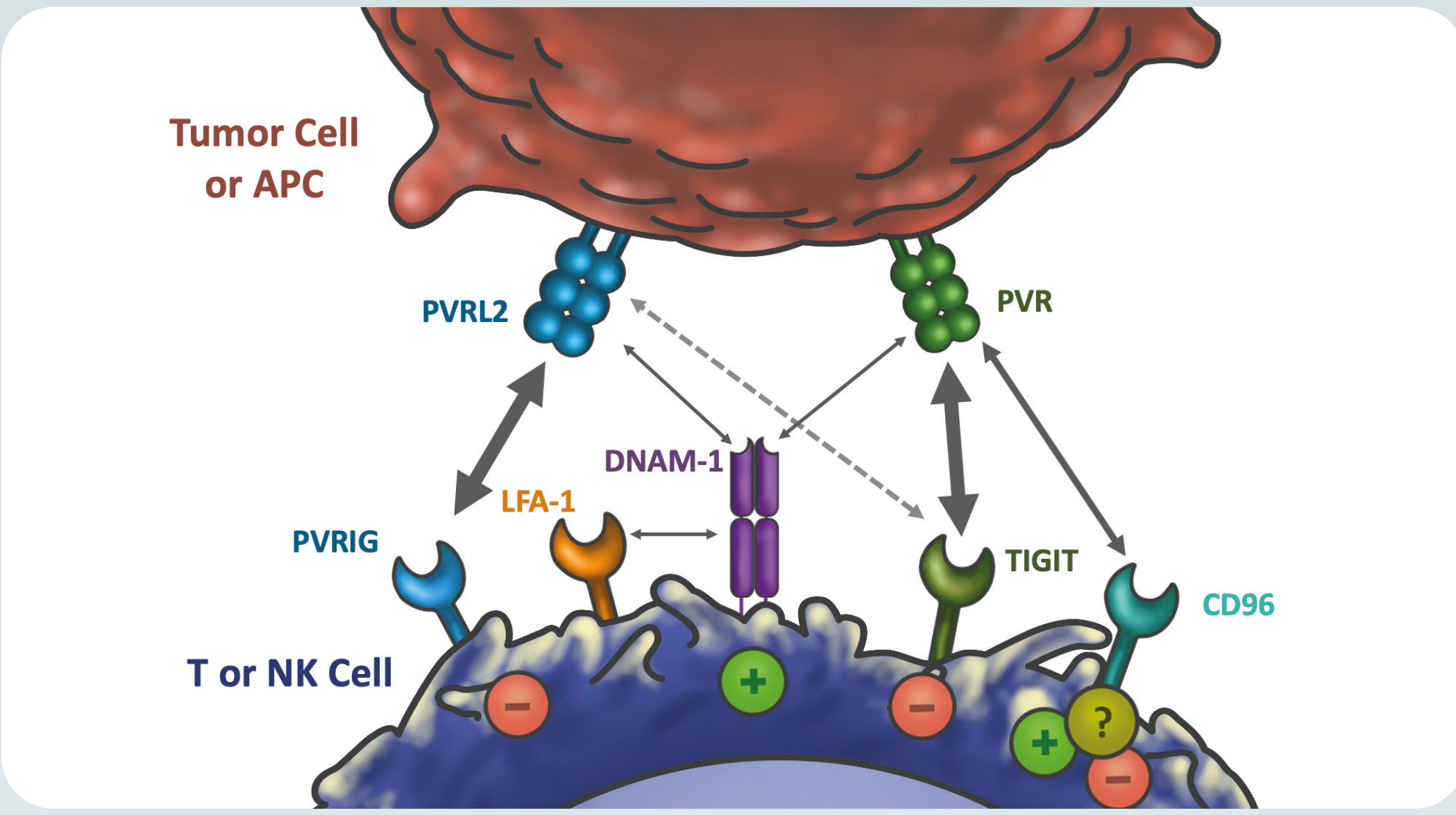
# The expression of the PVRIG/TIGIT pathway is dominant in the bone marrow of patients with multiple myeloma

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## BACKGROUND

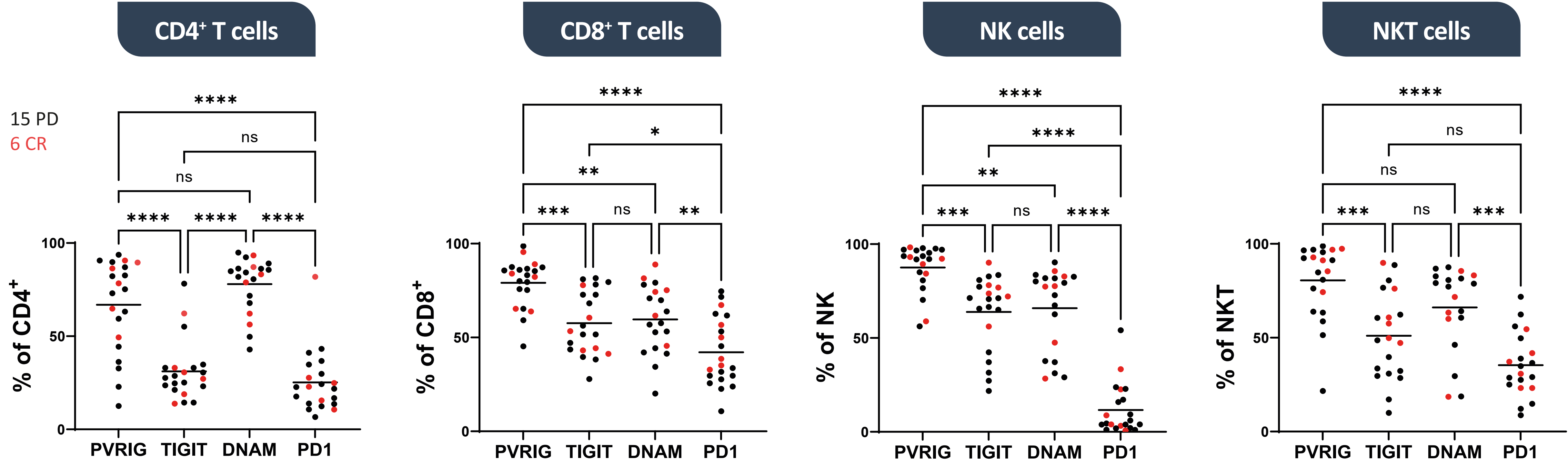
**Background:** Blocking inhibitory immune receptors has shown limited clinical benefit in patients with multiple myeloma (MM), warranting the discovery of alternative immune inhibitory pathways. Blockade of the immune checkpoint TIGIT was shown to enhance anti-tumor immunity in MM pre-clinical models. In addition to TIGIT, the DNAM1 axis includes the novel inhibitory receptor PVRIG. Both TIGIT and PVRIG deliver inhibitory signals to T and NK cells and compete with the co-activating receptor DNAM1 for binding to PVR and PVRL2, respectively.



Accordingly, TIGIT and PVRIG co-blockade was shown to synergize in enhancing anti-tumor immunity in preclinical models. PVRL2 and PVR were shown to be expressed on MM plasma cells in the bone marrow (BM). In this study, we evaluated DNAM1 axis receptor expression in the BM of patients with MM.

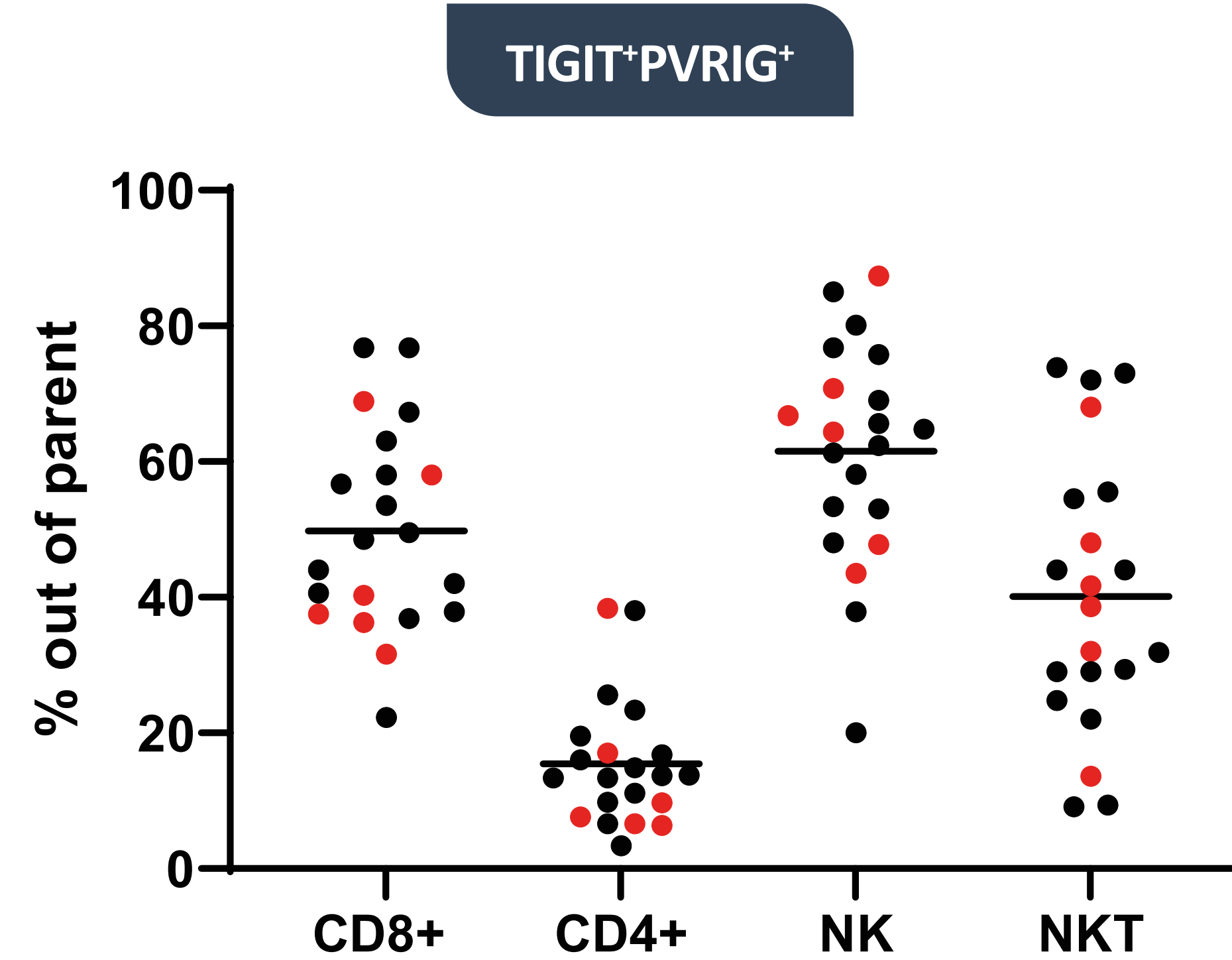
**Methods:** BM mononuclear cells derived from 21 patients with MM were analyzed for the expression of PD1 and DNAM1 axis molecules by flow cytometry. Patients classified with progressed disease (PD), or complete response (CR) were treated with multiple lines of therapies including targeted therapies, chemotherapies, proteasome inhibitors.

## DNAM1 AXIS RECEPTORS ARE MORE DOMINANTLY EXPRESSED THAN PD1 IN MM BM ASPIRATES



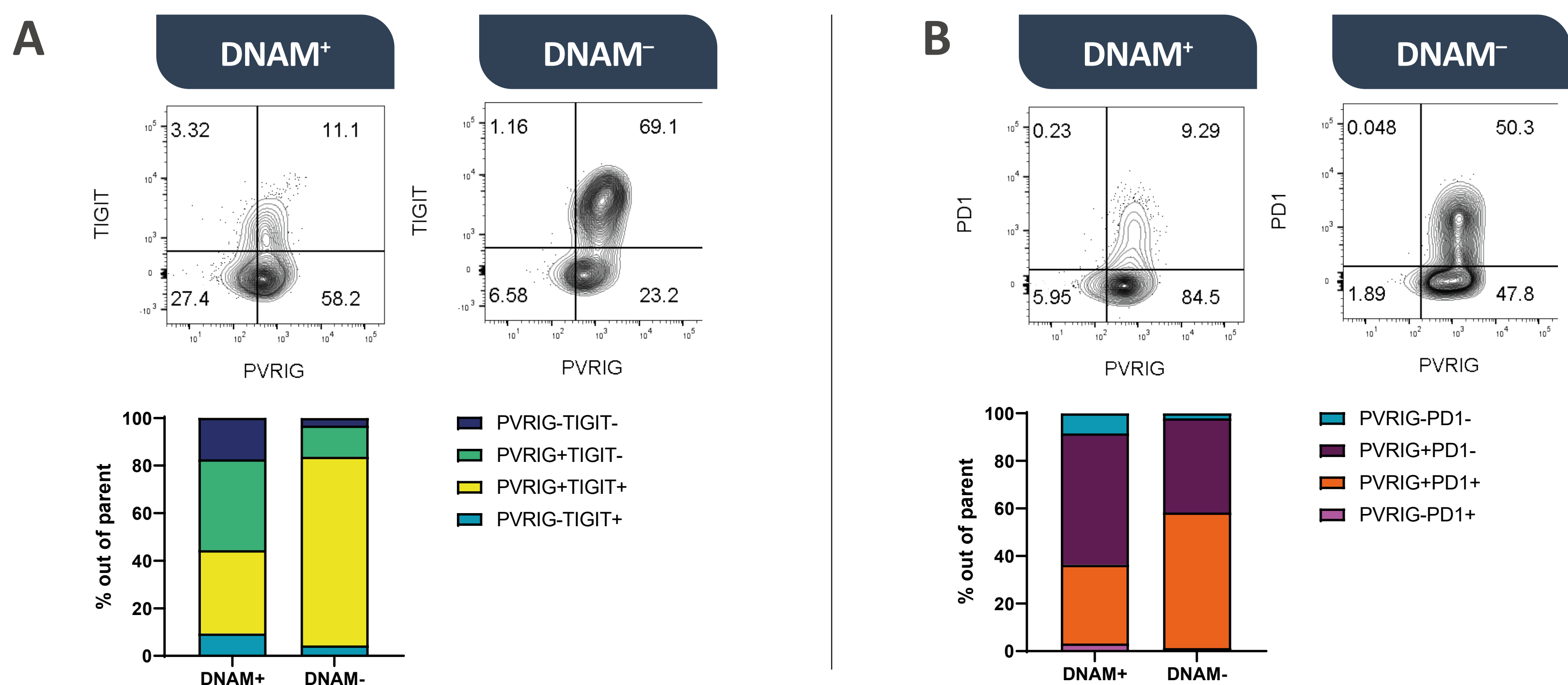
**Figure 1:** PVRIG demonstrated the highest expression among all evaluated receptors on NK, NKT, and CD8<sup>+</sup> T cells, significantly higher than PD1 ( $p < 0.0001$ ) and TIGIT ( $p < 0.001$ ). TIGIT showed substantially increased expression on NK ( $p < 0.0001$ ) and CD8<sup>+</sup> T cells ( $p < 0.05$ ) compared to PD1.

## PVRIG AND TIGIT ARE CO-EXPRESSED ON MM INFILTRATING LYMPHOCYTES



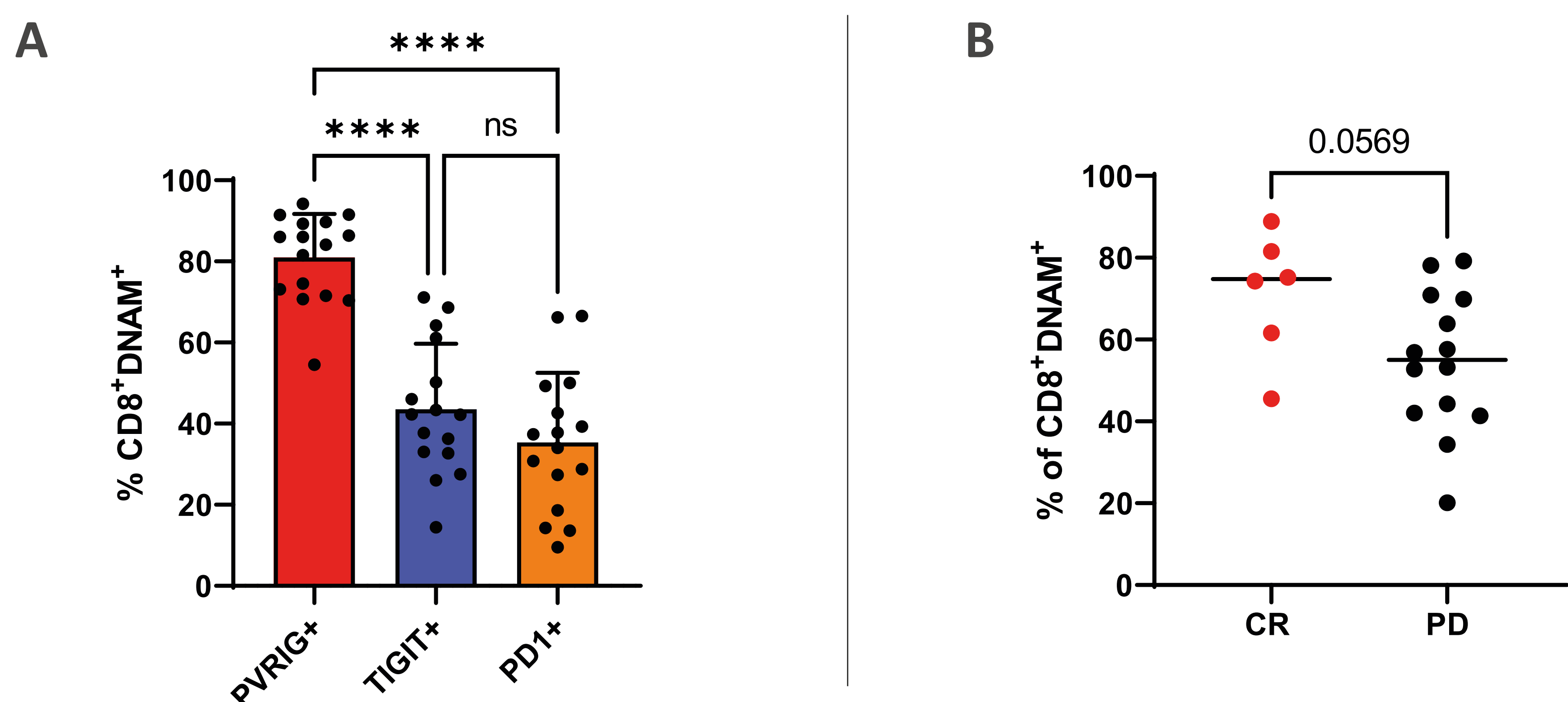
**Figure 2:** CD8<sup>+</sup> T and NK cells co-expressed TIGIT and PVRIG.

## EXHAUSTED T CELLS ACCUMULATE IN BM OF MM PATIENTS



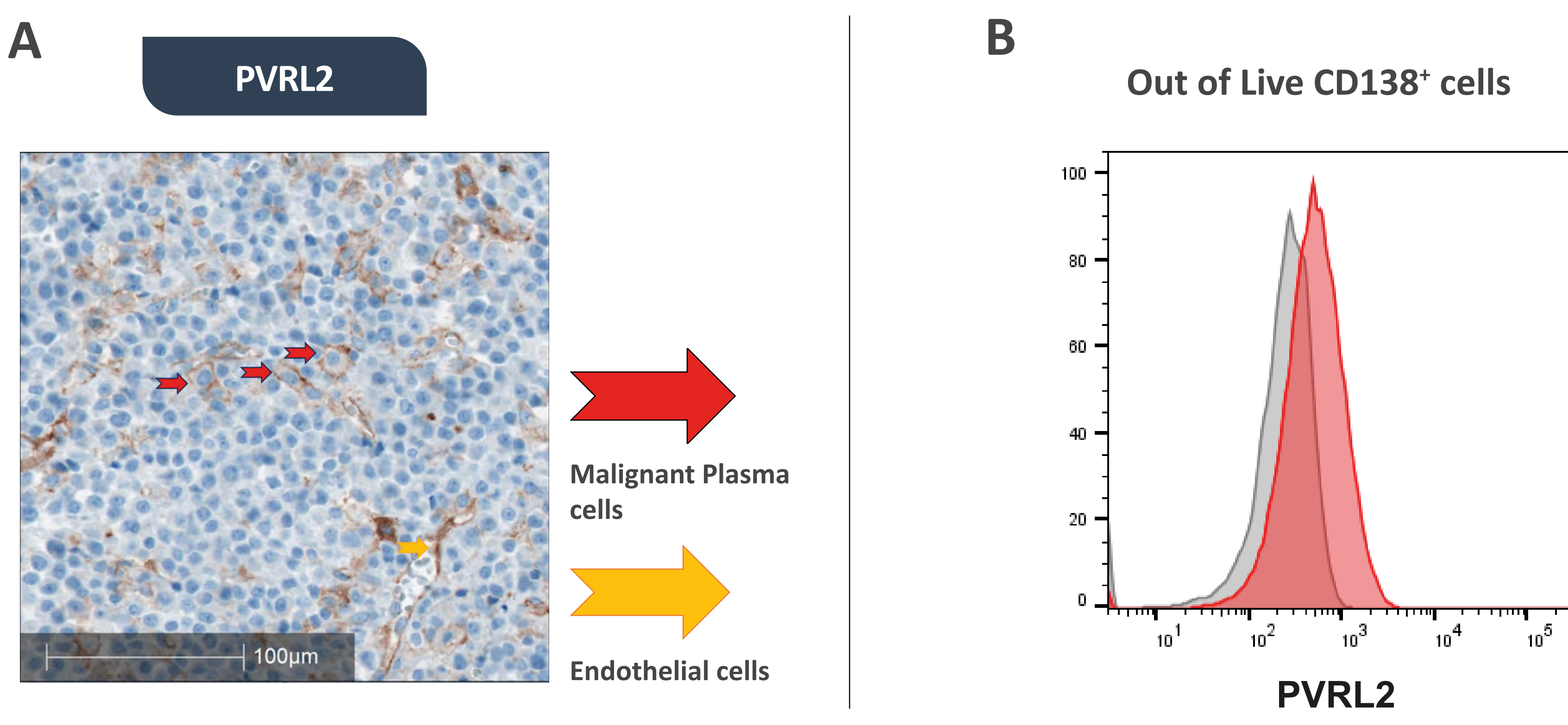
**Figure 3:** Exhausted DNAM<sup>+</sup> PVRIG<sup>+</sup> TIGIT<sup>+</sup> PD1<sup>+</sup> T cells accumulate in BM of MM patients. Co-expression of PVRIG and TIGIT (A) and PVRIG and PD1 (B) on DNAM<sup>+</sup> and DNAM<sup>-</sup> cells.

## DNAM1 IS CO-EXPRESSED WITH PVRIG, AND ITS EXPRESSION IS CORRELATED WITH RESPONSE IN MM



**Figure 4:** PVRIG showed significantly higher ( $p < 0.0001$ ) expression on DNAM<sup>+</sup> CD8<sup>+</sup> T cells, compared to TIGIT and PD1 (A). Patients with CR had a trend towards higher DNAM1 expression on CD8<sup>+</sup> T cells compared to PD patients ( $p = 0.057$ ) (B).

## PVRL2 IS EXPRESSED ON BM PLASMA CELLS IN MM PATIENTS



**Figure 5:** The expression of PVRIG ligand, PVRL2, on BM plasma cells from 6 patients with MM was demonstrated by immuno-histochemistry (A) and by flow cytometry (B).

## CONCLUSION

DNAM1 axis receptors are more dominantly expressed than PD1 on MM BM lymphocytes, with PVRIG exhibiting the most prominent expression. The reduced expression of DNAM1 in patients with PD suggests a link between DNAM1 axis and clinical outcome. Our findings highlight for the first time the dominant expression of PVRIG, as well as TIGIT and suggest that combined blockade of these checkpoints may potentially benefit patients with MM, placing the DNAM1 axis as a promising therapeutic pathway in MM therapy.