

# OR502, a best-in-class anti-LILRB2 antibody that enhances both innate and adaptive anti-tumor immune responses

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## Abstract #494

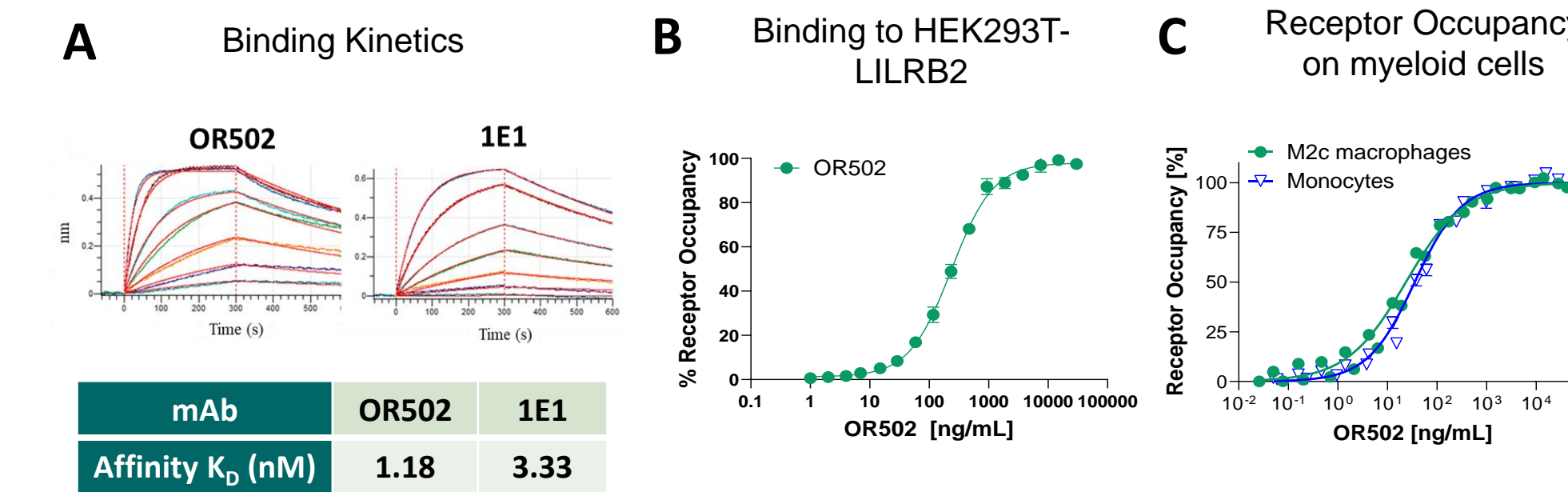
**Background:** The inhibitory receptor leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2, ILT4) is mostly expressed on immunosuppressive myeloid cells, and its expression correlates with poor survival in multiple cancers. OR502 is a humanized IgG1 antibody that blocks the interaction of LILRB2 with its ligands including HLA class I (e.g., HLA-G, HLA-A, B, etc.) to relieve LILRB2-mediated immune suppression by myeloid cells and diminish immune evasion in the tumor microenvironment. OR502 parental antibody demonstrated significant tumor growth inhibition and tumor regression in a humanized SK-MEL-5 tumor model. Antibodies targeting LILRB2 are currently being evaluated in clinical trials for the treatment of cancer as monotherapy and in combination with checkpoint inhibitors.

**Methods:** OR502 functional activity was compared to other anti-LILRB2 antibodies for its ability to prevent the generation of new suppressive macrophages, to reprogram the suppressive function of existing macrophages, in M2c/CD8+ T cell coculture assays, and to assess the modulation of LPS-induced IFN- $\gamma$  and IL-10 production by human PBMCs.

**Results:** OR502 binds specifically to human myeloid cells without binding to lymphocyte cell populations. OR502 antagonizes LILRB2 binding to its main ligand HLA-G expressed on cancer cells as well as to classical HLA class I molecules. Compared to other anti-LILRB2 antibodies, OR502 is superior in enhancing LPS-induced IFN- $\gamma$  and reducing IL-10 production by PBMCs, preventing the generation of immune suppressive macrophages, relieving macrophage-mediated suppression of T cell proliferation, and enhancing IFN- $\gamma$  and perforin secretion by CD8+ T cells. Furthermore, OR502 restored the ability of exhausted T cells to secrete IFN- $\gamma$  in the presence of M2c macrophages and significantly enhanced the activity of pembrolizumab in combination studies. These data demonstrate that OR502 has superior activity in relieving LILRB2-mediated immune suppression and enhancing both innate and adaptive anti-tumor immunity.

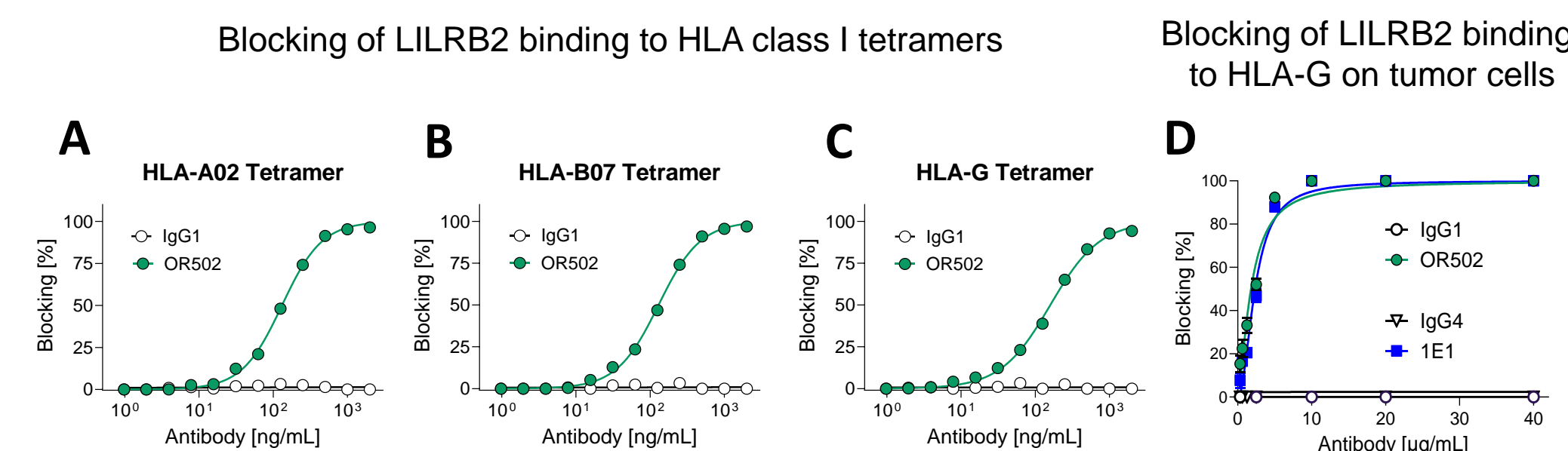
**Conclusions:** OR502 is an anti-LILRB2 antibody with best-in-class activity to restore both innate and adaptive immune responses by modulating immunosuppressive phenotype of myeloid cells.

## 2 OR502 demonstrates high affinity binding to LILRB2



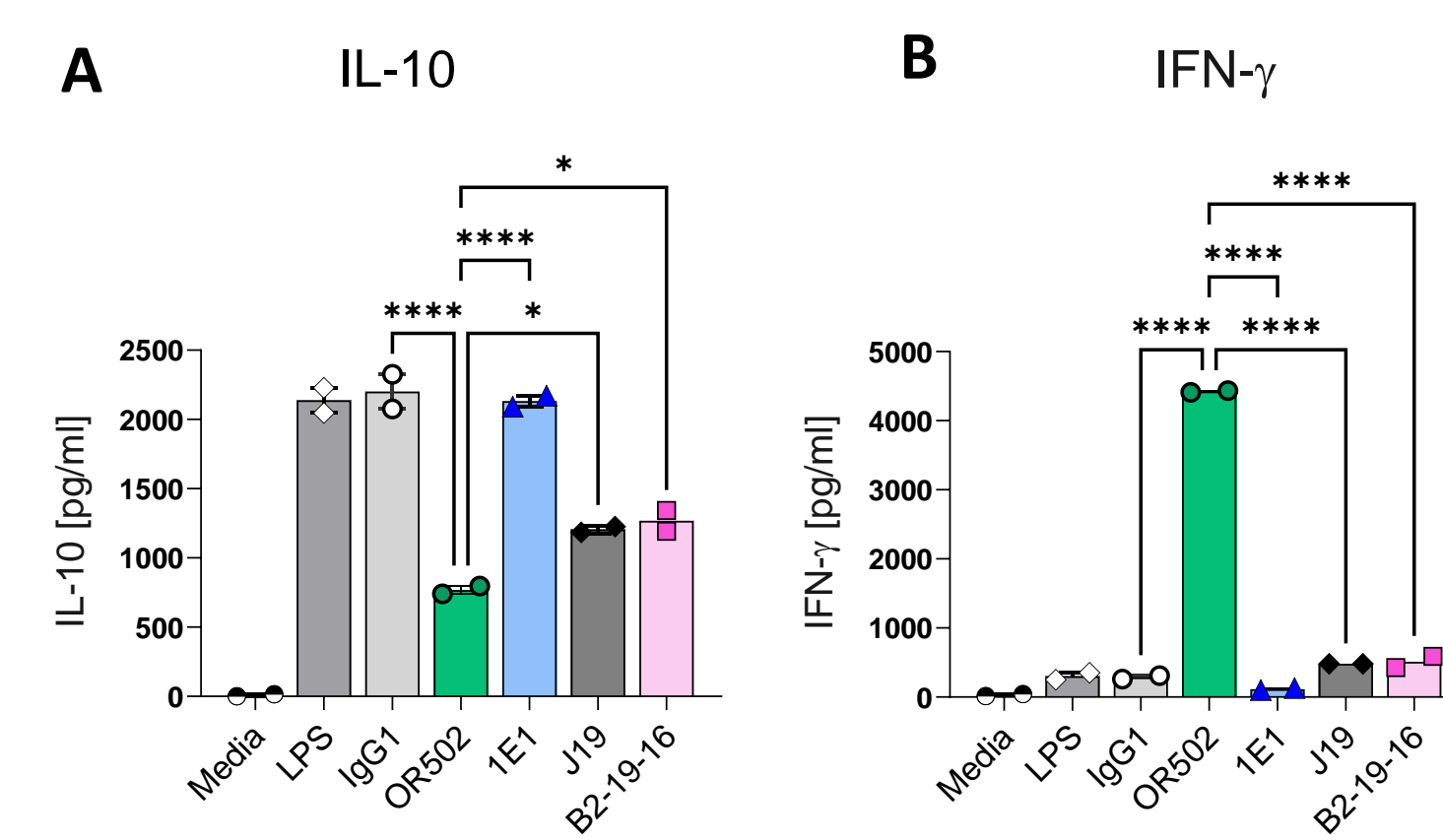
**Figure 2.** A) Binding kinetics of soluble human LILRB2-His tag protein to immobilized OR502 or 1E1 benchmark antibody by Bio-layer Interferometry. B) OR502 binding to LILRB2 expressing HEK293T cells. C) Binding of OR502 to human monocytes and monocyte-derived M2c macrophages.

## 3 OR502 blocks LILRB2 – HLA class I ligand interactions



**Figure 3.** OR502 blocks LILRB2 protein binding to A) HLA-A, B) HLA-B and C) HLA-G tetramers. D) OR502 blocks the interaction of LILRB2-Fc with HLA-G expressed on B-cell lymphoma 721.221 cells.

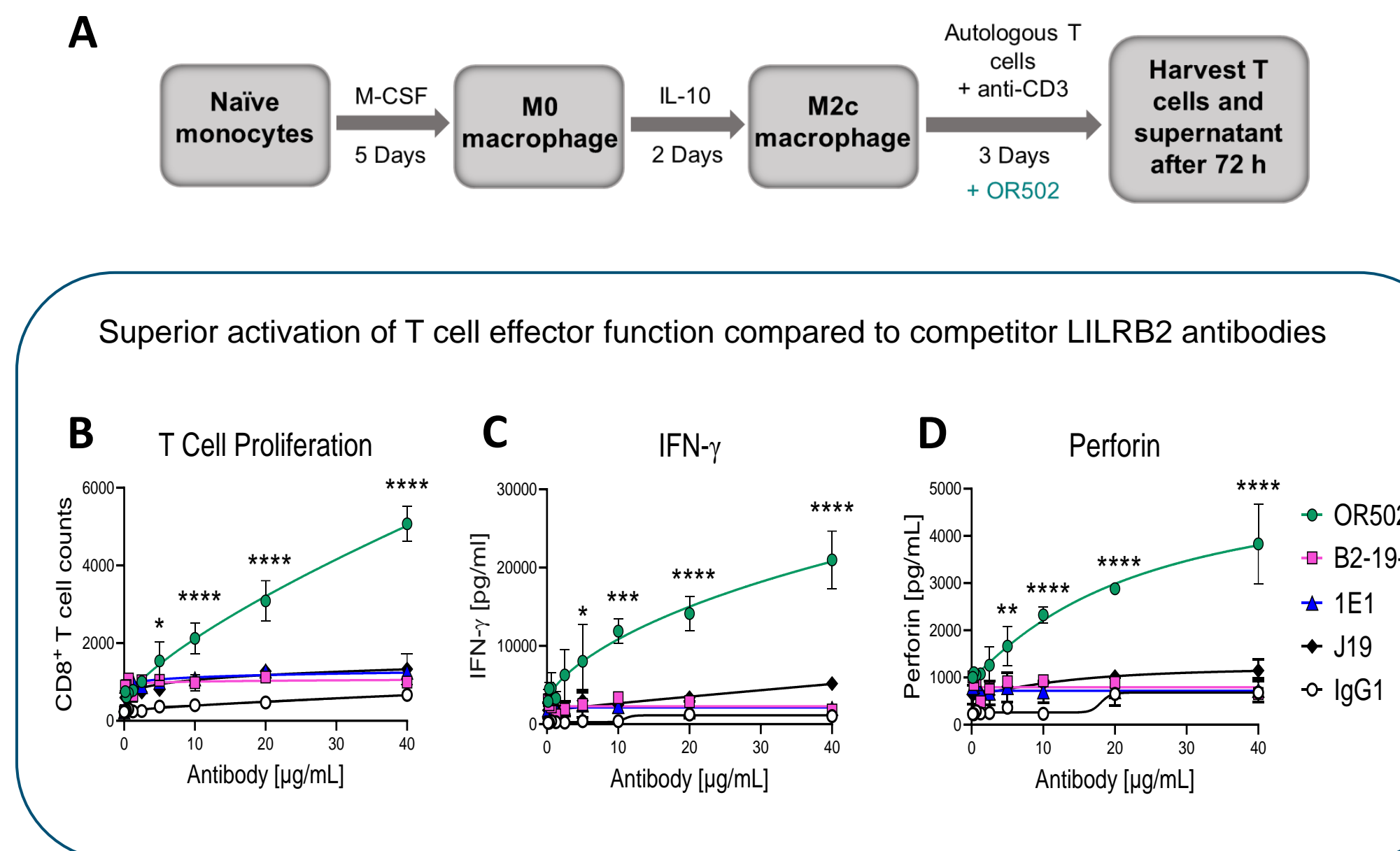
## 4 OR502 enhances Th1-like innate immune responses



**Figure 4.** Human PBMCs were treated with OR502, benchmark anti-LILRB2 antibodies (1E1, J19 and B2-19-16) or human IgG1 isotype control and stimulated with LPS for 24 hr prior to assessment of IFN- $\gamma$  and IL-10 secretion. OR502 treatment A) decreases IL-10 secretion and B) enhances IFN- $\gamma$  release.

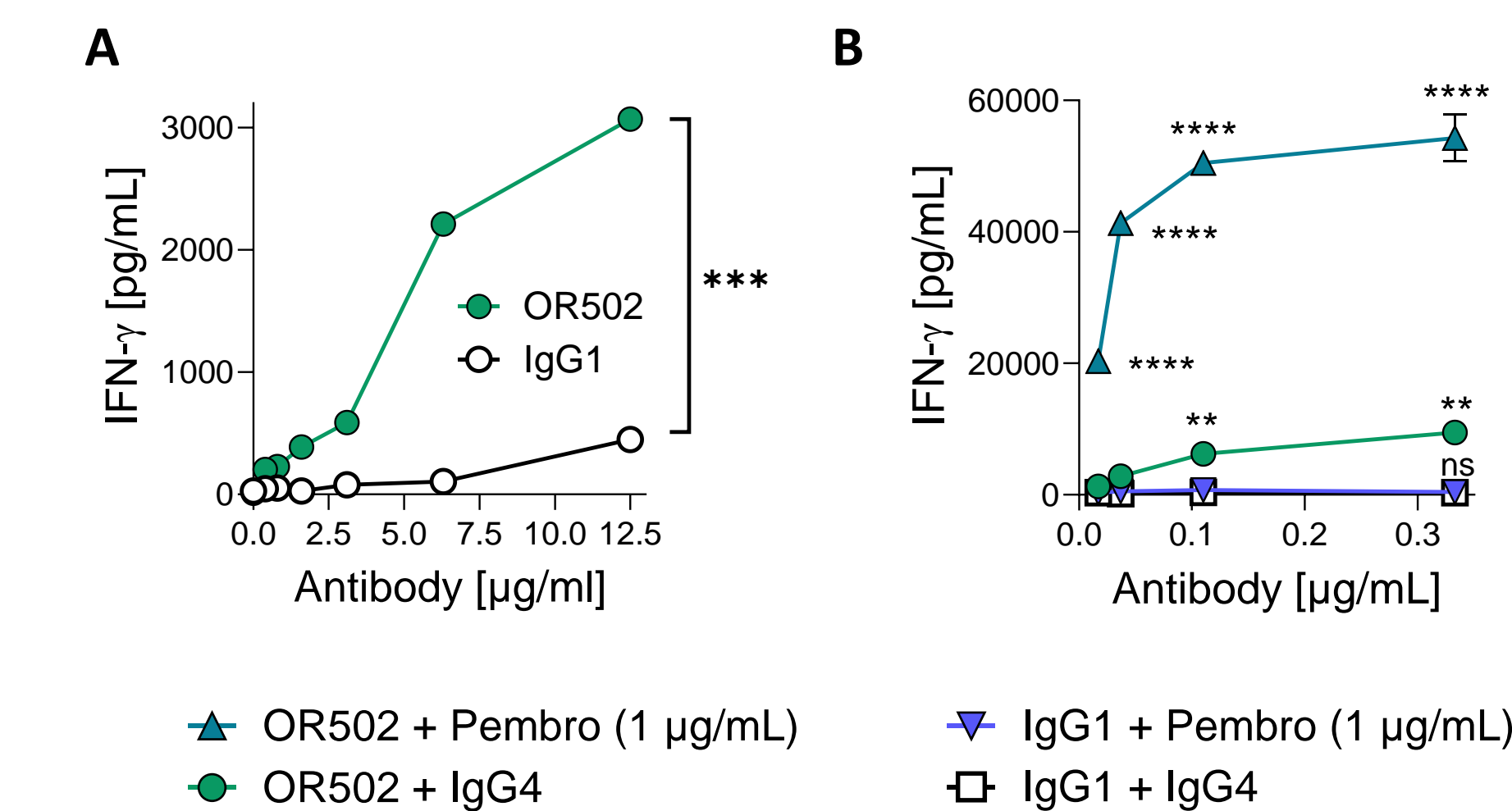
## RESULTS

## 5 OR502 relieves CD8+ T cells from M2c macrophage-mediated immune suppression



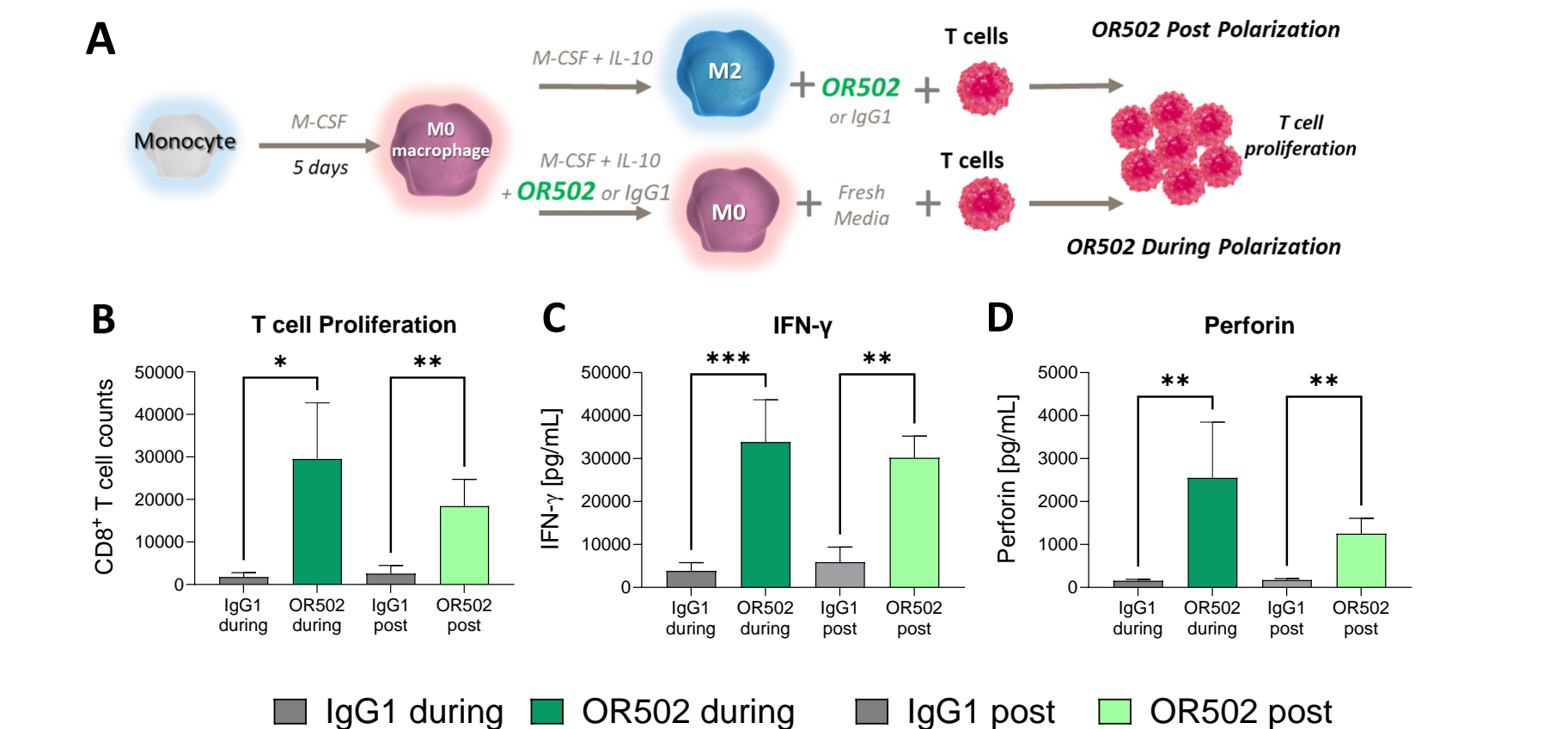
**Figure 5.** A) Schematic for M2c macrophage/T cell coculture assay. M2c macrophages were incubated with anti-CD3 and anti-LILRB2 antibodies or isotype control then cocultured with CD8+ T cells for 72 hr. Cell and supernatants were collected for assessment of B) T cell proliferation and C) IFN- $\gamma$  and D) Perforin secretion. 2-way ANOVA analysis: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$ .

## 6 Combination with OR502 amplifies anti-PD-1 activity in M2c/exhausted T cell coculture assay



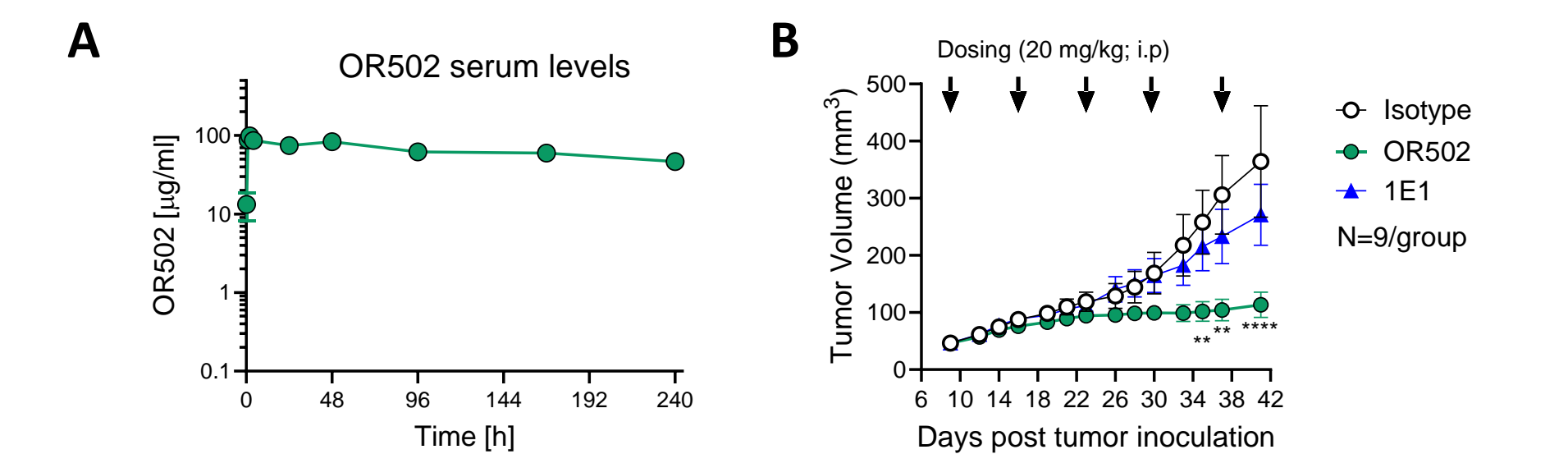
**Figure 6.** OR502 rescues exhausted T cells from M2c macrophage-mediated immune suppression. A) OR502-treated M2c macrophages enhance IFN- $\gamma$  secretion by exhausted T cells. B) OR502-treated macrophages amplifies the anti-PD-1 (Pembro, 1  $\mu$ g/mL) induced IFN- $\gamma$  production by exhausted T cells. 2-way ANOVA; \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$ ; ns: not significant.

## 7 OR502 reduces and prevents immunosuppressive phenotype of existing and new M2-like TAMs



**Figure 7.** A) CD8+ T cells from healthy donors were activated with anti-CD3 in the presence of macrophages treated with OR502 and IgG1 isotype control under the "During" and "Post-polarization" regimens" as indicated in the schematic. On day 3, cells and supernatants were collected for assessment of A) T cell proliferation, B) IFN- $\gamma$  and C) Perforin secretion. One-way ANOVA: \*  $p < 0.05$ , \*\*  $p < 0.01$ , and \*\*\*  $p < 0.001$ .

## 8 OR502 pharmacokinetic profile and in vivo anti-tumor activity of parental antibody



**Figure 8.** A) OR502 has a half-life of ~10 days in humanized FcRn mice following intraperitoneal (i.p.) single dose (10 mg/kg). B) OR502 parental antibody demonstrates anti-tumor activity in SK-MEL-5 tumor model in humanized NSG-SGM3 mice. Mice were injected i.p. with 20 mg/kg antibody every 7 days starting on day 9 post SK-MEL-5 subcutaneous tumor inoculation (N=9/group).

## Summary

OR502 is a high affinity, humanized IgG1, LILRB2 antagonist antibody with potential best-in-class activity:

- Demonstrates superior preclinical characteristics versus benchmark antibodies.
- Enhances Th1-like innate immune responses.
- Reverses and prevents immunosuppressive phenotype of new and existing TAMs.
- Amplifies anti-PD-1 activity in M2/T cell coculture assays.
- Superior in vivo anti-tumor activity in SK-MEL-5 tumor model compared to 1E1 benchmark.
- Blocks classical (HLA-A and B) and non-classical (HLA-G) HLA class I ligands binding of LILRB2.
- Co-engagement of Fc $\gamma$ R provides an additional signal for myeloid reprogramming.
- OR502 has advanced to Phase 1 clinical study.

## Acknowledgements

We would like to acknowledge the contributions of Phil Hammond, Bob Lechleider, and Cliff Stocks at OncoResponse. We would also like to acknowledge our Scientific advisors: Michael Curran, David DeNardo, Mike Gallatin, David Hong, Miriam Merad, Anil Singhal, and James Welsh.