



ULTIMATE PREDICTABILITY

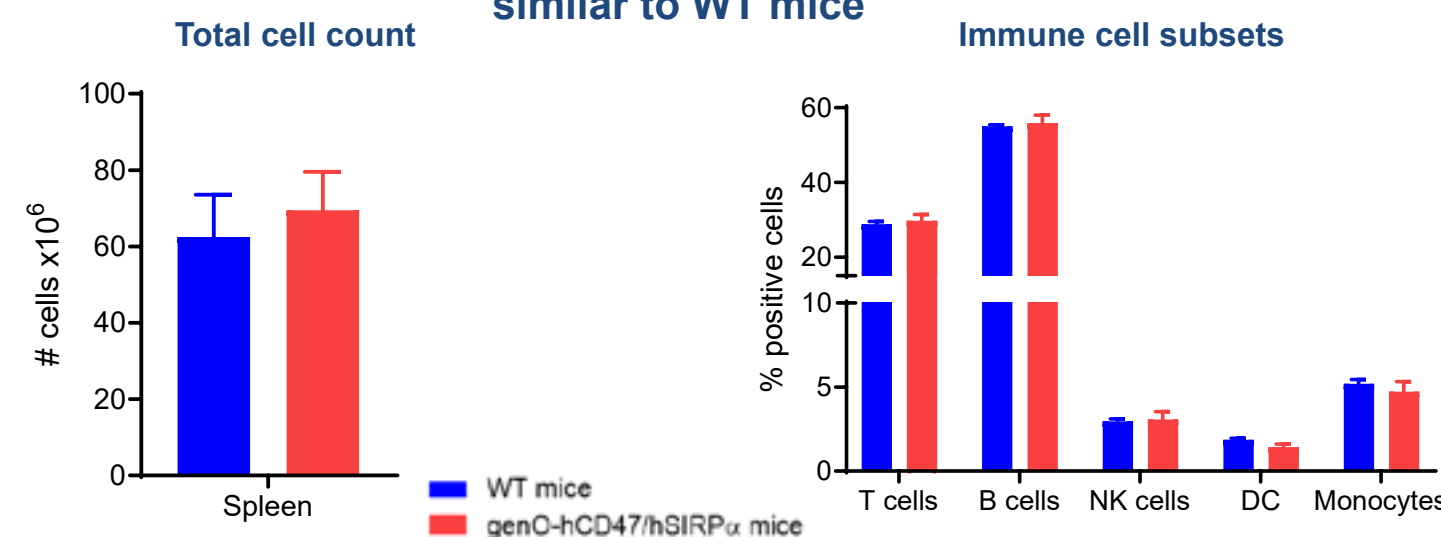
Preclinical double humanized genO-hCD47/hSIRPα mouse model and MC38 cell line expressing human CD47 for efficacy and safety assessment of anti-CD47/SIRPα-targeting therapies

EACR 2025
Abstract #0518

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Background: CD47 is overexpressed on many human tumor cells and interacts with its ligand, the signal-regulating protein alpha (SIRPα), a protein expressed on macrophages and dendritic cells, to induce a “don’t eat me” signal. CD47 and its interaction with phagocytes is therefore a promising therapeutic target to treat cancer⁽¹⁾. Herein, we describe a double humanized genO-hCD47/hSIRPα model for efficacy, safety assessment and biodistribution of human CD47/SIRPα-targeting therapies in immunocompetent mice. The double humanized genO-hCD47/hSIRPα mouse model (genO-hCD47/hSIRPα) was generated by intercrossing genO-hCD47 and genO-hSIRPα mice models whose designs enable expression of all human isoforms at physiological levels.

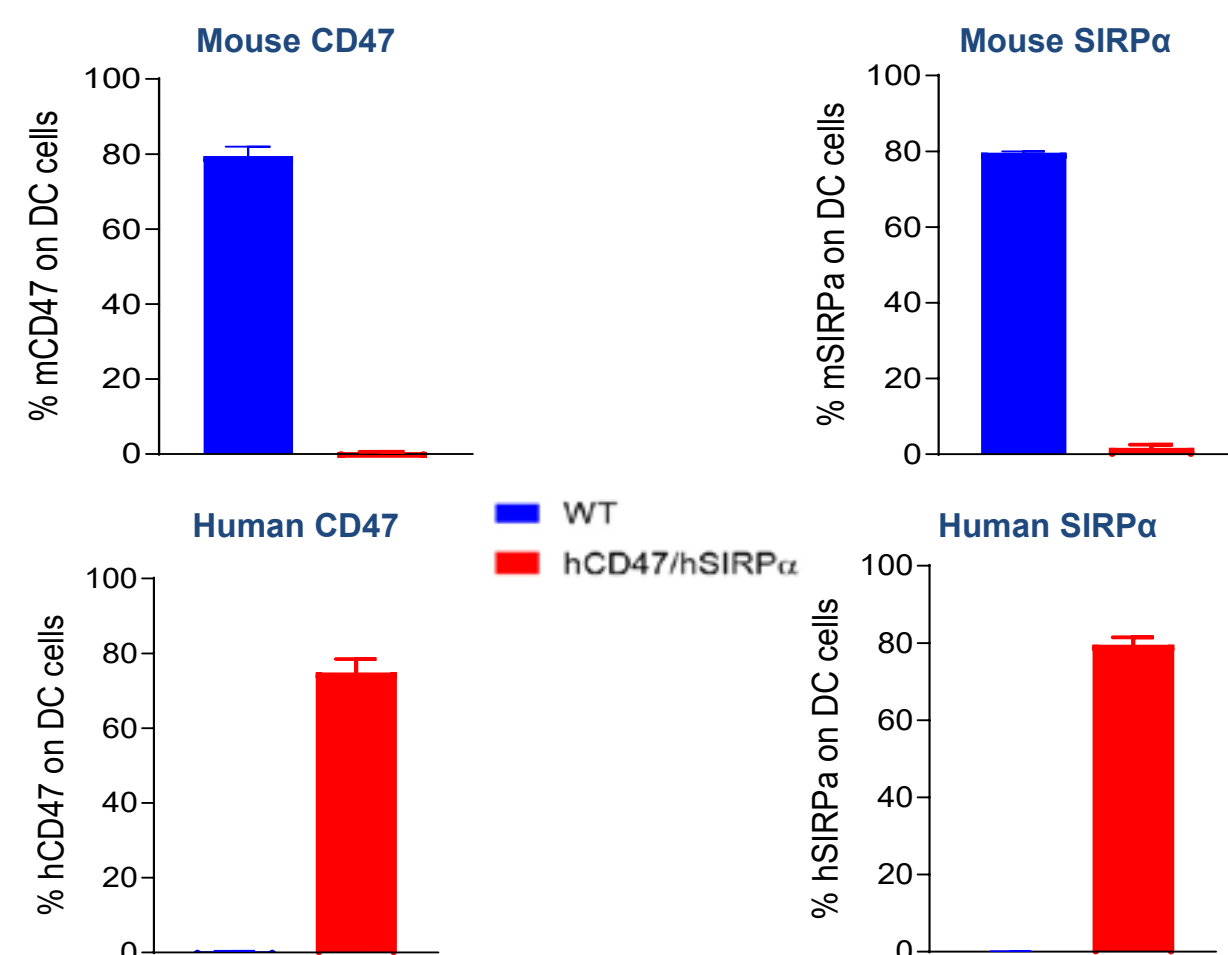
1. Immune cells distribution in spleen from genO-hCD47/hSIRPα is similar to WT mice



⇒ Immune cell distributions in blood and bone marrow of genO-hCD47/hSIRPα are also similar to WT mice (data not shown)

Immune cell distribution assessed by flow cytometry on freshly isolated splenocytes from WT and genO-hCD47/hSIRPα mice. Cells were gated on live cells: T cells (CD3⁺CD19⁻), B cells (CD3⁺CD19⁺), NK cells (CD3⁻CD19⁻NKp46⁺), DC (CD3⁻CD19⁻CD11b⁺CD11c⁺) and Monocytes (CD3⁻CD19⁻CD11b⁺CD11c⁻).

2. Human CD47 and SIRPα expression patterns recapitulate the murine expression of CD47 and SIRPα on splenic dendritic cells (DCs)

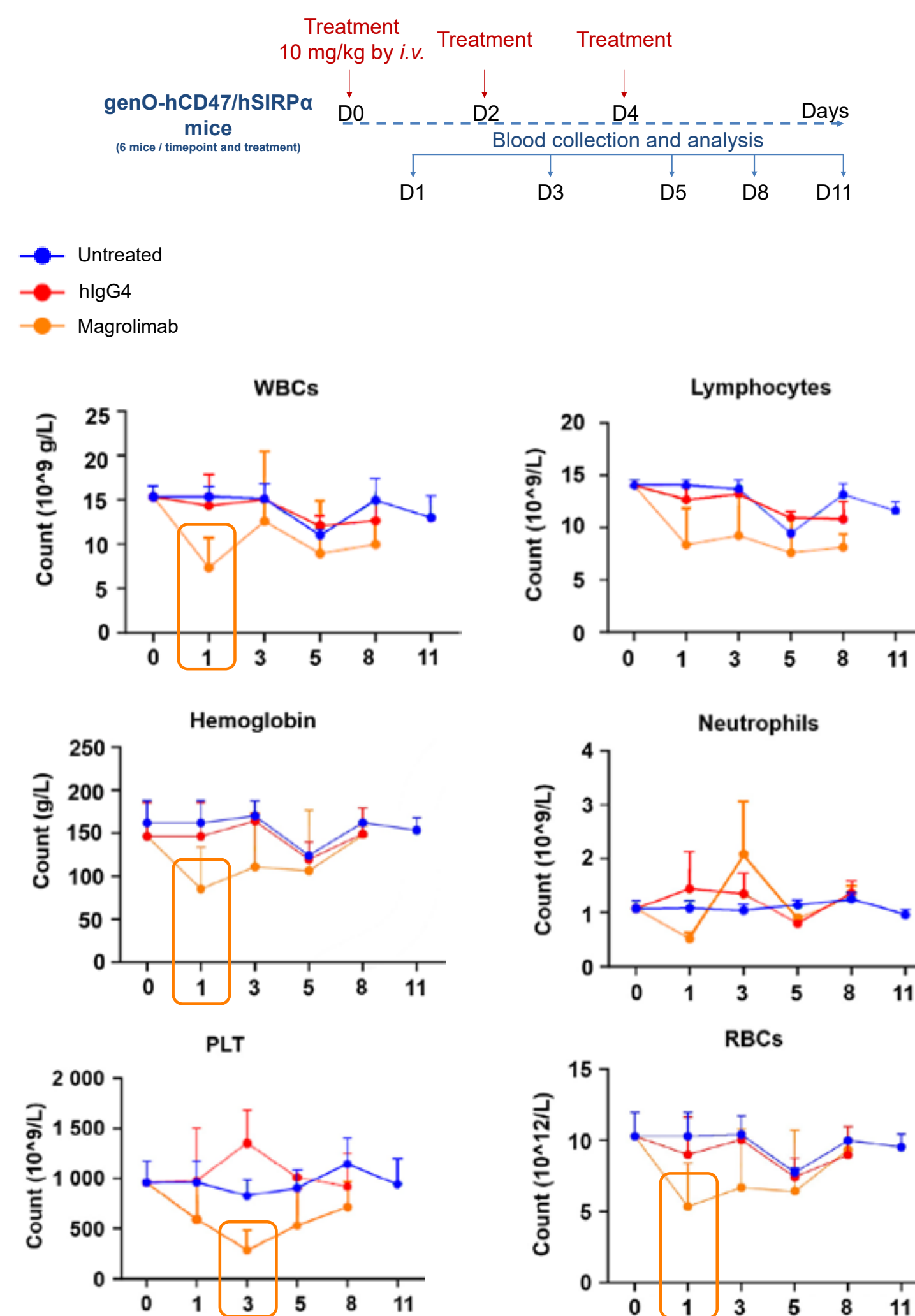


CD47 and SIRPα expressions assessed by flow cytometry on freshly isolated splenocytes from WT and genO-hCD47/hSIRPα mice (anti-mouse CD47 clone miap301, anti-human CD47 clone B6H12, anti-mouse SIRPα clone P84, anti-human SIRPα, clone REA144). Cells were gated on single live CD3⁺CD19⁻CD11b⁺CD11c⁻.

Other application reported: Biodistribution evaluation of hSIRPα-targeting nanobody (Nb) in genO-hCD47/hSIRPα mouse model (“Two birds with one stone: human SIRP nanobodies for functional modulation and *in vivo* imaging of myeloid cells”, Wagner *et al.*, 2023⁽³⁾):

- Nanobodies binding hSIRPα without blocking its interaction with CD47 have been developed and are suitable as radiotracers for PET-imaging
- Anti-hSIRPα Nb used as radiotracers would enable patient stratification and monitoring of individual responses during cancer immunotherapies

3. Safety of Magrolimab in naïve genO-hCD47/hSIRPα mice



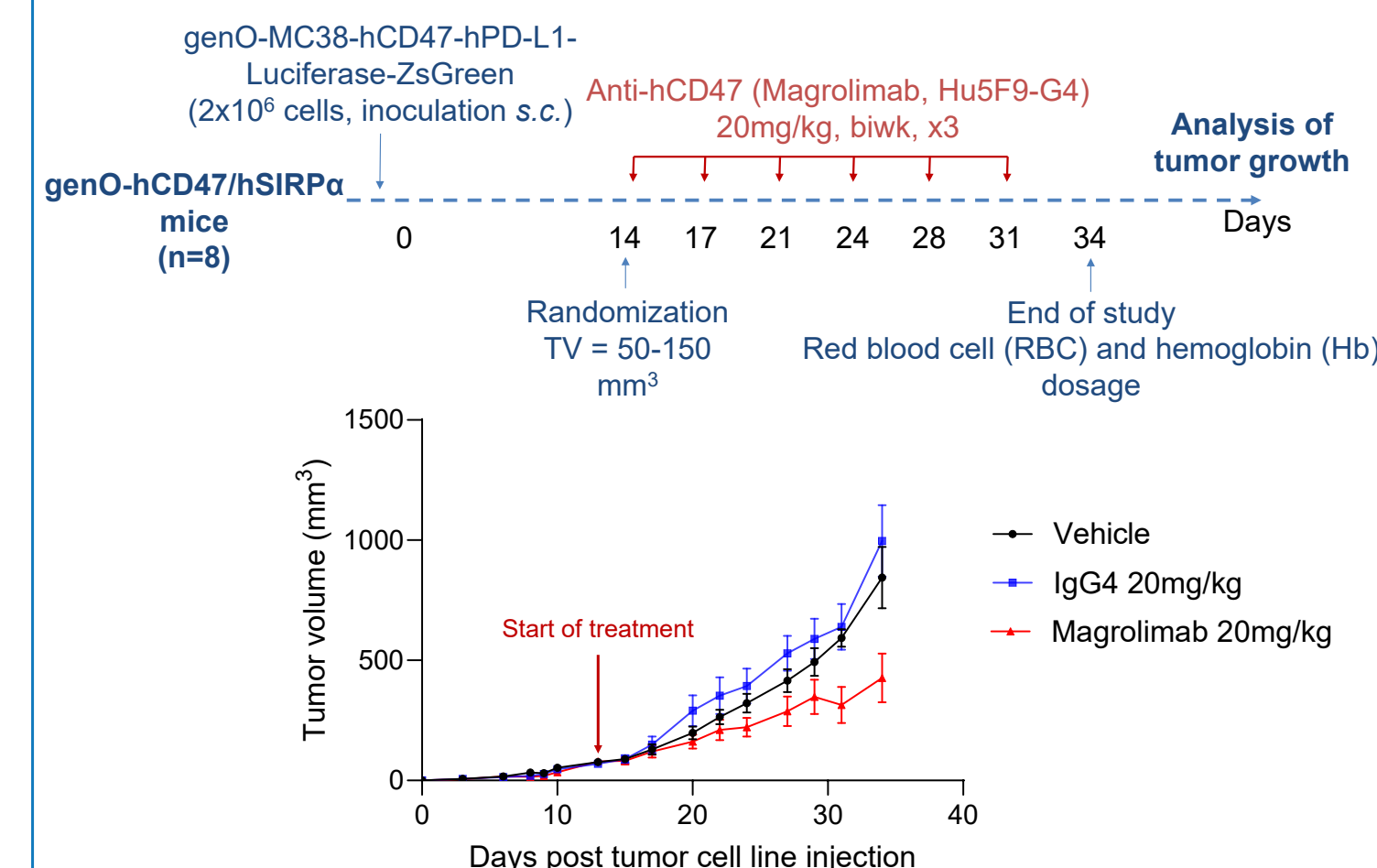
⇒ Magrolimab causes a transient reduction in RBCs and Hb level after 1 injection

⇒ Magrolimab caused a 48% drop in WBCs after 1 injection and a 65% drop in platelets after 2 injections

⇒ Double humanized genO-hCD47/hSIRPα model enables safety assessment of CD47-targeting compounds

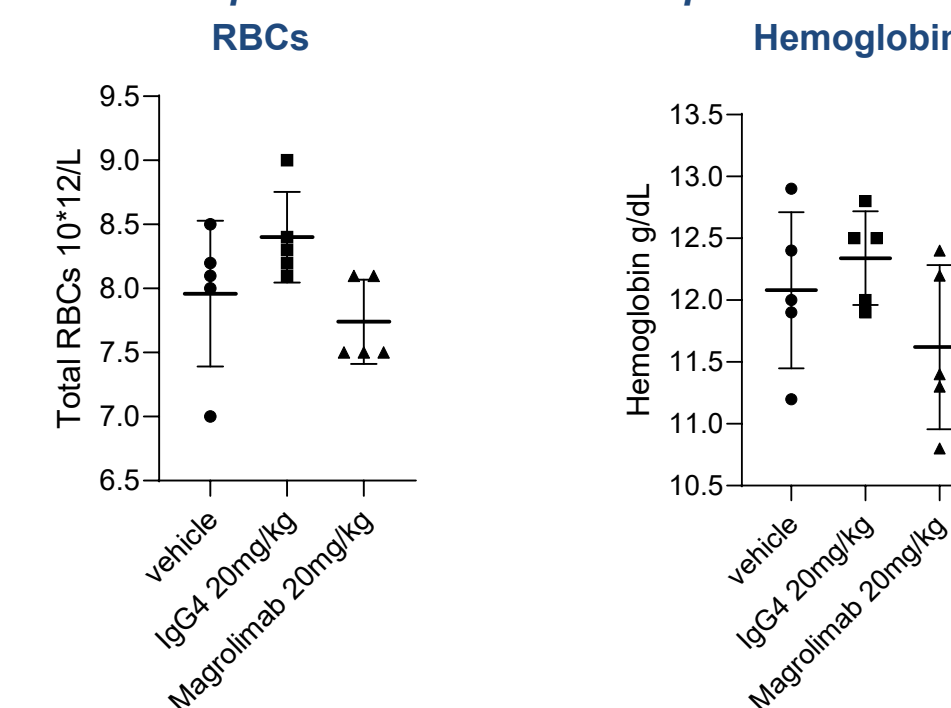
4. Magrolimab efficacy and safety assessment in tumor-bearing genO-hCD47/hSIRPα double humanized mice

4.1. Magrolimab induces tumor growth inhibition in tumor-bearing genO-hCD47/hSIRPα double humanized mice



⇒ Magrolimab shows an anti-tumor activity on MC38-hCD47-hPD-L1 cells engrafted in genO-hCD47/hSIRPα mice

4.2. genO-hCD47/hSIRPα double humanized mouse model recapitulates safety parameters observed in patients



⇒ Magrolimab shows a slight effect on RBC and hemoglobin in genO-hCD47/hSIRPα mice, as observed in patients⁽²⁾

Conclusion: Altogether, these data suggest that genO-hCD47/hSIRPα model enables assessment of efficacy and safety of CD47 and/or SIRPα-targeting agents as well as biodistribution for non-invasive *in vivo* imaging of tumors. The model has been upgraded by intercrossing genO-hCD47/hSIRPα mouse with the humanized genO-hFcγR model to enable assessment of Fc-mediated function of human antibodies targeting human CD47 and/or SIRPα.

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Abbreviation:

- PLT: Platelets
- WBCs: White blood cells
- RBCs: Red blood cells

References:

- (1): S.B. Willingham *et al.*, Proc. Natl. Acad. Sci. U.S.A., 2012
- (2): C.K. Brierley *et al.*, Transfusion., 2019
- (3): T.R. Wagner *et al.*, Front. Immunol., 2023