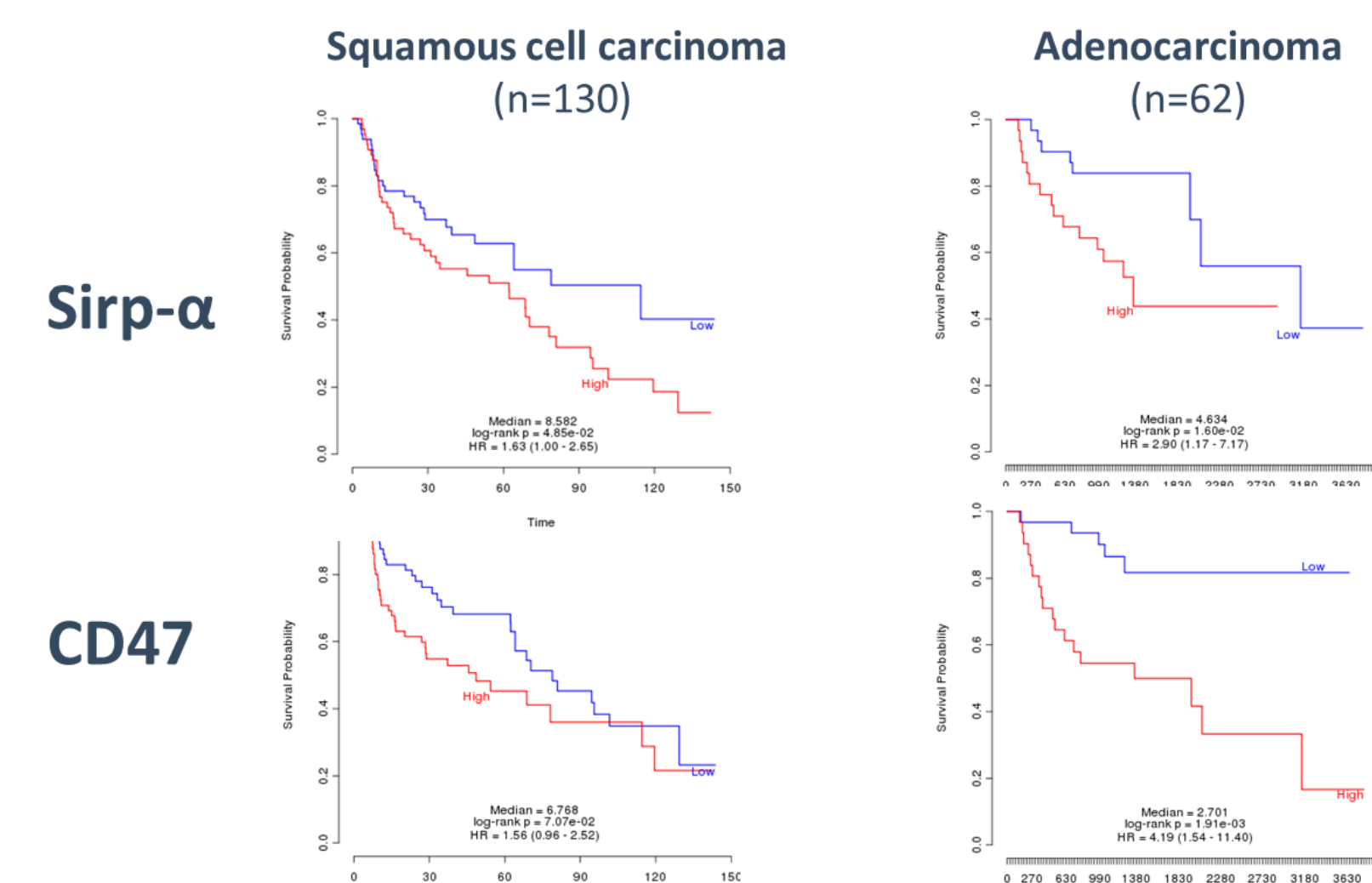


Introduction

Targeting immune checkpoints of the adaptive immunity has shown great therapeutic efficacy to fight numerous cancers, but in a limited proportion of patients. Immune checkpoint on myeloid cells (macrophages, dendritic cells, MDSC, PMN) remain poorly studied while these cells represent the most abundant immune cell type in many solid tumors and are often associated with a poor outcome. Interaction of SIRP α (SIRP α), expressed by myeloid cells, with the ubiquitous receptor CD47 is an important immune checkpoint of the innate response, involved in the regulation of myeloid functions. Furthermore, it was shown that abundance of CD47 as well as SIRP α receptors in tumors is inversely correlated with patient overall survival and constitute an adverse prognostic factor for several cancer types (Figure below extracted with the PRECOG software from data of Raponi et al. Cancer Res 2006; Lee et al. Clin Cancer Res 2008).

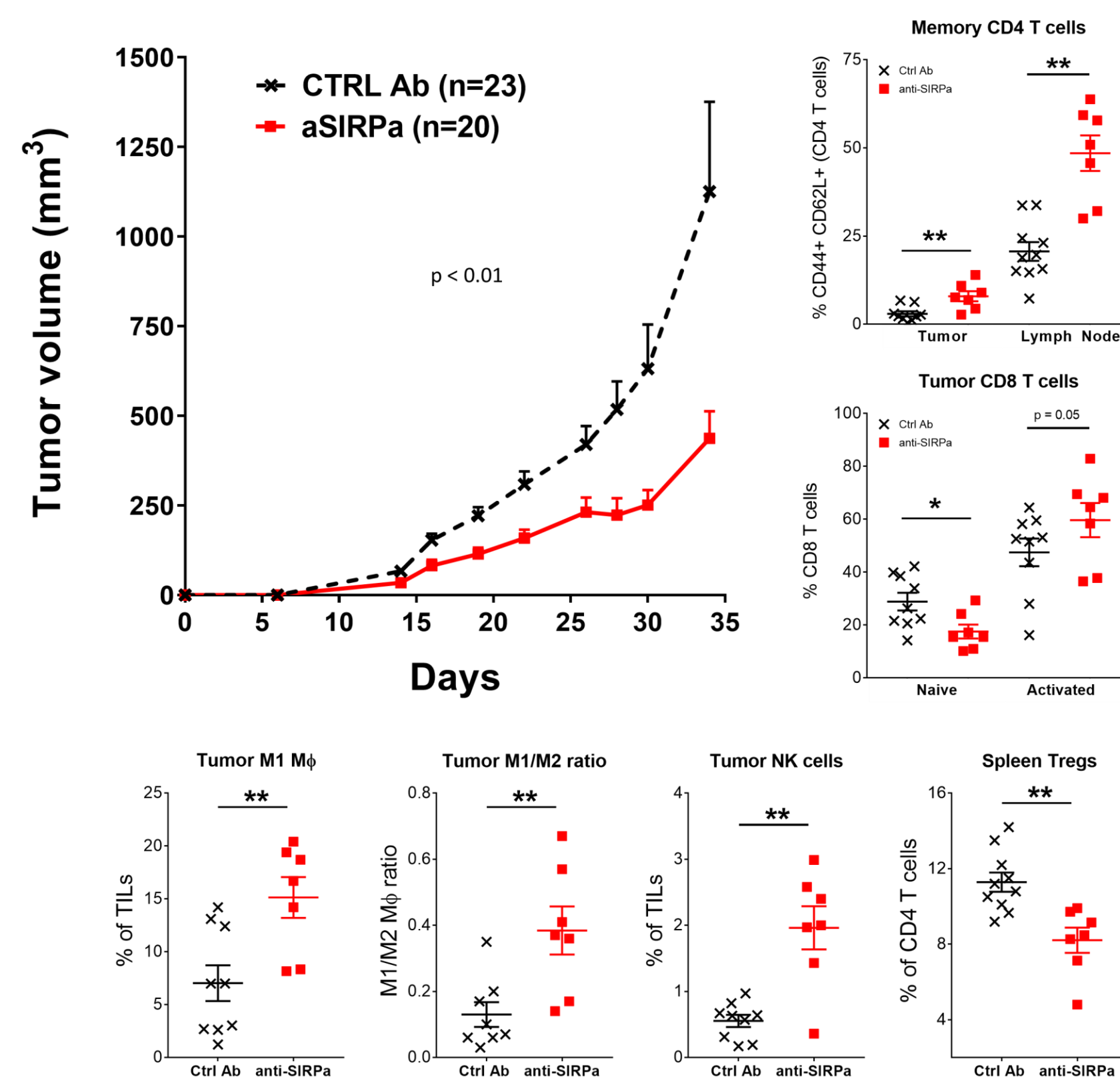


Since agents targeting CD47 (anti-CD47 or SIRP α -Fc) recently experienced hematological toxicity (anemia or thrombocytopenia) related to CD47 physiological role, we evaluated the preclinical safety and efficacy of selective antagonistic anti-SIRP α monoclonal antibodies (mAb) without binding to RBC and Platelets. Furthermore, CD47 interacts with several others ligands and physiological functions, such as the CD47/SIRP γ axis, another member of the SIRP family, described to play a role in human T cell proliferation. Selective antagonist of SIRP α are not binders of SIRP γ avoiding deleterious impact on T cell immune responses. Thus, combining immunotherapies Targeting both adaptive and innate immune cells, through selective targeting at SIRP α , could represent a safe and promising therapeutic strategy against cancer.

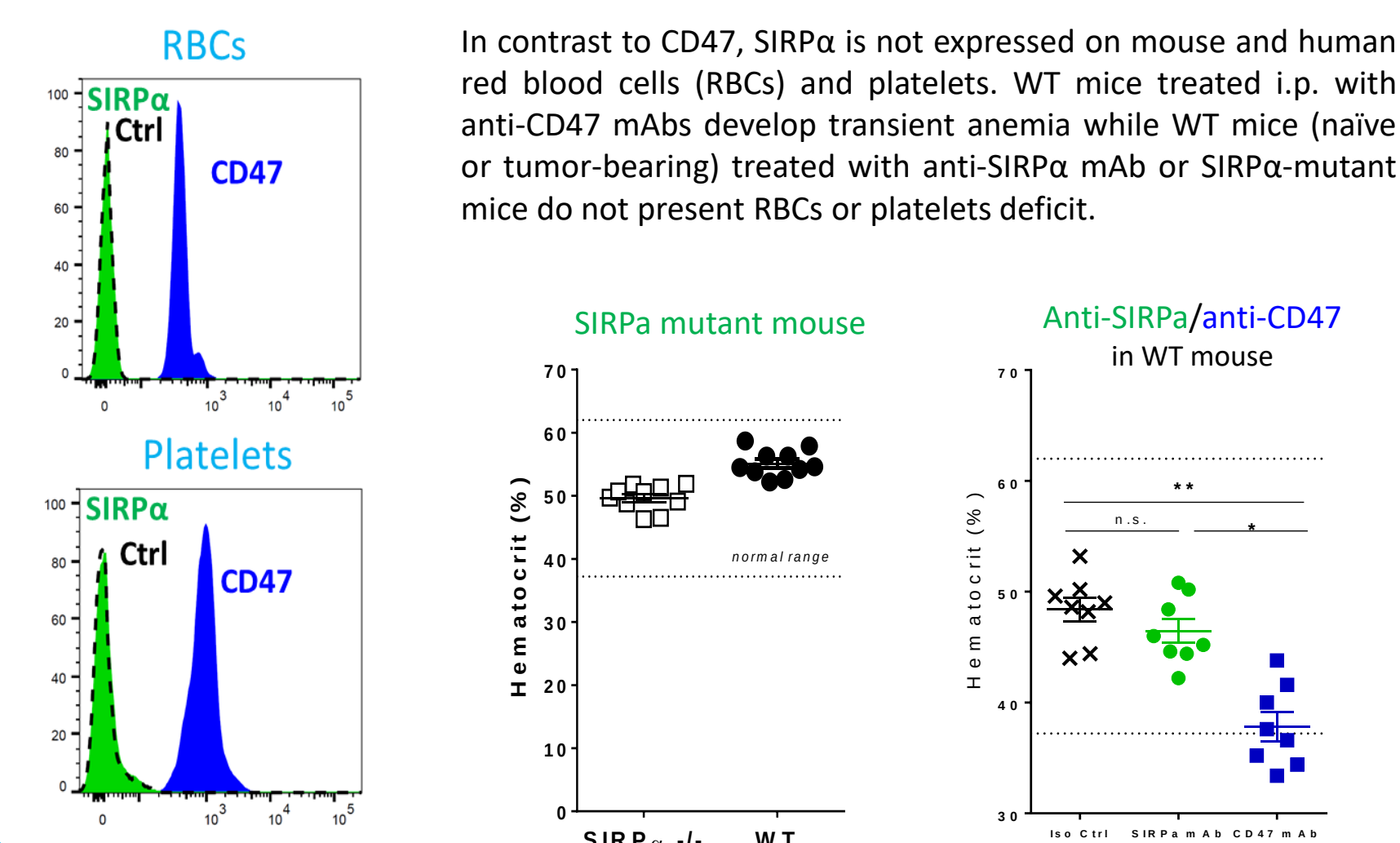
Anti-SIRP α monotherapy in orthotopic TNBC

Inhibits tumor growth and modifies tumor micro-environment

Mammary carcinoma 4T1 cells were injected into the mammary gland of female Balb/c mice. Mice were treated three times a week for one month with a control monoclonal antibody (mAb) or an anti-SIRP α mAb.



Without hematological toxicity (no SIRP α on RBCs and platelets)

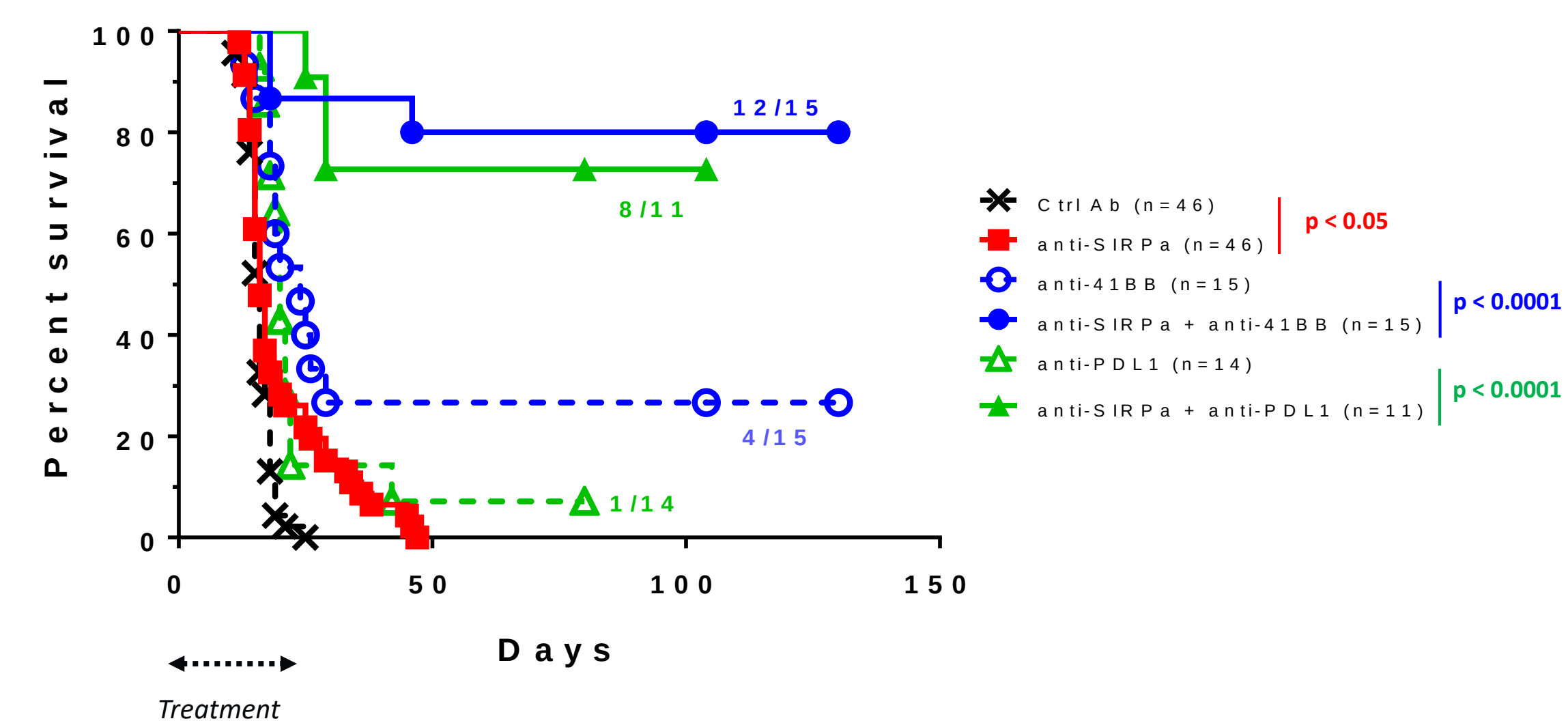


In contrast to CD47, SIRP α is not expressed on mouse and human red blood cells (RBCs) and platelets. WT mice treated i.p. with anti-CD47 mAbs develop transient anemia while WT mice (naïve or tumor-bearing) treated with anti-SIRP α mAb or SIRP α -mutant mice do not present RBCs or platelets deficit.

Anti-SIRP α combination with PD-1 blockade or 4-1BB activation

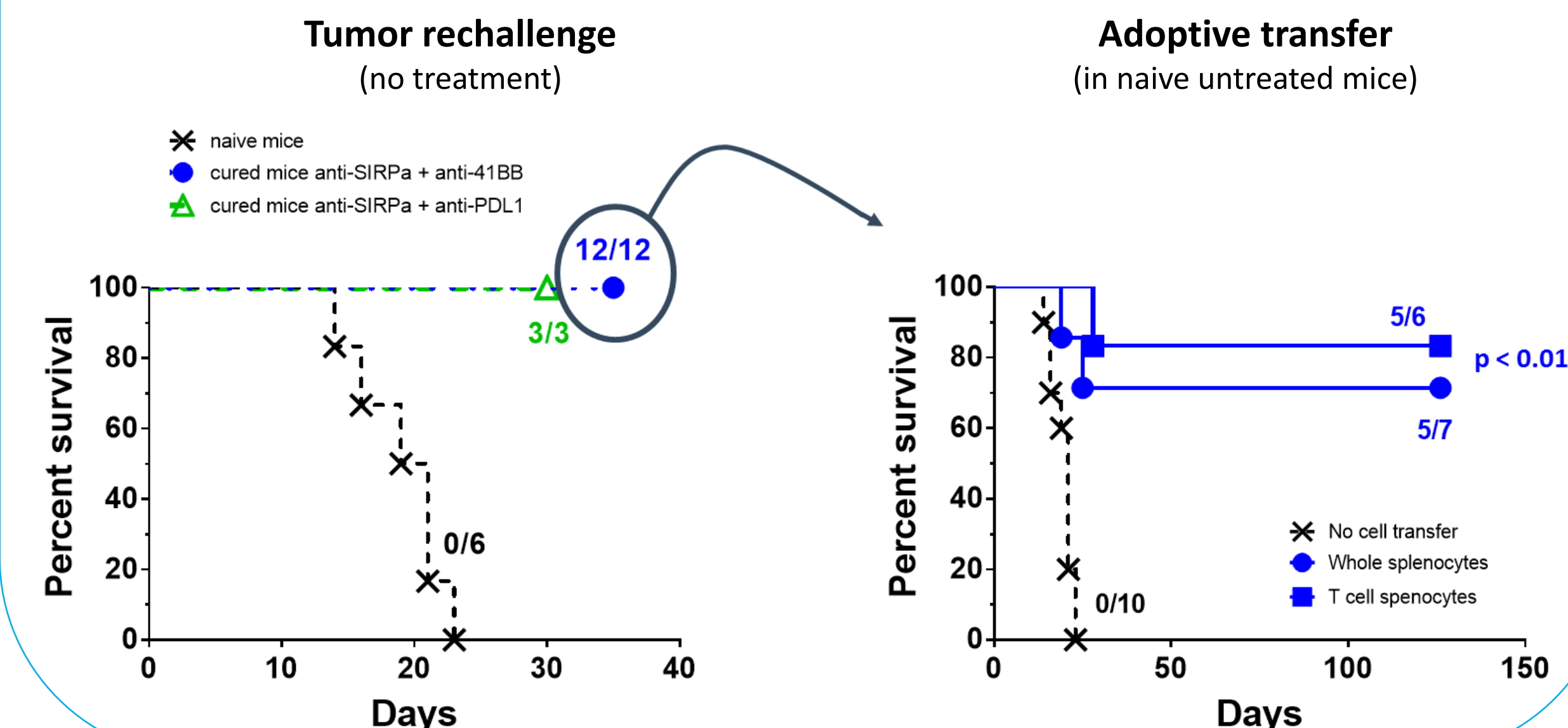
Induces high response rate and tumor elimination in orthotopic HCC mouse model

Syngeneic hepatoma Hepa 1.6 cells were injected intraportally into C57Bl/6 male mice. Mice were treated three times a week for one month with a control monoclonal antibody (mAb) or an anti-SIRP α mAb. The anti-PD-L1 mAb was injected two times a week for one month and the anti-4-1BB mAb was injected twice (Day 4 & 8). All treatments have been started four days after tumor inoculation.



Induces durable and robust anti-tumor memory T lymphocytes responses

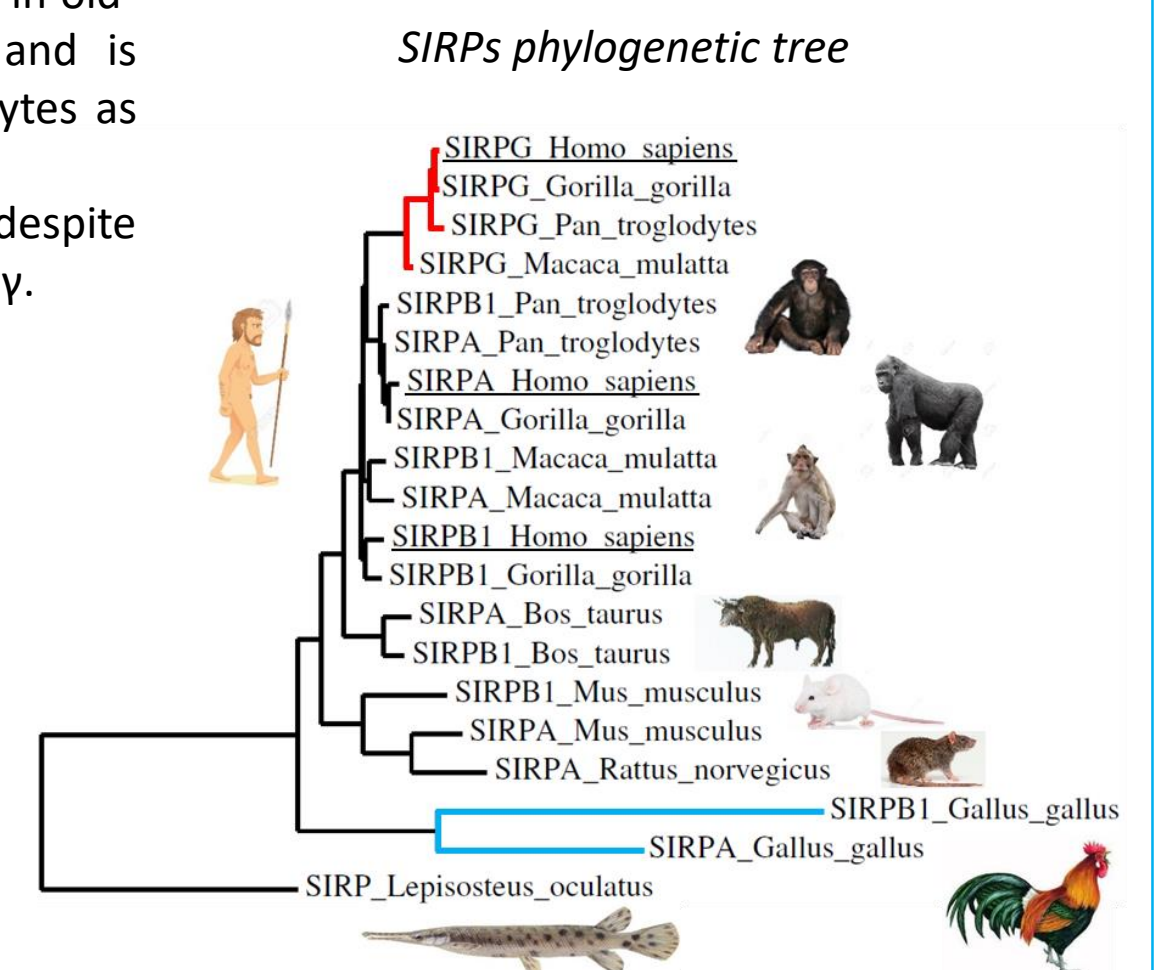
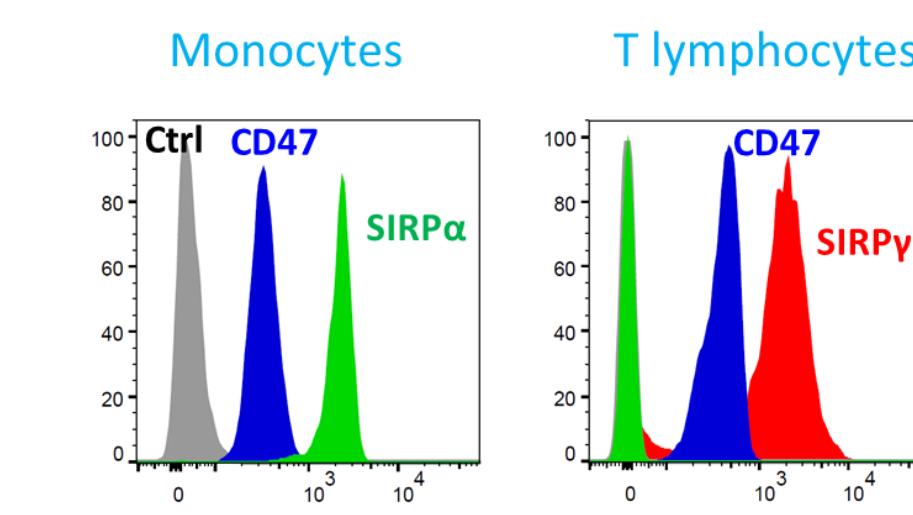
Mice previously cured with combination of anti-SIRP α + anti-PD-L1 or anti-4-1BB mAbs rejected spontaneously (without new treatment) a second intra-splenic tumor challenge, demonstrating combination induces anti-tumor memory immune responses. Adoptive transfer of splenocytes (10⁷) or isolated T lymphocytes (2.5x10⁶) from cured-mice protects naïve and untreated mice from intraportal injection of Hepa 1.6 cells, demonstrating T cells are responsible of immune memory anti-tumor responses.



OSE-172 does not disturb CD47/SIRP γ and enables human T-cell responses

SIRP γ is absent in mice and is expressed by human T lymphocytes

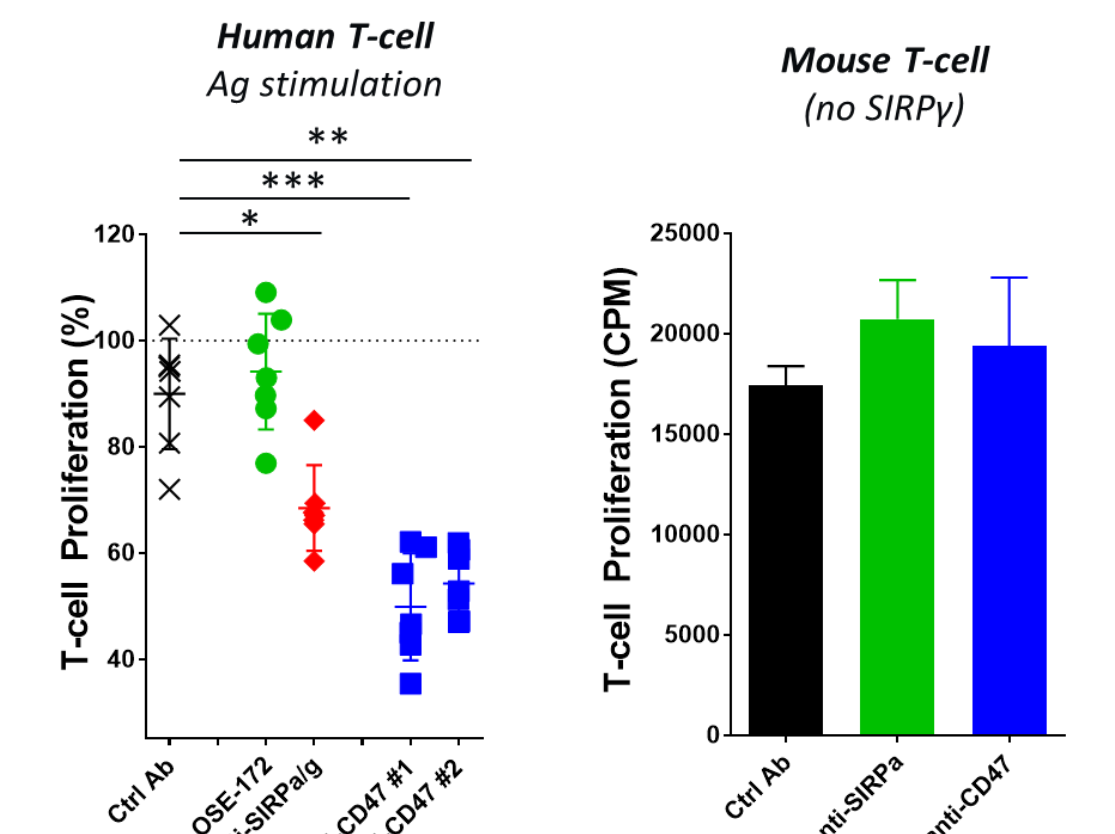
SIRP γ is the result of a duplication of SIRP β gene in old-world primates nearly 35 million years ago and is expressed in a restricted manner on T lymphocytes as opposed to SIRP α expression on myeloid cells. OSE-172 is a selective anti-SIRP α mAb which, despite high homology with SIRP α , does not bind to SIRP γ .



SIRP γ /CD47 interaction is required for human T lymphocyte proliferation

Non-selective anti-SIRP α mAb (interacting also with SIRP γ) and anti-CD47 mAbs significantly inhibit human antigen-specific T lymphocytes proliferation while OSE-172 has no negative impact.

SIRP γ gene being absent in rodent, immunosuppression induced by anti-CD47 mAbs can not be appreciated in xenograft or syngeneic mouse models.



Conclusion

Selective blockade of SIRP α :

- Is devoid of hematological toxicity due to restricted expression
- Reduces tumor growth and modifies tumor microenvironment in monotherapy
- Synergizes with checkpoint inhibitors or costimulatory agents
- Induces durable anti-tumor memory T lymphocytes responses
- Is not immunosuppressive on human T-cell responses