Dual targeting of adaptive and innate checkpoints induce potent memory anti-tumor response

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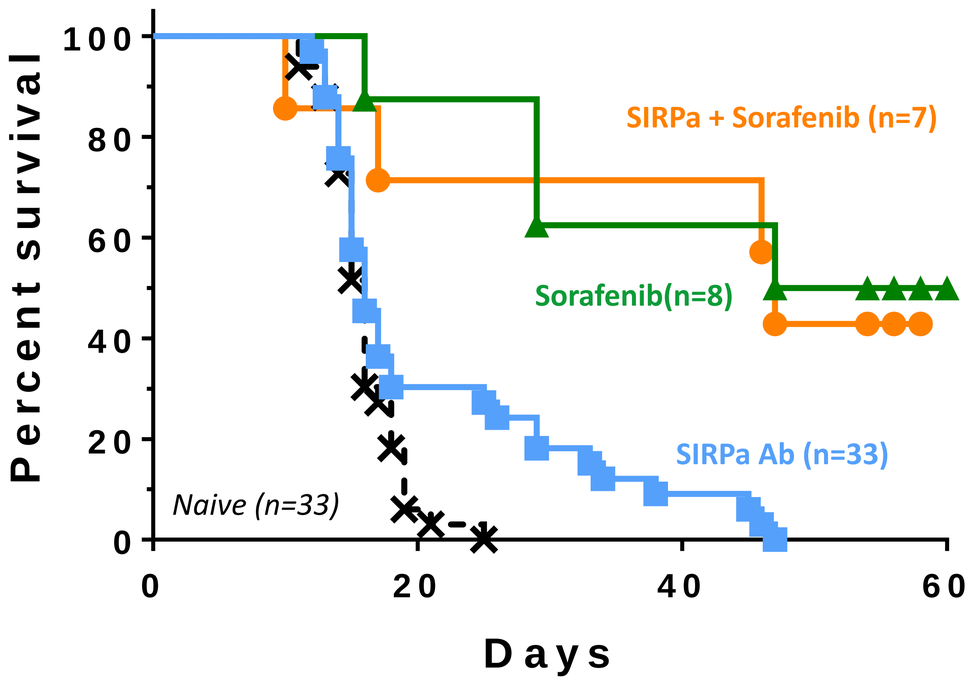
Introduction

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) remains poorly studied while they represent the most abundant immune cell type in many solid tumors, and are often associated with a poor outcome. Interaction of SIRPalpha (SIRPα), 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. CD47 receptor upregulation on cancer cells is inversely correlated with patient overall survival and constitute an adverse prognostic factor for several cancer types. Thus, combining immune checkpoint blockade of both adaptive and innate immune cells could represent a promising therapeutic strategy against cancer.

Results

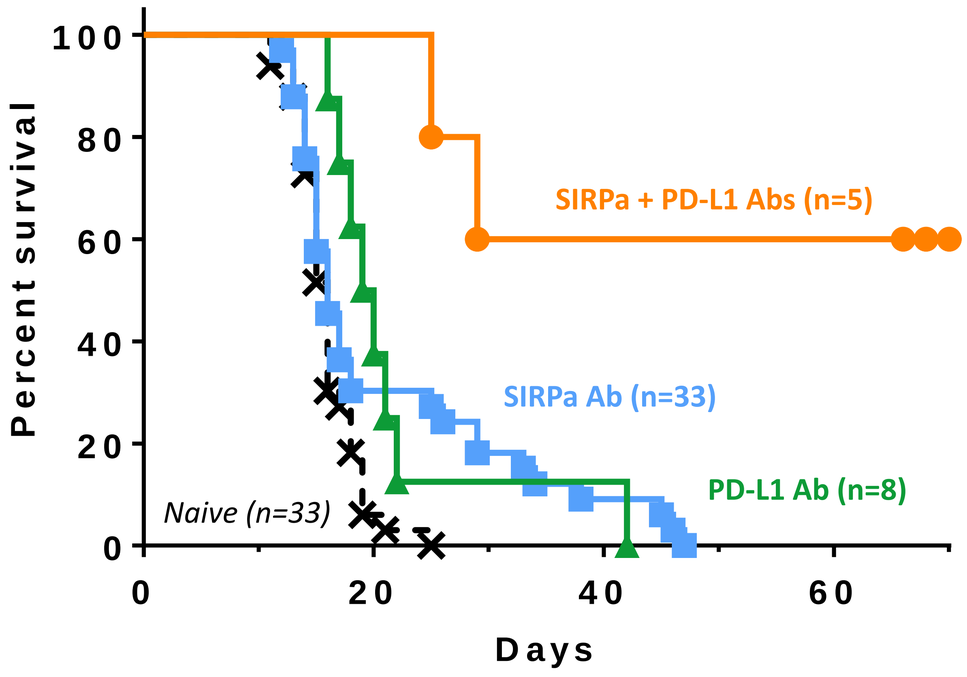
Antagonistic anti-SIRPα does not synergize with chemotherapy (Sorafenib) …

Syngeneic orthotopic mouse model of hepatocellular carcinoma (Hepa1.6): Mice were treated 3 times/week for 1 month with ctrl Ab or anti-SIRPa mAb
+/- Sorafenib administered daily for 1 month



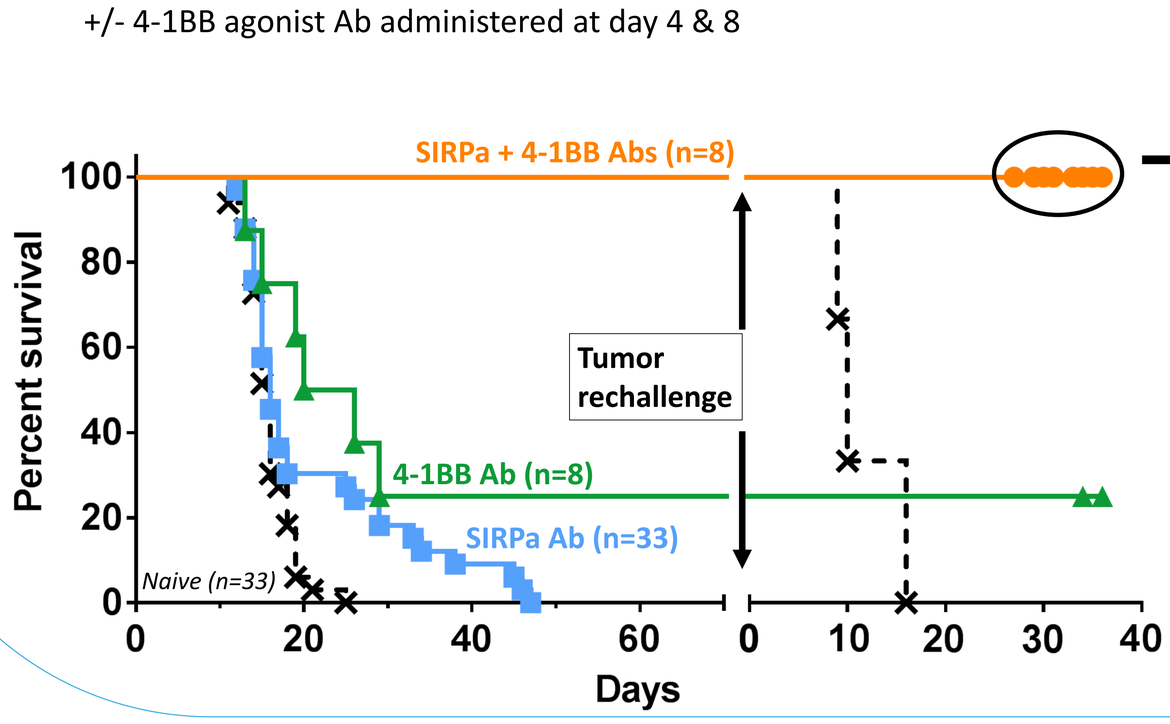
… but potentiates T-cell checkpoint inhibitor (anti-PD-L1 mAb)

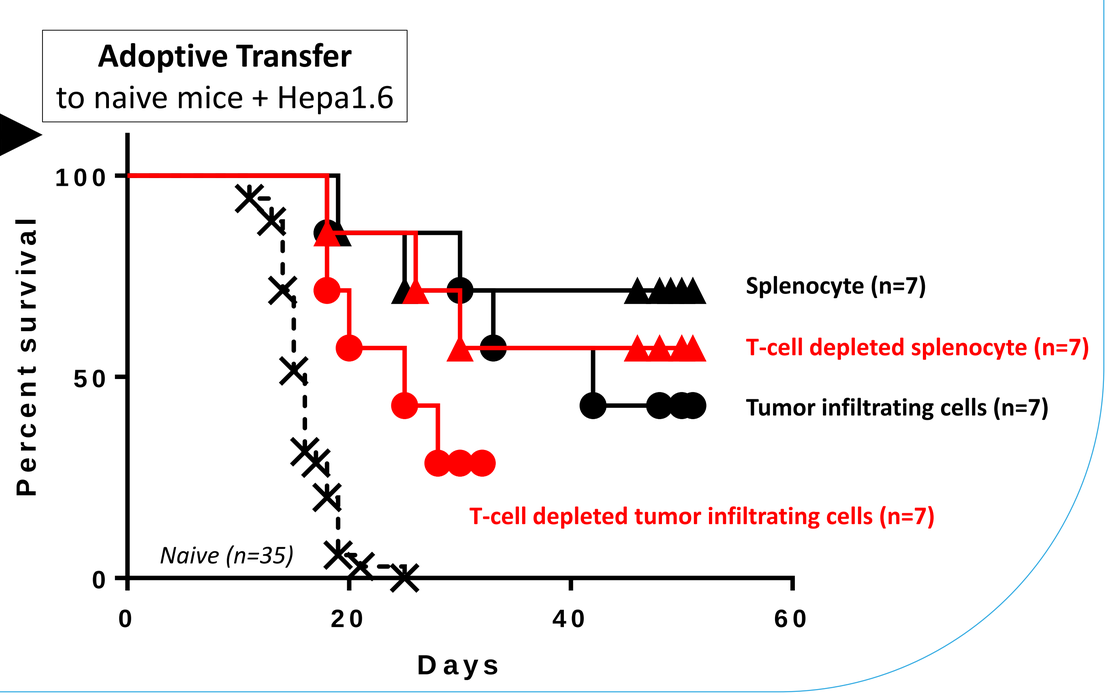
+/- PD-L1 antagonist Ab administered 3 times/week for 1 month



Antagonistic anti-SIRPα synergizes with T-cell checkpoint co-stimulatory mAbs (4-1BB)

Syngeneic orthotopic mouse model of hepatocellular carcinoma (Hepa1.6): Mice were treated 3 times/week for 1 month with ctrl Ab or anti-SIRPa antagonist
+/- 4-1BB agonist Ab administered at day 4 & 8





Conclusion

These findings indicate that anti-SIRPα checkpoint inhibitor could potentiate T-cell checkpoint inhibitor or costimulatory strategies and lead to therapeutic benefit for refractory patients. Combined targeting of immune checkpoints targeting of both adaptive and innate immune cells is promising and could generate anti-tumor memory immunity.