Combination therapies augment the anti-tumor activity of agonist anti-CD27 mAb in human CD27 transgenic mouse models

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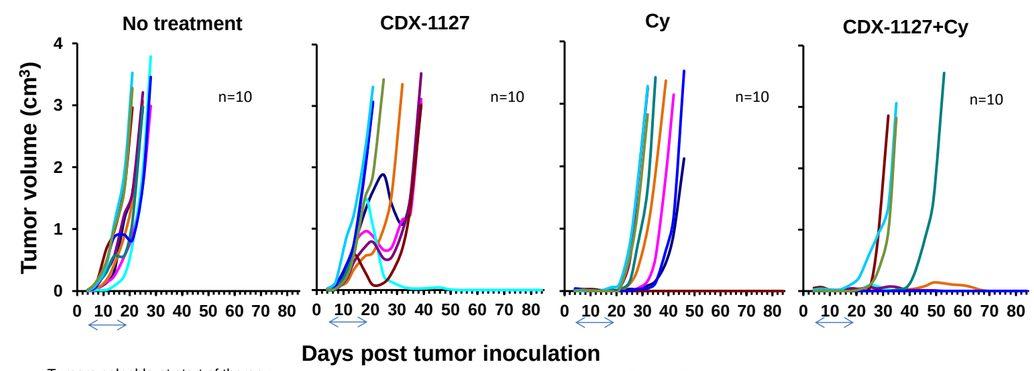
Introduction

- CD27 is a potent co-stimulatory molecule that drives T cell activation and survival through interaction with its ligand, CD70
- Monoclonal antibodies to the CD27 molecule have been shown to enhance immune responses and promote antitumor immunity in preclinical models (French RR et al.2007 Blood, Roberts, DJ et al. 2010 J. Immunotherapy)
- CDX-1127 is an agonist anti-CD27 IgG1 fully human mAb that induces activation and proliferation of human T cells when combined with T-cell receptor stimulation that is currently being evaluated in a Phase 1 trial of hematologic (poster 144) and solid tumors (poster 146).
- We have previously shown that CDX-1127 can be effective in syngeneic murine tumor models when dosing is initiated early. In this study, using more challenging tumor models we investigated combinations with conventional and checkpoint blockade therapies.
- There is strong rationale for combining an immune activating agent (CDX-1127) with other therapies, in particular agents that induce tumor killing to provide a source of antigen and agents that block T cell inhibitory molecules.

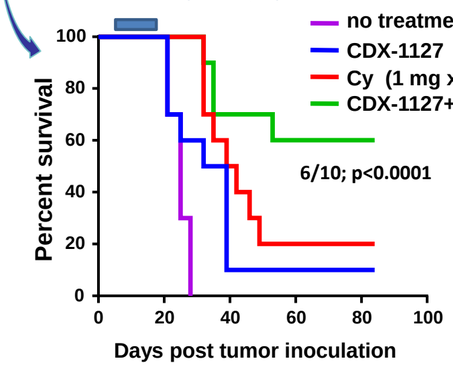
Combination of CDX-1127 with cyclophosphamide

Synergistic activity of CDX-1127 and cyclophosphamide in aggressive E.G7 tumor model



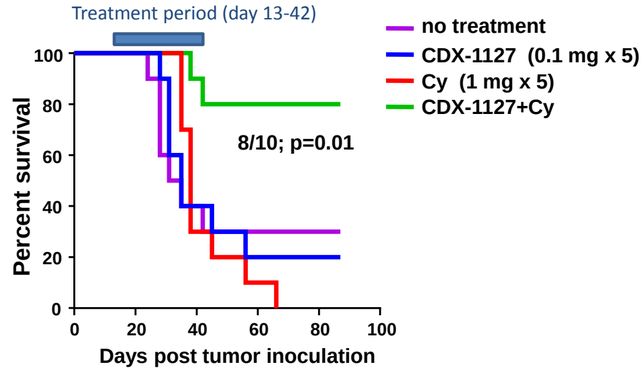
Tumors palpable at start of therapy

Treatment period (day 4-19)



Tumors 50 mm³ at start of therapy

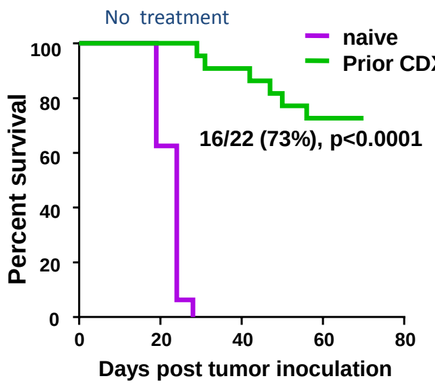
Treatment period (day 13-42)



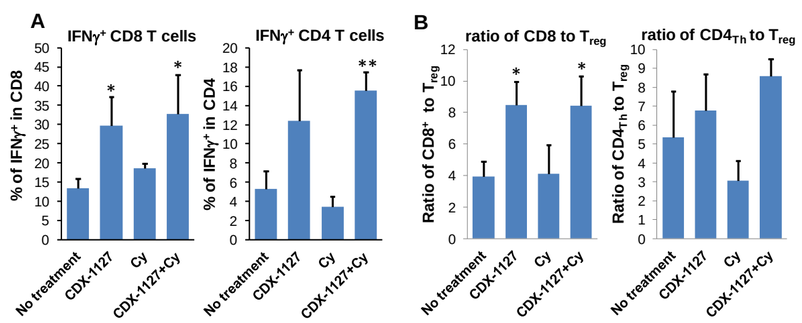
Mice that were inoculated with 10^6 E.G7 tumor cells and treated as indicated.

Combination therapy elicits immunity to rechallenge and favorable T cell profile in tumors

No treatment



Mice that were treated with the combination therapy (from above) and survived were rechallenged with 10^6 E.G7 tumor cells. Naïve mice served as controls.

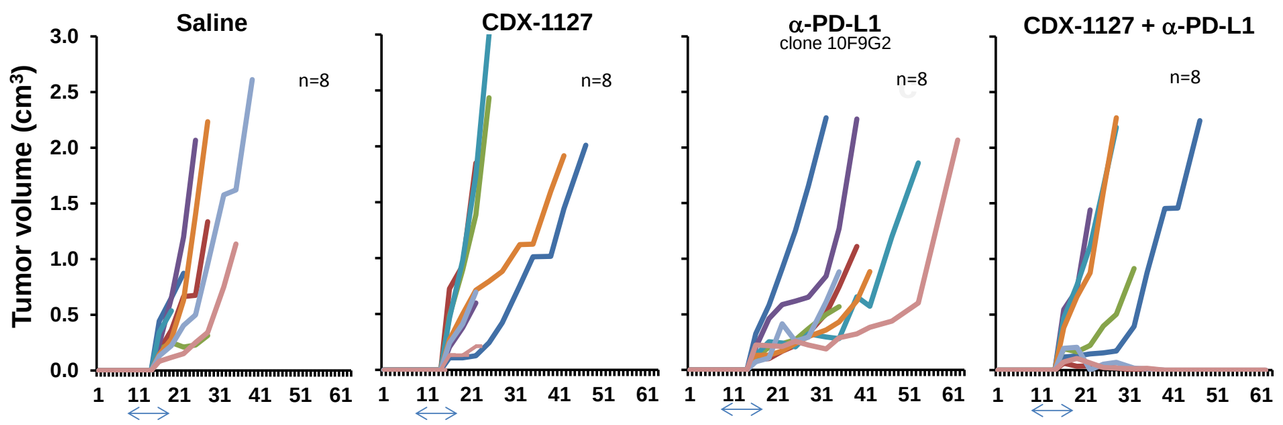


E.G7 tumor bearing mice (~100 mm³) were treated with Cy 1 mg i.p. on day 1; CDX-1127 0.1 mg i.p. on day 2 and 5; or the combination. On day 12, tumor was collected and processed for TIL analysis. (A) Surface CD8 and CD4 and intracellular IFNγ were stained and analyzed by flow cytometry after 5 hr incubation with 2 μg/ml of α-CD3 and α-CD28. (B) Surface CD3, CD4, CD25 and hCD27and intracellular Foxp3 were stained and analyzed. Student *t* test: * p<0.05; ** p<0.01 compared to no treatment.

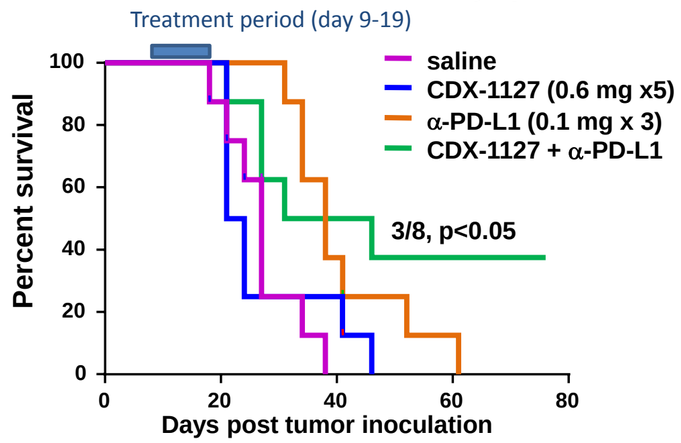
Combination of CDX-1127 with anti-PD-L1 mAb

Improved survival in CT26 and E.G7 models with CDX-1127 and anti-PD-L1 mAb

CT26 model (colon carcinoma)

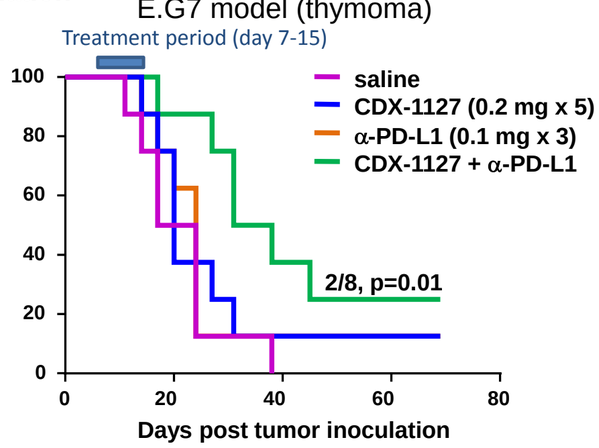


Treatment period (day 9-19)



E.G7 model (thymoma)

Treatment period (day 7-15)



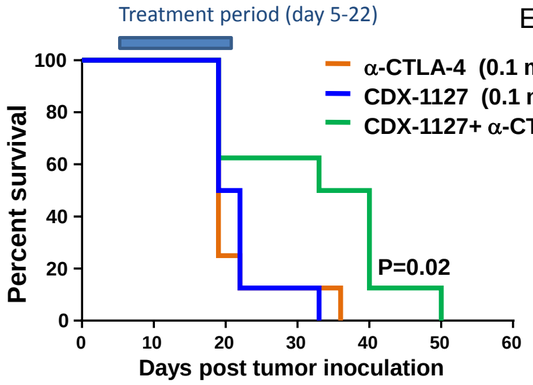
Mice that were inoculated with 1.5×10^4 CT26 tumor cells and treated as indicated.

Mice that were inoculated with 10^6 E.G7 tumor cells and treated as indicated.

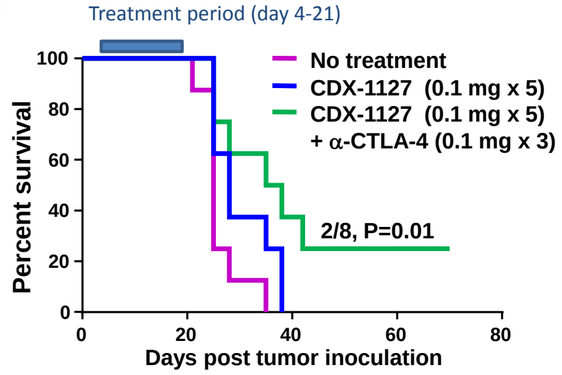
Combination of CDX-1127 with anti-CTLA-4 mAb

E.G7 model

Treatment period (day 5-22)



Treatment period (day 4-21)



Mice that were inoculated with 10^6 E.G7 tumor cells and treated as indicated.

Conclusions:

- We observed significant anti-tumor activity in challenging tumor models when CDX-1127 was combined with either cyclophosphamide or checkpoint blocking antibodies.
- Combination of CDX-1127 with cyclophosphamide resulted in durable immunity against rechallenge and an increase in the T_{eff} to T_{reg} ratio among the tumor associated lymphocytes.
- Optimization of combination therapy may require variation of dose and timing of the regimen. These studies are on-going.
- These studies, together with the favorable safety profile and activity data from the Phase 1 trial with CDX-1127, support the initiation of combination trials with conventional and immune-based therapies.

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