Synergistic anti-tumor activity with a combination of anti-PD1 antibody and the cyclophilin inhibitor, rencofilstat, in the Hep53.4 fatty liver model of hepatocellular carcinoma

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INTRODUCTION

Cyclophilins are pleiotropic, regulatory enzymes that have been shown in preclinical studies to contribute to progression of hepatocellular carcinoma (HCC) and other types of cancer. Immunomodulation is one of the proposed mechanisms by which cyclophilin inhibitors may in turn show anti-cancer activity. Rencofilstat (formerly CRV431) is a cyclophilin inhibitor currently in clinical phase evaluation in NASH and HCC.

AIMS

1. To investigate the anti-tumour activity of the cyclophilin inhibitor, rencofilstat, in combination with anti-PD1 in a murine orthotopic tumor transplant model of HCC.
2. To compare the background of normal livers to fatty livers in the orthotopic model to determine if fatty livers influence rencofilstat and anti-PD1 activities.

METHODS

Hep53.4 Orthotopic HCC Transplant Model

Optional 3 months lead-up Western diet → Surgically implant murine Hep53.4 HCC cells into livers → Days 14-28 vehicle, rencofilstat, anti-PD1, or combination → Day 28 Sacrifice, measure tumors

Drug Treatments, Starting 14 Days Post HCC Implantation

- Rencofilstat – daily oral gavage 80 mg/kg
- Anti-PD1 IgG – 200 µg 2x/week intraperitoneal
- Combination rencofilstat + anti-PD1 IgG

Survival Analysis

- Orthotopic model on fatty liver background
- Treatments from Day 14 until termination

Immunohistochemical detection of tissue-infiltrating immune cells in tumor and nontumor tissue

CONTACT INFORMATION

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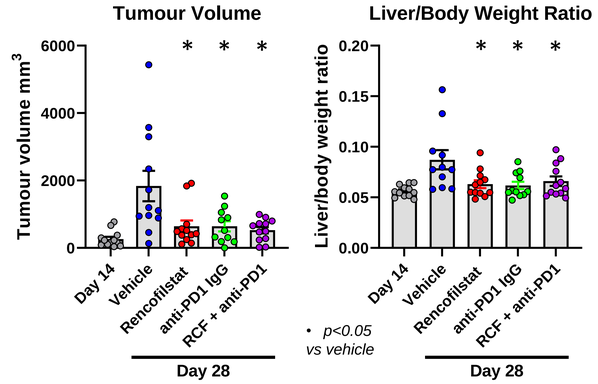
RESULTS

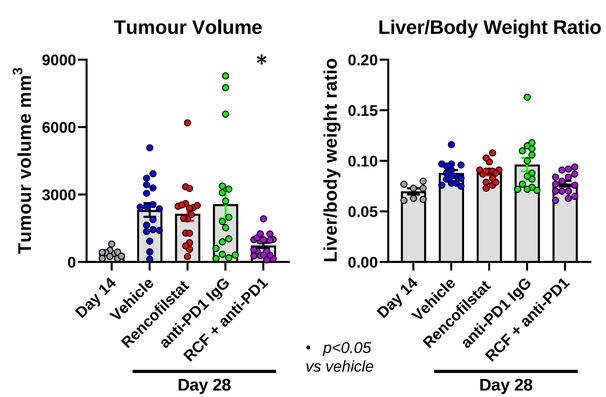
Orthotopic Tumors in Normal Livers

Monotherapy, anti-tumor effects from both rencofilstat and anti-PD1 IgG (~ 80% ↓)



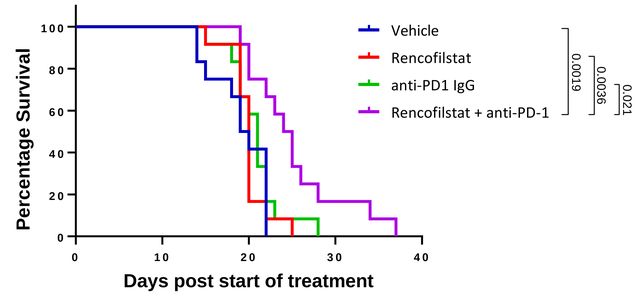
Orthotopic Tumors in Fatty Livers

Tumor size decreased only with combination rencofilstat plus anti-PD1 IgG treatment (84% ↓)

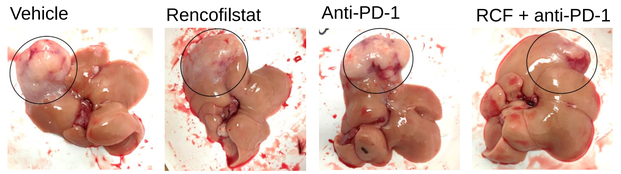


Survival Analysis (orthotopic – fatty livers)

Rencofilstat plus anti-PD1 IgG combination extended survival by 26%



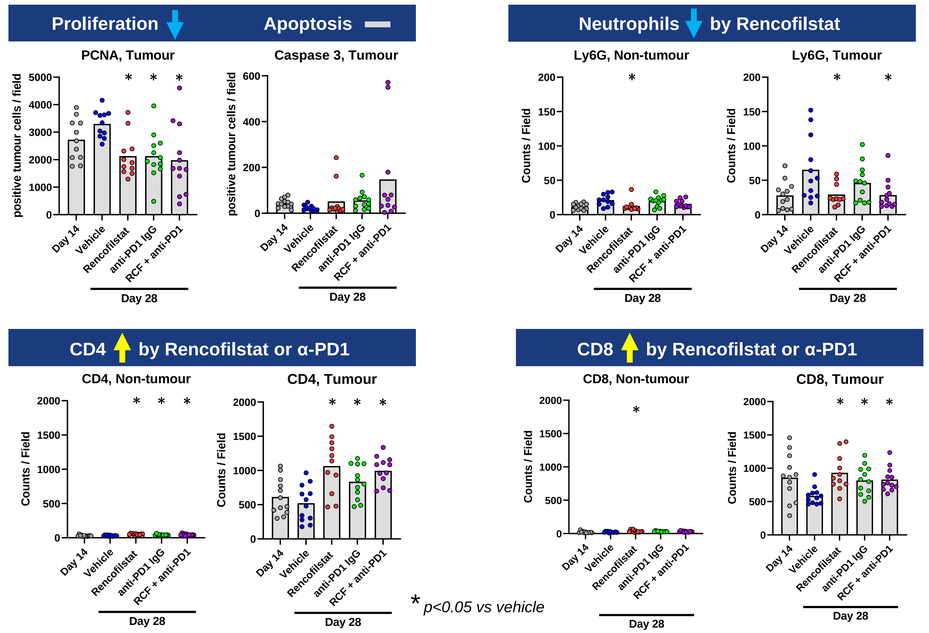
Representative Images (orthotopic – fatty livers)



Tissue-Infiltrating Immune Cells (orthotopic – normal livers)

RENCOFILSTAT:

- decreased neutrophils in tumors and non-tumor liver
- increased CD4 T cells in tumors and non-tumor liver
- increased CD8 T cells in tumors and non-tumor liver



CONCLUSIONS

Normal Liver Background

- monotherapy anti-tumor effects of rencofilstat and anti-PD1 ~ 80%

Fatty Liver Background

- resistant to anti-tumor monotherapy
- rencofilstat synergized with anti-PD1 to decrease tumor growth 84% and extend survival 26%

Rencofilstat Mechanism

- increase in CD4 and CD8 tumor-infiltrating lymphocytes similar to anti-PD1
- additional decrease in tumor-infiltrating neutrophils