Effect of Combined PD-1 and STAT3 Pathway Blockade Treatment on K-ras Mutant Lung Cancer

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Background

- Lung adenocarcinoma (LUAD) is an aggressive form of non-small cell lung cancer[1]
- 30% of LUAD patients have mutations in the Kirsten rat sarcoma viral oncogene (K-ras)[1]
- K-ras mutations are challenging to directly treat due to drug resistance[2]
- Transcription factor STAT3 is a major component of tumor associated inflammation in K-ras mutant tumors[3]
- STAT3 upregulates immune checkpoint molecules PD-1/PD-L1[4]
- Targeting downstream or co-occurring pathways of K-ras may provide new targeted therapy

Aim

We treated a K-ras mutant lung cancer mouse model, CC-LR, with TTI-101 (a STAT3 inhibitor) and/or anti-PD-1 to investigate the significance of targeting downstream/co-occurring pathways of K-ras

Methodology

- CC-LR lung cancer mice were treated with TT1-101 (provided by Tweardy and Eckols) and/or anti-PD-1 from 10 to 14 weeks of age
- Lung samples were extracted and stained with Hematoxylin and Eosin (H&E) staining to determine tumor area percentage

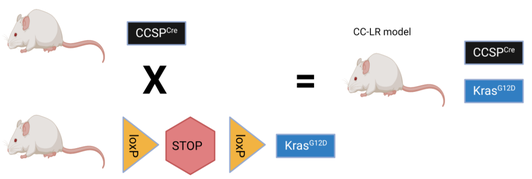

Figure 1. K-ras induced lung cancer mouse model, CC-LR, breeding scheme.

Results

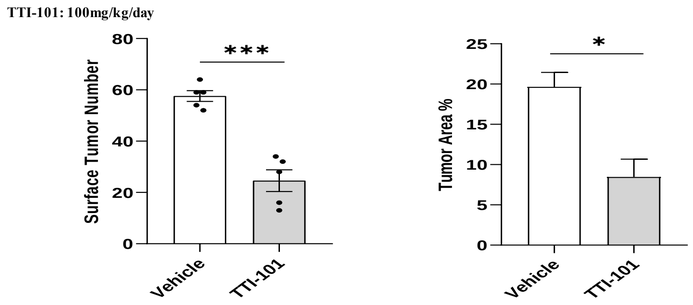

Figure 2. Injection of TTI-101 reduces tumor number and area in CC-LR mice. Figures produced by Marco A. Ramos-Castaneda and Stephen Peng.

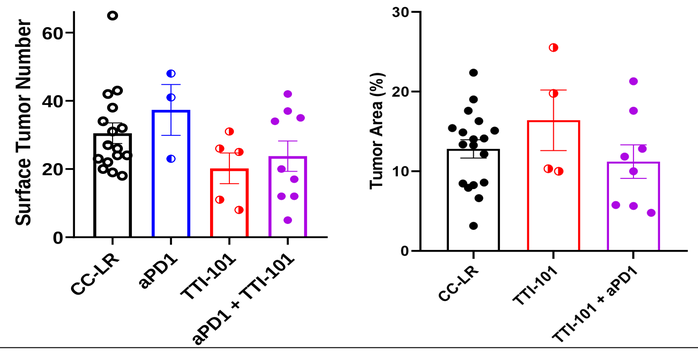

Figure 3. TTI-101 +/- anti-PD1 treatment trends toward reduced surface tumor number, but not tumor area, in CC-LR mice. Figures produced by Michael J. Clowers and Cody Chou

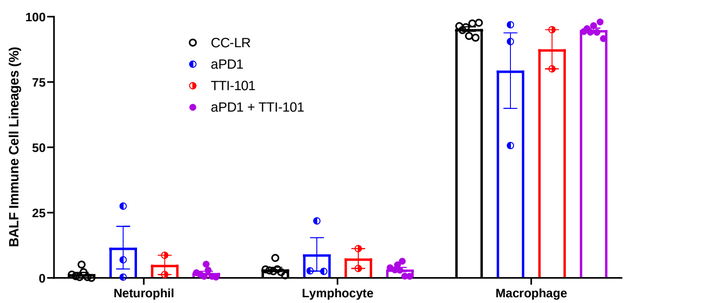

Figure 4. immune cell composition of different treatments in CC-LR mice. Figures produced by Michael J. Clowers

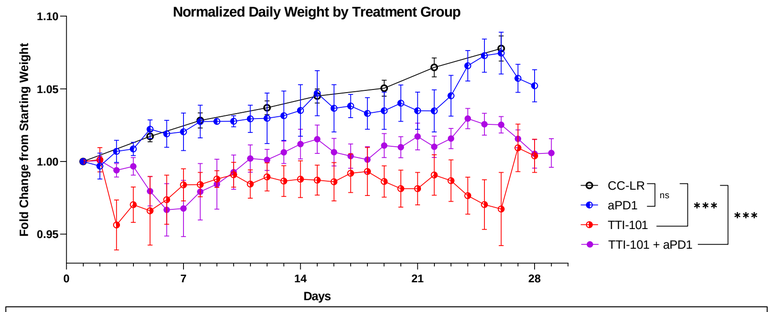

Figure 5. TTI-101 oral gavage causes modest weight loss in CC-LR mice. Figures produced by Michael J. Clowers and Cody Chou

Conclusion

- Based on preliminary data, single treatment of TTI-101 trends toward reduced tumor number
- Combination treatment of TTI-101 and anti-PD-1 trends toward reduced tumor number and area.
- Combination treatment, when compared to single treatment, is not significant
- Personalized treatment with TT1-101 and anti-PD-1 may serve as an alternative approach in the future

Future Work

- We plan to perform immunohistochemistry staining to detect pSTAT3
- We also plan to perform qPCR to detect inflammatory markers in the tumor environment

References

1) Goldstraw, P. et al. Non-small-cell lung cancer. *The Lancet* **378**, 1727-1740 (2011).
2) Mayekar, M. K. & Bivona, T. G. Current landscape of targeted therapy in lung cancer. *Clinical Pharmacology & Therapeutics* **102**, 757-764 (2017).
3) Ji, H. et al. K-ras activation generates an inflammatory response in lung tumors. *Oncogene* **25**, 2105-2112 (2006).
4) Bu, L L et al. "STAT3 Induces Immunosuppression by Upregulating PD-1/PD-L1 in HNSCC." *Journal of dental research* vol. 96,9 (2017): 1027-1034. doi:10.1177/0022034517712435