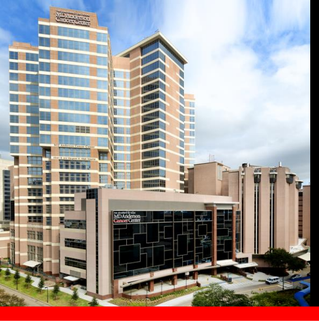

Effect of Combined PD-1 and IL-6 Blockade on K-ras Mutant Lung Cancer

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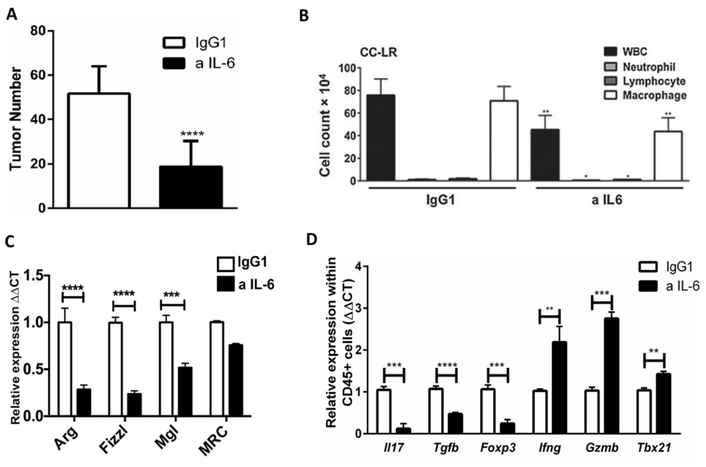
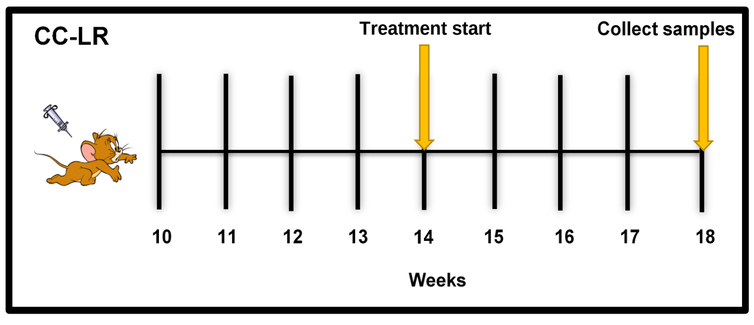
Background

- Kras mutations are the most common oncogenic mutation in non-small cell lung cancer.
- Unfortunately, **targeting Kras directly has substantially failed thus far, and there are no therapies that adequately address most forms of mutant Kras.**
- Immune checkpoint blockade, ICB (e.g., PD-1 blockade) has shown promise patients with non-small cell lung cancer.
- Our laboratory has previously shown that IL-6 blockade reprograms the myeloid tumor microenvironment (TME), leading to a more robust cytotoxic immune response[1].



- Accordingly, we hypothesized that there might be an additive/ synergistic effect of modulating the immunosuppressive TME and augmenting anti-tumor immunity through combined PD-1 and IL-6 blockade. We would also like to see the effectivity of anti-PD-1 treatment alone in Kras mutant lung cancer.

Methodology



Treatment	Conditions	Duration
Control (IgG)	200µL IP	Twice a week for 4 weeks
Anti-PD-1	Clone: 29F.1A12 (Bioxcell – BE0273-CUST)(200µg IP)	Three times a week for 4 weeks
Anti-IL-6	Clone: MP5-20F3 (Bioxcell – BE0046-CUST)(20 mg/kg IP)	Twice a week for 4 weeks
Anti-PD-1 + Anti-IL-6	Given separately	Two regimes combined

Results

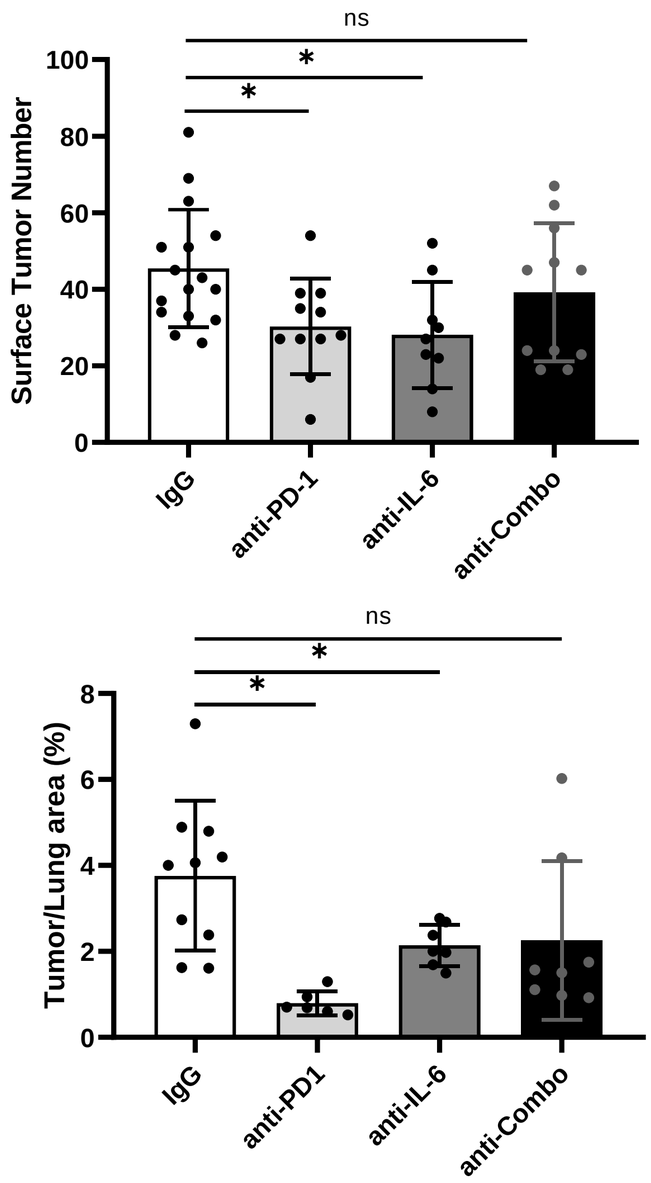


Figure 1. Anti-PD-1 and anti-IL-6 treatment reduce tumor burden while their combination leads to clustered responses.

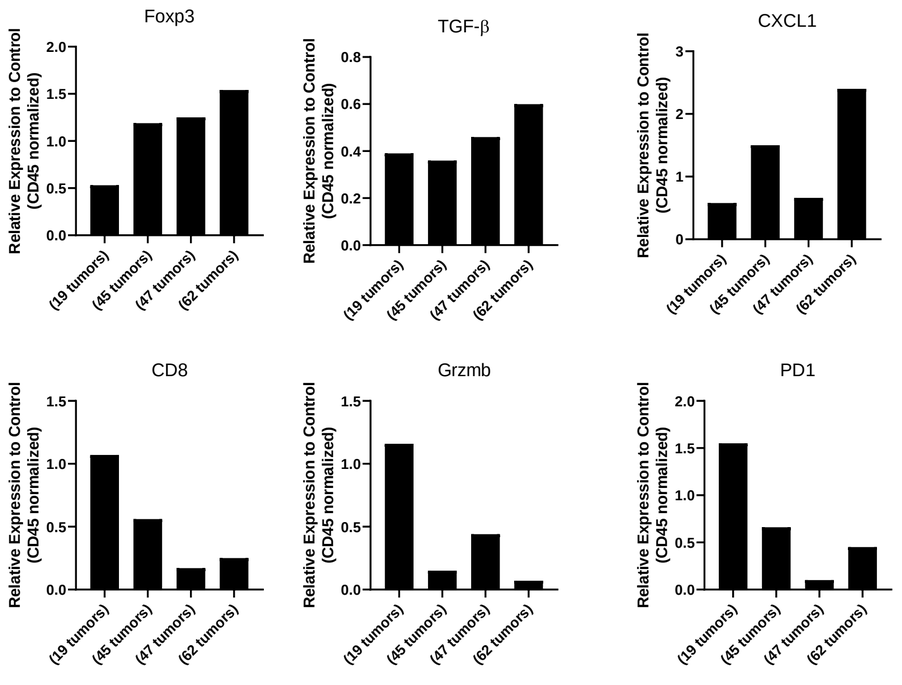


Figure 2. Increase in surface tumor number correlates with increased immunosuppressive hallmarks and weakened cytotoxic signature in combination treatment mice.

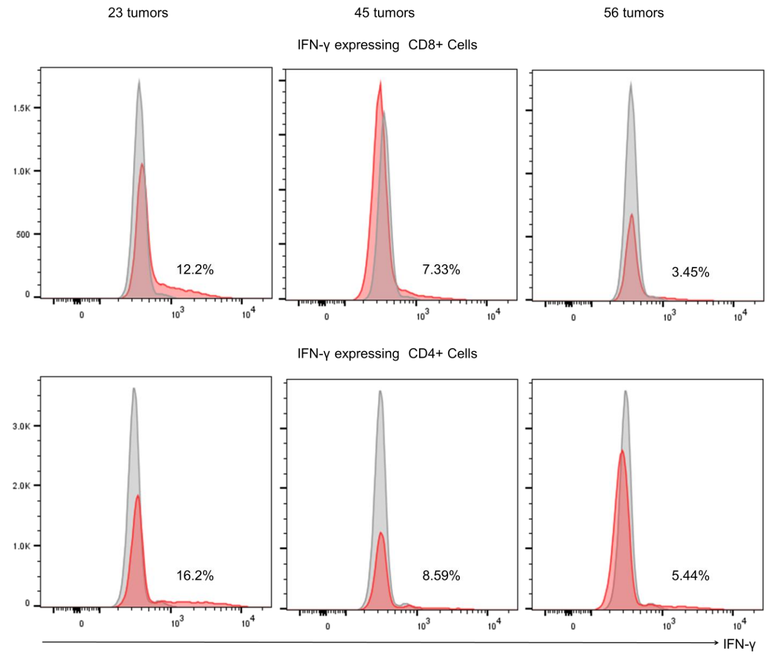


Figure 3. Flow cytometry analysis reveals a weaker cytotoxic immune response as surface tumor number increases in combination treatment mice.

Conclusions

- Consistent with previous results, anti-IL-6 treatment results in decrease in tumor burden.
- Anti-PD-1 treatment significantly reduces tumor burden in our Kras-mutant lung cancer mouse model.
- Personalized treatment with anti-IL-6 alone might be an alternative modality for ICB in patients with Kras mutant lung cancer.
- Combination treatment results in clustered responses, with some mice responding extremely well and others receiving no benefit.
- Responders in the combination treatment group have lower expression of Treg signatures and higher CD8 T-cell cytotoxic activation, as well as lower CXCL1 and higher PD1 expression.

Future Work

- More repeat experiments of each group
- Dissection of why certain mice are responders or nonresponders will elucidate resistance mechanisms and help clinicians create individualized treatment strategies.

References

1. Caetano MS, Zhang H, Cumpian AM, et al. IL6 Blockade Reprograms the Lung Tumor Microenvironment to Limit the Development and Progression of K-ras–Mutant Lung Cancer. *Cancer Res*. 2016;76(11):3189-3199.

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