KCRS22 Kidney Cancer Research Summit

Circulating biomarkers associated with resistance to nivolumab and ipilimumab based regimens indicate persistent immunosuppression and activation of STAT3 signaling

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Introduction

- Nivolumab (PD-1 blockade) and ipilimumab (CTLA-4 blockade) are front line therapy for metastatic RCC (1)
- Resistance involves many factors including the innate and adaptive immunity, the activation of oncogenic pathways and the tumor microenvironment (TME) including: exhausted T cells, T regulatory cells, myeloid-derived suppressor cells and tumor associated macrophages (TAMs)
- There are currently no established predictive biomarkers to anticipate lack of response to immune checkpoint inhibitors (ICIs) in RCC

In this study we aimed to:

(1) Humans: Investigate associations in immune alterations in lack of response to nivolumab/ipilimumab
(2) Mice: Assess a novel drug combination to target innate and adaptive immune alterations

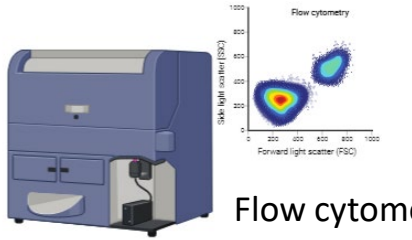
(1) Motzer RJ et al. N Engl J Med (2018)

Methods: Part 1

RCC patients treated with nivolumab/ipilimumab at City of Hope

Timepoint 1: Baseline

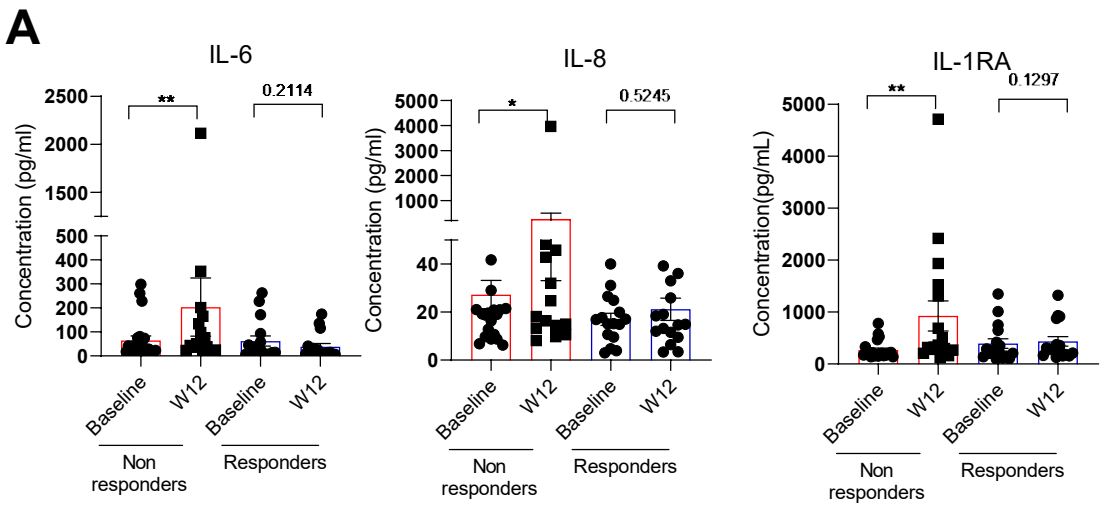
Timepoint 2: Week 12

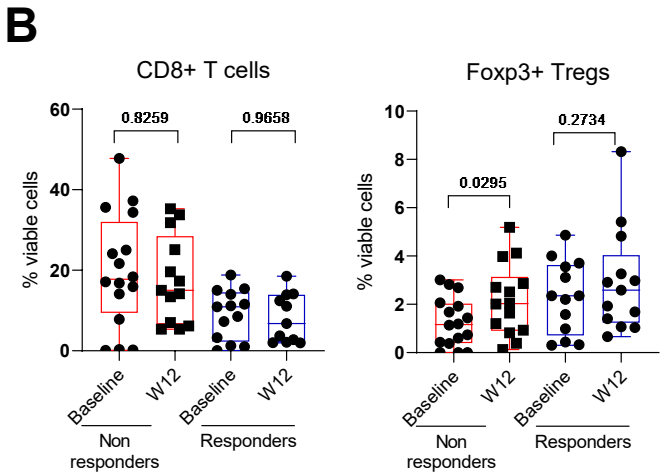


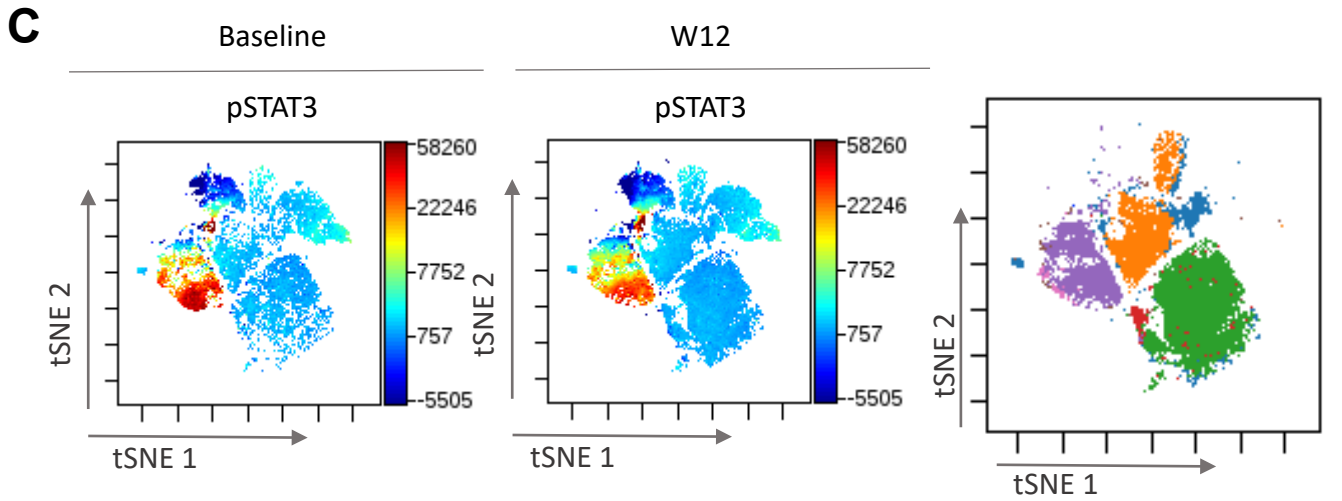
Flow cytometry

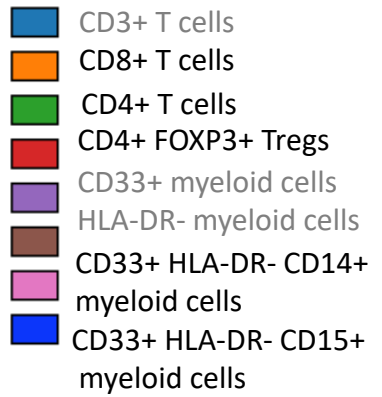
Luminex

Results: Part 1

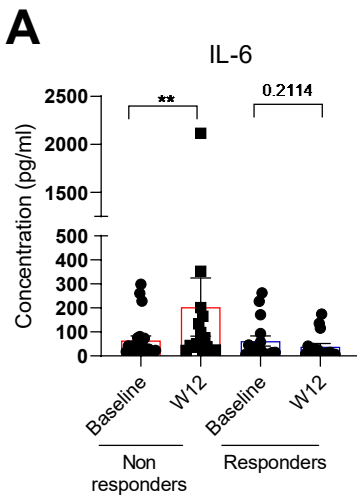


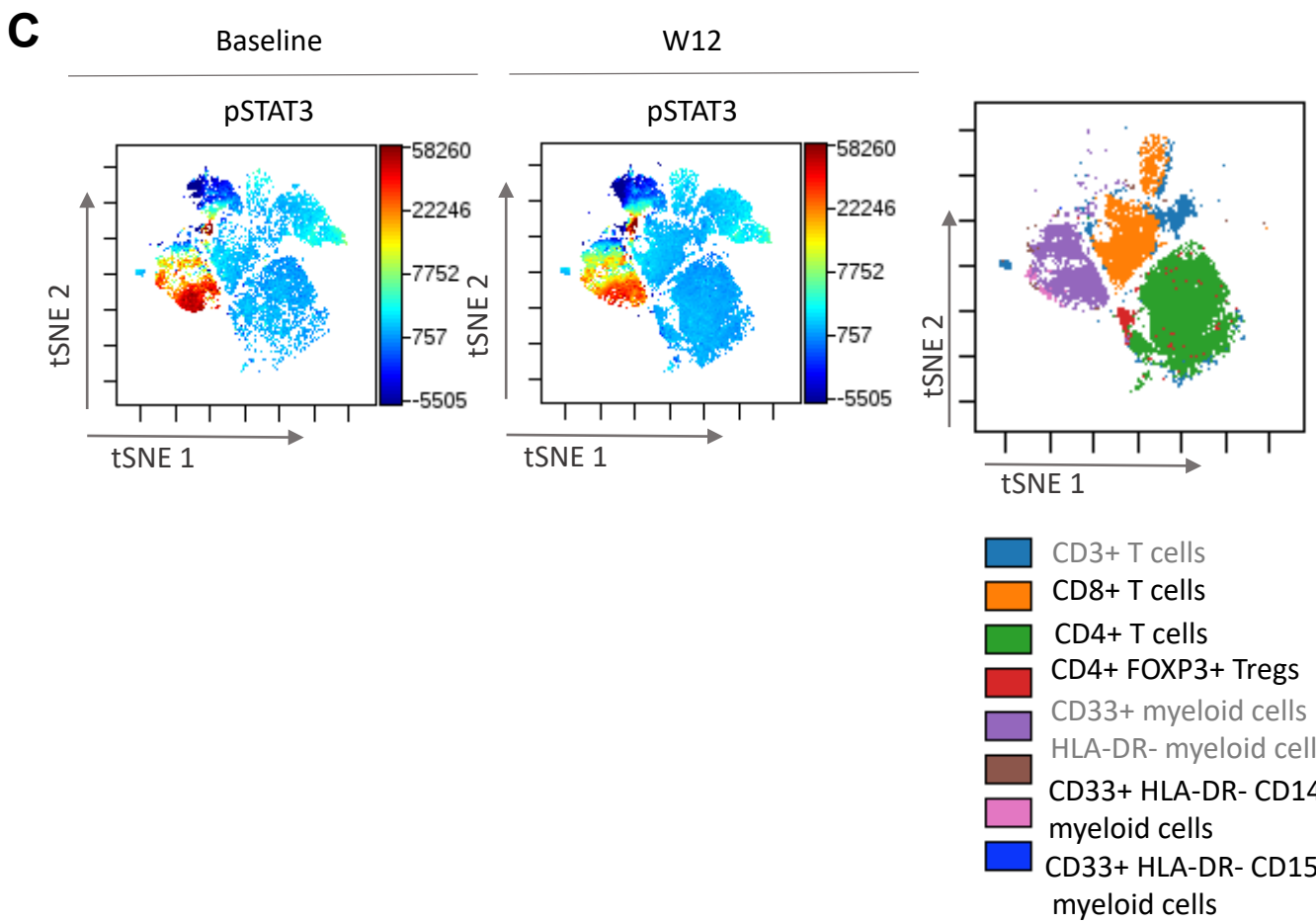






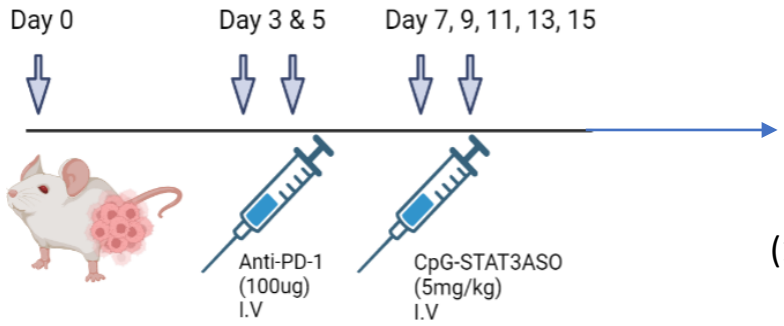
Results: Part 1





Methods: Part 2

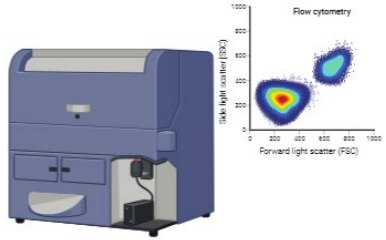
Syngeneic mouse model of RCC: RENCA mouse model



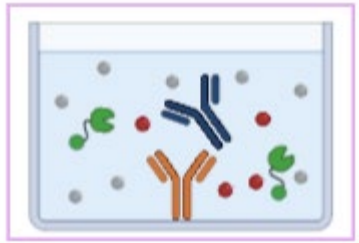
(1) Peripheral blood

(2) Tumors

(3) Tumor draining lymph nodes



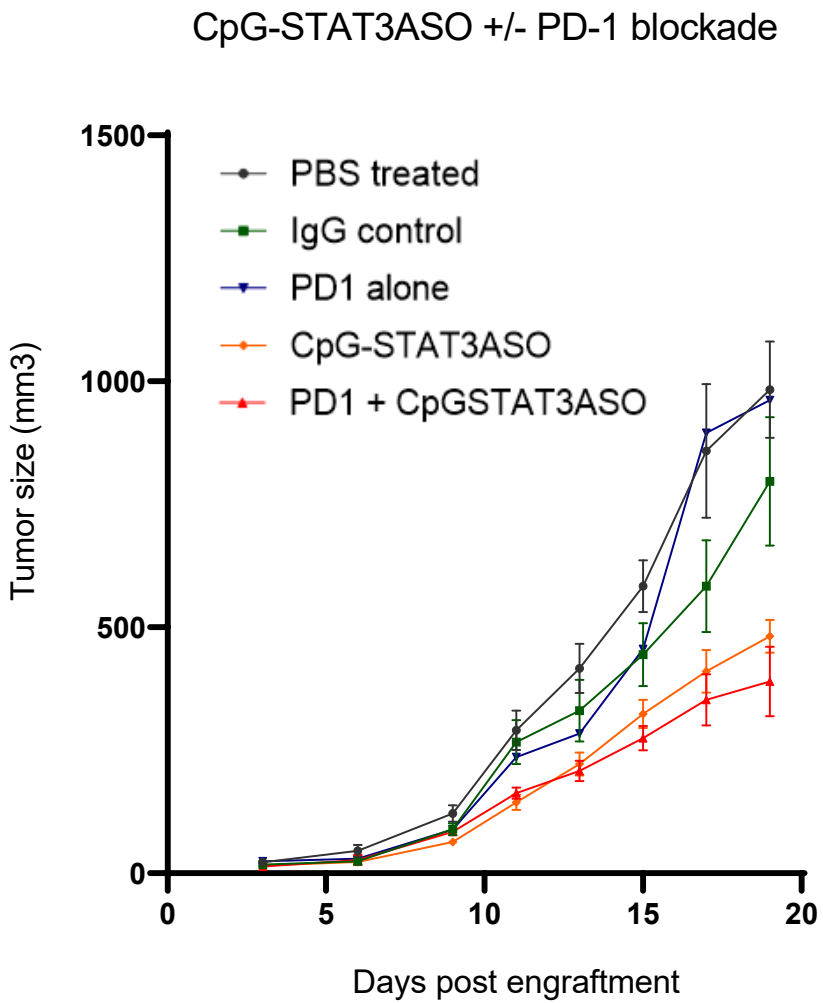
Flow cytometry



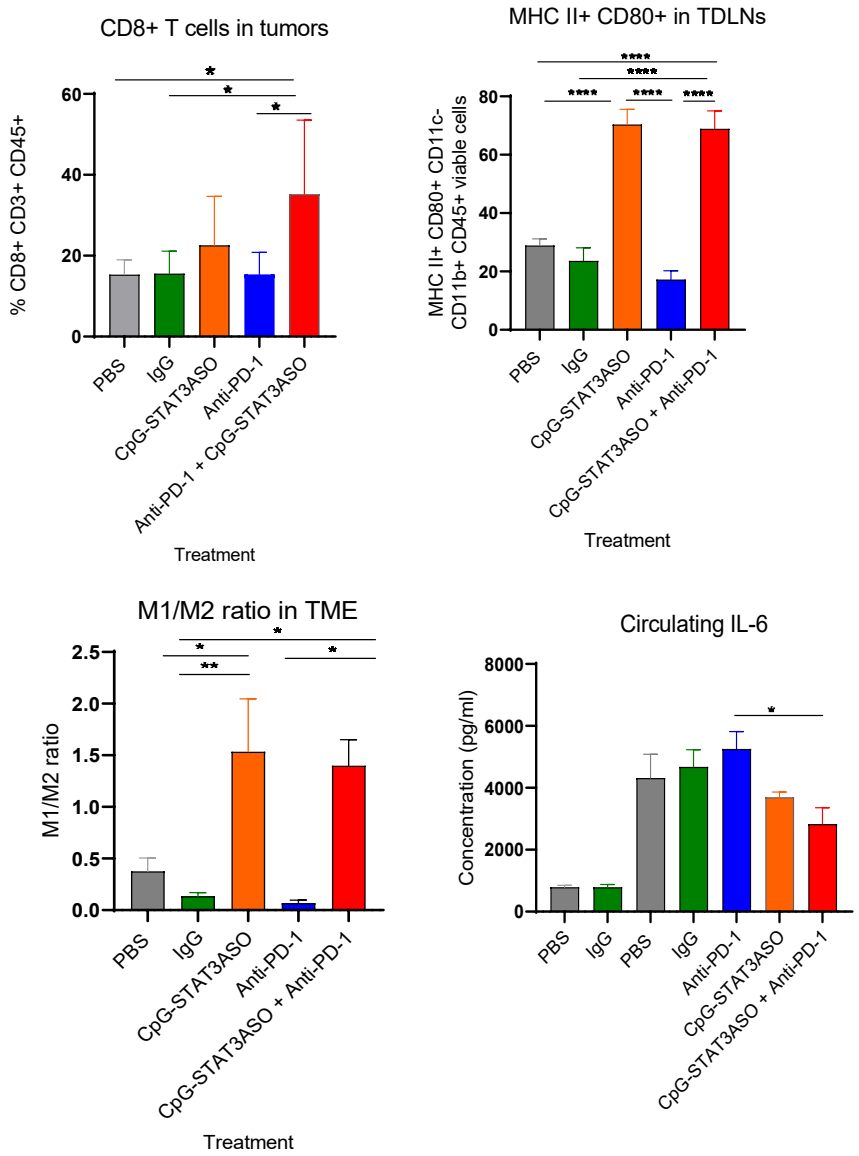
ELISA

Results

A


CpG-STAT3ASO +/- PD-1 blockade
PBS treated
IgG control
PD1 alone
CpG-STAT3ASO
PD1 + CpGSTAT3ASO
Tumor size (mm3)
1500
1000
500
0
0
5
10
15
20
Days post engraftment

B


CD8+ T cells in tumors
% CD8+ CD3+ CD45+
60
40
20
0
PBS
IgG
CpG-STAT3ASO
Anti-PD-1
Anti-PD-1 + CpG-STAT3ASO
Treatment
MHC II+ CD80+ in TDLNs
MHC II+ CD80+ CD11c- CD11b+ CD45+ viable cells
80
60
40
20
0
PBS
IgG
CpG-STAT3ASO
Anti-PD-1
CpG-STAT3ASO + Anti-PD-1
Treatment
M1/M2 ratio in TME
M1/M2 ratio
2.5
2.0
1.5
1.0
0.5
0.0
PBS
IgG
CpG-STAT3ASO
Anti-PD-1
CpG-STAT3ASO + Anti-PD-1
Treatment
Circulating IL-6
Concentration (pg/ml)
8000
6000
4000
2000
0
PBS
IgG
PBS
IgG
Anti-PD-1
CpG-STAT3ASO
CpG-STAT3ASO + Anti-PD-1

Summary

- Non-responders to Nivo/Ipi have increased immunosuppressive Tregs, circulating cytokines IL-6, IL-8, Il-1RA and high levels of phosphorylated STAT3 suggesting immune suppression particularly within innate immune system
- IL-6, IL-8 and IL-1RA should be investigated further as potential biomarkers for resistance to nivolumab and ipilimumab
- Finally, our animal studies suggest, combining STAT3 inhibitor with PD-1 blockade could be a way to overcome immune suppression in RCC

Acknowledgments

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