# Adenosine signature genes associate with tumor regression in renal cell carcinoma (RCC) patients treated with the adenosine A2A receptor (A2AR) antagonist, CPI-444.

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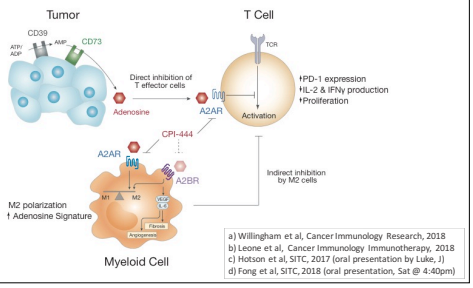
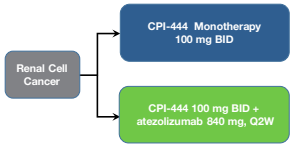
## Background

- Adenosine blocks T-cell activation and promotes myeloid suppression
- CPI-444 is an oral small molecule antagonist of the adenosine 2A receptor (A2AR) that has shown efficacy in animal models and is associated with T cell activation. [a,b]
- Ongoing clinical trial of CPI-444 +/- anti-PD-L1 atezolizumab demonstrates tumor responses to monotherapy and combination in multiple indications including renal cell carcinoma (RCC). [c,d]
- Future trials in RCC would benefit from a biomarker that predicts patient response.




a) Willingham et al, Cancer Immunology Research, 2018
b) Leone et al, Cancer Immunology Immunotherapy, 2018
c) Hotson et al, SITC, 2017 (oral presentation by Luke, J)
d) Fong et al, SITC, 2018 (oral presentation, Sat @ 4:40pm)

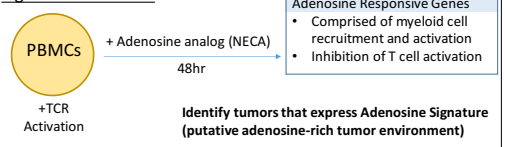
## Phase 1/1b Clinical Study with CPI-444




Eligibility
- Heavily pretreated (median 3 prior therapies)
- Prior anti-PD-(L)1 allowed
- Progressive disease on prior therapy
- No selection for PD-L1 expression

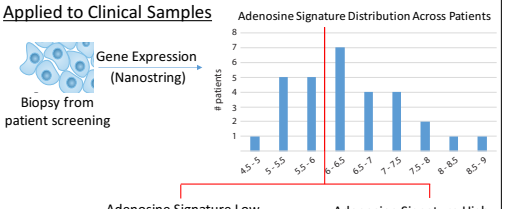
## Adenosine Signature: *In vitro* Discovery and *In vivo* Application

Signal Identification




**Identify tumors that express Adenosine Signature (putative adenosine-rich tumor environment)**

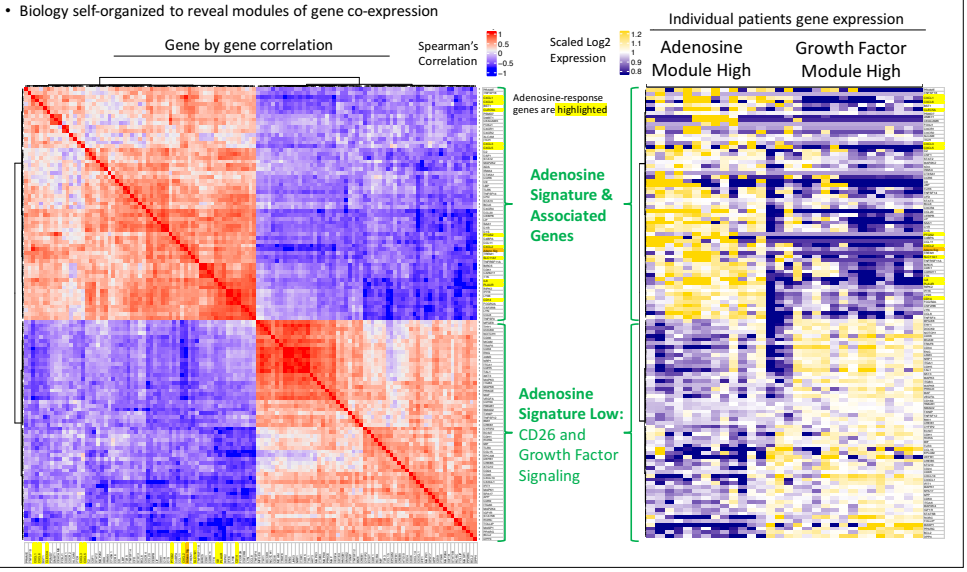
Applied to Clinical Samples



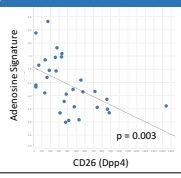

## Adenosine Signature and Co-expressed Genes Identified in Patient Subset by Unsupervised Clustering

***A separate patient subset is low for adenosine signature and expresses alternate biological pathways***

- Gene expression was collected from pre-treatment biopsies
- Expression was correlated across patients and clustered
- Biology self-organized to reveal modules of gene co-expression




## CD26 Negatively Correlates with Adenosine Signature



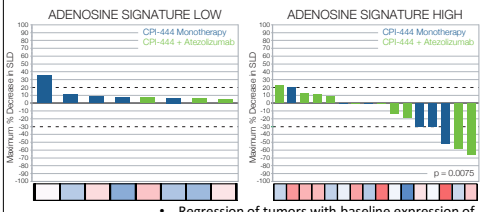

- CD26 is a binding partner for soluble adenosine deaminase (ADA)
- ADA decreases local adenosine concentration

## Adenosine Signature and Associated Biology

***Model of distinct RCC subclasses***

| Adenosine Microenvironment | Non-Adenosine Microenvironment |
|---|---|
| • Myeloid recruitment<br>• +/- T cell infiltration<br>• Complement | • Growth factor response<br>• +/- T cell infiltration<br>• Complement inhibition<br>• CD26 |
| *Responsive to A2AR inhibition* | *Adenosine pathway independent tumor* |

## Adenosine Signature Biomarker and Outcome




- Regression of tumors with baseline expression of Adenosine Signature
- Tumor response independent of underlying T cell infiltration

## Summary

- Adenosine-response genes define an Adenosine Signature biomarker that enriches for patients with tumors that respond to A2AR antagonism by CPI-444
- Gene clustering analysis identified two distinct populations of RCC
  1) Adenosine Signature high / growth factor low
  2) Adenosine Signature low and high for growth factor response genes & CD26
- Enables future studies to employ Adenosine Signature for identification of sub-groups that associate with tumor response