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

1Andrew Hotson, 1Stephen Willingham, 1Lawrence Fong, 1John Powderly II, 1Jason Luke, 1Mario Szol, 1Saby George, 1Toni K. Choueiri, 1Marios Giannakis, 1Brian Rini, 1Shivaani Kummur, 1Erik Evesen, 1Ian McCaffery, 1Chunyan Gu, 1Long Kwei, 1Ginni Laport, 1Joe Buggy and 1Richard Miller

Background

- Adenosine blocks T-cell activation and promotes myeloid suppression
- CPI-444 is an oral small molecule antagonist of the adenosine A2 receptor (A2AR) that has shown efficacy in animal models and is associated with T cell activation. 1,2
- Ongoing clinical trial of CPI-444 +/- anti-PO-L1 atezolizumab demonstrates tumor responses to monotherapy and combination in multiple indications including renal cell carcinoma (RCC). 3,4
- Future trials in RCC would benefit from a biomarker that predicts patient response.

Adenosine Signature: In vitro Discovery and In vivo Application

Signal Identification

- PBMC + Adenosine analog (NECA)
- TCR Activation

Adenosine Responsive Genes
- Comprised of myeloid cell recruitment and activation
- Inhibition of T cell activation

Adenosine Signature Distribution Across Patients

- Adenosine Signature Low: No tumor regression
- Adenosine Signature High: Enriched for tumor responders to CPI-444

Adenosine Signature and Co-expressed Genes Identified by Unsupervised Clustering

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

Adenosine Signature and Associated Biology

Model of distinct RCC subclases

- Adenosine Microenvironment
  - Myeloid recruitment
  - +/− T-cell infiltration
  - Complement

- Non-Adenosine Microenvironment
  - Growth factor response
  - +/− T-cell infiltration
  - Complement inhibition

Adenosine Signature Biomarker and Outcome

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

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