MUNICH 2018 ESMO congress

IDENTIFICATION OF ADENOSINE PATHWAY GENES ASSOCIATED WITH RESPONSE TO THERAPY WITH THE ADENOSINE RECEPTOR ANTAGONIST CPI-444

Presentation #:1137PD

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Slides For Discussant

Adenosine Signaling Through A2AR Induces a Specific Gene Signature in Human Immune Cells.

- Extracellular adenosine within the tumor microenvironment creates an immunosuppressive niche
- Extracellular adenosine has a short half life and it is not feasible to routinely measure in human tumors.

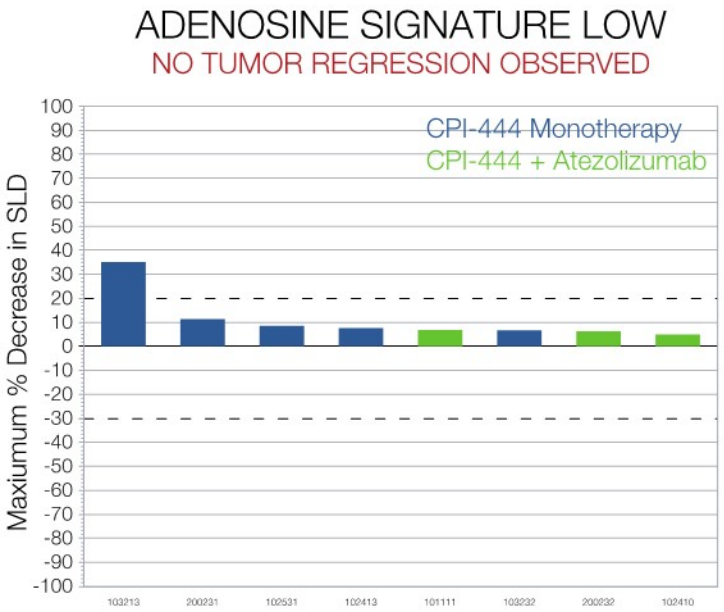
ADENOSINE SIGNATURE - NANOSTRING

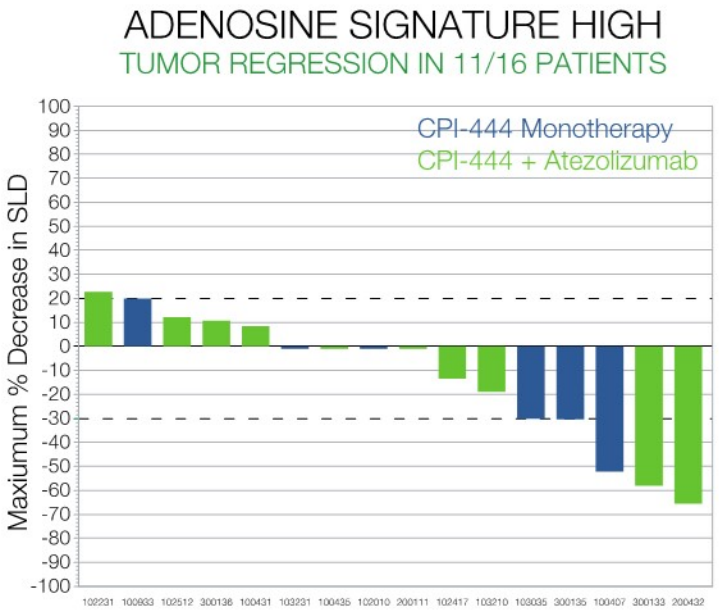
	Adjusted p Value	Function	Receptor
IL23A	1.44E-04	Increases angiogenesis and reduces CD8+ T-cell infiltration	
SLC11A1	1.27E-03	Natural resistance-associated macrophage protein 1	
CXCL2	1.27E-03	MIP2a: macrophage inflammatory protein 2, alpha	CXCR2
CXCL7	1.27E-03	PPBP, Pro-Platelet Basic Protein	CXCR2
CXCL6	1.40E-03	GCP2: Granulocyte chemotactic protein 2	CXCR2
CXCL3	1.40E-03	Controls migration and adhesion of monocytes	CXCR2
IL-6	1.48E-03	Pro- and anti-inflammatory cytokine	
IL-1α	1.73E-03	Inflammation	
CXCL8	1.98E-03	IL-8. Nutrophil chemotactic factor	CXCR1/2
CXCL5	1.98E-03	Attracts and activates neutrophils	CXCR2
THBS1	2.28E-03	Multiple functions. Inhibits angiogenesis & immune regulation	
IL-1β	2.38E-03	Inflammation	
PTGS2	2.65E-03	COX-2. Elevated during inflammation and cancer	
IL-24	2.70E-03	Cell survival and proliferation. Activates STAT1/3	
CXCL1	3.92E-03	Neutrophil chemotractant	CXCR2
CD86	5.31E-03	B7-2: Costimulatory signal for T cell activation and survival	
CLEC5A	5.82E-03	Interacts with DAP-12 and may play a role in cell activation	
CD14	6.24E-03	Expressed by myeloid cells	

- This study aims to determine genes/proteins modulated by adenosine as surrogate signature to identify patients with adenosine rich tumors

- Adenosine induces a specific gene signature in human immune cells. Induction of these genes shifts the balance away from T effector responses and toward myeloid suppressor functions.

Expression of the "Adenosine Signature" Correlates with Tumor Regression in Corvus' Ongoing Ph 1/1b trial with CPI-444 Treatment in RCC





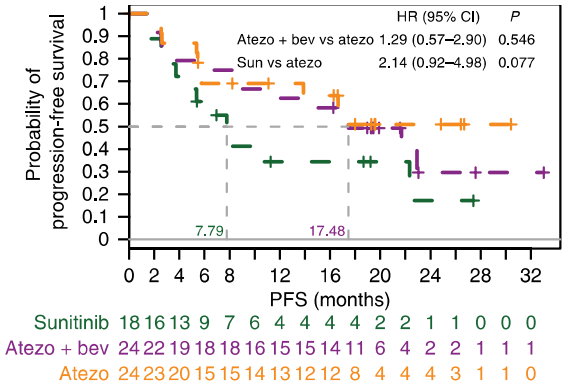
p-value = 0.0075

Adenosine signature determined in archive or pre treatment biopsy tissue

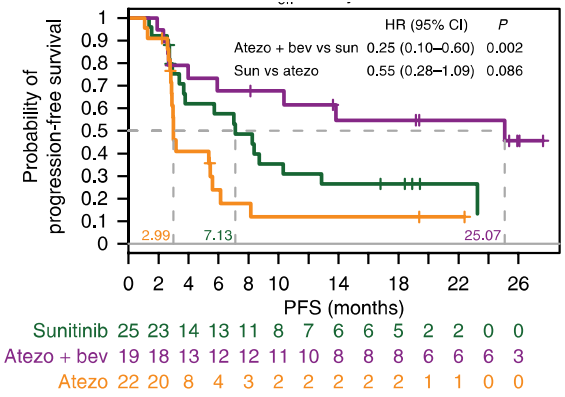
Adenosine Signature Is Nearly Identical To GNE "Myeloid Signature" That Associates with Poor Response to Atezolizumab Monotherapy in RCC Patients

IMMotion150: Ph2 study of atezolizumab ± bevacizumab (anti-VEGF) versus sunitinib in 305 patients with treatment-naive metastatic RCC

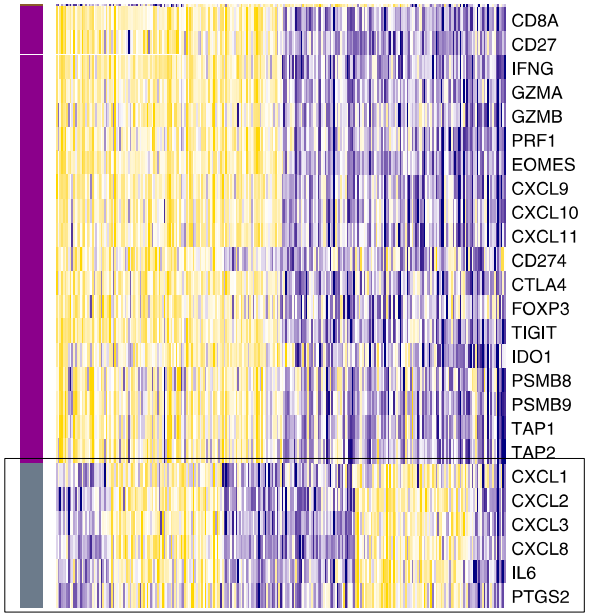
T_{eff}^{High} / $Myeloid^{Low}$



T_{eff}^{High} / $Myeloid^{High}$



Supports role of adenosine in tumor escape from anti-PD-(L)1 therapy



GNE Myeloid Signature

McDermott et al, Nature Medicine, 2018

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Conclusions

- A2AR agonists induce a specific gene signature in human immune cells. This "Adenosine Signature" is dominated by inflammatory myeloid cytokines and chemokines that signal through CXCR2.
- Adenosine induction of these genes dampens T cell immunity and shifts the balance away from T effector responses and toward myeloid suppressor functions.
- CPI-444 blocks the induction of the Adenosine Signature by A2AR agonists in vitro.
- Expression of the "Adenosine Signature" correlates with tumor regression in Corvus' ongoing Ph 1/1b trial with CPI-444 treatment in RCC. Patients with high expression of the Adenosine Signature were more likely to have tumor regression than those patients with low expression
- The Adenosine Signature may be used as a predictive biomarker that can be used to select patients most likely to respond to therapy with agents that antagonize adenosine production or signaling.
- Neutralization of the Adenosine Signature confirms the mechanism of action of CPI-444 as an A2AR antagonist.

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