Inhibition of A2AR induces anti-tumor immunity alone and in combination with anti-PD-L1 in preclinical and clinical studies.

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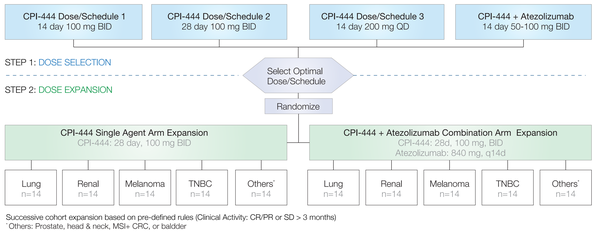
PHASE 1/1B CLINICAL TRIAL DESIGN

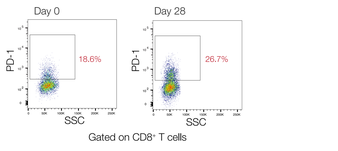


Successive cohort expansion based on pre-defined rules (Clinical Activity: CR/PR or SD > 3 months)
*Others: Prostate, head & neck, MSI+ CRC, or baldder

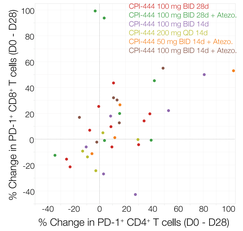
IMMUNE MODULATION BY CPI-444 IN PERIPHERAL BLOOD

PD-1+ T cells are reportedly enriched for neo-antigen specific anti-tumor clones, indicating CPI-444 may induce tumor-specific T cell expansion

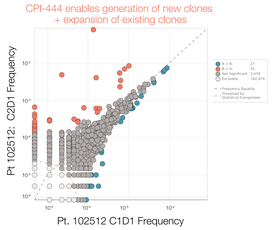
PD-1 expression is induced in most patients following CPI-444 treatment.



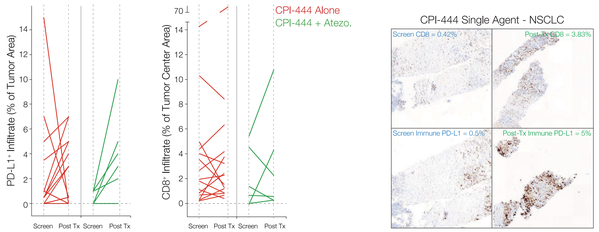
Fresh blood was collected at day 0 and day 28 and the following day cells were stained for PD-1 and T cell lineage markers for flow cytometry



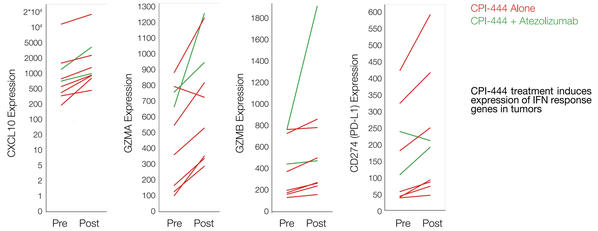
CPI-444 MODULATES TCR REPERTOIRE IN PERIPHERY



CPI-444 INCREASES IMMUNE INFILTRATION INTO TUMORS



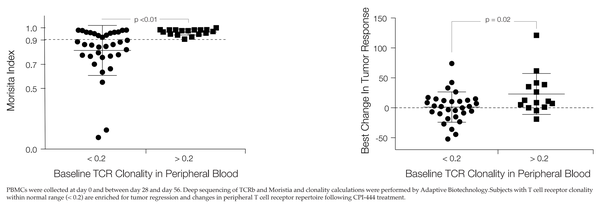
CPI-444 INCREASES T EFFECTOR GENE SIGNATURE



CPI-444 treatment induces expression of IFN response genes in tumors

TCR CLONALITY ASSOCIATES WITH TUMOR REGRESSION

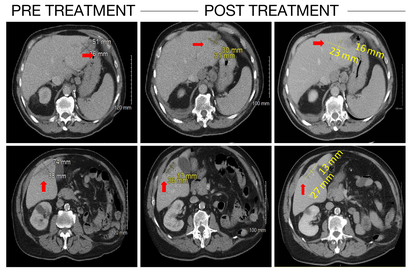
Subjects with TCR diversity are enriched for tumor regression and changes in peripheral TCR repertoire following CPI-444 treatment.



PBMCs were collected at day 0 and between day 28 and day 56. Deep sequencing of TCRb and Morisita and clonality calculations were performed by Adaptive Biotechnology. Subjects with T cell receptor clonality within normal range (< 0.2) are enriched for tumor regression and changes in peripheral T cell receptor repertoire following CPI-444 treatment.

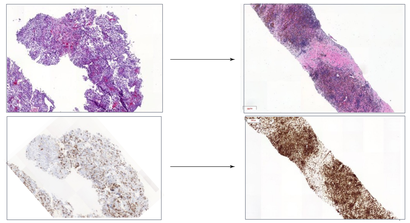
ANTI-TUMOR IMMUNITY INDUCED IN RESPONDING RCC PT.

REGRESSION OF TUMORS

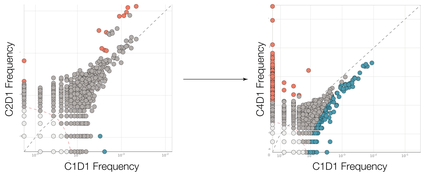


INCREASED IMMUNE INFILTRATION

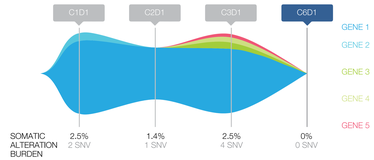
INCREASED CD8 TIL INFILTRATION



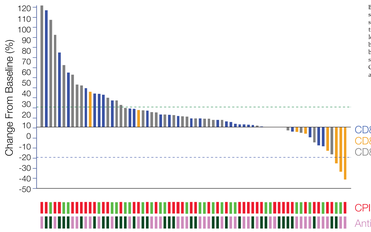
EXPANSION OF TCR REPERTOIRE



ELIMINATION OF CIRCULATING TUMOR DNA

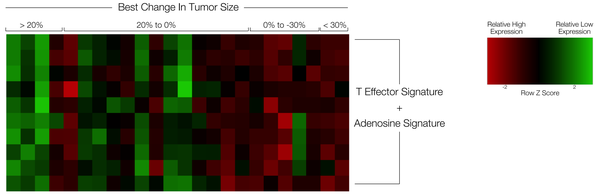


CLINICAL ACTIVITY OF CPI-444 ± ATEZOLIZUMAB



Best overall change in tumor size for all subjects. Colored by CD8+ infiltration of screening biopsy. Corresponding treatment cohort and PD-1 resistant/refractory status is color-coded below. CT scans of target lesions were performed prior to treatment and every 8 weeks post-treatment or at optional time points. Target lesions were measured and the sum of longest dimensions (SLD) calculated. The best change in SLD for each subject is shown in the waterfall plot and colored by the percentage of CD8 infiltration in the center of the pre-treatment biopsy sample as measured by immunohistochemistry. Treatment with single agent CPI-444 or combination with atezolizumab and prior anti-PD-1 treatment status are indicated with colored rectangles under each subject on the waterfall plot

GENE SIGNATURE CORRELATES WITH CLINICAL RESPONSE



Gene expression levels were determined from pre treatment tumor biopsies using the Nanostring Pan Cancer Immune Profiling panel with the addition of custom genes. Differential expression analysis was performed to determine gene expression differences between subjects with a best change in tumor size showed no growth (less than or equal to zero) vs. those with tumor growth (greater than zero). A composite T-effector was calculated as the geometric mean of its composite genes; both the t-effector signature and a number of its component genes were expressed more highly in screen biopsy samples from subjects with no tumor compared to subects with tumor growth. For each gene shown, the z-score for each individual was calculated and used to display by color on the heatmap.

CONCLUSIONS

- Immune activation in both peripheral blood and tumor tissues observed in patients treated with single agent CPI-444 or in combination with atezolizumab
  1. Increased frequencies of PD-1+ activated T cells in peripheral blood
  2. Significant expansion of TCR repertoires in peripheral blood in patients with high TCR diversity at baseline
  3. Increased tumor CD8 infiltration as well as induction of interferon induced genes in tumor tissues
- Early clinical data suggests pre-existing T cell infiltration or activation is not required for tumor regression with either single agent or combination regimens
- This is consistent with the hypothesis that inhibition of A2AR signaling stimulates T cell infiltration and activation in the tumor microenvironment in both inflamed and non-inflamed tumors