

# Immunobiology, Preliminary Safety and Efficacy of CPI-006, an Anti-CD73 Antibody with Immune Modulating Activity, in a Phase 1 Trial in Advanced Cancers

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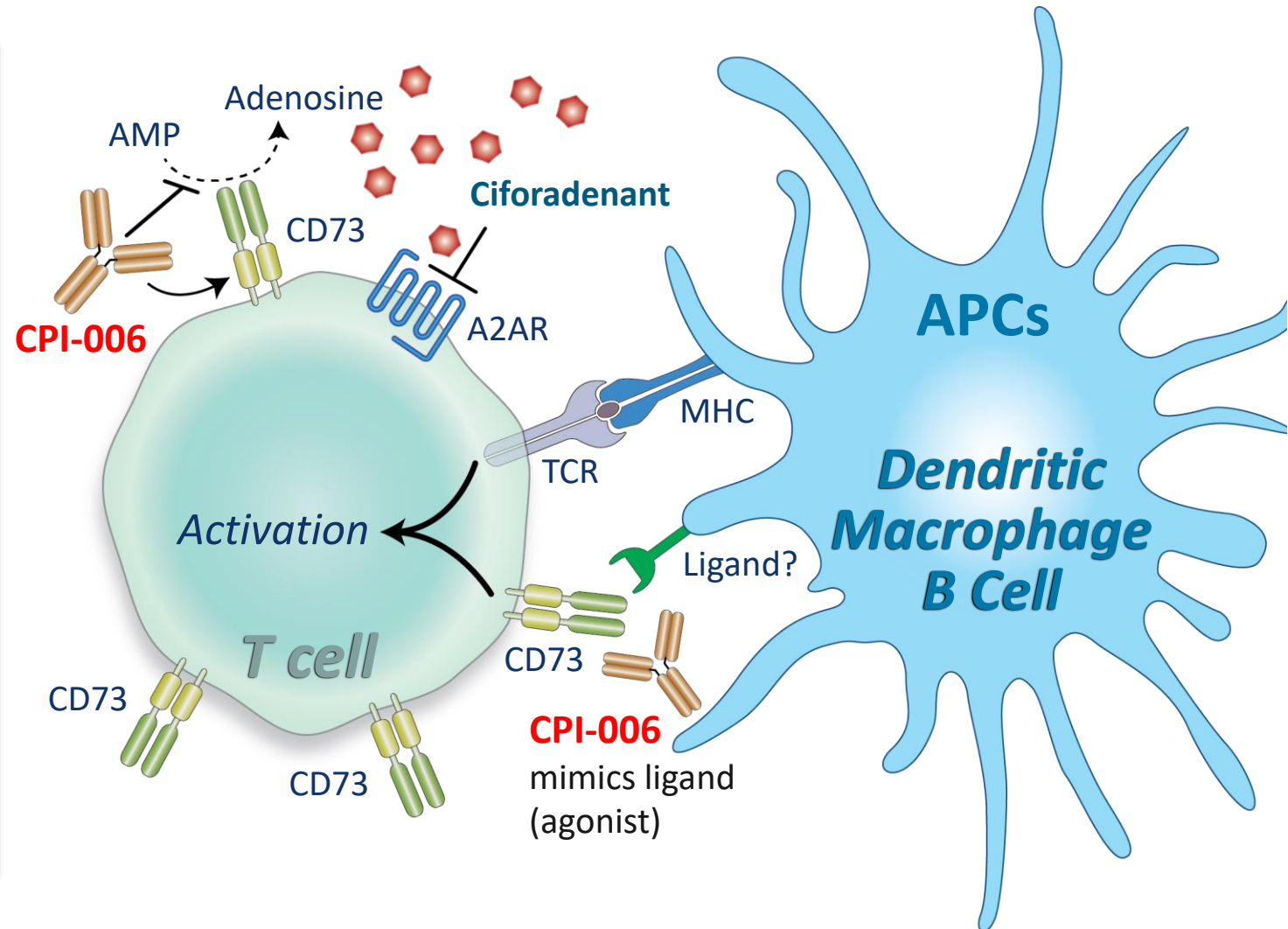
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# Background

- Adenosine in the tumor microenvironment is immunosuppressive
- CD73 is an ectoenzyme present on many tissues including subsets of T and B cells
  - Converts AMP to adenosine
  - Functions in lymphocyte adhesion, migration and activation\*
- CPI-006 is a humanized IgG1 Fcγ receptor deficient anti-CD73 with unique properties
  - Blocks catalytic activity
  - Has agonistic immunomodulatory activity on CD73 positive cells
- Ciforadenant (CPI-444) is an adenosine 2A receptor (A2AR) antagonist with anti-tumor activity in animals and in human clinical trials
  - Adenosine gene signature in tumor correlates with response

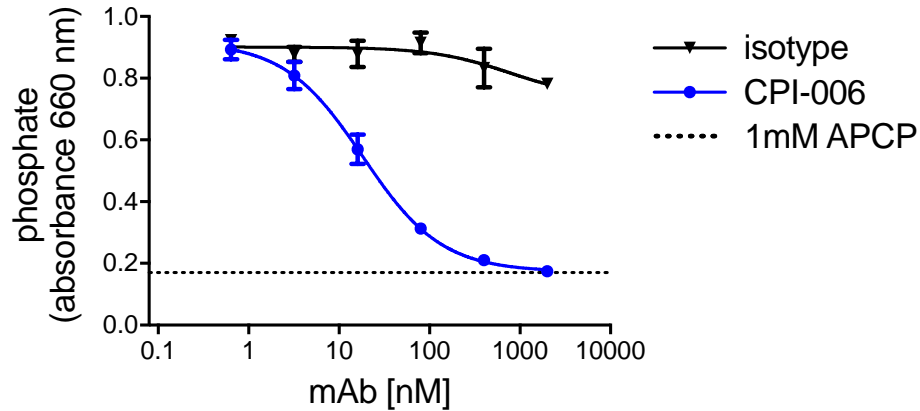
\*Resta & Thompson, Cell Signaling, 1997



# CPI-006 Blocks CD73 Enzymatic Activity

## CD73 Catalytic Activity

AMP → Adenosine + Phosphate



CD73 IHC

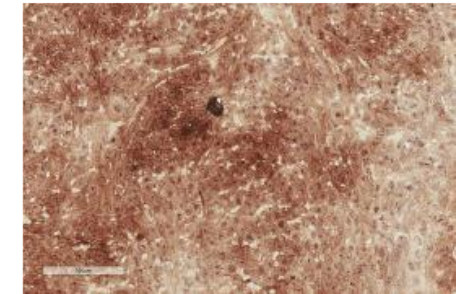
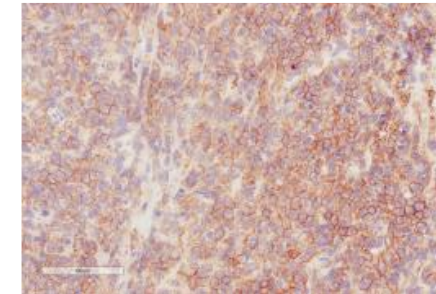
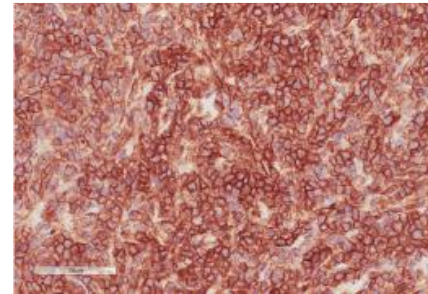
(Non-Competitive Anti-CD73)

CD73 IHC

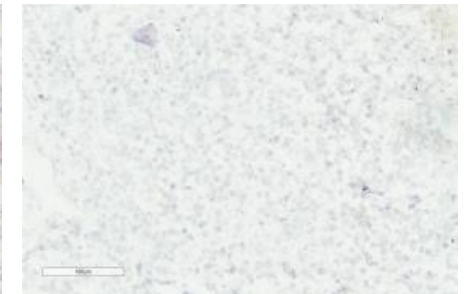
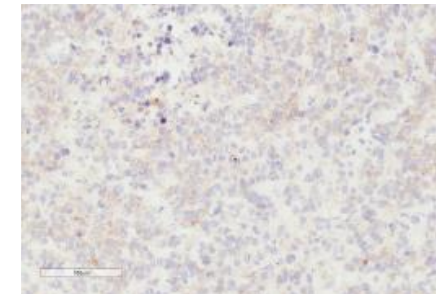
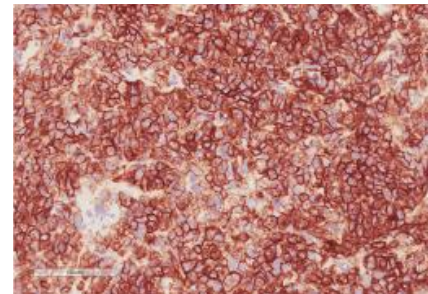
(Competitive Anti-CD73)

CD73 Enzyme activity\*

PBS  
Control  
Animal

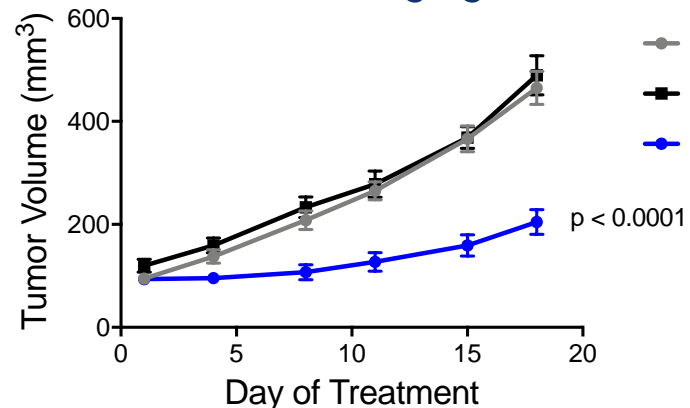


CPI-006  
Treated  
Animal



## MDA-MB-231 Xenograft

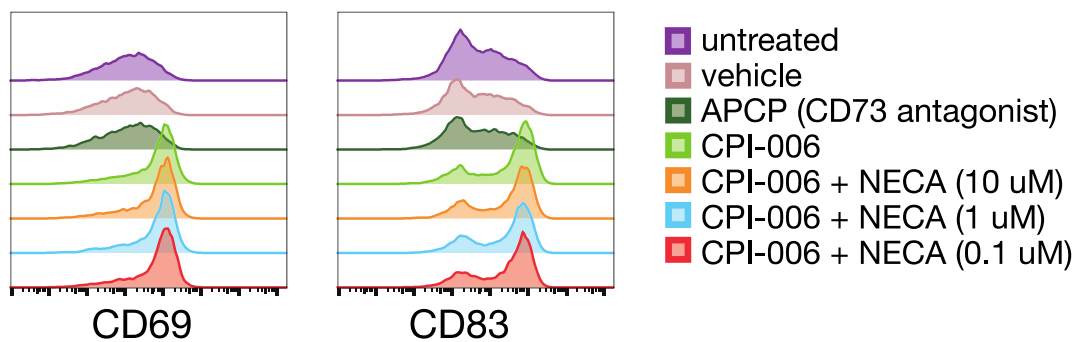
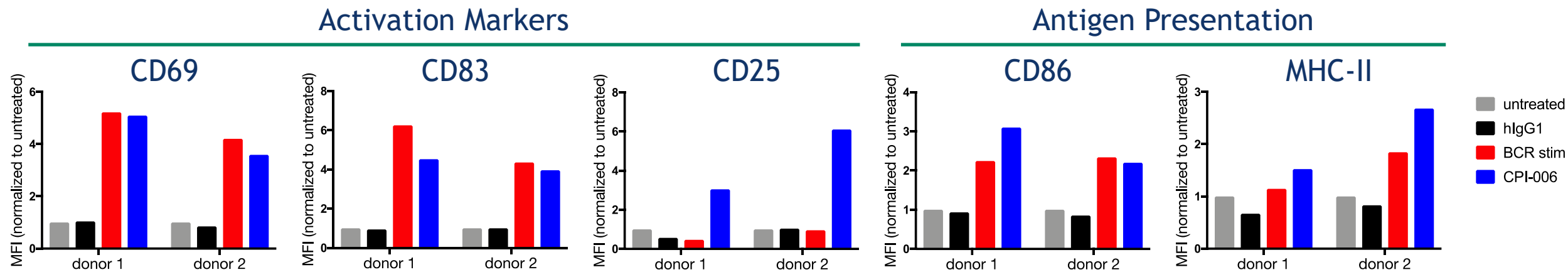
Dosed with 10 mg/kg CPI-006 daily



MDA-MB-231: Human TNBC Xenograft Model

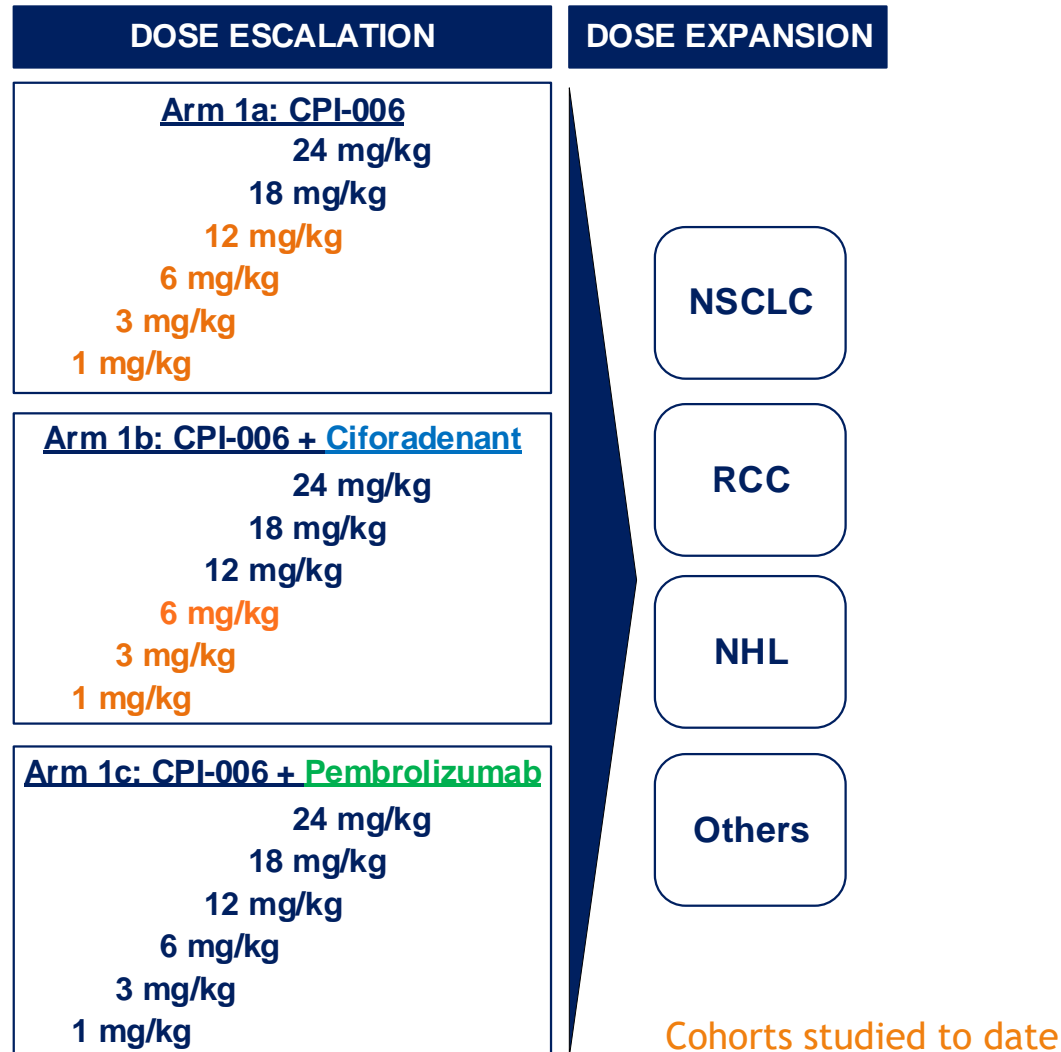
\*Method: Silber et al. J Clin Invest, 1975, 56(5): 1324-7.

# Immunomodulatory Activities of CPI-006 are Adenosine Independent



- Healthy donor PBMC treated overnight
- Flow cytometry analysis of surface markers on B cells (CD19<sup>POS</sup>CD3<sup>NEG</sup>)
- Lymphocyte markers are consistent with activation of B cells as well as other antigen presenting cell populations, e.g., APCs

# Clinical Trial Design



## Design

- Phase 1/1b open label, 3 + 3 dose escalation/dose expansion
- CPI-006 given as 1 hour IV infusion every 3 weeks; fixed dose of ciforadenant (100 mg po BID) for combo

## Eligibility

- Advanced cancers progressed on 1-5 prior therapies
- ECOG status 0 or 1
- CD73 expression: required in expansion, not in dose escalation
- Adenosine gene signature not used to select patients

## Objectives

- Primary: Safety and tolerability
- Secondary: PK/PD, efficacy, biomarkers

## Biomarker Assessments

- Effects on CD73 expression in tumors
- Peripheral blood lymphocyte subsets
- Antibody occupancy of target
- Serum cytokines



# Patient Characteristics

Baseline Demographics		
Description	CPI-006 (N=12)	CPI-006 + ciforadenant (N=8)
Age (yrs), median (range)	62 (46, 78)	64 (36, 86)
Gender, male n (%)	10 (83)	8 (100)
No. of prior therapies, median (range)	4 (1, 5)	4 (3, 7)
Histologies	N	N
Bladder Cancer	1	0
Colorectal Cancer	2	2
Head and Neck Cancer	2	1
Pancreatic Cancer	2	2
Prostate Cancer	3	1
Renal Cell Cancer	1	2
Sarcoma	1	0

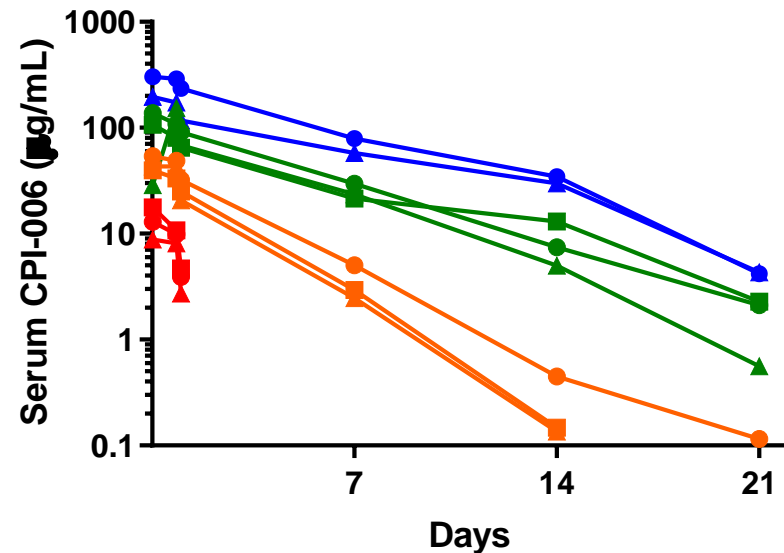
# Adverse Events

Adverse Events N(%)	CPI-006 Monotherapy (N=12)		CPI-006 + Ciforadenant (N=8)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Subjects with any TEAE	8 ( 66.7)	1 ( 8.3)	5 ( 62.5)	0 ( 0.0)
Anemia	1 ( 8.3)	1 ( 8.3)	1 ( 12.5)	0 ( 0.0)
Diarrhea	1 ( 8.3)	0 ( 0.0)	1 ( 12.5)	0 ( 0.0)
Nausea	3 ( 25.0)	0 ( 0.0)	2 ( 25.0)	0 ( 0.0)
Chills	4 ( 33.3)	0 ( 0.0)	1 ( 12.5)	0 ( 0.0)
Fatigue	2 ( 16.7)	0 ( 0.0)	2 ( 25.0)	0 ( 0.0)
Infusion related reaction	2 ( 16.7)	0 ( 0.0)	1 ( 12.5)	0 ( 0.0)
Headache	2 ( 16.7)	0 ( 0.0)	1 ( 12.5)	0 ( 0.0)
Pruritus	2 ( 16.7)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

- Treatment related adverse events: Any grade 3 or 4 events, or 2 or more all grades

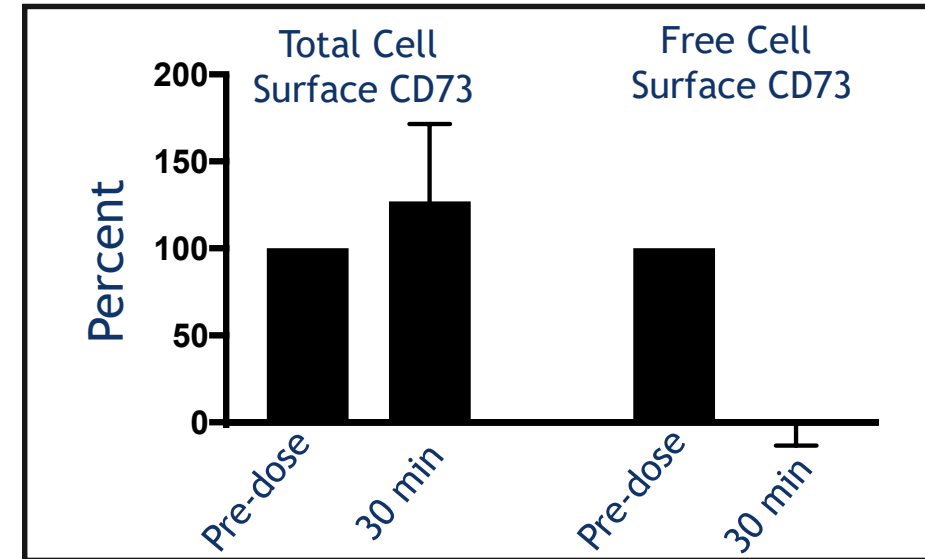
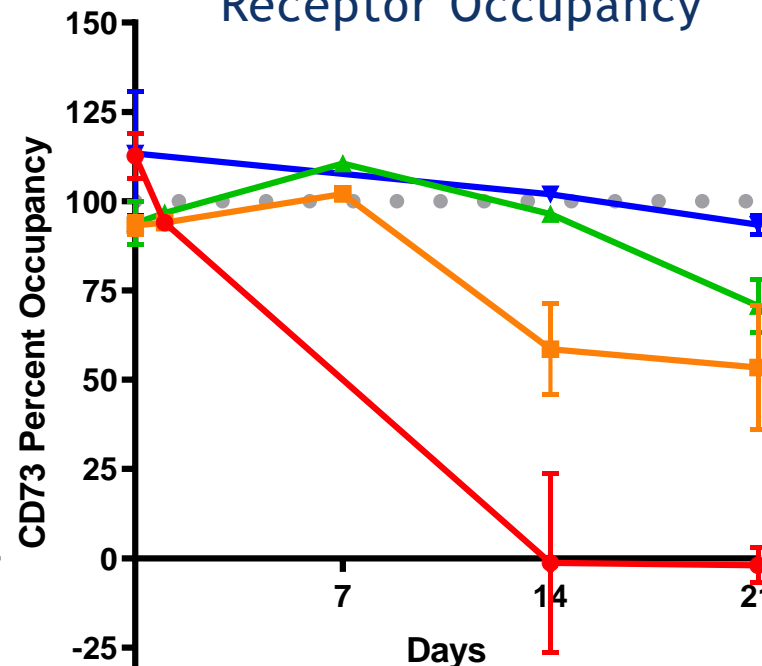
# Pharmacokinetics and Receptor Occupancy

## Serum Pharmacokinetics



— 1mg/kg — 3mg/kg — 6mg/kg — 12mg/kg

## Peripheral CD8 Receptor Occupancy



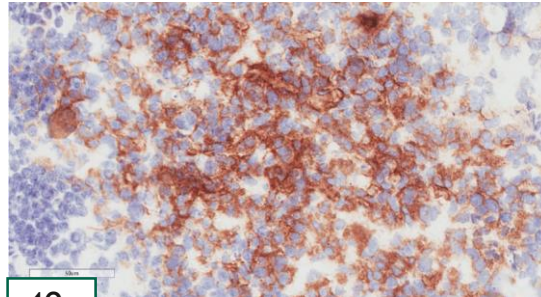
- Exposure increases and clearance decreases with increasing dose
- CPI-006 detectable for 21 days after a single dose of 6 mg/kg or higher
- Total cell surface CD73 unchanged; CPI-006 epitope blocked



# Occupancy and Inhibition of CD73 in the Tumor

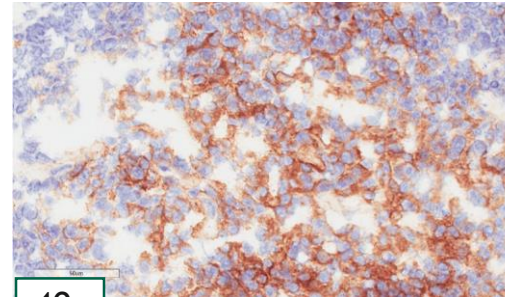
Positive  
Control  
(Tonsil)

Non-Competitive Anti-CD73



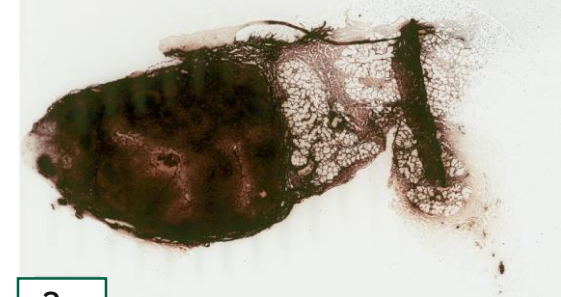
40x

Competitive Anti-CD73



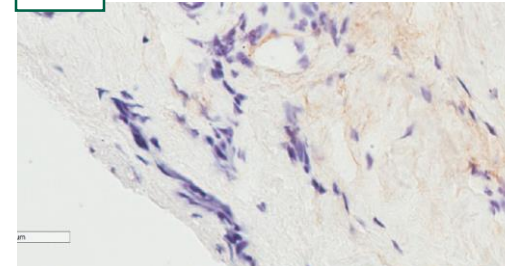
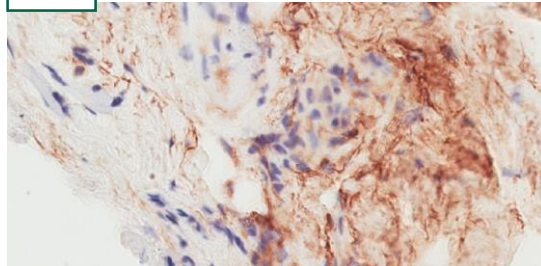
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CD73 Enzyme Activity



2x

On-Treatment  
Bx

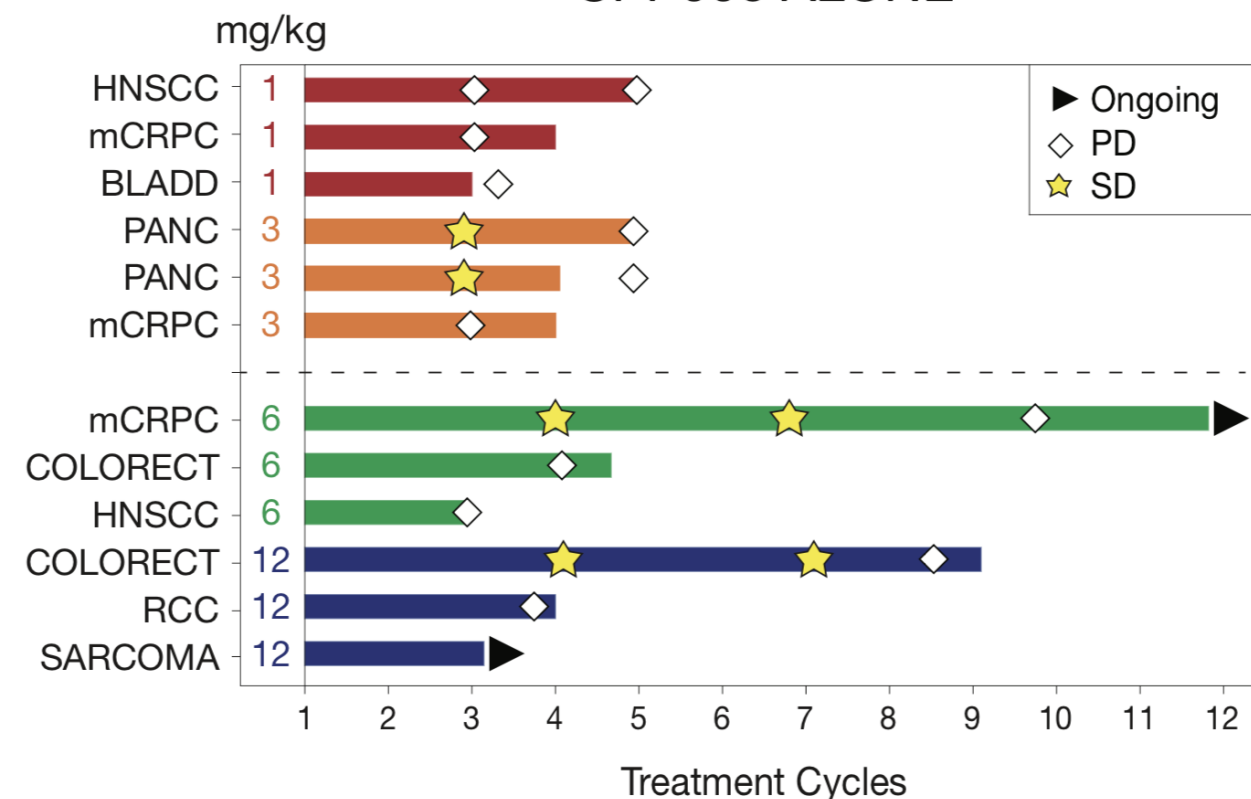


- Colorectal patient treated with 12 mg/kg CPI-006
- Tumor biopsy of retroperitoneal lesion obtained at trough pre-dose 3

- Tumor biopsy demonstrates presence of CD73 which is occupied by CPI-006
- CPI-006 saturates CD73 and inhibits enzymatic activity

# Disease Assessment

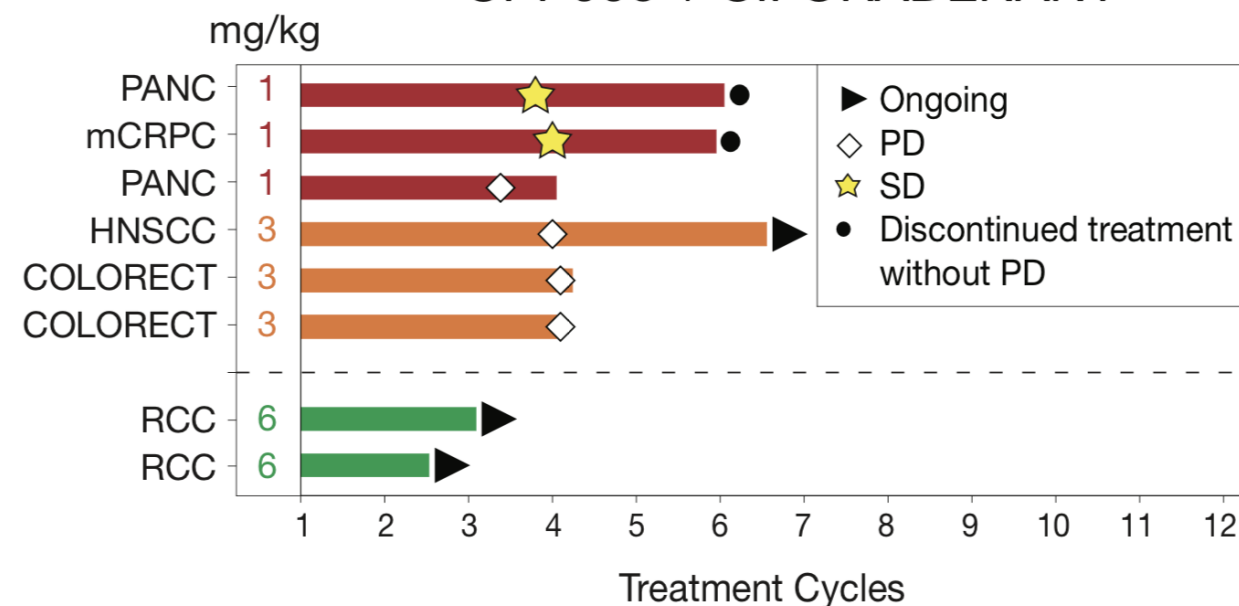
## CPI-006 ALONE



Cycle = 21 days

Disease assessment every 3-4 cycles

## CPI-006 + CIFORADENANT

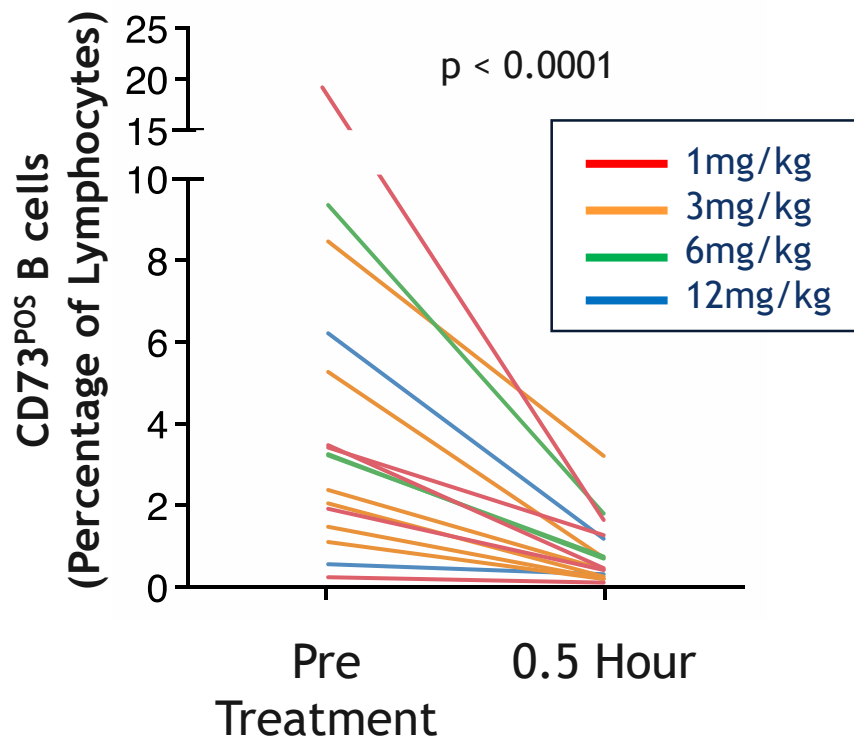


--- Sustained CD73 occupancy in peripheral blood

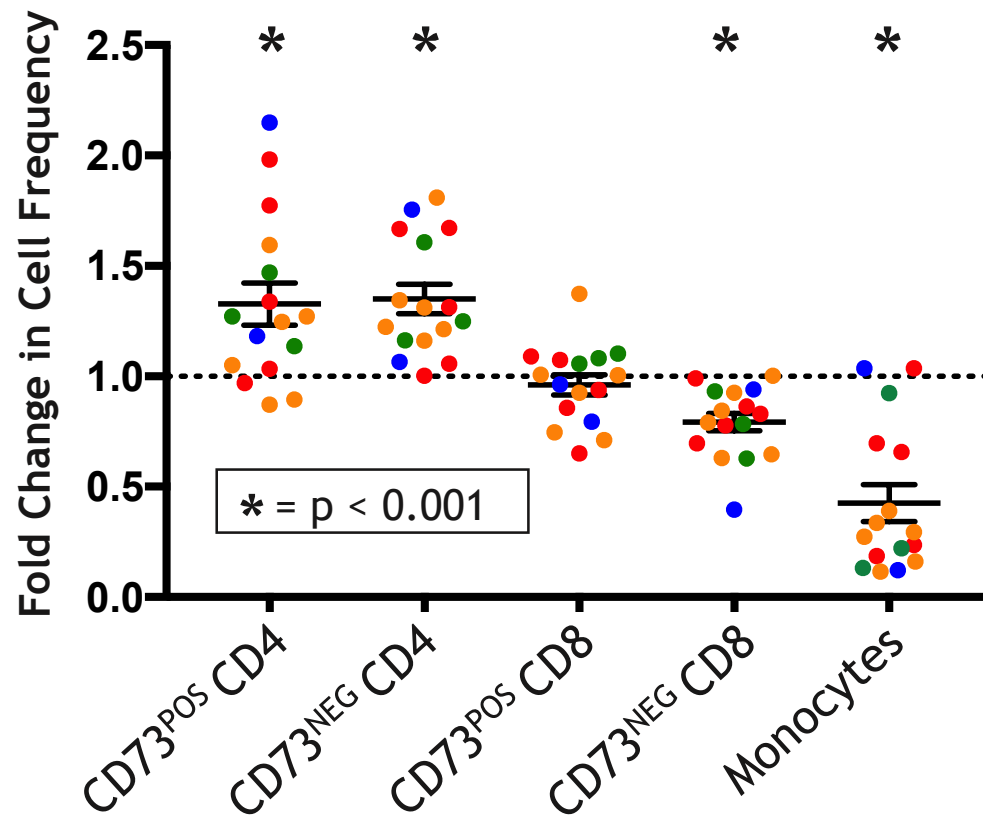
- Higher doses appear to be providing longer term disease control with monotherapy
- Combination appears to improve disease control

# Treatment Induces Rapid Changes in PBMCs

CD73<sup>POS</sup> B cells



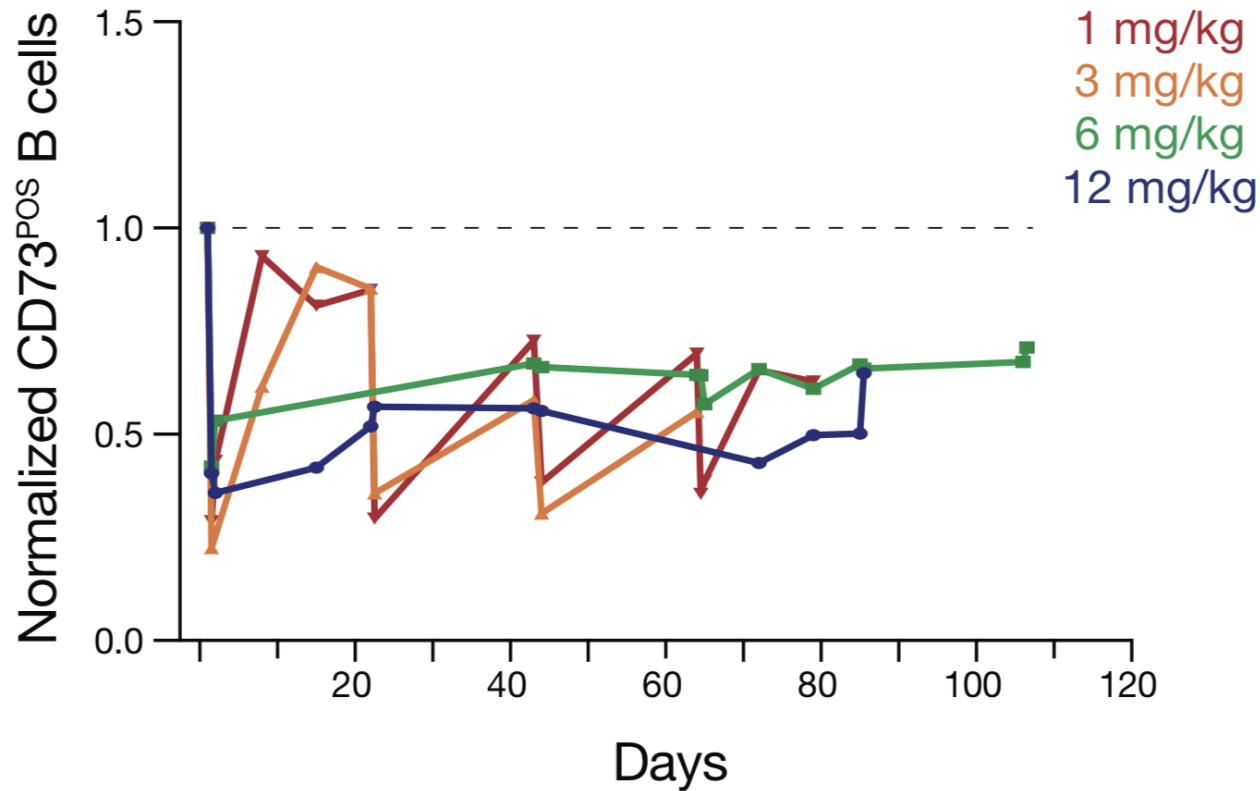
Changes in PBMCs at 0.5 Hour



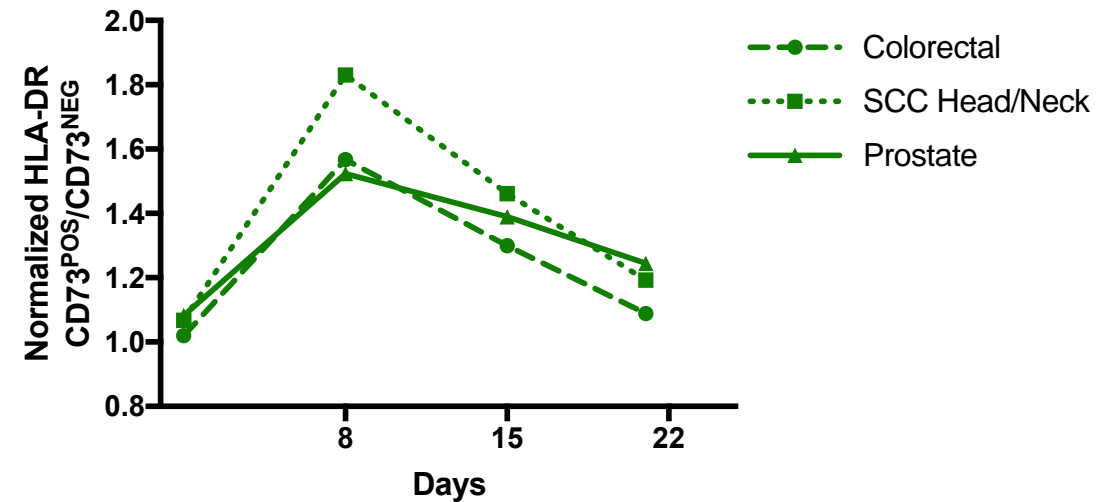
- Consistent with
  - Trafficking of CD73<sup>POS</sup> B cells out of the blood
  - Redistribution of T cells & monocytes (CD73<sup>NEG</sup>)
- Increase in CD4/CD8 ratios – including CD73<sup>NEG</sup> subsets

# Changes in Blood B Cells Over Time

Changes in CD73<sup>POS</sup> B cells



Changes in HLA-DR Expression  
6 mg/kg Monotherapy cohort

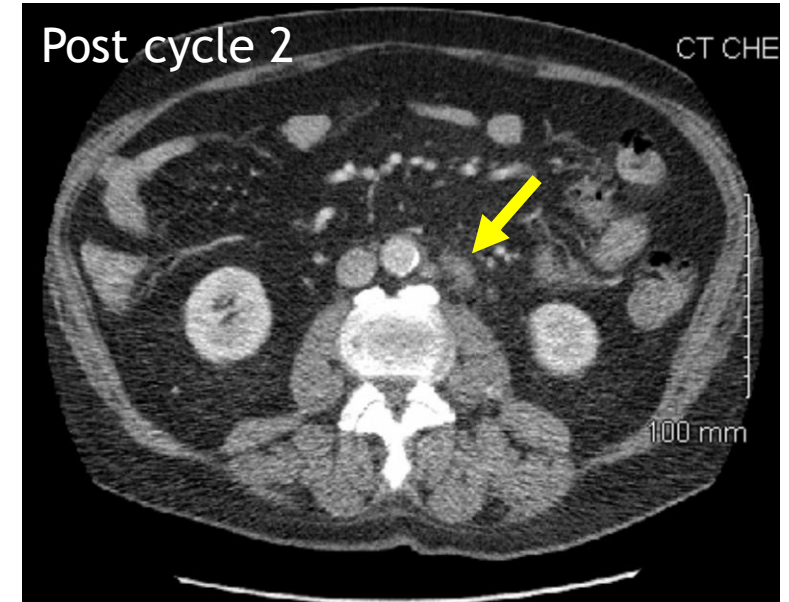
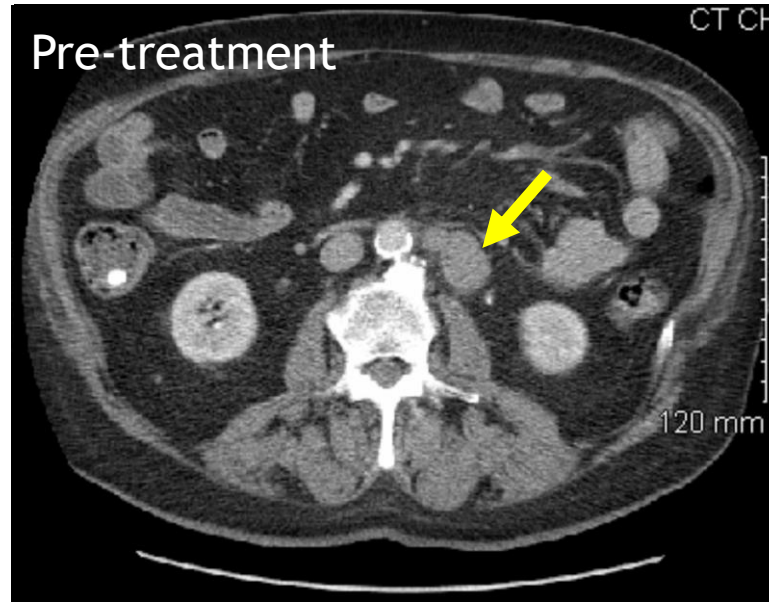
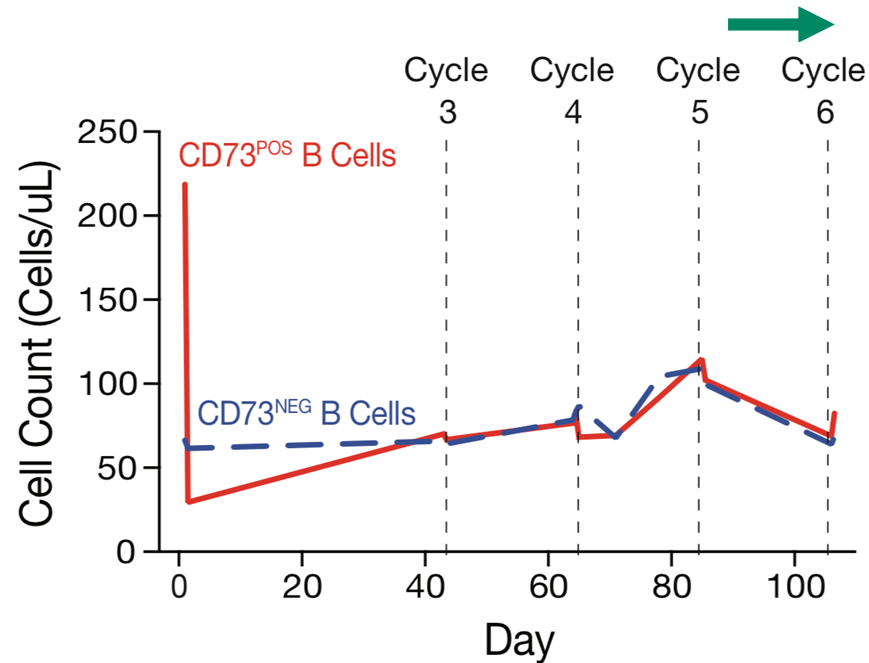


- CD73<sup>POS</sup> B cells drop with each infusion and partially return reaching new steady state
- Consistent with redistribution of B cells to lymphoid tissue
- Increased expression of HLA-DR



# Changes in CD73<sup>POS</sup> B Cells & Tumor Reduction in a Prostate Cancer Patient

Changes in Circulating B Cells

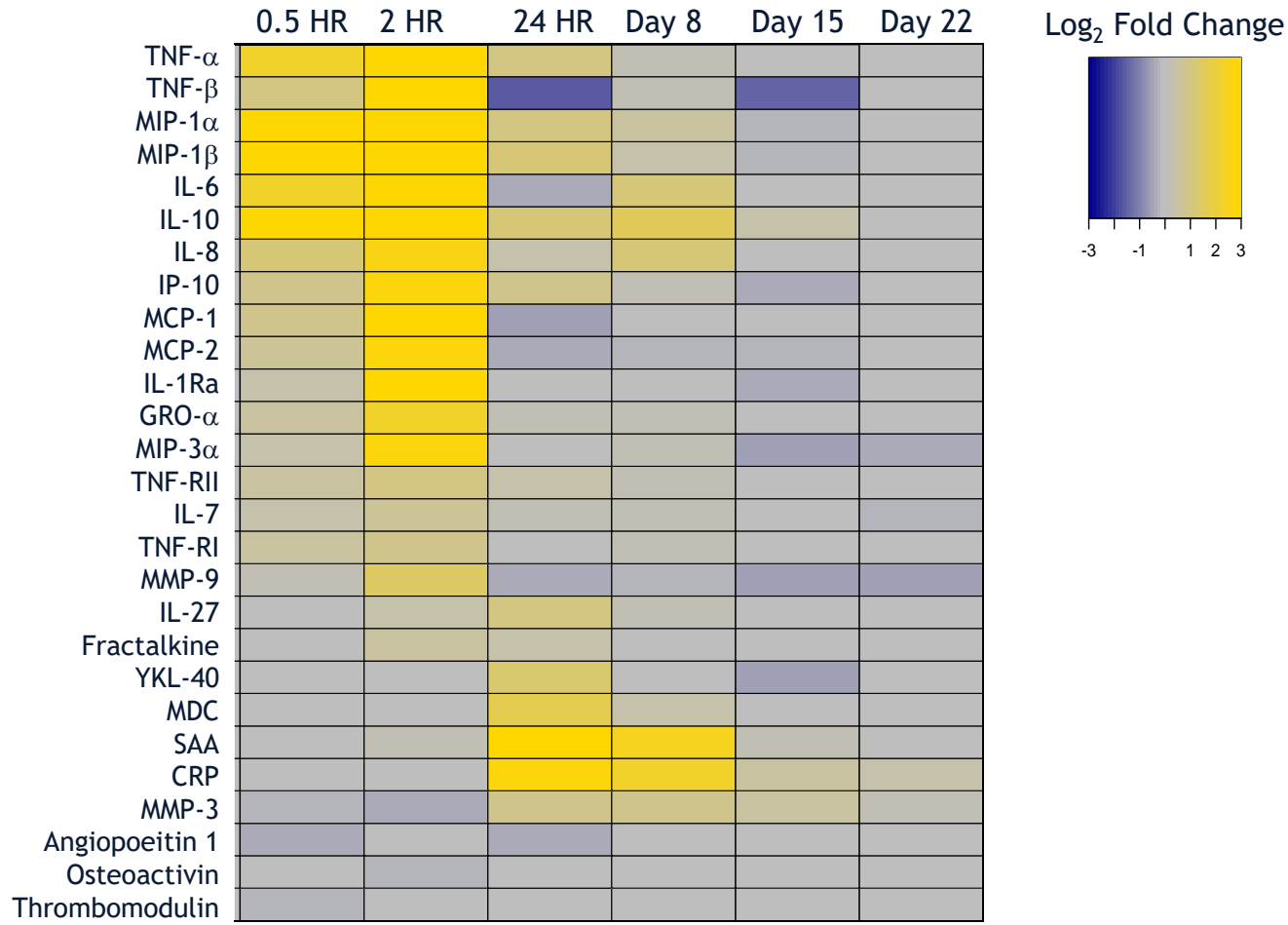


- 72 year old man with widely metastatic prostate cancer; previous therapies include leuprolide/bicalutamide, abiraterone, enzalutamide and docetaxel

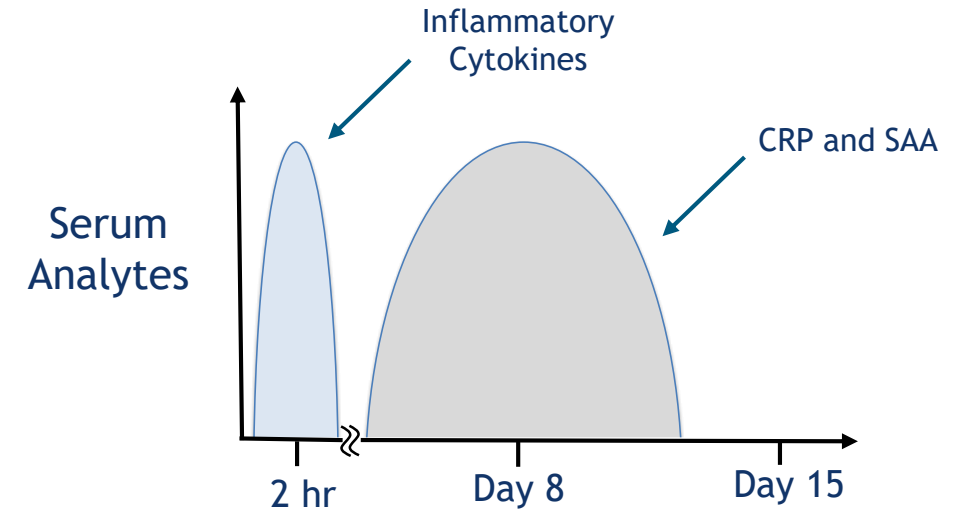
- Decrease in target lesion in patient receiving 6 mg/kg monotherapy, treatment ongoing through 11 cycles

# Treatment Induces Cytokines Consistent with Immune Activation

## Fold change in Serum Analytes N=3, 6mg/kg Cohort



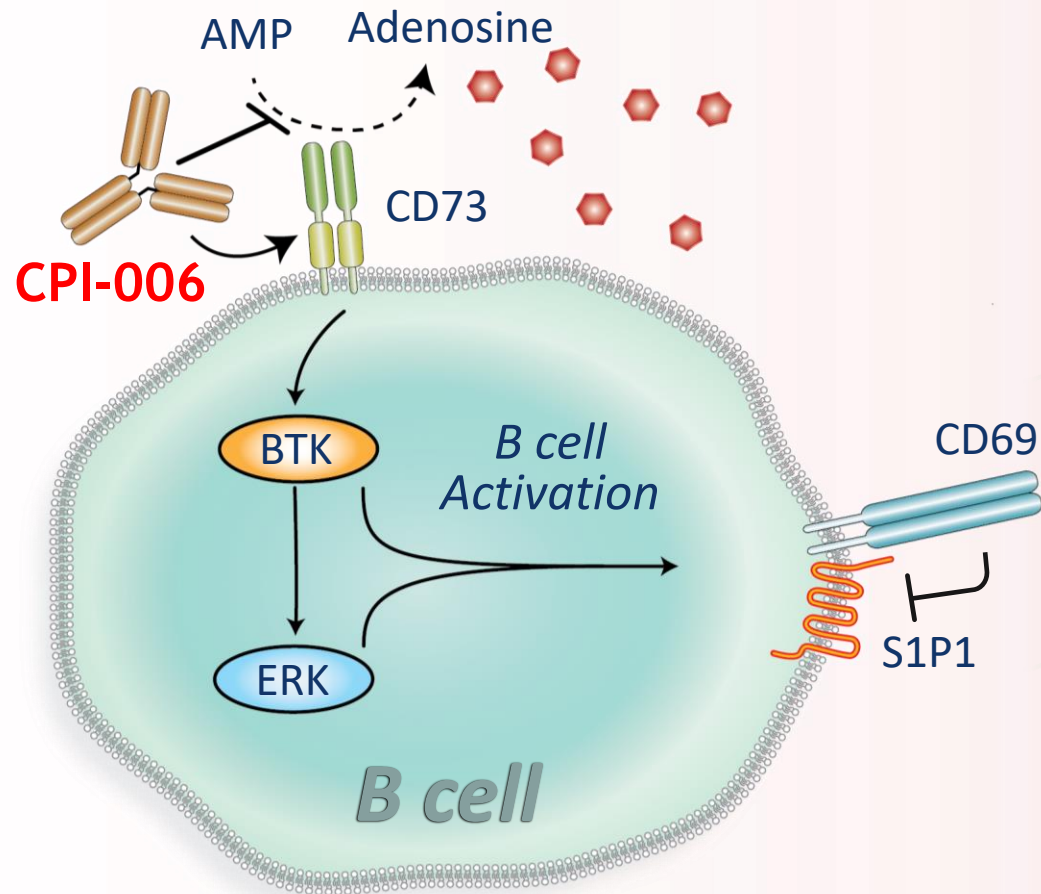
- Rapid induction of inflammatory cytokines
- Subsequent induction of C-reactive protein and serum amyloid A
- These findings are consistent with early inflammatory response





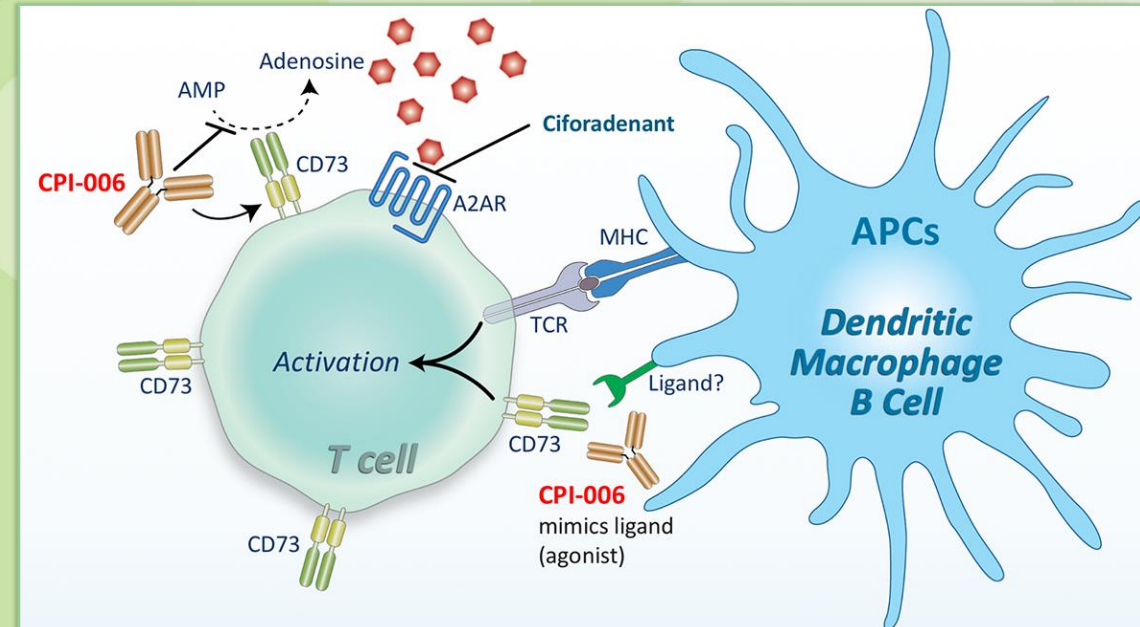
# Proposed Model for CPI-006 Immunomodulatory Activity

**Blood**



**Lymphoid tissue**

- Migration to and retention in lymph nodes.
- Increased antigen presentation.



# Conclusions

- CPI-006 has novel immunomodulatory activity with dual mechanisms of action:
  - Affects B cell trafficking and increases expression of CD69 and other markers consistent with increased antigen presentation by APCs
  - Complete inhibition of CD73 enzyme activity without internalization
- CPI-006 is safe as monotherapy at least to doses of 12 mg/kg and in combination with ciforadenant to 6 mg/kg. No DLTs reported and MTD not reached.
- Doses of 12 mg/kg achieve:
  - Sustained occupancy of PBL
  - Target saturation and complete inhibition of enzyme activity in tumor biopsies
- Treatment with CPI-006 induces serum cytokines that mediate inflammatory response
- Preliminary data suggest increasing disease control with higher doses and enhancement with combination therapy
- Enrollment in this study continues with both monotherapy and combination in dose escalation

# Acknowledgements

- **The patients and their families**
- **Participating Centers:** *Carolina BioOncology Institute, University of Chicago, Medical College of Wisconsin, Roswell Park Cancer Institute, Yale University, Mount Sinai, Icahn School of Medicine, Dana Farber Cancer Institute, Mary Crowley Cancer Center, University of Miami, City of Hope, Sarah Cannon Research Institute, University of Oklahoma, Monash Health*
- **Colleagues at Corvus**