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Immunobiology and Clinical Activity of CPI-006, an Anti-CD73 Antibody with Immunomodulating Properties in a Phase 1/1b Trial in Advanced Cancers

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Disclosures

Jason J. Luke: University of Pittsburgh Medical Center, Pittsburgh

The following relationships exist related to this presentation:

- **Data and Safety Monitoring Board:** TTC Oncology
- **Scientific Advisory Board:** 7 Hills, Actym, Alphamab Oncology, Mavu, Pyxis, Springbank, Tempest
- **Consultancy**: Abbvie, Akrevia, Array, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Compugen, EMD Serono, Ideaya, Immunocore, Incyte, Janssen, Leap, Merck, Mersana, Novartis, RefleXion, Silicon, Vividion
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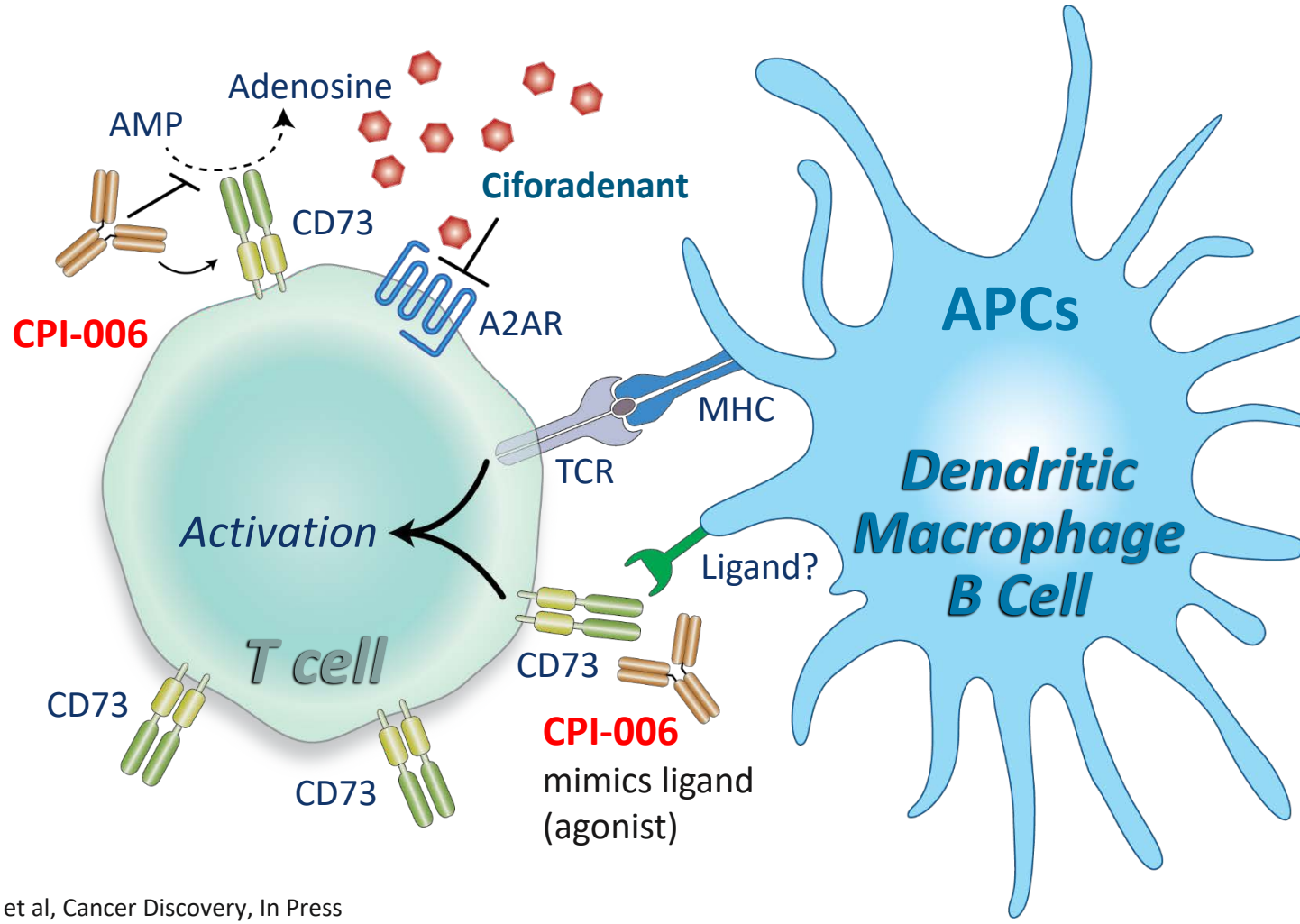
- **Patents**: (both provisional) Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)

Corvus Pharmaceutical Inc. is the sponsor of this study.

Background

CPI-006 is an Anti-CD73 with Adenosine Independent Immunomodulatory Properties

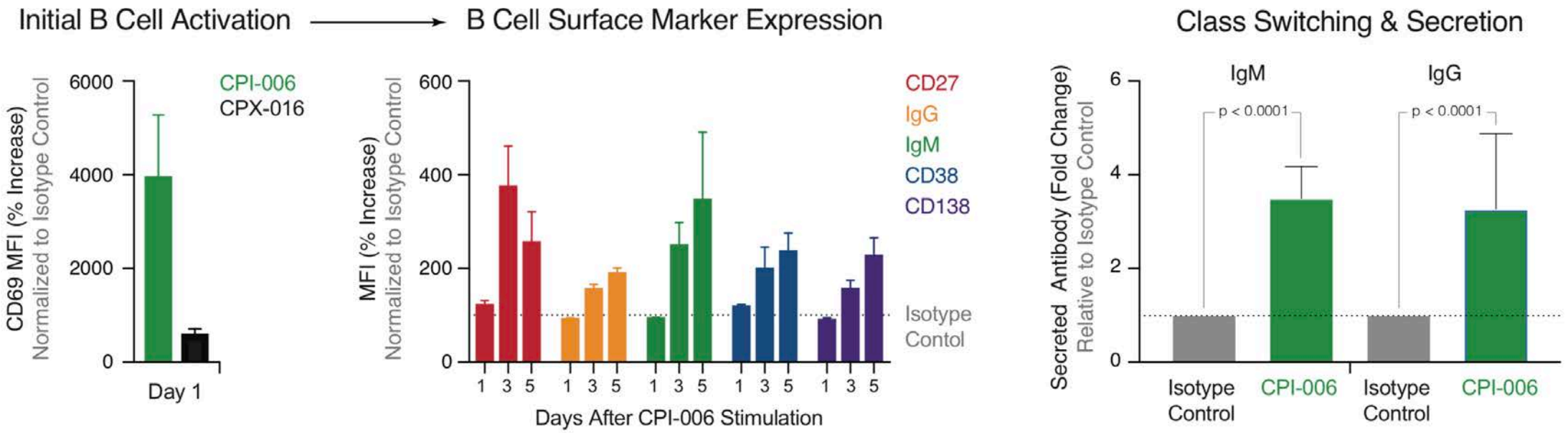
- CD73 is an ectoenzyme present on many tissues including subsets of T and B cells
  - Converts AMP to adenosine
  - Functions in lymphocyte adhesion, migration and activation[1]
- CPI-006 is a humanized IgG1 Fcγ receptor deficient anti-CD73 with unique properties[2]
  - Blocks catalytic activity
  - Has agonistic immunomodulatory activity on CD73 positive cells that are **adenosine independent**
  - Increases expression of CD69, HLA-DR, etc. on APC
- Early results from Ph1 dose escalation trial demonstrate lymphocyte activation and effects on trafficking[2]
- Ciforadenant (CPI-444) is an adenosine 2A receptor (A2AR) antagonist with reported anti-tumor activity in mCRPC, RCC and NSCLC[3]
  - Adenosine gene signature in tumor correlates with response in RCC

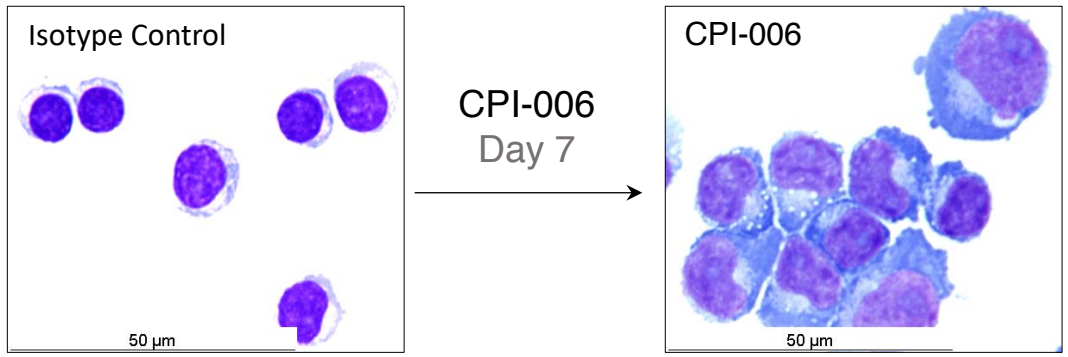


[1]Resta & Thompson, Cell Signaling, 1997 [2]Luke, ASCO Annual Meeting, 2019 [3]Fong et al, Cancer Discovery, In Press

CPI-006 is an Anti-CD73 with Unique Properties

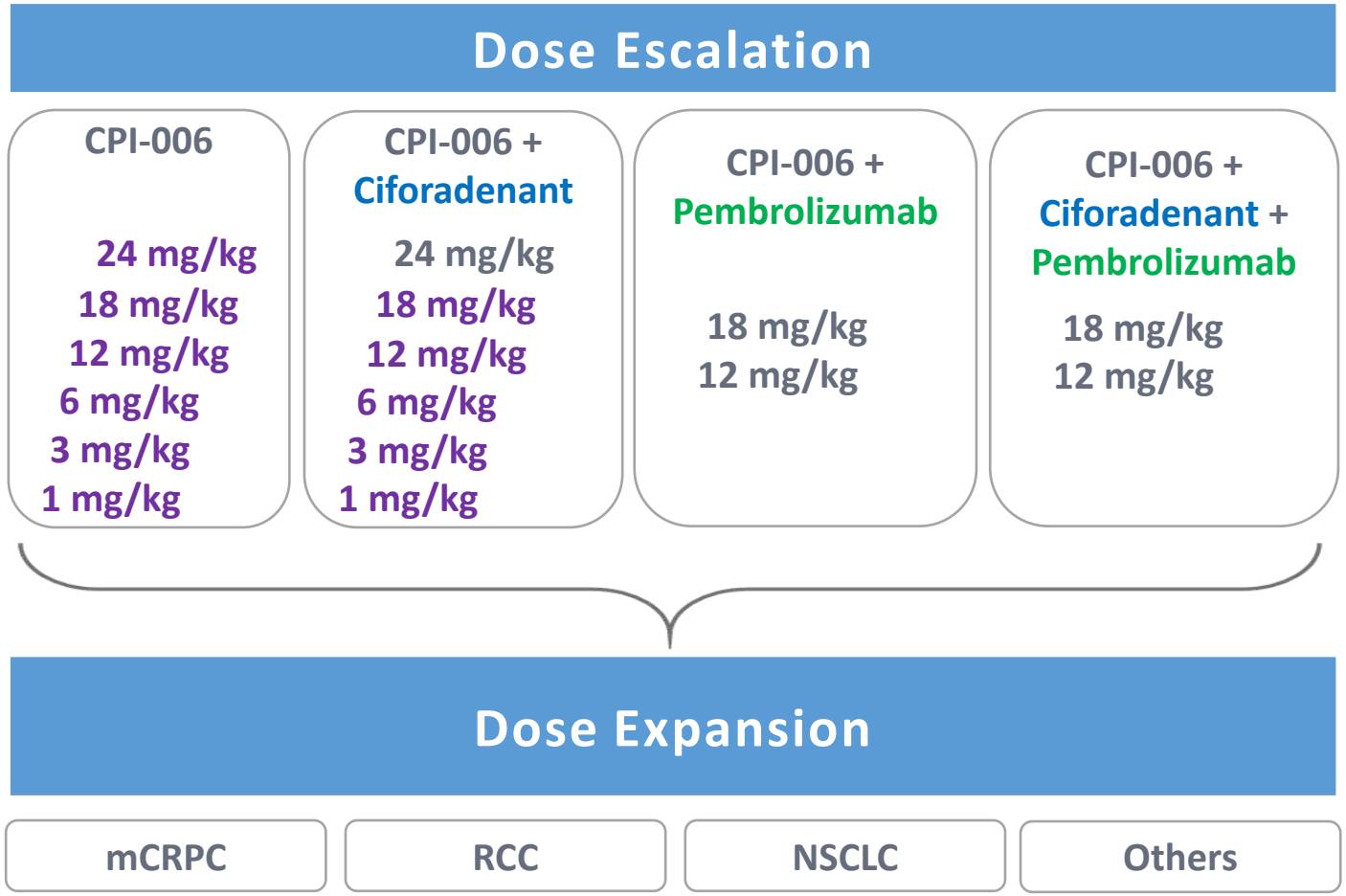
CPI-006 induces B cell differentiation: isotype switching and immunoglobulin secretion in vitro





- CPI-006 activates B cells, resulting in morphological and surface marker changes consistent with B cell differentiation and isotype class switching
- Comparison to adenosine blocking anti-CD73 antibody (CPX-016) demonstrates unique CPI-006 property

CPI-006-001 Clinical Trial Design



Design
- Phase 1/1b dose escalation/dose expansion in disease specific cohorts
- CPI-006 every 3 weeks; fixed dose of ciforadenant

Eligibility
- Cancers progressed on 1-5 prior therapies
- 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
- Tumor markers, cytokines, etc.

Doses explored to date & planned doses

See Poster P434, Saturday Nov 9th

Patient Characteristics

Total Patients N=40	CPI-006 (N = 24)	CPI-006 + Ciforadenant (N=16)
Age (yrs), median (range)	62 (46, 78)	67 (36, 86)
Gender, male N (%)	18 (75)	12 (75)
No. of prior therapies, median (range)	4 (1, 6)	4 (2, 7)
Histologies	**N**	**N**
Renal Cell Cancer	2	4
Non-small cell lung cancer	2	1
Prostate Cancer	5	1
Colorectal Cancer	7	5
Head and Neck Cancer	3	2
Pancreatic Cancer	3	3
Sarcoma	1	0
Bladder Cancer	1	0

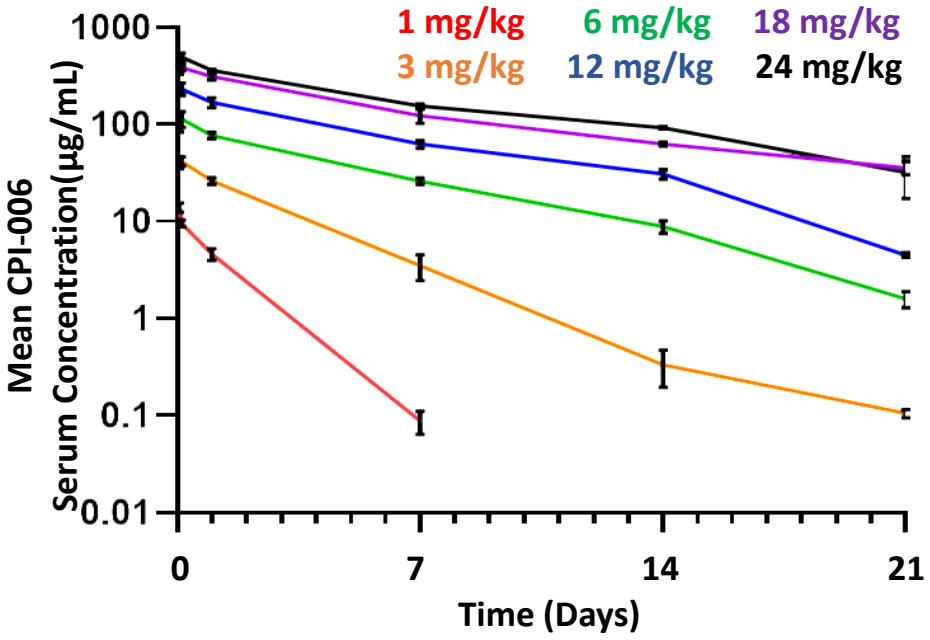
Adverse Events

Adverse Events N (%)	CPI-006 Monotherapy (N=24)		CPI-006 + Ciforadenant (N= 16)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Patients with any TEAE	18 (75.0)	4 (16.7)	12 (75.0)	2 (12.5)
Anemia	1 (4.2)	1 (4.2)	2 (12.5)	1 (6.3)
Lymphopenia	2 (8.3)	1 (4.2)	0 (0.0)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)
Diarrhea	1 (4.2)	0 (0.0)	3 (18.8)	1 (6.3)
Nausea	4 (16.7)	0 (0.0)	2 (12.5)	0 (0.0)
Vomiting	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Chills	11 (45.8)	0 (0.0)	3 (18.8)	0 (0.0)
Fatigue	3 (12.5)	0 (0.0)	3 (18.8)	0 (0.0)
Pyrexia	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion related reaction	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Liver enzymes increased (AST & ALP)	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)
WBC decreased	1 (4.2)	0 (0.0)	3 (18.8)	0 (0.0)
Decreased appetite	1 (4.2)	0 (0.0)	1 (6.3)	0 (0.0)
Hyponatremia	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)
Tumor pain	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	2 (8.3)	0 (0.0)	1 (6.3)	0 (0.0)
Pruritus	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (4.2)	0 (0.0)	2 (12.5)	0 (0.0)

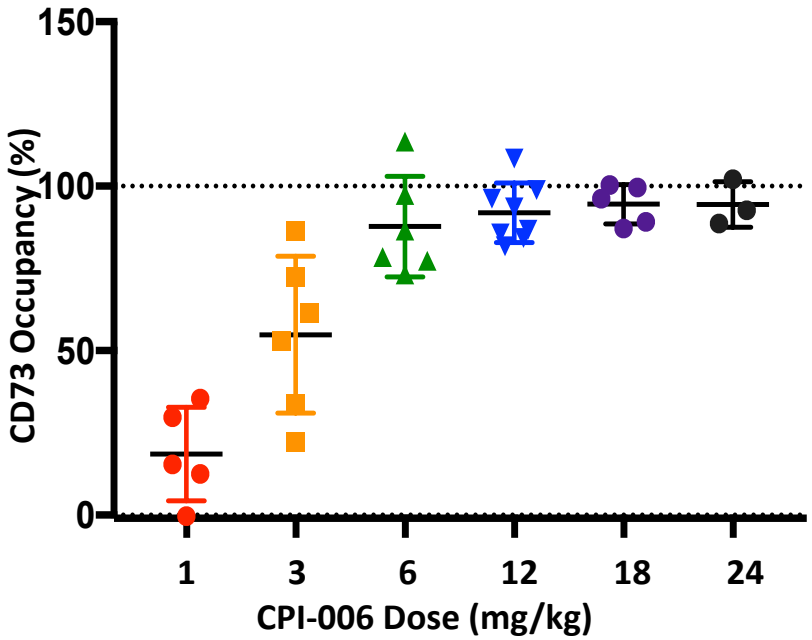
Treatment related adverse events: Any grade 3 or 4 events, or 2 or more all grades

Pharmacokinetics and Receptor Occupancy

Serum Pharmacokinetics



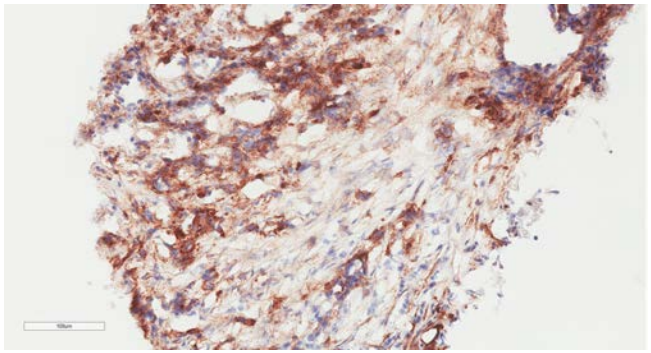
Target Occupancy on Peripheral B Cells



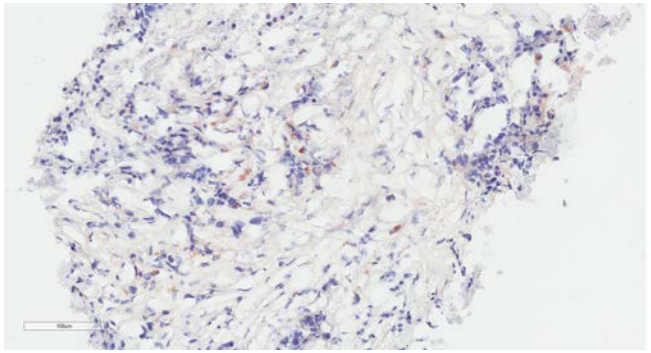
Tissue Occupancy

(18 mg/kg CPI-006)

CD73 with non-cross blocking antibody (total CD73)

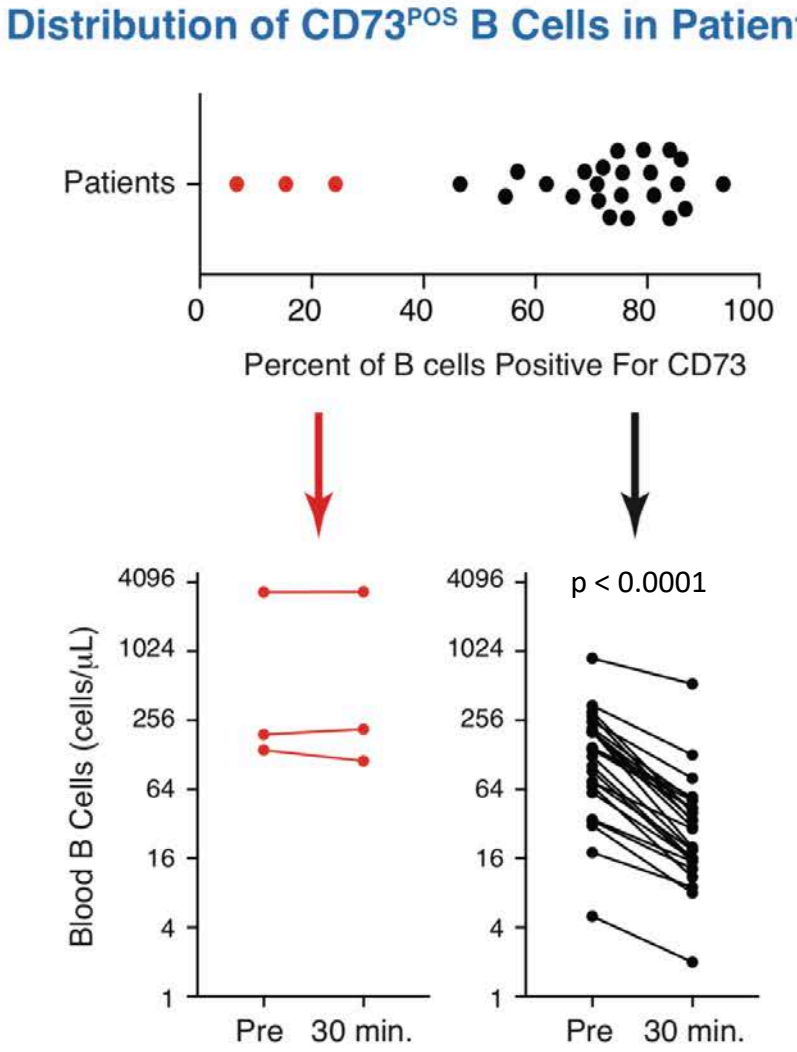


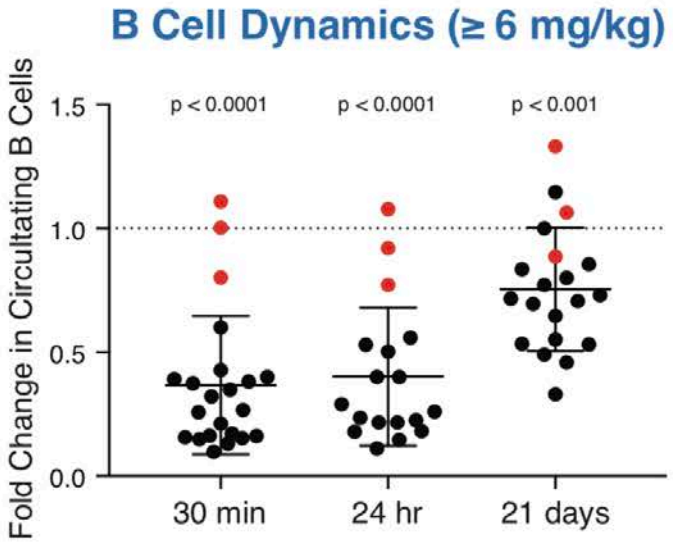
CD73 with CPI-006 demonstrates sites occupied

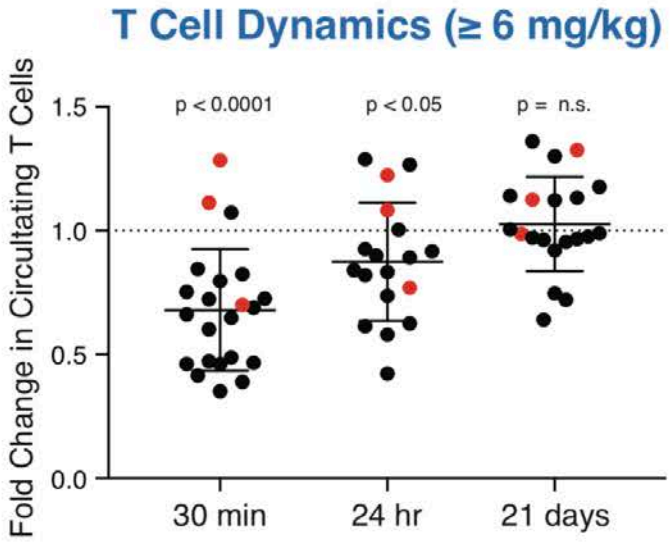


- Sustained CD73 occupancy of peripheral blood at ≥ 6 mg/kg
- Full tumor occupancy observed at ≥ 18 mg/kg

Treatment Induces Rapid Changes in Blood B and T Cells



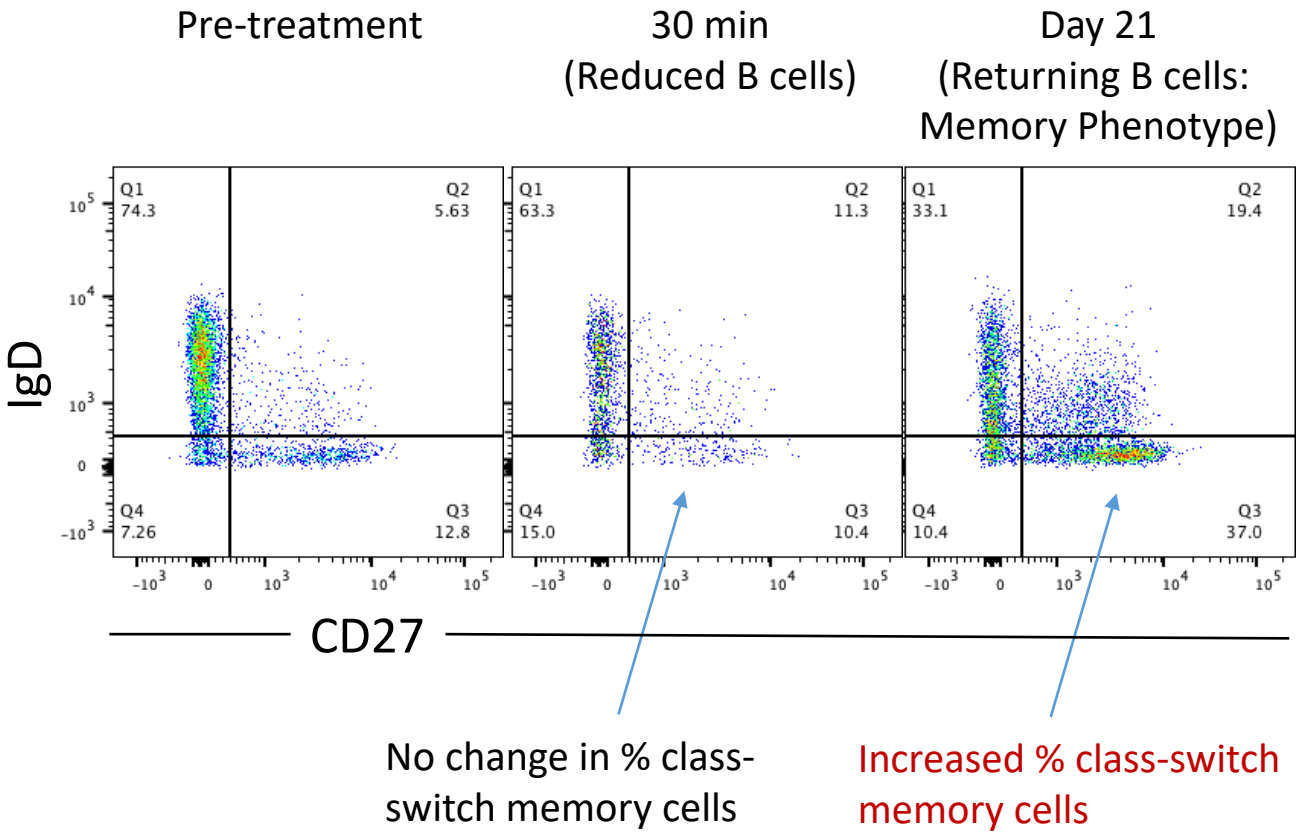




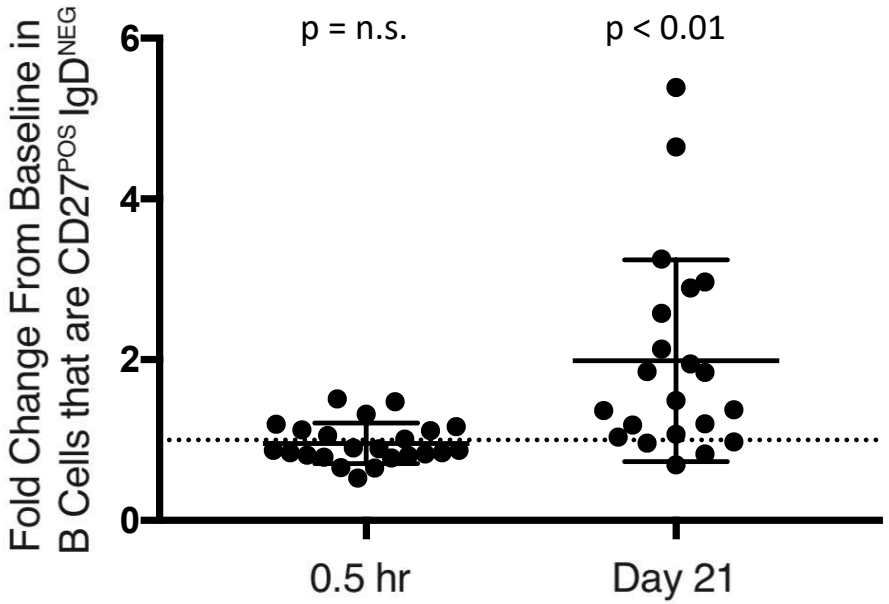
- Changes in B cells (but not T cells) appear to be CD73 expression dependent
- B cell numbers partially return by 21 days; T cells fully return

Increase in Memory B Cells in Returning Lymphocytes

Peripheral Blood Gated on CD19+ and CD20+ B Cells



Increased Memory B Cells at Day 21

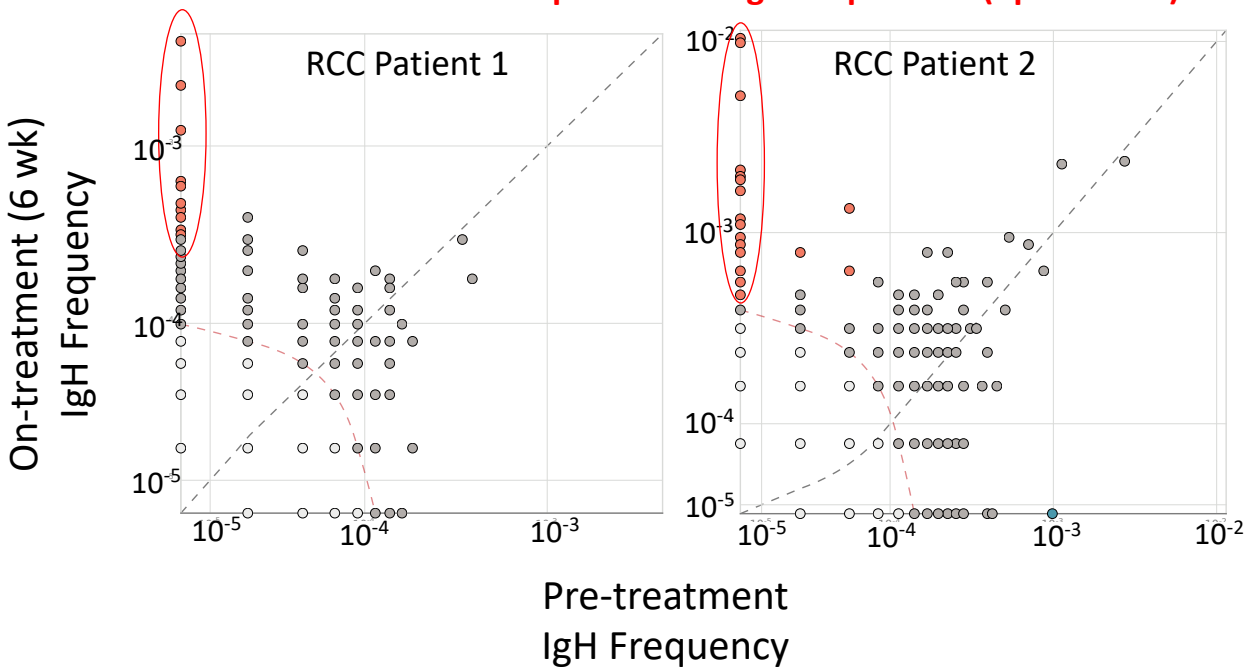


- At 0.5 hours no change in proportion of naïve and memory B cells; returning cells have a greater proportion of memory B cells
- These findings are consistent with a humoral adaptive response

Significant Expansion of New B and T cell Clones

Differential Abundance Plots of B cell Clonal Expansion

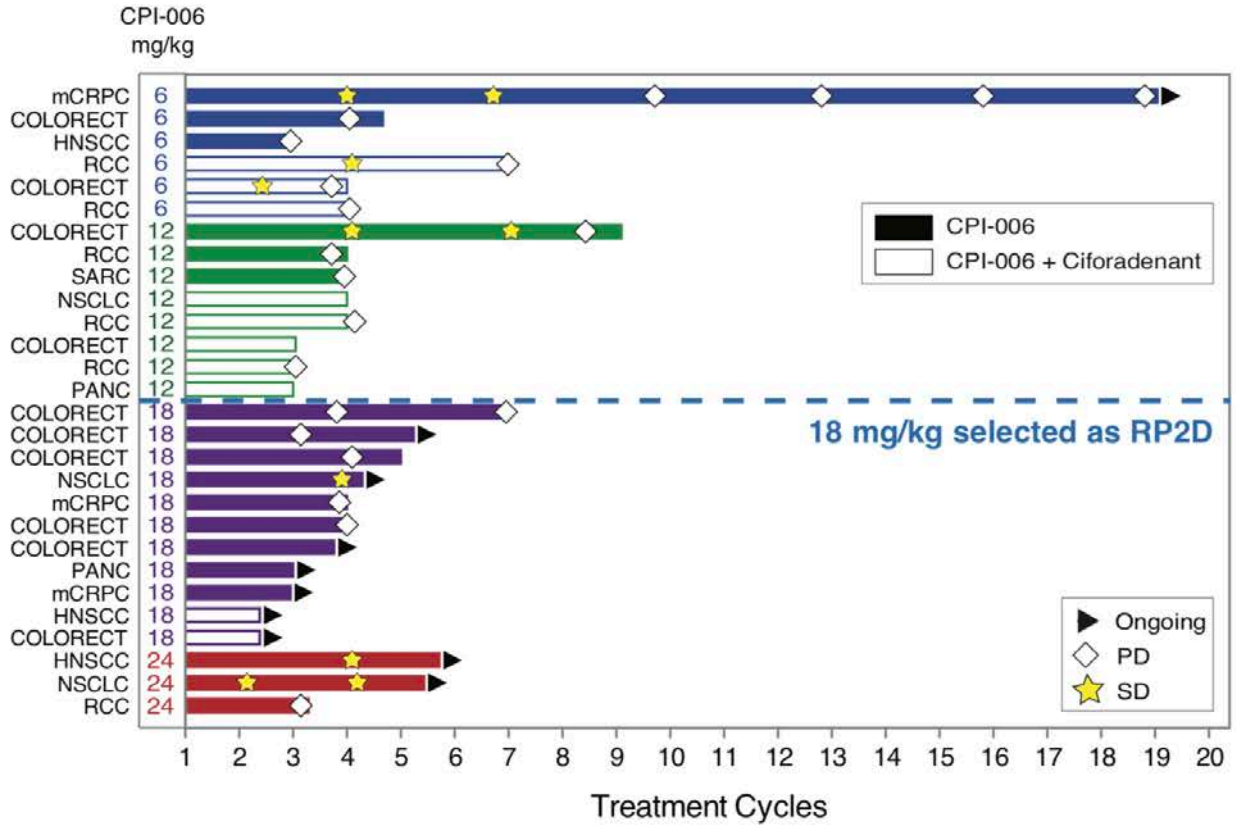
New B cell clones on treatment present at high frequencies (up to 1:100)

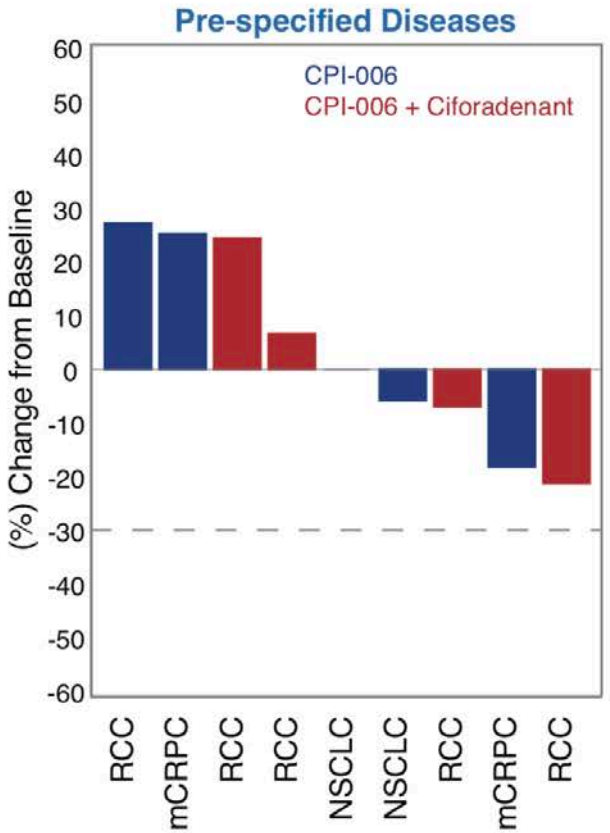


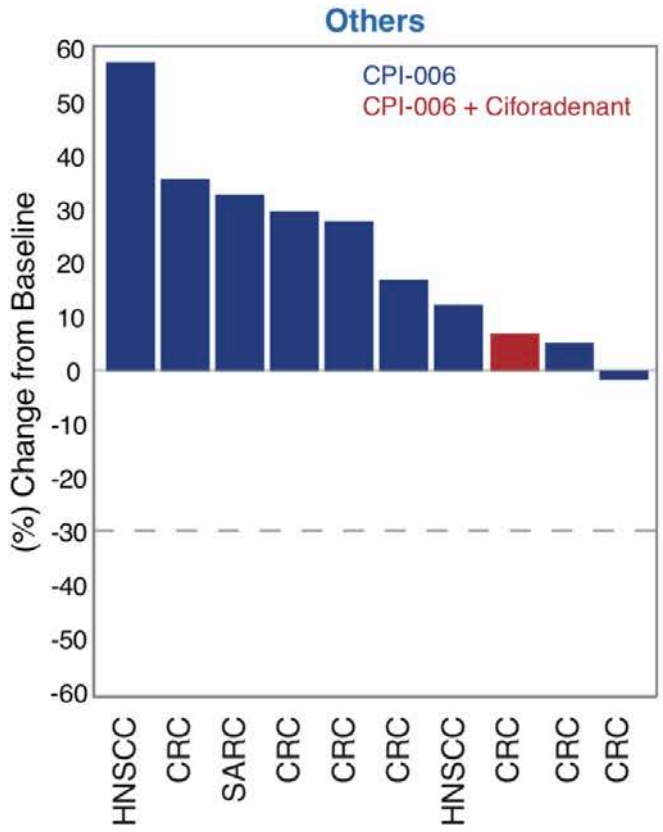
Cohort	Number of Patients with B Cell Expansion	Number of Patients with T Cell Expansion
CPI-006 monotherapy	5 of 7	2 of 4
CPI-006 + ciforadenant	2 of 4	1 of 4
Total	7 of 11	3 of 8

- Generation of prevalent B and T cell clones on therapy
- Consistent with antigen-driven clonal selection
- No change in serum immunoglobulins observed

Response Assessments



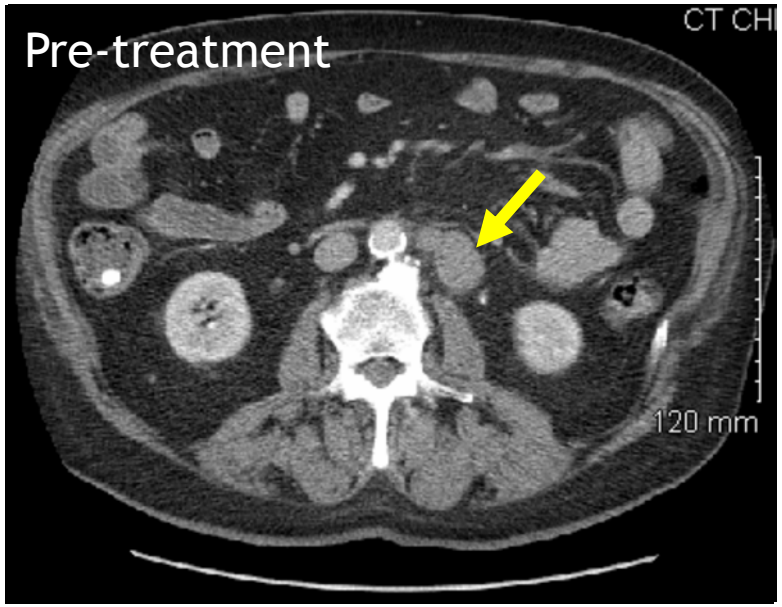


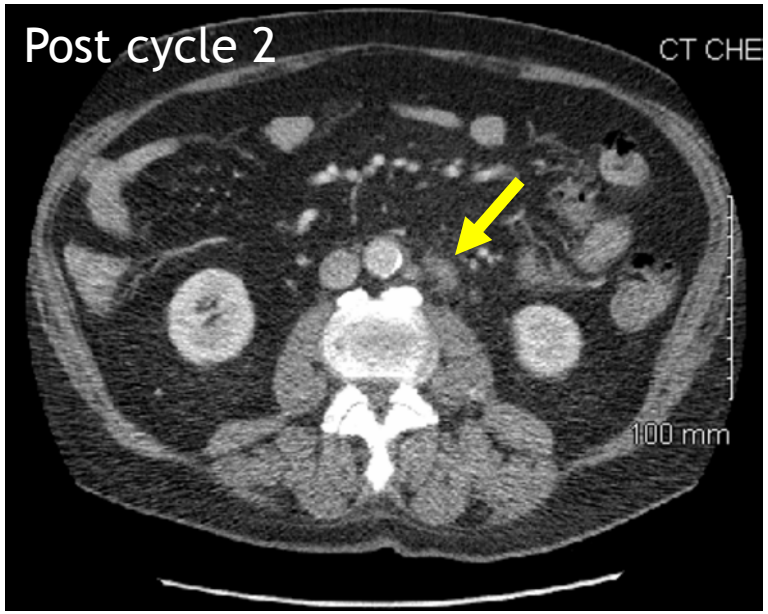


- Response assessments in patients receiving ≥ 6 mg/kg dose

Tumor Reduction in a Prostate Cancer Patient

CPI-006 monotherapy





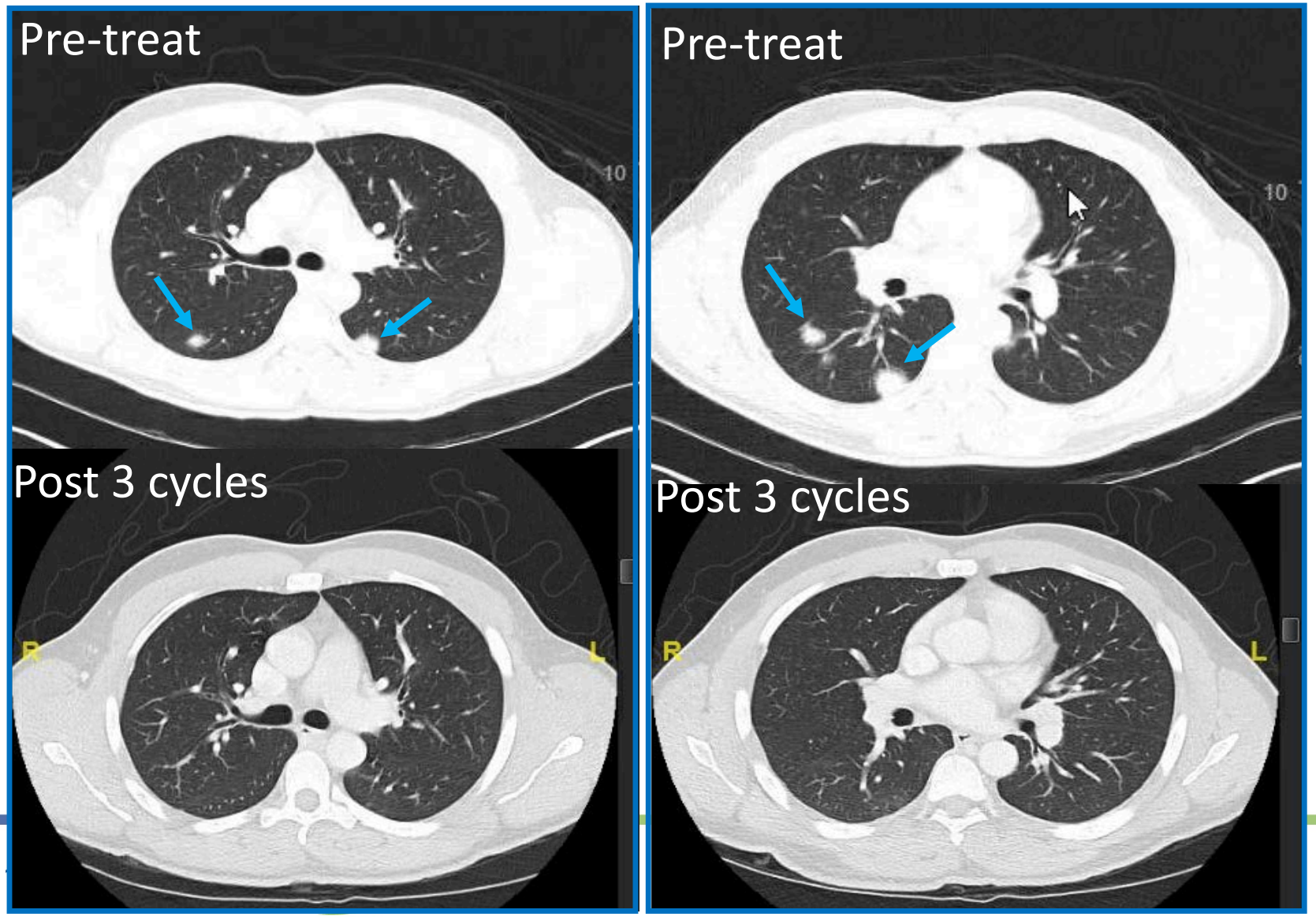
- 72 year old man with widely metastatic prostate cancer; previous therapies include leuprolide/bicalutamide, abiraterone, enzalutamide and docetaxel

- Decrease in target lesion in patient receiving 6 mg/kg monotherapy, treatment ongoing through 19 cycles

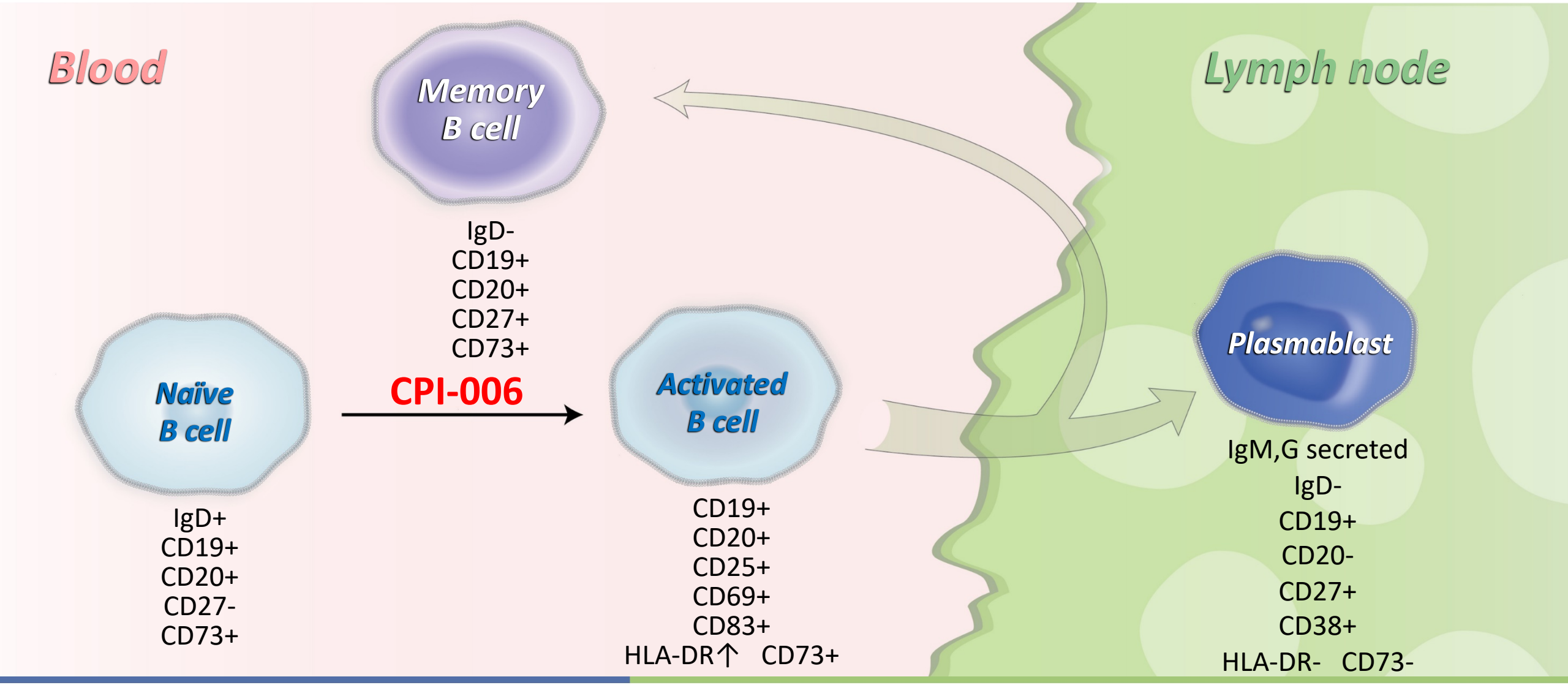
Responding Pulmonary Metastases in RCC Patient

CPI-006 6 mg/kg plus ciforadenant combination

- 36 year old male presented in 2015 with renal mass and bone metastases
- Failed TKI, nivo and nivo/ipi with increase pulmonary mets
- Regression of multiple biopsy proven pulmonary metastases on CPI-006 + ciforadenant



Model for CPI-006 Effects on Cells



Conclusions

- CPI-006 has novel immunomodulatory activities:
  - Induces differentiation of B cells, class switching, secretion of immunoglobulin (in vitro), and generation of memory B cells
  - Increases expression of CD69 and other markers consistent with increased antigen presentation by APCs
- The optimum and well tolerated dose of CPI-006 is 18 mg/kg
- Treatment with CPI-006 induces redistribution of T and B cells with an increase in returning memory B cells and expansion of new B cell clones
- Changes in lymphocytes are consistent with induction of adaptive humoral immunity
- Tumor regression observed in RCC and prostate
- *Treatment with CPI-006 may represent an opportunity to identify novel anti-tumor antibodies*

Acknowledgements

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