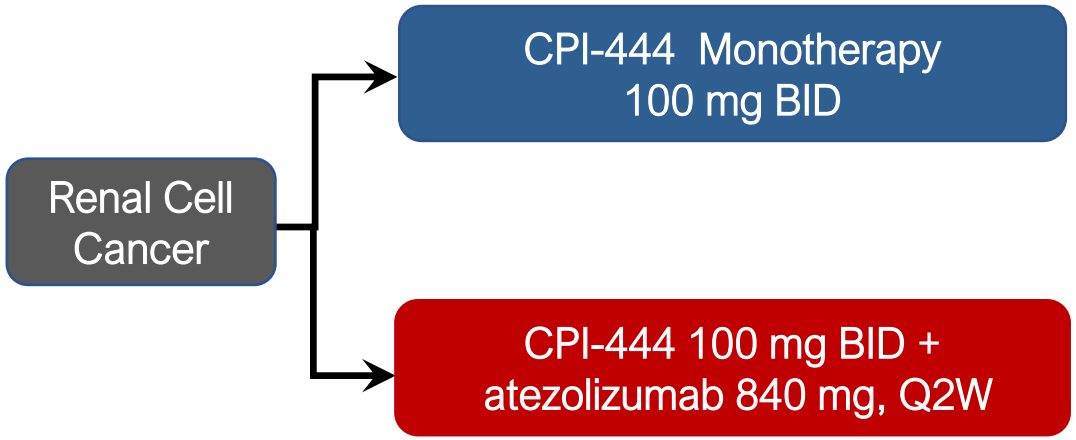
Refractory Renal Cell Cancer (RCC) Exhibits High Adenosine A2A Receptor (A2AR) Expression and Prolonged Survival Following Treatment With the A2AR Antagonist CPI-444

Lawrence Fong, John Powderly II, Jason Luke, Drew Hotson, Mario Sznol, Saby George, Toni Choueiri, Brian Rini, Matthew Hellmann, Shivaani Kummar, Leonel Hernandez-Aya, Daruka Mahadevan, Brett Hughes, Ben Markman, Matthew Riese, Joshua Brody, Daniel Renouf, Rebecca Heist, Rachel Goodwin, Amy Weise, Leisha Emens, Stephen Willingham, Long Kwei, Ginna Laport and Richard Miller

sitc
Society for Immunotherapy of Cancer
#SITC2018

TRIAL DESIGN & PATIENT CHARACTERISTICS



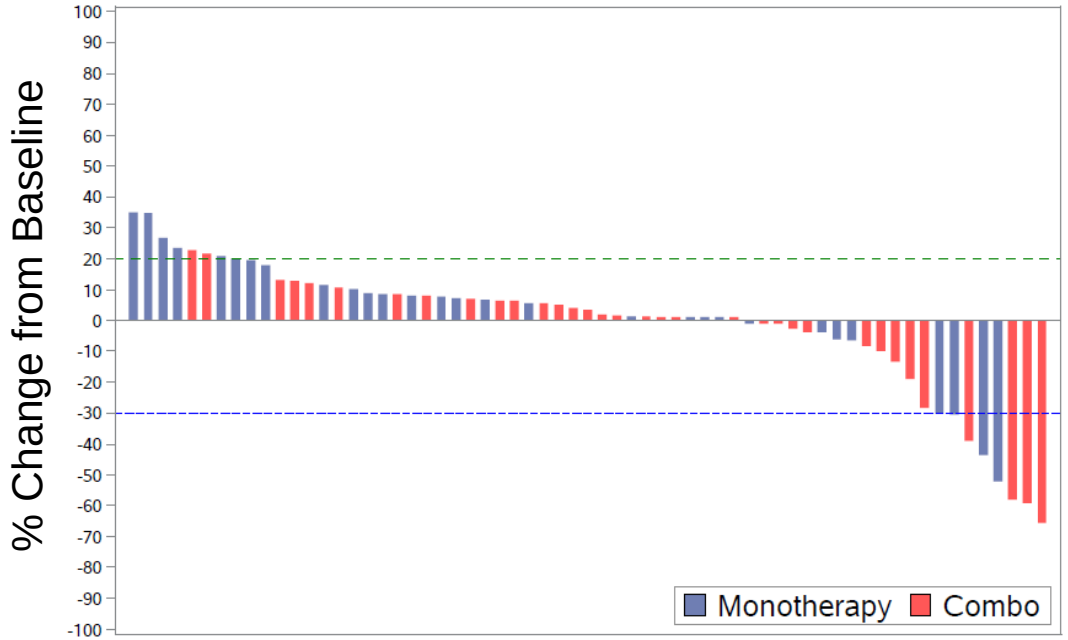
Eligibility

- Prior anti PD-(L)1 allowed
- Progressive disease at time of entry
- No selection for PD-L1 expression

Baseline Demographics	CPI-444 (n=33)	CPI-444 + atezolizumab (n=35)
Age (years), median (range)	60 (47, 76)	65 (44, 77)
Gender, male n (%)	25 (75.8)	28 (80.0)
Number of prior therapies median (range)	3 (1, 5)	3 (1, 5)
Prior IO, number of subjects n (%)	24 (72.7)	25 (71.4)
Months since prior IO therapy, median (range)	3.1 (1.2, 70.4)	1.7 (0.9, 23.6)
Prior Anti-Cancer Therapy n (%)		
TKI	27 (81.8)	30 (85.7)
mTor	9 (27.3)	11 (31.4)
anti-PD-1	23 (69.7)	25 (71.4)
anti-VEGF, Bevacizumab	6 (18.2)	4 (11.4)
IL-2	7 (21.2)	9 (25.7)

TUMOR RESPONSE TO TREATMENT

Best Response of All Patients

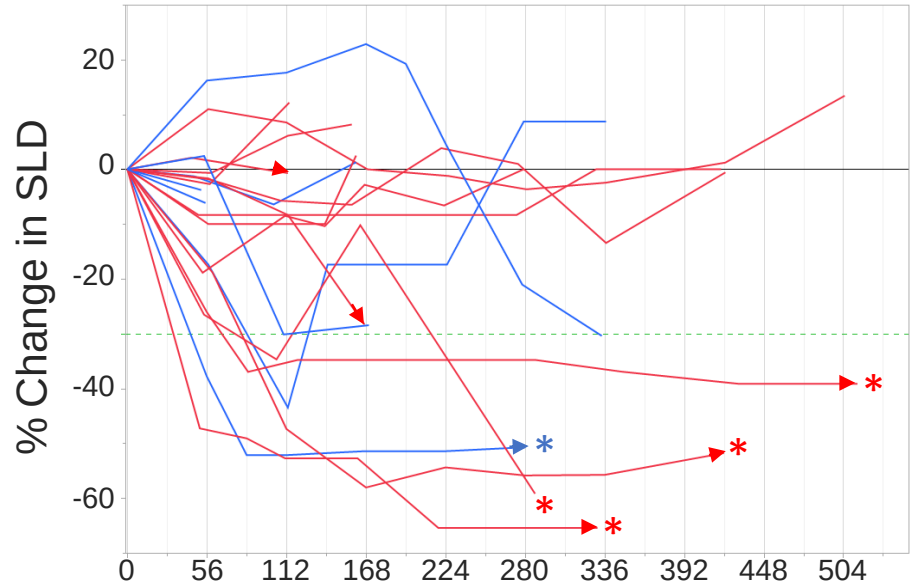


6 Month Disease Control Rate

	Mono*	Combo*
Prior PD(L)-1	25% (5/20)	32% (7/22)
Naive	0% (0/9)	44% (4/9)
Total	17% (5/29)	35% (11/31)

* Disease control % (# Disease control patients/total)

Spider Plot of Patients with Tumor Regression

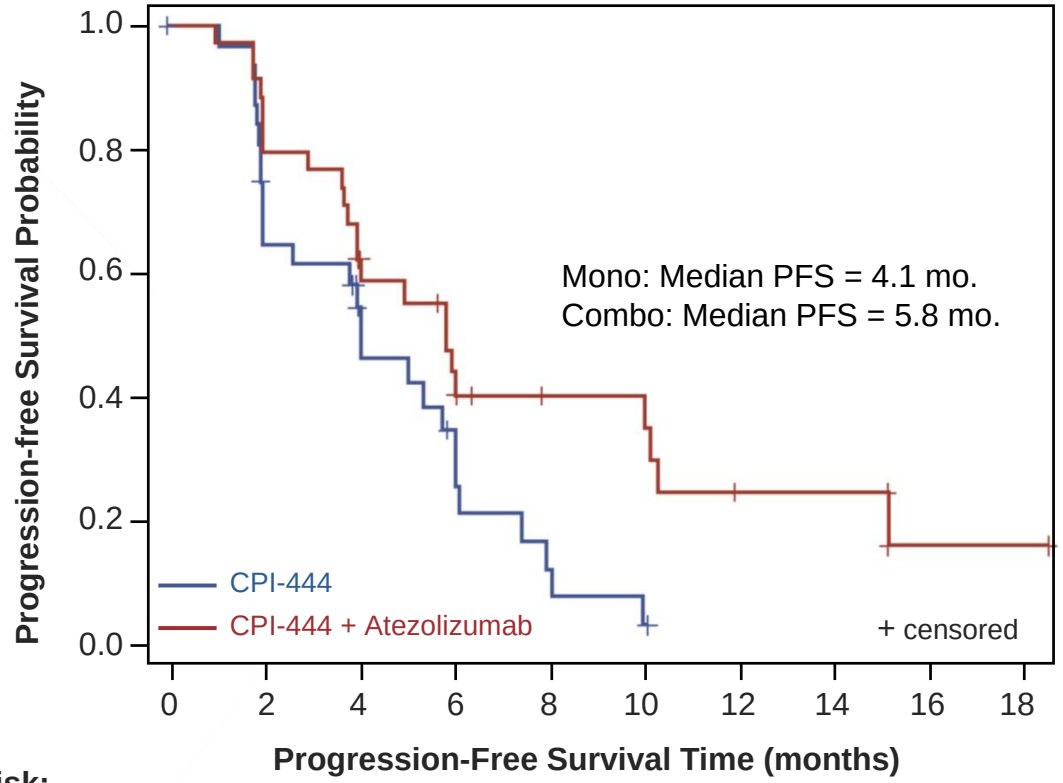


Median time to best tumor reduction:

- Monotherapy 3.4 months
- Combination 5.5 months

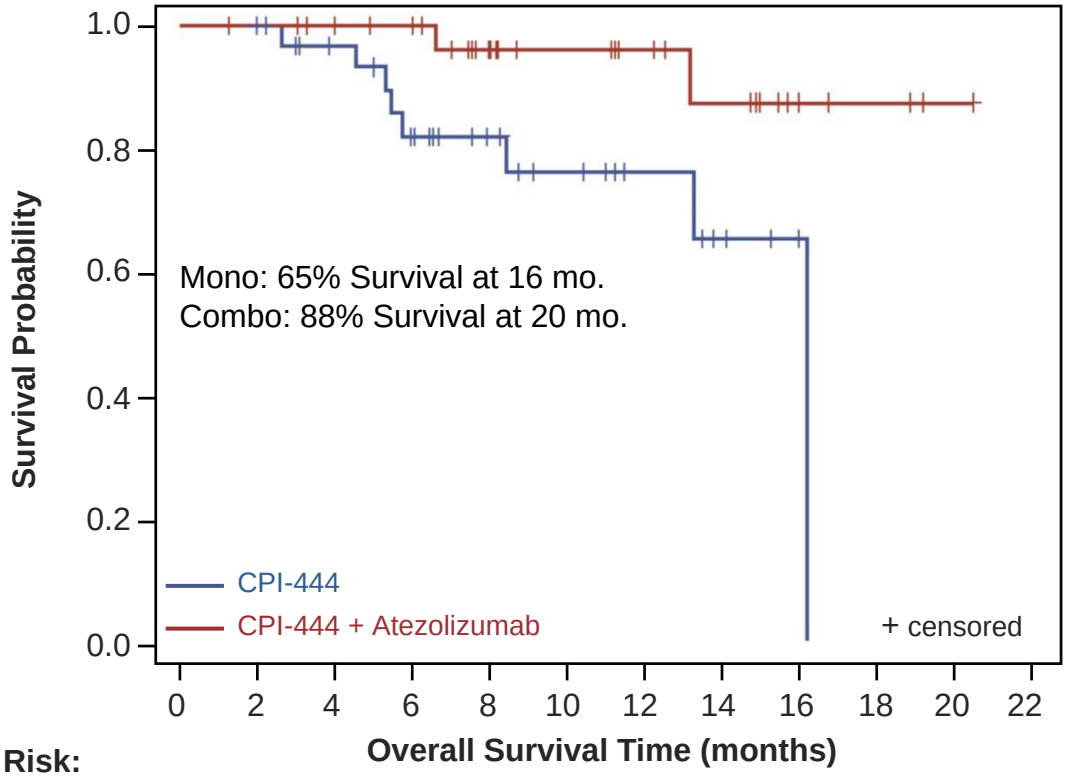
PROGRESSION FREE AND OVERALL SURVIVAL

Median follow-up 8.7 months



N. At Risk:

CPI-444	33	23	15	8	3	1				
CPI-444 + Atezolizumab	35	31	23	12	8	7	4	4	1	1



N. At Risk:

CPI-444	33	33	27	22	15	11	7	4	2	0		
CPI-444 + Atezolizumab	35	34	32	30	22	16	13	10	5	3	1	0

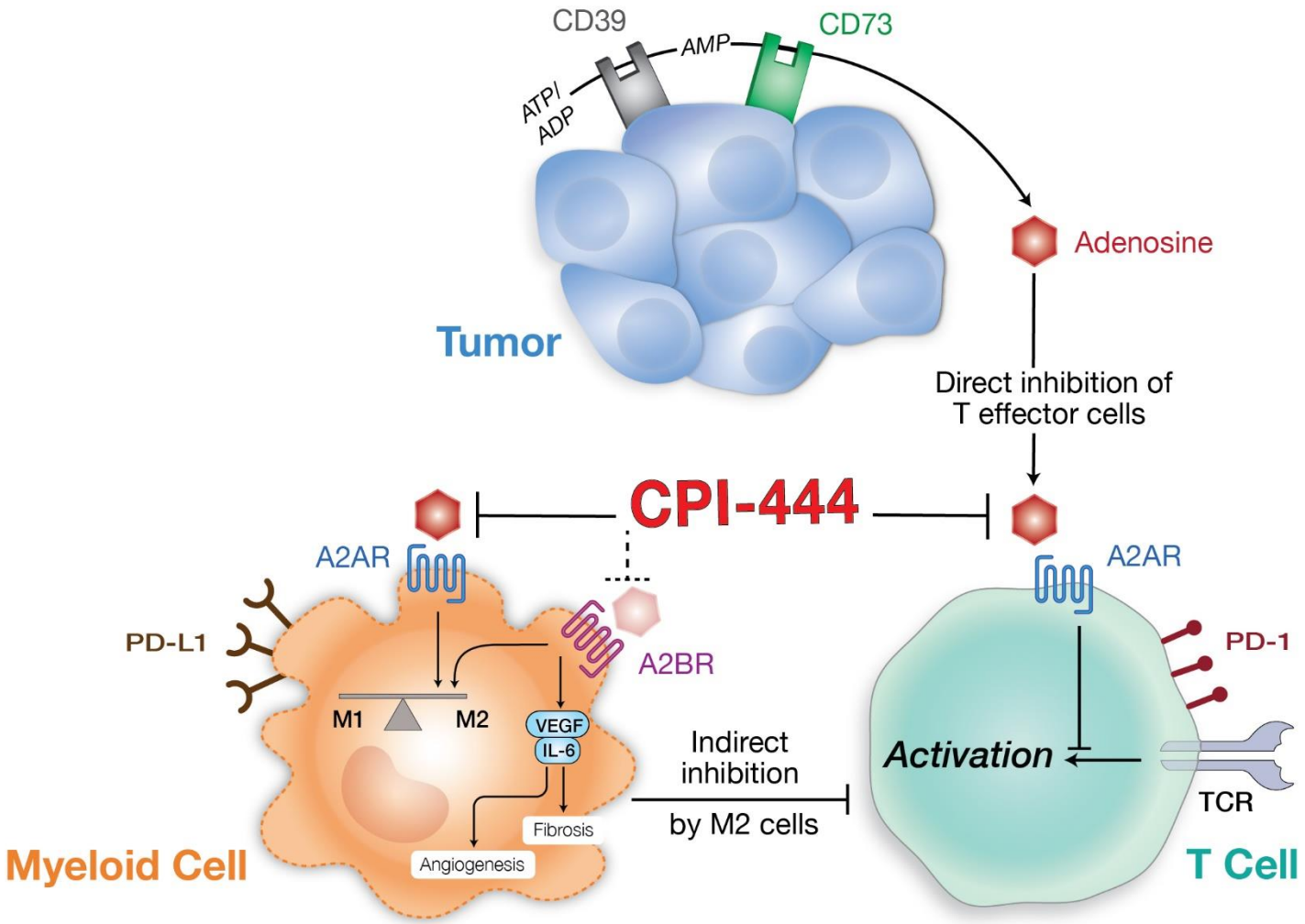
BIOMARKERS TO ASSESS IMMUNE FUNCTION AND CLINICAL ACTIVITY

Intra tumoral adenosine leads to:

- T cell suppression
- M2 polarization

Hypothesis:

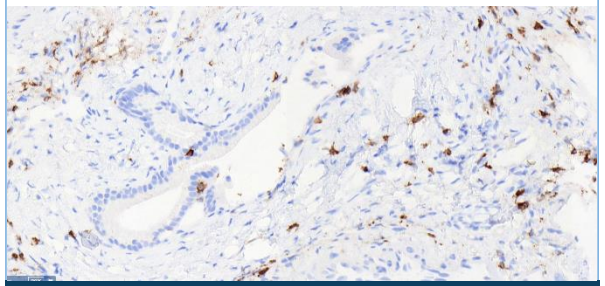
- CPI-444 treatment will enhance T cell responses
- Patients with M2 skewed tumors may be most sensitive to treatment



CD8+ T CELL INFILTRATION CORRELATES WITH DISEASE CONTROL

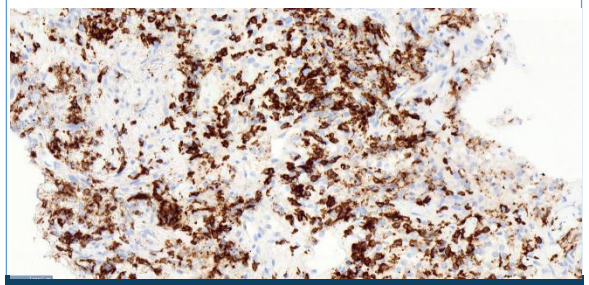
CD8 IHC in subject with disease control > 6 mo.

1.4%



Pre-treatment

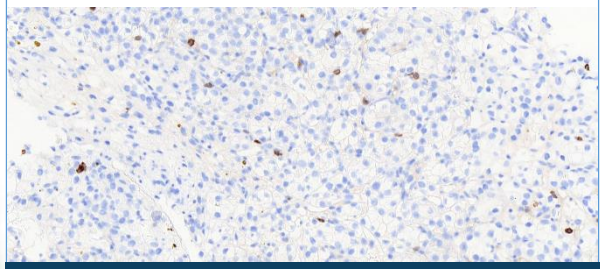
4.4%



On-treatment

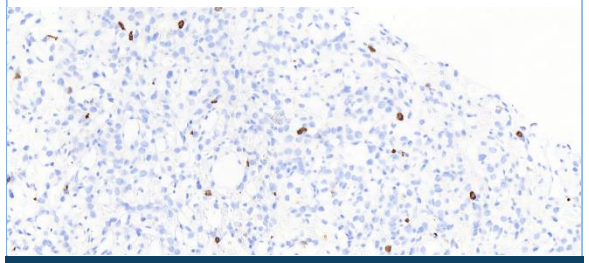
CD8 IHC in subject with disease control < 6 mo.

0.5%

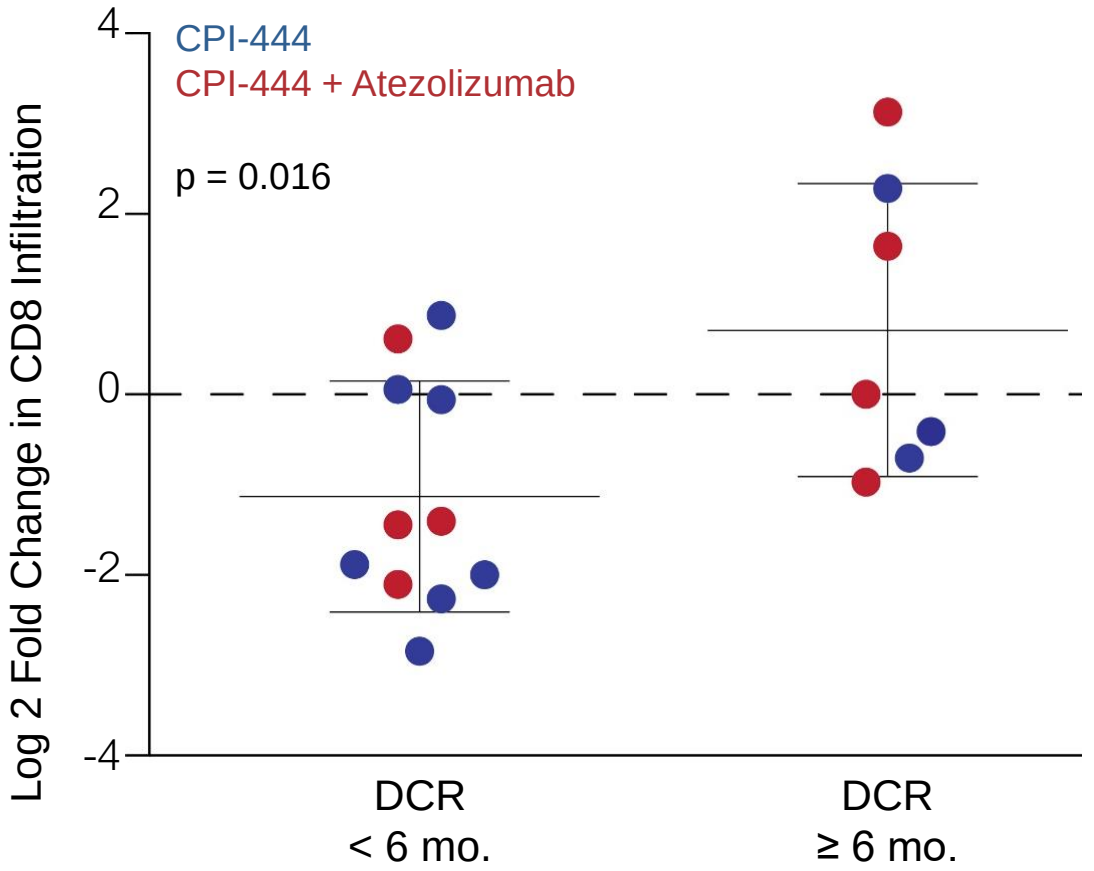


Pre-treatment

0.4%

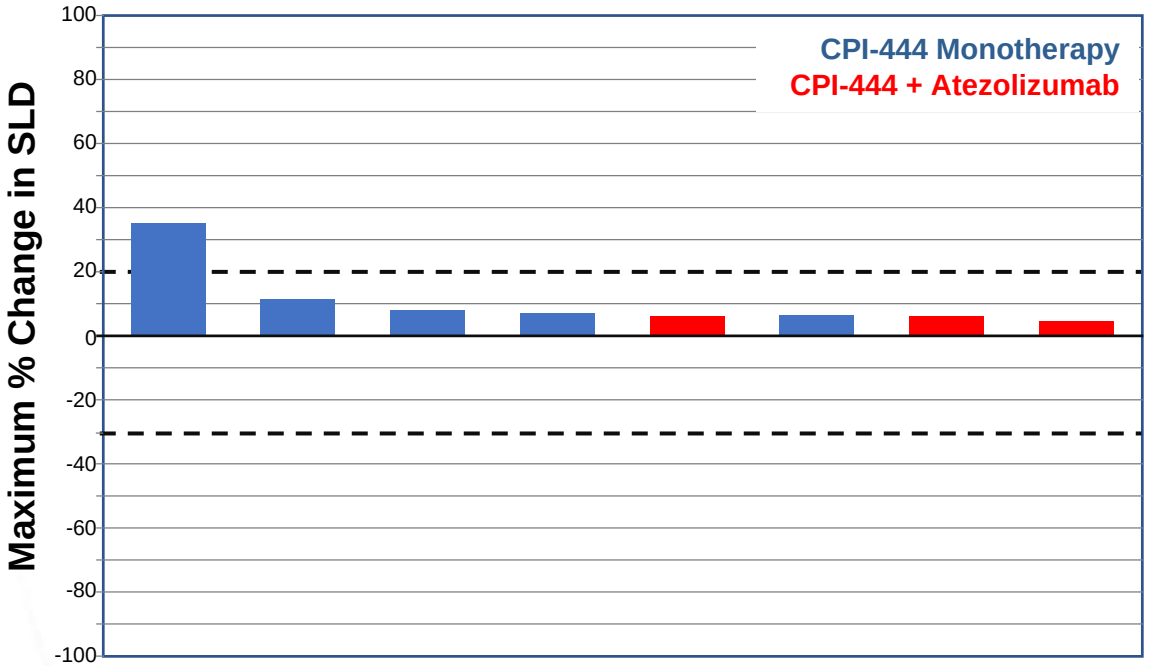


On-treatment

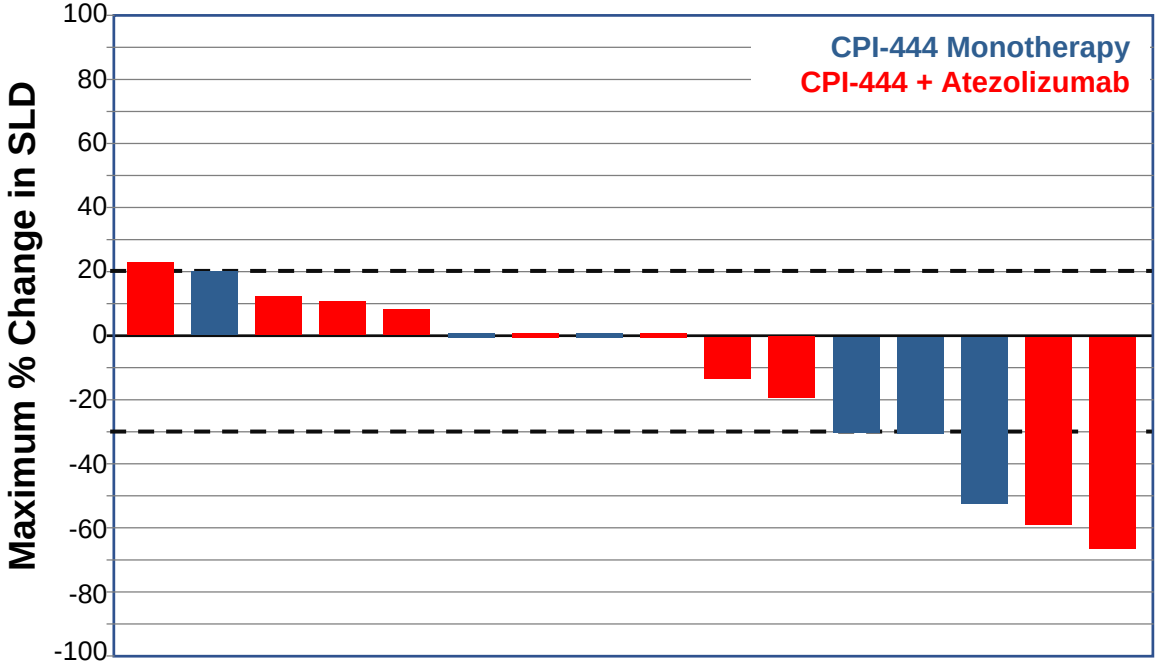


TUMOR EXPRESSION OF THE "ADENOSINE SIGNATURE" CORRELATES WITH RESPONSE

Adenosine Signature Low



Adenosine Signature High



Responders in Adenosine Signature High vs Low: $p < 0.008$

CONCLUSIONS

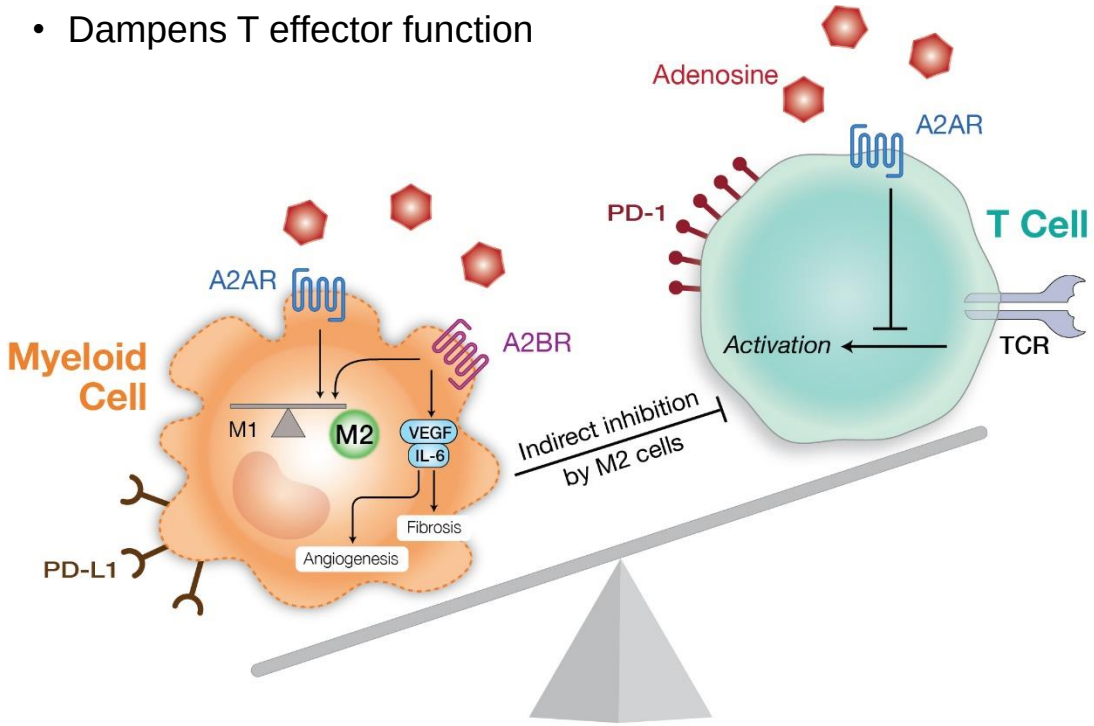
- CPI-444 is active as monotherapy and in combination with atezolizumab in
  - PD-(L)1 naive patients
  - PD-(L)1 resistant/refractory patients
- Combination therapy appears more active than monotherapy
- Combination efficacy results in heavily pretreated patients:
  - PR = 11%
  - DCR at 6 months = 35%
  - PFS = 5.9 months
  - OS = 88% at 20+ months
- Treatment-induced CD8+ T cell infiltration associates with an improved disease control rate
- The adenosine gene signature is associated with tumor response to therapy with CPI-444, and could be used as a biomarker for future patient selection
- CPI-444 is currently being evaluated in RCC patients in earlier lines of therapy

ROLE OF ADENOSINE IN THE TUMOR MICROENVIRONMENT

PRE-TREATMENT

Adenosine

- Promotes myeloid suppression
- Dampens T effector function



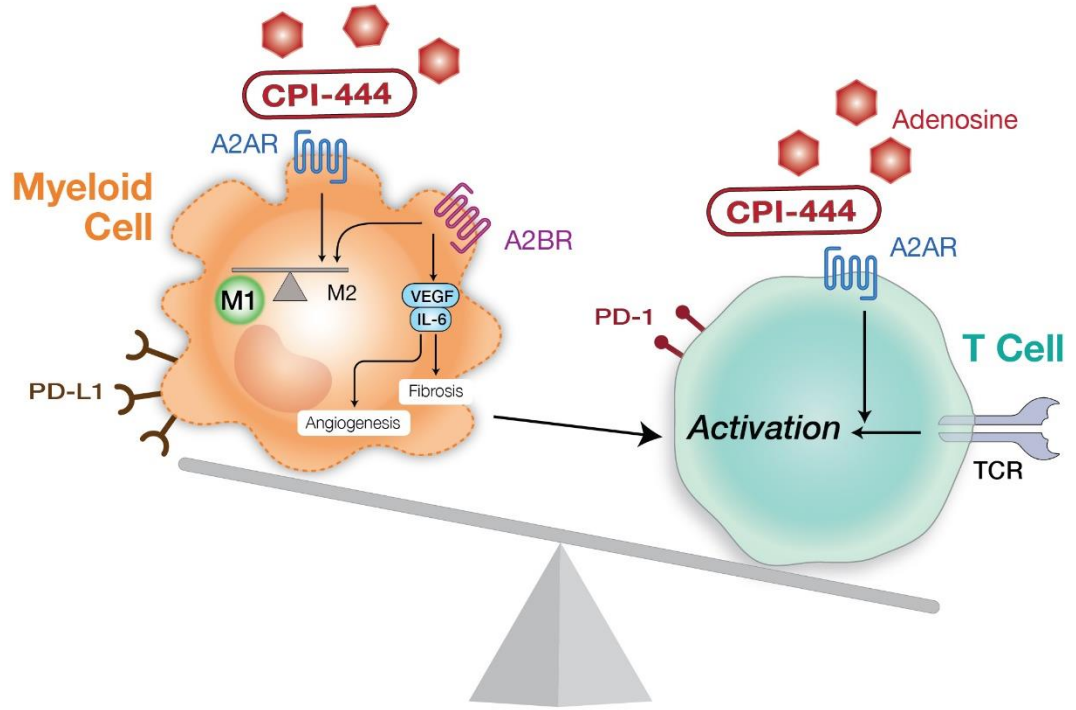
M2 polarization
↑ Adenosine Signature

↑ PD-1 expression
↓ IL-2 & IFNγ production
↓ Proliferation

Immunosuppressive

TREATED WITH CPI-444

- Inhibits adenosine and restores immune balance



M1 polarization
Blocks Adenosine Signature

↓ PD-1 expression
↑ IL-2 & IFNγ production
↑ Proliferation

Immunostimulatory

COMPARISON OF RCC THERAPIES

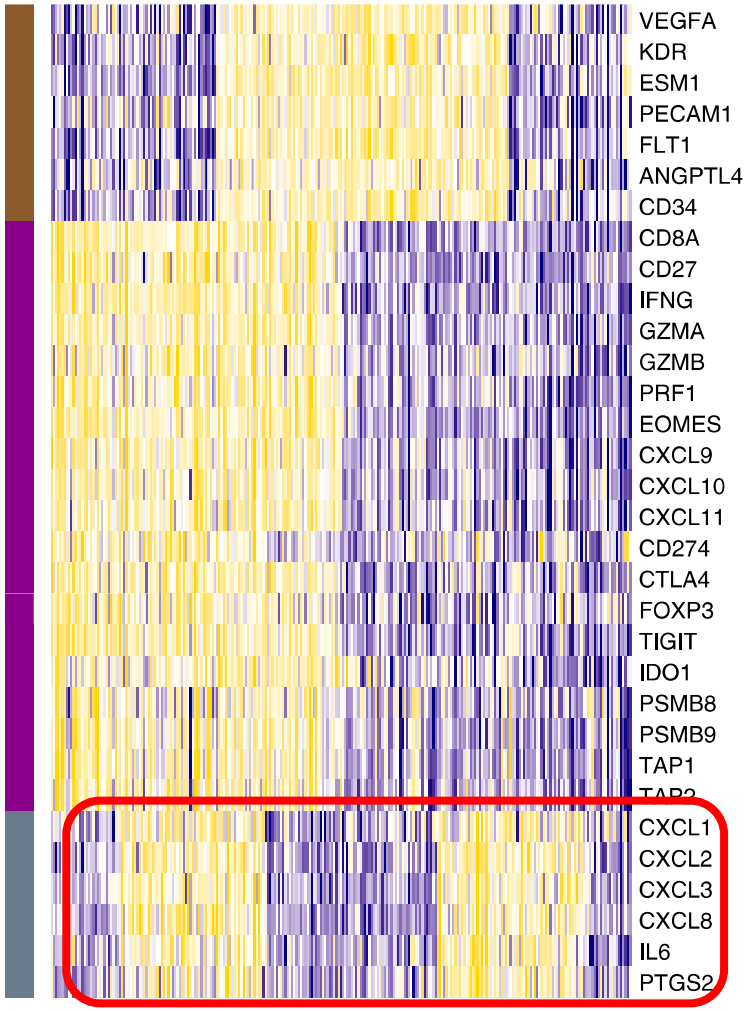
	Line of Rx	No. Pts	Prior IO	ORR %	PFS (mo) / OS
CPI-444/Atezo[1]	4th	35	72%	11	5.8 / 88% 20 mo.
Atezo[2]	3rd	70	No	15	5.6 /28.9 mo. median
Nivo[3]	2nd	410	No	24	4.6 / 25 mo. median
Everolimus[3]	2nd	411	No	5	4.4 / 19.6 mo. median
Nivo/Ipi[4]	1st	425	No	42	11.6 / 75% 18 mo.
Sutent[4]	1st	422	No	27	8.4 / 26 mo. median
Cabozantanib[5]	2nd or 3rd	223	No	16	~8.3* / 22 mo. median
Cabozantanib[6]	3rd **	25	100%	28	4.7 / 40% 12 mo.

1. Fong et al, SITC 2018
2. McDermott et al, JCO 2016
3. Motzer et al, NEJM 2015
4. Motzer et al, NEJM 2018
5. Powles et al, BJC 2018
6. McGregor ESMO 2018

*Prior sunitinib 9.1 months; prior pazopanib 7.4 months

** Prior IO+TKI

Gene Expression Distinguishes Subgroups of RCC with Different Response to Anti-PD(L)-1



Gene expression distinguishes biological subgroups of RCC with differential response rates to PD-1 pathway inhibition

Signature
- Angiogenesis
- Immune and antigen presentation
- Myeloid inflammation

Expression
2
1
0
−1
−2

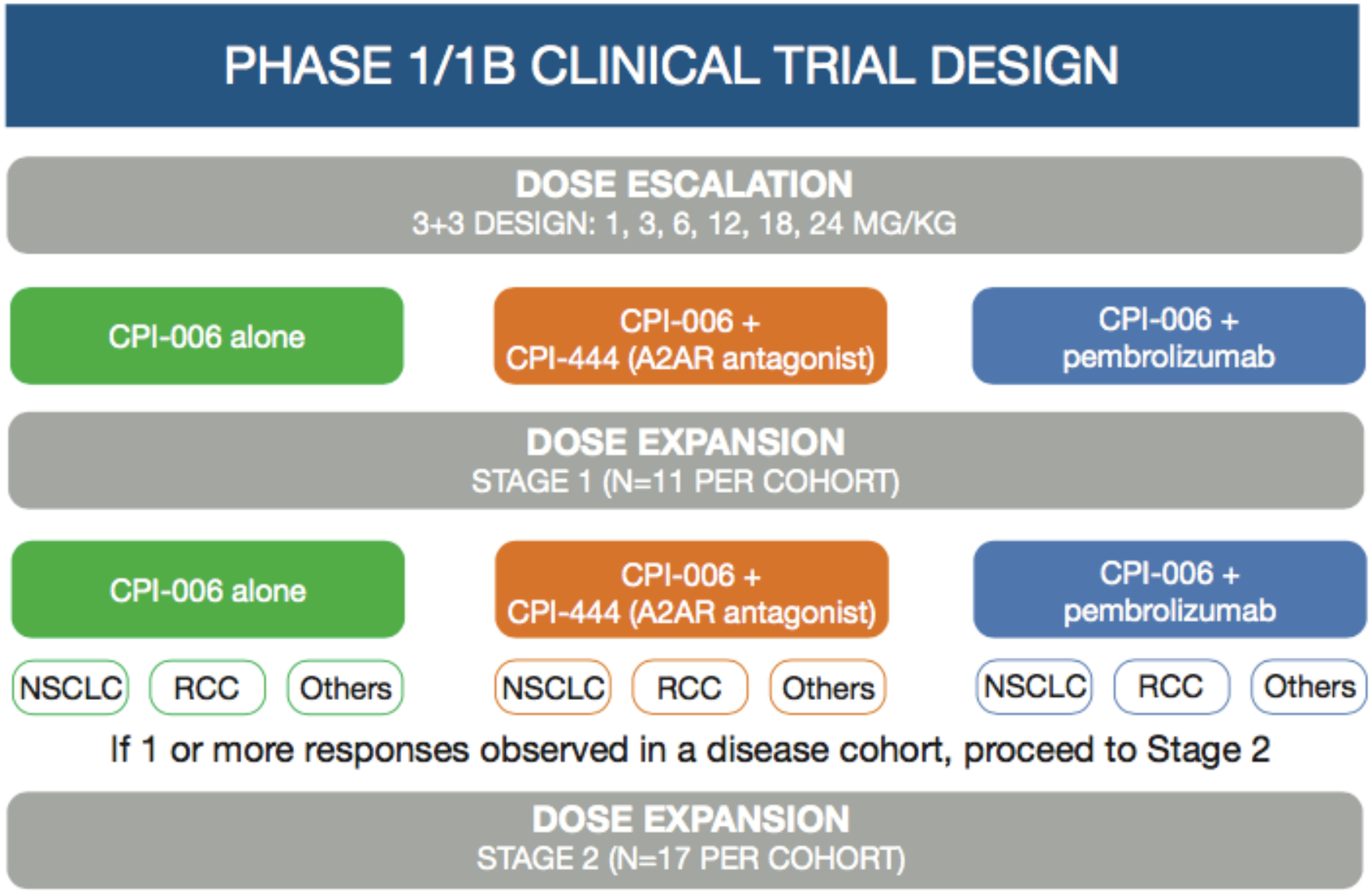
Myeloid Inflamed tumors show reduced response to atezolizumab
PFS HR = 2.98 (1.68-5.29), $p < 0.001$

McDermott et al Nature Medicine 2018

CPI-006, a Novel anti-CD73 Monoclonal Antibody

- CPI-006 targets a novel epitope on CD73
  - Blocks production of adenosine
  - Activates B lymphocytes
- Phase 1 monotherapy clinical data indicate that CPI-006 is
  - Well tolerated (no DLTs) at 1, 3, and 6 mg/kg
  - Dose-proportional PK and receptor occupancy
  - Affects B cell trafficking from blood to lymph nodes
- Dose escalation continues with monotherapy and combination with A2AR antagonist CPI-444

Anti-CD73 (CPI-006) Clinical Trial

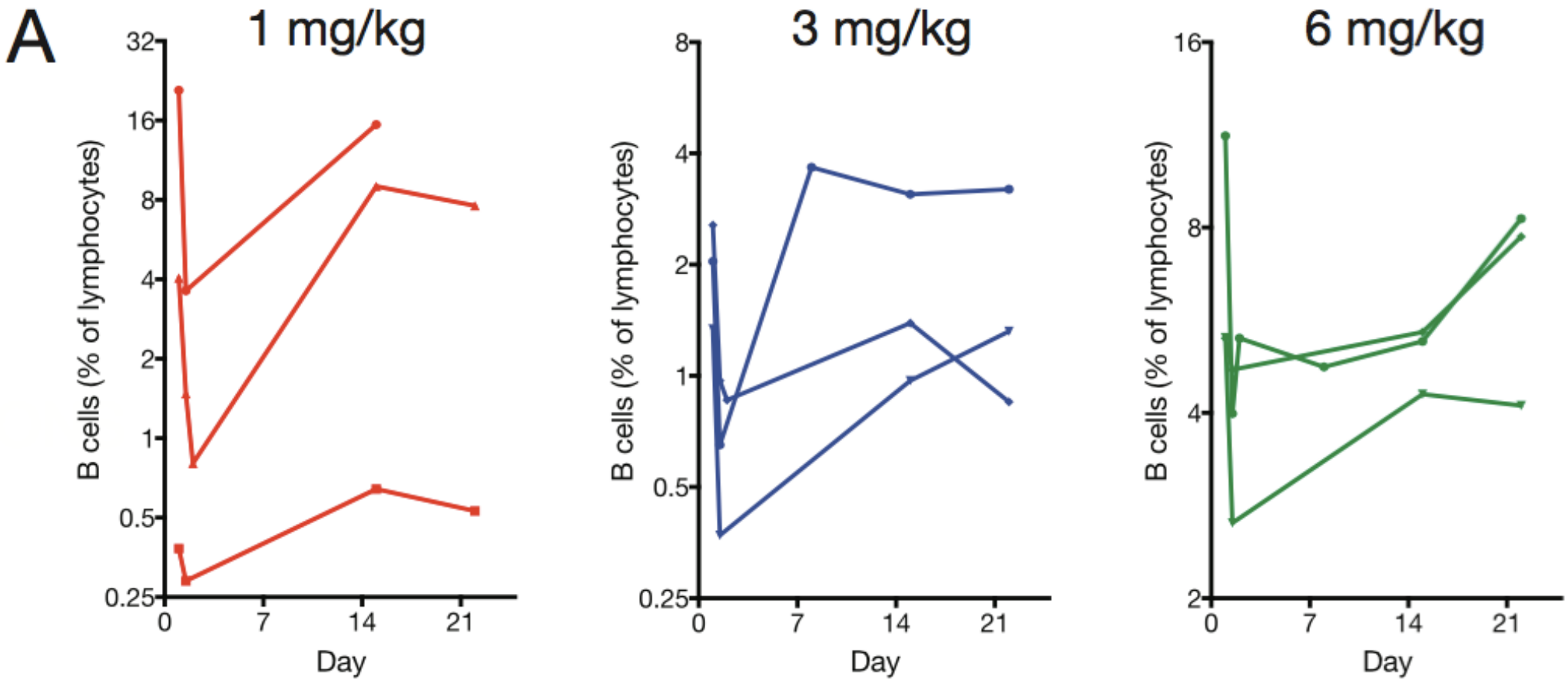


Patient Treatment Summary

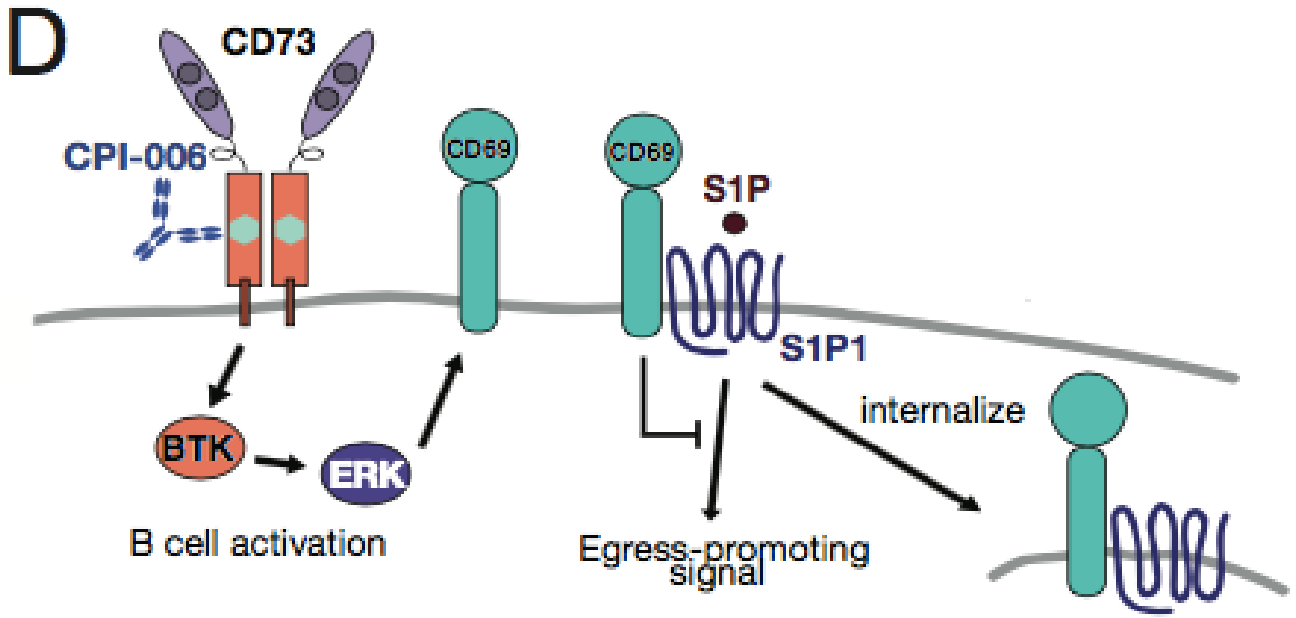
- No

Patient	Dose	Disease	Occupancy of Peripheral B cells at C1D15	% Decrease of Peripheral B cells at C1D1 (0.5h)	Serum CPI-006 [µg/mL] at C1D8
1		bladder	-1.35%	24.6%	BLQ
2	1 mg/kg	prostate	65.83%	82.6%	BLQ
3		SCHN	22.96%	63.7%	BLQ
4		pancreatic	88.12%	71.2%	2.461
5	3 mg/kg	pancreatic	74.57%	62.3%	5.032
6		prostate	58.19%	68.1%	2.937
7		colorectal	97.90%	49.3%	23.60
8	6 mg/kg	prostate	98.31%	64.6%	TBD
9		SCHN	101.60%	11.1%	TBD

Transient Redistribution of B Cells from Blood



A Model of CPI-006 Induced Signaling



- Peripheral lymphocytes have low S1P1
- S1P1 is involved in lymphocyte retention in lymphoid organs
- Downregulation of S1P1 inhibits egress from lymphoid organs
- Trafficking and activation of lymphocytes to lymphoid tissues is necessary for immune responses