Clinical Activity of Adenosine A2A Receptor (A2aR) Inhibitor CPI-444 is Associated with Tumor Expression of Adenosine Pathway Genes and Tumor Immune Modulation

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Disclosures

Consultancy

7 Hills, Actym, Amgen, Array, AstraZeneca, BeneVir, Bristol-Myers Squibb, Castle, CheckMate, EMD Serono, Gilead, Janssen, Novartis, Merck

Clinical Trial Support to Institution

AbbVie, Boston Biomedical, Bristol-Myers Squibb, Celldex, Corvus, Delcath, Five Prime, Genentech, Immunocore, Incyte, Intensity, MedImmune, Macrogenics, Novartis, Pharmacyclics, Merck, Tesaro

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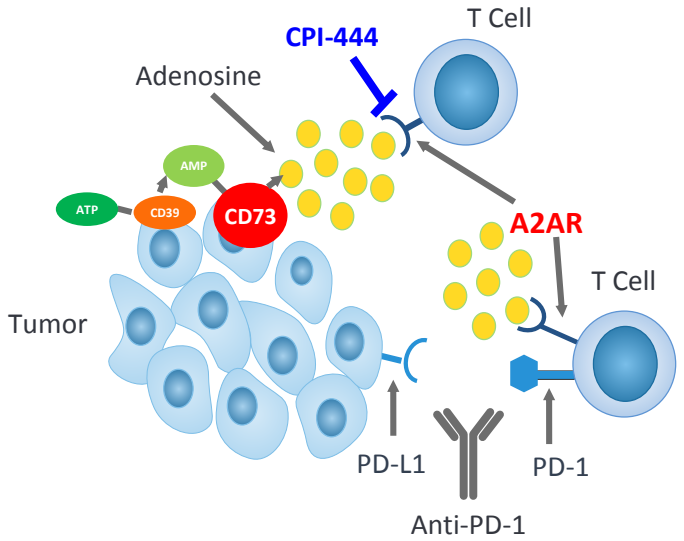
Background

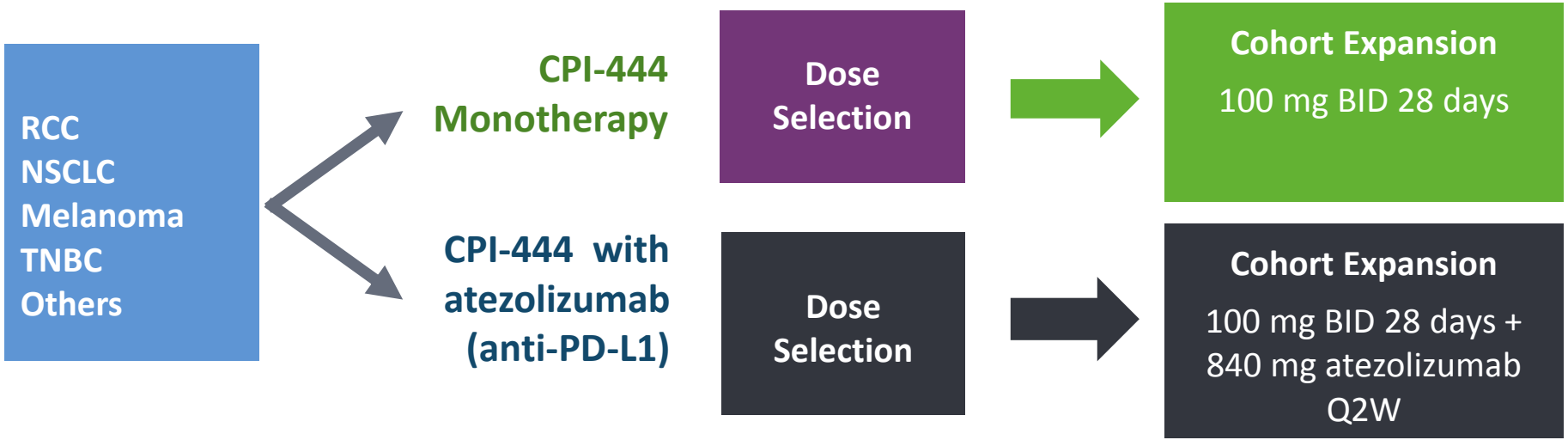
- Anti-PD-(L)1 antibodies are approved for treatment of several cancers but a small proportion of patients benefit
- Mechanisms of anti-PD-(L)1 resistance are not well understood and no agents are approved to overcome resistance
- Adenosine pathway mediates tumor immunosuppression; may be a resistance mechanism to anti-PD-(L)1 therapy
- CPI-444 is an oral, small molecule inhibitor of A2AR that has shown anti-tumor activity in anti-PD-(L)1 resistant/refractory, and PDL-1 negative patients[1]

Adenosine in the tumor microenvironment[2,3]



[1]Fong, ASCO 2017; [2]Beavis *et al*., Can Immun Res 2015; [3]Sharma *et al*., Cell 2017

Phase 1/1b Clinical Study with Oral Drug CPI-444



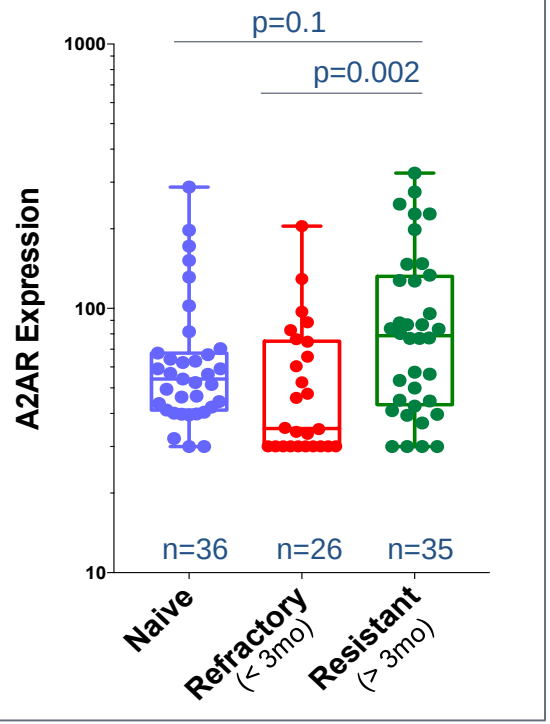
Eligibility

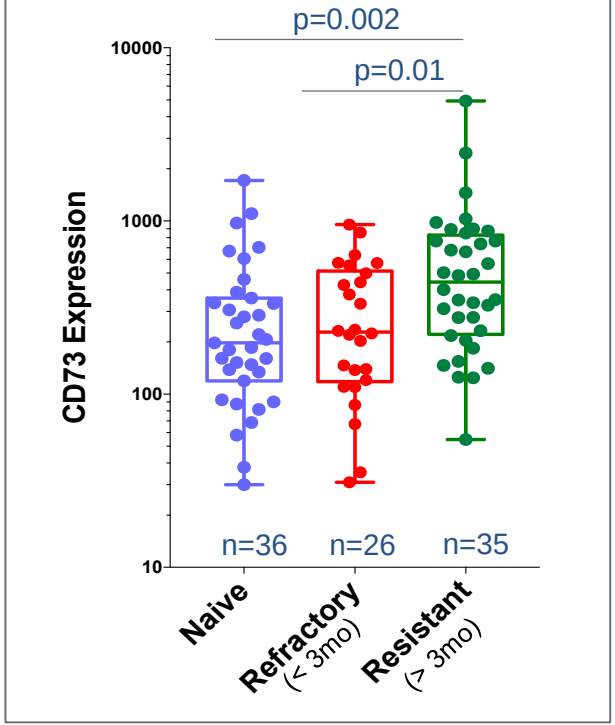
- Prior anti-PD-(L)1 allowed
  - **Resistant:** SD or better > 3 months of treatment
  - **Refractory:** progression within 3 months
- Must have progressive disease on prior therapy
- No selection for PD-L1 expression

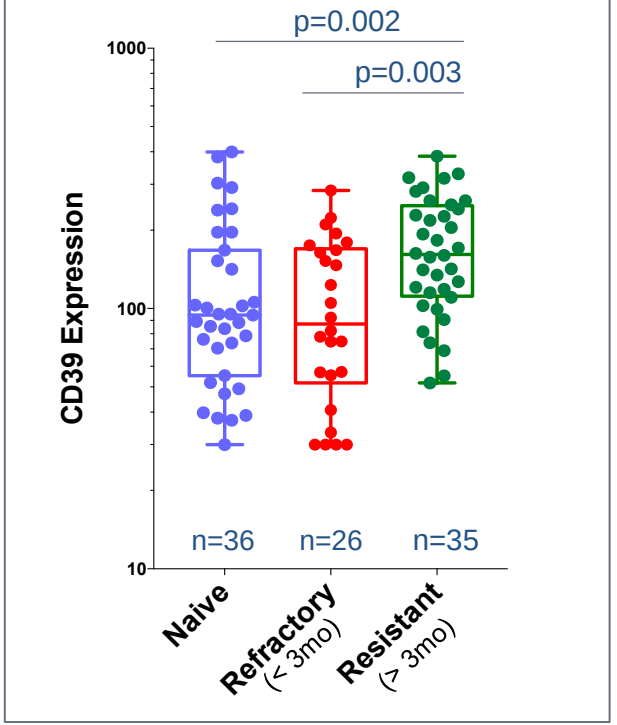
Prior Anti-PD-(L)1 Treatment Increases A2AR, CD73 and CD39

Adenosine pathway is a potential mechanism of resistance

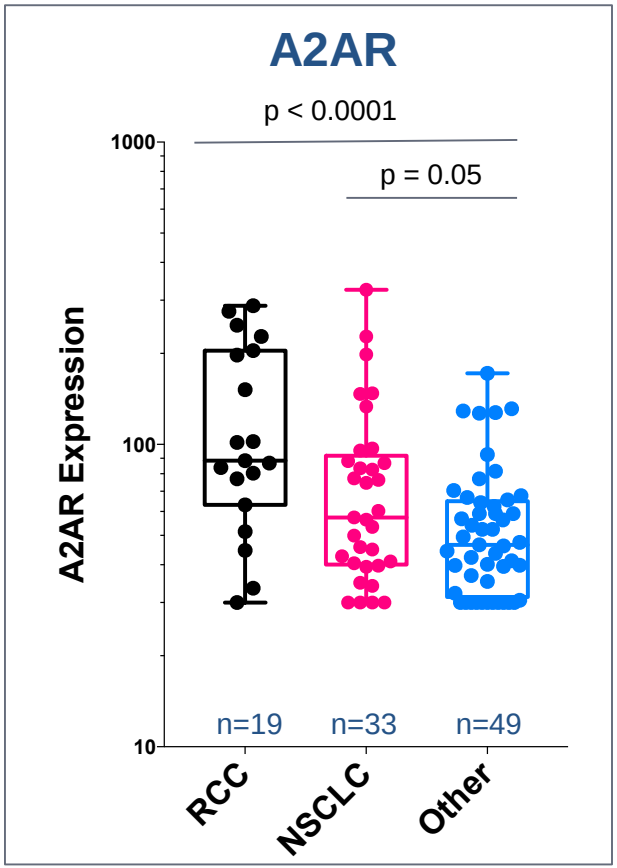
Exposure to anti-PD-(L)1 therapy (> 3 months) increases A2AR, CD73, and CD39 expression

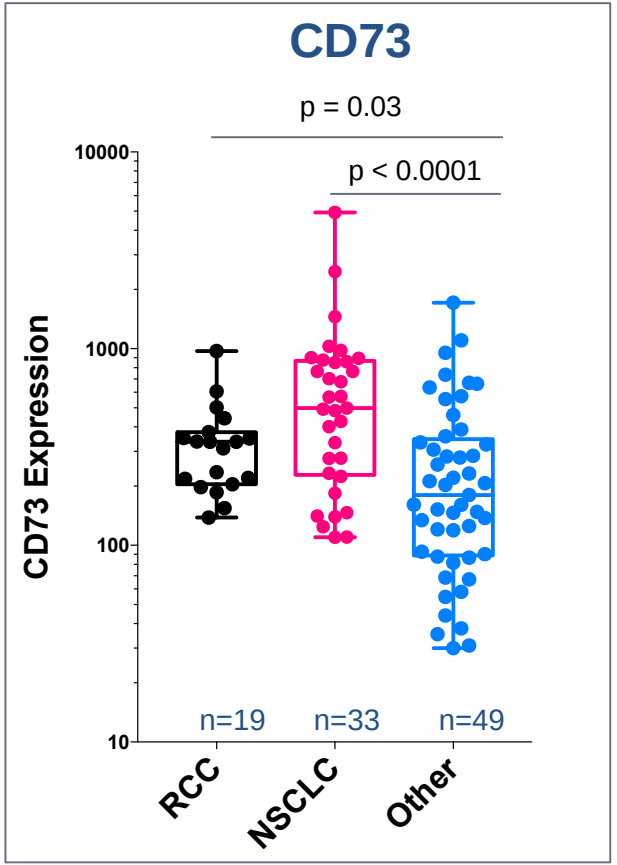


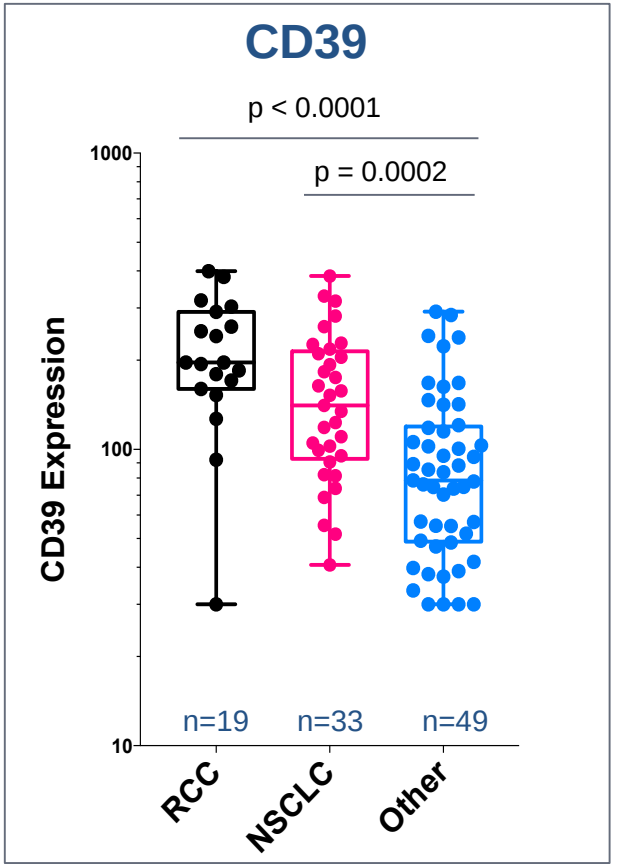




Adenosine Pathway Expression is Higher in RCC and NSCLC Pre-Treatment Biopsies







Other = bladder, colorectal, triple-negative breast, melanoma, prostate

Renal Cell Cohorts Expanded
Patient characteristics

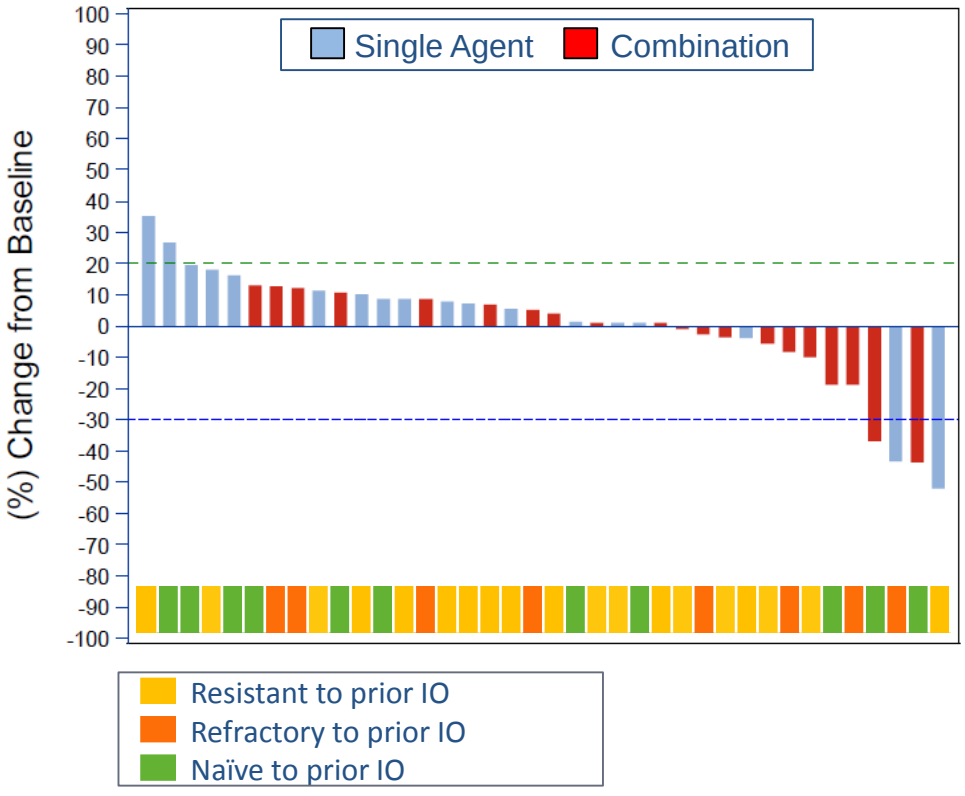
	Renal Cell Cancer (N=51)
Prior anti-PD-(L)1 exposure Naïve Resistant/Refractory	 16 (31%) 35 (69%)
PD-L1 Negative (archival) *	91%
Median time since IO agent, months (range)	1.6 (1 – 71)
Histology	50 (98%) Clear cell 1 (2%) Papillary
Median age, years (range) **No. of patients: single agent /combination** **Median number prior therapies (range)**	64 (44-70) 25/26 3 (1-5)
Adverse Prognostic Factors (%) **Visceral metastases** **Hepatic metastases** **Anemia** **Elevated LDH**	 88% 20% 45% 21%

* PD-L1 status determined using FDA-approved assay (SP142, cutoff = 5%)

Data cutoff 10/26/17

CPI-444 Anti-Tumor Activity in Renal Cell Cancer

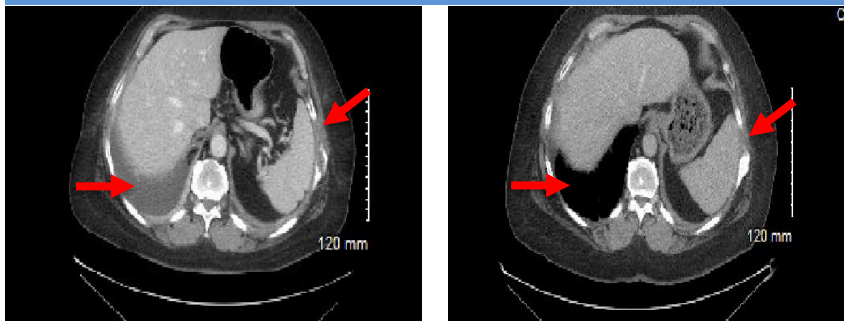
Responses with single agent and combination



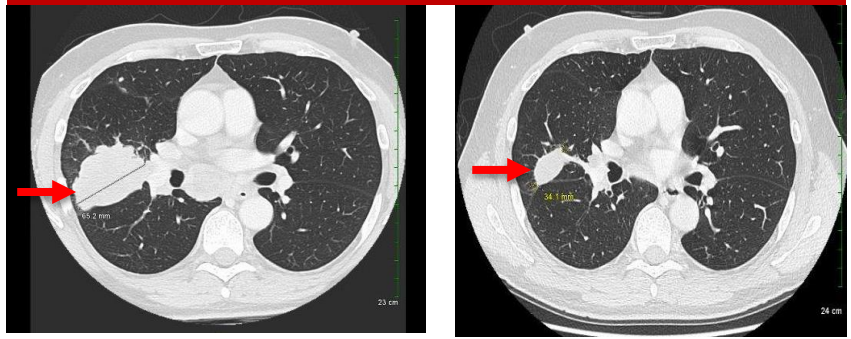
Data cutoff 10/26/17

Partial Responses in RCC

Single agent CPI-444 (atezolizumab-refractory)



Combination CPI-444 + atezolizumab

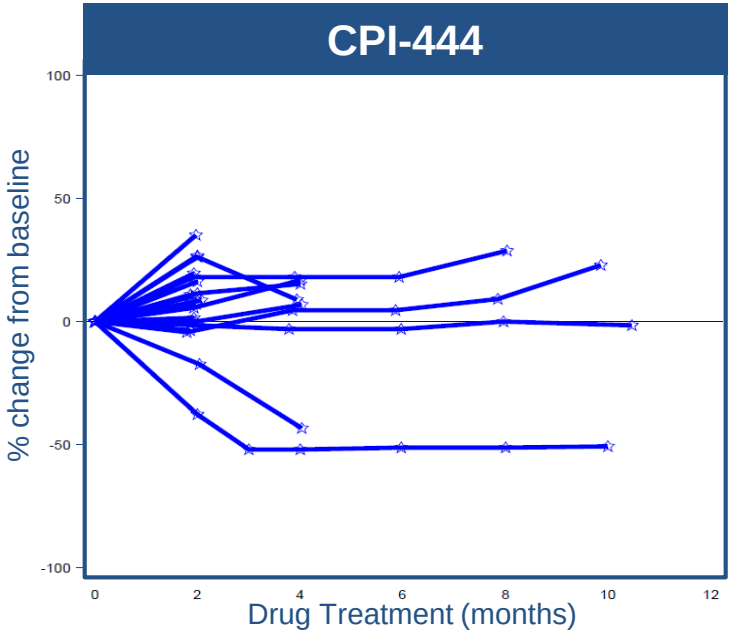


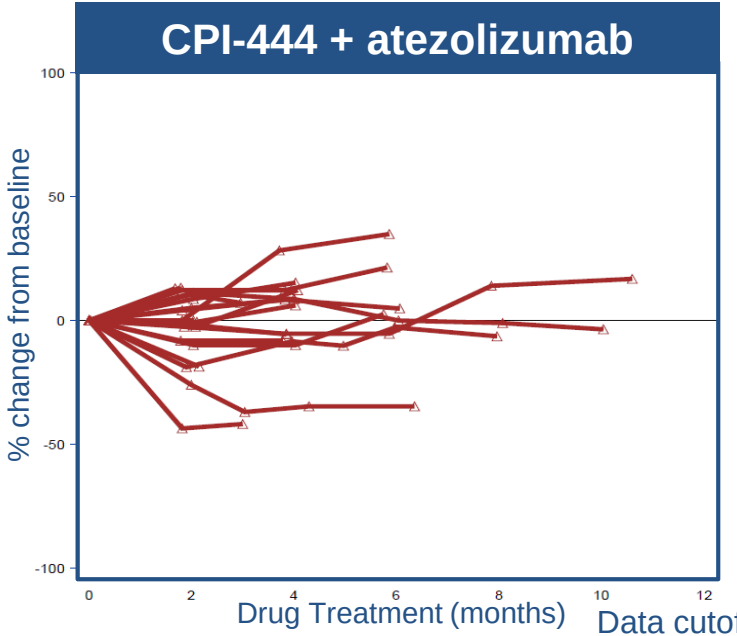
Renal Cell Cancer

Response rate and disease control rate in evaluable patients

Treatment	Objective Response Rate	Disease Control Rate
CPI-444	2*/14 (14%)	4/14 (29%)
CPI-444 + atezolizumab	2/16 (13%)	11/16 (69%)

*1 unconfirmed





Data cutoff 10/26/17

Treatment-Related Adverse Events

Adverse Events (Gr1/2) ≥ 5% Frequency (n=210)		
	CPI-444 (%)	CPI-444/Atezo (%)
Fatigue	21	29
Nausea	12	14
Pruritus	11	10
Pyrexia	5	9
Decreased appetite	6	7
Diarrhea	7	5
Anemia	6	4
Vomiting	3	6
Rash	3	6

Grade ≥ 3 Serious Adverse Events

CPI-444 (n=1)

- Gr 3 nausea/vomiting/diarrhea

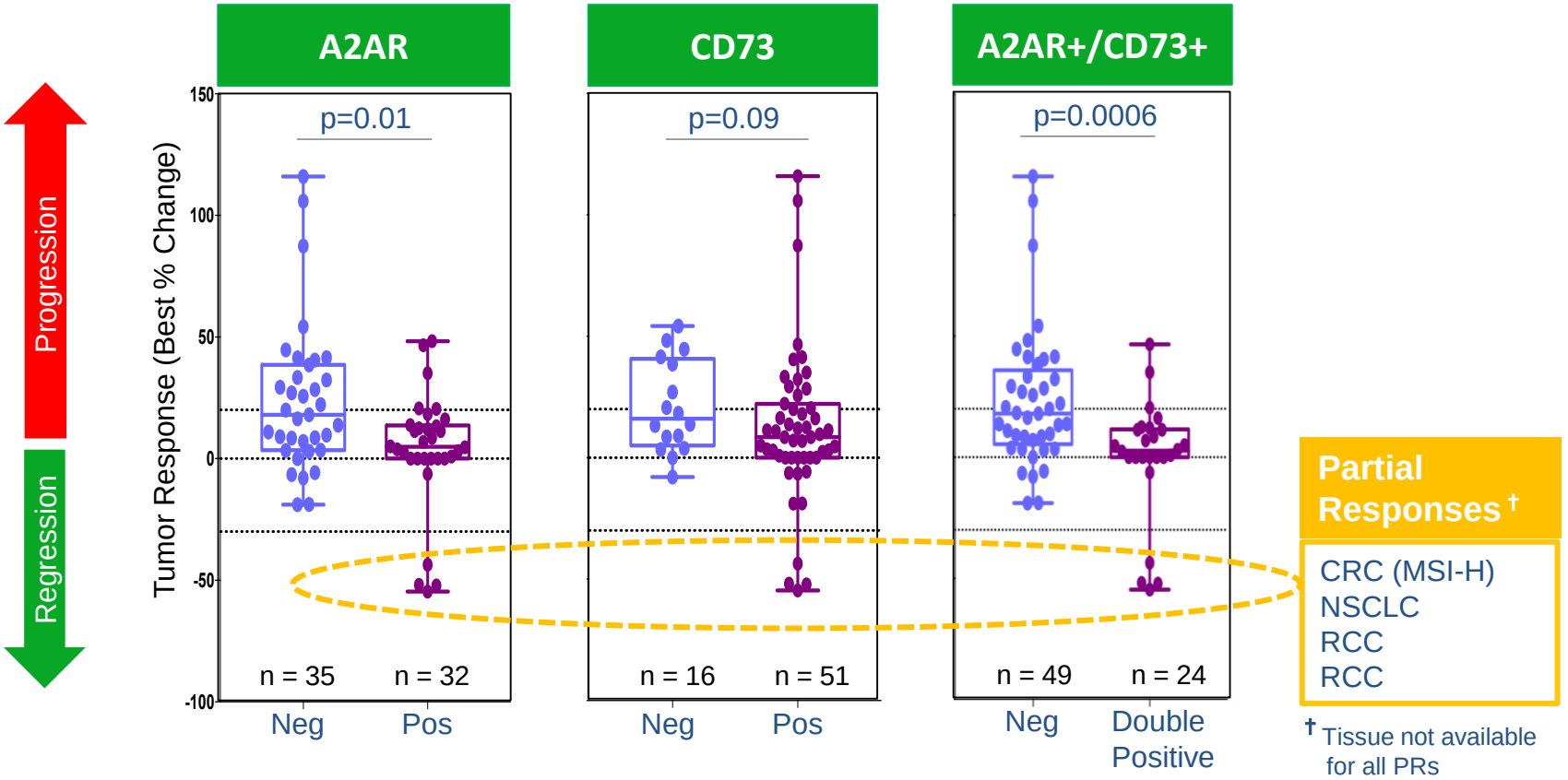
CPI-444/Atezolizumab (n=5)

- Gr 3 immune related hepatitis, dermatitis, mucositis, pneumonitis
- Gr 3 autoimmune hemolytic anemia
- Gr 3 increased ALT/AST
- Gr 3 thrombocytopenia/ Gr 4 encephalitis
- Gr 3 pneumonitis

Data cutoff 10/26/17

Screening A2AR and CD73 Associated with Response

Double positive A2AR, CD73 may be predictive



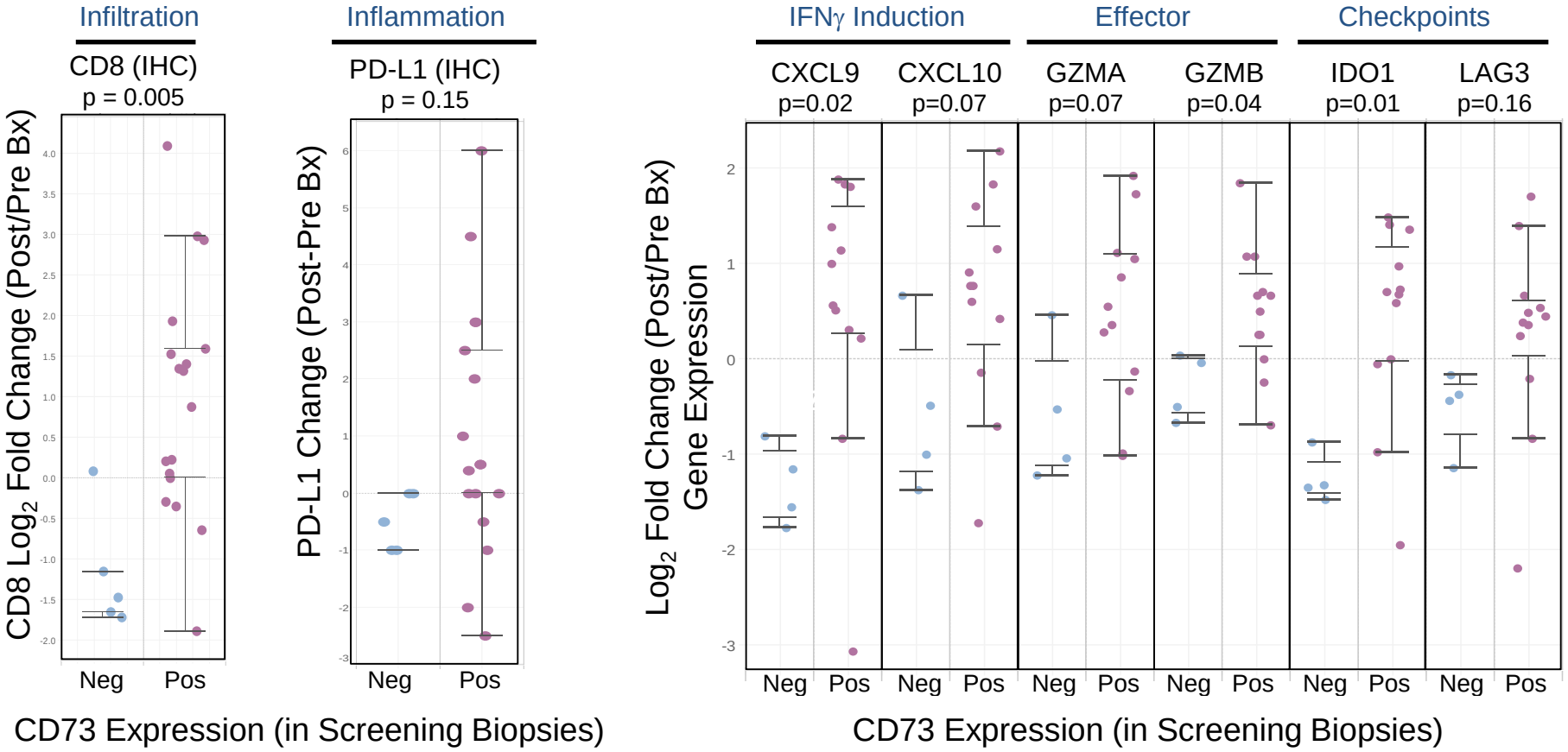
Screening A2AR, CD73 Associated with Disease Control Rate

Double positive A2AR, CD73 may be predictive

Disease Control Rate (all indications; biomarker assessable)		
	Negative	**Positive**
A2AR	4/39 (10%)	10/34 (29%)
CD73	2/22 (9%)	12/51 (24%)
A2AR + CD73 (Double Positive)	**4/49 (8%)**	**10/24 (42%)***

*p=0.0007

In CD73+ Tumors, Single Agent CPI-444 Induces Expression of T cell Activation Markers in Post-Dose Biopsies



Summary

- Tumor expression of A2AR, CD73 and CD39 are increased in patients that are resistant to prior treatment with anti-PD-(L)1
- RCC and NSCLC have high tumor expression of adenosine pathway genes A2AR, CD73 and CD39
- CPI-444 has anti-tumor activity in RCC
  - Reponses seen in anti-PD-(L)1 resistant/refractory patients
  - A2AR and CD73 expression in screening biopsies is associated with response to therapy
- CPI-444 increases CD8+ infiltration in tumors and induces expression of IFNγ-dependent genes and Th1 activation
- This study continues to enroll patients with RCC and NSCLC in expansion cohorts

Acknowledgements

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