PD-L1 in renal and bladder carcinomas

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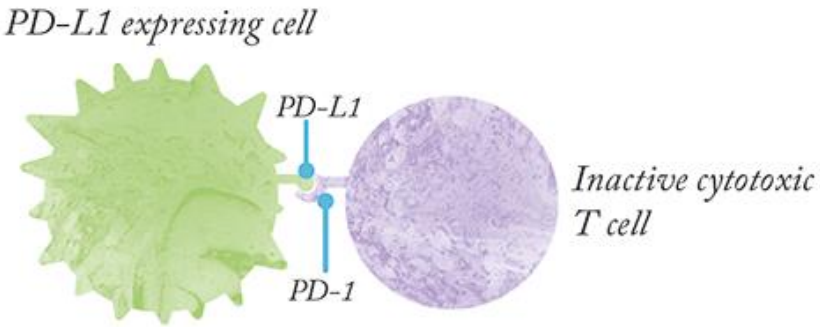
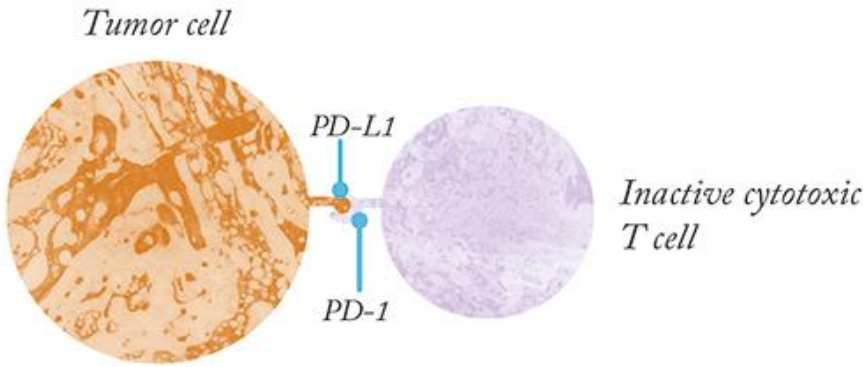
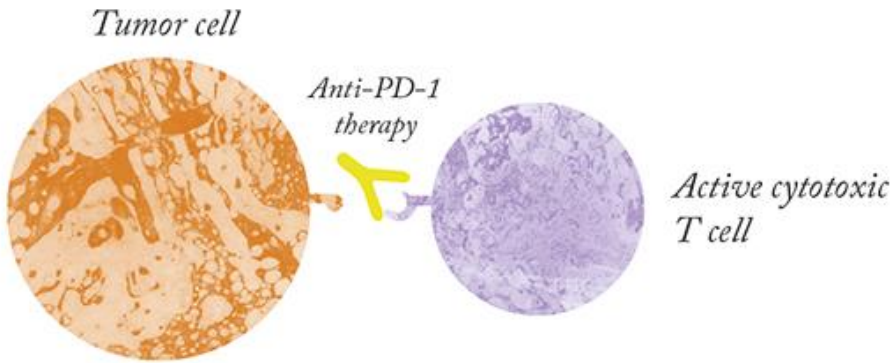
The Role of the PD-1/PD-L1 Pathway in Cancer



Limiting damage to healthy tissue
Inactivation of T cells limits damage to healthy tissue



The tumor escapes detection
Inactivation of T cells reduces tumor cell killing



Immuno-oncology therapies harness the immune response to fight tumors
Blocking PD-L1 enables cytotoxic T cells to actively remove tumor cells

Mutational heterogeneity in cancer creates opportunities for immune recognition

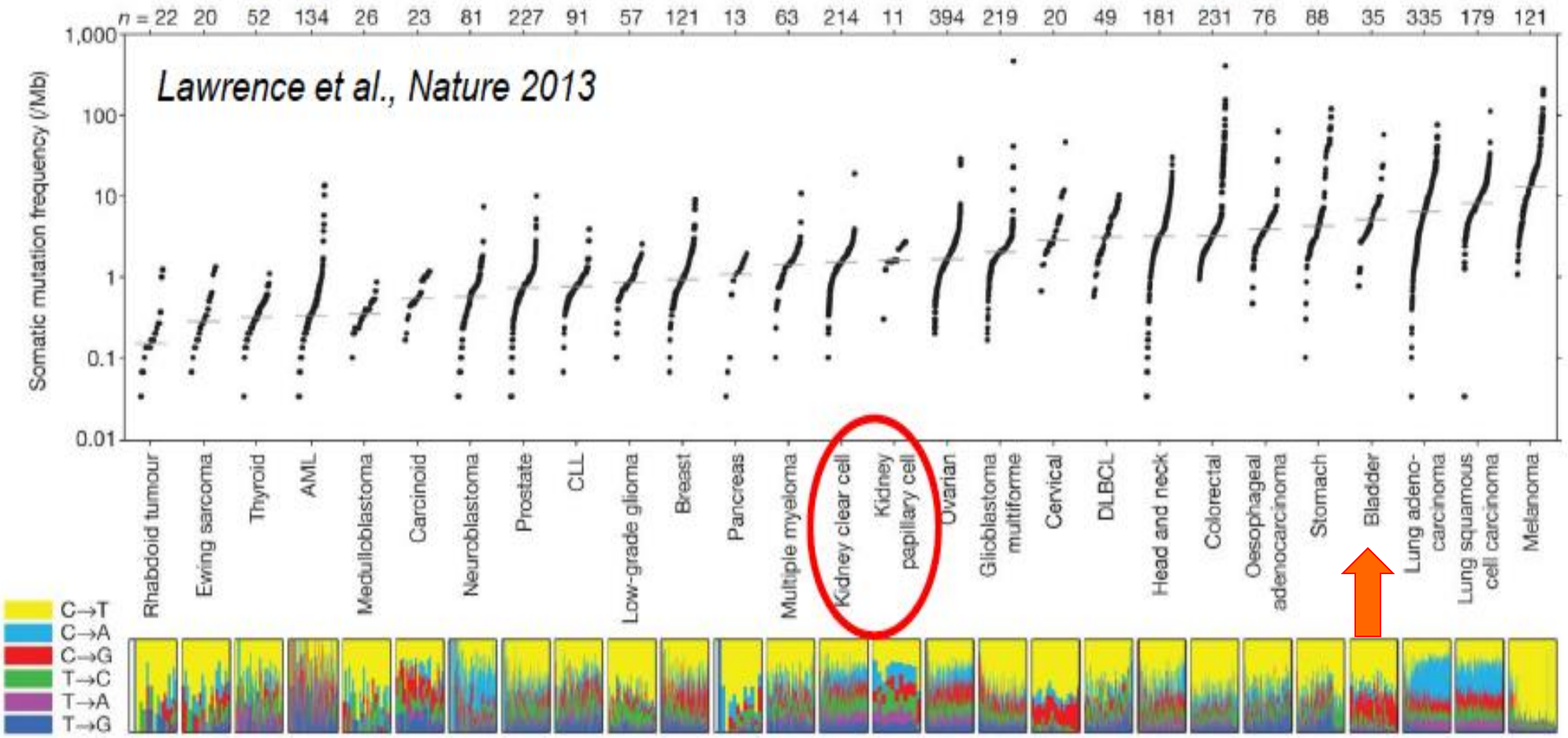


Table 1. Overview of PD-1 and PD-L1 expression in various types of solid tumors

Tumor types (n = 437 total)	PD-1 expression (% and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Carcinomas (n = 380 total)			
Breast (n = 116)	51% (1–20)	45%	29%
Colon (n = 87)	50% (1–>20)	21%	12%
NSCLC (n = 44)	75% (1–20)	50%	43%
Pancreas (n = 23)	43% (1–16)	23%	9%
Prostate (n = 20)	35% (1–6)	25%	5%
Merkel cell carcinoma (n = 19)	17% (1–4)	0%	0%
Endometrium (n = 16)	86% (1–13)	88%	79%
Ovary (n = 14)	93% (1–16)	43%	36%
Liver (n = 13)	38% (1–5)	8%	0%
Bladder (n = 11)	73% (1–10)	55%	55%
Kidney (n = 11)	36% (1–3)	67%	33%
CUP (n = 6)	50% (1–4)	33%	33%
Sarcomas (n = 33 total)	30% (1–>10)	97%	30%
Melanoma (n = 24 total)	58% (1–15)	92%	58%

Renal cell carcinomas

PD-L1 significantly associated to

- size (OR = 2.28, 95% CI: 1.61-3.23)
- stage TNM (OR = 4.37, 95% CI: 2.99-6.39),
- ISUP nuclear grading (OR = 7.58, 95% CI: 5.26-10.92)
- necrosis (OR = 6.77, 95% CI: 4.73-9.71)

Clinicopathological and prognostic value of programmed death ligand-1 (PD-L1) in renal cell carcinoma: a meta-analysis

F Xu, et al Int J Clin Exp Med. 2015 Sep 15;8(9).

CCR and anti PD-1 or anti PD-L1

Table 1. Single agent anti-PD-1 (nivolumab) studies in RCC.

Phase	Total number of patients (with RCC)	Dose of nivolumab in RCC (mg/kg)	Objective response rate in RCC	Stable disease in RCC	Immune-related grade 3 or 4 adverse events	Reference
I	39 (1)	10.0	n/a	n/a	3%	Brahmer *et al.* [2010]
I	296 (33)	1.0, 10.0	29%	27%	6%	Topalian *et al.* [2012b]
II	168 (168)	0.3, 2.0, 10.0	21%	40%	**	Motzer *et al.* [2014]

Table 2. Single agent anti-PD-L1 studies in RCC.

Agent	Phase	Total number of patients (with RCC)	Dosing in RCC (mg/kg)	Objective response rate in RCC	Stable disease in RCC	Treatment-related grade 3 or 4 adverse events	Reference
BMS-936559	I	207 (17)	10.0	12%	41%	5%	Brahmer *et al.* [2012]
Atezolizumab	I	277 (69)	⩽1, 3.0, 10.0, 15.0, 20.0	15%	54%	1%	Herbst *et al.* [2013], Herbst *et al.* [2014], McDermott *et al.* [2014]

CCR and PD-L1 in association

Table 3. Anti-PD-1/PD-L1 in combination with angiogenesis inhibition or other immune checkpoint inhibition in RCC.

Agents	Phase	Total Number of Patients (with RCC)	Dosing in RCC	Objective Response Rate in RCC	Stable Disease in RCC	Grade 3 or 4 Adverse Events	Reference
Atezolizumab, Bevacizumab	IB	33 (10)	Atezolizumab 20 mg/kg q3weeks, Bevacizumab 15 mg/kg q3weeks	40%	50%	49%	Lieu *et al.* [2014]
Nivolumab, Sunitinib, Pazopanib, (CheckMate 016)*	I/II	53 (53)	N2, N5	52% (nivolumab/ sunitinib), 45% (nivolumab/ pazopanib)	30% in N/ sunitinib arms	71.4% in N2/sunitinib arm, 84.6% in N5/ sunitinib arm	Amin *et al.* [2014] [ClinicalTrials.gov identifier: NCT01472081]
Nivolumab, Ipilimumab (CheckMate 016)*	I/II	44 (44)	N3/I1, N1/I3	43% (N3/I1), 48% (N1/I3)	24% (N3/I1), 35% (N1/I3)	28.6% (N3/ I1), 60.9% (N1/I3)	Hammers *et al.* [2014] [ClinicalTrials.gov identifier: NCT01472081]

Abbreviations: N2, nivolumab 2.0 mg/kg; N5, nivolumab 5.0 mg/kg; N3, nivolumab 3.0 mg/kg; I1, ipilimumab 1.0 mg/kg; N1, nivolumab 1.0 mg/kg; I3, ipilimumab 3.0 mg/kg; RCC< renal cell carcinoma.
*This study is ongoing but is not currently recruiting participants.

Nivolumab : FDA approved in CCRCC in second line chemotherapy

Urothelial carcinomas

PD-L1 expression correlated to stage
No correlation with grading (p = 0.25)

OS variable results

Wang Y et al. 2009. *J. Huazhong Univ. Sci. Technol. Med. Sci*. 29: 77-79. (50 patients)
Xylinas E et al. 2014. *Eur. J. Surg. Oncol.* 40: 121-127. (302 parients)
Faraj, SF. Urology. 2015 Mar; 85(3): 703 (56 patients)
Huang Y et al Oncol Rep. 2015 Jun;33(6):3075-84 (data base 696 patients)

Probably because of variable evaluation in PD-L1 (% ? targets ?) (see later)

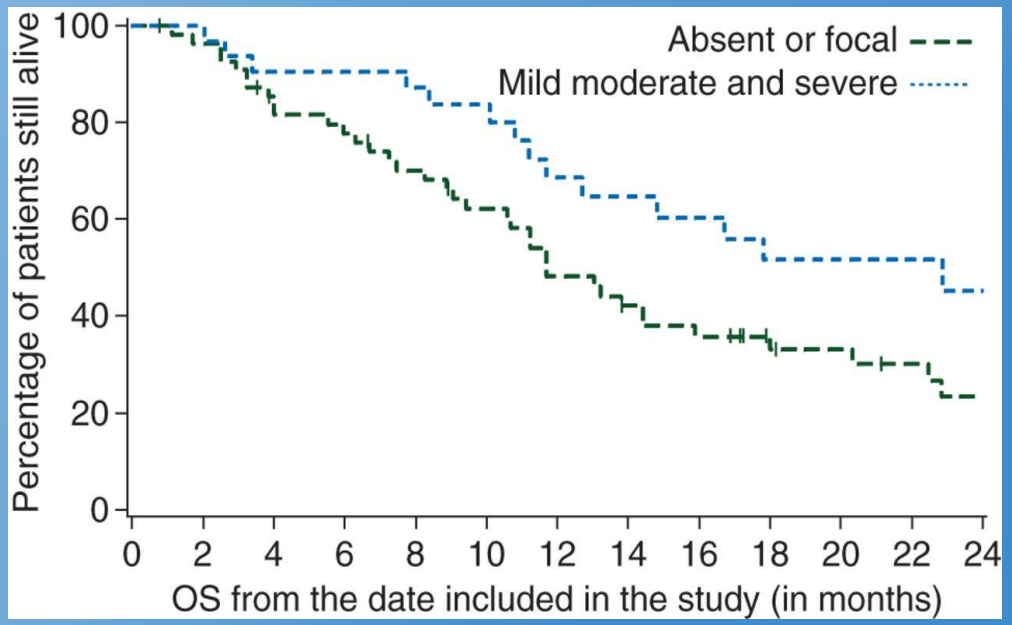
Mukherji D et al. Clin Genitourin Cancer. 2016 Apr;14(2):183-7

UC and OS

PD-L1 expression on
- 20% tumor cells (14% if metastasis)
- Peri tumoral lymphocytes or immune cells (PTL or IC)
  37% (2+, 3+)

OS significatively increased if
IC PD-L 1+ (<10%) vs (2+ (<25%), 3+ (>25%))
23 vs 12 mois (univariate p=0,04, multivariate p = 0,0007)
(89 patients)

Bellmunt J et al Ann Oncol. 2015 Apr;26(4):812-7



UC : PD-L1 and treatment

2014 : phase 1 study in metastatic urothelial Bladder Cancer (UBC)

As some might expect
Overall response rate (ORR)
- 43% PD-L1 2+ et 3+ patients
- 11% PD-L1 0+ ou 1+ patients

Atezolizumab FDA approved in june 2016 for metastatic UBC
IMvigor 210 : 315 patients with UBC

CU : PD-L1 and treatment

IMVIGOR 210 (atezolizumab) phase 2
315 patients locally advanced

Strong PD-L1 expression correlated to response
But negative patients have response

Overall response rate (ORR) of 15% with significant durability (in 38/45 patients)

OS 11,4 months (IC 95% 9-NE) vs 7,9 (IC 95% 6,6-9,3)

CU : PD-L1 and treatment

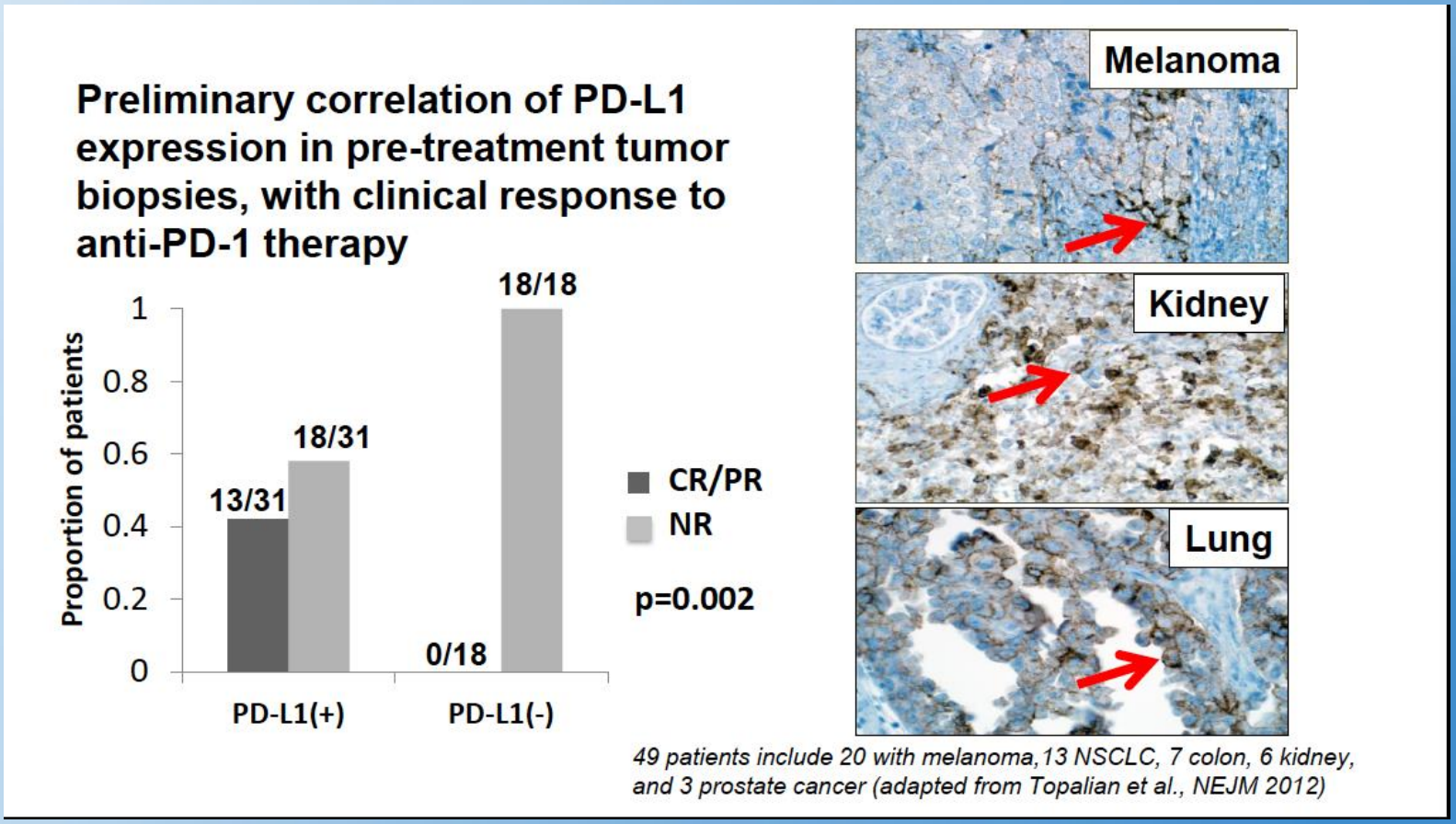
Massard et al JCO Sept 2016
phase I/II trial metastatic UBC
61 patients
anti–PD-L1 monoclonal antibody durvalumab

significant activity in UBC,
ORR of 31% in a population that was enriched for PD-L1–positive patients

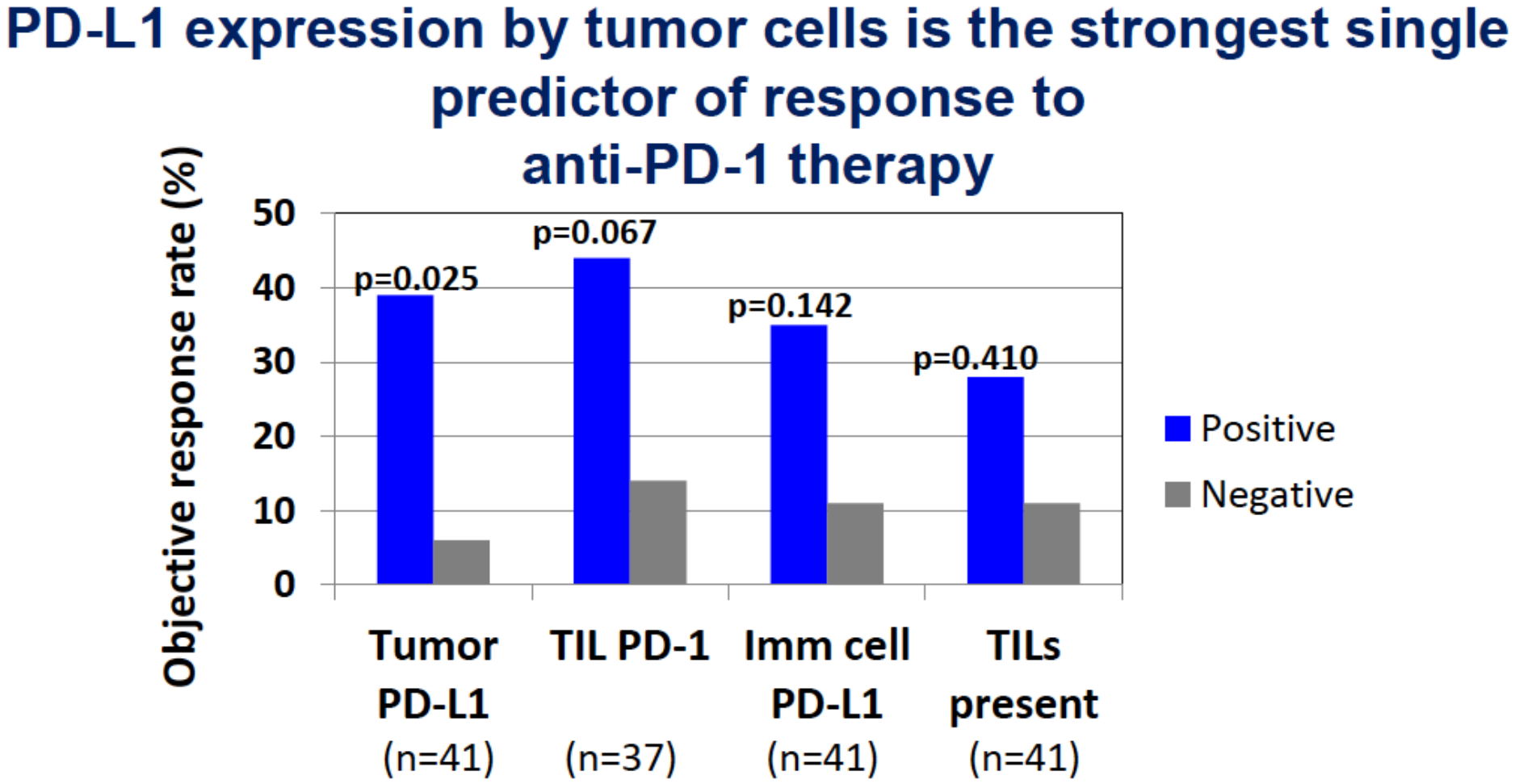
PD-L1 expression on either tumor cells (TCs) or immune cells (ICs) .

CU : PD-L1 and treatment

IMvigor used SP142 antibody (spring bioscience)
Durvalumab study used SP263 antibody (Ventana)



PD-L1 and therapeutic response



J Taube, R Anders, et al., CCR 2014

PD-L1 and Immunohistochemistry

PD-L1 IHC methods currently in testing

	JHU	BMS	Merck	Roche
mAb clone	5H1	28-8	22C3	SP142
Automated	No	Yes	Yes	Yes
Staining location scored	Membrane	Membrane	Membrane	Membrane
Cell type(s) scored	Tumor cells	Tumor cells	Tumor and/or infiltrating imm. cells	Infiltrating immune cells

Companion tests used

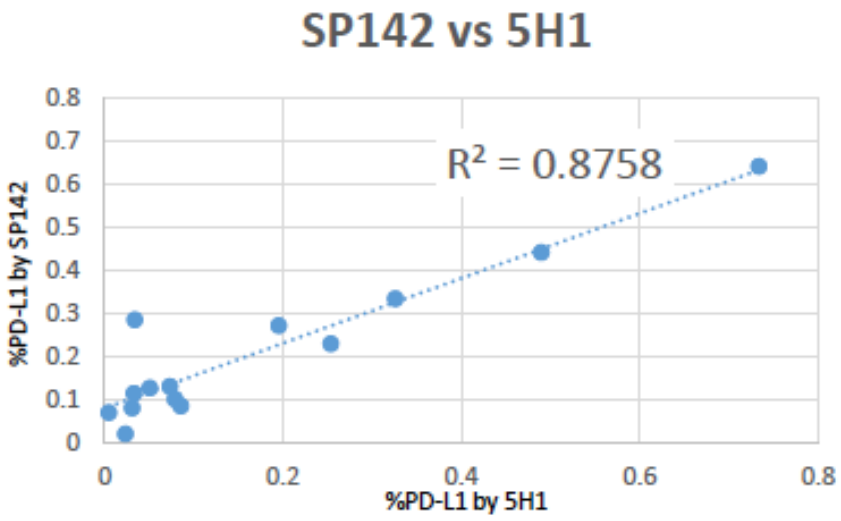
	Nivolumab (Anti PD1)	Pembrolizumab (Anti PD1)	Atezolizumab (Anti PDL1)	Durvalumab (Anti PDL1)
anti PDL1 antibody	28-8 (Dako) (abcam)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretation and IHC scoring	1-10% Membranous TC	1-50% Membranous TC	1-50% Membranous TC and IC	> 25% Membranous TC
system	Autostainer Link 48	Autostainer Link 48	Benchmark ULTRA	Benchmark ULTRA
Pharmaceutic laboratory	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

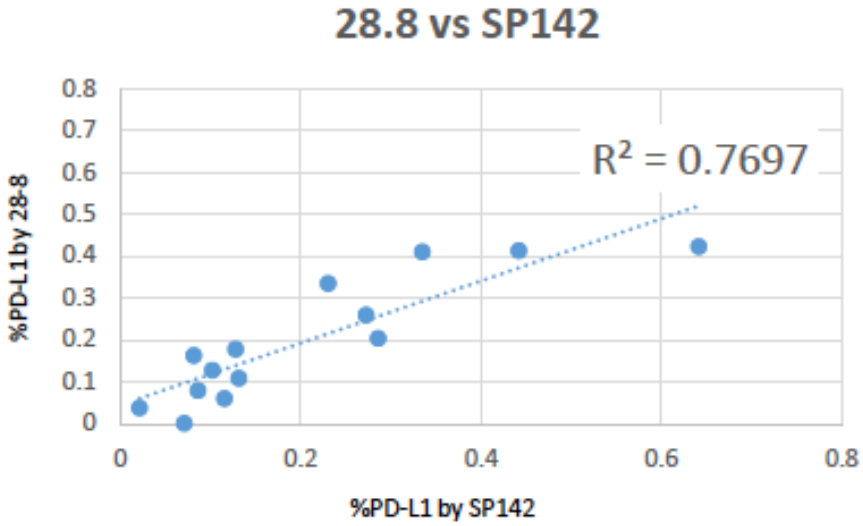
PD-L1 threshold in companion diagnosis

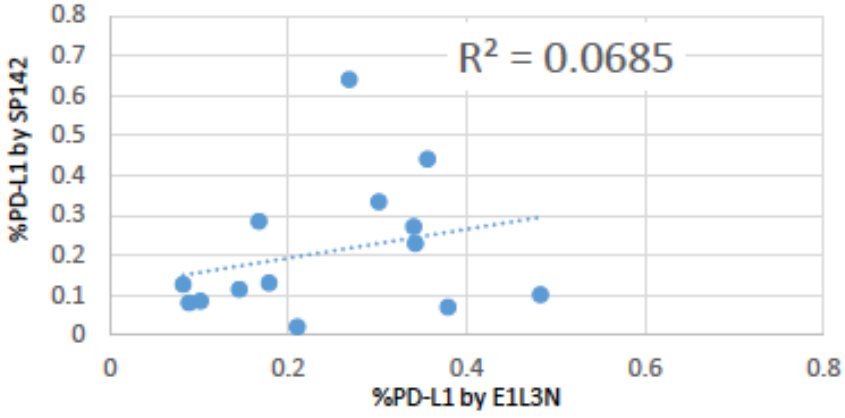
Tumor celle positivity	
<1%	Negatve all trials
>1% <5%	Nivolumab and Pembrolizumab
>5% <10%	Nivolumab and Atezolizumab
>10% <25%	Nivolumab and Durvalumab
>25% <50%	Durvalumab
>50%	Pembrolizumab and Atezolizumab

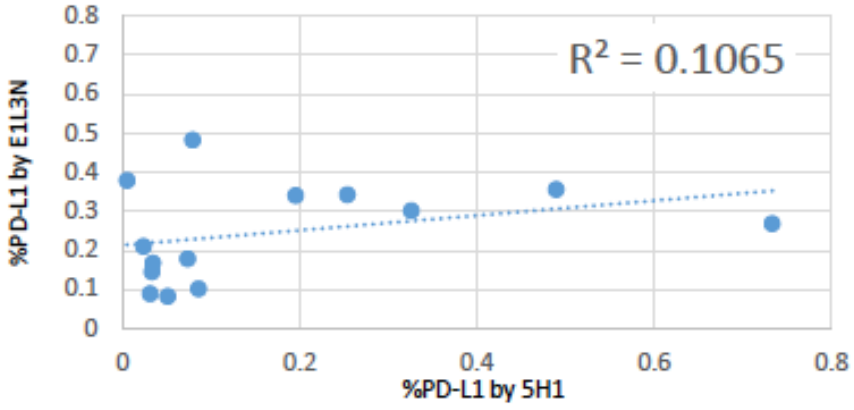
Immune cells positivity	
<1%	Negatve all trials
>1% <10%	Atezolizumab
>10%	Avelimab and Atezolizumab

PD-L1 Antibody Comparisons



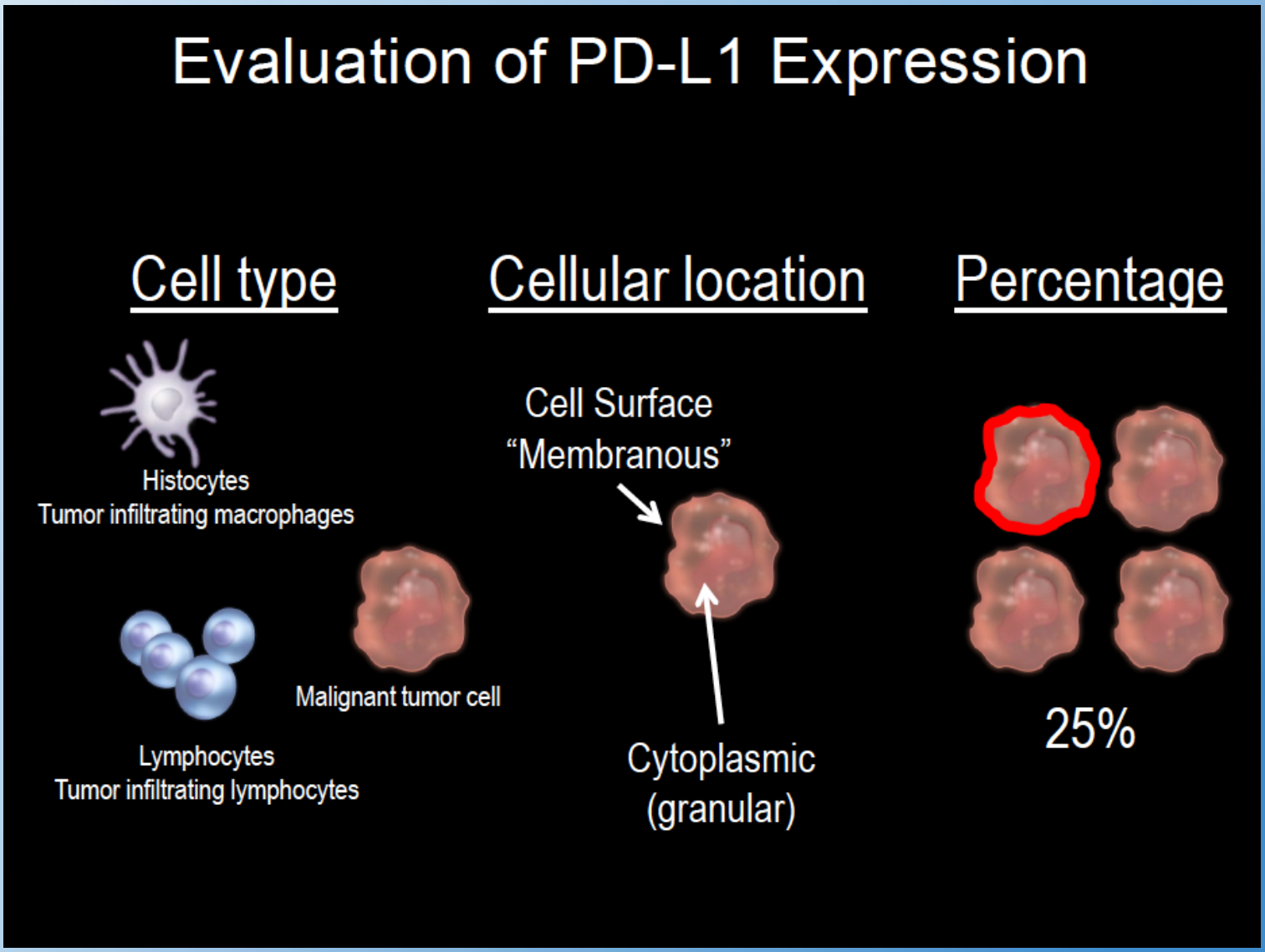






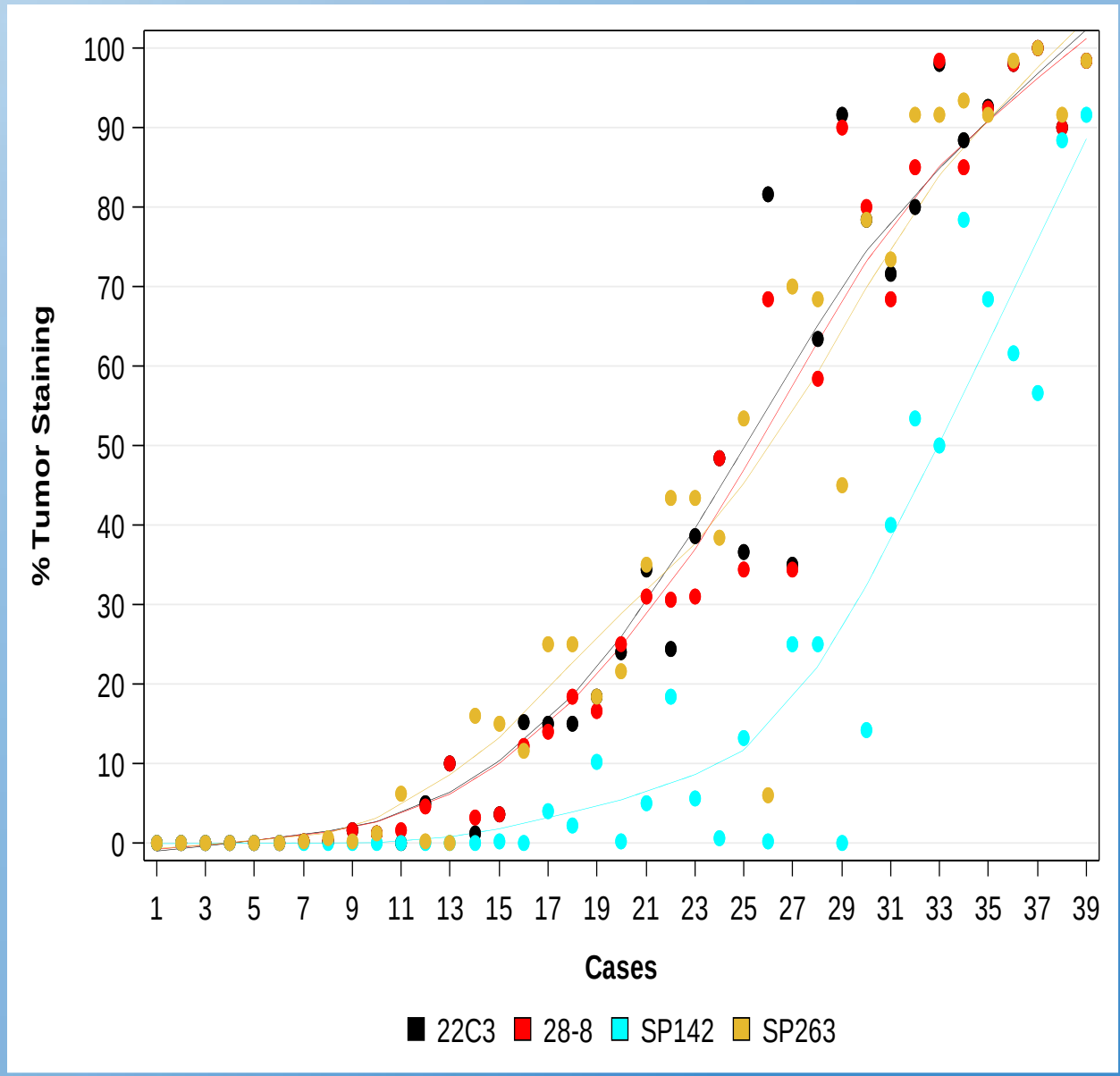
J Sunshine, RA Anders, JM Taube (unpublished data)

PD-L1 and pathologist



Blue print : Evaluation of mean IHC staining on TC per case with 3 senior pathologists

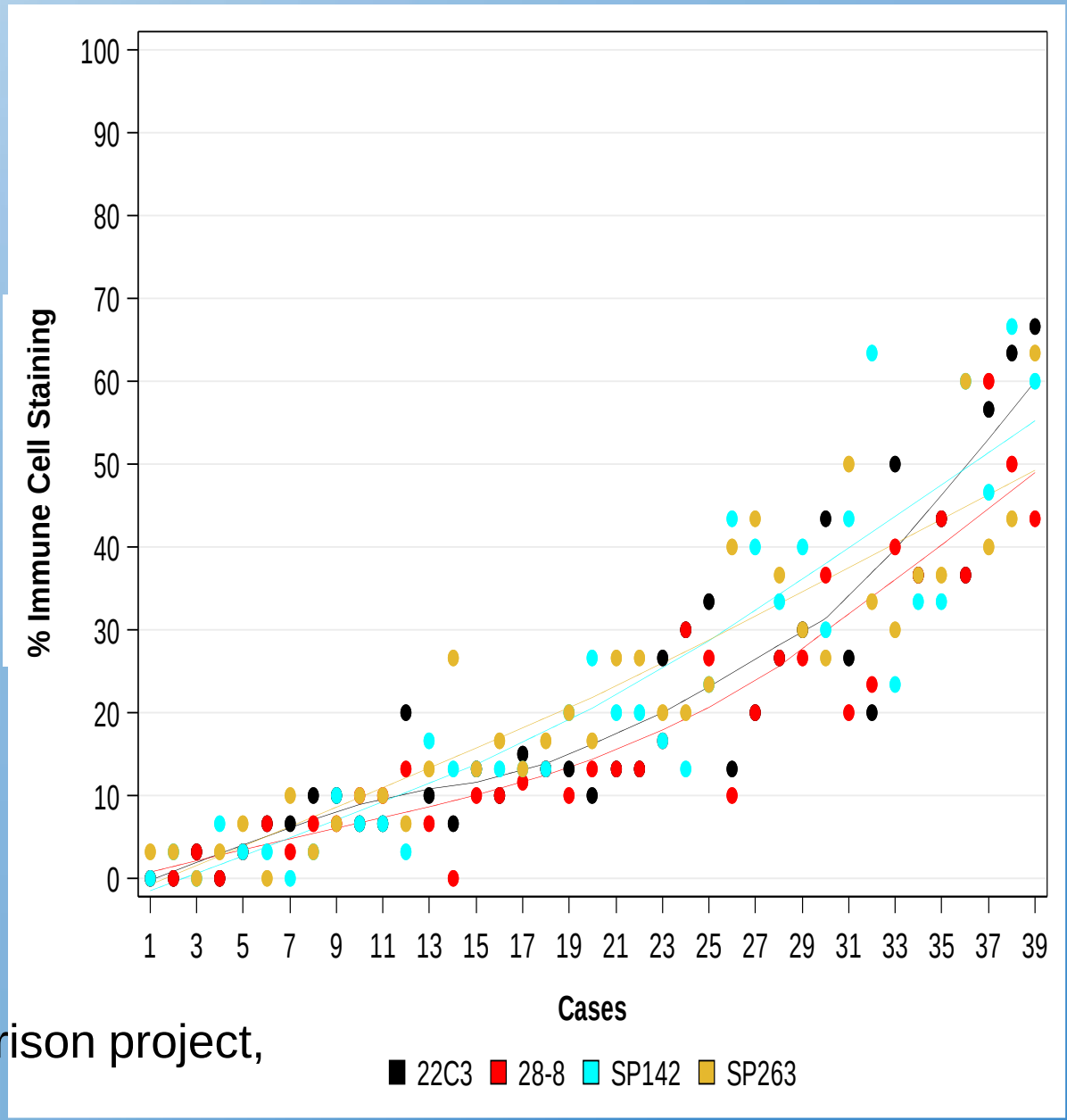
- Comparison of positive TC %
- Mean score of 3 pathologists for each trial on each case



Blueprint PD-L1 IHC assay comparison project, Dr. Fred R. Hirsch, AACR

Blue print : Evaluation of mean IC staining per case by 3 senior pathologists

- Comparison of positive IC %
- Mean score of 3 Pathologsts for each case in each trial
- Conclusion: quantification mare variable than TC staining evaluation



Blueprint PD-L1 IHC assay comparison project,
Dr. Fred R. Hirsch, AACR

CU : PD-L1 and treatment

IMvigor analysis focused on Immune cells (IC) staining.

ORR : 26% in patients PD-L1 + (IC2/3 >5%)
10% in the IC0/1 patients.

Atezolizumab is likely to be administrated to patients with both PD-L1–positive and PD-L1–negative bladder cancer.

CU : PD-L1 and treatment

Durvalumab responses correlated with PD-L1 expression on either TC or IC.

Considering TC only, ORR is 47% for positive vs 22% for negative staining.

Considering IC staining ORR : 57% for positive vs 13% for negative staining

CU : PD-L1 and treatment

Durvalumab study introduced a novel approach :

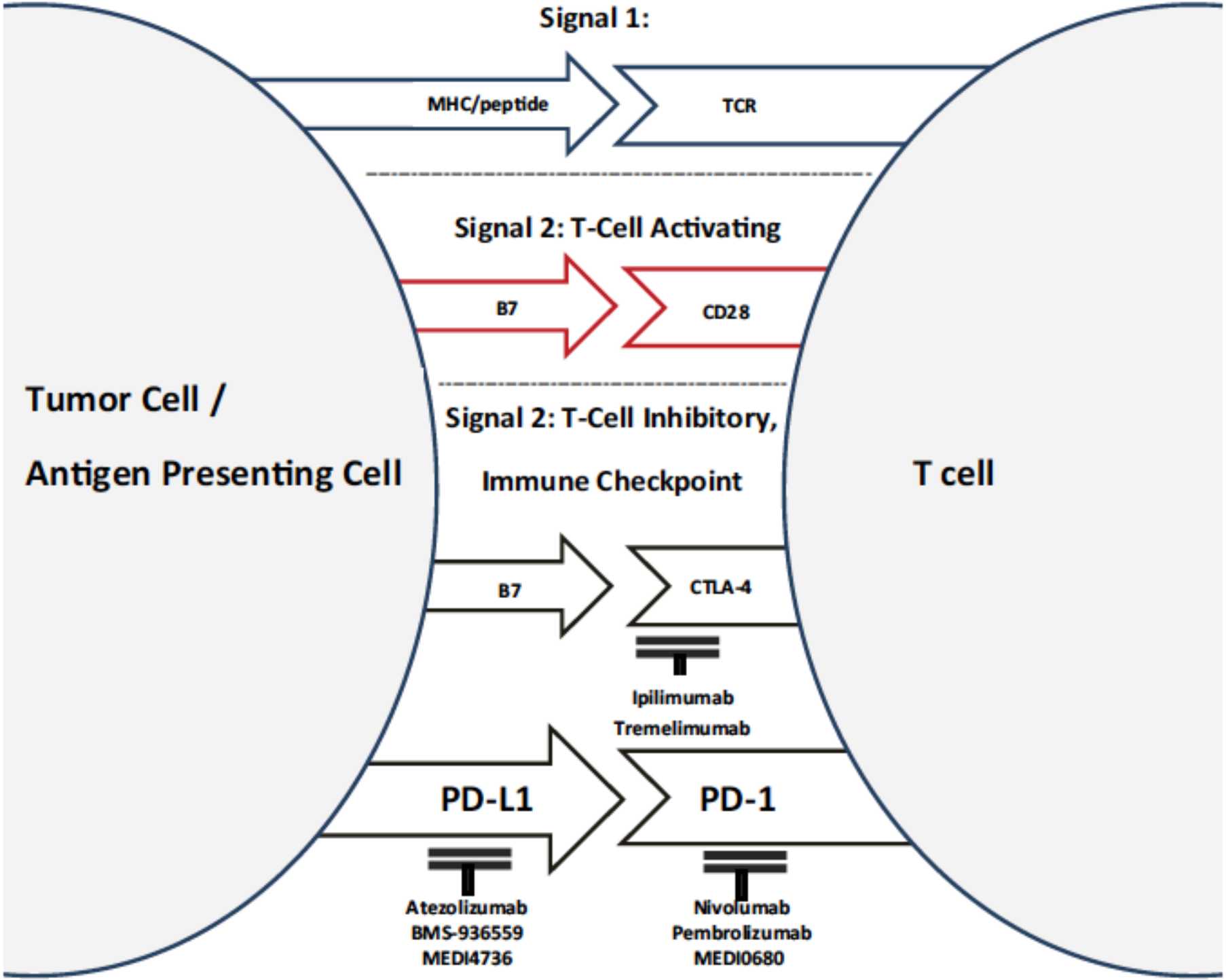
composite positive and negative categories
PD-L1 positive : ≥ 25% staining in either ICs or TCs,
PD-L1 negative (≤ 25%) in both the IC and TC

Patients negative for PD-L1 in both compartments : ORR of 0% (0 of 14),
Patients positive for PD-L1 in either compartment : ORR of 46%.

CU : PD-L1 and treatment

striking negative predictive value is premature :
Because : small population (61 patients)
population enriched in PDL1+ patients

On the other hand,
PD-1 or PD-L1 antinody are supposed to block the inhibitory signal transmitted from TCs or ICs to the CD8 T cells that infiltrate a tumor


Signal 1:
MHC/peptide
TCR
Signal 2: T-Cell Activating
B7
CD28
Tumor Cell /
Antigen Presenting Cell
Signal 2: T-Cell Inhibitory,
Immune Checkpoint
T cell
B7
CTLA-4
Ipilimumab
Tremelimumab
PD-L1
PD-1
Atezolizumab
BMS-936559
MEDI4736
Nivolumab
Pembrolizumab
MEDI0680

CU : PD-L1 and treatment

Therefore
Why PD-L1 expression is not more powerful in terms of predictive value ?
(together with previously exposed technical reasons)

intratumoral heterogeneity ?
PD-1/PD-L1 interaction in the tumor-draining lymph nodes ?
PD-L1 expression controlled by the cytokine milieu, meaning : dynamic changes in the tumor microenvironment over time ?

CU : PD-L1 and treatment

Durvalumab is being further evaluated in DANUBE trial,
525 patients with metastatic UBC
randomly assigned to either

durvalumab,

standard platinum-based chemotherapy, or

combination of durvalumab + the anti–CTLA-4 antibody tremelimumab.

Expected completion in September 2019.

CU : PD-L1 and treatment

Indeed

Future : Combination of treatment ? antiPDL1 anti CTL4 (melanoma)
First line treatment (Keynote 24 in lung carcinoma)

Technical guidelines in PD-L1 immunostaining ?

New biomarker approach ?