Overview of Immune Checkpoint Inhibitors: RCC and UBC

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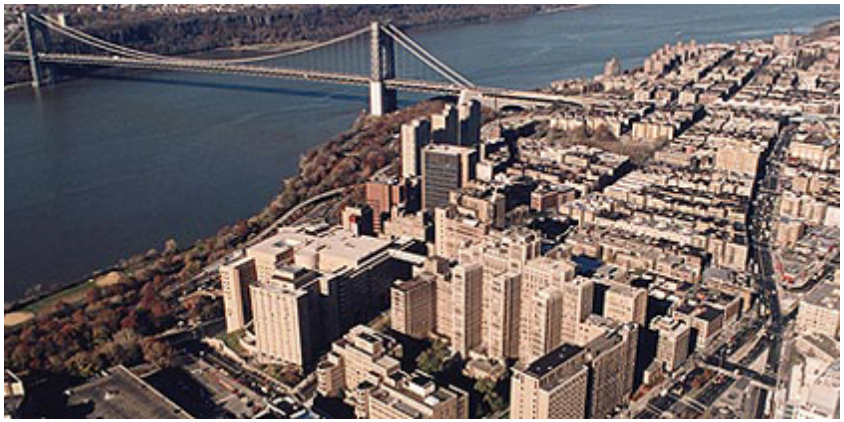

Columbia University
Medical Center
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Case

- 64 yo with recurrent bladder CA
- Presented 3 years PTV with nocturia, TURP showed MIBC
- GEM / CIS x 6 cycles with goal of bladder sparing surgery, well tolerated
- At surgery, multiple positive LN, cystectomy aborted
- Rx with docetaxel + ramicurimab, multiple AE's (neuropathy, tearing, severe rash, etc)
- Presents with PS 70% (ongoing fatigue)
- CT = multiple retroperitoneal LN c/w metastatic UBC

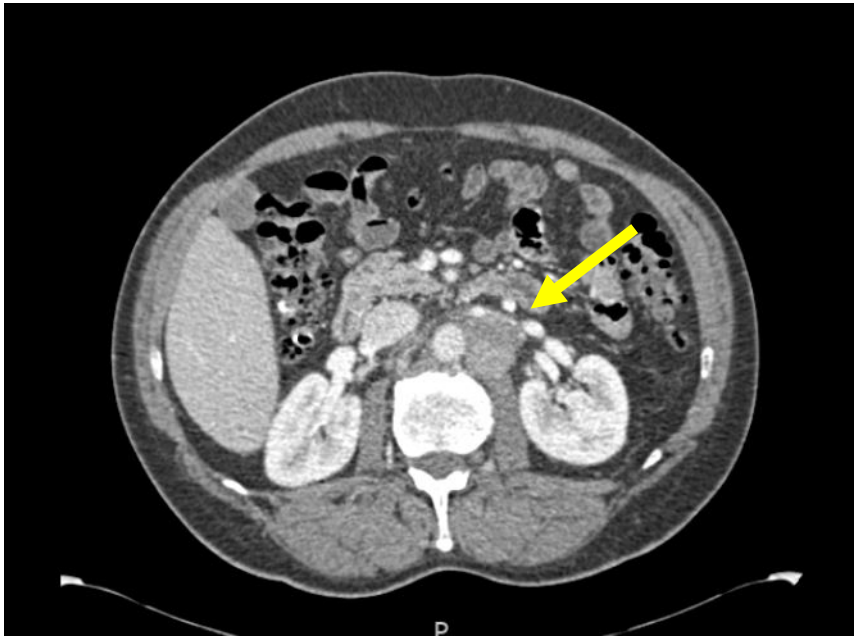
Case (cont)

- Enrolled on Phase I of MPDL3280A (now atezolizumab)
- Rx on study x 2 years total (q 2 weeks)
- AE = Rash upper R scapula
- CT = 70% decrease in SLD by RECIST 1.1, stable PR
- 1 yr later – elevated CEA on “executive” physical (20) (now age = 67)
- GI W/U Negative
- CEA continues to rise (45)
- PET / CT = focal intensity in R lobe prostate

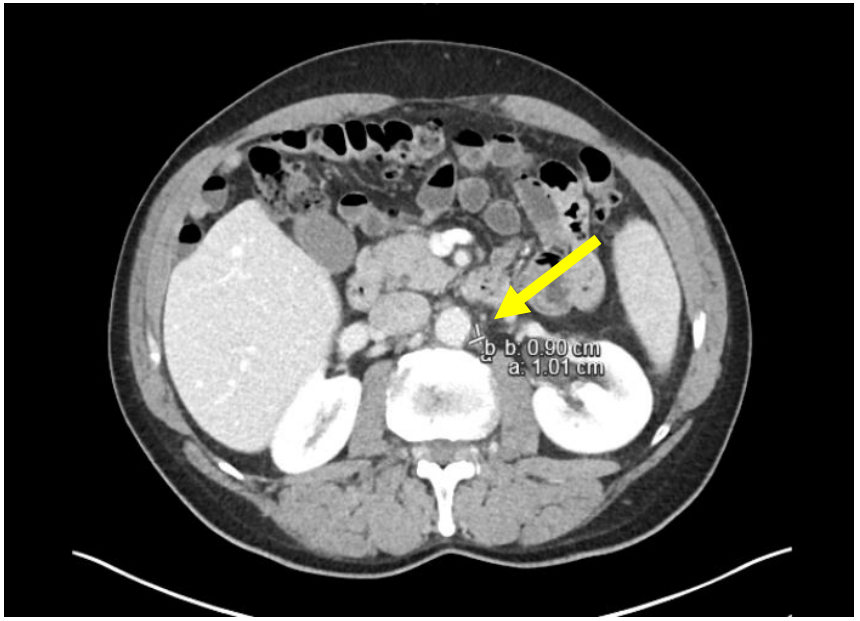
Case (cont)

- BX = UBC, c/w primary
- No other disease foci
- RX: Cystoprostatectomy
- Following

Case Images



Study Initiation



24 Months

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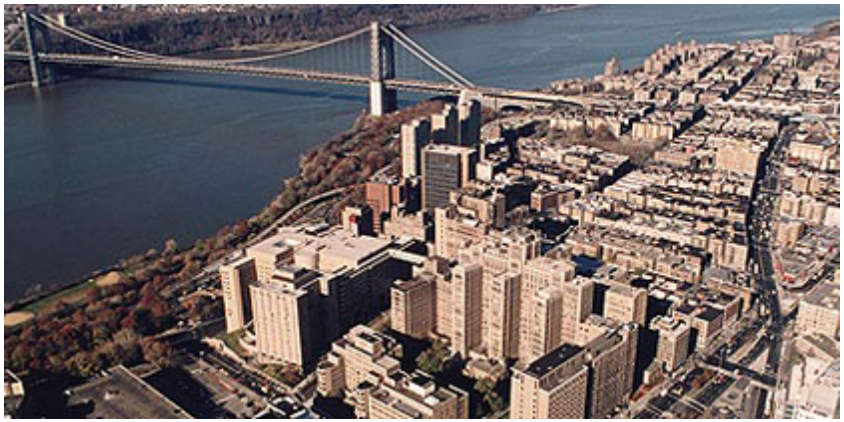

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Complete Disclosure

- Consulting:
  Agenus Inc, Dendreon Pharmaceuticals Inc, ImmunExcite, Janssen Biotech Inc, Lilly, Merck, NexImmune, Pierre Fabre, Roche Laboratories Inc / Genentech BioOncology

- Patents
  Amplimmune, Bristol-Myers Squibb Company, Janssen Biotech Inc

- Stockholder
  Compugen, NexImmune, Potenza Therapeutics, Tizona Therapeutics

- Sponsored Research Agreement
  Aduro Biotech, Bristol-Myers Squibb Company, Janssen Biotech Inc

Several of the agents discussed are NOT FDA approved for use in cancer treatment

Sixty Years Ago:

"…the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease…"

Lewis Thomas, 1957

"It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence."

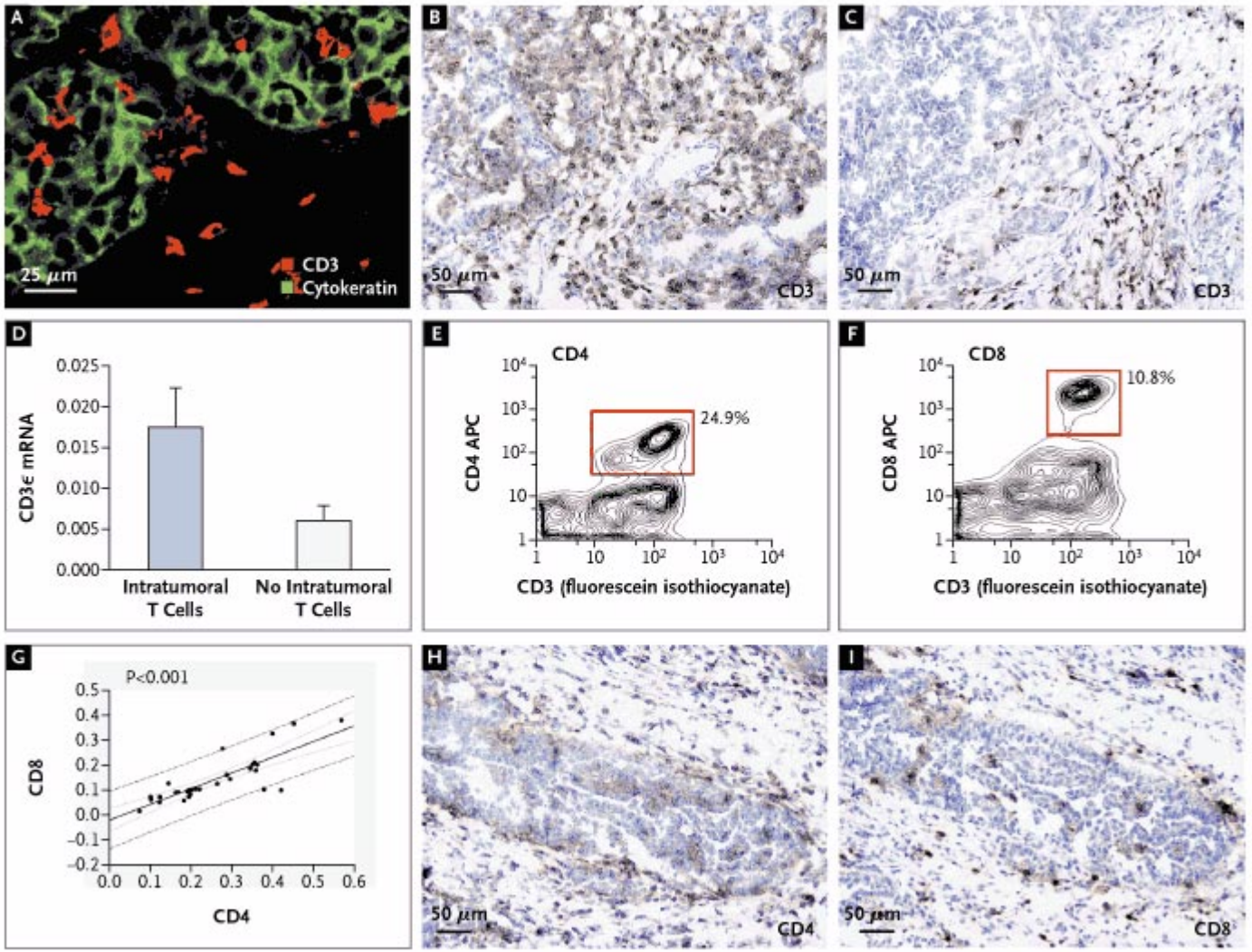
Sir Macfarlane Burnet, 1957

Lots of Tumors Have Infiltrating T Cells
Are they SURVEYING?

CD3 (All T Cells)

CD4 or CD8
(By Flow)

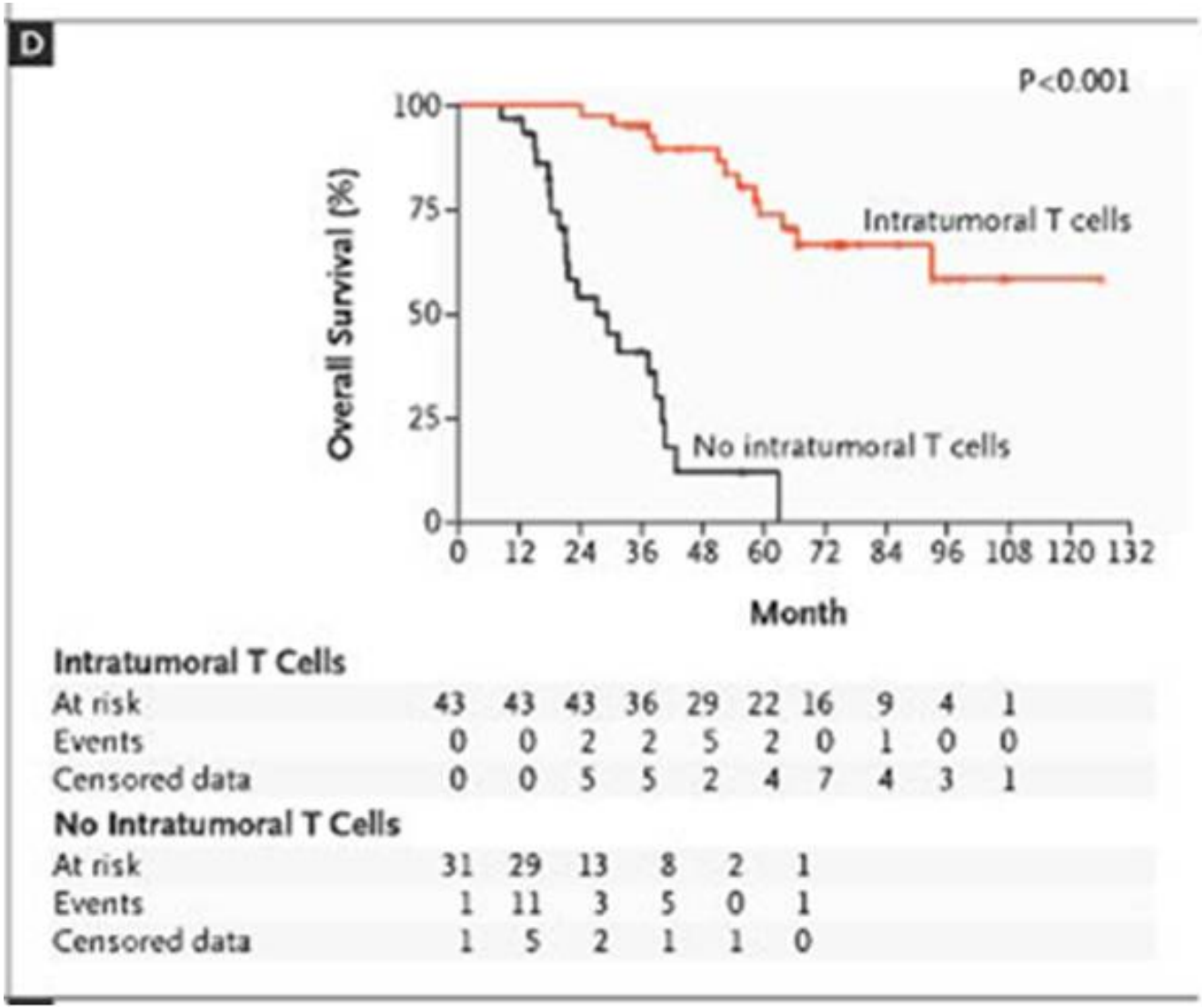
CD4 or CD8
(By IHC)



Zhang et al. N Engl J Med 2003;348:203-213

T Cells in Ovarian Cancer: A Life or Death Matter

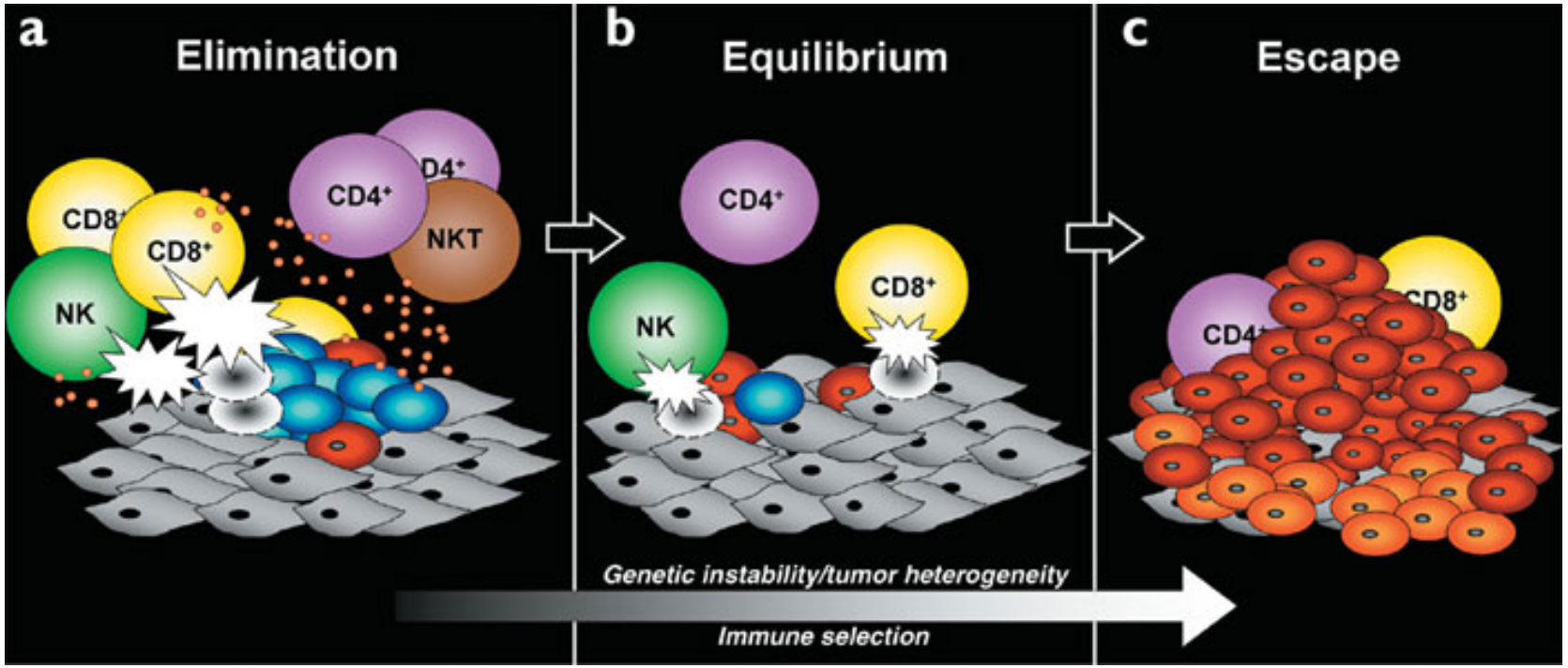
Stage IV Ovarian CA
Complete response to treatment



Intratumoral T Cells										
At risk	43	43	43	36	29	22	16	9	4	1
Events	0	0	2	2	5	2	0	1	0	0
Censored data	0	0	5	5	2	4	7	4	3	1
No Intratumoral T Cells										
At risk	31	29	13	8	2	1				
Events	1	11	3	5	0	1				
Censored data	1	5	2	1	1	0				

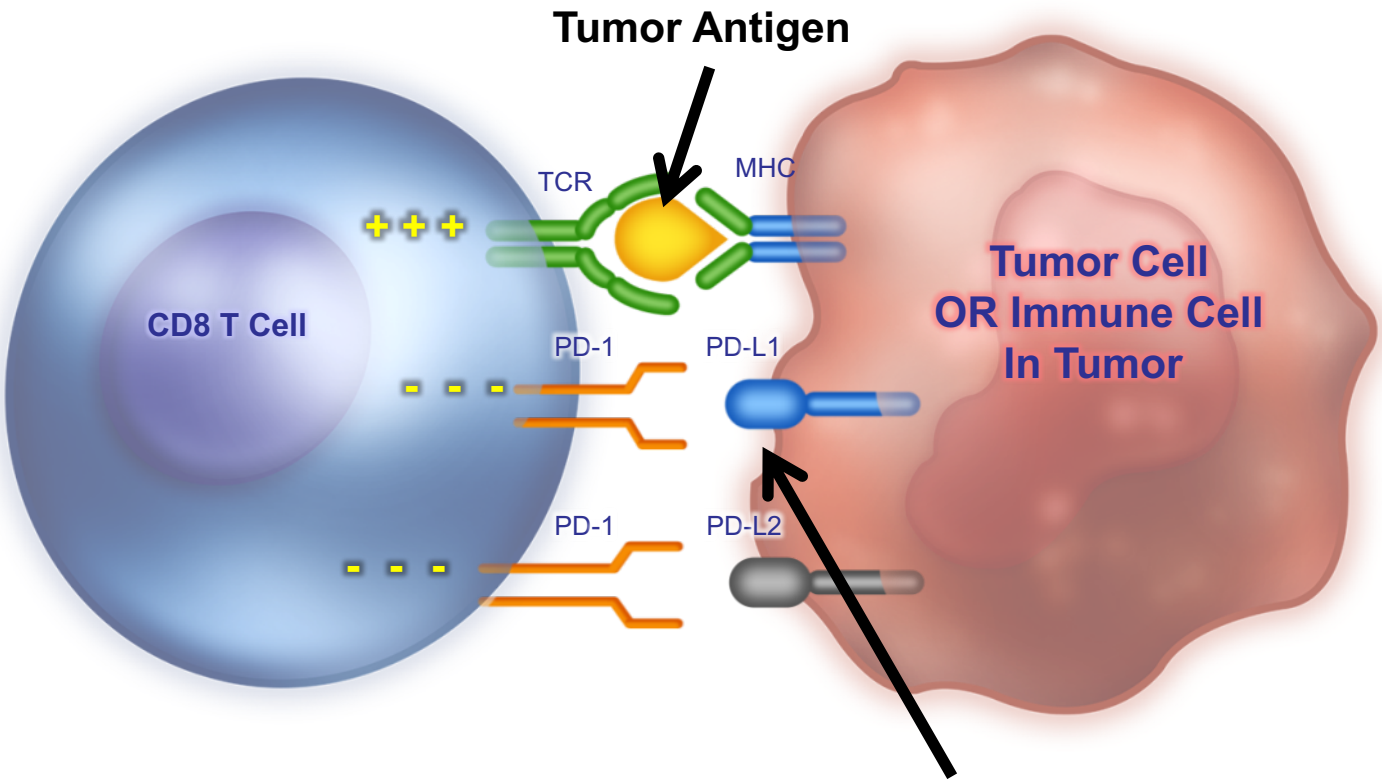
Zhang et al. N Engl J Med 2003;348:203-213

The Immune Editing Hypothesis (3 E's)

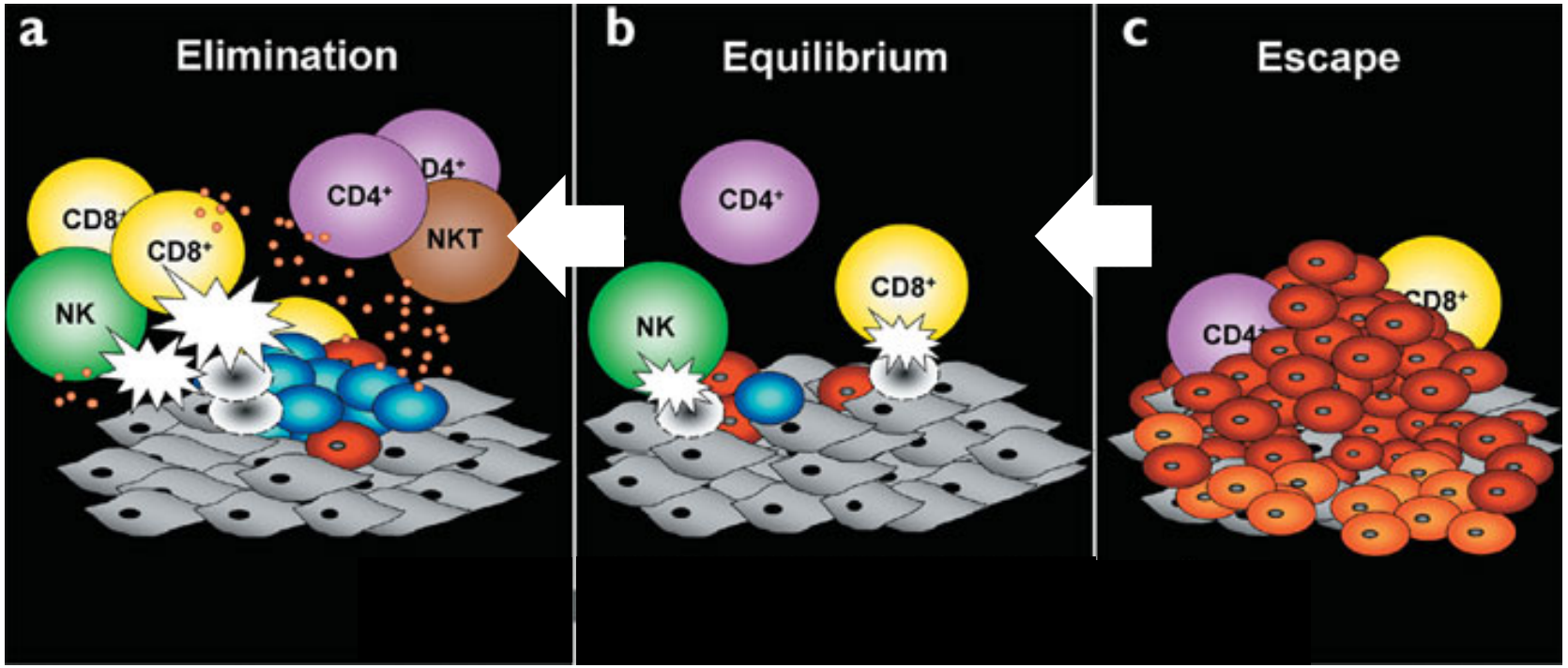


Dunn GP, et al. Nat Immunol. 2002;3:991-998

The PD-1 / PD-L1 Axis Is One Major Component of Escape

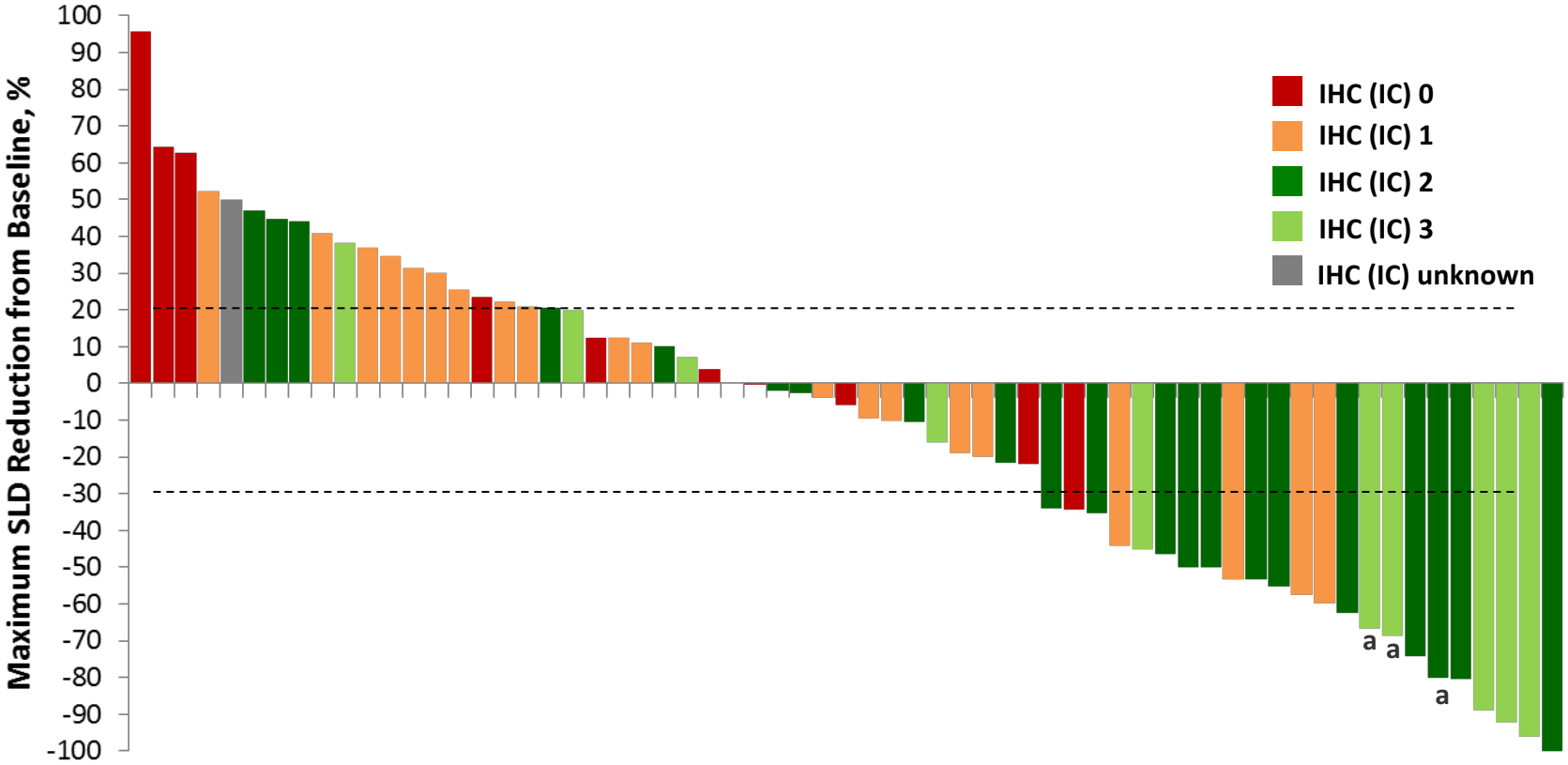


Reversing Escape?



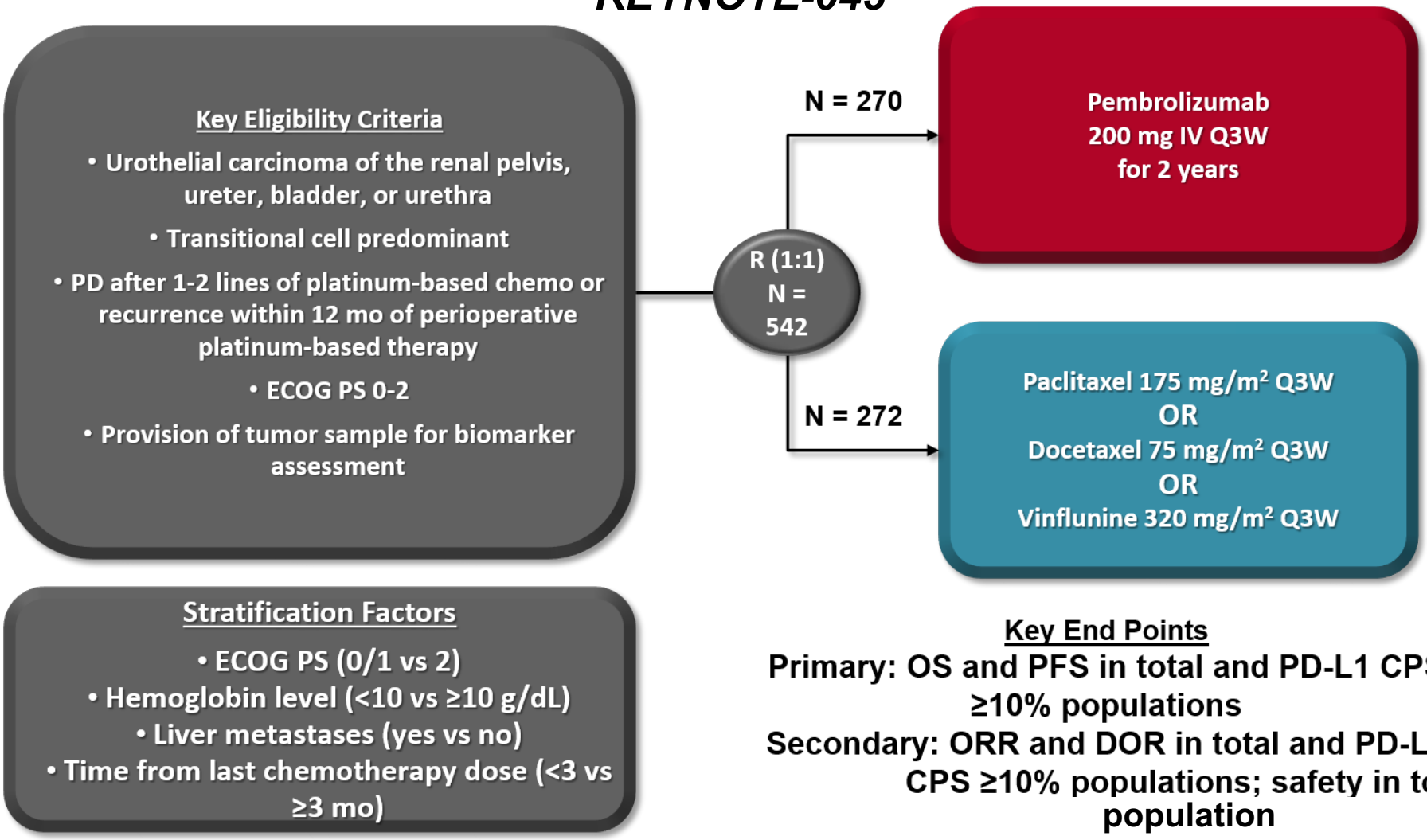
Dunn GP, et al. Nat Immunol. 2002;3:991-998

Blocking PD-1 / PD-L1 Tilts the Balance Back To Elimination: Objective Responses to Anti-PD-L1 (Atezolizumab) in Urothelial Bladder Cancer



Powles et al, Nature 2014

Level 1 Evidence: Pembrolizumab (Anti-PD-1) in Second Line UBC KEYNOTE-045



Key End Points

Primary: OS and PFS in total and PD-L1 CPS ≥10% populations

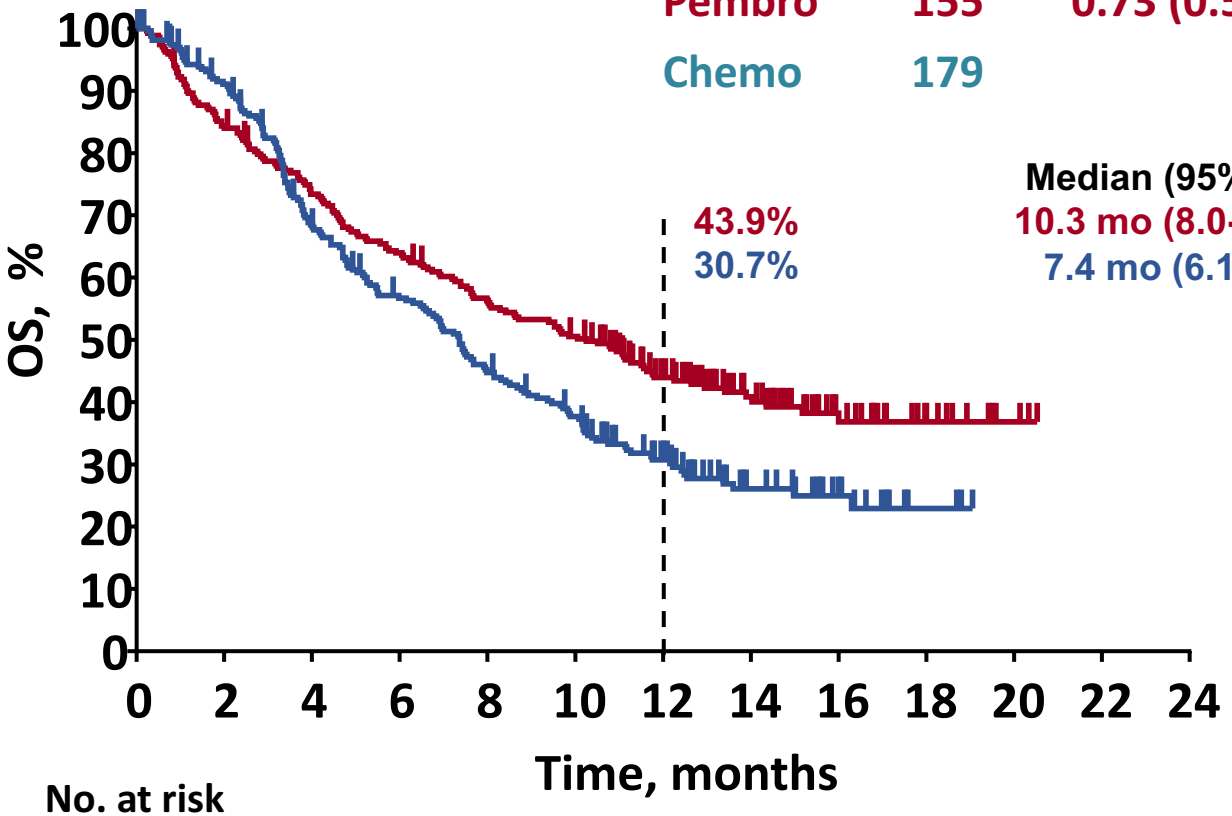
Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

CPS = combined positive score

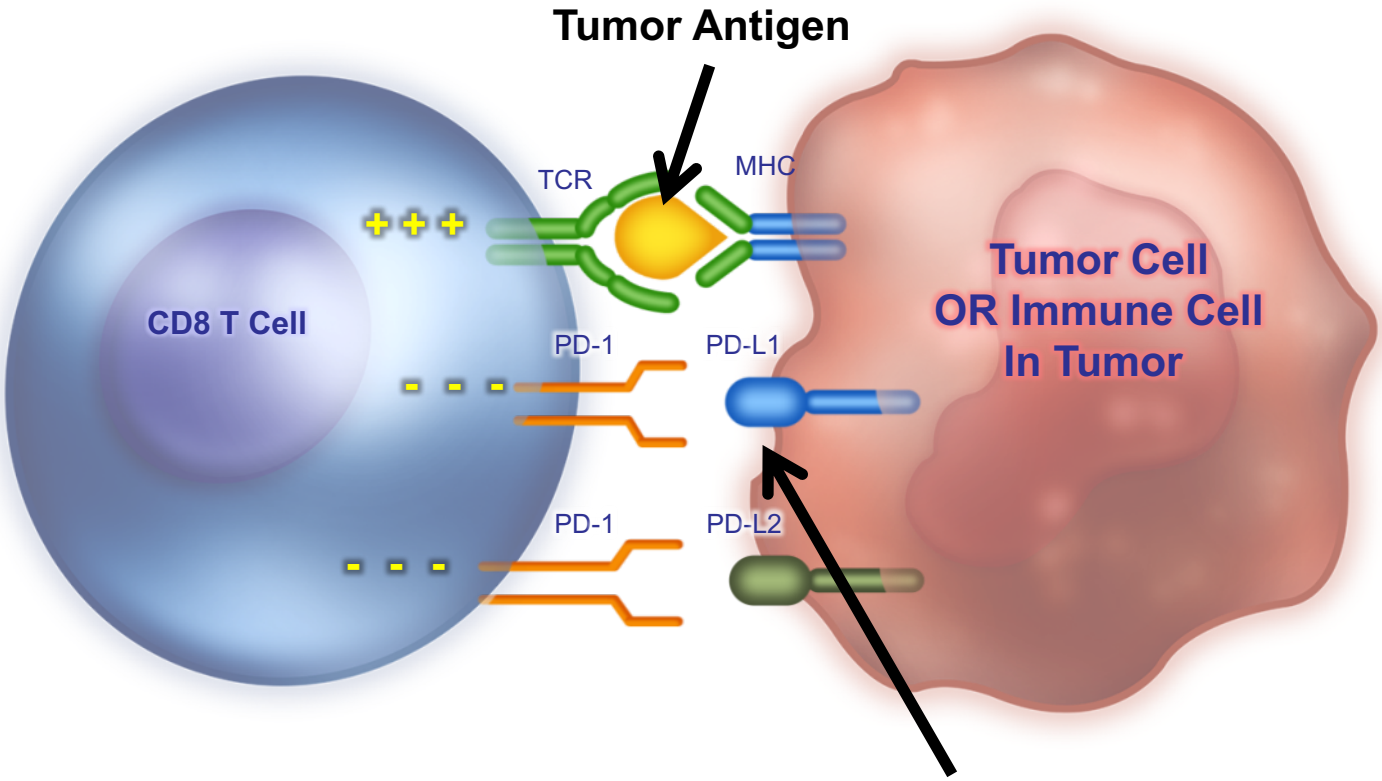
Bellmunt J et al NEJM 2017

Improved Overall Survival

	Events, n	HR (95% CI)	*P*
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		



If PD-1 Is Mediating Escape
Then Response Should Correlate with PD-L1 Expression in the Tumor Microenvironment

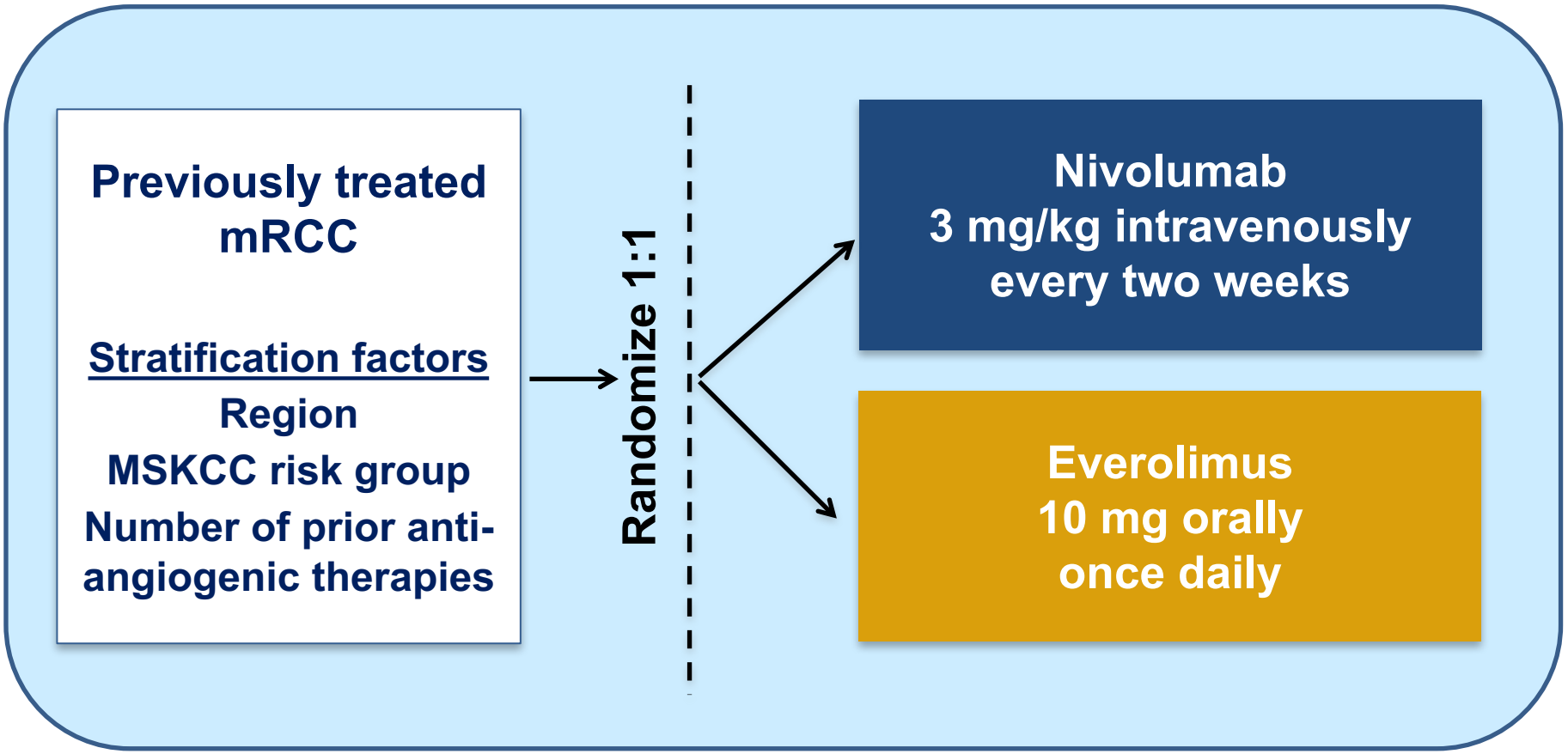


In UBC:
PD-L1 Expression on Myeloid Cells Is an Imperfect Predictive Biomarker

	IC2/3 (n = 100)	IC1/2/3 (n = 207)	All (N = 310)	IC1 (n = 107)	IC0 (n = 103)
ORR (95% CI) per confirmed IRF RECIST v1.1	26% (18, 36)	18% (13, 24)	15% (11, 19)	10% (5, 18)	8% (3, 15)
ORR (95% CI) per investigator mRECIST	27% (19, 37)	22% (16, 28)	19% (15, 24)	17% (10, 25)	13% (7, 21)
Complete response (CR) per confirmed IRF RECIST v1.1	11%	6%	5%	2%	2%

Hoffman-Centis, ASCO GU 2016

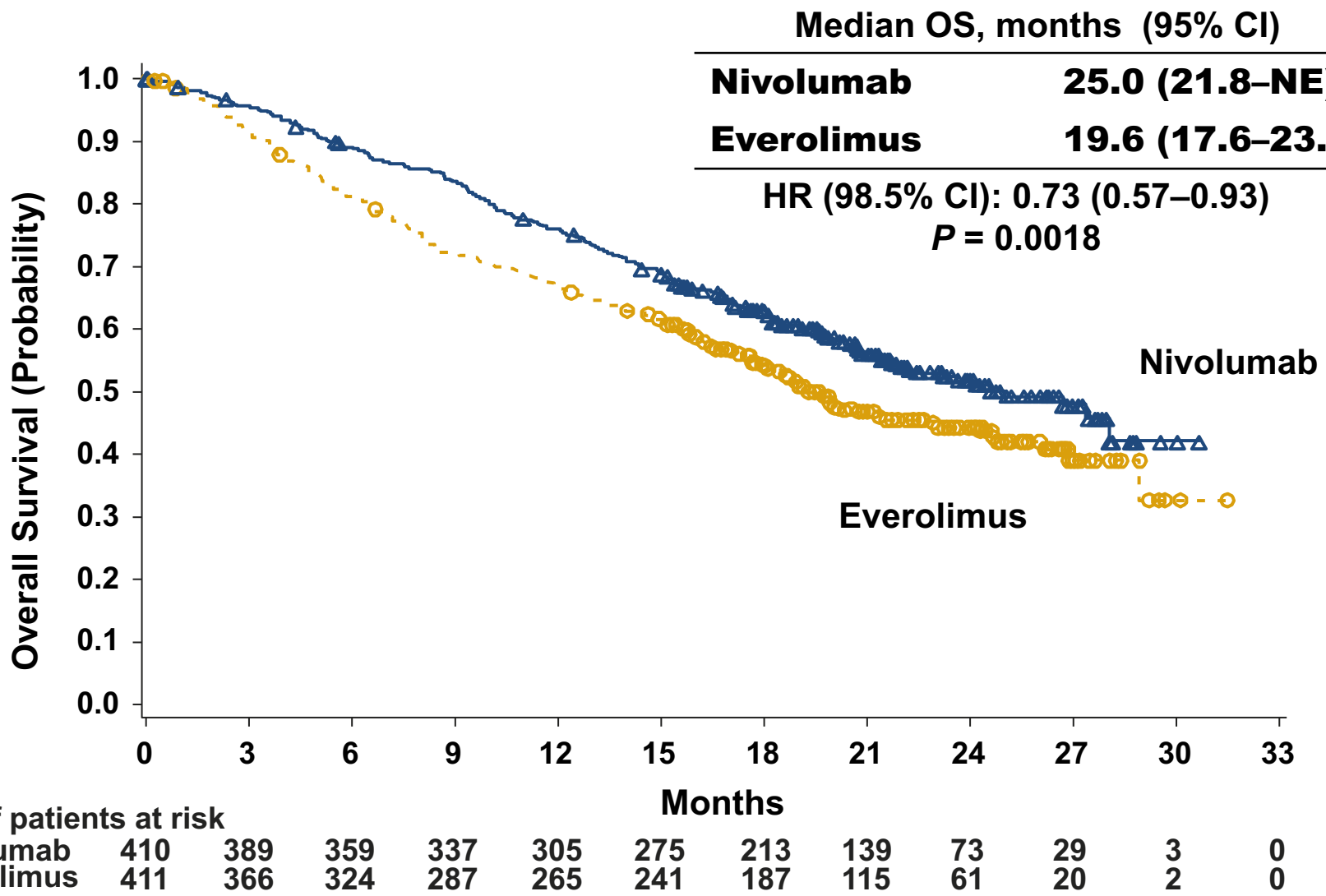
PD-1 Blockade in RCC (Phase III)



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

MSKCC, Memorial Sloan Kettering Cancer Center.

Efficacy of PD-1 Blockade in RCC



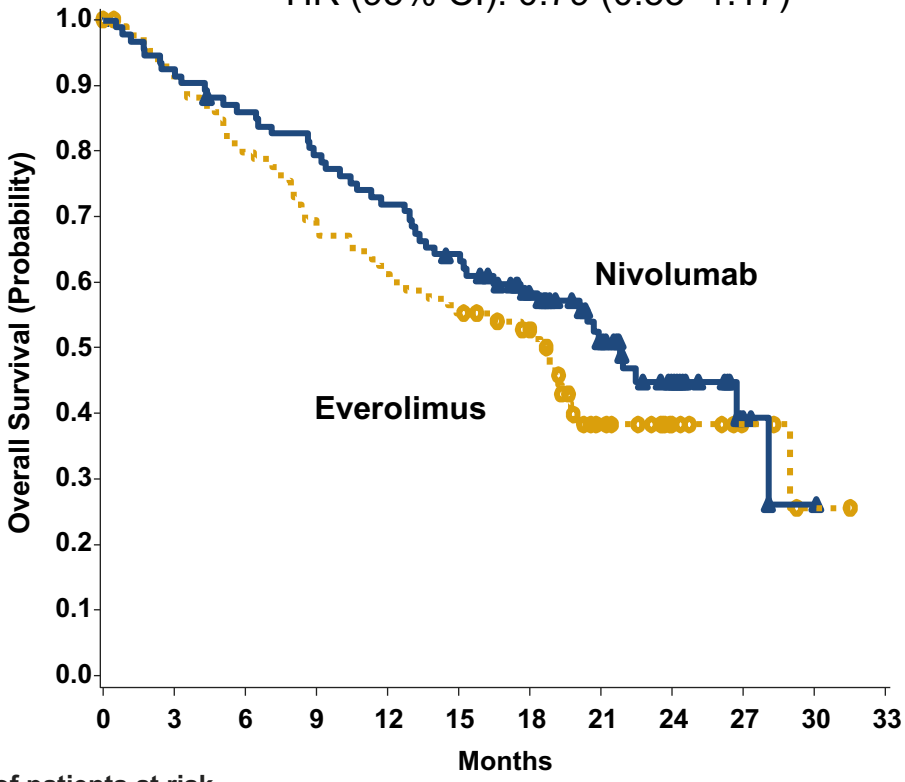
Motzer et al NEJM 2015

In RCC:
PD-L1 Expression Is NOT a Predictive Biomarker

PD-L1 ≥1% (n = 24%)

Median OS, months (95% CI)	
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)

HR (95% CI): 0.79 (0.53–1.17)



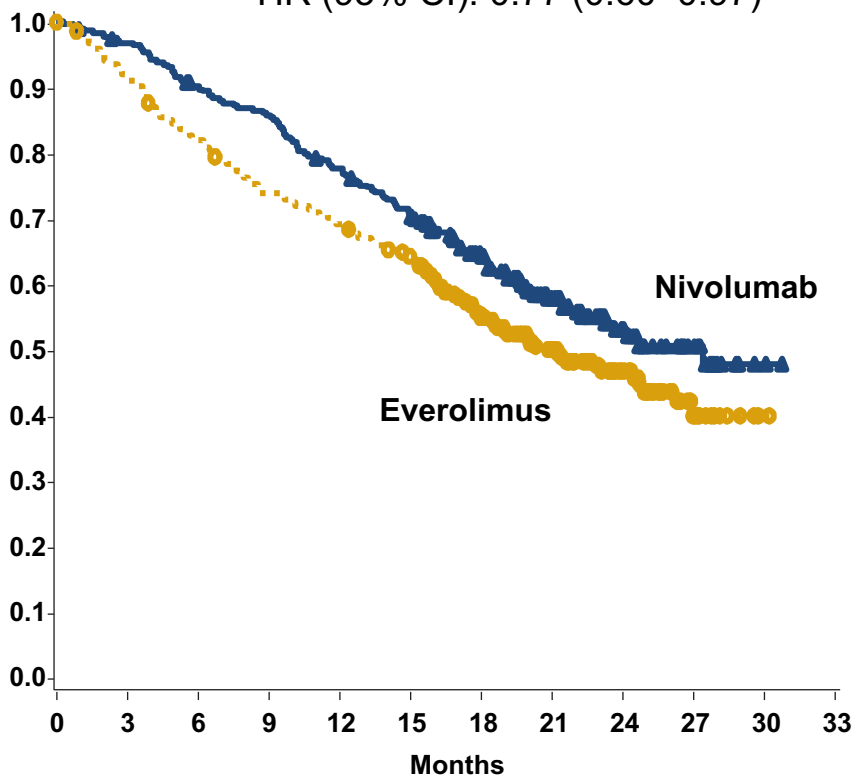
No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

PD-L1 <1% (n = 76%)

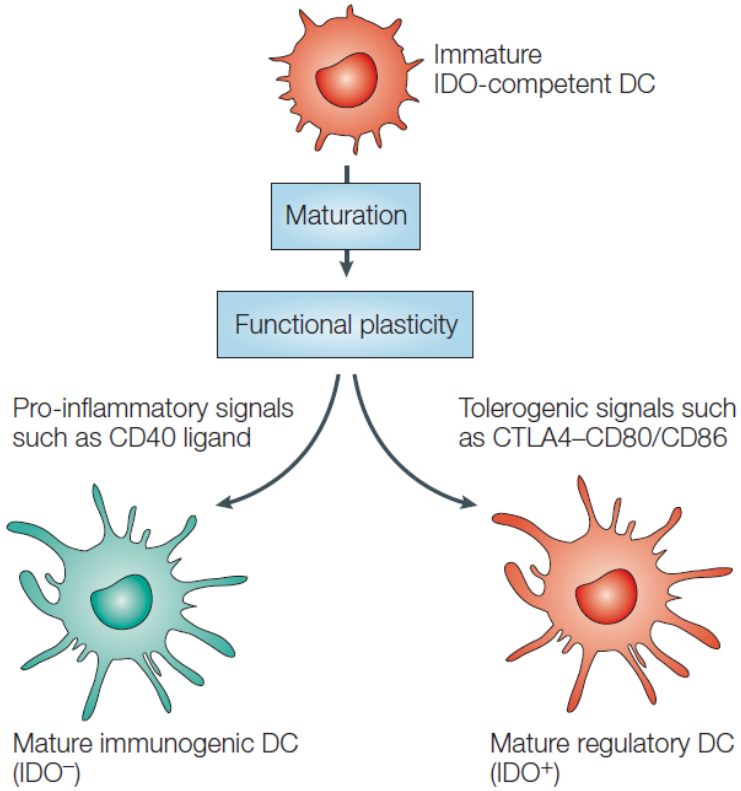
Median OS, months (95% CI)	
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

HR (95% CI): 0.77 (0.60–0.97)



	276	265	245	233	210	189	145	94	48	22	2	0
	299	267	238	214	200	182	137	92	51	16	1	0

Additional Mediators of Escape #1: IDO in the Tumor Microenvironment



Mellors and Munn, *Nat. Rev. Immunol.* (2004)

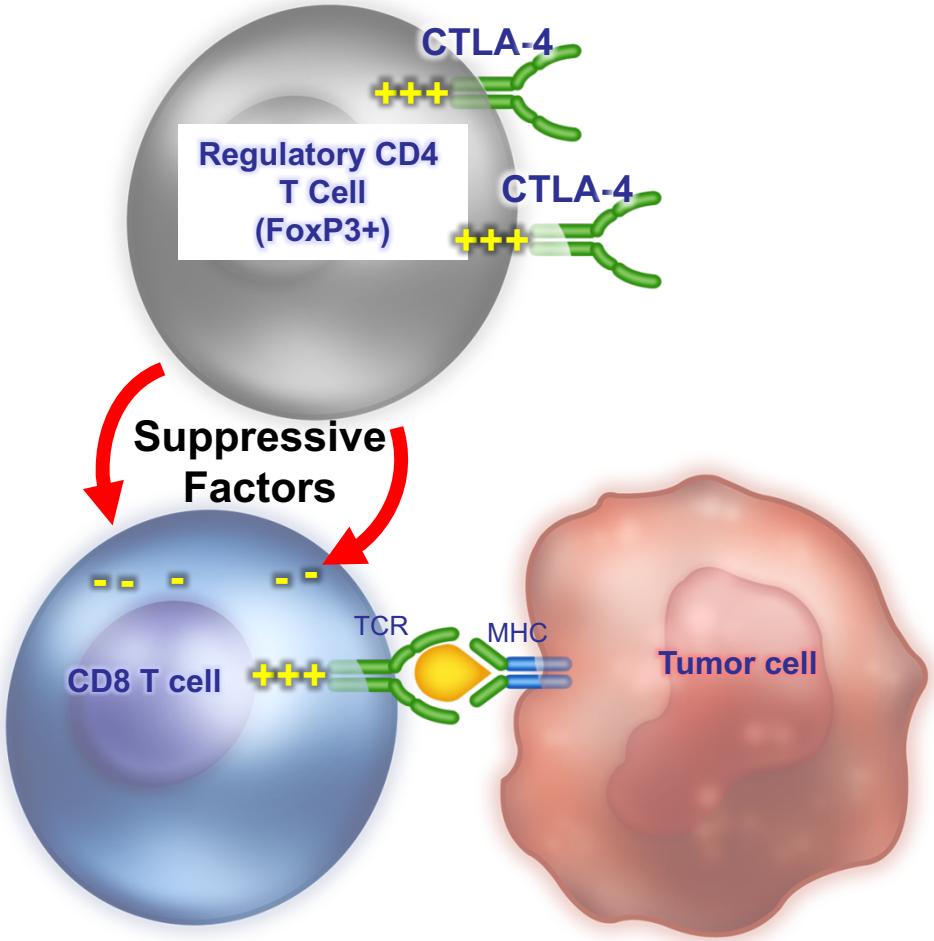
Preliminary results from a phase 1/2 study of epacadostat (INCB024360) in combination with pembrolizumab in patients with selected advanced cancers

Evaluable patients*, n (%)	Melanoma (n=7)	RCC (n=5)	TCC (n=2)	NSCLC (n=2)	EA (n=2)	SCCHN (n=1)
ORR (CR+PR)	4 (57)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
CR	2 (29)	0	0	0	0	0
PR	2 (29)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
SD	2 (29)	2 (40)	0	1 (50)	0	0
DCR (CR+PR+SD)	6 (86)	4 (80)	1 (50)	2 (100)	1 (50)	1 (100)
PD	1 (14)	0	1 (50)	0	0	0
Not assessable	0	1 (20)	0	0	1 (50)	0

*Patients with ≥ 1 post-baseline response assessment or discontinued from study or died before response could be assessed.

Gangadhar TC et al, *JITC* 2015

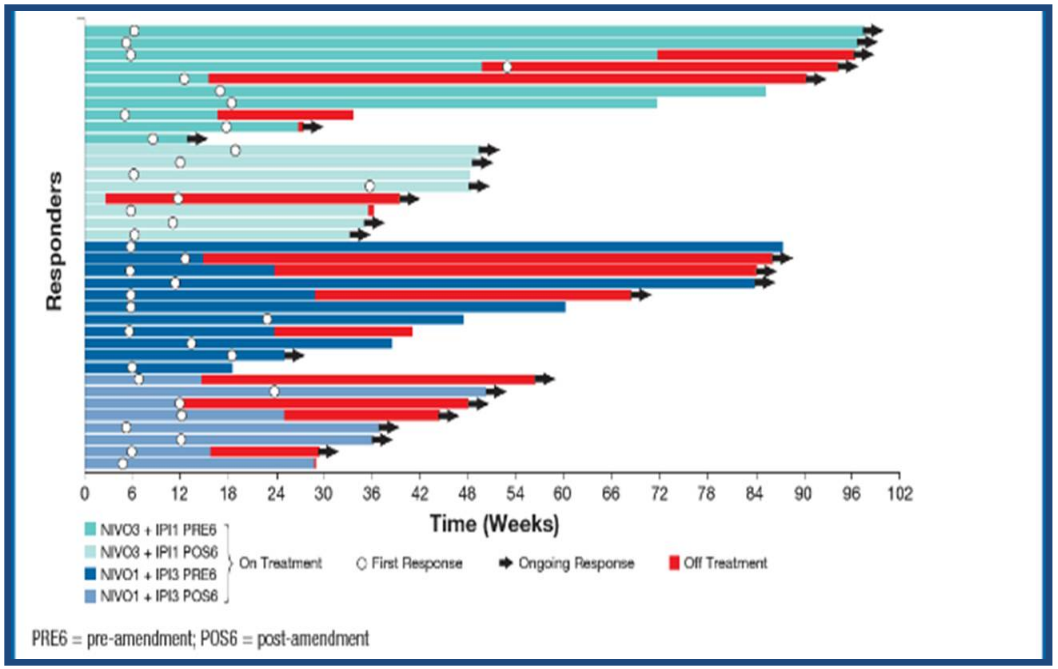
Additional Mediators of Escape #2: CTLA-4 on Treg in the Tumor Microenvironment



Combination Immunotherapy in RCC

- PD-1 Increases CD8 T Cell Function / Trafficking
- CTLA-4 Highly Expressed on Treg in Tumor Microenvironment
- Additional Inhibitory Checkpoints
  - LAG-3
  - TIM-3
  - TIGIT

- **38% Overall Response Rate (ORR)**
- **34% Grade III / IV AE**



Hammers HJ et al
ASCO 2014

Conclusions

- Clear efficacy for PD-1/L1 blockade in UBC
- Clear efficacy for PD-1 blockade in RCC
- PD-L1 as an imperfect biomarker
- Combination Immunotherapy to Address Additional Mechanisms of Escape

Cancer Immunotherapy Answers and Questions

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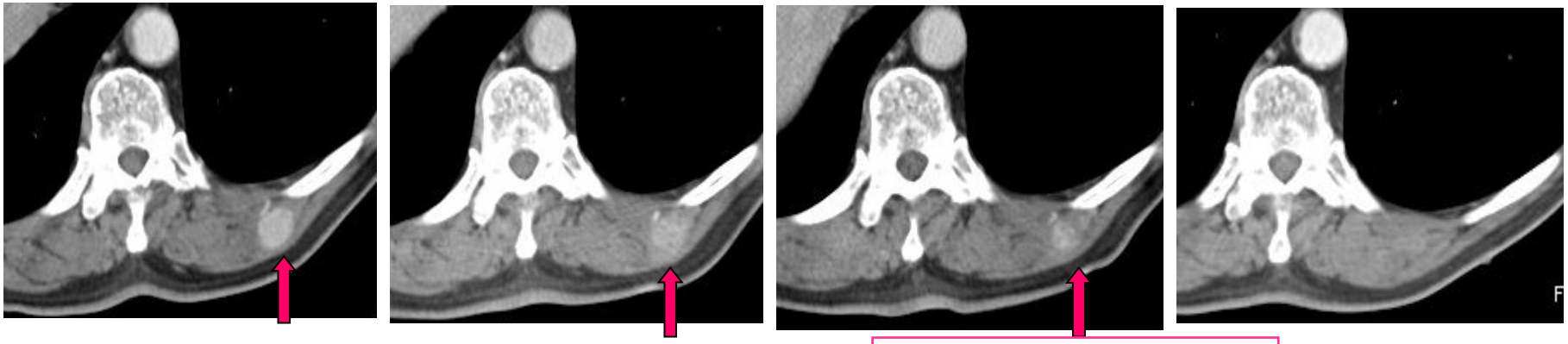
Case: A Patient With Kidney Cancer

- 66 year old man with recurrent RCC
- s/p nephrectomy 6 years prior to visit
- Relapsed 4 years prior to visit with multiple pulmonary nodules
- Rx on clinical trials of sorafenib, HDAC inhibitor
- CT: Multiple metastatic lesions in lungs, bone (R scapula), soft tissue
- Labs WNL

Continued

- Enrolled on first Phase I of MDX-1106 (now nivolumab)
- Received 3 on-study treatments
- Side Effects = hypothyroidism, GI disturbance
- Discontinued due to stable partial response
- Last seen 10/**2016**, CT Scan = Complete Response

01/15/08 (pre-Rx) **03/25/08** **04/22/08** **07/22/08**



US-guided biopsy: No viable tumor