Immunotherapy of Prostate Cancer, Bladder Cancer and Renal Cell Cancer

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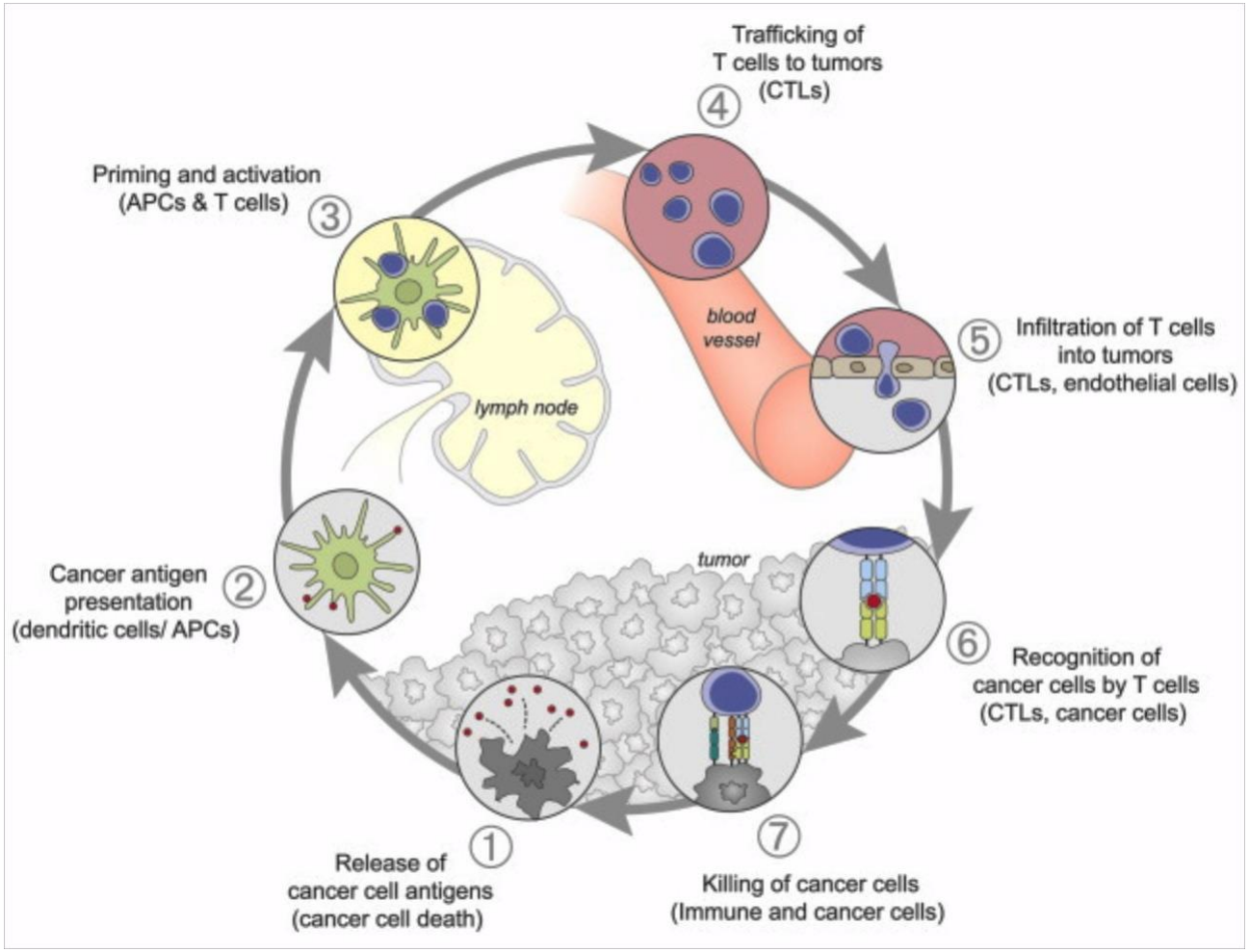
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Introduction to Immunotherapy

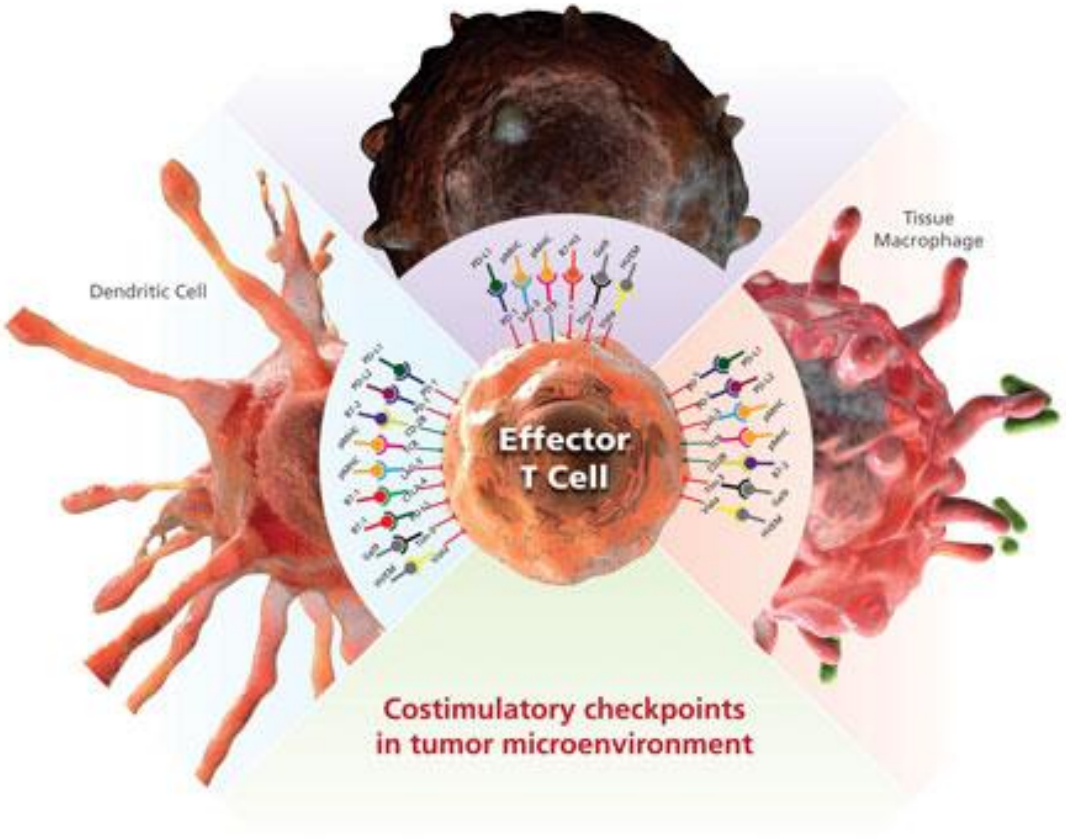


DS. Chen and I. Mellman.
Oncology Meets Immunology:
The Cancer-Immunity Cycle.
Immunity 39, July 25, 2013

Introduction to Immunotherapy

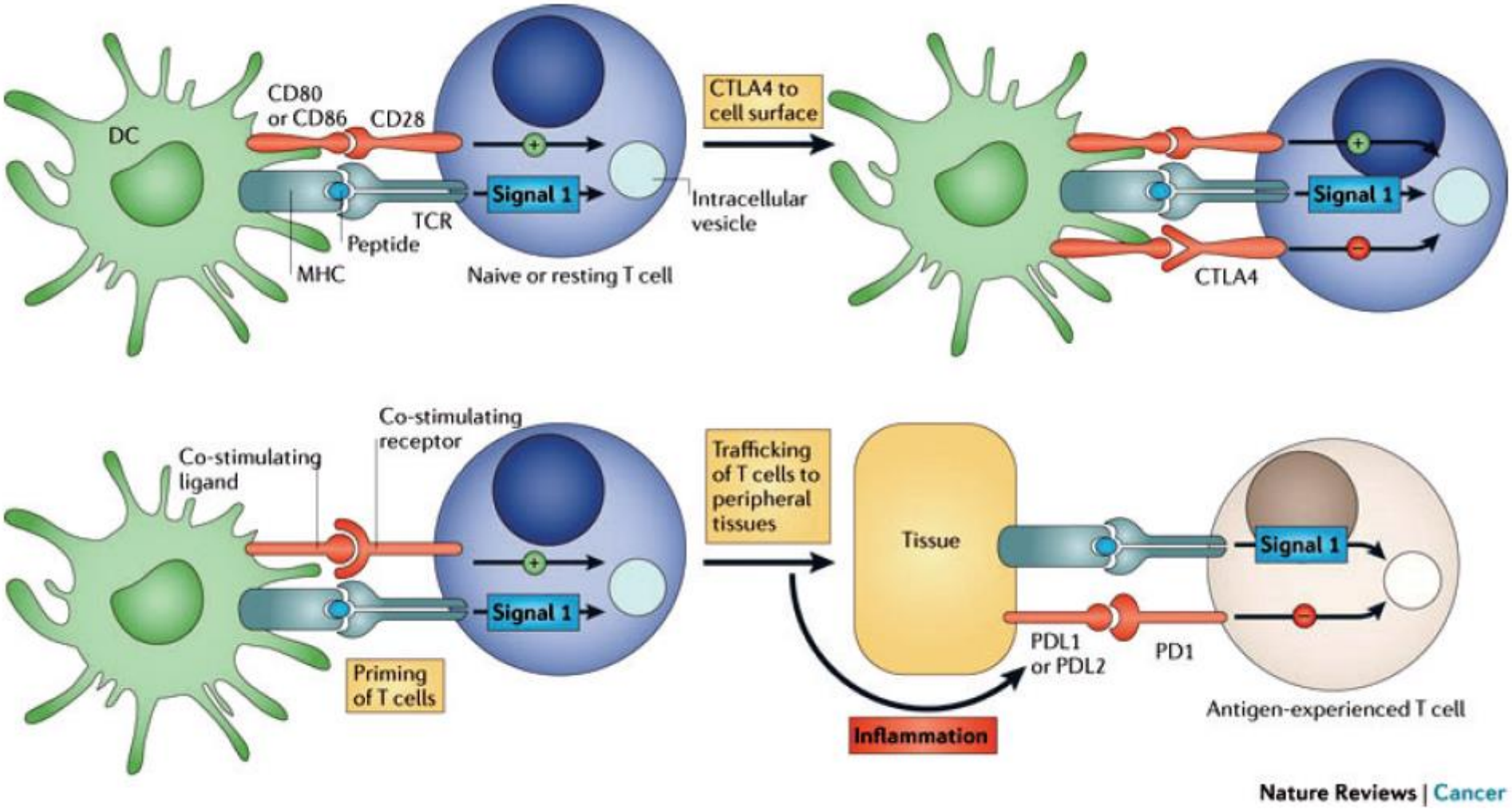
Tumor Cell

Dendritic Cell



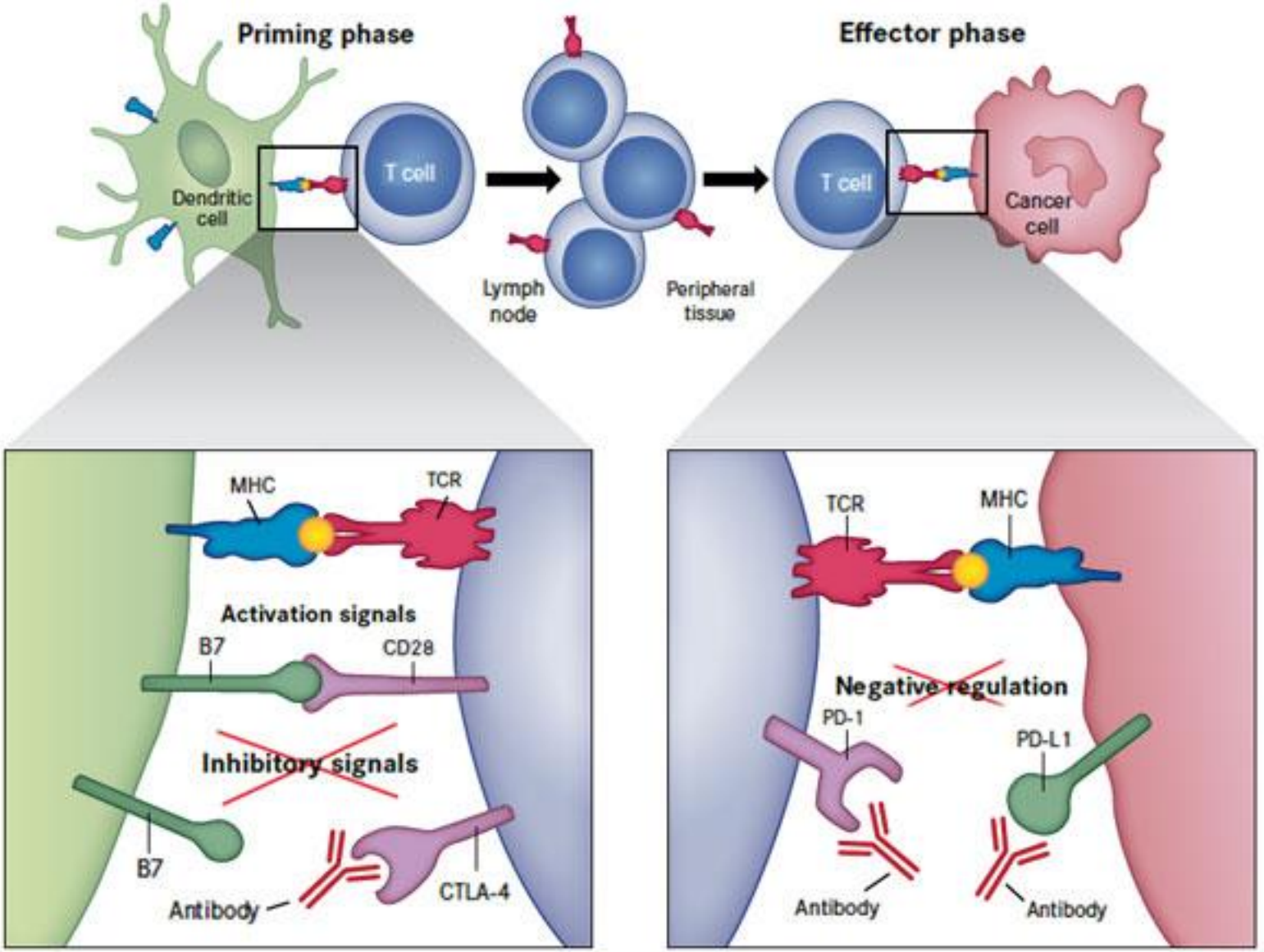
Tissue Macrophage

Introduction to Immunotherapy

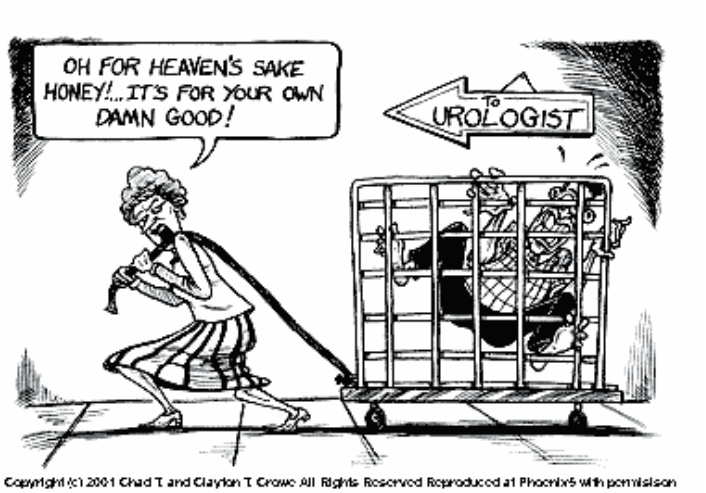


Nature Reviews | Cancer

Introduction to Immunotherapy

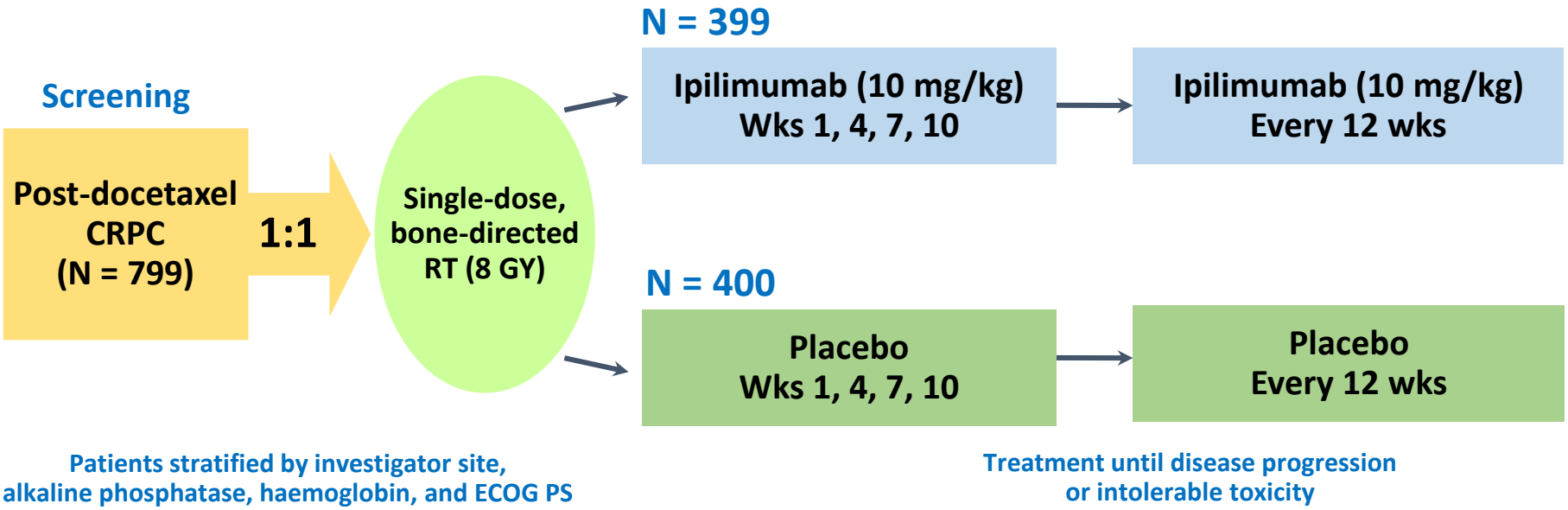


Immune Checkpoint Inhibitors
Prostate Cancer



Immune Checkpoint Inhibitors
Prostate Cancer: Ipilimumab (post-docetaxel)

CA184-043: Study design

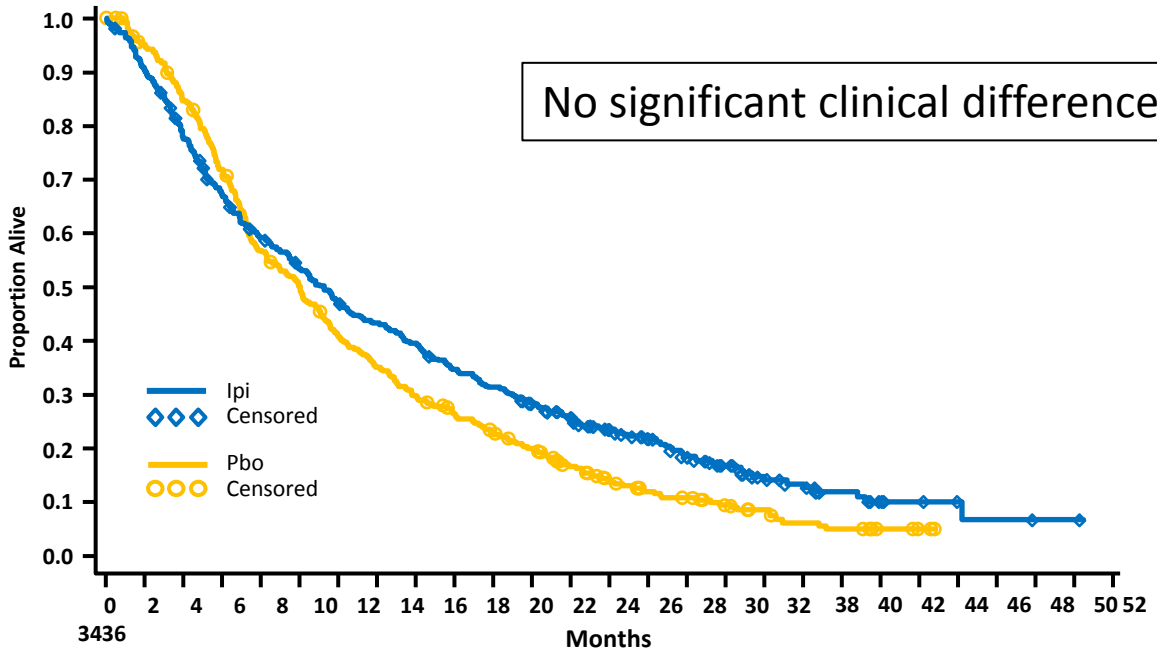


- Primary endpoint: OS
- Secondary endpoints: Progression-free survival, safety
- Exploratory endpoint: PSA response rate

Gerritsen W, et al. ESMO 2013. Abstract 2850.

Immune Checkpoint Inhibitors
Prostate Cancer: Ipilimumab (post-docetaxel)

Van den Eertwegh AJ, et al. *Lancet Oncol.* 2012;13:509-517; Fizazi K et al, ESMO 2014.

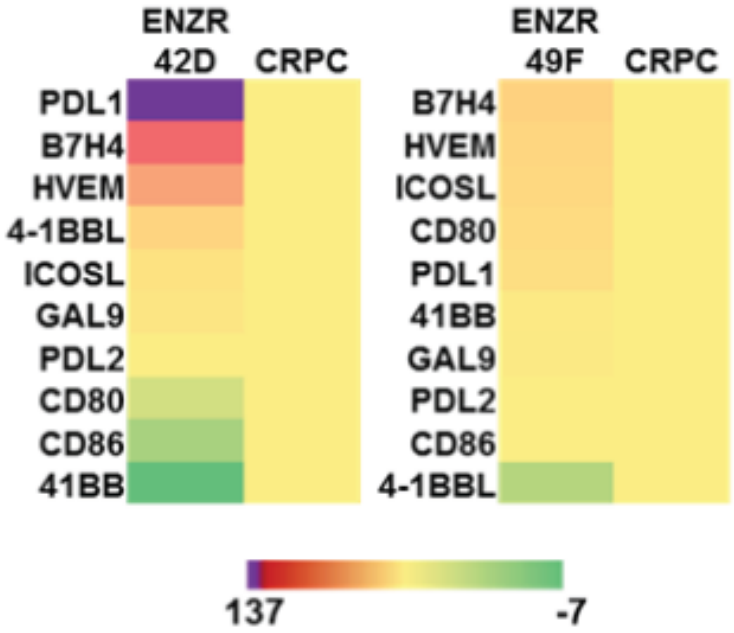


No significant clinical difference

Ipilimumab (pre-docetaxel): no significant difference

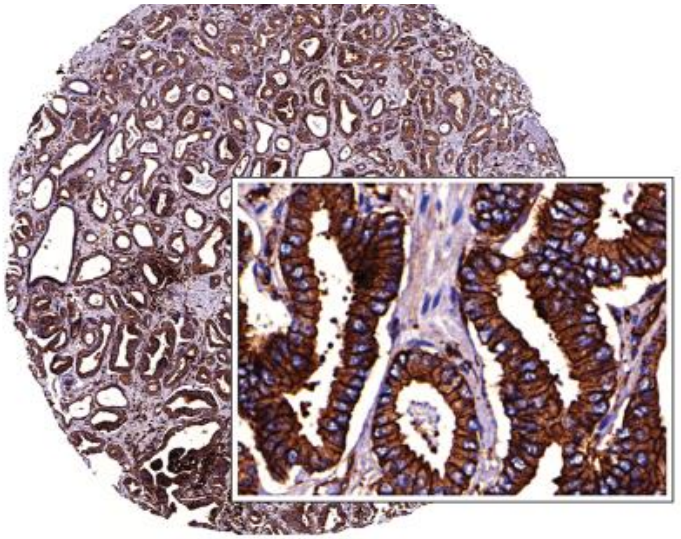
Immune Checkpoint Inhibitors
Prostate Cancer: PDL-1 expression

Enzalutamide resistent PC cell lines



Jennifer Bishop et al. Oncotarget 2014:6: 234

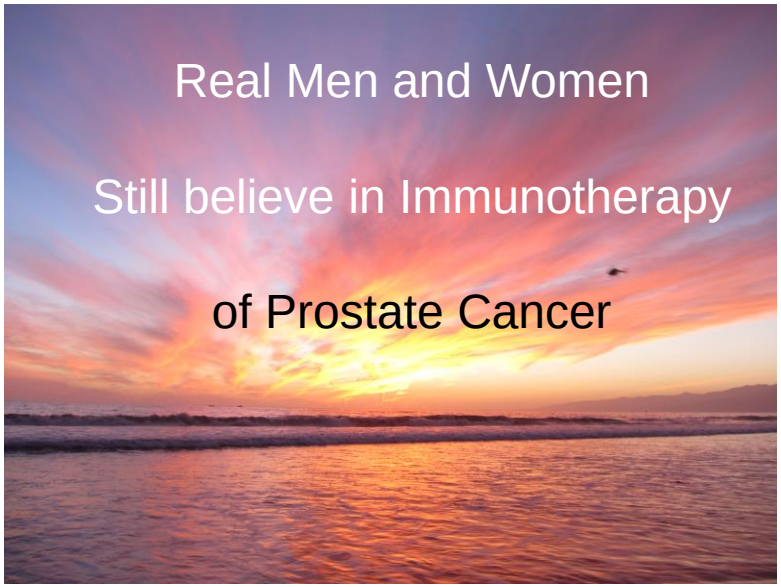
High eexpression PDL-1 in human primary PC



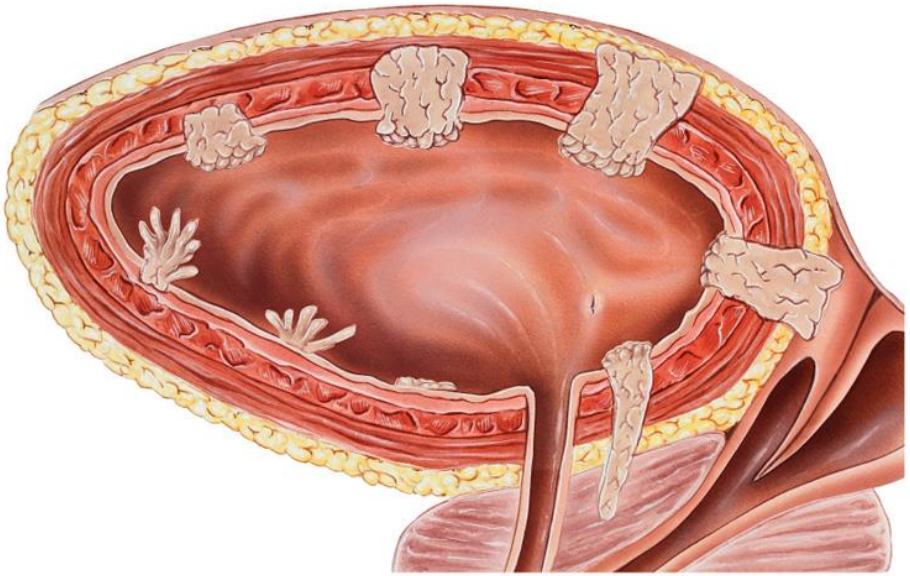
Heidrun Gebensleben et al, CCR nov 2015

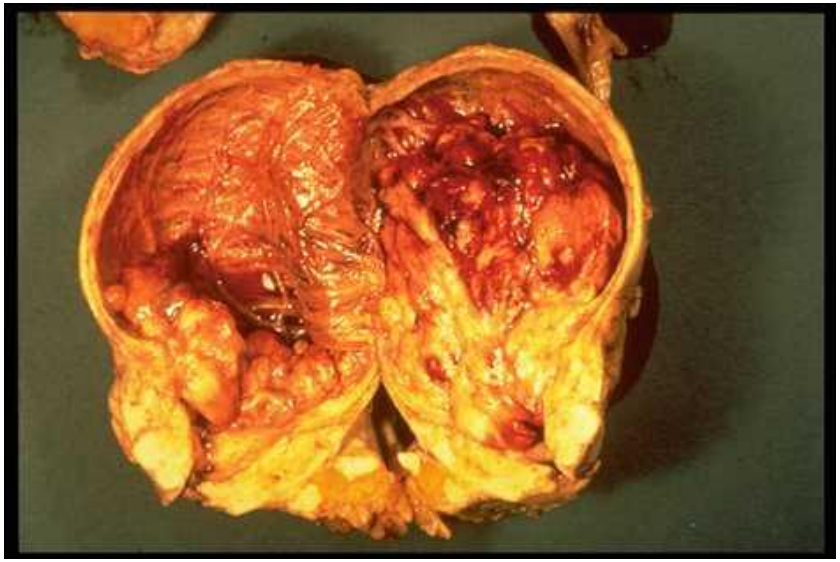
Massari et al. Target Oncol nov 2015

Immune Checkpoint Inhibitors
Prostate Cancer

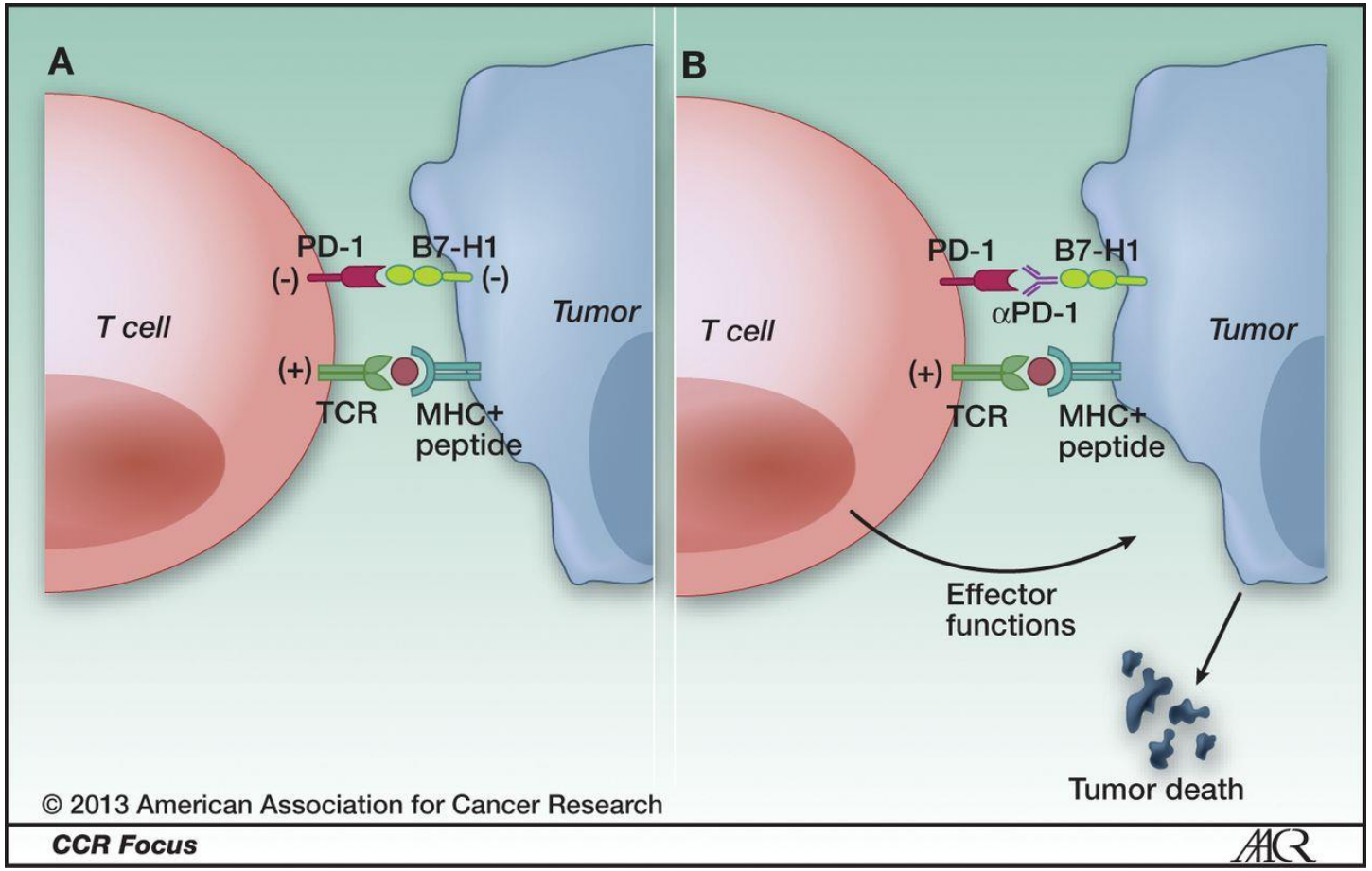


Immune Checkpoint Inhibitors
Bladder Cancer



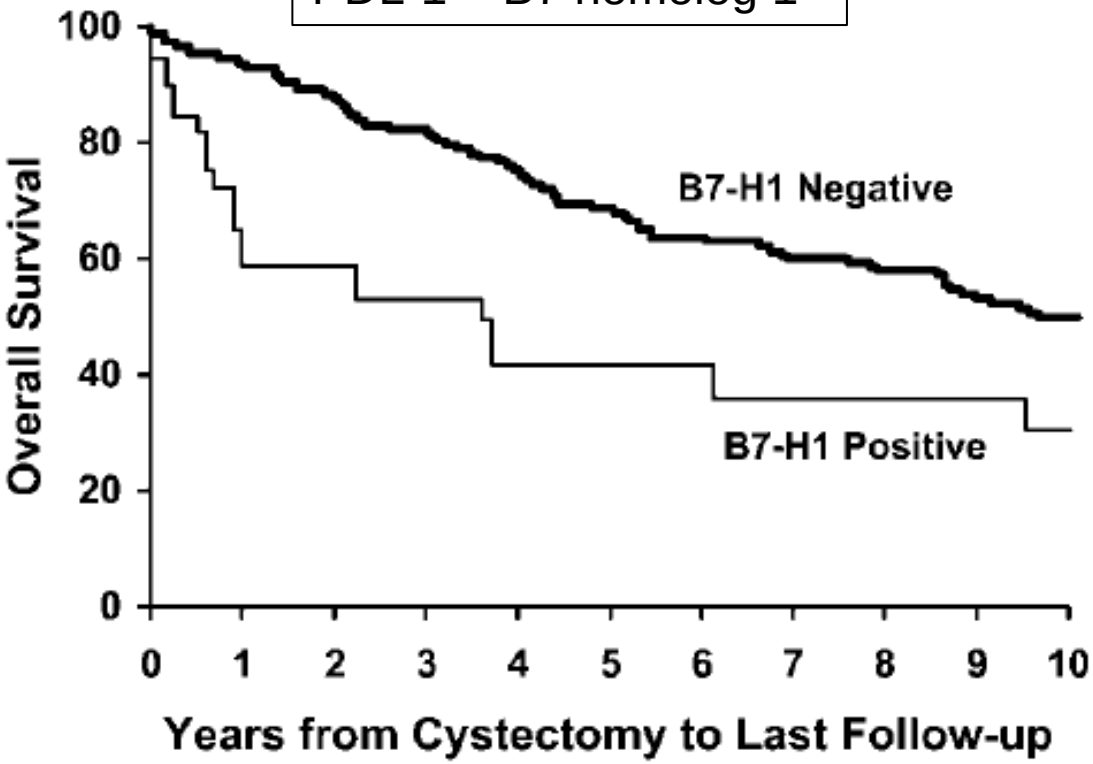


Immune Checkpoint Inhibitors
Bladder Cancer



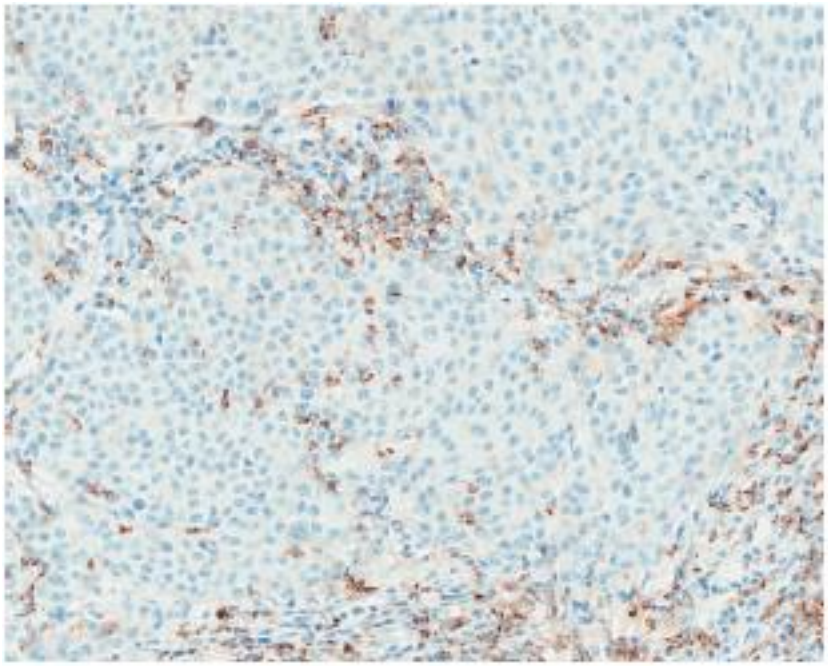
Immune Checkpoint Inhibitors
Bladder Cancer

PDL-1 = B7 homolog 1

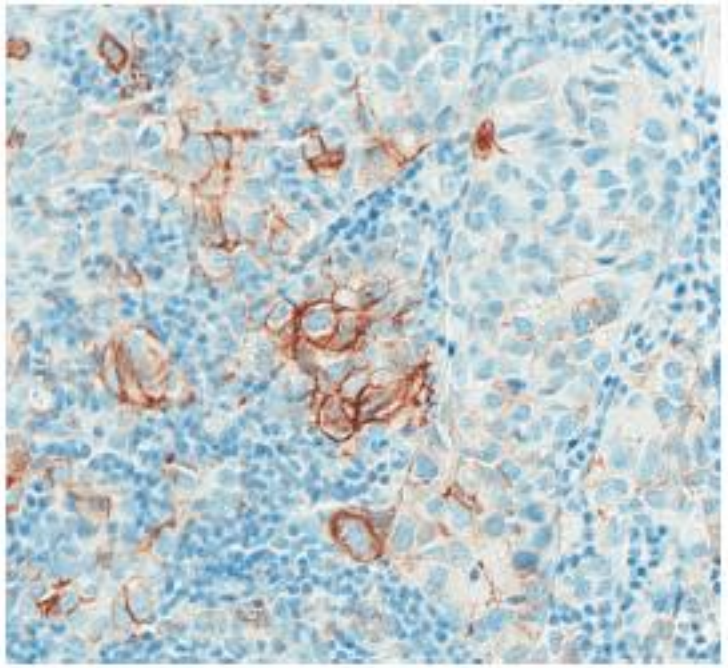


Boorijan SA et al, CCR 2008

Immune Checkpoint Inhibitors
Bladder Cancer: PDL-1 expression



Tumour-infiltrating immune cells



Tumour cells

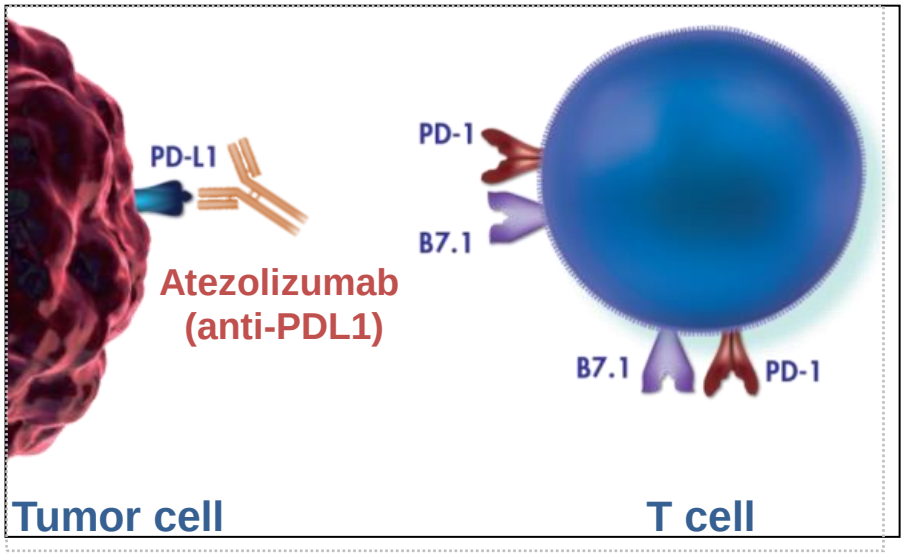
T Powles *et al. Nature* **515**, 558-562 (2014)

Immune Checkpoint Inhibitors
Bladder Cancer

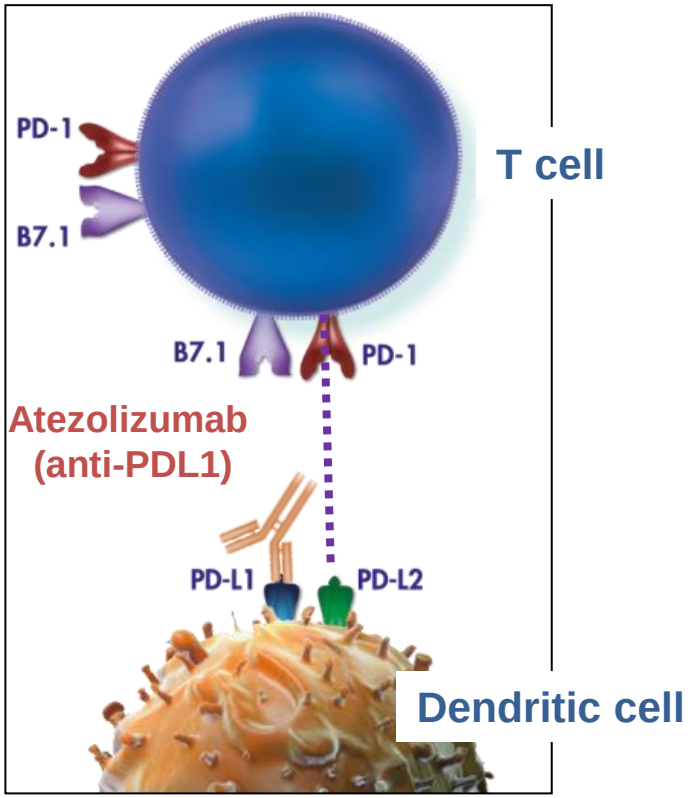
PD-L1 prevalence in UBC tumours by IHC		
$n = 205$	PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))	PD-L1-positive tumour cells (no. of specimens (%))
IHC 3	18 (9)	14 (7)
IHC 2	37 (18)	8 (4)
IHC 1	89 (43)	37 (18)
IHC 0	61 (30)	146 (71)

T Powles *et al. Nature* **515**, 558-562 (2014)

Immune Checkpoint Inhibitors
Bladder Cancer: Atezolizumab



By leaving the PD-L2/PD-1 interaction intact, atezolizumab has the potential to preserve peripheral immune homeostasis



Immune Checkpoint Inhibitors
Bladder Cancer: PDL-1 expression and response

Tumour-infiltrating immune cells and objective response rates

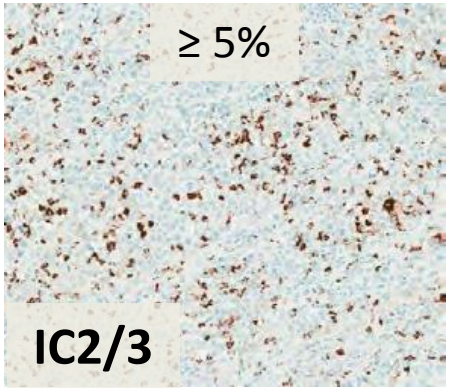
	Objective response rate *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
IHC 2/3 (*n* = 30)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 (*n* = 10)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 (*n* = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (*n* = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 (*n* = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 (*n* = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)

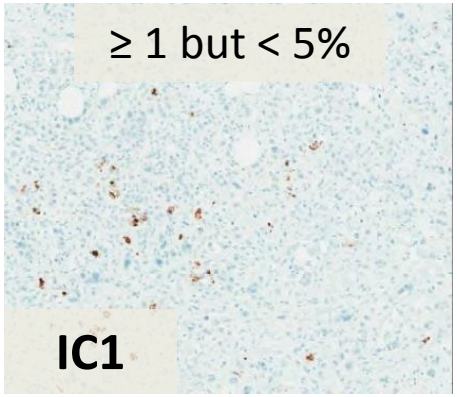
T Powles *et al. Nature* **515**, 558-562 (2014)

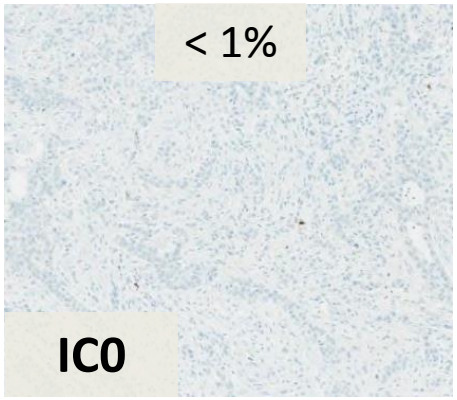
IMvigor 210: PD-L1 IHC

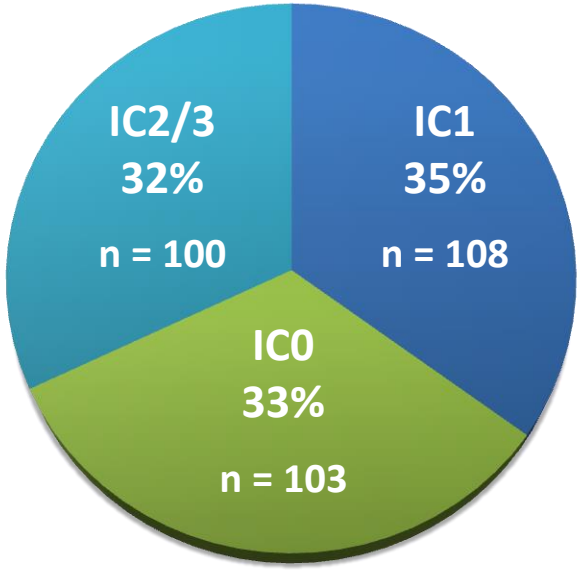
PD-L1 Immune Cell Expression and Prevalence

IHC Status of Treated Patients in IMvigor 210 Study (N = 311)







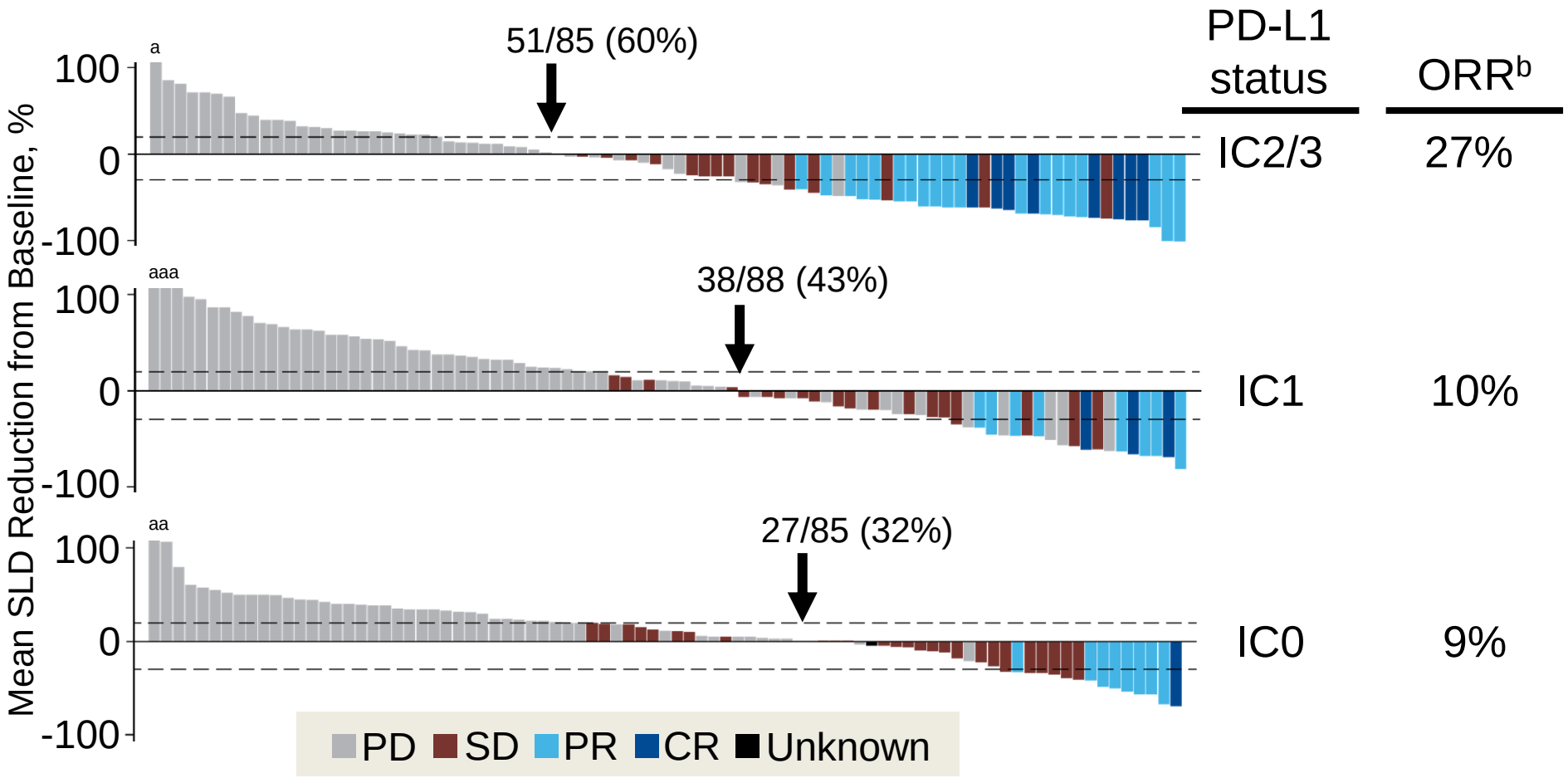


- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating immune cell (IC) PD-L1 expression based on 3 IHC scoring levels

Images at 10x magnification.

IMvigor 210: Efficacy

Changes in Target Lesions by PD-L1 Subgroup



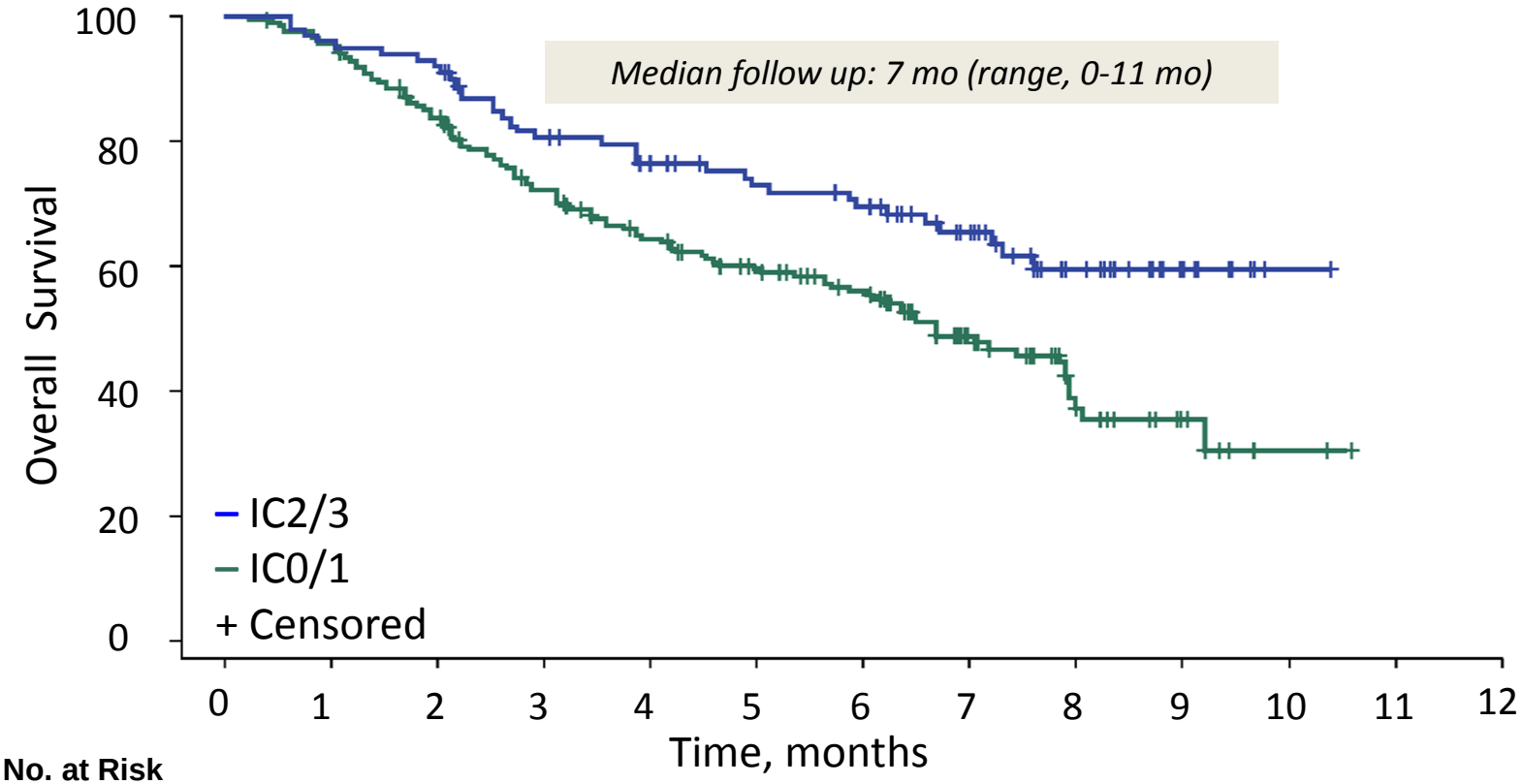
111/258 (43%) patients with tumor assessments had SLD reduction

SLD, sum of longest diameters. [a]> 100% increase. [b]Per confirmed RECIST v1.1 (independent review).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.
Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

IMvigor 210: Efficacy

Preliminary Analyses of Overall Survival

Survival	IC2/3 n = 100	IC0/1 n = 211	All N = 311
Median OS, mo (95% CI)	NR (7.6, NE)	6.7 (5.7, 8.0)	7.9 (6.7, NE)



No. at Risk

IC2/3:	100	96	92	78	71	64	60	41	22	11	1
IC0/1:	211	201	173	143	123	107	90	50	23	10	2

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC

IMvigor 210: Safety
Summary

AE (N = 311)	All Cause	Treatment Related
Any Grade	96%	66%
Serious AEs	45%	11%
Grade 3-4	50%	15%
Grade 5[a]	1%	0%
AEs leading to withdrawal	3%	N/A
AEs leading to dose modification/interruption	27%	N/A

- Median treatment duration 12 weeks (range, 0-46 wk) with median of 5 doses (range, 1-16 doses)
- Atezolizumab was well tolerated with no treatment-related deaths
- AE profile was consistent across IC2/3, IC1/2/3 and all-comer populations

[a]2 all-cause Grade 5 AEs were seen: pulmonary sepsis and subileus (intestinal occlusion).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Immune Checkpoint Inhibitors
Bladder Cancer

Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Elizabeth R. Plimack,[1] Joaquim Bellmunt,[2] Shilpa Gupta,[3] Raanan Berger,[4] Bruce Montgomery,[5] Karl Heath,[6] Jonathan Juco,[6] Kenneth Emancipator,[6] Kumudu Pathiraja,[6] Jared Lunceford,[6] Rodolfo Perini,[6] Peter H. O'Donnell[7]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA,
[2]Dana-Farber Cancer Institute, Boston, MA, USA,
[3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA,
[4]Sheba Medical Center, Tel Hashomer, Israel, [5]University of Washington, Seattle, WA, USA, [6]Merck & Co., Inc., Kenilworth, NJ, USA, [7]University of Chicago, Chicago, IL, USA

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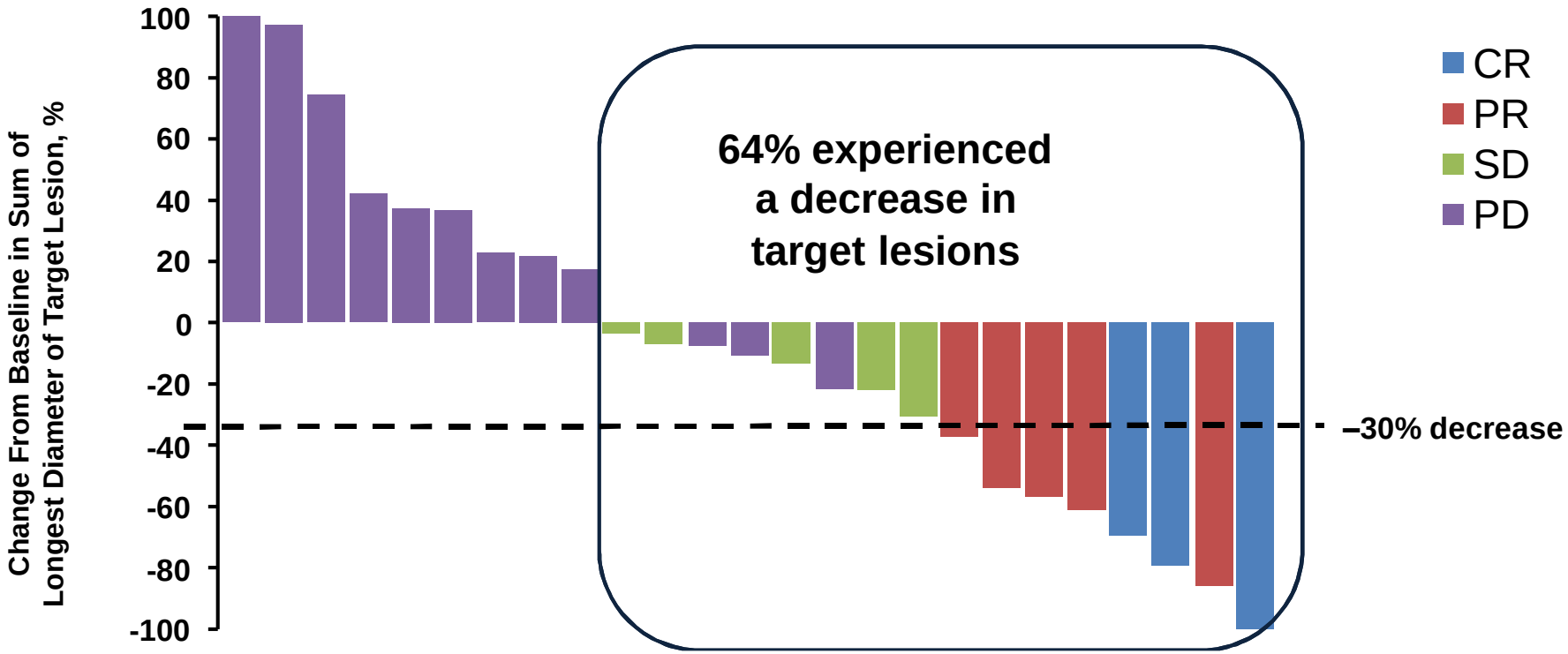
Immune Checkpoint Inhibitors
Bladder Cancer:Pembroluzimab

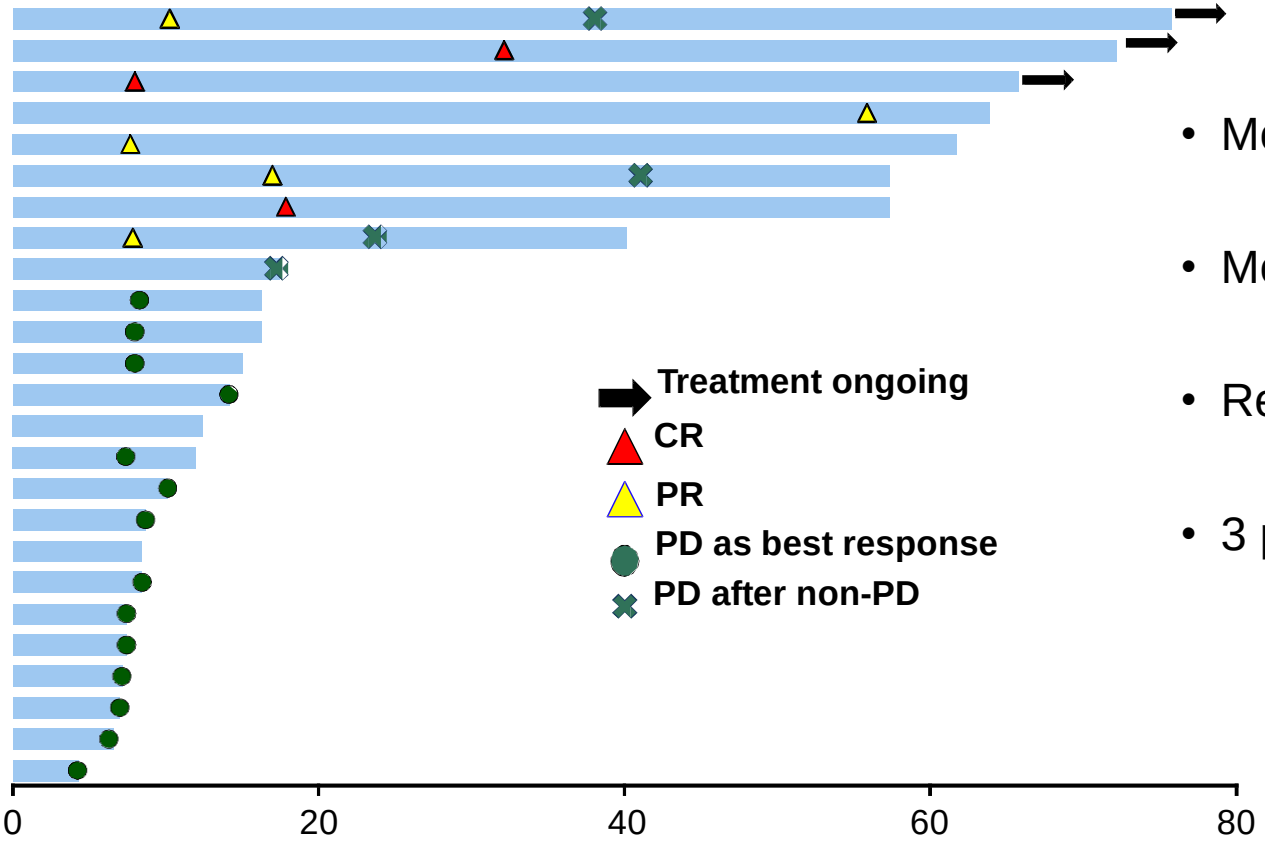
Overall Response Rate = 28% (8/33)



Plimack, E.R., *et al. ASCO Meeting Abstracts* **33**, 4502 (2015).

Immune Checkpoint Inhibitors
Bladder Cancer: Pembroluzimab

Duration of Response



- Median follow-up duration:
  - 15 (0.6-20) months
- Median time to response:
  - 9 (7.7−55.9) weeks
- Response duration:
  - 8.1 to 64.1+ weeks
- 3 patients remain on therapy

RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

Plimack, E.R., *et al. ASCO Meeting Abstracts* **33**, 4502 (2015).

Immune Checkpoint Inhibitors
Bladder Cancer: summary

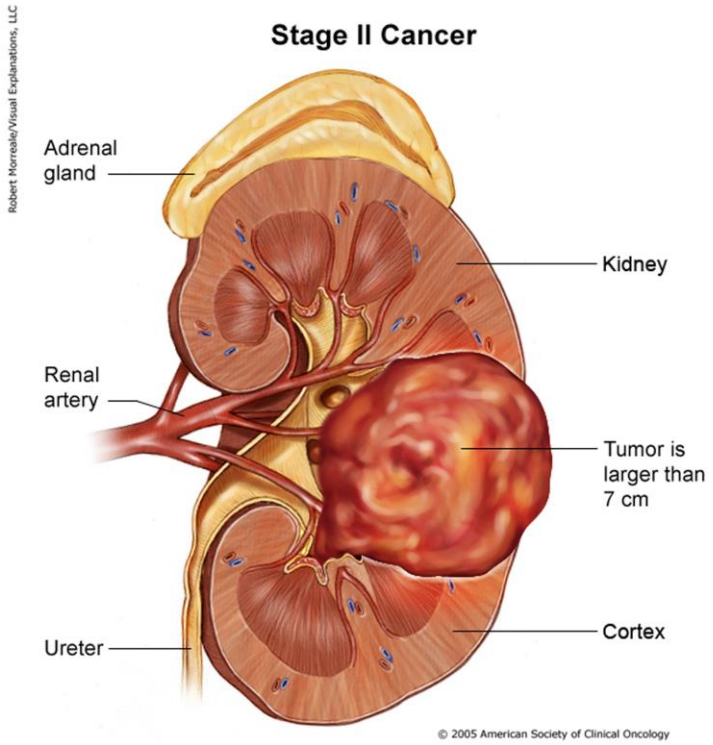
20 years no improvement in overall survival

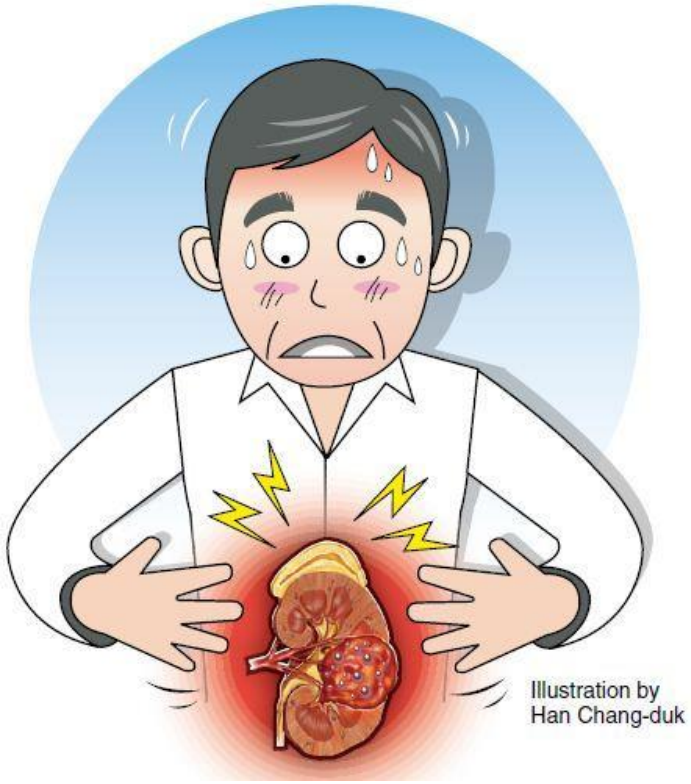
Atezoluzimab (anti-PDL-1):
- 15% grade 3-4 toxicity
- 37% response rate
- OS: 10-14 months

Pembroluzimab (anti-PD-1):
- 15% grade 3-4 toxicity
- 28% response rate
- OS: 13 months

Docetaxel:
- 15-20% response rate
- OS: 7 months

Immune Checkpoint Inhibitors
Renal Cell Cancer





The NEW ENGLAND JOURNAL of MEDICINE

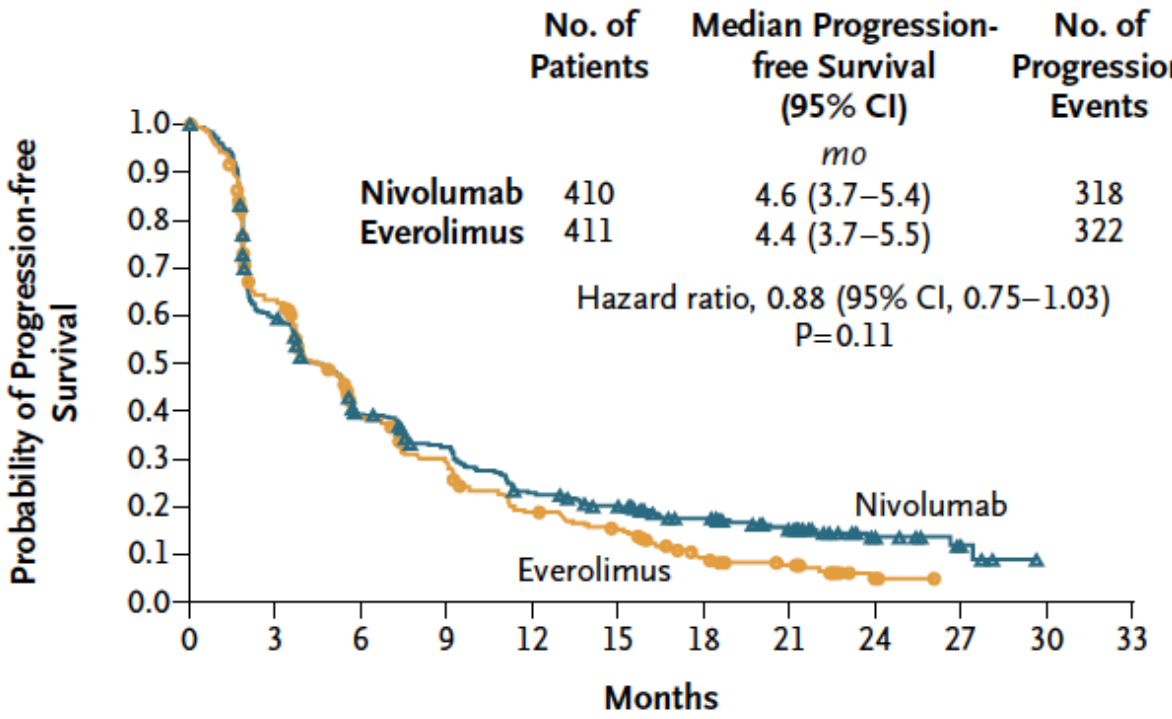
ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

B **Kaplan–Meier Curve for Progression-free Survival**

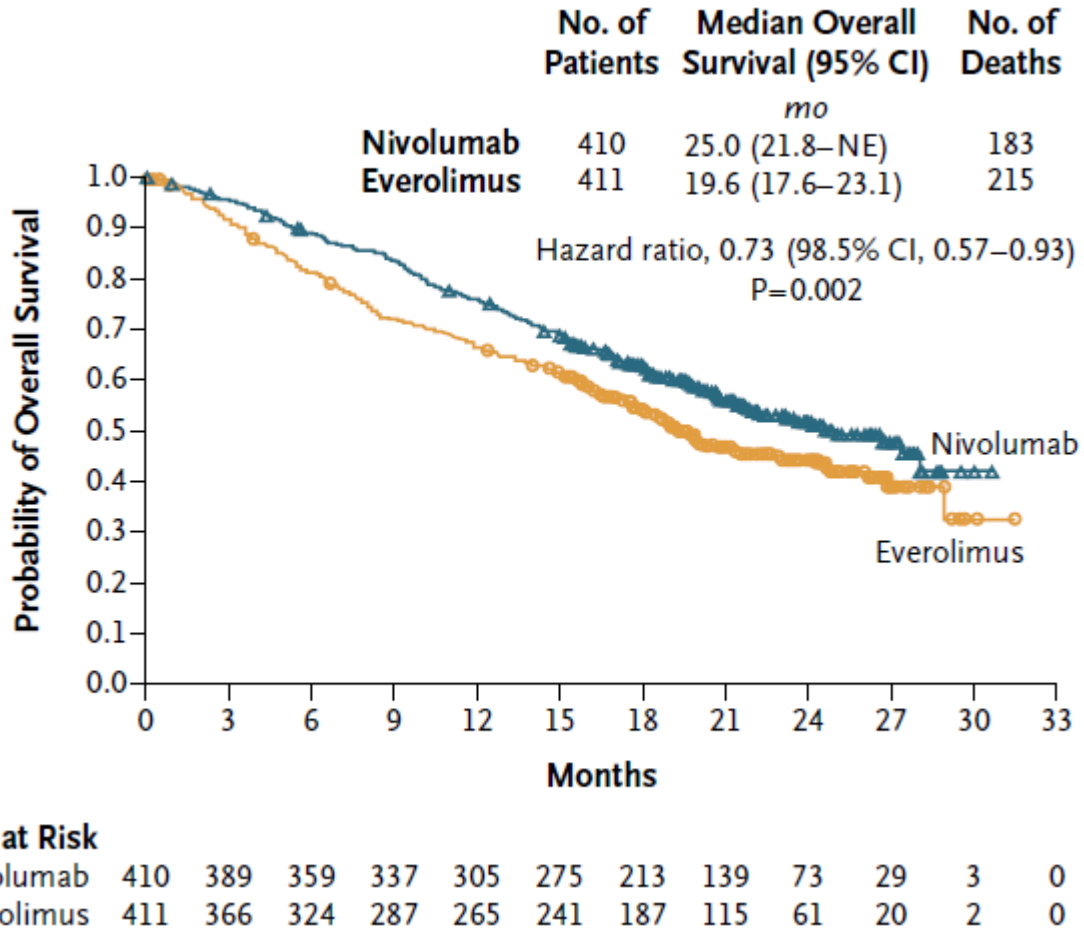


No. at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0	0

Motzer et al *NEJM* 2015

Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

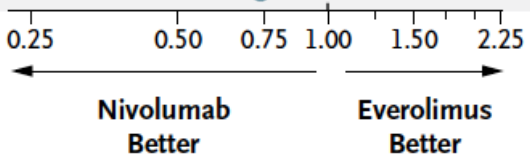


Motzer et al *NEJM* 2015

Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

A Subgroup Analyses of Overall Survival

Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic regimens			
1	128/294	158/297	0.71 (0.56–0.90)
2	55/116	57/114	0.89 (0.61–1.29)
Region			
United States or Canada	66/174	87/172	0.66 (0.48–0.91)
Western Europe	78/140	84/141	0.86 (0.63–1.16)
Rest of the world	39/96	44/98	0.78 (0.51–1.20)
Age			
<65 yr	111/257	118/240	0.78 (0.60–1.01)
≥65 to <75 yr	53/119	77/131	0.64 (0.45–0.91)
≥75 yr	19/34	20/40	1.23 (0.66–2.31)
Sex			
Female	48/95	56/107	0.84 (0.57–1.24)
Male	135/315	159/304	0.73 (0.58–0.92)



Motzer et al *NEJM* 2015

Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)

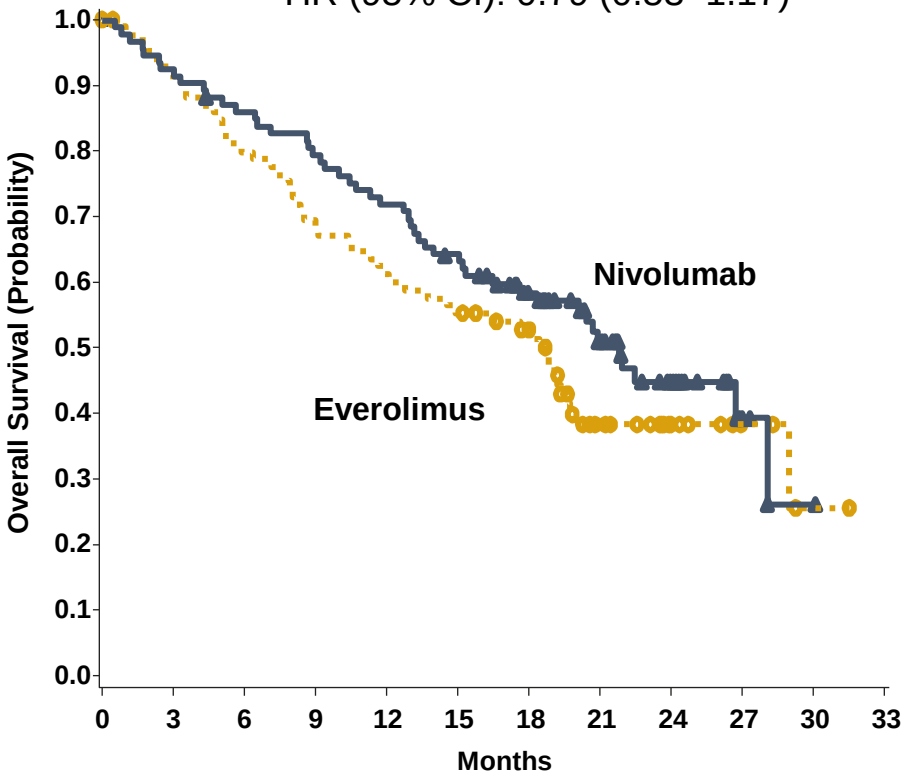
Motzer et al *NEJM* 2015

Overall survival by PD-L1 expression

PD-L1 ≥1% (n = 24%)

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

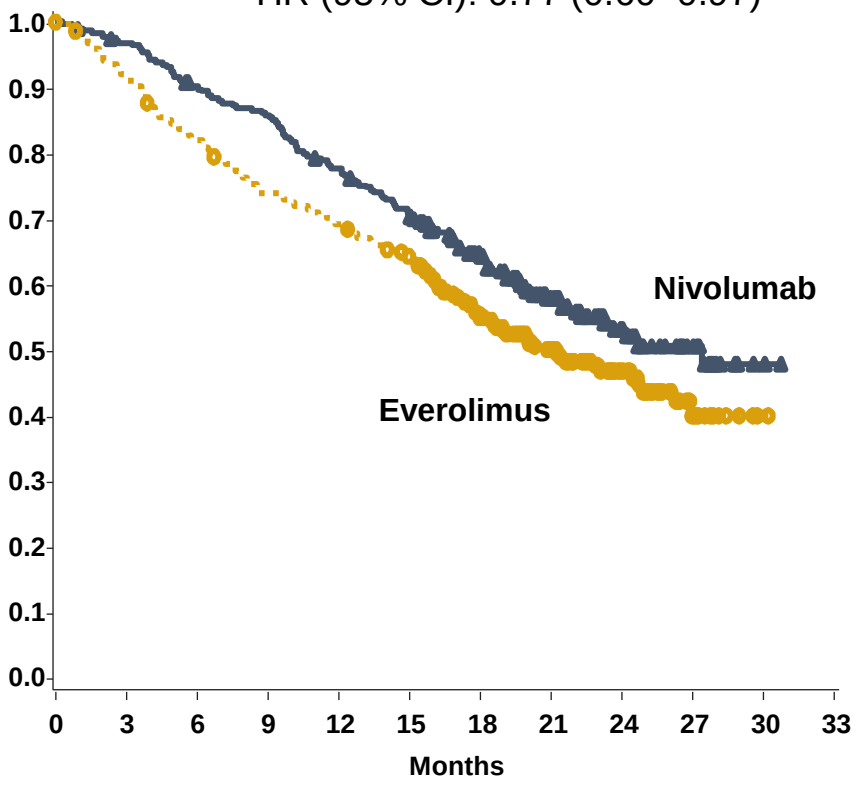
HR (95% CI): 0.79 (0.53–1.17)



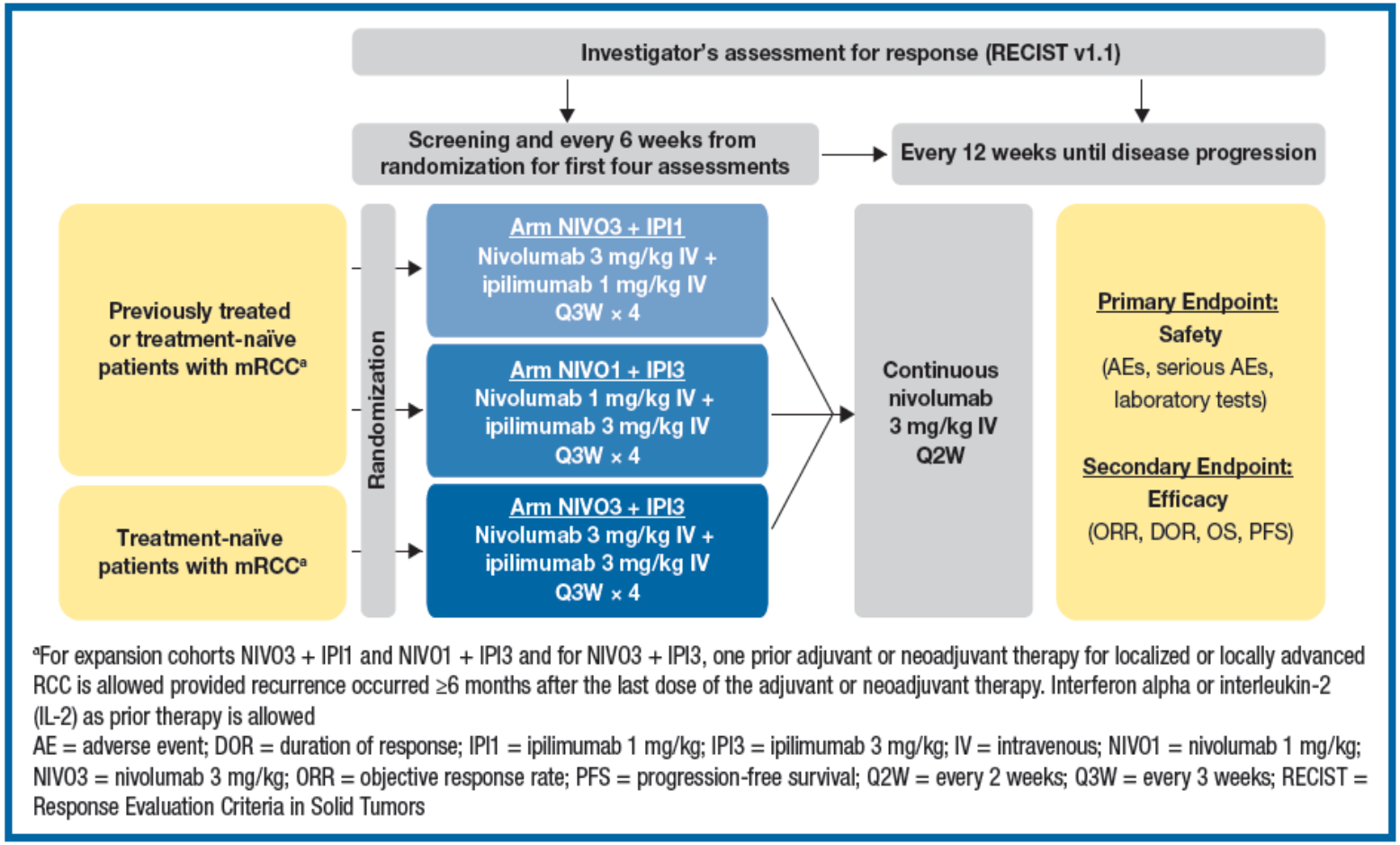
PD-L1 <1% (n = 76%)

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)



Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab



[a]For expansion cohorts NIVO3 + IPI1 and NIVO1 + IPI3 and for NIVO3 + IPI3, one prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred ≥6 months after the last dose of the adjuvant or neoadjuvant therapy. Interferon alpha or interleukin-2 (IL-2) as prior therapy is allowed

AE = adverse event; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; IV = intravenous; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; ORR = objective response rate; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

Hammers et al ASCO 2014
Motzer et al al ASCO 2015

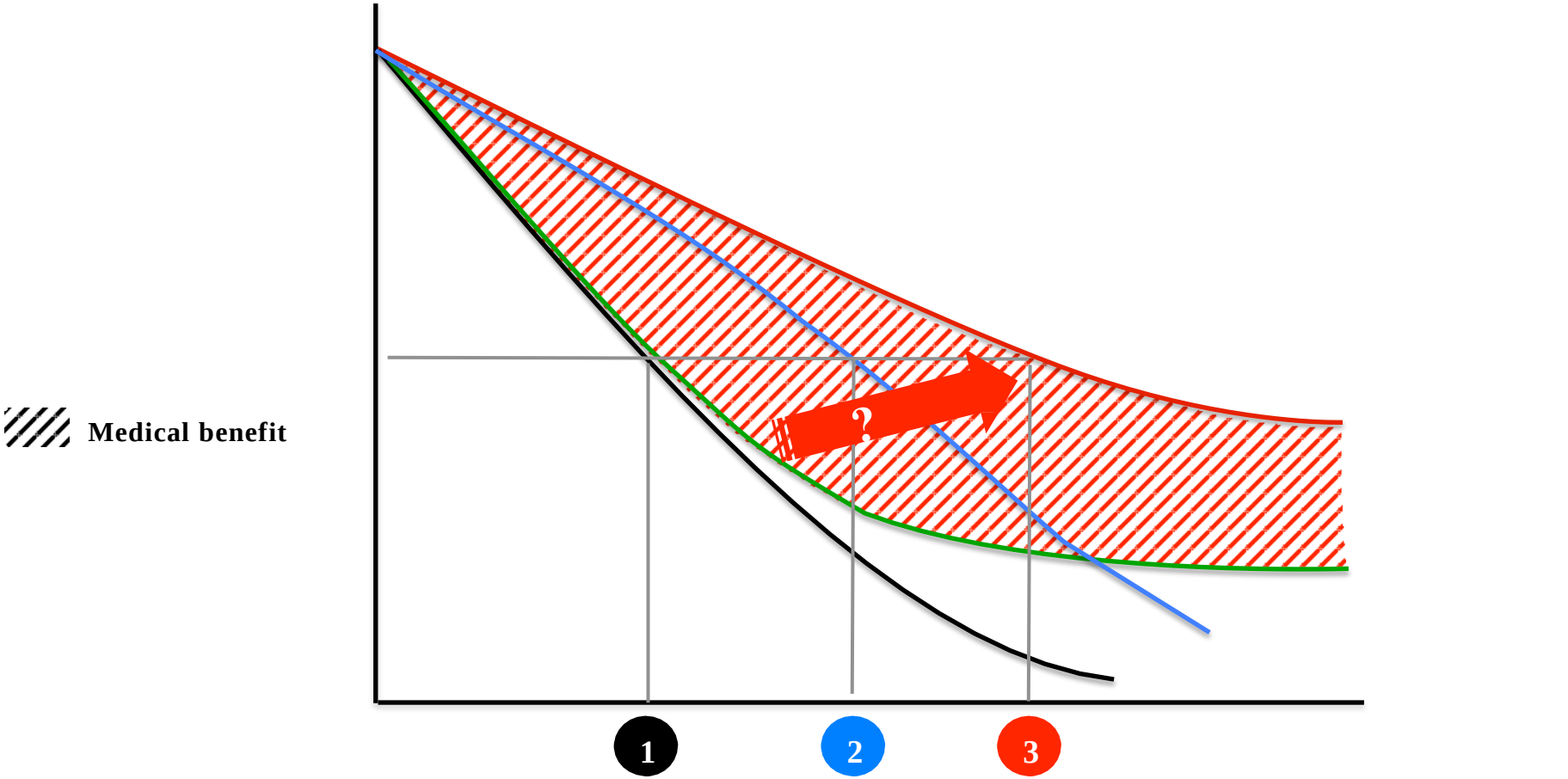
Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab

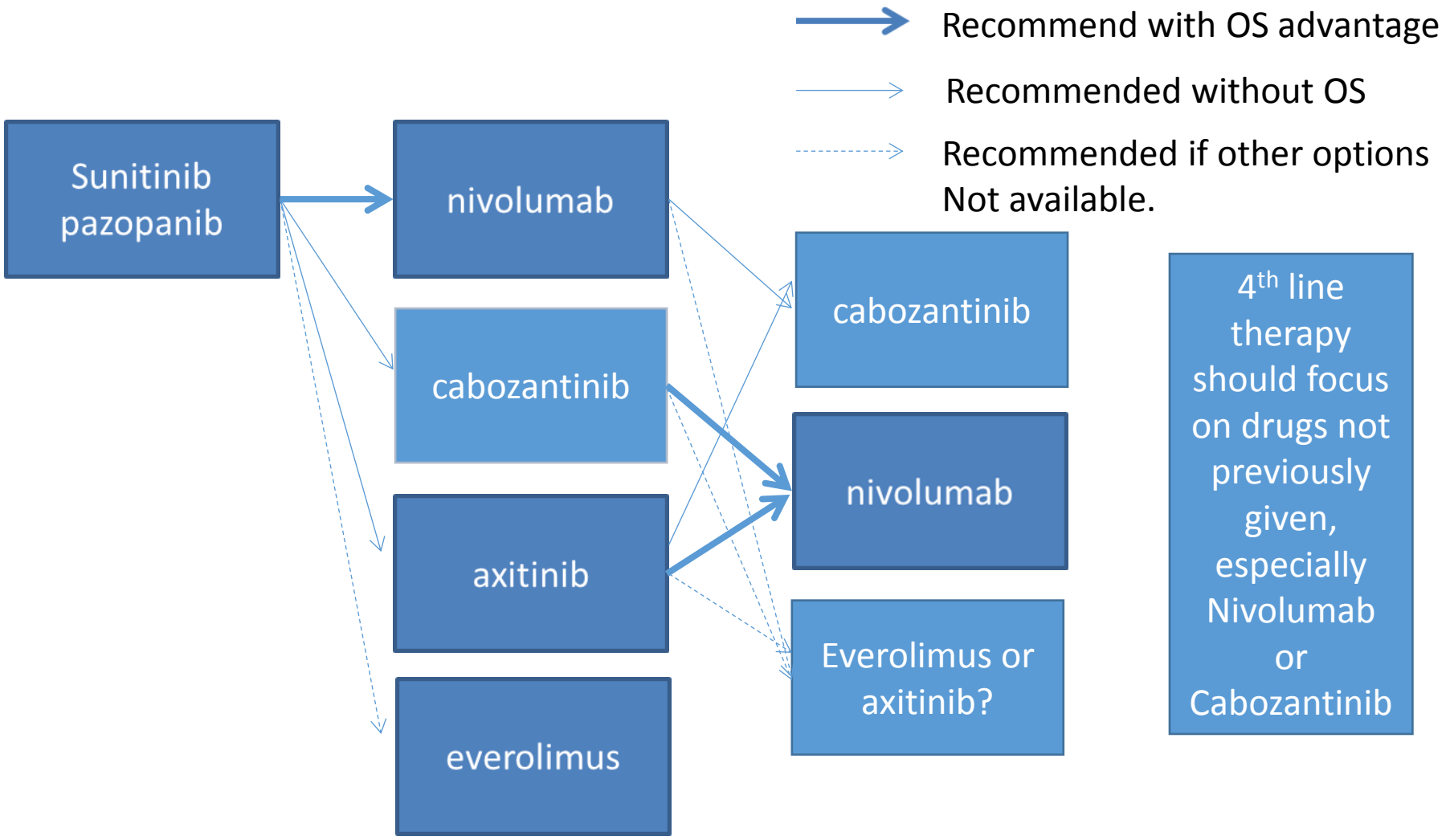
	NIVO3 + IPI1	NIVO1 + IPI3	NIVO3 + IPI3
	N = 47	N =47	N = 6
Confirmed ORR[a], n (%) 95% CI	18 (**38.3**) 24.5-53.6	19 (**40.4**) 26.4–55.7	0
Best overall response[b], n (%) Complete response Partial response Stable disease Progressive disease	 **4 (8.5)** 14 (29.8) 17 (36.2) 10 (21.3)	 1 (2.1) 18 (38.3) 17 (36.2) 7 (14.9)	 0 0 5 (83.3) 1 (16.7)

Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab
Adverse Events

	NIVO3 + IPI1		NIVO1 + IPI3	
	N = 47		N = 47	
Preferred term, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Total patients with an event	**39 (83.0)**	**16 (34.0)**	**44 (93.6)**	**30 (63.8)**

Immune Checkpoint Inhibitors
Renal Cell Cancer





Immune Checkpoint Inhibitors