Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the treatment of GU Malignancies

Edwin M Posadas, MD FACP
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center

Advances in Cancer Immunotherapy™ - Los Angeles
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Society for Immunotherapy of Cancer

Disclosures

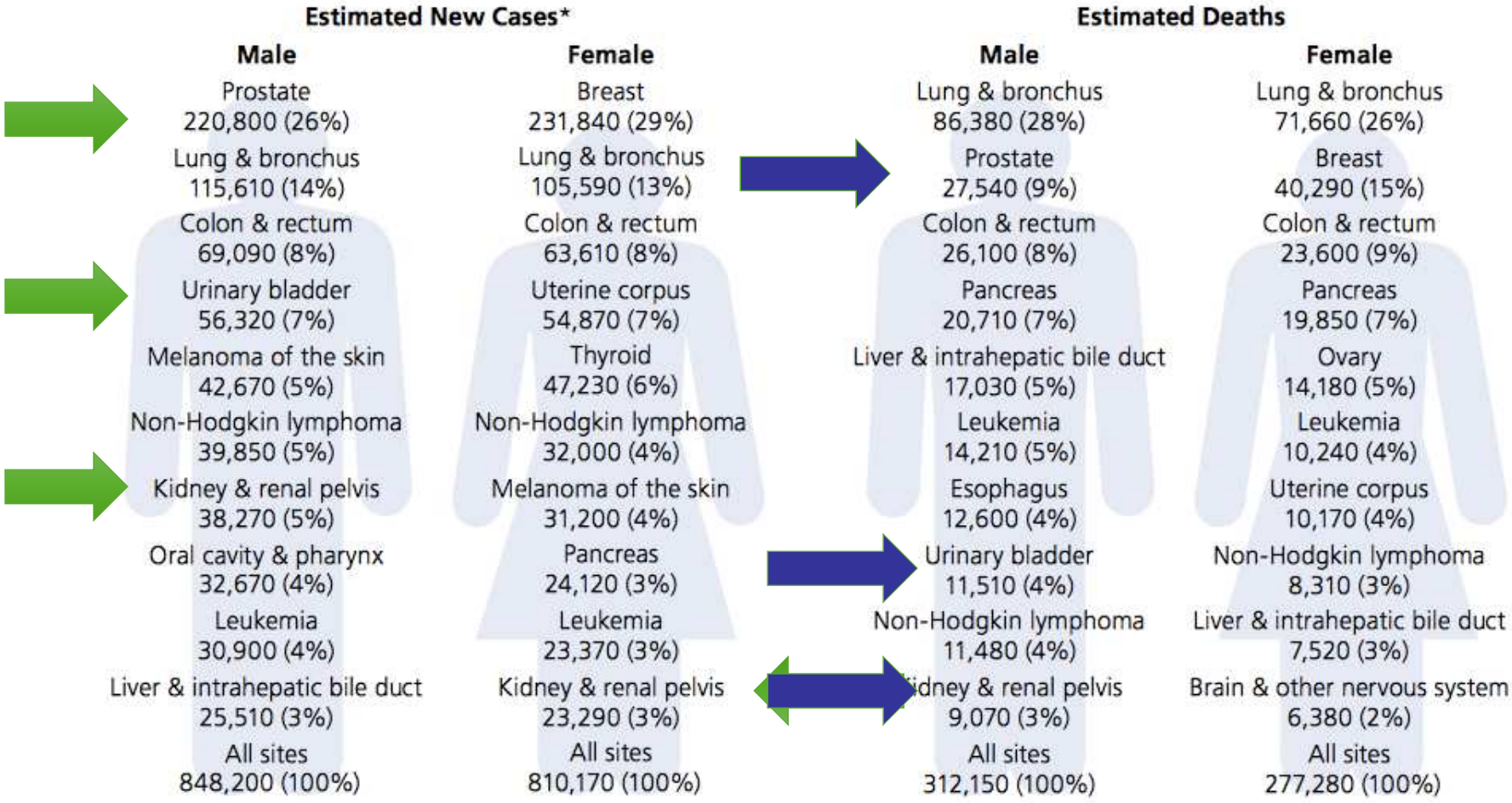
- Research support: BNIT, Tracon
- Honoraria: Medivation, Astellas, Pharamcyclics

Outline

1. *General Principles*
2. *Urothelial Carcinomas*
3. *Renal Cell Carcinoma*
4. *Prostate Cancer*

Genitourinary Malignancies

Leading Sites of New Cancer Cases and Deaths – 2015 Estimates



Cancer Facts and Figures, 2015

General Principles – Immunotherapy

Cancer Immunotherapy Given the "Breakthrough of the Year" Title.

Science magazine deems advances in cancer immunotherapy as the scientific breakthrough of the year.

Immunotherapy referred to as a "turning point in cancer".

Classes of Immunotherapies

Active

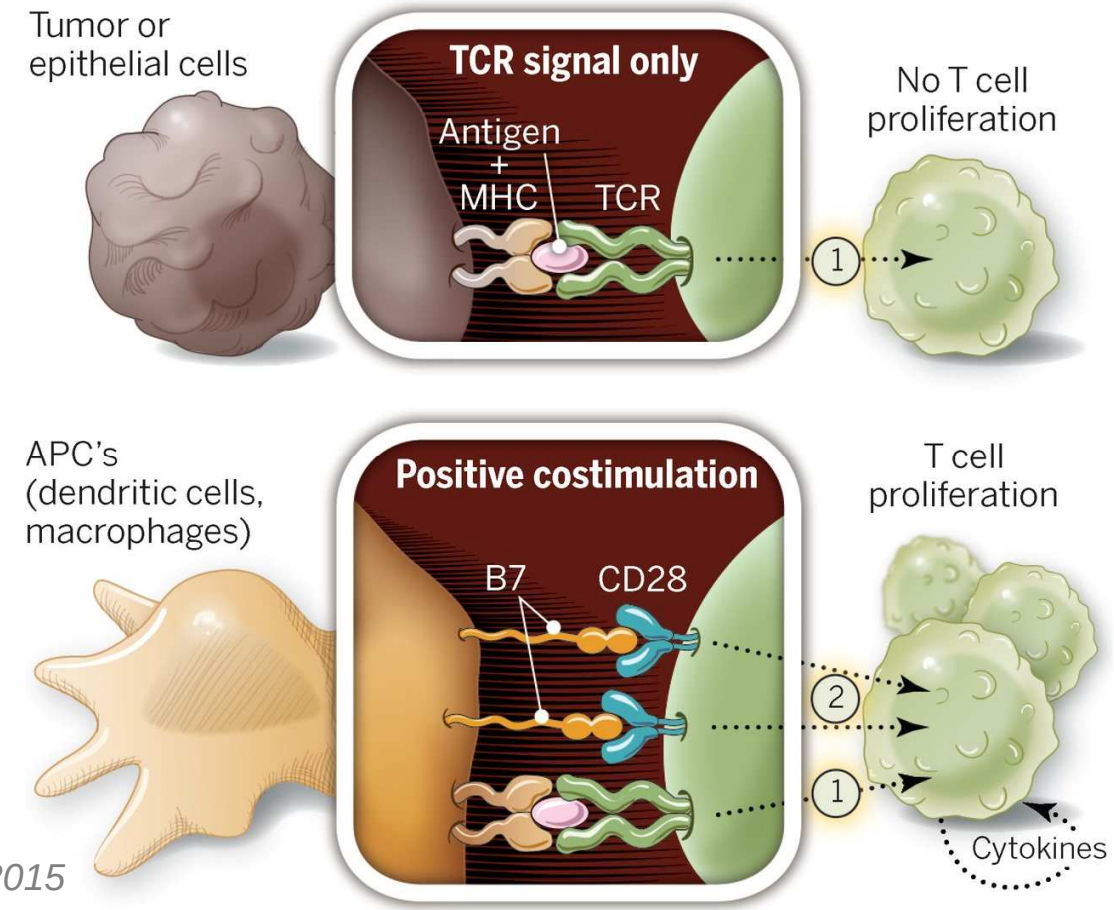
- Vaccines
- IC BCG
- Cytokine Therapy

Passive

- Monoclonal antibody therapy
- Cell-based therapy
  - T cell
  - APC
- Infusion of gamma globulin

What is the nature of the immune response towards tumors?

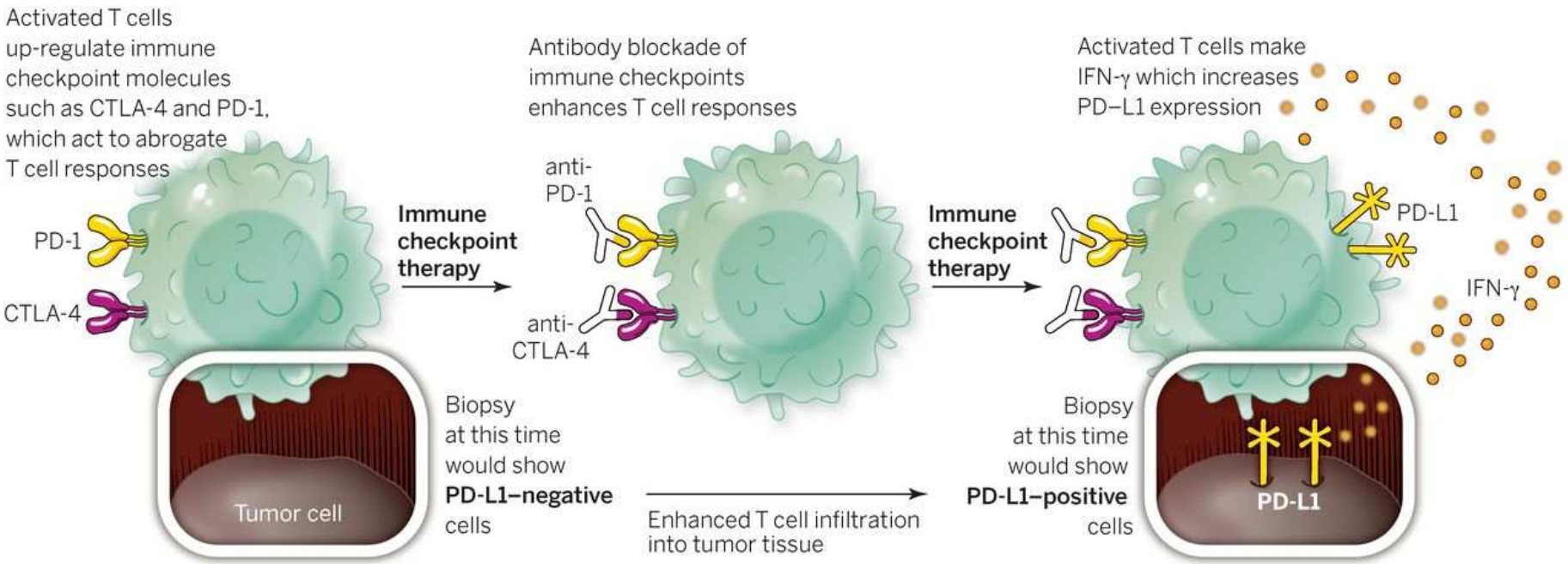
Tumors fails to elicit immune response.



Sharma and Allison
Science 348:6230, 2015

What is the nature of the immune response towards tumors?

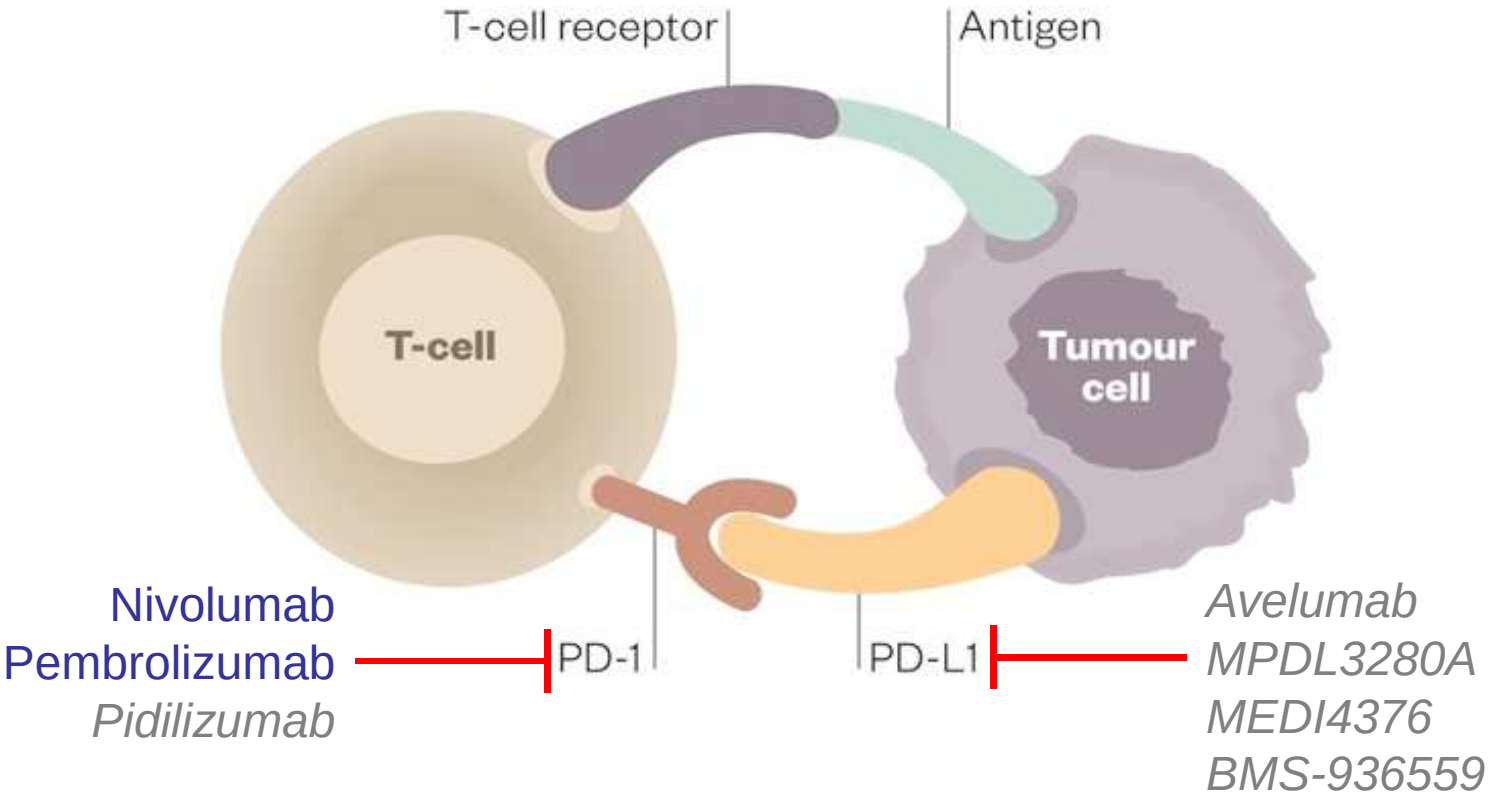
Tumors actively suppress the immune response via 'checkpoint' inhibitors.



Sharma and Allison
Science 348:6230, 2015

Checkpoint inhibitors

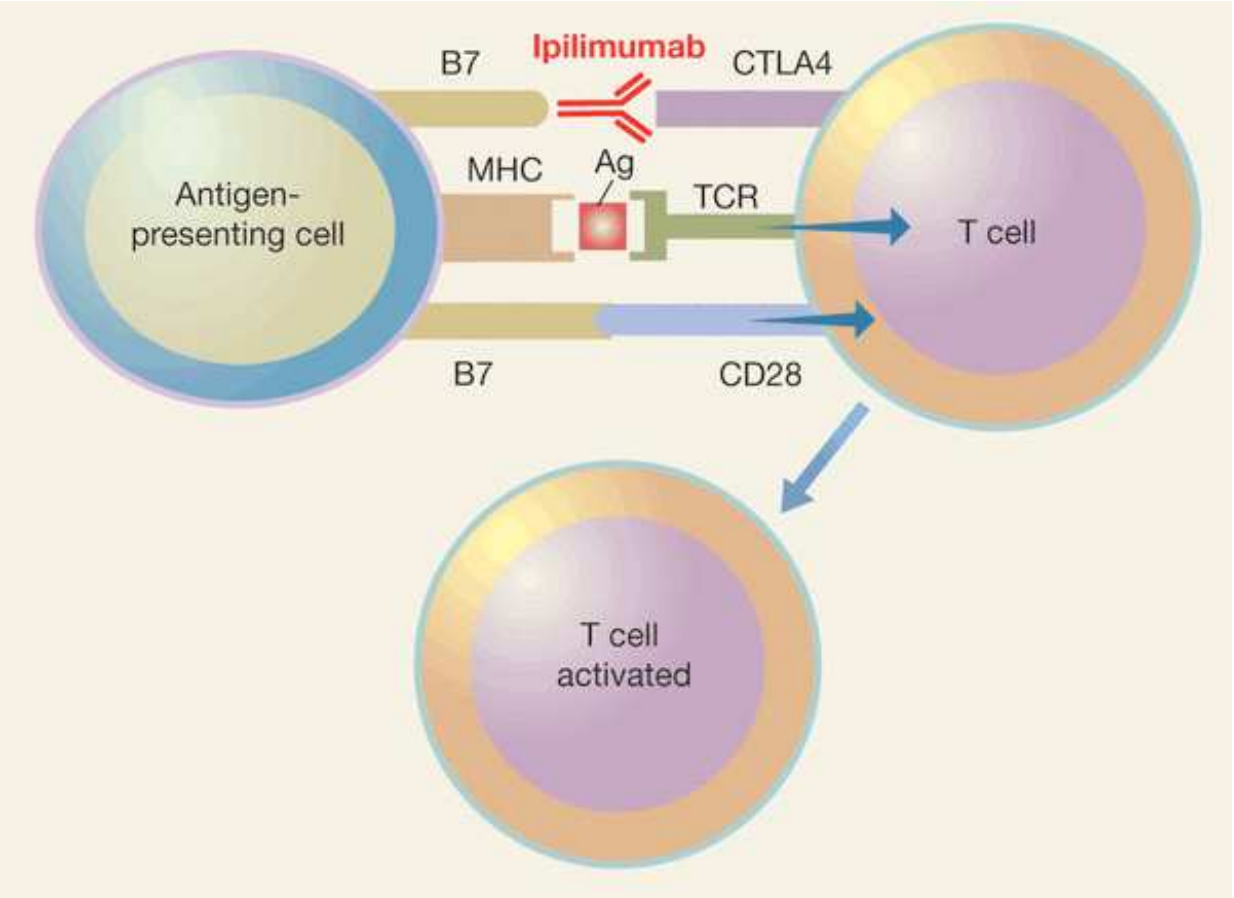
Tumor cells evade the body's immune system by turning it off by expressing PD-L1, which binds to PD-1 leading to the arrest of the immune response directed against the tumor.



Targeting immune checkpoint inhibitors with monoclonal antibodies

Ipilimumab

FDA approval Jan. 1, 2011.



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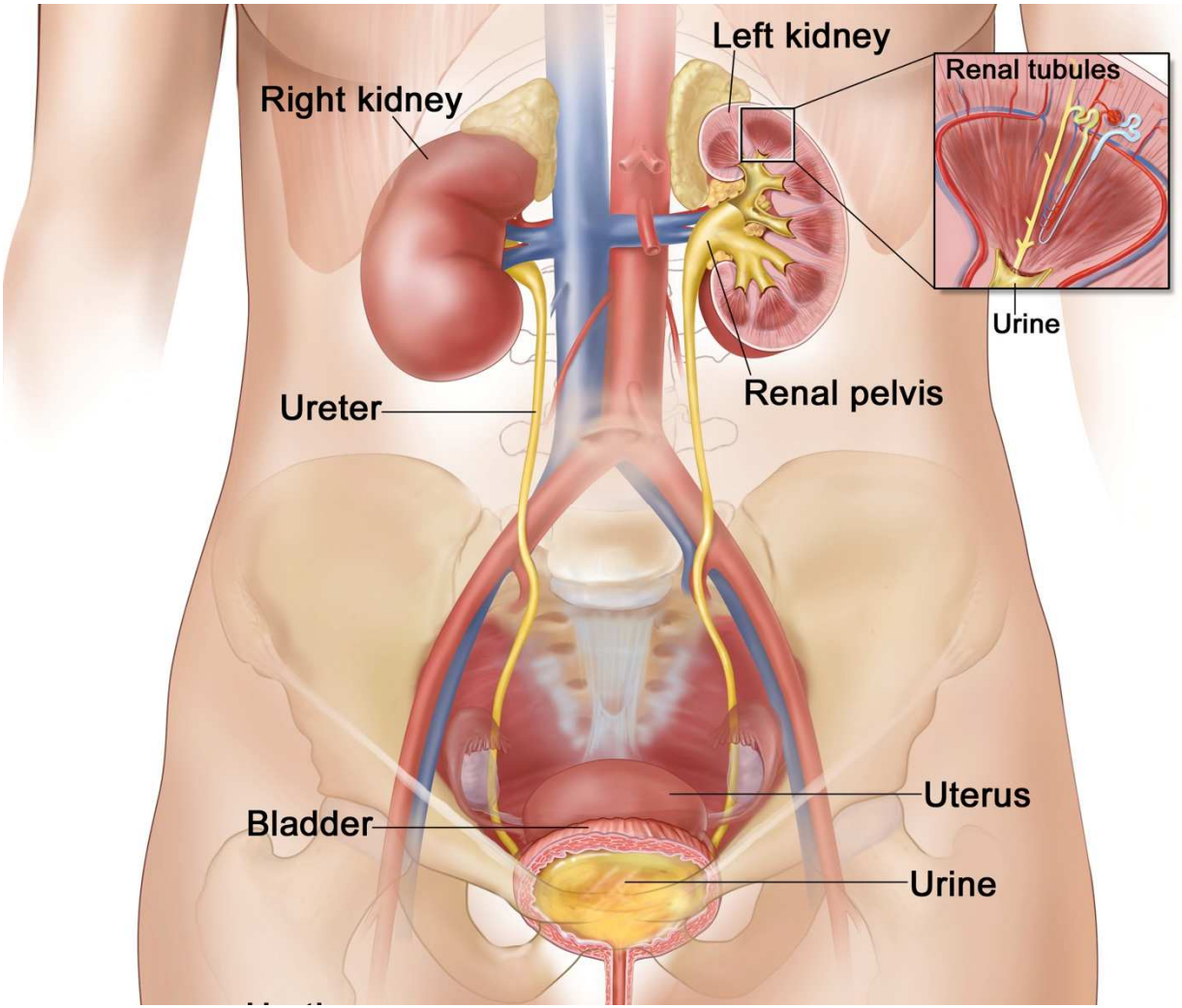
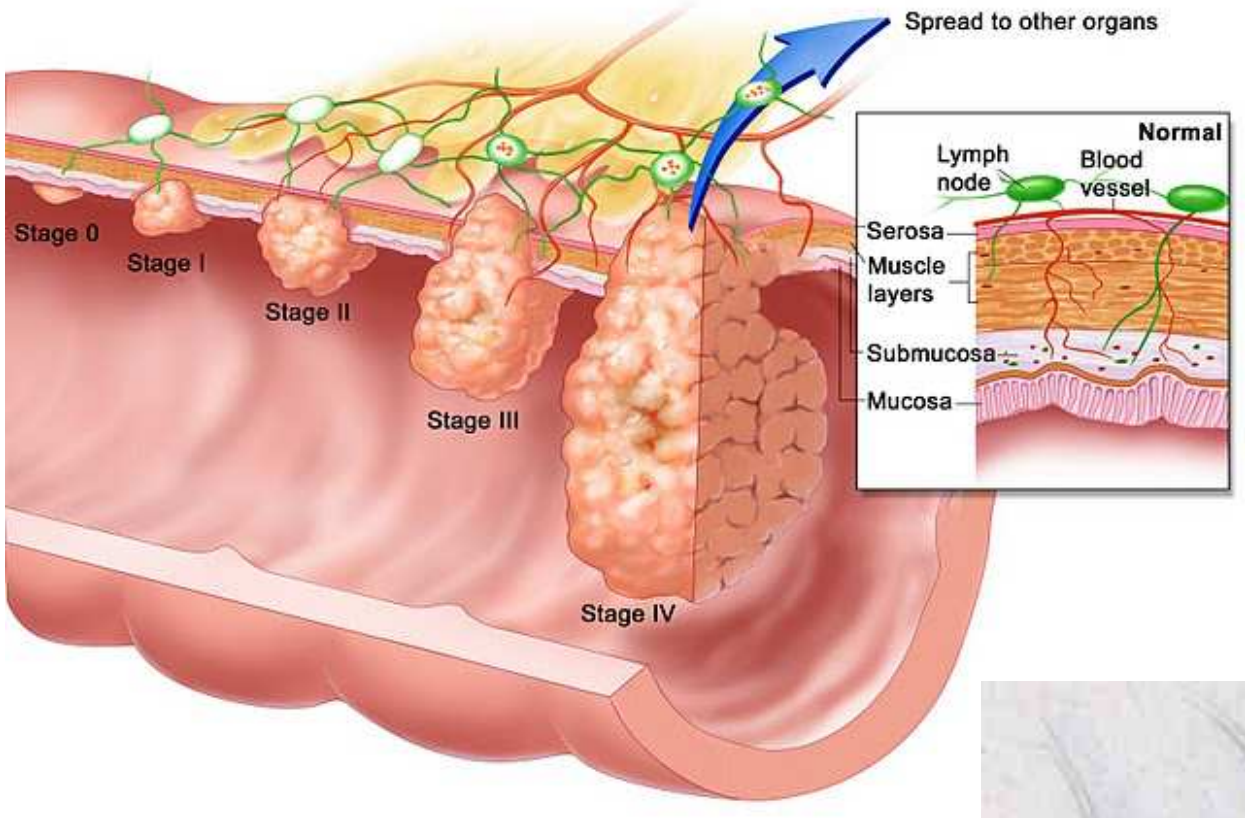
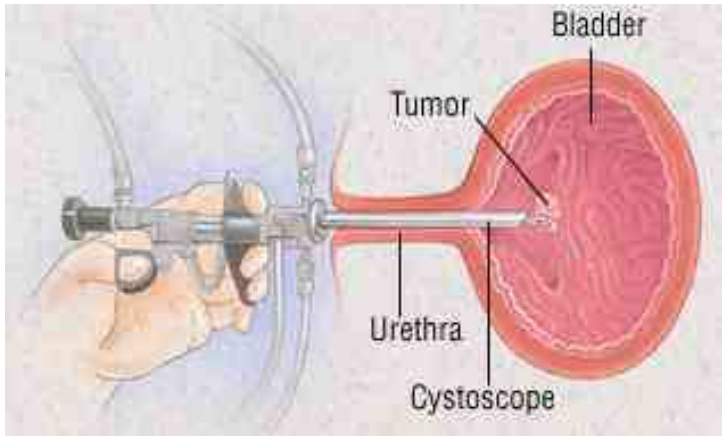
Urothelial Cancers



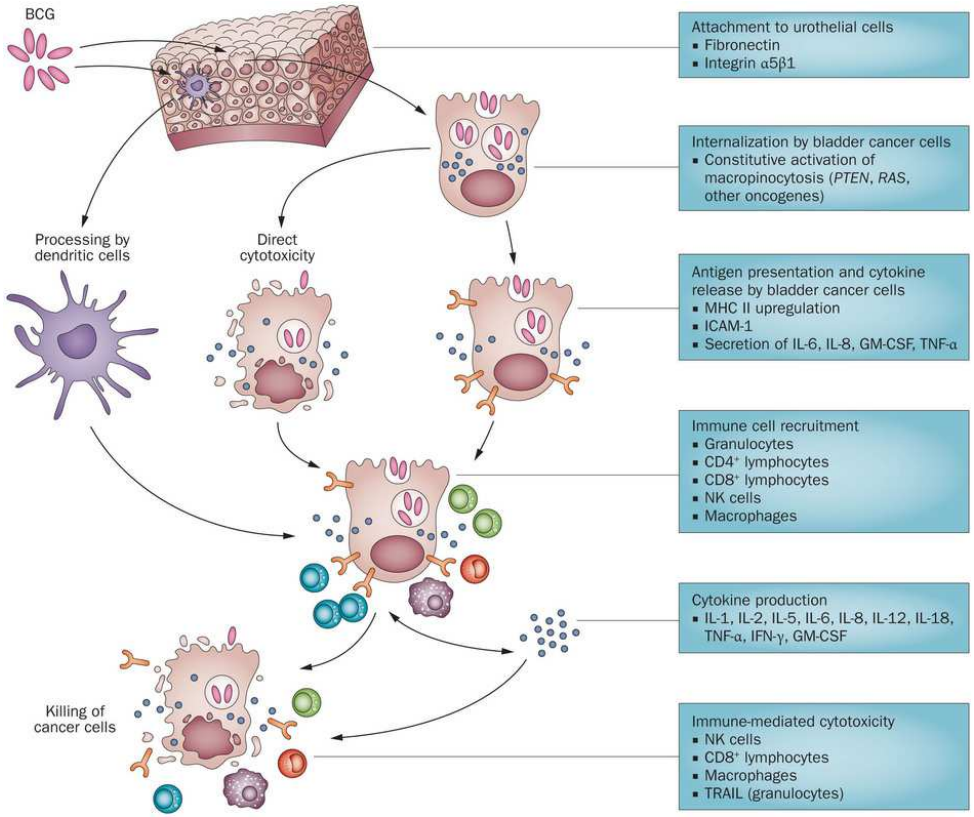
Superficial Urothelial Cancers





BCG for refractory tumors

- Bacillus Calmette-Guerin (BCG)
  - Instilled into bladder
  - Prevents recurrence of high risk disease



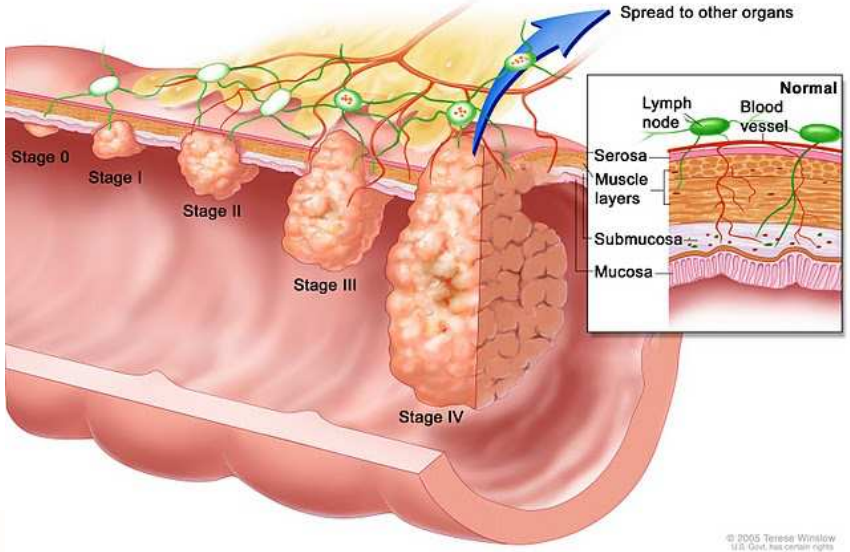
Urothelial CA- BCG immunotherapy

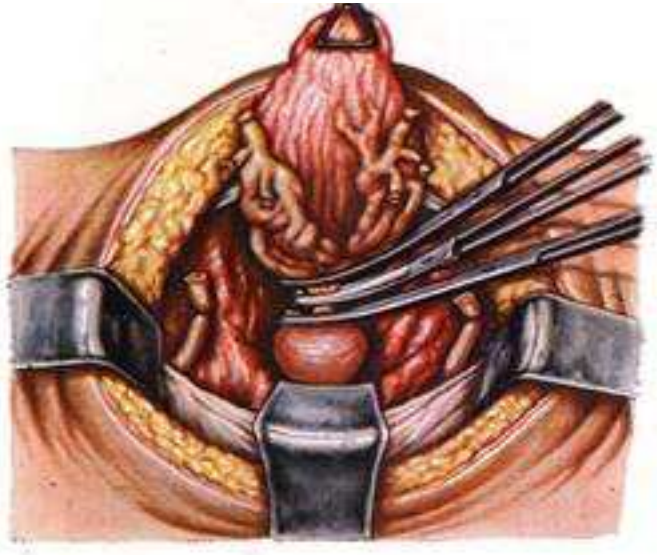
- 1929- 1st association of TB and cancer
- 1976- first use in superficial bladder cancer

- Mechanism of action unknown

Pearl, AM J Hygeine 1929; Morales, J Urol 1976;

Muscle Invasive Cancer



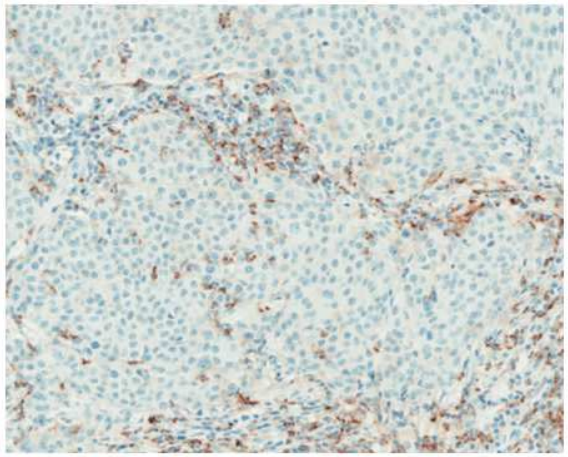


PD-L1 inhibition in refractory urothelial cancers

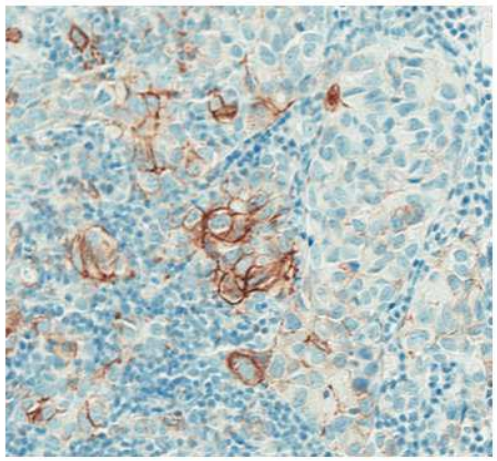
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[3], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]

b



Tumour-infiltrating immune cells



Tumour cells

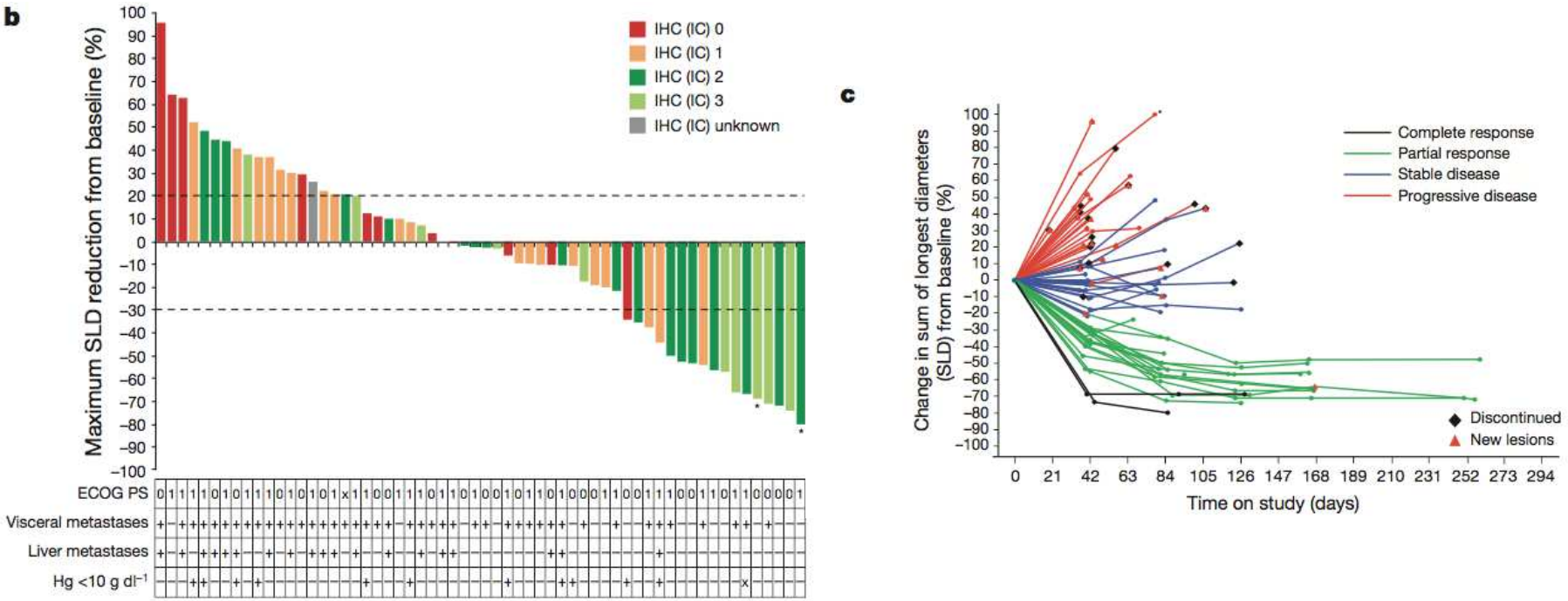
c

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)

Powles, Nature 2014

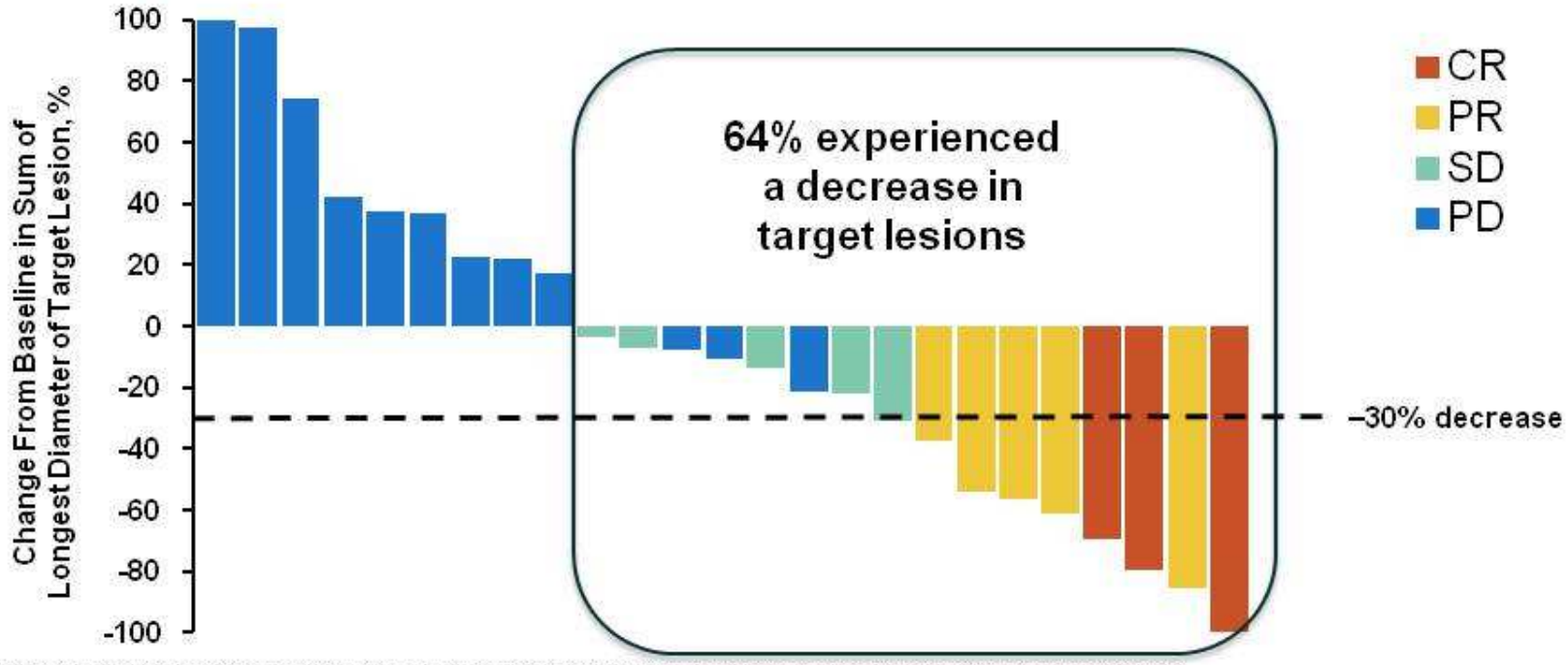
PD-L1 inhibition in refractory urothelial cancers



Powles, Nature 2014

KEYNOTE-012: Pembrolizumab

Maximum Percent Change From Baseline in Target Lesions



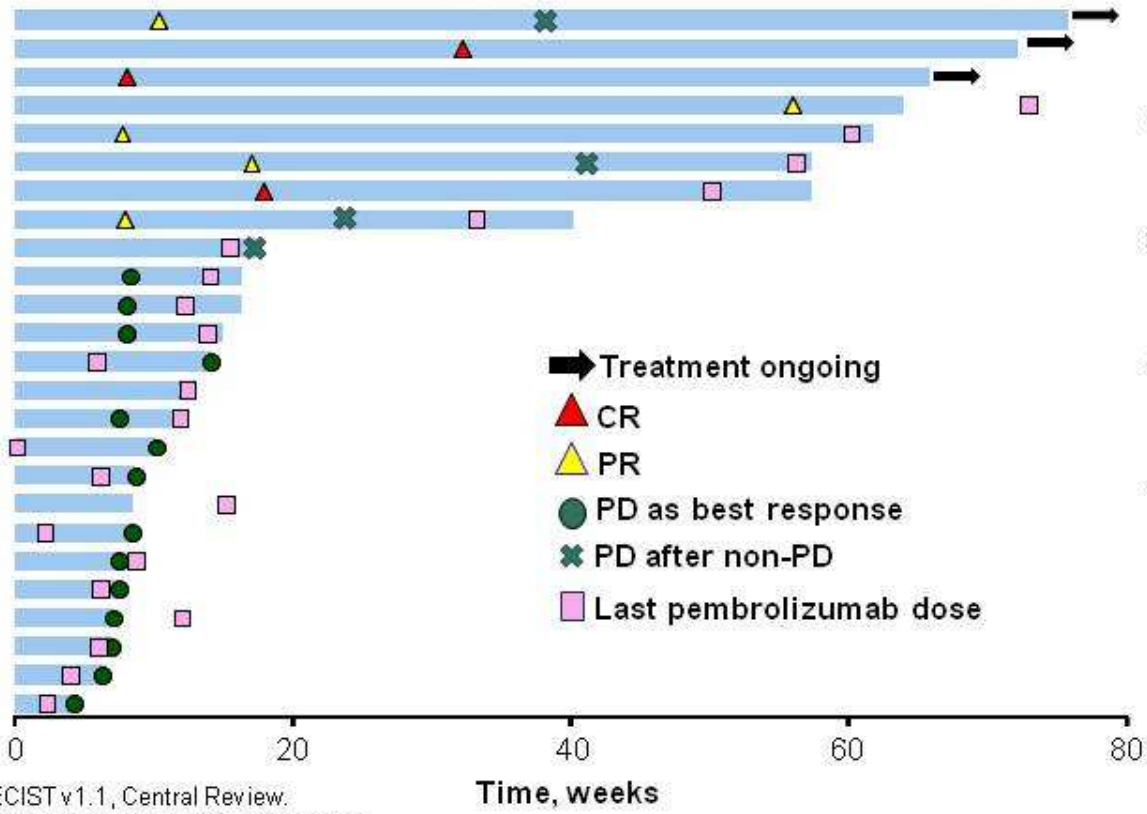
Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline tumor assessment (n = 25).
RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

PRESENTED AT: ASCO Annual '15 Meeting

With kind permission from E. Plimack

KEYNOTE-012: Pembrolizumab

Treatment Exposure and Response Duration



- 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.

PRESENTED AT: ASCO Annual '15 Meeting

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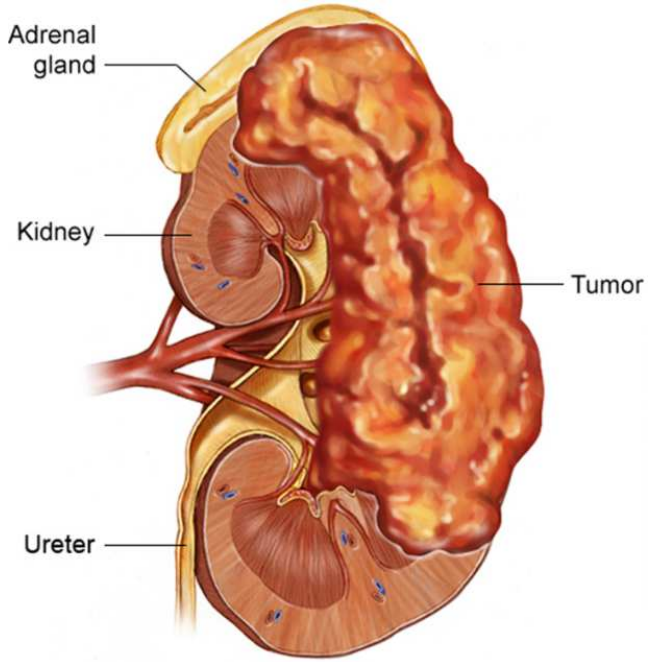
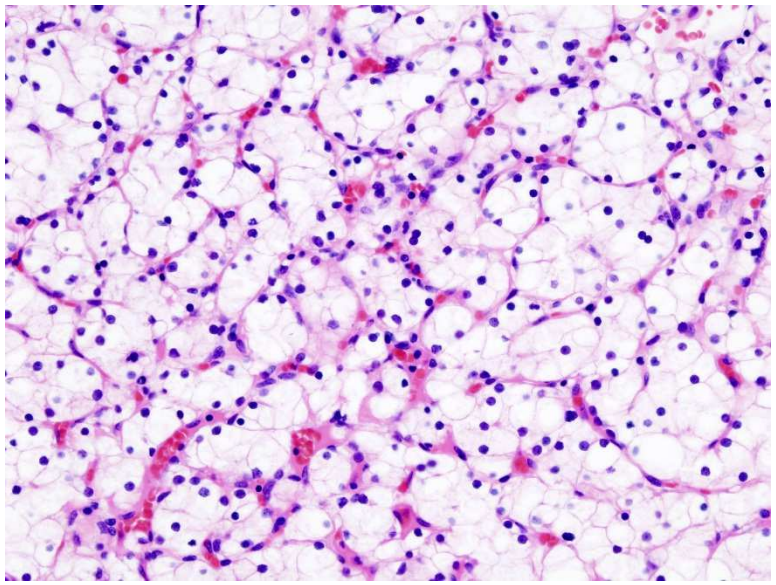
Renal Cell Cancers





- Cytokine Therapies: IL-2 & IFN-alpha
- Tyrosine Kinase Inhibitors

- Checkpoint Inhibitors: Ipilimumab and PD-1
- Vaccine Therapy: AGS-003

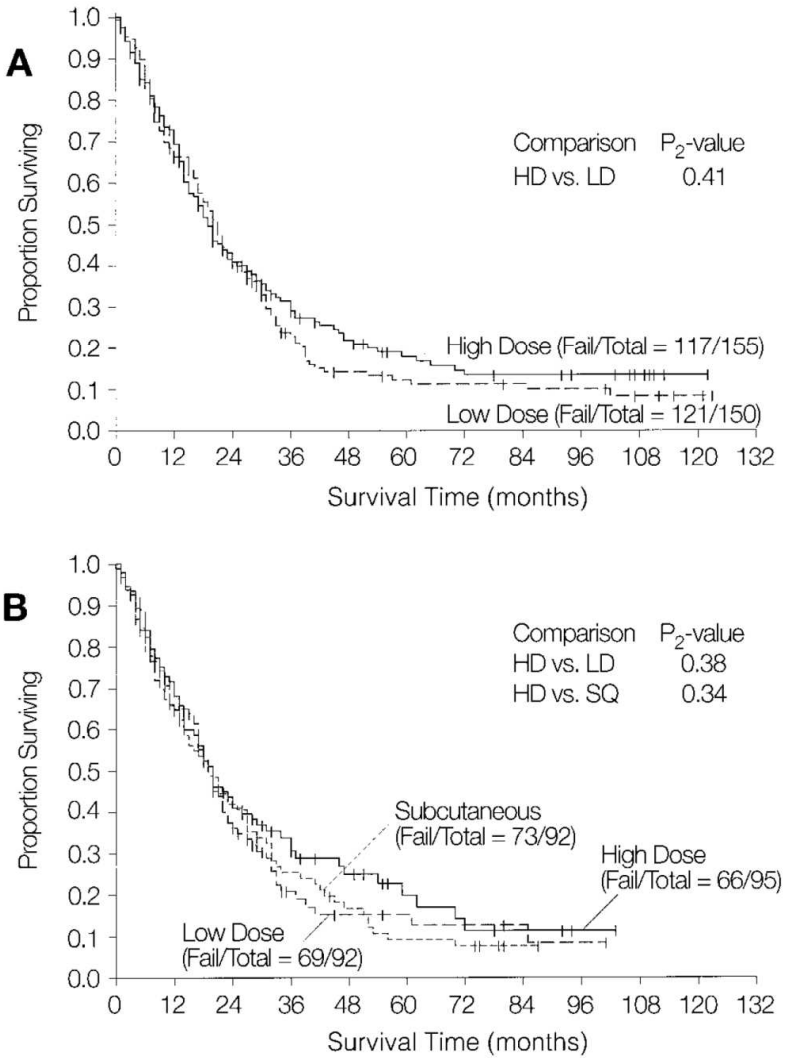
HD-IL2 therapy for RCC

Table 4. Response Durations

Duration (months)					
High-Dose IV IL-2		Low-Dose IV IL-2		Subcutaneous IL-2	
CR	PR	CR	PR	CR	PR
130+	**37**	128+	**24**	**78**+	**28**
121+	**28**	113+	23	**13**	**28**
115+	**24**	**40**+	22		**17**
114+	**23**	20	**21**+		**15**
103+	**19**	19	**15**		**9**
100+	**17**	3	**13**+		**8**
90+	**17**		11		**2**
52+	16		**11**		
45	15		**8**+		
23	14		7		
19	**14**		**7**		
	14+		**4**		
	13		**4**		
	10				
	9				
	8+				
	8				
	8				
	7				
	6				
	4				
	4				

NOTE. Bold values are for patients concurrently randomly assigned between three arms. + indicates response is ongoing.

Abbreviations: IV, intravenous; IL-2, interleukin-2; CR, complete response; PR, partial response.



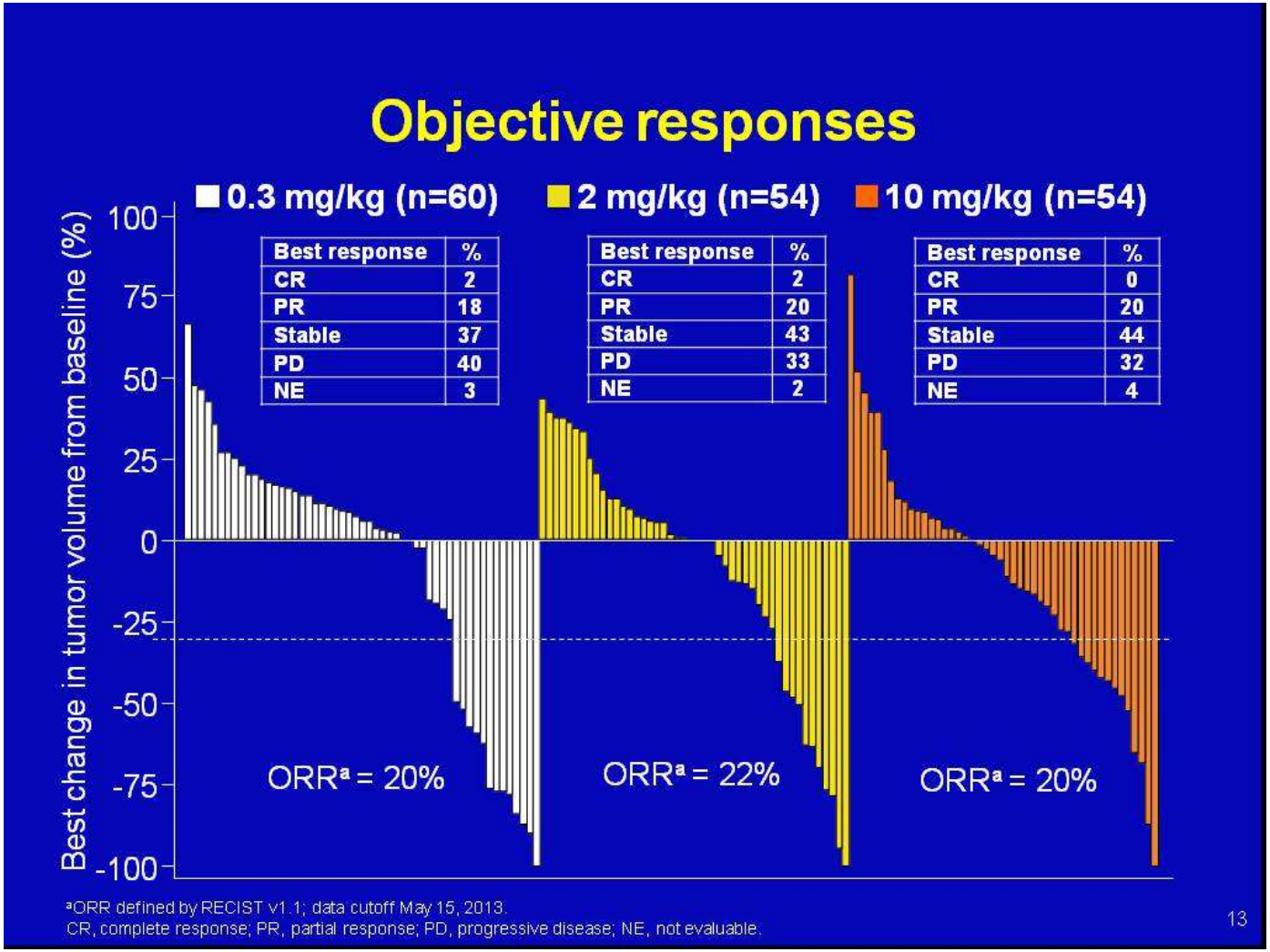
720,000 U/kg vs. 72,000 U/kg

Yang, JCO 2003

Summary of RCC Clinical Trials

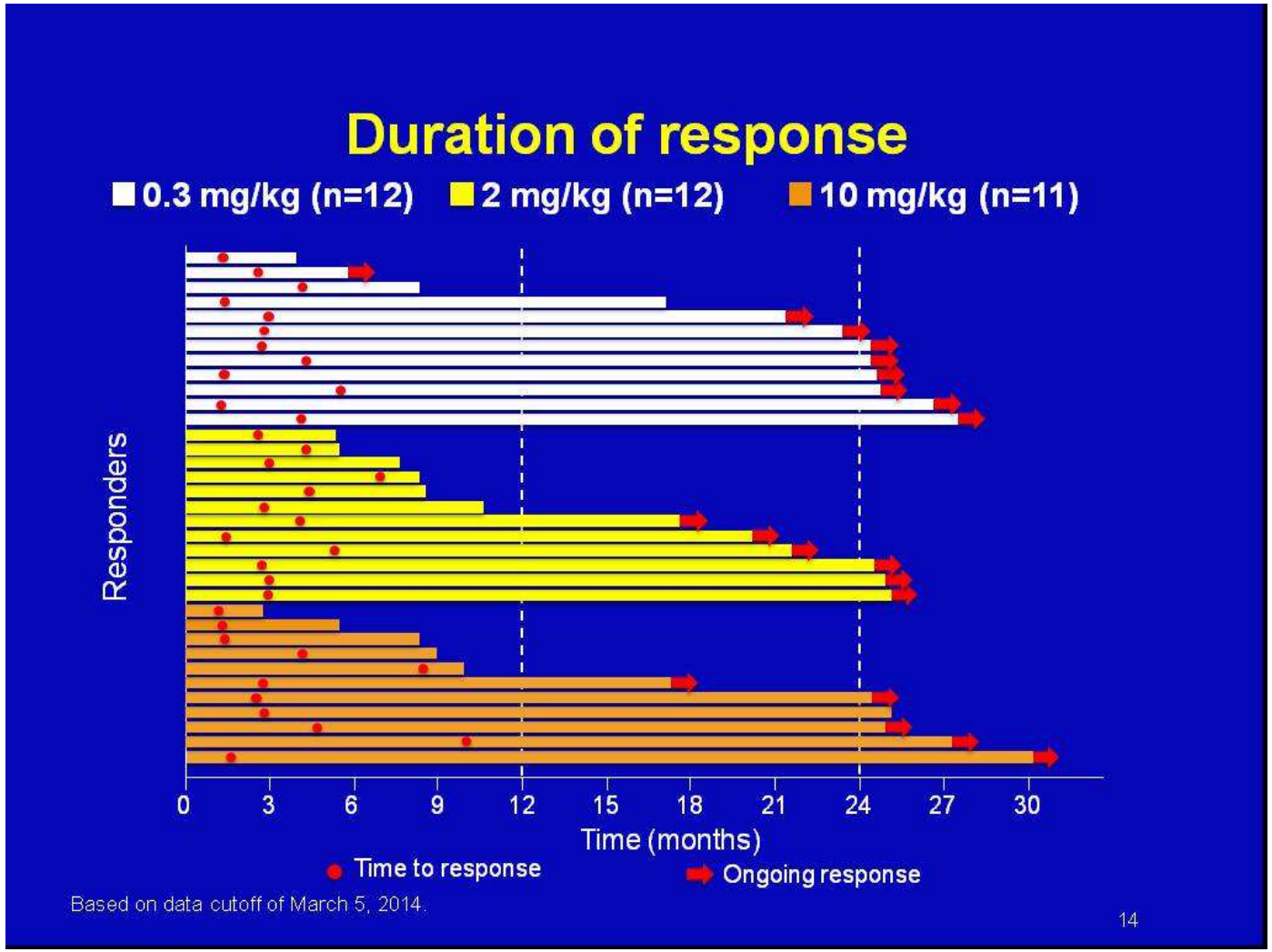
		Therapy	Alternative
First Line	Good px	Sunitnib or Pazopanib IFN + bev or HD-IL2	Sorafenib
	Poor px	Temsirolimus	
Second Line	Cytokine Refractory	Sorafenib Pazopanib	Sunitinib
	VEGF(R) or mTOR Refractory	Everolimus Axitinib	Sequential TKIs
Non-Clear Cell		Temsirolimus Sunitinib Everolimus	

Nivolumab in RCC



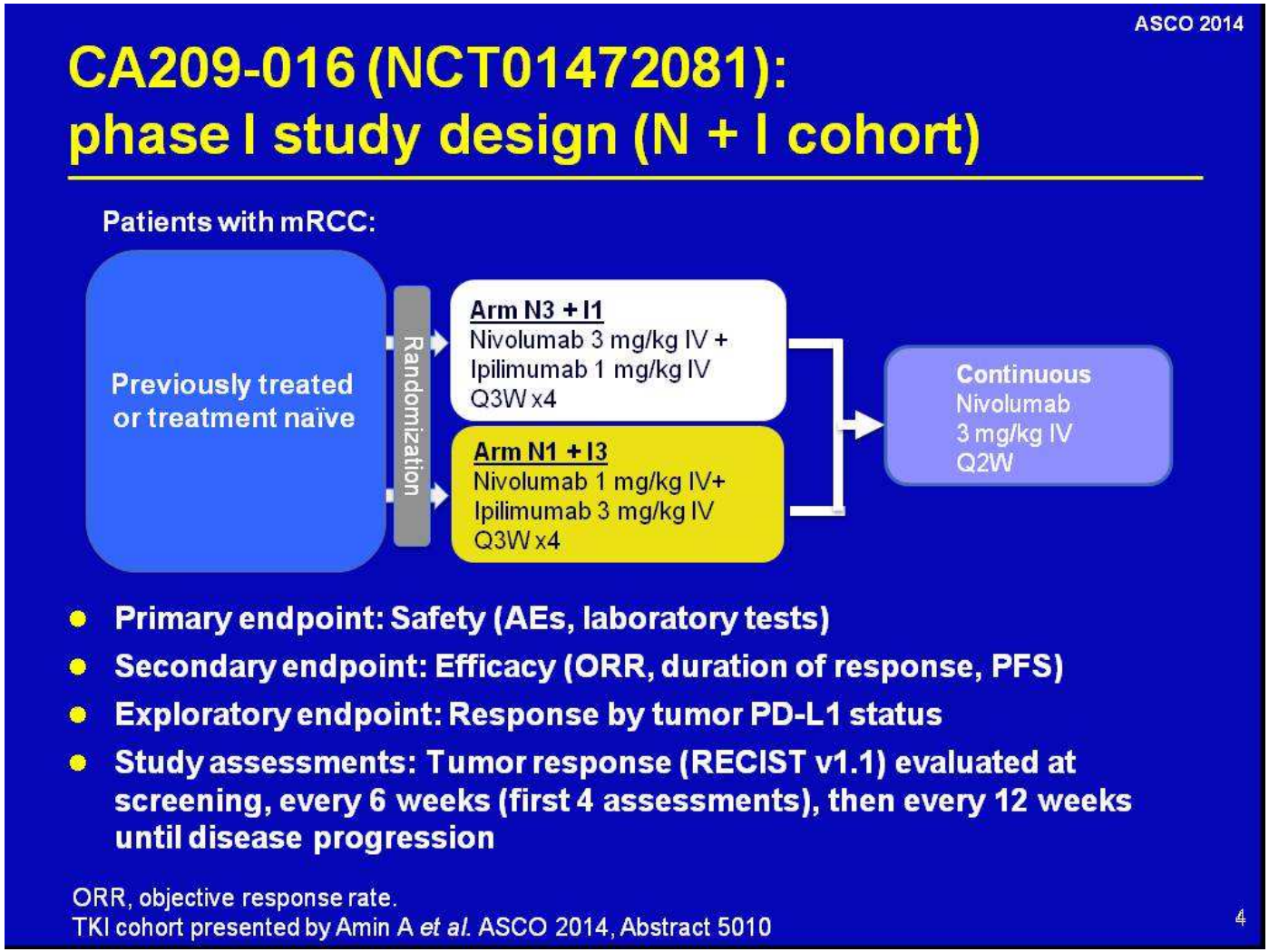
With kind permission from R. Motzer

Nivolumab in RCC



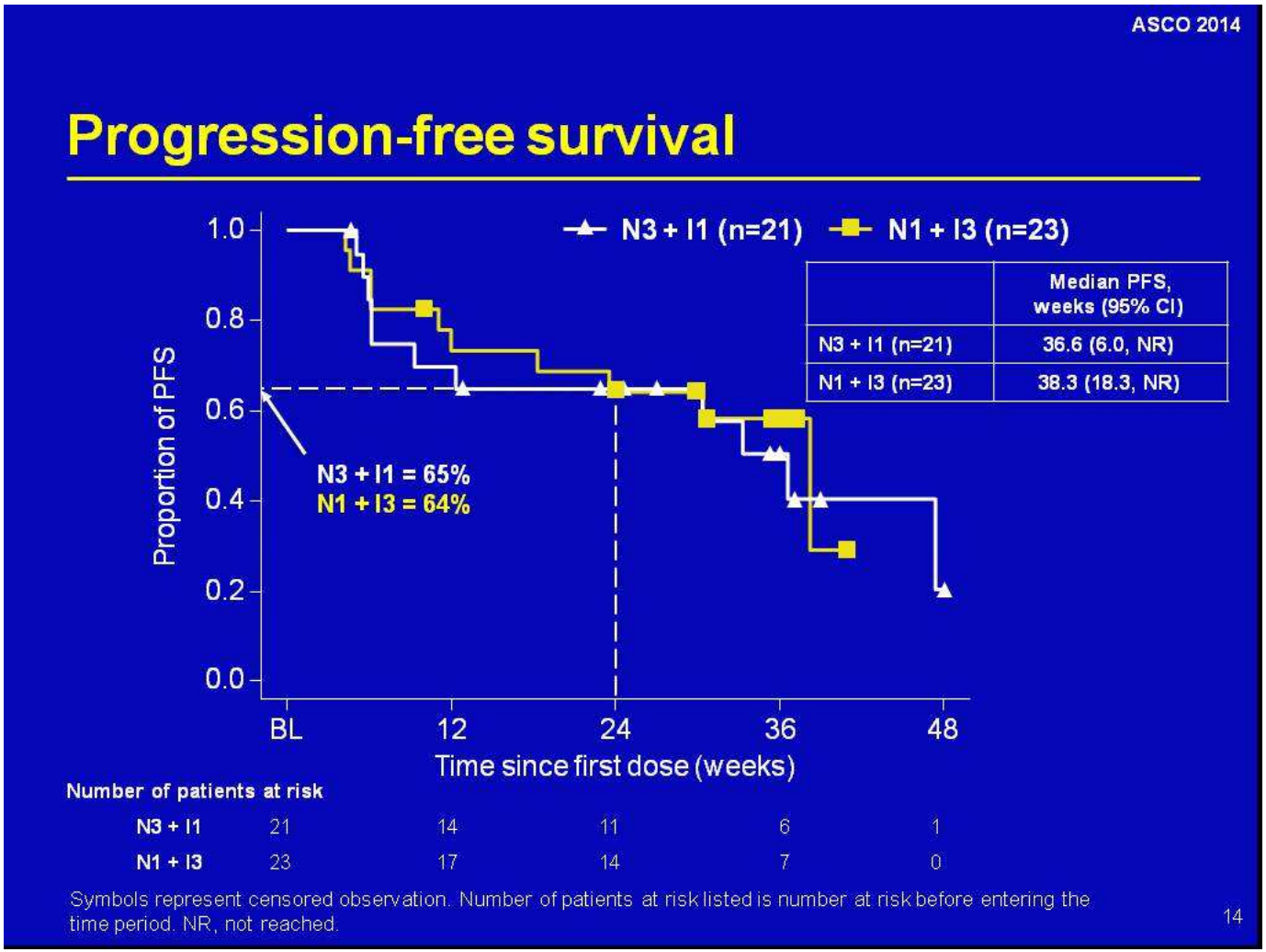
With kind permission from R. Motzer

CheckMate 016



With kind permission from H. Hammers

CheckMate 016



With kind permission from H. Hammers

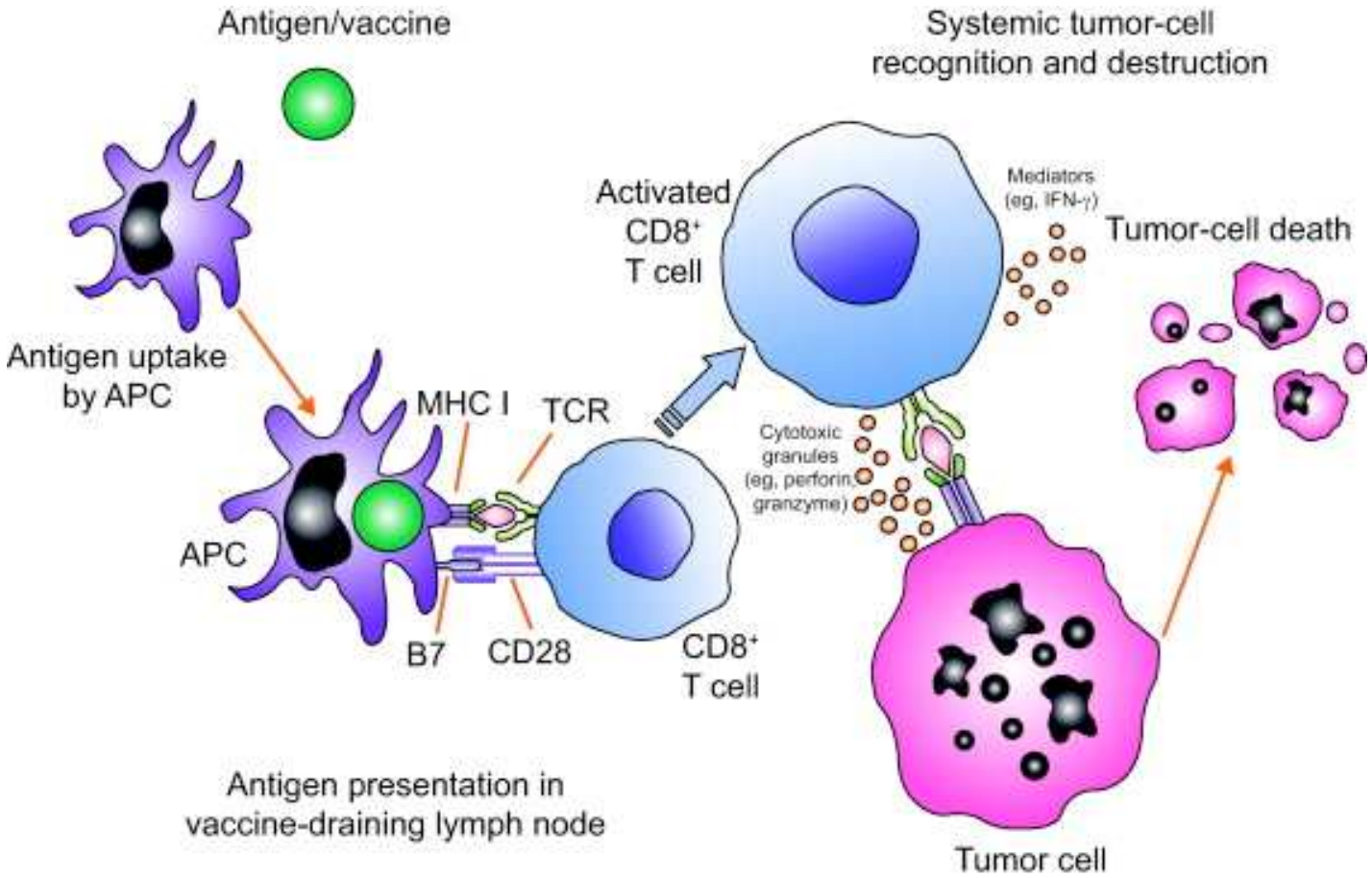
Active phase 3 studies in RCC

- CheckMate phase 3 RCC
  - Ipilimumab + Nivolumab vs. sunitnib
    - First line metastatic RCC

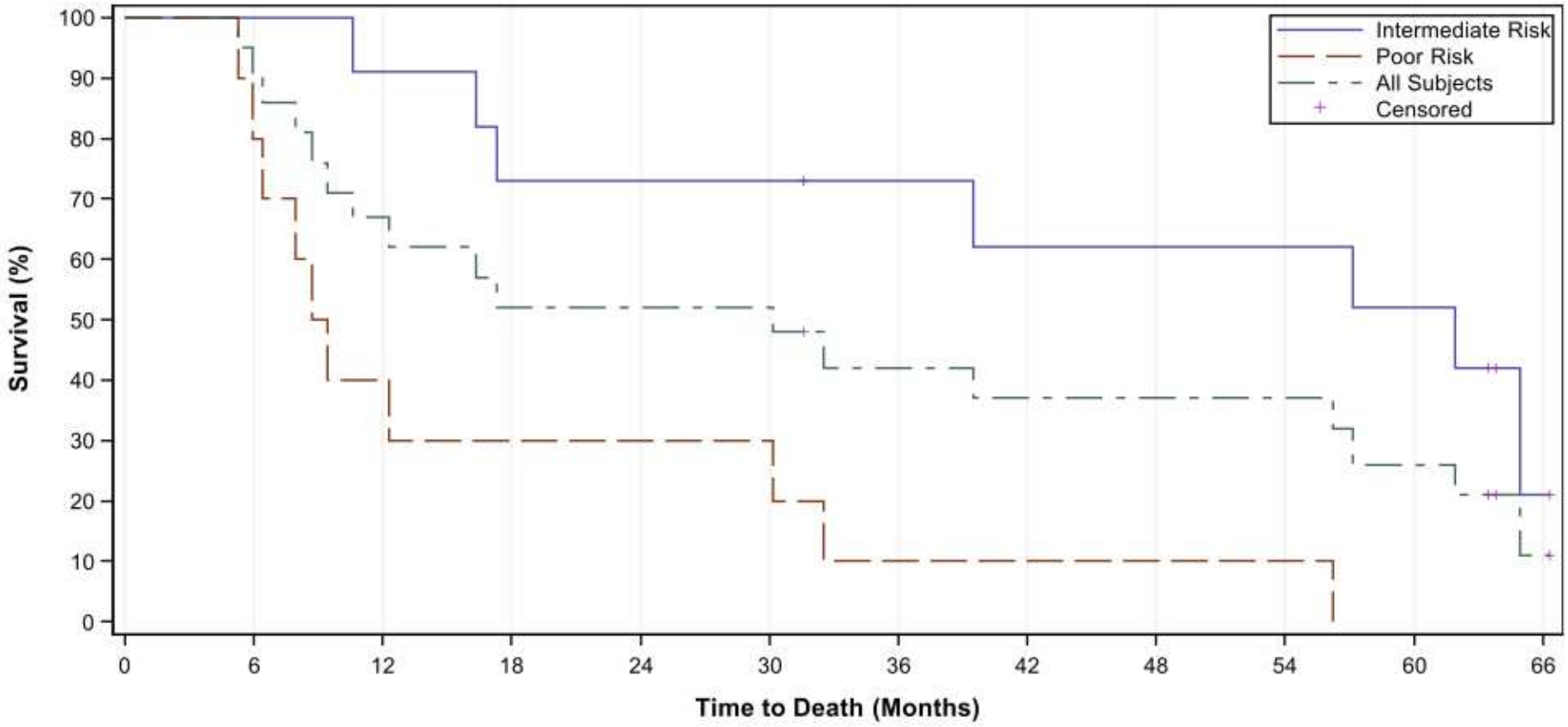
- ADAPT
  - Sunitinib +/- AGS-003 (autologous dendritic cell vaccine)

Open and accruing at CSMC

AGS-003: mechanism of action



Sunitinib + AGS-003



Number at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	median (95% CI)
Intermediate Risk	11	11	11	9	9	9	8	7	7	7	6	2	1	61.9 (16.32, NE)
Poor Risk	10	9	5	4	4	4	2	2	2	2	1	1	1	9.1 (5.26, 30.16)
All Subjects	21	20	15	12	12	12	9	8	8	8	6	2	1	30.2 (9.44, 57.14)

Amin et al, J Immunother Cancer. 2015; 3: 14.

Outline

1. *General Principles Immunotherapy*
2. *Urothelial Carcinomas*
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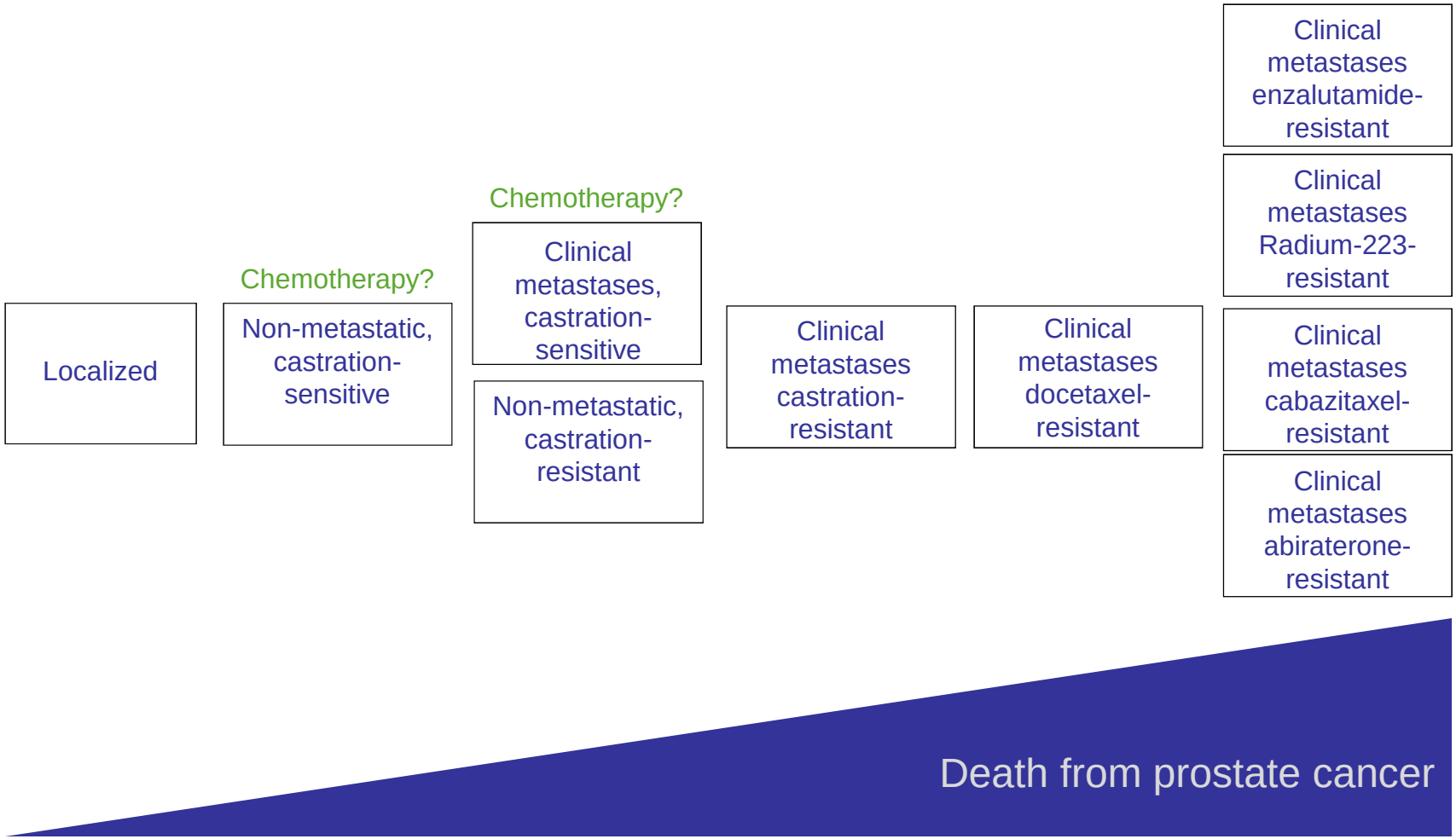
4. *Prostate Cancer*

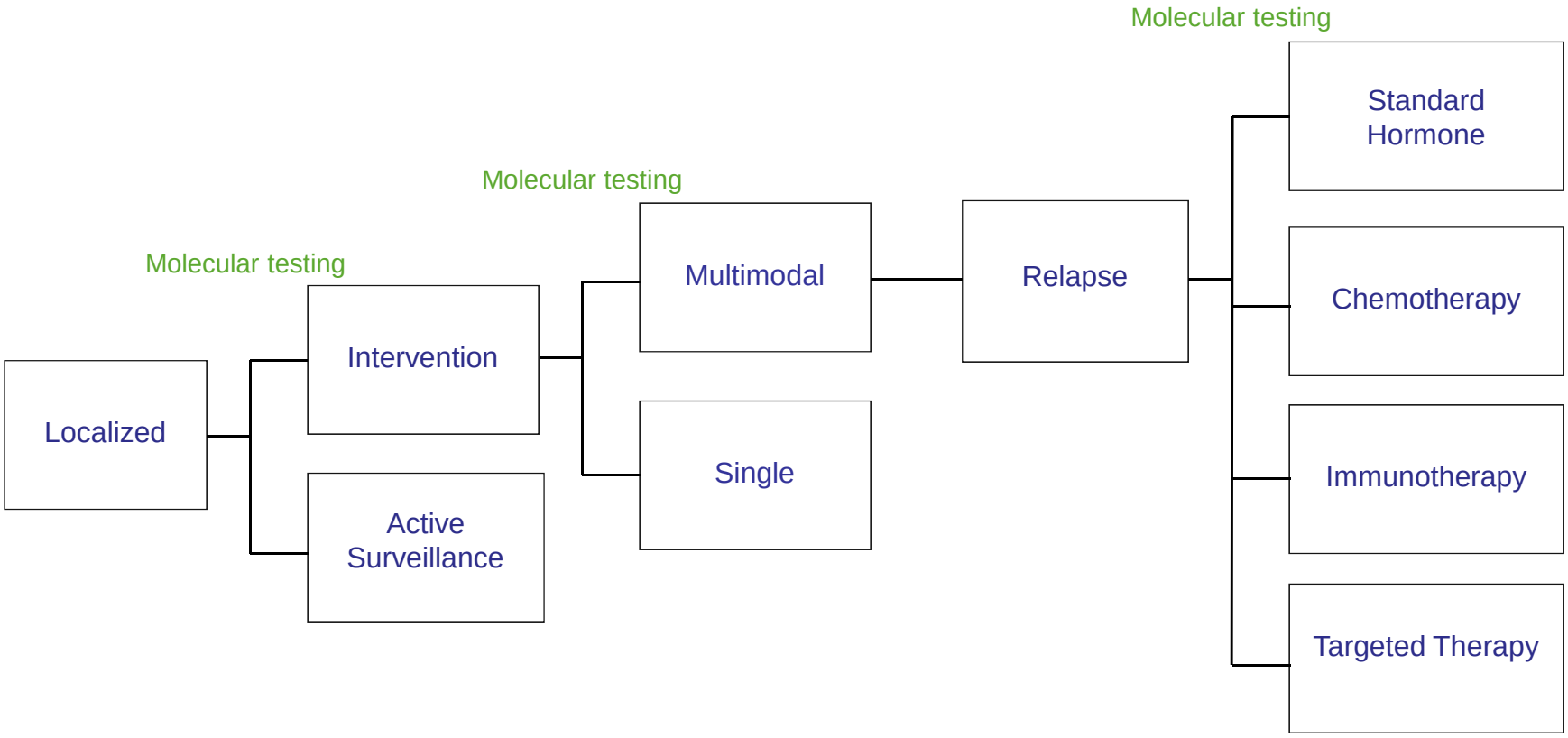
Prostate Cancer Systemic Therapy

- Androgen receptor inhibition
  - First line castration
    - Surgical
    - LHRH analogs
  - Next generation hormonal therapy
    - Androgen biosynthesis: abiraterone
    - Non-steroidal anti-androgens: bicalutamide, enzalutamide
- Cytotoxic chemotherapy: docetaxel, cabaziatxel
- Radionucleides: radium-223

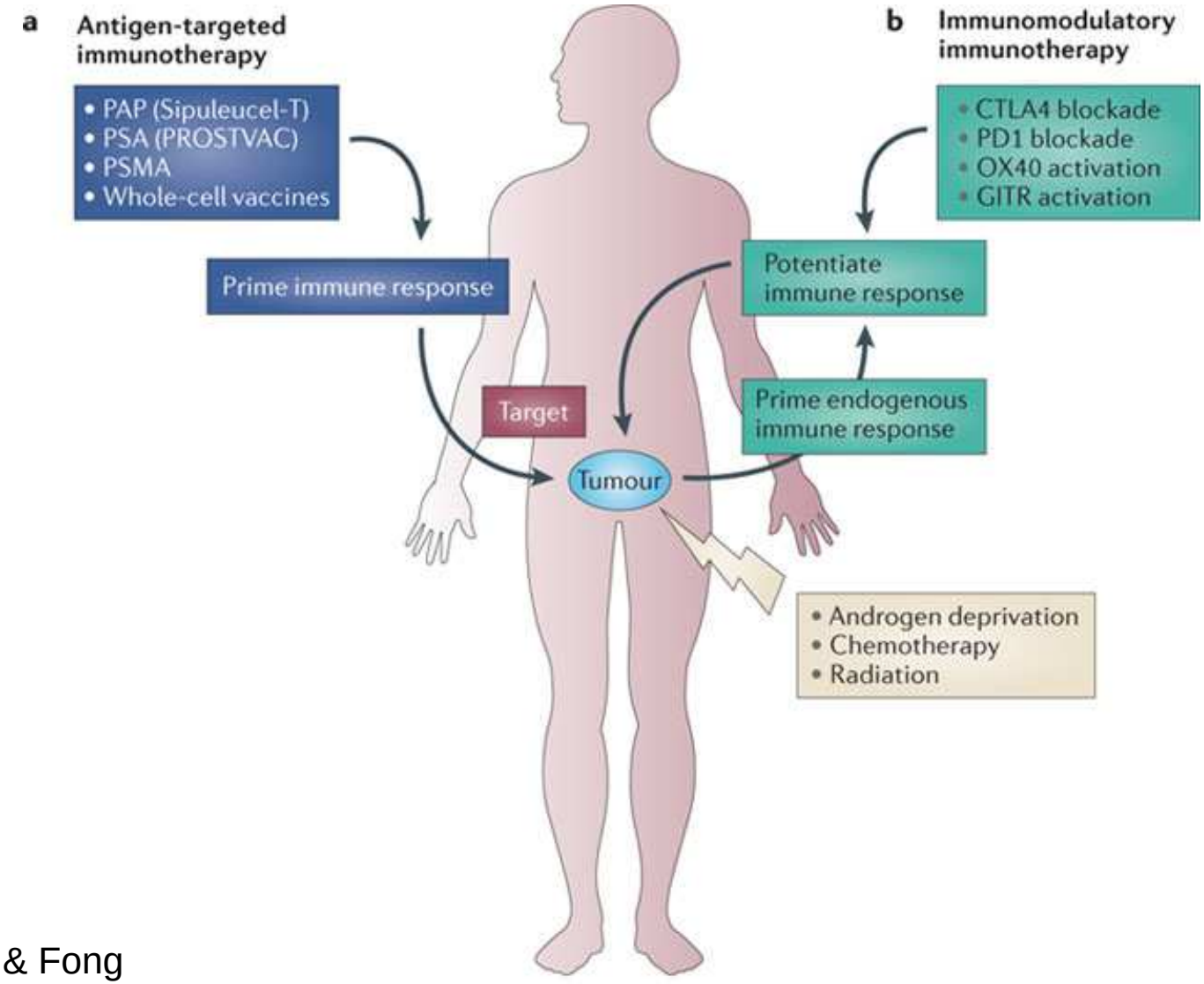
Clinical States Model (2015)



Prostate Cancer Therapy: soon to come



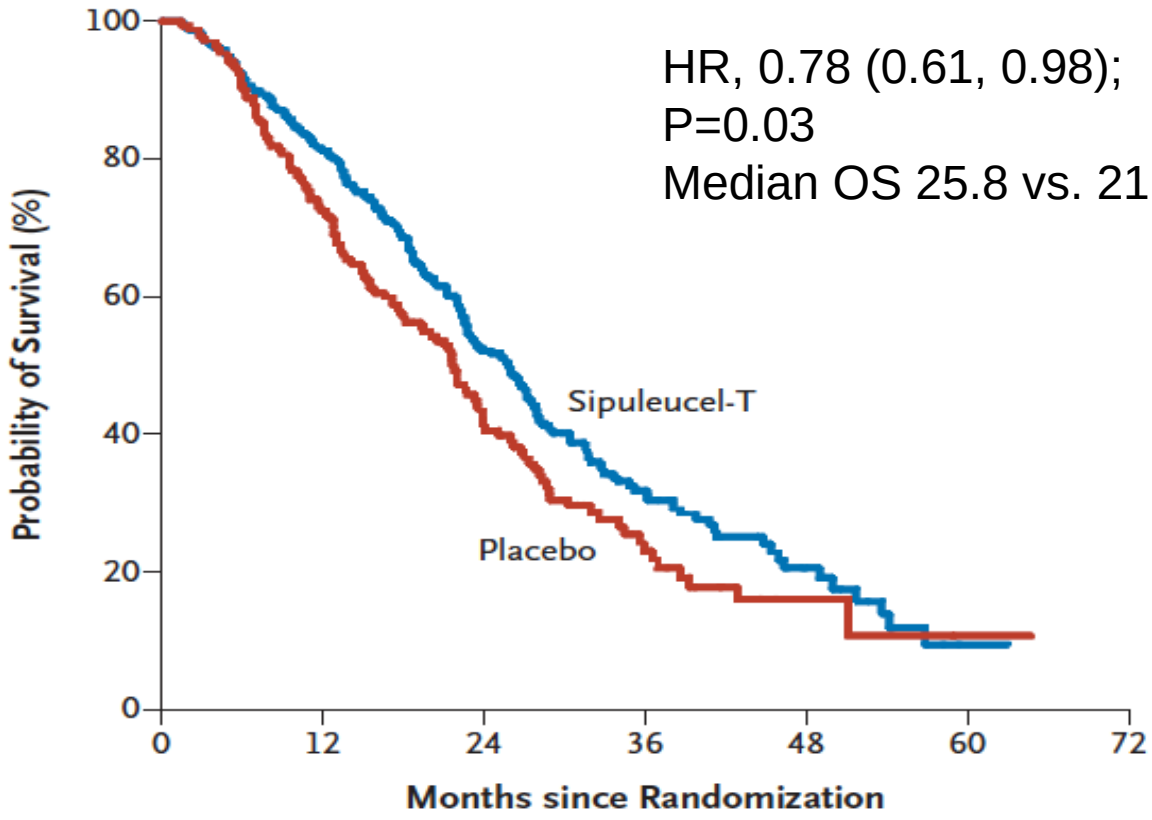
Prostate Cancer Immunotherapies



Kwek, Cha & Fong
Nature Reviews Cancer 12:289, 2012

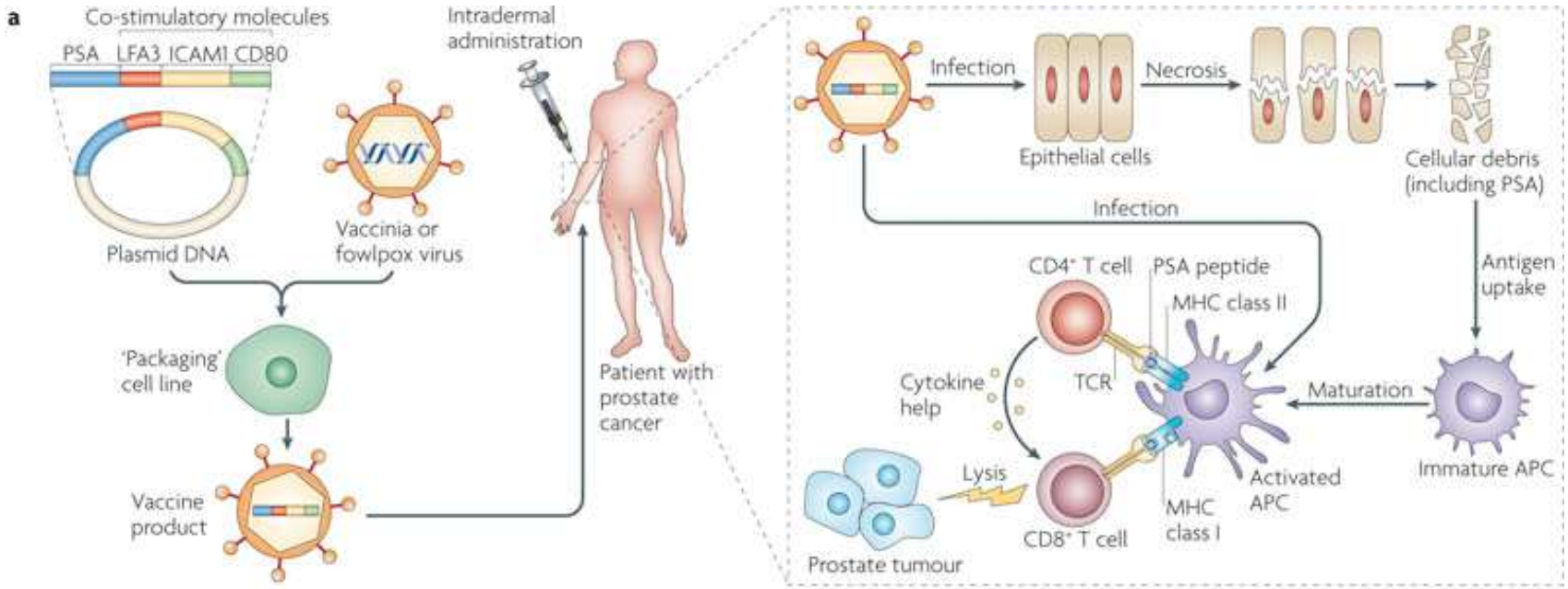
Sipuleucel-T

- First FDA-approved immunotherapy for prostate cancer.
- PAP-GMCSF and dendritic cells



HR, 0.78 (0.61, 0.98);
P=0.03
Median OS 25.8 vs. 21.7 mo

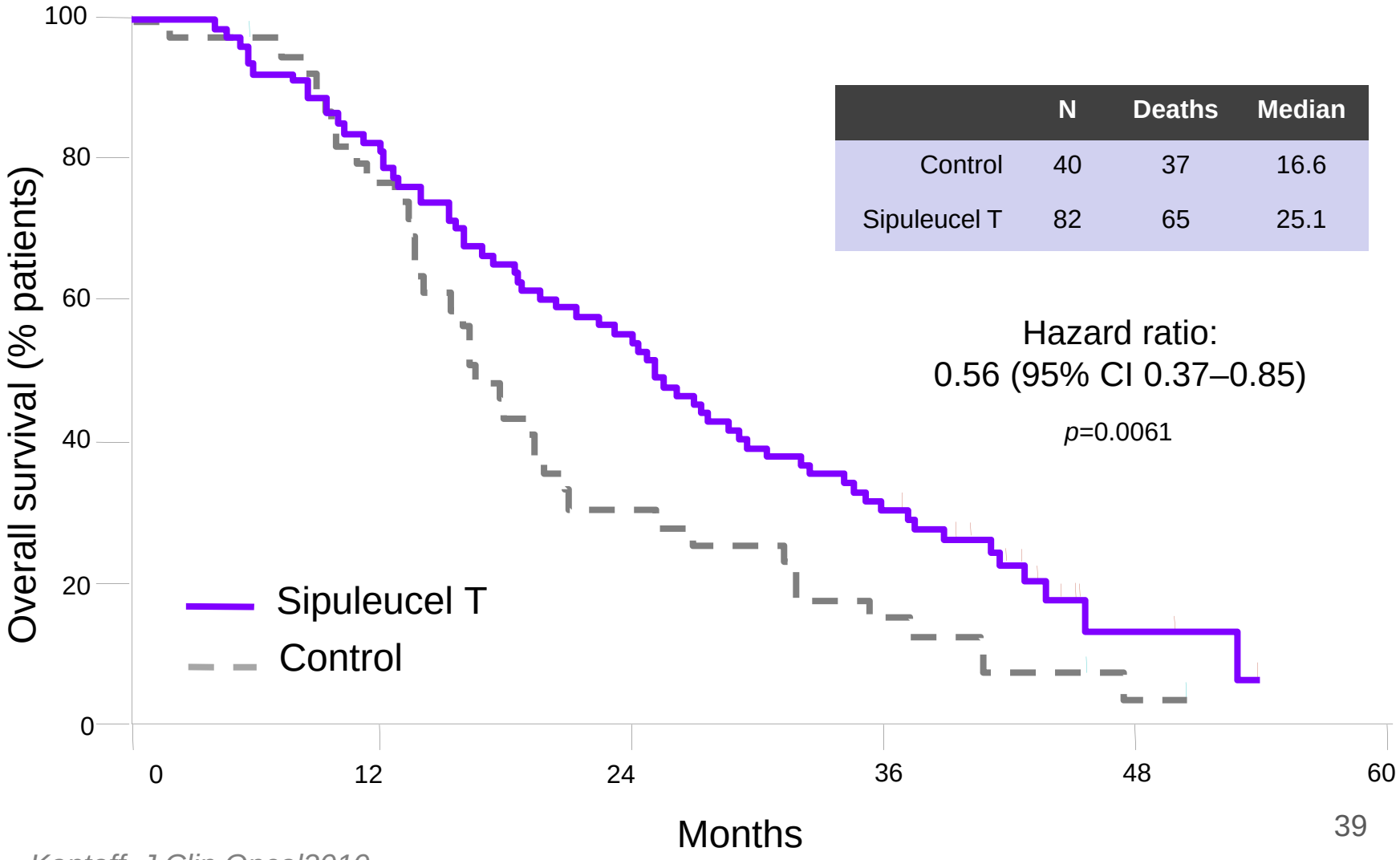
Prostate Cancer
Sipuleucel T VF: virus-based vaccine



Sipuleucel T had a median overall survival that was 8.5 months longer than the control group (25.1 versus 16.6 months) and a 44% reduction in the risk of death.

Scientific rationale for combination therapy with Sipuleucel T (hormone therapies, immune checkpoints inhibitor)

Sipuleucel T improves overall survival in mCRPC



	N	Deaths	Median
Control	40	37	16.6
Sipuleucel T	82	65	25.1

Hazard ratio:
0.56 (95% CI 0.37–0.85)

p=0.0061

Kantoff J Clin Oncol2010

Key Takeaways

- Bladder cancer:
  - BCG immune therapy is a standard treatment
  - Checkpoints inhibitors show great promise that needs to be developed in phase 3 trials
- Kidney cancer:
  - HD IL-2 (though not FDA approved) is an effective and historic treatment
  - Both vaccines and checkpoint inhibitors are developing strategies that show great promise
- Prostate cancer:
  - Dendritic cell therapy is effective
  - Other treatments are in active development