sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Malignancies

Brendan D. Curti, MD

Earl A. Chiles Research Institute, Providence Cancer Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

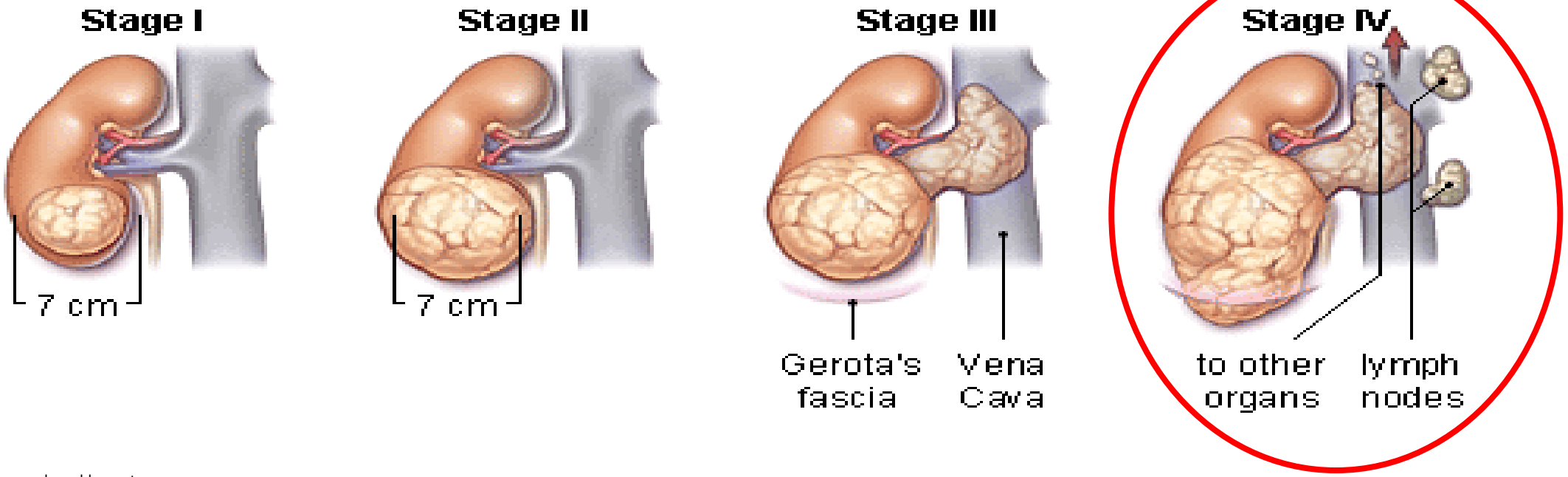
sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees: BMS, Eisai, Alligator
- Contracted Research: Astra-Zeneca
- I will not be discussing non-FDA approved indications during my presentation.

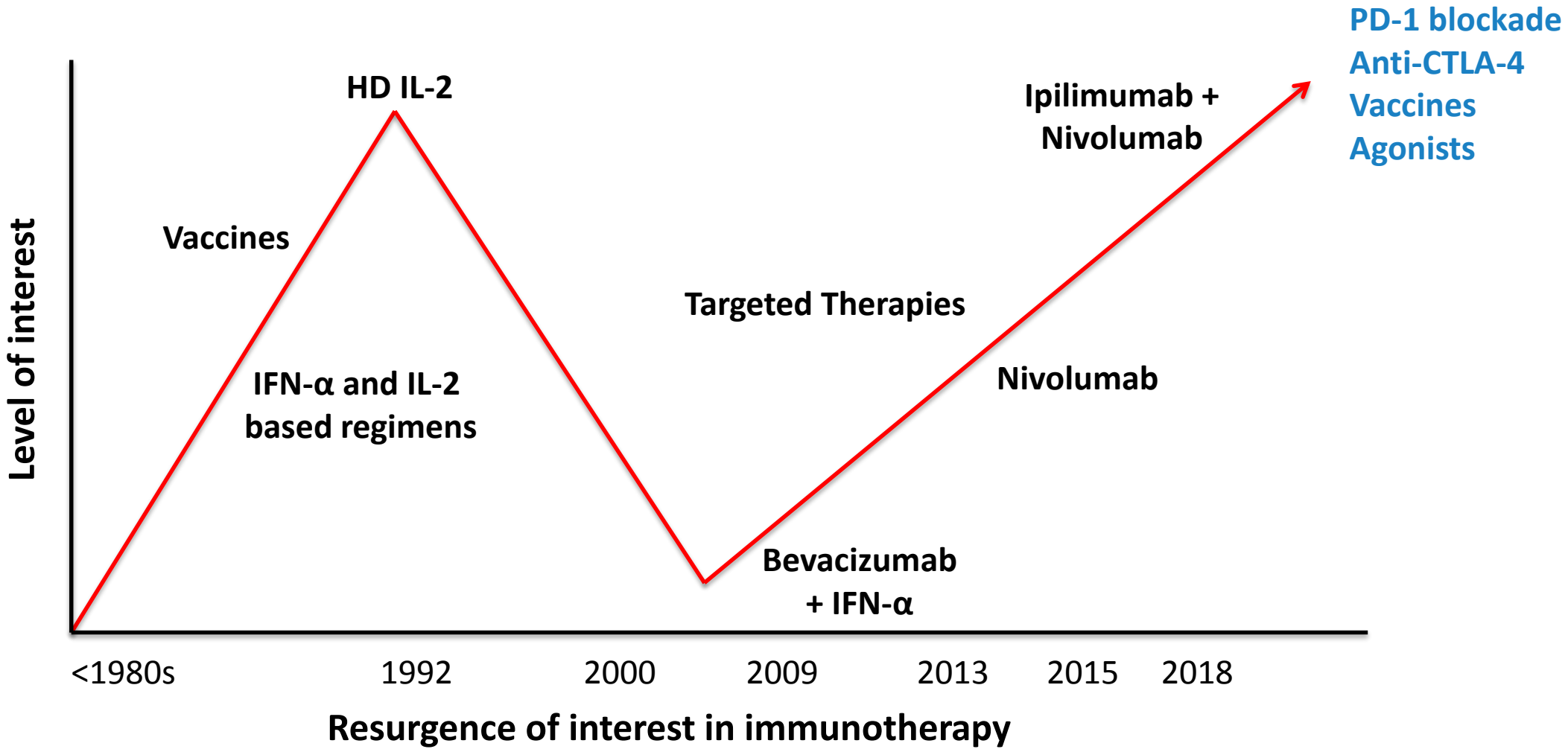
Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)

Surgically resectable → Oligo-metastatic → Metastatic



reemakeup.blogspot.com

History of Immunotherapy in mRCC



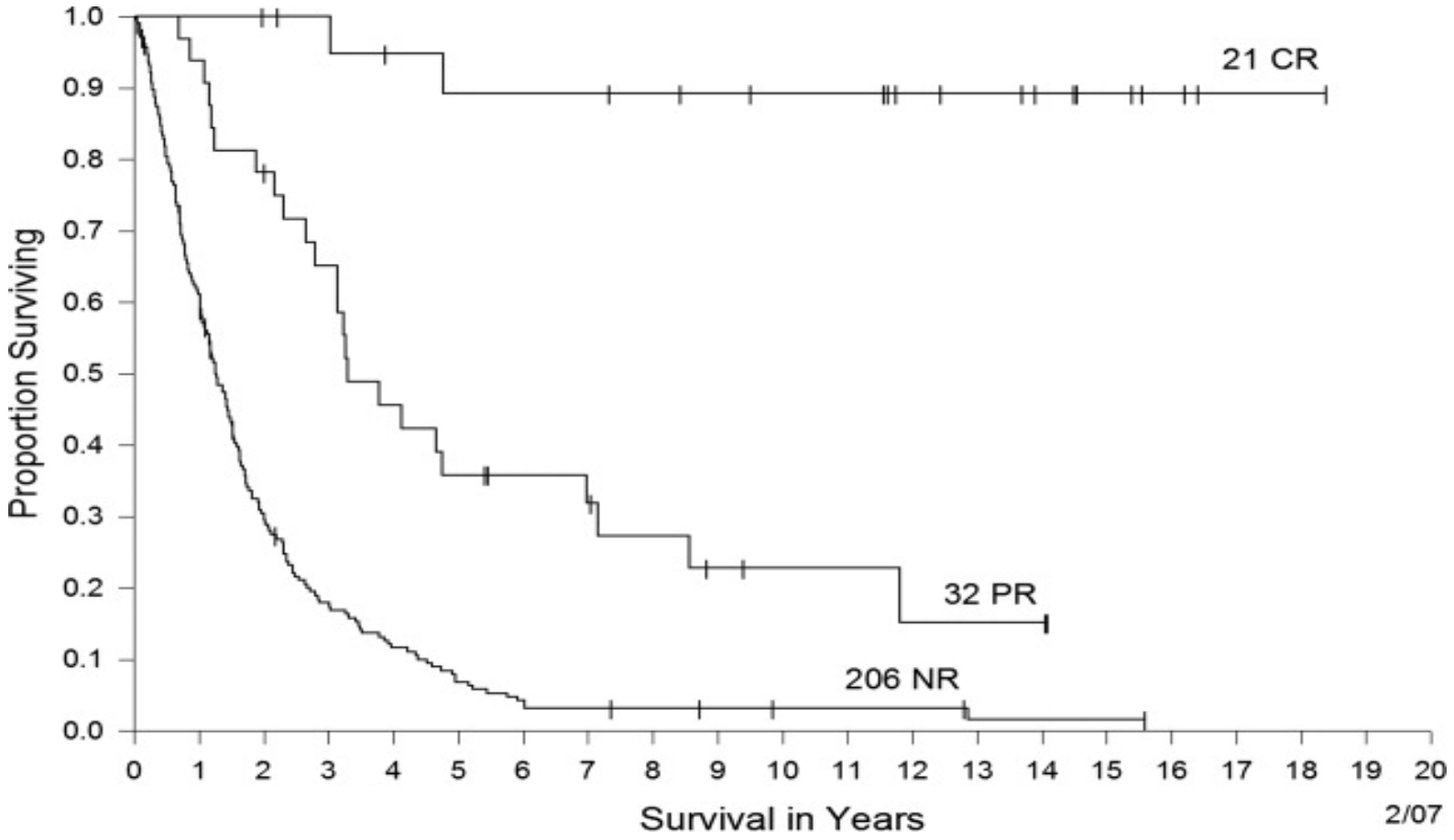
FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Dose
High dose Interluekin-2	1992	Metastatic RCC	600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)*
Interferon-a (with bevacizumab)	2009	Clear cell RCC***	9 MIU s.c. three times a week
Nivolumab	2015	Clear cell RCC Refractory to prior VEGF Targeted therapy	3mg/kg 240mg IV q 2 week or 480mg IV q 4 wks
Nivolumab +ipilimumab	2018	Clear cell RCC, treatement naïve	3mg/kg nivo plus 1mg/kg ipi q3 wks x 4 doses then nivo maintenance at flat dosing

*Retreatment: Evaluate after 4 weeks, advisable only if tumor shrinkage and no retreatment contraindications (see package insert for details)

High Dose IL-2 in mRCC

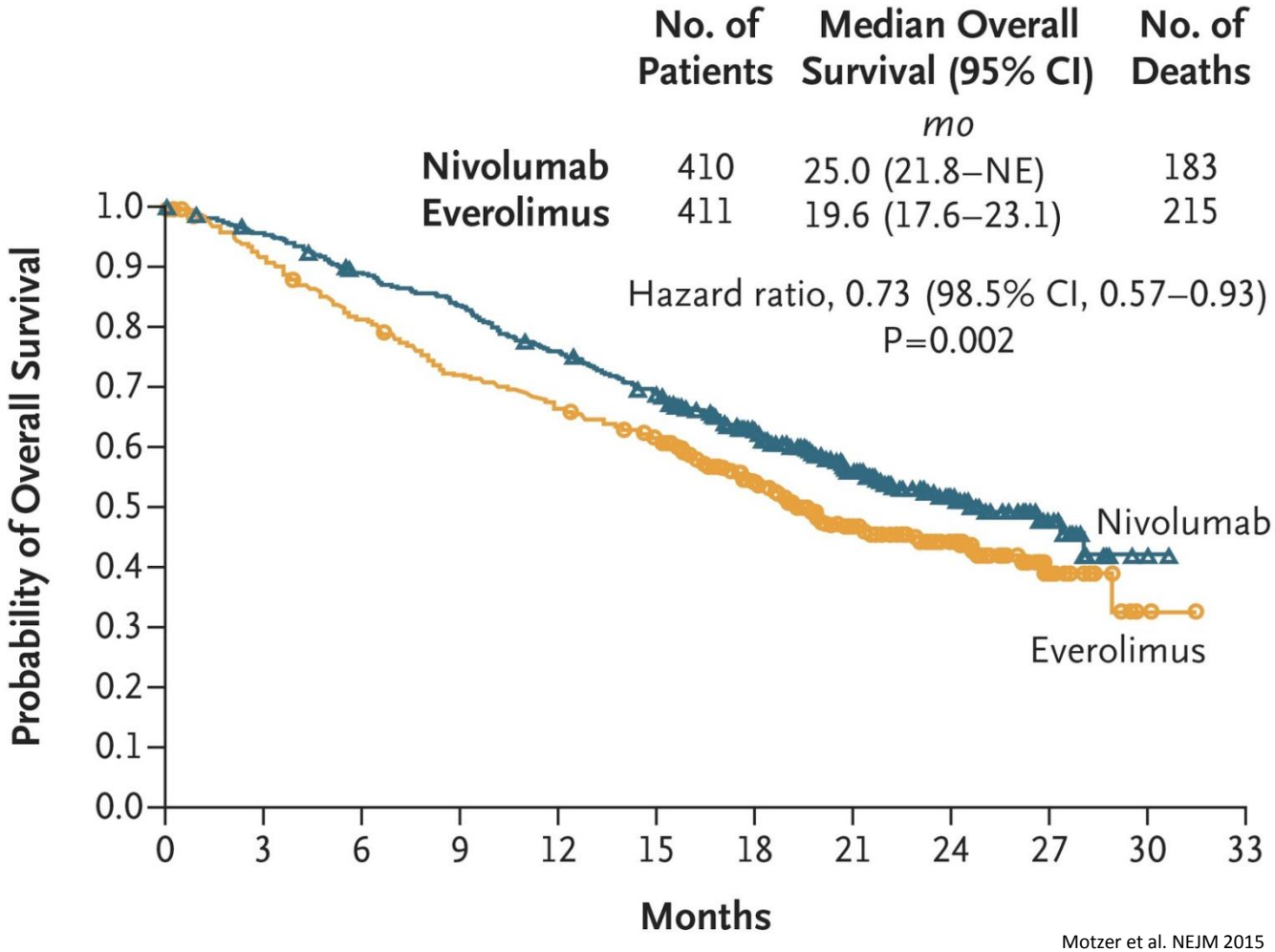
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

Second-Line Nivolumab in mRCC

- CheckMate 025 Phase III trial
- Nivolumab = anti-PD-1 antibody
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)

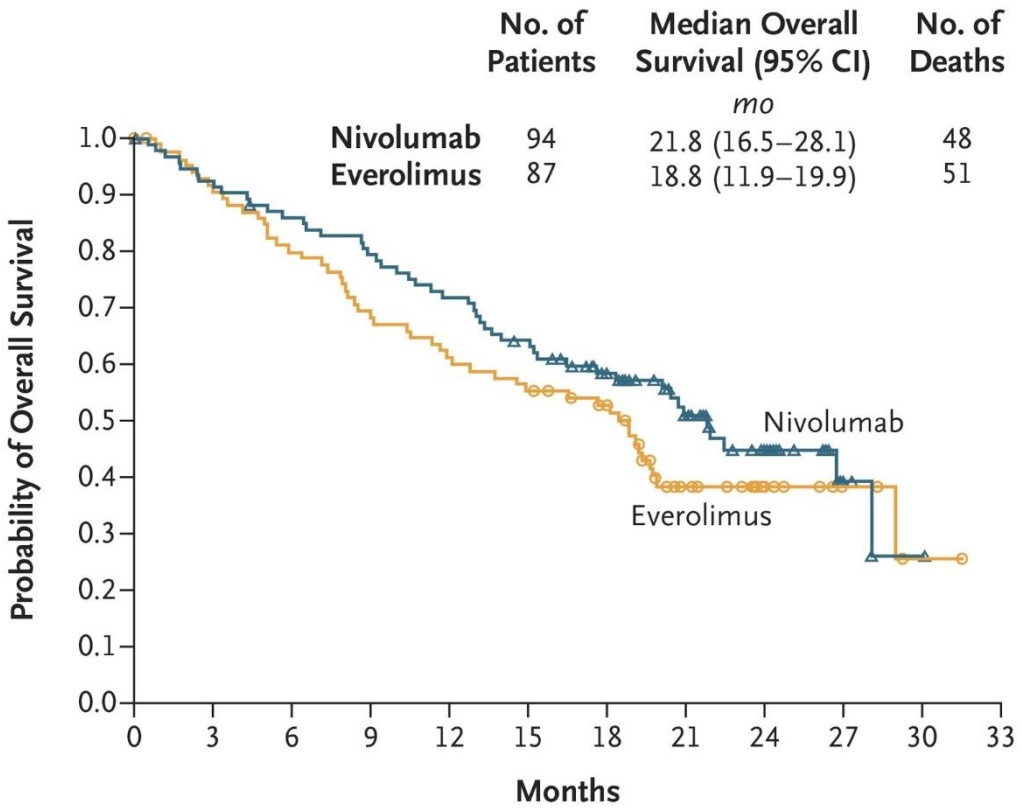


Motzer et al. NEJM 2015

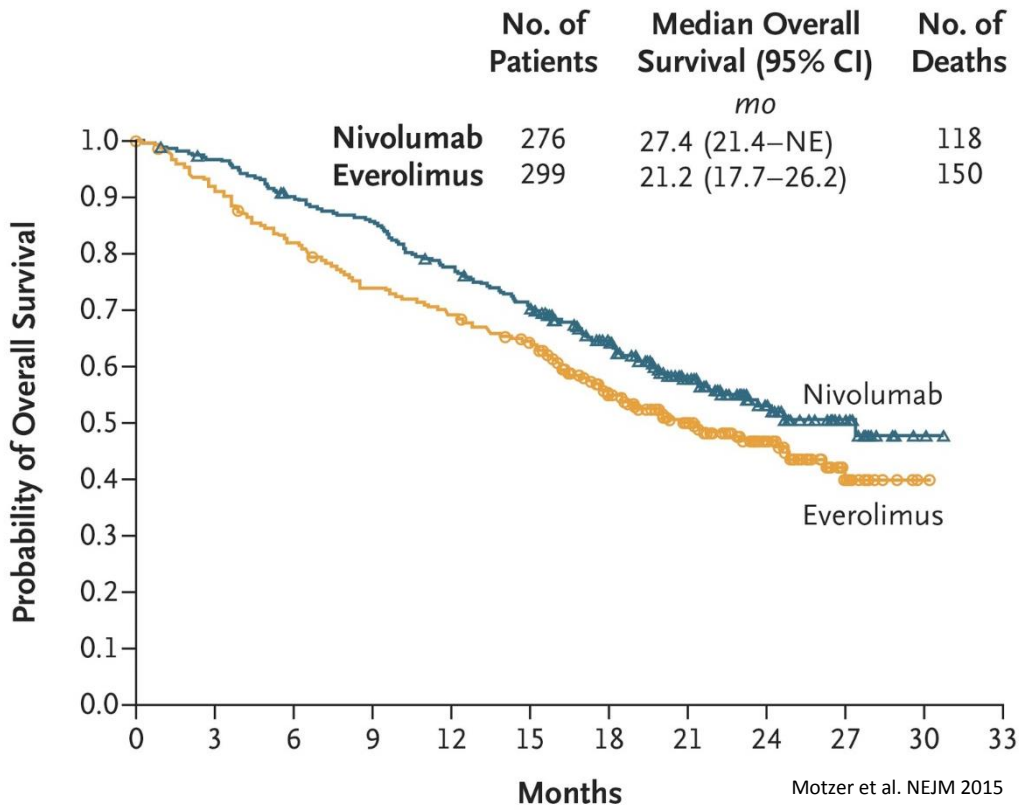
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%



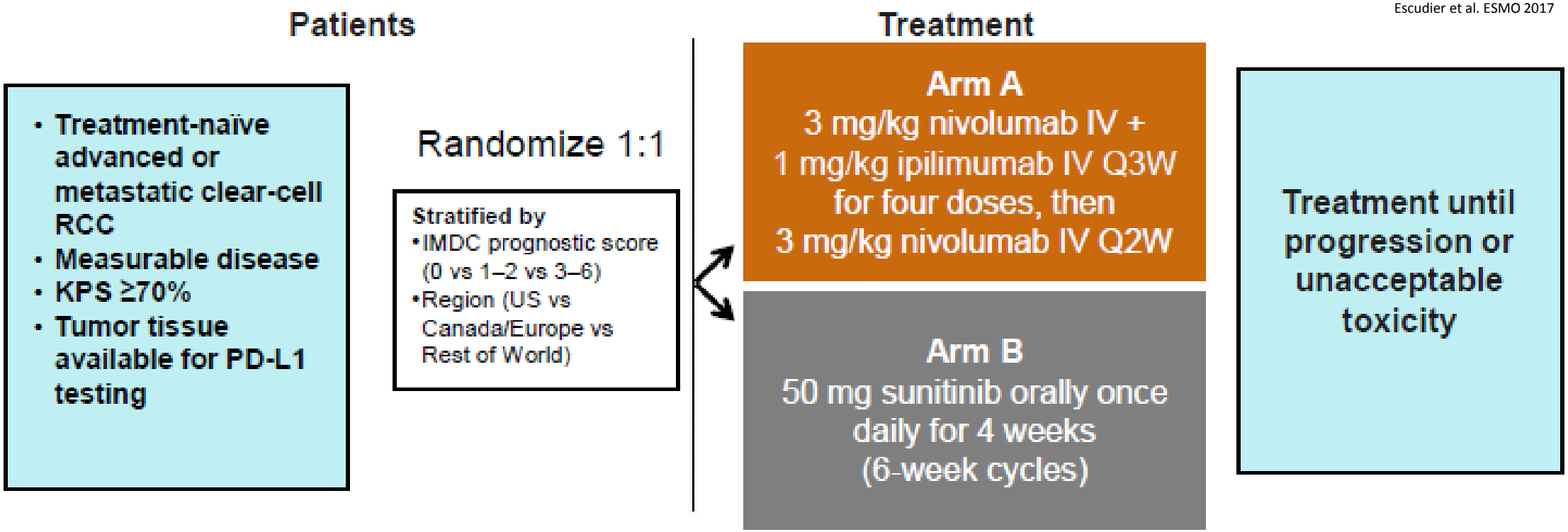
PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC

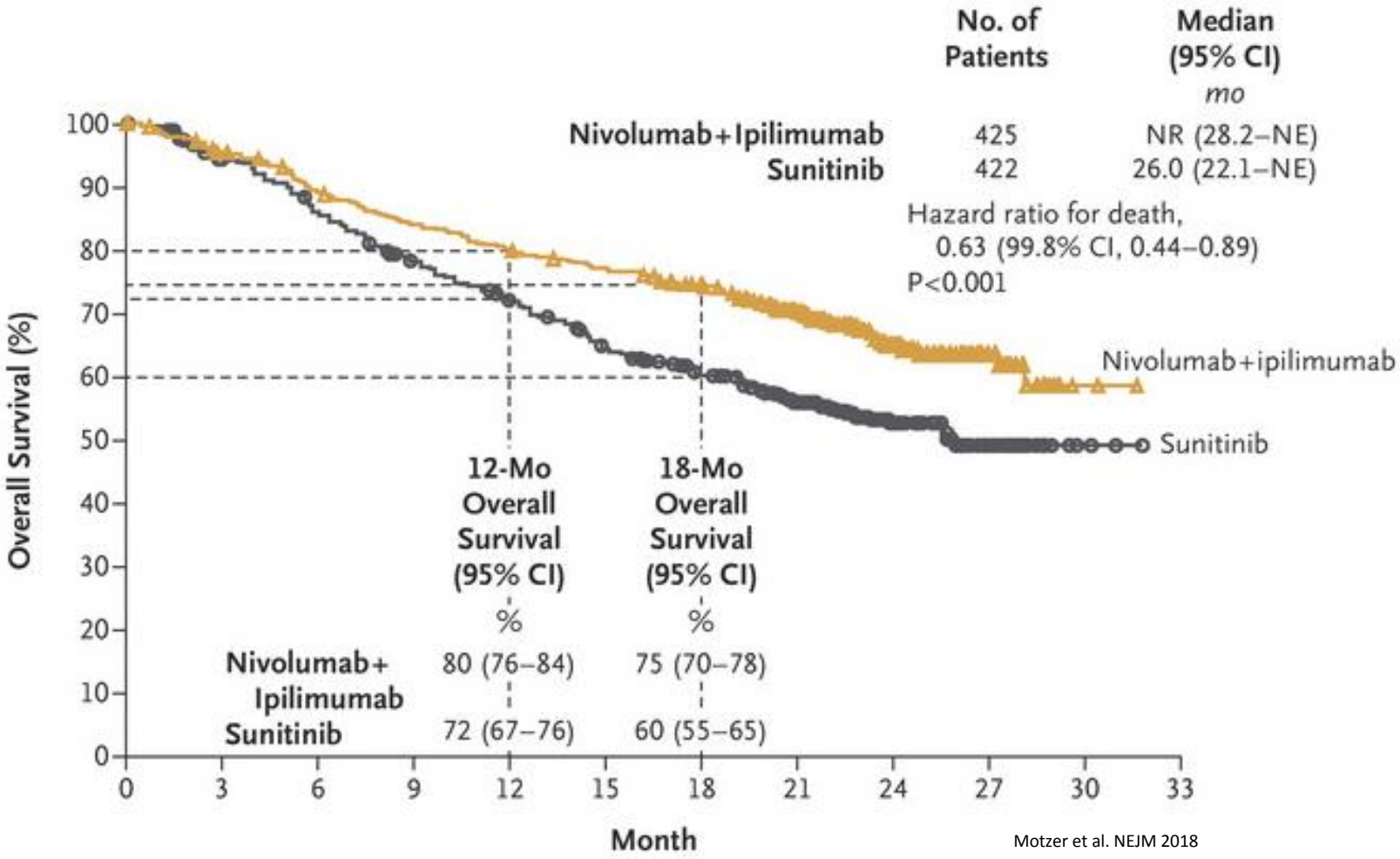
Escudier et al. ESMO 2017



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

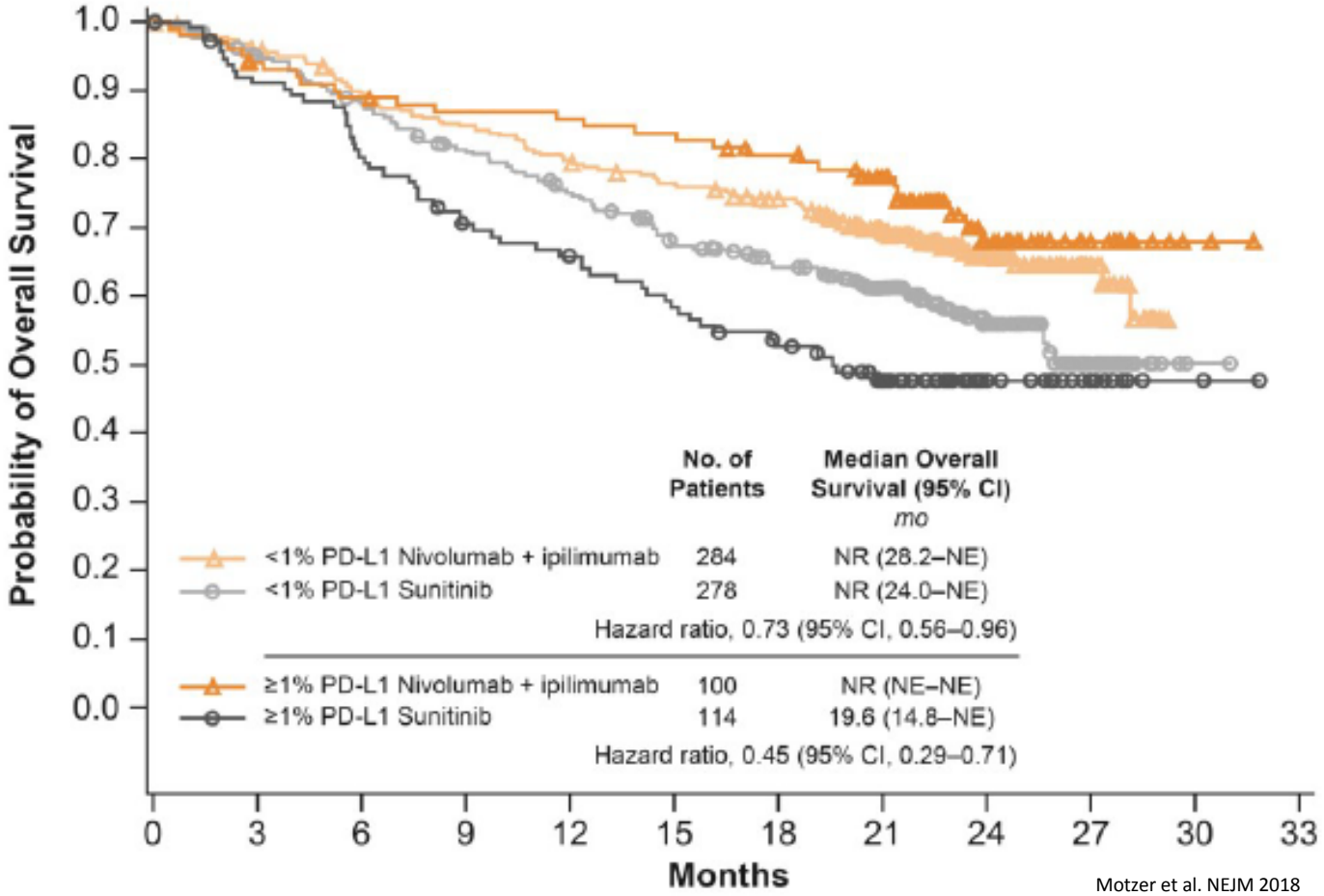
First-line Nivolumab + Ipilimumab in mRCC



Motzer et al. NEJM 2018

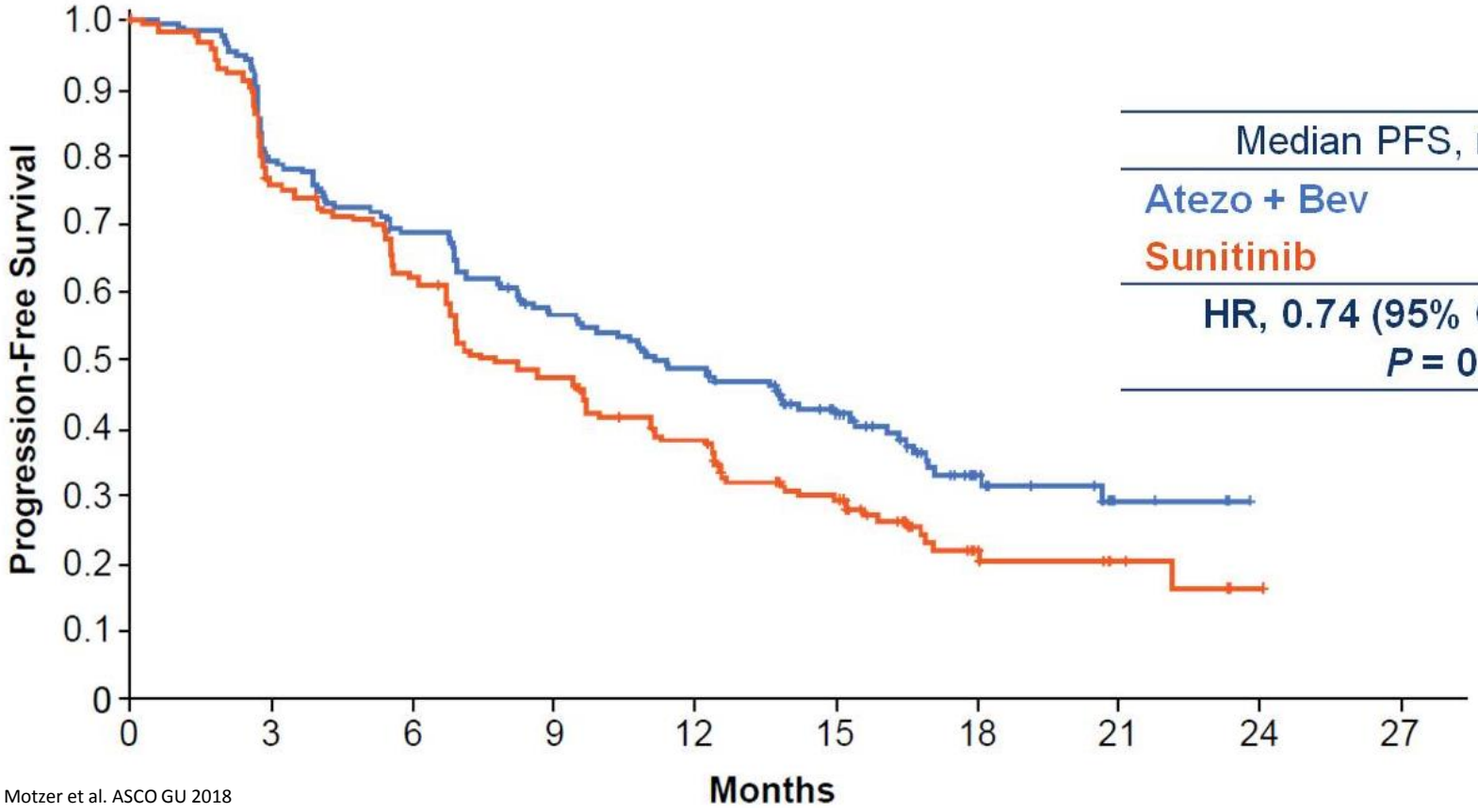
First-line Nivolumab + Ipilimumab in mRCC

PD-L1 Subgroups



Motzer et al. NEJM 2018

In Development: First-line Atezolizumab + Bevacizumab in PD-L1+ mRCC

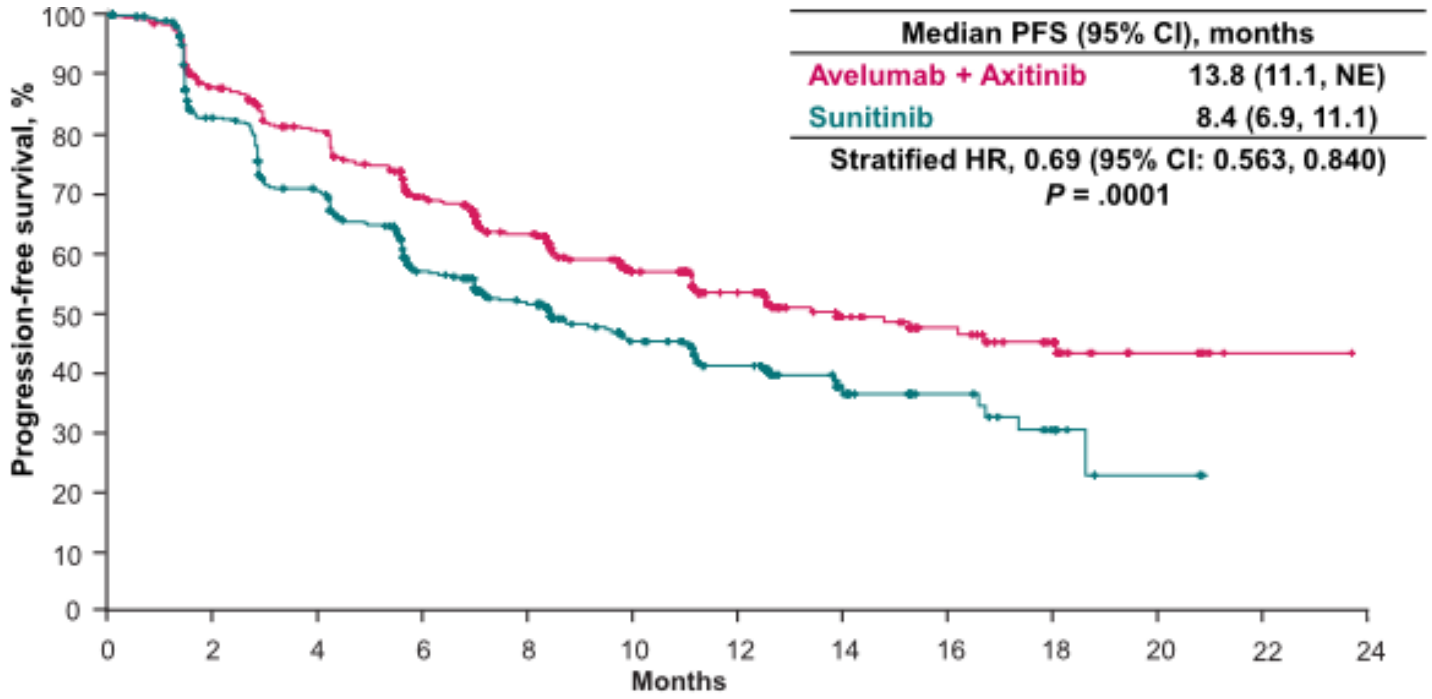


Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96)	
P = 0.02[a]	

Motzer et al. ASCO GU 2018
Escudier et al. ASCO 2018

In Development: First-line Checkpoint Inhibitors + Axitinib in mRCC

JAVELIN Renal 101

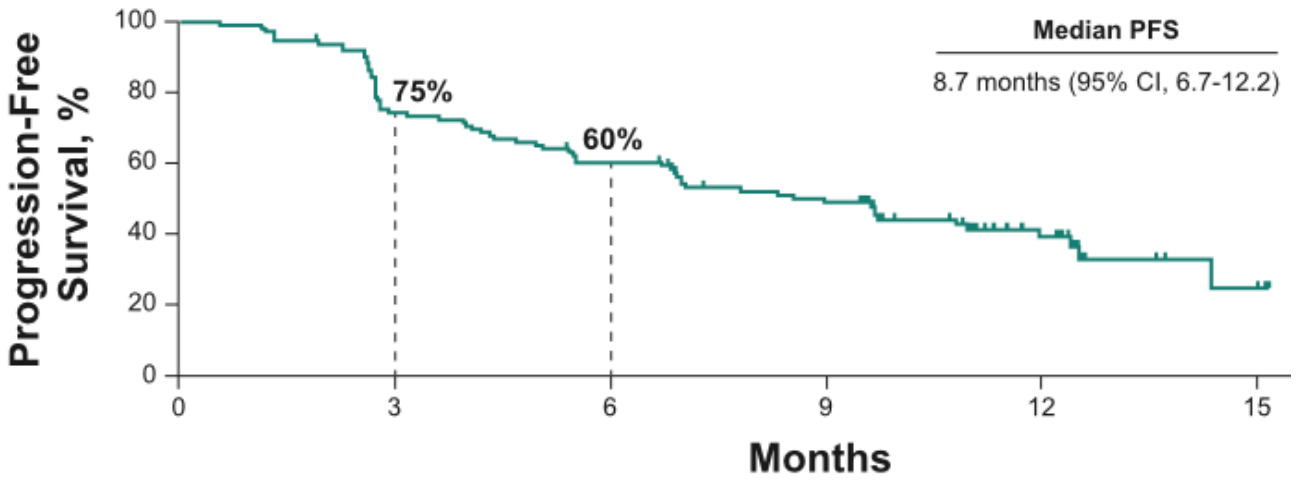


Motzer et al. ESMO 2018

- KEYNOTE-426
  - Pembrolizumab + axitinib in mRCC
  - Positive for OS and PFS (10/18/2018)

In Development: First-line Pembrolizumab in mRCC

KEYNOTE - 427



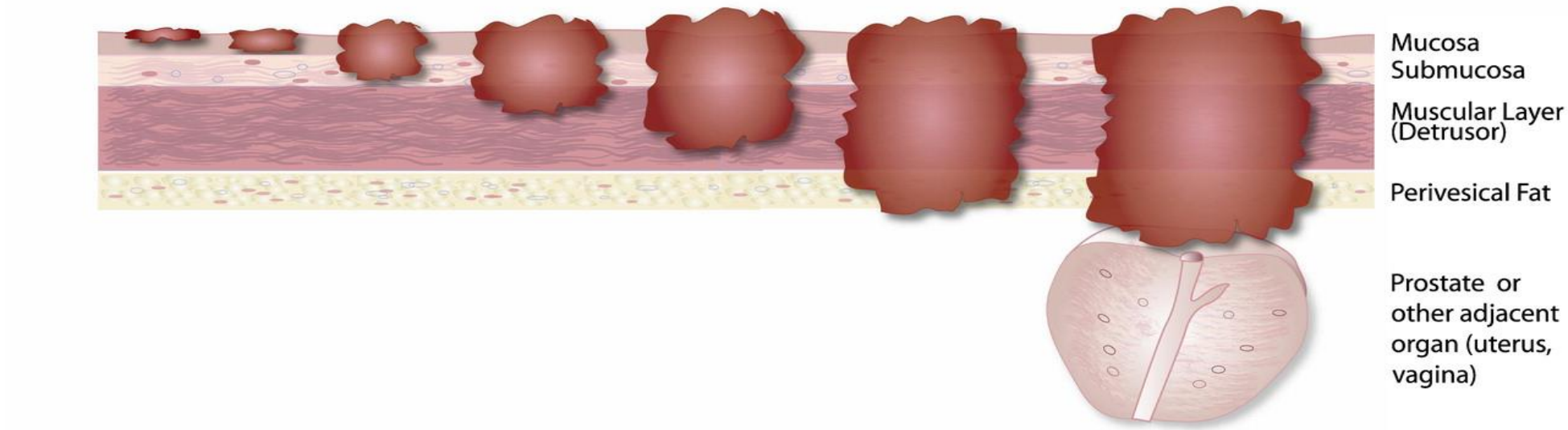
	N = 110
Confirmed ORR, % (95% CI)	38 (29 – 48)
Confirmed BOR, n (%)	
CR	3 (3)
PR	39 (35)
SD	35 (32)
PD	31 (28)
No assessment	2 (2)

Donskov et al. ESMO 2018

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)

Non-Muscle Invasive → Muscle Invasive → Metastatic

TNM	TIS	T_a	T_1	T_{2A}	T_{2B}	T_{3B}	T_{4A}
JSM	0	0	A	B_1	B_2	C	D_1



Approved Checkpoint Inhibitors for mUC

Cisplatin Refractory

Drug/Trial name	Phase	No. of patients	ORR	PFS	OS	Duration of response	Grade 3/4 AE (treatment related deaths)	Maximal duration of treatment
CISPLATIN REFRACTORY								
Atezolizumab IMvigor210 cohort 2	II	310	16% (6% CR)	2.1 mo	7.9 mo (1yr 29%)	22.1 mo	18% (0 deaths)	NR
Atezolizumab IMvigor211	III	931	13%	NR	8.6 mo	21.7 mo	20%	NR
Pembrolizumab KEYNOTE-045	III	542	21%	2.1 mo	10.3 mo	NR	14% (4 deaths)	2 years
Nivolumab CheckMate275	II	265	19.6% (2% CR)	2 mo	8.7 mo	NR	18% (3 deaths)	NR
Avelumab JAVELIN	Ib	242*	17% (6% CR)	6.6 weeks	6.5 mo	NR	10% (1 death)	NR
Durvalumab	I/II	191	17.8% (4% CR)	1.5 mo	18.2 mo	NR	7% (2 deaths)	1 year

Anti-PD-L1 Antibodies

1) Atezolizumab
2) Avelumab
3) Durvalumab

Anti-PD-1 Antibodies

1) Nivolumab
2) Pembrolizumab

In development: Combinations

1) IO + IO
2) IO + Chemotherapy

Ghatalia et al. Ther Adv Med Oncol 2018

Approved Checkpoint Inhibitors for mUC

Cisplatin Ineligible

CISPLATIN INELIGIBLE								
Atezolizumab IMvigor210 cohort 1	II	119	23% (9% CR)	2.7 mo	15.9 mo, 1yr 57%	NR	16% (1 death)	NR
Pembrolizumab KEYNOTE-052	II	370	29% (7% CR)	6mo 30%	6 mo 67%	NR	19% (1 death)	2 years

Anti-PD-L1 Antibodies

1) Atezolizumab
   - PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area

Anti-PD-1 Antibodies

1) Pembrolizumab
   - PD-L1 CPS ≥ 10

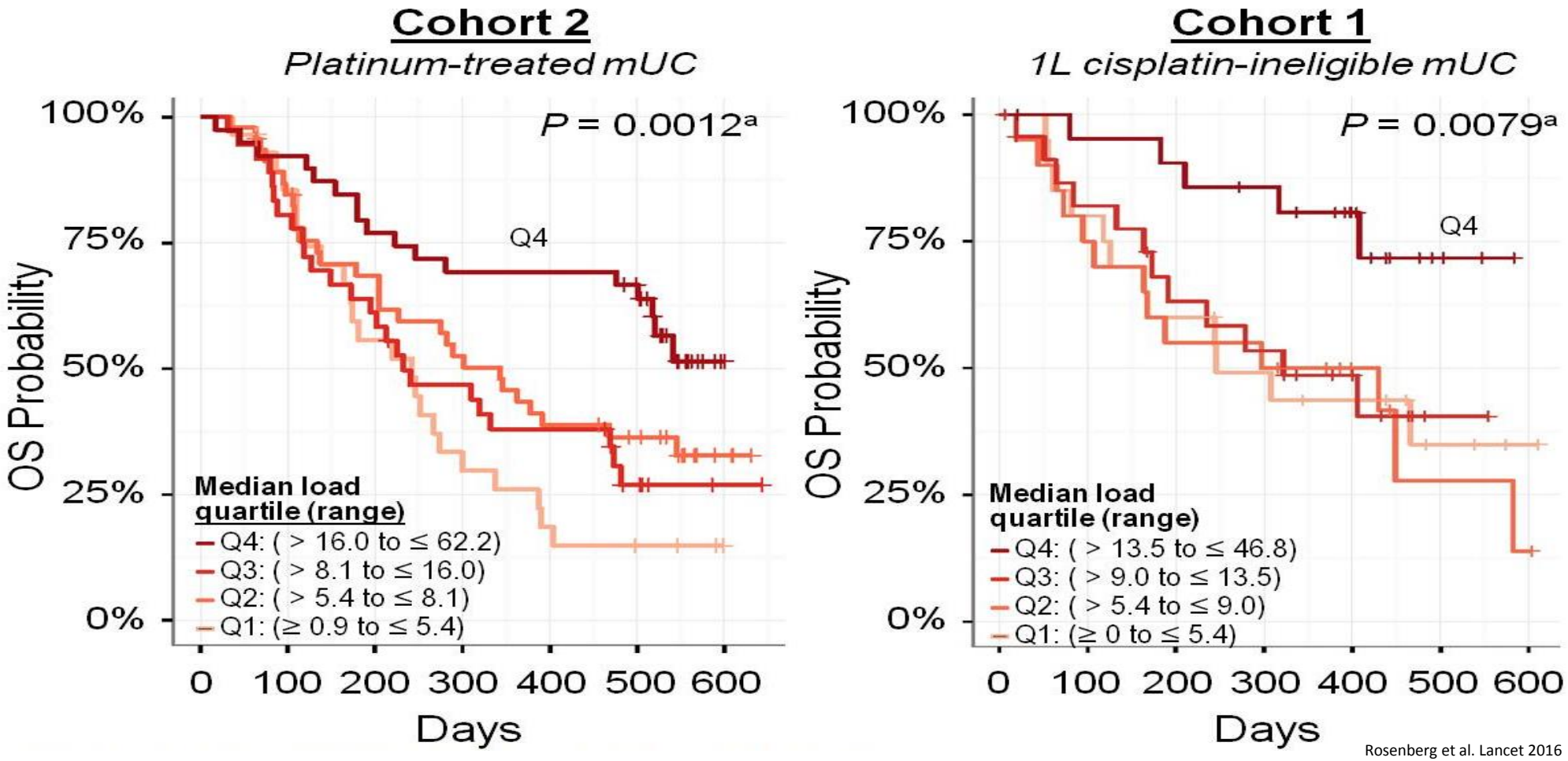
In development: Combinations

1) IO + IO
2) IO + Chemotherapy

Ghatalia et al. Ther Adv Med Oncol 2018

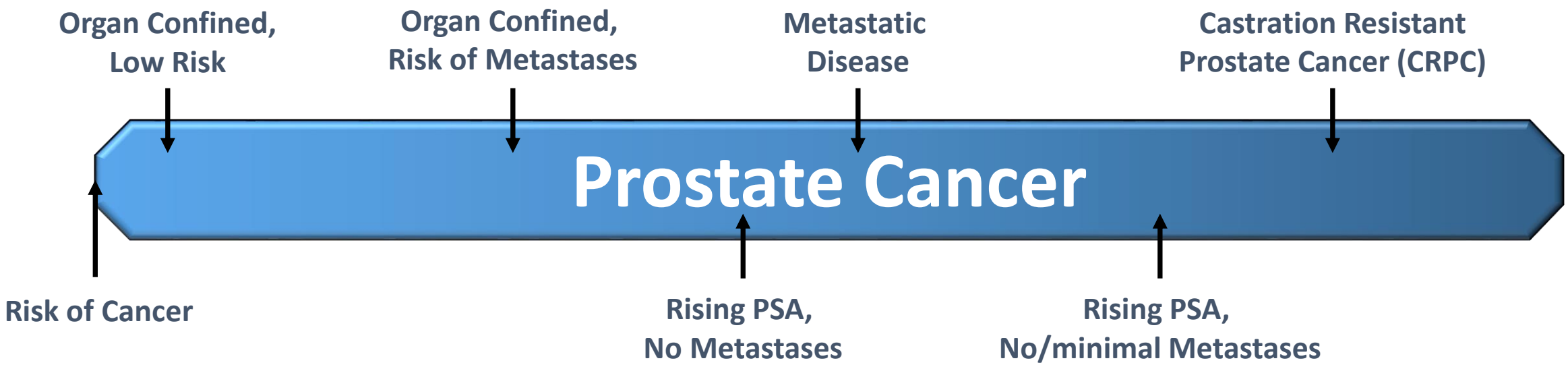
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



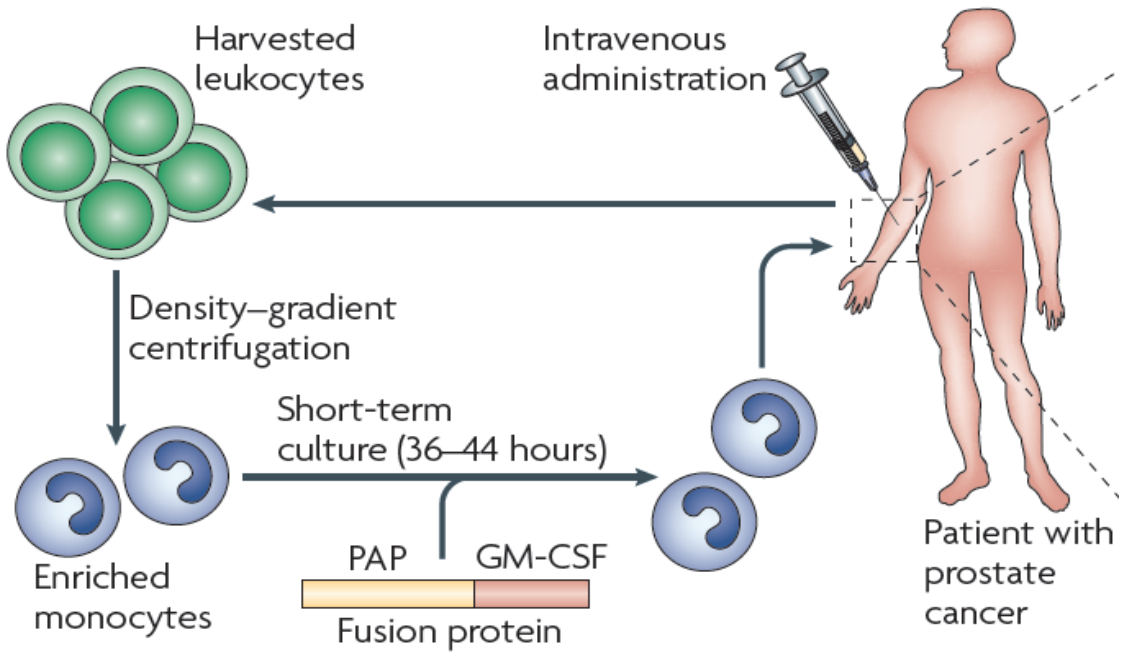
Rosenberg et al. Lancet 2016

The Spectrum of Prostate Cancer

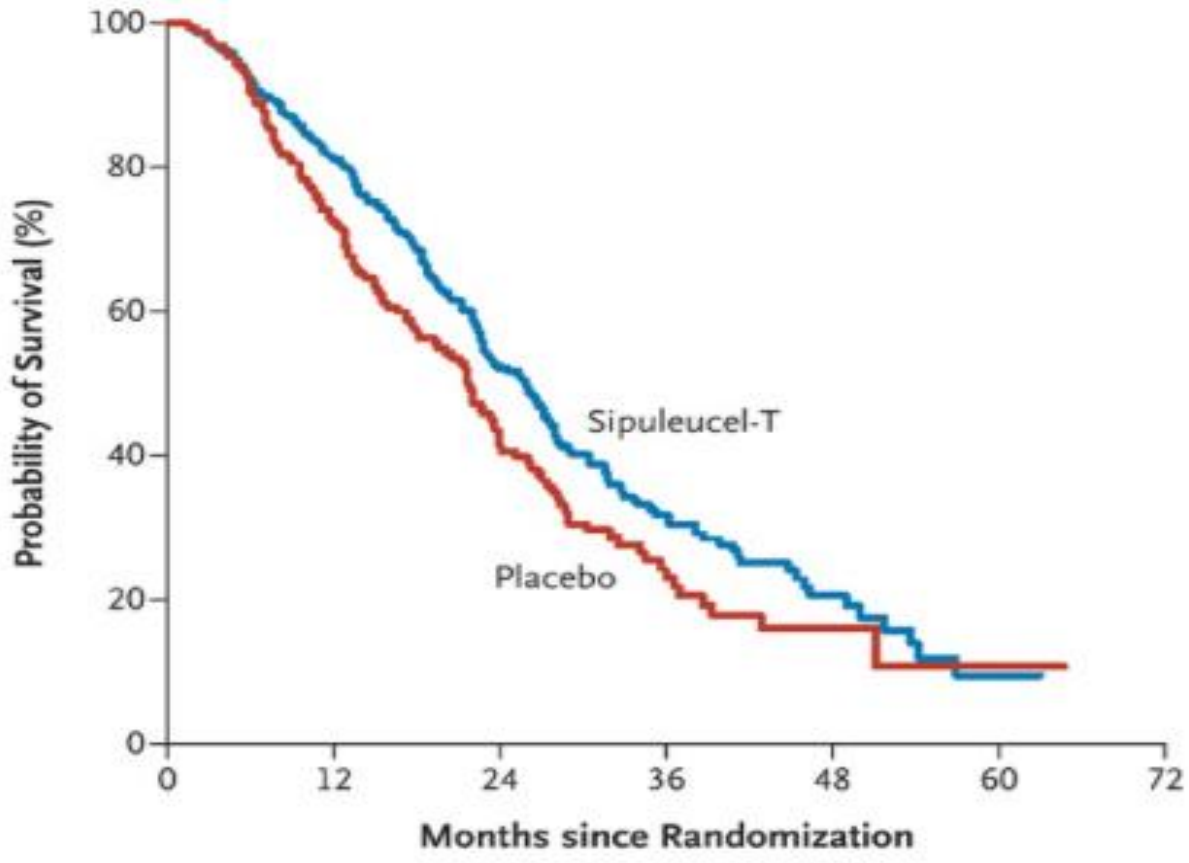


Sipuleucel-T in mCRPC

- First anticancer therapeutic vaccine



Drake et al. Curr Opin Urol 2010

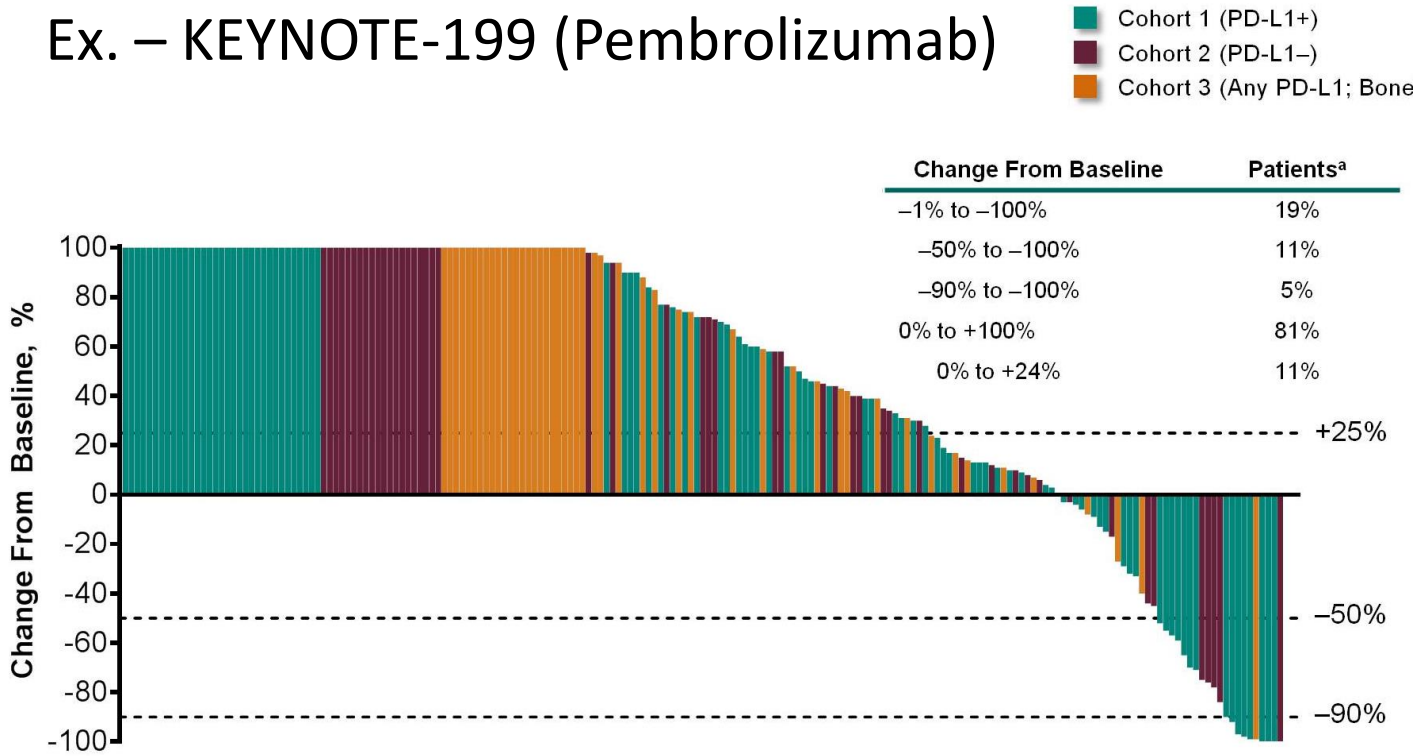


Kantoff et al. NEJM 2010

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

Ex. – KEYNOTE-199 (Pembrolizumab)

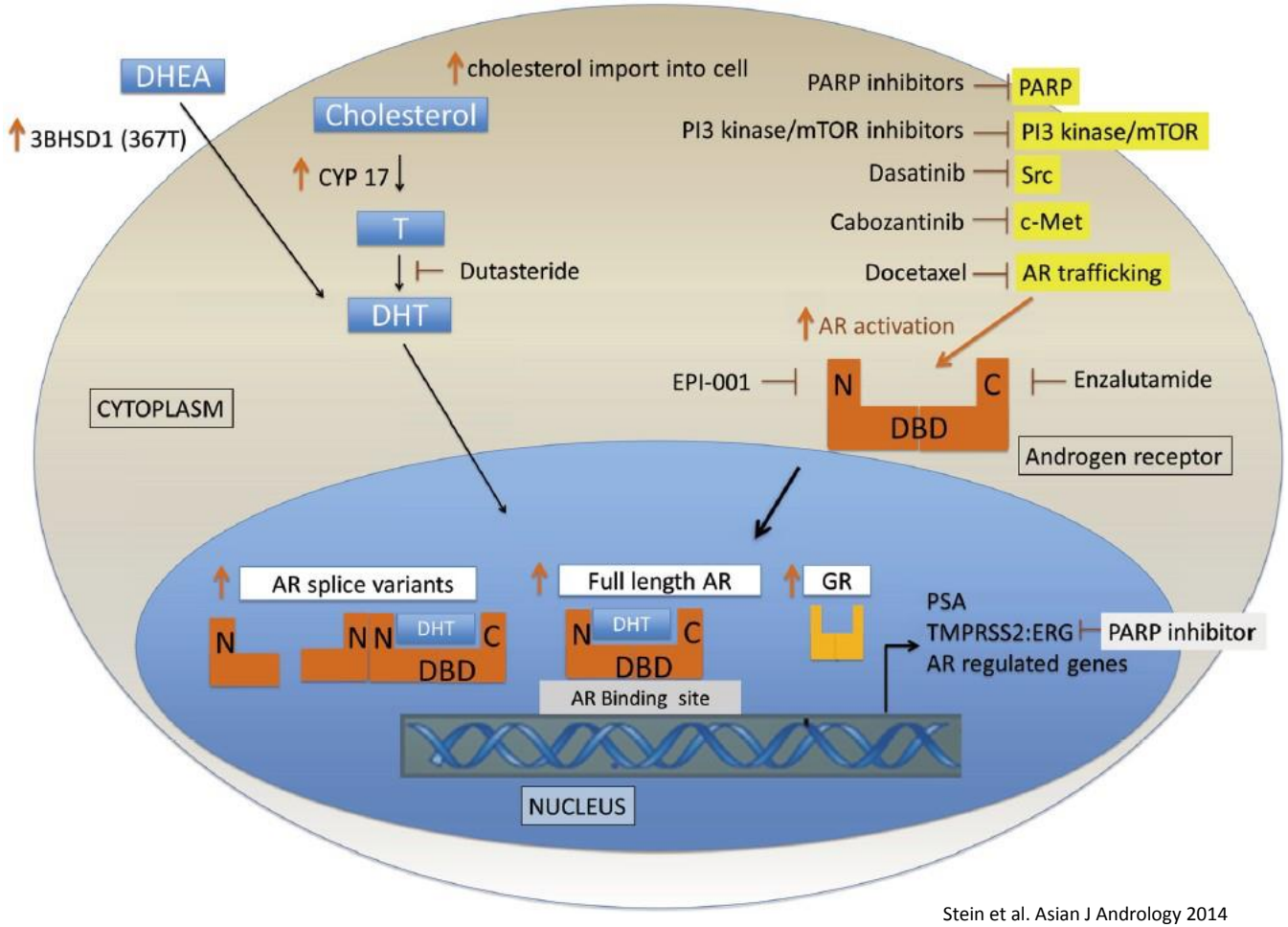


DeBono et al. ASCO 2018

- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

Future Combinations in mCRPC to Engage Immune System

- Hormonal therapy
- Radiation
- Radium-223
- PARP inhibitors
- Chemotherapy
- New targets



Stein et al. Asian J Andrology 2014

irAEs with Immune Checkpoint Inhibitors in GU Cancers

Meta-analysis of 8 studies

- Similar incidence overall

Adverse event	Incidence, any grade (GU only trials) (%)	Incidence, grades 3–5 (GU only trials) (%)	Incidence any grade (non-GU clinical trials) (%)	Incidence, grades 3–5 (non-GU clinical trials) (%)
Hypothyroid/ thyroiditis	0.8–9	0–0.6	3.9–12	0–0.1
Diabetes/DKA	0–1.5	0–0.7	0.8–0.8	0.4–0.7
LFT changes/ hepatitis	1.5–5.4	1–3.8	0.3–3.4	0.3–2.7
Pneumonitis	2–4.4	0–2	1.8–3.5	0.25–1.9
Encephalitis	NR	NR	0.2–0.8	0.0–0.2
Colitis/diarrhea	1–10	1–10	2.4–4.1	1.0–2.5
Hypophysitis	0–0.5	0–0.2	0.2–0.9	0.2–0.4
Renal Dysfunction/ nephritis	0.3–1.6	0–1.6	0.3–4.9	0.0–0.5
Myositis	0.8–5	0–0.8	NR	NR

Maughan et al. Front Oncol 2017

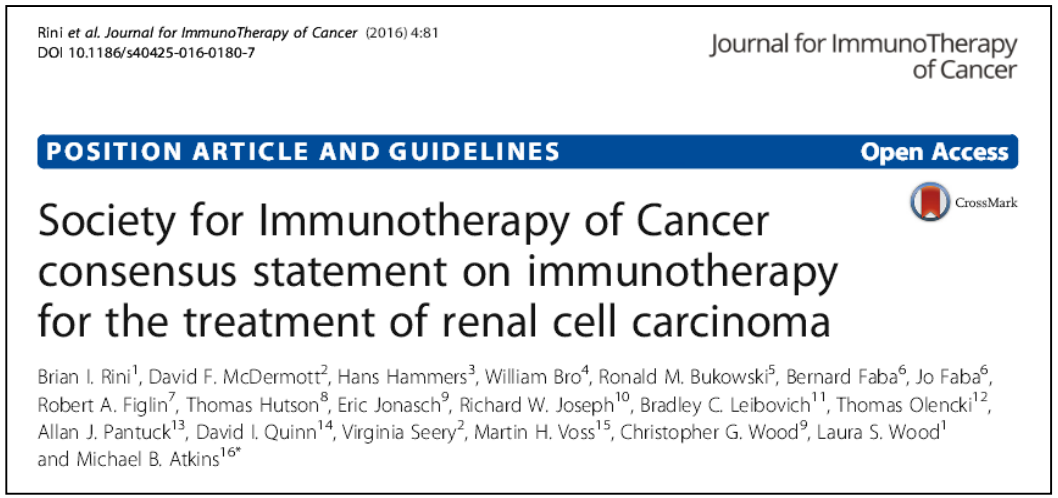
Immune-related Adverse Events

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov Journal for ImmunoTherapy of Cancer 2017

Additional Resources



Rini *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:81
DOI 10.1186/s40425-016-0180-7

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma

Brian I. Rini[1], David F. McDermott[2], Hans Hammers[3], William Bro[4], Ronald M. Bukowski[5], Bernard Faba[6], Jo Faba[6], Robert A. Figlin[7], Thomas Hutson[8], Eric Jonasch[9], Richard W. Joseph[10], Bradley C. Leibovich[11], Thomas Olencki[12], Allan J. Pantuck[13], David I. Quinn[14], Virginia Seery[2], Martin H. Voss[15], Christopher G. Wood[9], Laura S. Wood[1] and Michael B. Atkins[16*]

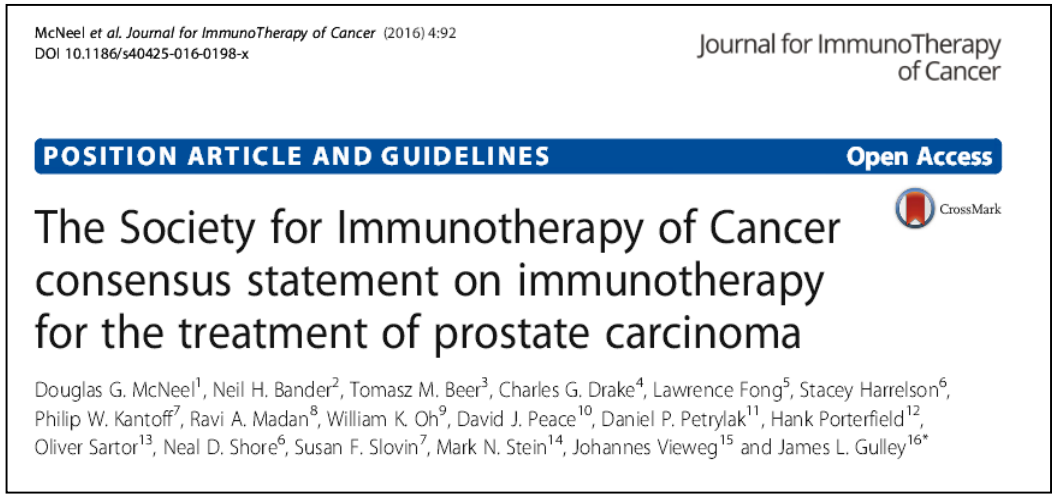
Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma

Ashish M. Kamat[1*], Joaquim Bellmunt[2], Matthew D. Galsky[3], Badrinath R. Konety[4], Donald L. Lamm[5], David Langham[6], Cheryl T. Lee[7], Matthew I. Milowsky[8], Michael A. O'Donnell[9], Peter H. O'Donnell[10], Daniel P. Petrylak[11], Padmanee Sharma[12], Ella C. Skinner[13], Guru Sonpavde[14], John A. Taylor III[15], Prasanth Abraham[16] and Jonathan E. Rosenberg[17]



McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

Douglas G. McNeel[1], Neil H. Bander[2], Tomasz M. Beer[3], Charles G. Drake[4], Lawrence Fong[5], Stacey Harrelson[6], Philip W. Kantoff[7], Ravi A. Madan[8], William K. Oh[9], David J. Peace[10], Daniel P. Petrylak[11], Hank Porterfield[12], Oliver Sartor[13], Neal D. Shore[6], Susan F. Slovin[7], Mark N. Stein[14], Johannes Vieweg[15] and James L. Gulley[16*]

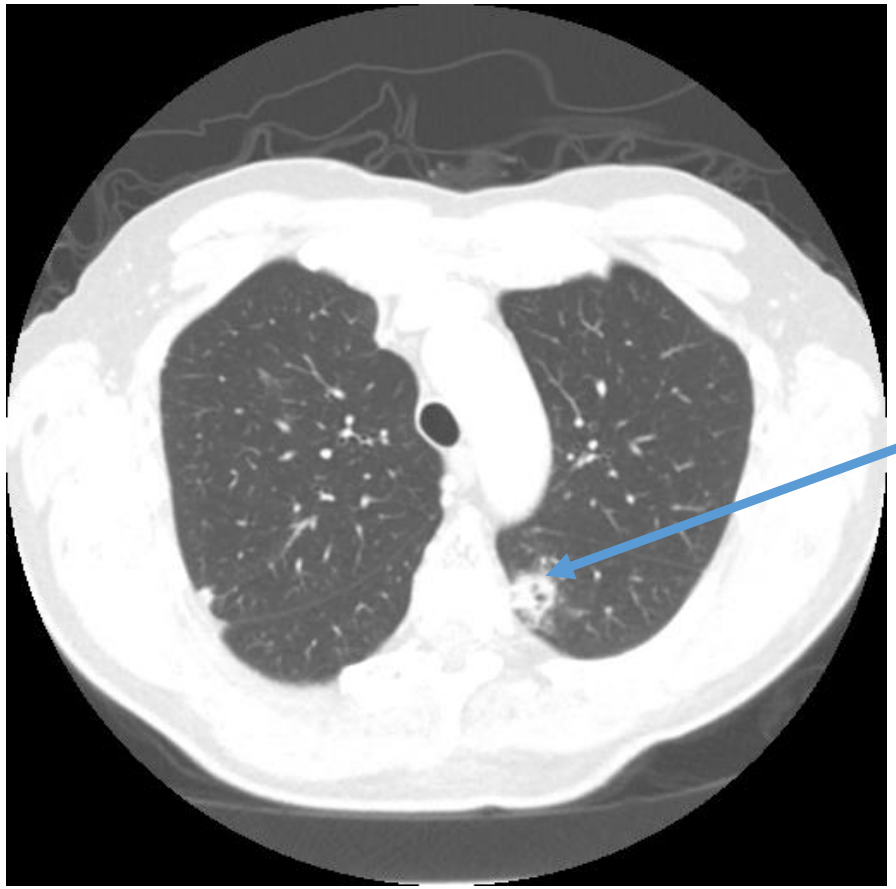
Case Study 1

Cancer History

- 74 year old man who presented with hematuria and a left renal mass in May 2014. Clinical diagnosis was primary renal cancer. Imaging showed no metastatic disease.
- Initial therapy was left radical nephrectomy. Pathology revealed high grade urothelial carcinoma measuring 5.8 cm. One of 12 regional lymph nodes contained carcinoma (pT4pN1M0, stage IV).
- Post surgical adjuvant gemcitabine and cisplatin were administered x 4 cycles.

Cancer History continued…

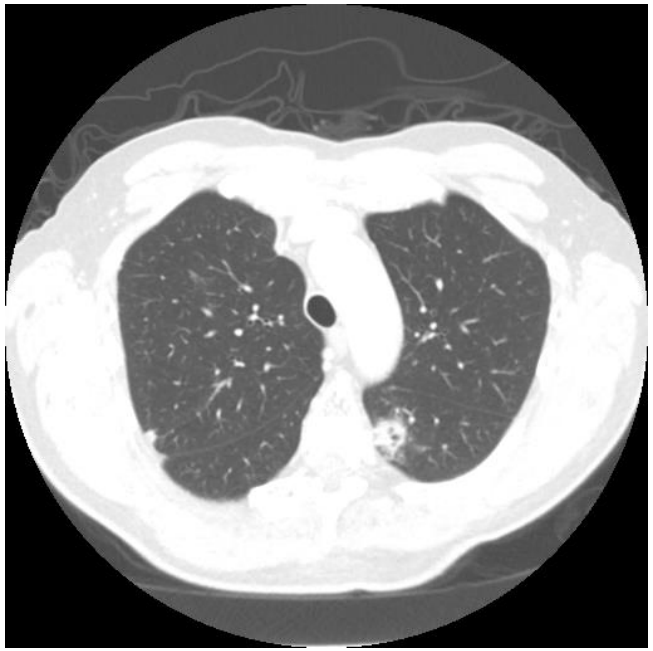
- The patient did well until July, 20 2015 when imaging revealed:

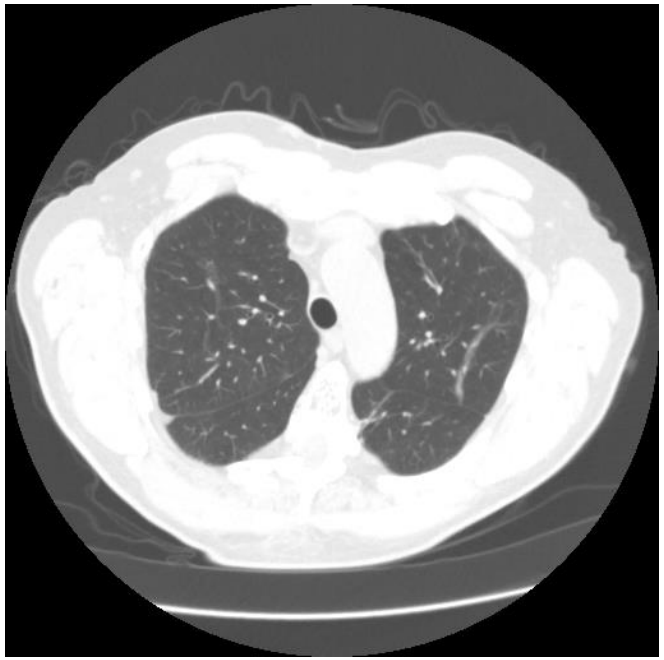


Biopsy confirms metastatic urothelial carcinoma

Cancer History continued…

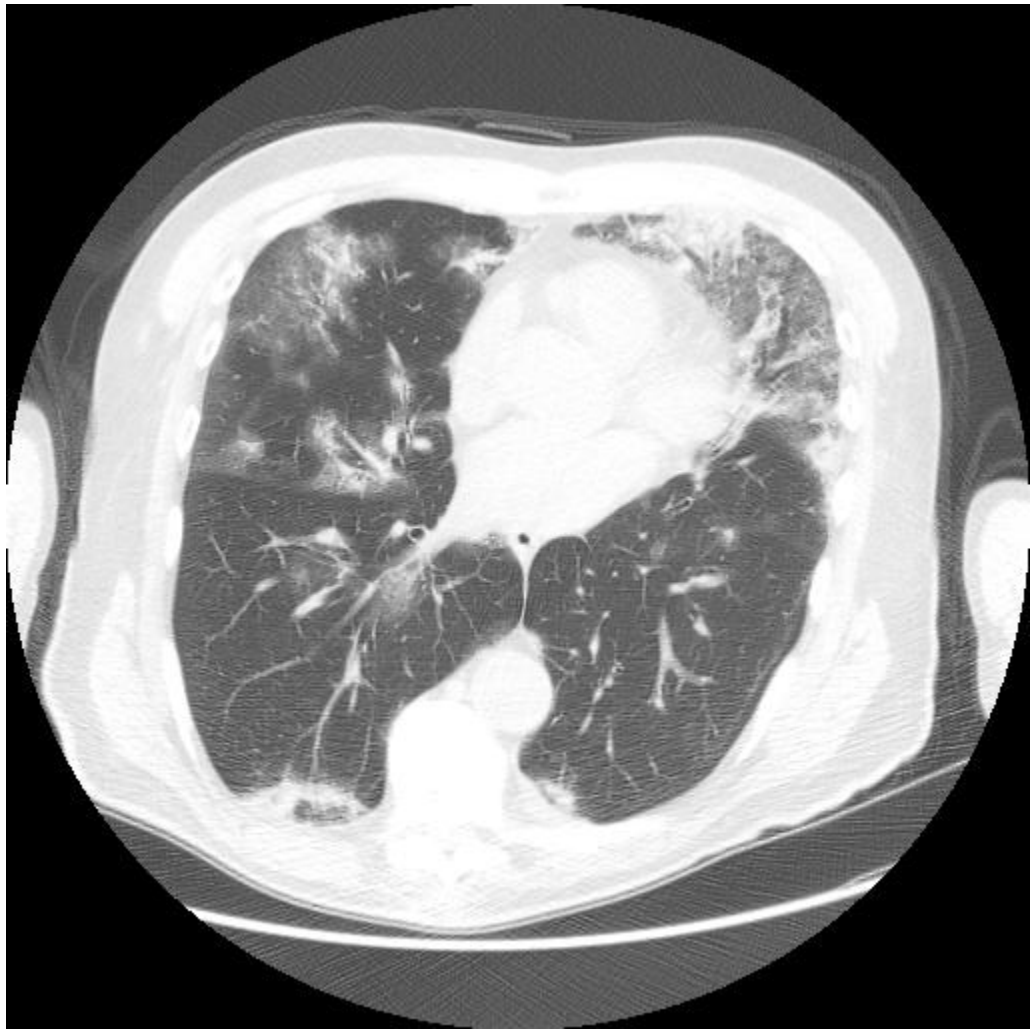
- Patient enrolled in the BMS CA209-275 clinical trial
  - Nivolumab administered at 3 mg/kg IV every 2 weeks
  - Response:





Other Events…

- Nivolumab resulted in:
  - Pneumonitis that appeared after ~9 months of therapy and required high dose steroids with a slow taper.
  - The radiologist report interpreted this and many other scans as disease progression (beware . . .).
  - He is recurrence-free now 31 months after the last nivolumab dose.



Case Study 2

Initial Presentation

- 63 year old woman who presents with painless hematuria x 3. The patient has no other symptoms, normal labs and ECOG 0. She has a 20 pack-year smoking history and quit 5 years ago. She works in telemarketing.
  - Initial evaluation?

Case Continued

- Physical exam revealed a palpable large left renal mass.
- CT imaging showed multiple bilateral lung nodules and a 14 cm left renal mass.
  - Treatment options?

Case Continued…

- The patient had left radical nephrectomy and pathology revealed a conventional (clear cell) renal cancer measuring 14 cm and Fuhrman nuclear grade 4. One out of 7 lymph nodes contained RCC.
  - Systemic therapy options?

Case Continued…

- The patient volunteered for a clinical trial investigating SBRT + IL-2 versus IL-2. Pulmonary function tests and ETT were sufficient for high-dose immunotherapy. During the IL-2 evaluation, she presented with a left sided weakness and brain MRI showed 2 right-sided brain metastases amenable to gamma knife radiosurgery.
  - Would you still offer this patient IL-2 or another therapy?

… and then:

- She recovered from gamma knife radiosurgery, was weaned off steroids and received IL-2 (off protocol). A total of 4 cycles were administered and she achieved a partial regression of pulmonary and brain metastases, but a new lytic right femur lesion.
- RT was administered to the femur she was started on sunitinib.
- After 1 cycle of TKI there were new bone and pulmonary metastases.
- Nivolumab was started and 12 months of therapy were given. Best response was PR.
- Within 3 months of stopping nivolumab, there were new bone metastases.
- She has recently started cabozantinib and has initial regression of disease