Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Malignancies

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ACCC Association of Community Cancer Centers

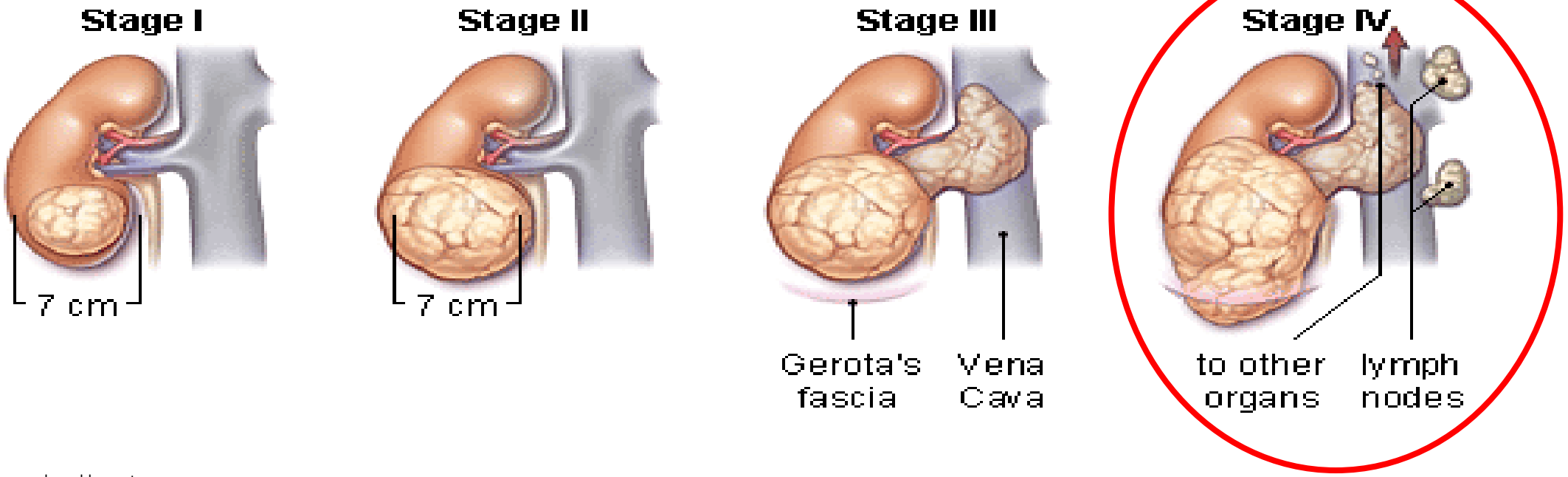
Society for Immunotherapy of Cancer

Disclosures

- I do not have any conflict of interest to disclose
- I will not be discussing non-FDA approved indications during my presentation.

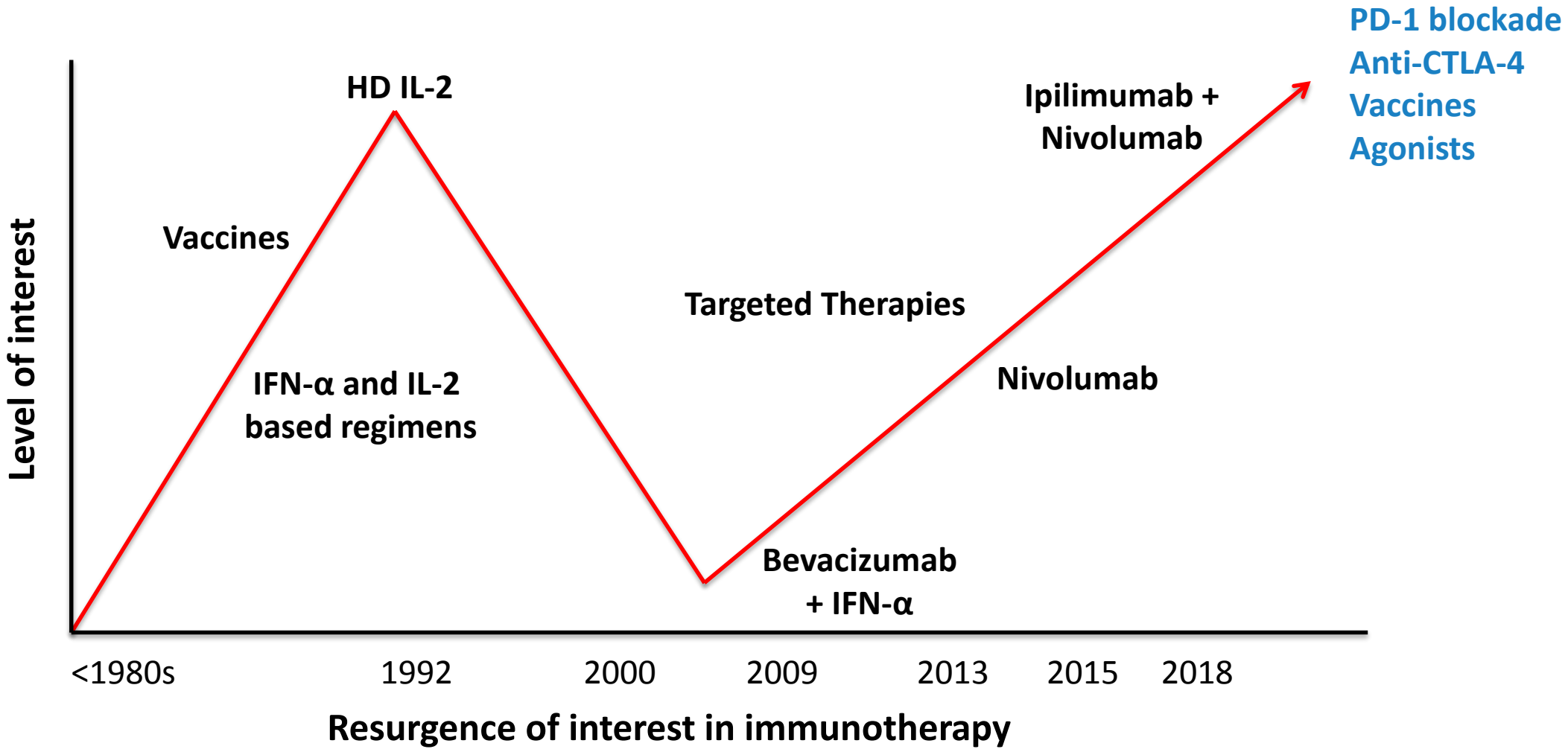
Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)

Surgically resectable → Oligo-metastatic → Metastatic



reemakeup.blogspot.com

History of Immunotherapy in mRCC



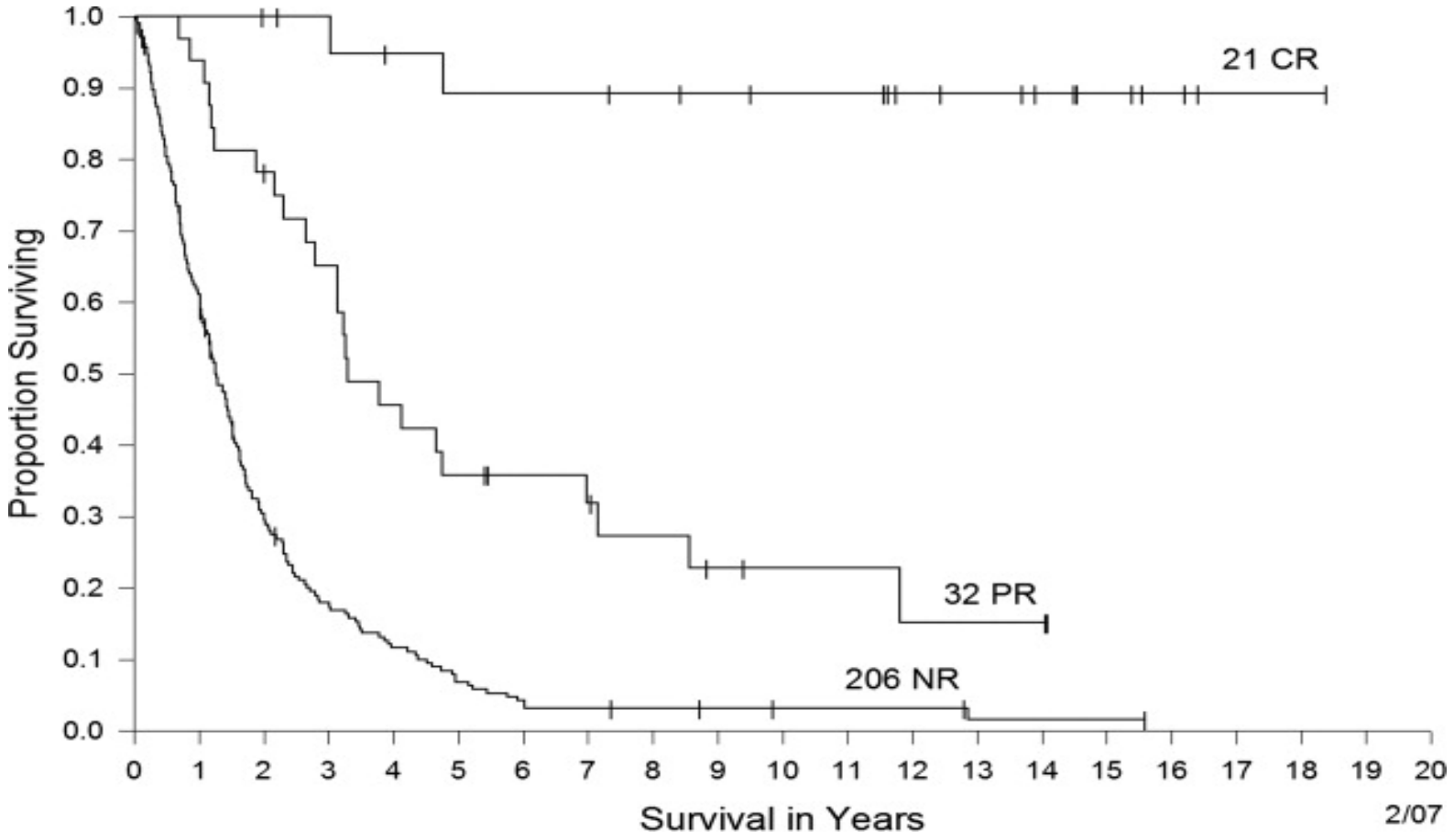
FDA-approved Immunotherapies for mRCC

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

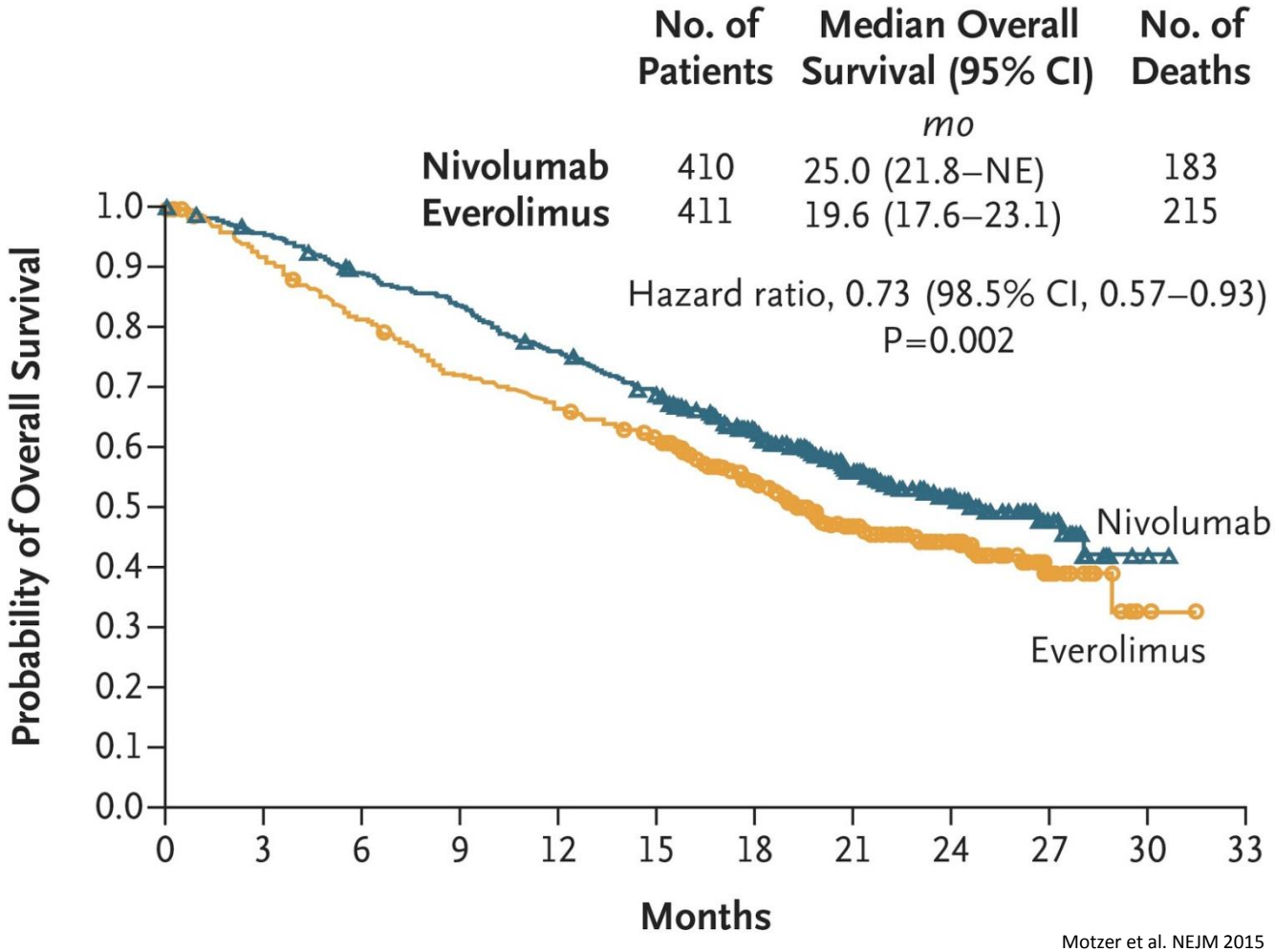
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



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)

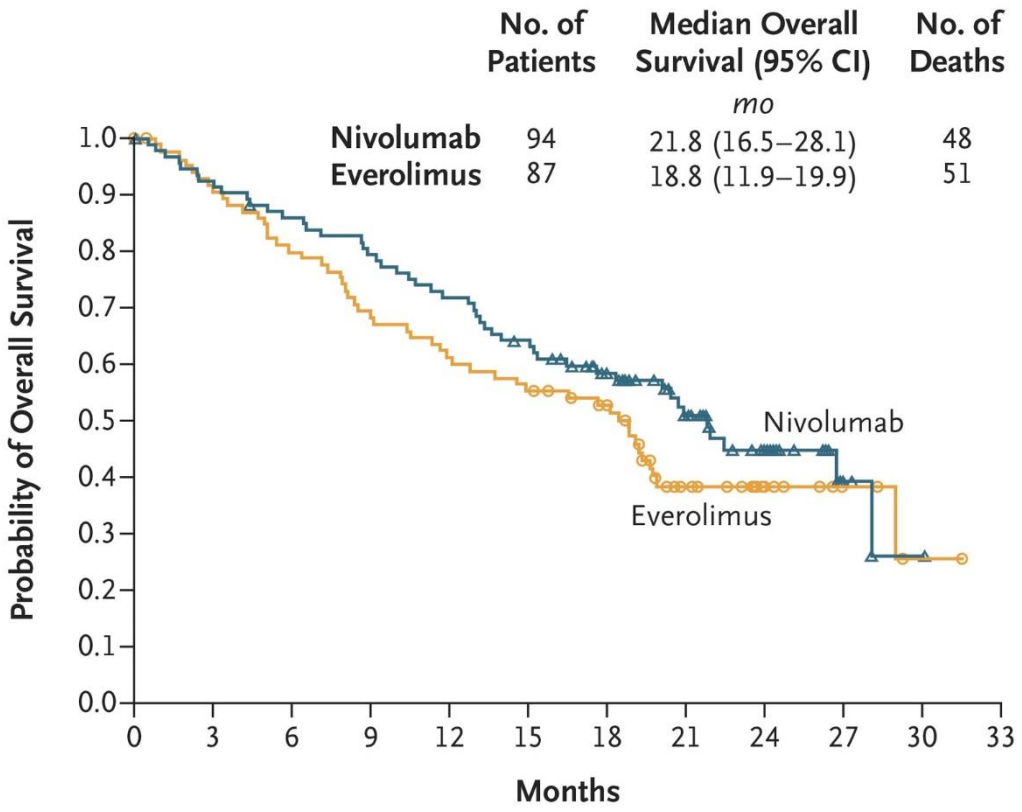


Motzer et al. NEJM 2015

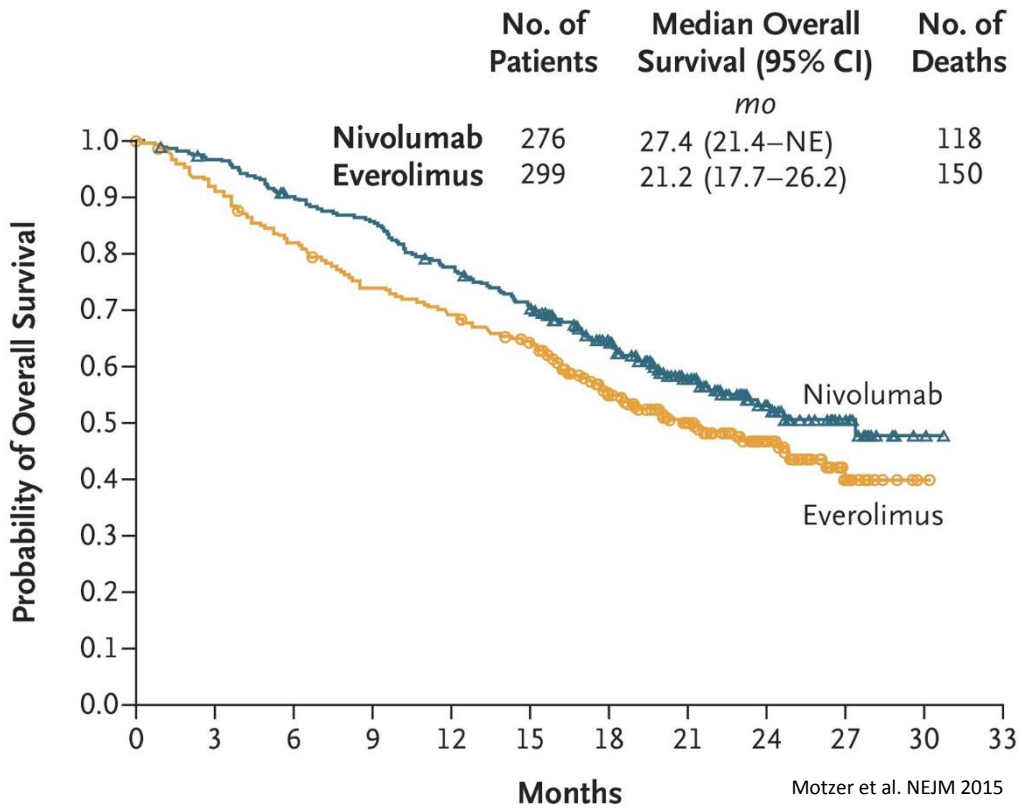
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%



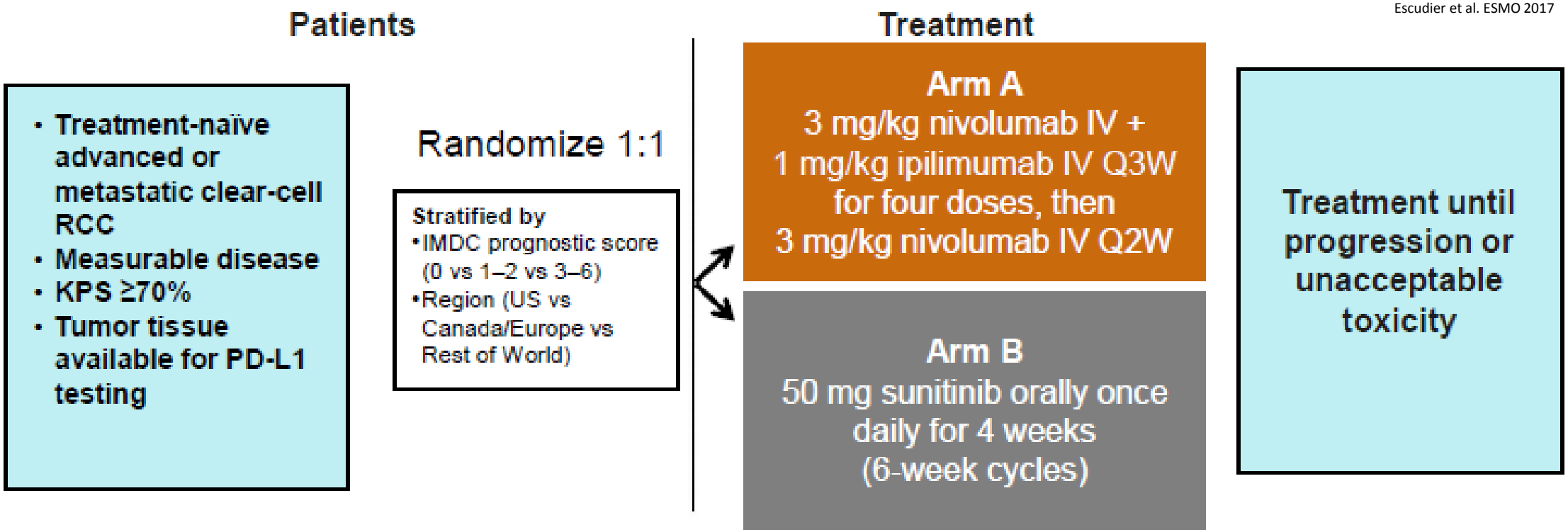
PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC

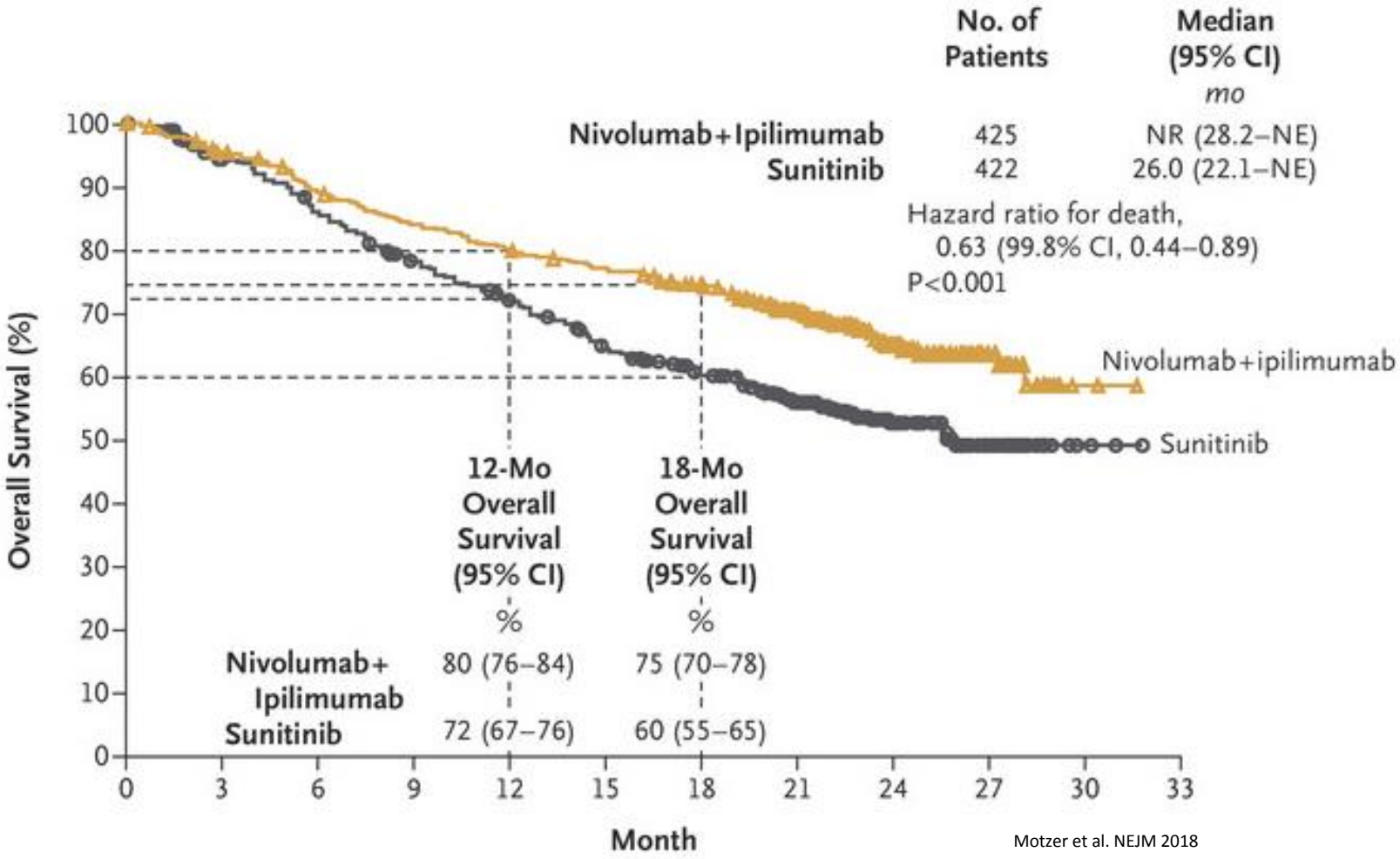
Escudier et al. ESMO 2017



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

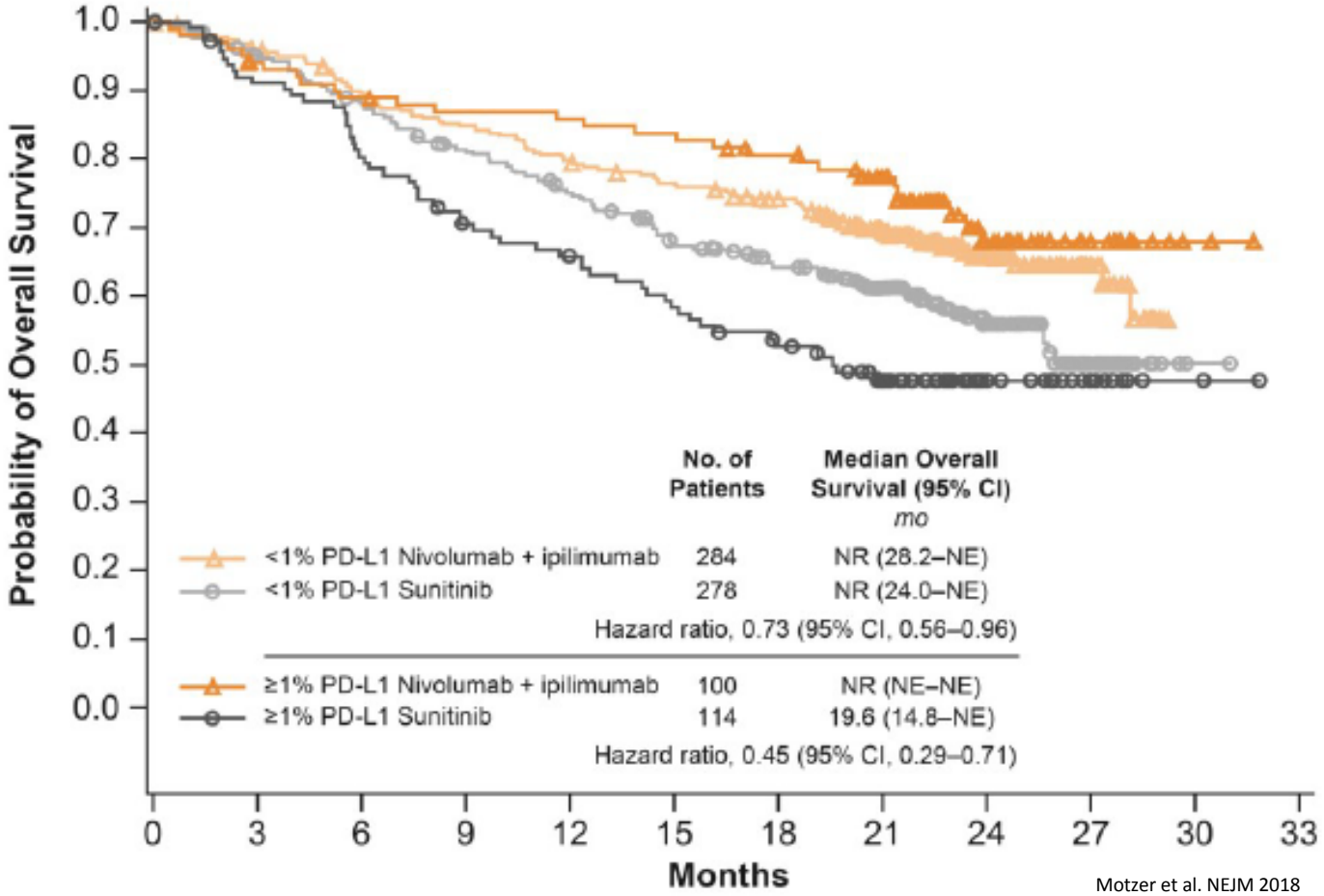
First-line Nivolumab + Ipilimumab in mRCC



Motzer et al. NEJM 2018

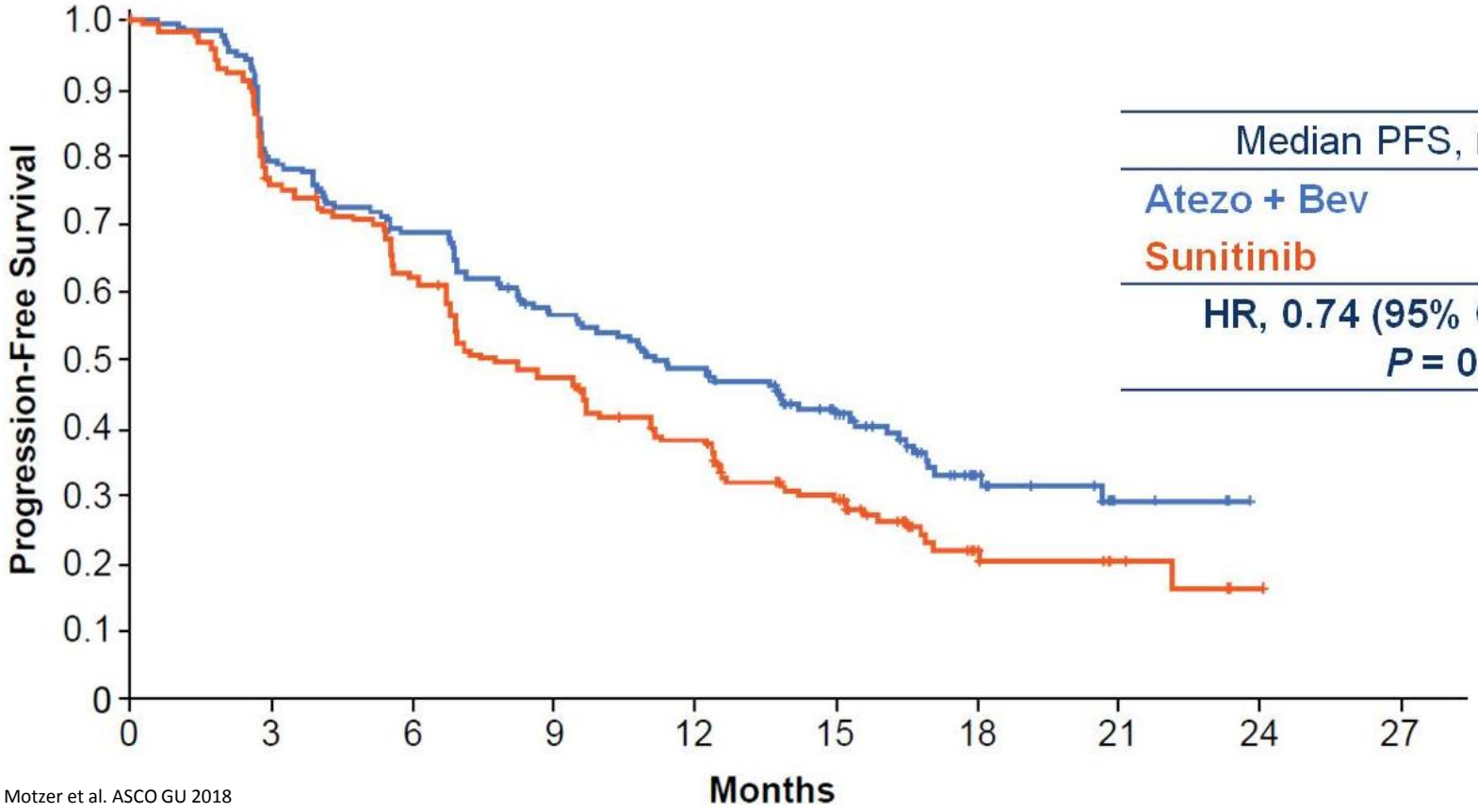
First-line Nivolumab + Ipilimumab in mRCC

PD-L1 Subgroups



Motzer et al. NEJM 2018

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

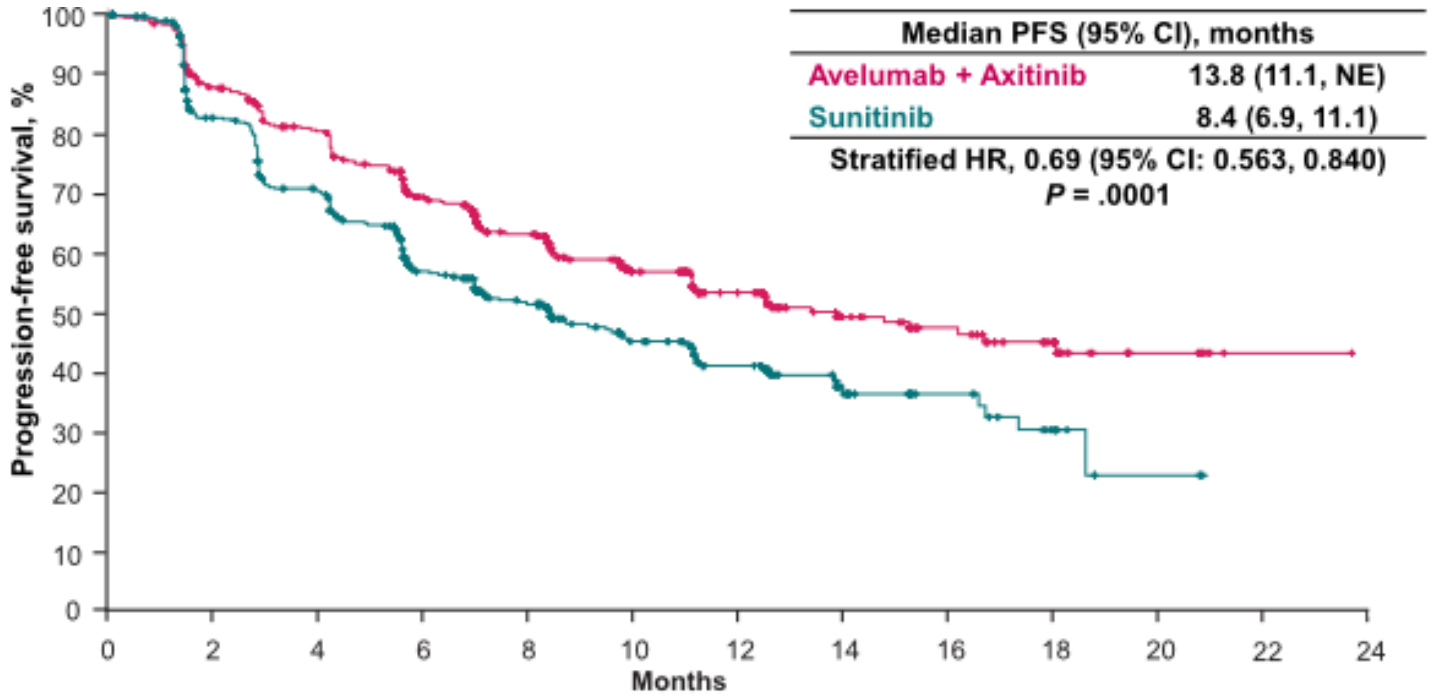


Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96)	
P = 0.02[a]	

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

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

JAVELIN Renal 101

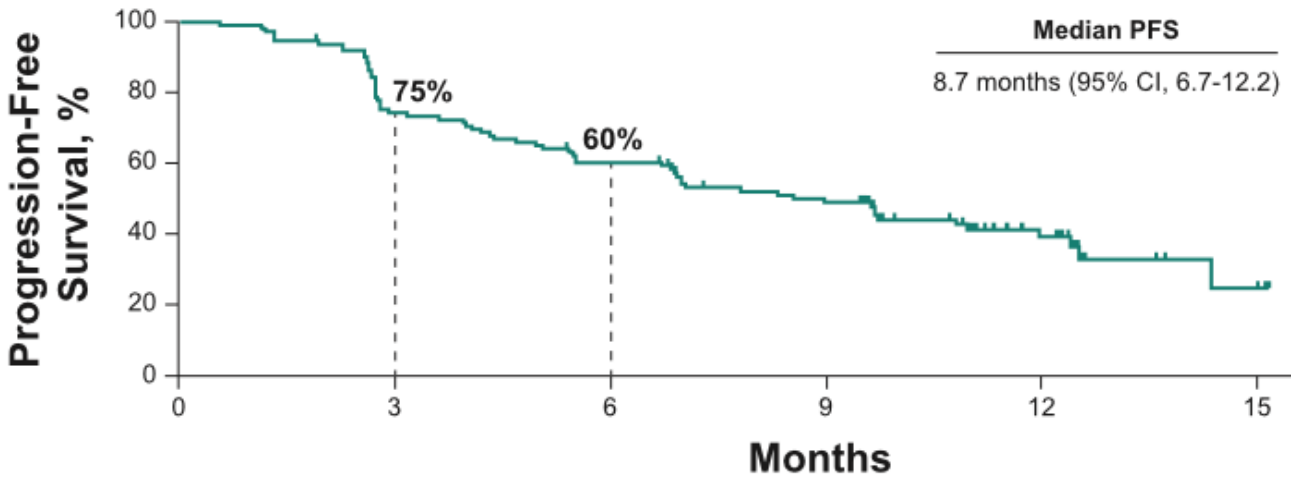


Motzer et al. ESMO 2018

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

In Development: First-line Pembrolizumab in mRCC

KEYNOTE - 427



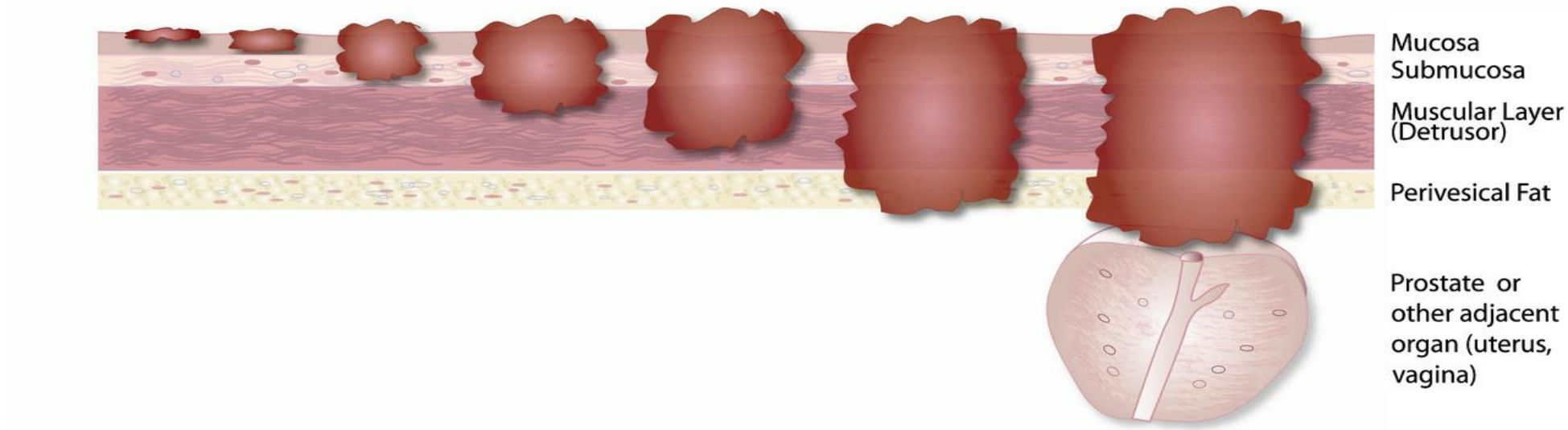
	N = 110
Confirmed ORR, % (95% CI)	38 (29 – 48)
Confirmed BOR, n (%)	
CR	3 (3)
PR	39 (35)
SD	35 (32)
PD	31 (28)
No assessment	2 (2)

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

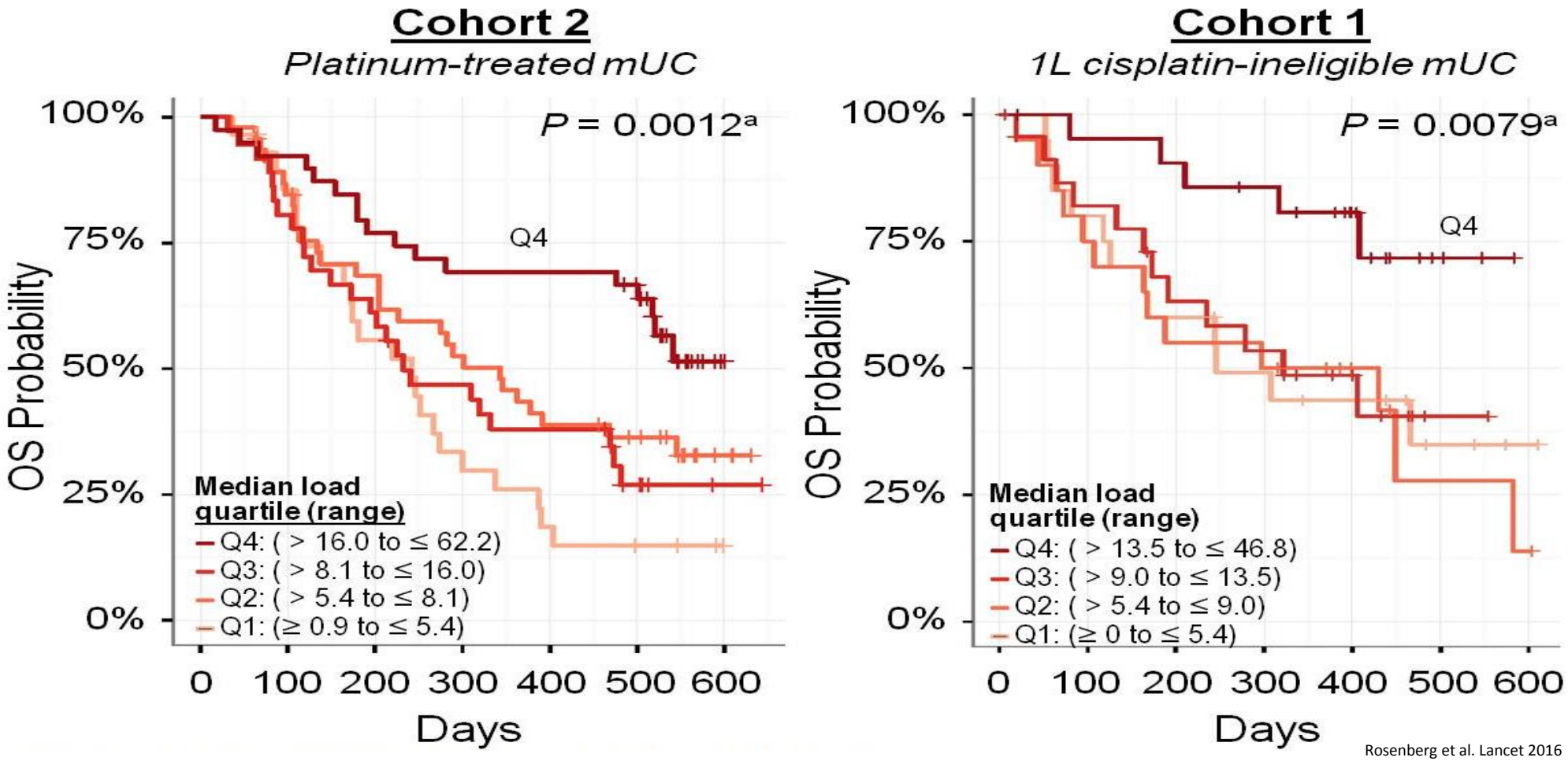
In development: Combinations

1) IO + IO
2) IO + Chemotherapy

Ghatalia et al. Ther Adv Med Oncol 2018

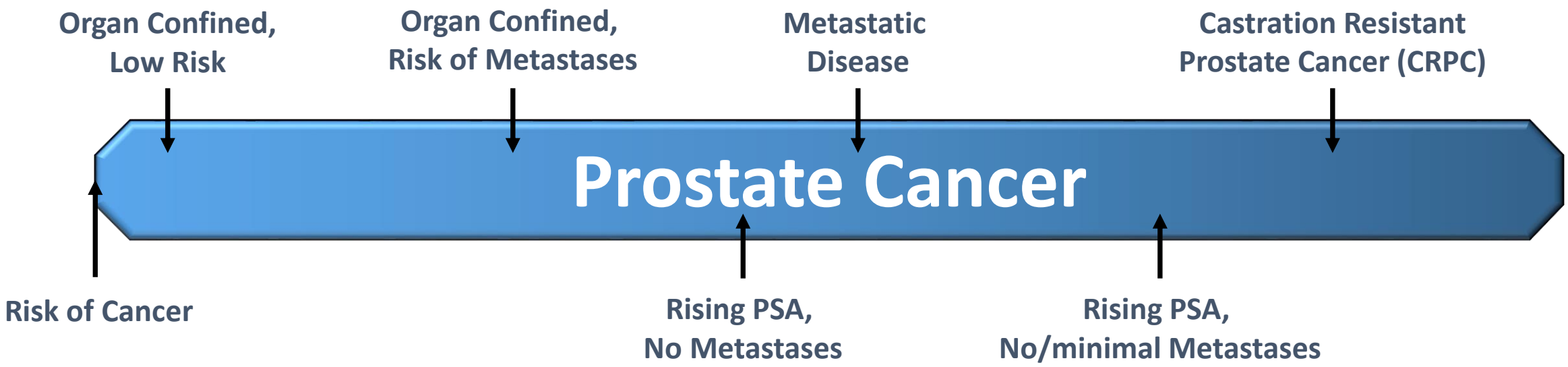
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



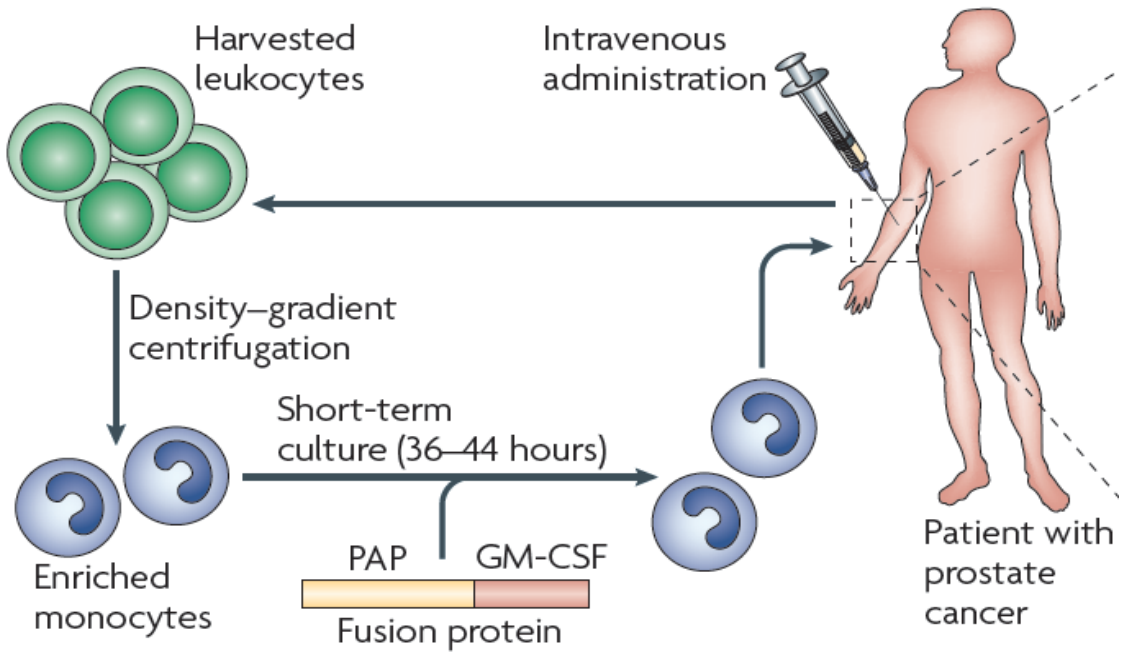
Rosenberg et al. Lancet 2016

The Spectrum of Prostate Cancer

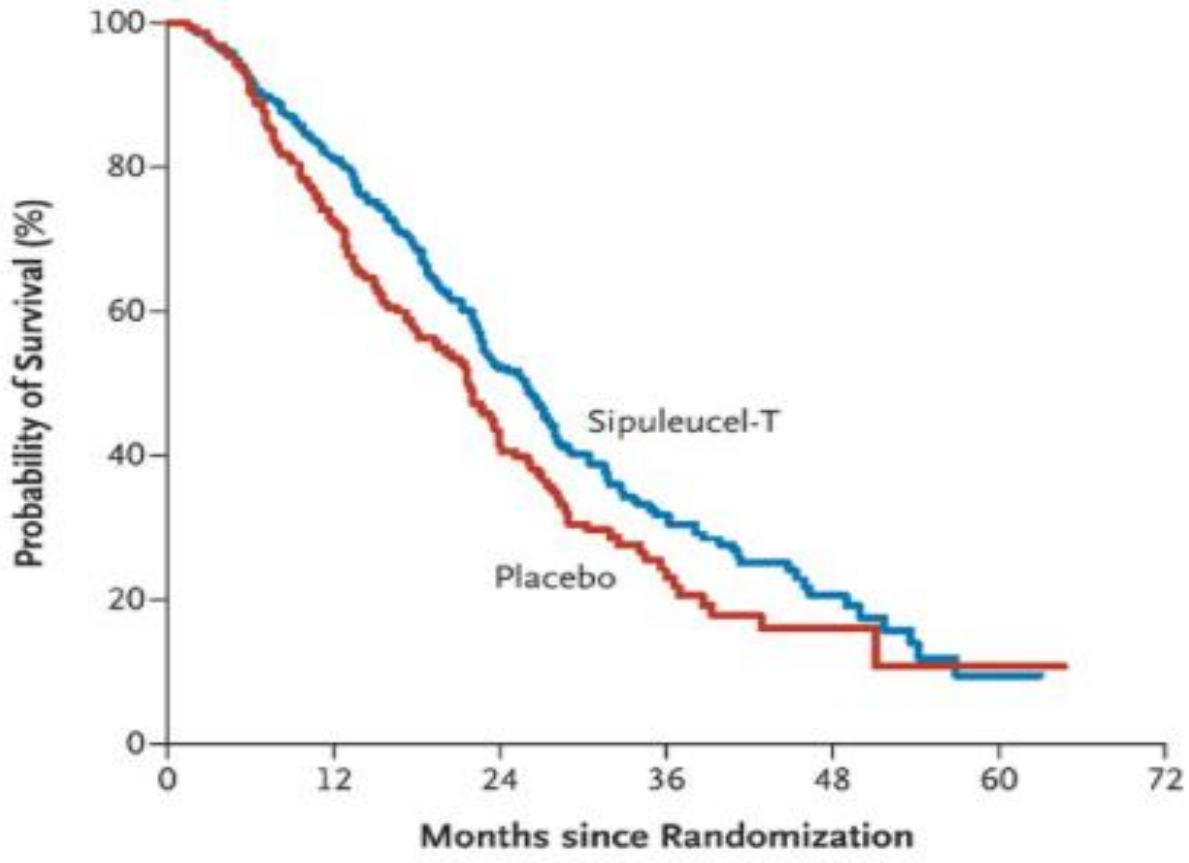


Sipuleucel-T in mCRPC

- First anticancer therapeutic vaccine



Drake et al. Curr Opin Urol 2010

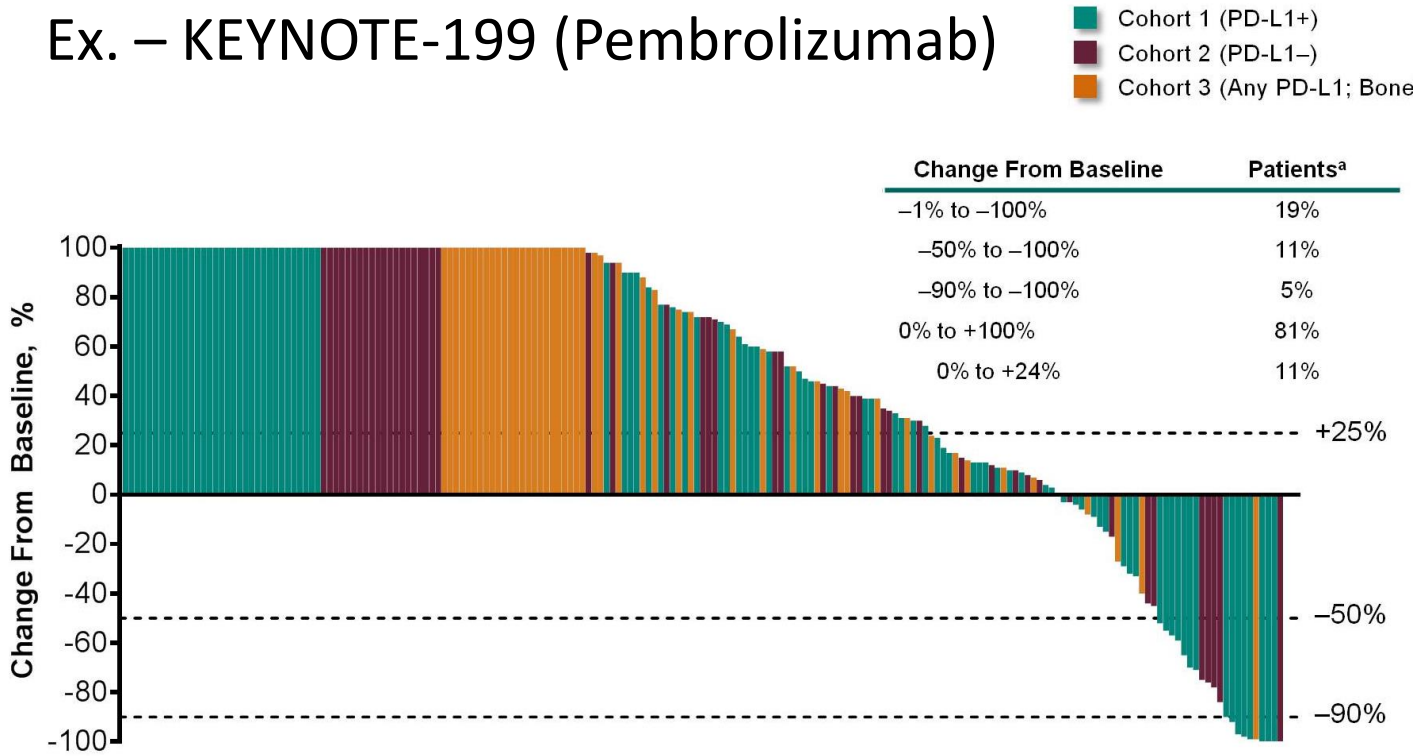


Kantoff et al. NEJM 2010

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

Ex. – KEYNOTE-199 (Pembrolizumab)

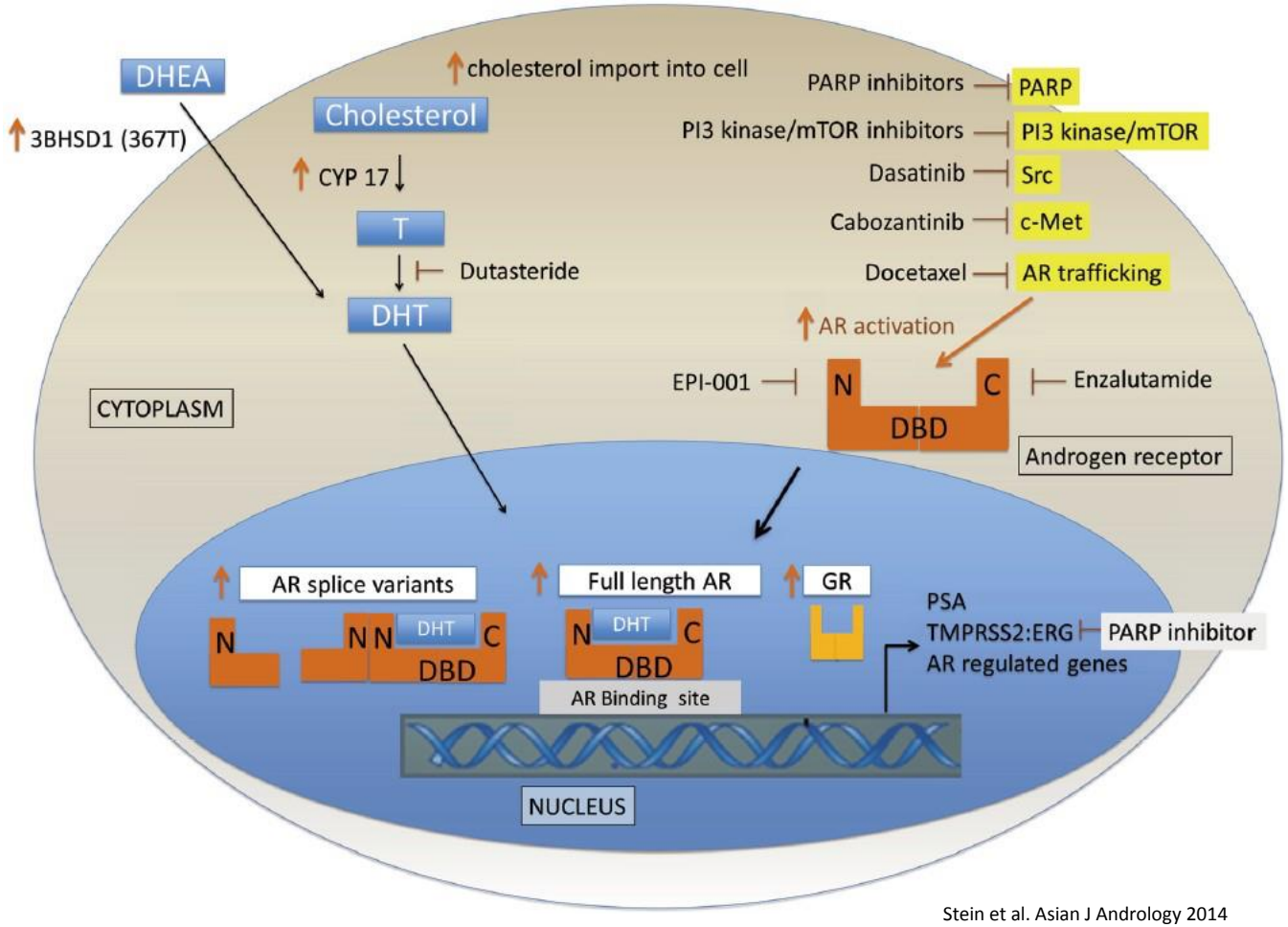


DeBono et al. ASCO 2018

- 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

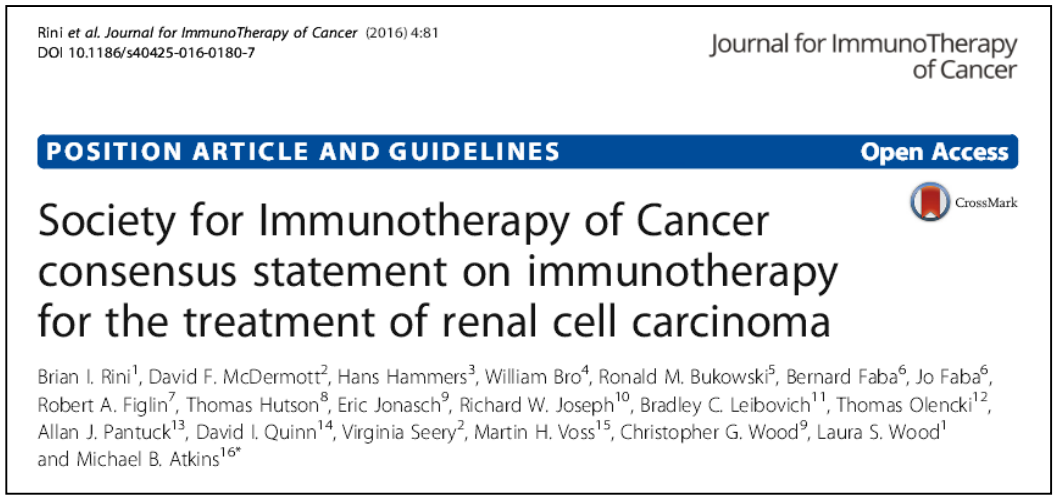
Immune-related Adverse Events

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*]

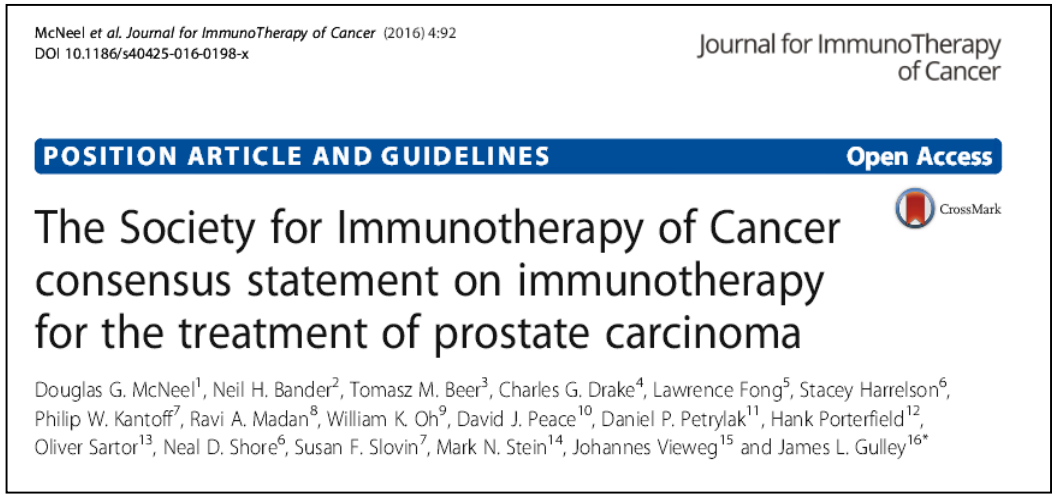
Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

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: Metastatic Kidney Cancer

You are seeing a 65 year old woman with kidney cancer that was resected 3 years ago but has now recurred in the lungs and liver. She was initially treated with sunitinib but progressed after 9 months. What would immunotherapy option is most proven to treat her disease in the post VEGF targeted therapy setting?

A. Interferon-alfa

B. Thalidomide

C. Nivolumab

D. Atezolizumab

Case Study 2: Bladder Cancer

You are seeing a 60 y/o man who was diagnosed with superficial bladder cancer 5 years ago. After several courses of resection and intravesical BCG therapy, he developed muscle-invasive disease 2 years ago and underwent radical cystoprostatectomy. He then did well until 4 months ago when he was found to have lung and liver metastases. He started treatment with gemcitabine and cisplatin chemotherapy, but unfortunately had progressive disease after 3 cycles of therapy. What is the best immunotherapy treatment option for him?

A. IL-2

B. Atezolizumab

C. Pembrolizumab