

Immunotherapy for the Treatment of Genitourinary Malignancies

Michael Schweizer, MD

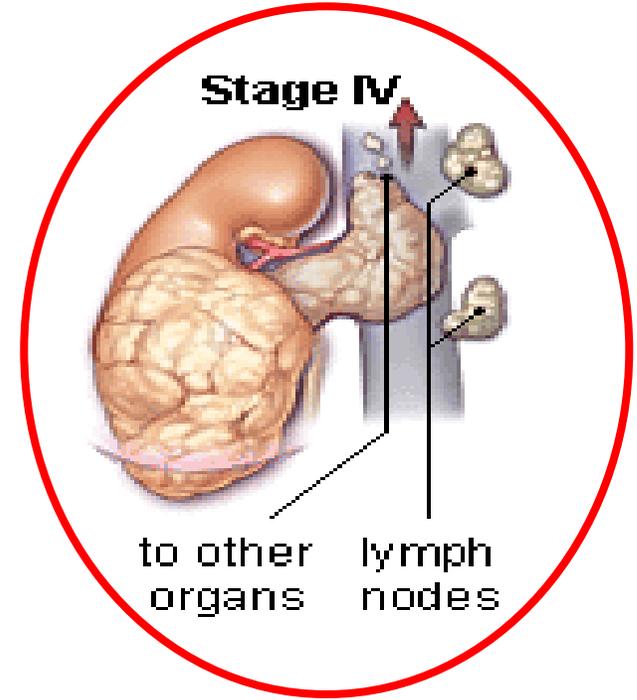
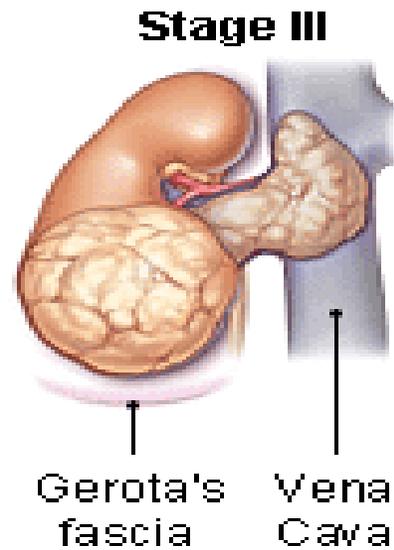
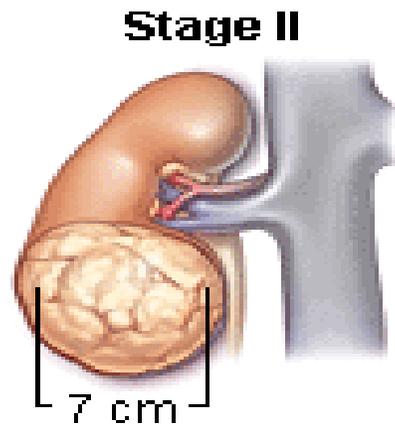
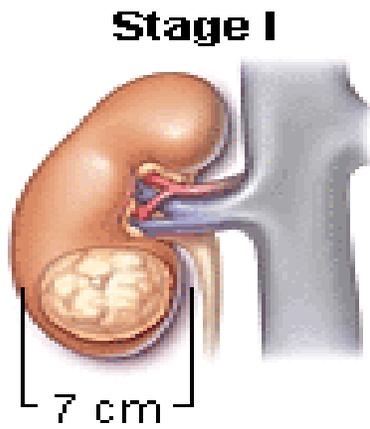
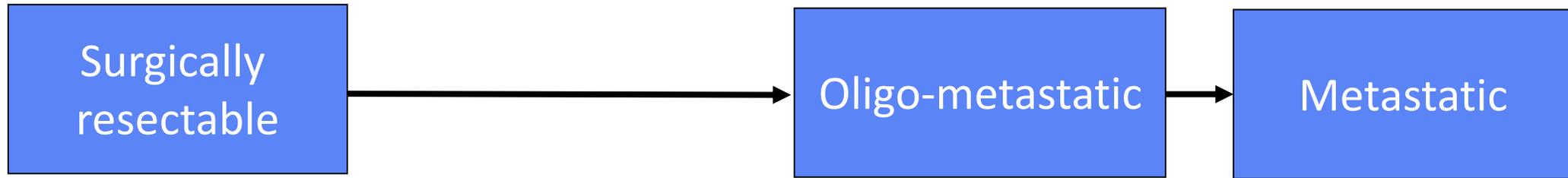
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Disclosures

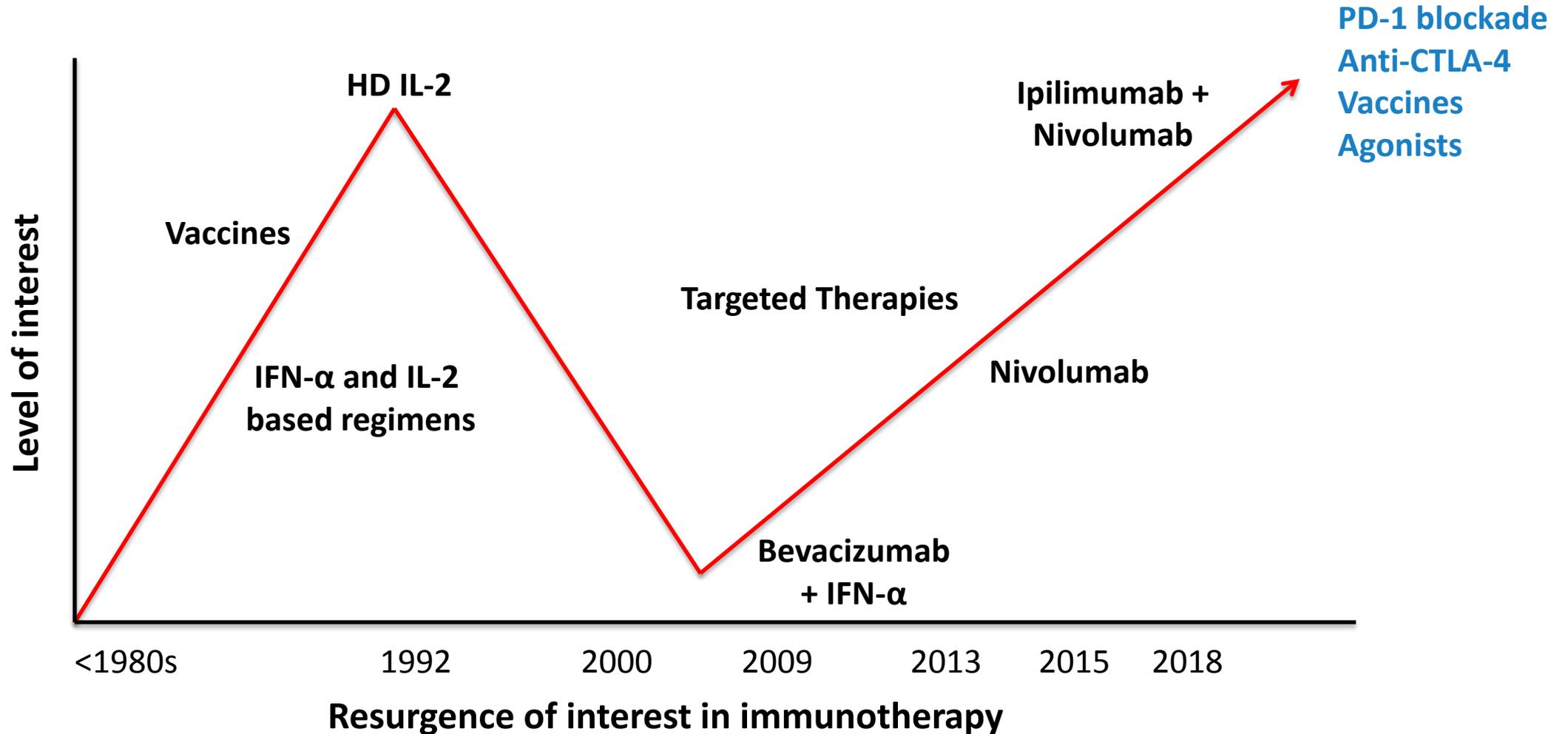
- Consulting Fees: Janssen
- Contracted Research: Janssen, AstraZeneca, Zenith, Pfizer, Hoffmann-La Roche
- I will not be discussing non-FDA approved indications during my presentation.

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



reemakeup.blogspot.com

History of Immunotherapy in mRCC



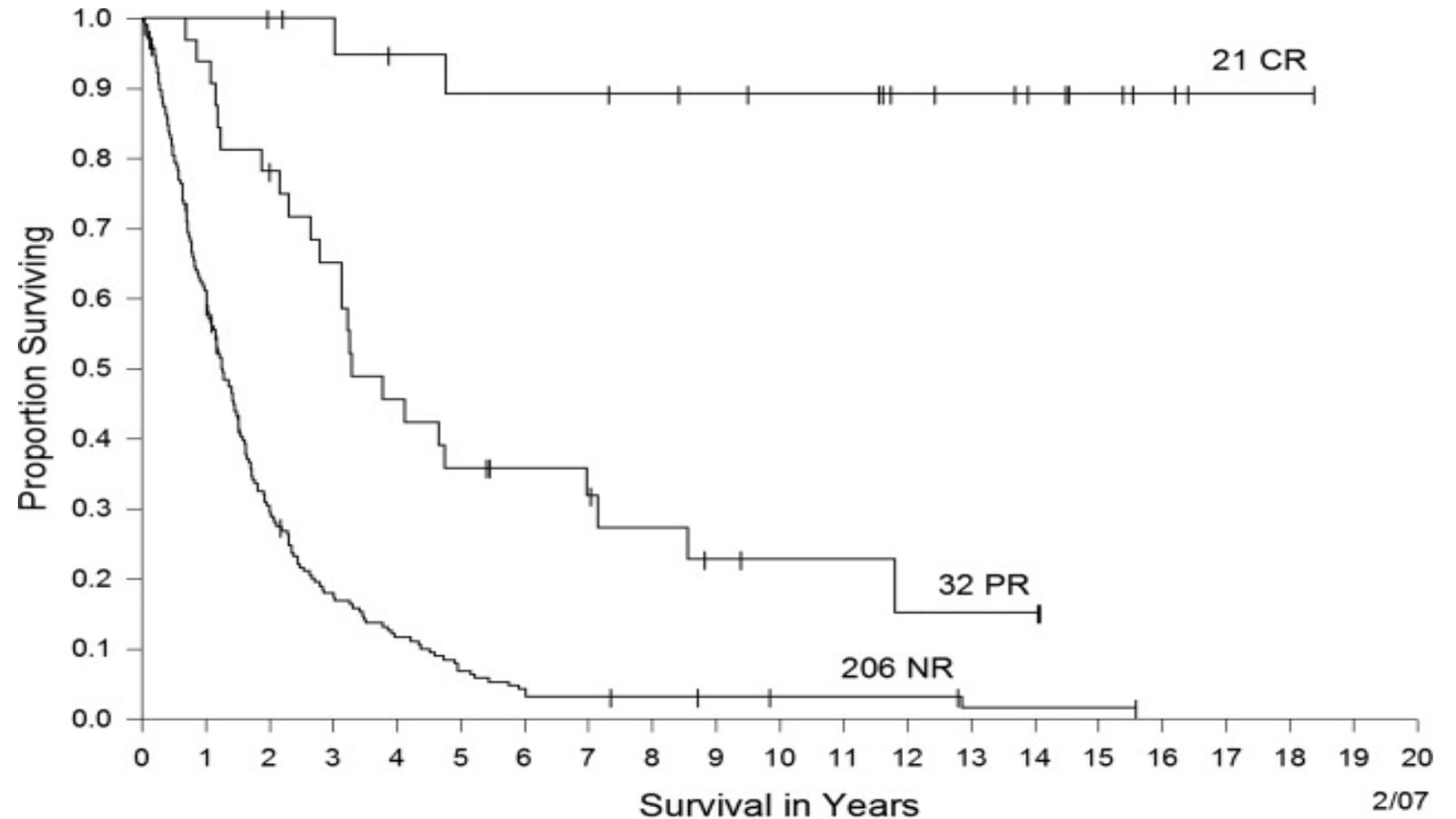
FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Dose
High dose Interleukin-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, treatment 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

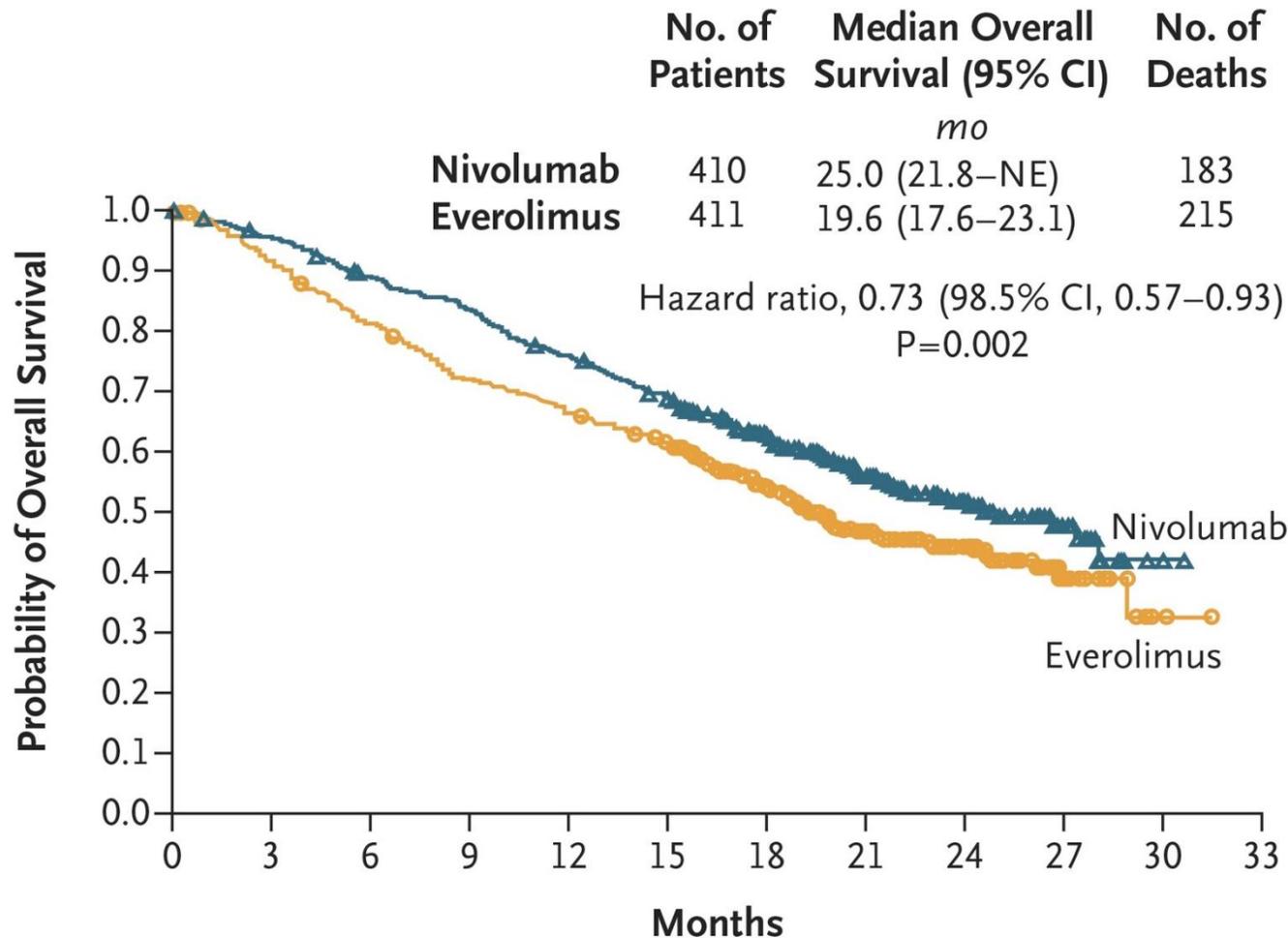
- 20 year analysis of 259 patients
- ORR = 20%
 - 9% CR (n = 23)
 - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



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)

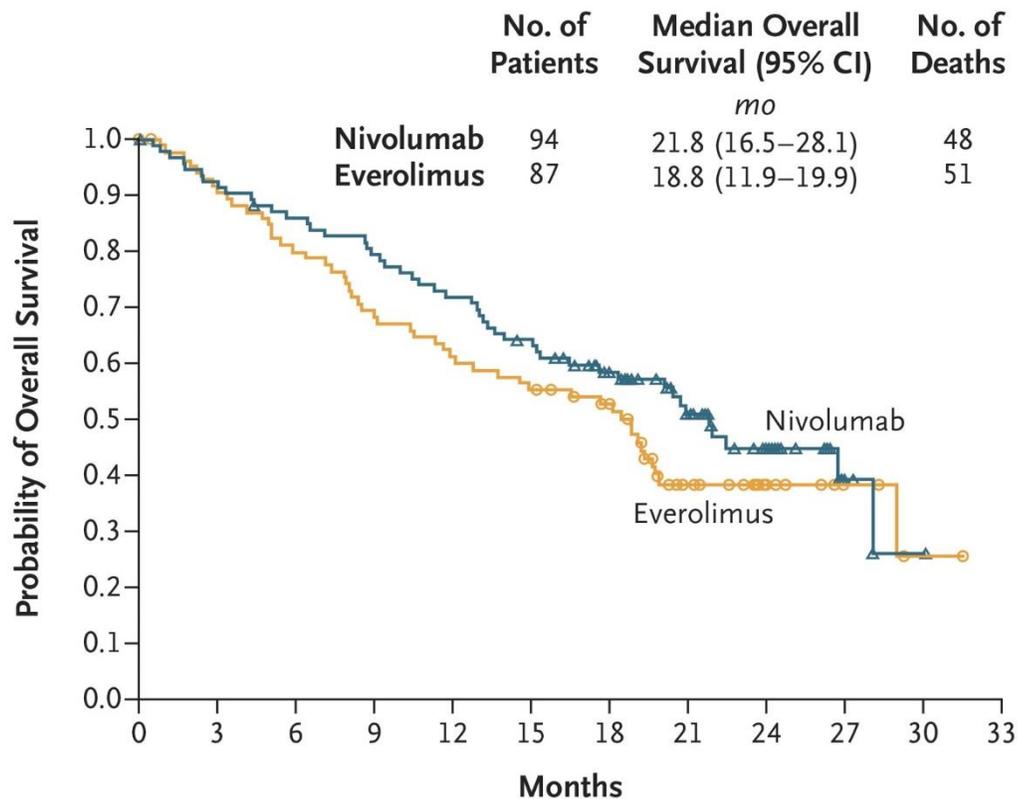


Motzer et al. NEJM 2015

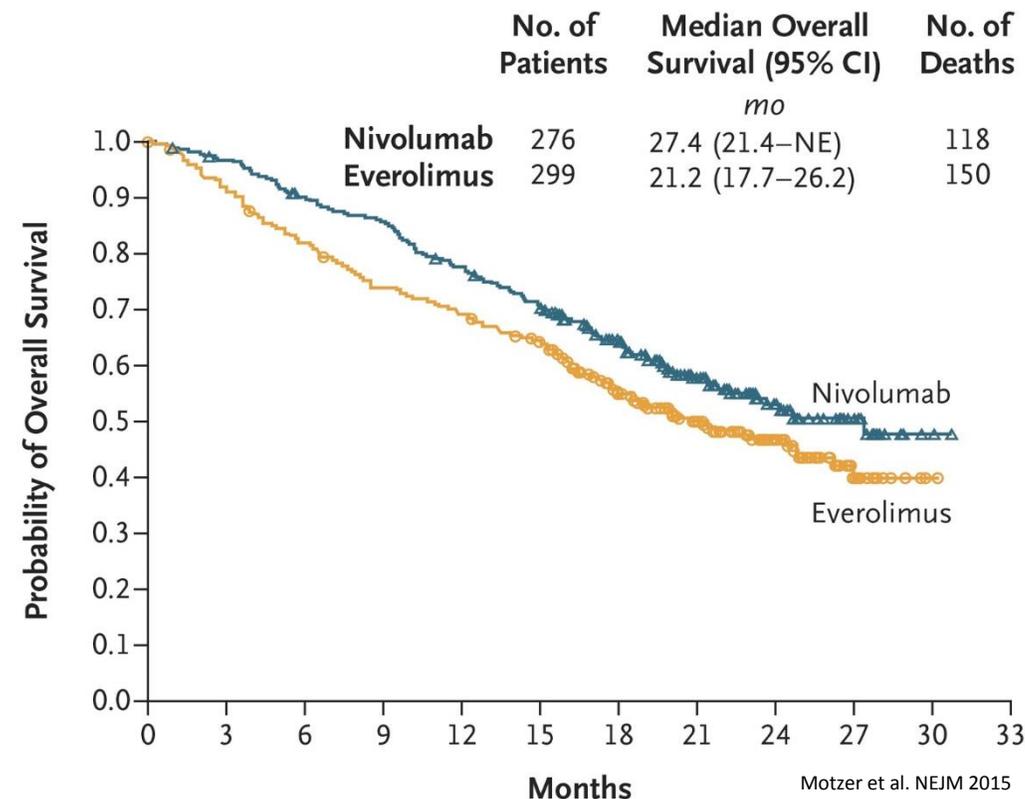
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%



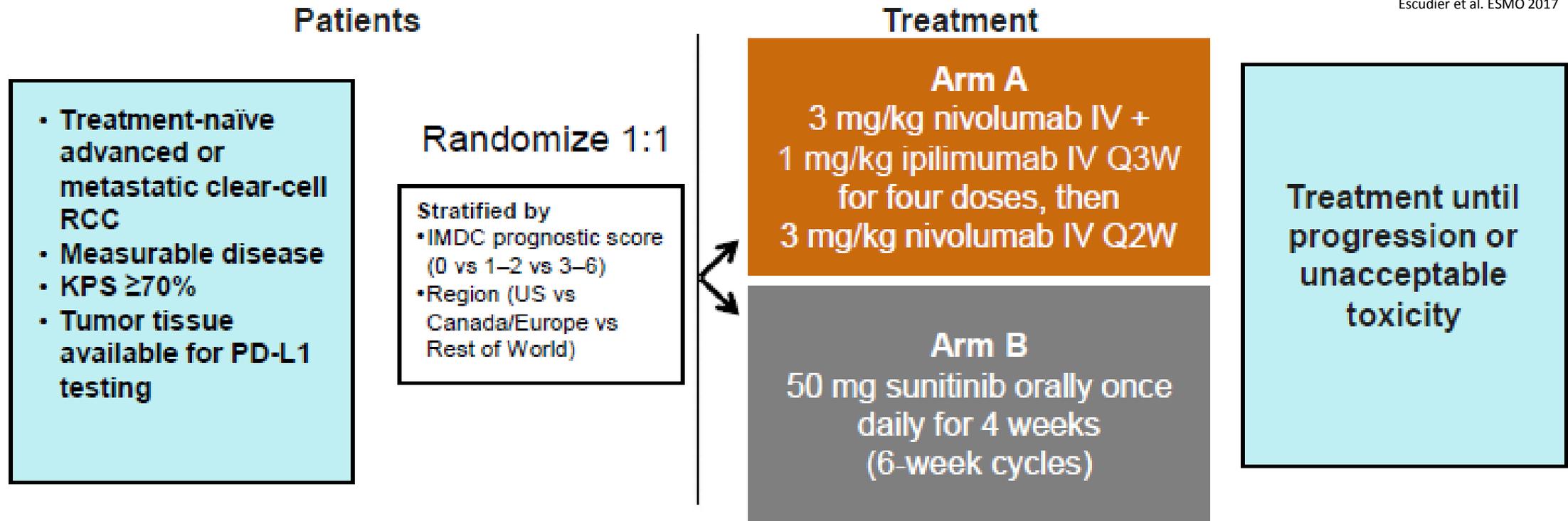
PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC

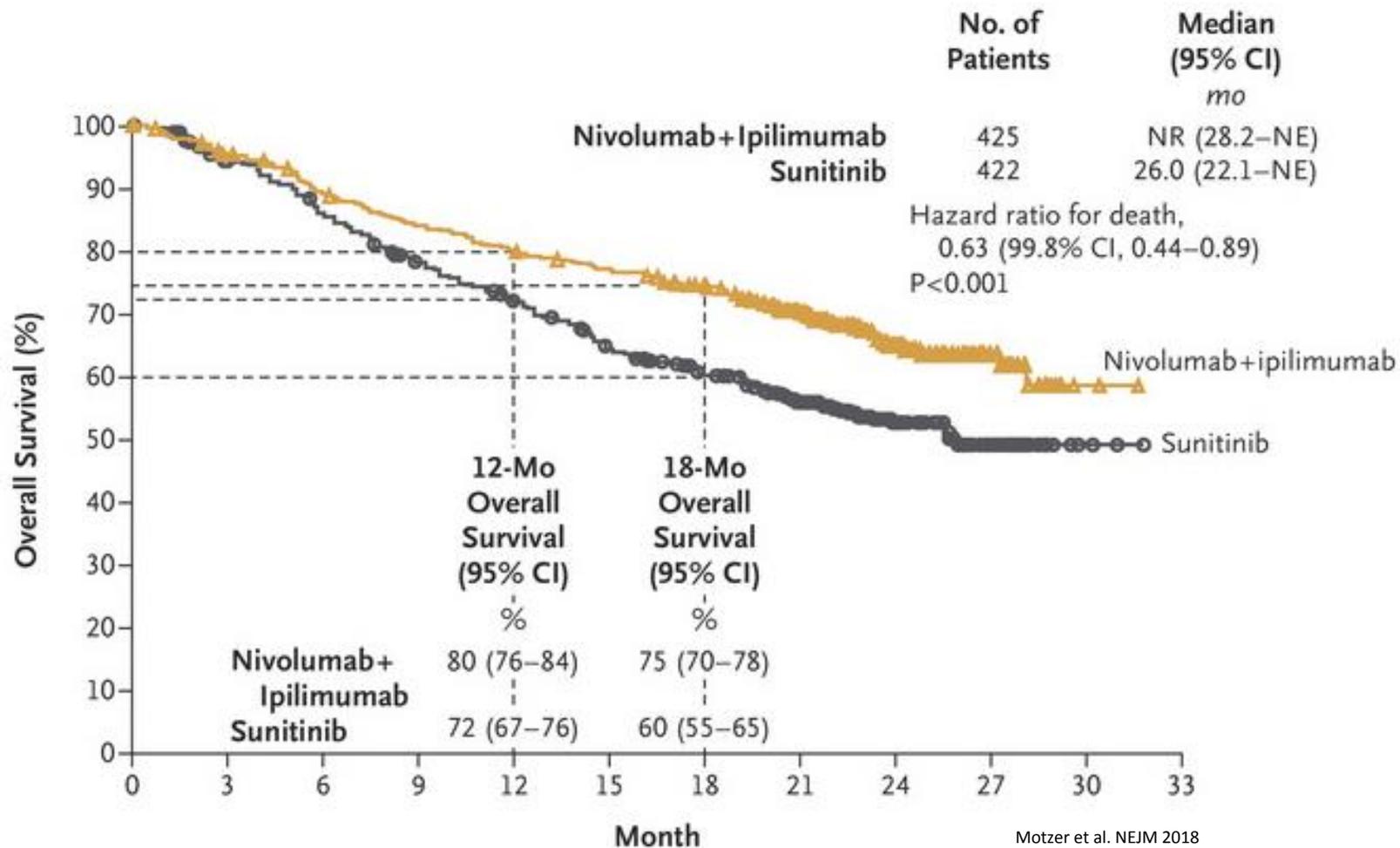
Escudier et al. ESMO 2017



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

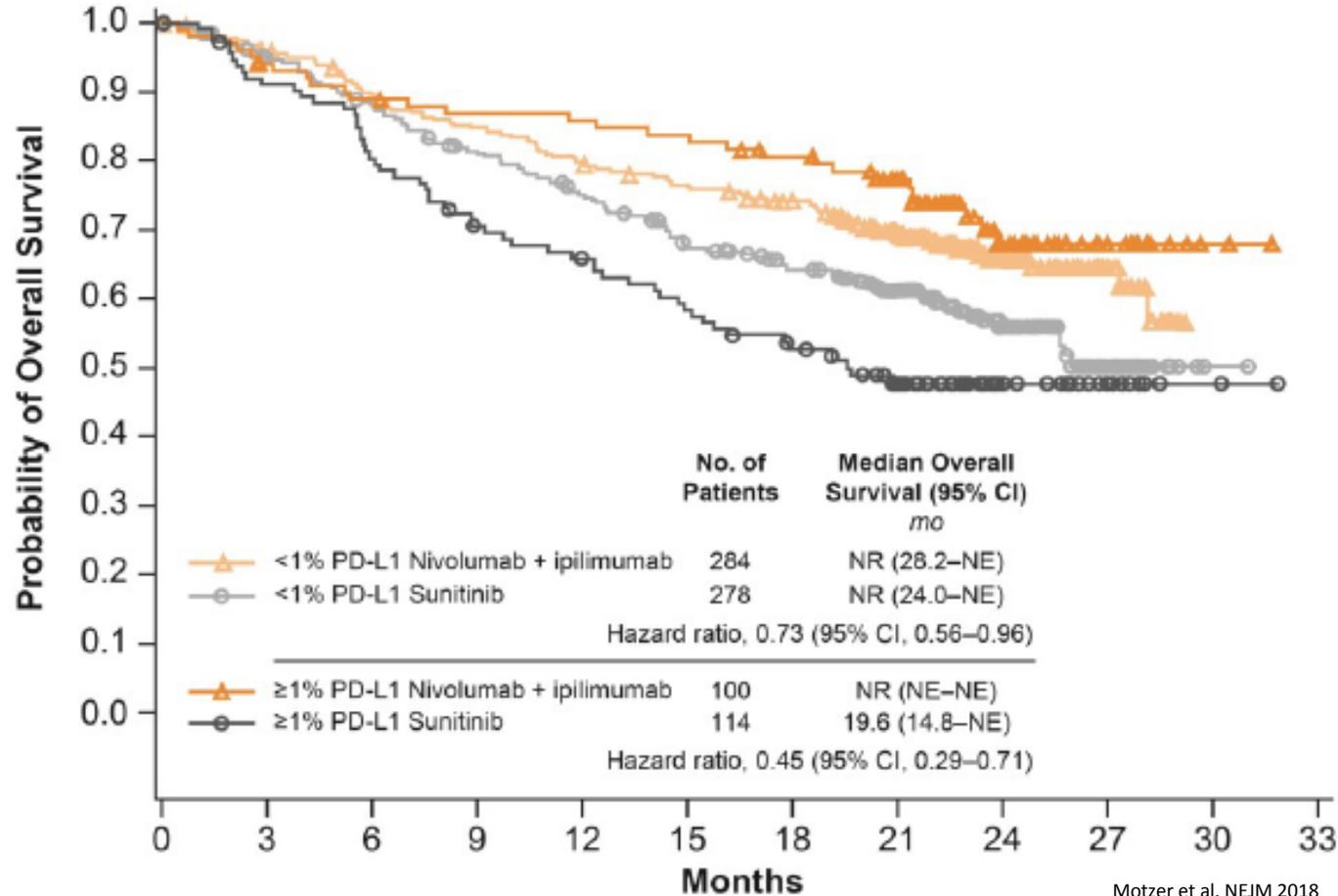
First-line Nivolumab + Ipilimumab in mRCC



Motzer et al. NEJM 2018

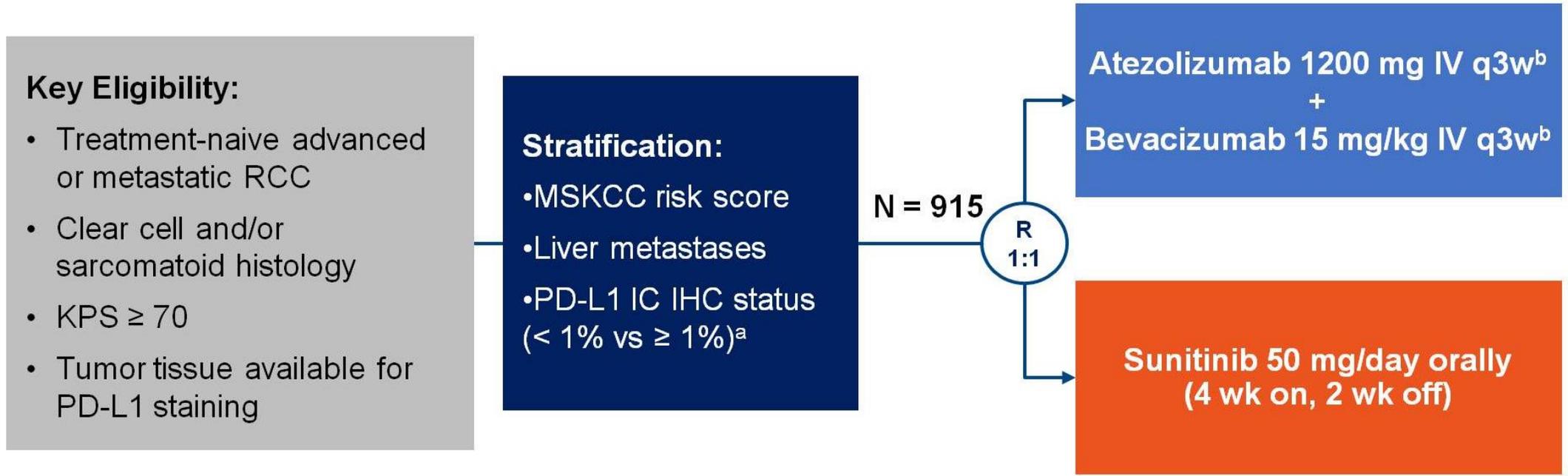
First-line Nivolumab + Ipilimumab in mRCC

PD-L1 Subgroups



Motzer et al. NEJM 2018

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

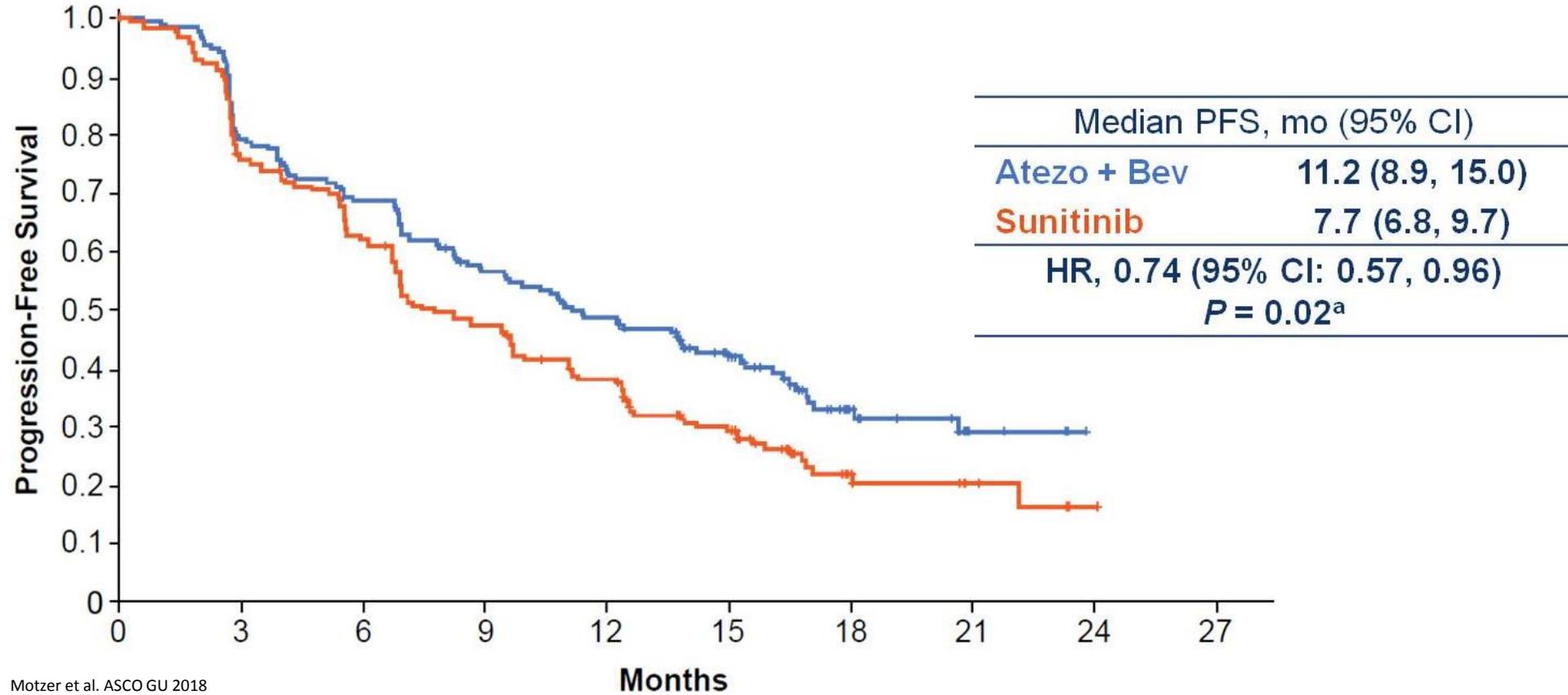


Motzer et al. ASCO GU 2018

Atezolizumab = anti-PD-L1 antibody

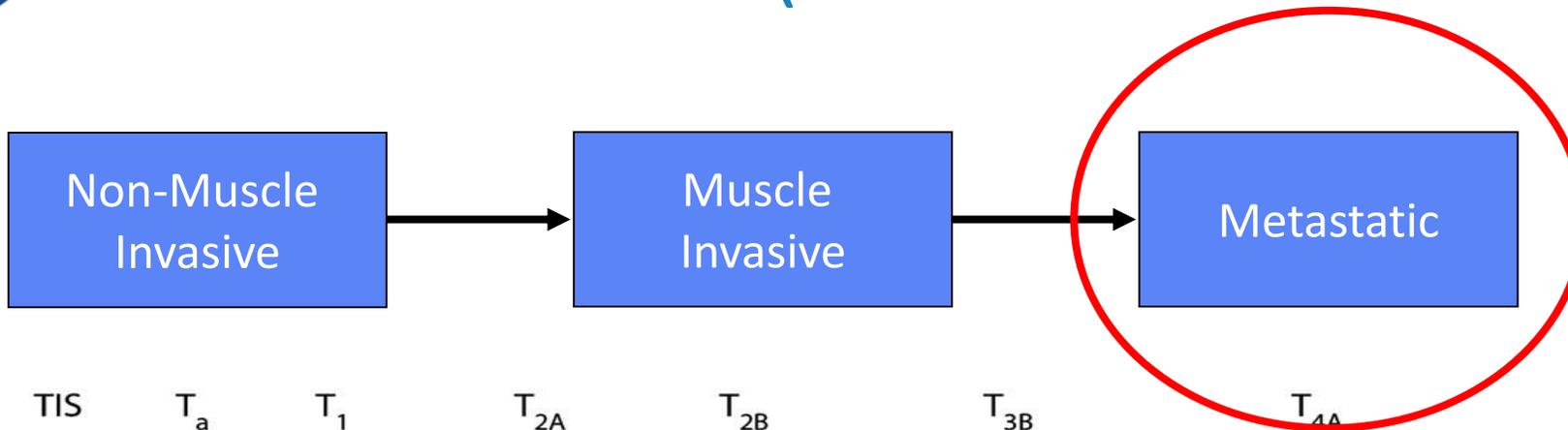
bevacizumab = anti-VEGF antibody

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

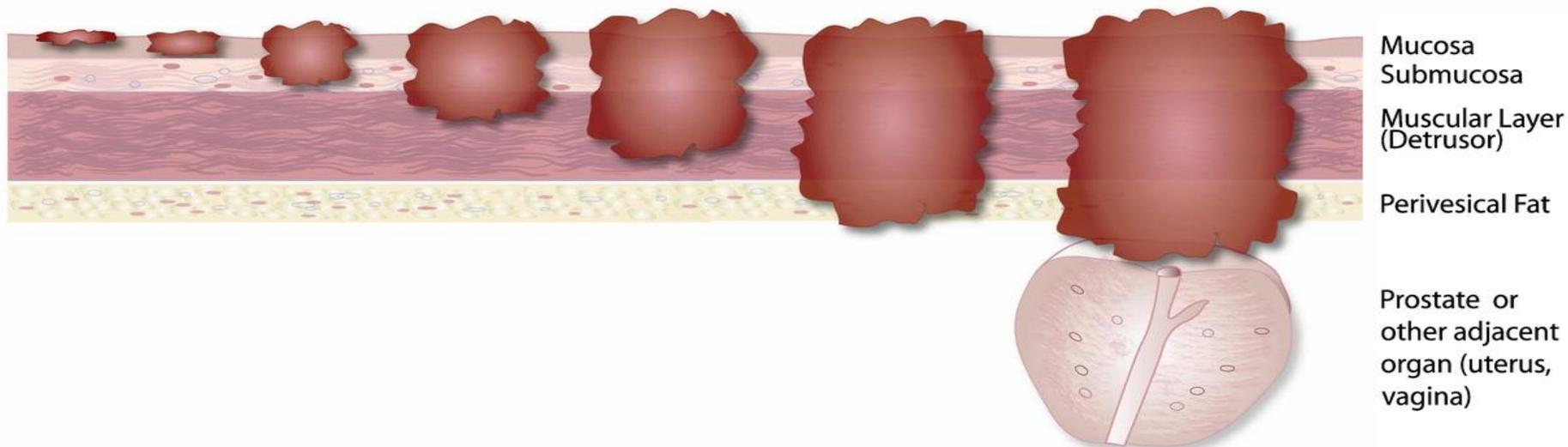


Motzer et al. ASCO GU 2018
 Escudier et al. ASCO 2018

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



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

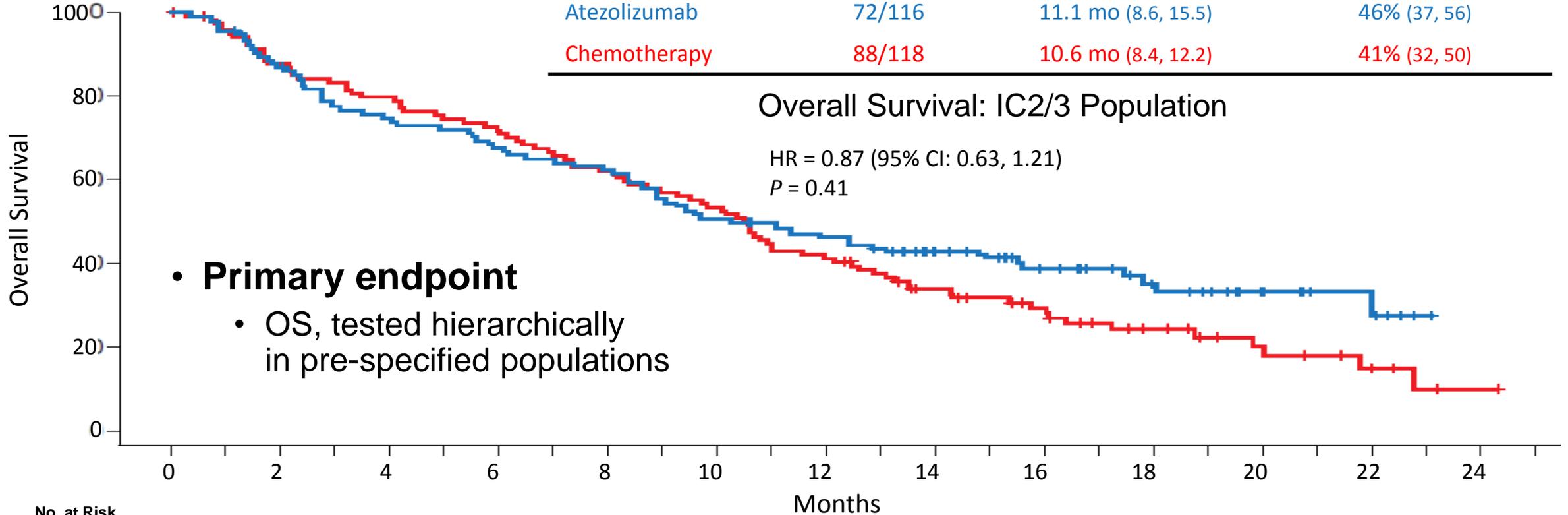
- 1) Nivolumab
- 2) Pembrolizumab

In development: Combinations

- 1) IO + IO
- 2) IO + Chemotherapy

Imvigor 211: Atezolizumab vs Chemo

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



- **Primary endpoint**
 - OS, tested hierarchically in pre-specified populations

No. at Risk

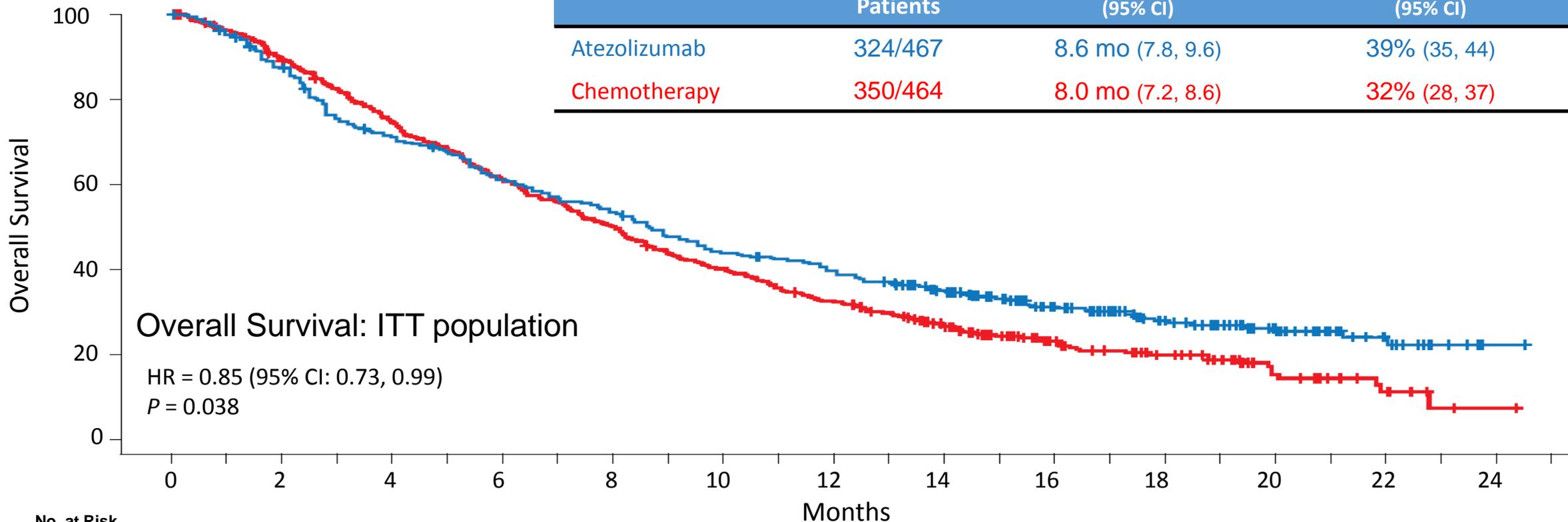
Atezolizumab
 Chemotherapy

Months	0	2	4	6	8	10	12	14	16	18	20	22	24
Atezolizumab	116	100	85	77	71	58	51	39	27	19	11	6	0
Chemotherapy	118	100	91	82	71	61	47	32	24	15	9	5	1

Powles T et al. Lancet 2018; 391:748-57.

Imvigor 211: Atezolizumab vs Chemo

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)

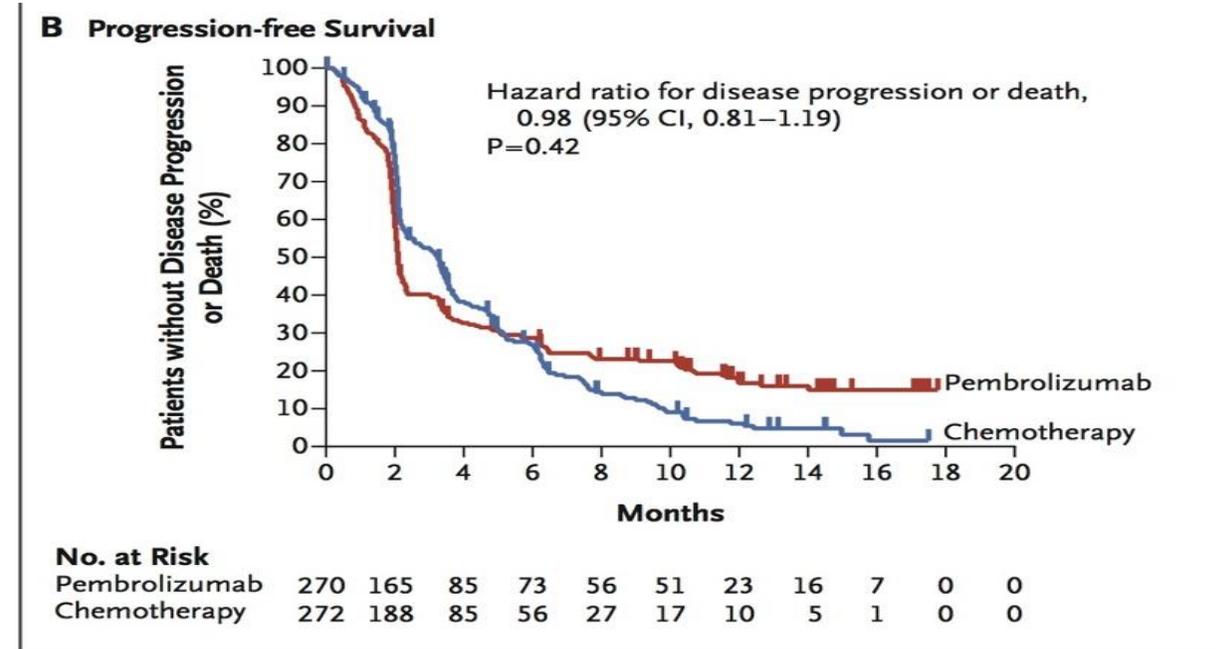
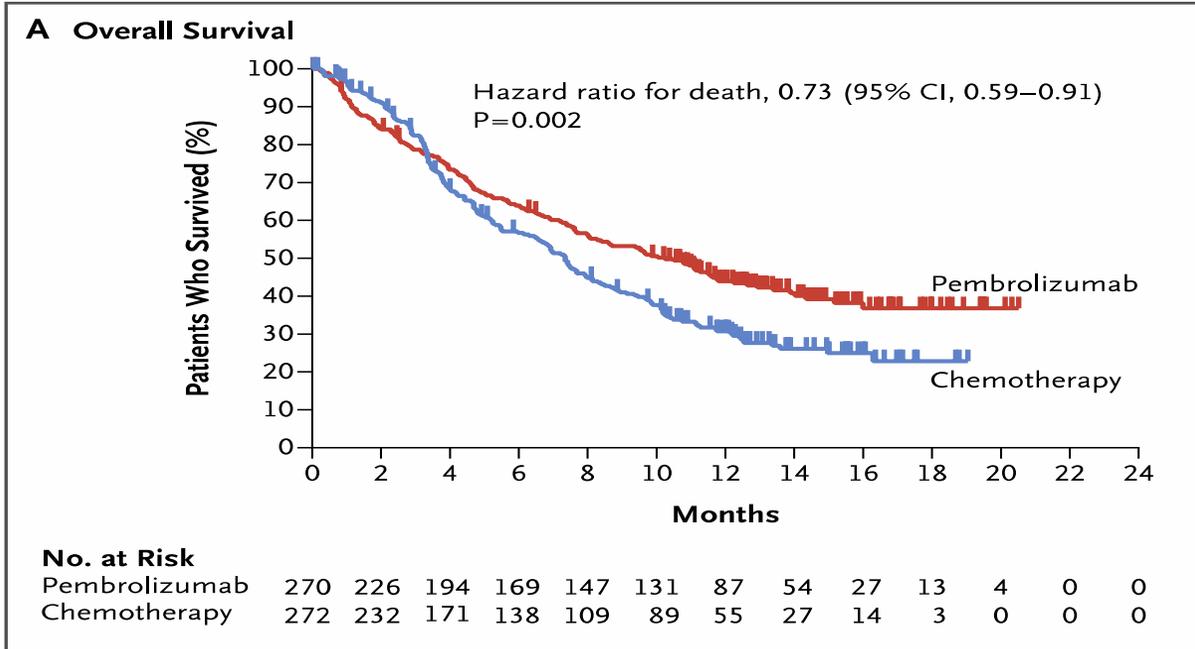


No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24
Atezolizumab	467	405	327	280	245	201	177	138	90	59	34	13	1
Chemotherapy	464	397	330	268	219	175	140	99	60	42	17	7	1

- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T et al. Lancet 2018; 391:748-57.

KEYNOTE-045: Pembrolizumab vs Chemo



- Primary endpoint: OS and PFS
- Median OS (pembro vs. chemo): 10.3 mos vs. 7.4 mos (P=0.002)
- Median PFS: 2.1 mos vs. 3.3 mos (P=NS)
 - 18 mos PFS: 16.8% vs. 3.5%
- Response rate: 21.1% vs. 11% (P=0.001)

Bellmunt J et al. N Engl J Med 2017; 376:1015-26.

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 $\geq 5\%$ of the tumor area

Anti-PD-1 Antibodies

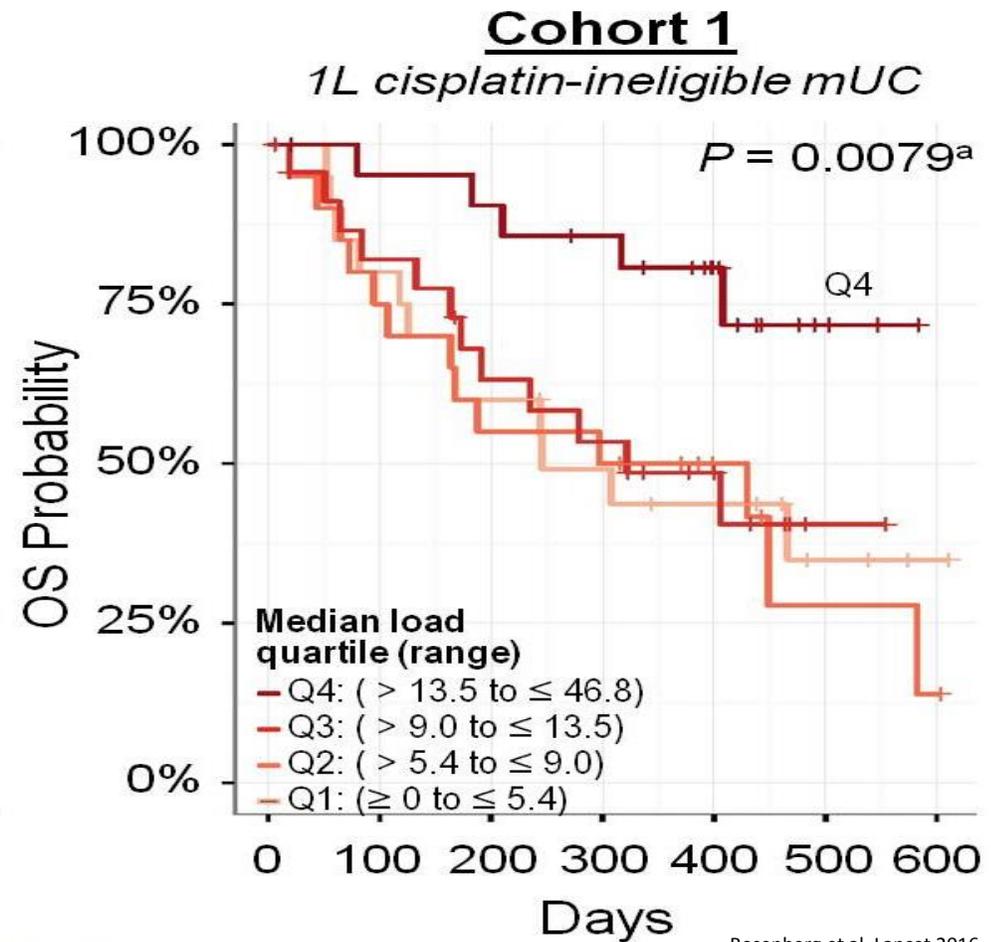
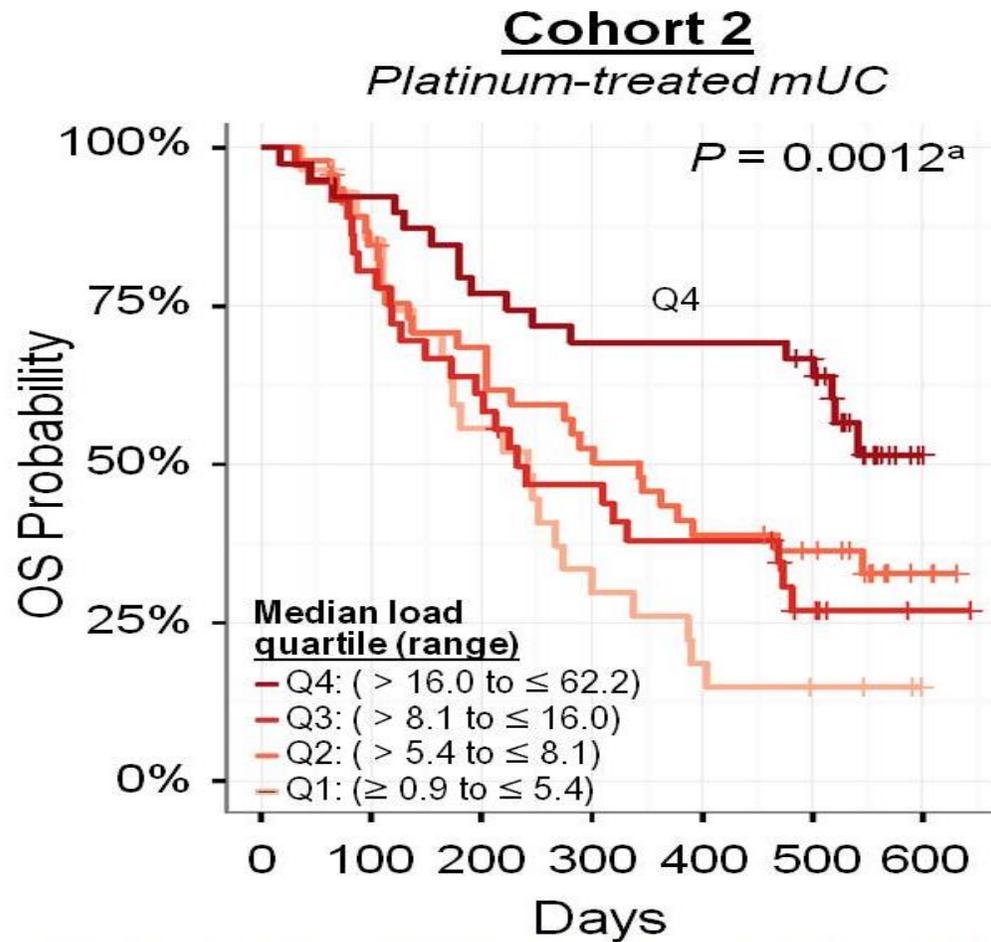
- 1) Pembrolizumab
 - PD-L1 CPS ≥ 10

In development: Combinations

- 1) IO + IO
- 2) IO + Chemotherapy

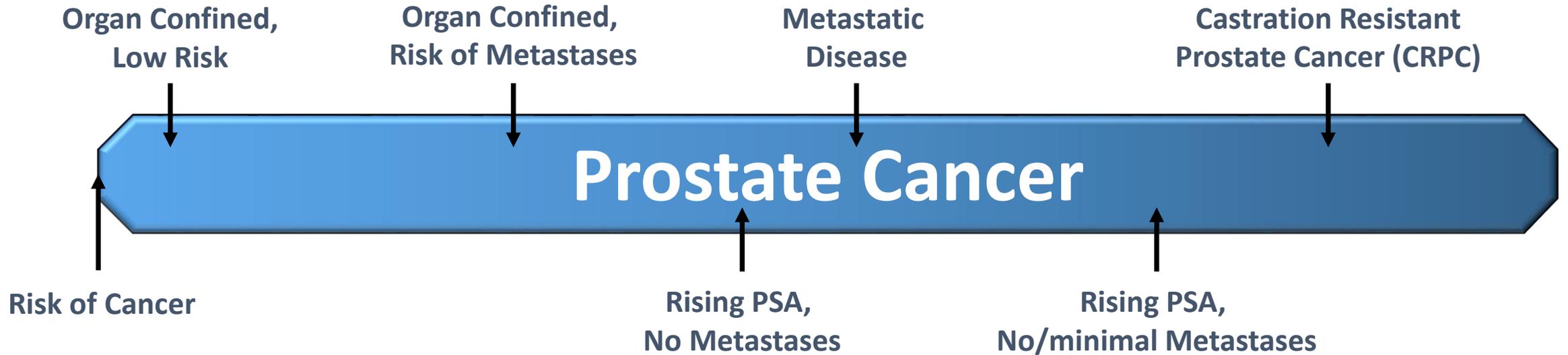
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



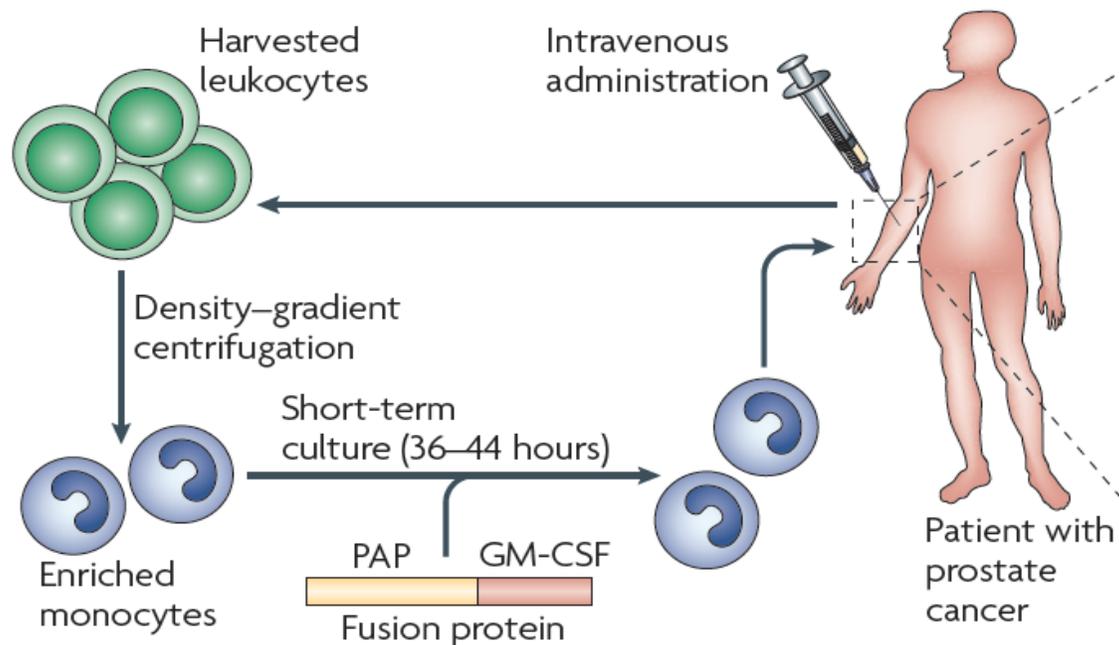
Rosenberg et al. Lancet 2016

The Spectrum of Prostate Cancer

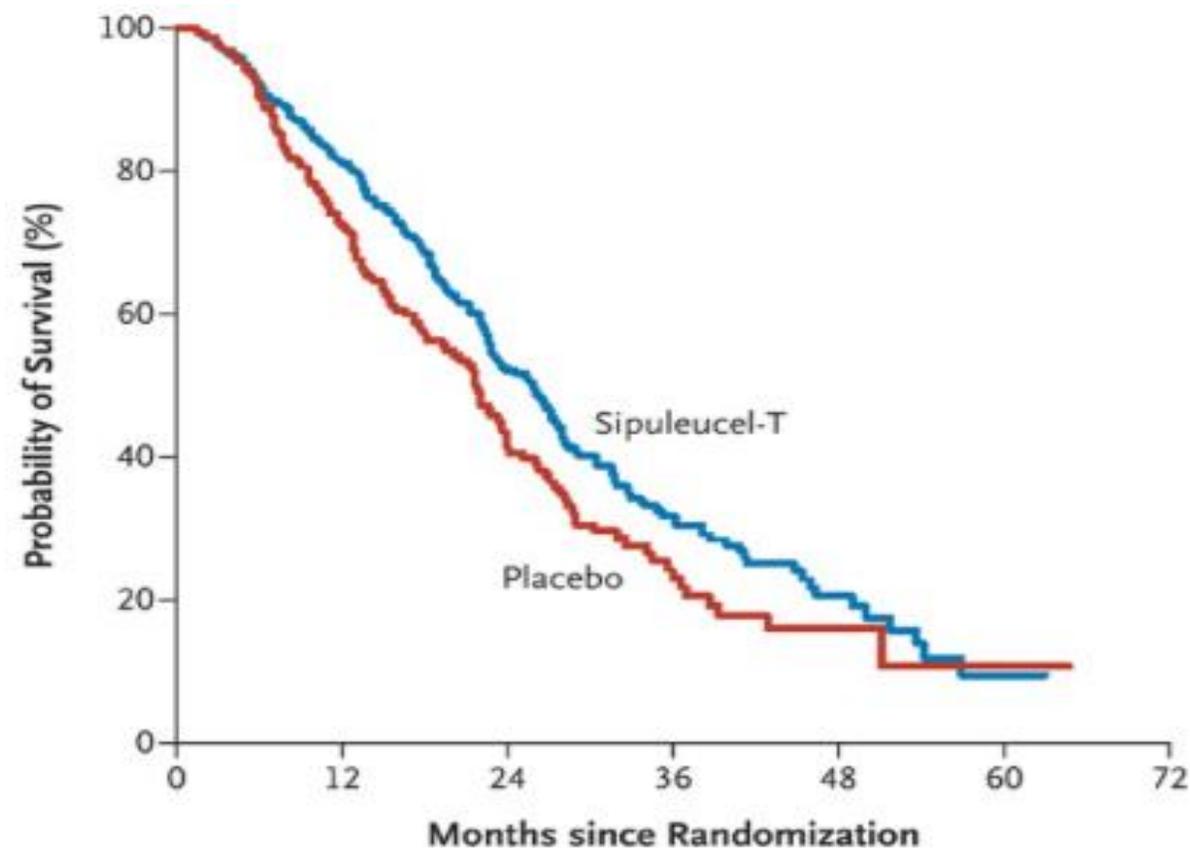


Sipuleucel-T in mCRPC

- First anticancer therapeutic vaccine



Drake et al. Curr Opin Urol 2010



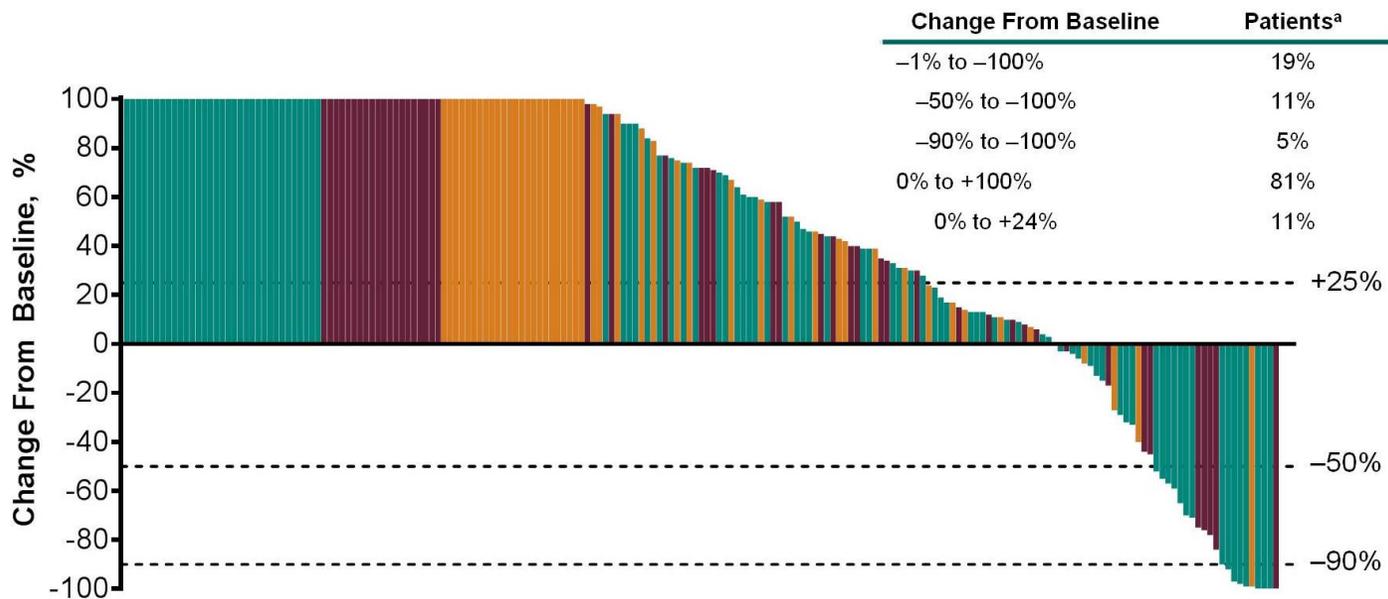
Kantoff et al. NEJM 2010

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

Ex. – KEYNOTE-199 (Pembrolizumab)

■ Cohort 1 (PD-L1+)
 ■ Cohort 2 (PD-L1-)
 ■ Cohort 3 (Any PD-L1; Bone)

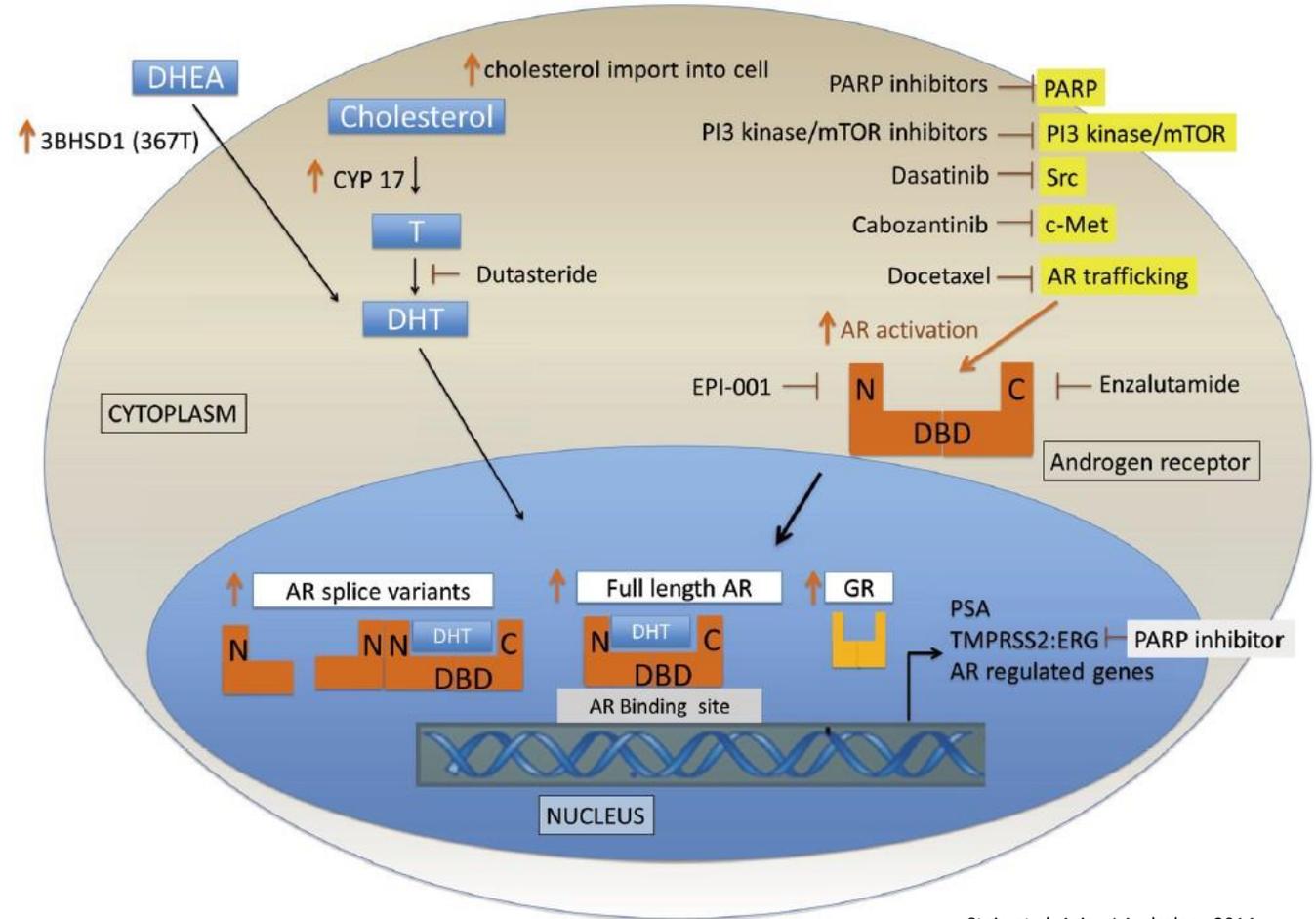


- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
 - Localized PC ~2%
 - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

DeBono et al. ASCO 2018

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	<ul style="list-style-type: none"> Corticosteroids not usually indicated 	<ul style="list-style-type: none"> Continue immunotherapy
2	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Hold immunotherapy during corticosteroid use Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids Start proton pump inhibitor for GI prophylaxis
3	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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**

 CrossMark

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

Brian I. Rini¹, David F. McDermott², Hans Hammers³, William Bro⁴, Ronald M. Bukowski⁵, Bernard Faba⁶, Jo Faba⁶, Robert A. Figlin⁷, Thomas Hutson⁸, Eric Jonasch⁹, Richard W. Joseph¹⁰, Bradley C. Leibovich¹¹, Thomas Olencki¹², Allan J. Pantuck¹³, David I. Quinn¹⁴, Virginia Seery², Martin H. Voss¹⁵, Christopher G. Wood⁹, Laura S. Wood¹ 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**

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

Ashish M. Kamat^{1*}, Joaquim Bellmunt², Matthew D. Galsky³, Badrinath R. Konety⁴, Donald L. Lamm⁵, David Langham⁶, Cheryl T. Lee⁷, Matthew I. Milowsky⁸, Michael A. O'Donnell⁹, Peter H. O'Donnell¹⁰, Daniel P. Petrylak¹¹, Padmanee Sharma¹², Ella C. Skinner¹³, Guru Sonpavde¹⁴, John A. Taylor III¹⁵, Prasanth Abraham¹⁶ and Jonathan E. Rosenberg¹⁷

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**

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

Douglas G. McNeel¹, Neil H. Bander², Tomasz M. Beer³, Charles G. Drake⁴, Lawrence Fong⁵, Stacey Harrelson⁶, Philip W. Kantoff⁷, Ravi A. Madan⁸, William K. Oh⁹, David J. Peace¹⁰, Daniel P. Petrylak¹¹, Hank Porterfield¹², Oliver Sartor¹³, Neal D. Shore⁶, Susan F. Slovin⁷, Mark N. Stein¹⁴, Johannes Vieweg¹⁵ 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: Prostate Cancer

You are seeing a 68 y/o man who was diagnosed with a Gleason 5+4 prostate cancer 5 years ago. He had evidence of metastases to the bone and retroperitoneal lymph nodes, and was started on treatment with leuprolide and bicalutamide. His PSA initially declined, but then began rising two years ago, and the bicalutamide was discontinued. His PSA continued to slowly rise, and is currently 5 ng/mL. Bone scan shows new metastases, but he remains asymptomatic. No new liver or other visceral disease. What are appropriate immunotherapy treatment options for him?

- A. Nivolumab
- B. Sipuleucel-T
- C. Pembrolizumab
- D. B or C

Case Study 3: 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