Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Malignancies

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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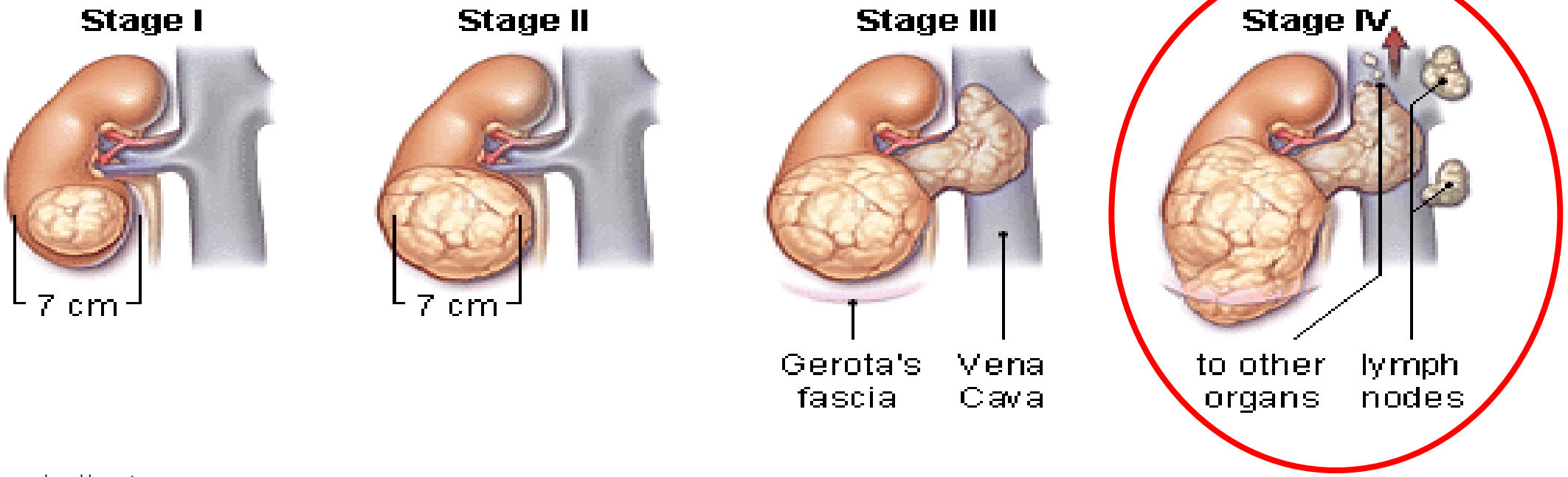
Disclosures

- Research funding: Syndax, Merck, Genenetech
- I will not be discussing non-FDA approved indications during my presentation.

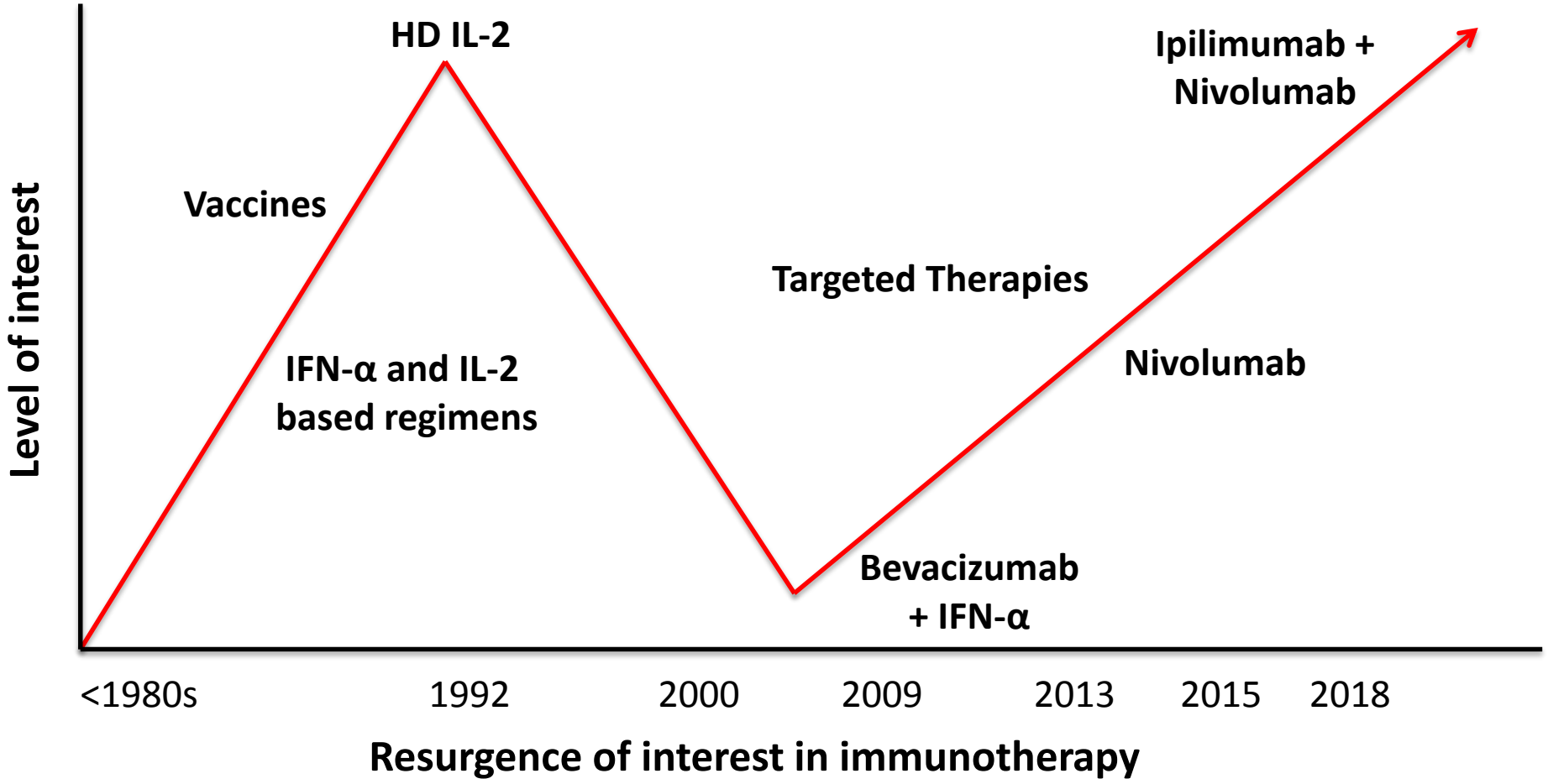
Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)

Surgically resectable → Oligo-metastatic → Metastatic



reemakeup.blogspot.com

History of Immunotherapy in mRCC



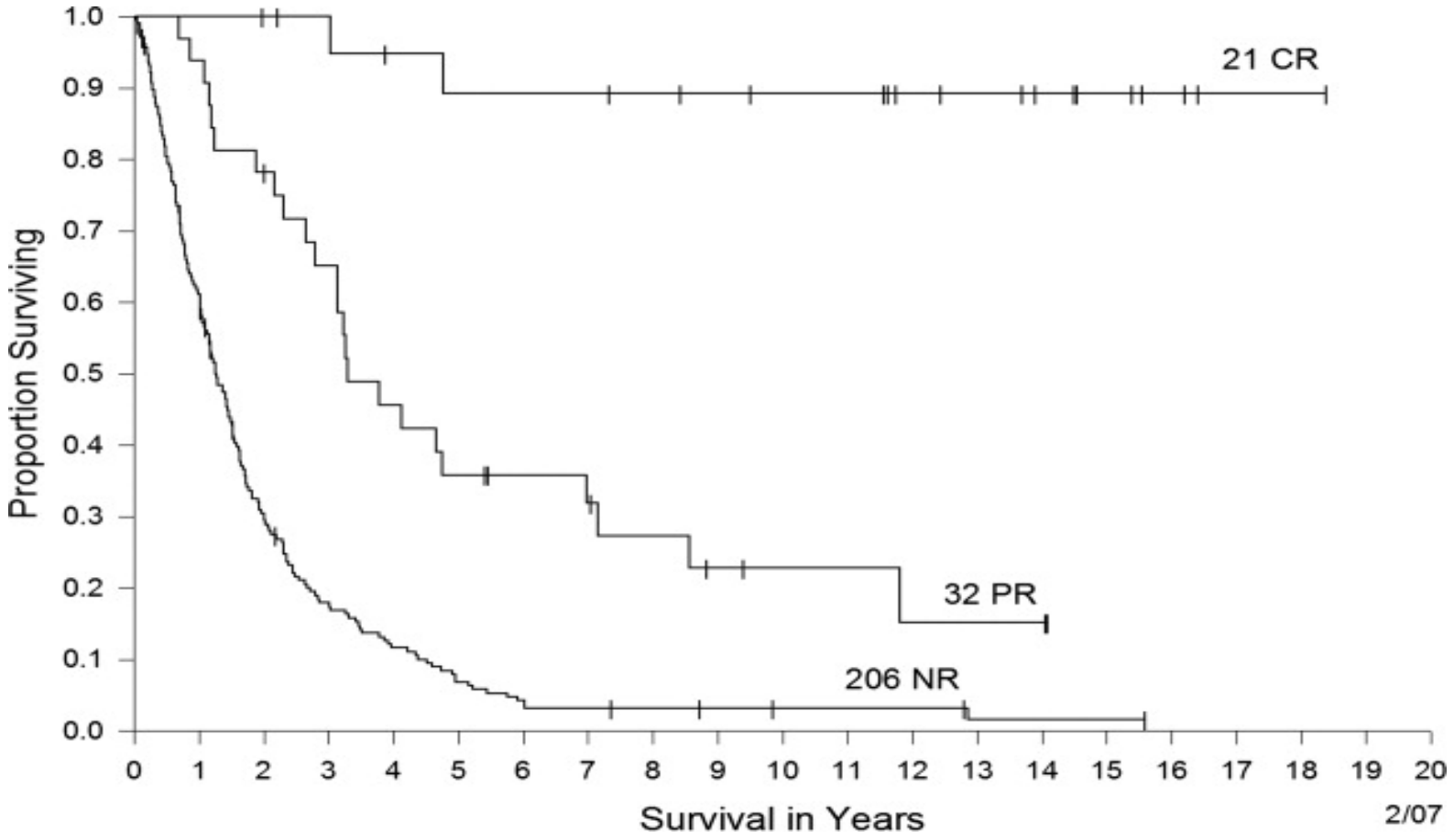
FDA-approved Immunotherapies for mRCC

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)

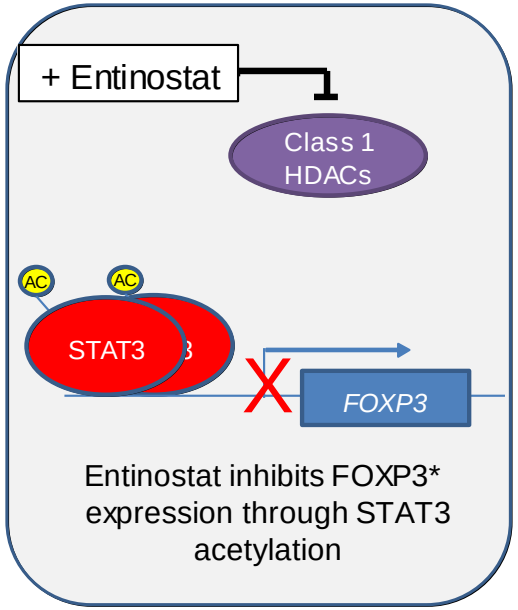
High Dose IL-2 in mRCC

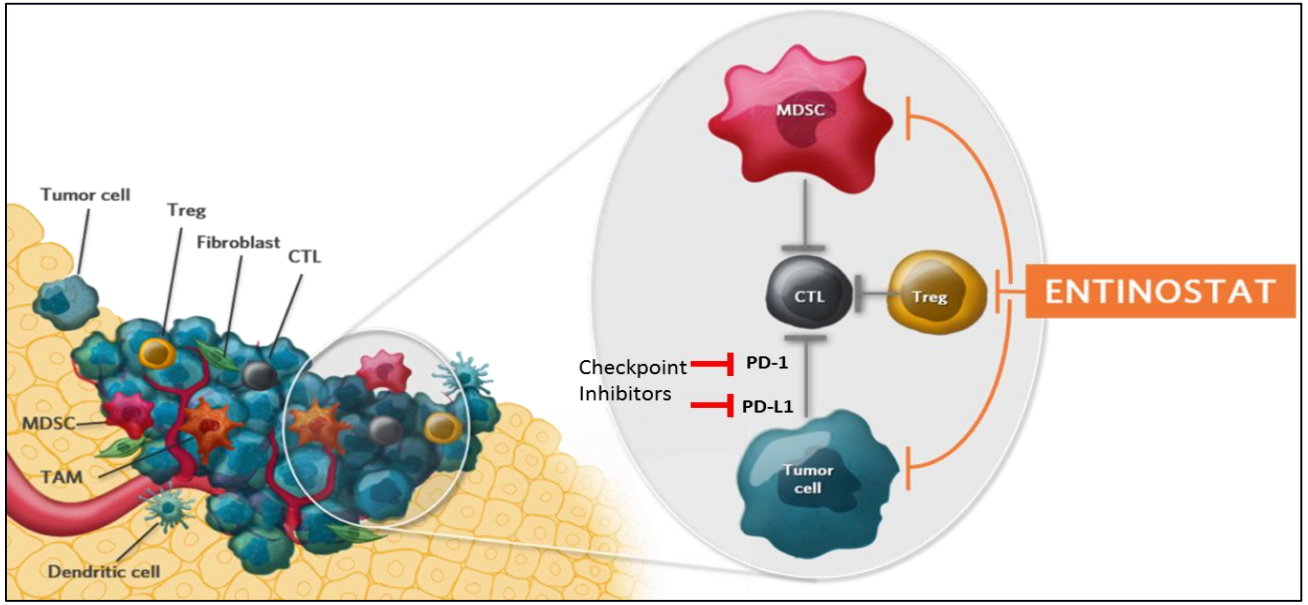
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months

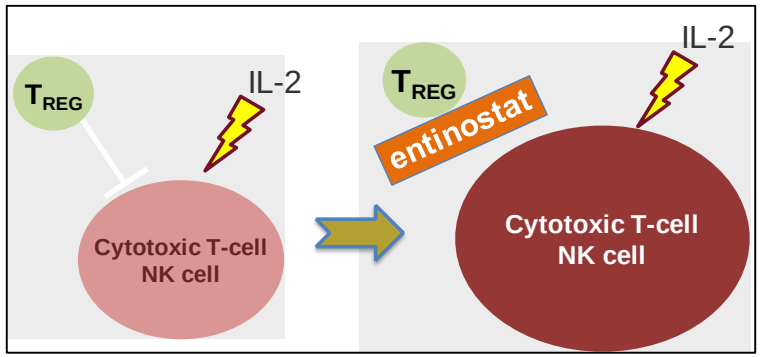


Klapper et al. Cancer 2008

Proposed mechanism(s) of action of HDAC inhibitors to enhance immunotherapies in RCC

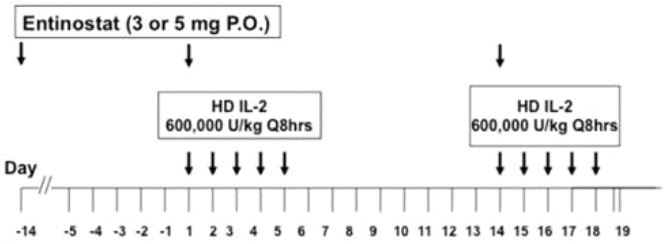


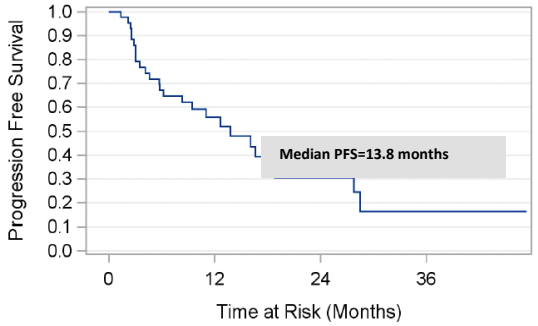




Kato Y & Pili R Clin Cancer Res 2007; Shen L & Pili R PLoS ONE 2012; Pili R et al Clin Cancer Res 2017

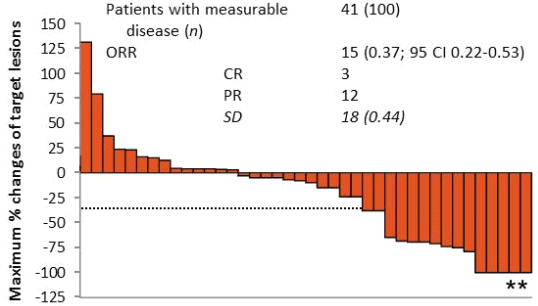
Combination of high-dose IL-2 and the HDAC inhibitor entinostat



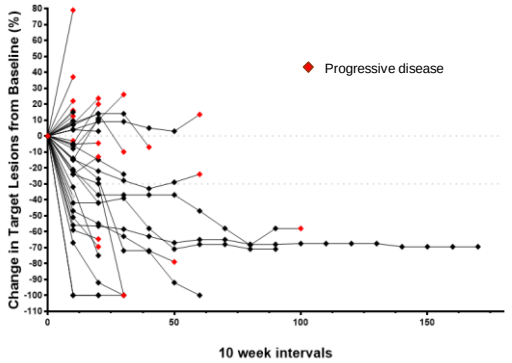


Unadjusted Kaplan Meier Estimates

Objective response	*N* (%)
Patients with measurable disease (*n*)	41 (100)
ORR	15 (0.37; 95 CI 0.22-0.53)
CR	3
PR	12
SD	*18 (0.44)*



* Subcentimeter non-target lesions present

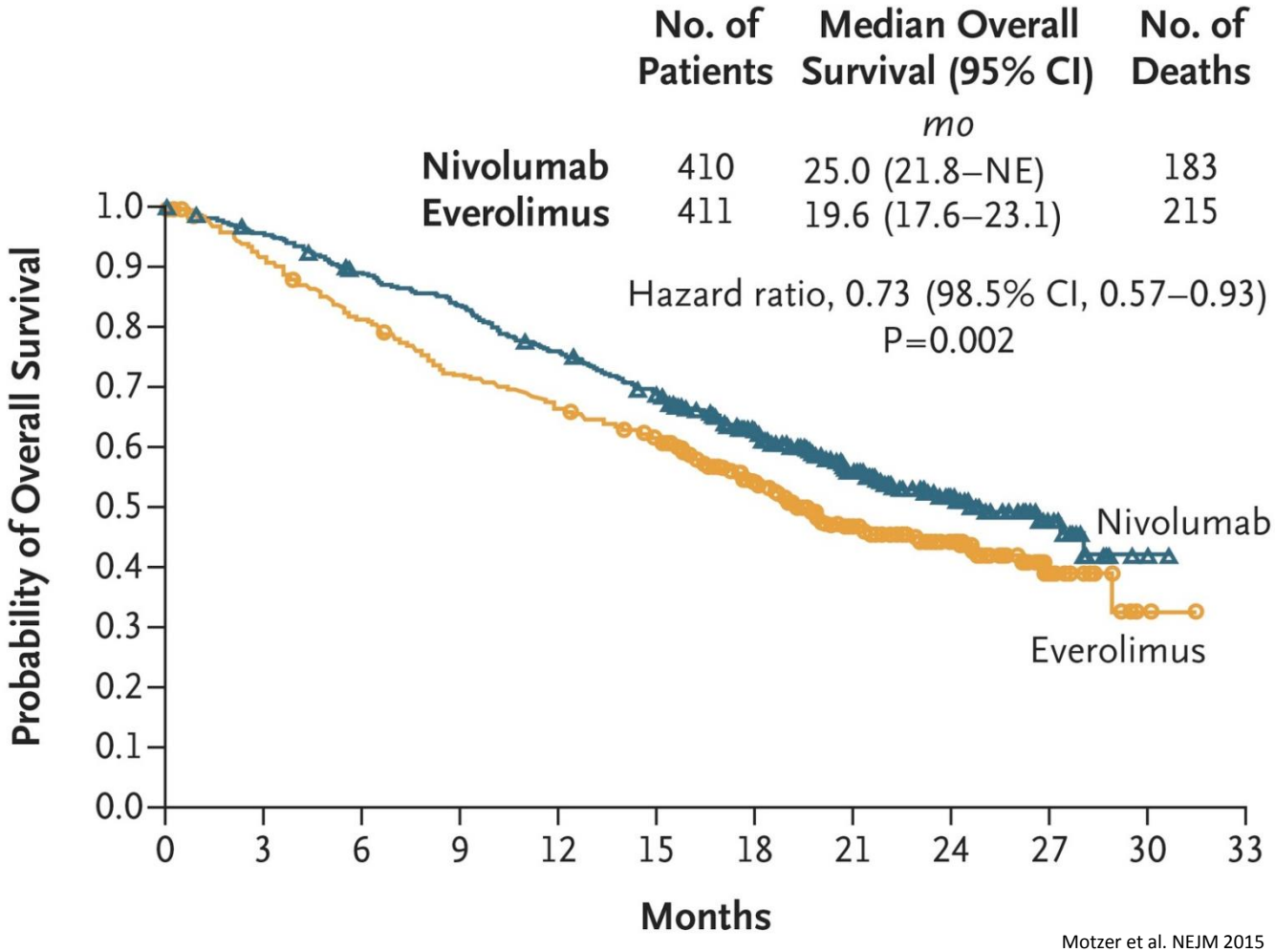


Patients with metastatic kidney cancer → **Clinical Trial Enrollment** → **Randomized Phase II study of HD-IL2 +/- entinostat (HCRN)**

Kato Y & Pili R Clin Cancer Res 2007; Pili R et al Clin Cancer Res 2017

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)

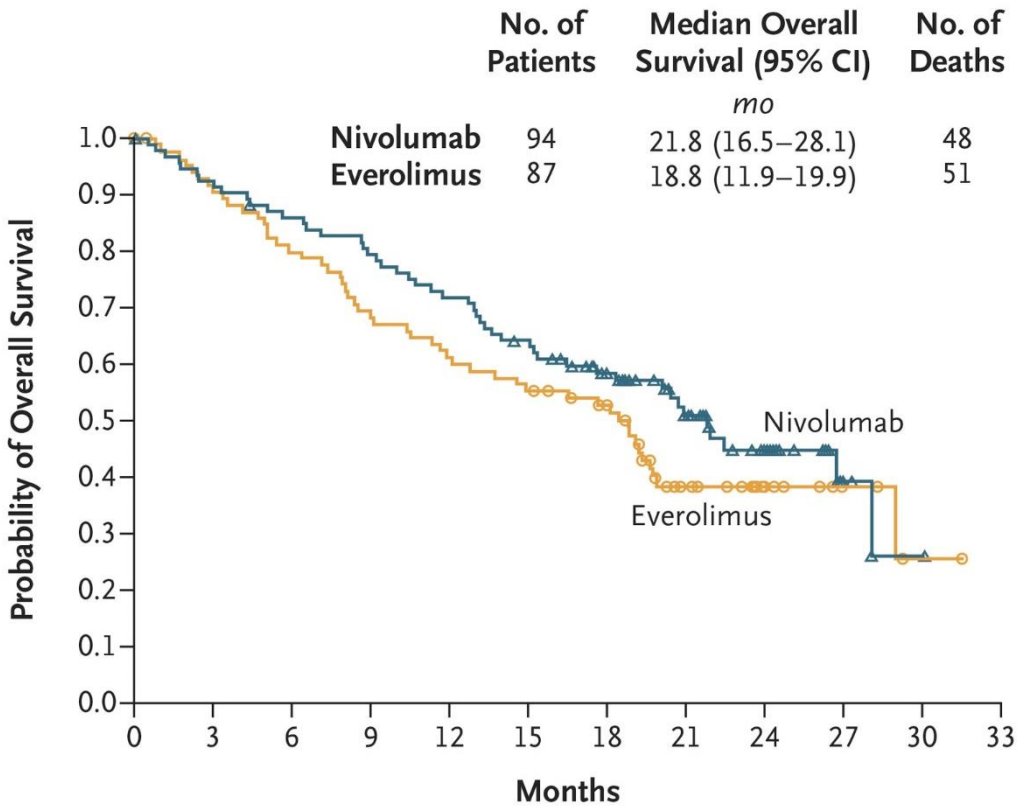


Motzer et al. NEJM 2015

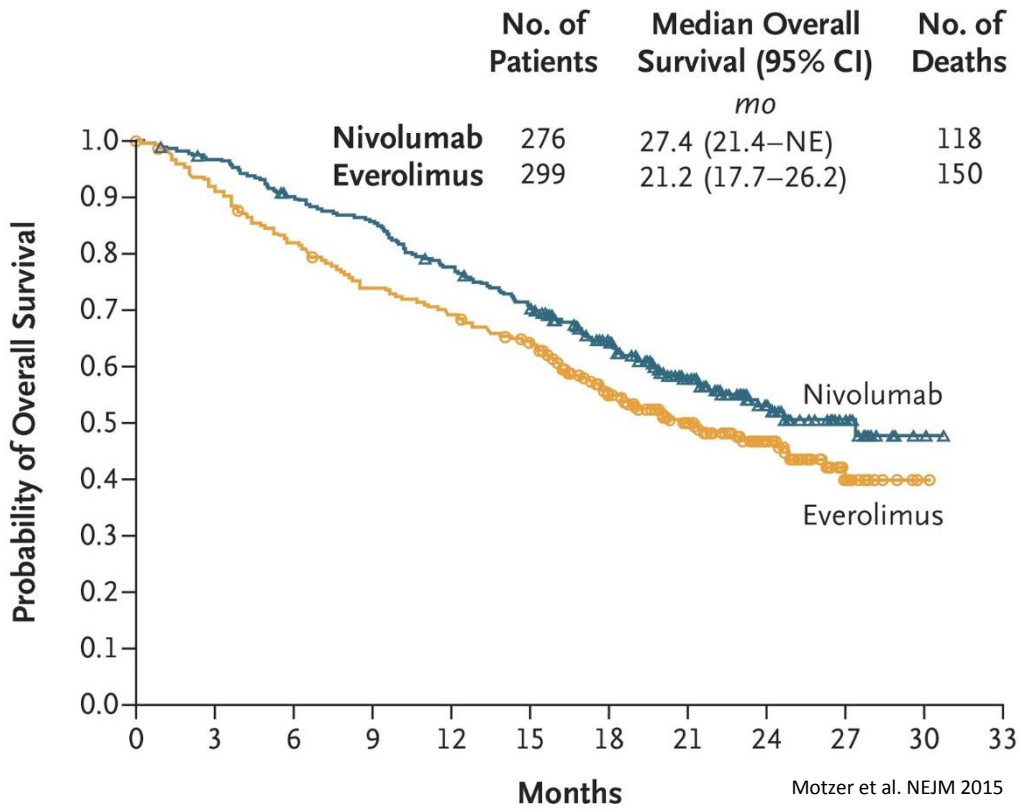
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%



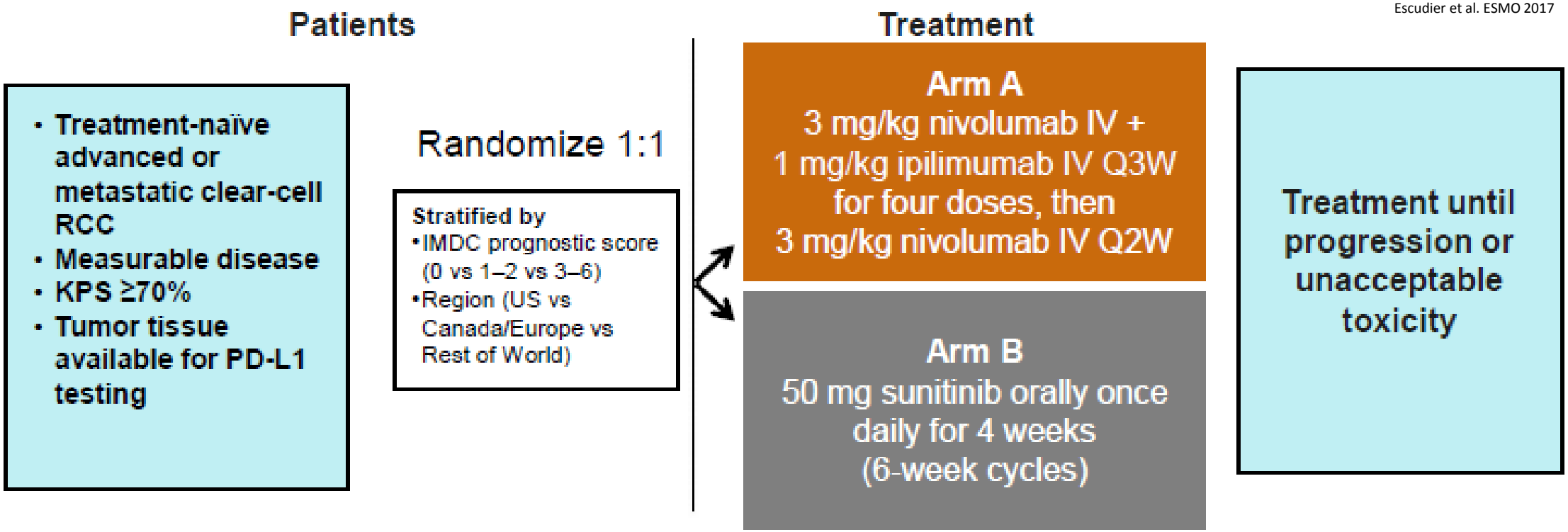
PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC

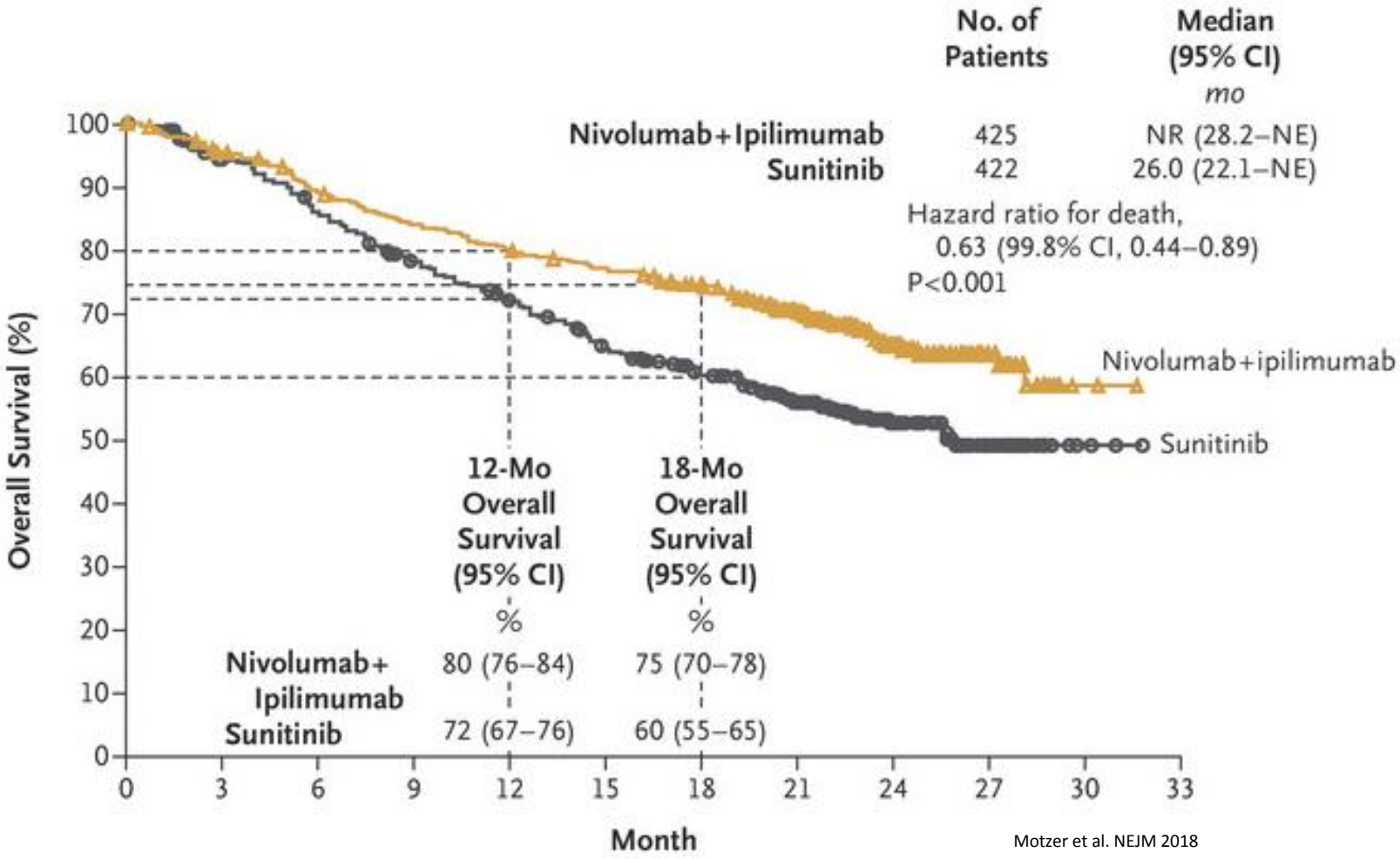
Escudier et al. ESMO 2017



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

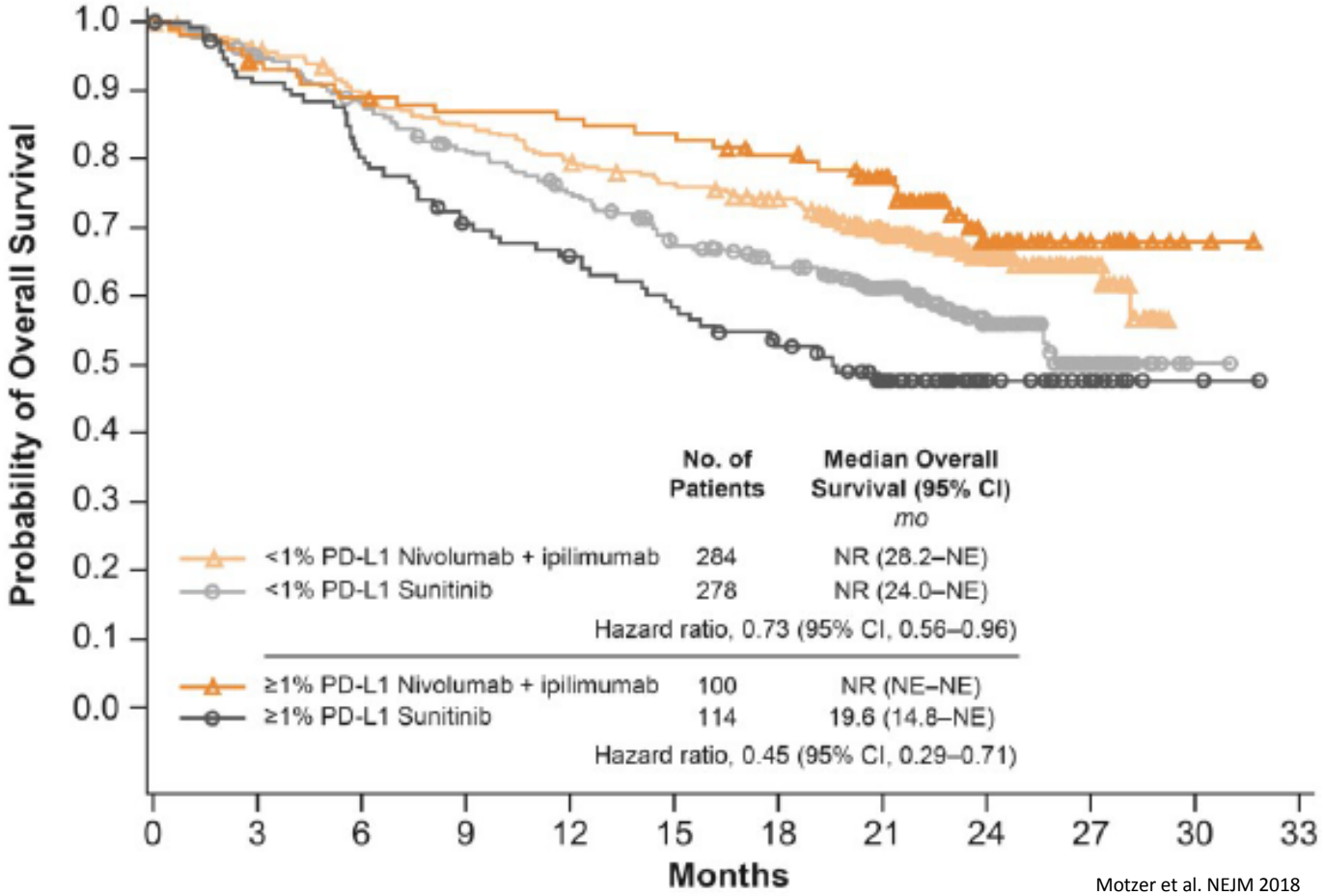
First-line Nivolumab + Ipilimumab in mRCC



Motzer et al. NEJM 2018

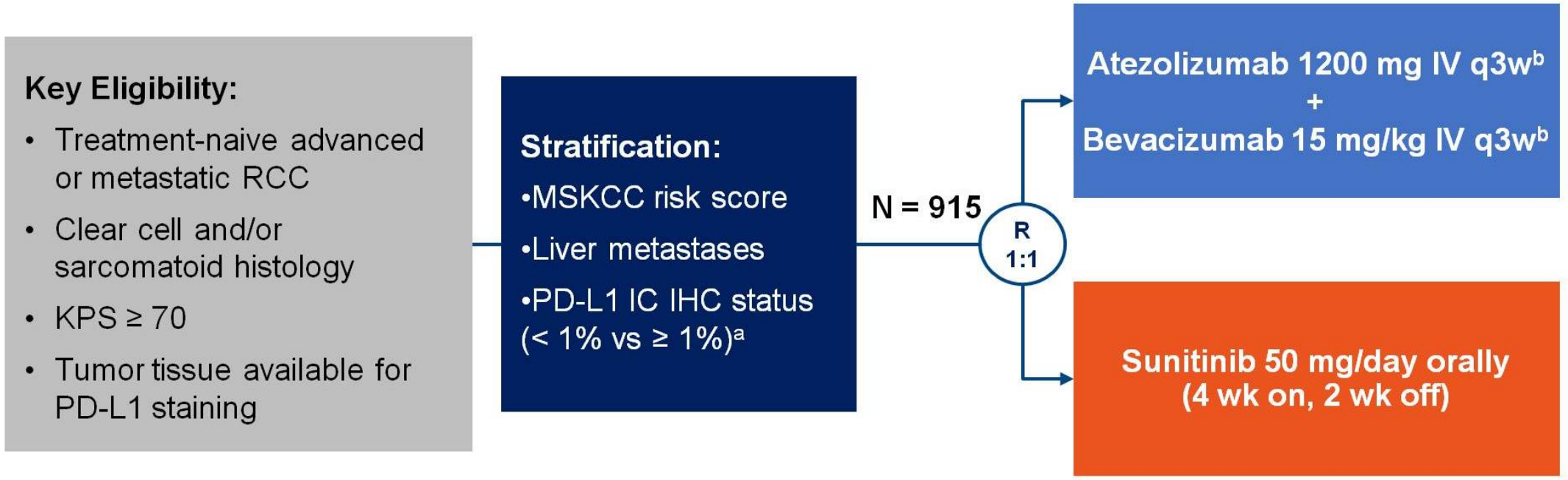
First-line Nivolumab + Ipilimumab in mRCC

PD-L1 Subgroups



Motzer et al. NEJM 2018

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

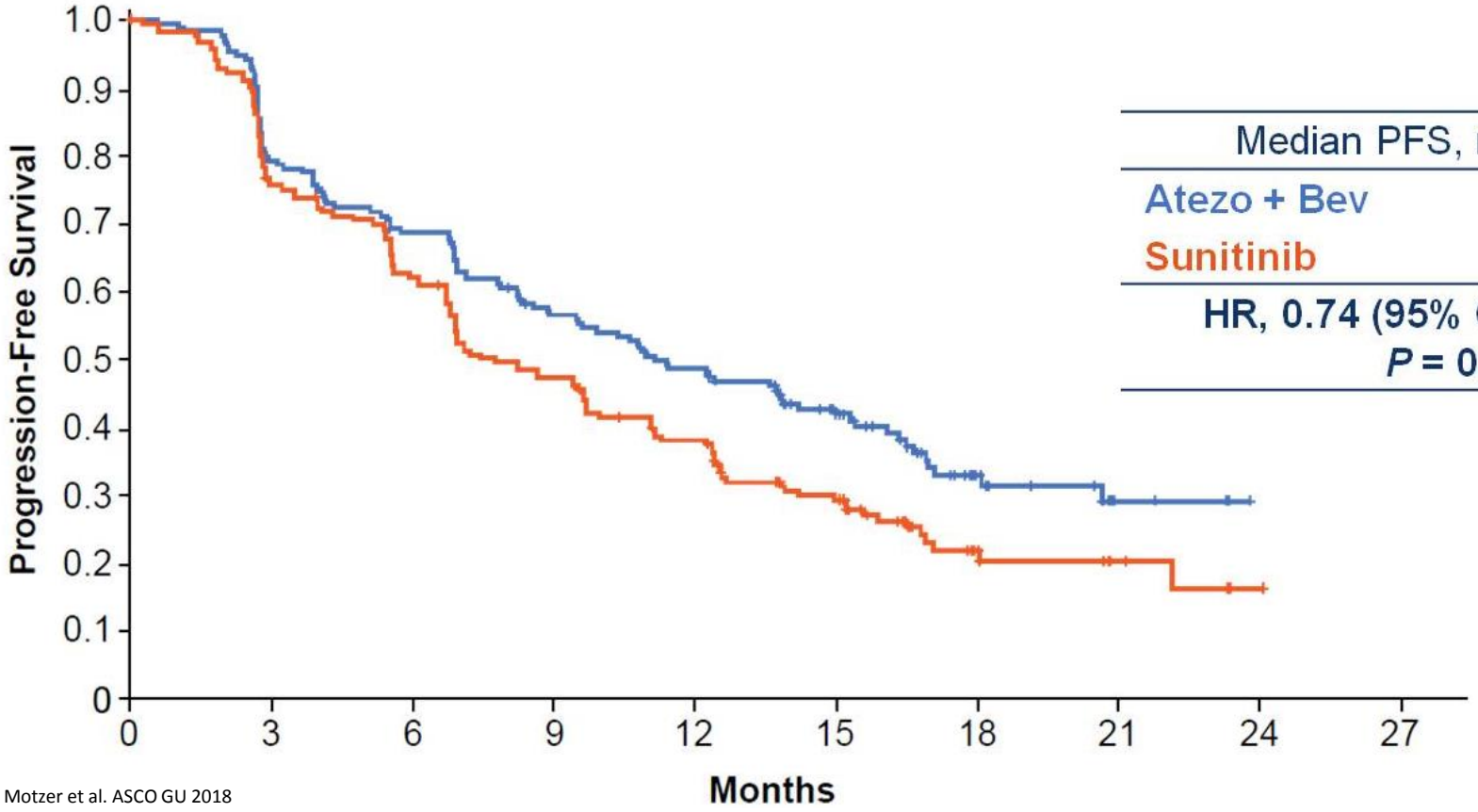


Motzer et al. ASCO GU 2018

Atezolizumab = anti-PD-L1 antibody

bevacizumab = anti-VEGF antibody

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



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

Immunomodulation by HDAC inhibition

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Cancer Therapy: Preclinical

Synergistic *In vivo* Antitumor Effect of the Histone Deacetylase Inhibitor MS-275 in Combination with Interleukin 2 in a Murine Model of Renal Cell Carcinoma

Yukihiko Kato,[1] Kiyoshi Yoshimura,[1] Tahiro Shin,[2] Henk Verheul,[1] Hans Hammers,[1] Tolib B. Sanni,[1] Brenda C. Salumbides,[1] Karen Van Erp,[1] Richard Schulick,[1] and Roberto Pili[1]

OPEN ACCESS Freely available online — PLoS one

Class I Histone Deacetylase Inhibitor Entinostat Suppresses Regulatory T Cells and Enhances Immunotherapies in Renal and Prostate Cancer Models

Li Shen[1], Michael Ciesielski[2], Swathi Ramakrishnan[1], Kiersten M. Miles[1], Leigh Ellis[1], Paula Sotomayor[1], Protul Shrikant[3], Robert Fenstermaker[2], Roberto Pili[1]*

Published OnlineFirst September 22, 2017; DOI: 10.1158/1078-0432.CCR-17-1178

Cancer Therapy: Clinical — Clinical Cancer Research

Immunomodulation by Entinostat in Renal Cell Carcinoma Patients Receiving High-Dose Interleukin 2: A Multicenter, Single-Arm, Phase I/II Trial (NCI-CTEP#7870)

Roberto Pili[1], David I. Quinn[2], Hans J. Hammers[3], Paul Monk[4], Saby George[5], Tanya B. Dorff[2], Thomas Olencki[4], Li Shen[5], Ashley Orillion[5], Dominick Lamonica[5], Roberto S. Fragomeni[3], Zsolt Szabo[3], Alan Hutson[6], Adrienne Groman[5], Susan M. Perkins[1], Richard Piekarz[6], and Michael A. Carducci[3]

Published OnlineFirst July 11, 2017; DOI: 10.1158/1078-0432.CCR-17-0741

Cancer Therapy: Preclinical — Clinical Cancer Research

Entinostat Neutralizes Myeloid-Derived Suppressor Cells and Enhances the Antitumor Effect of PD-1 Inhibition in Murine Models of Lung and Renal Cell Carcinoma

Ashley Orillion[1,2], Ayumi Hashimoto[3], Nur Damayanti[1], Li Shen[4], Remi Adelaiye-Ogala[1,5], Sreevani Arisa[1], Sreenivasulu Chintala[1], Peter Ordentlich[6], Chingai Kao[7], Bennett Elzey[7,8], Dmitry Gabrilovich[3], and Roberto Pili[1,7]

MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

A Phase I/Ib, Open Label, Dose Finding Study to Evaluate Safety, Pharmacodynamics and Efficacy of Pembrolizumab (MK-3475) in Combination with Vorinostat in Patients with Advanced Prostate, Renal or Urothelial Cell Carcinoma

Protocol Number:
IUSCC-0551

PROTOCOL

TITLE:	A PHASE I/II STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH ENTINOSTAT AND BEVACIZUMAB IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA
IUSCC STUDY NUMBER:	IUSCC-0574

B1G CANCER RESEARCH CONSORTIUM

Clinical Study Protocol
BTCRC-GU17-094

A Phase II Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Entinostat in Combination with Nivolumab plus Ipilimumab in Patients with Renal Cell Carcinoma Previously Treated with Nivolumab plus Ipilimumab

Sponsor Investigator
Roberto Pili, MD
Indiana University Melvin and Bren Simon Cancer Center

hoosier CANCER RESEARCH NETWORK

Clinical Study Protocol
HCRN GU17-289

A Phase II Randomized, Open label Study of High Dose Interleukin 2 *vs* High Dose Interleukin 2 *plus* Entinostat in Untreated Advanced Renal Cell Carcinoma HCRN GU17-289

Sponsor Investigator
Roberto Pili, MD
Indiana University

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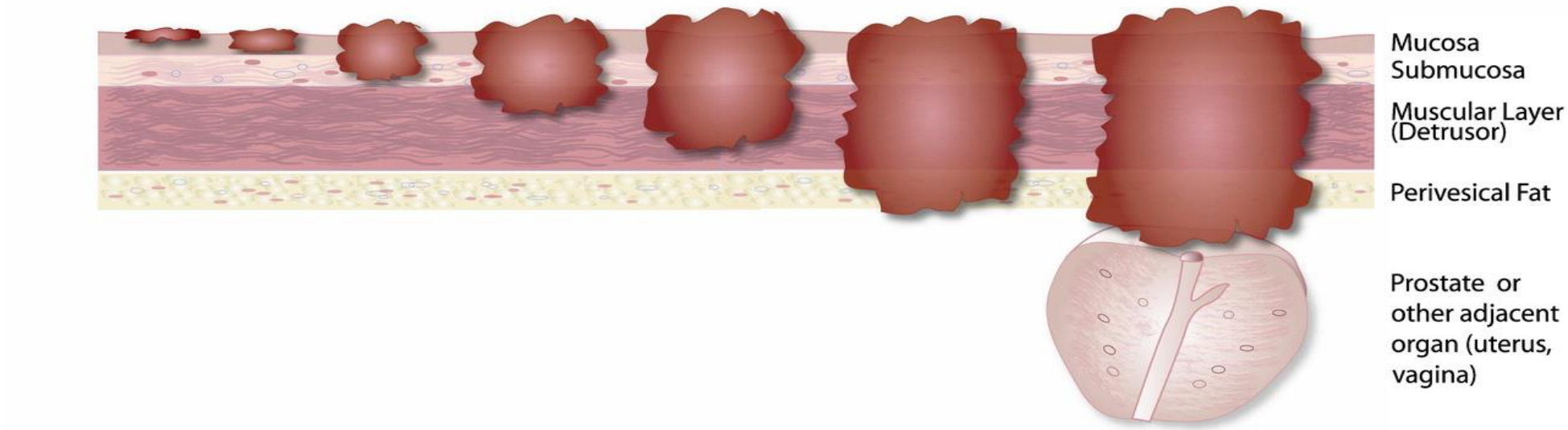
Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)

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 Inelgible

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

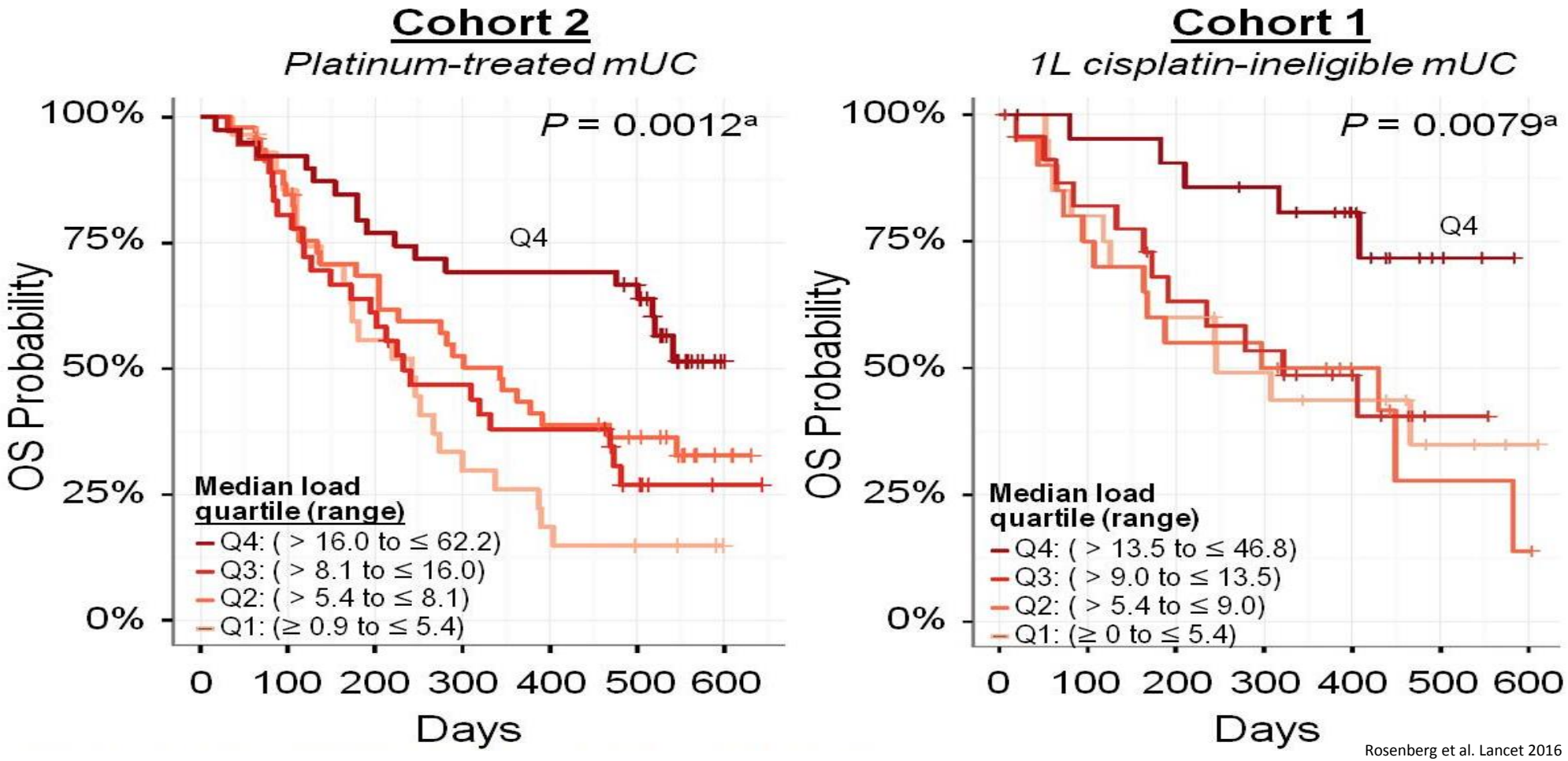
In development: Combinations

1) IO + IO
2) IO + Chemotherapy

Ghatalia et al. Ther Adv Med Oncol 2018

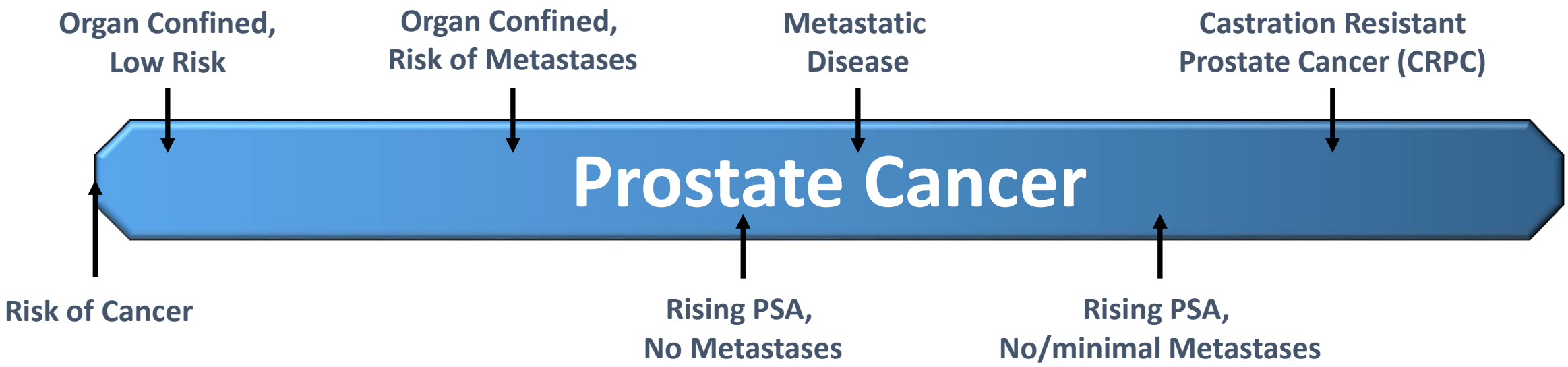
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



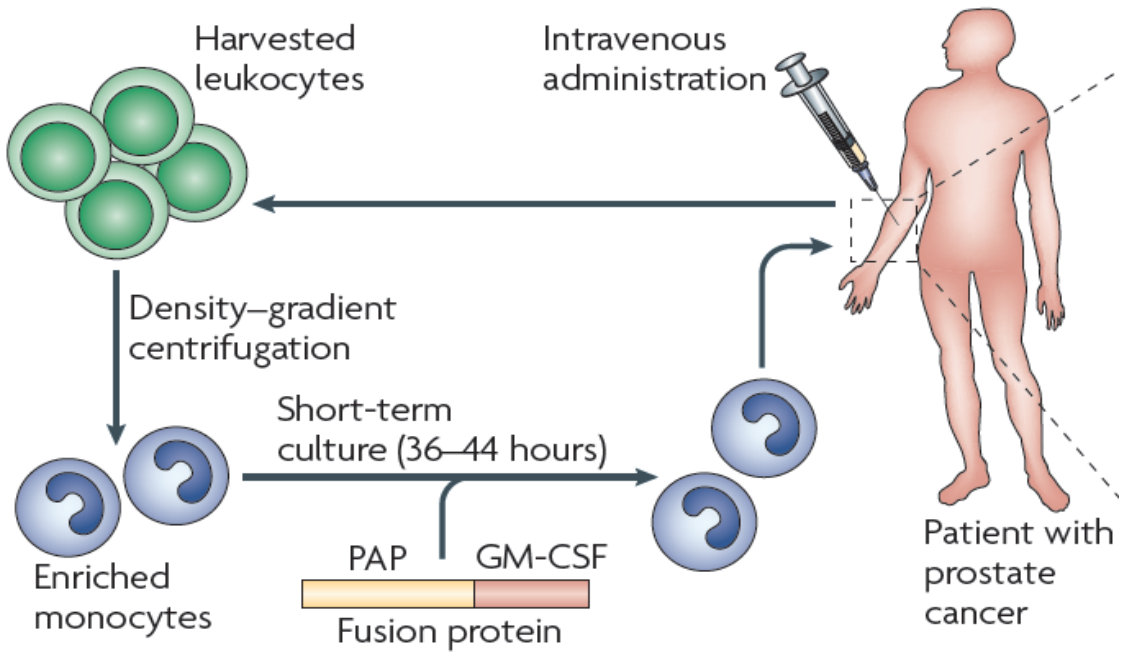
Rosenberg et al. Lancet 2016

The Spectrum of Prostate Cancer

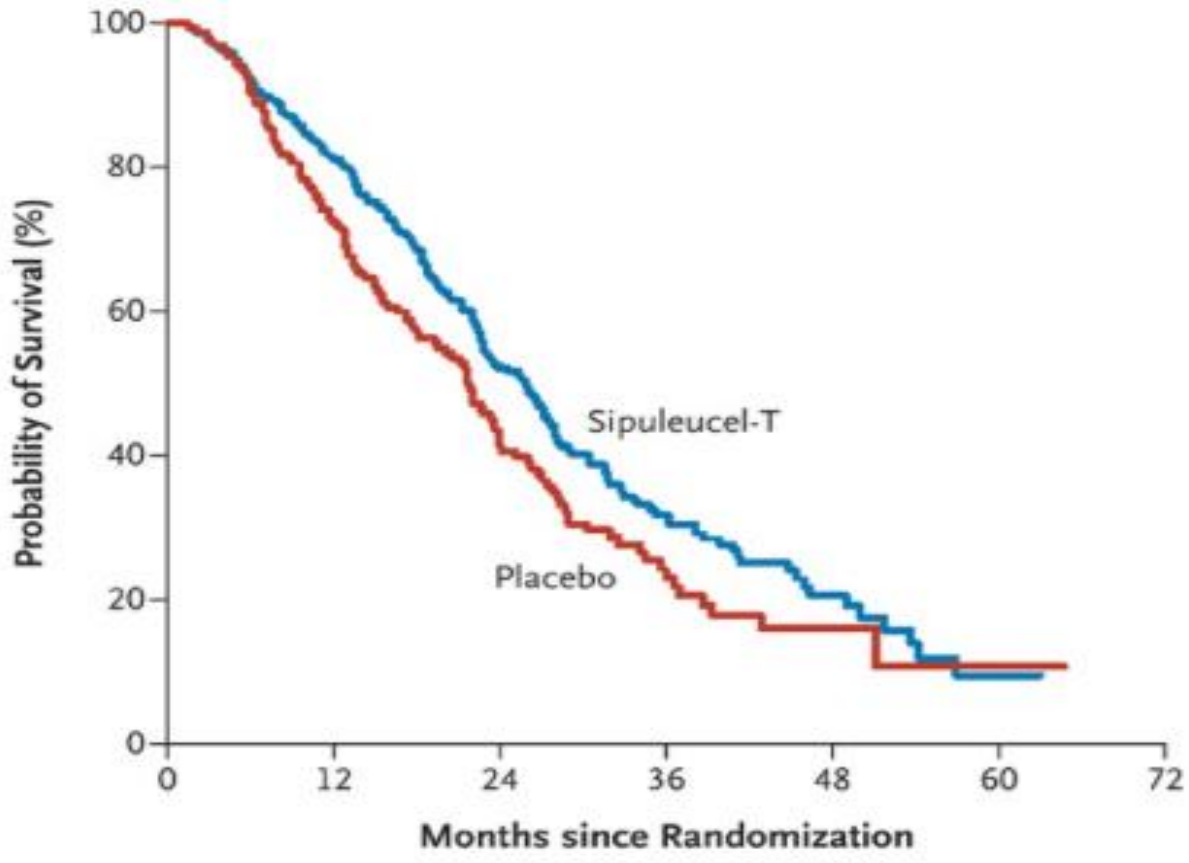


Sipuleucel-T in mCRPC

- First anticancer therapeutic vaccine

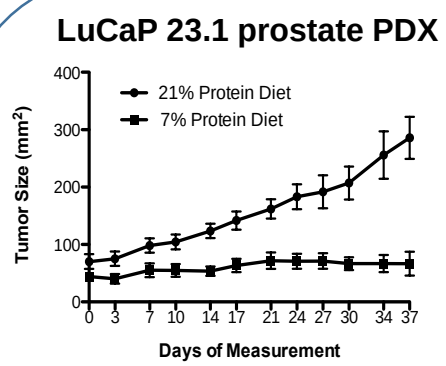


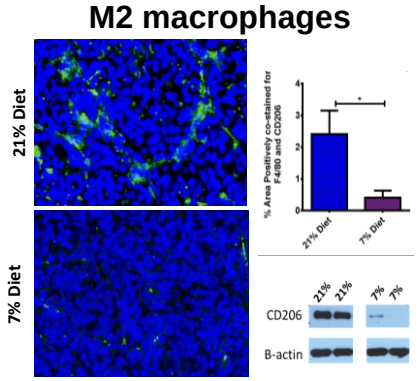
Drake et al. Curr Opin Urol 2010

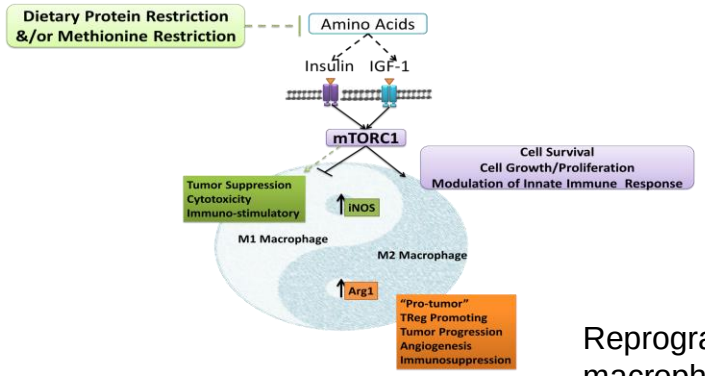


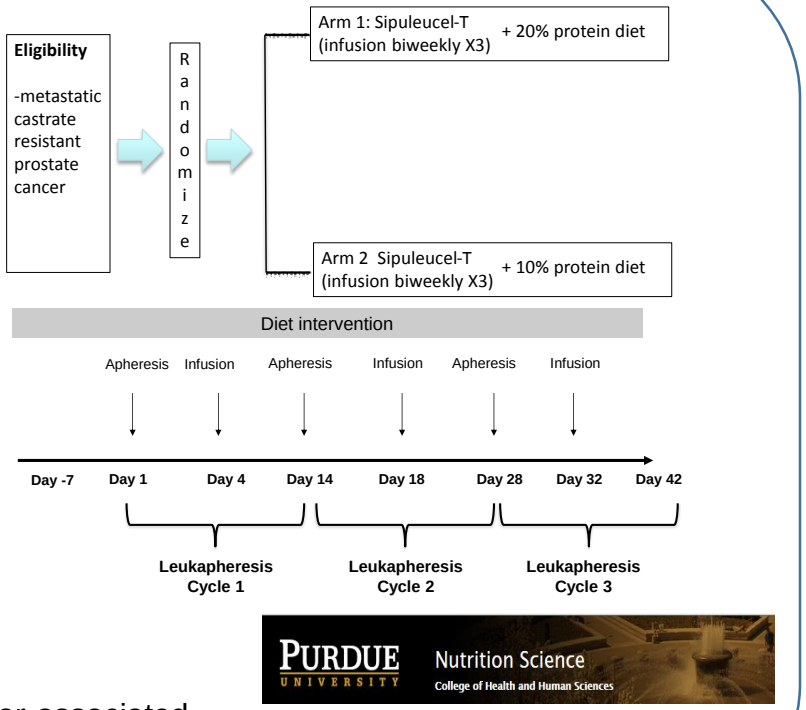
Kantoff et al. NEJM 2010

Immunomodulation by dietary protein restriction









PURDUE UNIVERSITY Nutrition Science College of Health and Human Sciences

Reprogramming of tumor-associated macrophages with dietary protein restriction increases the efficacy of immunotherapies

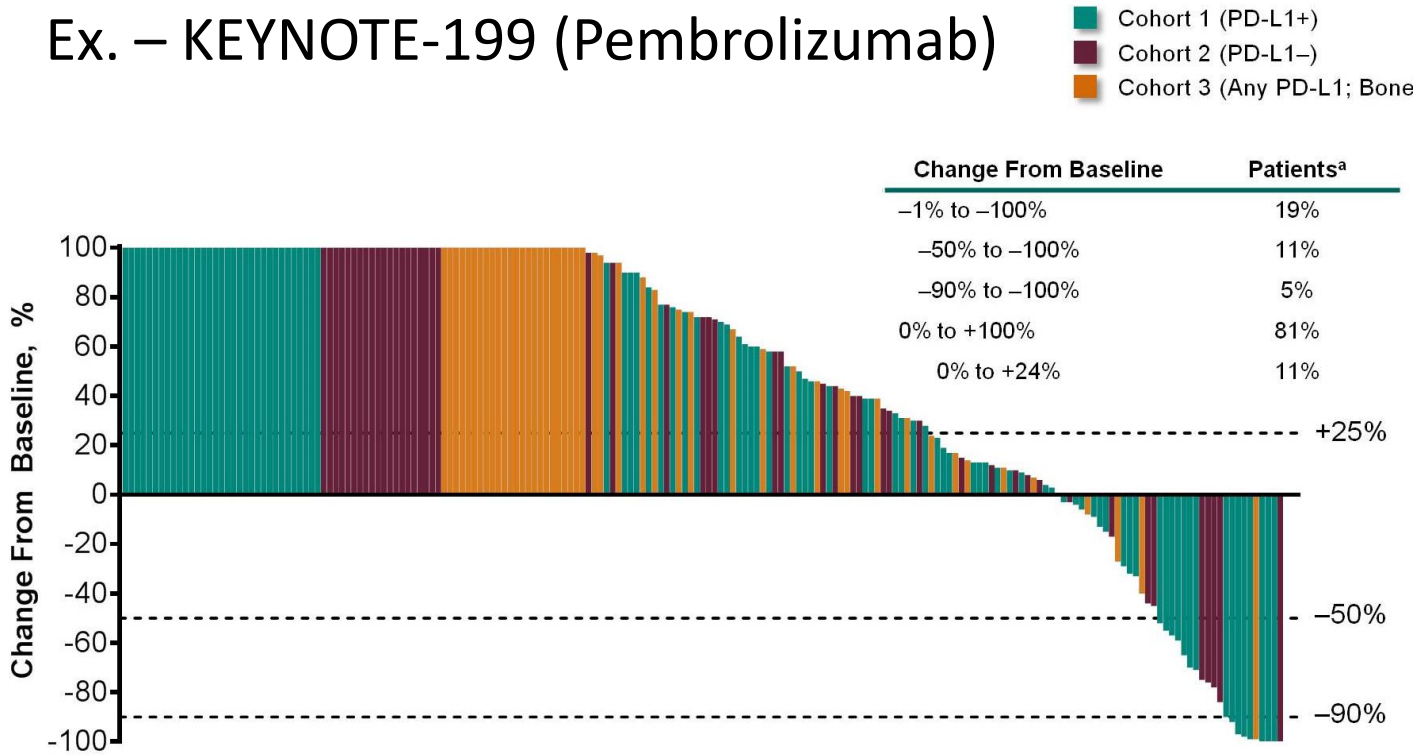
Patients with metastatic castration prostate cancer → **Clinical Trial Enrollment** → **Pilot randomized study normal vs low protein diet with sipuleucel-T**

Fontana L & Pili R Oncotarget 2013; Orillion A & Pili Clin Cancer Res 2018

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

Ex. – KEYNOTE-199 (Pembrolizumab)

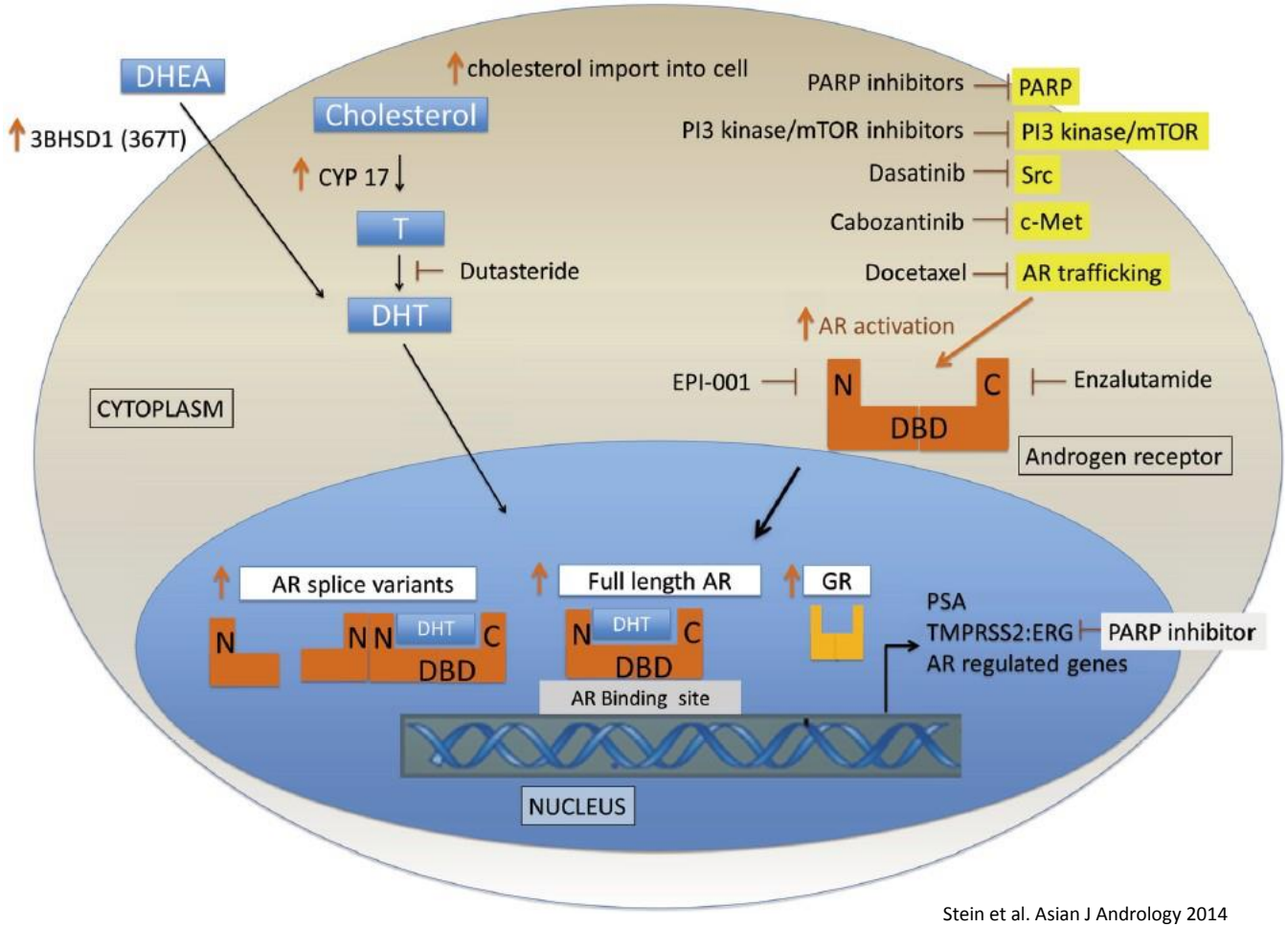


DeBono et al. ASCO 2018

- 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

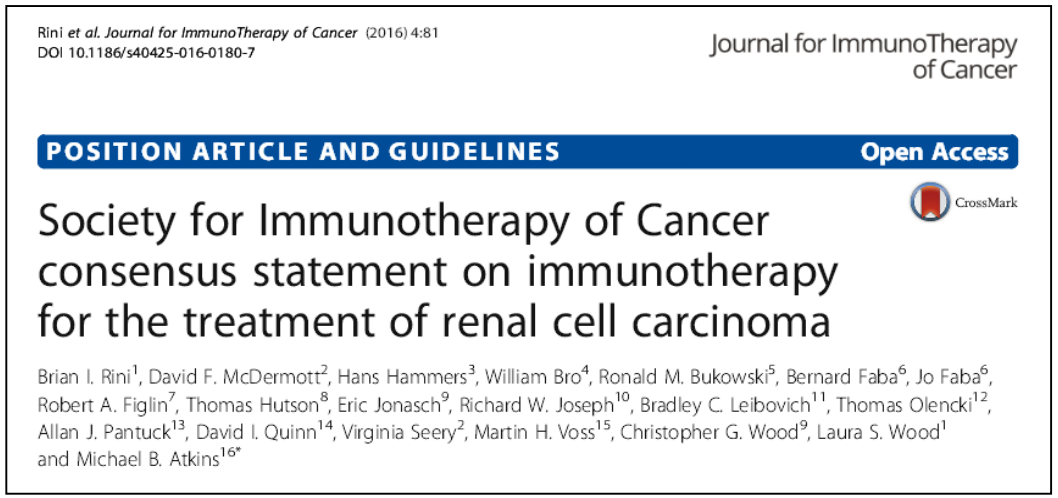
Immune-related Adverse Events

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*]

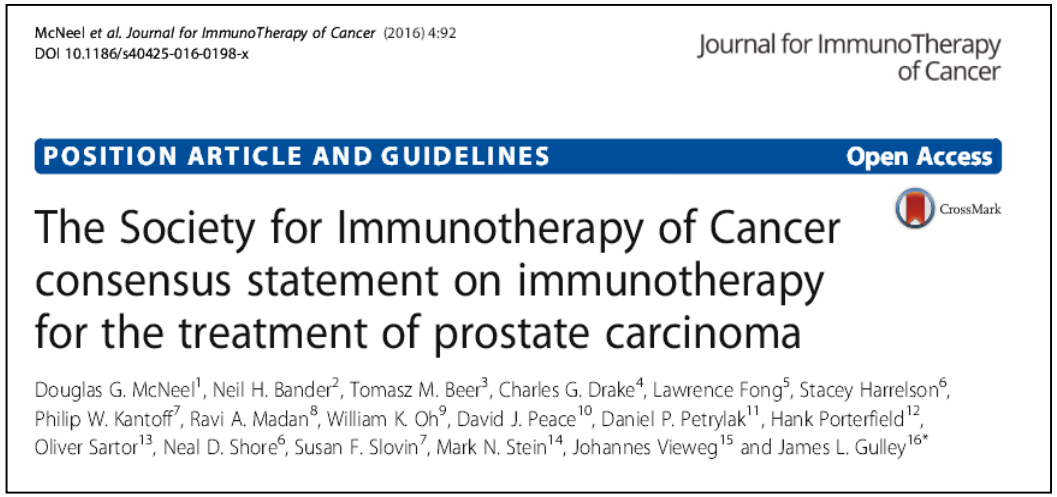
Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

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: 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