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

HOPA Hematology/Oncology Pharmacy Association

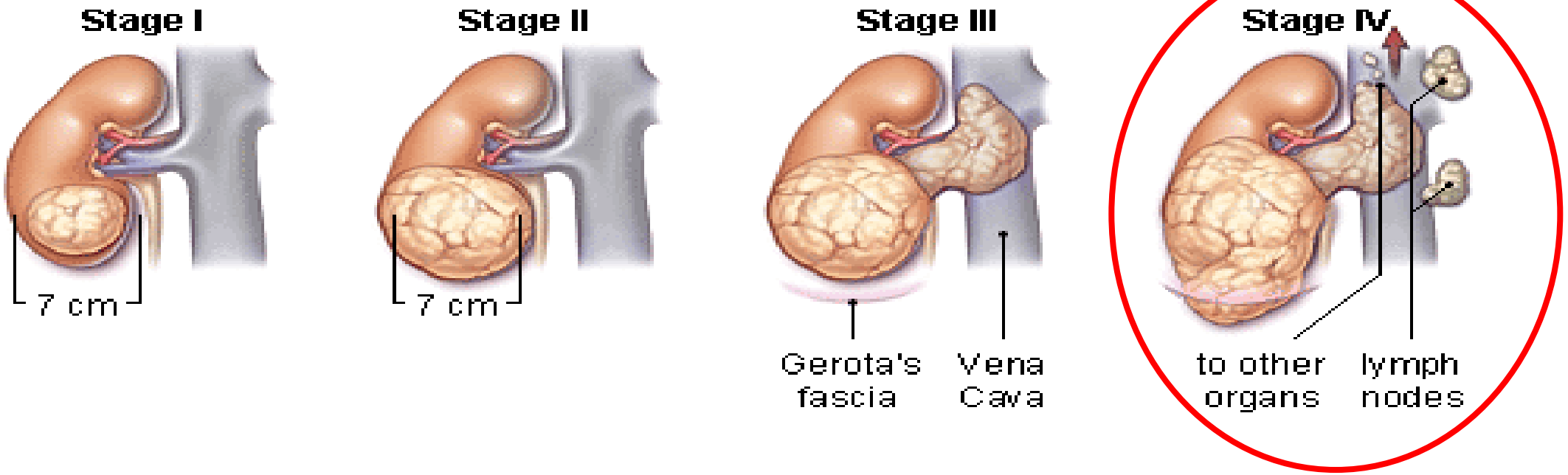
Society for Immunotherapy of Cancer

Disclosures

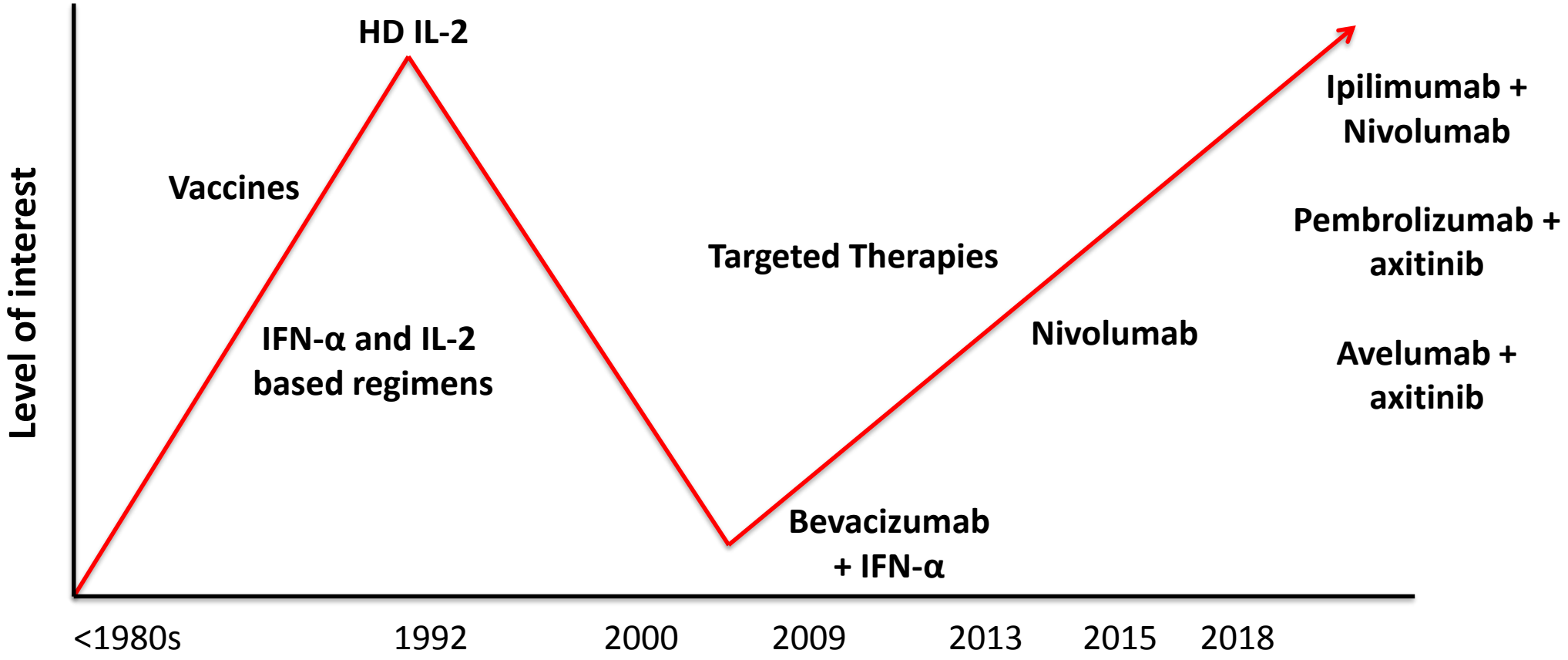
- Research Funding: Janssen, Incyte, Seattle Genetics, Neon Therapeutics
- Consulting: Janssen, EMD Serono, Pfizer, Abbvie, Astra Zeneca
- I will be discussing non-FDA approved indications during my presentation.

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

Surgically resectable → Oligo-metastatic → Metastatic



History of Immunotherapy in mRCC



Resurgence of interest in immunotherapy

FDA-approved Immunotherapies for mRCC

Class	Drug	Approved	Indication	Dose
Cytokine	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 + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
Checkpoint inhibitor	Nivolumab	2015	Clear cell RCC refractory to prior VEGF-targeted therapy	3mg/kg or 240mg IV Q2W or 480mg IV Q4W
	Nivolumab +ipilimumab	2018	Clear cell RCC, treatment naïve	3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
	Pembrolizumab + axitinib	2019	Advanced RCC, Treatment naïve	200 mg pembro Q3W + 5 mg axitinib twice daily
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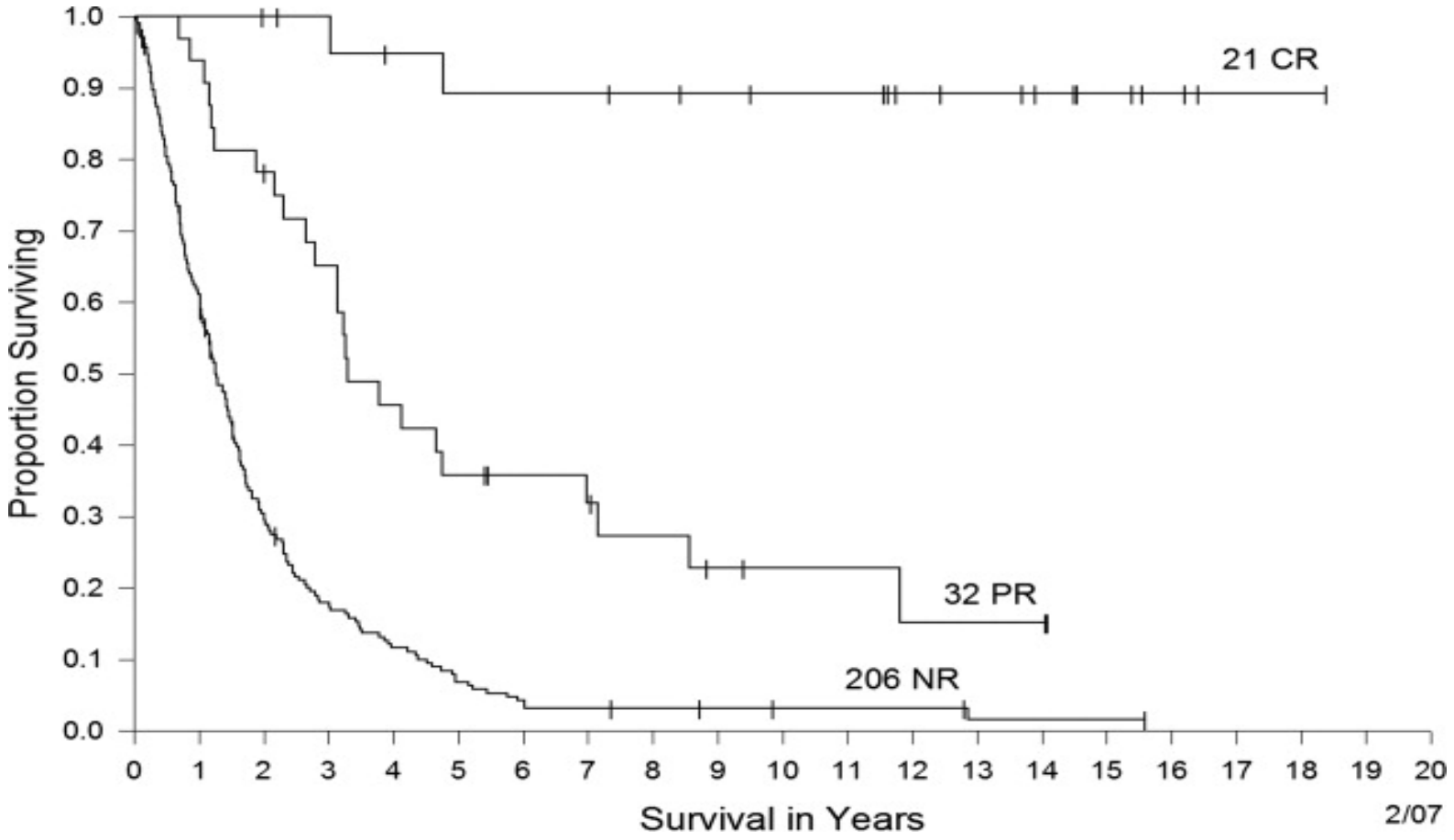
High Dose IL-2 is Active in mRCC

- N=259
- ORR = 20%
  - 9% CR
  - 12% PR
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

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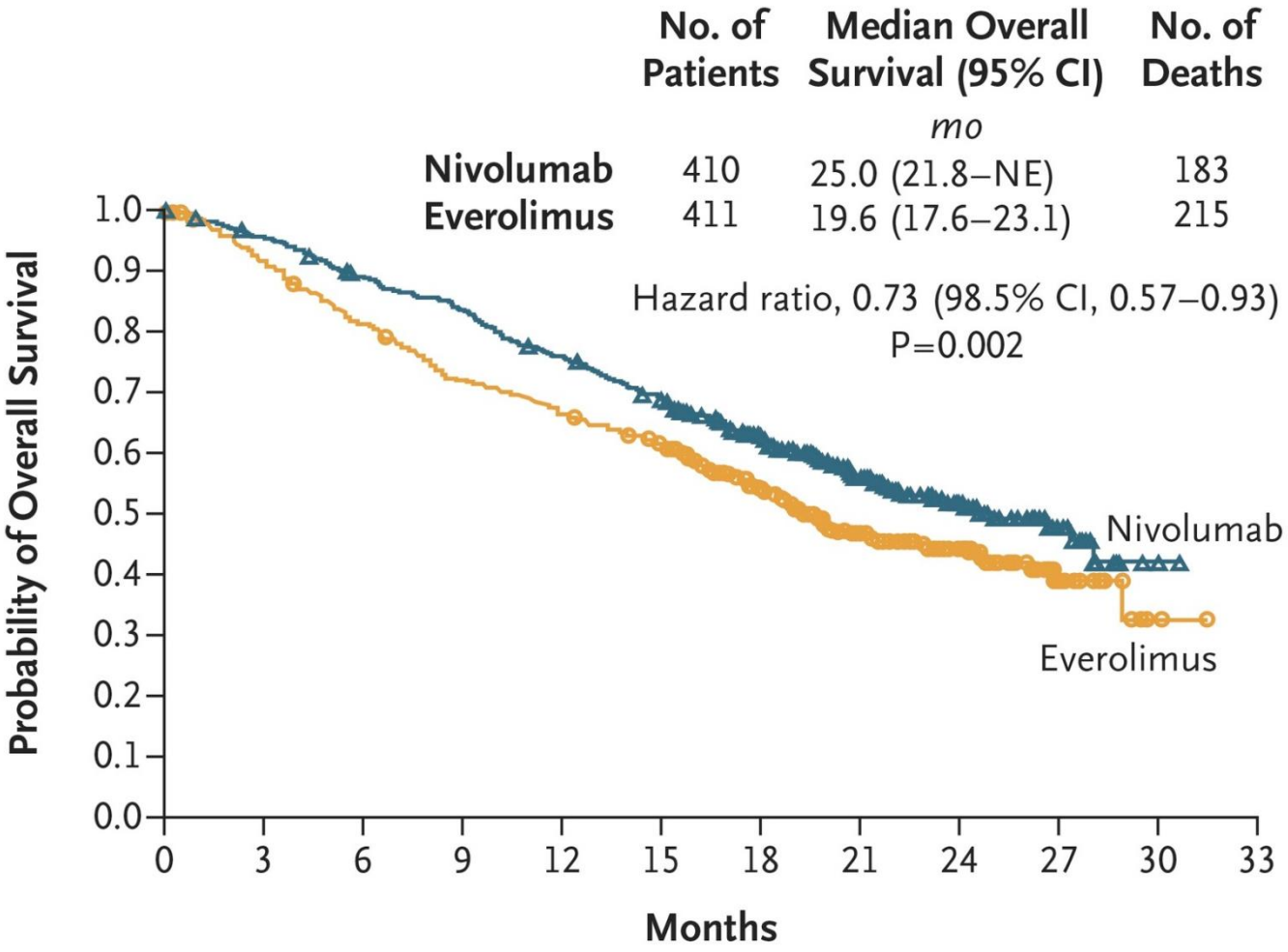
Second-Line Nivolumab in mRCC

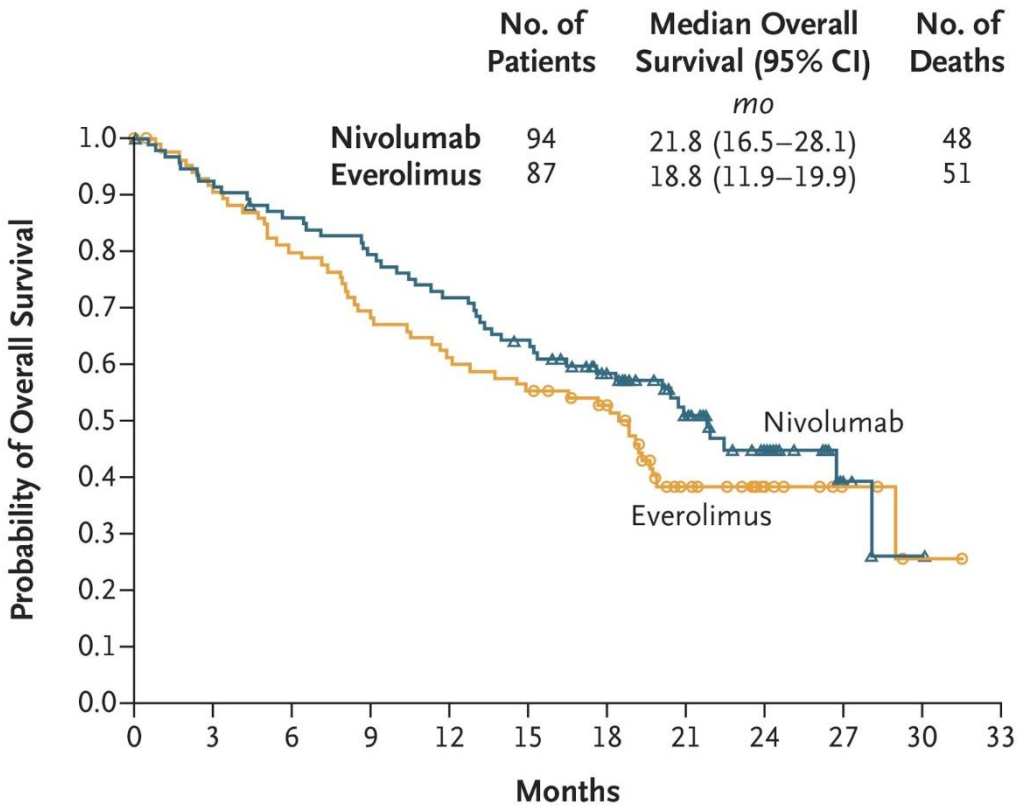
- Phase III "Checkmate 025" trial
- Metastatic, clear-cell RCC
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)



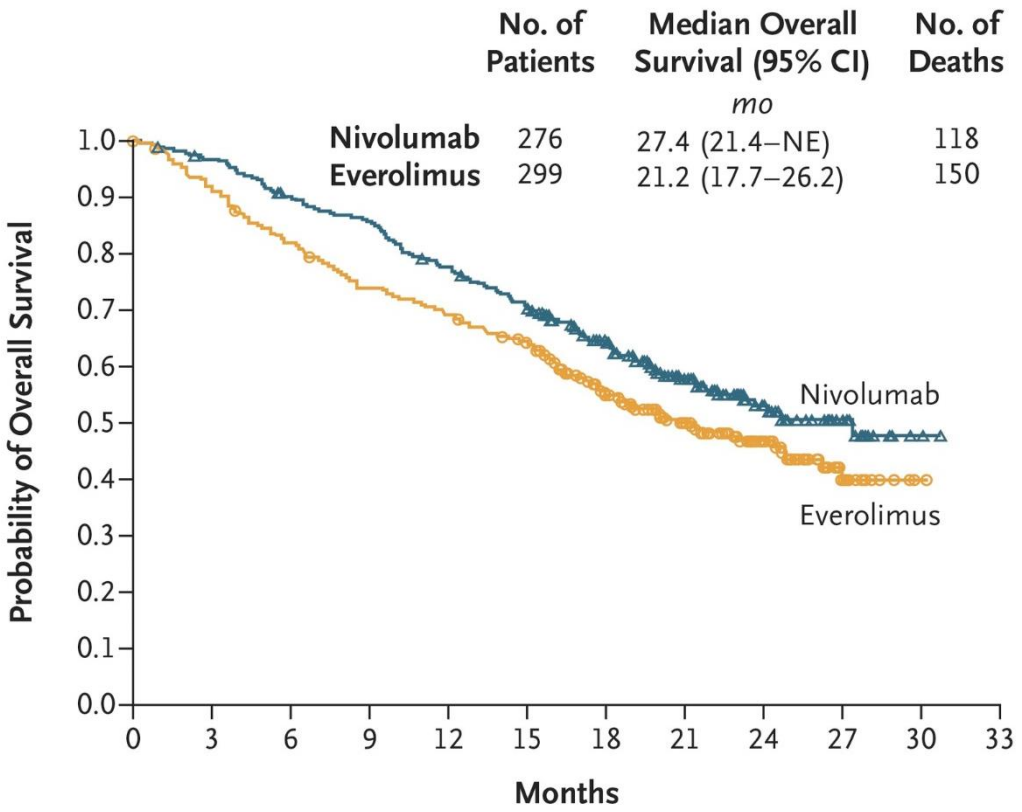
Motzer et al. NEJM 2015

PD-L1 Not a Useful Biomarker in RCC

PD-L1 ≥ 1%



PD-L1 < 1%



Motzer et al. NEJM 2015

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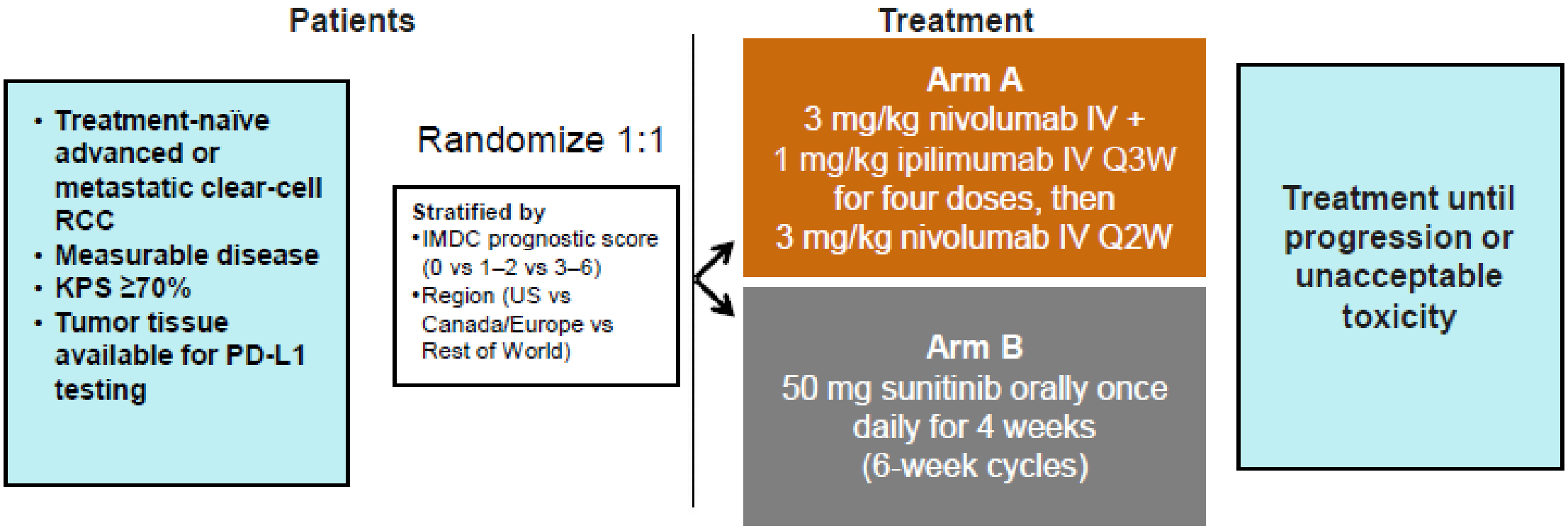
First-line Nivolumab + Ipilimumab in mRCC



Nivolumab = anti-PD-1 antibody Ipilimumab = anti-CTLA-4 antibody

IMDC = International Metastatic RCC Database Consortium

Escudier et al. ESMO 2017

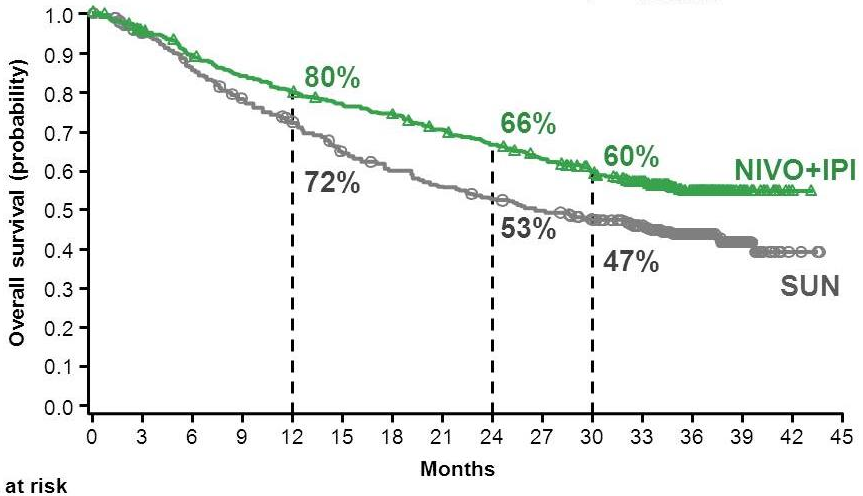
First-line Nivolumab + Ipilimumab in mRCC: Overall Survival

Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



No. at risk

NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

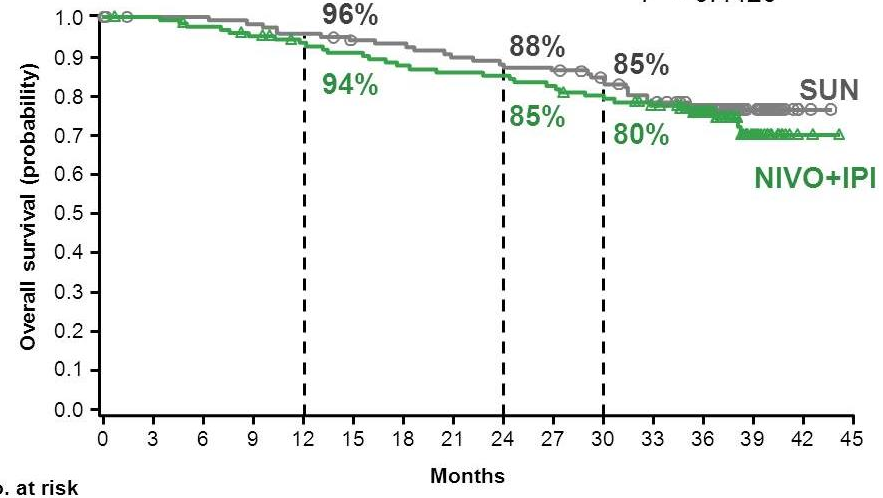
Favorable risk

Follow-up
= 30 months

Median OS, months (95% CI)

NIVO+IPI	NR (NE)
SUN	NR (NE)

HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk

NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Tannir et al. ASCO GU 2019

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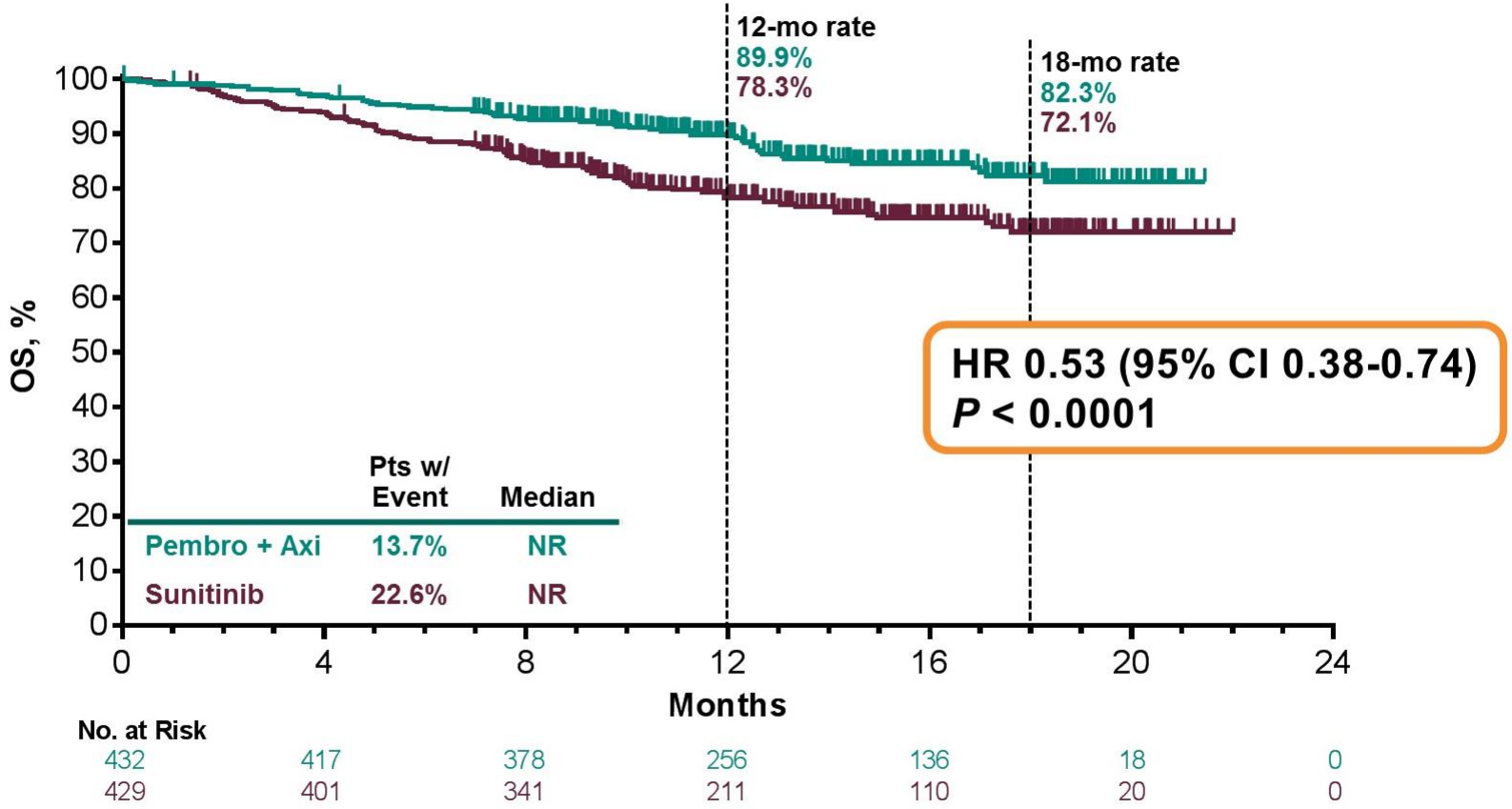
First-line Pembrolizumab + axitinib in advanced RCC: overall survival

KEYNOTE-426: OS in the ITT Population

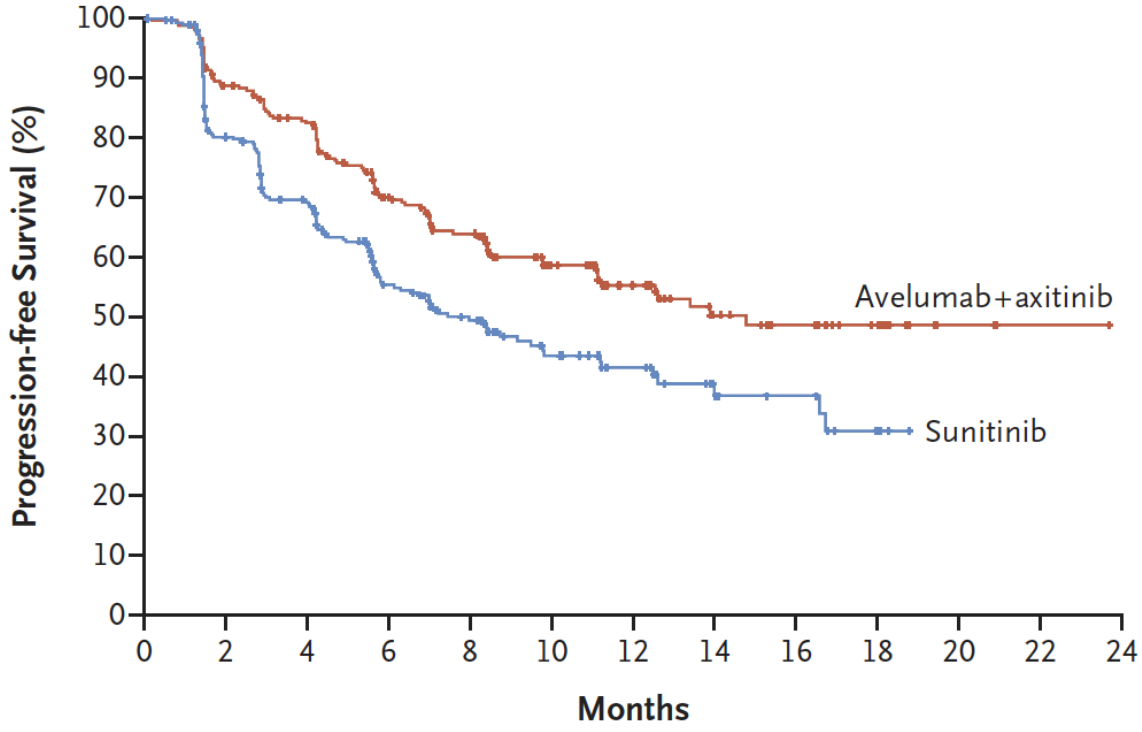


Rini, ASCO 2019

First-line avelumab + axitinib in mRCC

- Primary Endpoint: PFS and OS in PD-L1+
- Median PFS – 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR: 61.9% vs 29.7
- OS data: immature

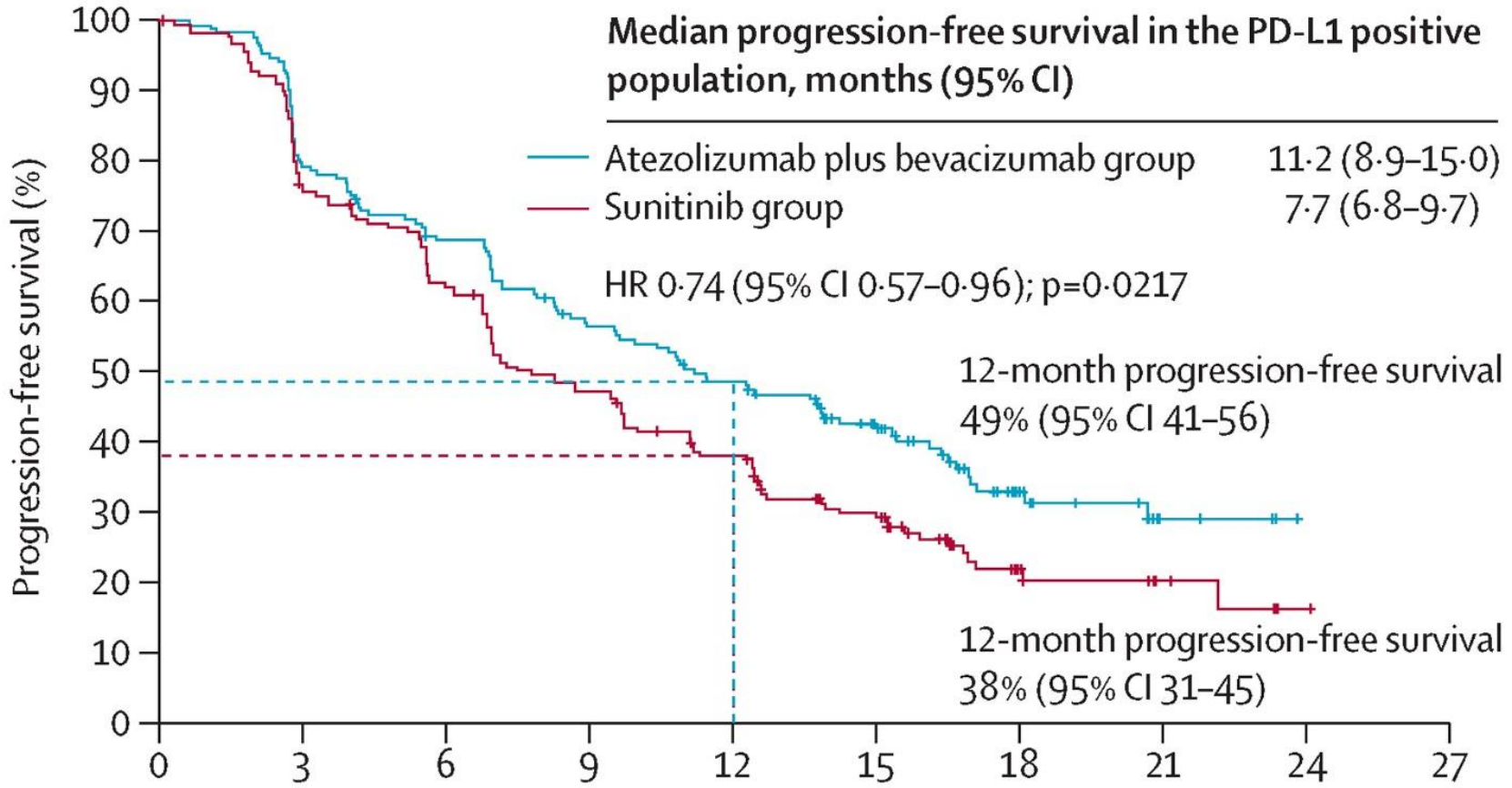
JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019.

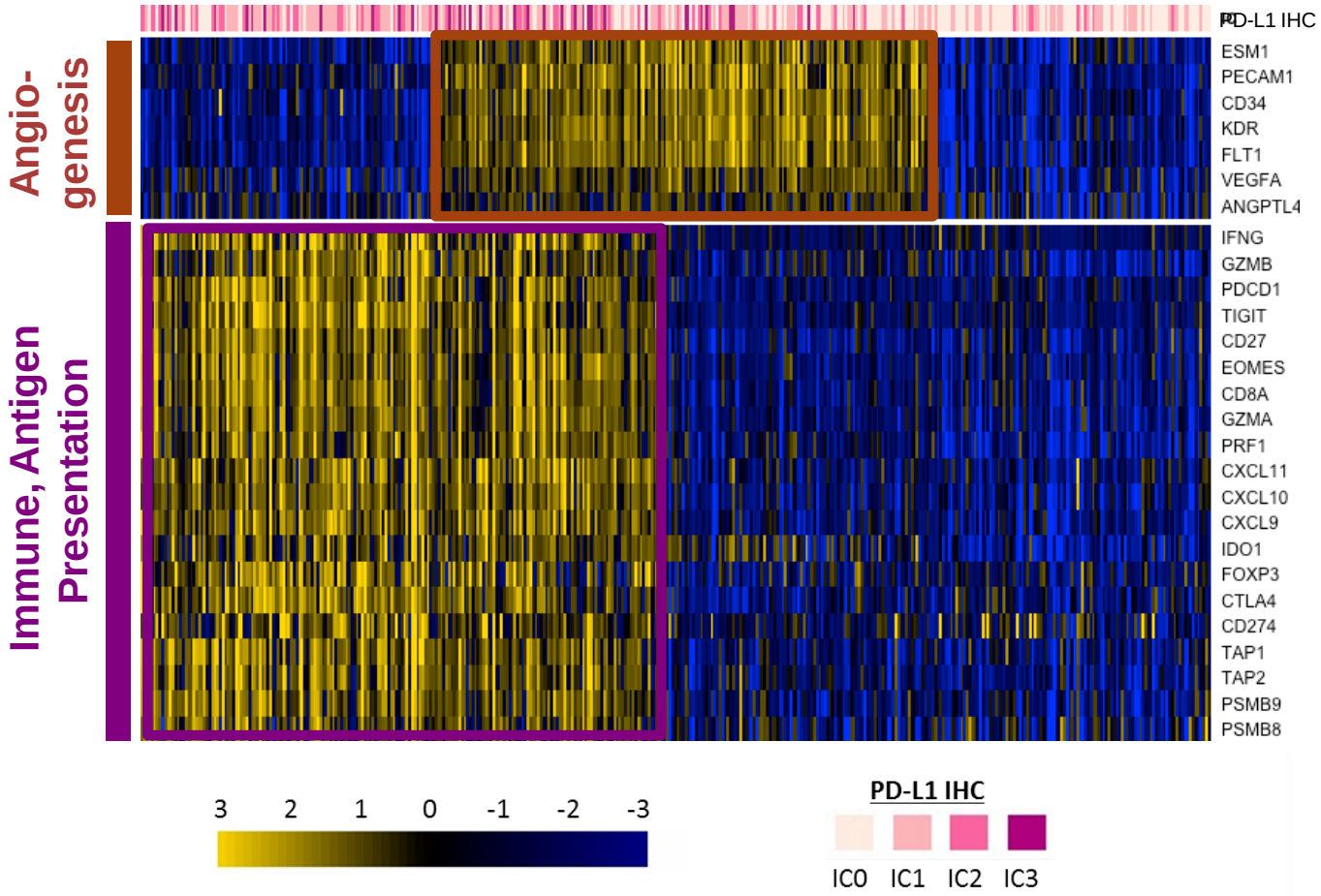
In Development?: First-line atezolizumab + bevacizumab

Immotion151



Rini, The Lancet 2019.

In Development: First-line atezolizumab + bevacizumab: molecular signatures



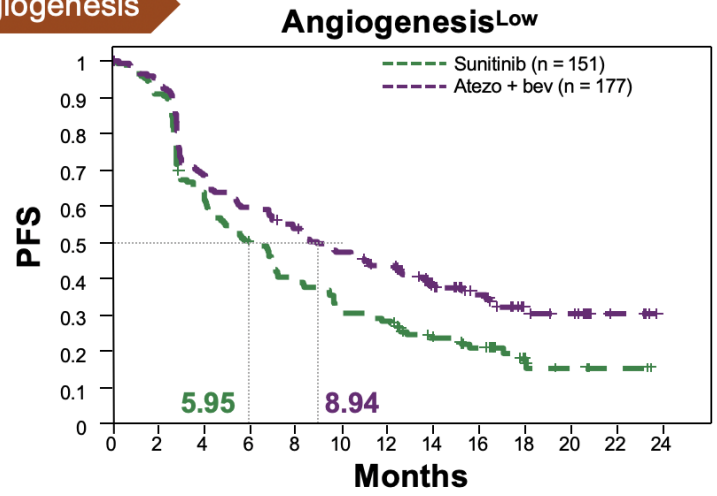
Identification of gene signatures based on association with clinicaloutcome

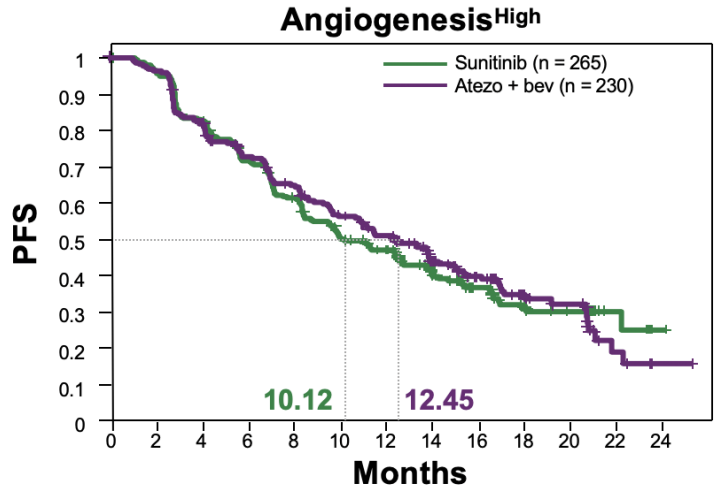
- T_{eff}: *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

Rini et al, ESMO 2018

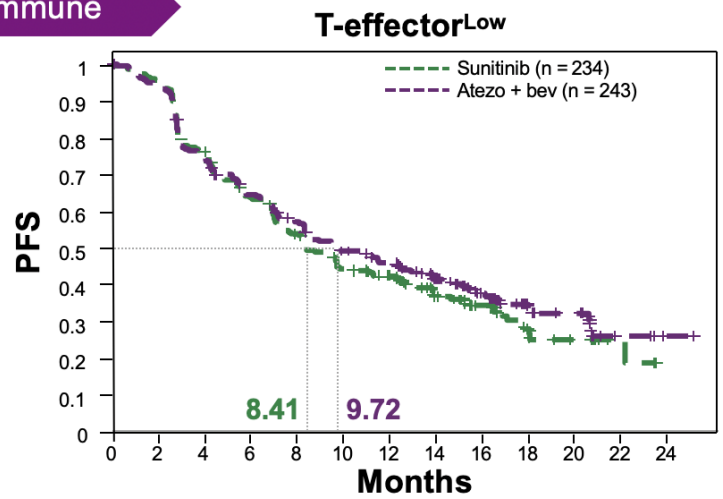
In Development: First-line atezolizumab + bevacizumab: molecular signatures

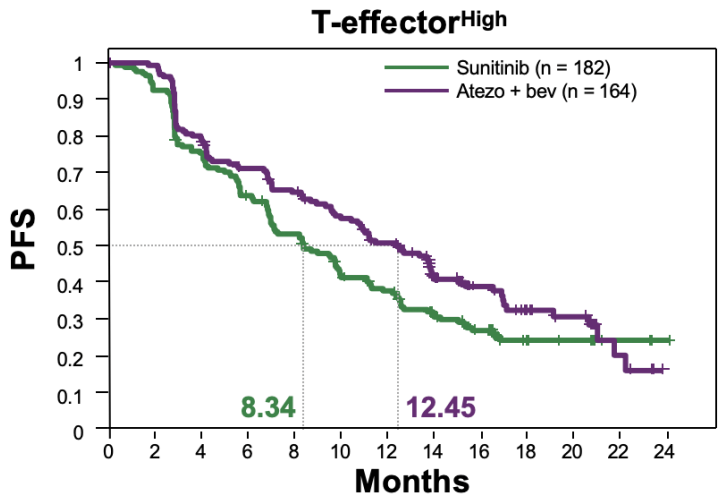
Angiogenesis





Immune





Rini et al, ESMO 2018

Front-line phase 3 trials with immunotherapy agents (efficacy summary)

	CheckMate 214	KEYNOTE-426	JAVELIN 101	IMmotion151
Intervention	Ipilimumab + Nivolumab	Pembrolizumab + Axitinib	Avelumab + Axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+	PFS in PD-L1+; OS
mOS, months	NR vs 37.9 (30 mo min followup)	NR vs NR (median 12.8 mo followup)	Not reported	33.6 vs 34.9 (median 24 mo followup)
PFS, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 7.2	11.2 vs 7.7
ORR (ITT), %	41% vs 34%	59.3% vs 35.7%	51.4% vs 25.7%	37% vs 33%
CR rate (ITT)	10.5% vs 1.8%	5.8% vs 1.9%	3.4% vs 1.8%	5% vs 2%

IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

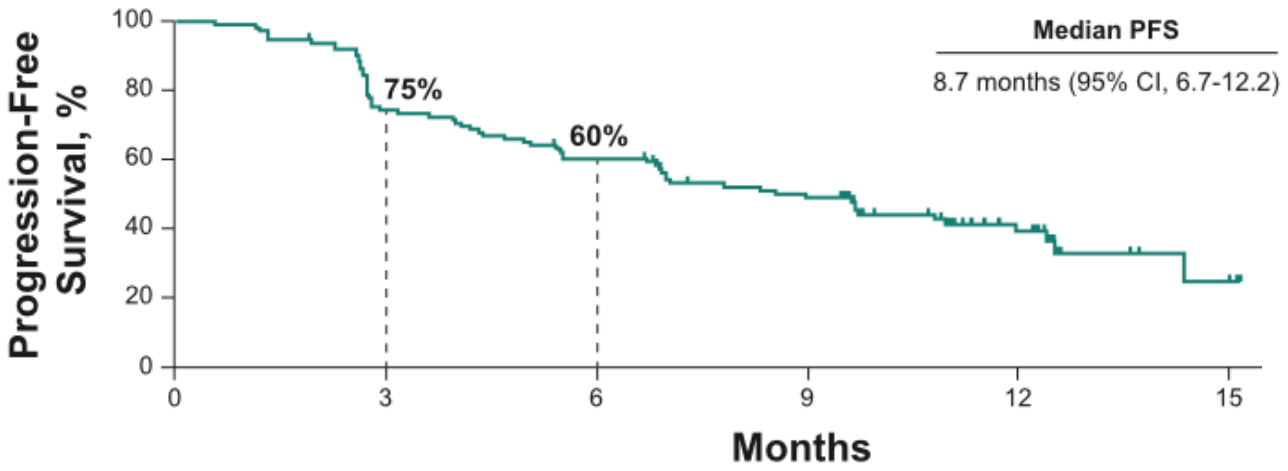
Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019.

Ongoing front-line phase 3 trials with immunotherapy agents for front-line ccRCC

Treatment Arm	Comparator Arm	Population Size	Primary End Point	Trial number	Trial Name
Cabozantinib + Nivolumab	Sunitinib	630	PFS	NCT03141177	CheckMate 9ER
Lenvatinib + Pembrolizumab or Everolimus	Sunitinib	1050	PFS	NCT02811861	CLEAR
NKTR-214 + Nivolumab	Sunitinib	600	ORR, OS	NCT03729245	CA045002
Cabozantinib + Ipilimumab + Nivolumab	Sunitinib	676	PFS	NCT03937219	COSMIC-313

PFS: progression-free survival; ORR: overall response rate; OS: overall survival

In Development: First-line pembrolizumab monotherapy in mRCC KEYNOTE – 427 Clear cell and Non-Clear Cell RCC



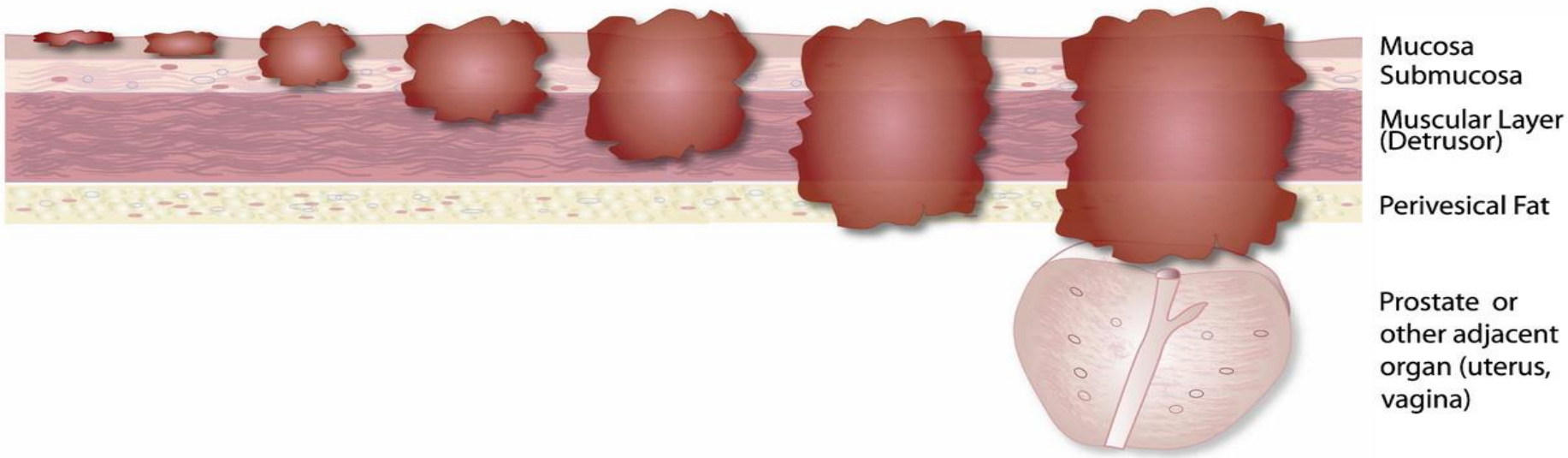
	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

Donskov et al. ESMO 2018
Tykodi et al, ASCO 2019

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	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC	1200 mg Q3W
Avelumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Durvalumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	2017	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC	200 mg Q3W

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Approved	Indication	Dose
Atezolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W

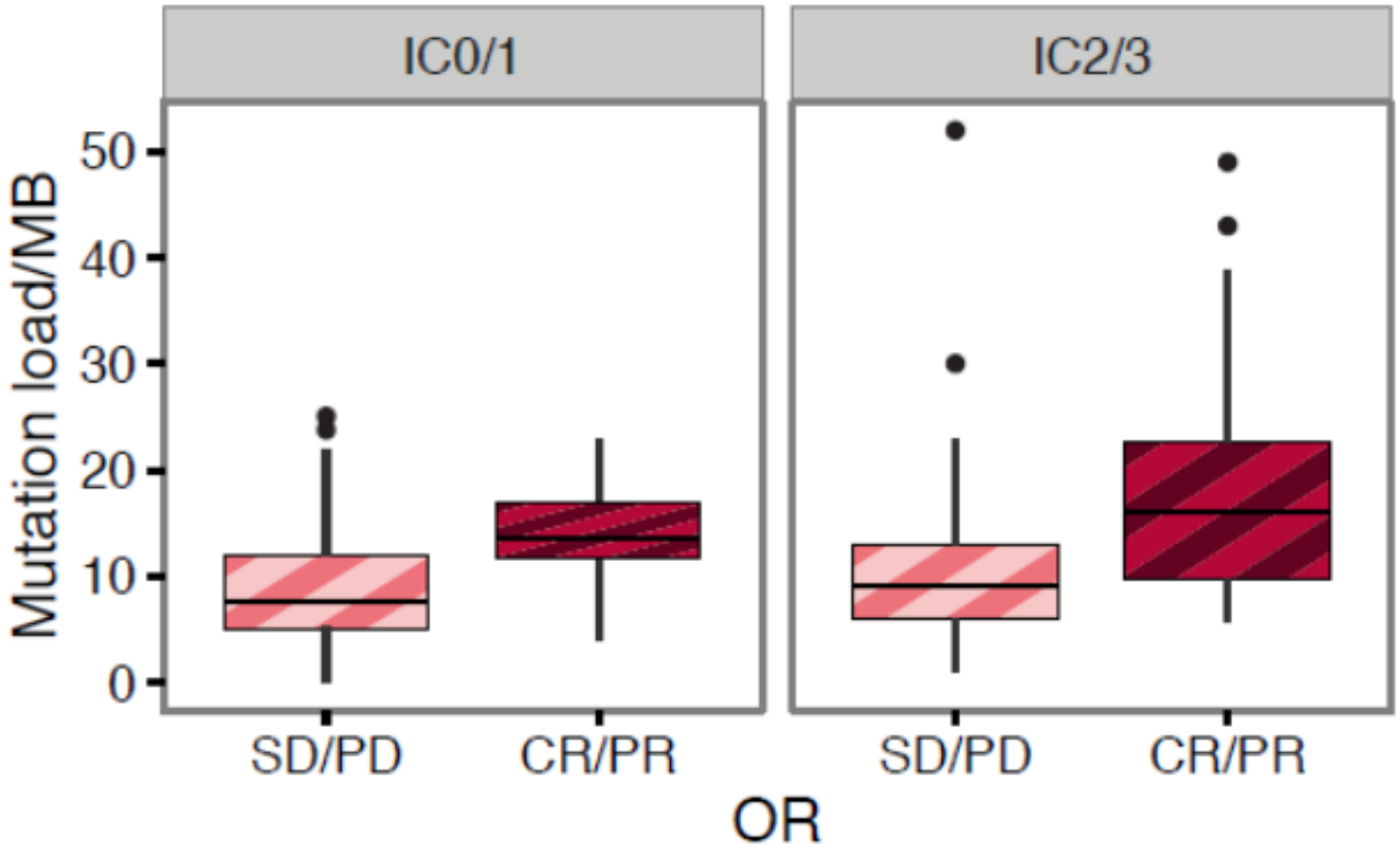
June 2018

FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients

- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and tumor PD-L1 (CPS ≥ 10, pembro; IC ≥ 5% tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status

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

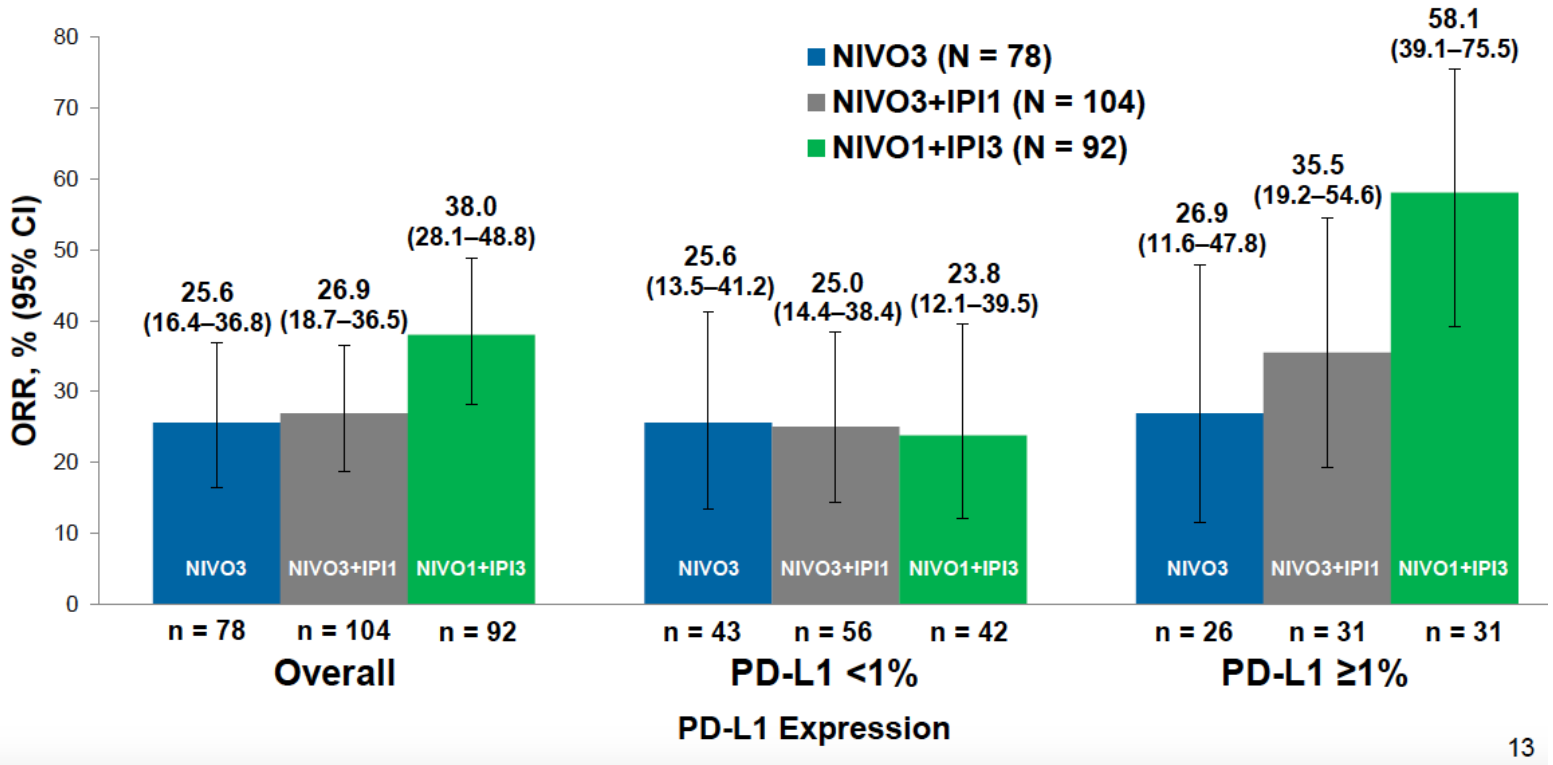
Atezolizumab in mUC



Rosenberg et al. Lancet 2016

In development: Ipilimumab + Nivolumab CheckMate 032

ORR by Baseline Tumor PD-L1 Expression per Investigator



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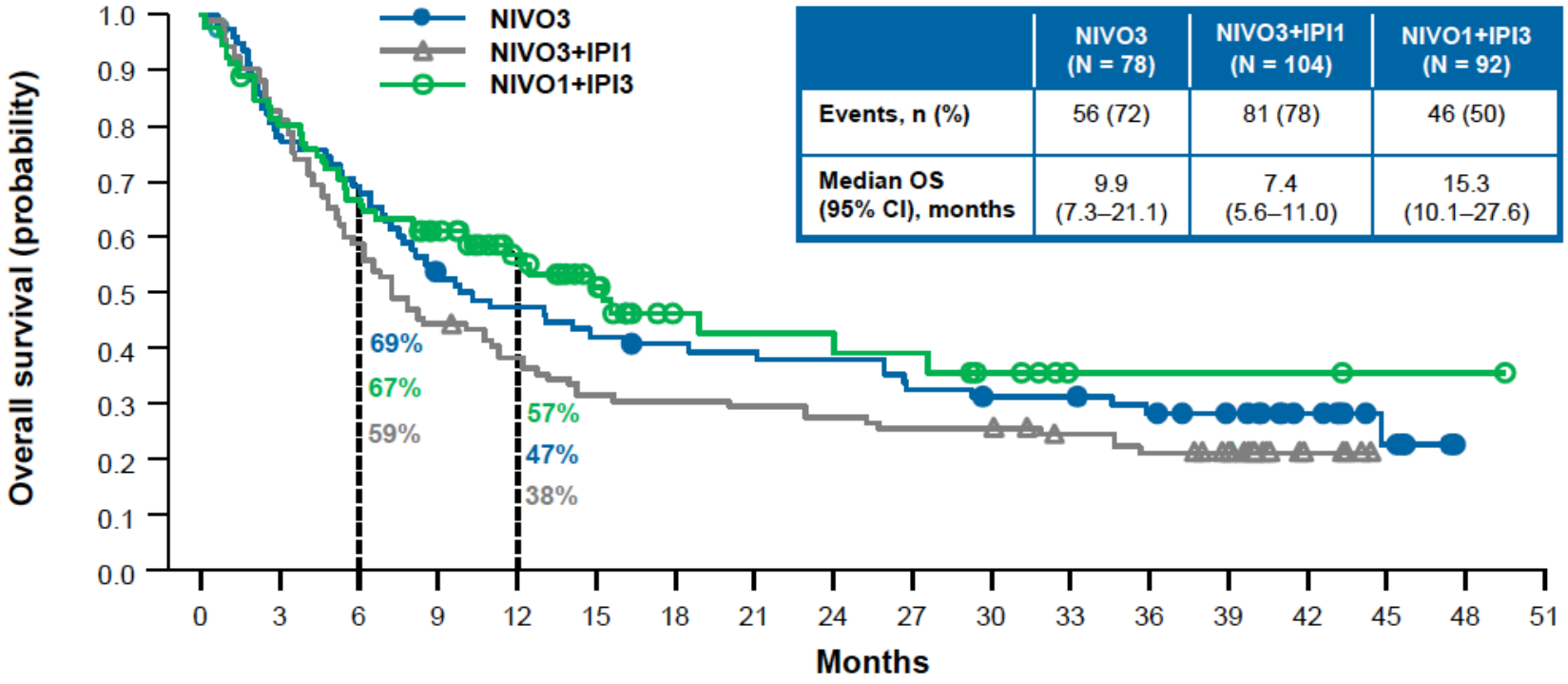
Rosenberg, ESMO 2018

In development: Ipilimumab + Nivolumab CheckMate 032



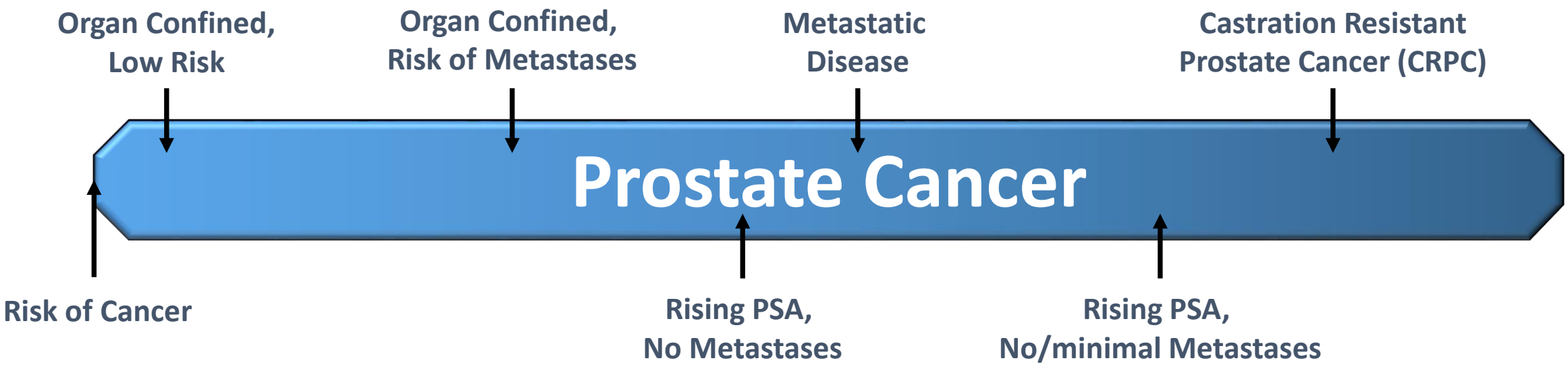
	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Number at risk

NIVO3	78	61	54	41	36	32	30	29	28	24	22	22	19	16	9	4	0	0
NIVO3+IPI1	104	86	61	46	39	32	31	30	28	26	26	22	19	15	5	0	0	0
NIVO1+IPI3	92	73	60	48	33	23	13	12	12	11	8	2	2	2	2	1	1	0

Rosenberg, ESMO 2018

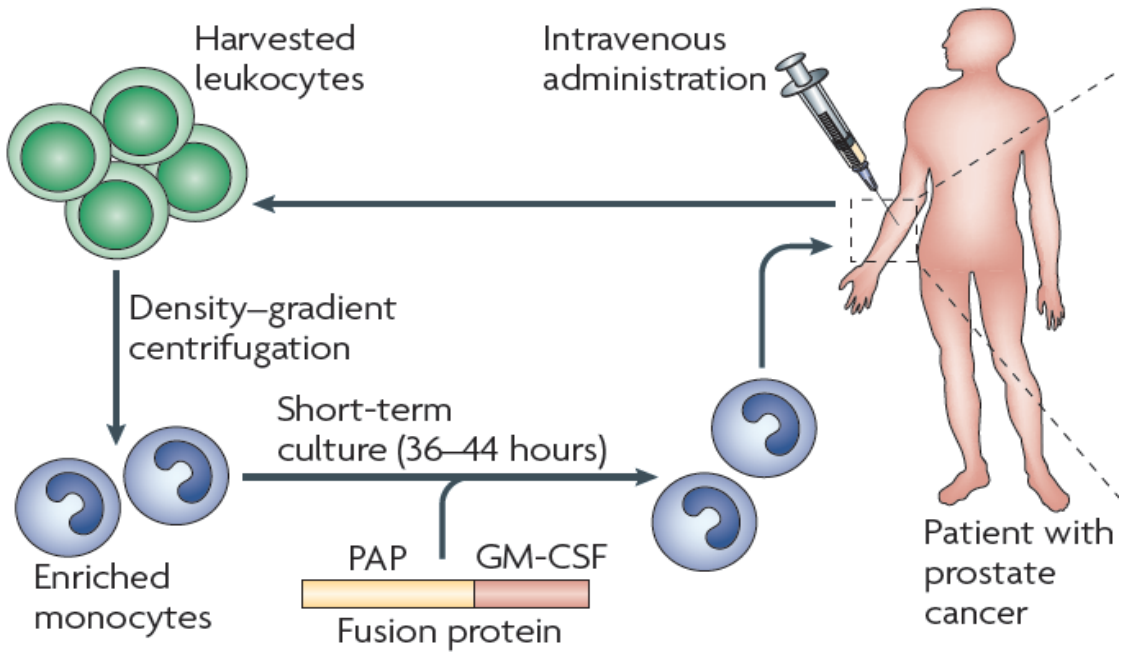
The Spectrum of Prostate Cancer

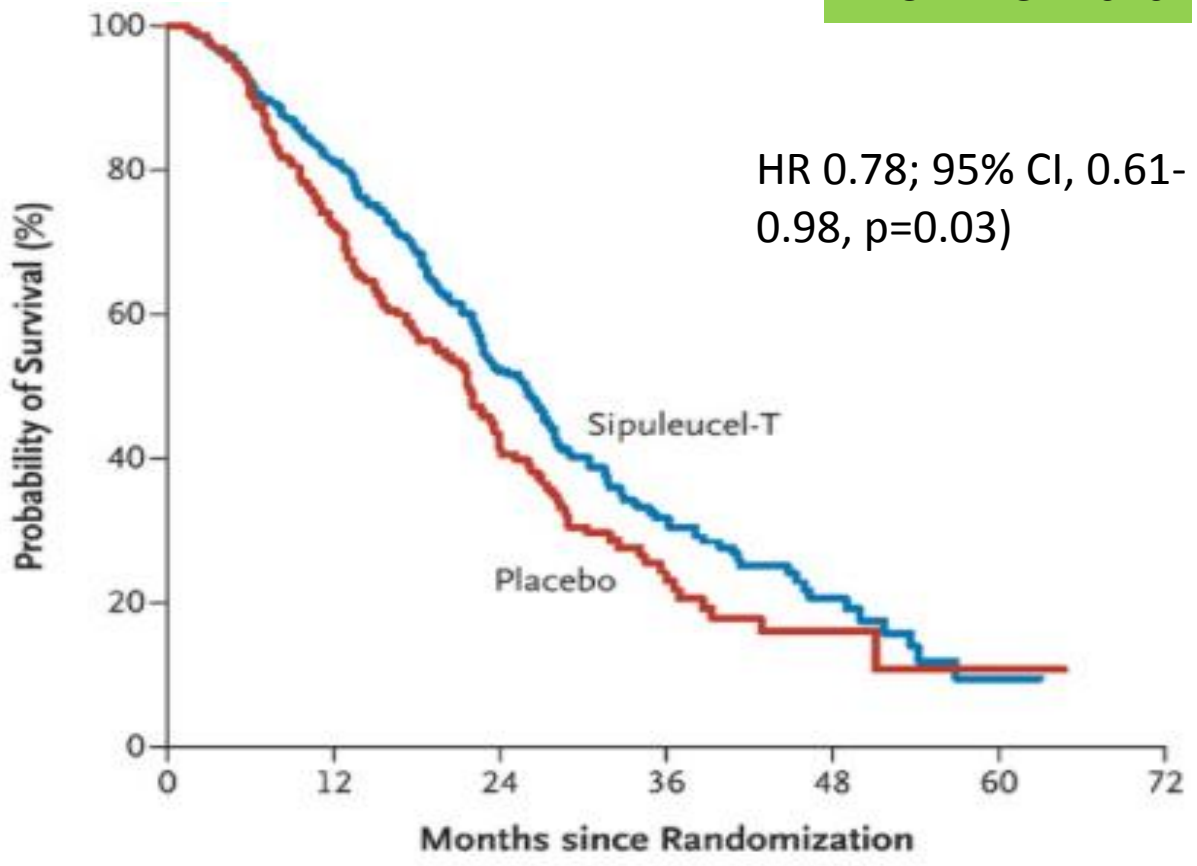


Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine





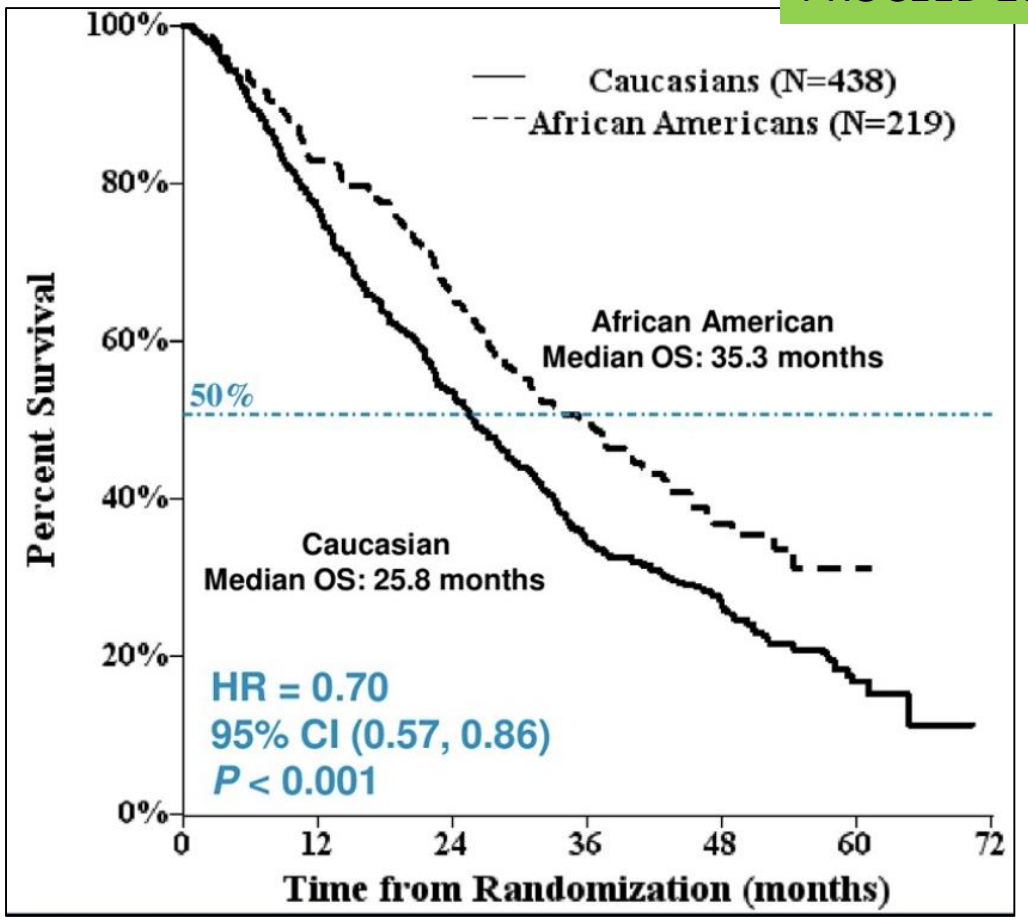
HR 0.78; 95% CI, 0.61-0.98, p=0.03)

Drake et al. Curr Opin Urol 2010
Kantoff et al. NEJM 2010

Sipuleucel-T in mCRPC

PROCEED 2019

- Post-hoc analysis of Phase 3 trial PROCEED (N = 1902 mCRPC patients)
- African-Americans (AA) = 438; Caucasians (CAU) = 219
- Median OS = 35.2 (AA) vs 29.9 mo (CAU); HR 0.81, 95% CI 0.68–0.97; p = 0.03.
- AA race was independently associated with prolonged OS on multivariate analysis (HR 0.60, 95% CI 0.48–0.74; p < 0.001)

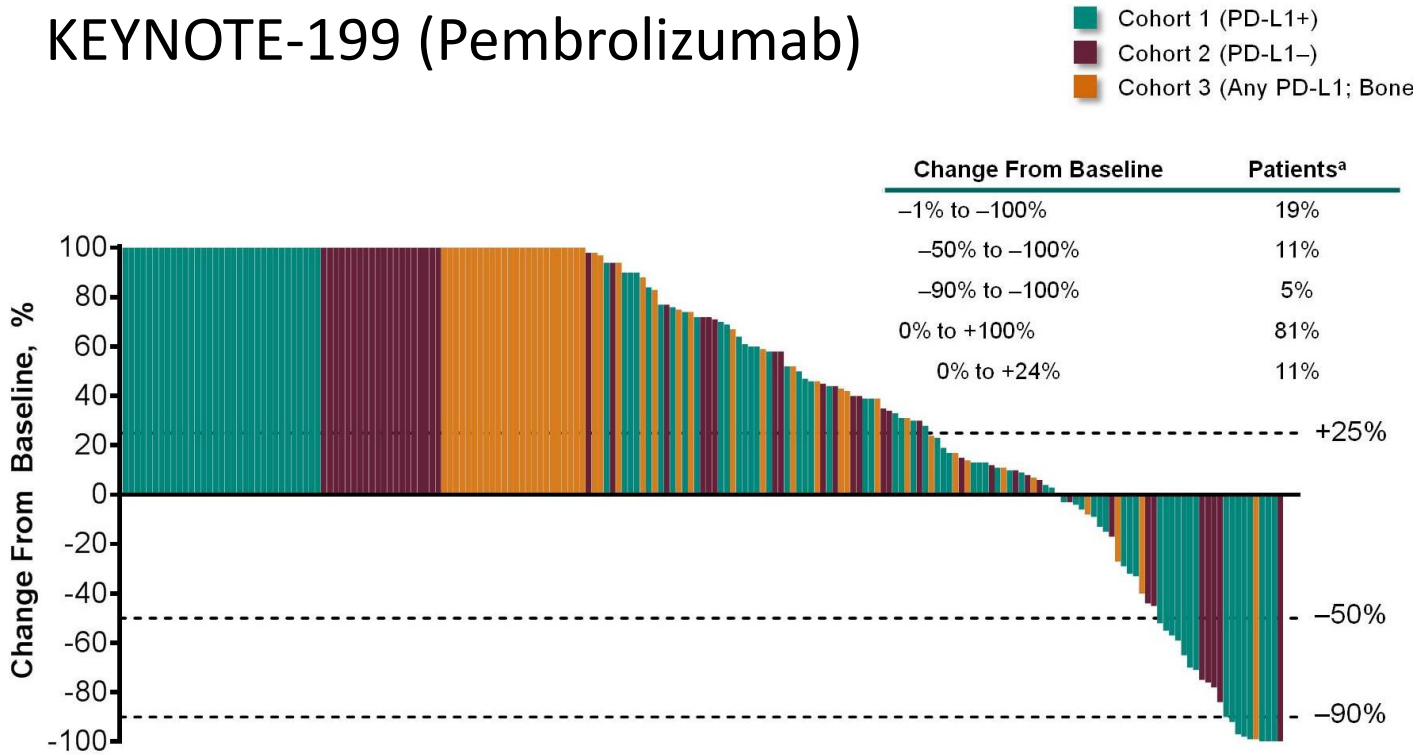


Sartor et al. ASCO 2019

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

KEYNOTE-199 (Pembrolizumab)



- 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

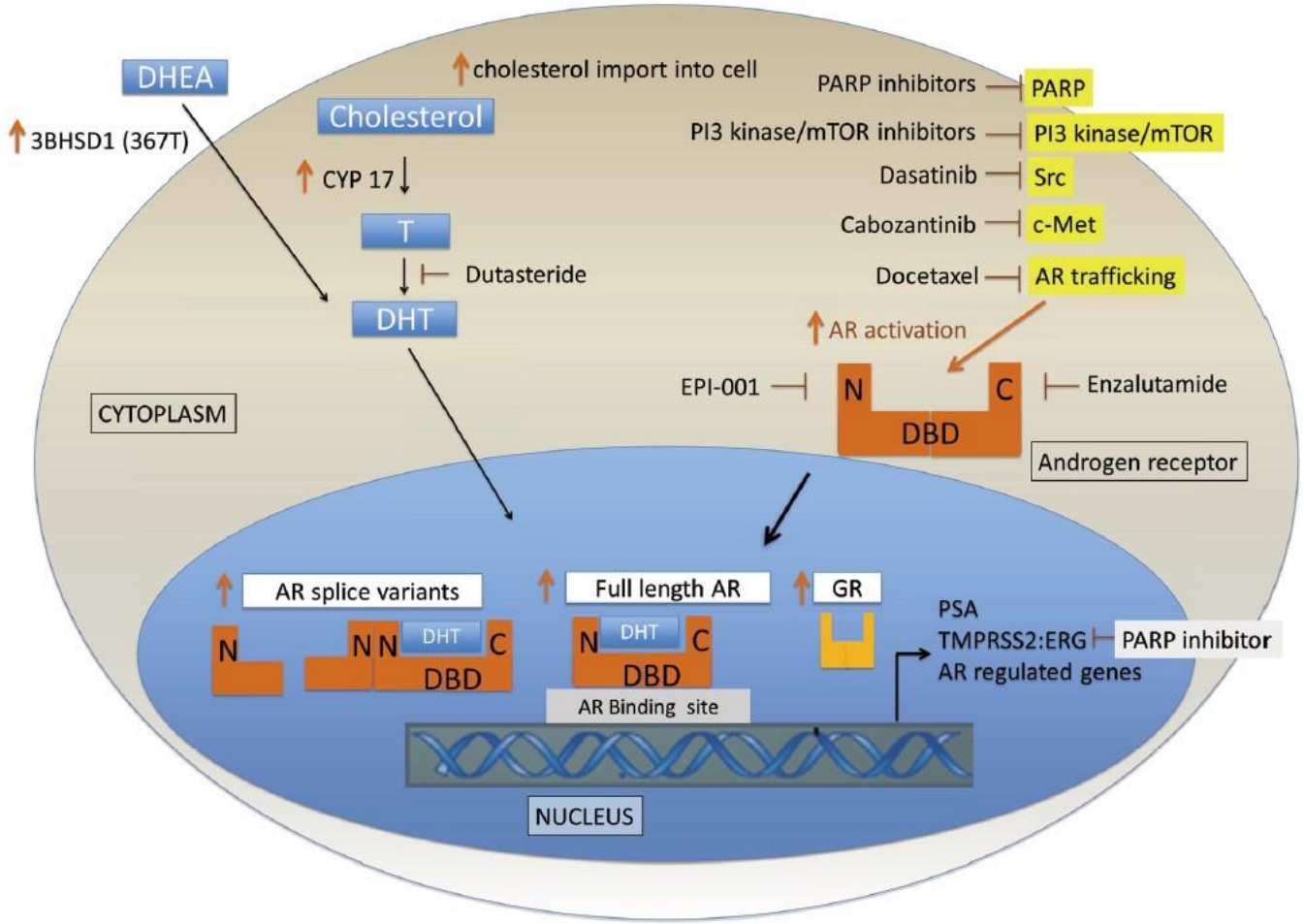
In development: nivolumab + ipilimumab in mCRPC

- Checkmate 650
- Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 doses, then Nivo 480 mg Q4W
- Progressed after 2nd-gen hormonal: 26% response @ 11.9 mo, 2 CR
- Progressed after chemo+hormonal: 10% response @ 13.5 mo, 2 CR
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

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

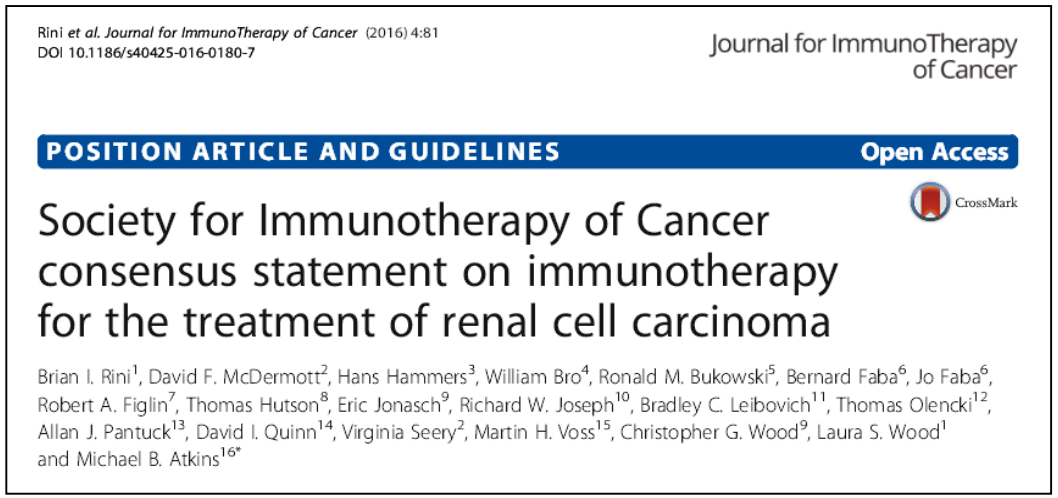
Adverse event	Incidence, any grade (GU only trials) (%)	Incidence, grades 3–5 (GU only trials) (%)	Incidence any grade (non-GU clinical trials) (%)	Incidence, grades 3–5 (non-GU clinical trials) (%)
Hypothyroid/ thyroiditis	0.8–9	0–0.6	3.9–12	0–0.1
Diabetes/DKA	0–1.5	0–0.7	0.8–0.8	0.4–0.7
LFT changes/ 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

Conclusions

- The role of immunotherapy in GU malignancies is increasing
- In RCC, many front-line checkpoint inhibitor options are approved
- Multiple checkpoint inhibitors approved for advanced/metastatic urothelial carcinoma
- Low immune engagement in prostate cancer has limited the application of immunotherapy in this disease

Additional Resources



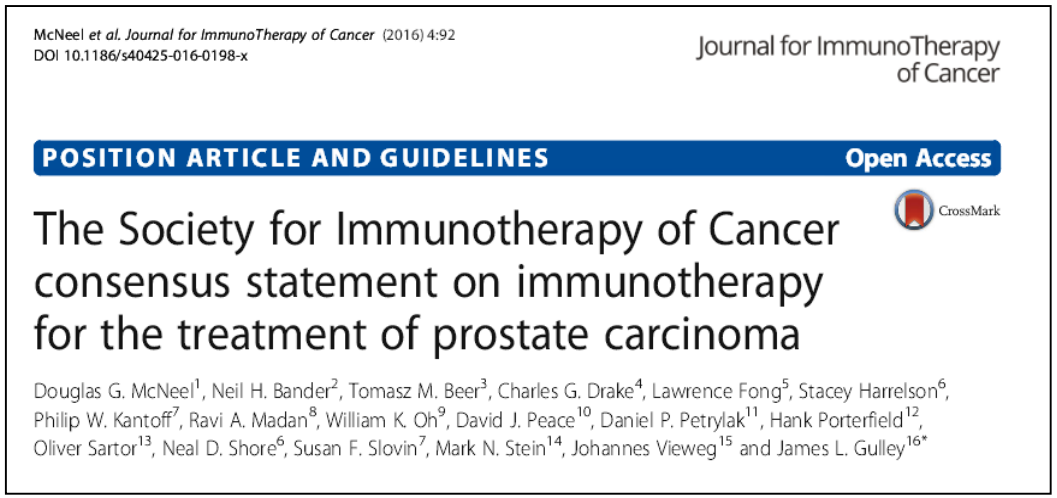
Rini *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:81
DOI 10.1186/s40425-016-0180-7

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*]



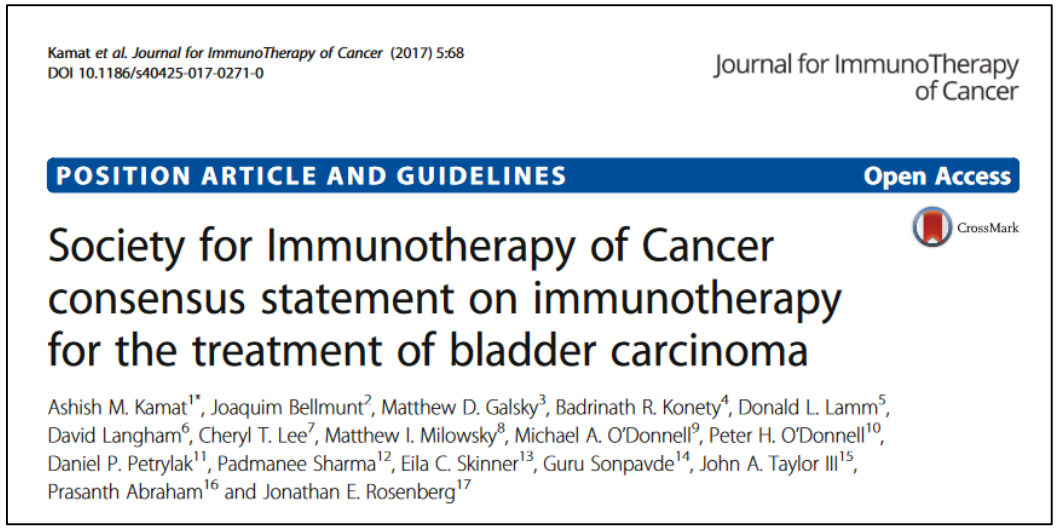
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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*]



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

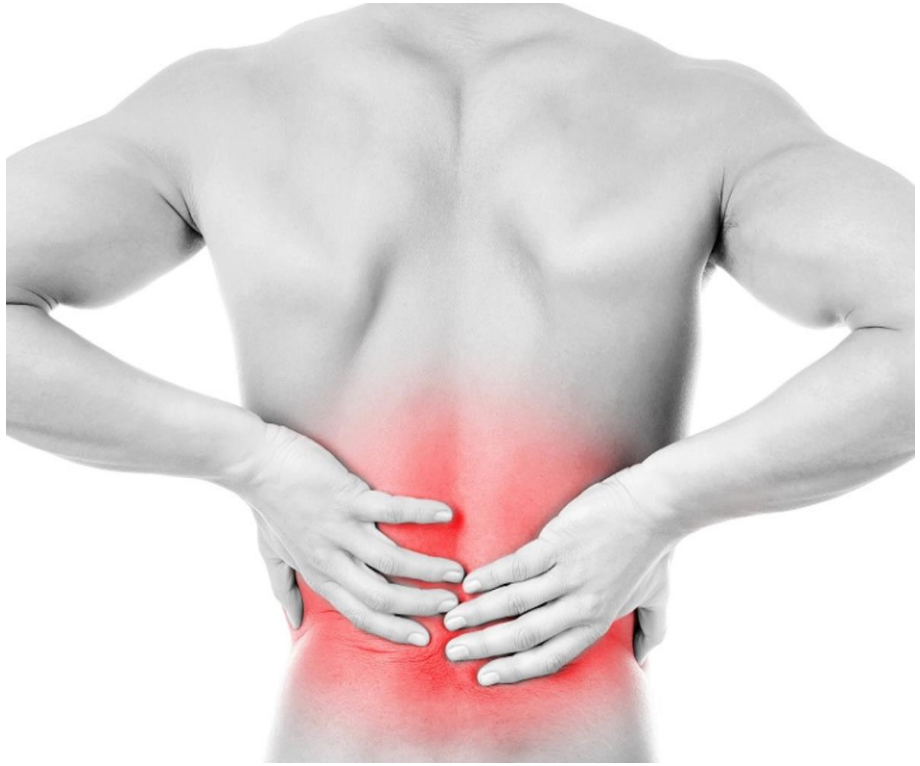
Ashish M. Kamat[1*], Joaquim Bellmunt[2], Matthew D. Galsky[3], Badrinath R. Konety[4], Donald L. Lamm[5], David Langham[6], Cheryl T. Lee[7], Matthew I. Milowsky[8], Michael A. O'Donnell[9], Peter H. O'Donnell[10], Daniel P. Petrylak[11], Padmanee Sharma[12], Eila C. Skinner[13], Guru Sonpavde[14],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

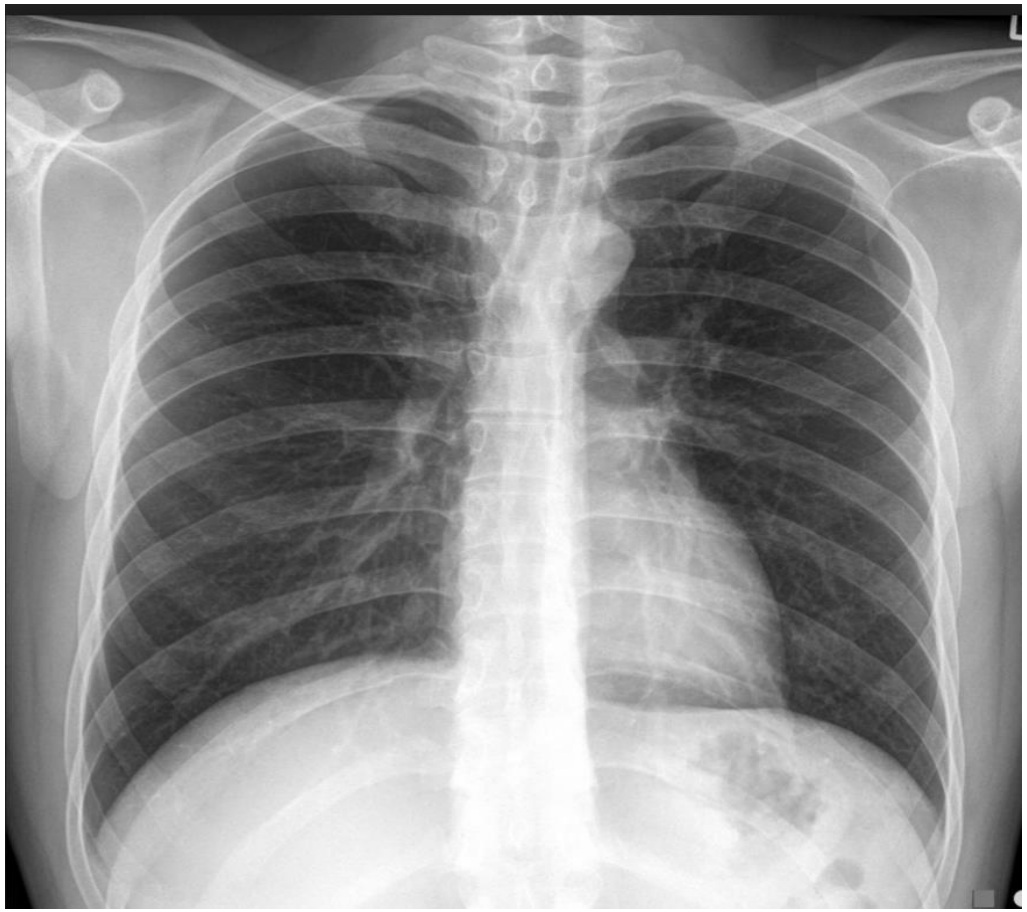
Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

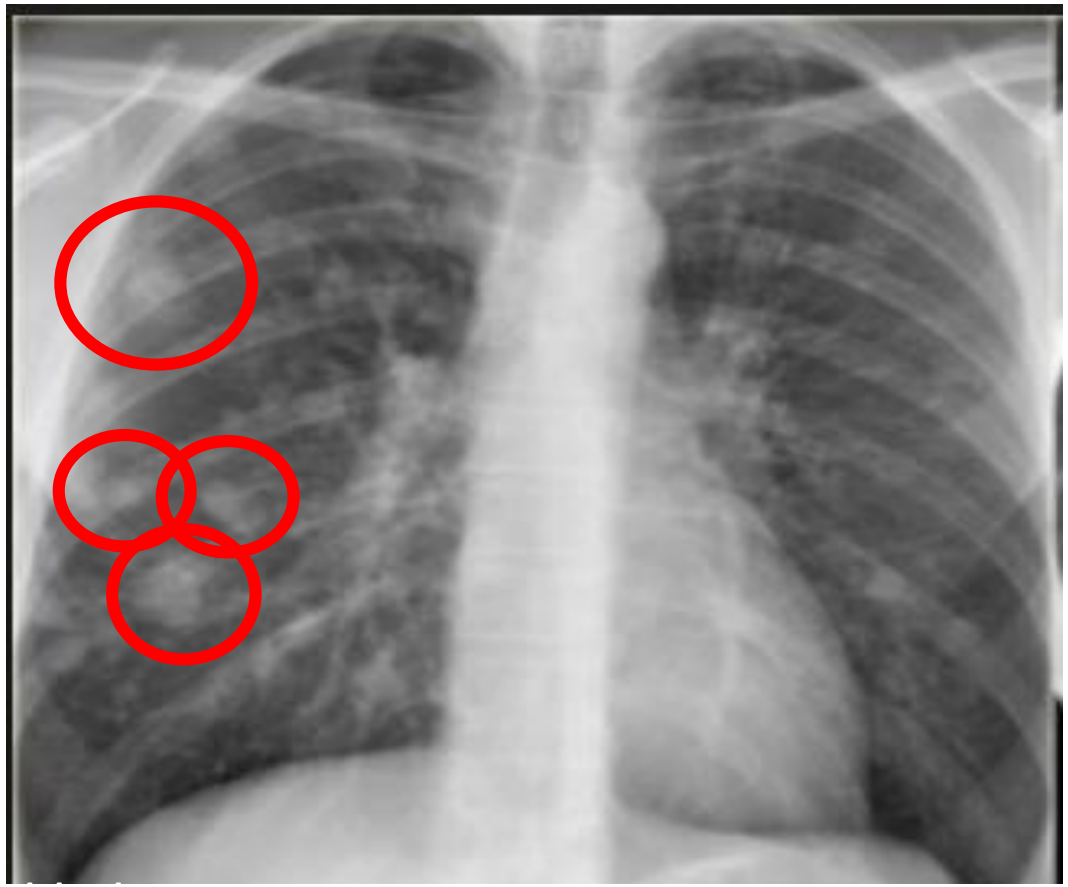
Case 1 – New back pain

- 55 year old woman
- History of rheumatoid arthritis
  - No regular medicines needed
- New back pain over 2 months, new “lump” in the left neck, just above collarbone
- No improvement with tylenol, heat, stretching.



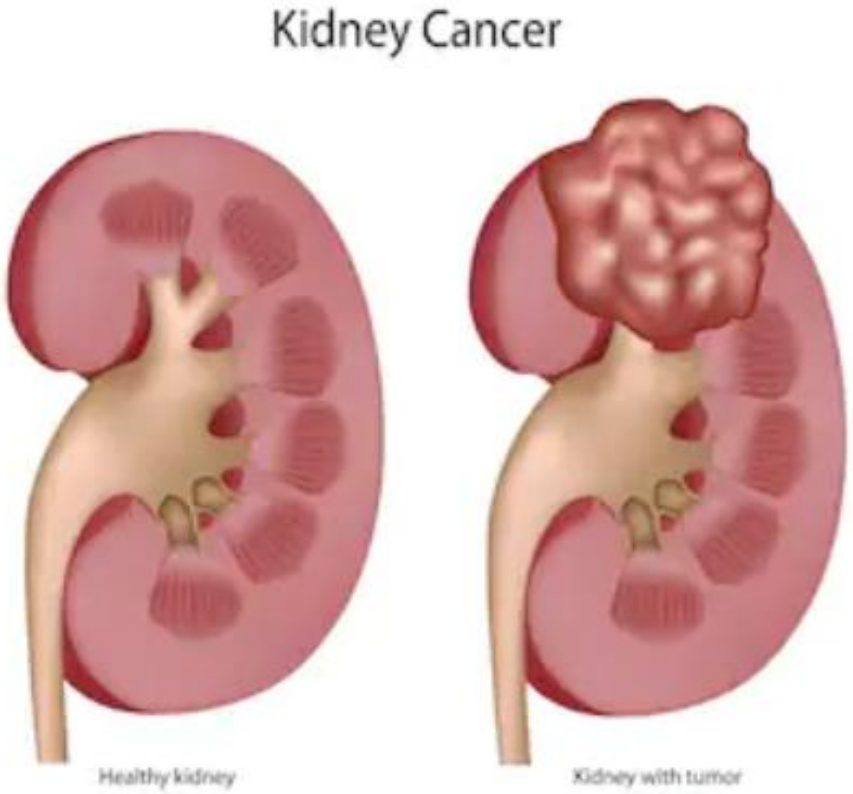


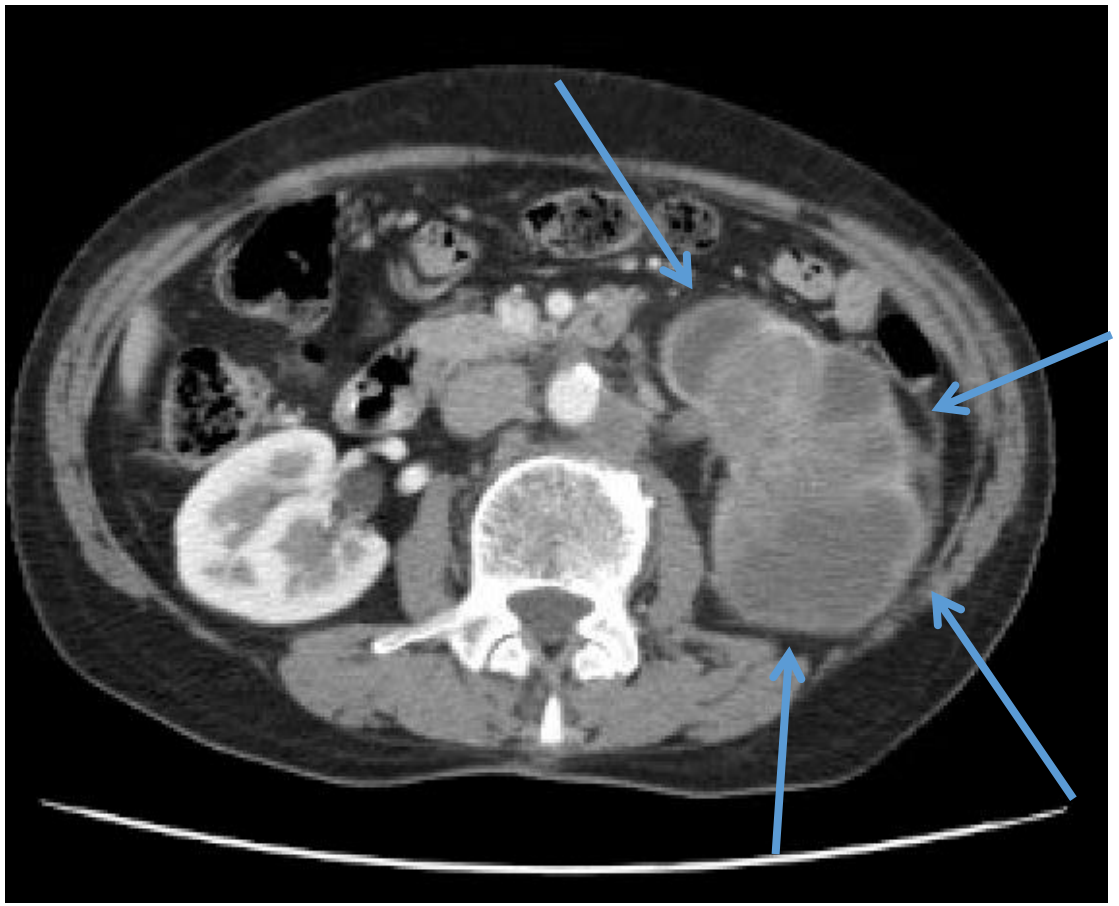
2016



2018

- CT scan of the abdomen = abnormal mass replacing most of the left kidney
  - "Suspicious for kidney cancer"

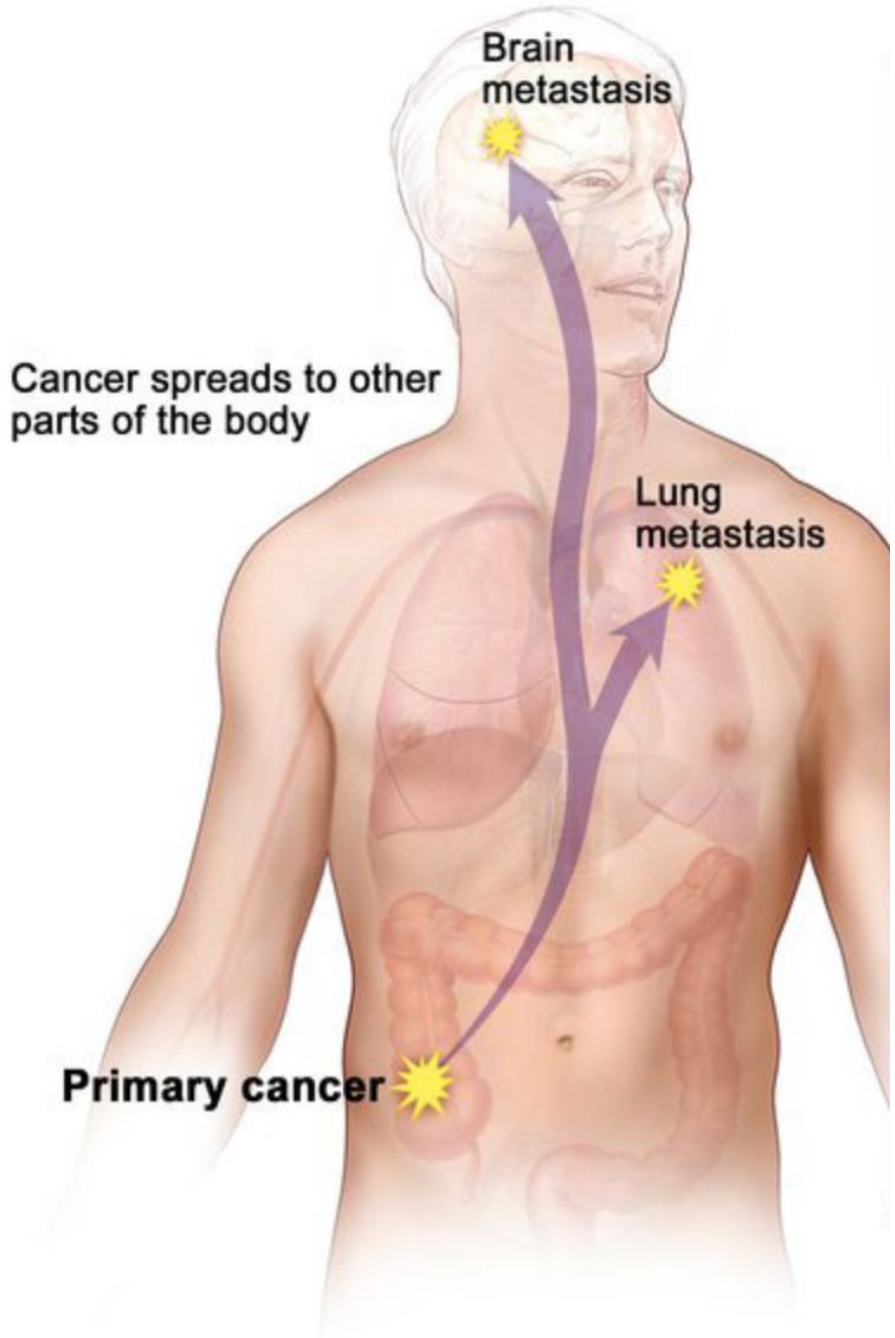




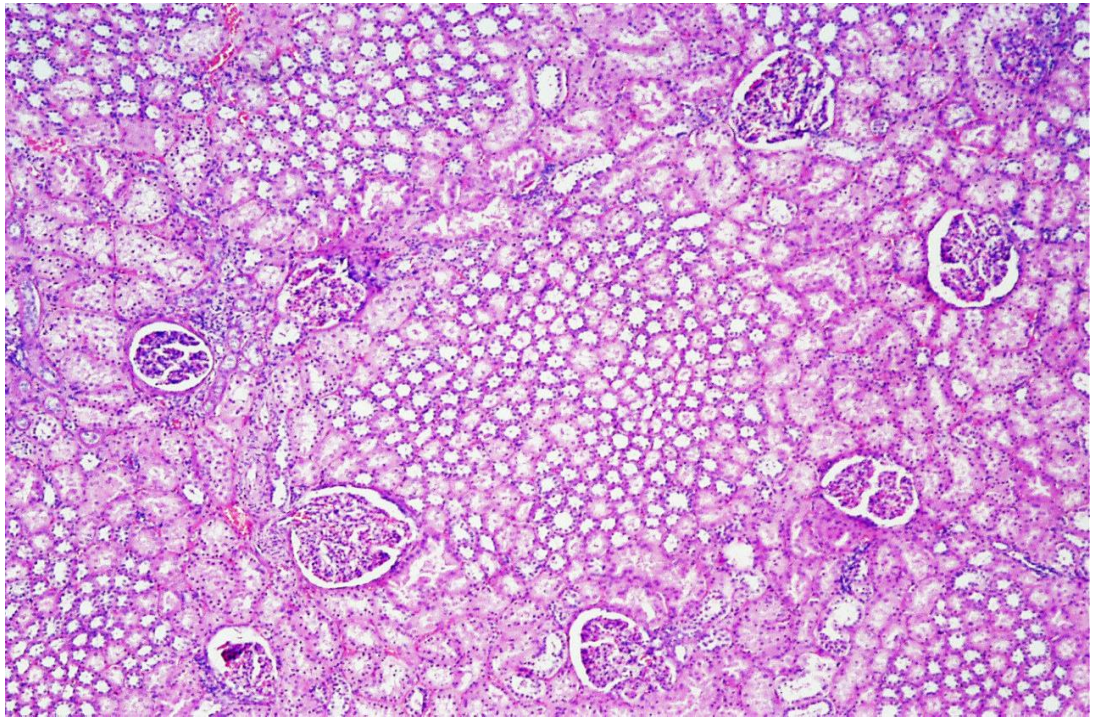
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

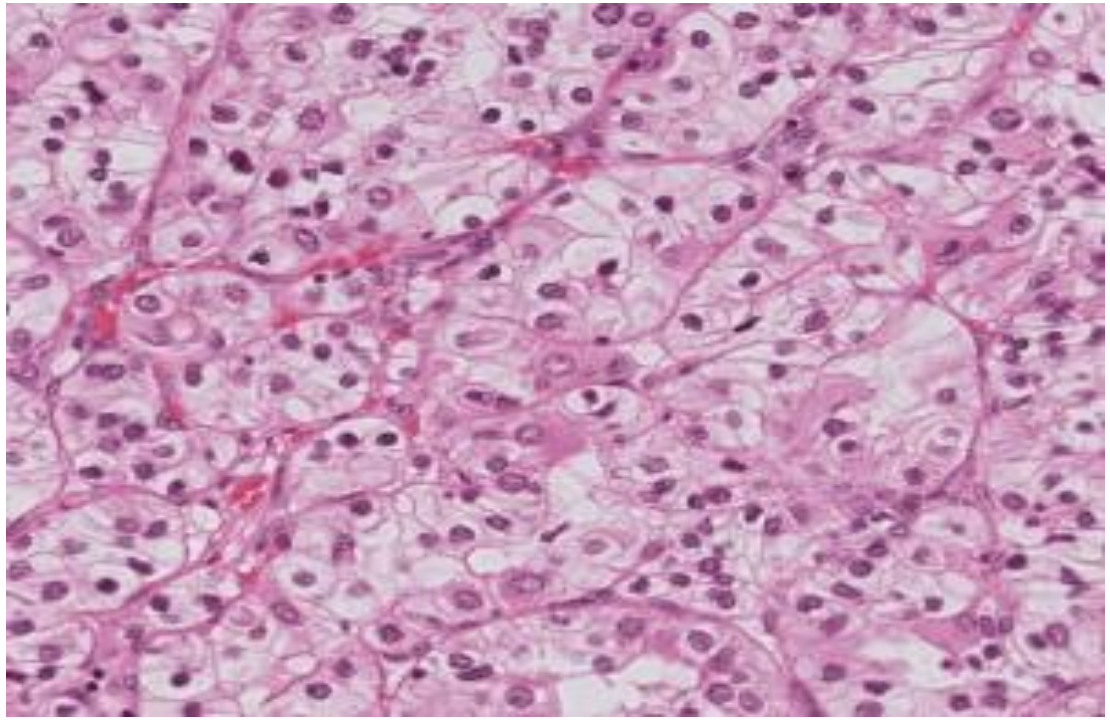
Metastasis



Neck biopsy confirms *Metastatic Kidney Cancer*



Normal kidney



Kidney cancer
(Clear cell type)

First meeting with Patient and husband

"I want to avoid getting chemotherapy, I hear it can have lots of side effects. Isn't it just toxic?"

"I hear there is a new treatment called immunotherapy. Can you tell me more about that?"

Question 1: Which of the following regimens are approved for kidney cancer?

a. Pembrolizumab plus Axitinib
b. Ipilimumab + Nivolumab
c. High-dose Interleukin-2
d. All of the above

Question 1: Which of the following regimens are approved for kidney cancer?

a. Pembrolizumab plus Axitinib
b. Ipilimumab + Nivolumab
c. High-dose Interleukin-2
d. All of the above

All are approved, currently high-dose IL-2 is used much less frequently

- Starts Ipilimumab + Nivolumab immunotherpy

- 7 weeks later: “My hands feel very stiff, and I have some pain in the joints. It is hard to open a jar.”

- Exam shows swelling of the joints in the fingers (proximal > distal) and you suspect she has autoimmune arthritis

Question 2: All of the following are reasonable except…

a. Start ibuprofen as needed
b. Aspiration of the swollen joint(s)
c. Referral to rheumatology (joint doctor)
d. Stop immunotherapy temporarily
e. Stop immunotherapy permanently

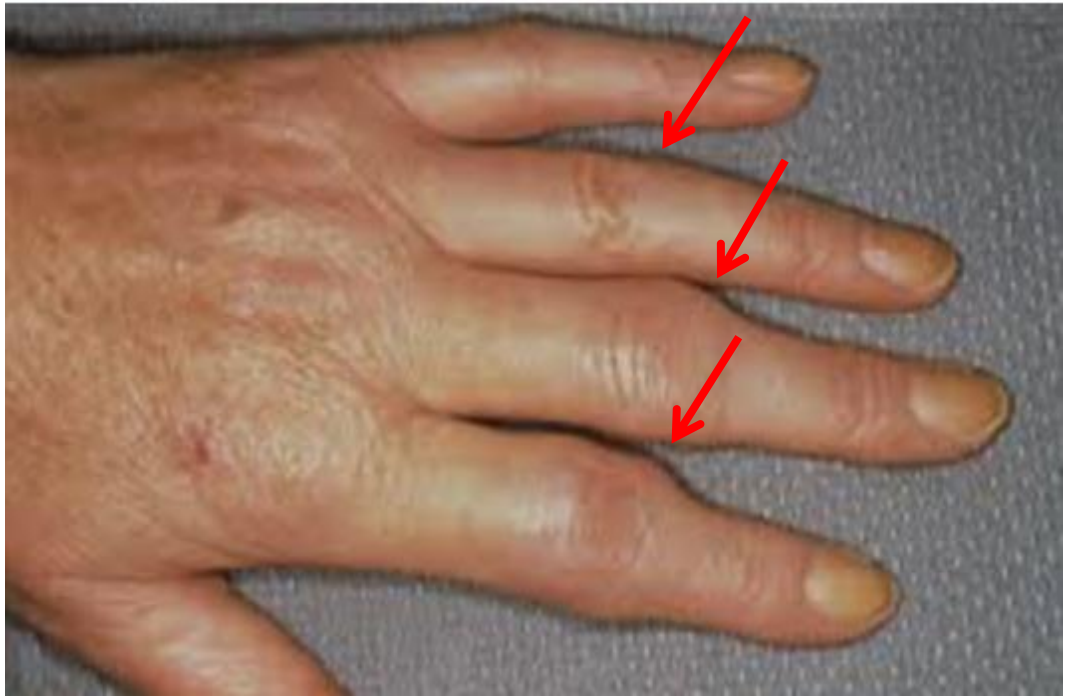
Question 2: All of the following are reasonable except…

a. Start ibuprofen as needed
b. Aspiration of the swollen joint(s)
c. Referral to rheumatology (joint doctor)
d. Stop immunotherapy temporarily
e. **Stop immunotherapy permanently**

Inflammatory Arthritis on Checkpoint Immunotherapy

- Occurs in up to 7% of patients
- Joint pain, stiffness, redness, warmth, swelling
- Early identification is key

- Treatment
  - Ibuprofen (NSAIDs)
  - Prednisone
  - Steroid injections
  - More potent immunosuppression (methotrexate, infliximab)



Inflammatory Arthritis on Checkpoint Immunotherapy

- Sees her rheumatologist (arthritis doctor)
- Starts around-the-clock ibuprofen
- Significant improvement in symptoms
  - No prednisone needed!

Question 3: Should we restart immunotheapy?

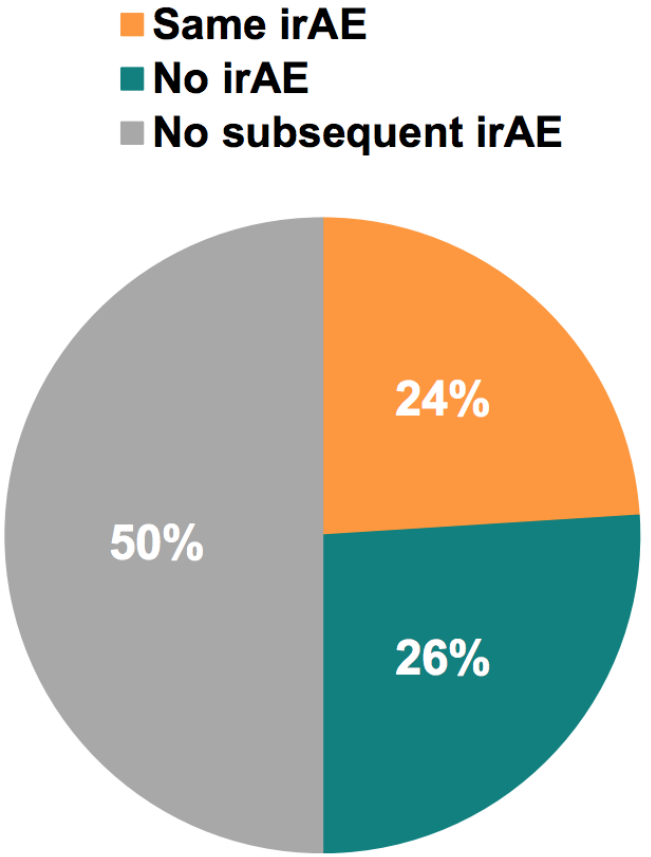
a. Yes – Ipilimumab and Nivolumab
b. Yes – Nivolumab alone
c. Maybe – Get a CT scan and see if she is responding
d. No - her risk of another adverse event is too high.

Question 3: Should we restart immunotheapy

a. **Yes – Ipilimumab and Nivolumab**
b. **Yes – Nivolumab alone**
c. **Maybe – Get a CT scan and see if she is responding**
d. No - her risk of another adverse event is too high.

Continuation of immunotherapy after adverse events

- Only half of patients will have another autoimmune adverse event
- Often in a different organ system
- Importance of being vigilant

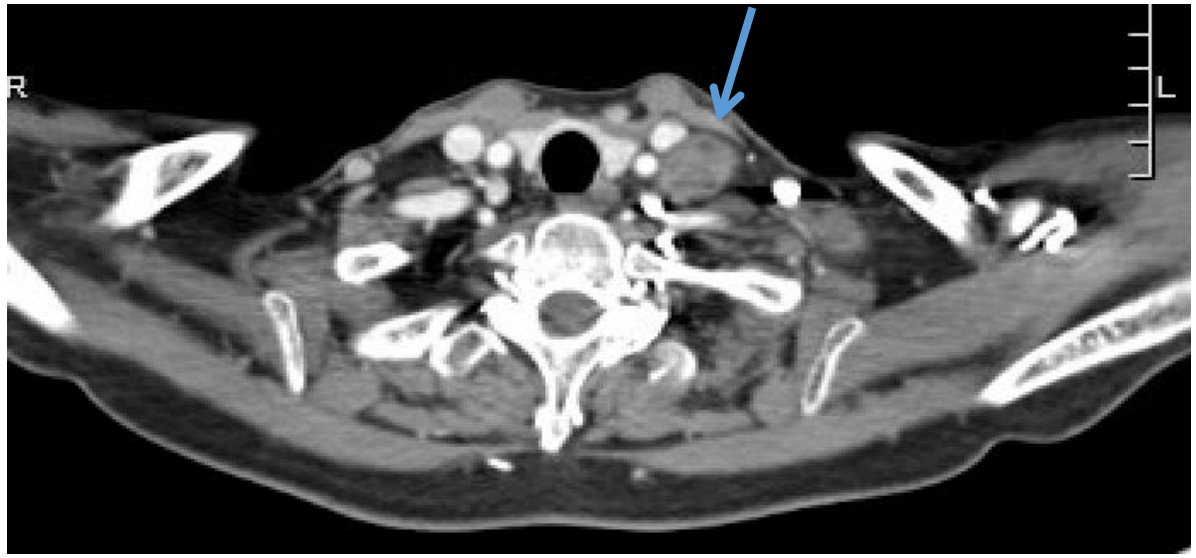


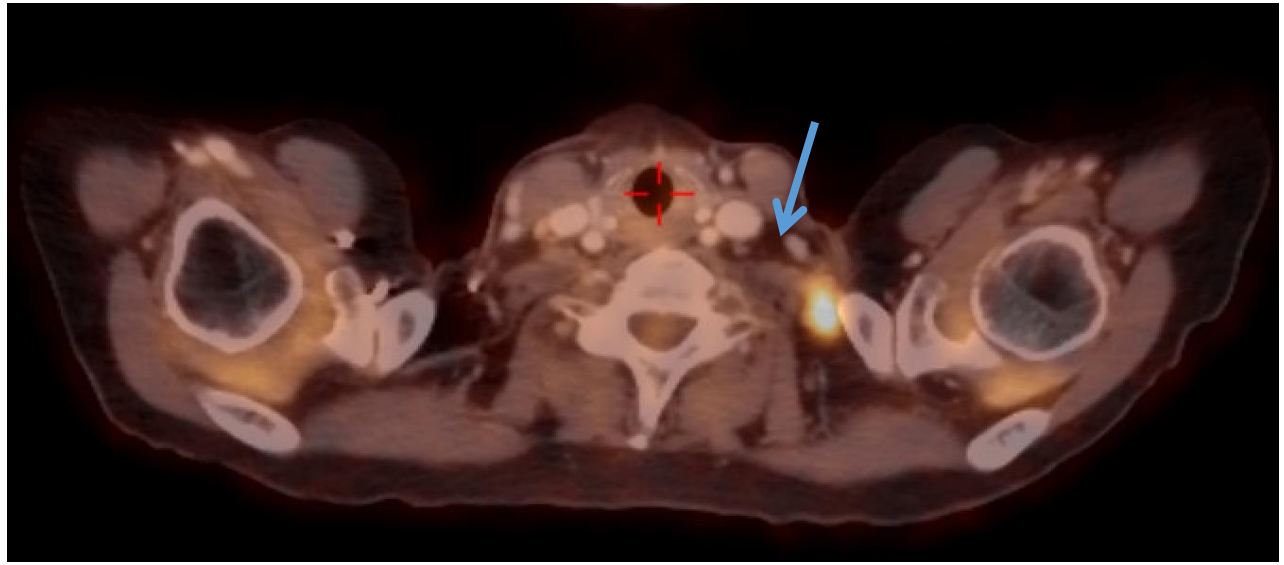
Santini JCO 35, no. 15_suppl (May 20 2017) 9012-9012.

- Ipilumumab stopped. Nivolumab continued.

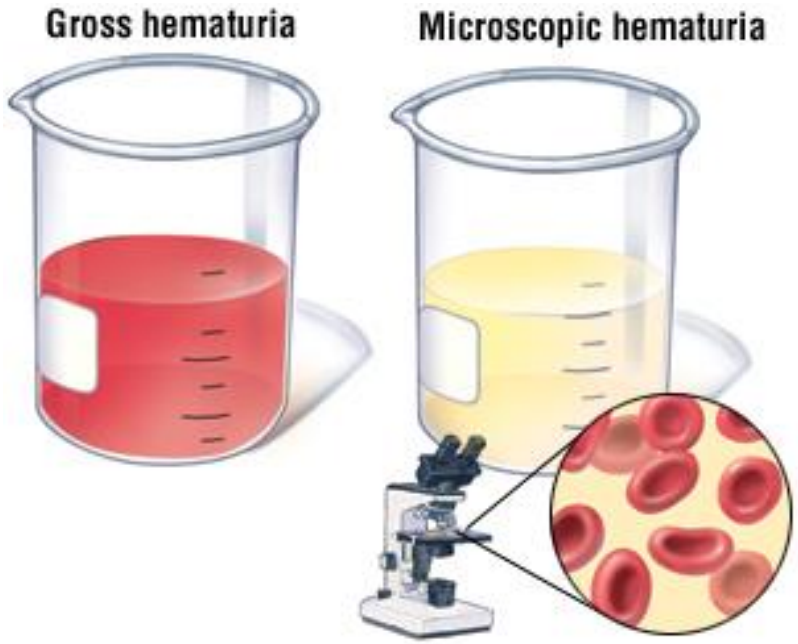
- Pt calls to report that she can no longer palpate the neck nodes

- PET CT:
  - Disappearance of the lymph node
  - Shrinkage of kidney mass
  - FDG uptake across multiple joints!

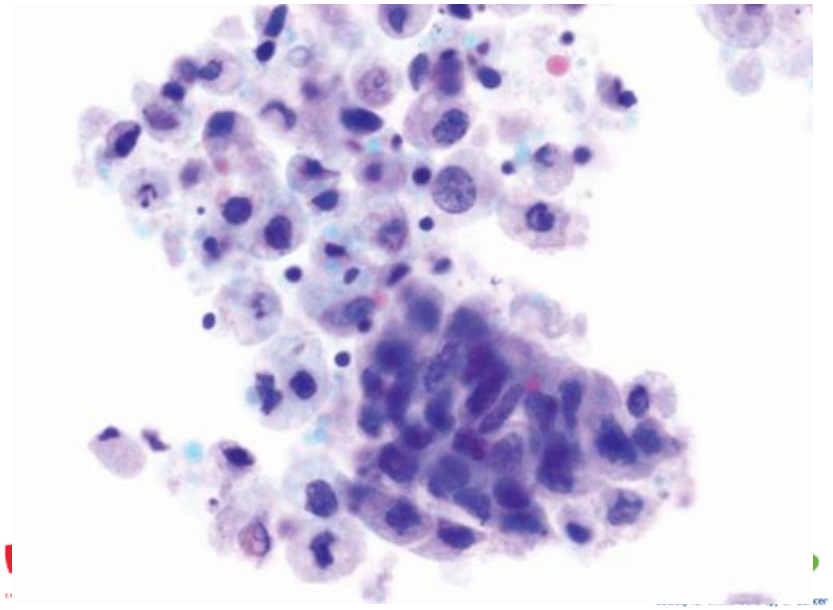




Case 2 - Hematuria

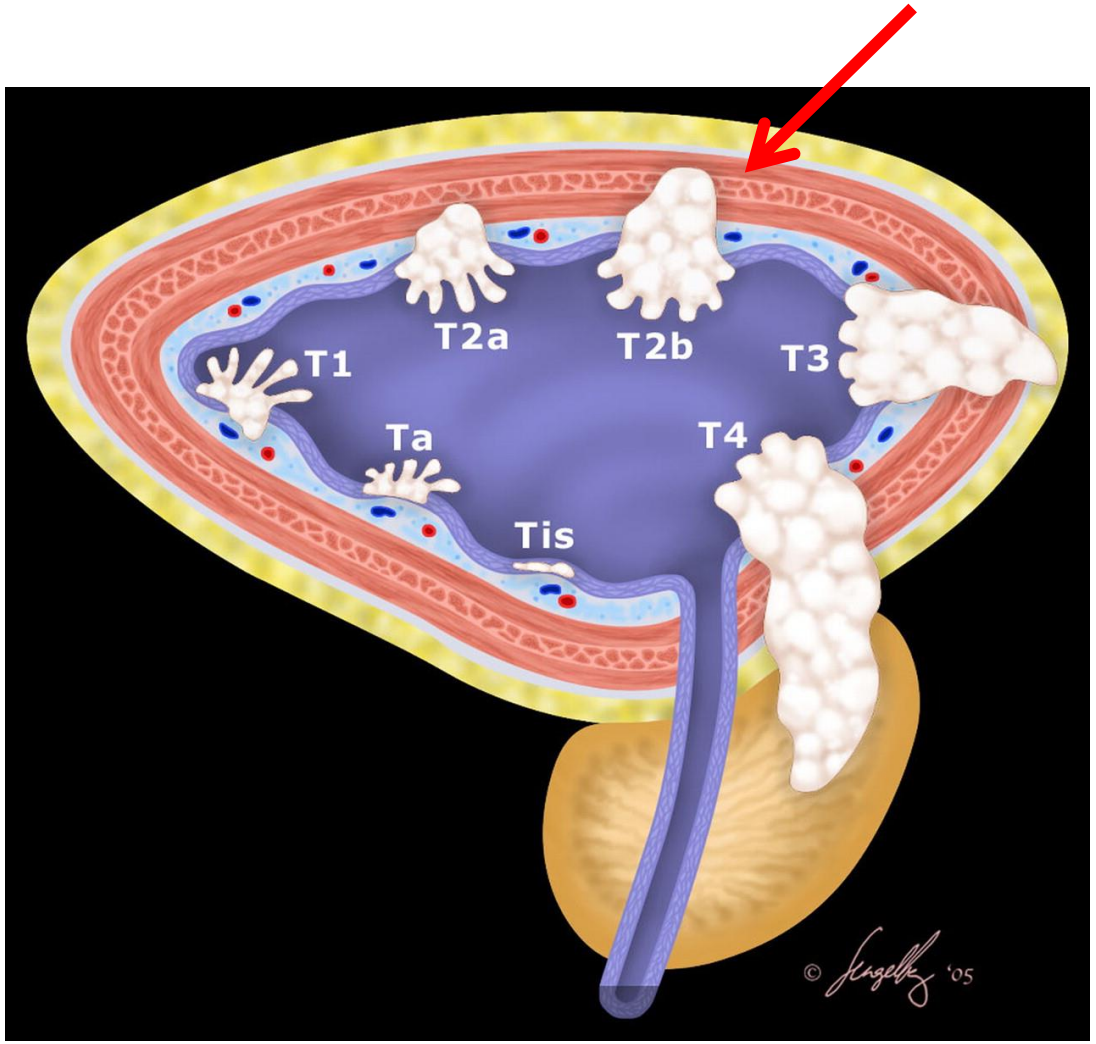


- 72 year old man - former smoker sees his Urologist
- “I’ve had a few episodes of red-colored urine”
- Exam, blood tests normal
- Urinalysis: +hemoglobin, many red blood cells
- Urine cytology: malignant



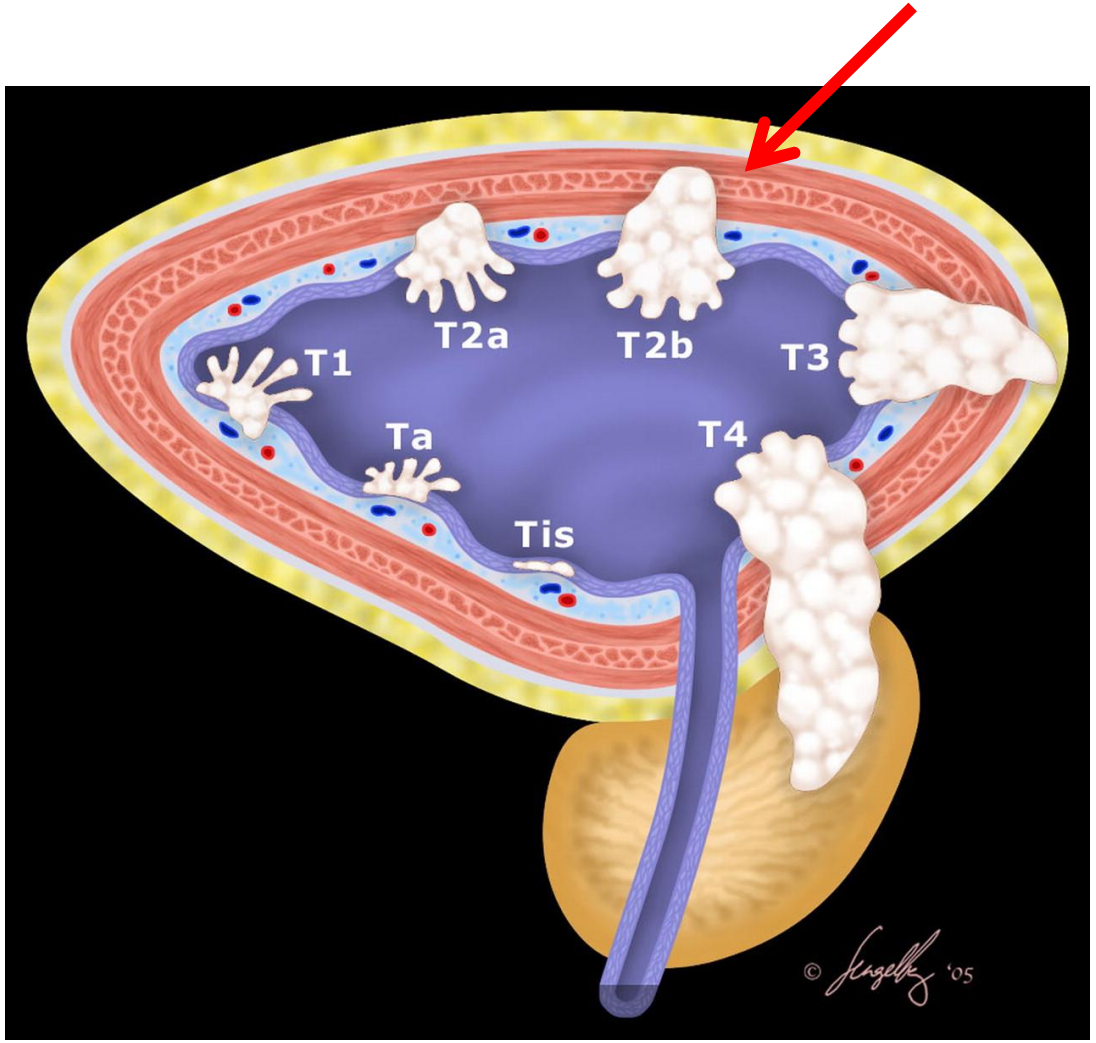
Case 2

- Cystoscopy (camera in the bladder) shows a suspicious mass
- Biopsy shows **urothelial cancer** (bladder cancer) invading the muscle wall of the bladder
- CT scans without metastases



Question 1: True or False?

"Immune checkpoint inhibitors are approved urothelial cancer in patients **without metastases**."

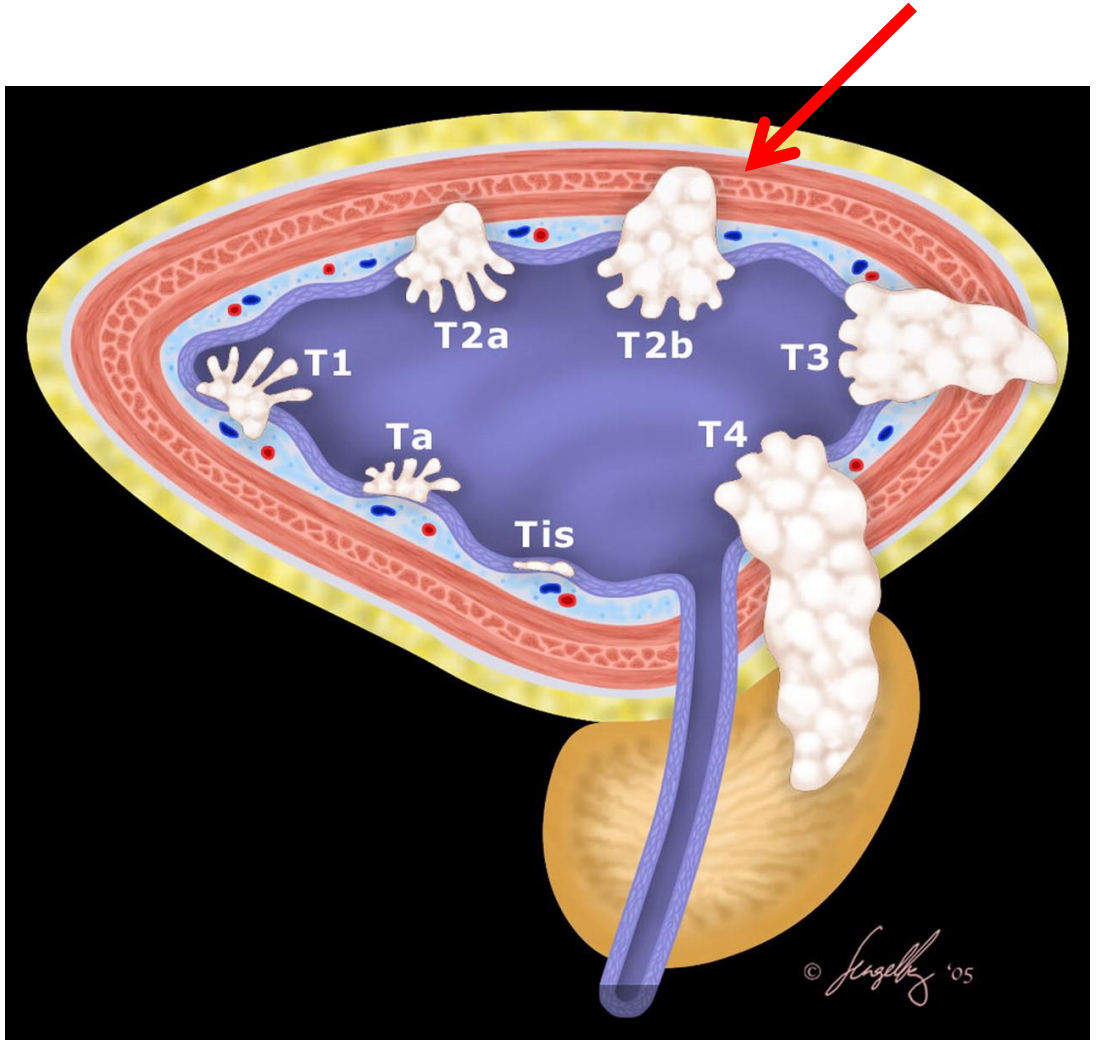


Question 1: True or False?

"Immune checkpoint inhibitors are approved urothelial cancer in patients **without metastases**."

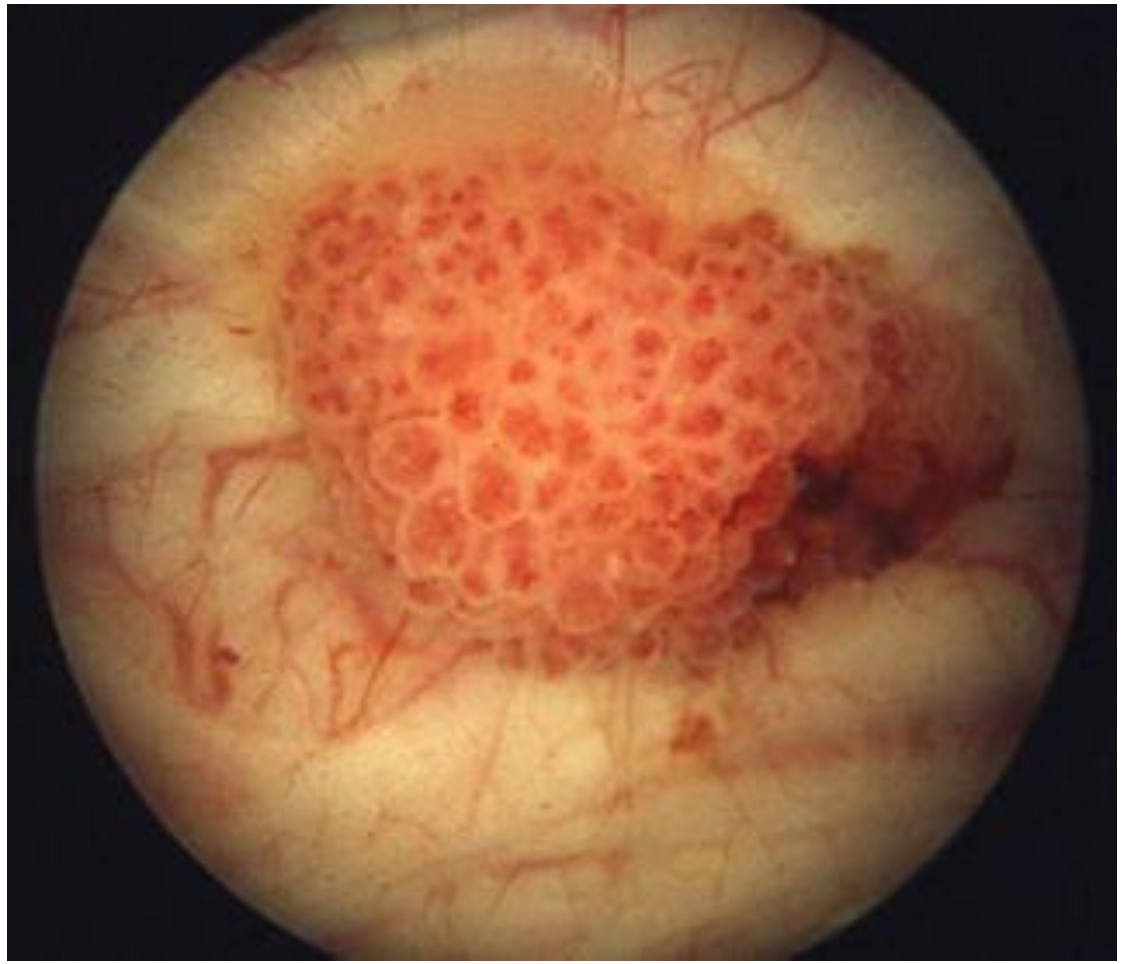
FALSE

- Only approved for ***metastatic urothelial cancer.***
- Ongoing studies are investigating checkpoint inhibitors in non-metastatic urothelial cancer



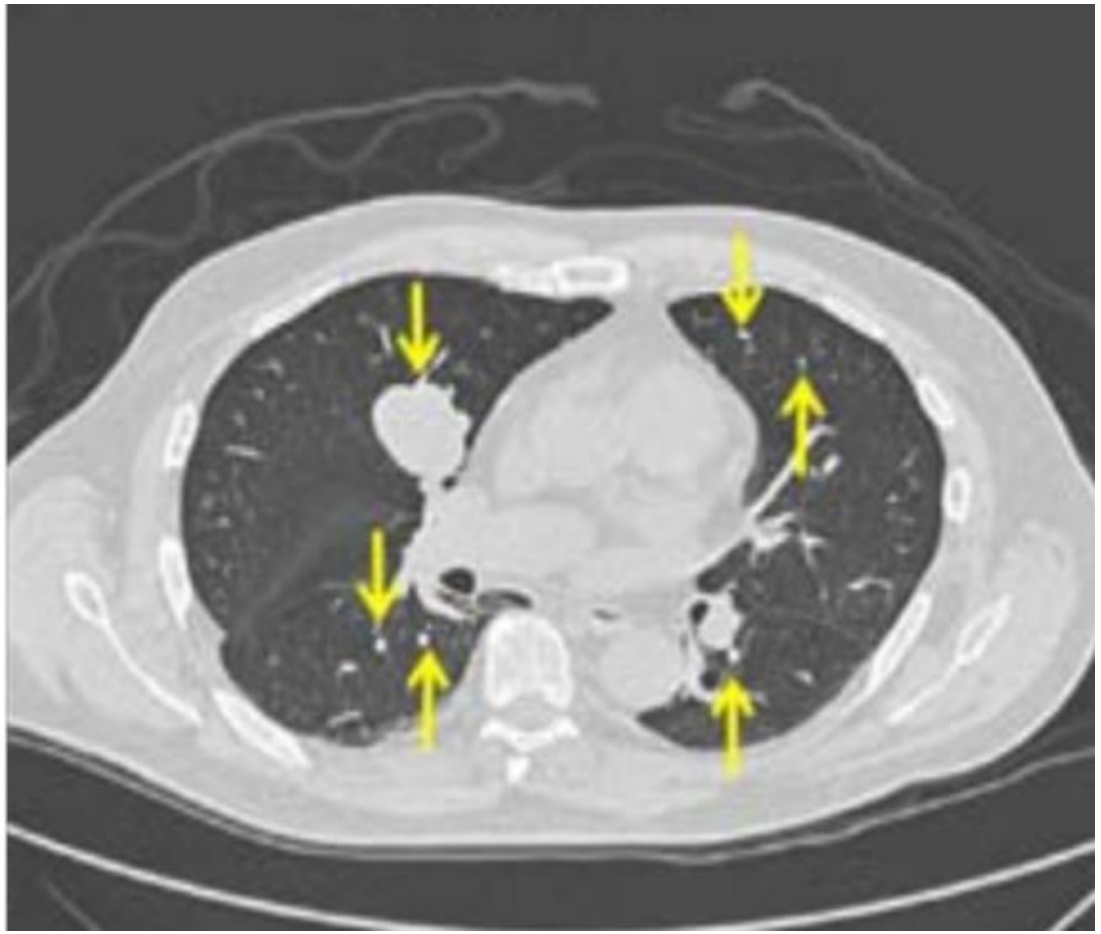
Case 2

- Patient undergoes chemotherapy for 4 cycles, then has his bladder removed.
- Pathology shows an aggressive tumor with multiple lymph nodes involved.
- “I know it might come back but I don’t want to more chemotherapy now.”



Case 2

- Does well for 8 months
- CT scan of the lungs
- And Biopsy shows **metastatic urothelial cancer.**



Question 2: Which of the following agents are **NOT** approved to treat him?

a. Pembrolizumab
b. Atezolizumab
c. Ipilimumab + Nivolumab
d. Taxane-based chemotherapy

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Question 2: Which of the following agents are not approved to treat him?

a. Pembrolizumab
b. Atezolizumab
c. Ipilimumab + Nivolumab
d. Taxane-based chemotherapy

This combination is in trials, but not yet approved for urothelial cancer

Case 2

- Starts Pembrolizumab

- 1 month later
  - “I am urinating a lot at night”
  - “I am thirsty all the time”
  - “I am *very* tired”

https://shutterstock.com/search/fatigue

What to do now?

a. Reassurance – pembrolizumab can cause fatigue
b. Add a sleep aid
c. Limit water intake in the afternoon and evenings
d. Check blood sugar

What to do now?

a. Reassurance – pembrolizumab can cause fatigue
b. Add a sleep aid
c. Limit water intake in the afternoon and evenings
d. **Check blood sugar**

- Blood surgar 532 mg/dL!
  - Normal is <200 mg/dL

- Dx: Type 1 Diabetes Mellitus
  - RARE complication of immunotherapy
  - Destruction of insulin-producing cells in the pancreas

Should we stop immunotherapy?

a. Yes
b. No

- Treatment
  - Starts insulin
  - No corticosteoids given
  - Continues on immunotherapy

- Scans 1 month later
  - Partial response to therapy

Summary

- Multiple checkpoint inhibitors approved for Kidney and Bladder Cancer
  - Under investigation for prostate cancer
- Severe toxicity is uncommon and generally manageable
- Treatment does not need to be stopped unless severe or recurrent toxicities.