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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

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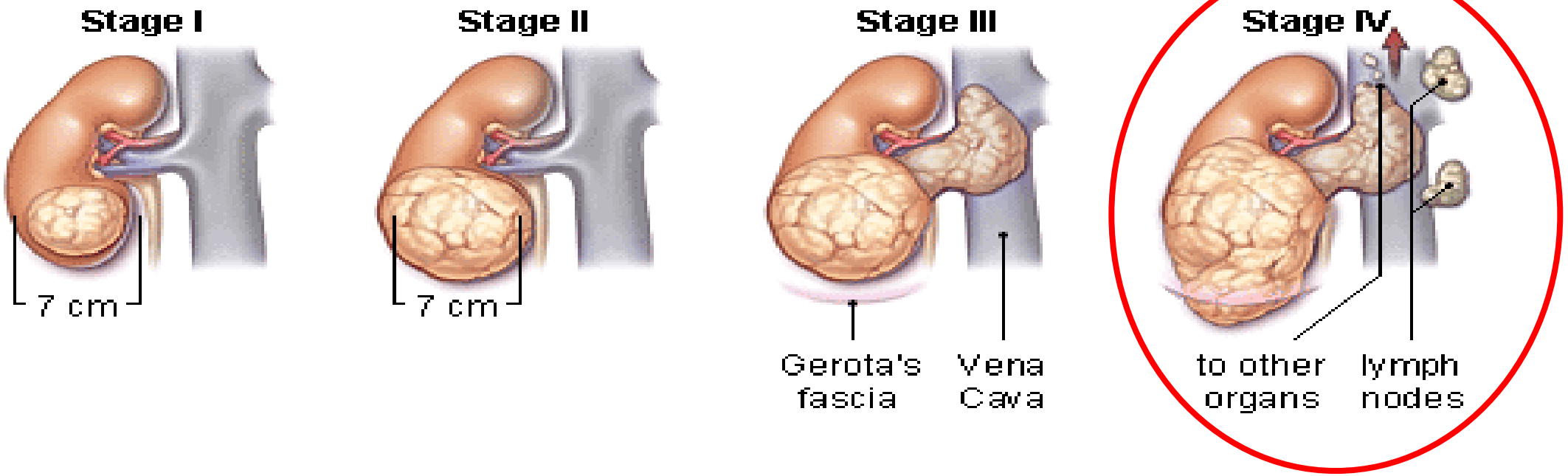
Disclosures

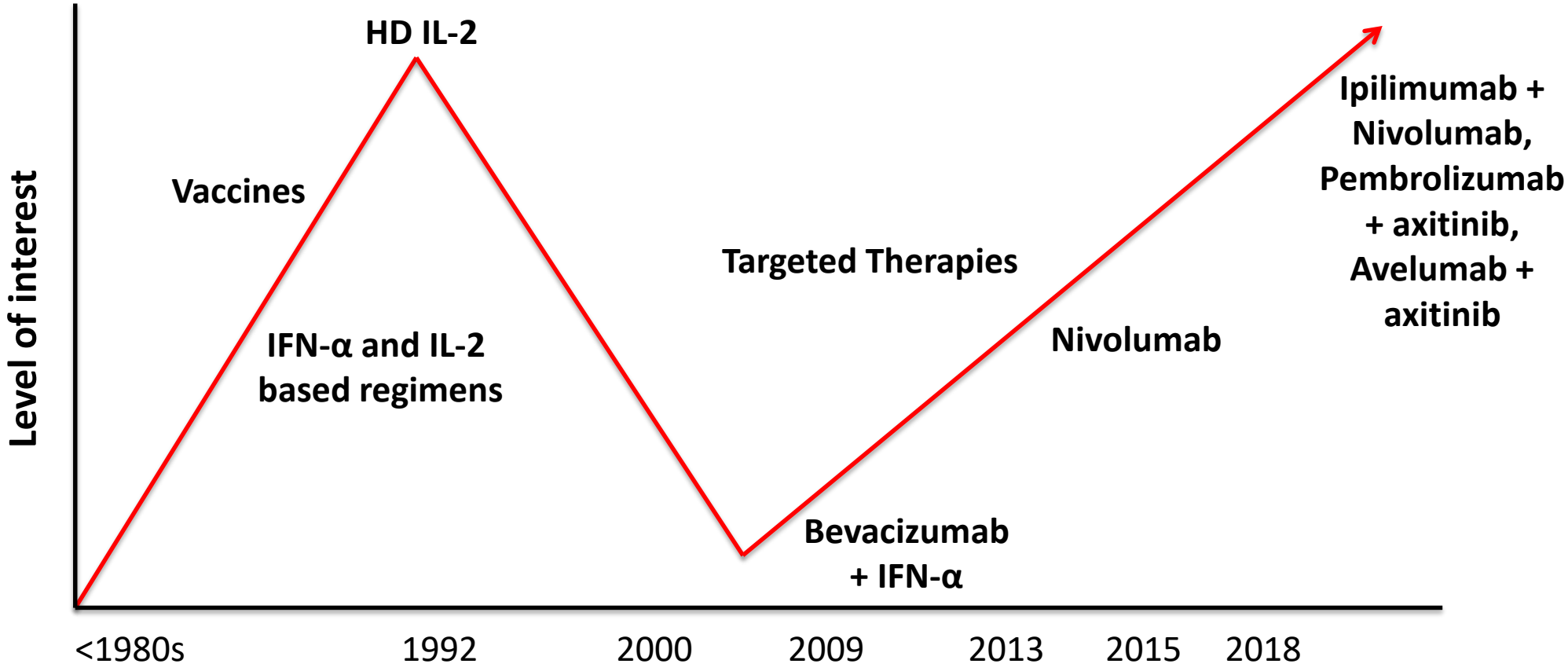
- Consulting Fees: Dendreon, Exelixis
- I will be discussing non-FDA approved indications during my presentation.

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

Surgically resectable → Metastatic



History of Immunotherapy in mRCC



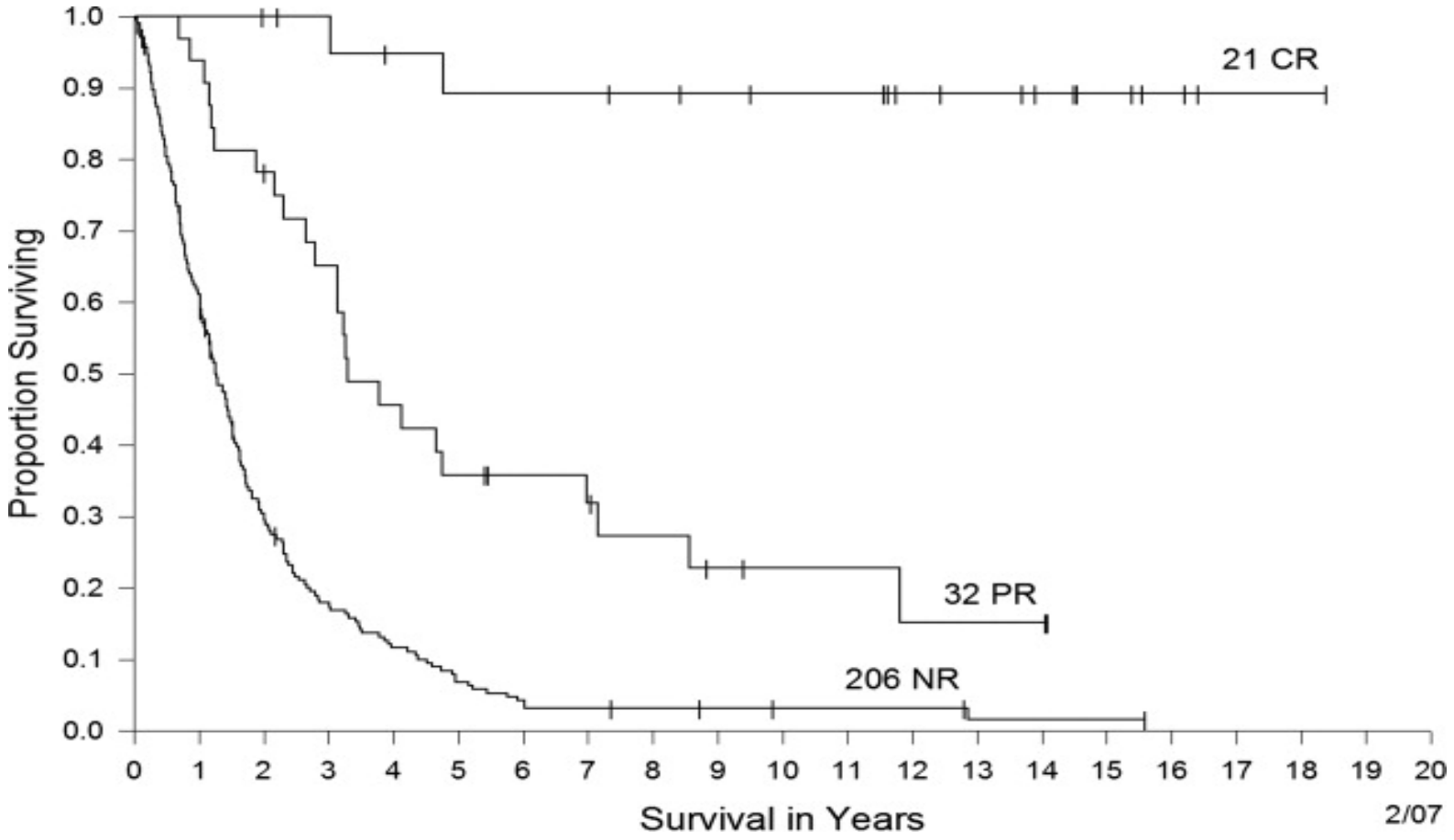
Resurgence of interest in immunotherapy

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 + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
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
Avelumab + axitinib	2019	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily

High Dose IL-2 in mRCC

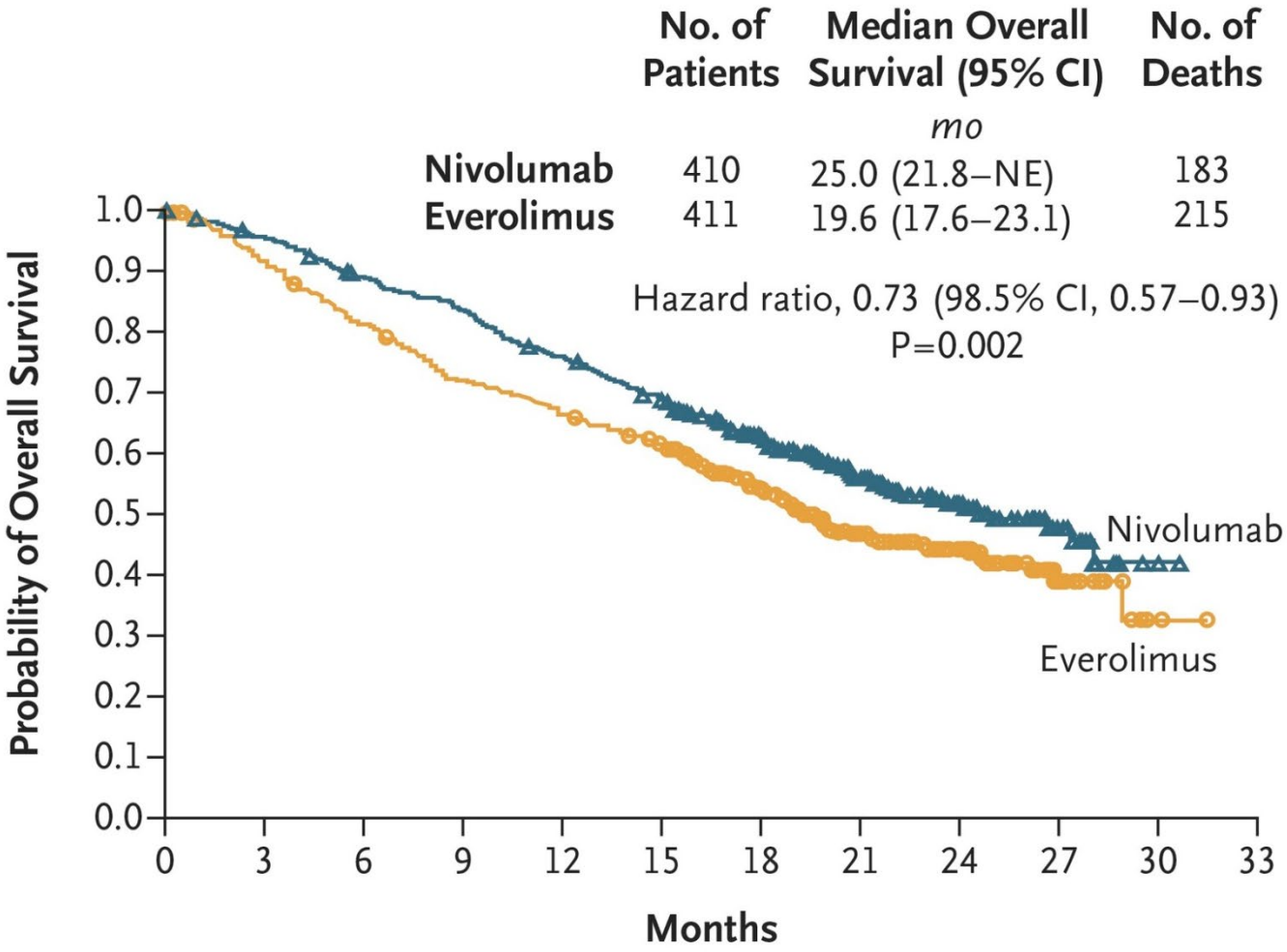
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

Second-Line Nivolumab in mRCC

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

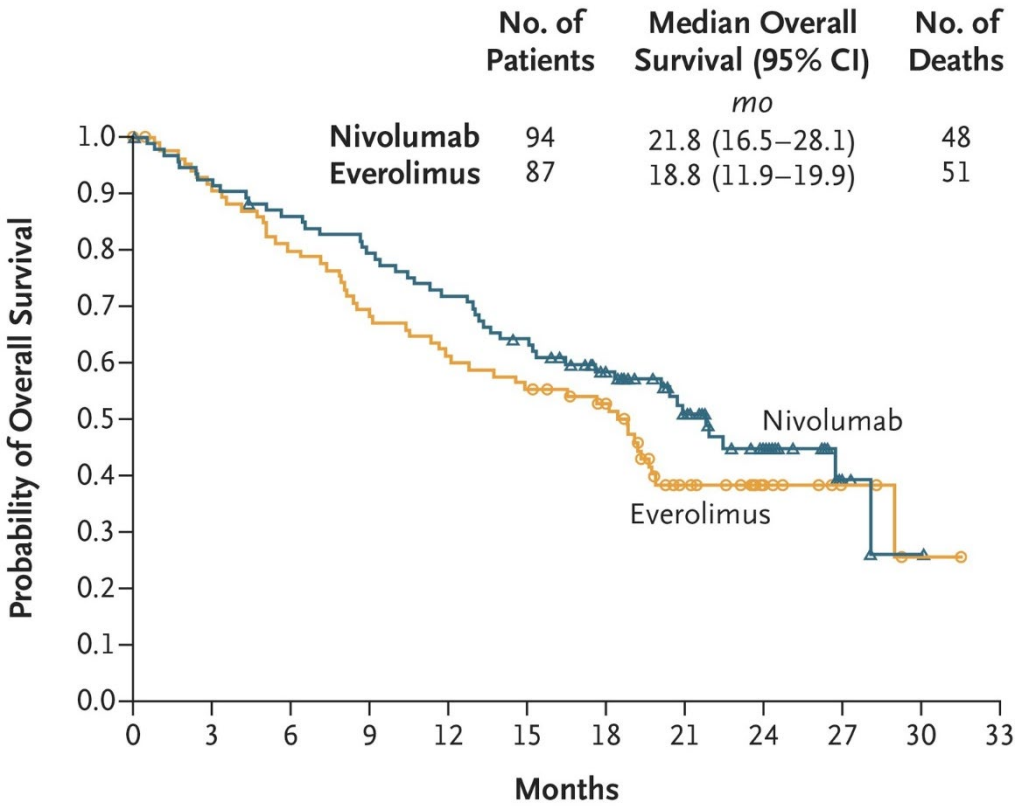


Motzer et al. NEJM 2015

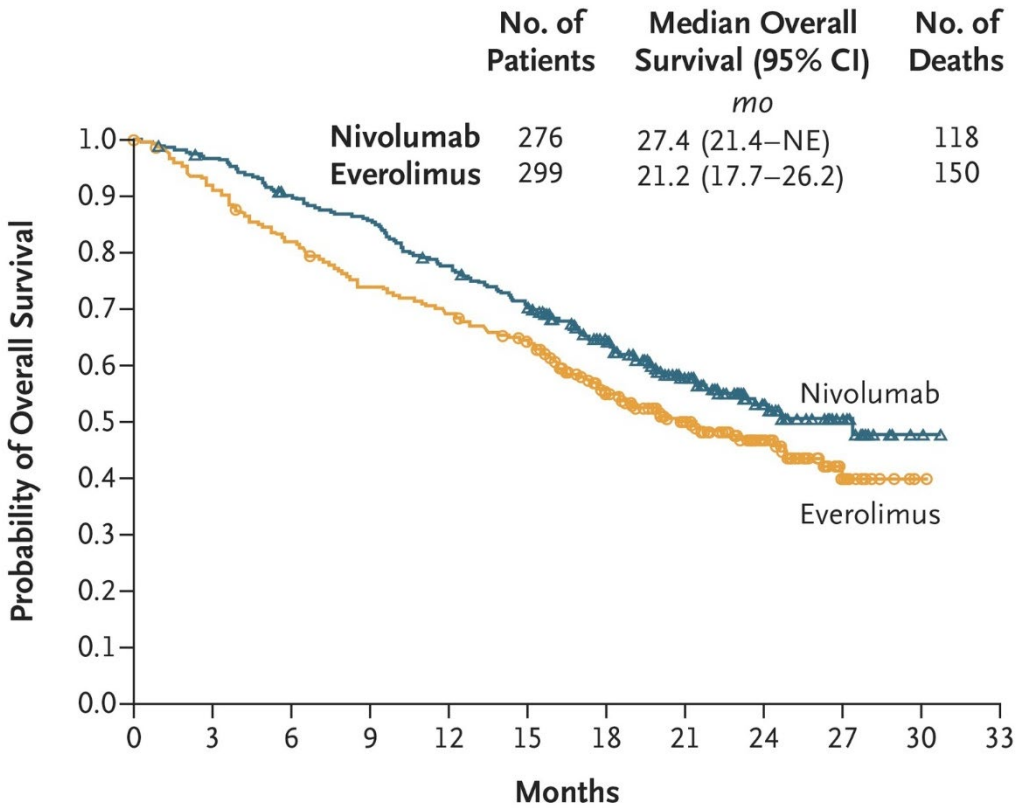
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%

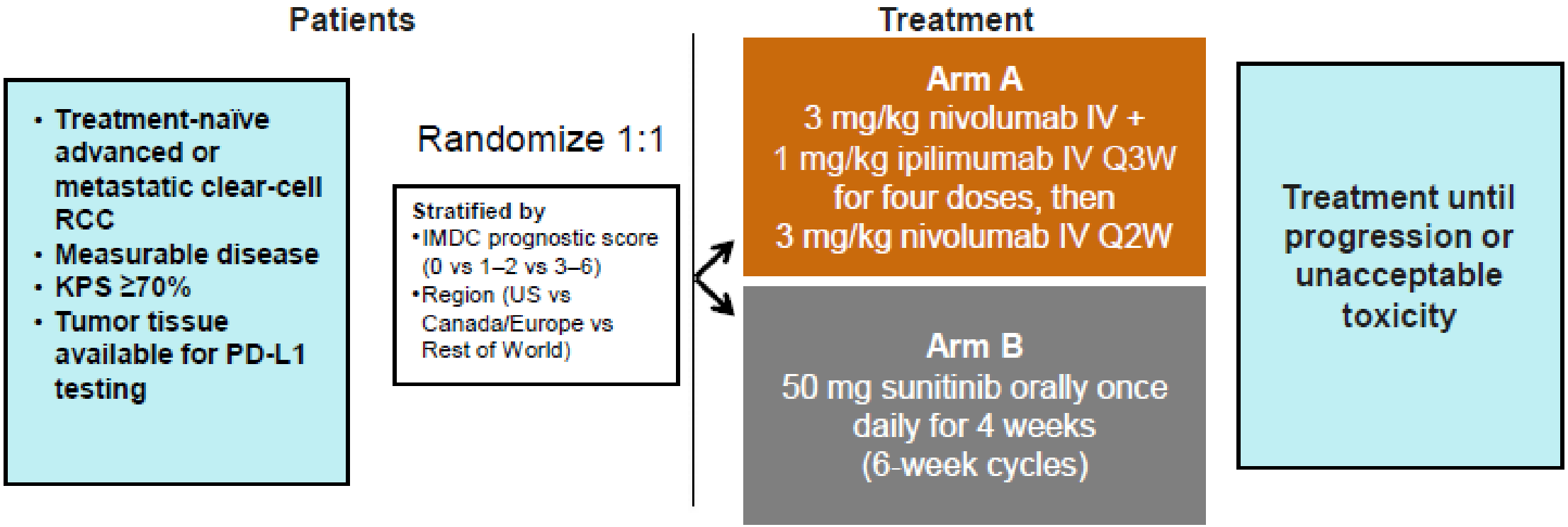


PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC



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

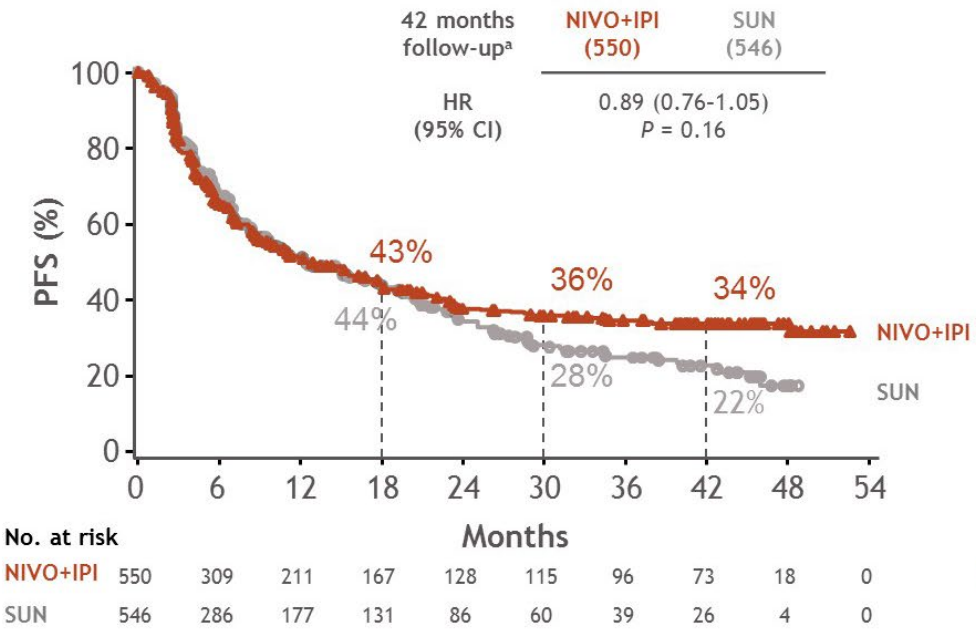
IMDC = International Metastatic RCC Database Consortium

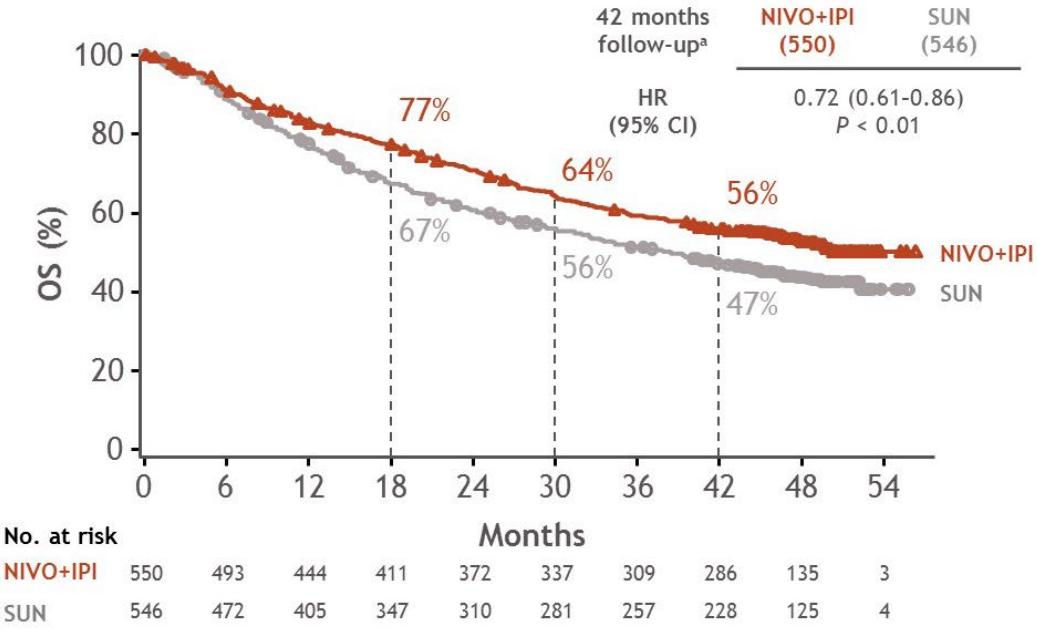
Escudier et al. ESMO 2017

First-line Nivolumab + Ipilimumab in mRCC by IMDC Risk: overall survival

CheckMate 214

Follow-up
= 42 months

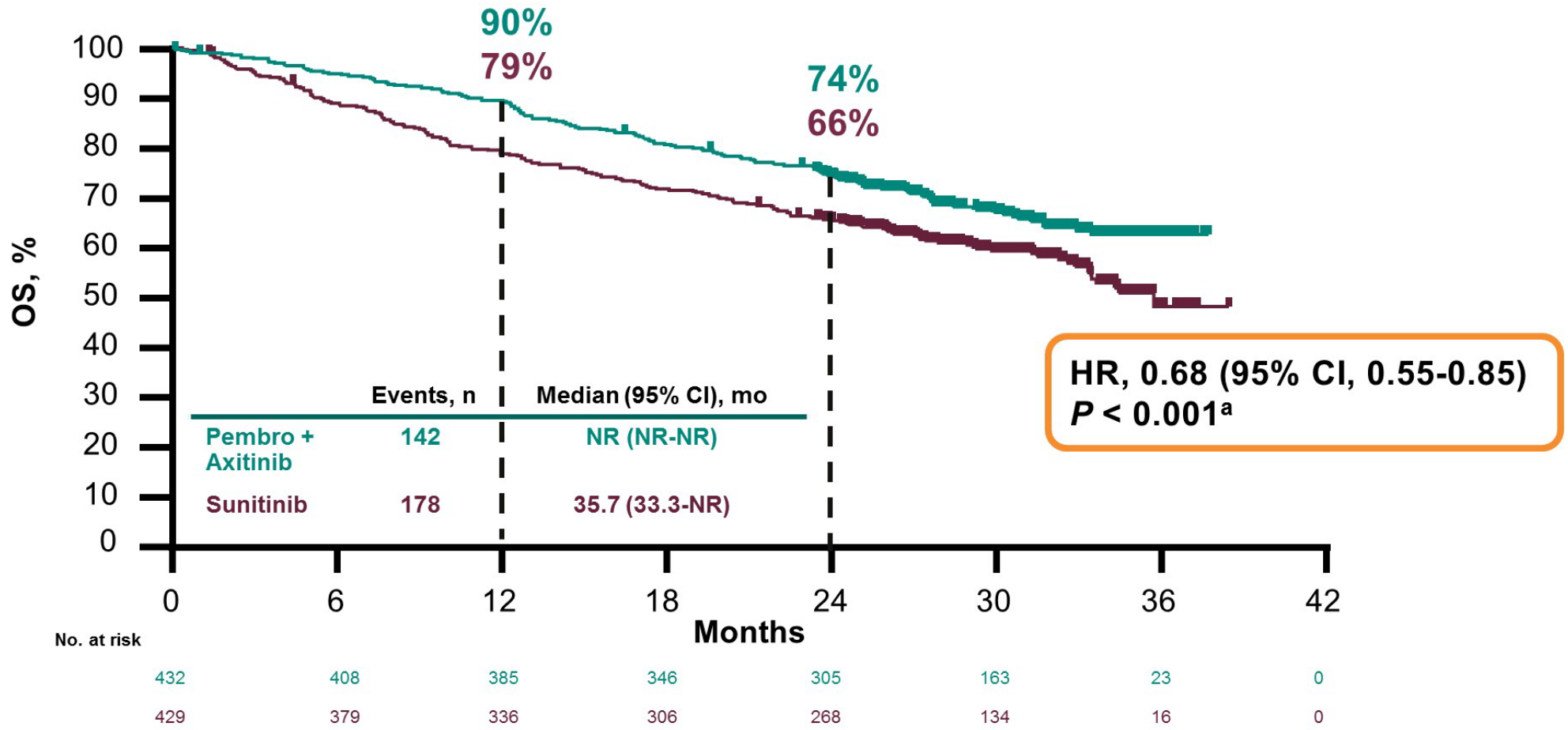




[a]N numbers represent the intention-to-treat population.
CI, confidence interval; HR, hazard ratio. 1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290; 2. Tannir NM, et al. Oral presentation at the ASCO Genitourinary Cancers Symposium; February 14-16, 2019; San Francisco, CA, USA. Abstract 547.

Tannir et al. ASCO GU 2020

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



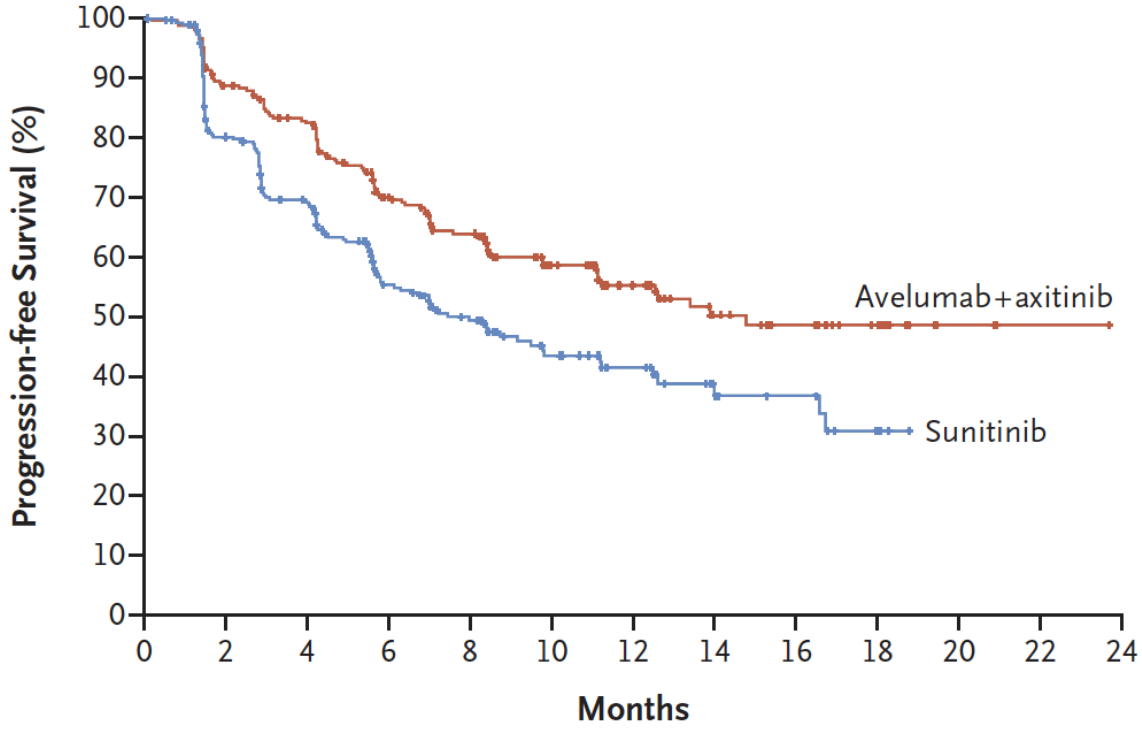
[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

Plimack, ASCO 2020

First-line avelumab + axitinib in mRCC: progression-free survival

- Primary Endpoint: PFS and OS in PD-L1+
- Median PFS in PD-L1+: 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR in PD-L1+: 55.2% vs 25.5%
- OS data: immature

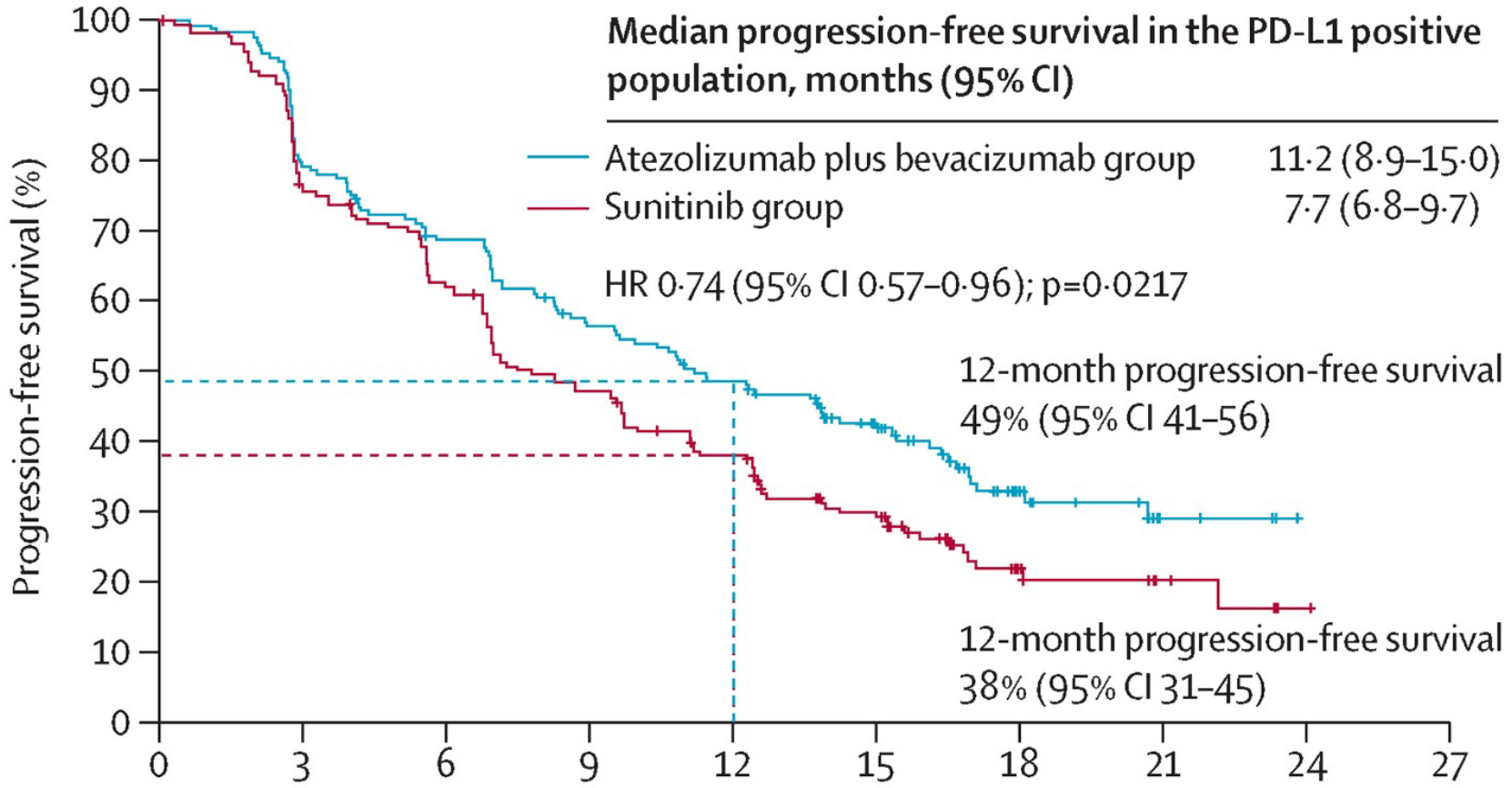
JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019.

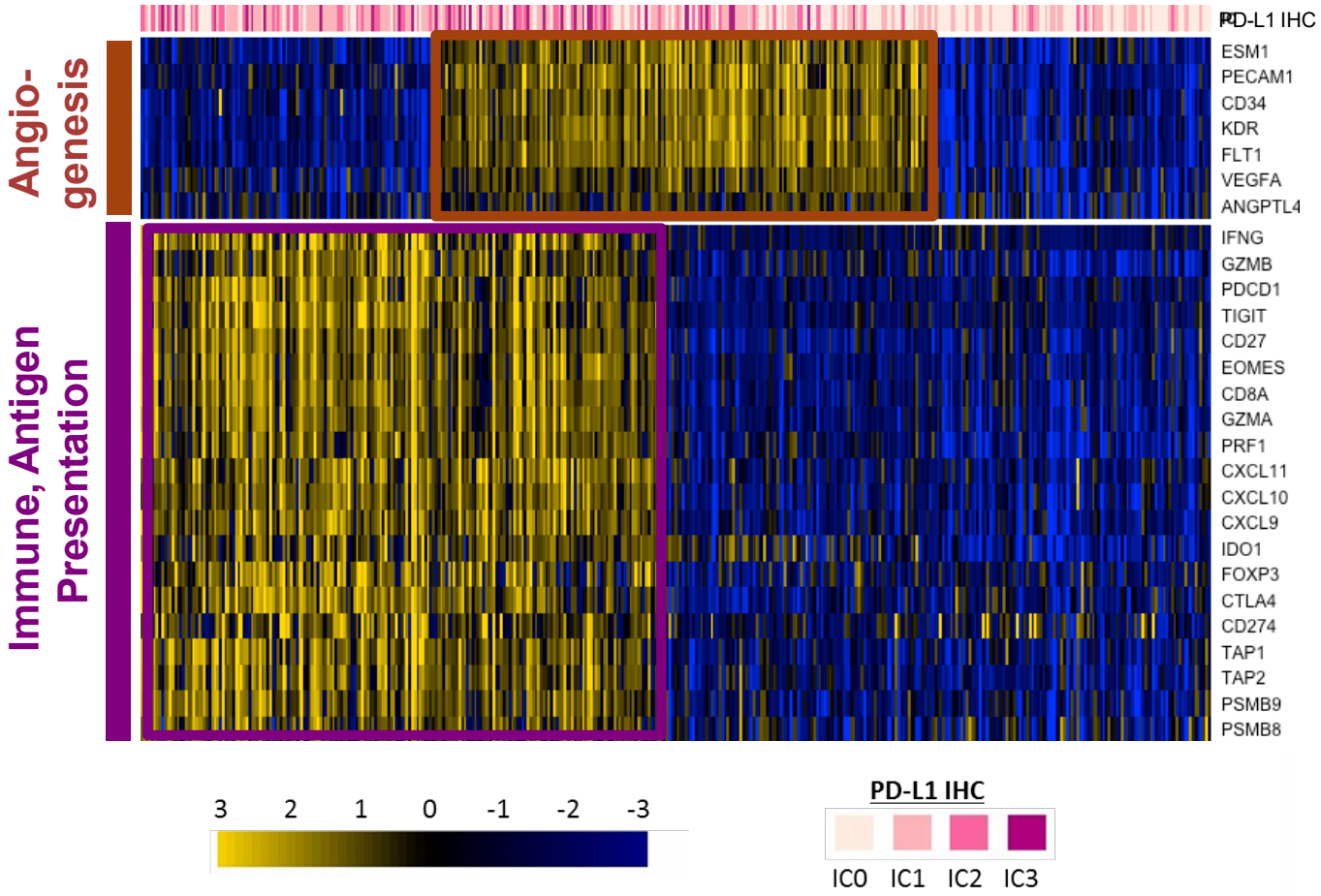
Under investigation: First-line atezolizumab + bevacizumab in PD-L1+ mRCC

Immotion151



Rini, The Lancet 2019.

Under investigation : First-line atezolizumab + bevacizumab: molecular signatures



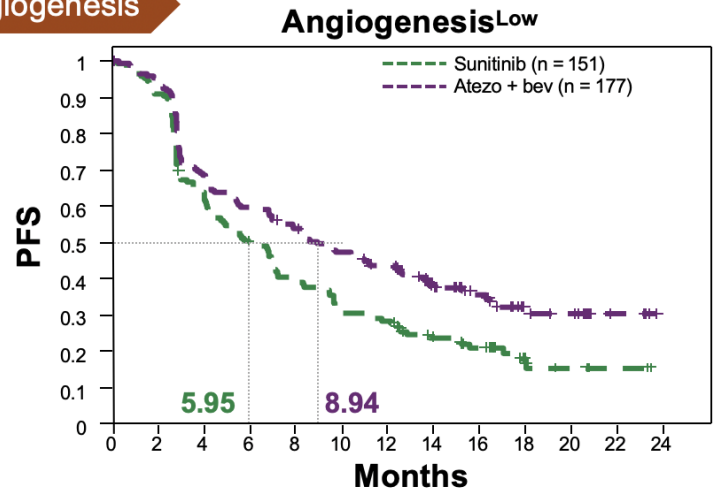
Identification of gene signatures based on association with clinicaloutcome

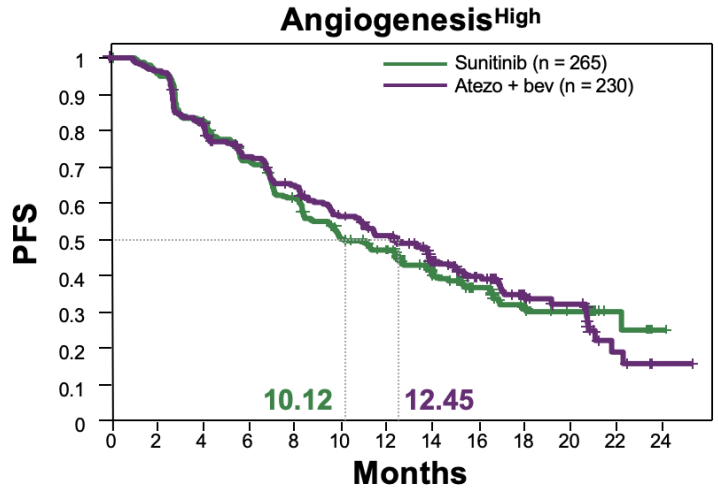
- T_{eff}: *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

Rini et al, ESMO 2018

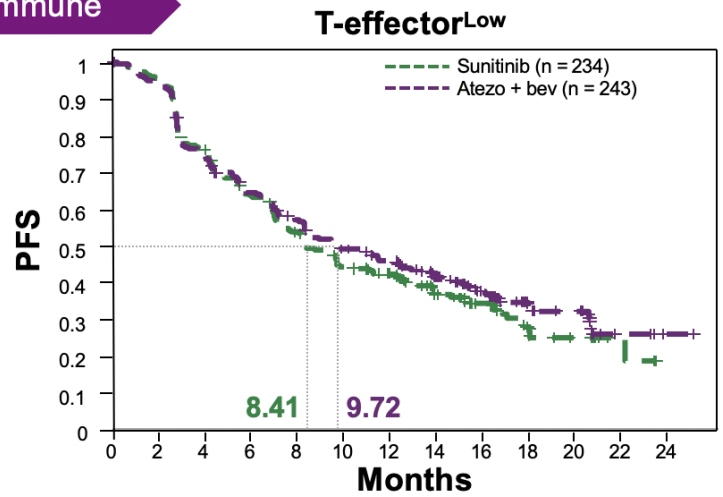
Under investigation : First-line atezolizumab + bevacizumab: molecular signatures

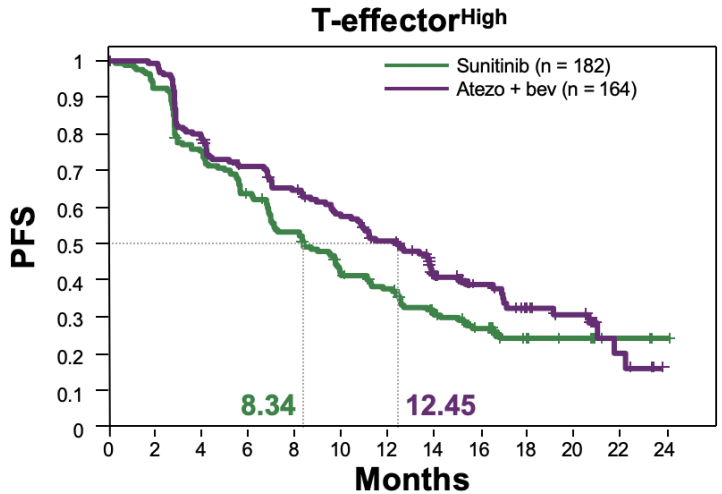
Angiogenesis





Immune





Rini et al, ESMO 2018

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

Study	Treatment arm(s)	Patient selection criteria	N	ORR	Median PFS (months)	Median OS (months)
CheckMate 214	Nivolumab + ipilimumab*	Untreated, advanced clear cell RCC (poor/intermediate risk)	550	42%	12.0	47.0
	Sunitinib		546	26%	8.3	26.6
KEYNOTE-426	Pembrolizumab + axitinb*	Untreated, advanced clear cell RCC	432	60%	15.4	NR
	Sunitinib		429	40%	11.1	35.7
JAVELIN Renal 101	Avelumab + axitinib*	Untreated, advanced clear cell RCC	442	52.5%	ITT: 13.3 PD-L1+: 13.8	ITT: NE PD-L1+: NE
	Sunitinib		444	27.3%	ITT: 8.0 PD-L1+: 7.0	ITT: NE PD-L1+: 25.6
IMmotion151	Atezolizumab + bevacizumab	Untreated, advanced clear cell or sarcomatoid RCC	454	ITT: 37% PD-L1+: 43%	ITT: 11.2 PD-L1+: 11.2	ITT: 33.6 PD-L1+: 34.0
	Sunitinib		461	ITT: 33% PD-L1+: 35%	ITT: 8.4 PD-L1+: 7.7	ITT: 34.9 PD-L1+: 32.7

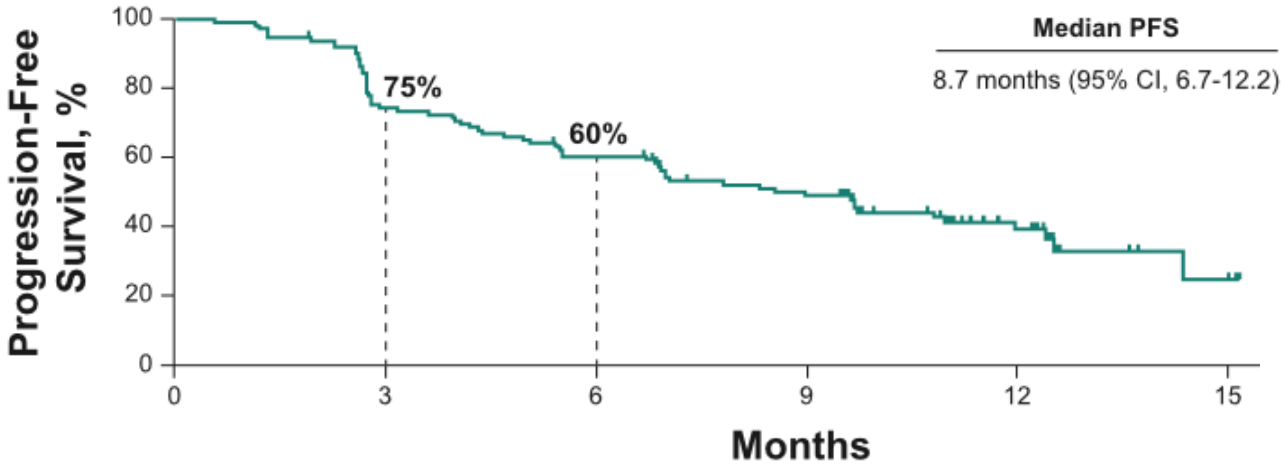
Tannir, ASCO-GU 2020; Pilmack, ASCO 2020; Choueiri, Ann Oncol 2020; Rini, Lancet 2019.

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

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

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

In Development: First-line pembrolizumab monotherapy in mRCC KEYNOTE - 427



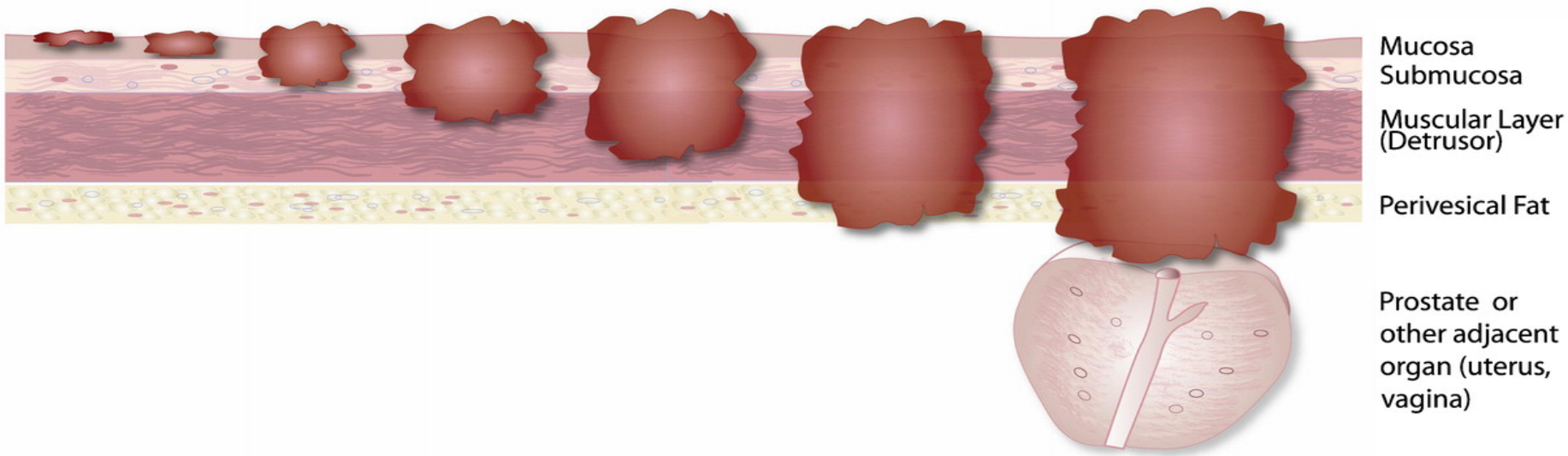
	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

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 inhibitor for non-muscle invasive bladder cancer

Drug	Approved	Indication	Dose
Pembrolizumab	January 2020	BCG-unresponsive, high-risk NMIBC, with CIS with or without papillary tumors and ineligible for cystectomy	200 mg Q3W For up to 24 months

Response, n (%)	KEYNOTE-057 cohort A (n=97)
Complete response	40 (41.2)
Non-complete response	56 (57.7)
Persistent	40 (41.2)
Recurrent	6 (6.2)
NMIBC stage progression	9 (9.3)
Progression to T2	0
Extravesical disease	1 (1.0)
Non-evaluable	1 (1.0)

FDA Advisory Committee Briefing Document, 2019.

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

Note that only pembrolizumab has positive phase 3 data – all others approved on phase 1/2 trials.

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

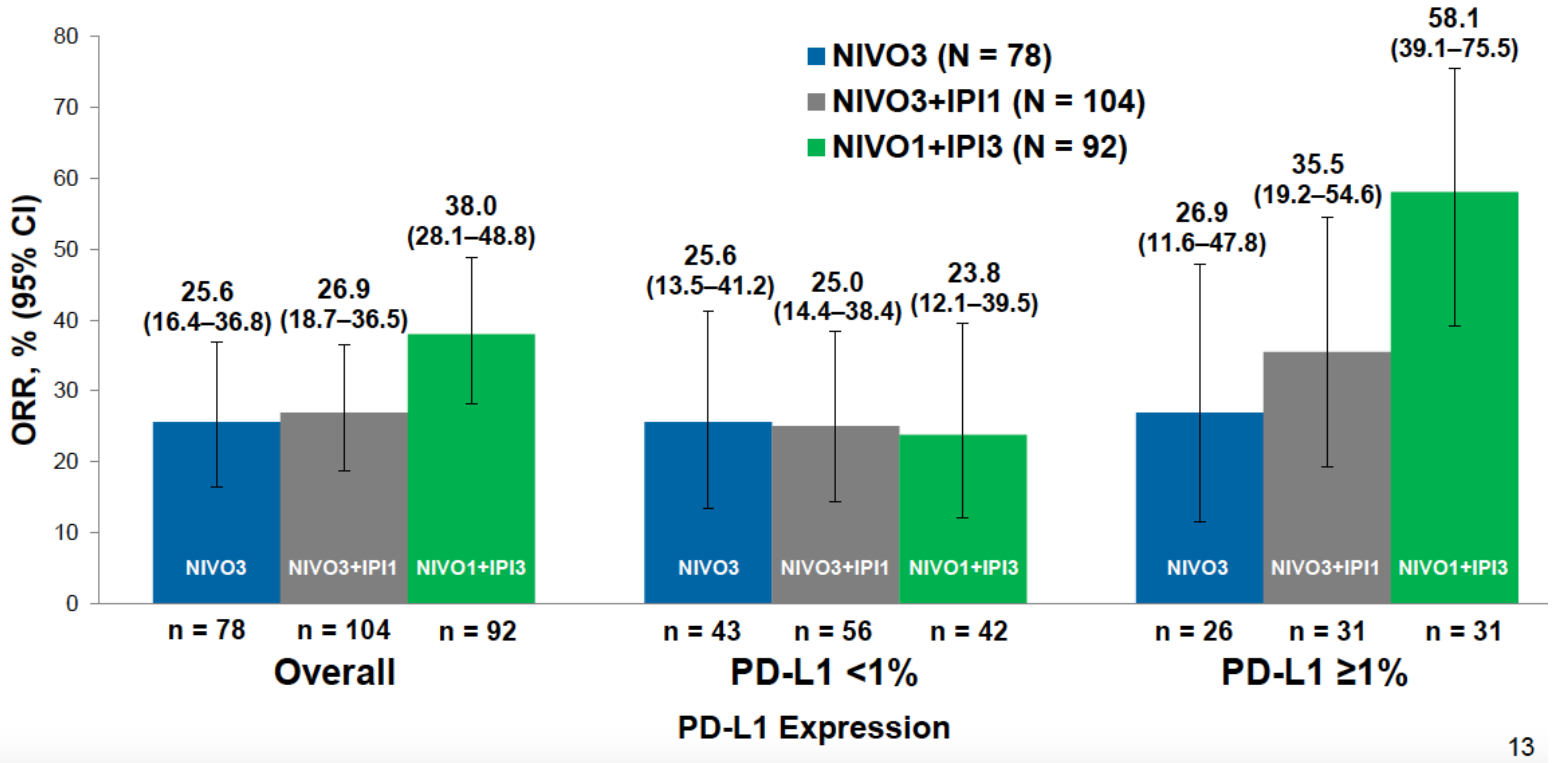
June 2018

FDA limits the use of Atezolizumab and Pembrolizumab 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

In development: Ipilimumab + Nivolumab CheckMate 032

ORR by Baseline Tumor PD-L1 Expression per Investigator



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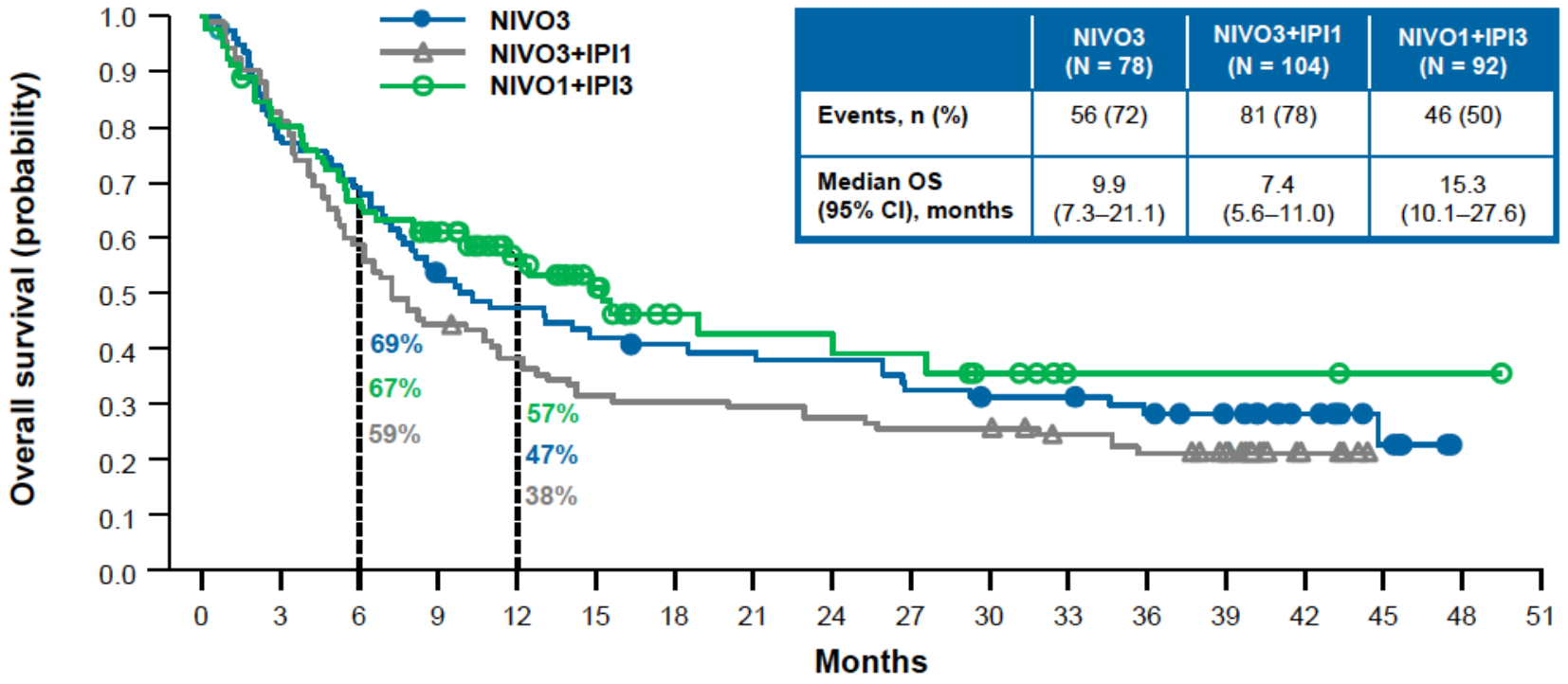
Rosenberg, ESMO 2018

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)

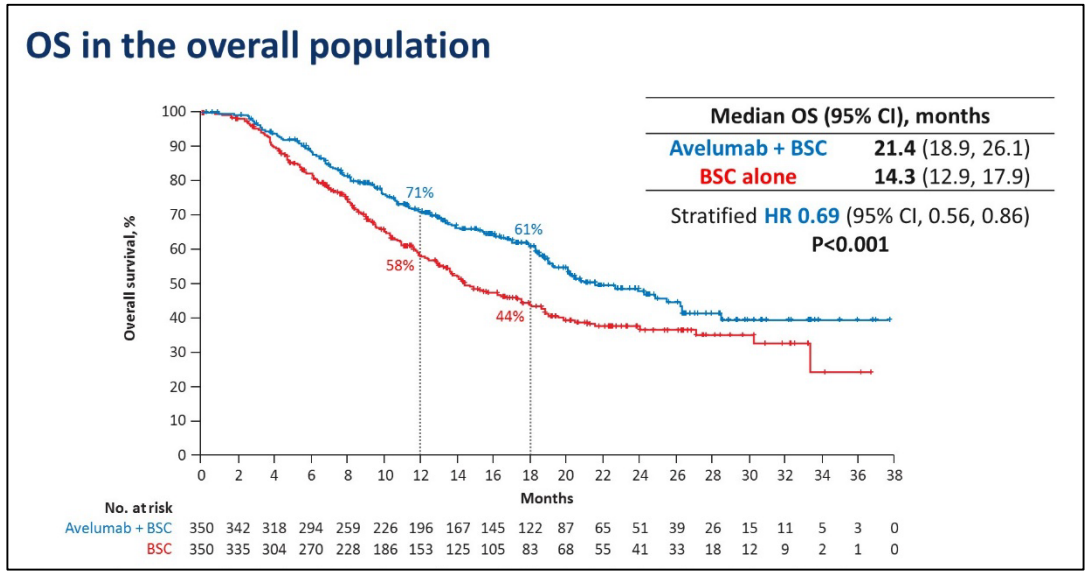
Number at risk

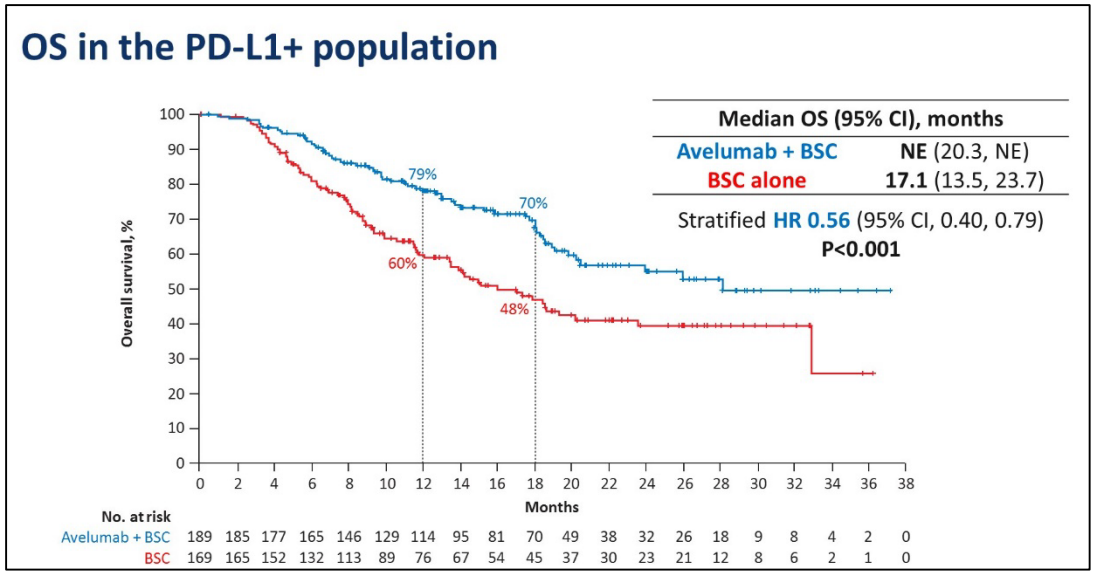
NIVO3	78	61	54	41	36	32	30	29	28	24	22	22	19	16	9	4	0	0
NIVO3+IPI1	104	86	61	46	39	32	31	30	28	26	26	22	19	15	5	0	0	0
NIVO1+IPI3	92	73	60	48	33	23	13	12	12	11	8	2	2	2	2	1	1	0

Rosenberg, ESMO 2018

Approved checkpoint inhibitor for maintenance treatment

Drug	Indication	Dose
Avelumab	Maintenance of locally advanced/metastatic UC without progression on first-line Pt chemotherapy	800 mg Q2W



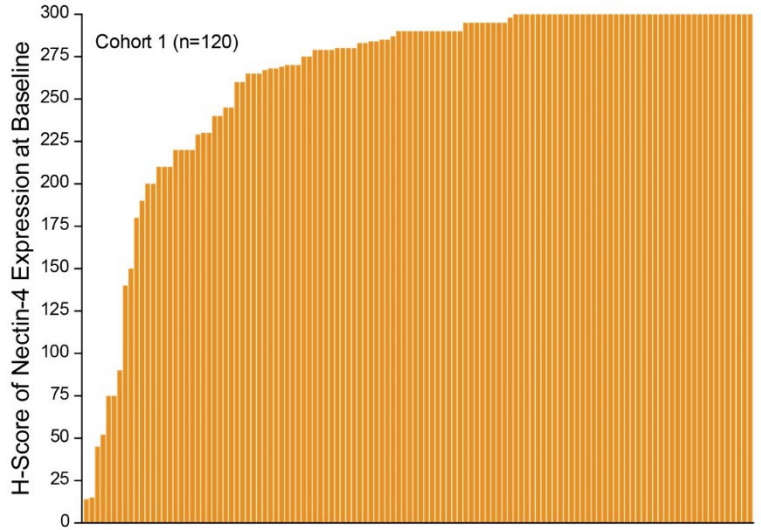


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

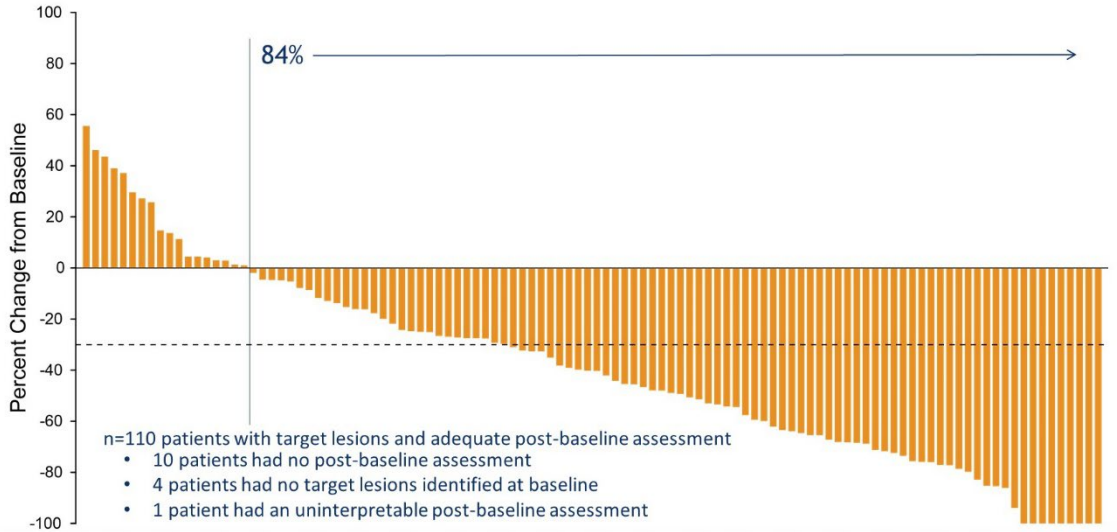
Drug	Approved	Indication	Dose
Enfortumab vedotin	December 2019	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



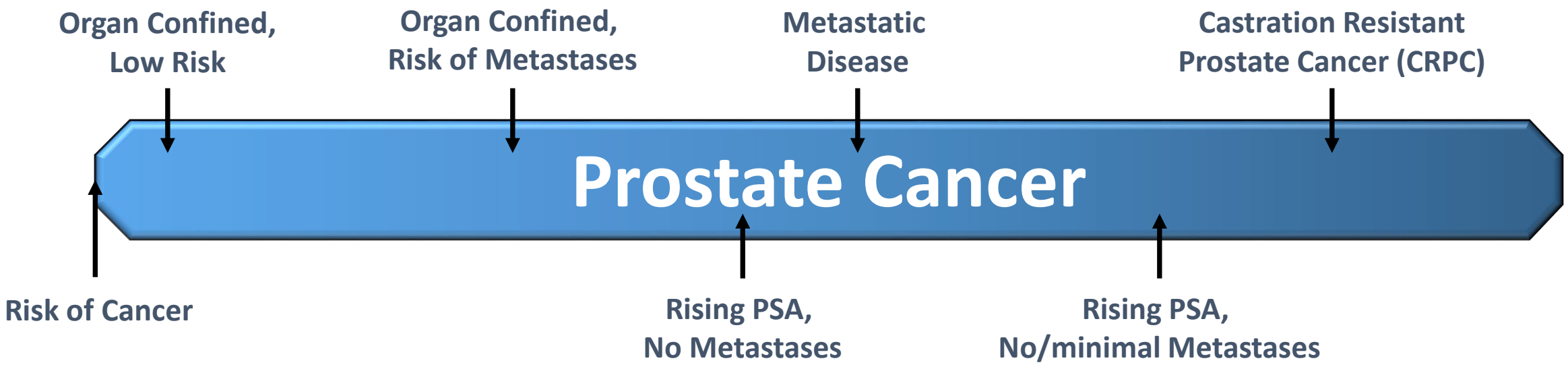
[1] Five patients did not have adequate tissue for Nectin-4 testing

EV-201: Cohort 1 Change in Tumor Measurements per BICR



Petrylak, ASCO 2019.

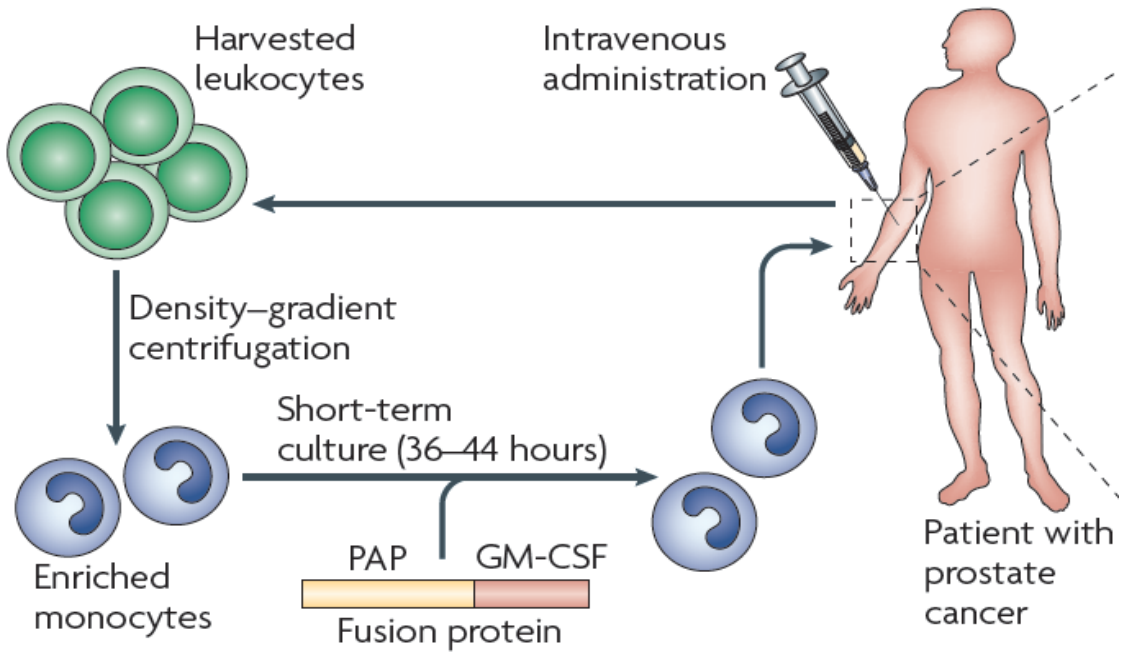
The Spectrum of Prostate Cancer

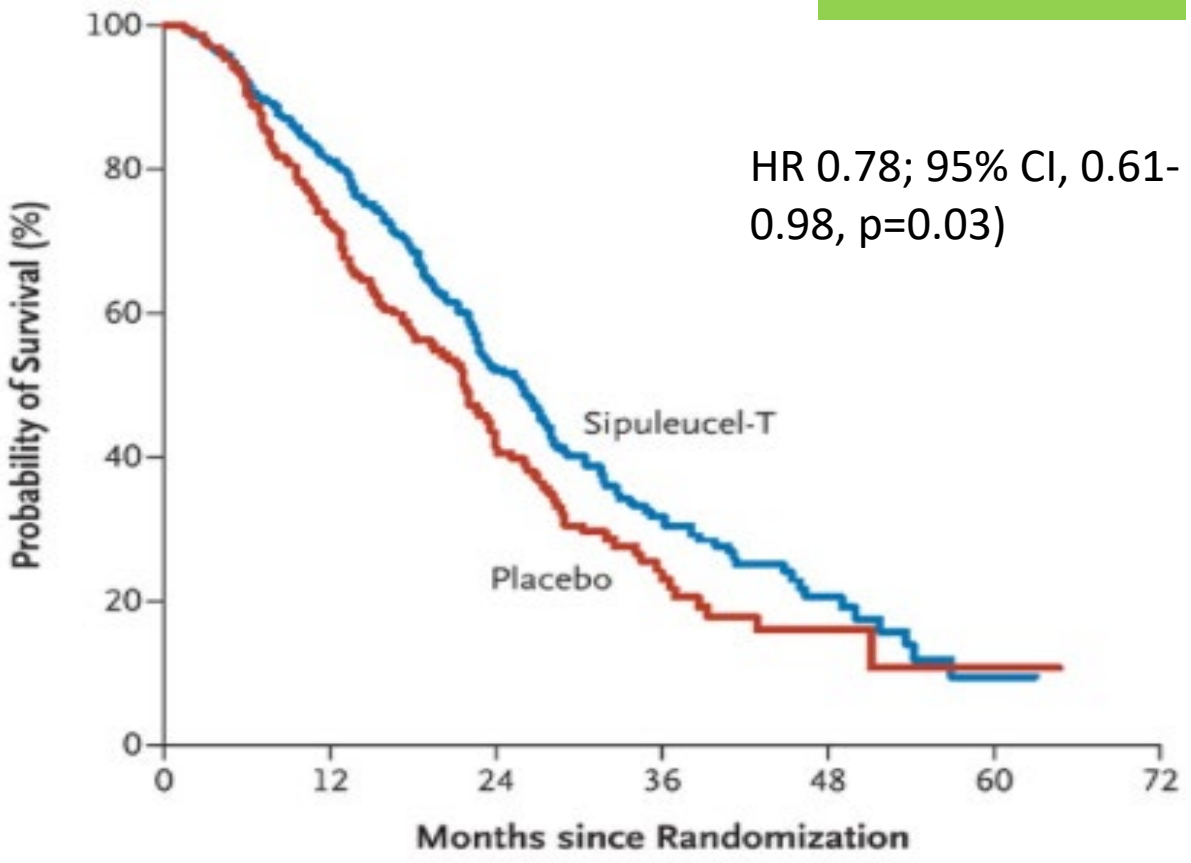


Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine





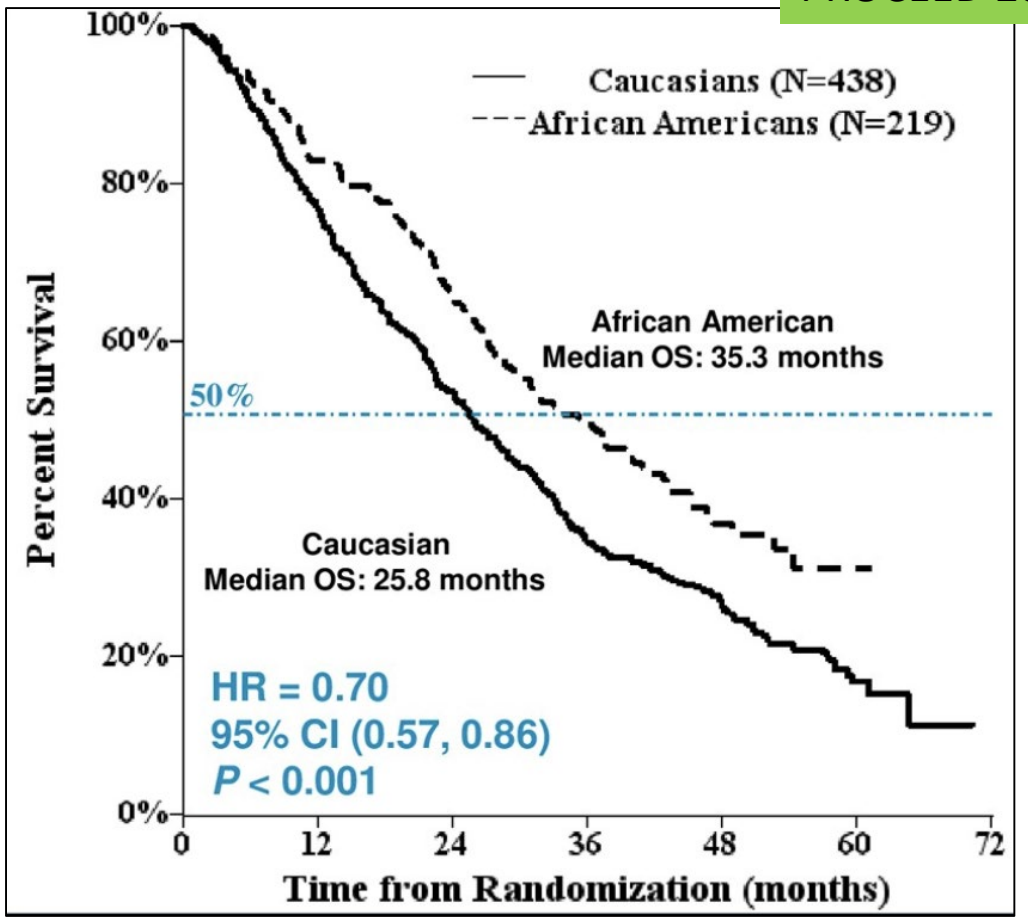
HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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)

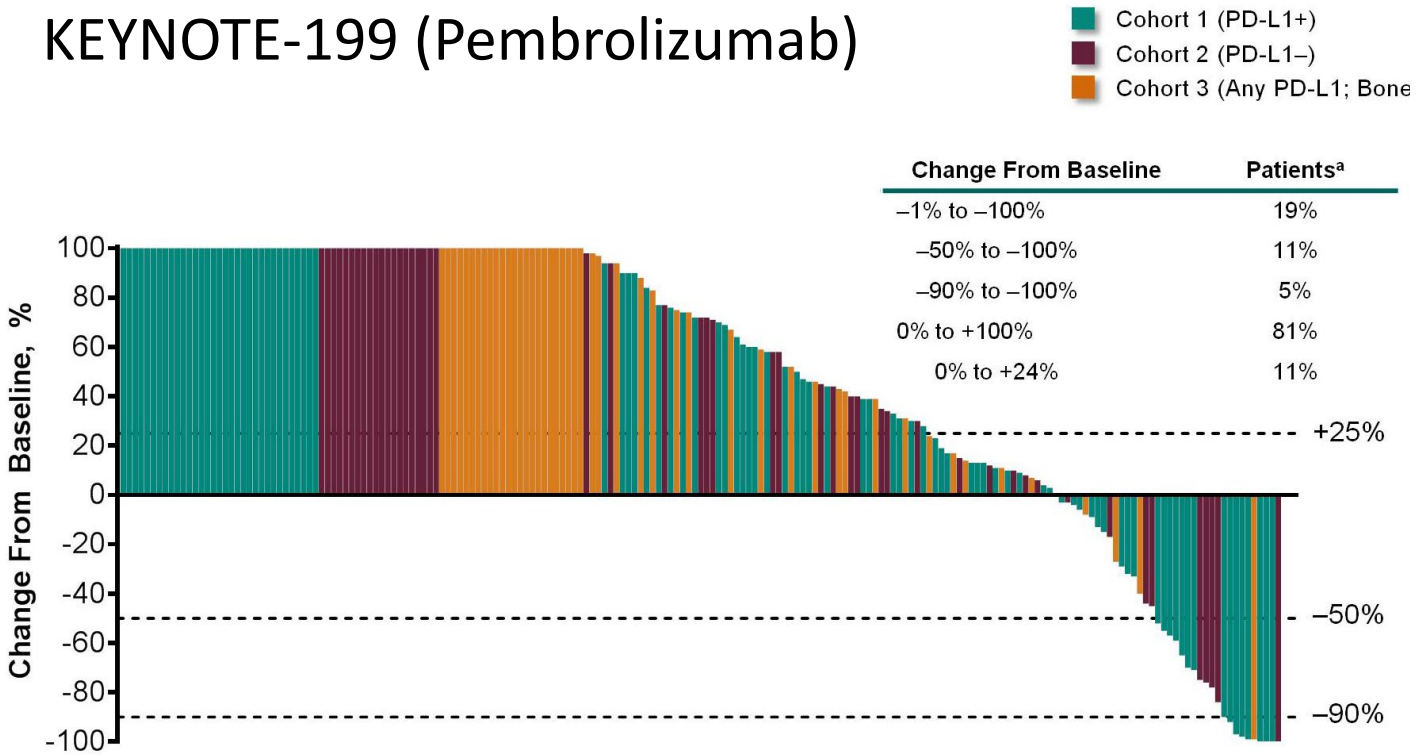


Sartor et al. ASCO 2019

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, Hempelmann J Immunother Cancer 2018

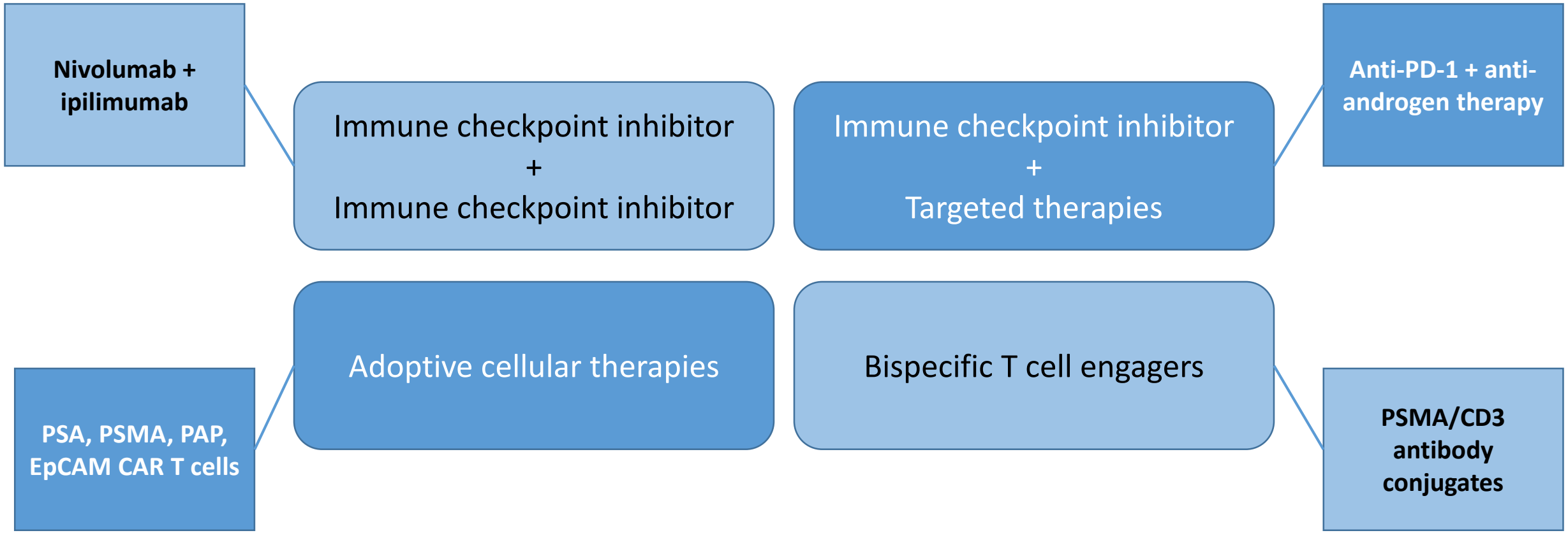
In development: nivolumab + ipilimumab in mCRPC

Trial	Treatment	Population	ORR	Median OS
CheckMate 650	Nivolumab + ipilimumab, then nivolumab maintenance	Progression on hormonal therapy, no chemotherapy	25%	19 months
		Progression on chemotherapy	10%	15.2 months

- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Future directions for prostate cancer immunotherapy



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

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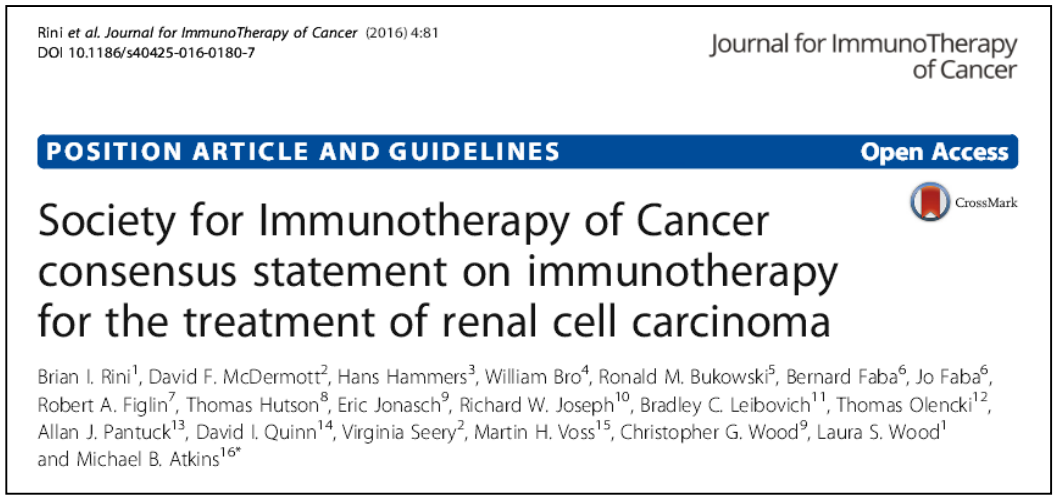
Additional Resources

Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES

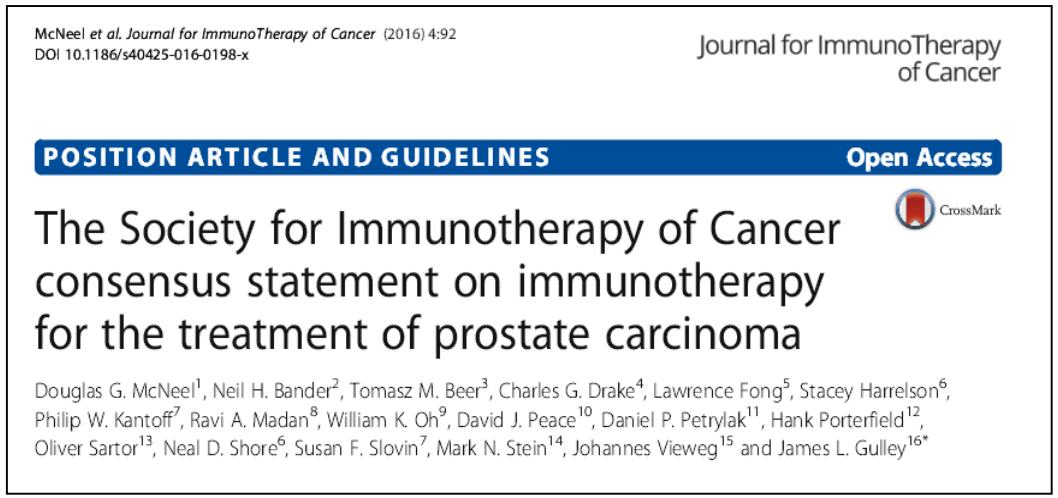

Rini et al. Journal for ImmunoTherapy of Cancer (2016) 4:81
DOI 10.1186/s40425-016-0180-7

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*]

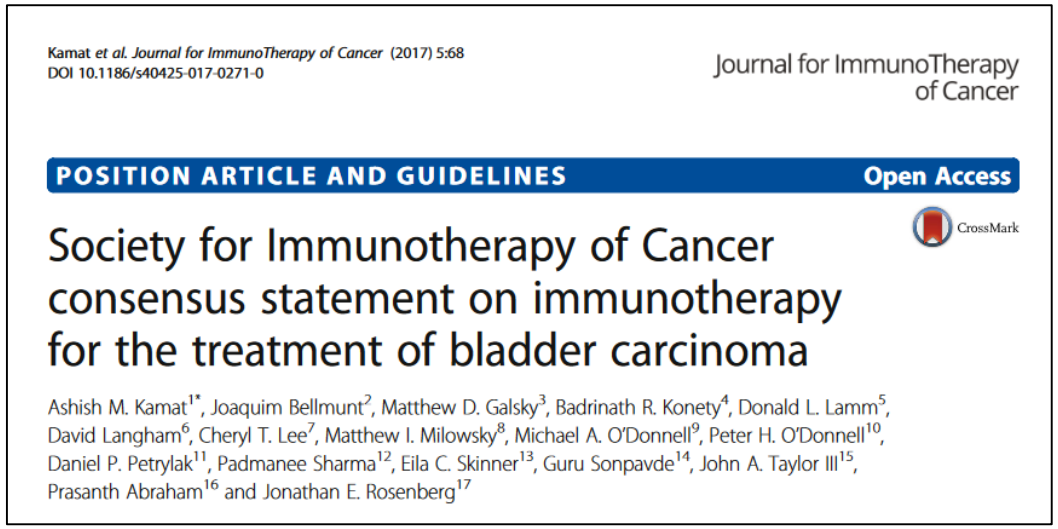

McNeel et al. Journal for ImmunoTherapy of Cancer (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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]

AAEM American Academy of Emergency Medicine
ACCC Association of Community Cancer Centers
HOPA Hematology/Oncology Pharmacy Association
sitc Society for Immunotherapy of Cancer

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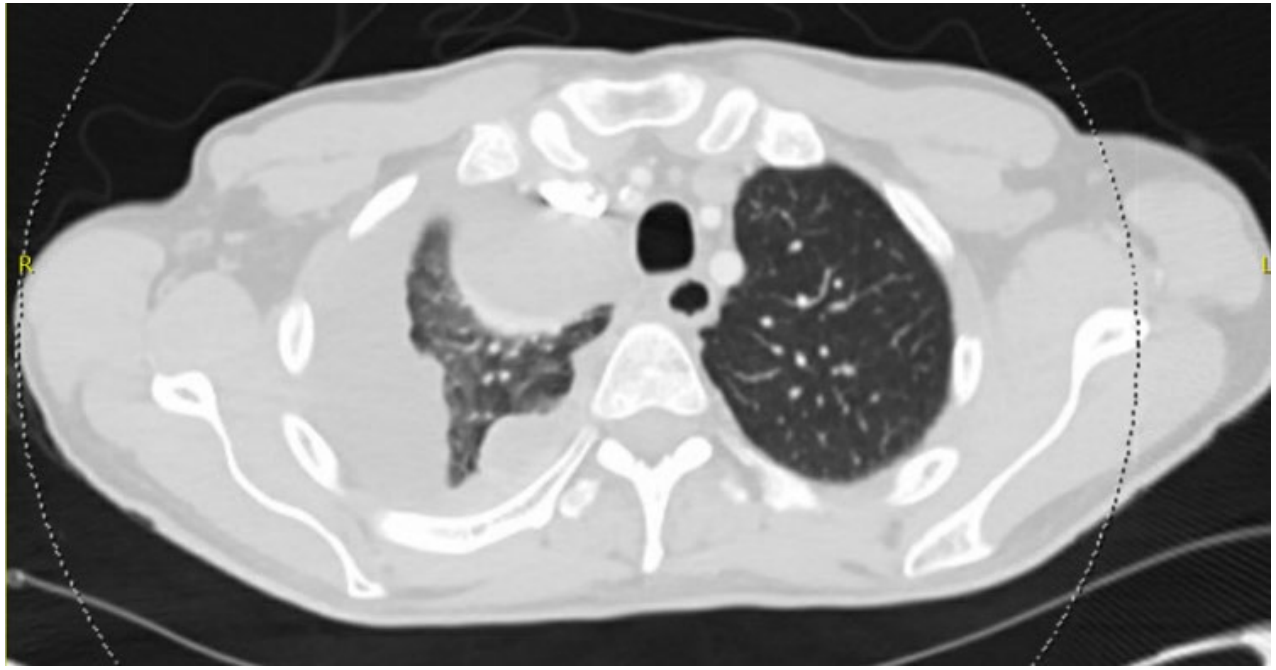
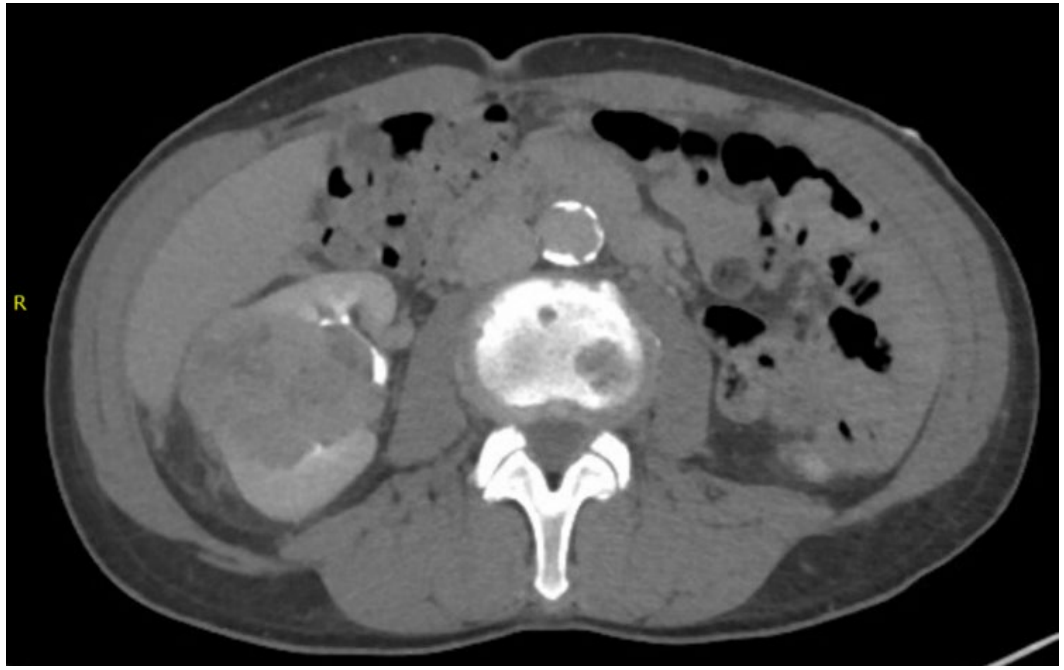
Case Studies

Case Study 1

- 68 y.o. man with HLD presented with progressive exertional dyspnea
- CXR showed a large right-sided pleural effusion. Subsequent CT showed additional pleural-based masses along with a 7 cm right renal mass
- Pleural mass biopsy showed metastatic renal cell carcinoma, clear cell type, Fuhrman grade 4/4 with focal sarcomatoid features
- Labs are notable for: Hgb 11.7. Calcium, PLT, Neutrophils were all within normal limits. ECOG PS 1

Case Study 1





Case Study 1

What first-line systemic therapy would you recommend for this patient?

A. Cabozantinib (Incorrect: the patient is eligible for immunotherapy and should receive immunotherapy-based first-line therapy)

B. Sunitinib (Incorrect: the patient is eligible for immunotherapy and should receive immunotherapy-based first-line therapy)

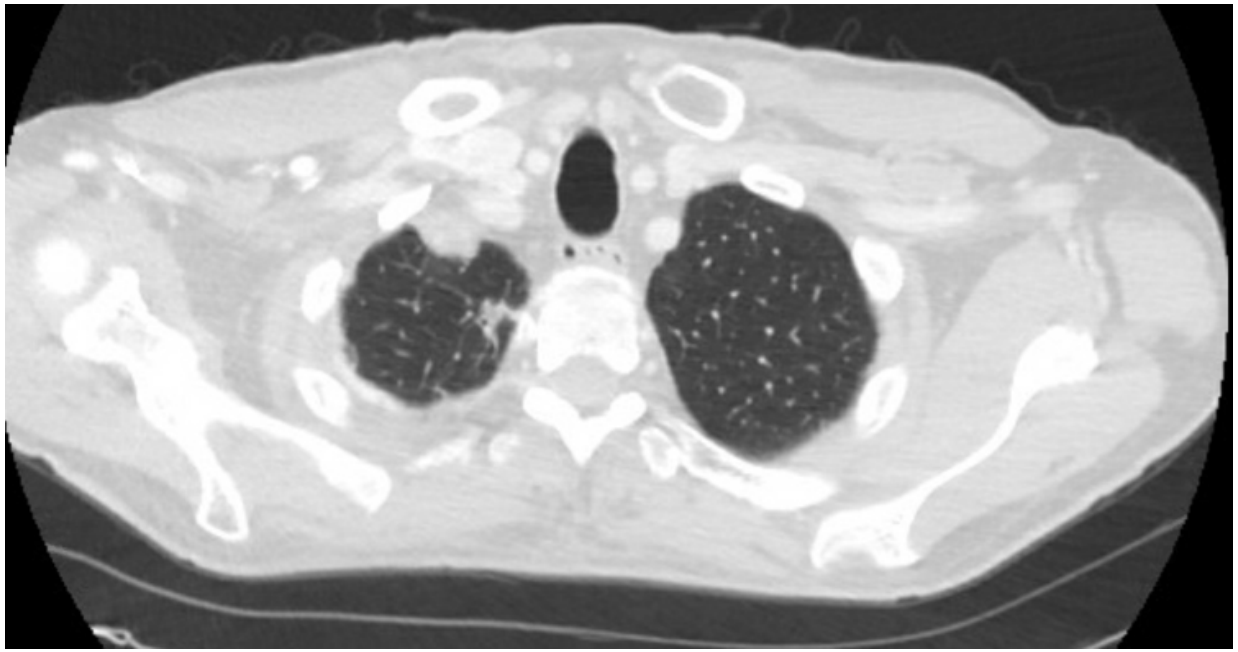
C. Nivolumab + Ipilimumab (Correct: the sarcomatoid histology is associated with a high objective response rate (57%) and complete response rate (18%))

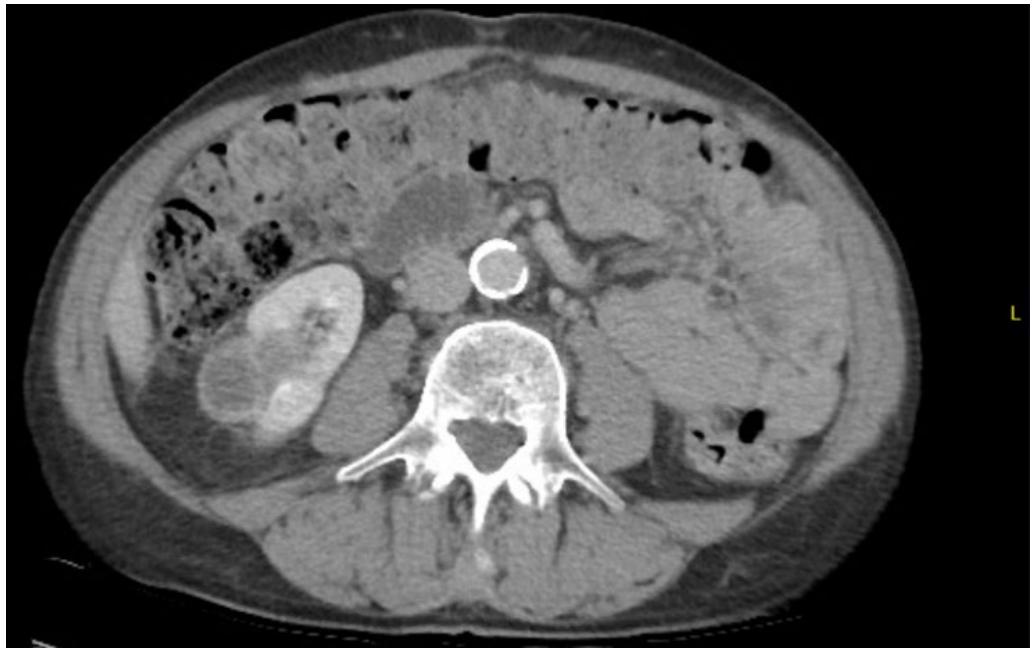
D. Avelumab + Axitinib (Incorrect: While this regimen may be discussed, there is no overall survival benefit shown to date and there are other more preferred regimens)

E. Pembrolizumab + Axitinib (Correct: This would also be a very reasonable first-line regimen to consider for the patient based on the KEYNOTE-426 data showing OS benefit compared to Sunitinib)

Case Study 1

- The patient was treated with Nivolumab + Ipilimumab
- Restaging scans at the conclusion of 4 cycles showed significant treatment response





Case Study 1

- He continues on Nivolumab monotherapy, but soon develops persistent anorexia, nausea, and weight loss of 10 lbs within 6 weeks of his last scans showing disease response

How would you approach the workup?

A. None needed – this is expected with nivolumab monotherapy (Incorrect: These are symptoms concerning for an adverse event)

B. Repeat imaging to evaluate for disease progression (Incorrect: The patient just had restaging scans very recently, and it is highly unlikely that there would be progression so quickly after response)

C. Hold Nivolumab and refer to Gastroenterology for EGD +/- Colonoscopy (Correct: these symptoms are concerning for immune-related enteritis and should be worked up)

D. Give empiric steroids as a diagnostic maneuver (Incorrect: The patient is stable and further workup is needed prior to initiation of immunosuppressive therapy)

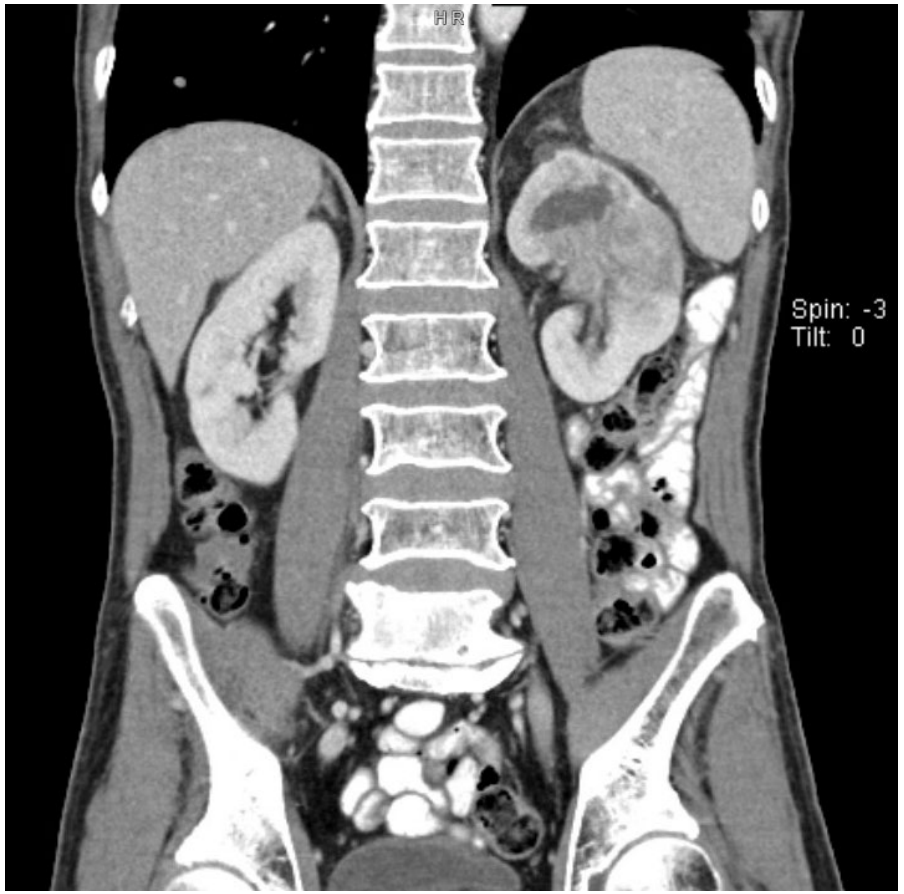
Case Study 1

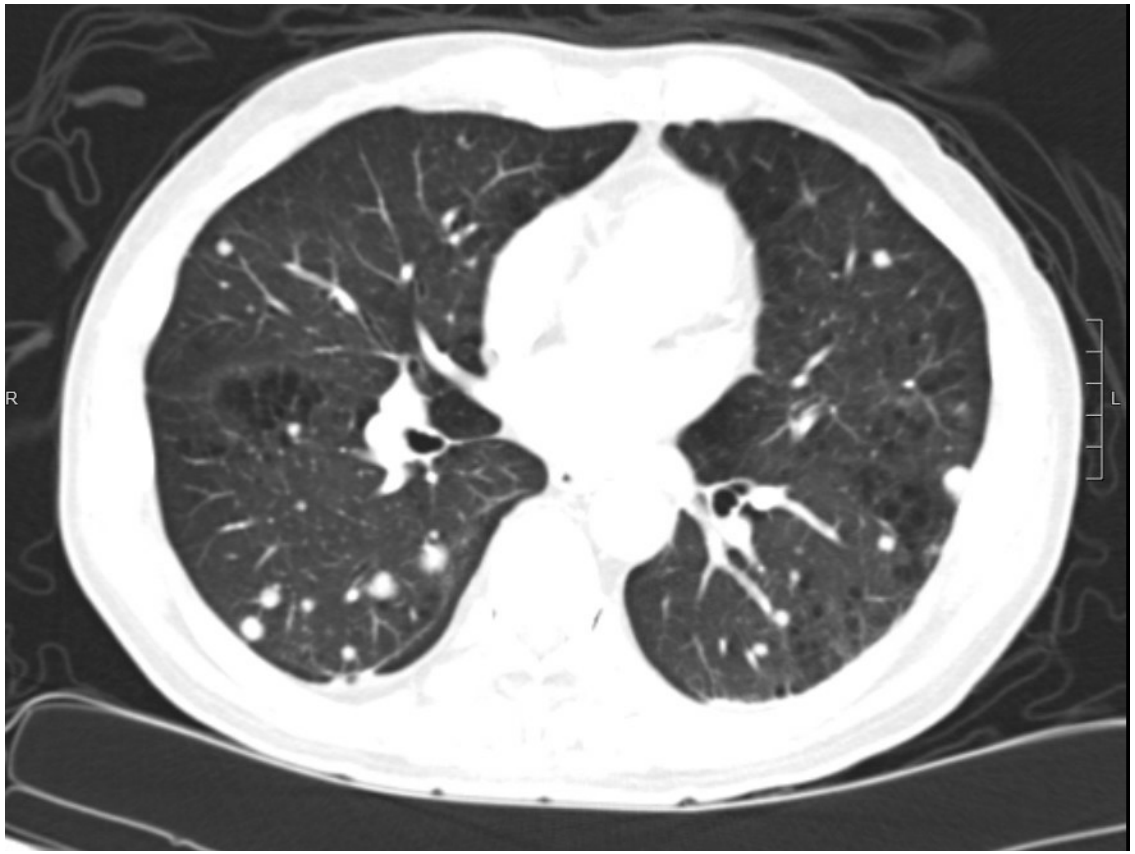
- CMP and CBC were WNL. The patient was referred to Gastroenterology and underwent EGD and Colonoscopy
- Duodenal biopsy showed villous blunting, patchy intraepithelial lymphocytosis and active duodenitis consistent with checkpoint inhibitor gastroenteritis
- He was started on prednisone 60 mg daily and gradually tapered over 2 months with resolution of GI symptoms. Nivolumab continued to be held during this time
- Restaging scans showed overall stability of tumor burden

Case Study 2

- 70 y.o. man with no known medical history presents with gross hematuria
- Workup showed a 5.6 x 4.3 cm left renal mass centered in the left renal collecting system, left adrenal lesions, bone lesions, and lung nodules consistent with metastatic disease
- Biopsy of the adrenal lesion confirmed metastatic urothelial carcinoma
- Labs are notable for creatinine 1.1, Hgb 9.9. ECOG PS 1

Case Study 2





Case Study 2

What additional testing should you request on the tumor specimen to help decide first-line therapy?

A. Tumor mutational burden (Incorrect: While there is an association between TMB and response to immunotherapy, the biomarker is not robust enough to be used clinically to select therapy in this disease)

B. PD-L1 combined positive score (CPS) in tumor and immune cells (Incorrect: While there is an association between PD-L1 staining and response to immunotherapy, the biomarker is not robust enough to be used clinically to guide first-line therapy for a patient who is eligible to receive cisplatin-based chemotherapy)

C. PD-L1 staining in infiltrating immune cells (IC) score (Incorrect: While there is an association between PD-L1 staining and response to immunotherapy, the biomarker is not robust enough to be used clinically to guide first-line therapy for a patient who is eligible to receive cisplatin-based chemotherapy)

D. None – no additional tumor testing is needed at this point (Correct: We have all the information needed to determine first-line therapy, which is generally cisplatin-based chemotherapy for such a patient who is eligible for cisplatin)

Case Study 2

What first-line systemic therapy would you recommend for this patient?

A. Nivolumab + Ipilimumab (Incorrect: This combination is approved for metastatic RCC and is not approved for urothelial cancer)

B. Cisplatin + Gemcitabine (Correct: Cisplatin-based chemotherapy remains first-line therapy for patients who are cisplatin-eligible)

C. Avelumab (Incorrect: Avelumab is not approved for first-line use in metastatic urothelial cancer. Avelumab is FDA-approved as maintenance therapy following completion of platinum-based chemotherapy or as second-line therapy at progression during or following platinum-based chemotherapy)

D. Pembrolizumab (Incorrect: This patient is cisplatin-eligible and chemotherapy-eligible. Pembrolizumab is FDA-approved for use as first-line therapy for patients who are ineligible for cisplatin-based chemotherapy and whose tumors have a PD-L1 CPS >=10, or for second-line therapy at progression during or following platinum-based chemotherapy)

E. Enfortumab vedotin (Incorrect: Enfortumab vedotin is FDA-approved for patients who have previously received an anti-PD-1/L1 therapy and a platinum-containing chemotherapy)

Case Study 2

- The patient states that he understands the pros/cons of first-line platinum-based chemotherapy vs immune checkpoint inhibitor. However, he declines first-line chemotherapy and would like to proceed with first-line pembrolizumab
- Restaging scans after 3 cycles of pembrolizumab 200 mg IV Q3W showed significant treatment response. He continues on pembrolizumab and switched to the 400 mg IV Q6W dosing with its recent FDA approval in April 2020.