Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Malignancies

Tanya Dorff, MD

Associate Clinical Professor of Medicine

City of Hope Comprehensive Cancer Center

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

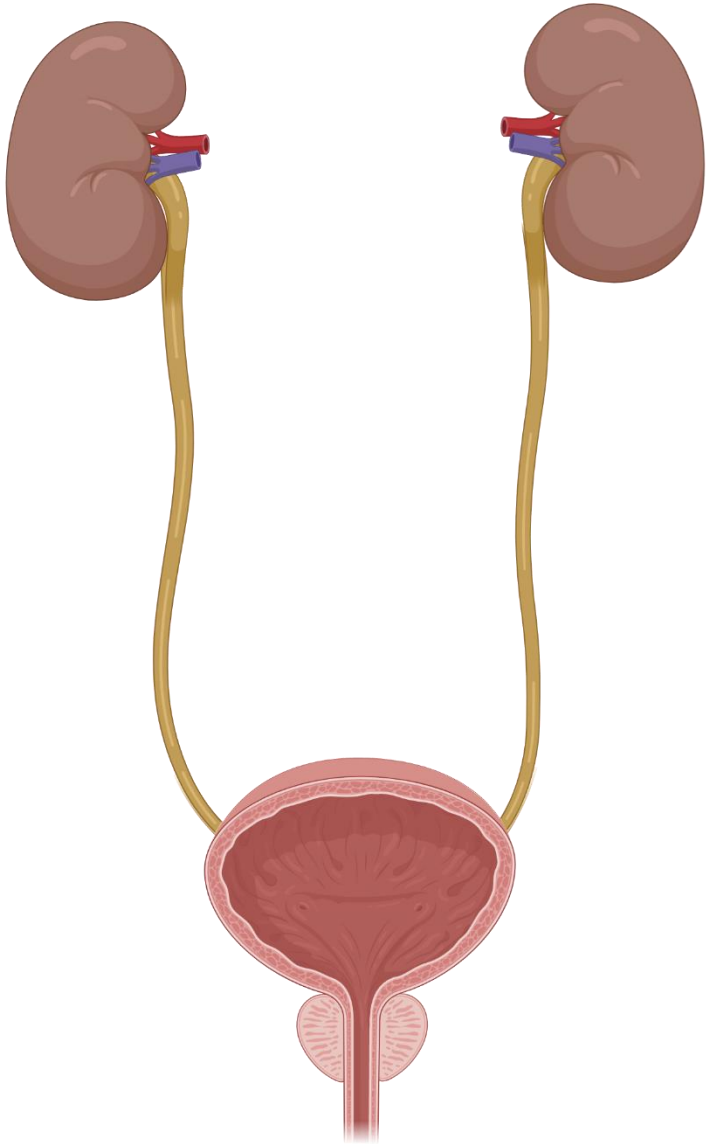
#LearnACI

Disclosures

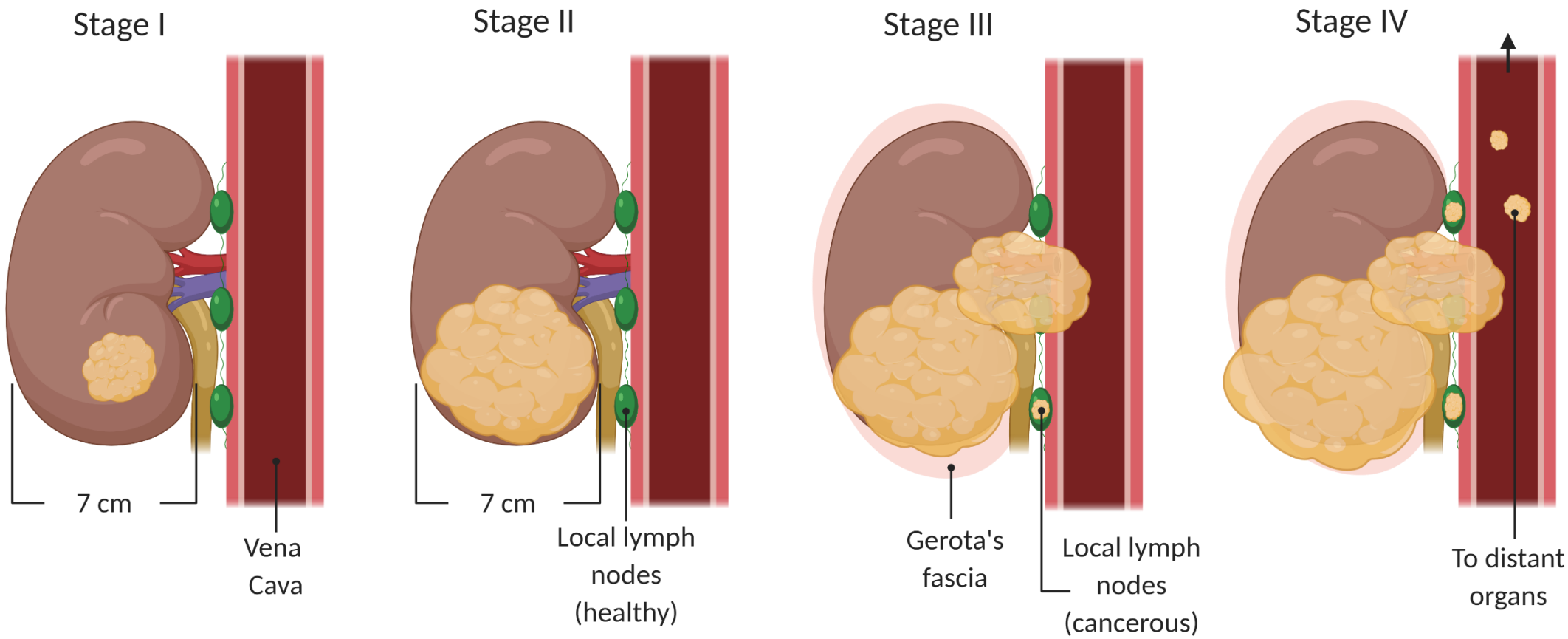
- Consulting Fees: SeaGen, Exelixis, Bayer, Janssen, ABBvie
- I will be discussing non-FDA approved indications during my presentation.

Outline

- Renal cell carcinoma
  - Approved immunotherapies
  - Future directions
- Urothelial carcinoma
  - Approved immunotherapies
  - Future directions
- Prostate cancer
  - Approved immunotherapies
  - Future directions



Renal cell carcinoma (RCC)



#LearnACI

FDA-approved immunotherapies for mRCC

Drug	Indication	Dose
High dose Interleukin-2	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-α + bevacizumab	Clear cell RCC	IFN 9 MIU s.c. three times a week + bevacizumab 10 mg/kg Q2W
Nivolumab	Clear cell RCC refractory to prior VEGF targeted therapy	240 mg Q2W or 480 mg Q4W
Nivolumab + ipilimumab	Clear cell RCC, treatment naïve	3 mg/kg nivo plus 1 mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	Advanced RCC, Treatment naïve	200 mg pembro Q3W or 400 mg Q6W + 5 mg axitinib twice daily
Avelumab + axitinib	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily
Nivolumab + cabozantinib	First-line advanced RCC	240 mg nivolumab Q2W or 480 mg Q4W + cabozantinib 40 mg daily

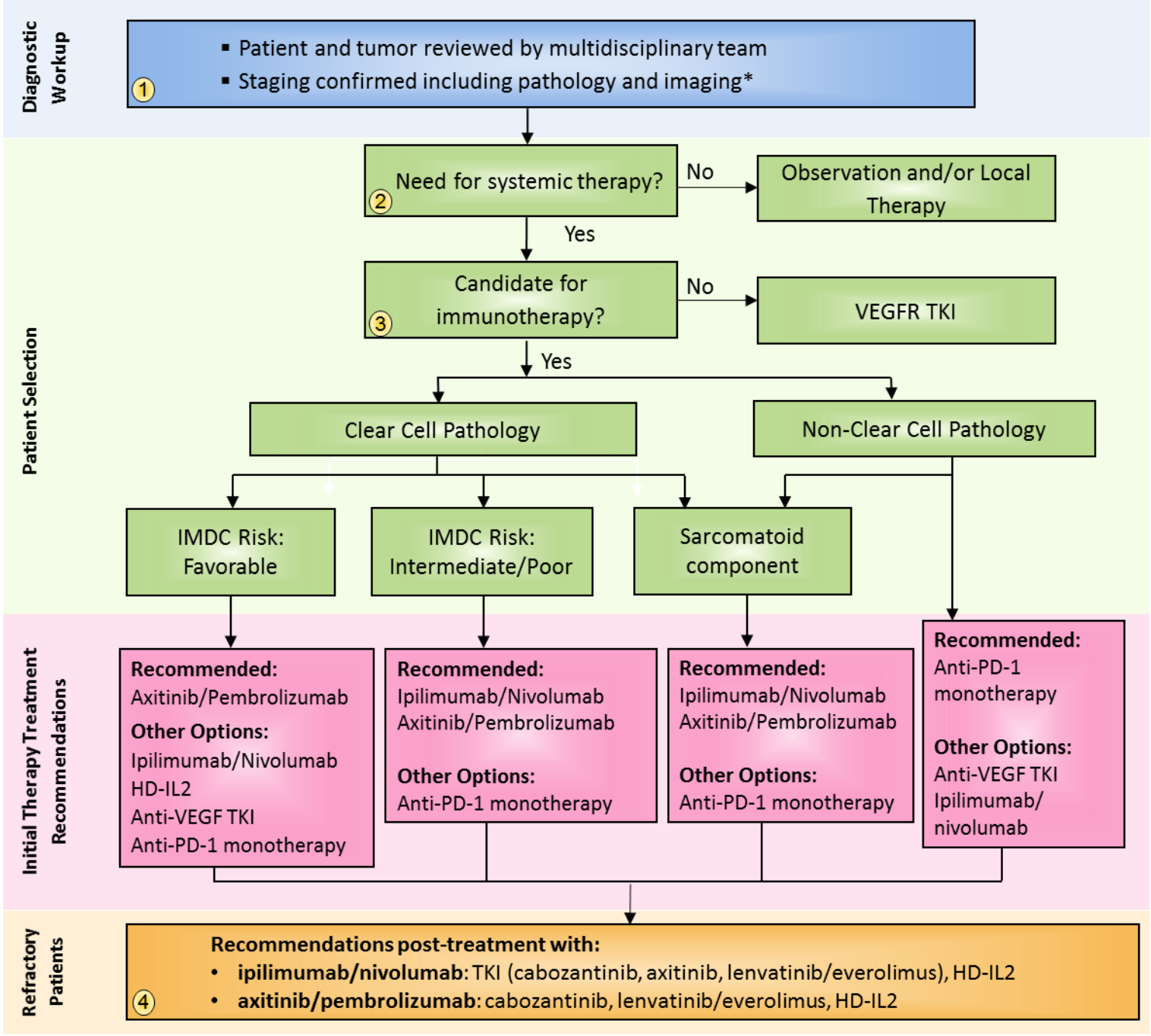
Front-line immunotherapy treatments for RCC

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

*FDA-approved IO regimen

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

SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma



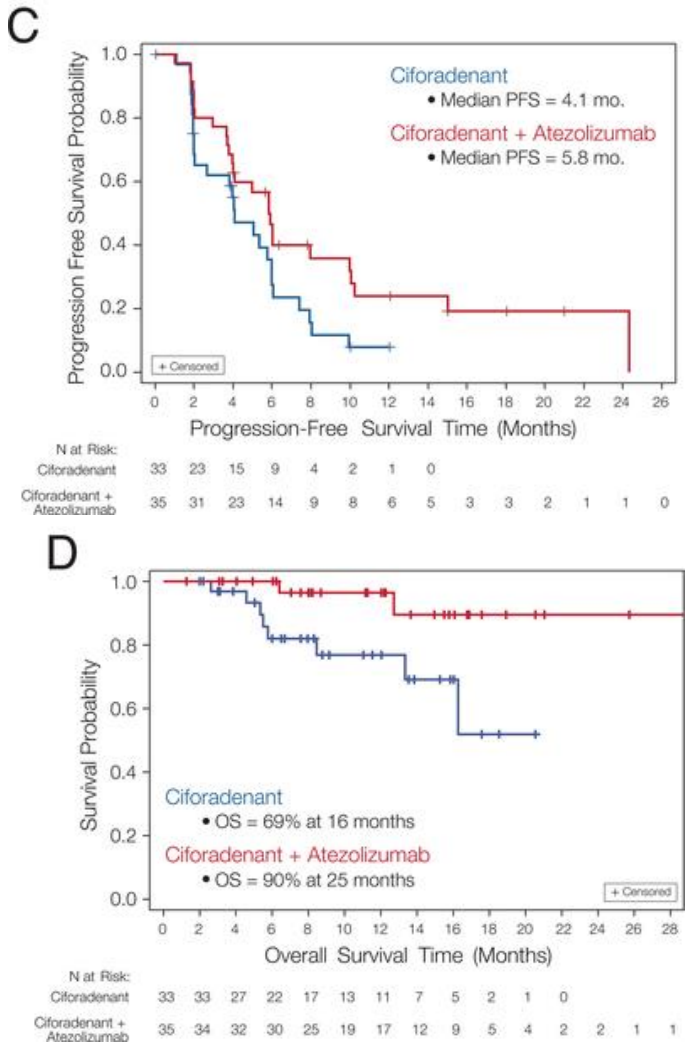
*Baseline imaging recommendations discussed in figure legend.

Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.

Rini, J Immunother Cancer 2019.

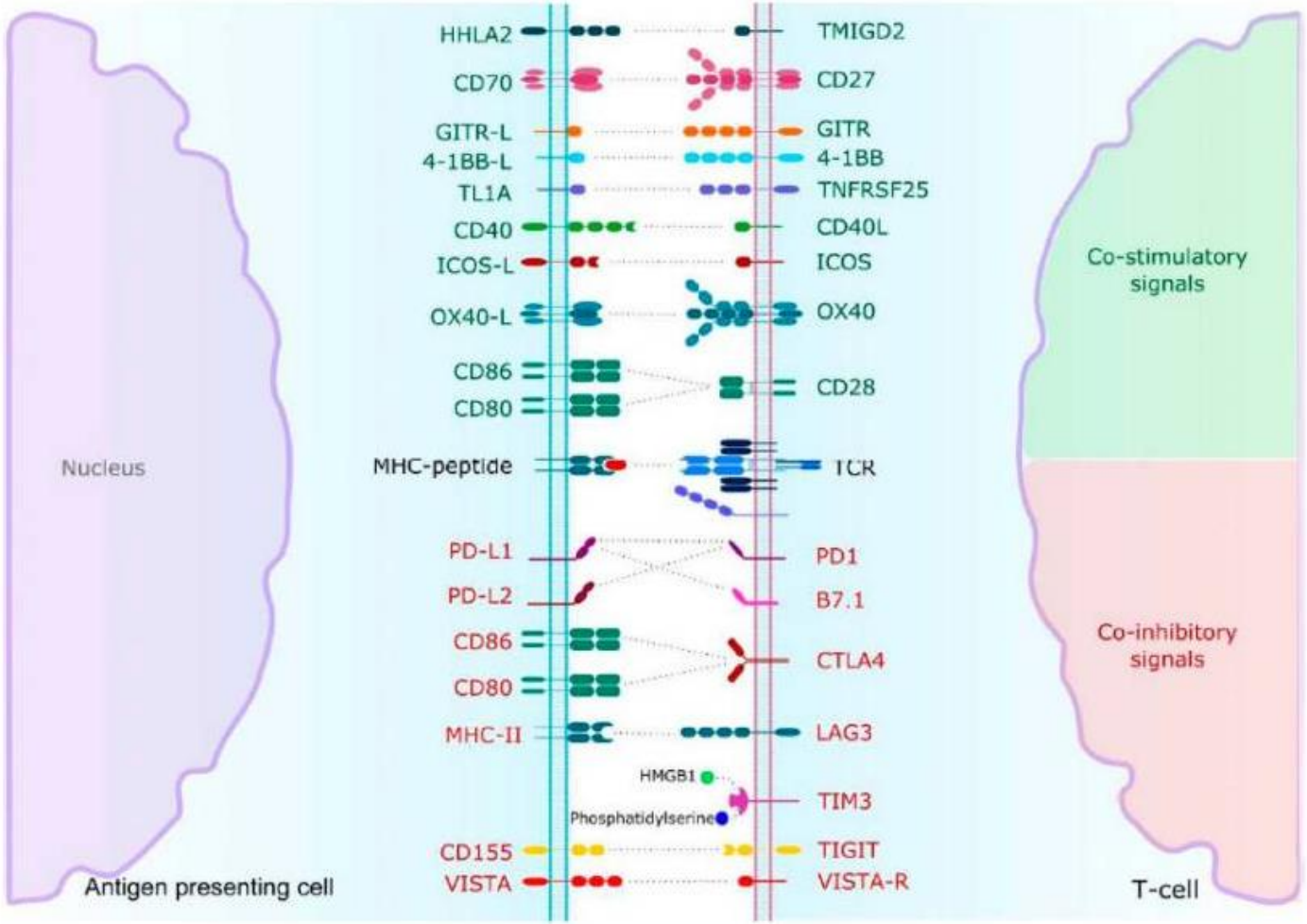
In development: A2AR antagonist + anti-PD-L1

Treatment arm	N	ORR	6-month disease control
Ciforadenant	33	3%	Naïve: 0%
			Prior ICI: 25%
Ciforadenant + atezolizumab	35	11%	Naïve: 50%
			Prior ICI: 35%



Fong, Ca Discov 2020

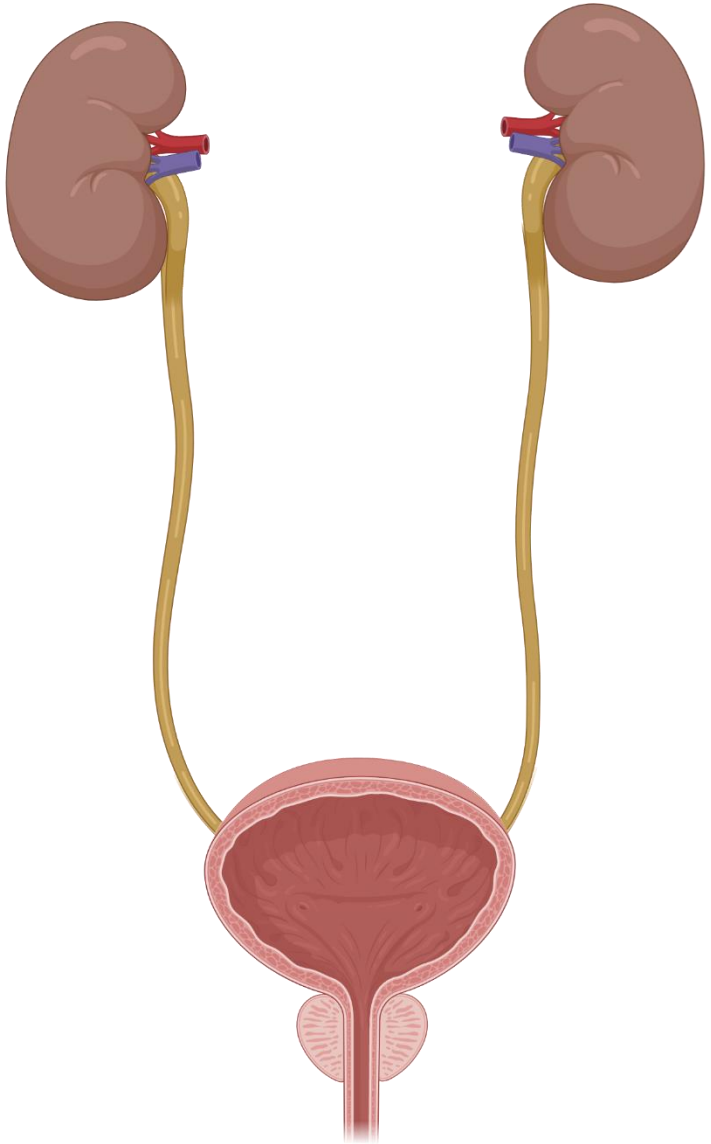
In development: additional immunotherapy approaches



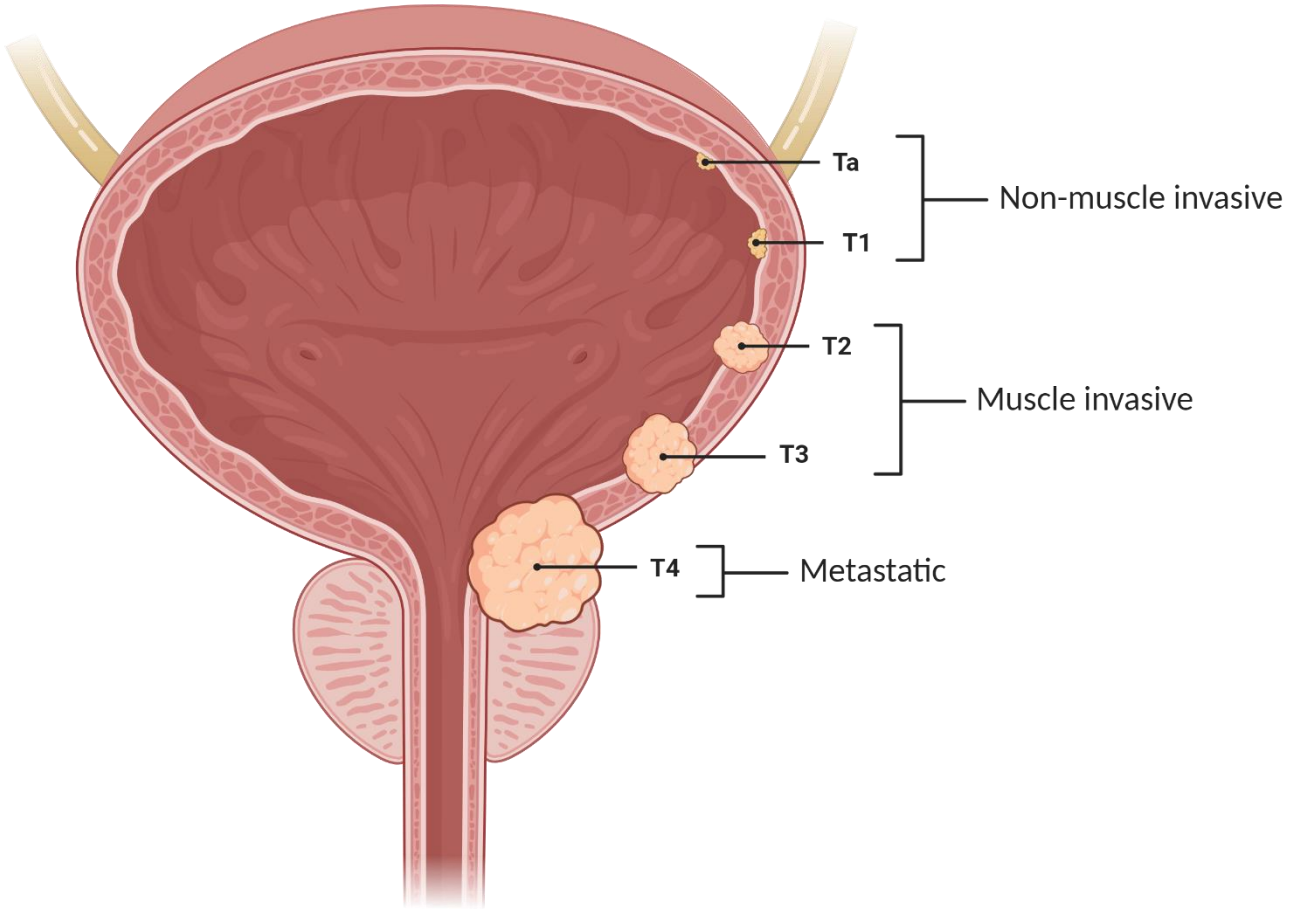
Deleuze, Int J Mol Sci 2020

Outline

- Renal cell carcinoma
  - Approved immunotherapies
  - Future directions
- Urothelial carcinoma
  - Approved immunotherapies
  - Future directions
- Prostate cancer
  - Approved immunotherapies
  - Future directions



Urothelial carcinoma (UC)



Approved checkpoint inhibitor for non-muscle invasive bladder cancer

Drug	Indication	Dose
Pembrolizumab	BCG-unresponsive, high-risk NMIBC, with or without papillary tumors and ineligible for cystectomy	200 mg Q3W or 400 mg Q6W

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	Indication	Dose
Avelumab	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Advanced/metastatic UC	200 mg Q3W or 400 mg Q6W

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Indication	Dose
Atezolizumab	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W or 400 mg Q6W

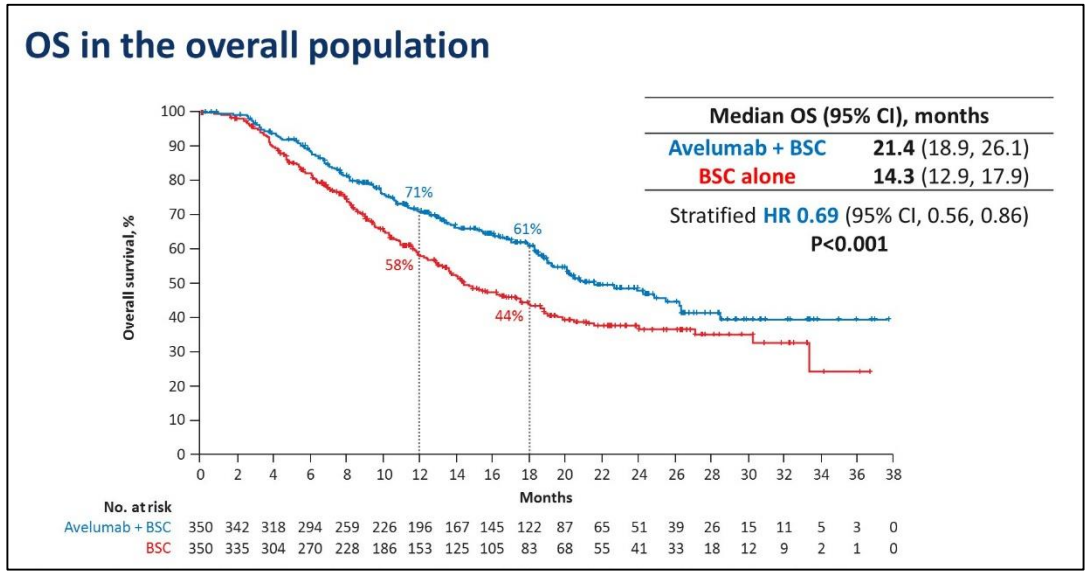
June 2018

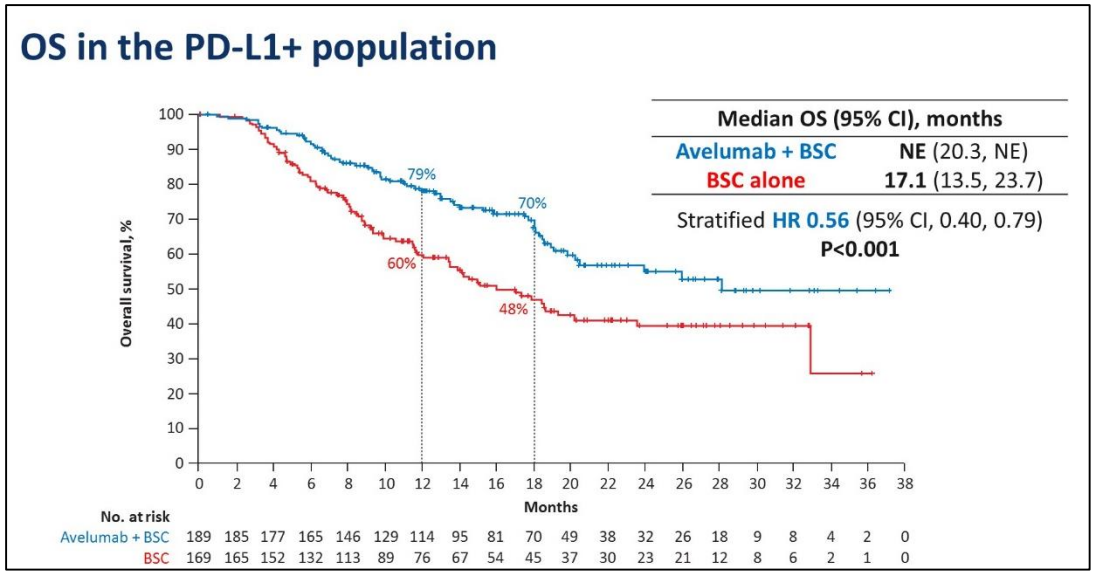
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

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

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



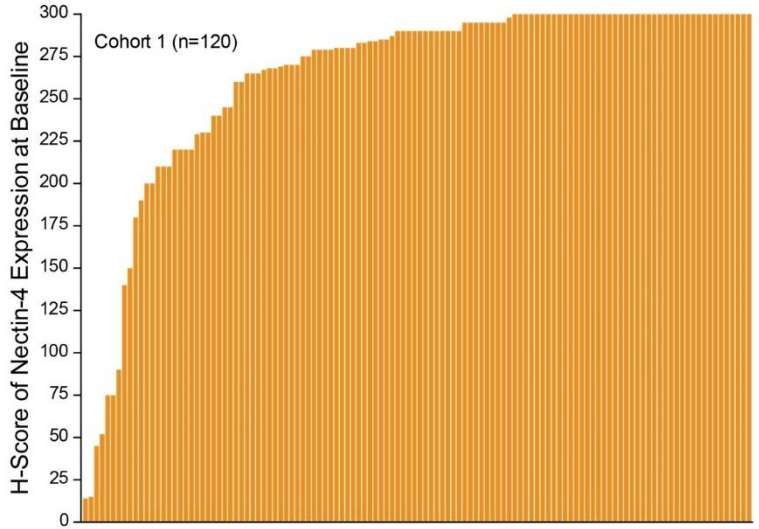


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

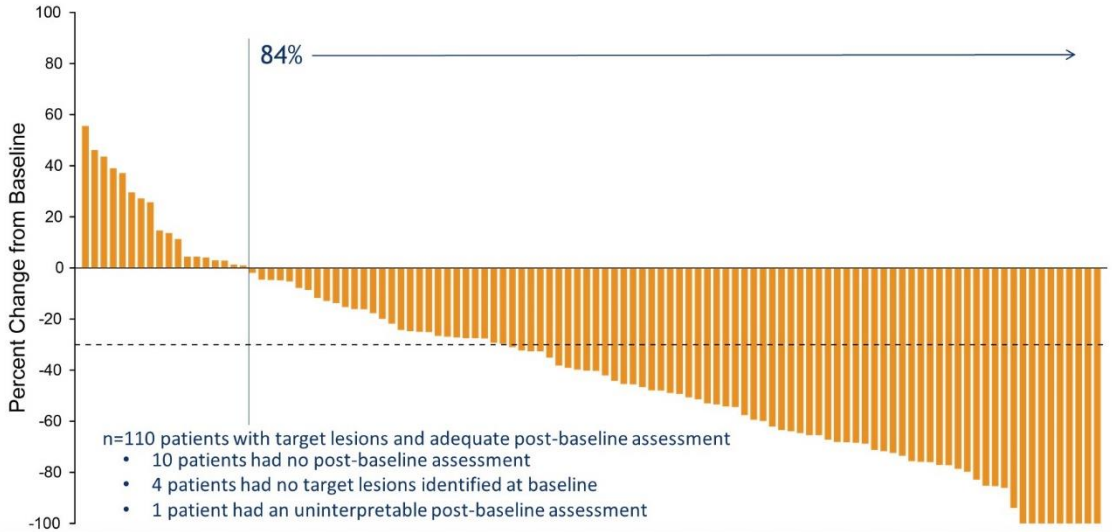
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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

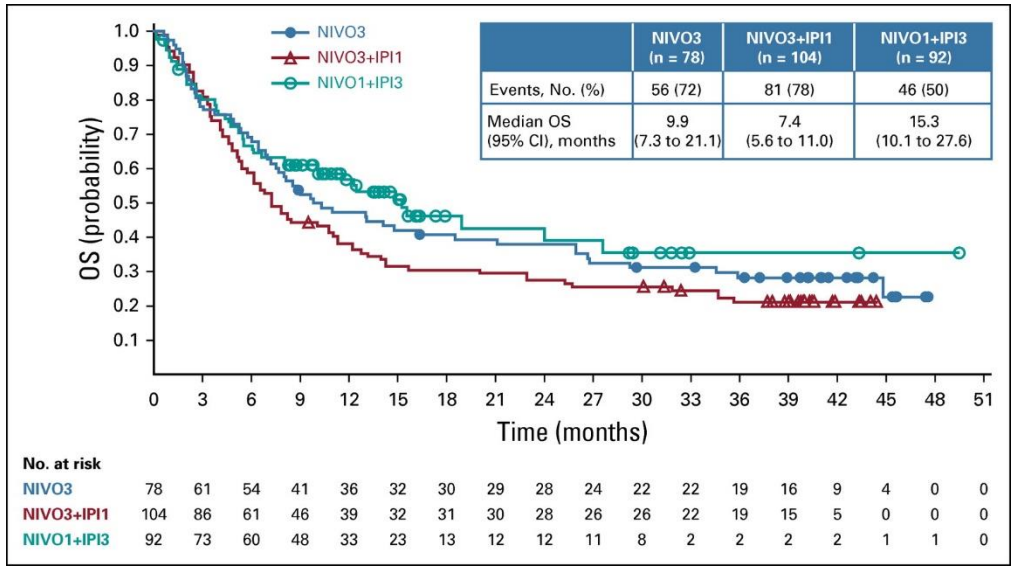


Petrylak, ASCO 2019.

#LearnACI

In development: Ipilimumab + Nivolumab CheckMate 032

Treatment arm	n	ORR	Median PFS	Median OS	Grade 3-4 TRAEs
Nivolumab 3 mg/kg Q3W	78	ITT: 25.6% PD-L1+: 26.9%	2.8 months	9.9 months	26.9%
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	104	ITT: 26.9% PD-L1+: 35.5%	2.6 months	7.4 months	30.8%
Nivolumab 1 mg/kg + ipilimumb 3 mg/kg	92	ITT: 38.0% PD-L1+: 58.1%	4.9 months	15.3 months	39.1%

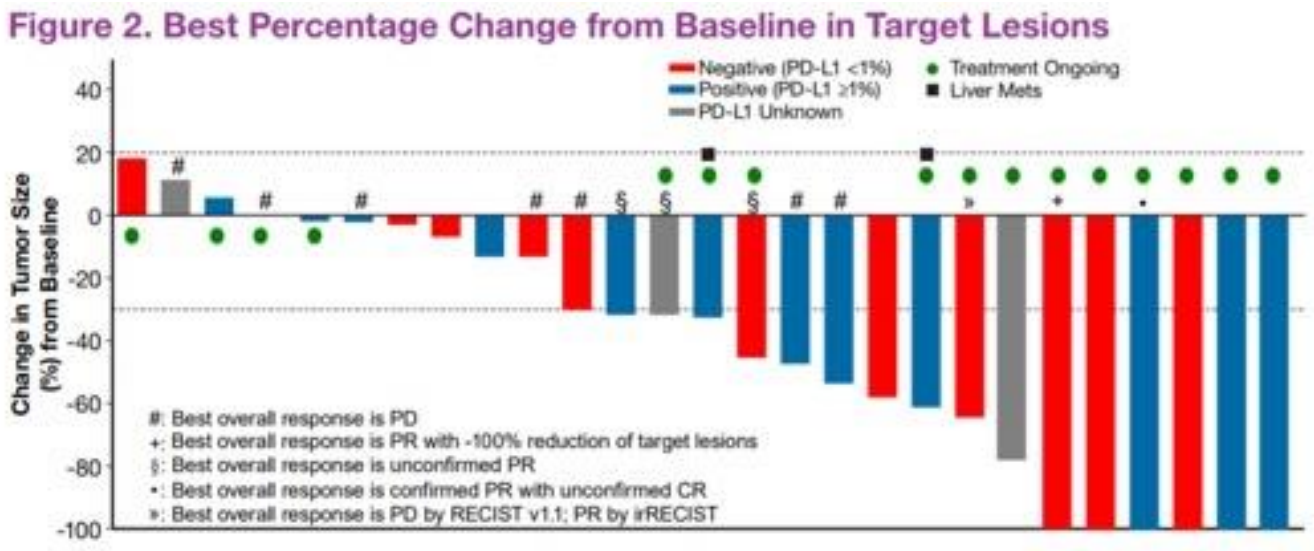


Sharma, J Clin Oncol 2019.

In development: NKTR-214 + nivolumab

Treatment	n	ORR
NKTR-214 + nivolumab	27	48%

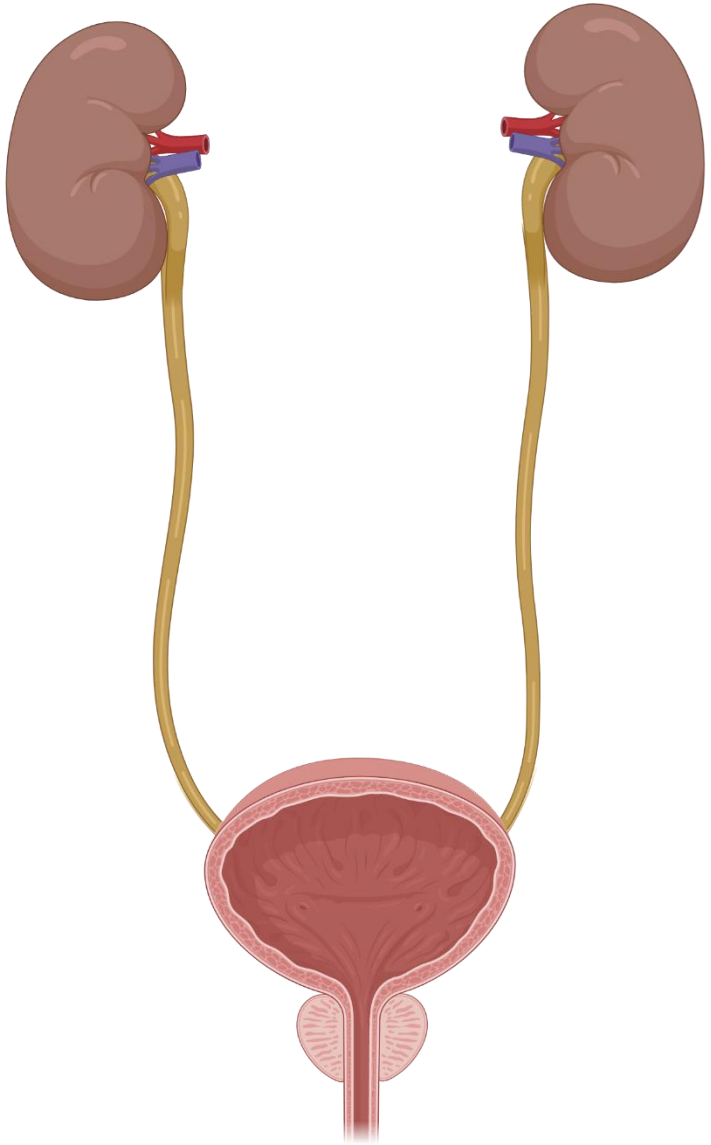
After treatment, 70% of patients with PD-L1-negative tumors converted to PD-L1-positive.



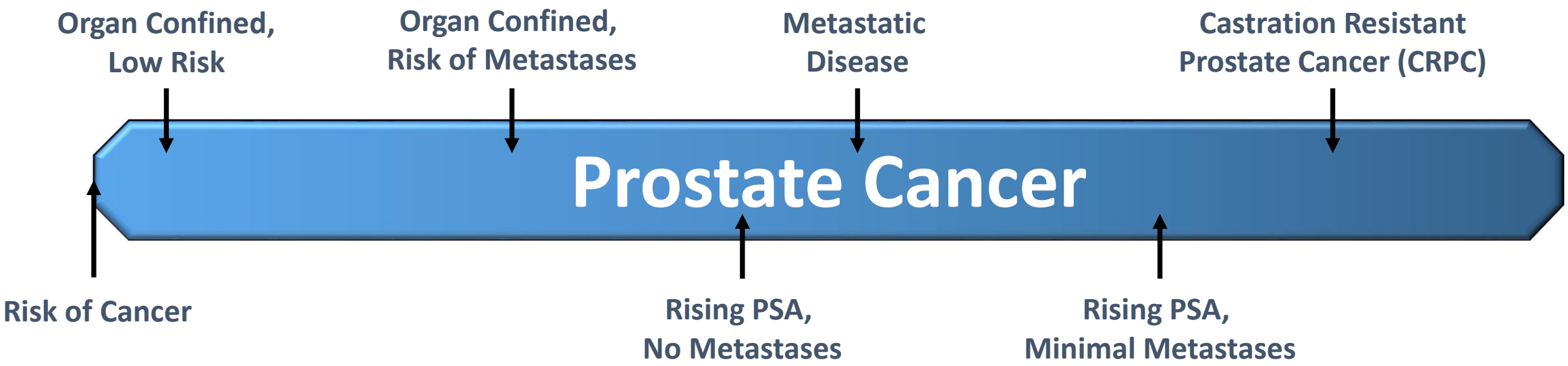
Siefker-Radtke, ASCO-GU 2020.

Outline

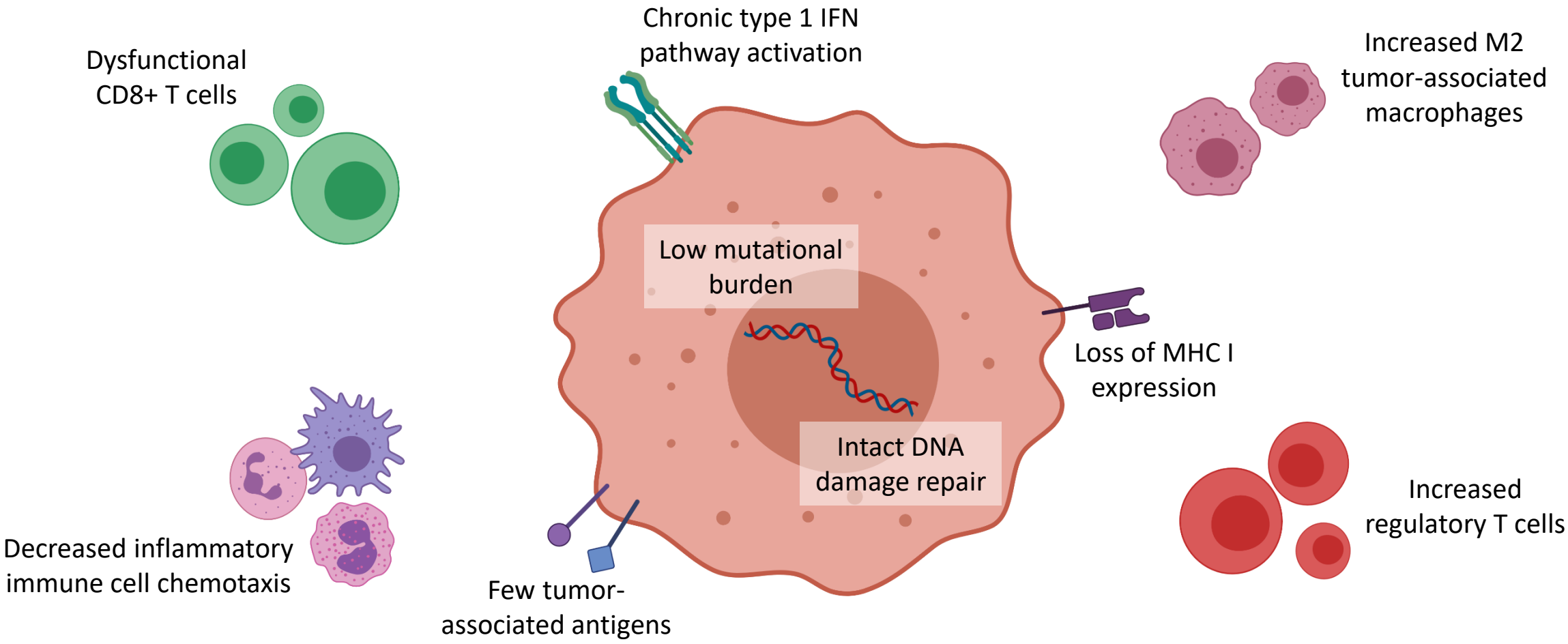
- Renal cell carcinoma
  - Approved immunotherapies
  - Future directions
- Urothelial carcinoma
  - Approved immunotherapies
  - Future directions
- Prostate cancer
  - Approved immunotherapies
  - Future directions



The Spectrum of Prostate Cancer



Immunology of prostate cancer



Vitkin, Front Immunol 2019.

#LearnACI

Immunotherapy landscape in prostate cancer

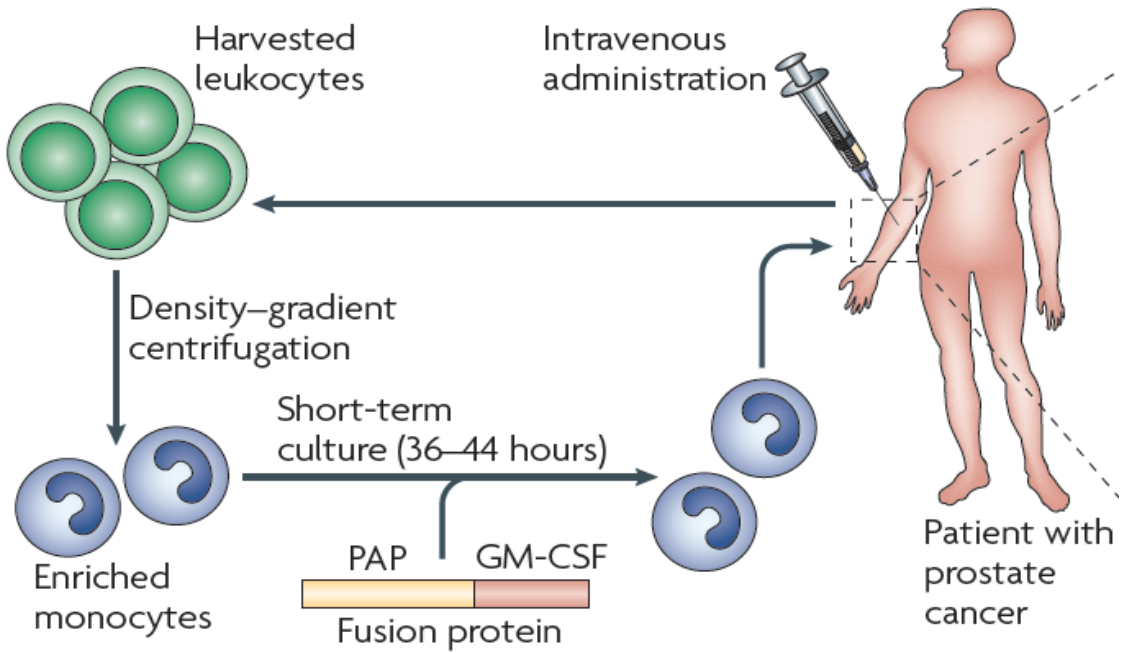
Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	RECIST-measurable PD-L1+ mCRPC	ORR: 5%
		RECIST-measurable PD-L1- mCRPC	ORR: 3%
		RECIST nonmeasurable mCRPC	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	PSA response rate: 21.8% Median OS: 20.4 months
	Pembrolizumab + olaparib		PSA response rate: 13% Median OS: 14 months
IMbassador250	Atezolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	Median OS: 15.2 vs 16.6 months
	Enzalutamide		

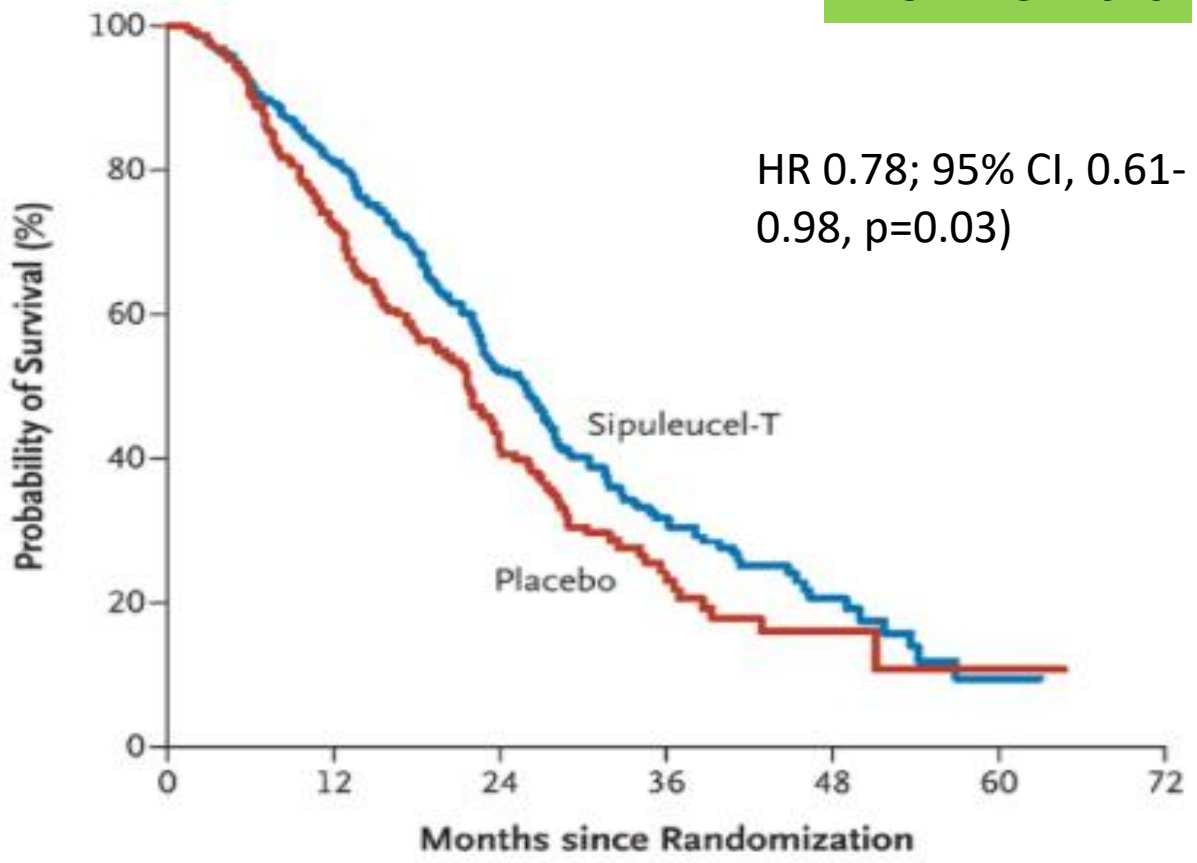
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

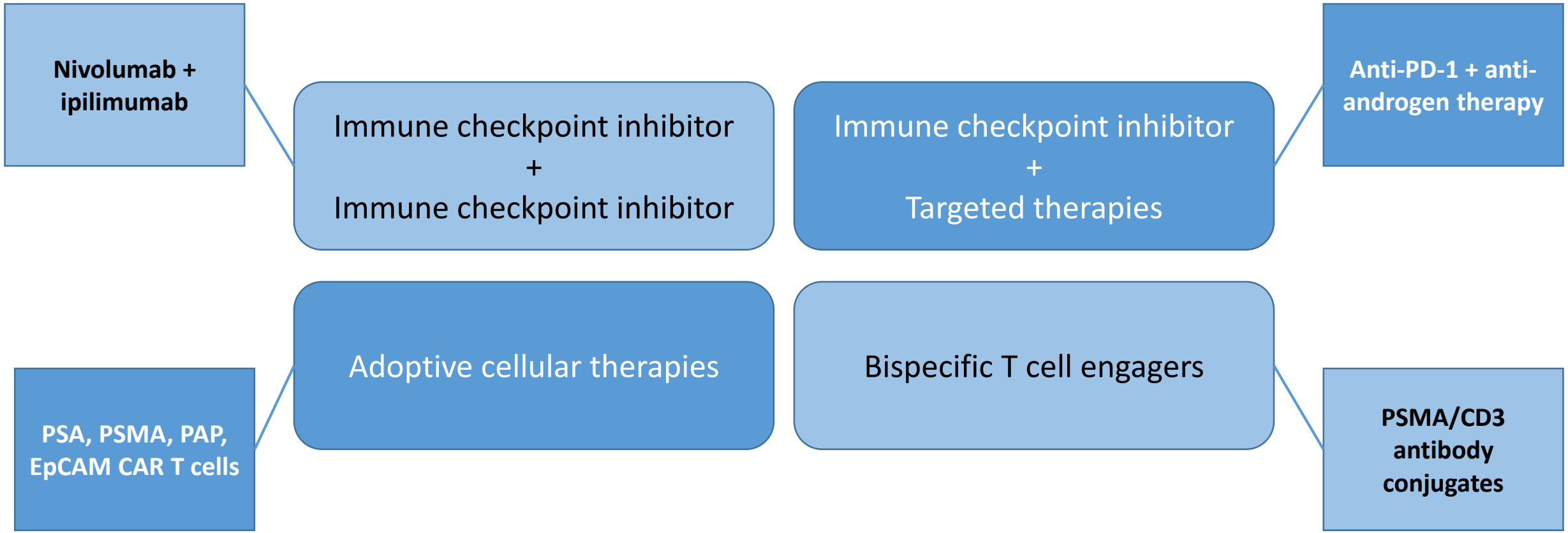




HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

Future directions for prostate cancer immunotherapy



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

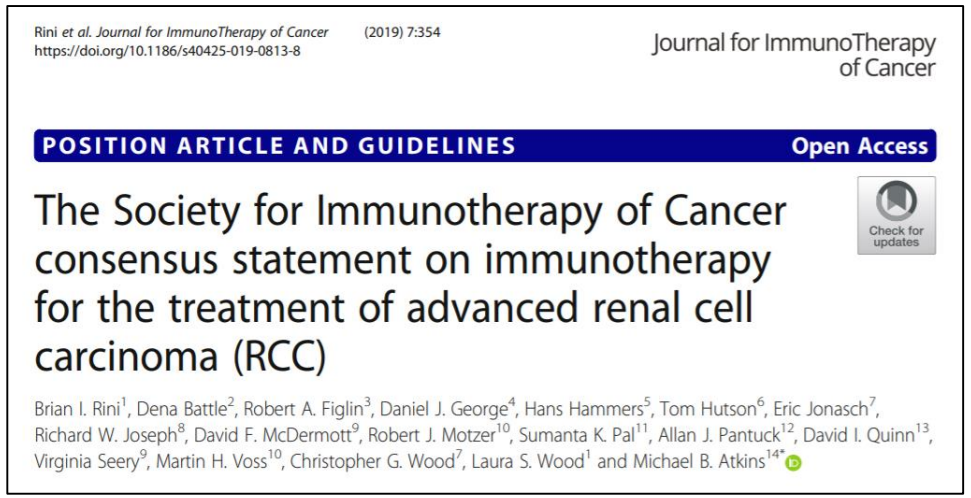
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

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, as well as other settings in UC
- 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* (2019) 7:354
https://doi.org/10.1186/s40425-019-0813-8

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 advanced renal cell carcinoma (RCC)

Brian I. Rini[1], Dena Battle[2], Robert A. Figlin[3], Daniel J. George[4], Hans Hammers[5], Tom Hutson[6], Eric Jonasch[7], Richard W. Joseph[8], David F. McDermott[9], Robert J. Motzer[10], Sumanta K. Pal[11], Allan J. Pantuck[12], David I. Quinn[13], Virginia Seery[9], Martin H. Voss[10], Christopher G. Wood[7], Laura S. Wood[1] and Michael B. Atkins[14*]

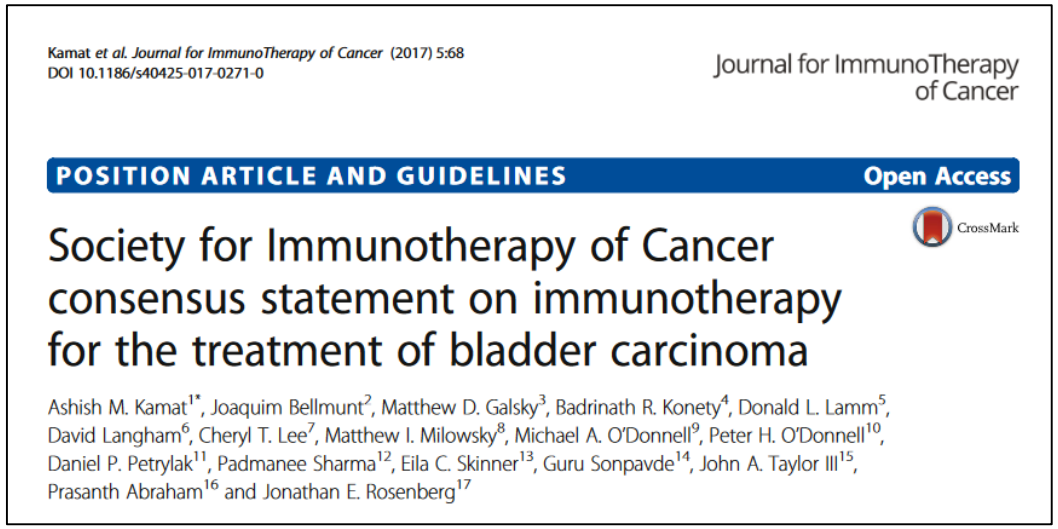
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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]

#LearnACI

Acknowledgements

- Some figures created using biorender.com

Case Studies

Case Study 1: mUC

A 68 year old man is referred to you by a urologist, after TURBT identified muscle invasive urothelial cancer. His Medical History is notable for CAD, for which he had 2 stents placed last year, no active angina. Last stress test reported as normal.

He has hypertension and hyperlipidemia which are well controlled.
Labs reveal creatinine of 1.1 which calculates to GFR of 60 mL/min

You perform staging and CT identifies enlarged RPLN, up to 2.5 cm in short axis, as well as 4 pulmonary nodules, largest 1.5 cm

What treatment would you recommend to this patient?

A) Pembrolizumab
B) Atezolizumab
C) Gemcitabine + Cisplatin
D) Gemcitabine + Carboplatin

Case Study 1 (mUC) continued

Because his GFR is good and he has no contraindication to cisplatin, you treat him with 6 cycles of Gem/Cis. He achieves a partial response. No major toxicities, just grade 1 nausea, fatigue, and thrombocytopenia.

You send his tissue for PD-L1 staining and identify that he has low PD-L1 staining.

He asks about additional treatment. What would be your recommendation?

A) Radical cystectomy
B) Avelumab maintenance
C) Observation
D) 2 additional cycles of gemcitabine + cisplatin

Case Study 1 (mUC) continued

Avelumab maintenance is offered due to the survival advantage seen in the JAVELIN Bladder 100 trial, which was present for the study population as a whole and not restricted to those with high PD-L1 expression. He receives 10 mg/k2 every 2 weeks, with acetaminophen and diphenhydramine pre-medication before the first 4 doses.

He develops new liver metastasis after 6 months. Performance status remains good. Genomic profiling is ordered to help determine whether he is a candidate for erdafitinib, with a plan for Enfortumab Vedotin while waiting for the results.

Case Study 2: mRCC

A 56 year old woman presents to the emergency room with cough and shortness of breath. She reports a history of nephrectomy 2 years earlier for renal cell carcinoma, but hasn't been following with her physician for surveillance because she lost her insurance during the pandemic. CT scan of the chest, abdomen and pelvis identifies multiple bilateral pulmonary nodules.

She has no significant medical history. Her mother had breast cancer in her 70's. Her grandmother had rheumatoid arthritis.
Labs reveal normal CBC, Calcium and LDH.
Biopsy of a lung nodule confirms clear cell renal carcinoma.

You perform staging MRI brain which is negative for metastases.
What treatment would you recommend to this patient?

A) Cabozantinib + nivolumab
B) Ipilimumab + nivolumab
C) Sunitinib
D) Lenvatinib + everolimus

Case Study 2 (mRCC) continued

Because she has good risk disease and is symptomatic, you recommend cabozantinib + nivolumab. She develops diarrhea and hand-foot syndrome. These are improved after holding cabozantinib for a week and reducing the dose upon resumption. Imaging shows a very good partial response.

6 months later she reports a new left sided headache. Mri brain reveals a 9 mm hemorrhagic focus in the left parietal lobe with mild surrounding vasogenic edema. She is started on dexamethasone, evaluated by neurosurgery, and the decision is made to treat with stereotactic radiation.

She returns to your office 2 weeks after the radiation. She has been tapered off dexamethasone and her headache has resolved. Her CT chest, abdomen and pelvis shows stability of the lung nodules. What do you advise her regarding treatment next:

A) Start second-line therapy with Lenvatinib + everolimus
B) Resume cabozantinib + nivolumab
C) Surgical resection of the brain metastasis
D) Observation

Case Study 2 (mRCC) continued

CNS metastases do not necessarily reflect systemic failure. Thus it would not be optimal to start second-line therapy.

Since she has residual active systemic disease and did not have major toxicity nor irAE, Cabozantinib + nivolumab may safely be resumed and would potentially be important for ongoing cancer control.

Surgical resection has not been shown to improve outcomes in mRCC after SRS to solitary brain metastases and would delay resumption of systemic therapy.

Observation is not favored, given active metastatic disease which was symptomatic at presentation.