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

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Disclosures

- Consulting Fees: HMP Global, Bayer, Bristol Myers Squibb, Seattle Genetics, Exelixis, EMD Serono, Immunomedics, Eisai
- 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
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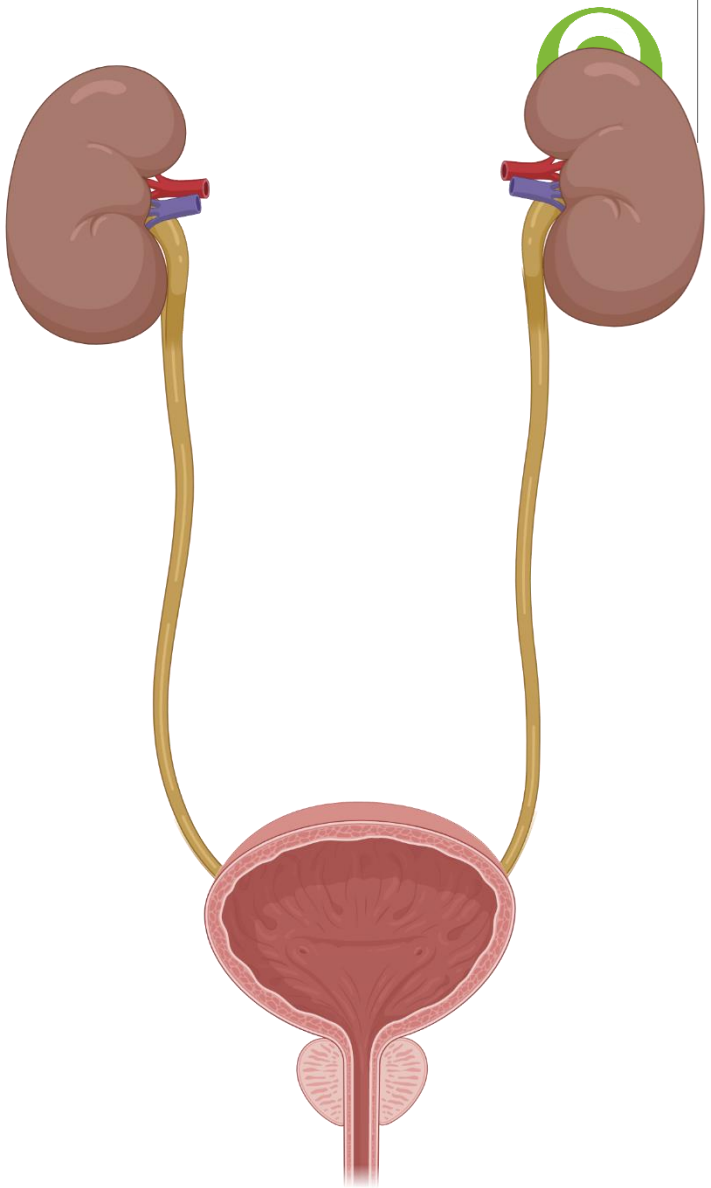
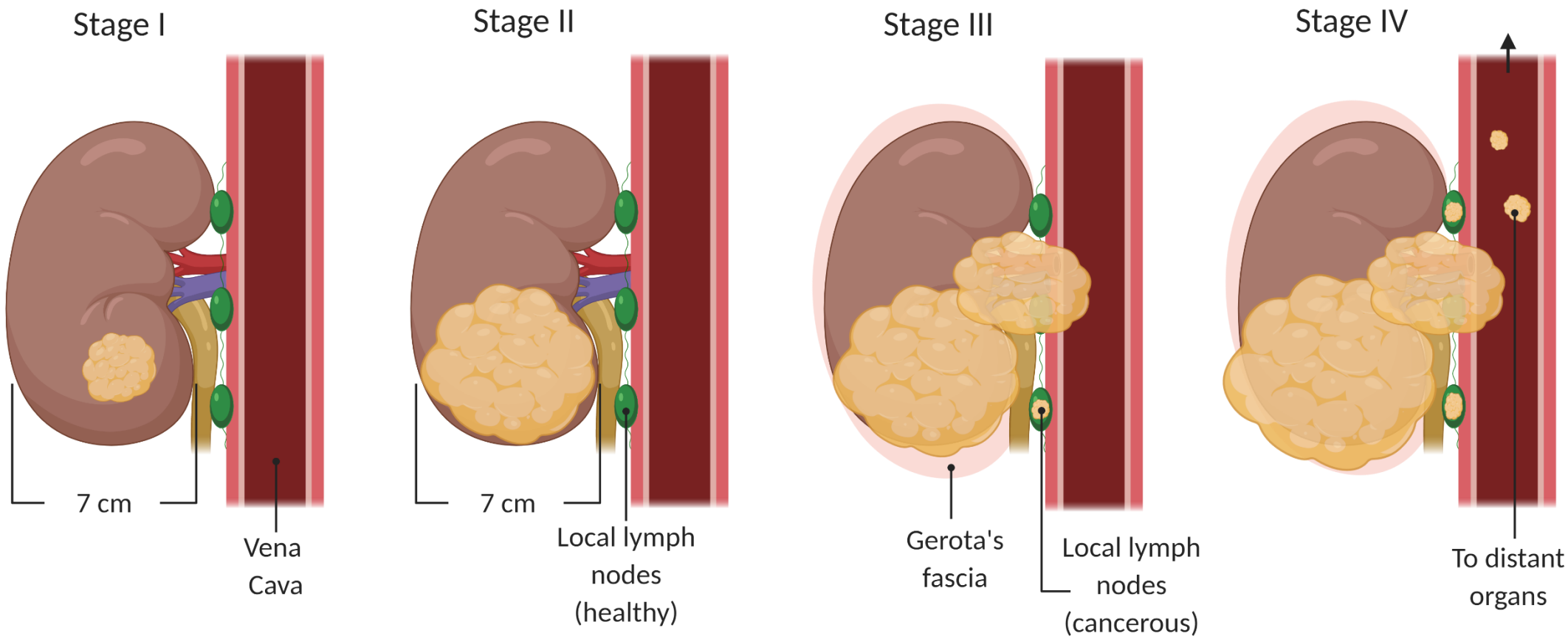


Renal cell carcinoma (RCC)



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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	CR 9%
	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	CR 5.6%
	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

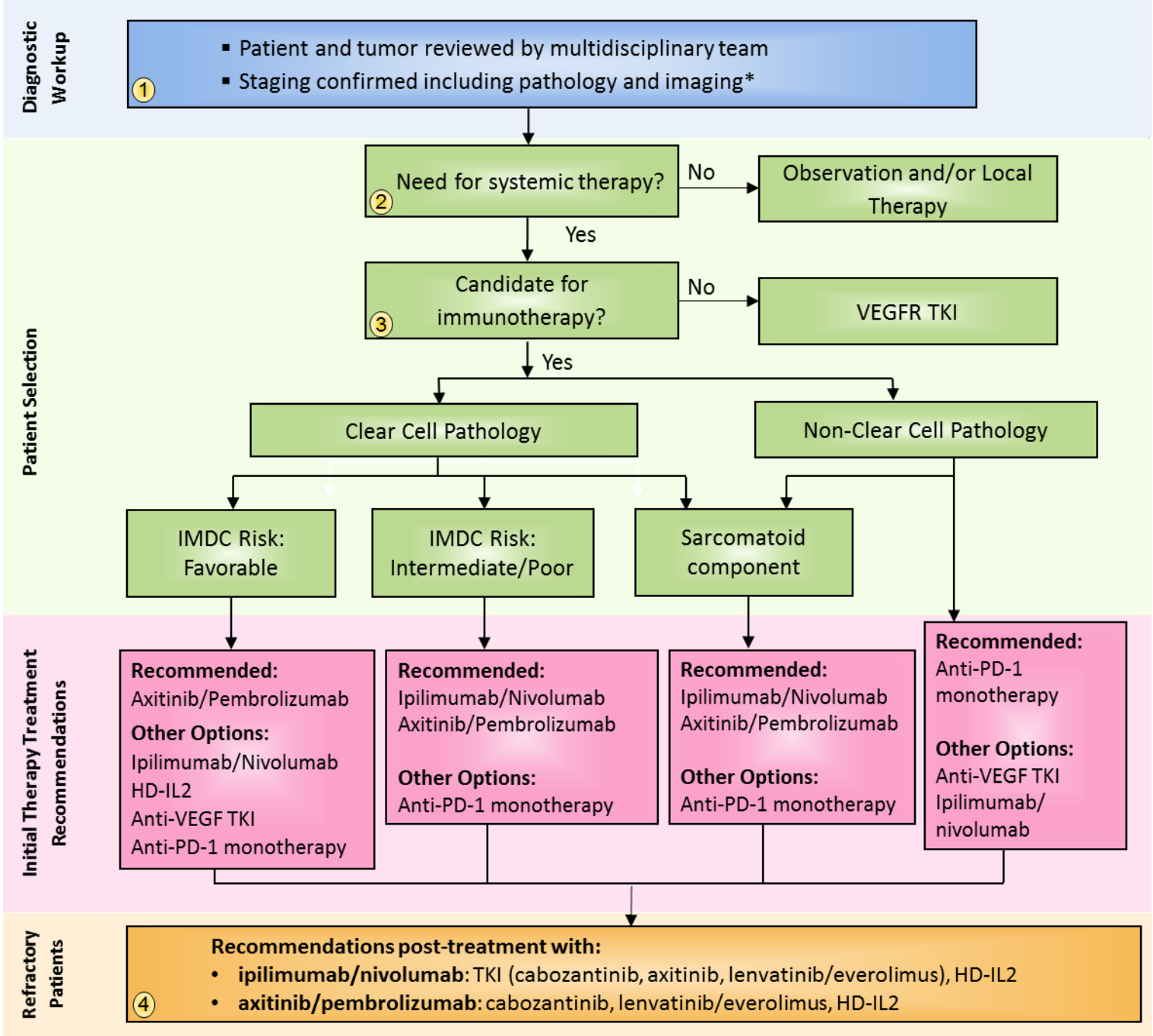
Tannir, ASCO-GU 2020; Pilmack, ASCO 2020; Choueiri, Ann Oncol 2020; Rini, Lancet 2019.

Frontline regimens continued

- CLEAR: pembrolizumab + lenvatinib (vs sunitinib) Motzer ASCO GU 2021
  - ORR 71%, mPFS 23.9 mo, mOS NR
  - CR 16.1%

- Checkmate-9ER: nivolumab + cabozantinib (vs sunitinib) Choueiri ESMO 2020
  - ORR 55.7%, mPFS 16.6 mo, mOS NR
  - CR 8%

SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma

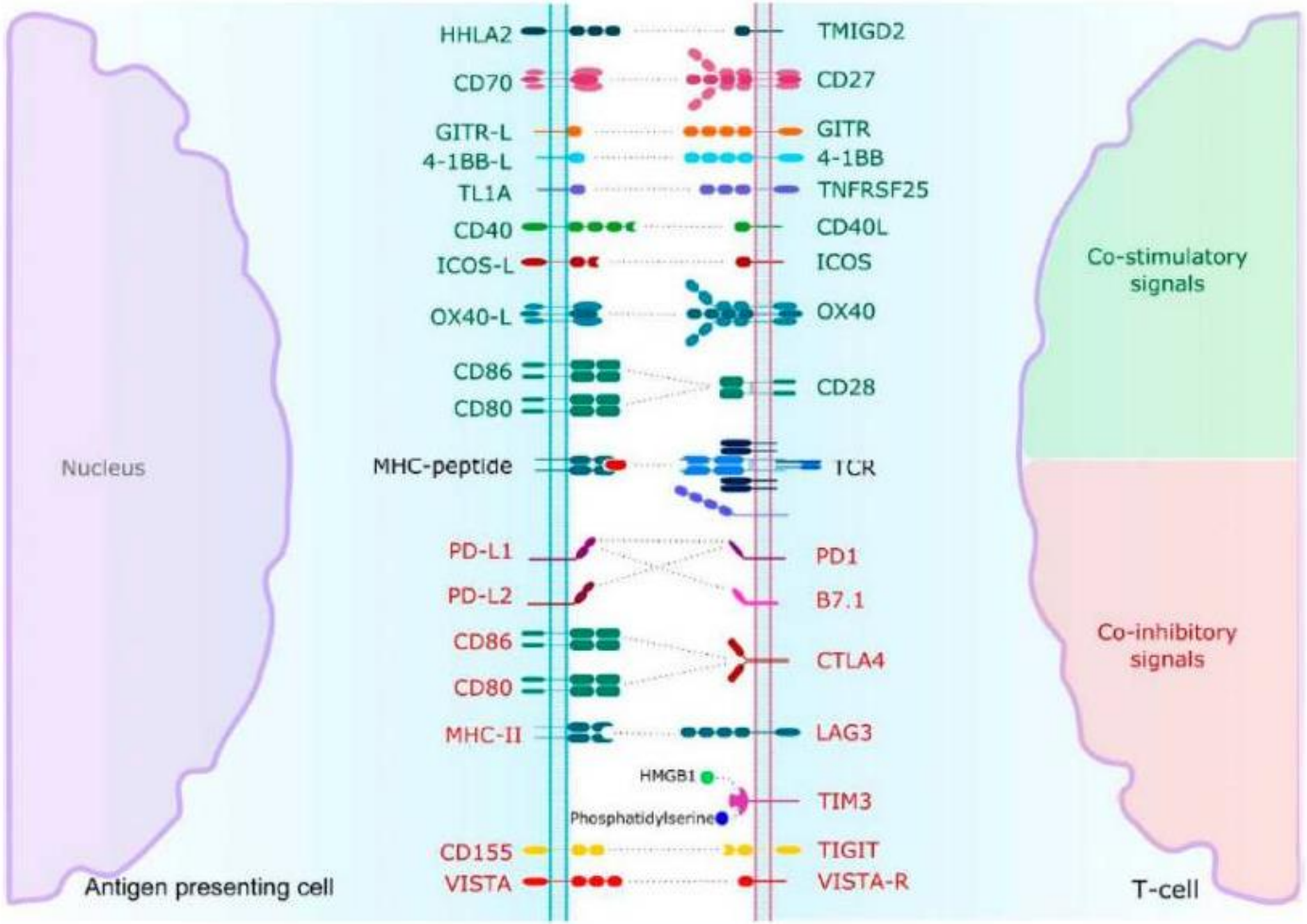


*Baseline imaging recommendations discussed in figure legend.

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: additional immunotherapy approaches



Deleuze, Int J Mol Sci 2020

What is the best sequence?

- Which second line therapy to use, depending on which first line combination was given?
- If patients have toxicity, how to differentiate IO from VEGF TKI toxicity and to address which treatment to use next?
- For oligometastatic cases, how do we utilize information on CR rates and role of possible subsequent surgery? Is there still a role for cytoreductive nephrectomy as well?

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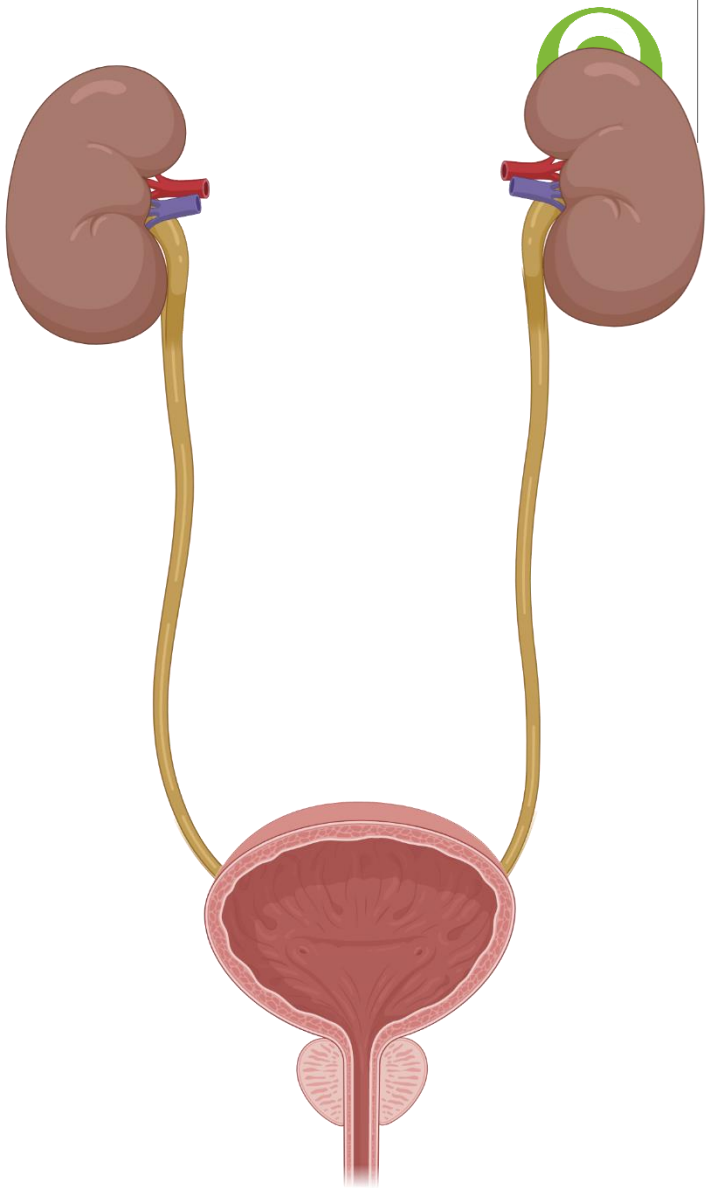
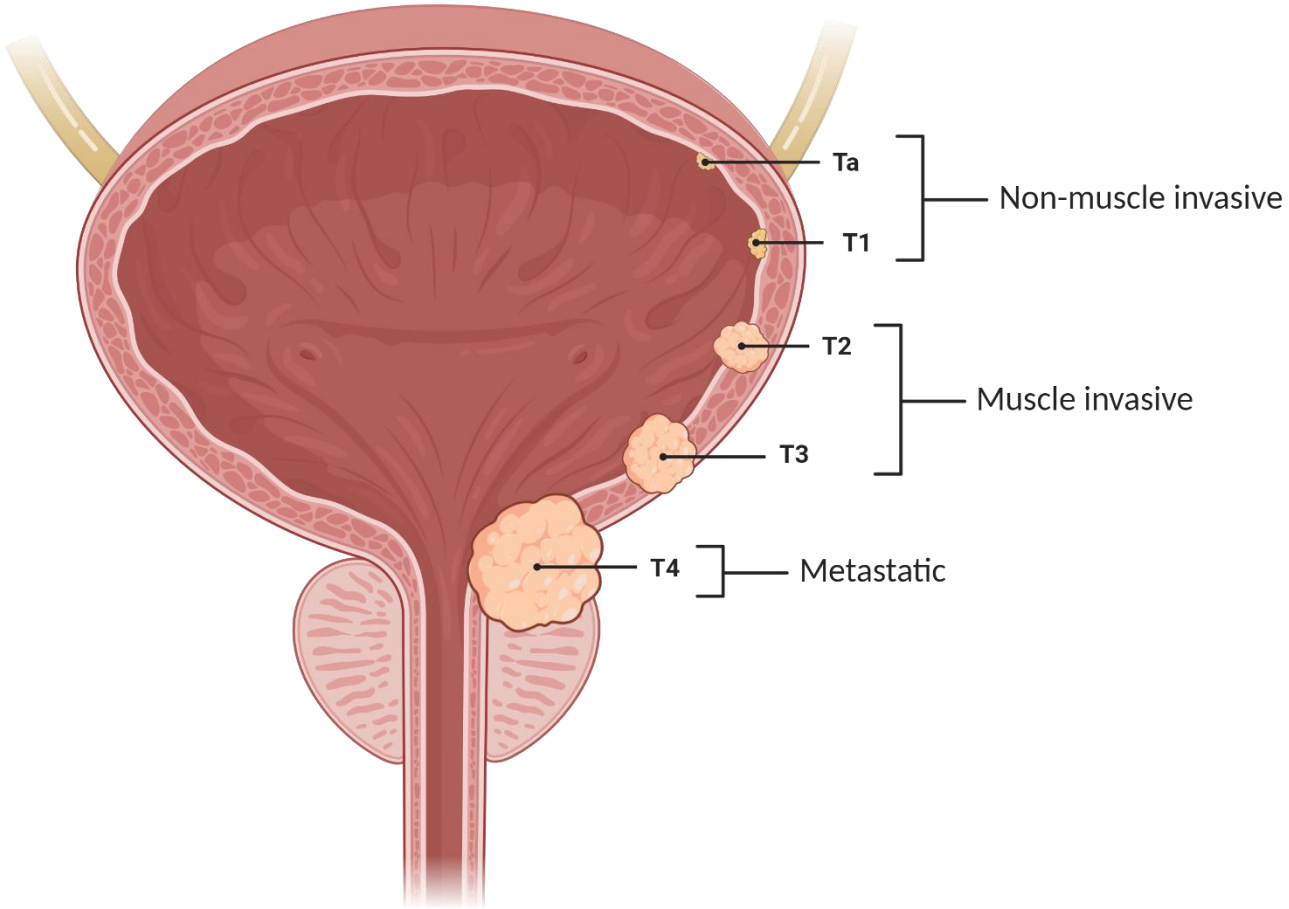


Urothelial carcinoma (UC)



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 progressing after cisplatin

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
Atezolizumab	Advanced/metastatic UC	840 mg q2w or 1200 q3w or 1680 q4w

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

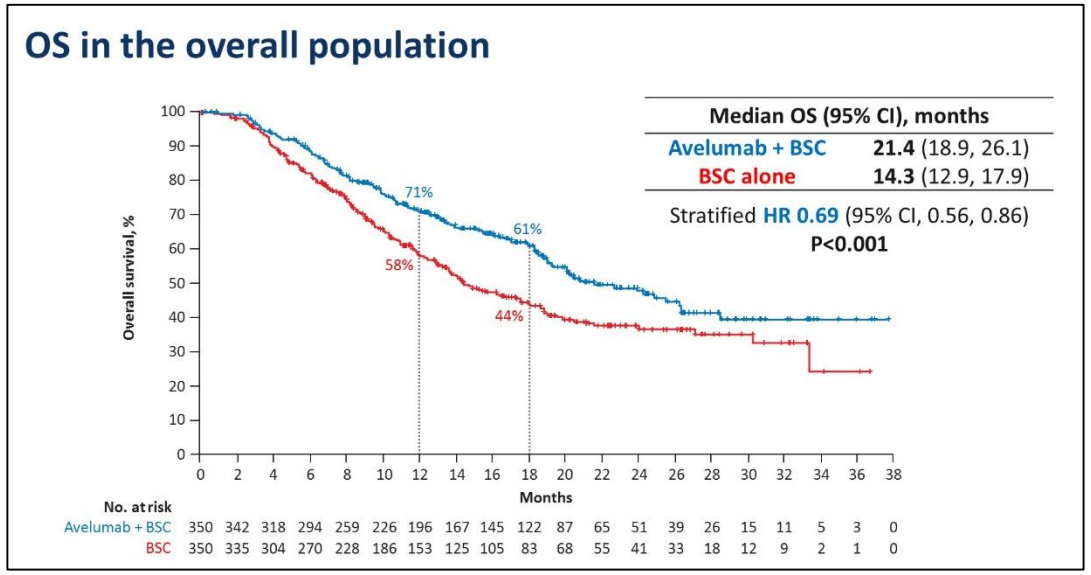
June 2018

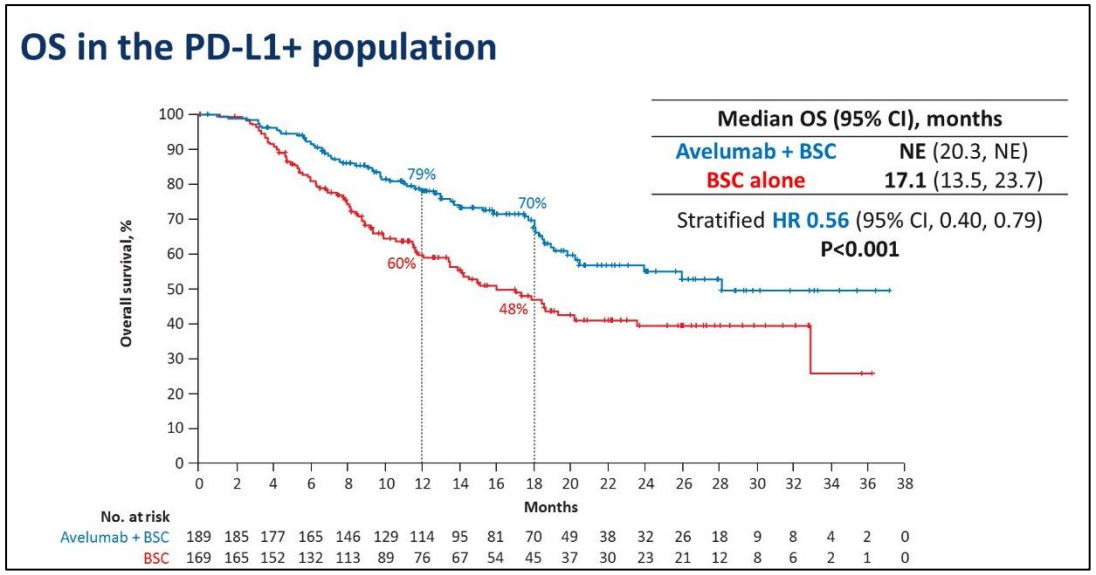
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- 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



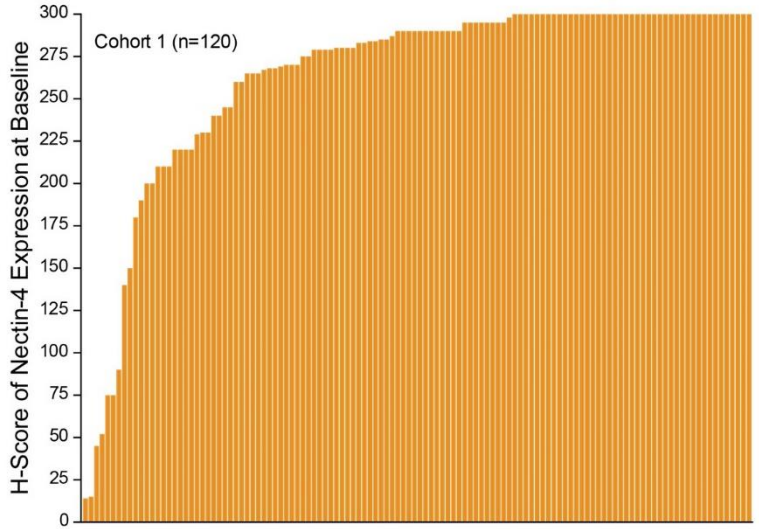


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

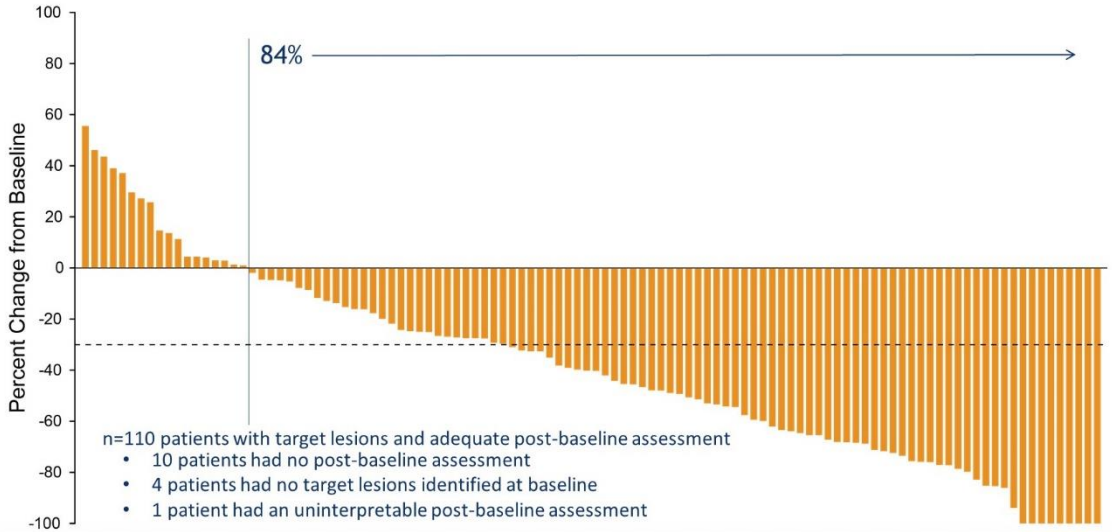
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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



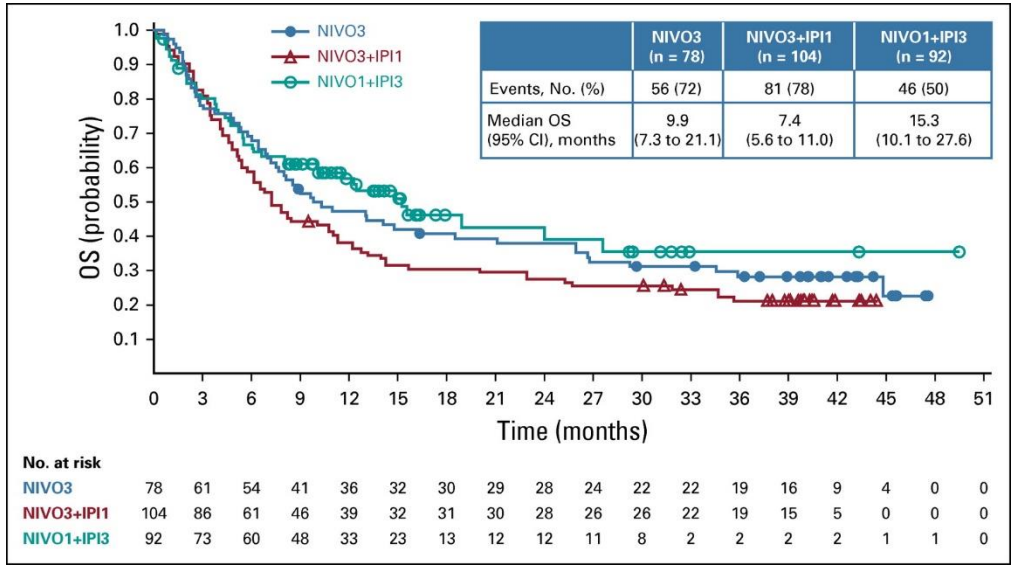
Petrylak, ASCO 2019.

Investigational approaches in mUC

- Chemoimmunotherapy and immunotherapy intensification approaches
  - IMvigor130: Role of concurrent chemoimmunotherapy (atezolizumab)
    - Positive for PFS but immature for OS
    - Galsky et al Lancet 2020; 395 (10236):1547
  - DANUBE: Role of double immunotherapy (durvalumab tremelimumab)
    - Powles et al Lancet Sept 21, 2020
  - KEYNOTE-361: Role of concurrent chemoimmunotherapy (pembrolizumab)
    - Alva ESMO 2020
  - Other chemoimmunotherapy ongoing trials
- Enfortumab vedotin combinations
- Novel targeted therapy for mutations and fusions
- Novel IO agents

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 + ipilimumab 3 mg/kg	92	ITT: 38.0% PD-L1+: 58.1%	4.9 months	15.3 months	39.1%

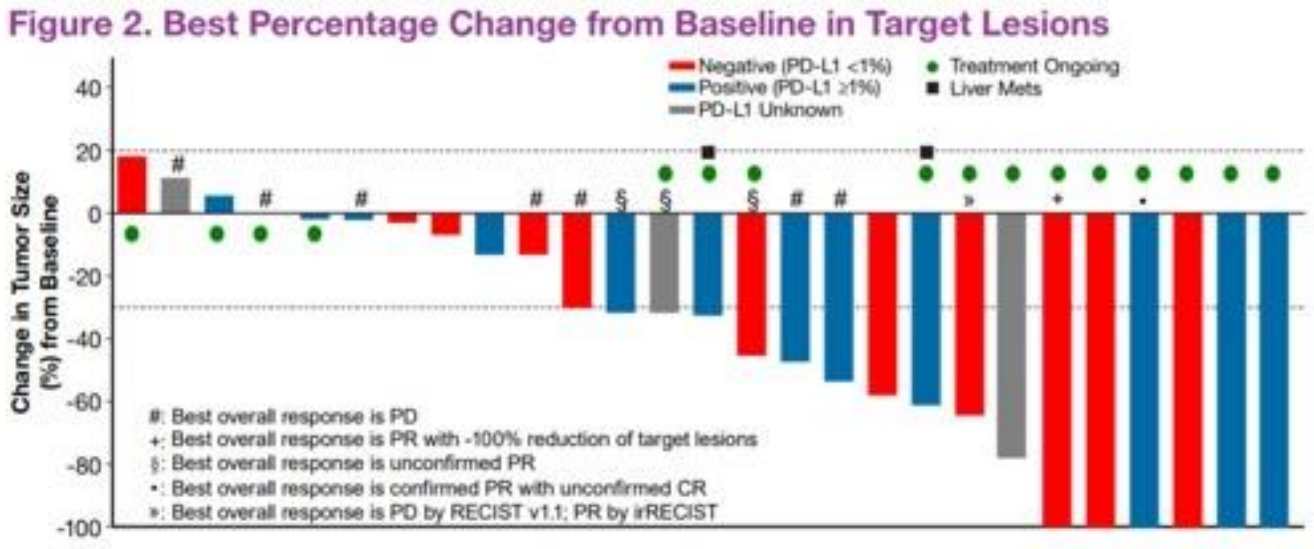


Sharma, J Clin Oncol 2019.

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.

How do I sequence mUC in 2021?

- First-line
  - Determine cisplatin eligibility (full dose or split dose D1/8)
  - Consider first-line cytotoxic chemotherapy, typically GC; then consider avelumab switch maintenance
  - Consider first-line clinical trials but take into account other recently reported trials and the pros and cons of maintenance avelumab, which may or may not be allowed in ongoing trials
  - While on first-line therapy, obtain comprehensive molecular profile from archival tissue to be ready for future decision-making upon progression

- Second-line
  - Role of immunotherapy and patient selection
  - Role of FGFR inhibition and patient selection
  - Role of enfortumab vedotin and patient selection
  - Combination clinical trials or novel molecular targets

- Third-line and beyond
  - Same as second-line options, depending on prior therapy
  - Combination clinical trials, novel molecular targets, or novel agents
  - Cytotoxic chemotherapy (taxanes or other)

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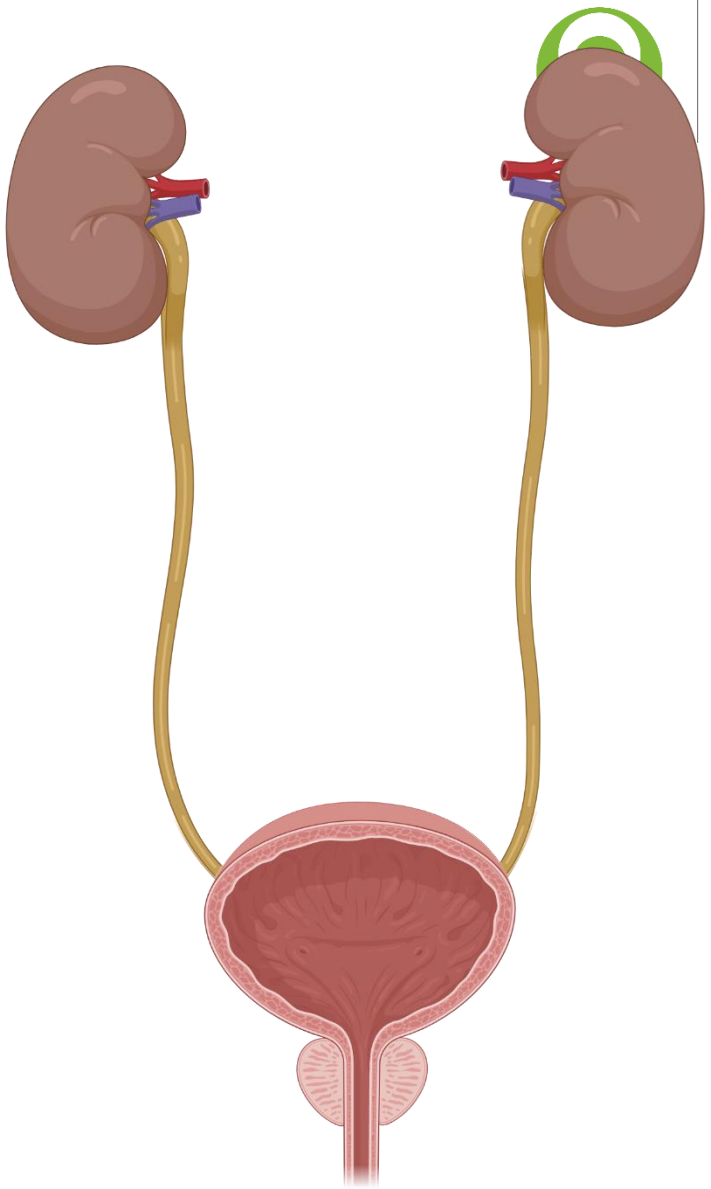
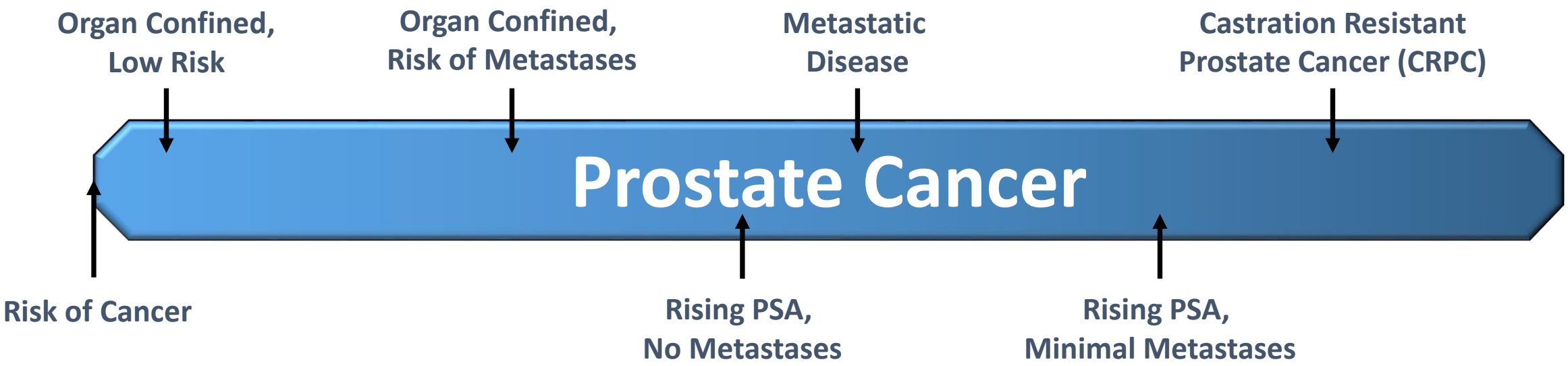


The Spectrum of Prostate Cancer



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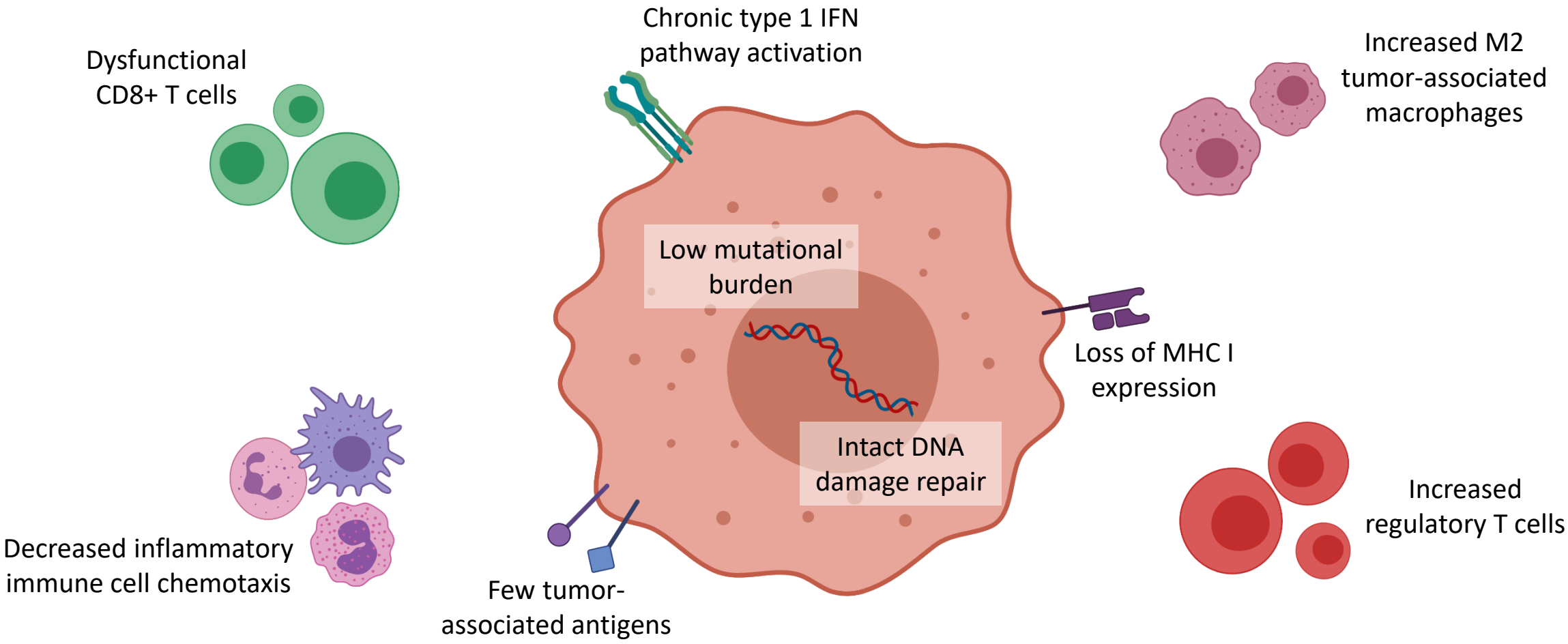
Immunology of prostate cancer

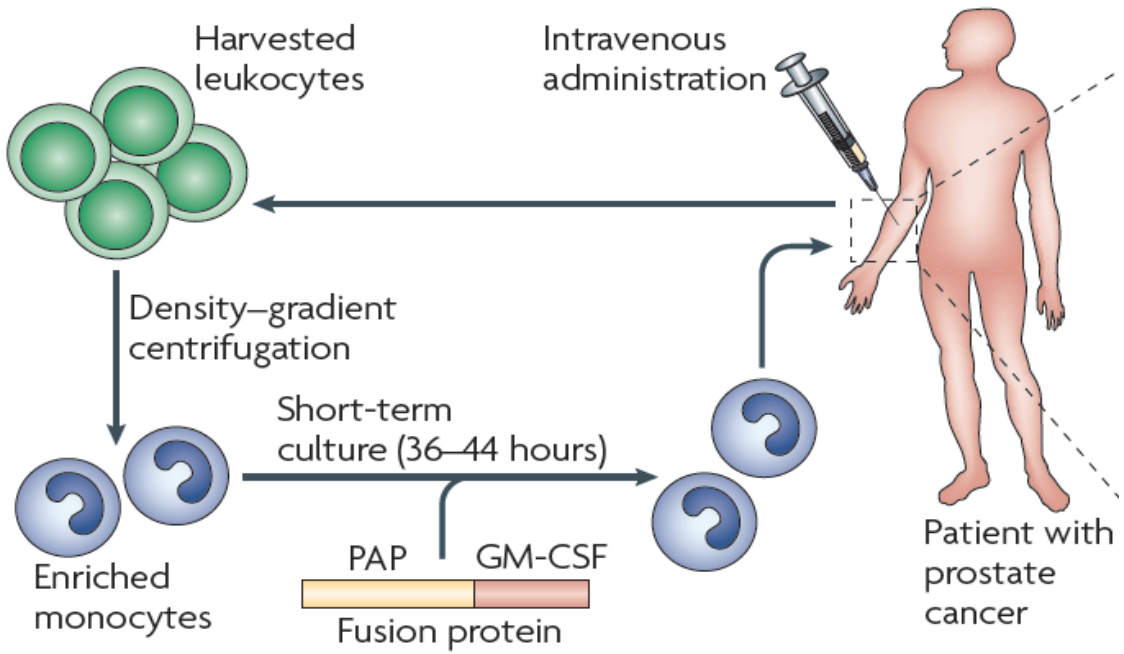


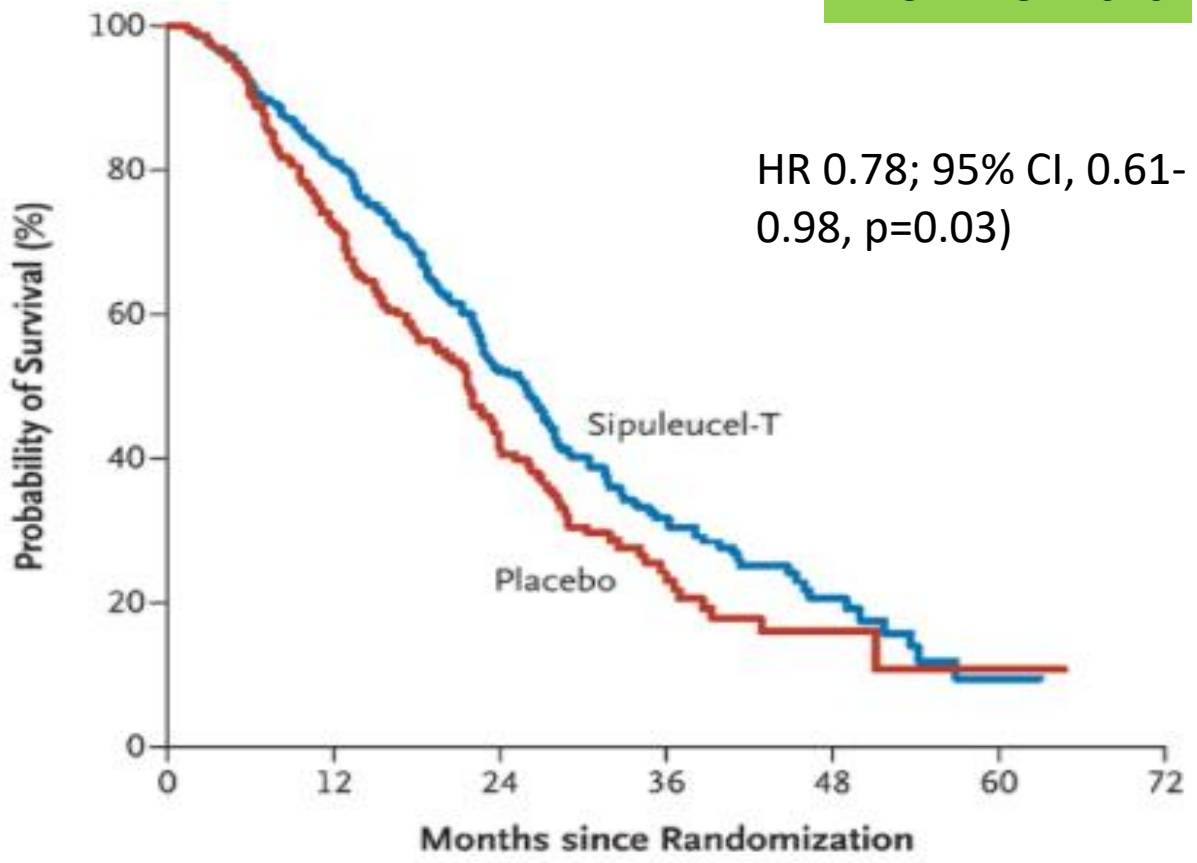
Vitkin, Front Immunol 2019.

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

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		

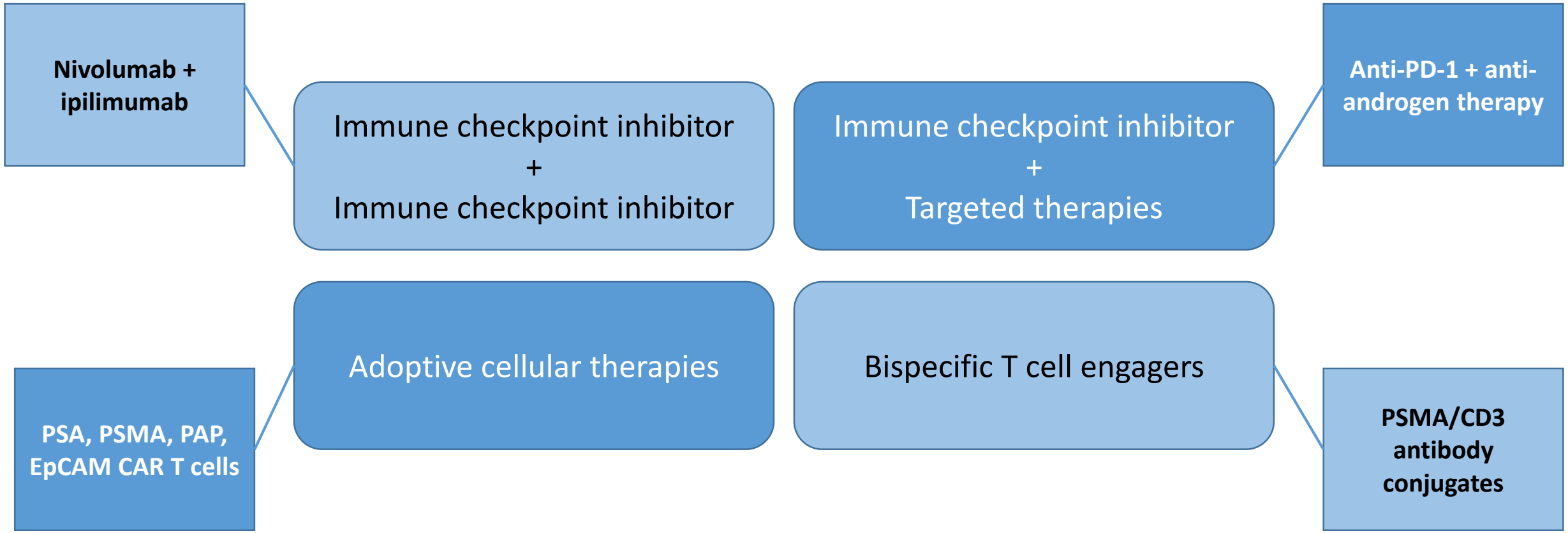
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

MSI high prostate cancer

- 3.1% incidence in 1033 patients at MSKCC
- 11 patients received checkpoint inhibitor therapy
- 6 patients had greater than 50% PSA decline
- 4 patients had radiographic responses
- 5 patients were still on therapy as long as 89 weeks

Abida et al JAMA Oncol 2019 April 1; 5(4):471

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

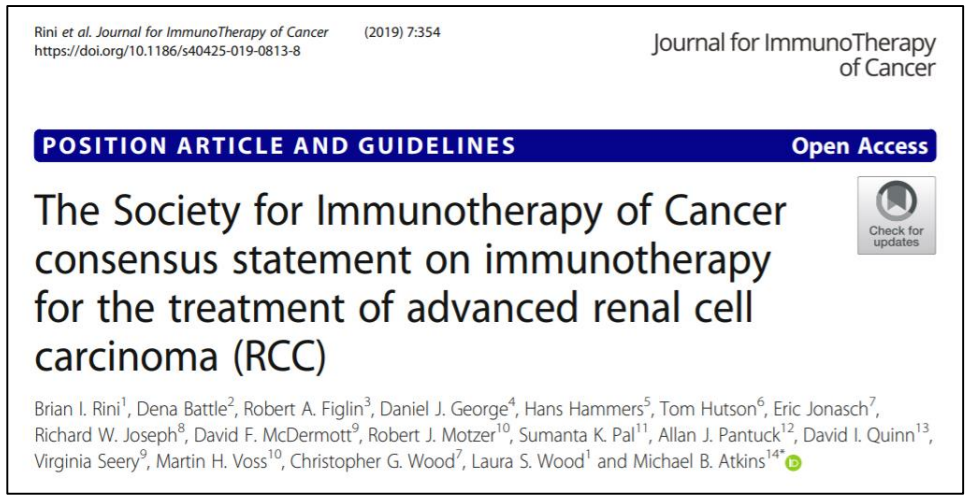
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Conclusions

- Established role of immunotherapy in RCC and urothelial carcinoma
- In RCC, many front-line checkpoint inhibitor combinations are approved
- Multiple checkpoint inhibitors approved for advanced/metastatic urothelial carcinoma, as well as other therapeutic spaces in UC
- Low immune engagement in prostate cancer has limited the application of immunotherapy in this disease however interest remains with multiple novel immunotherapy agents in development; molecular profile is commonly obtained and may also assist with MSI high detection

Additional Resources



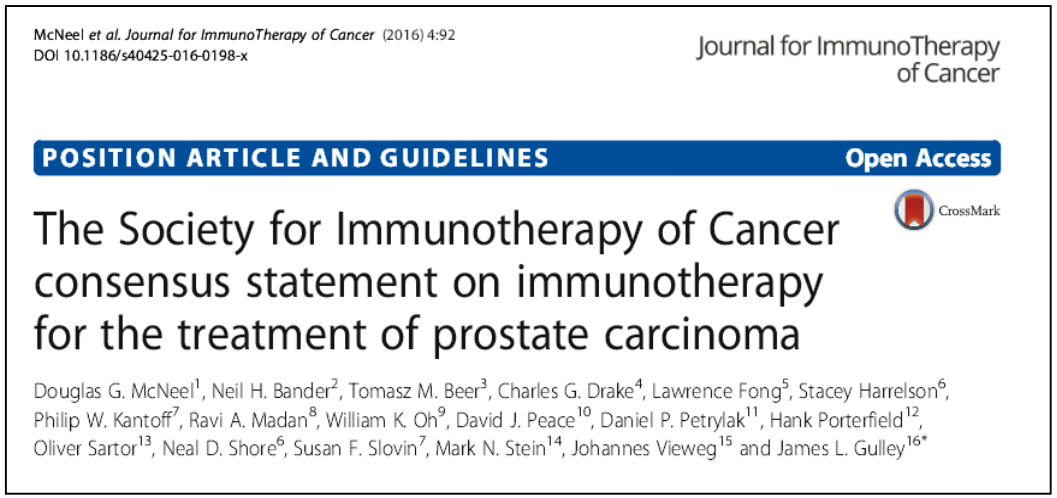
Rini *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:354
https://doi.org/10.1186/s40425-019-0813-8

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*]



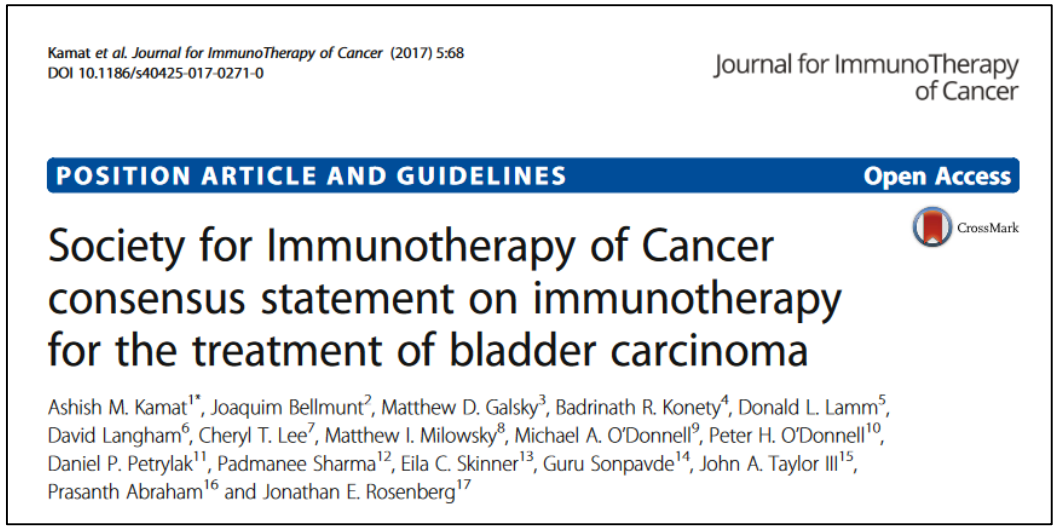
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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]

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