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

sitc Society for Immunotherapy of Cancer

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Disclosures

- Contracted Research: Bristol-Myers Squibb, Rexahn, Incyte, Novartis, LSK BioPharma, Five Prime, Mirati, QED Bioscience, Debiopharm, Merck, Pfizer, Astra Zeneca, MedImmune, Clovis, Immunocore
- Travel Fund: QED
- I will be discussing non-FDA approved indications during my presentation.

Types of Immune Therapies

Cytokines

IL2

IFN alfa2b

BCG

Checkpoint Inhibitors

PD-1

PD-L1/2

CTLA4

Agonism of costimulatory receptors

Manipulating T cells

Oncolytic viruses

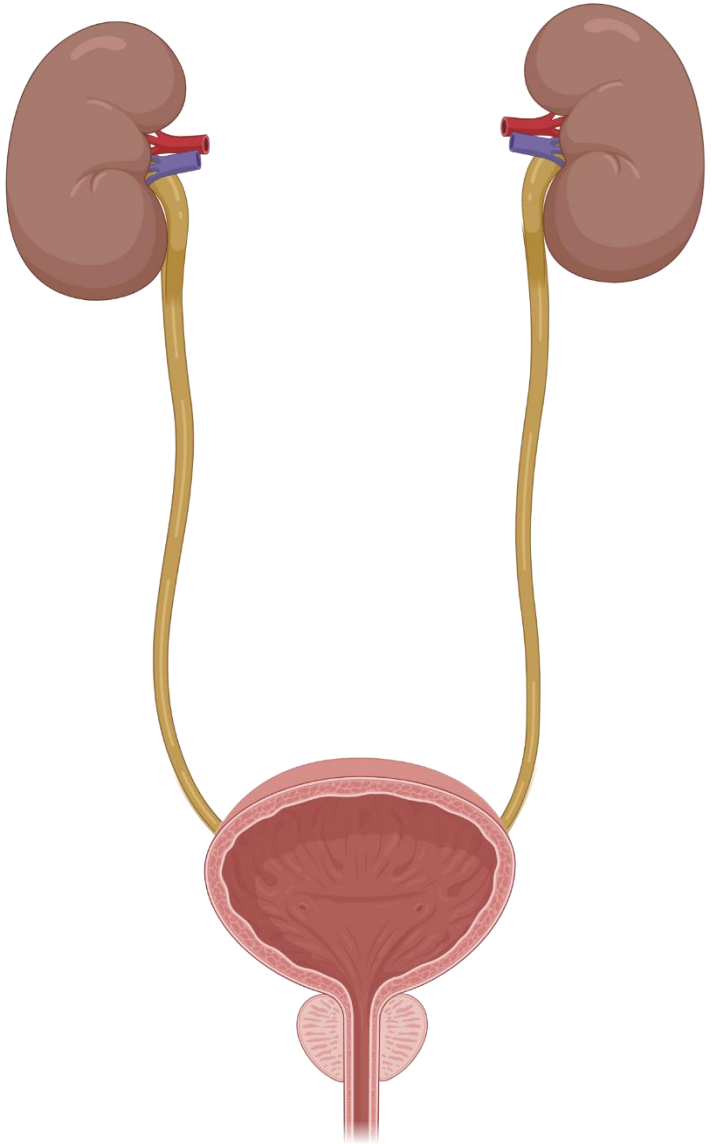
Vaccines

Sipuleucel-T

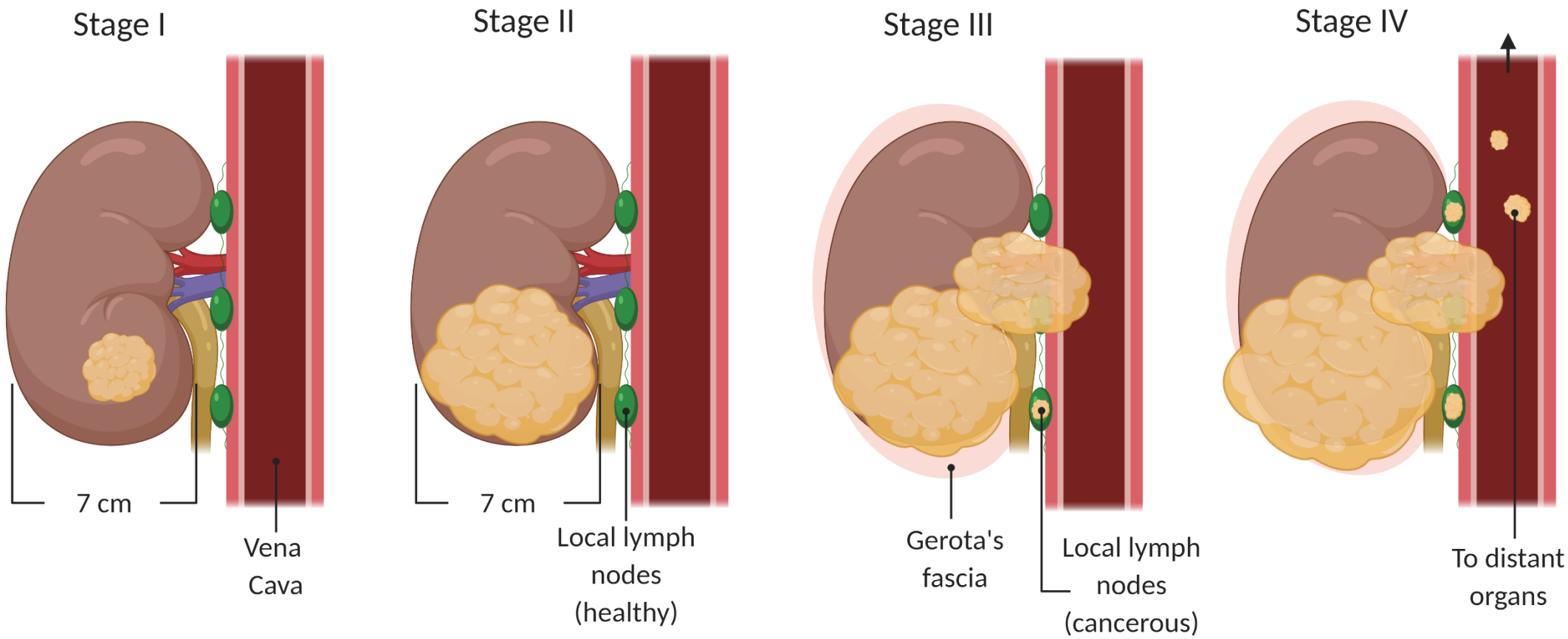
Therapies directed at other cell types in tumor microenvironment

Outline

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



Renal cell carcinoma (RCC)



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	Advanced RCC, Treatment naïve	240 mg nivolumab Q2 w + cabozantinib 40 mg once 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
CheckMate 9er	Nivolumab+ Cabozantinib*	Untreated, advanced clear cell RCC	323	55.7%	16.6	NR
	Sunitinib		328	27.1%	8.3	NR

 *FDA-approved IO regimen

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

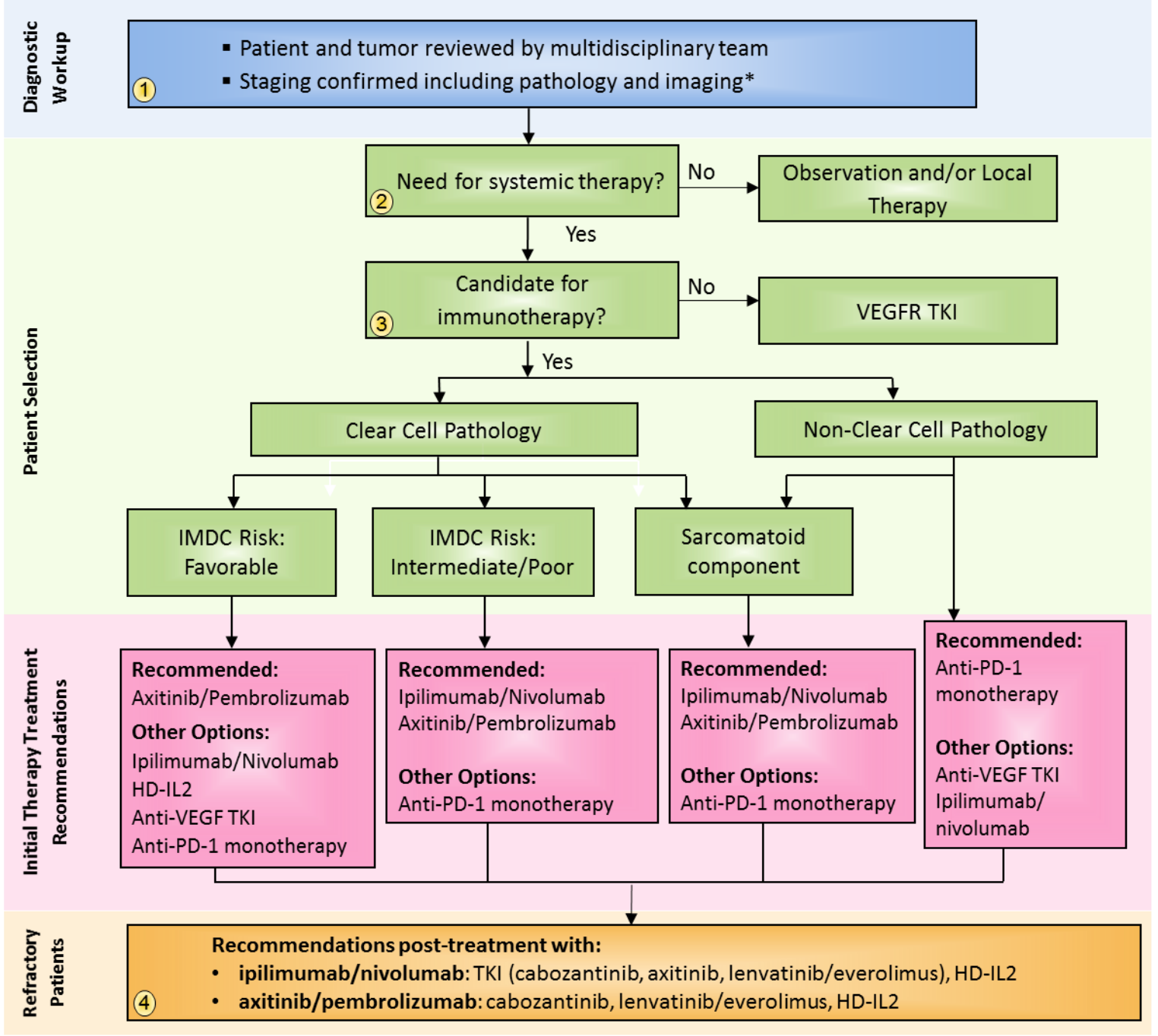
SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma

International Metastatic Renal Cell Carcinoma Database Consortium criteria:

Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 y
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

Nivolumab+Cabozantinib is now FDA approved as first line



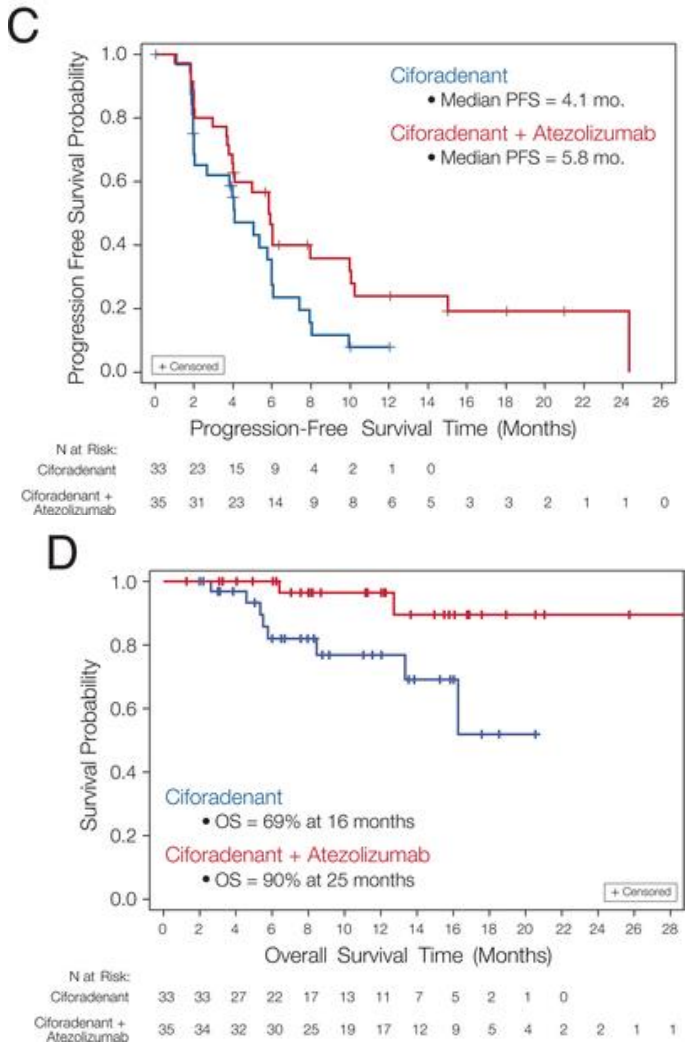
*Baseline imaging recommendations discussed in figure legend.

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

Heng, Lancet Oncol 2013; Rini, J Immunother Cancer 2019; Choueiri, Ann Oncol 2020.

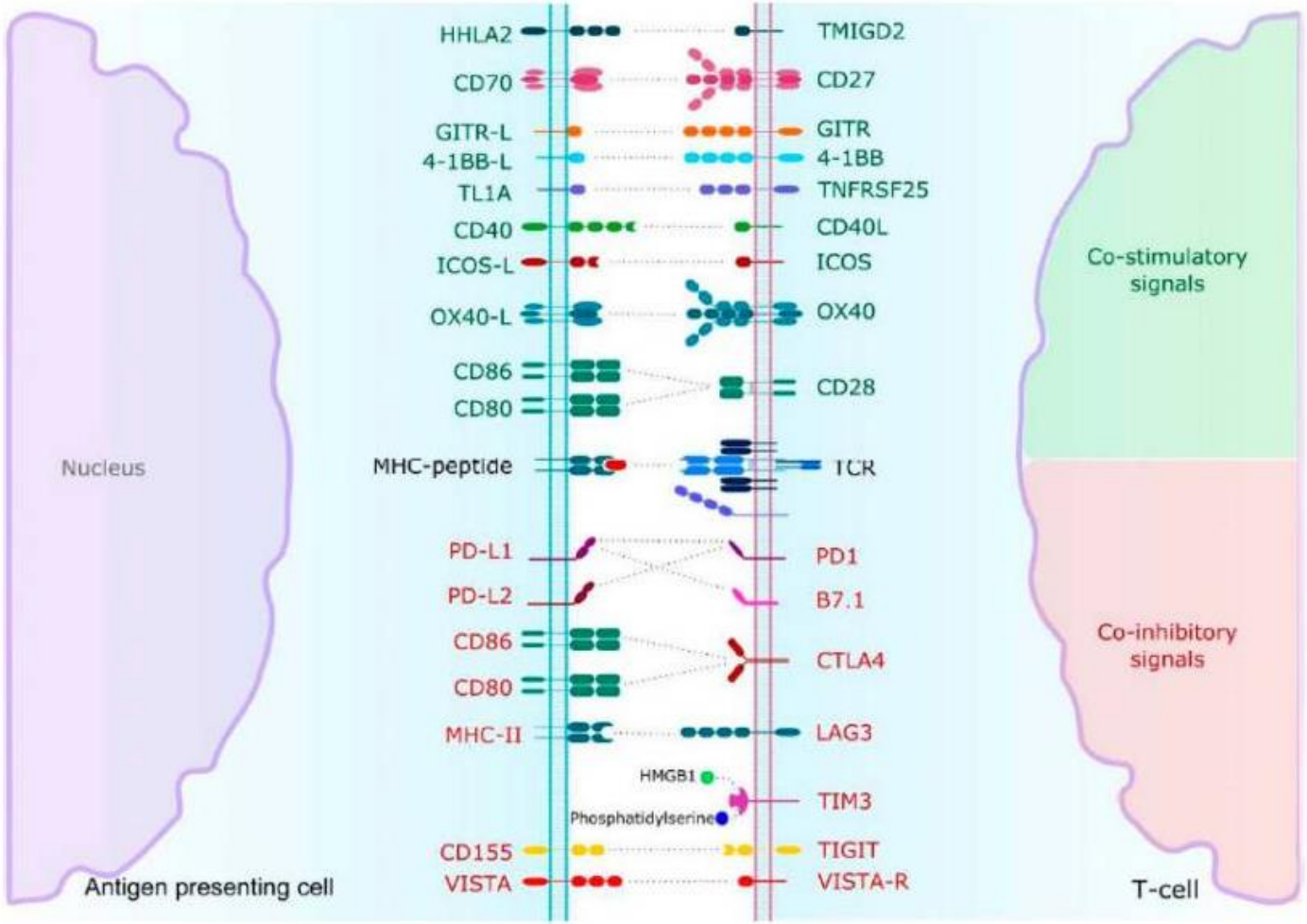
In development: A2AR antagonist + anti-PD-L1

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

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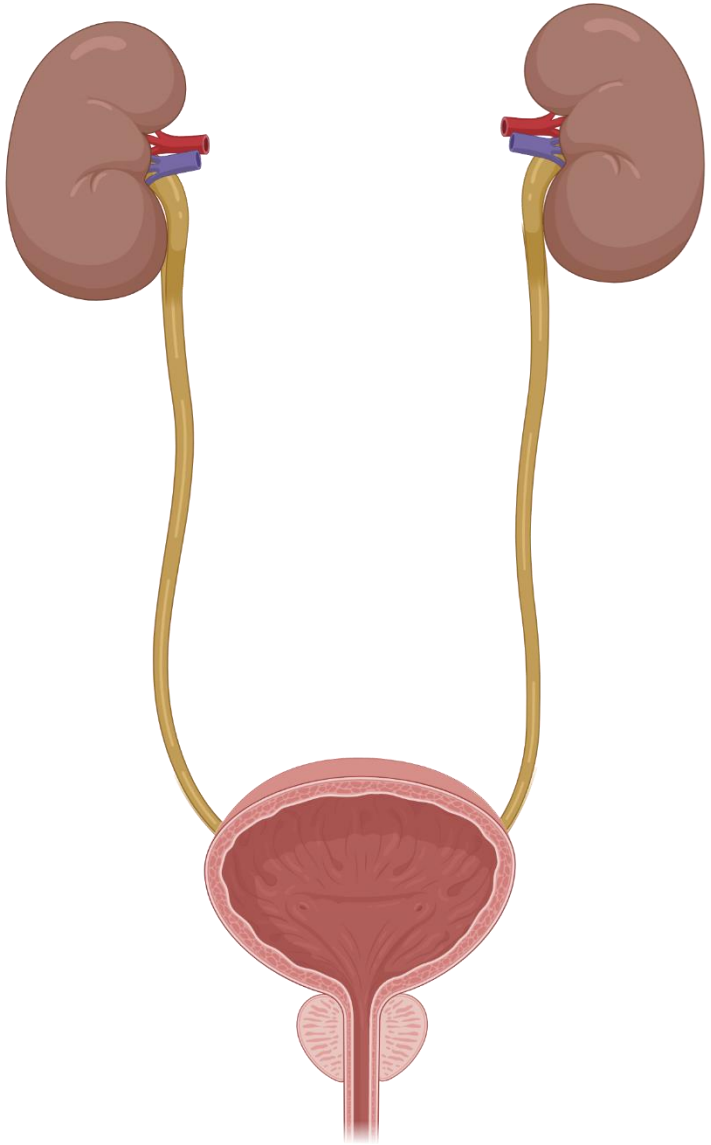
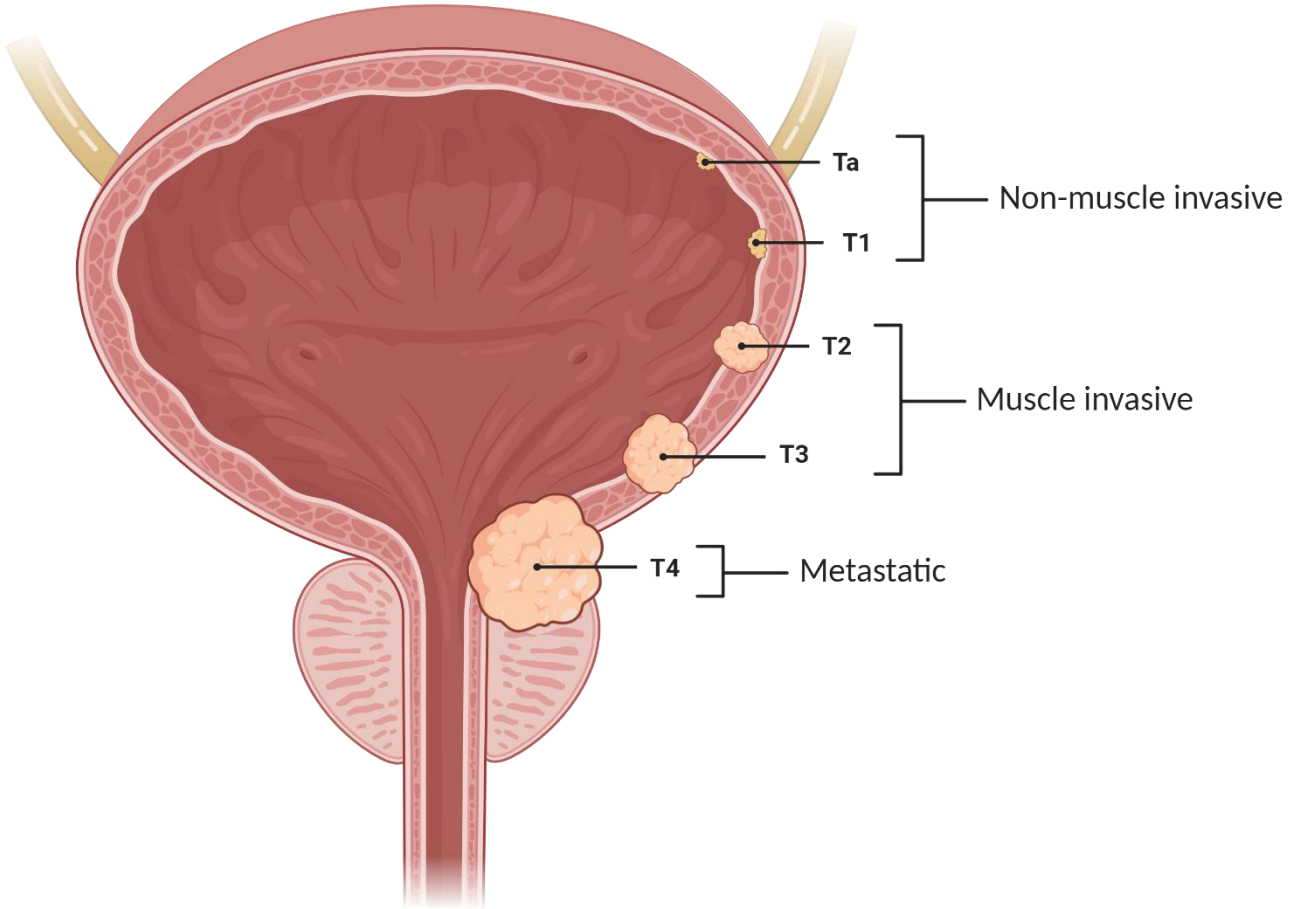
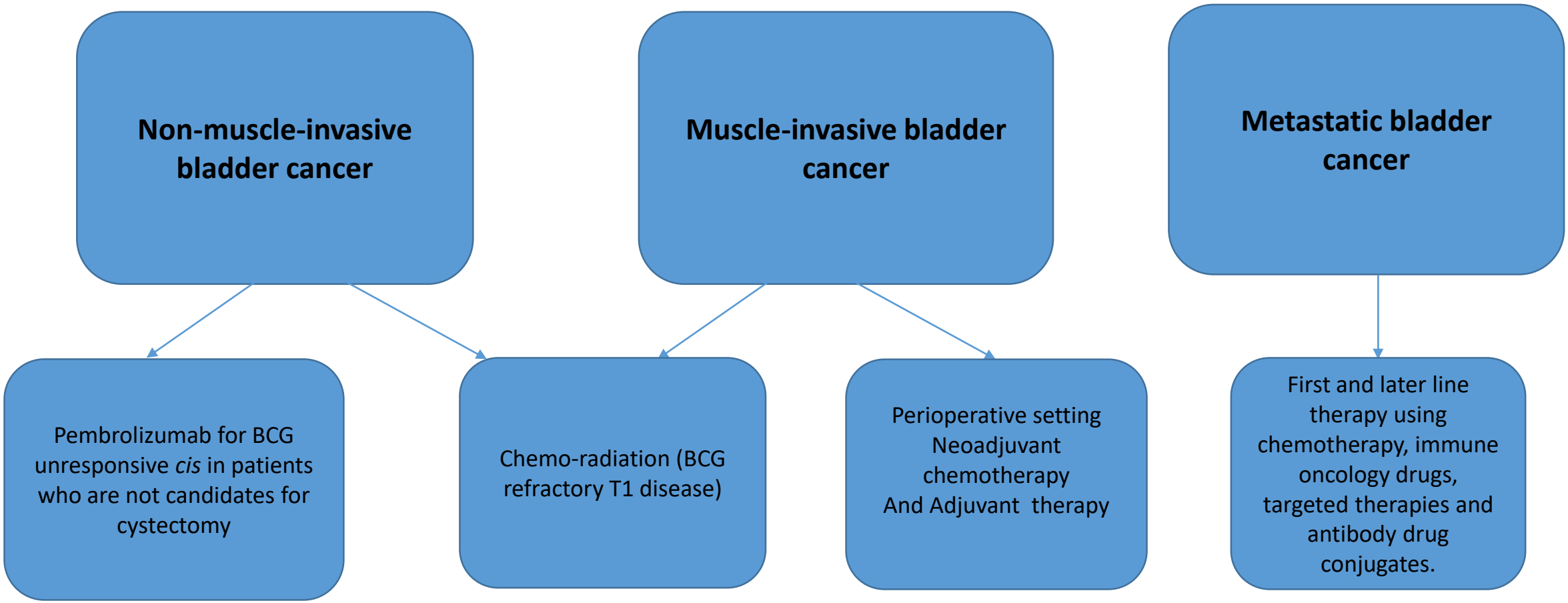


Urothelial carcinoma (UC)



Systemic Therapy in the Three Clinical Disease States of Urothelial Carcinoma



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.

In development :novel intra vesical agents for non-muscle invasive bladder cancer

1. Nadofaragene firadenovec, a novel recombinant adenovirus vector encoding the interferon alfa-2b gene, evaluated in a phase III study.

151 eligible patients BCG unresponsive, 55 (53·4%) of 103 patients with carcinoma in situ (with or without a high-grade Ta or T1 tumour) had a complete response within 3 months of the first dose and this response was maintained in 25 (45·5%) of 55 patients at 12 months. Micturition urgency was the most common grade 3-4 study drug-related adverse event (two [1%] of 157 patients, both grade 3), and there were no treatment-related deaths (1).

2. CG0070 CG0070 is a replication-competent oncolytic adenovirus that targets bladder tumor cells through their defective retinoblastoma pathway

CG0070 also carries the gene for granulocyte-macrophage colony-stimulating factor (GM-CSF), which is released at the time of virus-induced cell lysis and augments immune response to tumor antigens. In a phase II study, of 45 patients, 24 had pure CIS (BCG-unresponsive) The six-month complete response rate was 58 percent in patients with CIS and 50 percent in patients with CIS with or without Ta/T1 disease (2).

3. Oportuzumab monatox (VB4-845), a recombinant fusion protein that targets tumor cells expressing the epithelial cell adhesion molecule (EpCAM), The anti-EpCAM Ab is conjugated to a truncated *Pseudomonas* exotoxin A payload. Three studies with a total of more than 250 patients evaluated this therapy. It has efficacy in patients with BCG-unresponsive disease, with complete response rates of up to approximately 40 %at 3 months and 17% at 12 months.

1. Boorjian et al., Lancet Oncol. 2021
2. Packiam et al., Urol Oncol 2018
3. Kowalski et al., Drug Des Devel Ther. 2010, J Urol. 2012

MIBC In development: Neoadjuvant and Adjuvant setting

Multiple ongoing trials using immune checkpoint inhibitors perioperatively.

Checkmate 274 results: Press release by BMS 9/24/2020
Phase 3 study 709 patients with MIBC at high risk of recurrence after surgery(± NAC)
randomized 1:1 to receive either nivoluamb or placebo for up to 1 year.
Met its dual primary endpoints of improved DFS in all patients and those with PD-L1 expression ≥1.

Imvigor 010 used atezolizumab reported negative result.

Approved checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Indication	Dose
Atezolizumab	Advanced/metastatic UC	1200 mg Q3W
Avelumab	Advanced/metastatic UC	10 mg/kg Q2W
Durvalumab	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

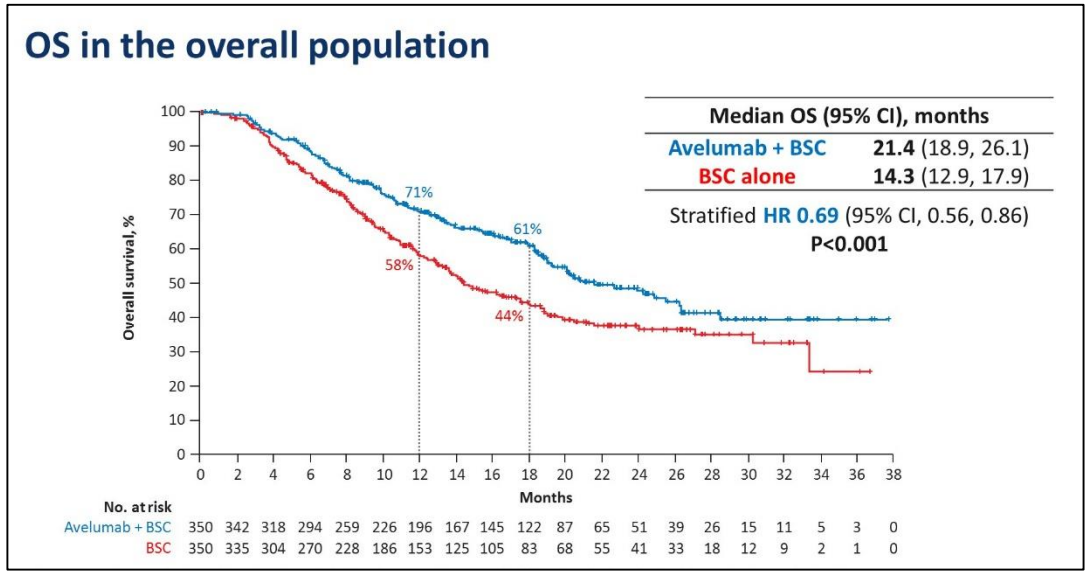
June 2018

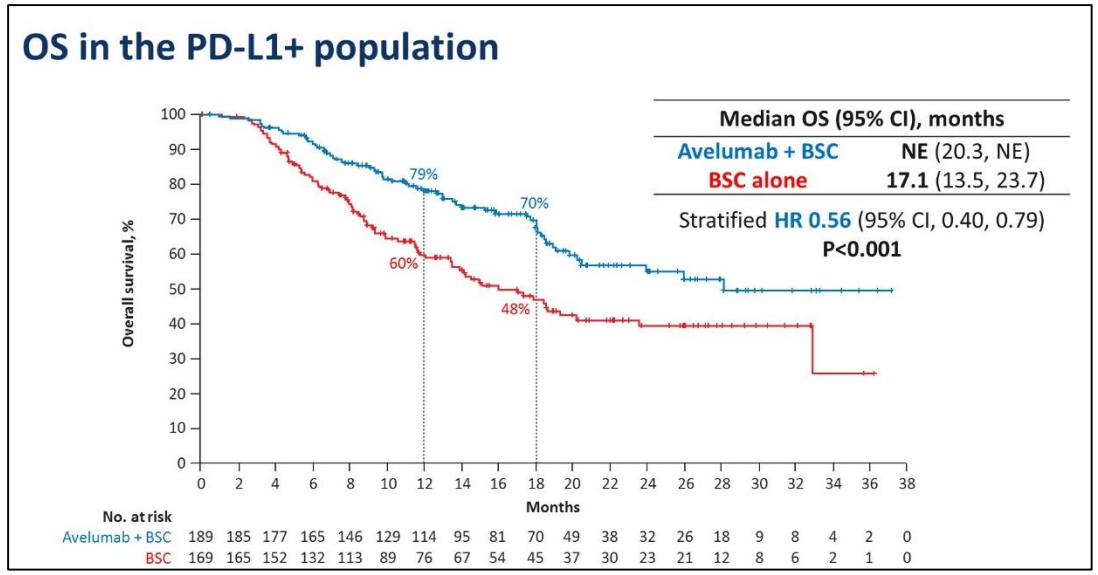
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- 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



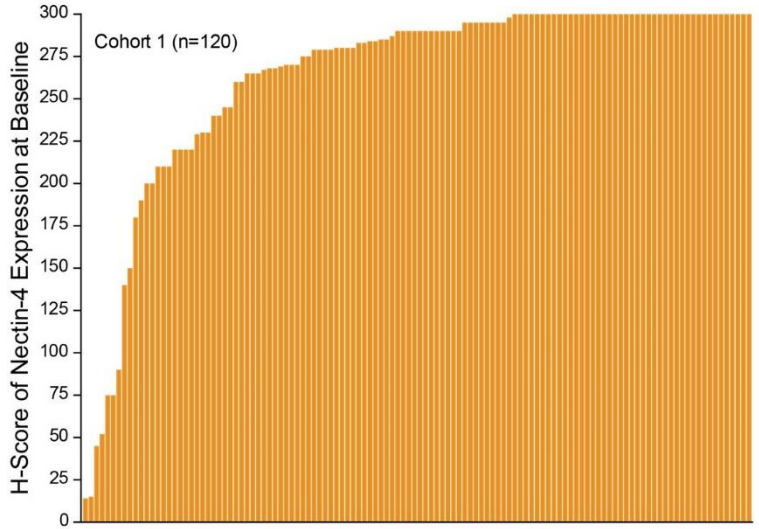


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

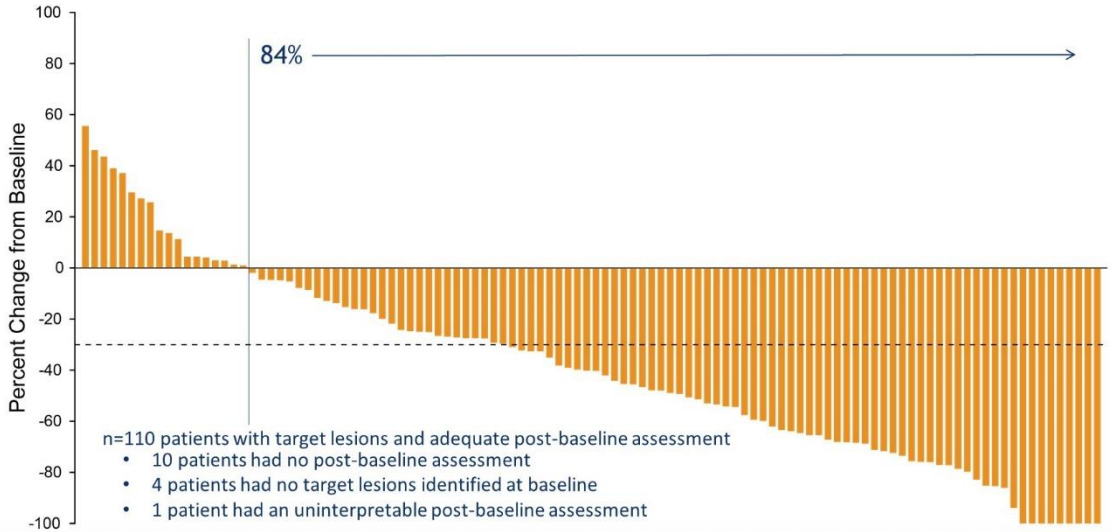
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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.

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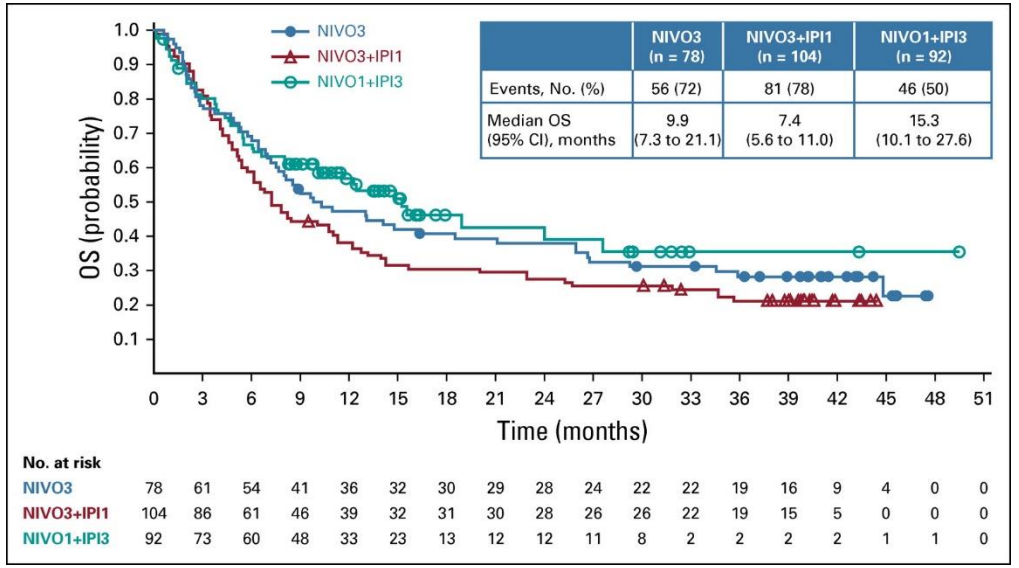
In development: Ipilimumab + Nivolumab CheckMate 032

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%

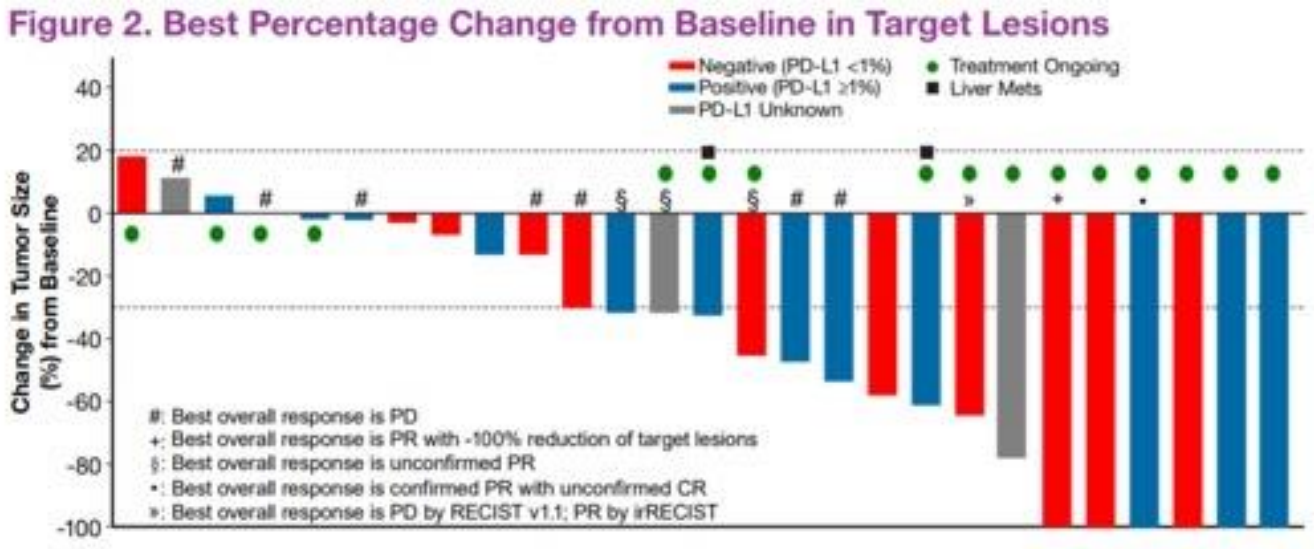


Sharma, J Clin Oncol 2019.

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.

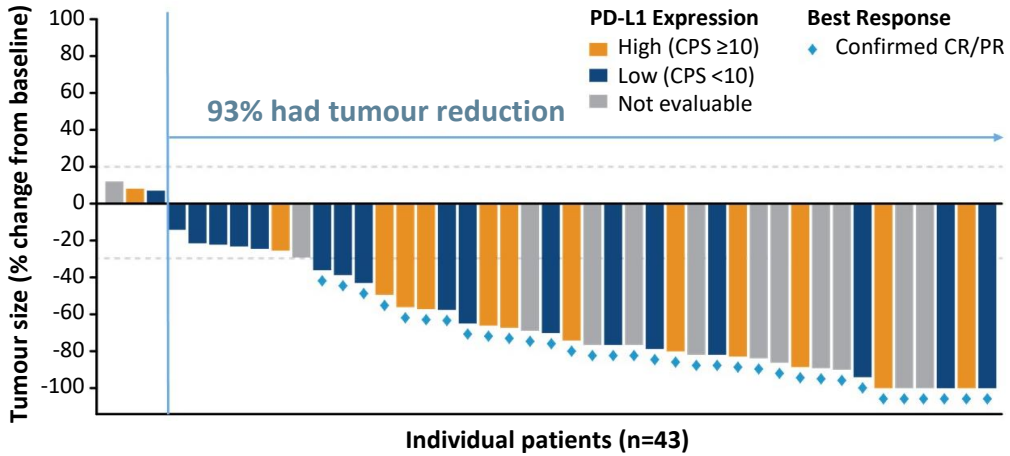


Siefker-Radtke, ASCO-GU 2020.

In development EV plus pembrolizumab based on EV 103 study results

Enfortumab vedotin 1.25 on days 1 and 8 and pembrolizumab (200 mg) on day 1 of every 3-week cycle in 1L cisplatin ineligible la/mUC patients (N=45)

MAXIMAL TARGET LESION REDUCTION BY PD-L1 STATUS



- Responses observed regardless of PD-L1 expression level

ORR PER INVESTIGATOR

Confirmed ORR 95% CI	**73.3% (33/45)** (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)
Best Overall Response Per RECIST v 1.1 by investigator (N=45)	

Rosenberg JE, et al. ASCO GU 2020. Abstract #441 (Oral presentation)

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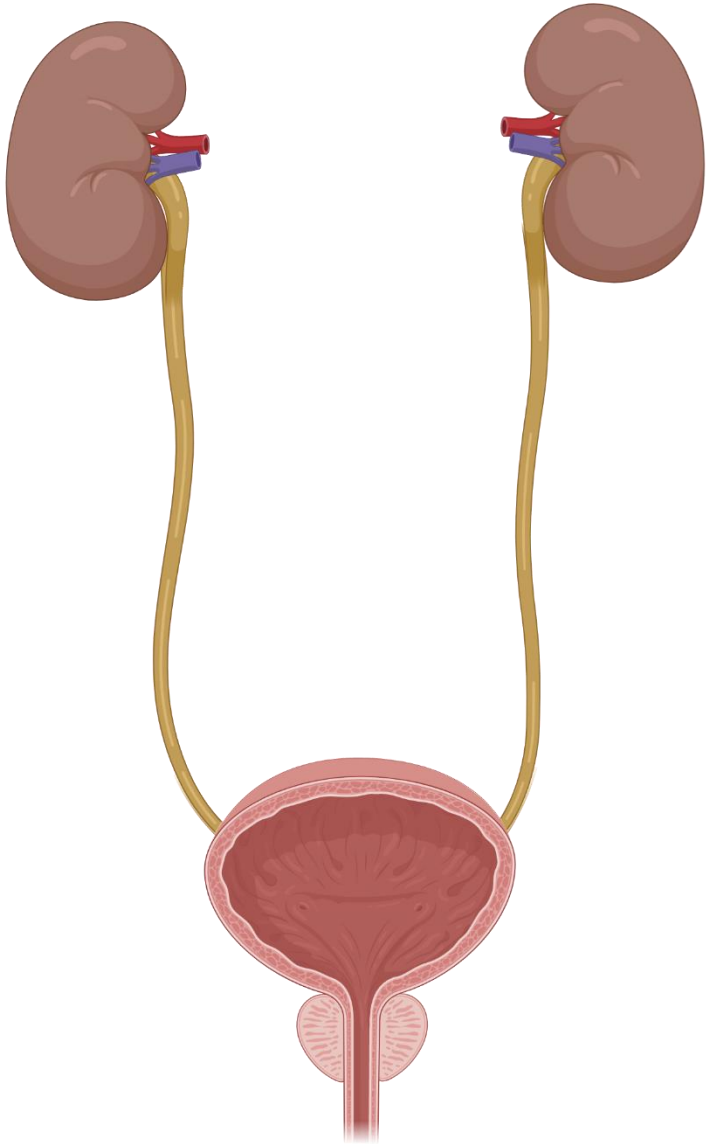
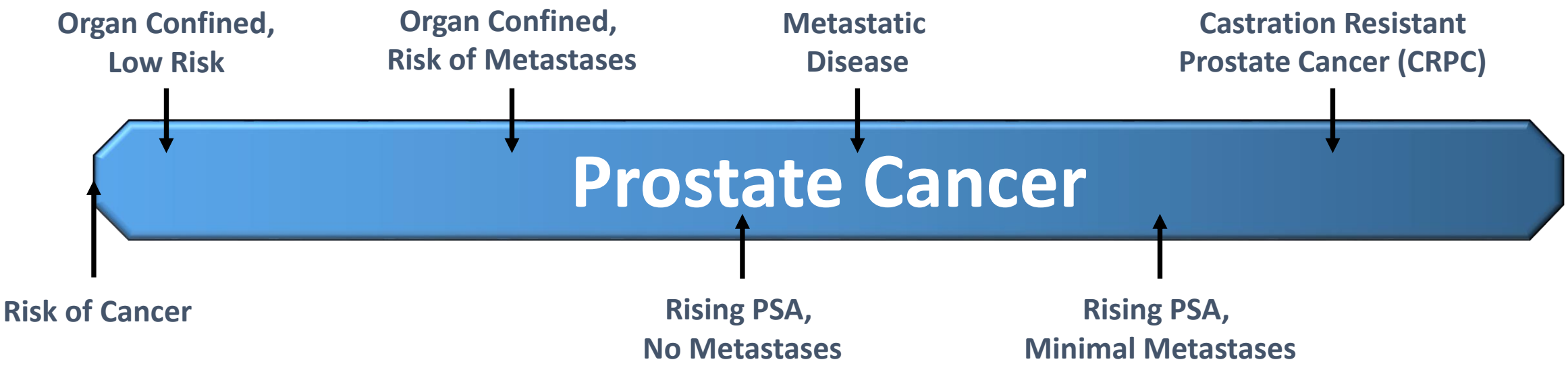
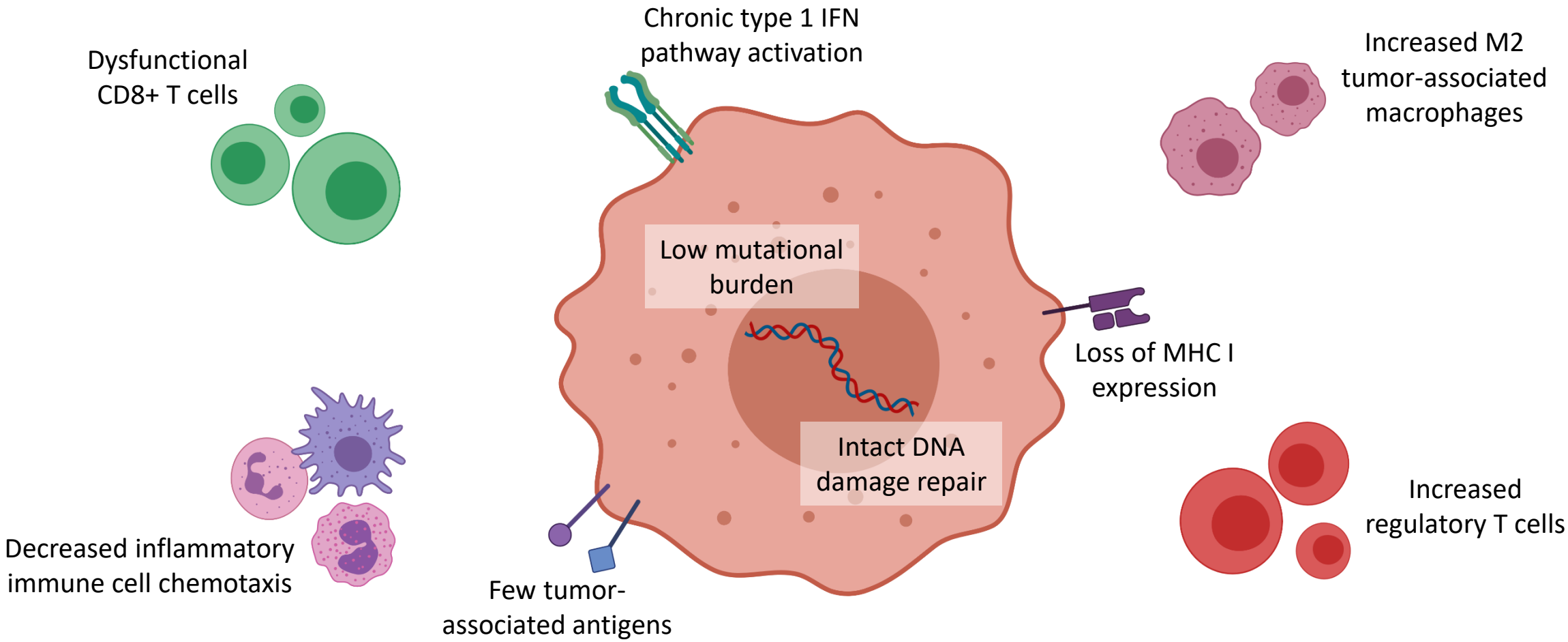


The Spectrum of Prostate Cancer



Immunology of prostate cancer



Vitkin, Front Immunol 2019.

Immunotherapy landscape in prostate cancer

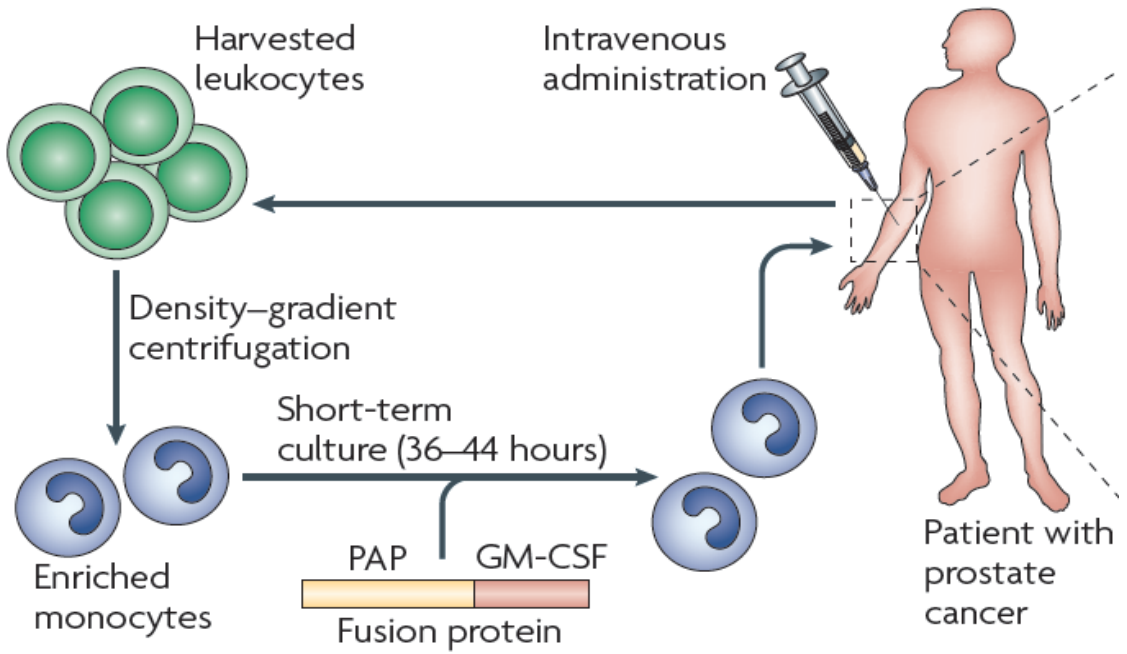
Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	RECIST-measurable PD-L1+ mCRPC	ORR: 5%
		RECIST-measurable PD-L1- mCRPC	ORR: 3%
		RECIST nonmeasurable mCRPC	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	PSA response rate: 21.8% 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		

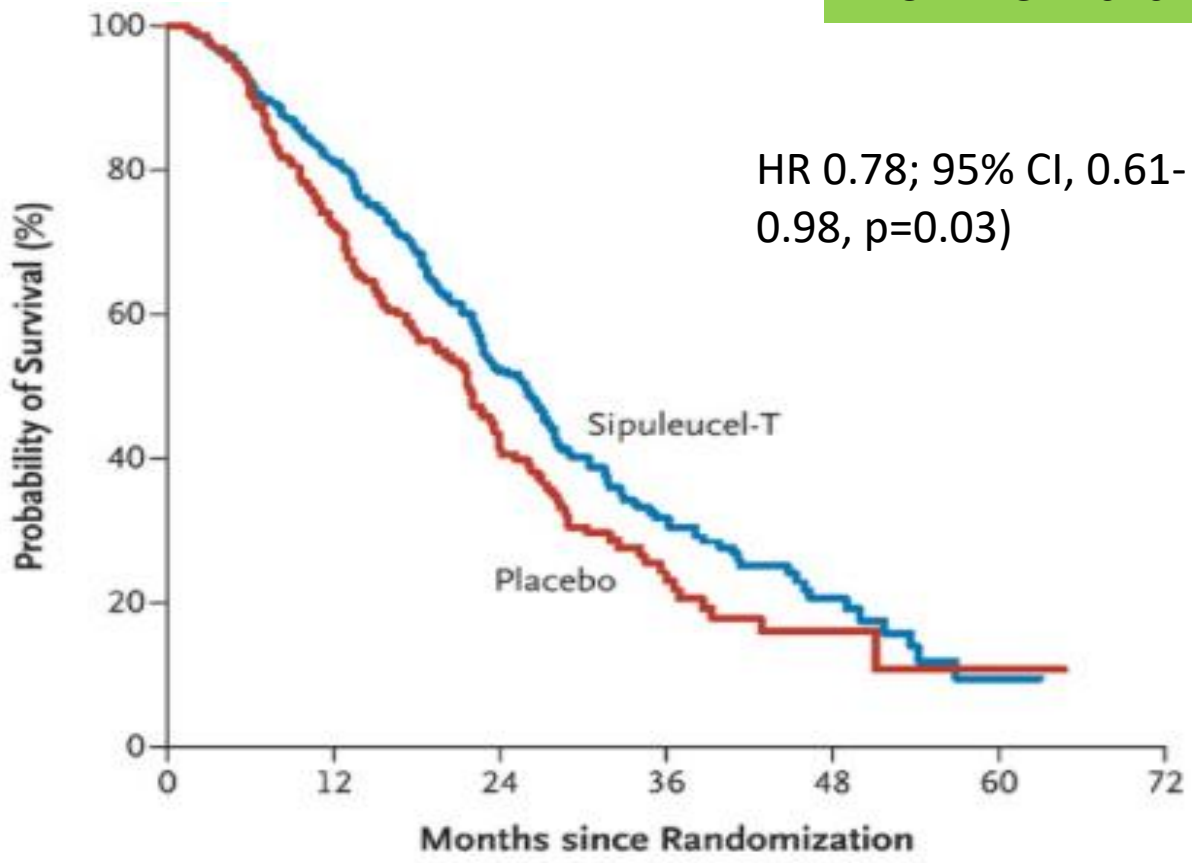
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

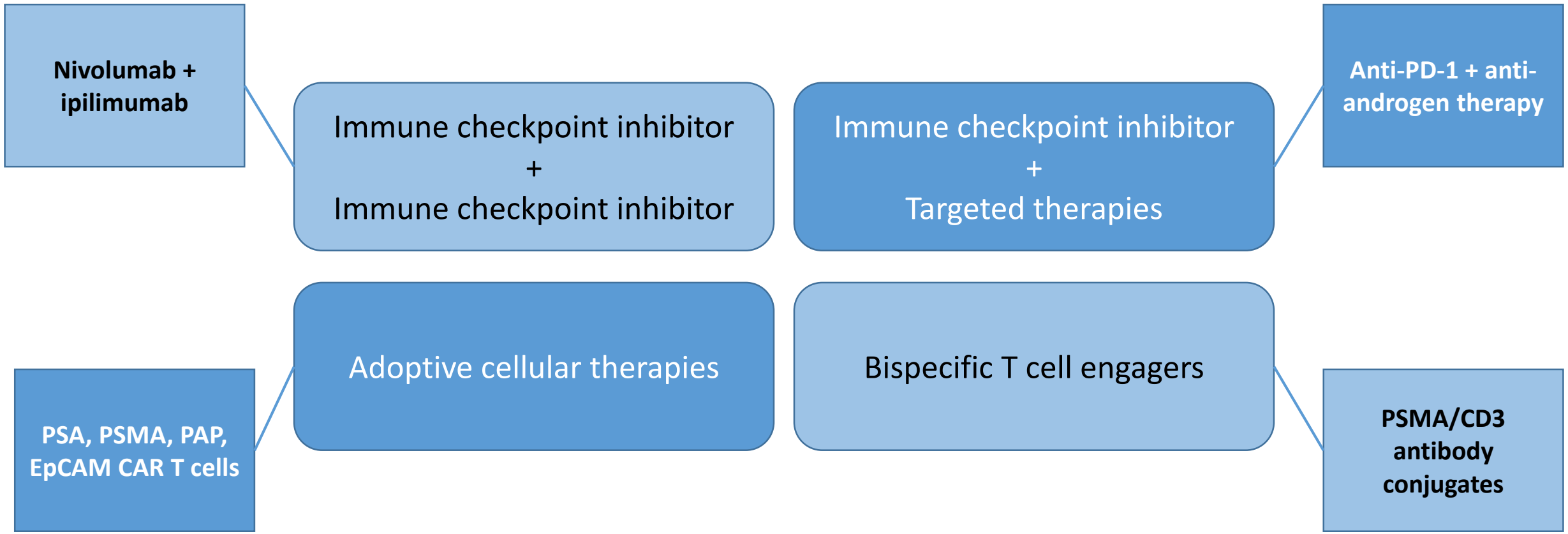




HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

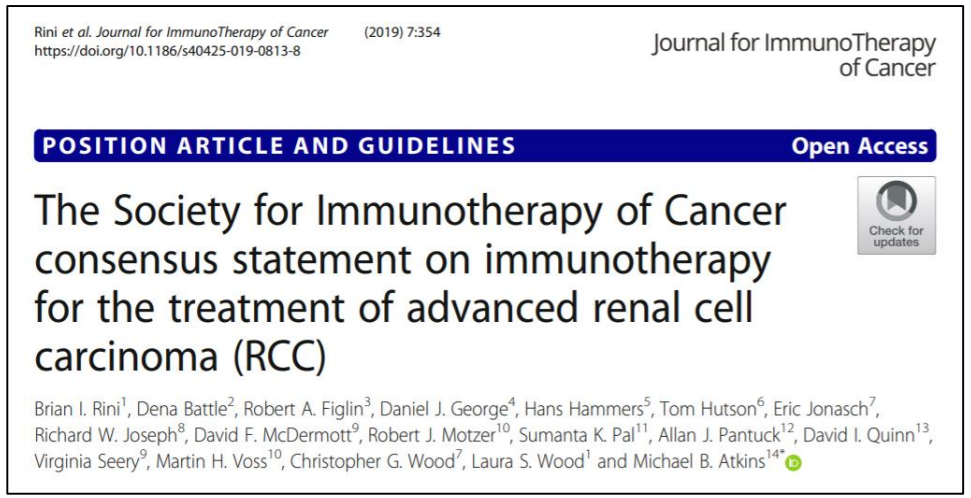
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

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*]

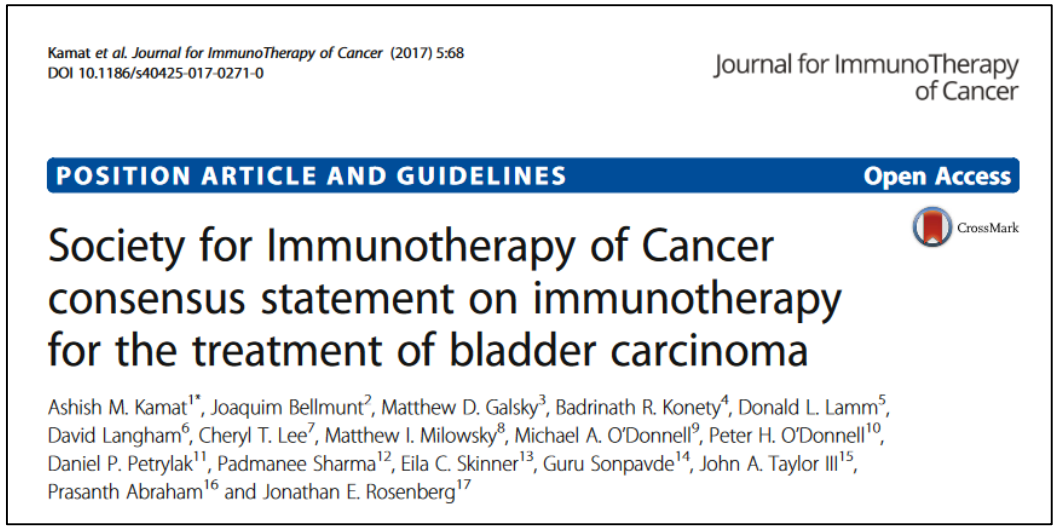
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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]

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- Dr. Umang Swami
- Dr. Manish Kohli
- GU Disease Center at Huntsman Cancer Institute

Case Studies

Case Study 1

1. A 64 year old male presents to your office for treatment of metastatic urothelial carcinoma. He presented with stroke and was treated ith TPA with improvement. A work up revealed lung nodules and subsequent scans revealed bladder tumors and metastatic disease in the liver. CT guided lung biopsy and TURBT confirm metastatic urothelial carcinoma. His ECOG performance status is 1 and he has a creatinine clearance of 100 ml/min. No heart failure or neuropathy or hearing loss. Question 1 What treatment will you offer this patient?
   A. Gemcitabine Cisplatin
   B. Pembrolizumab
   C. Atezolizumab
   D. Gemcitabine carboplatin

In a cisplatin eligible patient, cisplatin based combination chemotherapy is the preferred current standard of care. First line immunotherapy is FDA approved but is appropriate only if a patient is not eligible for chemotherapy and is more effective if there is PD-L1 expression in the tissue

1. He has partial response to 6 cycles of chemotherapy. His liver lesions completely disappear and his lung nodules get smaller What will you offer him next?
   A. Avelumab
   B. Pembrolizumab
   C. Best Supportive Care
   D. Enfortmumab vedotin

In a patient with stable disease or response to first line platinum based chemotherapy maintenance avelumab prolongs progression free survival and overall survival compared to best supportive care.

3. He has stable disease after 3 months of avelumab. After 6 months he has disease progression in the lungs and liver. What will you offer him for treatment?
   A. Pembrolizumab
   B. Best Supportive Care
   C. Enfortmumab vedotin
   D. Pemetrexed

In patients with metastatic urothelial carcinoma, enfortumab vedotin has a response rate of 44% post platinum and post PD-L1 therapy*

Case Study 2

A 56 year old male with no significant past medical history presents with hematuria and is found to have right renal mass with renal vein tumor throbus extemding to IVC, undergoes right radical nephrectomy with IVC thrombectomy. Path shows clear cell RCC with sarcomatoid features WHO/ISUP G4, pT3a,N0M0 disease. Scans in 6 months show multiple new lung metastases and patient is symptomatic with shortness of breath. His KPS is 80%, Hb, calcium, neutrophil and platelet count are normal. What is his IMDC risk category?

a. I

b. II

c. III

How will you treat him?

1. Cabozantinib plus nivolumab
2. Sunitinib
3. Axitinib plus pembrolizumab
4. Nivolumab plus Ipilimumab

You proceed with first line of treatment and the patient has a response. He develops immune mediated toxicity and stops immune therapy. His disease progresses, how will you treat him?

1. Cabozantinib
2. Sunitinib
3. Nivolumab
4. Lenvatinib plus everolimus