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

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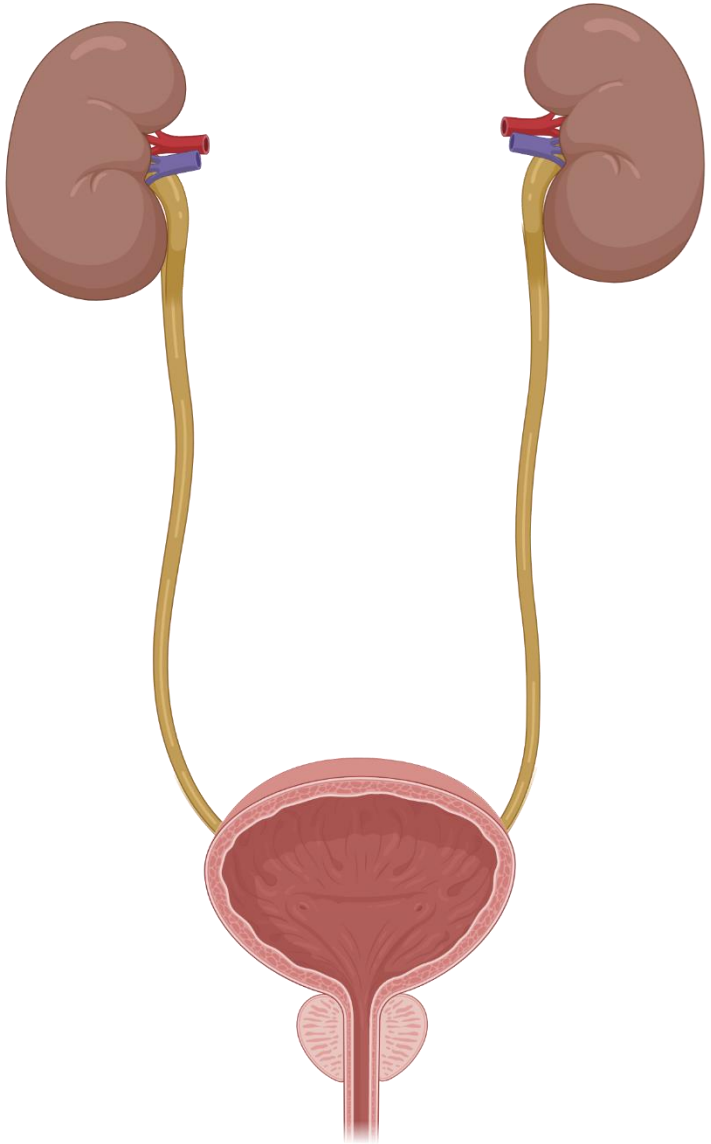
Disclosures

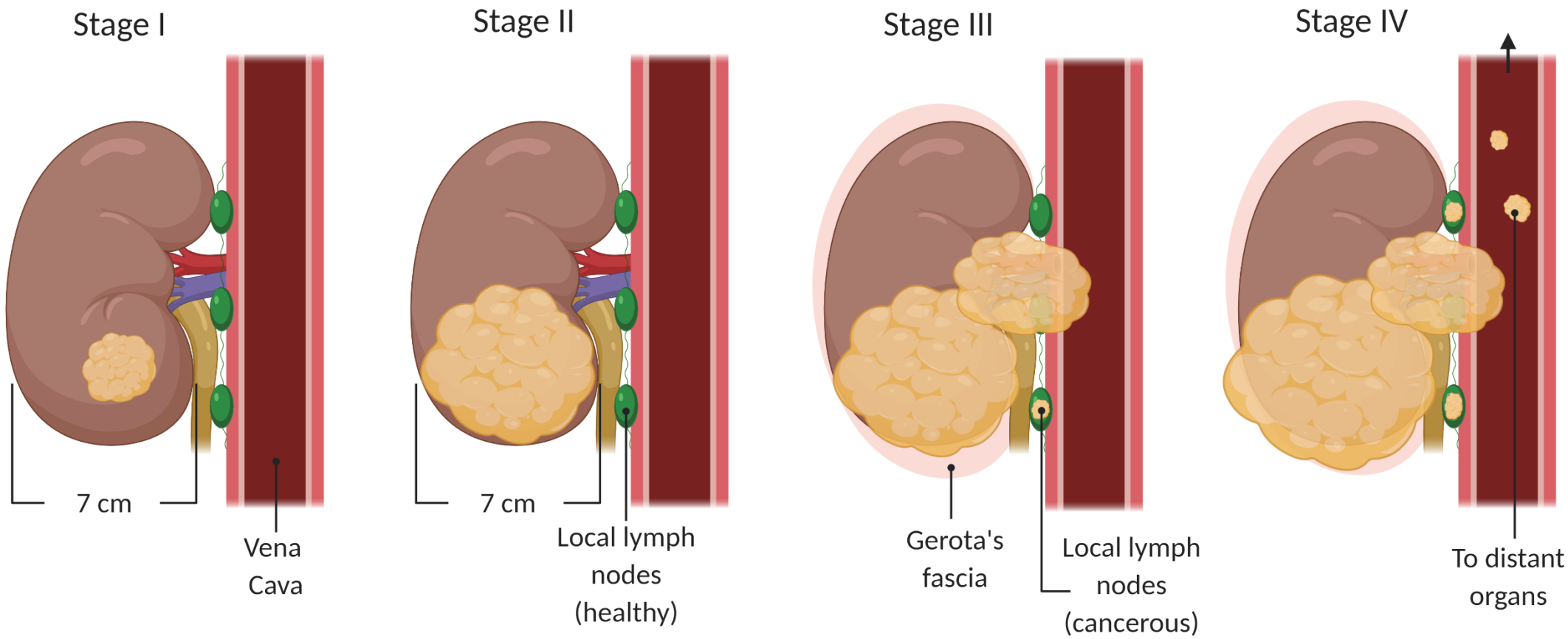
- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

Outline

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



Renal cell carcinoma (RCC)



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Risk Stratification

MSKCC Prognostic Factors	IMDC Prognostic Factors
Interval from diagnosis to treatment of less than 1 year	Interval from diagnosis to treatment of less than 1 year
KPS < 80%	KPS < 80%
LDH > 1.5 x ULN	Elevated Calcium
Elevated Corrected Calcium	Decreased Hemoglobin
Decreased Hemoglobin	Elevated Neutrophils
	Elevated Platelets

Prognostic Risk Group	Number of Prognostic Factors
Low Risk (MSKCC) Favorable Risk (IMDC)	0
Intermediate Risk	1 – 2
Poor Risk	3 or more

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
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

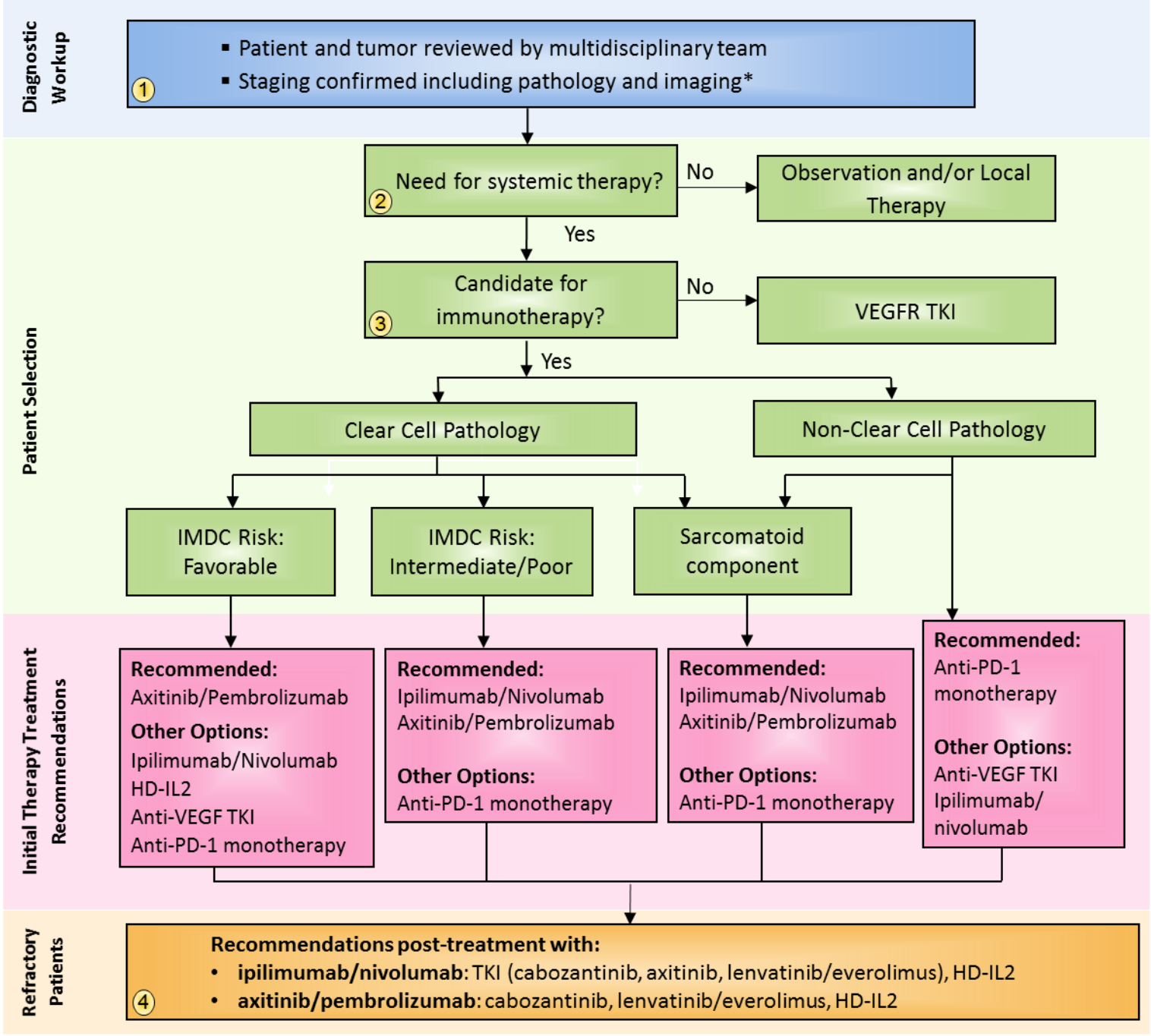
Tannir, ASCO-GU 2020; Pilmack, ASCO 2020; Choueiri, Ann Oncol 2020; Rini, Lancet 2019.

Front-line immunotherapy treatments for RCC

Study	Treatment arm(s)	Patient selection criteria	N	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-426	Pembrolizumab + axitinib*	Untreated, advanced clear cell RCC	432	60%	15.4	NE (HR 0.68, p=0.0003)
	Sunitinib		429	40%	11.1	35.7
CheckMate 9ER	Nivolumab + cabozantinib*	Untreated, advanced clear cell RCC	323	55.7%	16.6	NE (HR 0.60, p=0.001)
	Sunitinib		328	27.1%	8.3	NE
CLEAR	Pembrolizumab + lenvatinib	Untreated, advanced clear cell RCC	355	71%	23.9	NE (HR 0.66 vs sunitinib, p=0.005)
	Everolimus + lenvatinib		357	53.5%	14.7	NE (HR 1.15 vs sunitinib, p=0.30)
	Sunitinib		357	36.1%	9.2	NE

*FDA-approved IO regimen

SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma



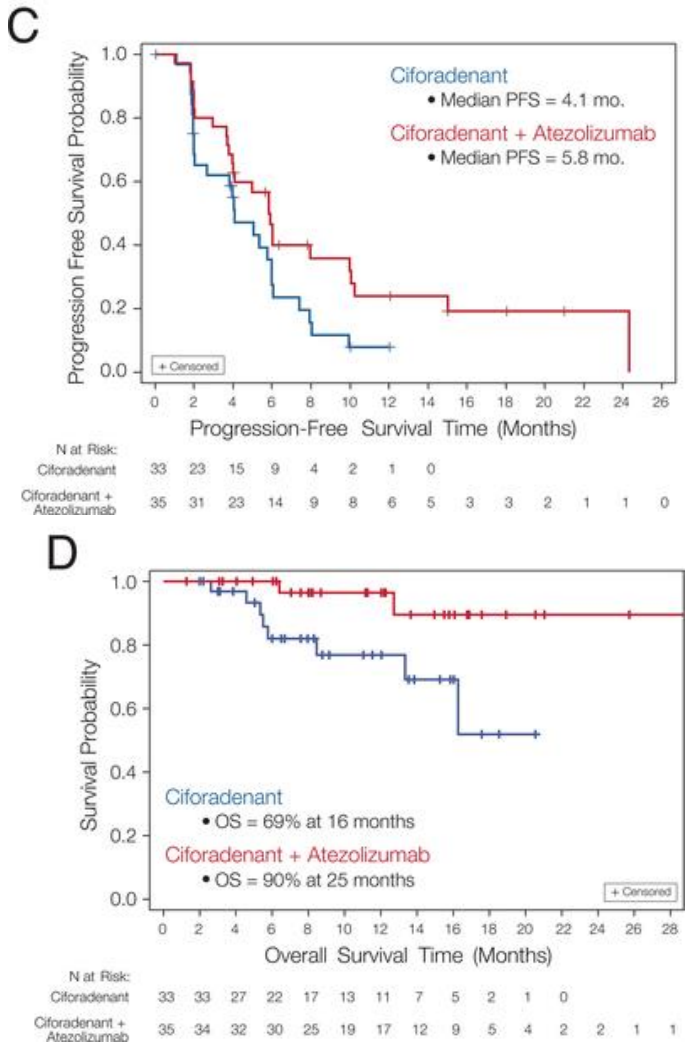
*Baseline imaging recommendations discussed in figure legend.

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.

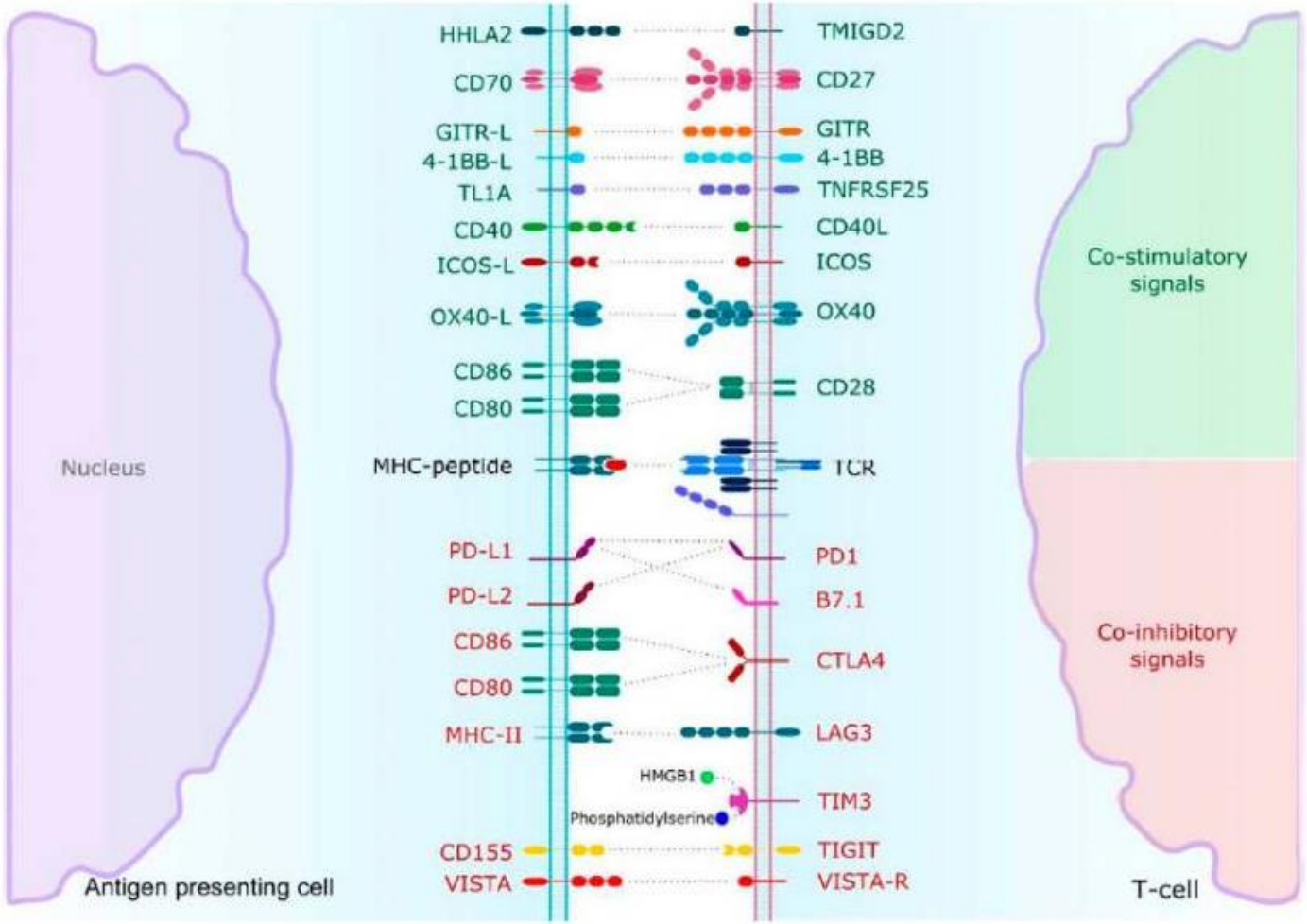
In development: A2AR antagonist + anti-PD-L1

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

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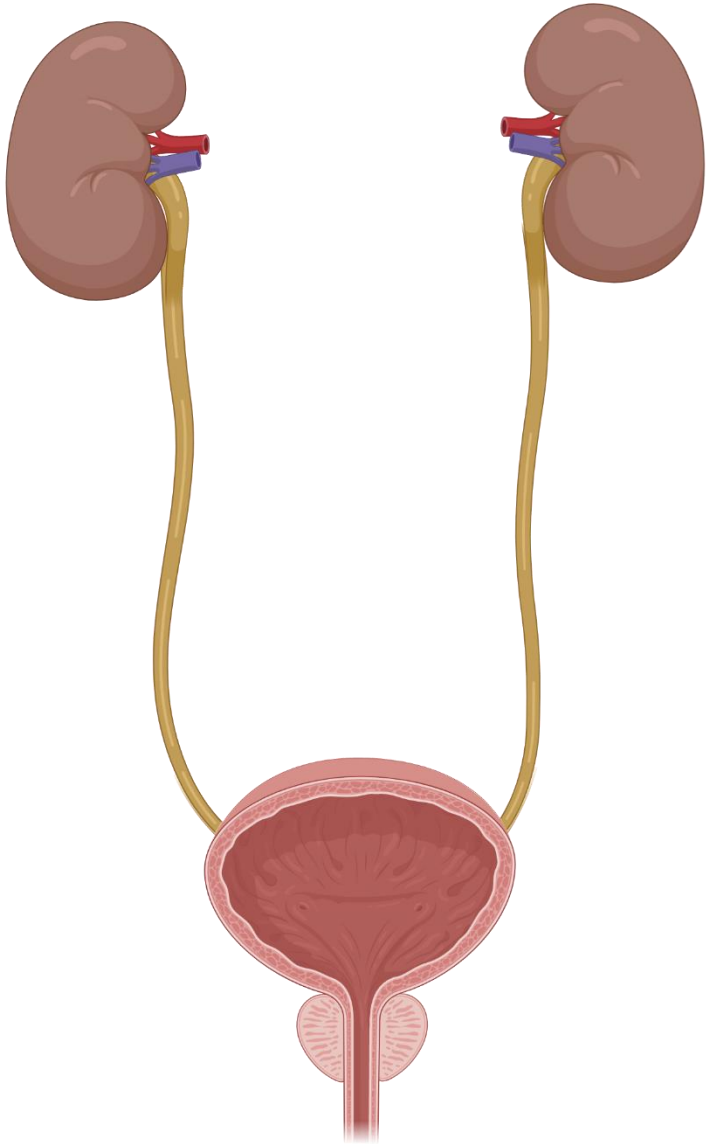
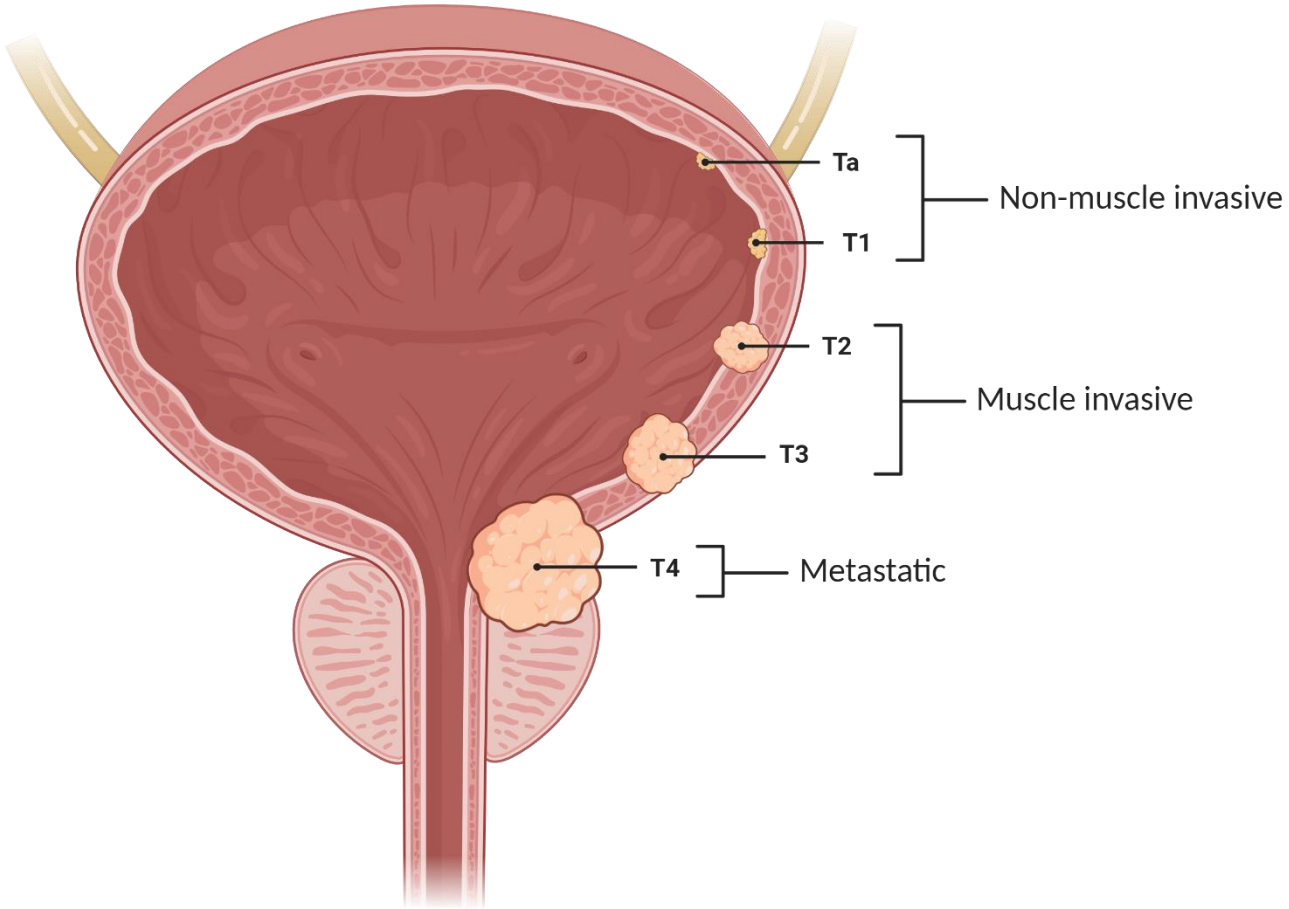


Urothelial carcinoma (UC)



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 – *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

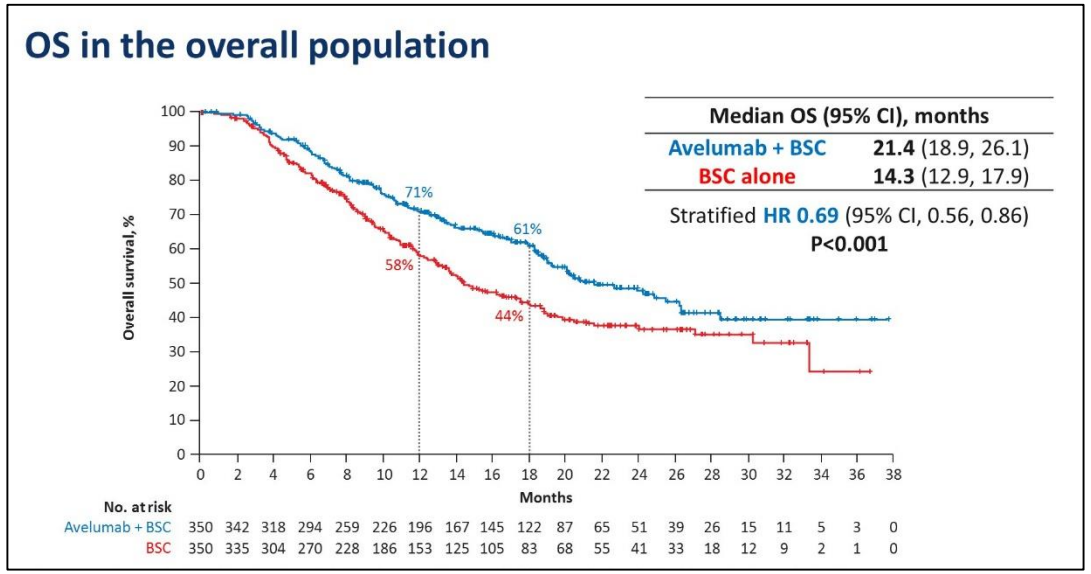
June 2018

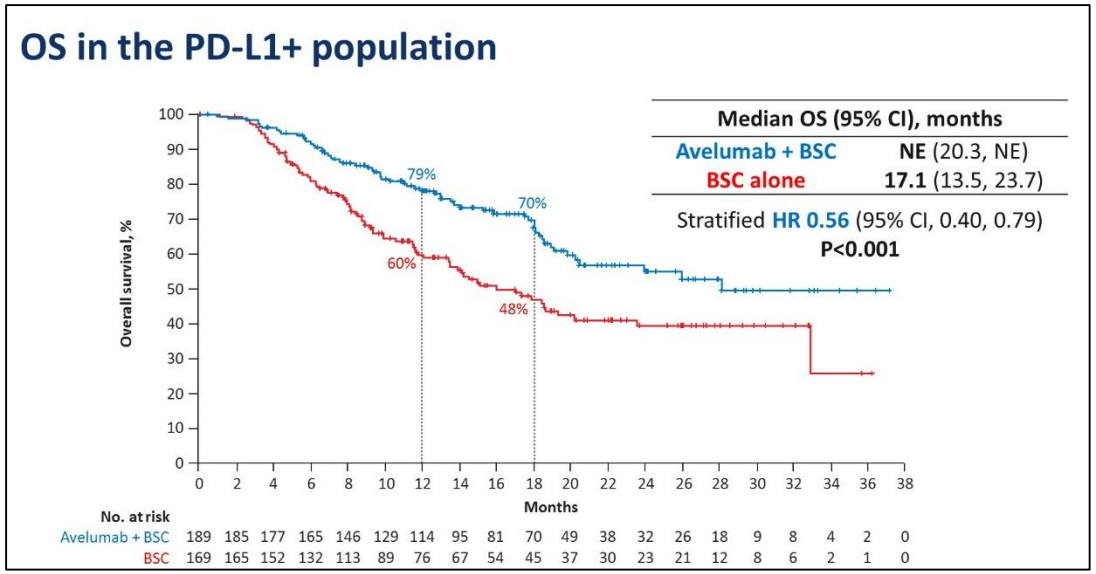
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- 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



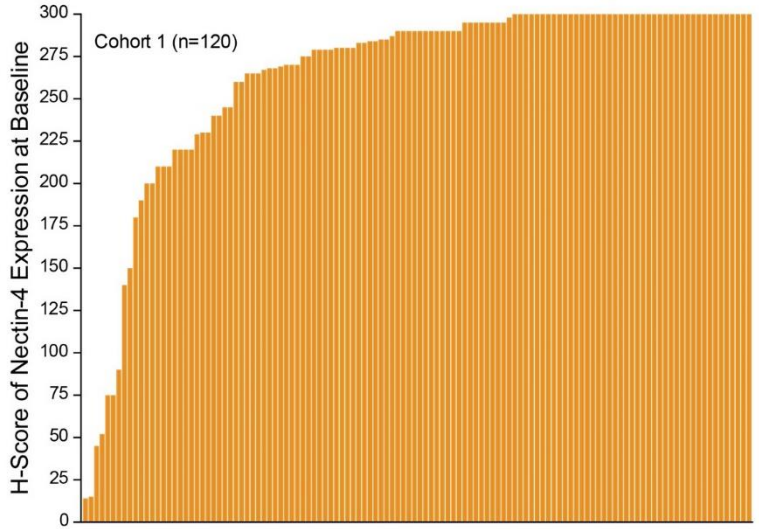


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

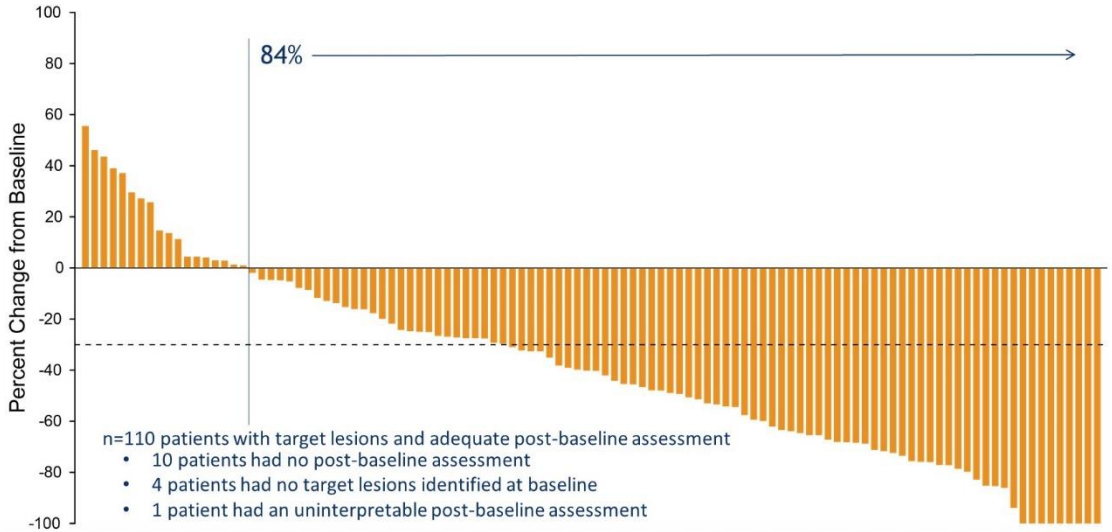
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metastatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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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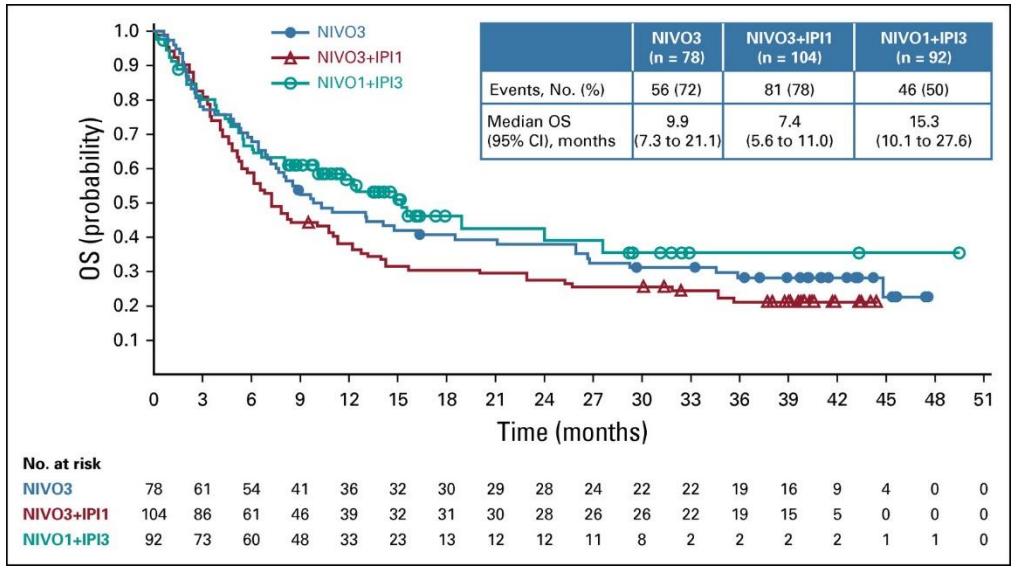
In development: Ipilimumab + Nivolumab CheckMate 032

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

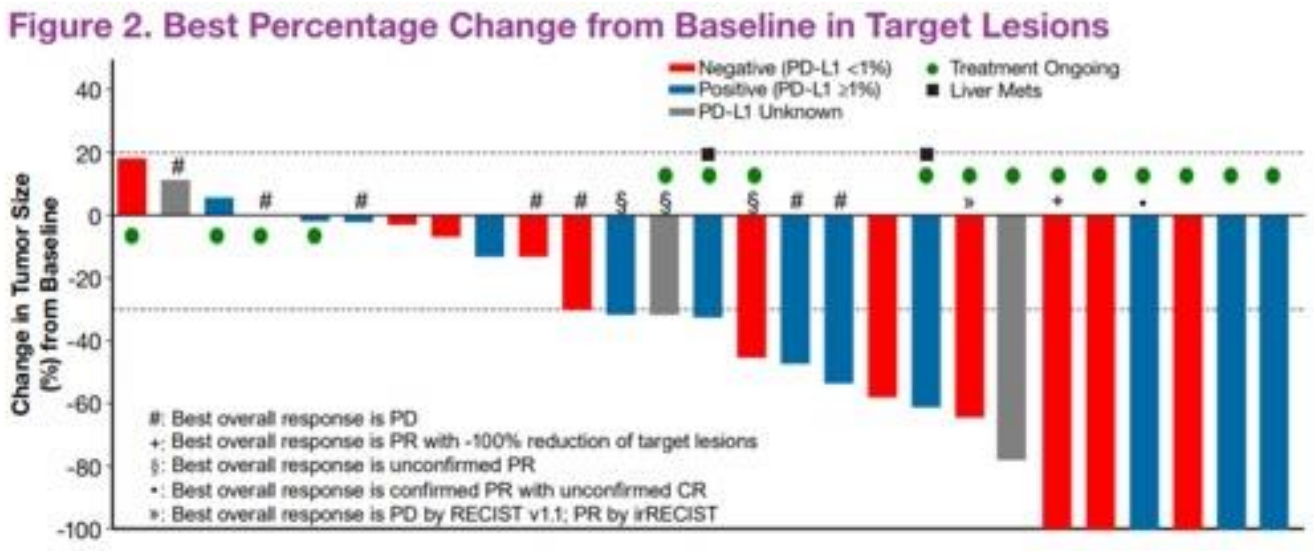


Sharma, J Clin Oncol 2019.

In development: NKTR-214 + nivolumab

Treatment	n	ORR
NKTR-214 + nivolumab	27	48%

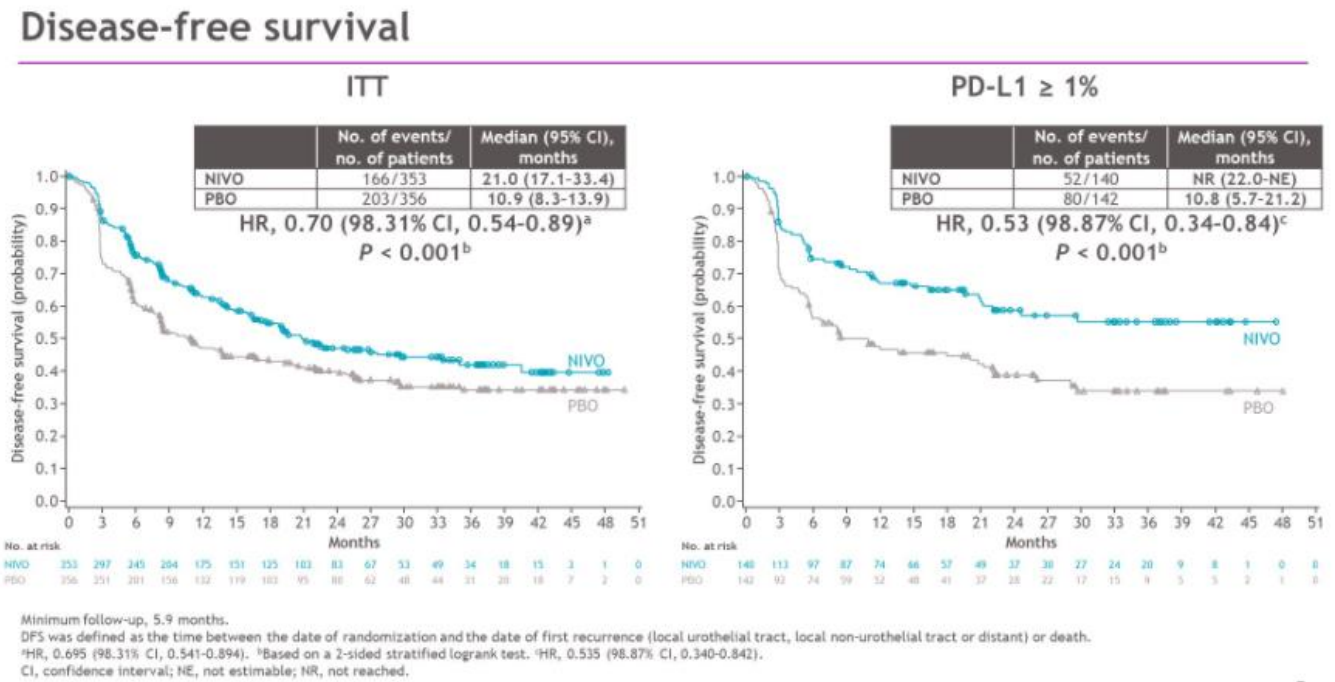
After treatment, 70% of patients with PD-L1-negative tumors converted to PD-L1-positive.



Siefker-Radtke, ASCO-GU 2020.

In development: Adjuvant nivolumab Checkmate 274

Treatment arm	n	Median DFS	Median NUTRFS	Median Distant Mets Free Survival
Nivolumab 240 mg Q3W	353 140	ITT: 21.0 (17.1 – 33.4) PD-L1+: NR (22.0 – NE)	ITT: 24.6 (19.2 – 35.0) PD-L1+: NR (26.0 – NE)	ITT: 35.0 (24.5 – NE) PD-L1+: NR (33.9 – NE)
Placebo	356 142	ITT: 10.9 (8.3 – 13.9) PD-L1+: 10.8 (5.7 – 21.2)	ITT: 13.7 (8.4 – 20.7) PD-L1+: 10.9 (5.8 – 22.1)	ITT: 29.0 (14.7 – NE) PD-L1+: 21.2 (10.6 – NE)



Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

Bajorin, ASCO-GU-2021.

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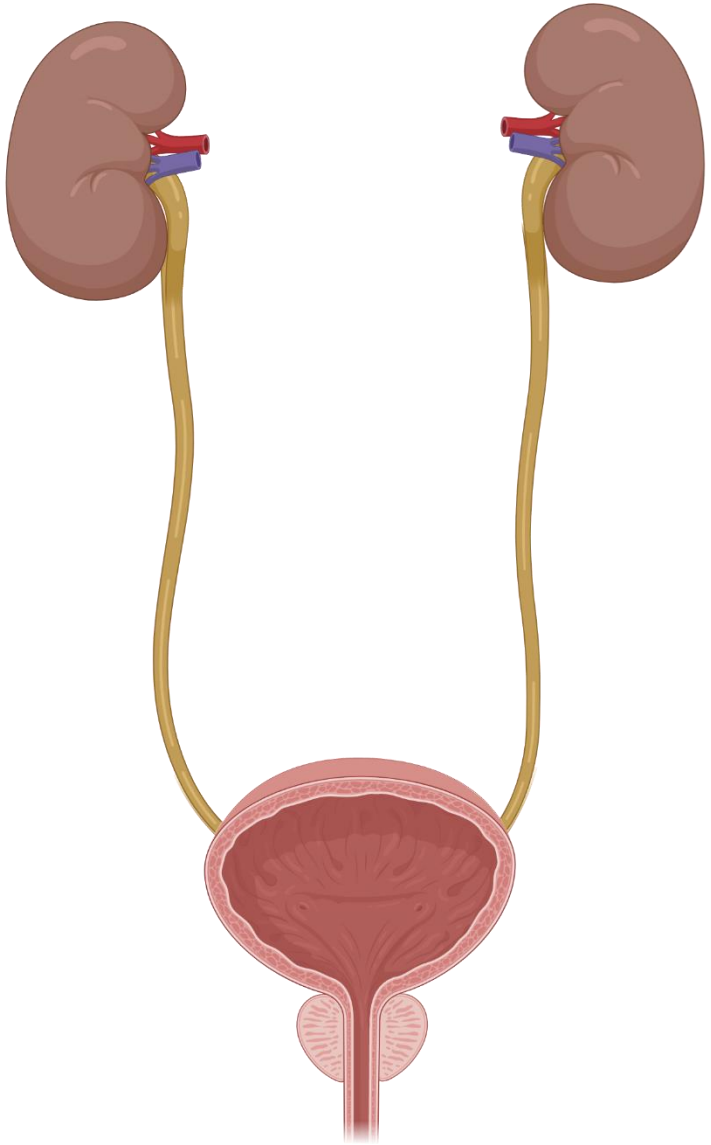
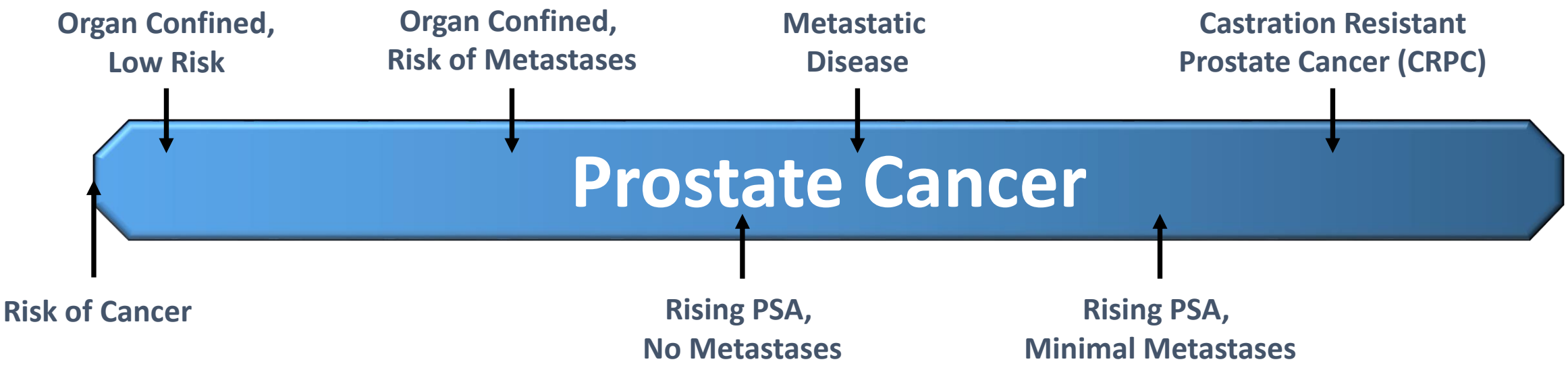
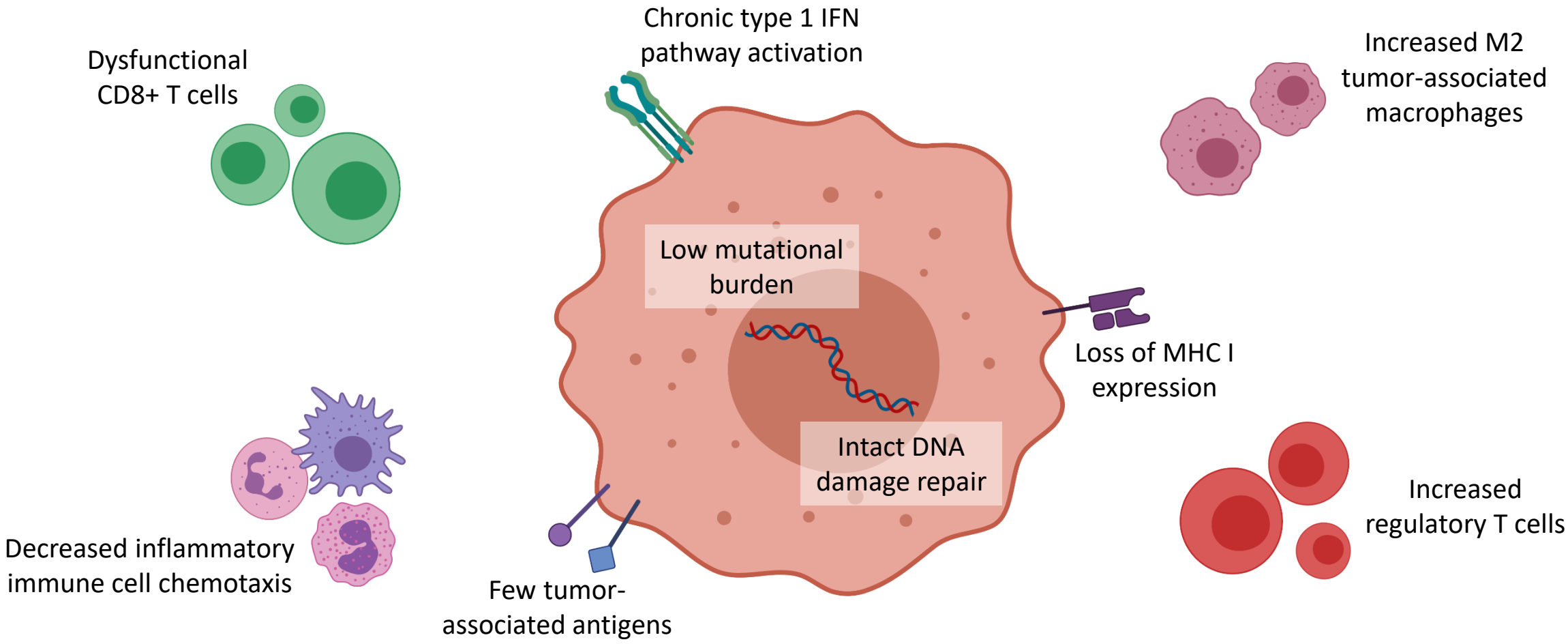


The Spectrum of Prostate Cancer



Immunology of prostate cancer



Vitkin, Front Immunol 2019.

Immunotherapy landscape in prostate cancer

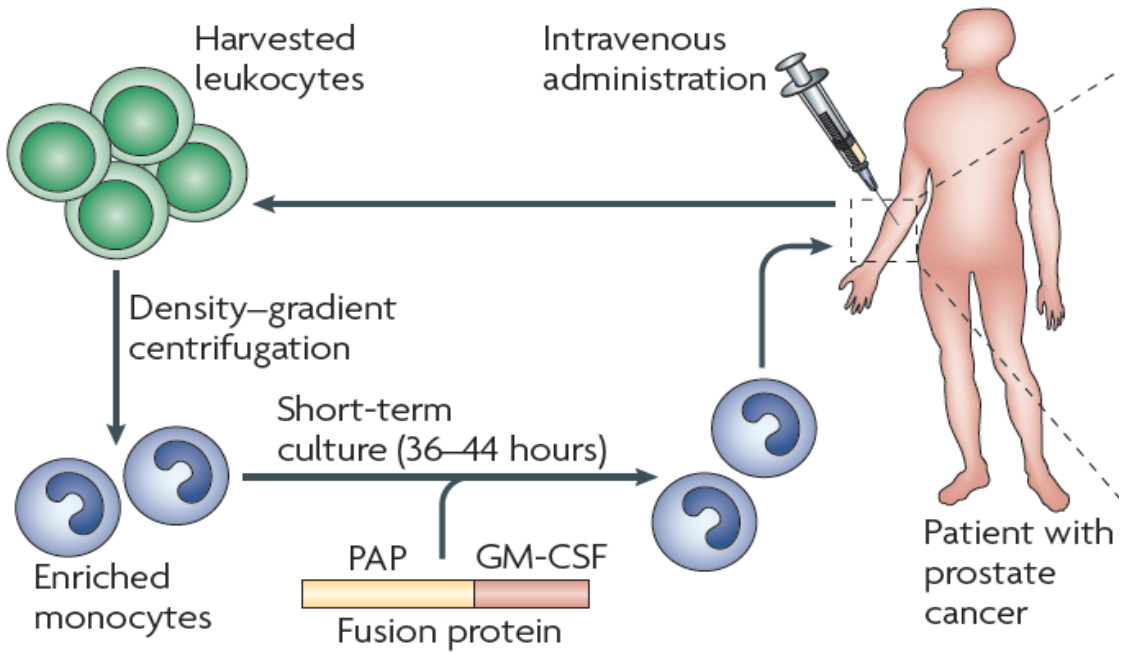
Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	RECIST-measurable PD-L1+ mCRPC	ORR: 5%
		RECIST-measurable PD-L1- mCRPC	ORR: 3%
		RECIST nonmeasurable mCRPC	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	PSA response rate: 21.8%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

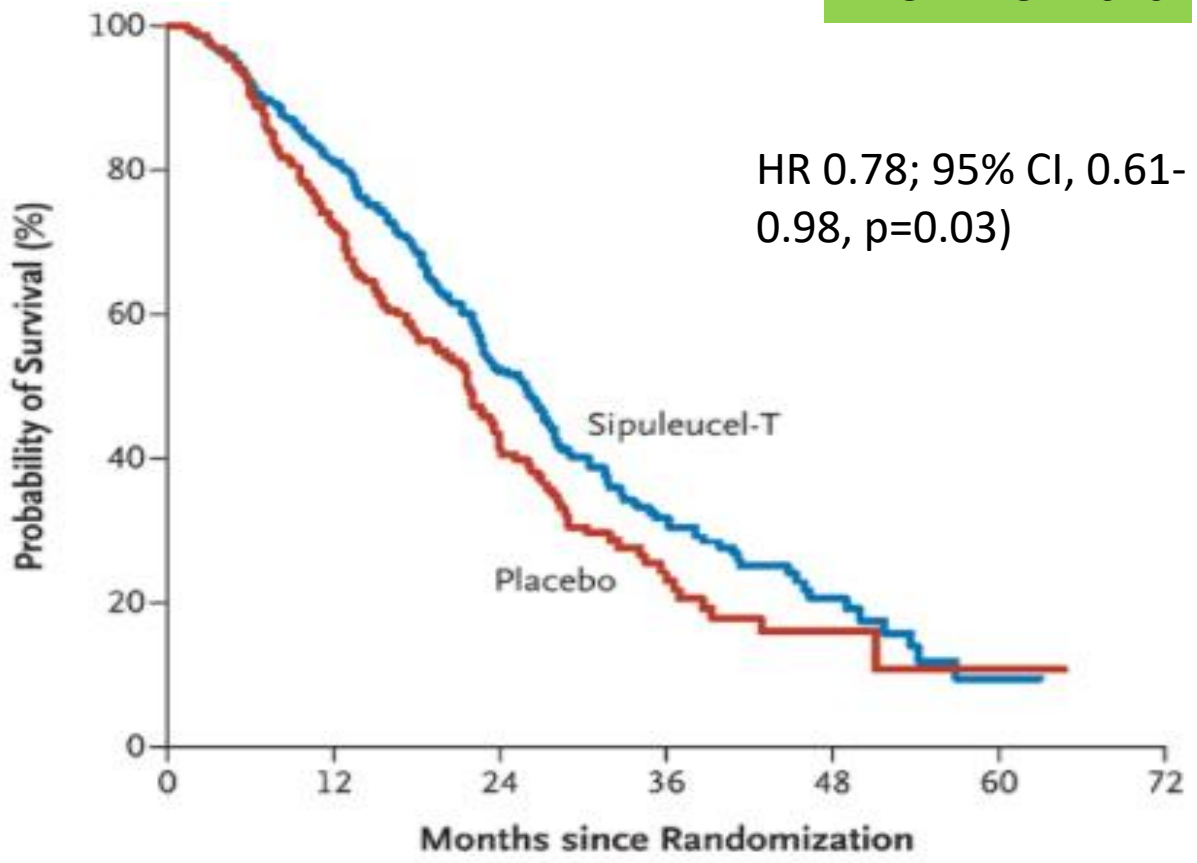
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

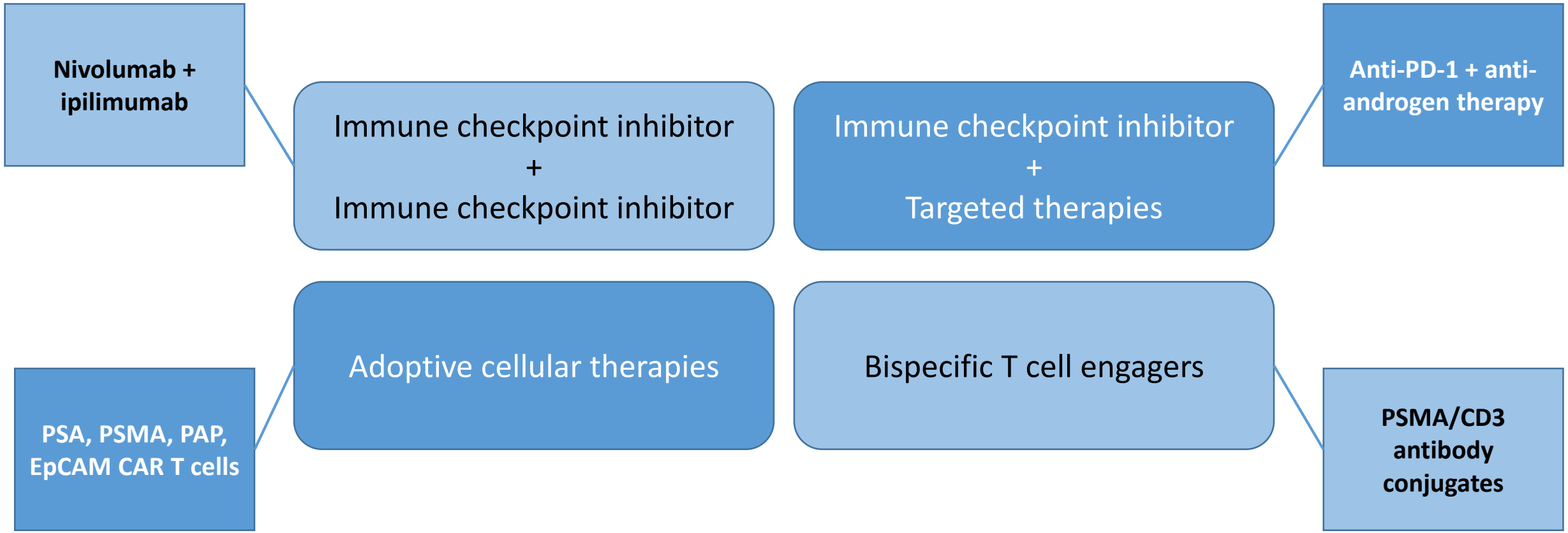




HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

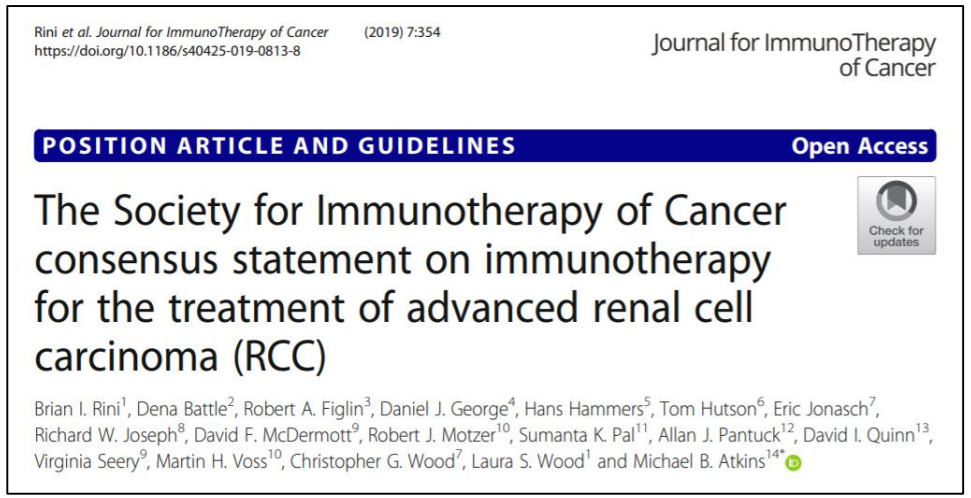
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

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*]

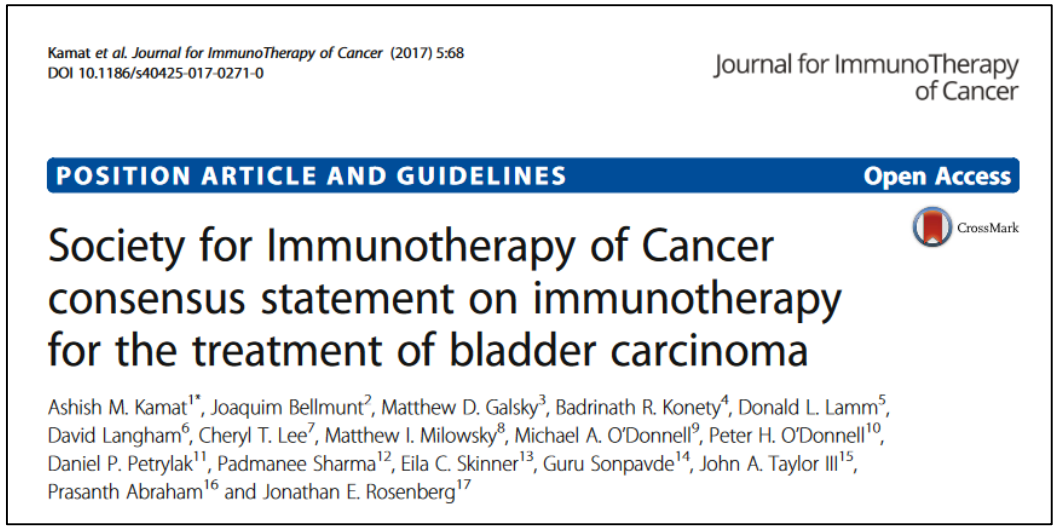
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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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Acknowledgements

- Some figures created using biorender.com

Case Studies

Case Study 1

56 year old man presents with 3 months of left flank pain, cough, progressive dyspnea and intermittent hematuria.

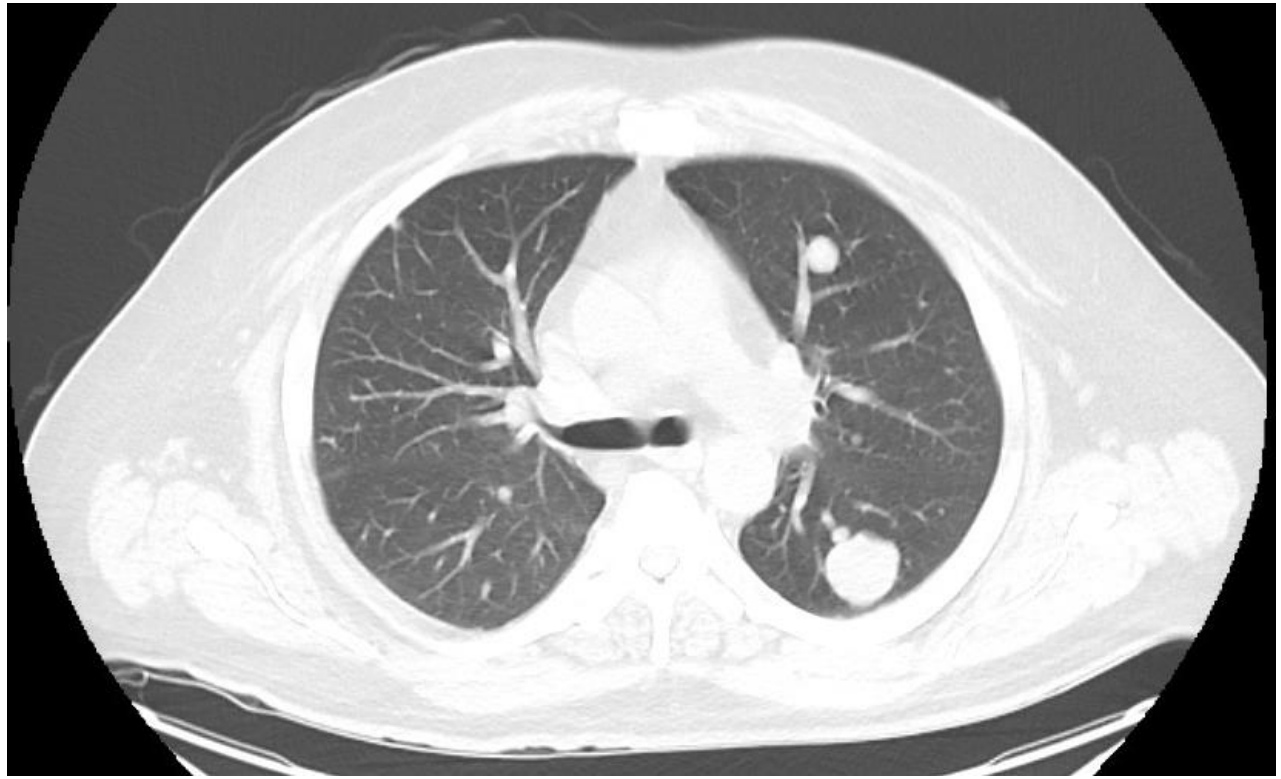
Vital Signs:

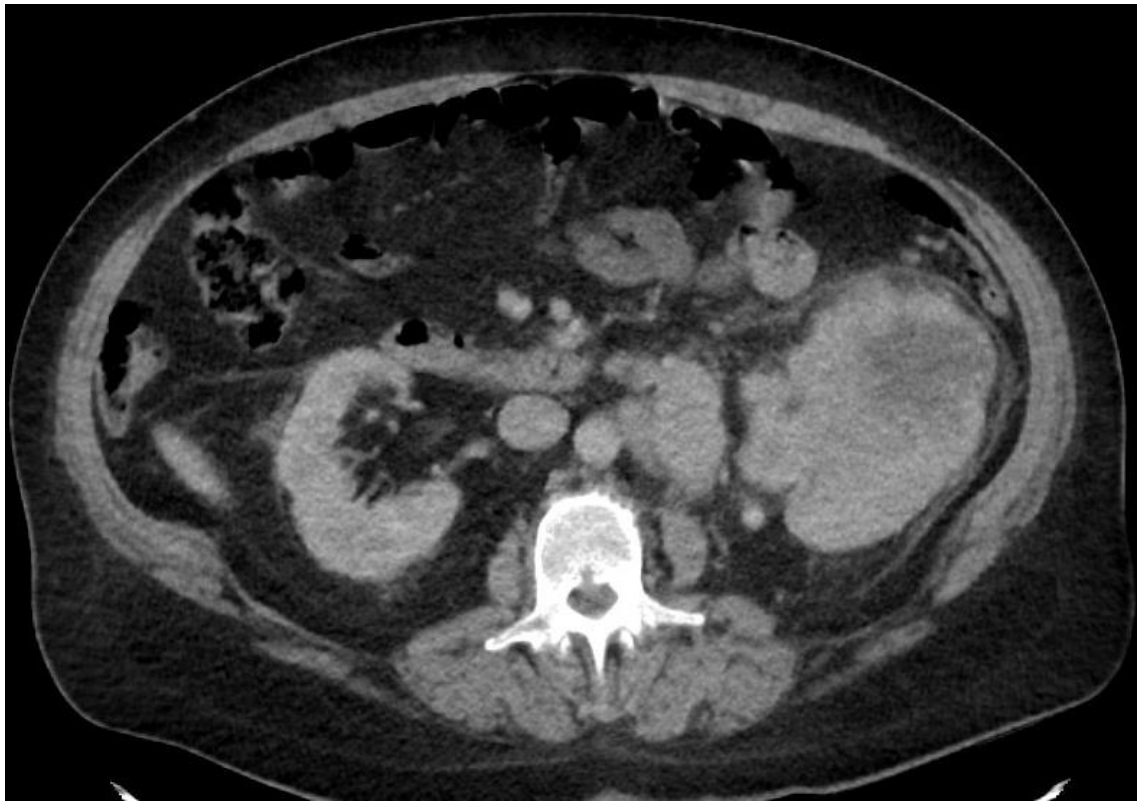
- T 97.2ºF HR 102 RR 16 BP 111/69 O2 Sat 98%

Labs:

- Hemoglobin 7.2
- Corrected Calcium 11.9
- ANC 14.6
- Platelets 959

CT Chest/Abd/Pelvis w/ contrast





Case Study 1

CT Chest/Abdomen/Pelvis

- Right lower lobe pulmonary embolism
- Numerous bilateral pulmonary nodules, largest 2.9 cm in left lower lobe
- 7.1 x 8.3 x 9.7 cm mass of the left kidney
- Adjacent metastatic seeding with lesions measuring 2.1 cm, 1.7 cm, 1.1 cm
- Bulky retroperitoneal lymph nodes, largest 4.5 x 4.0 cm
- No lytic bone metastases

Bone Scan:

- No metastases

Kidney Biopsy:

- Clear cell renal cell carcinoma

Question 1

Which of the following is the most appropriate first line therapy for this patient?

A) High-dose IL-2

B) Ipilimumab/Nivolumab

C) Sunitinib

D) Lenvatinib/Everolimus

Question 1

Which of the following is the most appropriate first line therapy for this patient?

A) High-dose IL-2: Reserved for selected patients with excellent performance status and normal organ function

B) Ipilimumab/Nivolumab: CheckMate 214 trial showed benefit over sunitinib, with 42% response rate, 12 month PFS and 47 month overall survival.

C) Sunitinib: Previous role as 1st line therapy has been replaced among all risk categories by combination IO/TKI or IO/IO.

D) Lenvatinib/Everolimus: FDA approved in 2016 to be used after prior anti-angiogenic therapy (2nd line). Arm in recent CLEAR trial showed improved PFS and response rate, but no overall survival benefit compared to sunitinib.

Case Study 2

77 year old woman presents with persistent cough.

- Diagnosed with recurrent pT1 high-grade urothelial carcinoma s/p multiple TURBTs
- Completed BCG x6 doses
- Recent admission for hemorrhagic shock from gross hematuria, now s/p TURBT with pT2 lesion and palliative radiation
- Ambulates at home, but requires wheelchair assistance from lobby to exam room due to dyspnea

- PMH:
  - Hypertension, Hyperlipidemia, DM2, CAD, HFrEF 30%, Carotid Artery Stenosis, TIA, PAD s/p femoral artery stent, Stage 4 CKD with Cr Cl 25 mL/min

- Social History:
  - 40 pack year cigarette smoking history, quit 5 years ago

Case Study 2

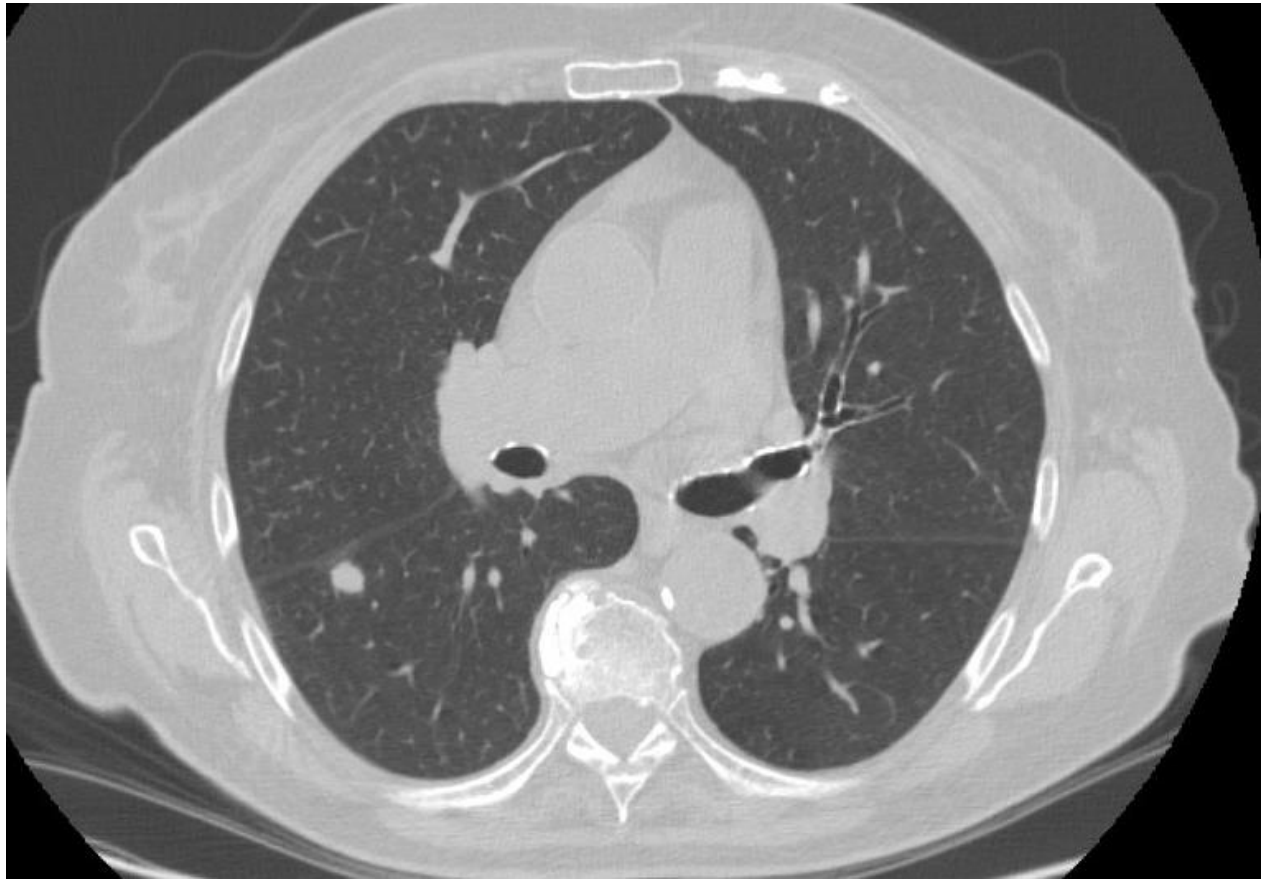
Vitals:

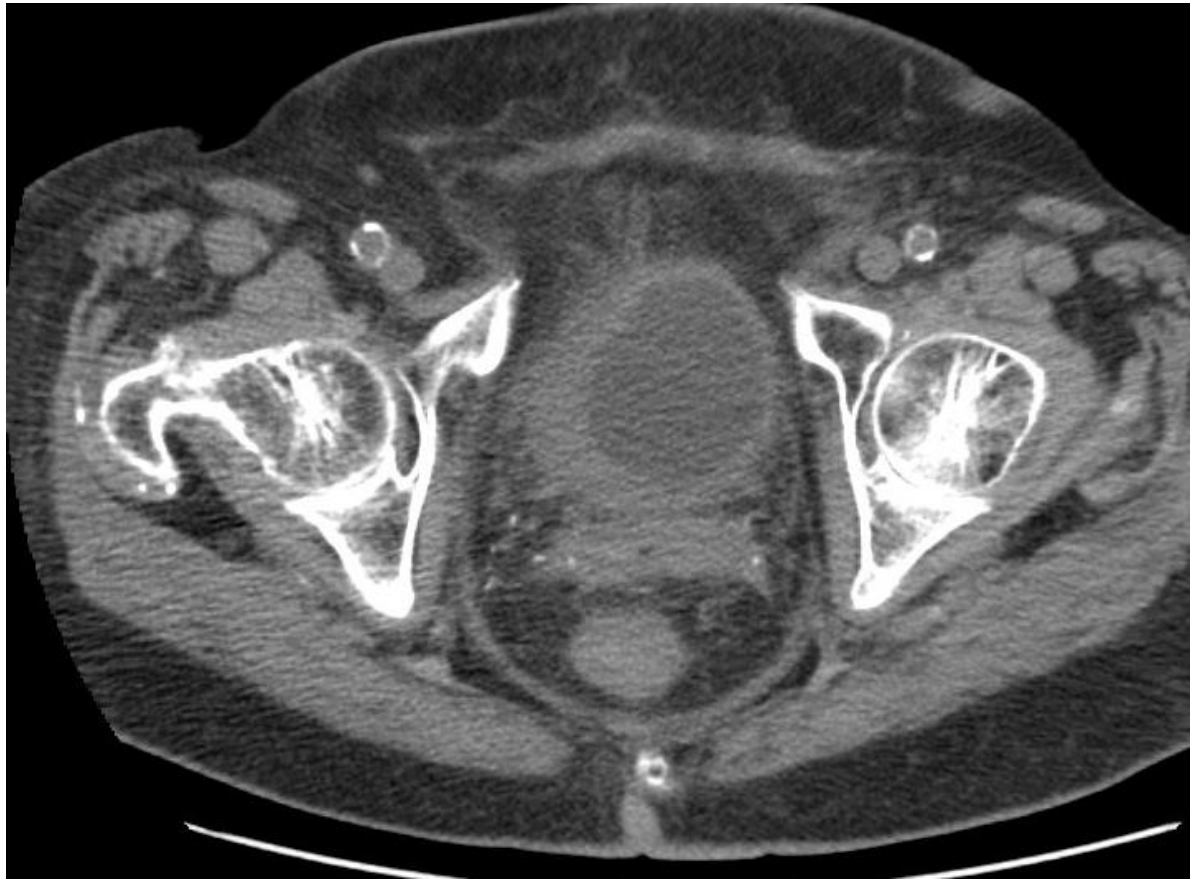
- T 97.7°F, HR 77 RR 16 BP 106/51 O2 sat 98%

Labs:

- WBC 7.7, Hemoglobin 10.3, Platelets 341
- BUN 25, Creatinine 2.02, K 5.0, eGFR 25
- LFTs normal

CT Chest/Abd/Pelvis w/o contrast





Case Study 2

CT: Chest/Abdomen/Pelvis without contrast

- Multiple pulmonary nodules bilaterally, new from prior, largest up to 15 mm in size
- Asymmetric right bladder wall thickening up to 19 mm

MR Pelvis w/o contrast:

- Bladder mass (1.9 x 2.6 x 2.8 cm) centered along the anterior bladder wall extending to the neck, with probable muscle invasion without definitive extension beyond the serosa.

CT Guided Lung Biopsy

- Urothelial Carcinoma

TURBT

- Urothelial Carcinoma
- PD-L1 CPS 50%
- No alterations in FGFR 2 or FGFR 3

Question 2

Which of the following is the most appropriate first line therapy for this patient?

A) Cisplatin/Gemcitabine

B) Carboplatin/Gemcitabine

C) Pembrolizumab

D) Enfortumab Vedotin

Question 2

Which of the following is the most appropriate first line therapy for this patient?

A) Cisplatin/Gemcitabine: Cisplatin ineligible due to low Cr Cl

B) Carboplatin/Gemcitabine: “Platinum ineligible” due to low GFR, NYHA Class 3 Heart Failure.

C) Pembrolizumab: Indicated as patient has CPS > 10%. It would also be indicated regardless of CPS as patient is “platinum ineligible” due to Cr Cl < 30 and NYHA Class 3 heart failure.

D) Enfortumab Vedotin: Indicated following progression on anti-PD1 therapy