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

- Consulting Fees: Ada Cap (Advanced Accelerator Applications) Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Mirati, Monopteros, Pfizer, Pharmacyclics, Roche, Seattle Genetics, Urogen
- Contracted Research: Ada Cap (Advanced Accelerator Applications), Agensys Inc, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Bristol Myers Squibb, Clovis Oncology, Eisai, Eli Lilly, Endocyte, Genentech, Innocrin, MedImmune, Medivation, Merck, Mirati, Novartis, Pfizer, Progenics, Replimune, Roche, Sanofi Aventis, Seattle Genetics
- Ownership Less than 5%: Bellicum (Sold 7/2020), Tyme (sold 10/2019)

- I will be discussing non-FDA approved indications during my presentation.

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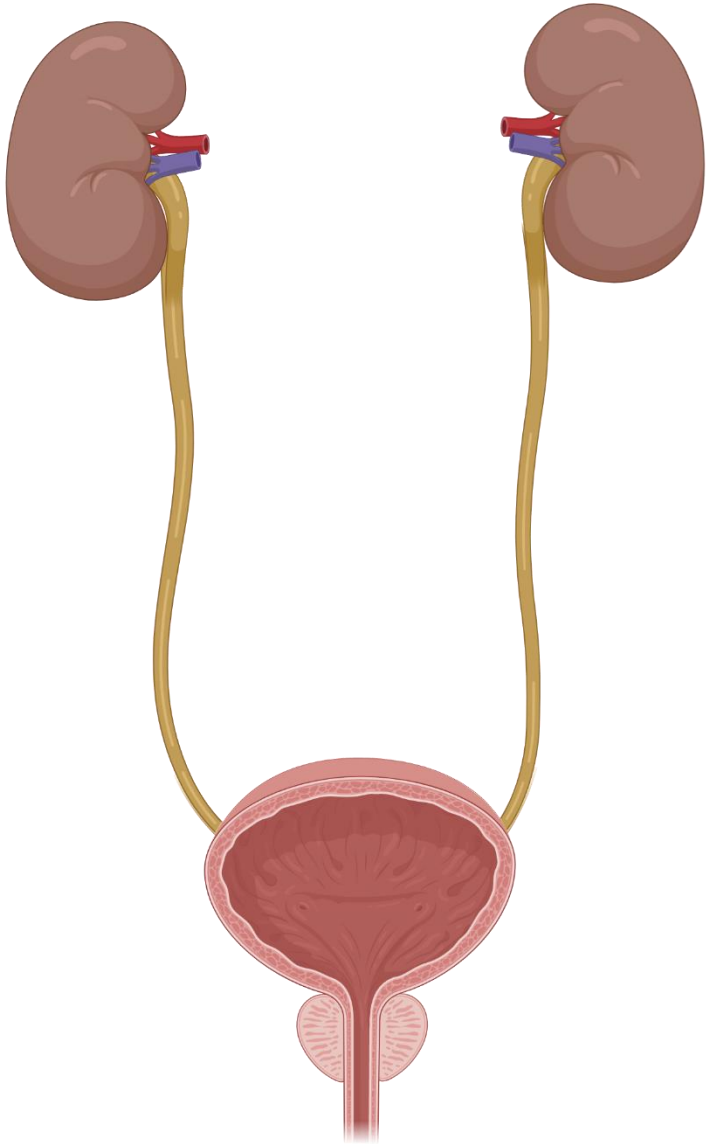
Outline

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



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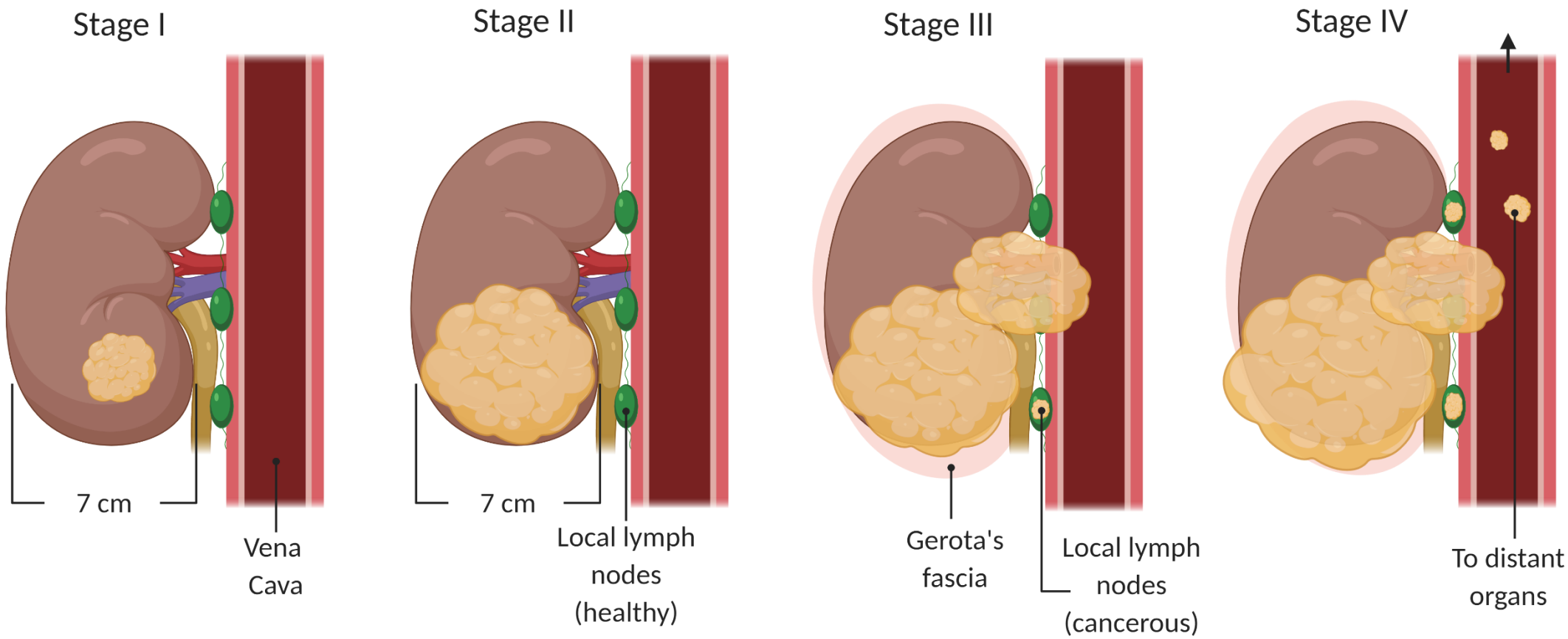
Renal cell carcinoma (RCC)



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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

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Comparing 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.

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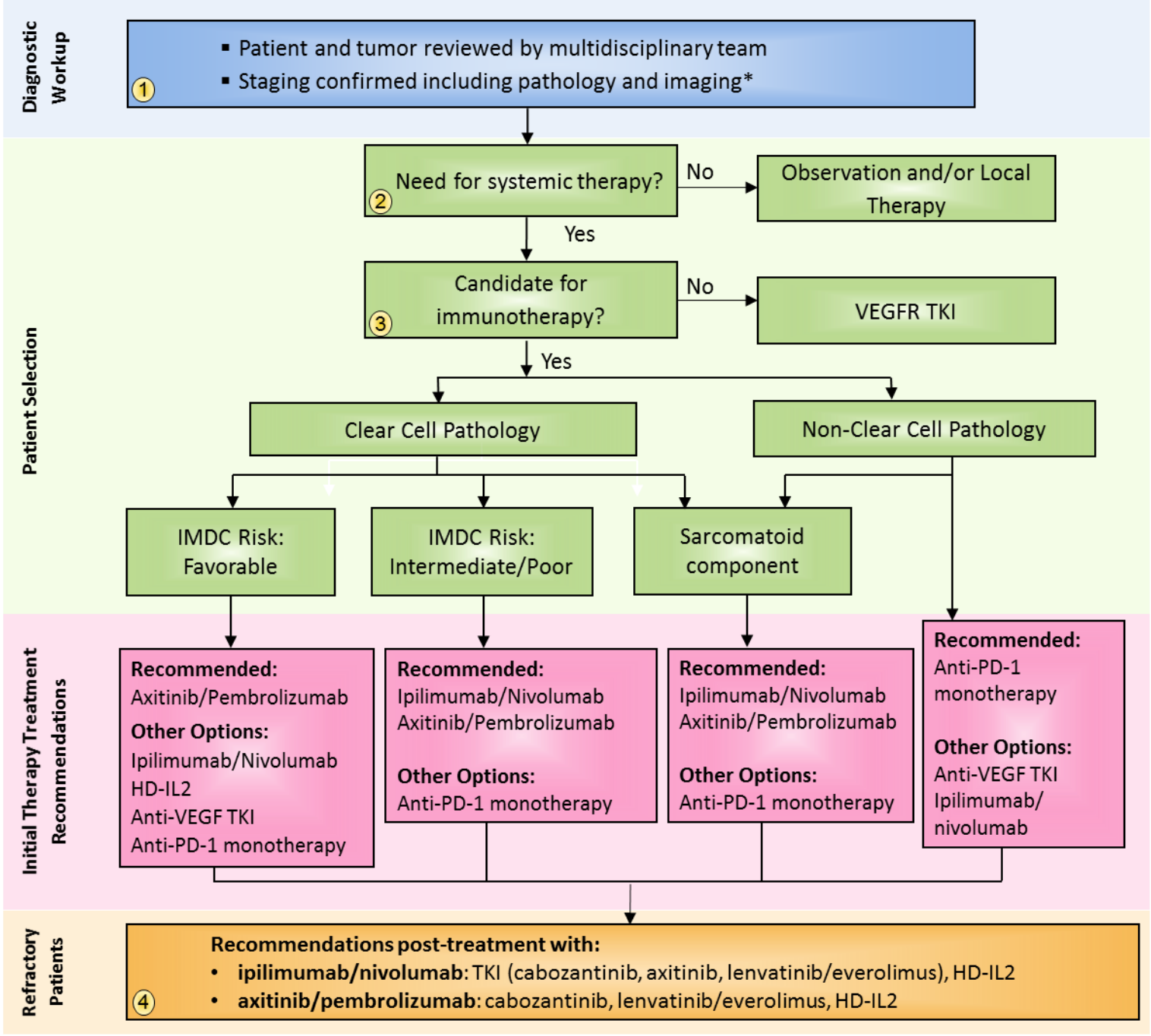
SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma



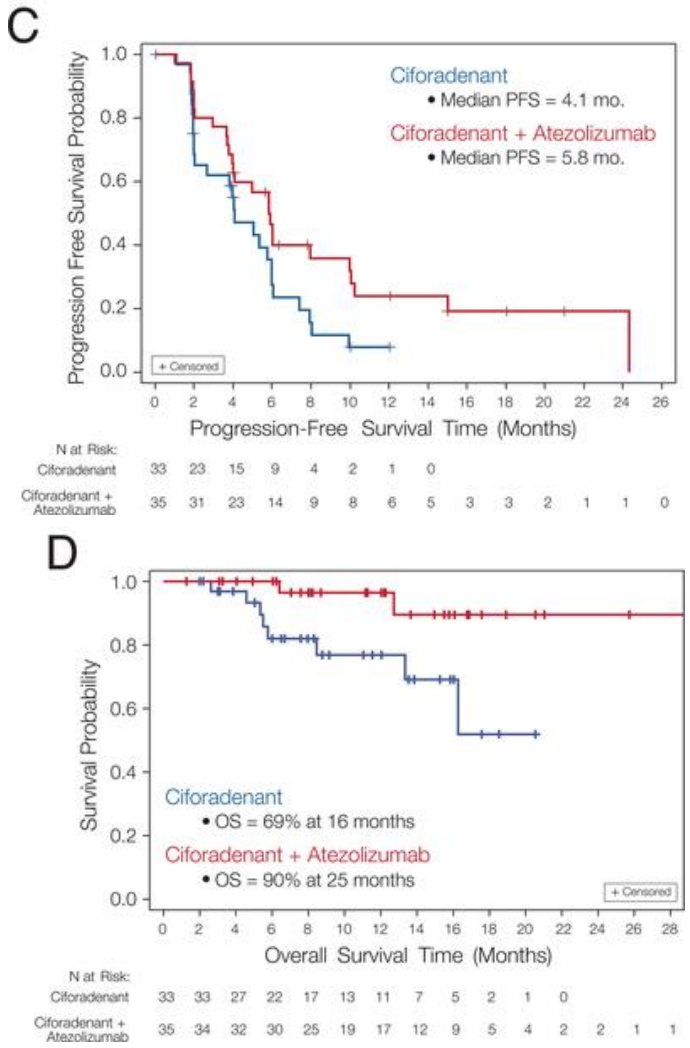
*Baseline imaging recommendations discussed in figure legend.

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

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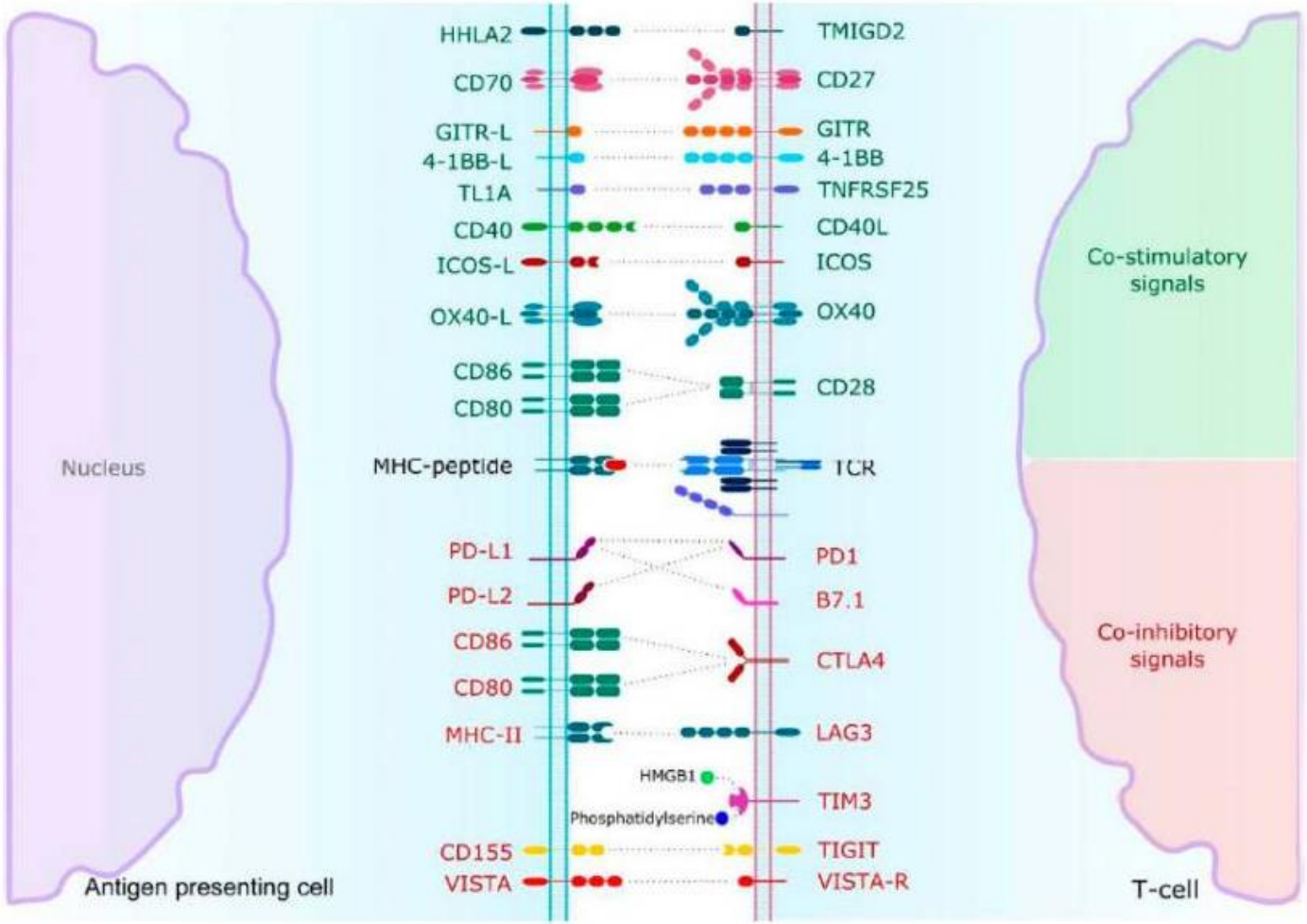
In development: additional immunotherapy approaches



Deleuze, Int J Mol Sci 2020

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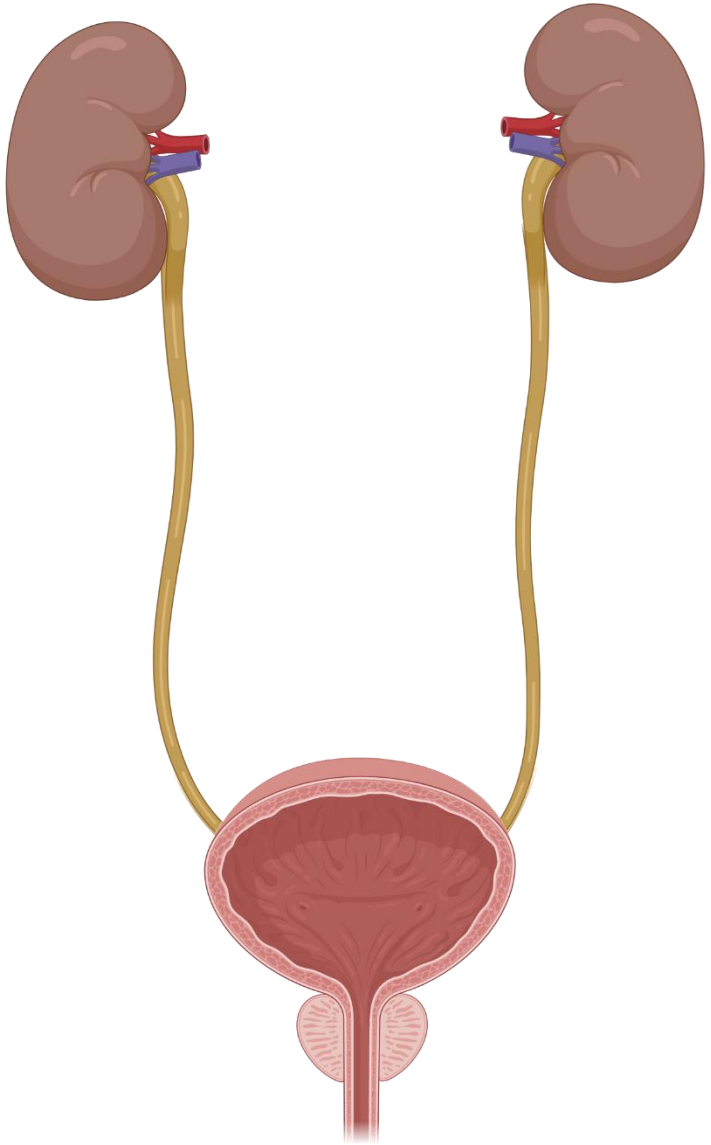

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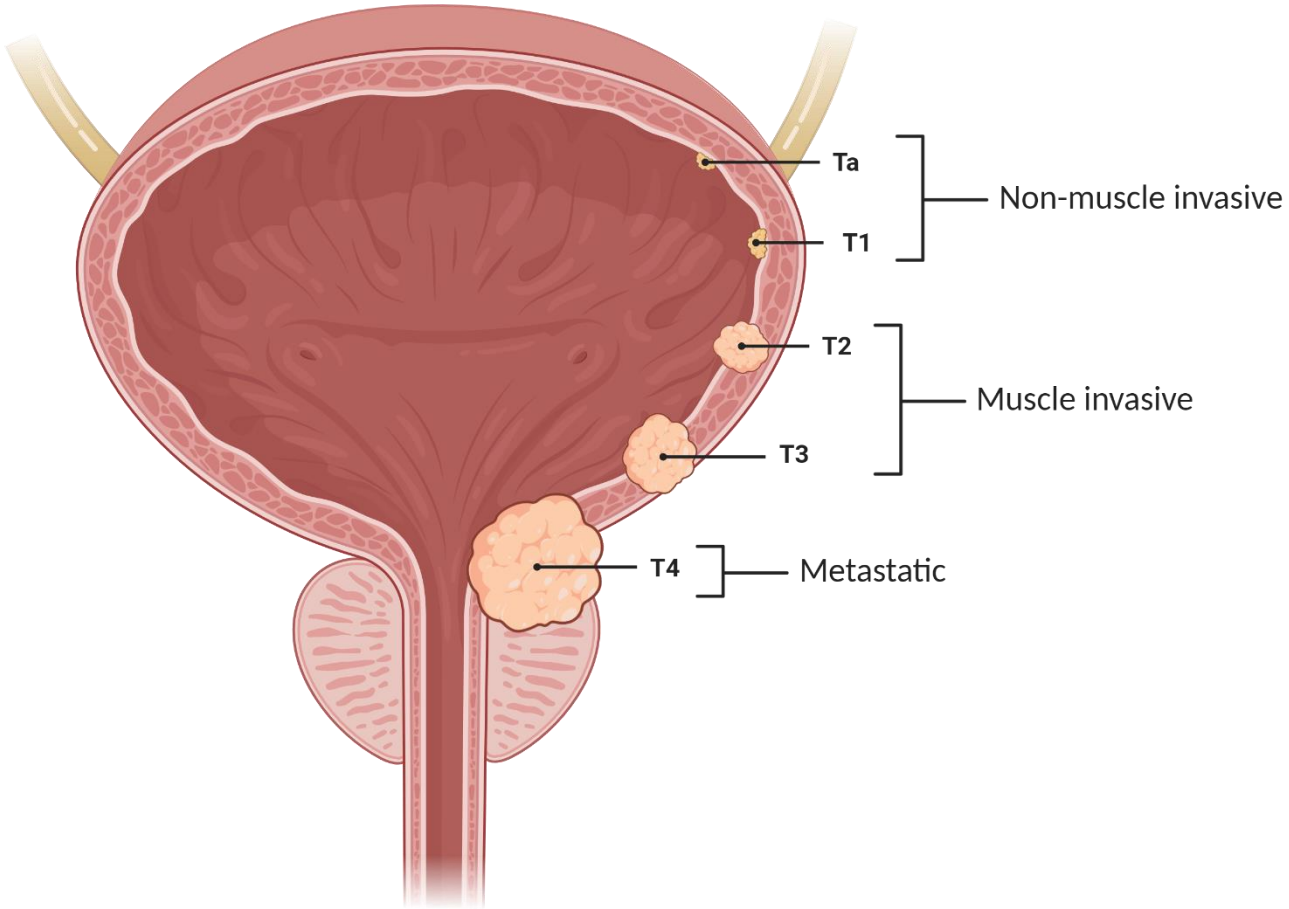
Urothelial carcinoma (UC)



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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.

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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

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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

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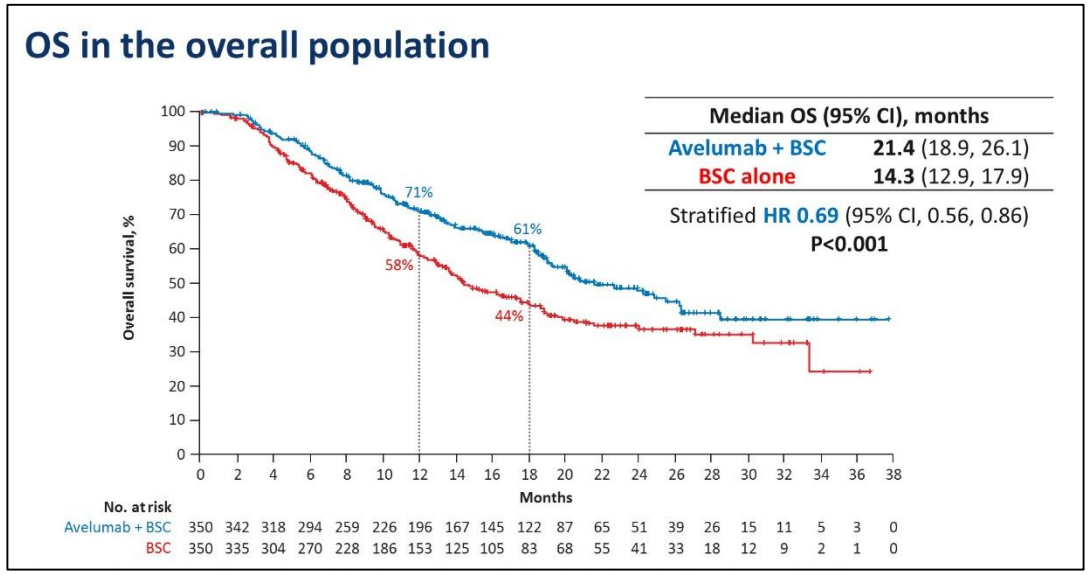
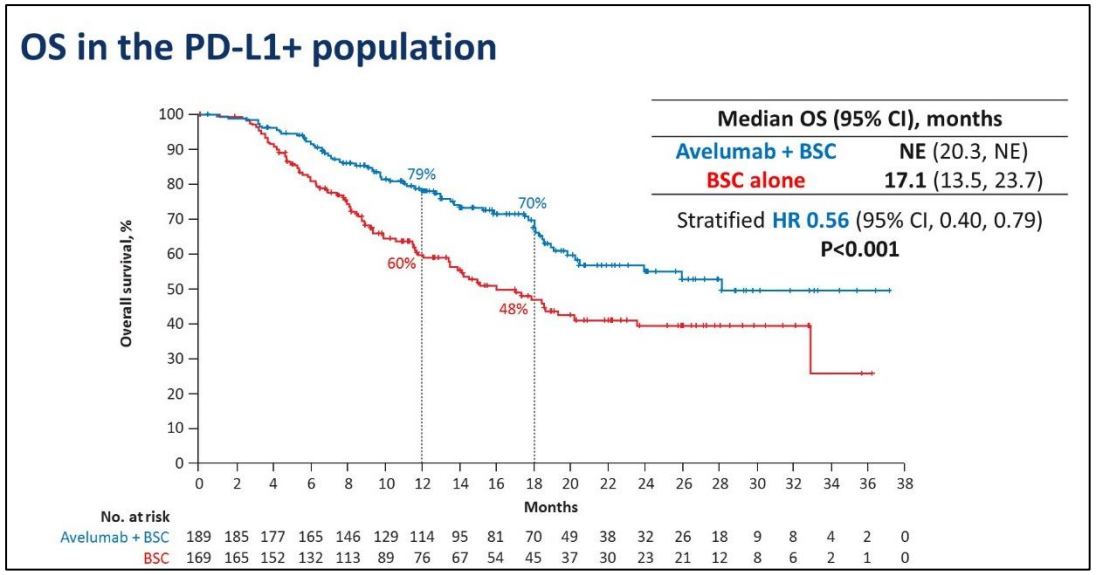
Approved checkpoint inhibitor for maintenance treatment

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





Powles, ASCO 2020.

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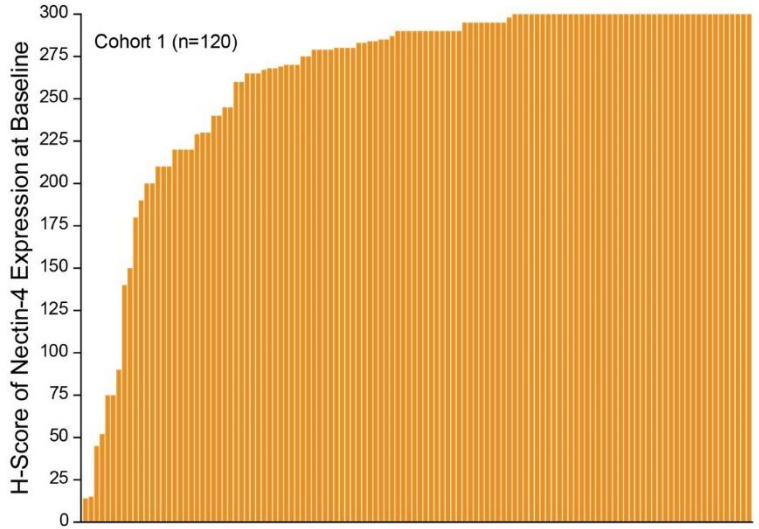
Approved antibody-drug conjugate for mUC

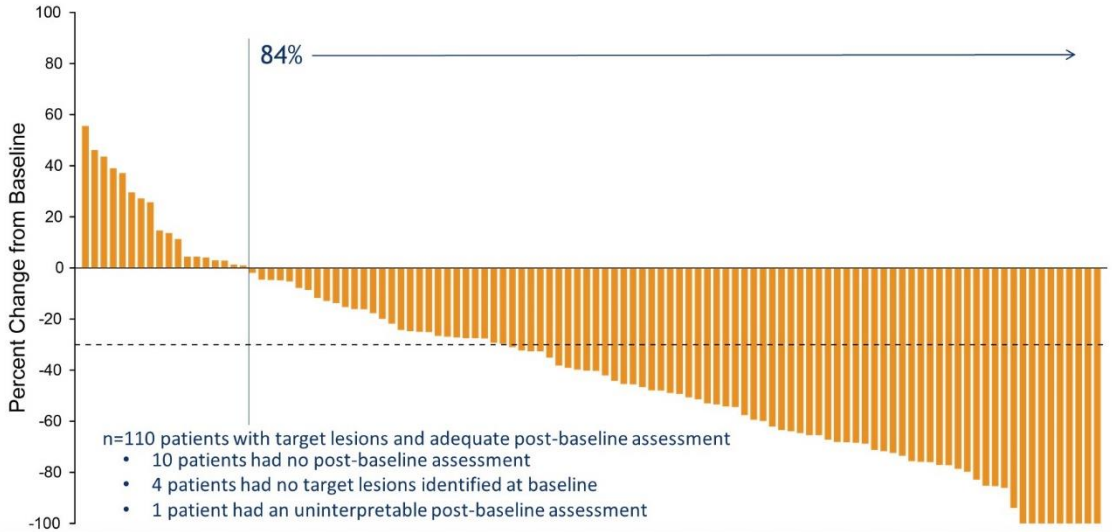
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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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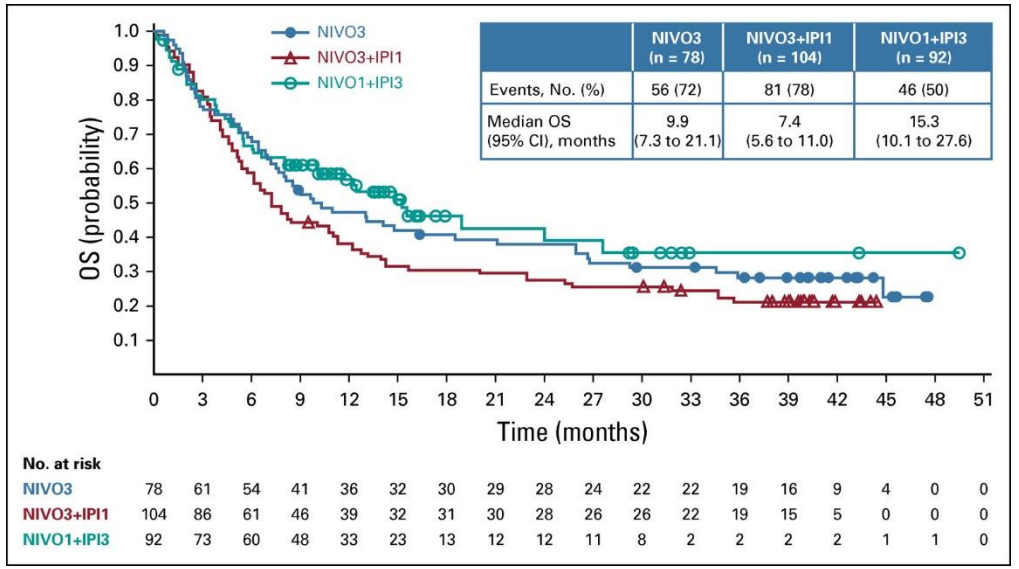
In development: Ipilimumab + Nivolumab CheckMate 032

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.

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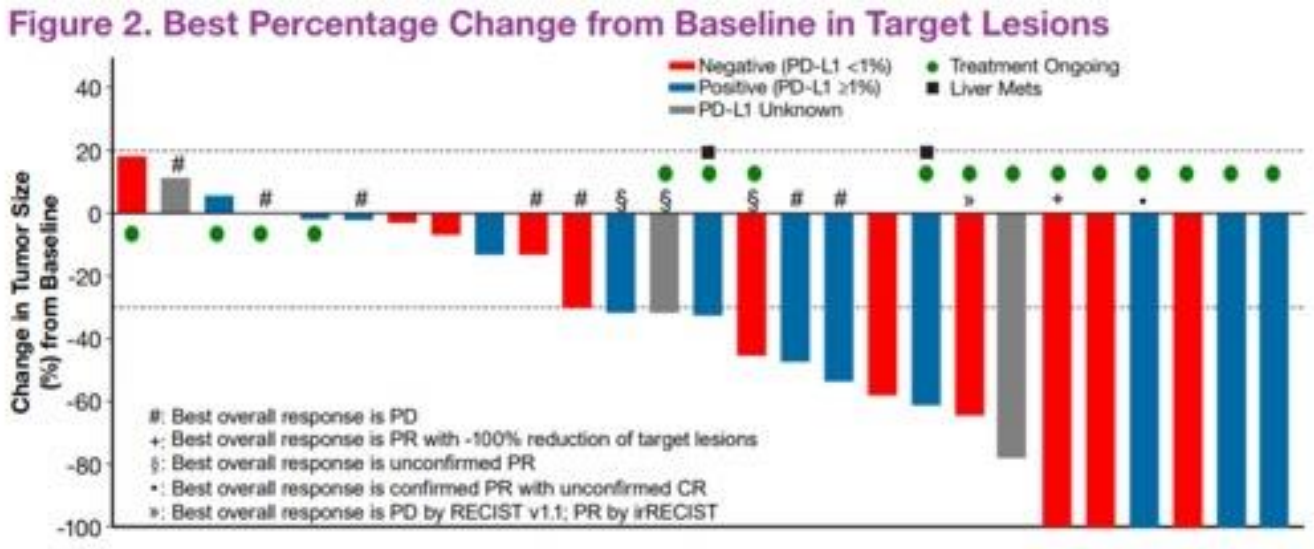
In development: NKTR-214 + nivolumab

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.

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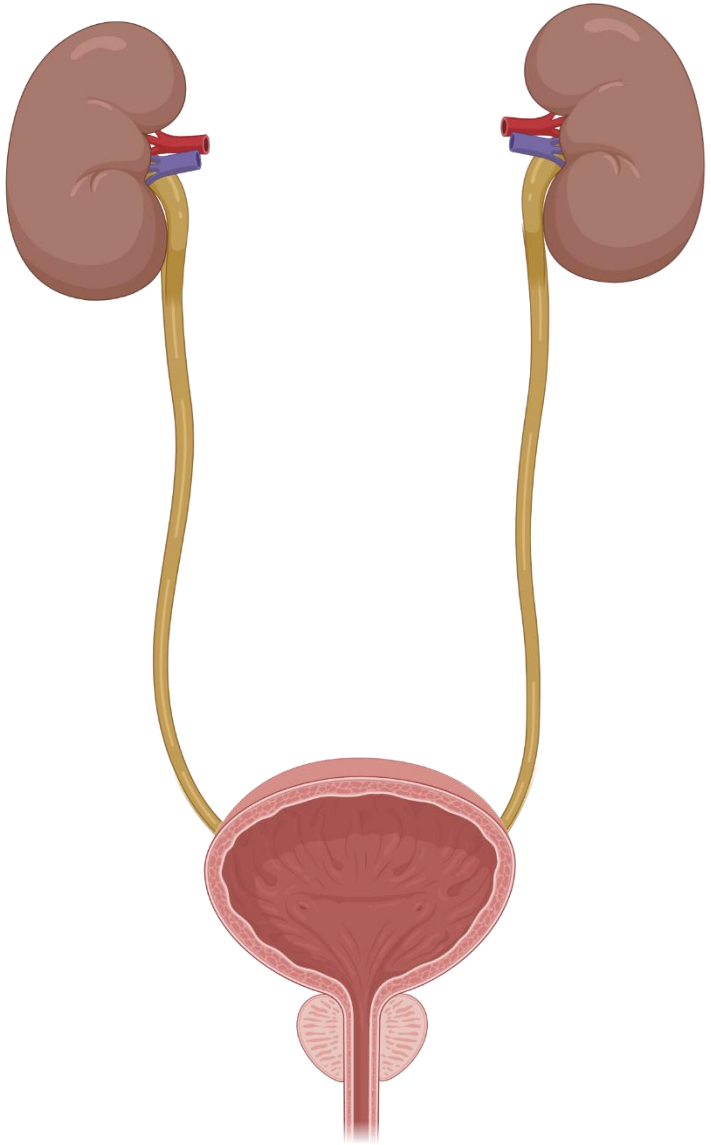

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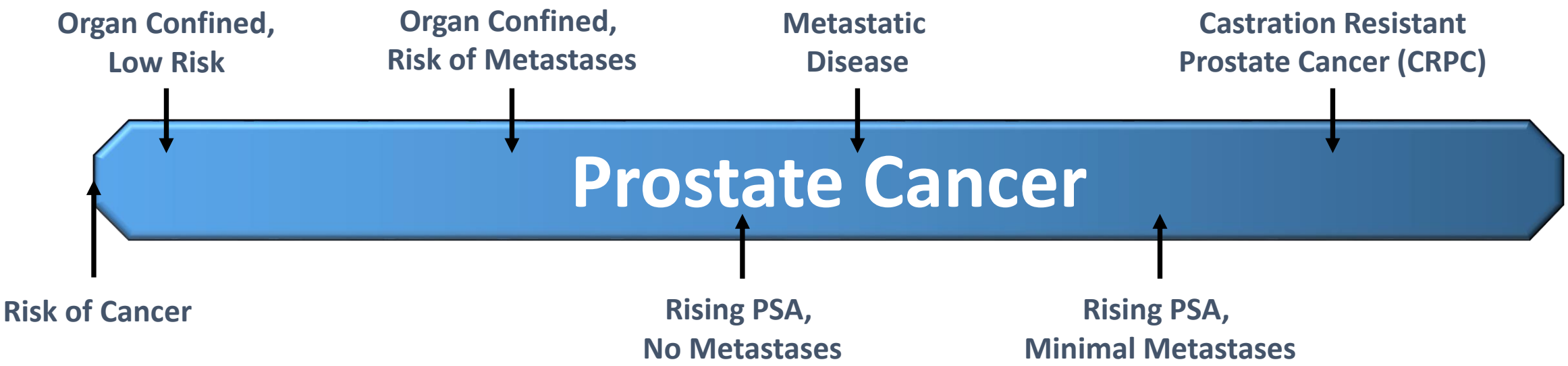
The Spectrum of Prostate Cancer



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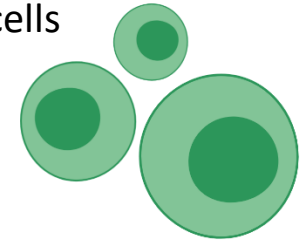
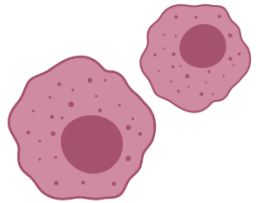
Immunology of prostate cancer

Dysfunctional CD8+ T cells



Chronic type 1 IFN pathway activation

Increased M2 tumor-associated macrophages



MSI in Prostate Cancer

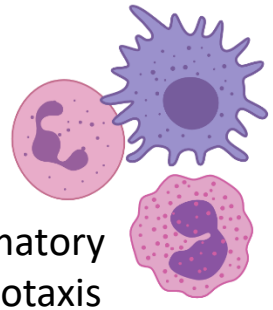
- 1033 patients who had adequate tumor quality for MSI sensor analysis 32 (3.1%) had MSI-H/dMMR prostate cancer.
- 23 of 1033 patients (2.2%) had tumors with high MSI sensor scores, and an additional 9 had indeterminate scores with evidence of dMMR.
- Seven of the 32 MSI-H/dMMR patients (21.9%) had a pathogenic germline mutation in a Lynch syndrome–associated gene.
- Six patients had more than 1 tumor analyzed, 2 of whom displayed an acquired MSI-H phenotype later in their disease course.

Abida et al JAMA Oncol. 2019;5(4):471-478.
doi:10.1001/jamaoncol.2018.5801
Published online December 27, 2018.

Loss of MHC I expression

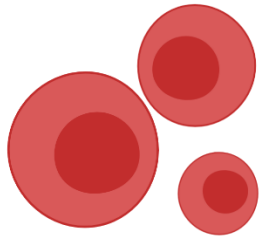
Intact DNA damage repair

Decreased inflammatory immune cell chemotaxis



Few tumor-associated antigens

Increased regulatory T cells



Vitkin, Front Immunol 2019.

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Immunotherapy landscape in prostate cancer

Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	F PC	ORR: 5%
		F PC	ORR: 3%
		F	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	F al and c	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		

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Abida et al JAMA Oncol. 2019;5(4):471-478.
doi:10.1001/jamaoncol.2018.5801
Published online December 27, 2018.

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

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Abida et al JAMA Oncol. 2019;5(4):471-478.
doi:10.1001/jamaoncol.2018.5801
Published online December 27, 2018.

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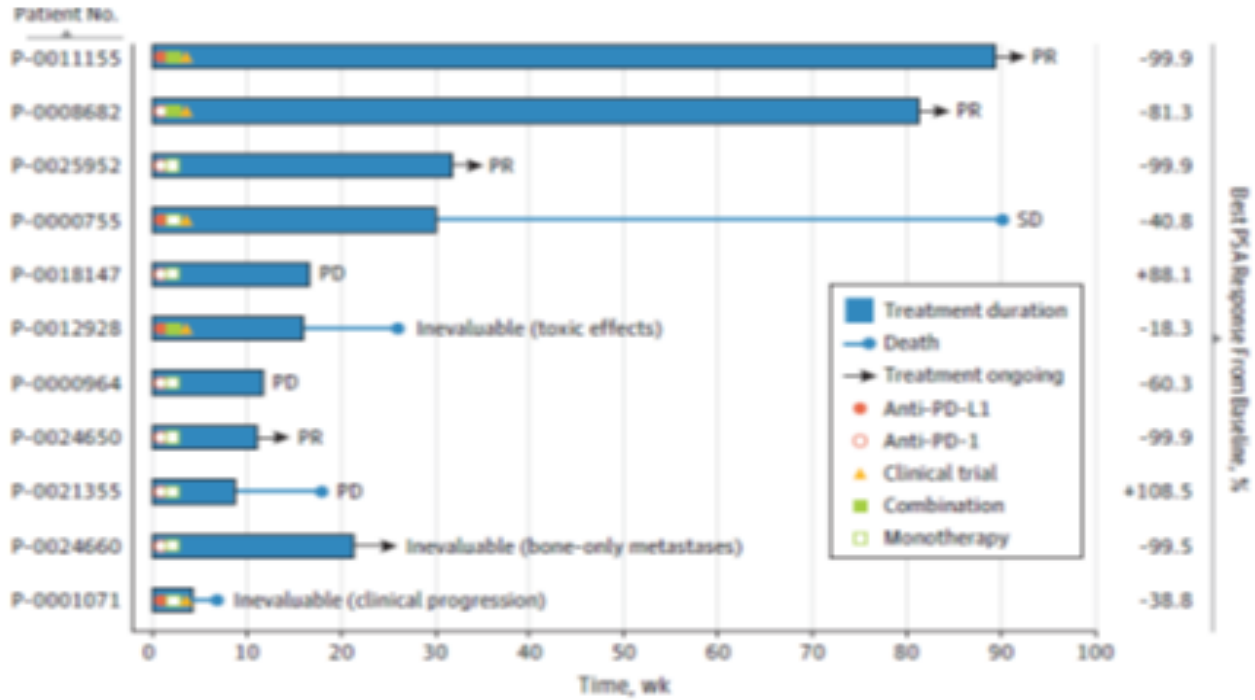
MSI in Castration Resistant Prostate Cancer



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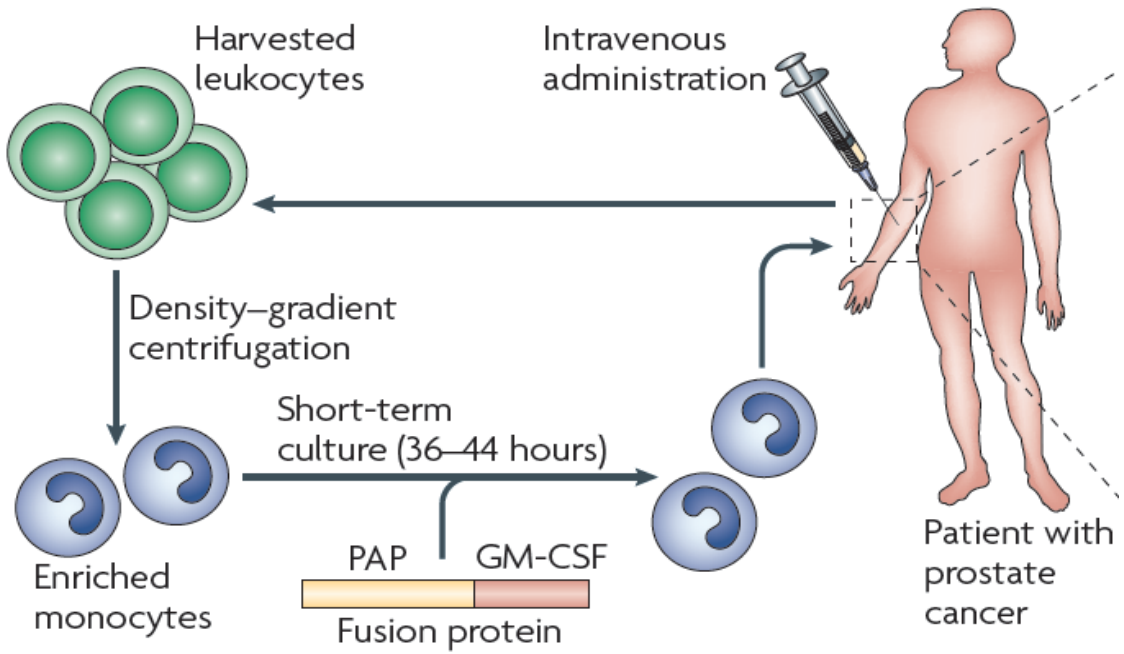
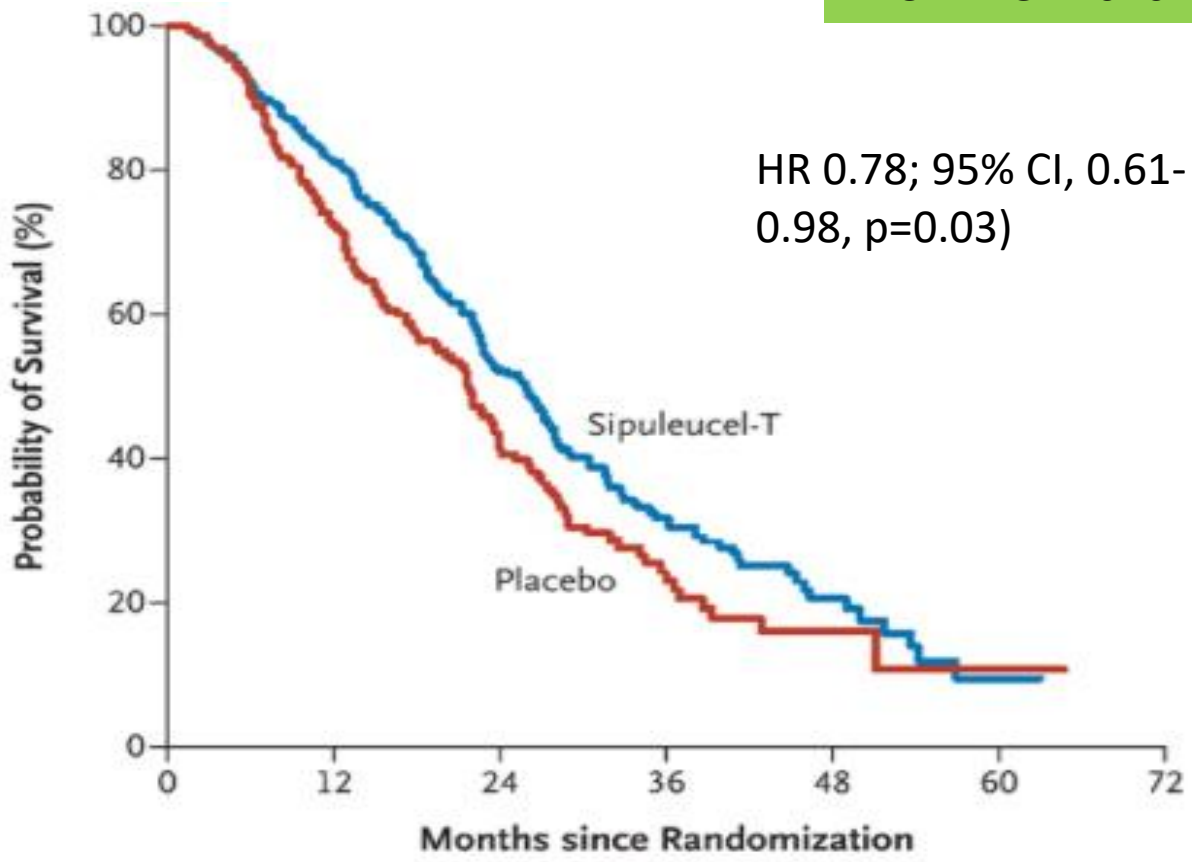
Sipuleucel-T in mCRPC

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

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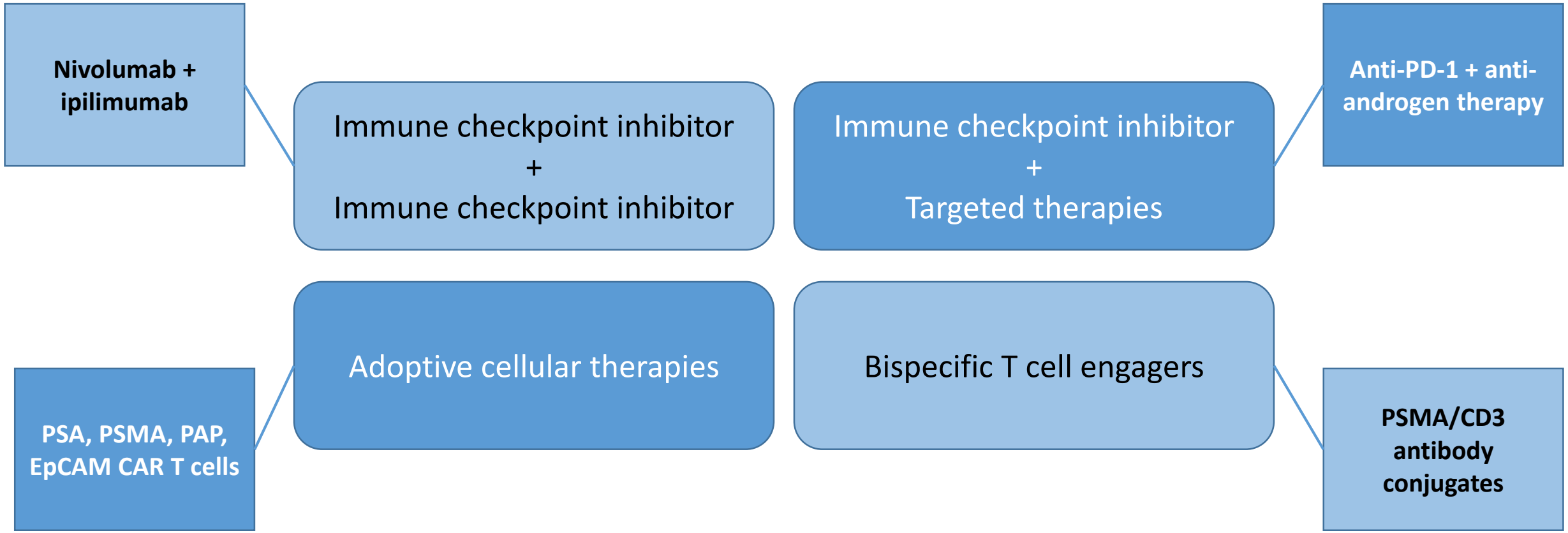
Future directions for prostate cancer immunotherapy



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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.

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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

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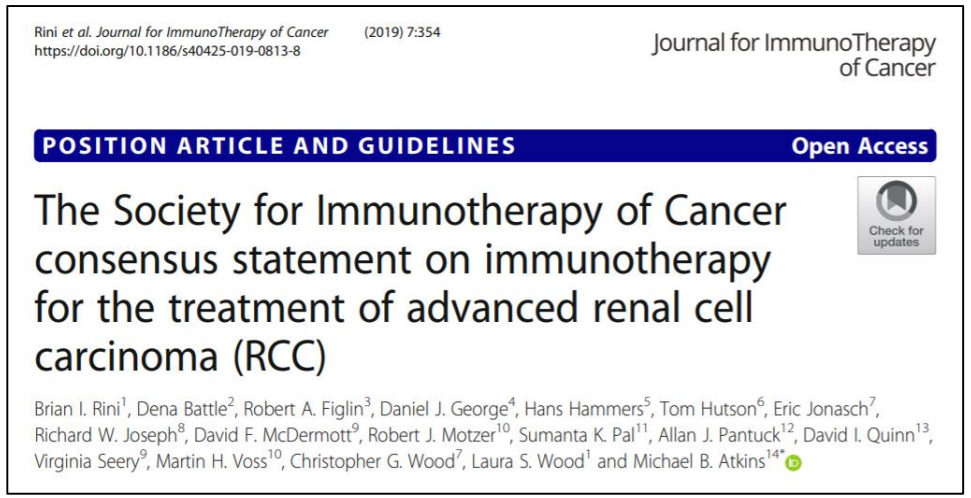
Additional Resources



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*]

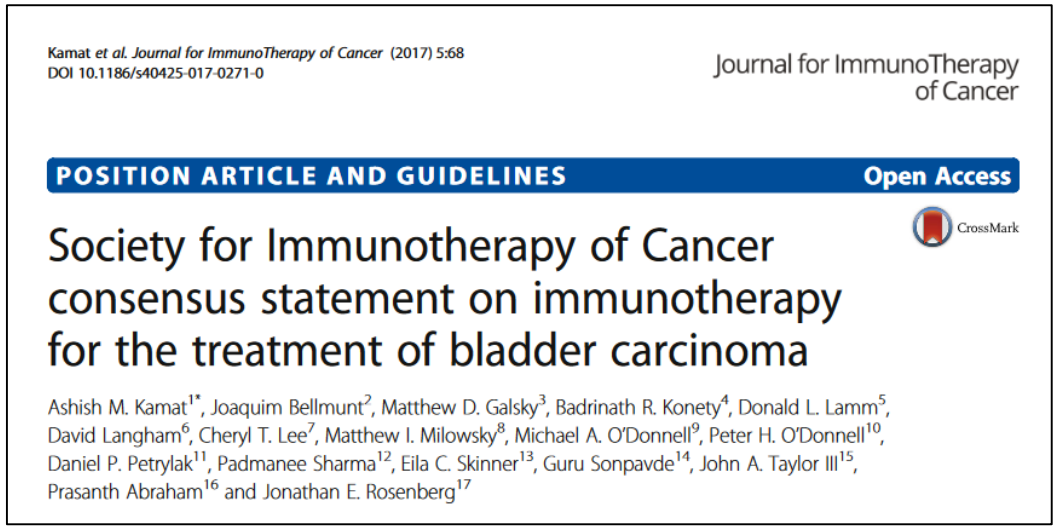
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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

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Case Studies

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Case Study

63 year old smoker develops gross hematuria. Cystoscopy demonstrates a large bladder mass; TURBT demonstrates a high grade urothelial cancer with muscle invasion. CT scan of the chest/abdomen/pelvis demonstrates a bladder mass and multiple pulmonary nodules. His creatinine clearance is 40 ml/min. His PDL-1 staining CPS $\geq$10

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Case Study

- Treatment options include all except
- 1) Avelumab
- 2) Pembrolizumab
- 3) Carboplatin/gemcitabine 4-6 cycles, if responding then avelumab
- 4) atezolizumab

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Since the patient is PDL-1 positive, single agent checkpoint inhibition is approved by the FDA for metastatic platinum ineligible urothelial cancer. Thus, both choices 2 and 4 are appropriate. Avelumab is not approved as a single agent for platinum ineligible patients. Based on the Javelin 100 trial, chemotherapy followed by maintenance therapy with avelumab is also appropriate.

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Case Study

- The patient decides to be treated with carboplatin/gemcitabine. After 6 cycles of therapy he is a partial response in lung. He elects for avelumab maintenance therapy. After 8 months of treatment he progresses in liver
- FDA approved treatments include
  - 1) Enfortumab vedotin
  - 2) Pemetrexed
  - 3) Sacituzumab Govitecan
  - 4) Docetaxel

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Case Study

- Of these agents, Enfotumab vedotin has received accelerated approval for the treatment of urothelial cancer in patients who have received chemotherapy and a checkpoint inhibitor. Sacituzumab Govitecan is currently in clincal trials.

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Case 2

- 62 year old male with a history of metaastatic prostate cancer diagnosed 18 motnsh ago ago with biopsy proven supraclavicular lymph nodes and retroperitoneal adenopathy. He underwent androgen blockade combined with docetaxel, and his PSA went from 32 to 0. The patient was treated with abiraterone/prednisone at progression. He had a response for 6 months and underwent treatment with cabazitaxel. His next generation sequencing demosntrated MSH2. What is the next treatemnt

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Case 2

Appropriate treatment options include

1) Pembrolizumab
2) Atezolizumab
3) Olaparib
4) Radium 223

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Case 2

- Answer pembrolizumab. This is an FDA approved treatment for MSI high tumors.

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