

Immunotherapy for the Treatment of Genitourinary Malignancies

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Medical Oncologist

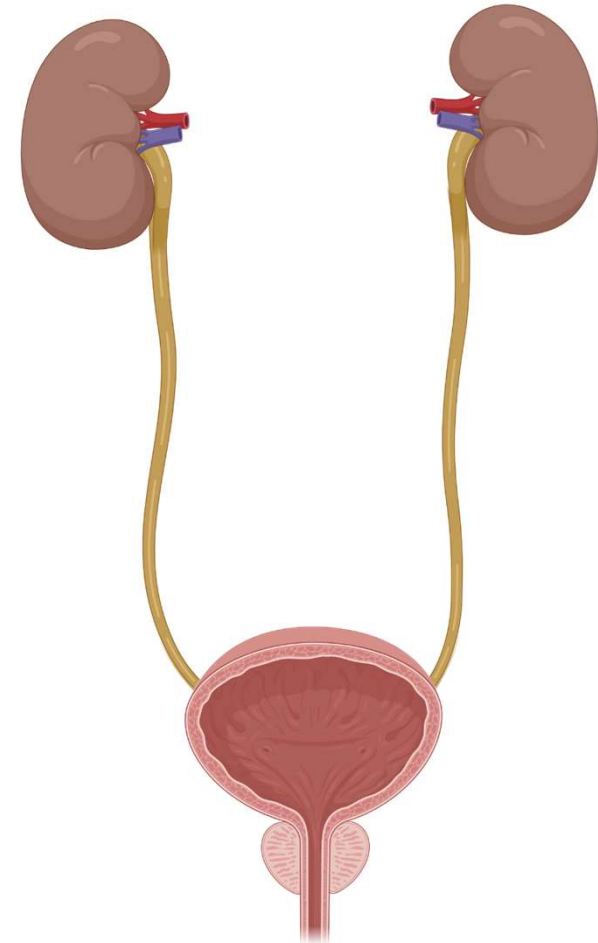
Norton Cancer Institute

Disclosures

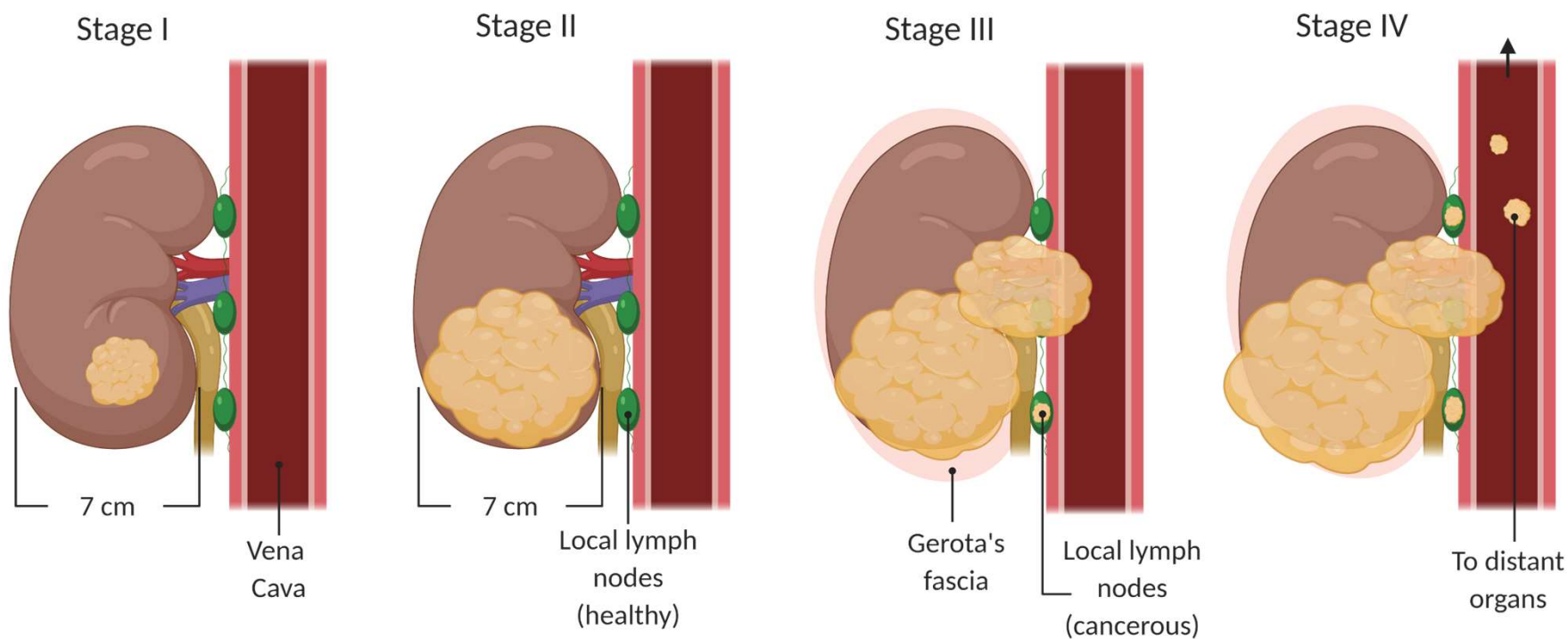
- Advisory Boards: Advisory Boards: Caris, Doximity, Astellas, Janssen, Merck, AstraZeneca, Pfizer, and SeaGen
- I will not be discussing non-FDA approved indications during my presentation.

Outline

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

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 + axitinib*	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

EE3

*FDA-approved IO regimen

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

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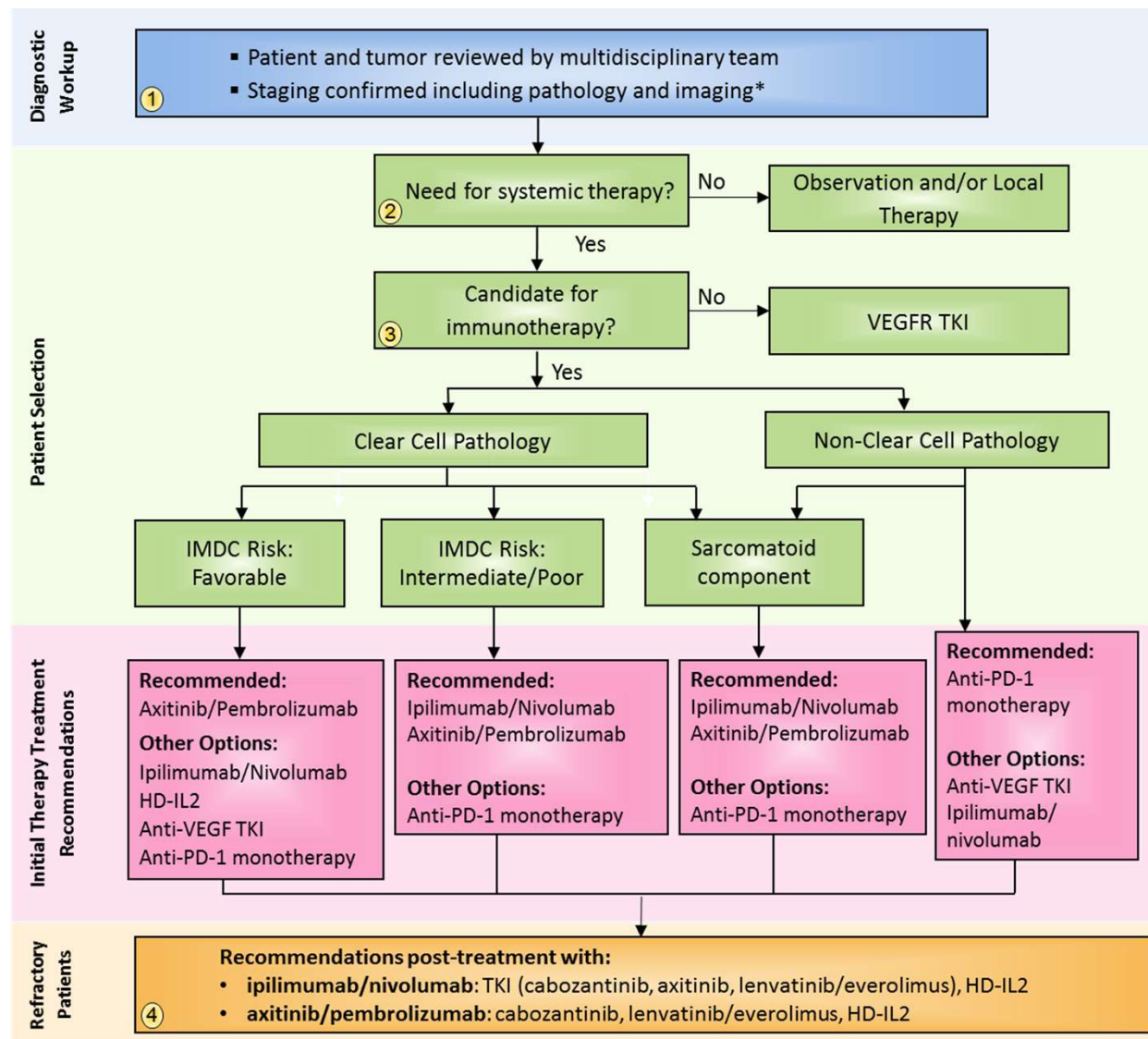
Slide 6

EE3

IMmotion151: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(19\)30723-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30723-8/fulltext)

Emily Ehlerding, 7/28/2020

SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma

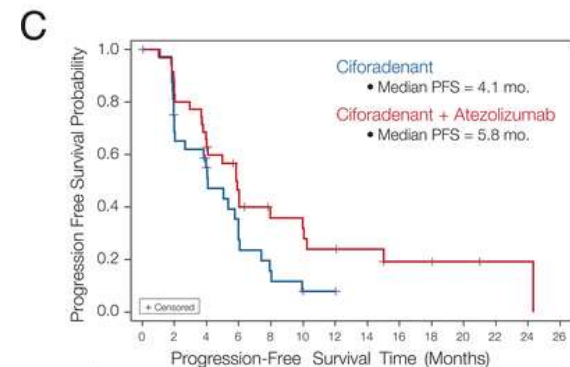


*Baseline imaging recommendations discussed in figure legend.

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

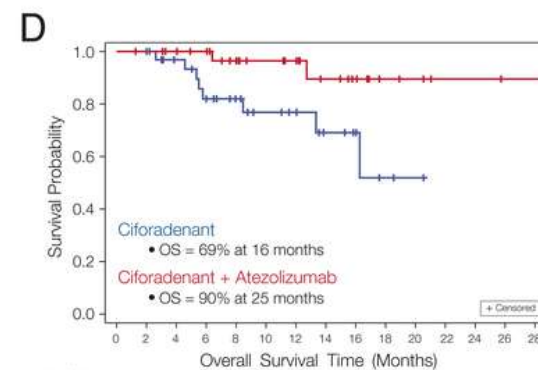
In development: A2AR antagonist + anti-PD-L1

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%



N at Risk:

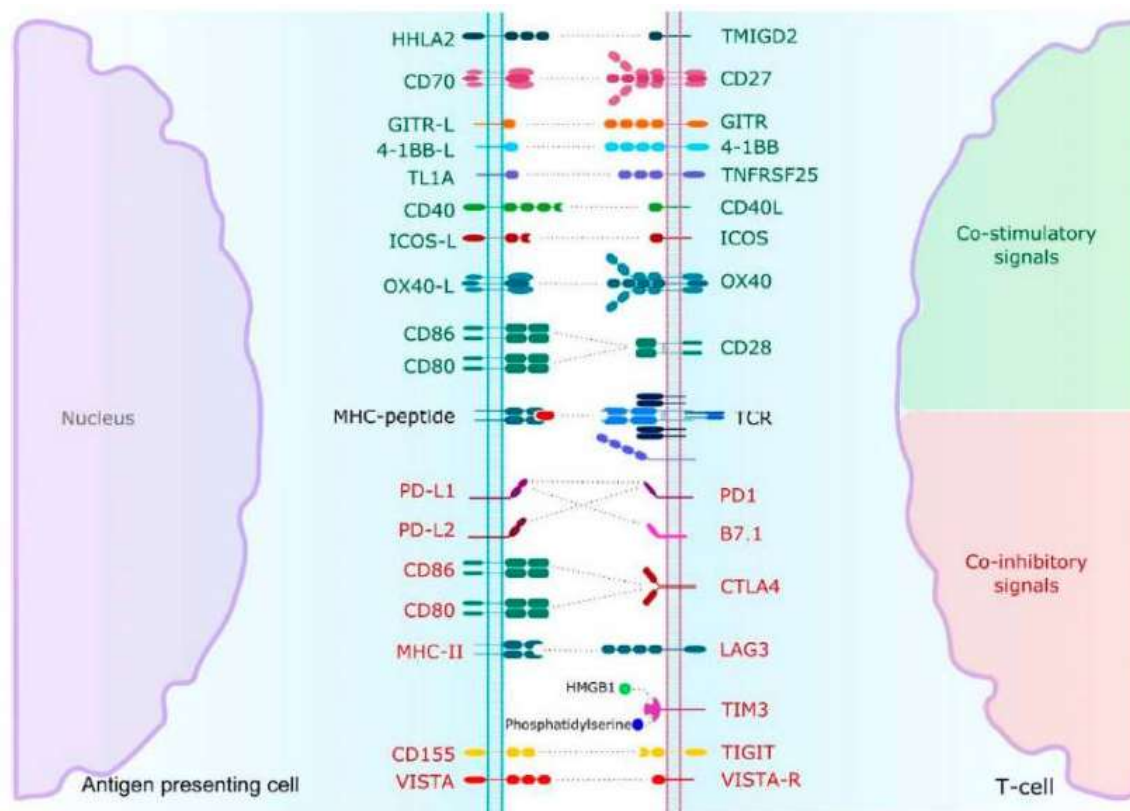
Ciforadenant	33	23	15	9	4	2	1	0
Ciforadenant + Atezolizumab	35	31	23	14	9	8	6	5



N at Risk:

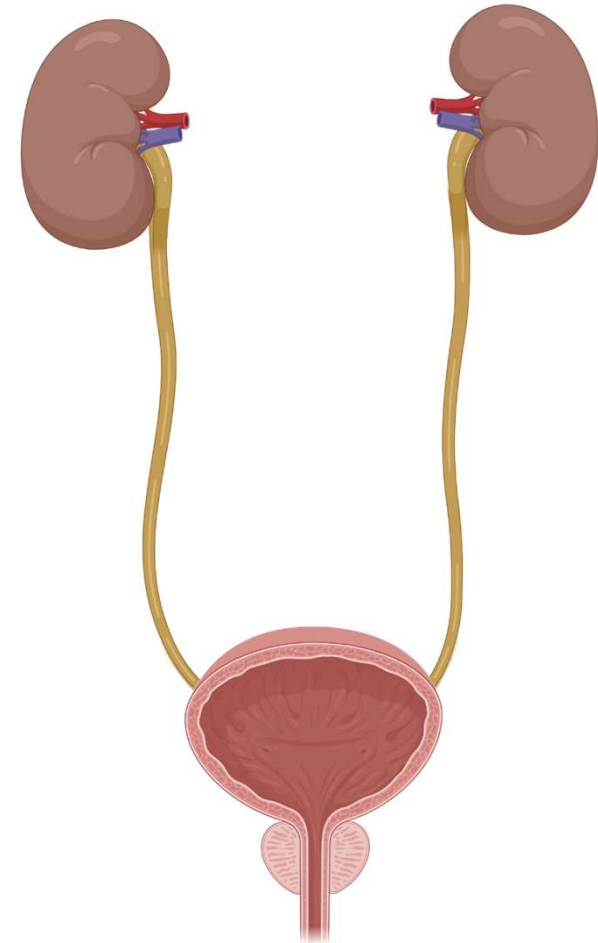
Ciforadenant	33	33	27	22	17	13	11	7	5	2	1	0
Ciforadenant + Atezolizumab	35	34	32	30	25	19	17	12	9	5	4	2

In development: additional immunotherapy approaches

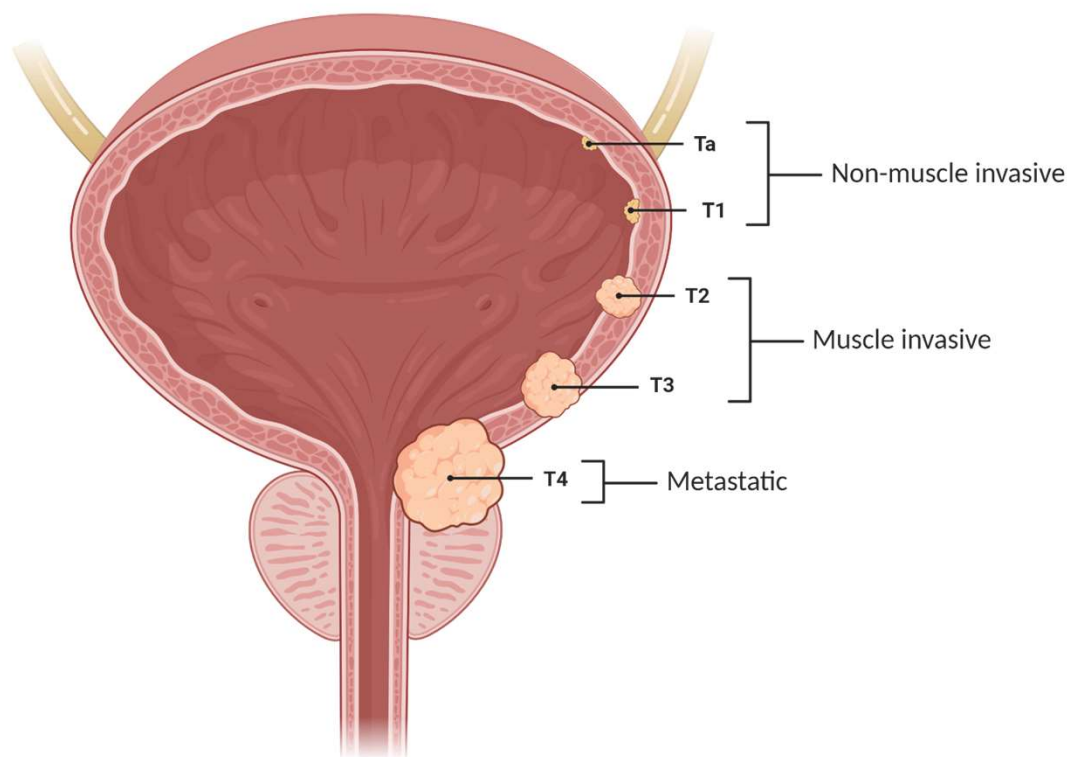


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Urothelial carcinoma (UC)



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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)

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 $\geq 5\%$)	1200 mg Q3W
Pembrolizumab	Advanced/metastatic UC (PD-L1 CPS ≥ 10)	200 mg Q3W or 400 mg Q6W

June 2018

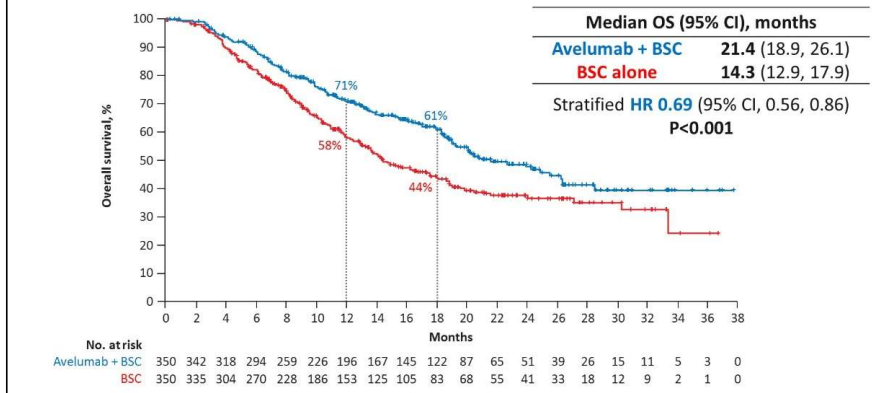
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

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

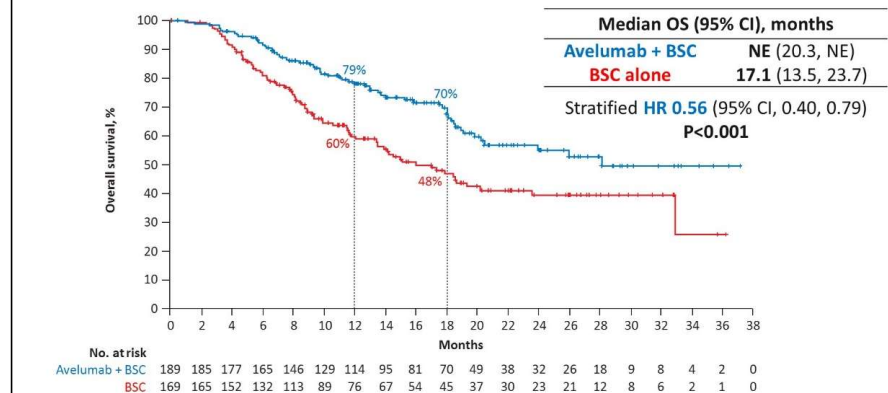
Approved checkpoint inhibitor for maintenance treatment

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

OS in the overall population



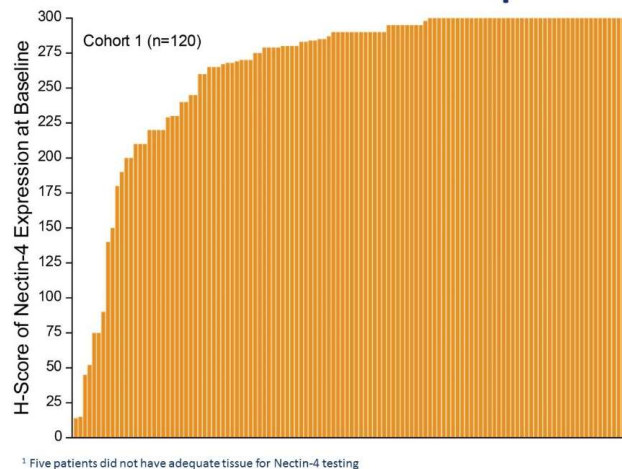
OS in the PD-L1+ population



Approved antibody-drug conjugate for mUC

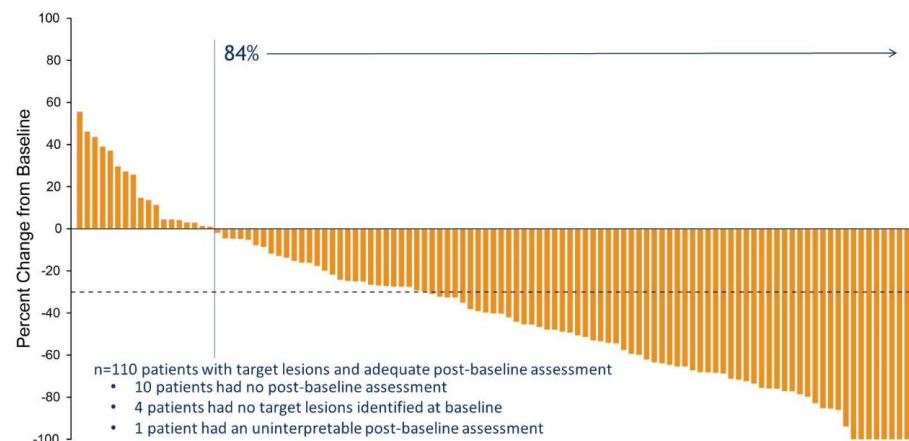
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metastatic UC with previous αPD-1/PD-L1 and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



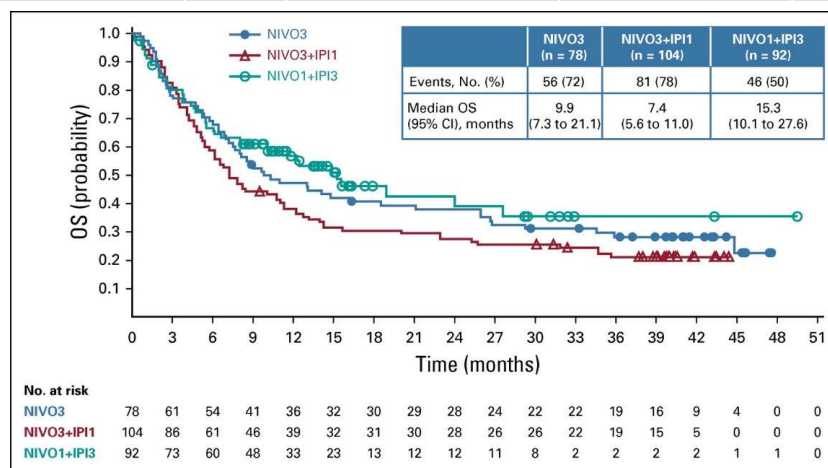
¹ Five patients did not have adequate tissue for Nectin-4 testing

EV-201: Cohort 1 Change in Tumor Measurements per BICR



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%



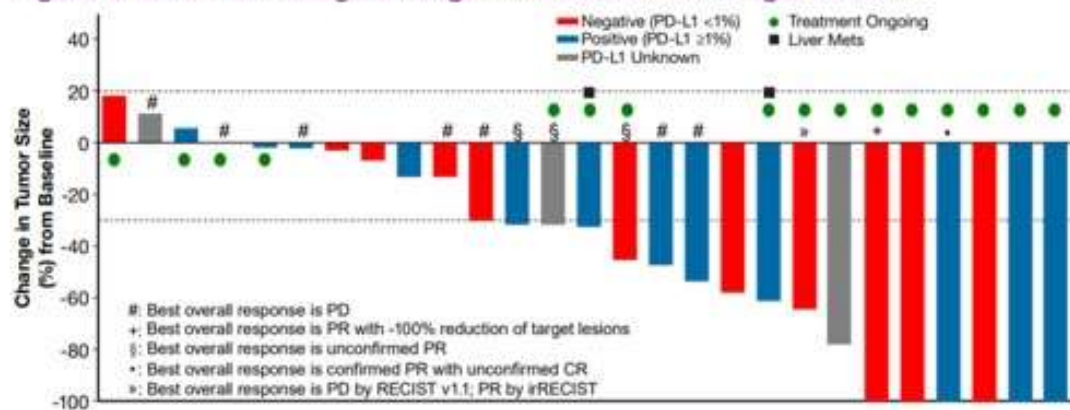
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In development: NKTR-214 + nivolumab

Treatment	n	ORR
NKTR-214 + nivolumab	27	48%

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

Figure 2. Best Percentage Change from Baseline in Target Lesions



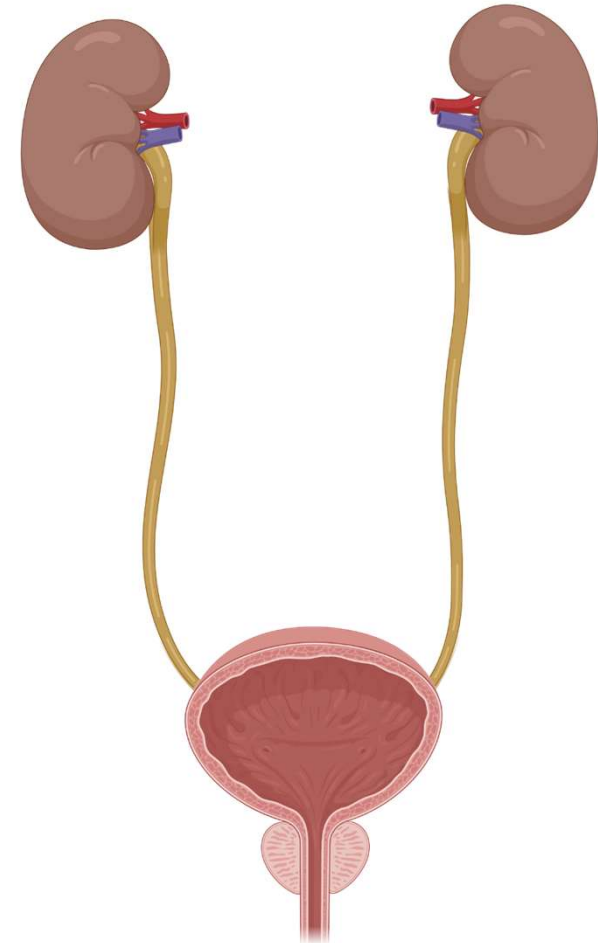
Siefker-Radtke, ASCO-GU 2020.

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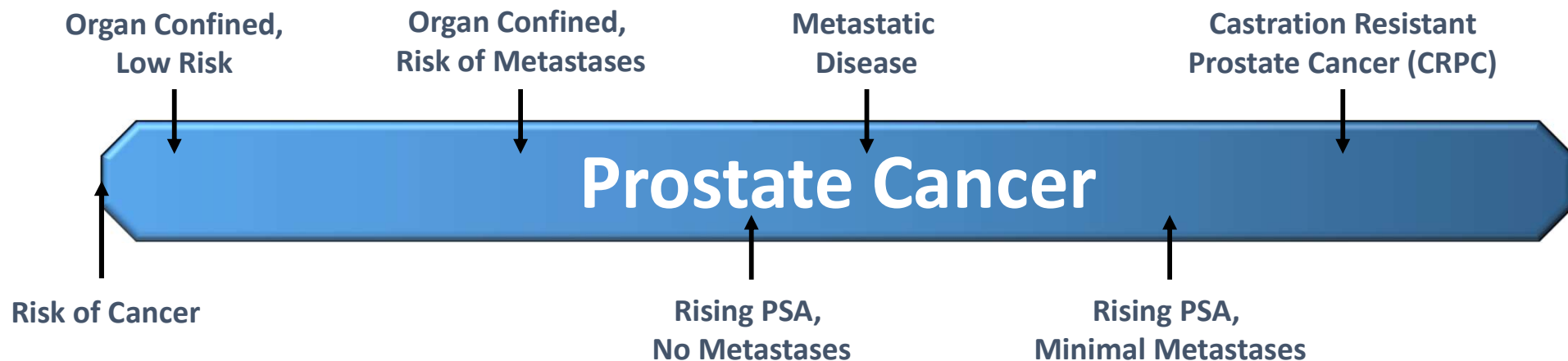
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Outline

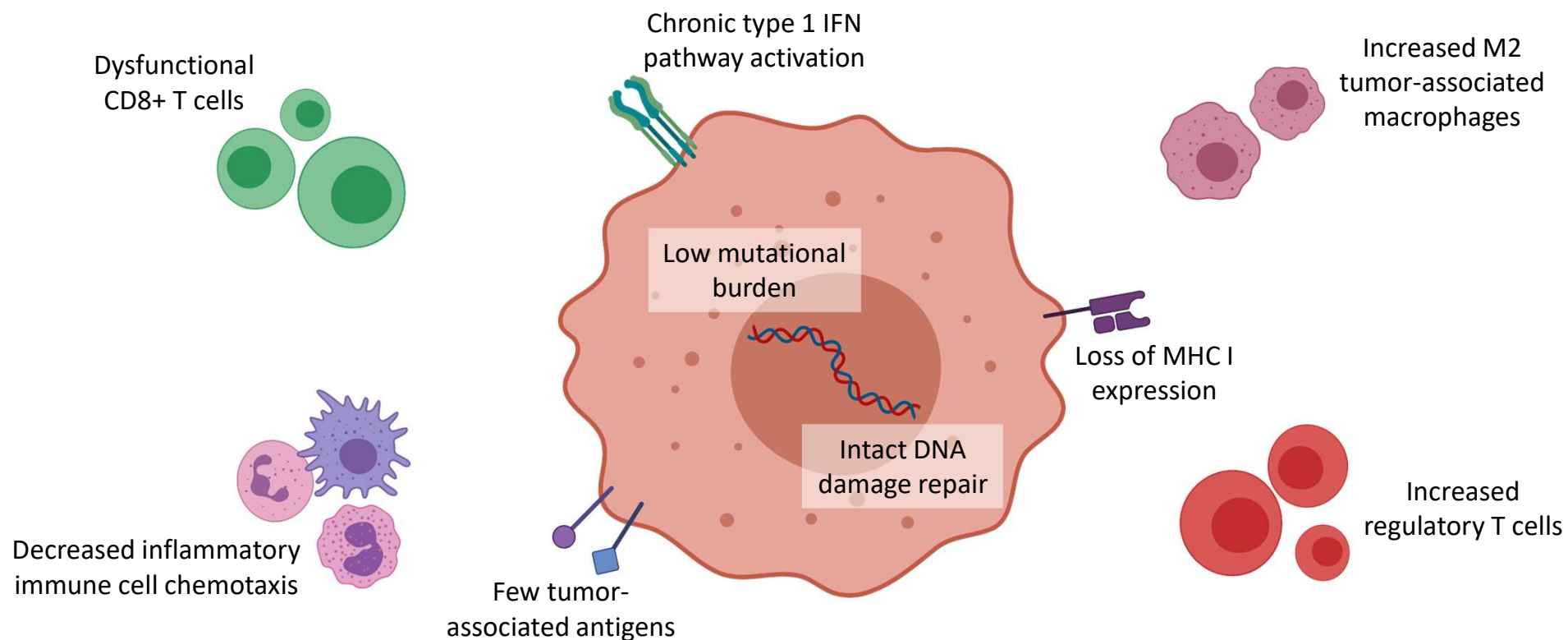
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The Spectrum of Prostate Cancer



Immunology of prostate cancer



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.

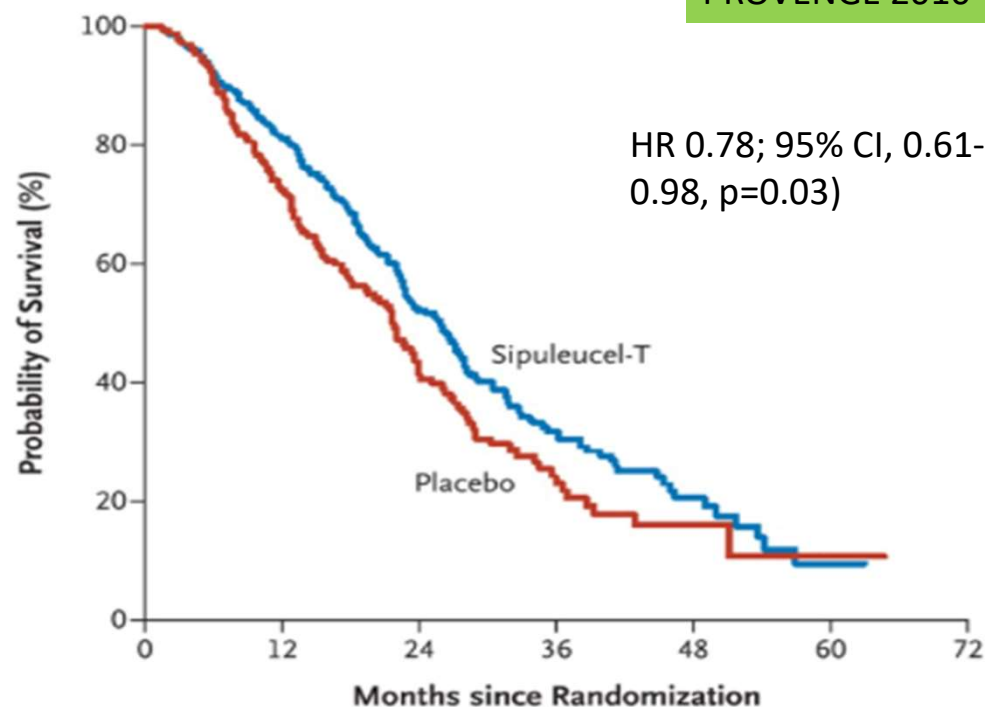
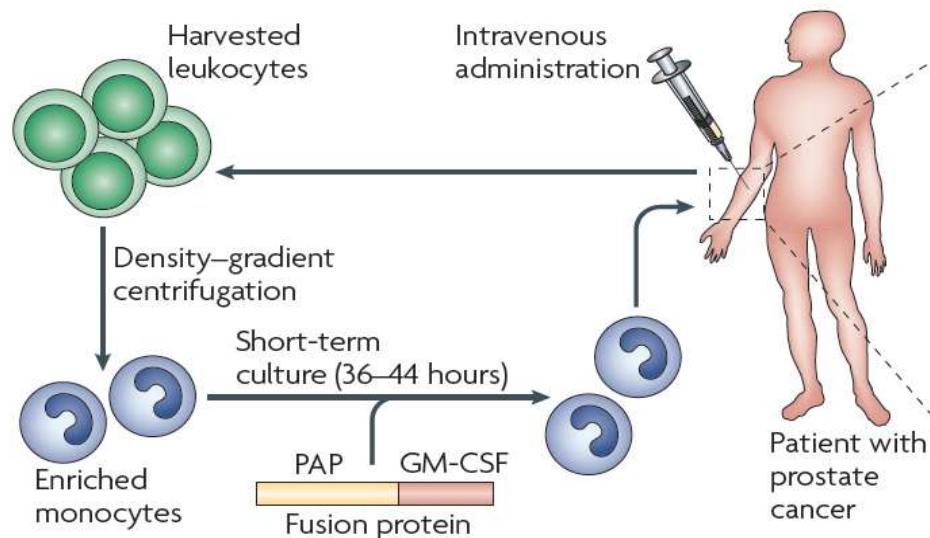
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Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

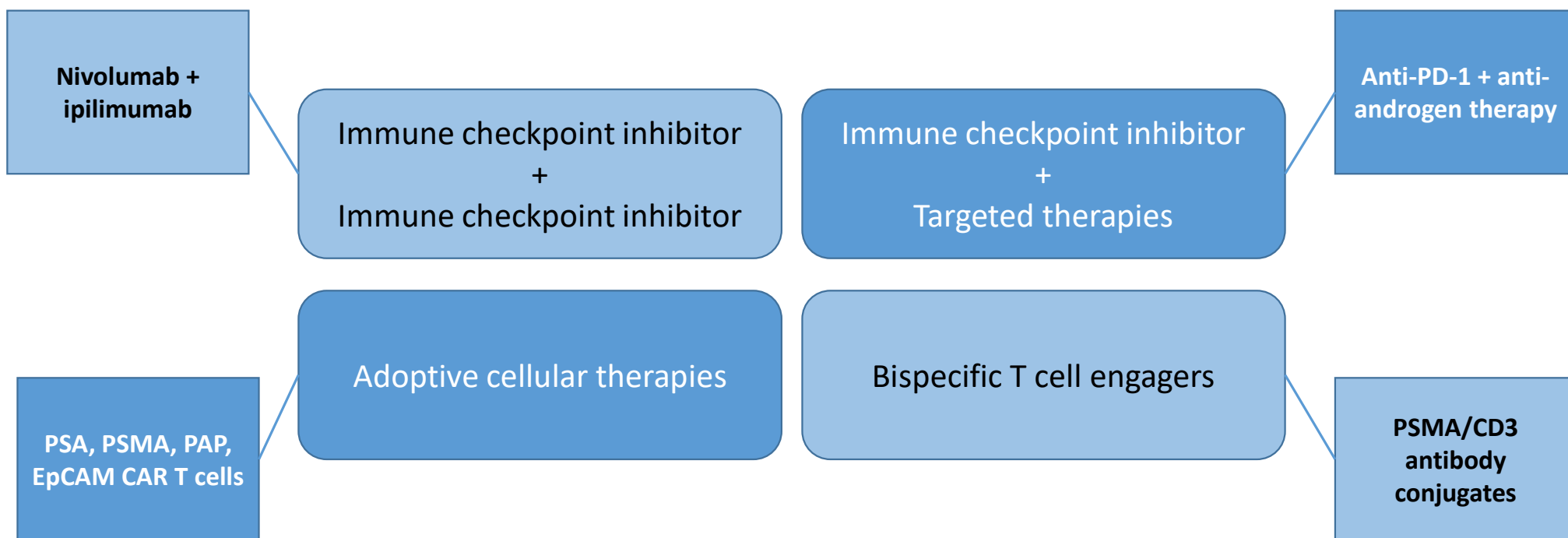


Drake et al. Curr Opin Urol 2010
 Kantoff et al. NEJM 2010

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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

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. Rini¹, Dena Battle², Robert A. Figlin³, Daniel J. George⁴, Hans Hammers⁵, Tom Hutson⁶, Eric Jonasch⁷,
 Richard W. Joseph⁸, David F. McDermott⁹, Robert J. Motzer¹⁰, Sumanta K. Pal¹¹, Allan J. Pantuck¹², David I. Quinn¹³,
 Virginia Seery⁹, Martin H. Voss¹⁰, Christopher G. Wood⁷, Laura S. Wood¹ and Michael B. Atkins^{14*}

Check for updates

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. McNeel¹, Neil H. Bander², Tomasz M. Beer³, Charles G. Drake⁴, Lawrence Fong⁵, Stacey Harrelson⁶,
 Philip W. Kantoff⁷, Ravi A. Madan⁸, William K. Oh⁹, David J. Peace¹⁰, Daniel P. Petrylak¹¹, Hank Porterfield¹²,
 Oliver Sartor¹³, Neal D. Shore⁶, Susan F. Slovin⁷, Mark N. Stein¹⁴, Johannes Vieweg¹⁵ and James L. Gulley^{16*}

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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 Bellmunt², Matthew D. Galsky³, Badrinath R. Konety⁴, Donald L. Lamm⁵,
 David Langham⁶, Cheryl T. Lee⁷, Matthew I. Milowsky⁸, Michael A. O'Donnell⁹, Peter H. O'Donnell¹⁰,
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