

Immunotherapy for the Treatment of Genitourinary Malignancies

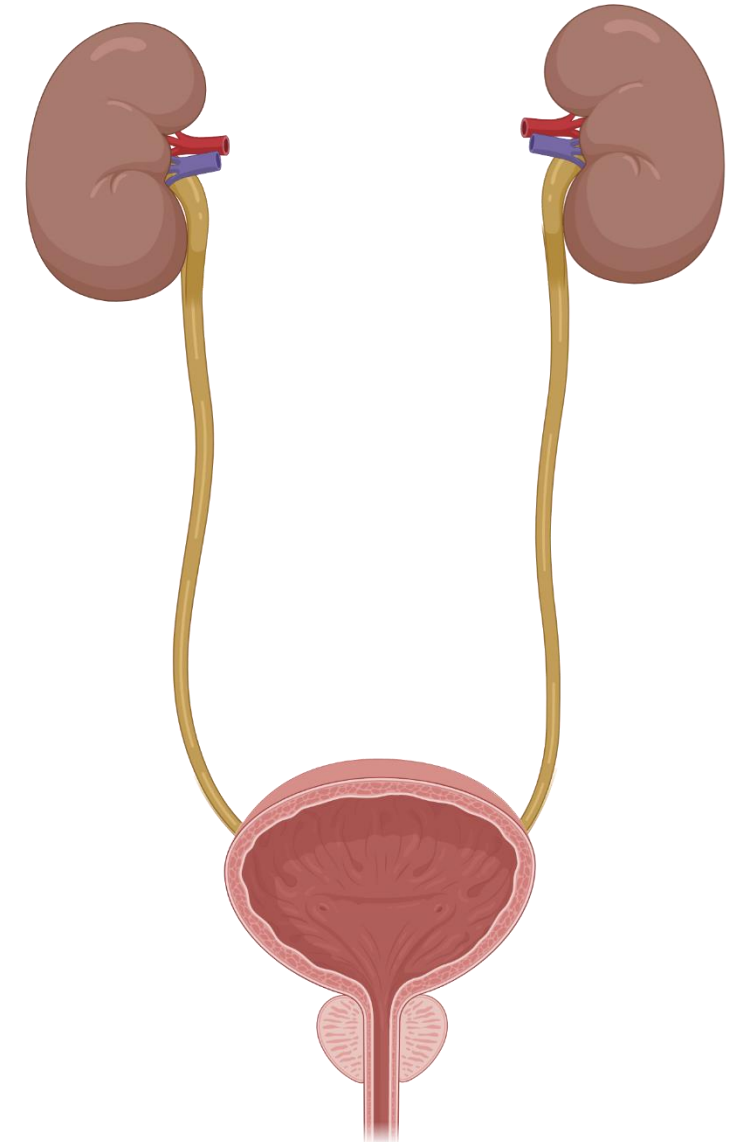
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Disclosures

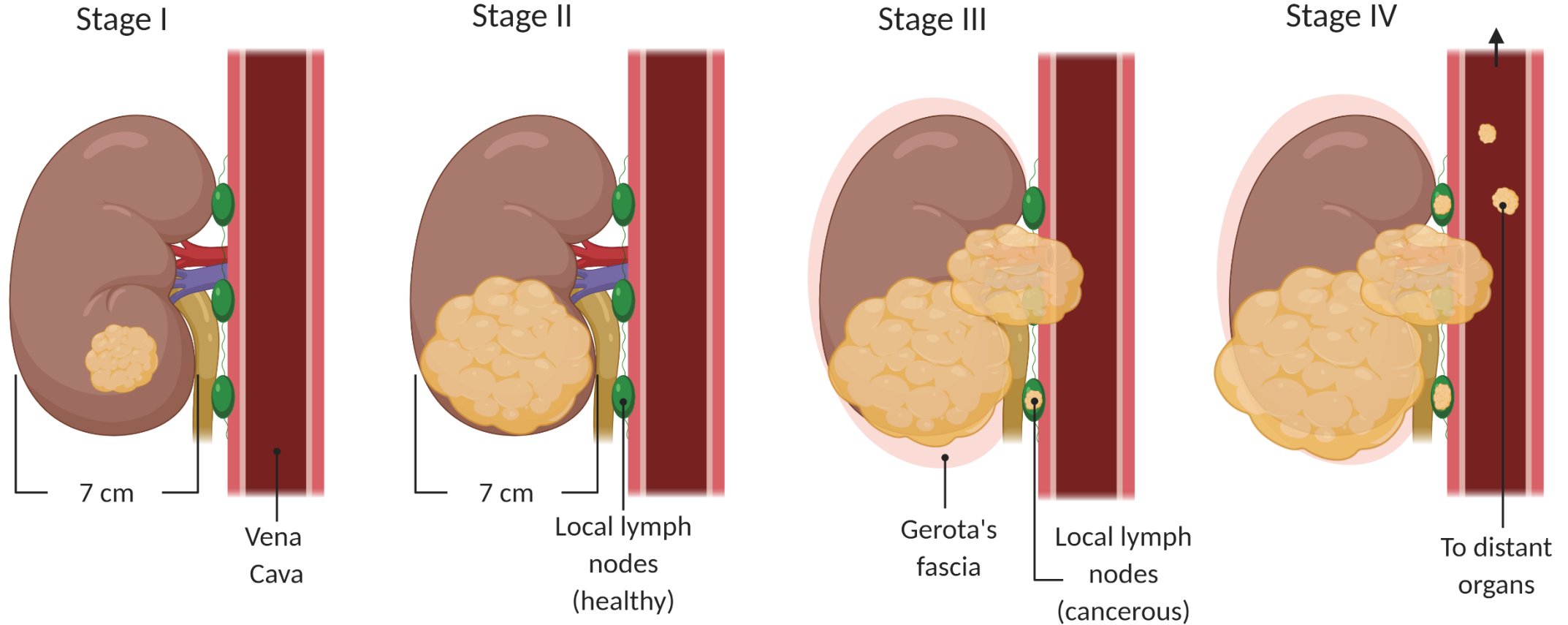
- Consulting Fees: Bayer Pharmaceuticals, Sanofi-Genzyme
- I will be discussing non-FDA approved indications during my presentation.

Outline

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

*FDA-approved IO regimen

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

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Front-line immunotherapy treatments for RCC

Study	Treatment arm(s)	Patient selection criteria	N	ORR	Median PFS (months)	Median OS (months)
CLEAR	Pembrolizumab + lenvatinib	Untreated, advanced RCC with a clear cell component	355	71%	23.9	NR
	Lenvatinib + everolimus		357	53.5%	14.7	NR
	Sunitinib		357	36.1%	9.2	NR
CheckMate 9ER	Nivolumab + cabozantinib*	Untreated, advanced RCC with a clear cell component	323	55.7%	16.6	NR
	Sunitinib		328	27.1%	8.3	NR

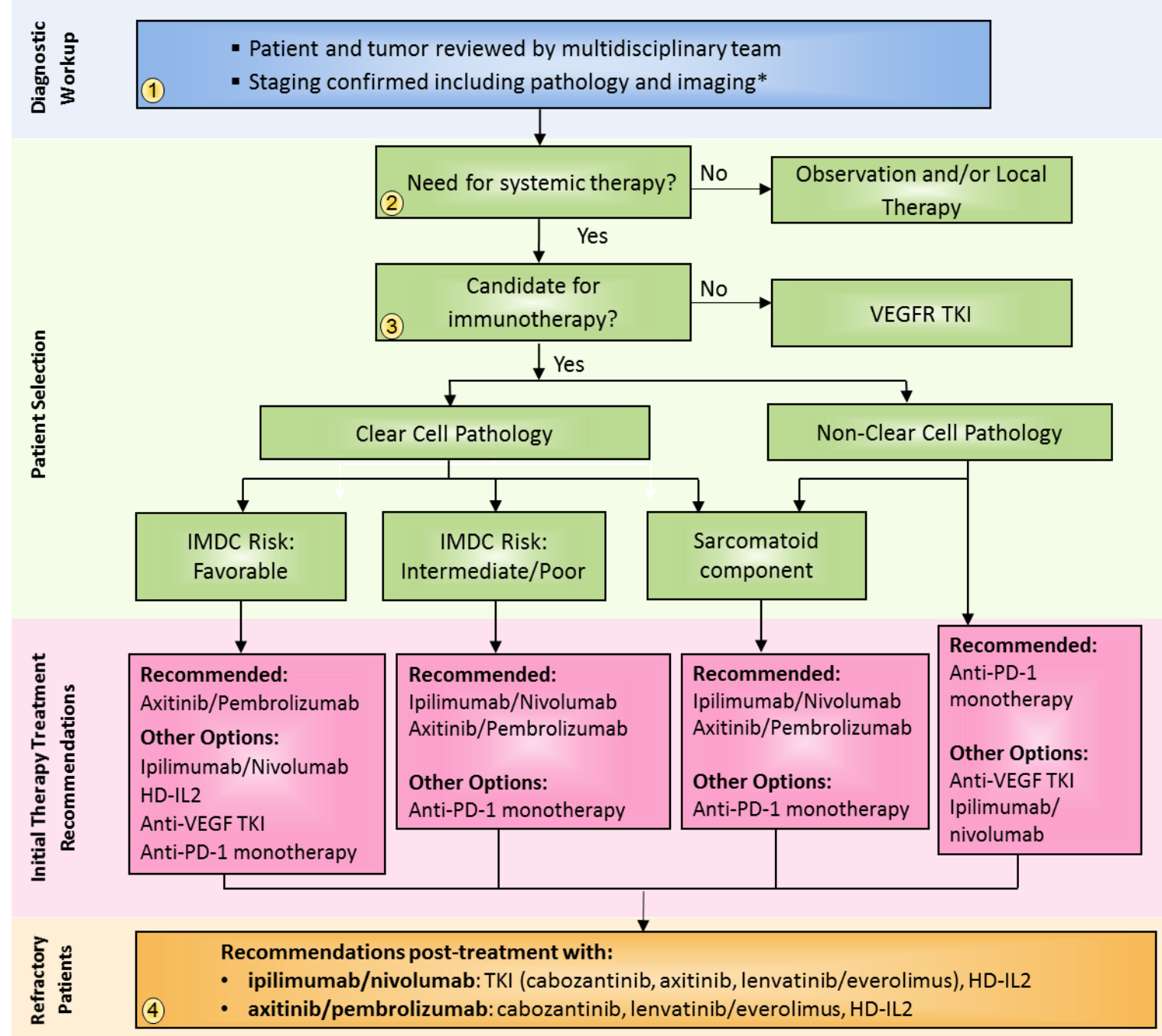
*FDA-approved IO regimen

Motzer, NEJM. April 2021
 Choueiri, NEJM. March 2021

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SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma

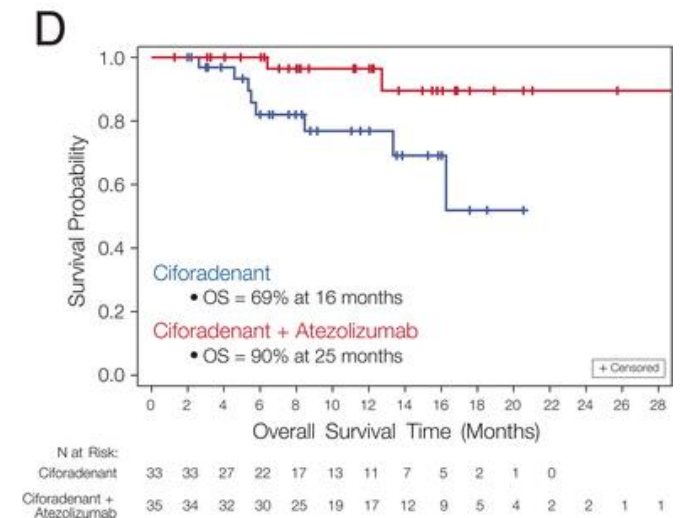
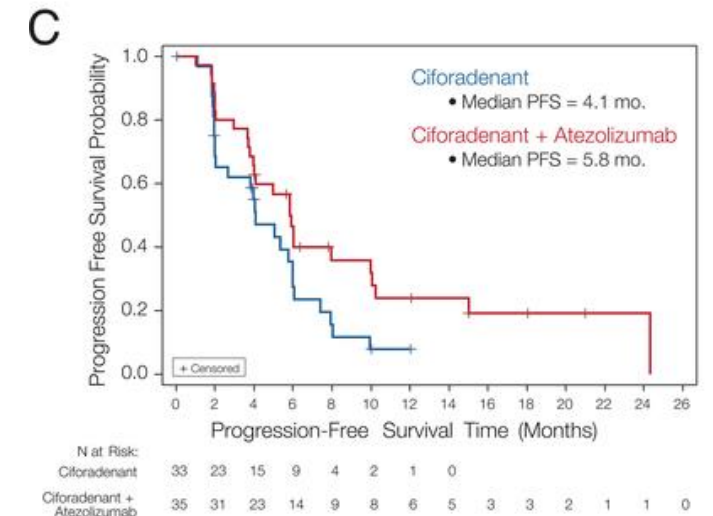


*Baseline imaging recommendations discussed in figure legend.

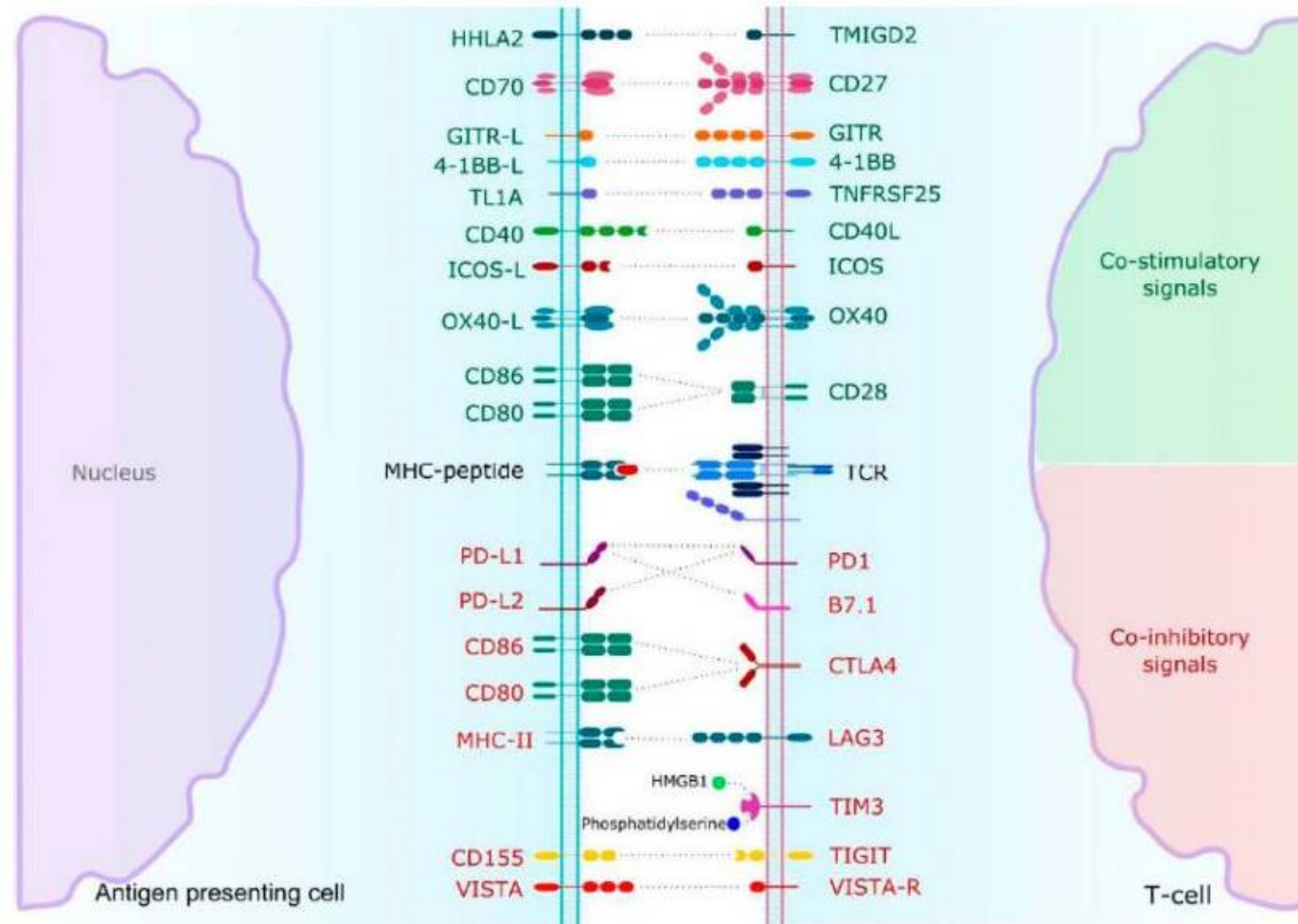
Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.

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%

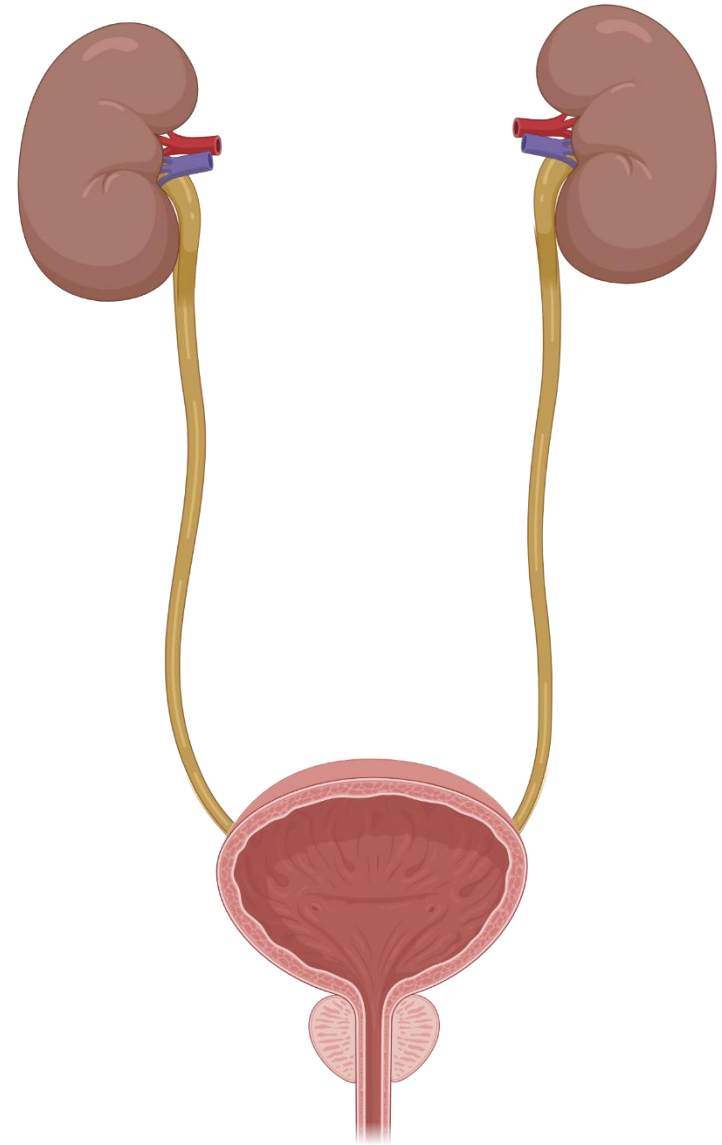


In development: additional immunotherapy approaches

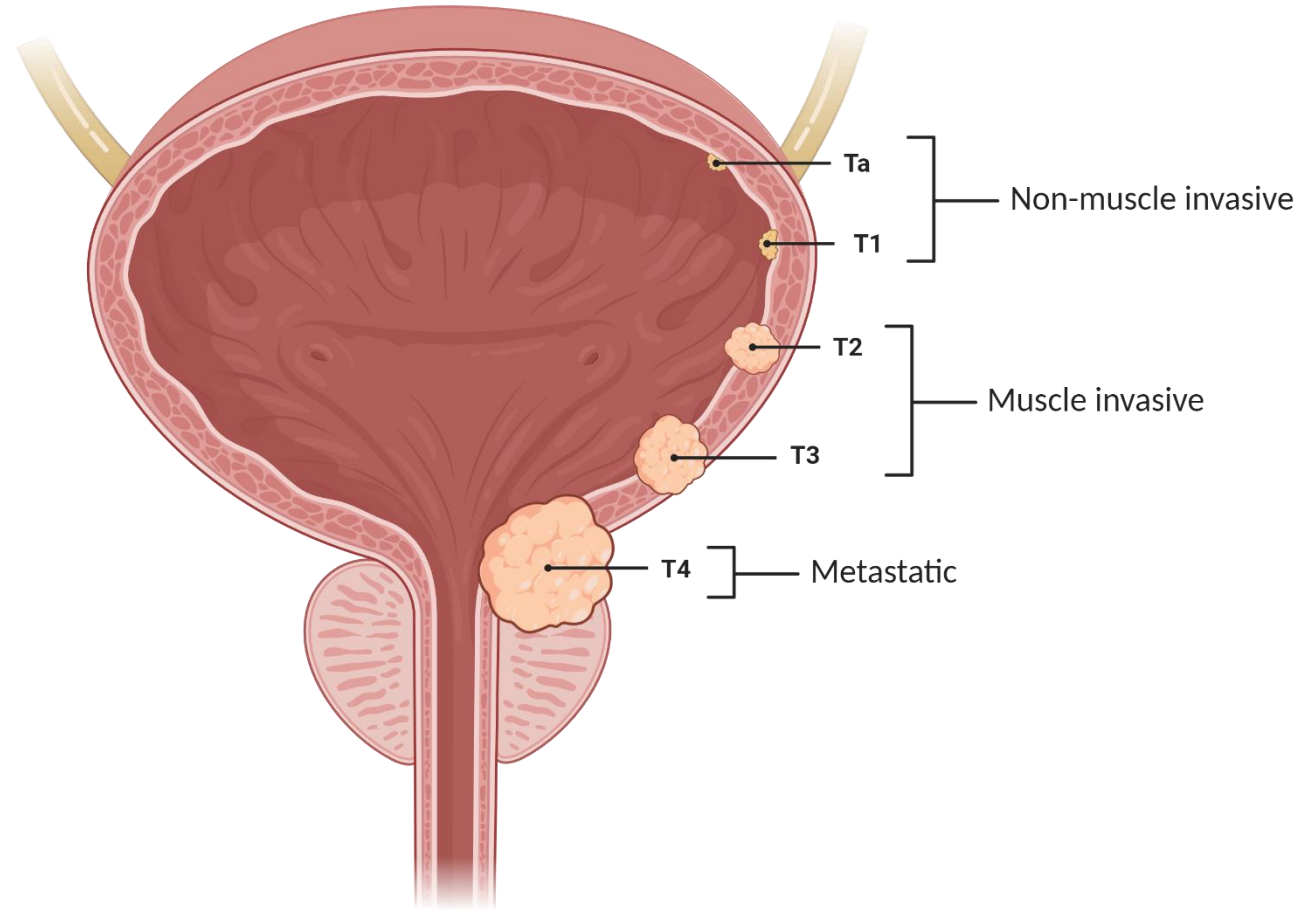


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Urothelial carcinoma (UC)



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)

Approved checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Indication	Dose
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

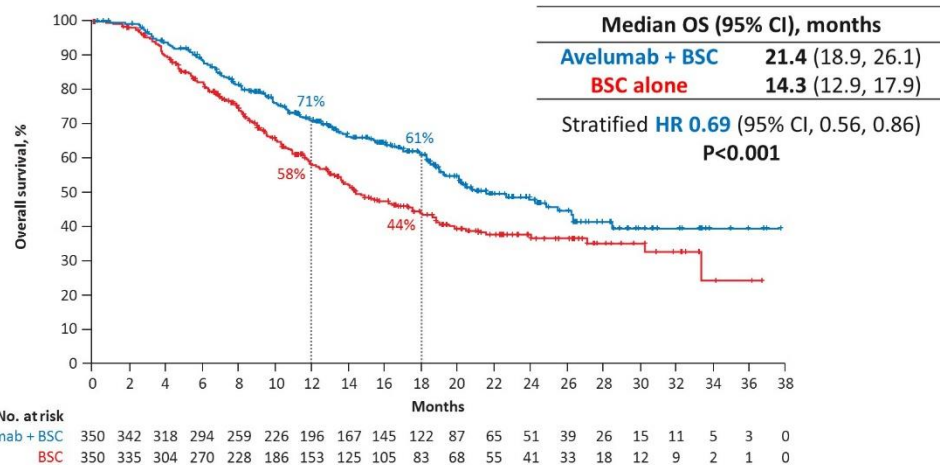
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- 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

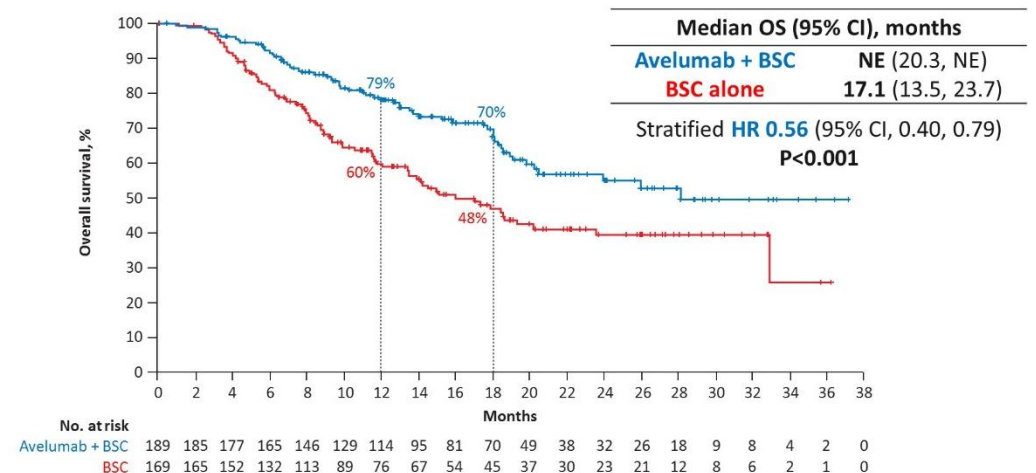
Approved checkpoint inhibitor for maintenance treatment

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



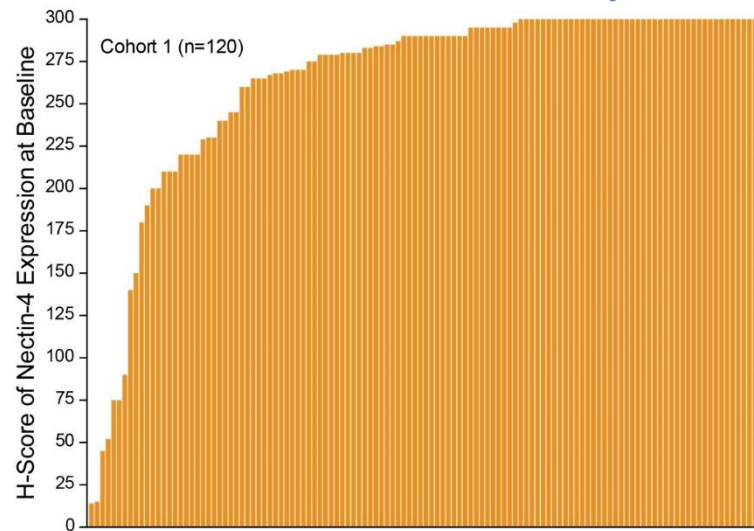
OS in the PD-L1+ population



Approved antibody-drug conjugate for mUC

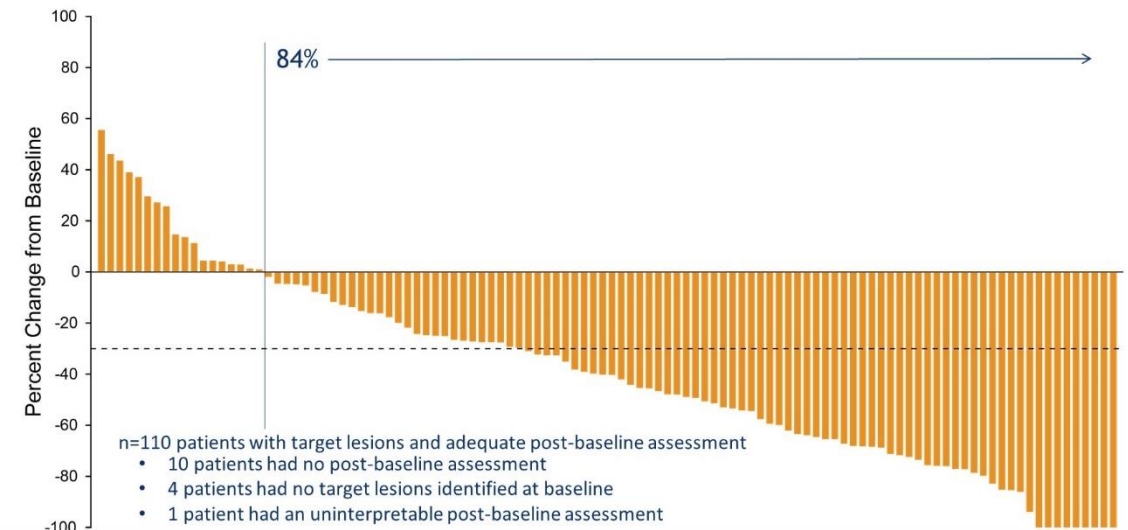
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metastatic UC with previous αPD-1/PD-L1 and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



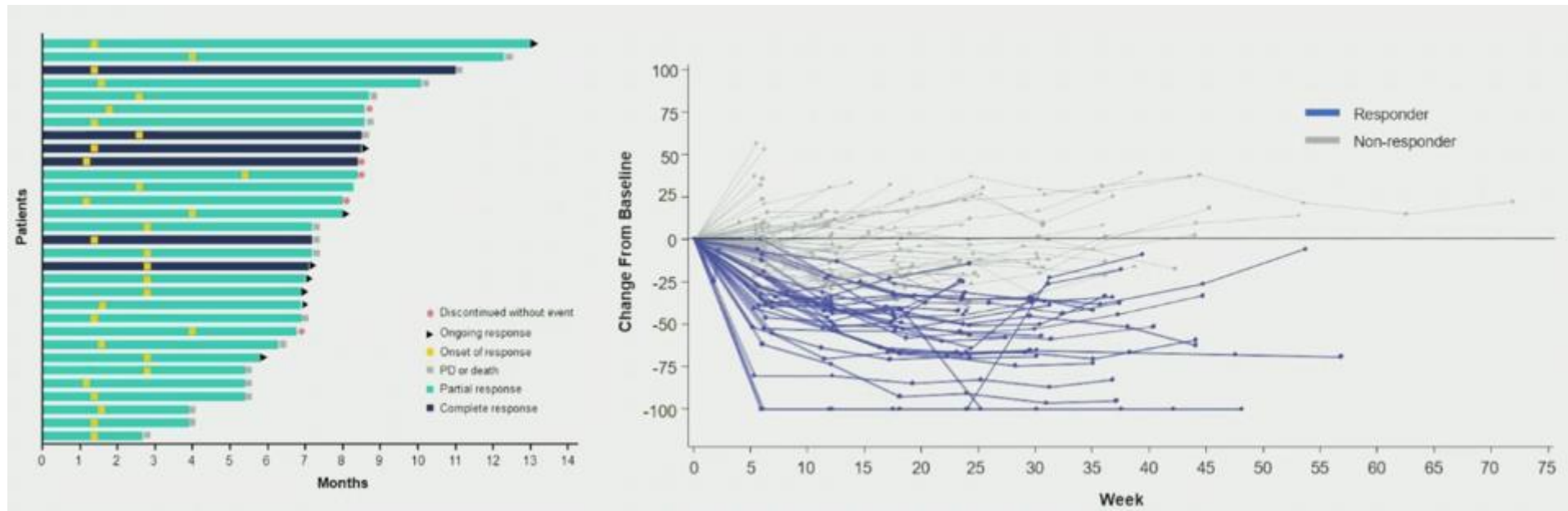
¹ Five patients did not have adequate tissue for Nectin-4 testing

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



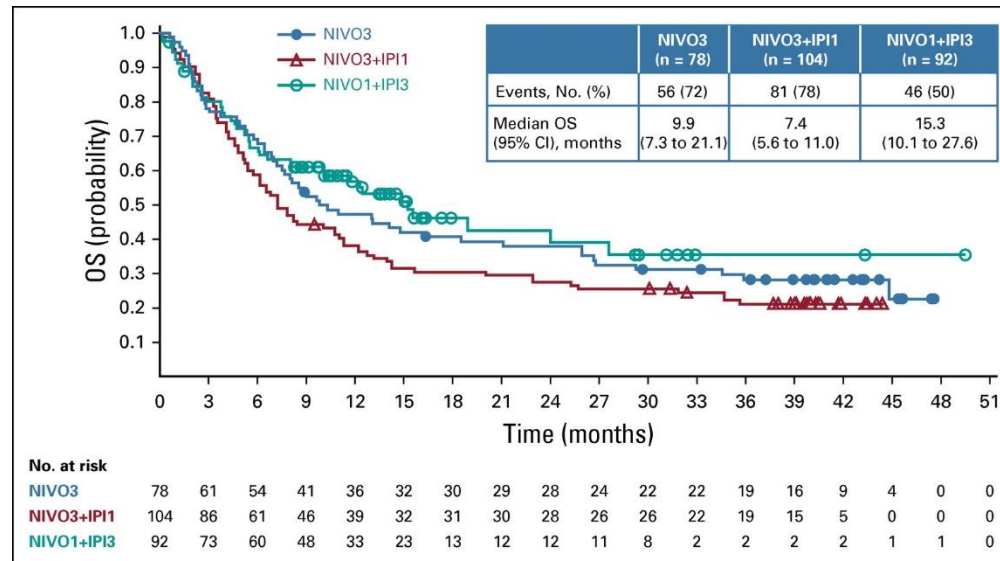
Approved antibody-drug conjugate for mUC

Drug	Indication	Dose
Sacituzumab govitecan	Locally advanced/metastatic UC with previous αPD-1/PD-L1 and Pt-based chemotherapy	10 mg/kg IV on days 1 and 8 of each 21-day cycle



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%

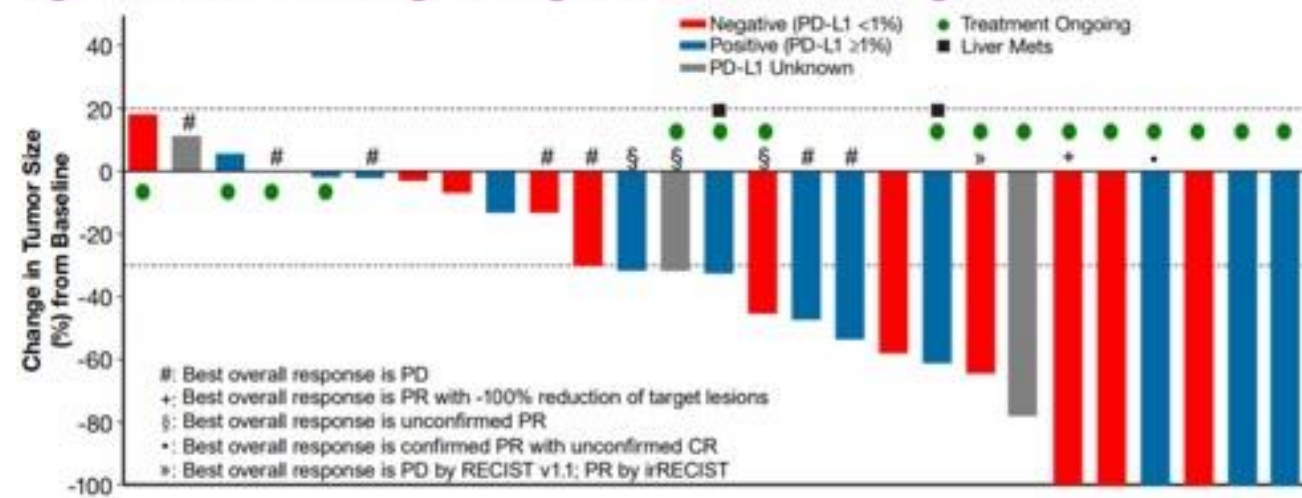


In development: NKTR-214 + nivolumab

Treatment	n	ORR
NKTR-214 + nivolumab	27	48%

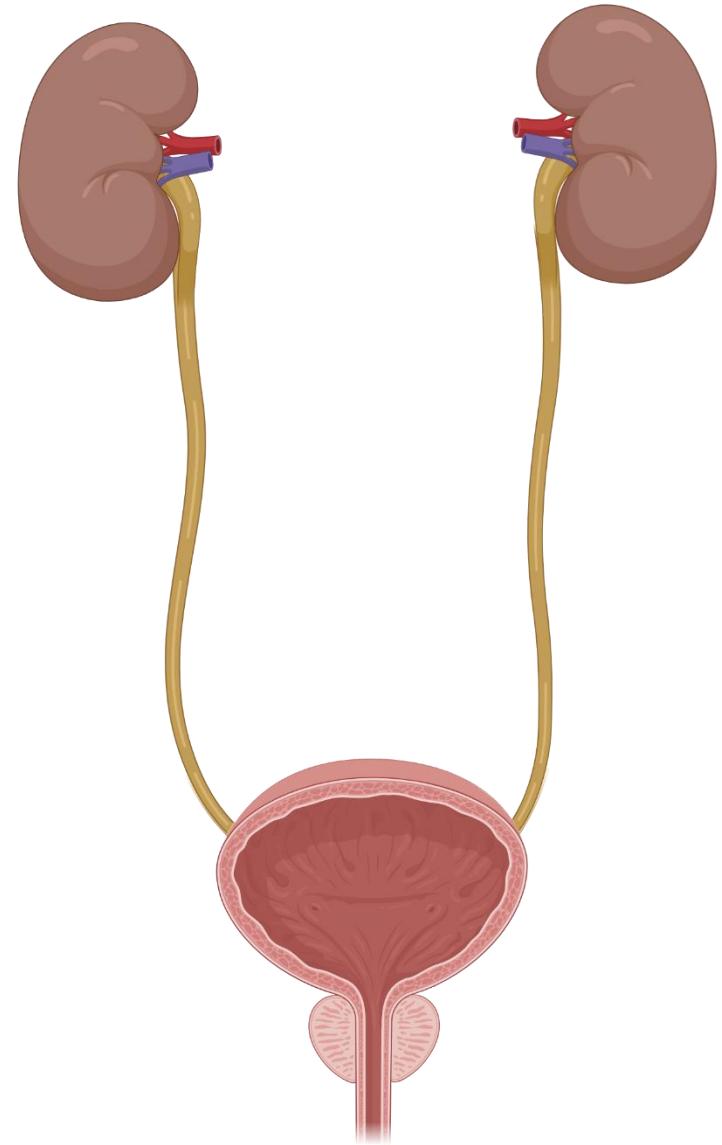
After treatment, 70% of patients with PD-L1-negative tumors converted to PD-L1-positive.

Figure 2. Best Percentage Change from Baseline in Target Lesions

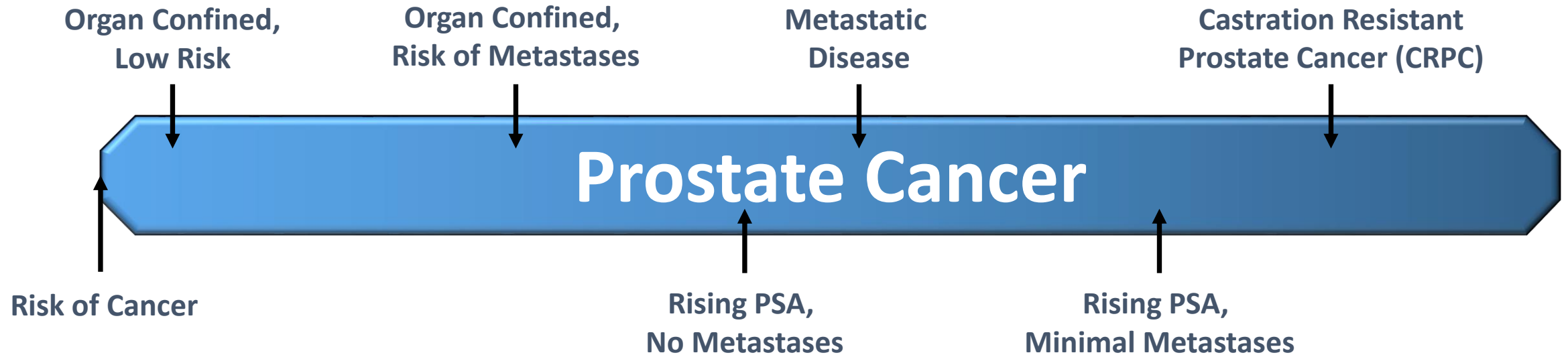


Outline

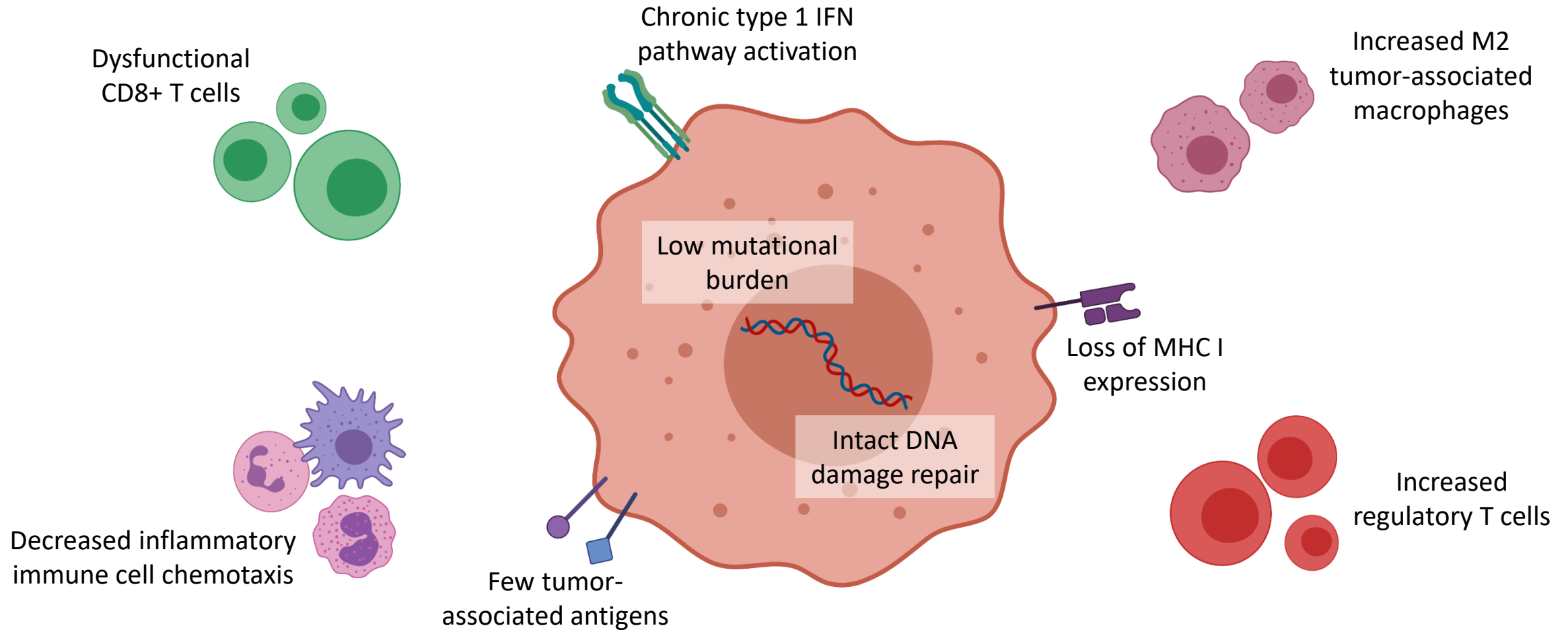
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The Spectrum of Prostate Cancer



Immunology of prostate cancer



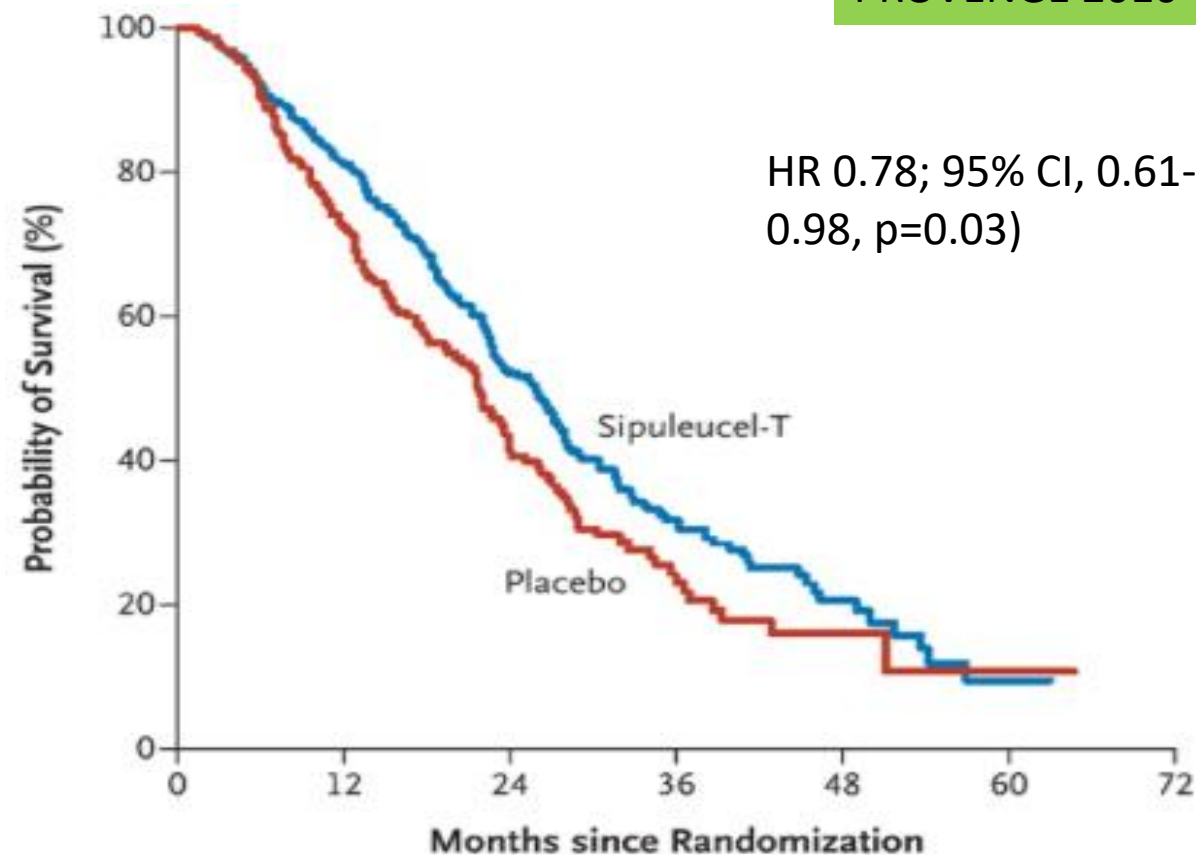
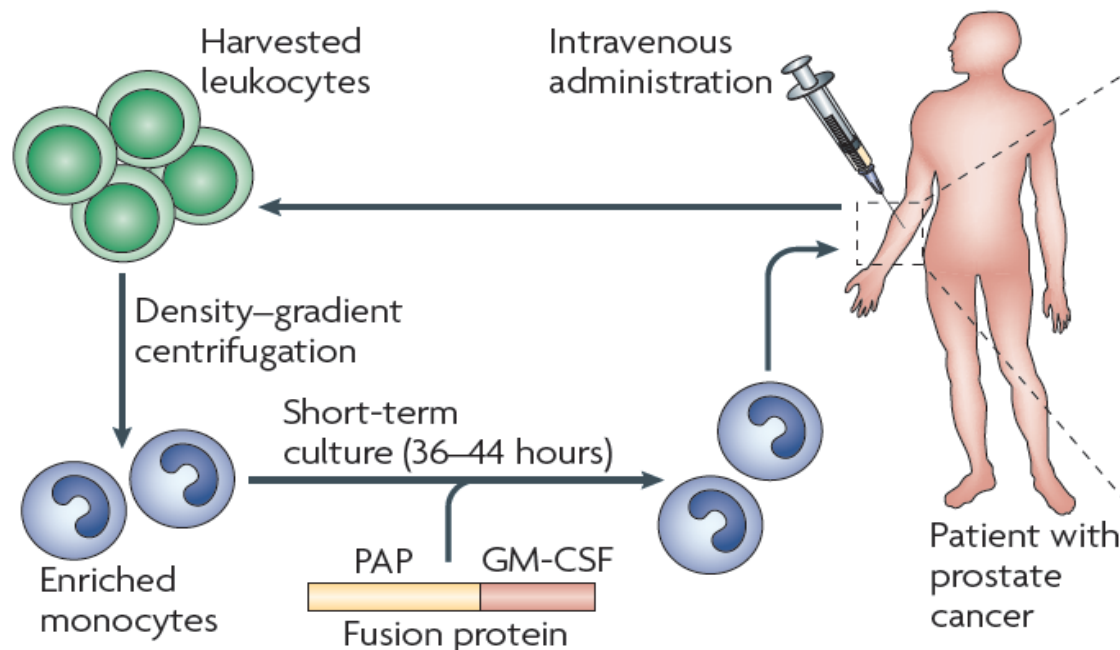
Immunotherapy landscape in prostate cancer

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		

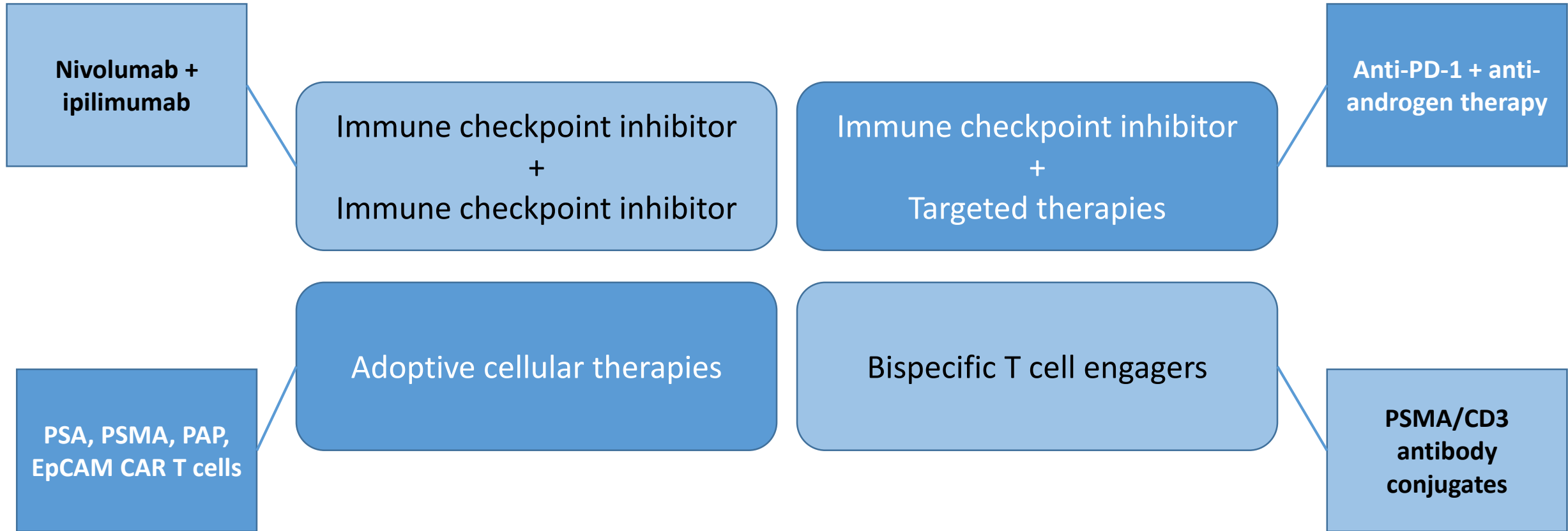
Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine



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)

Check for updates

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*}

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

CrossMark

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*}

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

CrossMark

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, Daniel P. Petrylak¹¹, Padmanee Sharma¹², Eila C. Skinner¹³, Guru Sonpavde¹⁴, John A. Taylor III¹⁵, Prasanth Abraham¹⁶ and Jonathan E. Rosenberg¹⁷

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Acknowledgements

- Some figures created using biorender.com

Case Studies

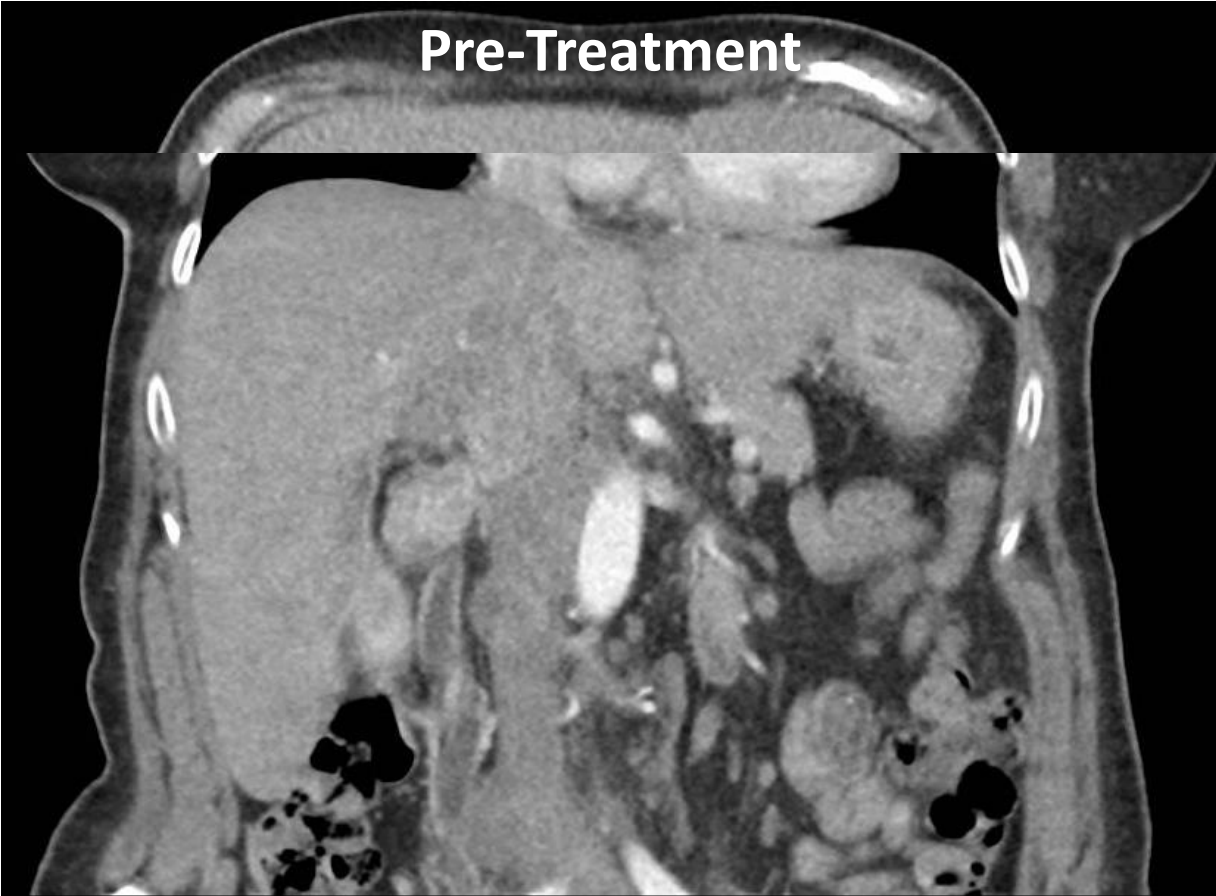
Case 1: A 68 year old female presents with biopsy-proven 10 cm clear cell renal cell carcinoma of the right kidney with tumor invading to the IVC to the level of the right atria, right retroperitoneal adenopathy, and multiple lytic bone lesions. MRI Brain is negative for CNS metastasis. She is IMDC intermediate risk due to anemia and need for treatment. She has a history of multinodular goiter and hypertension which is well controlled. What would you recommend for treatment?

- A. Sunitinib**
- B. Cabozantinib**
- C. Ipilimumab + nivolumab**
- D. Pembrolizumab + axitinib**
- E. Avelumab + axitinib**
- F. Nivolumab + cabozantinib**
- G. Pembrolizumab + lenvatinib**

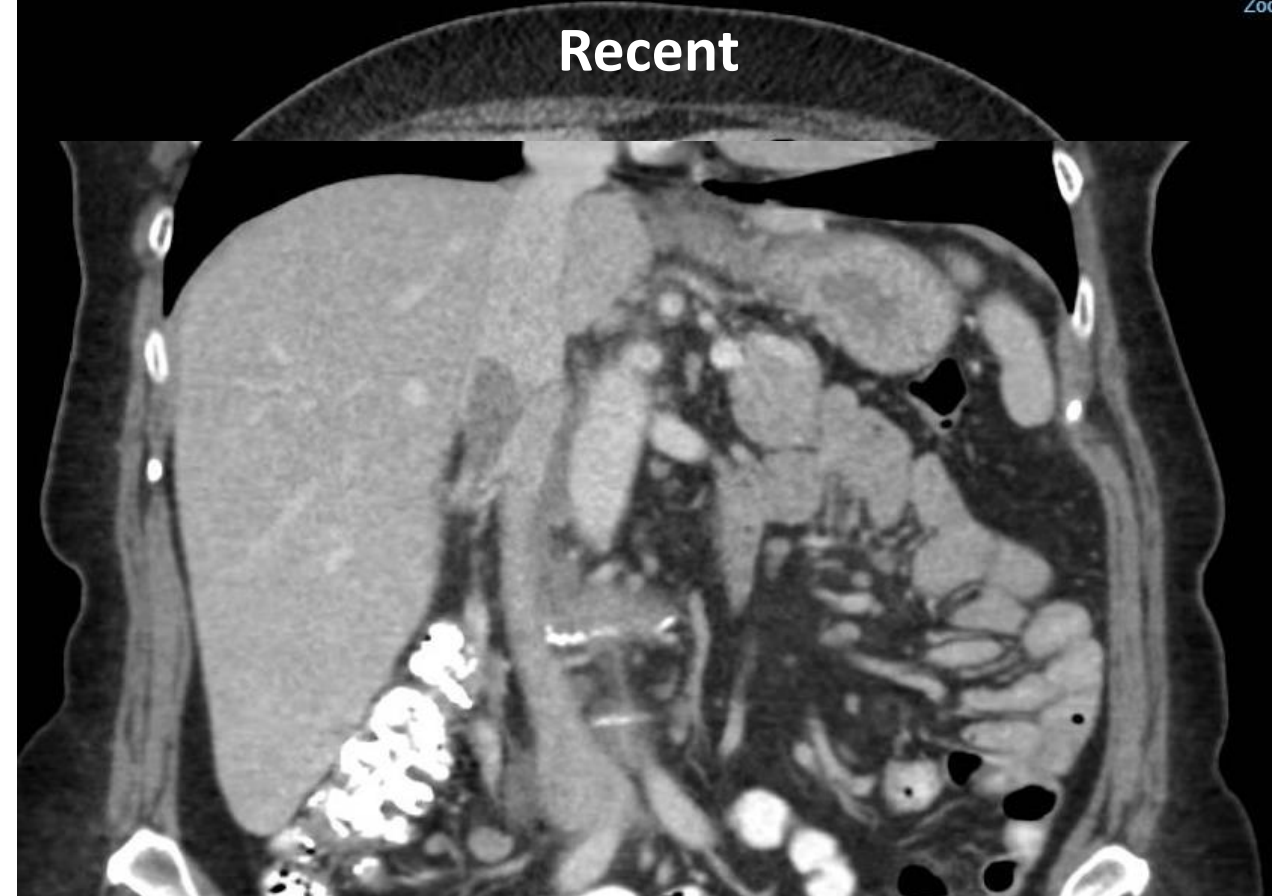
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Pre-Treatment



Recent



Case 2: A 63 year old female with a history of metastatic urothelial carcinoma presents for follow up 3 months after completing 6 cycles of carboplatin and gemcitabine with partial response now with progressing disease in mediastinal and cervical lymph nodes and bones. She has a history of autoimmune hepatitis previously on azathioprine and currently managed with budesonide. What treatment would you recommend?

- A. Paclitaxel**
- B. Pembrolizumab**
- C. Atezolizumab**
- D. Enfortumab vedotin**
- E. Sacituzumab-govitecan**