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

Outline

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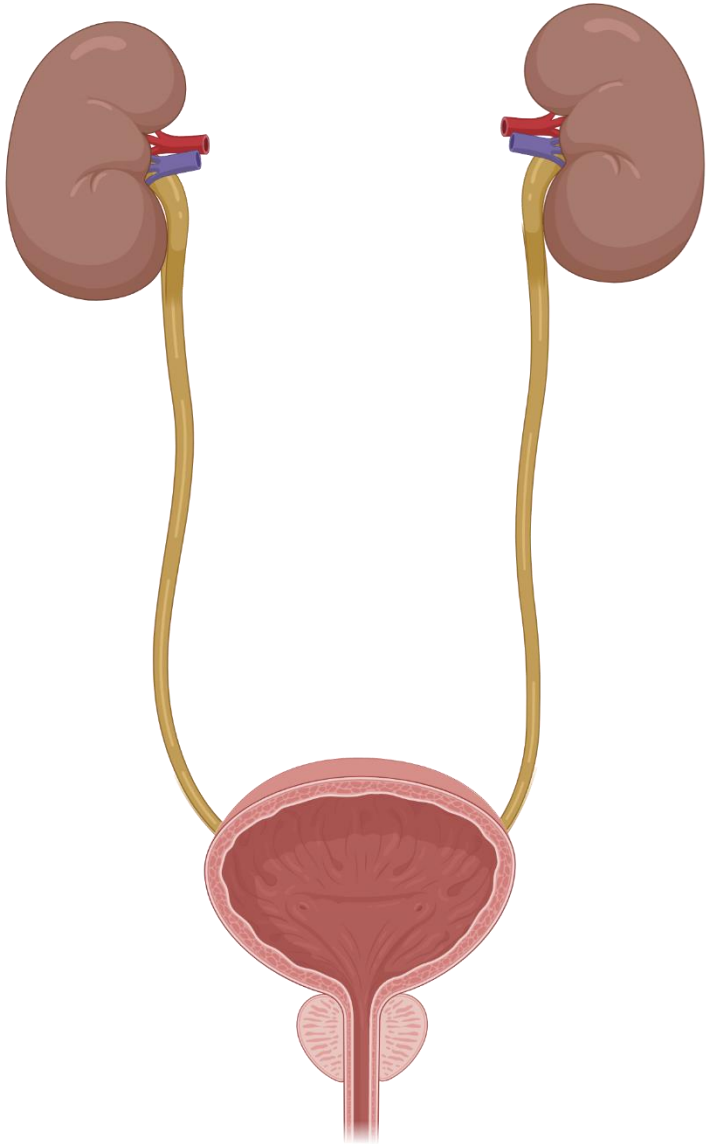
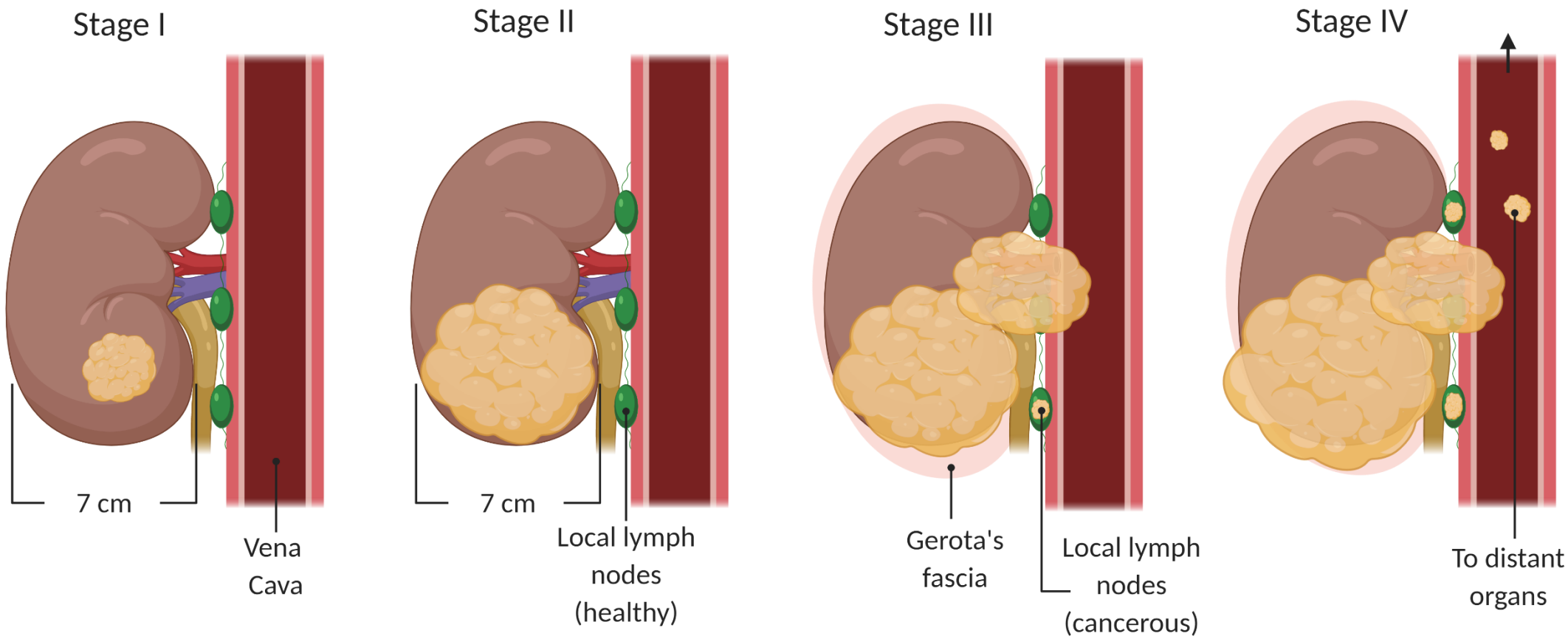
- Prostate cancer
  - Approved immunotherapies
  - Future directions



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

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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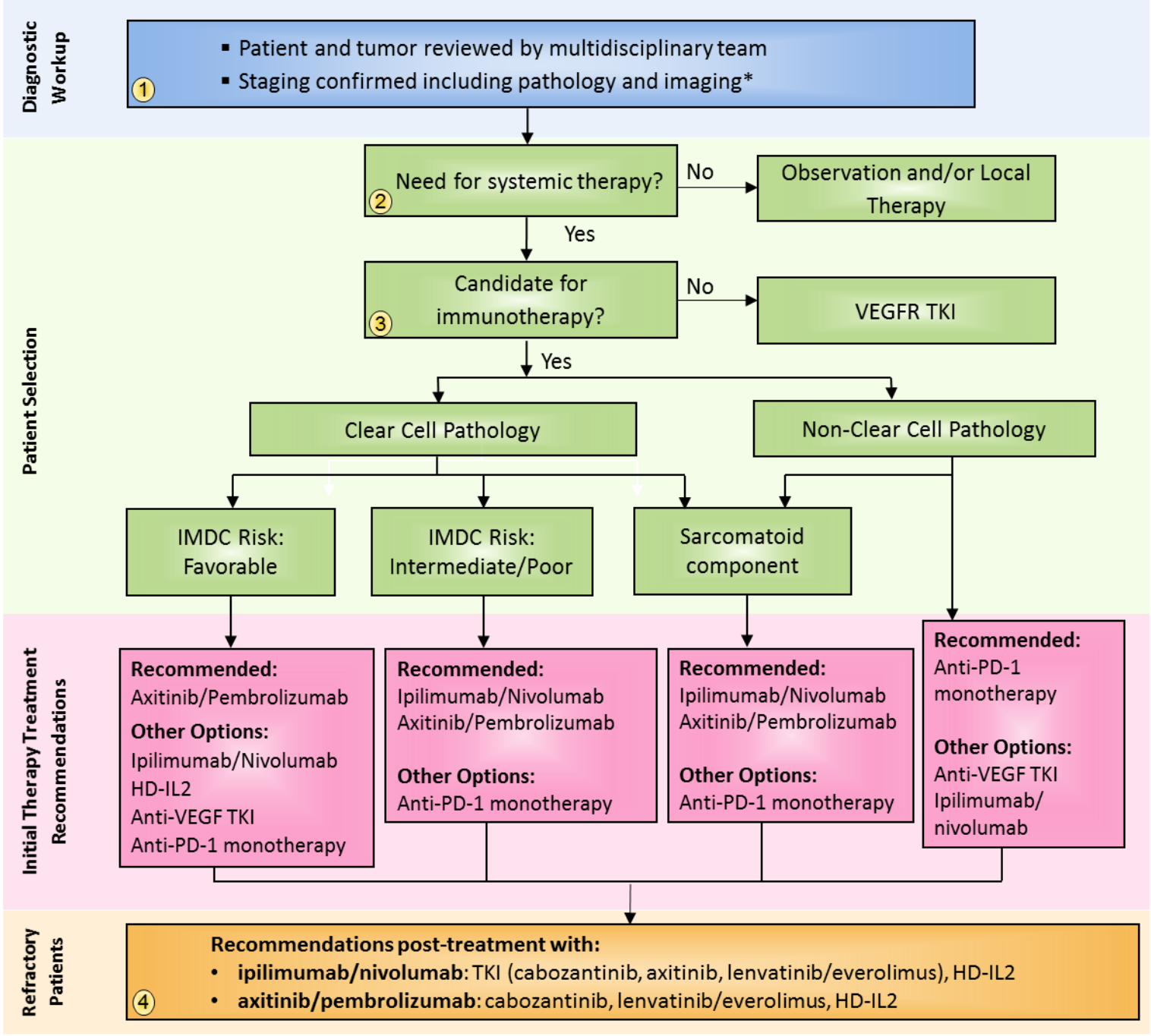
SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma



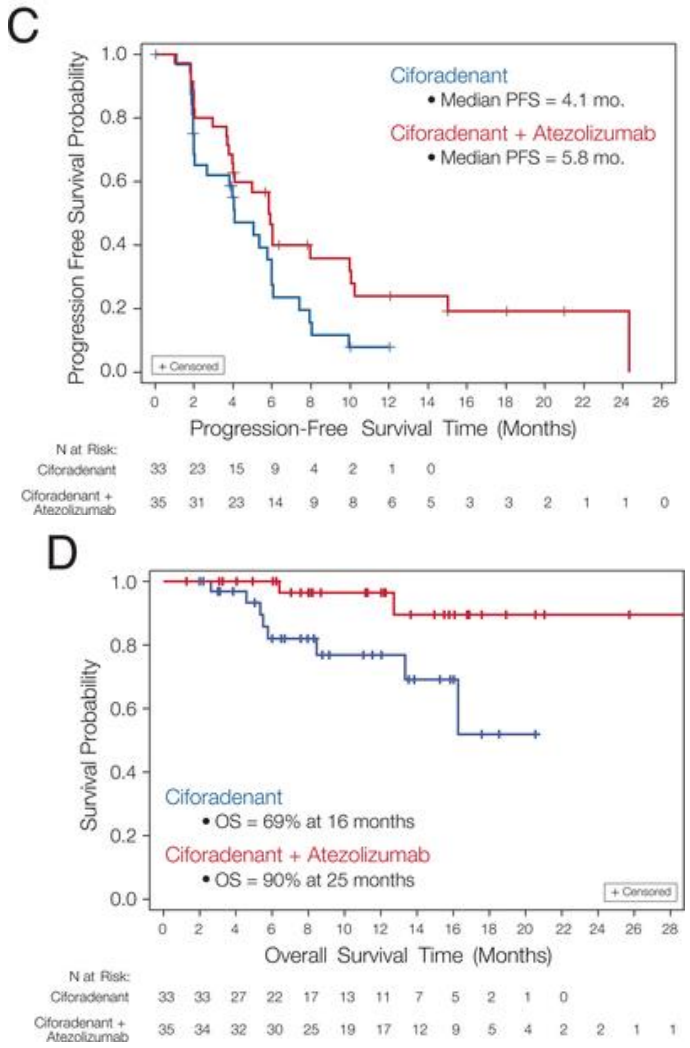
*Baseline imaging recommendations discussed in figure legend.

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.

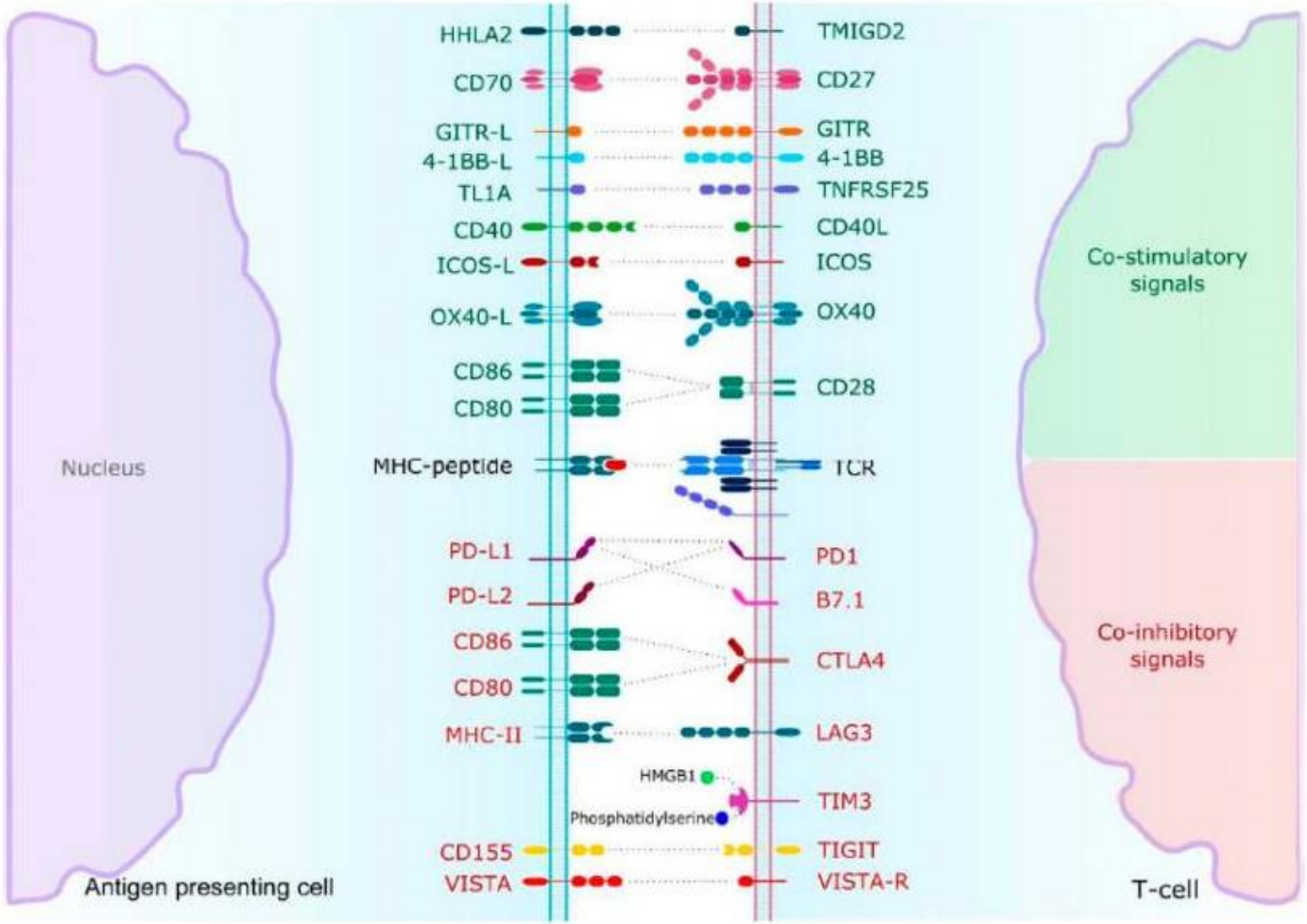
In development: A2AR antagonist + anti-PD-L1

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

In development: additional immunotherapy approaches



Deleuze, Int J Mol Sci 2020

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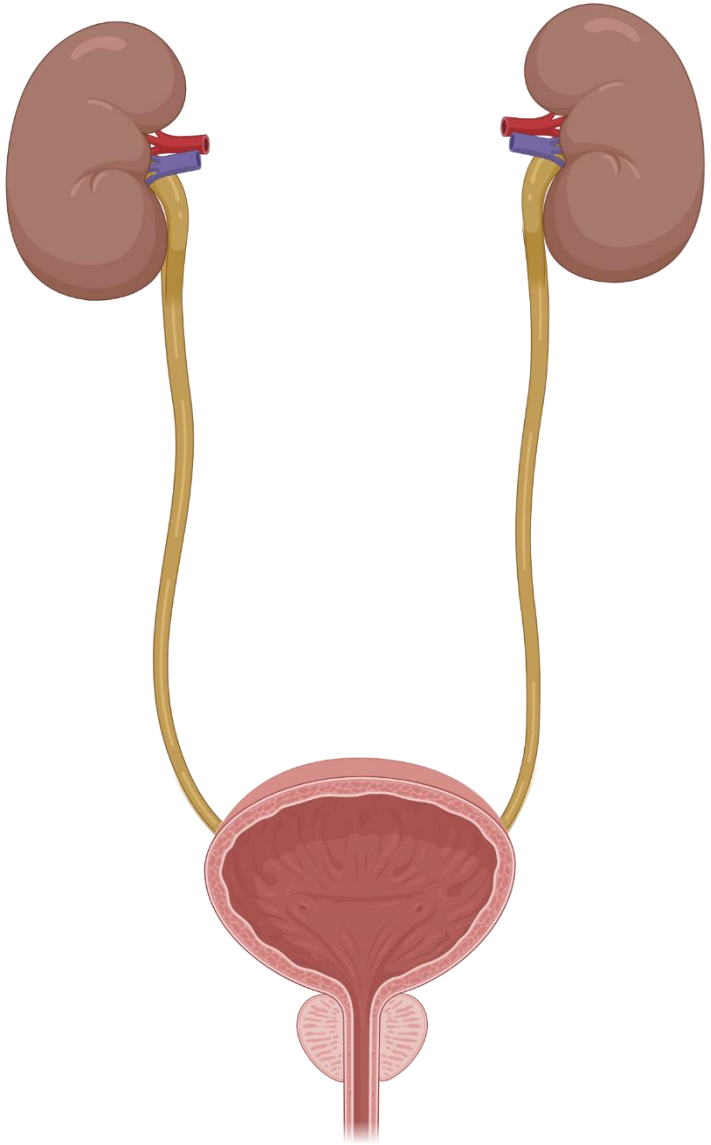
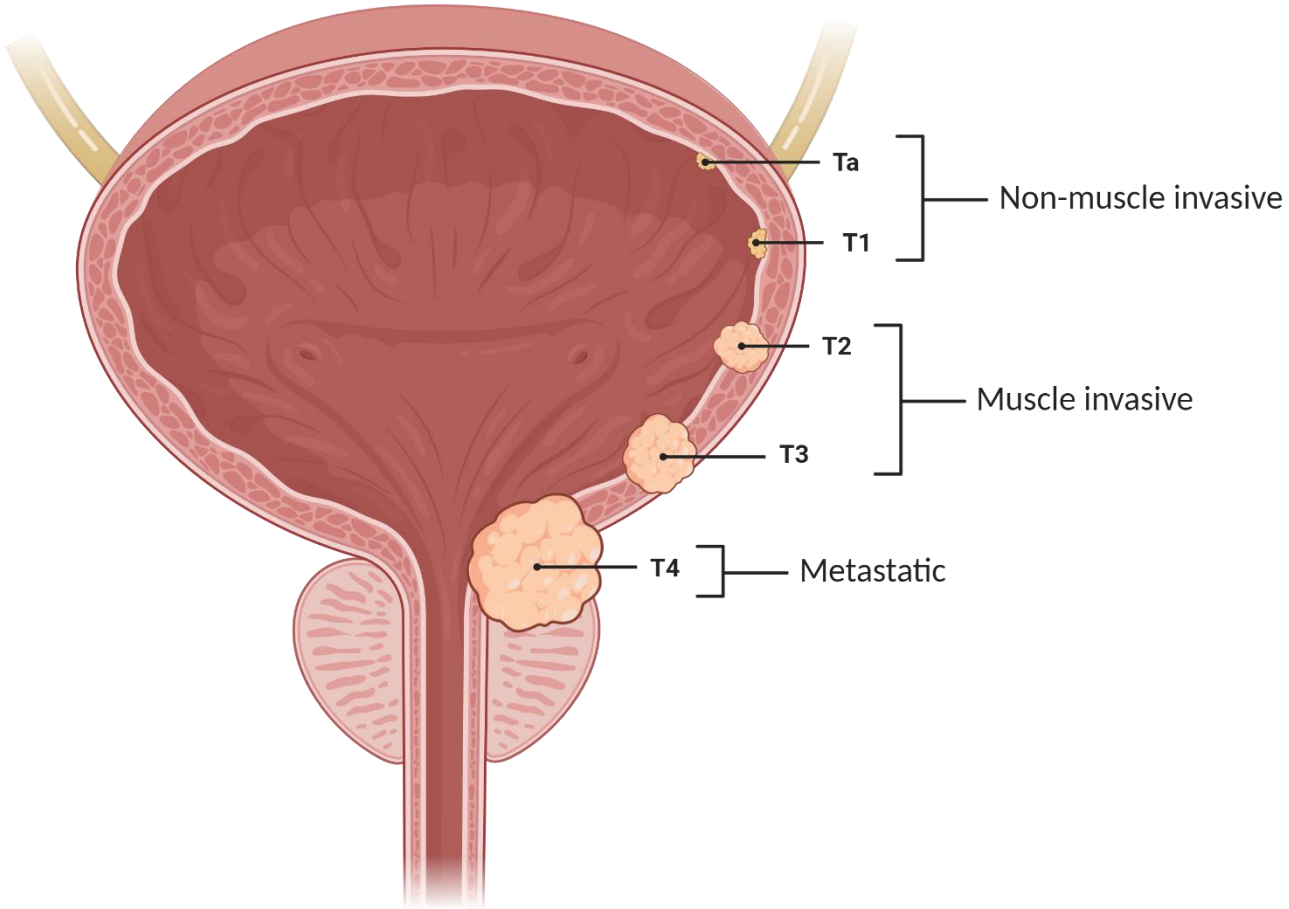


Urothelial carcinoma (UC)



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
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

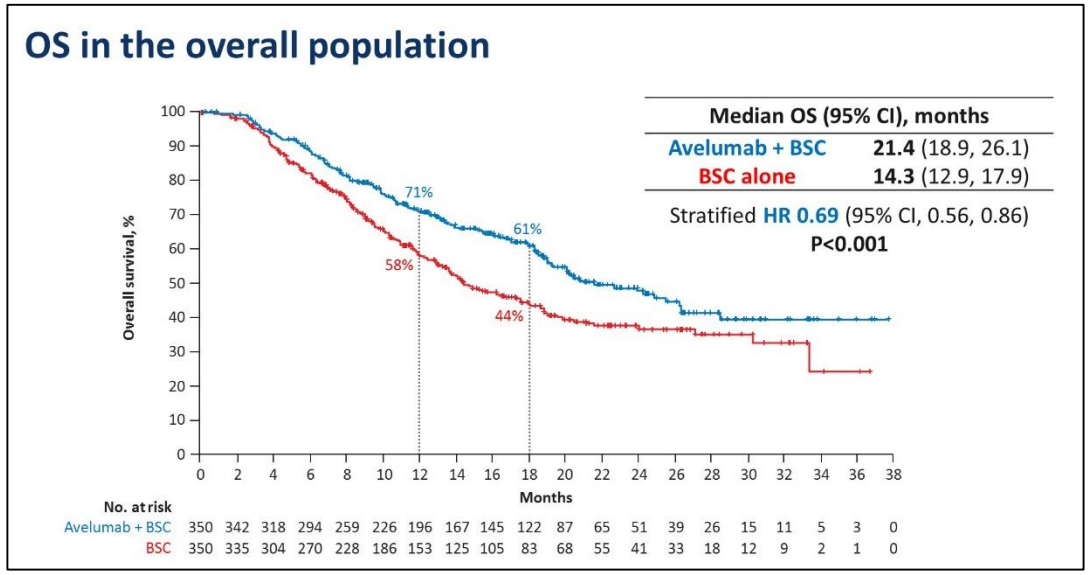
June 2018

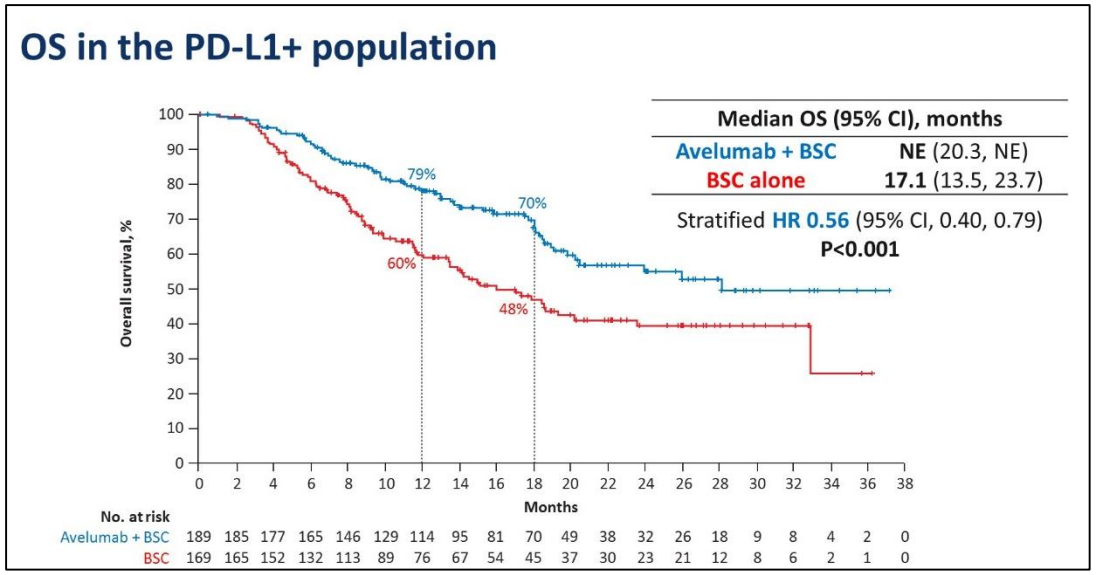
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- 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



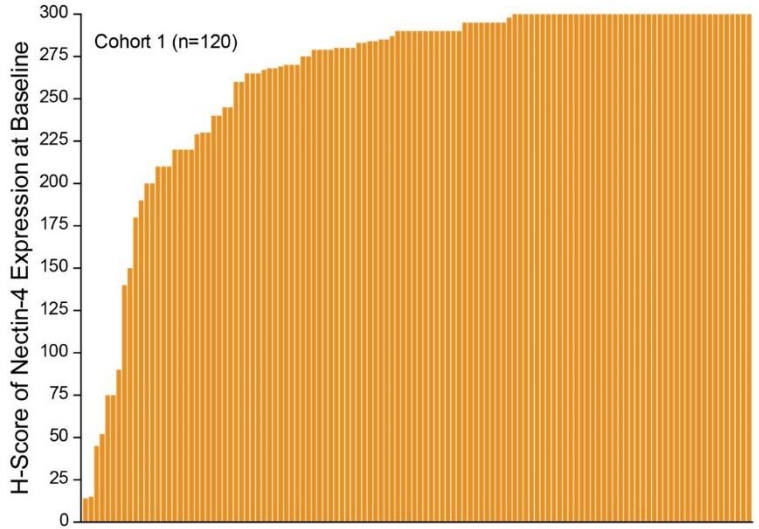


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

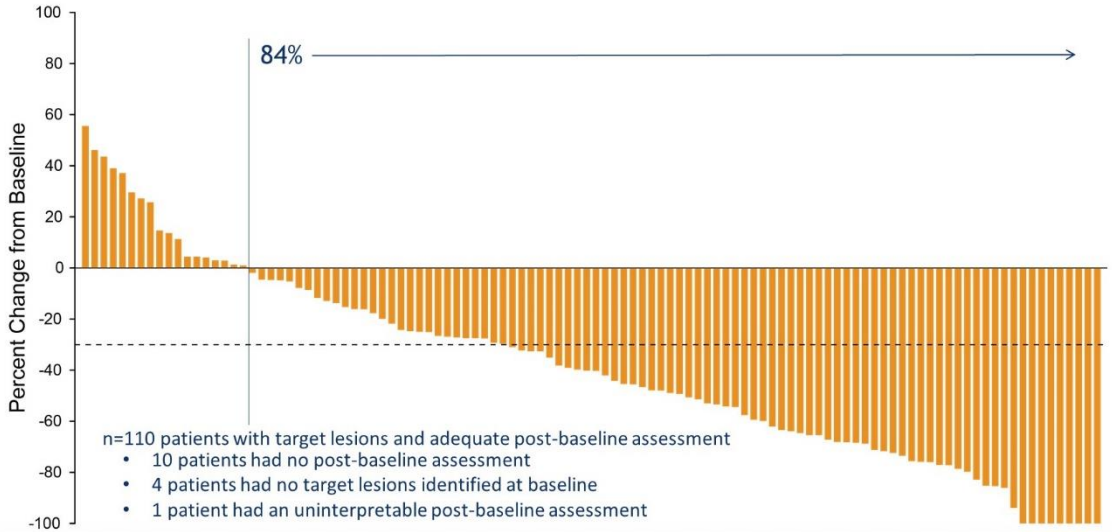
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

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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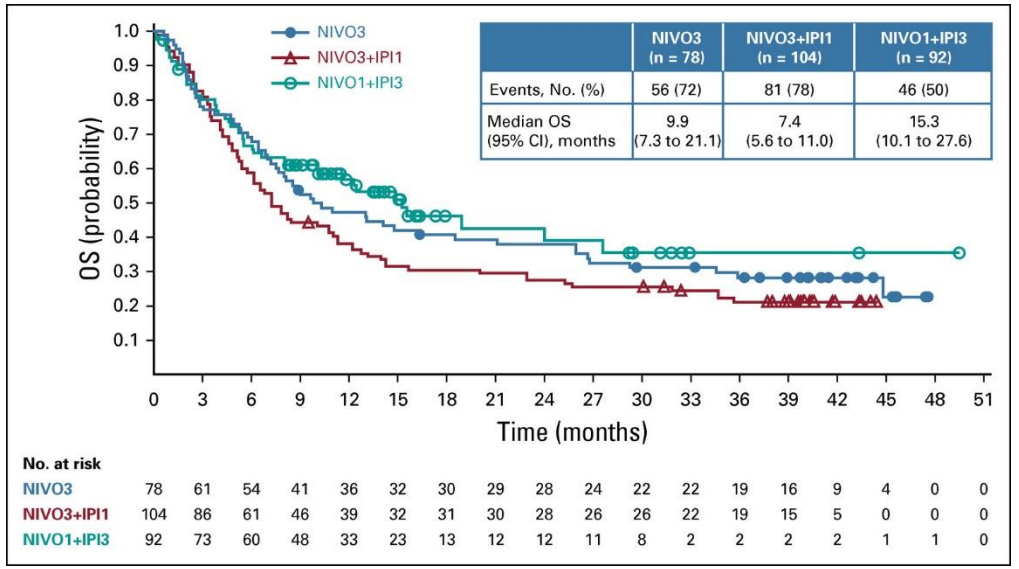
In development: Ipilimumab + Nivolumab CheckMate 032

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%

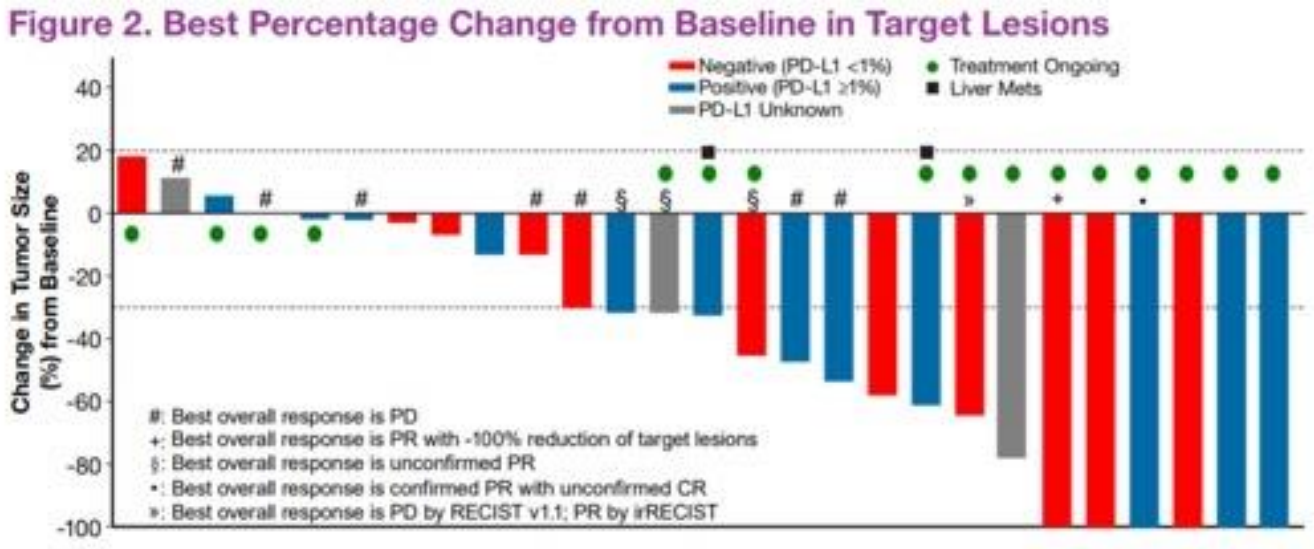


Sharma, J Clin Oncol 2019.

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.

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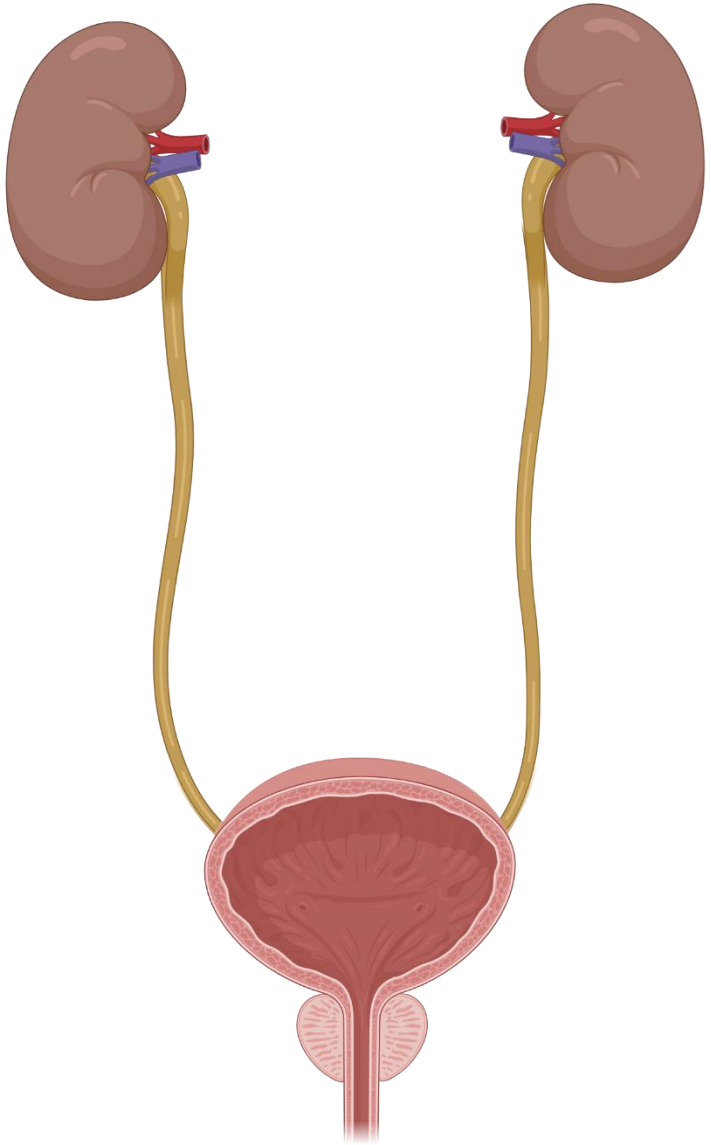
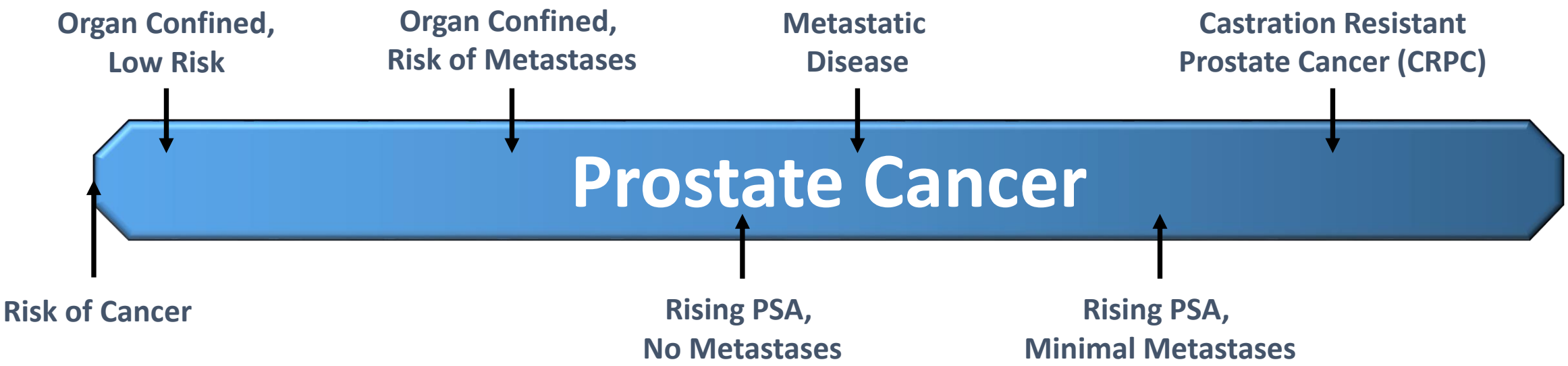


The Spectrum of Prostate Cancer



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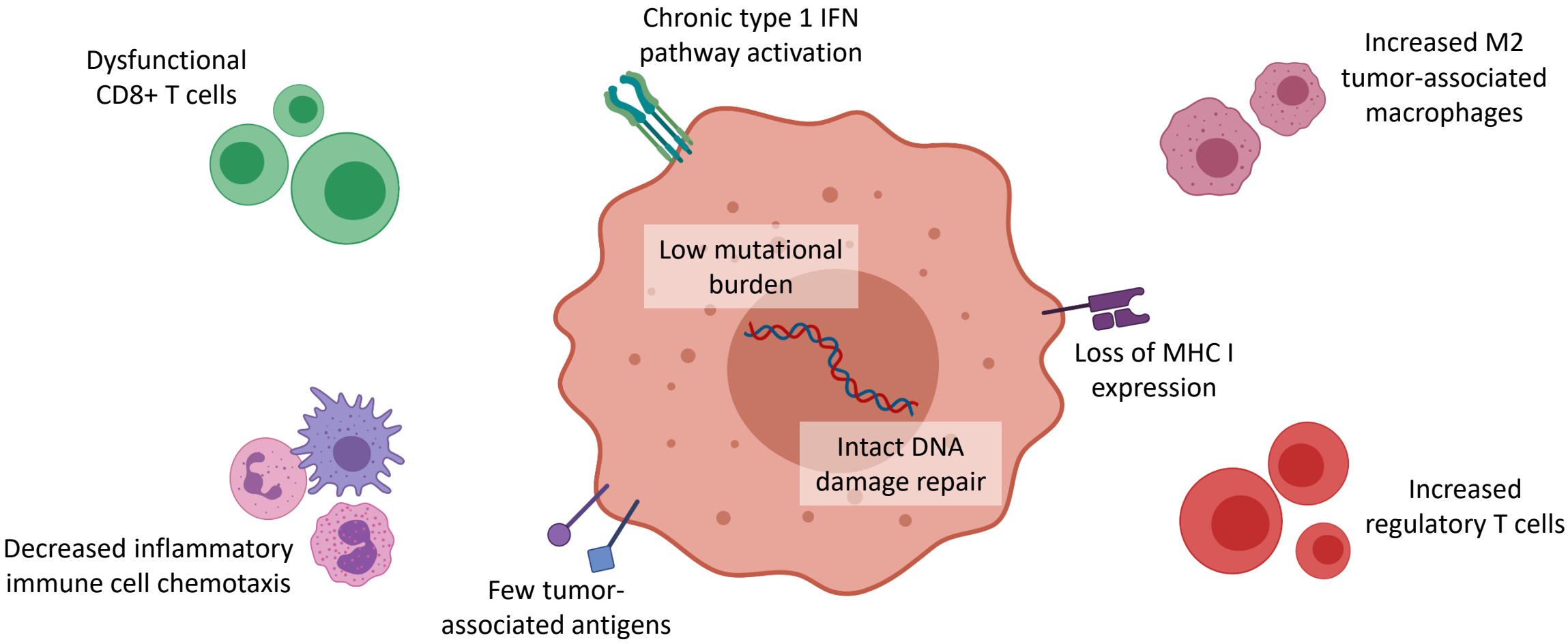
Immunology of prostate cancer



Vitkin, Front Immunol 2019.

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Immunotherapy landscape in prostate cancer

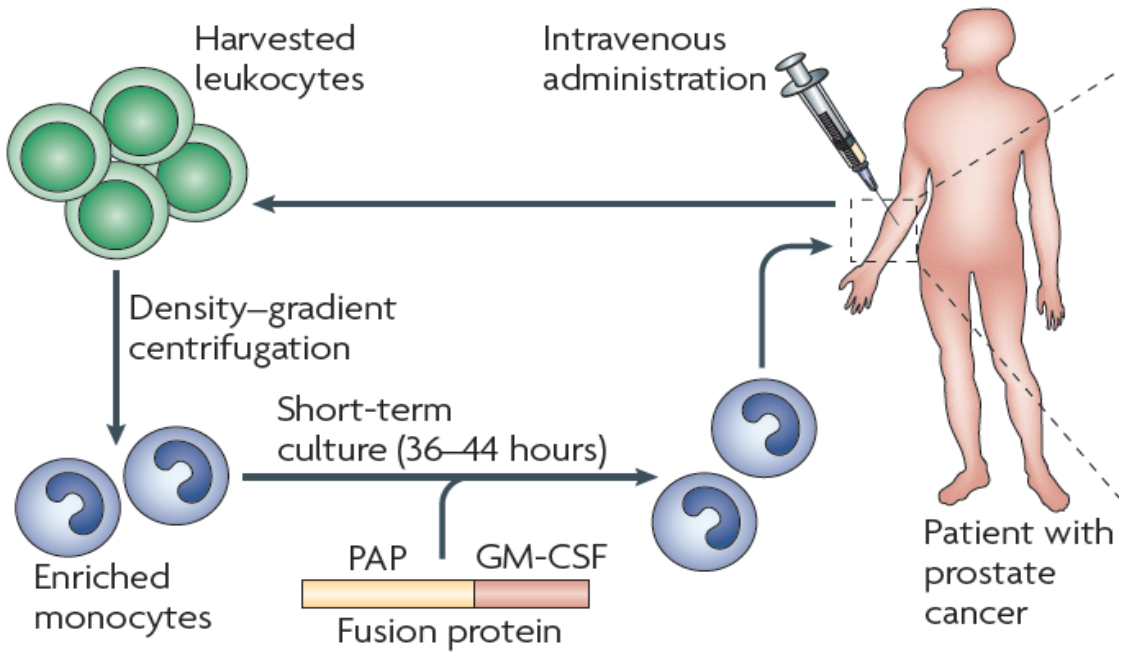
Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	RECIST-measurable PD-L1+ mCRPC	ORR: 5%
		RECIST-measurable PD-L1- mCRPC	ORR: 3%
		RECIST nonmeasurable mCRPC	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	PSA response rate: 21.8%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

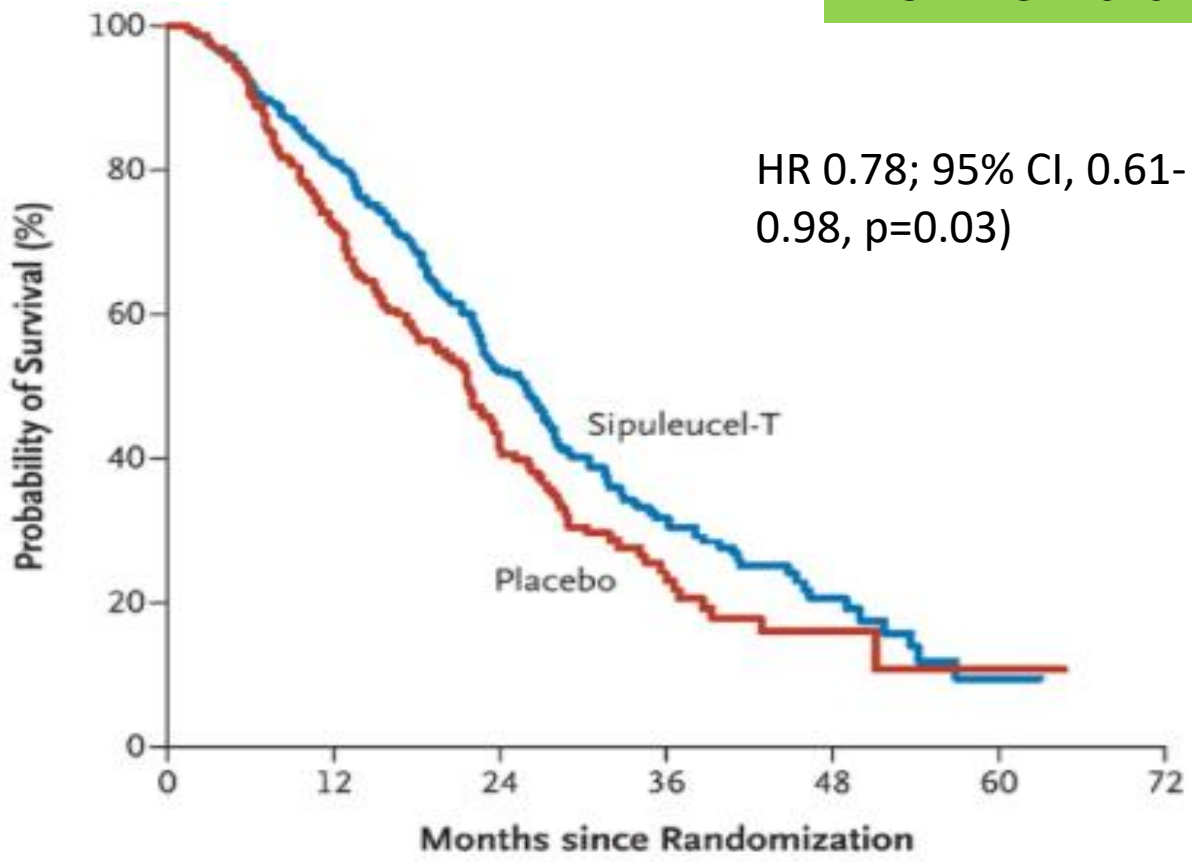
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

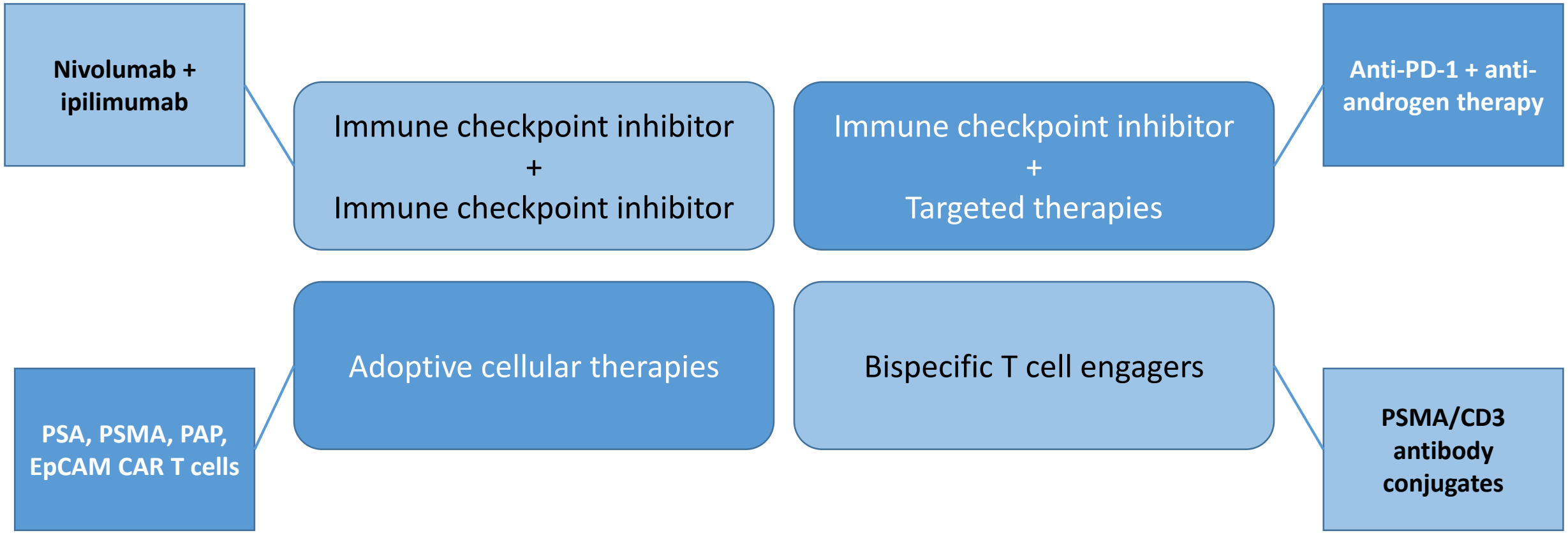




HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

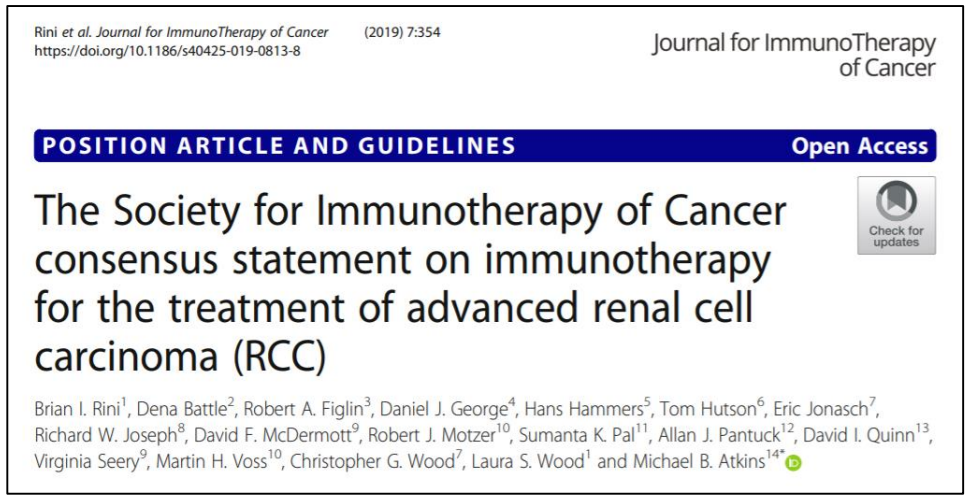
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

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*]

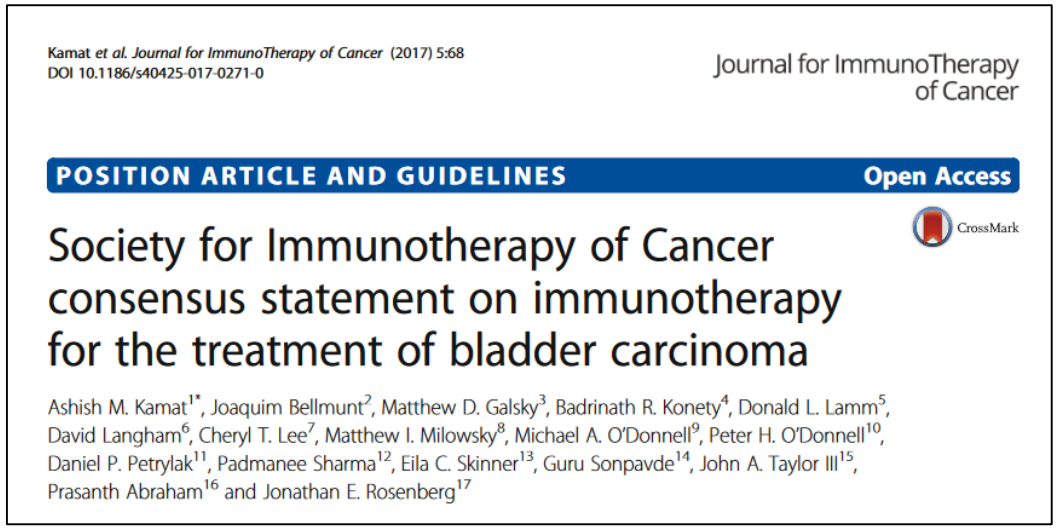
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

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

75 year old male with newly diagnosed metastatic renal cell carcinoma, metastases in the lung as well as bone with a large right renal mass with hematuria and right flank pain. Past medical history includes history of CAD s/p CABG, Hypertension and atrial fibrillation. He comes with his son for discussion of next steps.

What is the next option for the patient?

A. Proceed with cytoreductive nephrectomy
B. Initiation of systemic chemotherapy
C. Initiation of VEGF TKI
D. Initiation of VEGF TKI + IO
F. Initiation of IO + IO therapy

Checkmate 9ER

CheckMate 9ER: study design and endpoints

Randomized, multinational, phase 3 study of first-line NIVO+CABO versus SUN in patients with advanced RCC (NCT03141177)

N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

R 1:1

NIVO 240 mg intravenous every 2 weeks + **CABO** 40 mg oral daily

SUN 50 mg oral daily, cycle of 4 weeks on/2 weeks off

Treat until progression or unacceptable toxicity

Primary endpoint: Progression-free survival

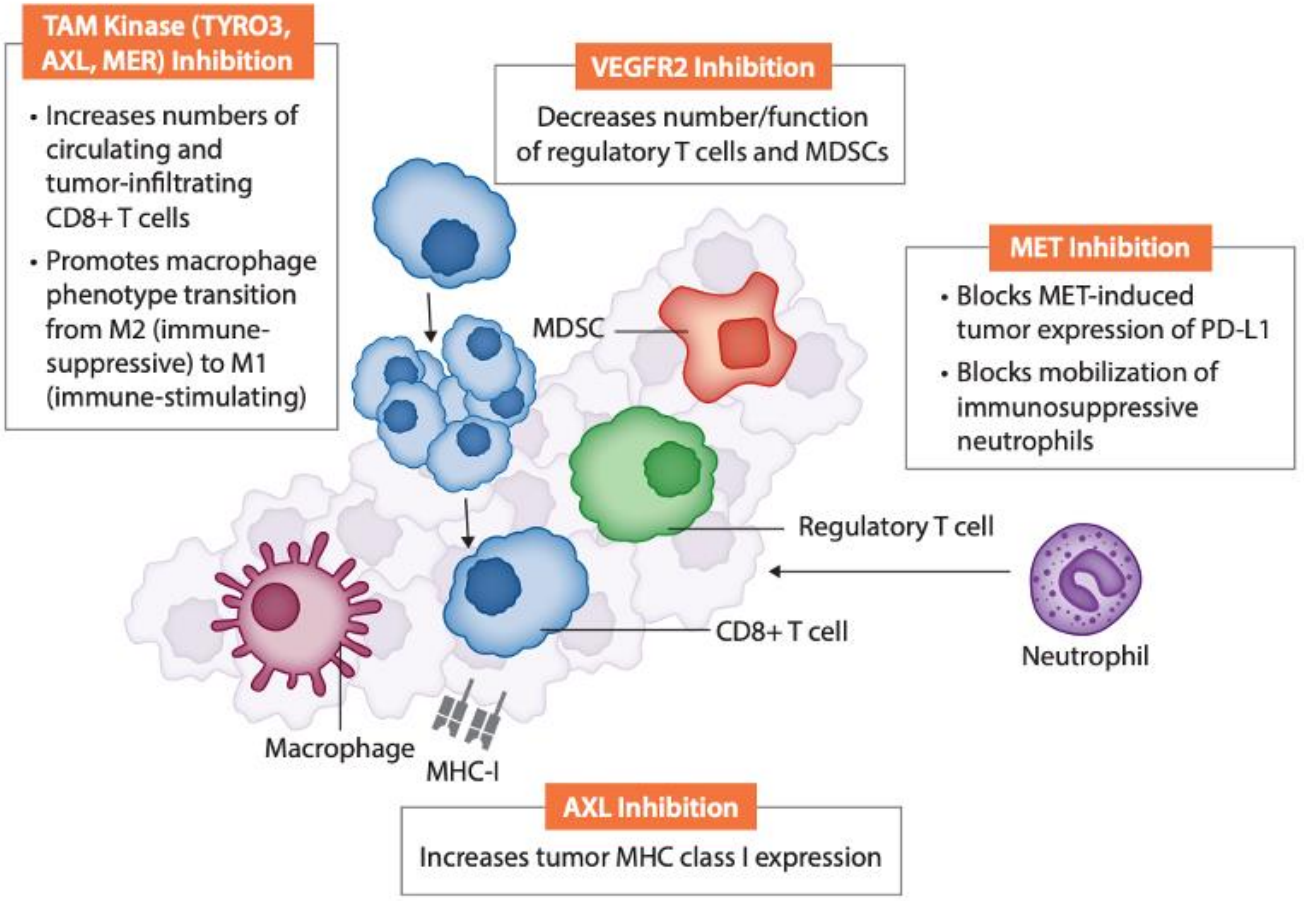
Secondary endpoints: Overall survival, objective response rate, and safety

Exploratory endpoints: Health-related quality of life (HRQoL)

Median study follow-up: 18.1 months (range, 10.6–30.6)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK, et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

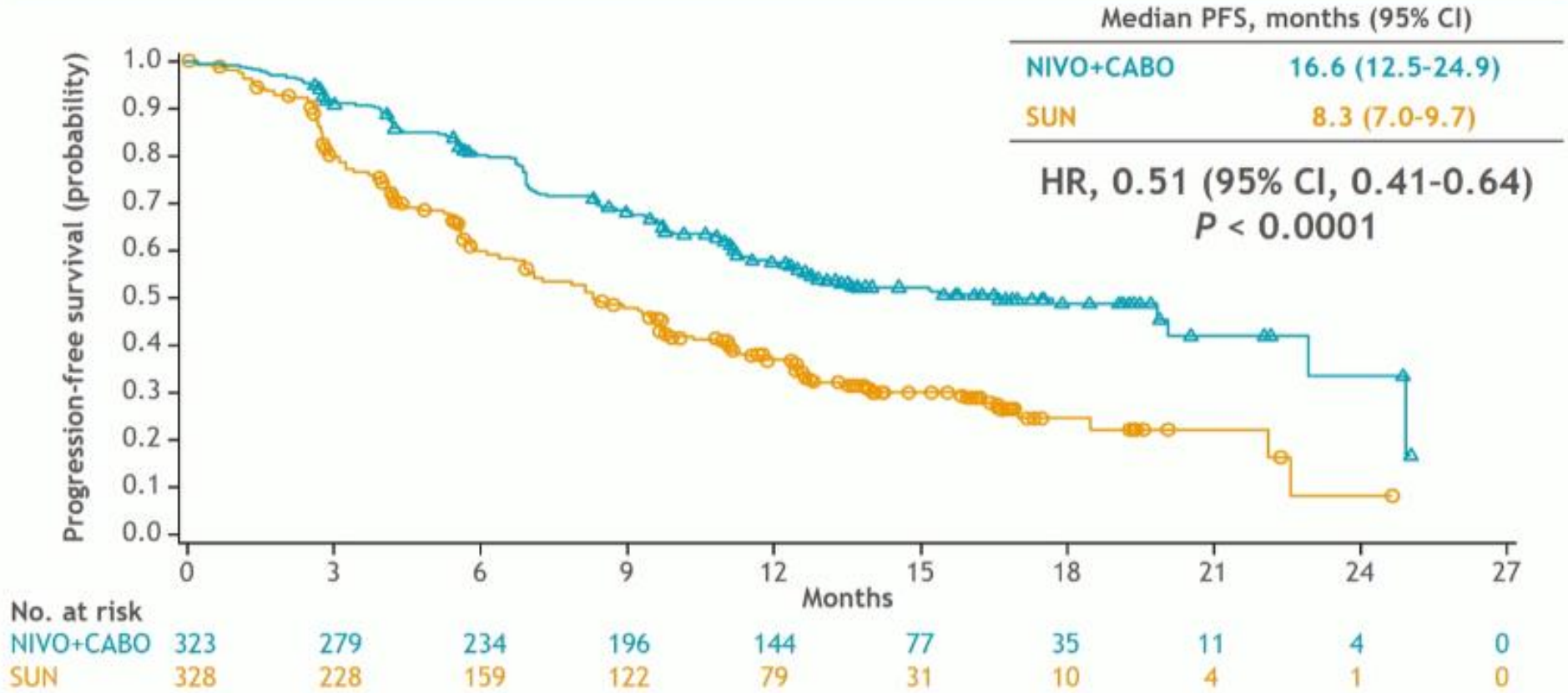
Cabozantinib Targets Pathways Associated with Tumor immune Suppression



Bradley McGregor, 2020 ESMO COSMIC-021 study

CheckMate 9ER

Progression-free survival per BICR



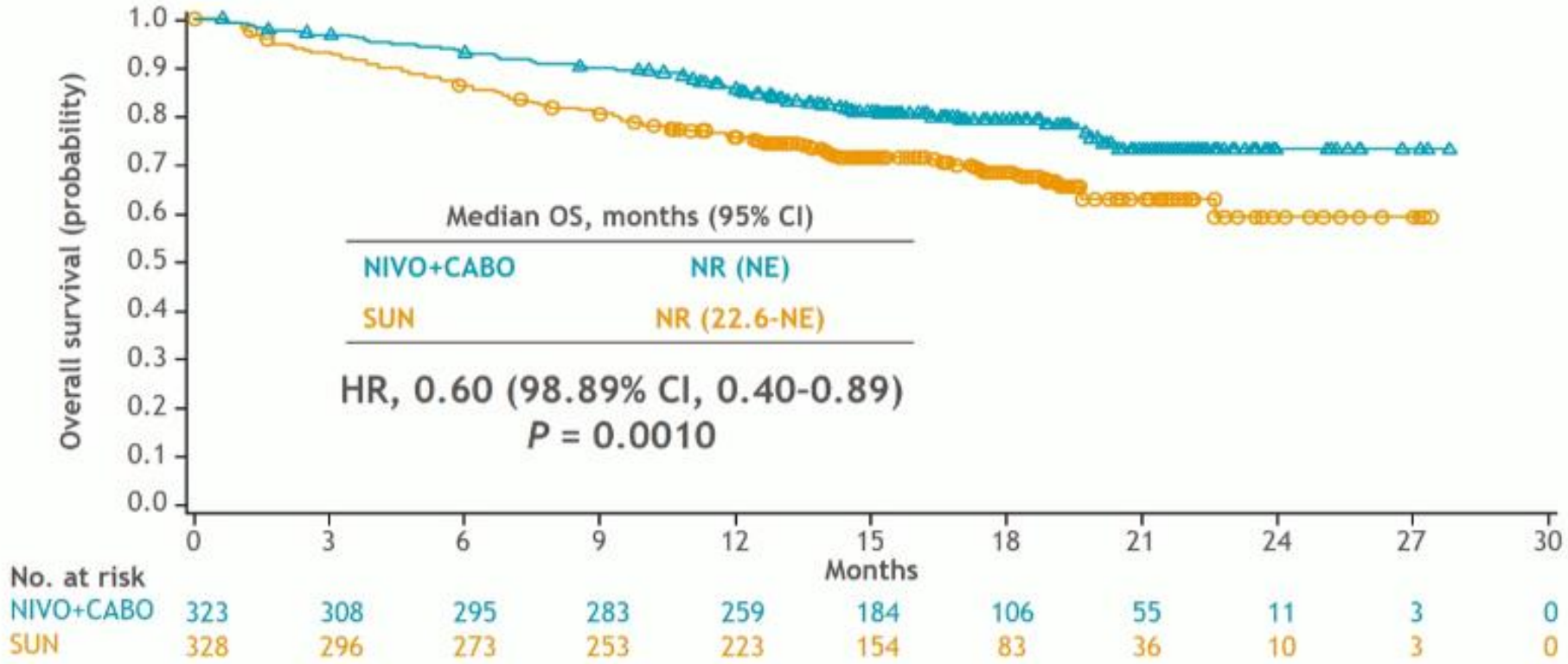
CheckMate 9ER

Progression-free survival per BICR in subgroups

Subgroup	NIVO+CABO	SUN	HR for progression or death (95% CI)
	Events/no. of patients		
Overall	144/323	191/328	0.51 (0.41-0.64)
Region			
US/Europe	61/158	85/161	0.46 (0.33-0.64)
Rest of world	83/165	106/167	0.57 (0.42-0.76)
IMDC prognostic risk			
Favorable	30/74	35/72	0.62 (0.38-1.01)
Intermediate	82/188	108/188	0.54 (0.40-0.72)
Poor	31/61	48/68	0.37 (0.23-0.58)
PD-L1 expression			
≥ 1%	42/83	54/83	0.49 (0.32-0.73)
< 1% or indeterminate	102/240	137/245	0.52 (0.40-0.67)
Age			
< 65 years	84/191	131/210	0.44 (0.33-0.58)
≥ 65 years	60/132	60/118	0.68 (0.48-0.98)
Sex			
Male	108/249	136/232	0.48 (0.37-0.62)
Female	36/74	55/96	0.61 (0.40-0.94)
Karnofsky performance status			
90-100	109/257	129/241	0.55 (0.43-0.71)
≤ 80	35/66	62/85	0.44 (0.29-0.68)
Bone metastases			
Yes	33/78	45/72	0.34 (0.22-0.55)
No	111/245	146/256	0.57 (0.44-0.73)
Previous nephrectomy			
Yes	90/222	136/233	0.46 (0.35-0.60)
No	54/101	55/95	0.63 (0.43-0.92)

CheckMate 9ER

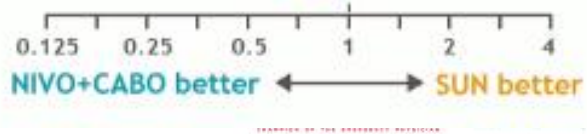
Overall survival



CheckMate 9ER

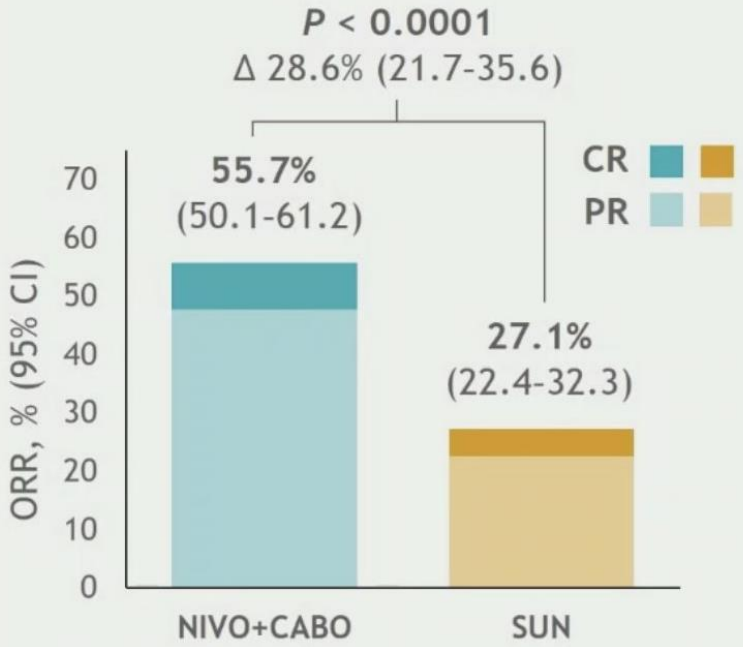
Overall survival in subgroups

Subgroup	NIVO+CABO Events/no. of patients	SUN Events/no. of patients	HR for death (95% CI)
Overall	67/323	99/328	0.60 (0.44-0.82)
Region			
US/Europe	26/158	45/161	0.48 (0.30-0.79)
Rest of world	41/165	54/167	0.71 (0.48-1.07)
IMDC prognostic risk			
Favorable	10/74	11/72	0.84 (0.35-1.97)
Intermediate	40/188	51/188	0.70 (0.46-1.07)
Poor	17/61	37/68	0.37 (0.21-0.66)
PD-L1 expression			
≥ 1%	28/83	30/83	0.80 (0.48-1.34)
< 1% or indeterminate	39/240	69/245	0.51 (0.34-0.75)
Age			
< 65 years	31/191	66/210	0.44 (0.29-0.67)
≥ 65 years	36/132	33/118	0.90 (0.56-1.44)
Sex			
Male	47/249	66/232	0.59 (0.40-0.85)
Female	20/74	33/96	0.68 (0.39-1.18)
Karnofsky performance status			
90-100	45/257	56/241	0.69 (0.47-1.03)
≤ 80	22/66	43/85	0.52 (0.31-0.86)
Bone metastases			
Yes	24/78	33/72	0.54 (0.32-0.92)
No	43/245	66/256	0.61 (0.41-0.89)
Previous nephrectomy			
Yes	36/222	66/233	0.49 (0.33-0.74)
No	31/101	33/95	0.79 (0.48-1.29)



CheckMate 9ER

Objective response and best overall response per BICR



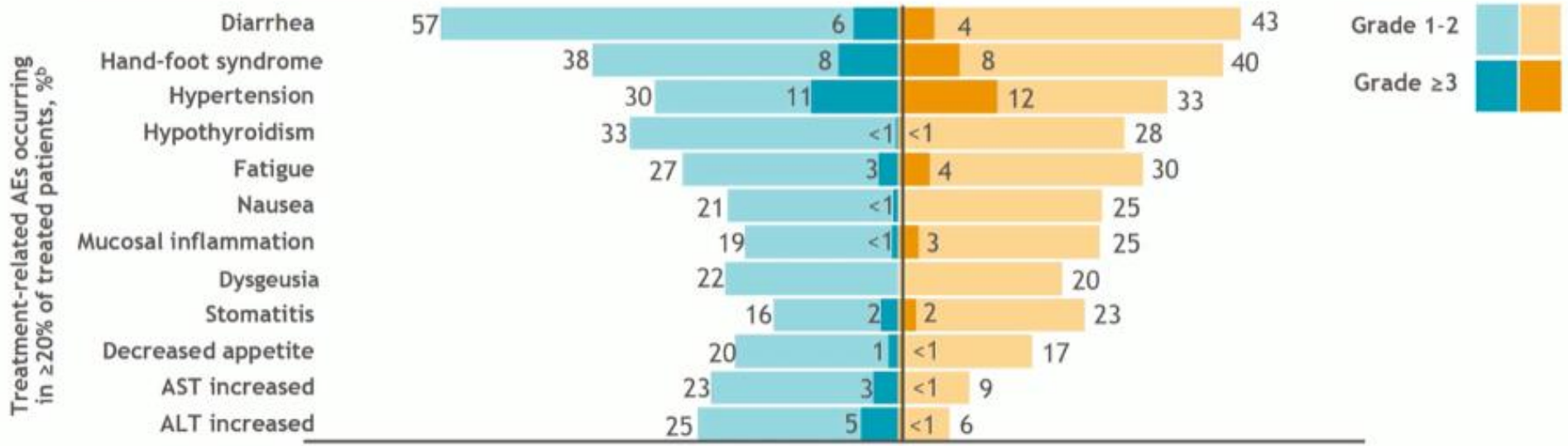
Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3-NE)	11.5 (8.3-18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not

CheckMate 9ER

Events, %[a]	NIVO+CABO, n = 320		SUN, n = 320	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



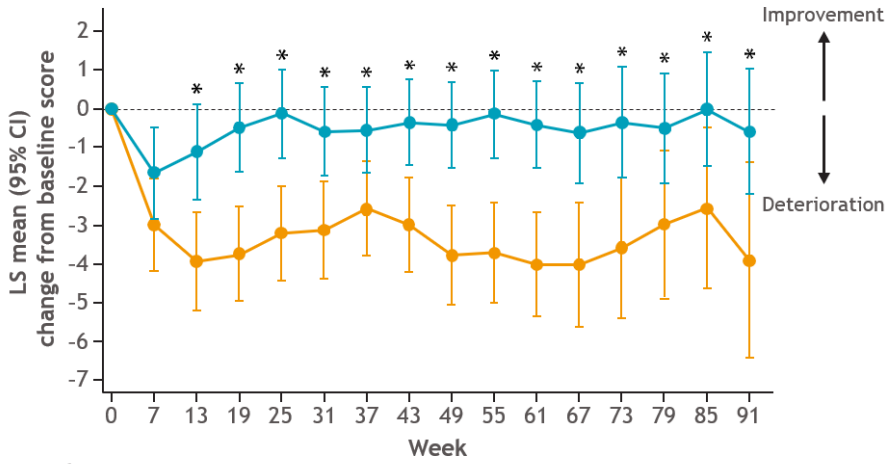
[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); [b]Total bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

15

CheckMate 9ER

Health-related quality of life

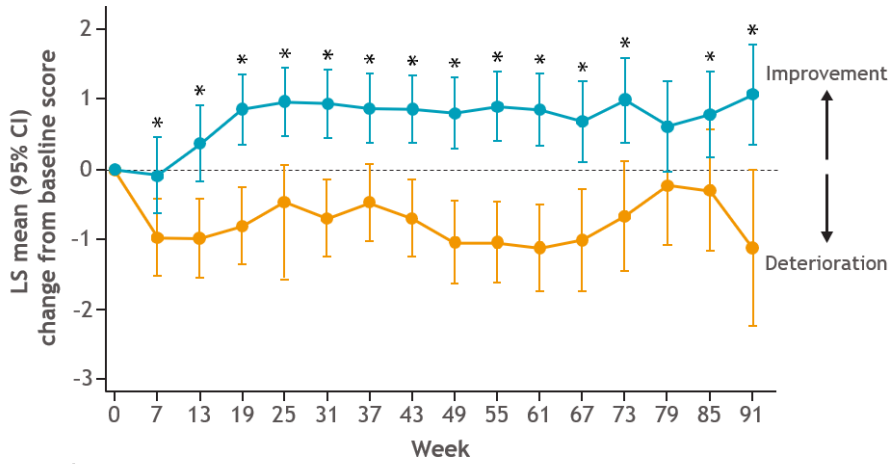
FKSI-19: Total Score



No. at risk

NIVO+CABO	299	261	246	242	228	217	199	191	173	153	147	124	90	67	53	42
SUN	310	262	226	201	179	163	152	142	116	110	87	67	49	34	25	16

FKSI: Disease-Related Symptom Subscale



No. at risk

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SUN	310	262	226	201	178	163	152	142	116	110	87	67	49	34	25	16

*Between-arm difference was statistically significant at this timepoint ($P < 0.05$).
Change from baseline was assessed using descriptive statistics and a mixed-model repeated measures analysis, which controlled for treatment arm, time point, baseline patient-reported outcomes score, IMDC prognostic score, PD-L1 tumor expression, and region. No. at risk denotes intention-to-treat patients with baseline plus at least 1 post-baseline HRQoL assessment with non-missing patient-reported outcome data. Time 0 indicates baseline.
FKSI-19, Functional Assessment of Cancer Therapy Kidney Symptom Index-19; LS, least square.

First line RCC

	CheckMate 214[1,2] ITT (n=550 vs n=546)	KEYNOTE-426[3,4] ITT (n=432 vs n=429)	CheckMate 9ER[5] ITT (n=323 vs n=328)
mOS, months HR (CI); P-value	NR vs 38.4 **0.72** (0.61–0.86); 0.0002	NR vs 35.7 **0.68** (0.55-0.85); <0.001	NR vs NR **0.60** (0.40–0.89); 0.001
Landmark OS at 12 months	**83%** vs. 78%	**90%** vs. 79%	**87%** vs. 78% (est)
mPFS, months HR (CI); p value	**12.4 vs 12.3** 0.88 (0.75–1.04); 0.127 (NS)	**15.4** vs 11.1 0.71 (0.60–0.84); <0.0001	**16.6** vs 8.3 0.51 (0.41–0.64); <0.0001
ORR, % p value	**39** vs 33 0.02	**60** vs 40 <0.0001	**56** vs 27 <0.0001
CR, %	**11** vs 2	**9** vs 3	**8** vs 5
Med f/u, months	**43.6**	**30.6**	**18.1**
Prognostic risk, % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19
Randomization period	Oct 2014 – Feb 2016	Oct 2016 – Jan 2018	
Subsequent therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)

Case Study 2

65 year old female with metastatic renal cell cancer to the liver, lung and bone, previously treated with pazopanib and had been most recently on maintenance nivolumab for the past 2 years has progression of disease in the lung. She comes to discuss next options:

A. Switch to TKI Cabozantinib

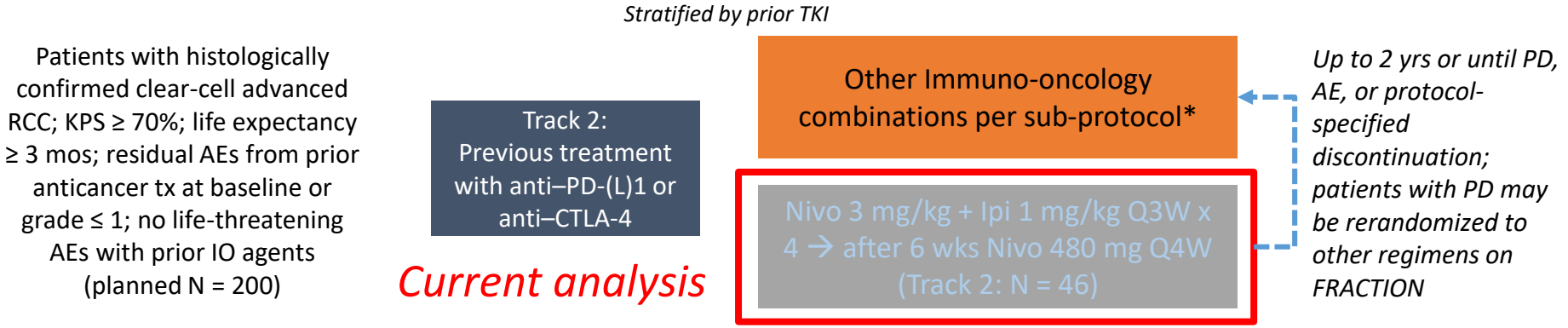
B. Rechallenge with Pazopanib

C. Add CTLA4 inhibitor

D. Radiation to sites of progression

Nivo + Ipi in RCC Progressing After ICI (FRACTION-RCC): Study Design

- Preliminary analysis of Track 2 treated with Nivo + Ipi in ongoing international, open-label, randomized phase II trial with adaptive-platform, Simon 2-stage design



Primary endpoints: investigator-assessed ORR per RECIST v1.1, DoR, probability of PFS up to 24 wks

Statistical assumptions for Track 2: if ≤ 1 of 21 respond, recommend early cohort termination; if ≥ 2 of 21 respond, recommend additional enrollment to stage 2

Key secondary endpoints: safety and tolerability up to 2 yrs

Slide credit: clinicaloptions.com

Choueiri. ASCO 2020. Abstr 5007. NCT02996110.

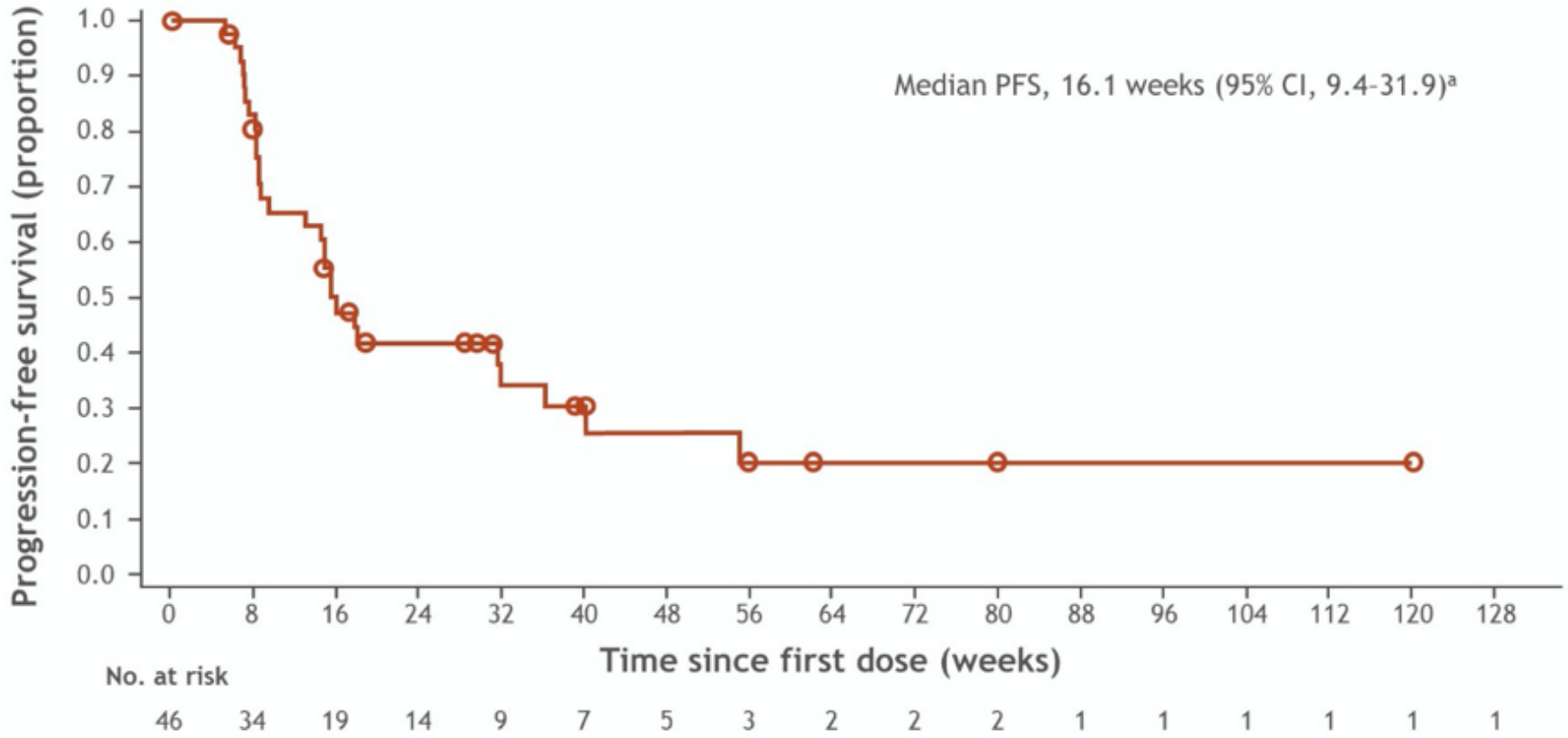
ASCO 2020: FRACTION-RCC

- 46 patients included, 13 had >4 lines of therapy
- None had prior CTLA 4 therapy, 37 progressed on TKI therapy, all had prior PDL1 therapy
- ORR 15.2%, (7/46 patients) Duration of response ranged from 2 to 19 months at a median follow up of 21.6 months

Response	Patients (N = 46)
ORR (co-primary endpoint), % (95% CI)	15.2 (6.3-28.9)
DCR (CR + PR + SD), % (95% CI)	52.2 (36.9-67.1)
Best overall response, n (%)	
▪ CR	0
▪ PR	7 (15.2)
▪ SD	17 (37.0)
▪ PD	15 (32.6)
▪ Not evaluable/available	7 (15.2)

ASCO 2020: FRACTION-RCC

Progression-free survival



IO+IO (Nivo+Ipi) JCO Anita Gul et al

- Retrospective analysis of 45 patients with metastatic RCC who received prior anti–PD-1 pathway-targeted therapy and subsequently received ipilimumab and nivolumab
  - 80% of patients had demonstrated clinical benefit; 53% had a partial response, and 27% had stable disease
  - response rate to salvage ipi+nivo was 20% with a median PFS of 4.0 months.
  - Most of the responders were off ICI for only a median of 2.8 months
  - immune-related adverse events were severe (grade 3 or 4) in six patients, and 38% received steroids, and one patient required infliximab therapy.

The role of NIVO → +IPI (salvage/rescue)

	HCRN GU16-260 ASCO 2020	TITAN RCC ESMO 2019	OMNIVORE ASCO 2020
N	123	207	83
Prior TKI	No	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo→Ipi
Ipi doses	4	4	2
ORR	13%	12%	4%
CR	0%	2.7%	0%

Nivo+ipi combo untreated ccRCC ORR 42%, CR 11% (Checkmate 214)[1]

1. Motzer et al, NEJM 2018

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PRESENTED BY: Toni Choueiri, Highlights of the Day, #ASCO 20

15

Summary: Post-IO (PD-1/L1) therapy

	VEGF TKI	IO	IO+IO (nivo+ipi)	IO→IO (nivo followed by ipi)	IO+VEGF
Evidence	Moderate	Low	Moderate	Moderate (to not do)	Moderate

- **Low:** few retrospective studies
- **Moderate:** retrospective, subgroups of phase 3, prospective non-randomized
- **High:** randomized studies

NEW TARGETS ALWAYS WELCOME

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27

Thoughts

- The addition of ipilimumab in patients with metastatic RCC who do not achieve an objective response to nivolumab monotherapy in the first line setting remains a question
- Of note, a subset of patients in this series with lack of an objective response to prior ICI-based therapy achieved a PR to salvage ipilimumab and nivolumab.
- Need to further define biomarkers for prediction of response
  - Molecular profiling, what constitutes immune sensitive, resistant, refractory (as well as prediction of toxicity)
- Upfront combination therapy is more effective than salvage therapy based on overall response rate and complete response rate.
- Need to balance toxicity/costs with benefit

Thank you