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

sitc Society for Immunotherapy of Cancer

Disclosures

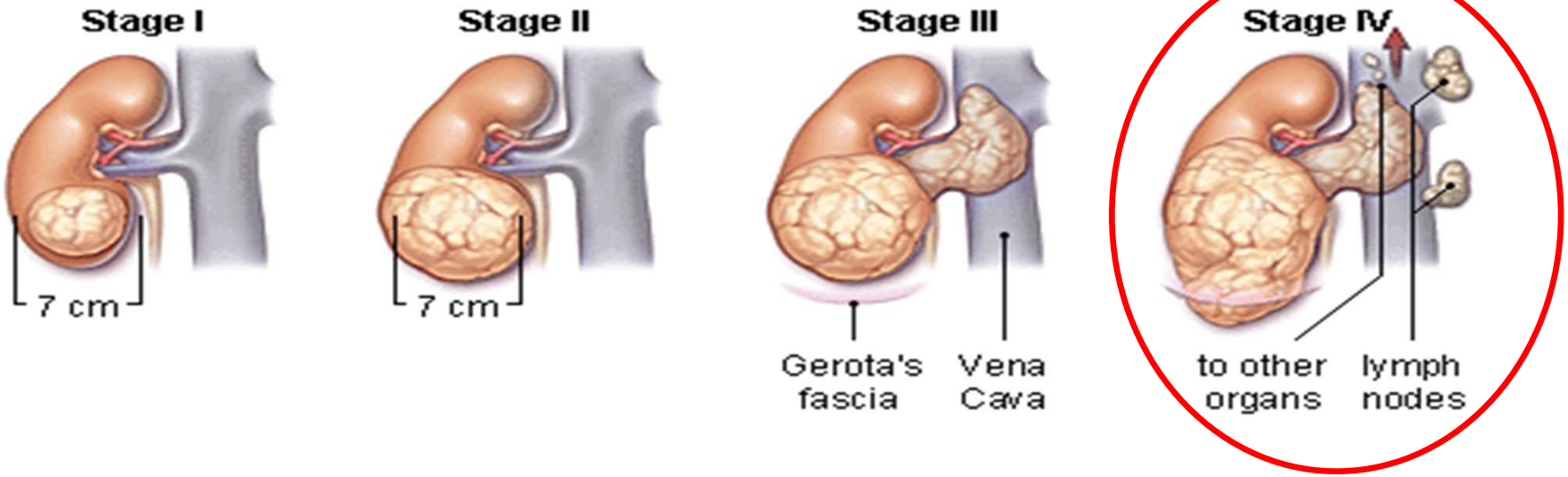
- **Relationships with financial sponsors:**
  - **Consulting Fees:** AbbVie, Astellas, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche, TerSera
  - **Contracted Research**: BioCanRx

No other relevant conflicts or bias directly related to this presentation

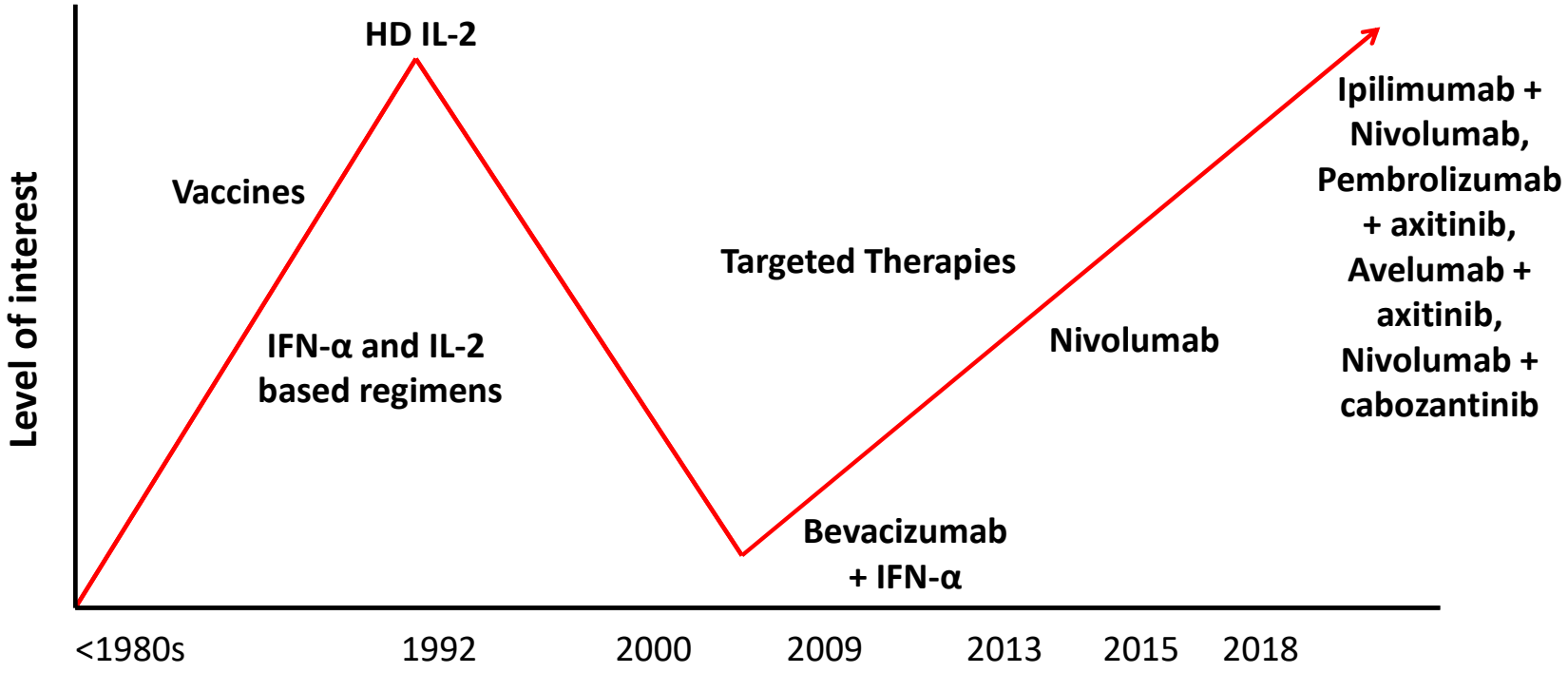
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)

Surgically resectable → Oligo-metastatic → Metastatic



History of Immunotherapy in mRCC

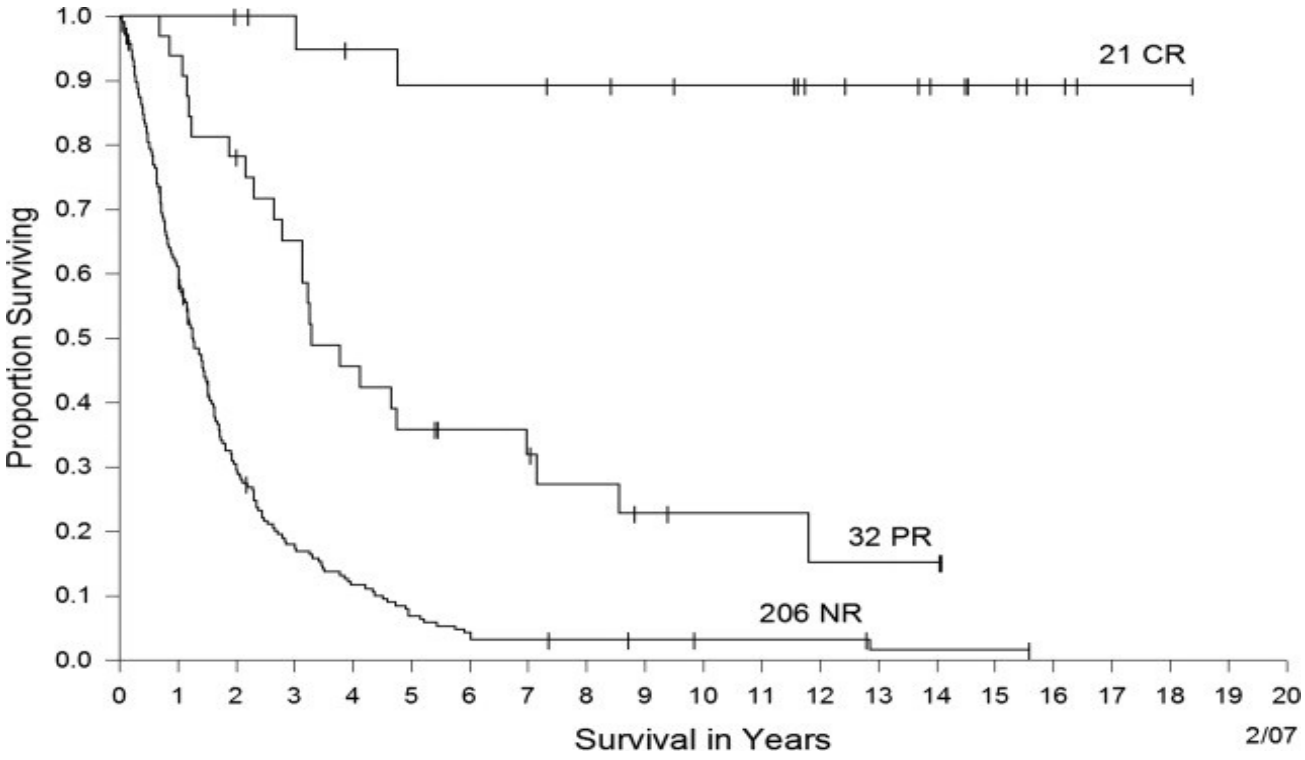


FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Dose
High dose Interleukin-2	1992	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-a + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
Nivolumab	2015	Clear cell RCC refractory to prior VEGF targeted therapy	3mg/kg or 240mg IV Q2W or 480mg IV Q4W
Nivolumab +ipilimumab	2018	Clear cell RCC, treatment naïve	3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	2019	Advanced RCC, Treatment naïve	200 mg pembro Q3W + 5 mg axitinib twice daily
Avelumab + axitinib	2019	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily

High Dose IL-2 in mRCC

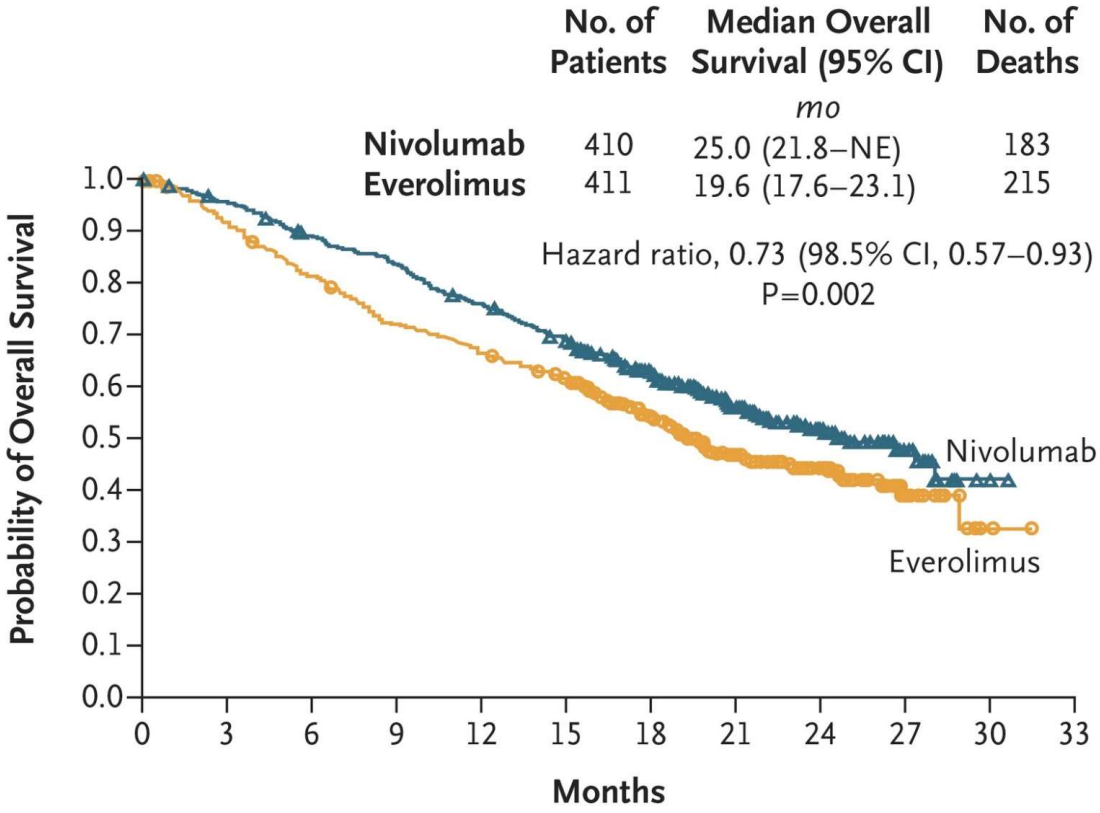
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

Second-Line Nivolumab in mRCC

- CheckMate 025 Phase III trial
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)

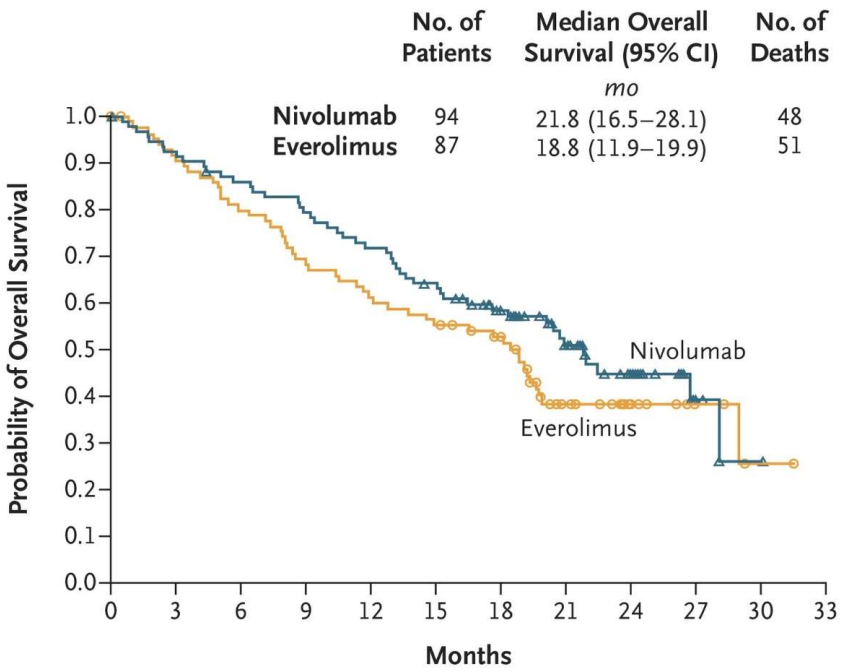


Motzer et al. NEJM 2015

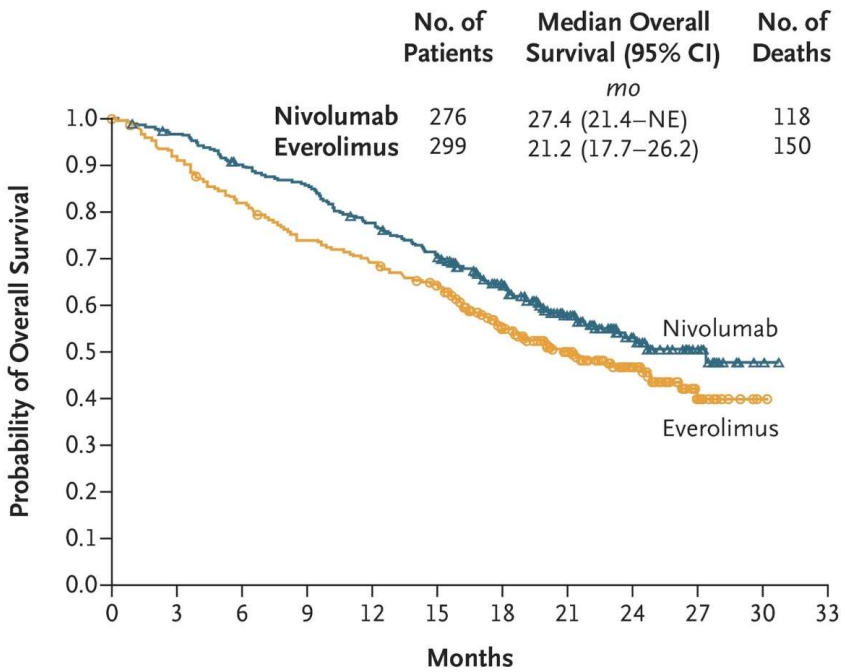
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%

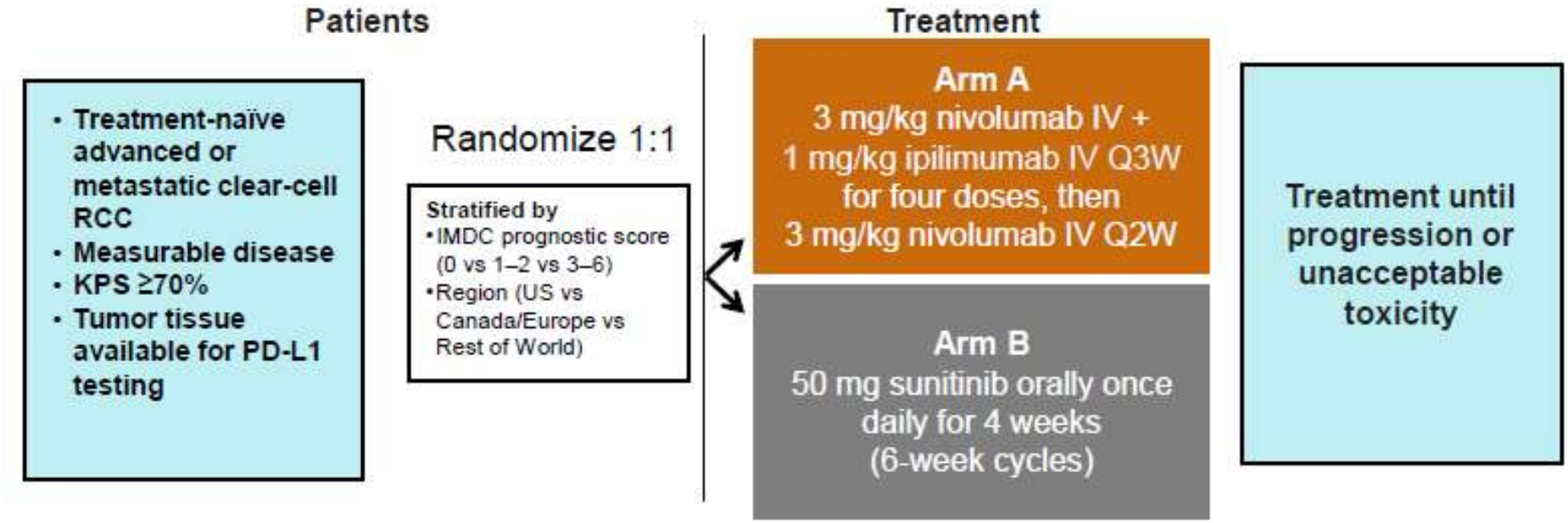


PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC



Nivolumab = anti-PD-1 antibody Ipilimumab = anti-CTLA-4 antibody

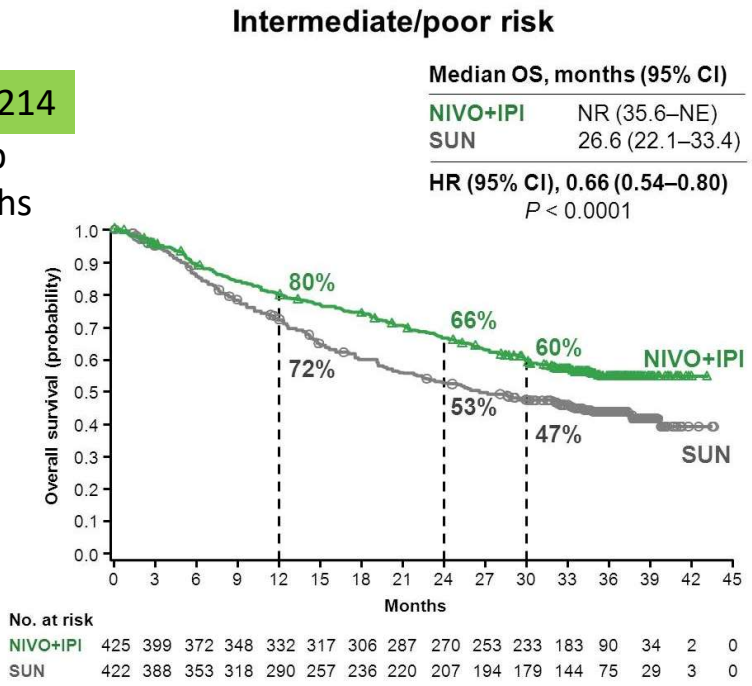
IMDC = International Metastatic RCC Database Consortium

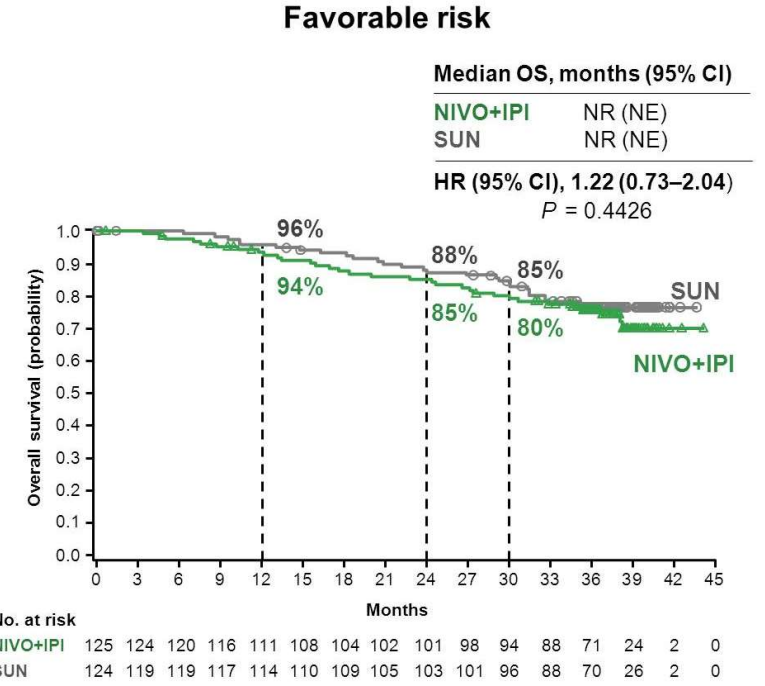
Escudier et al. ESMO 2017

First-line Nivolumab + Ipilimumab in mRCC by IMDC Risk: overall survival

CheckMate 214

Follow-up
= 30 months

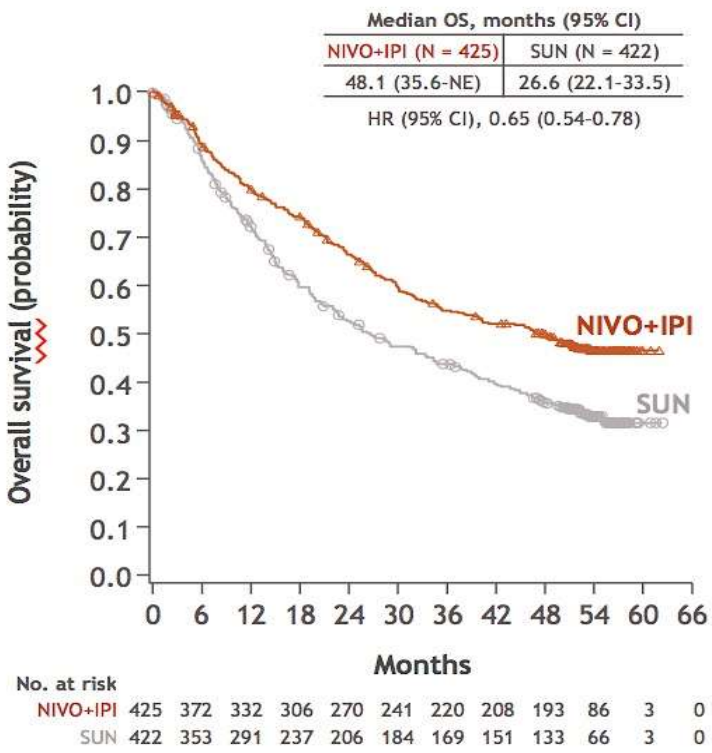


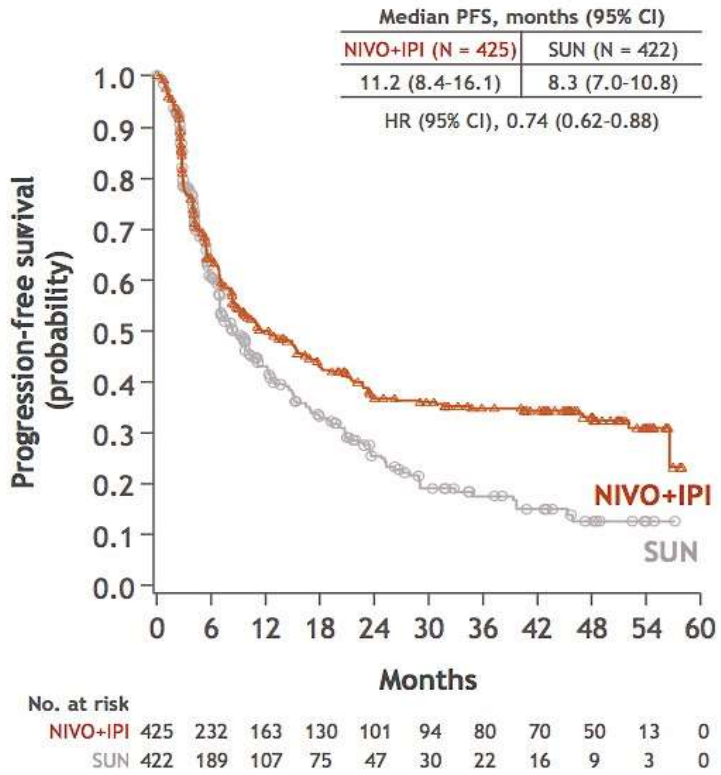


Tannir et al. ASCO GU 2019

Intermediate/poor risk - 48 month follow up

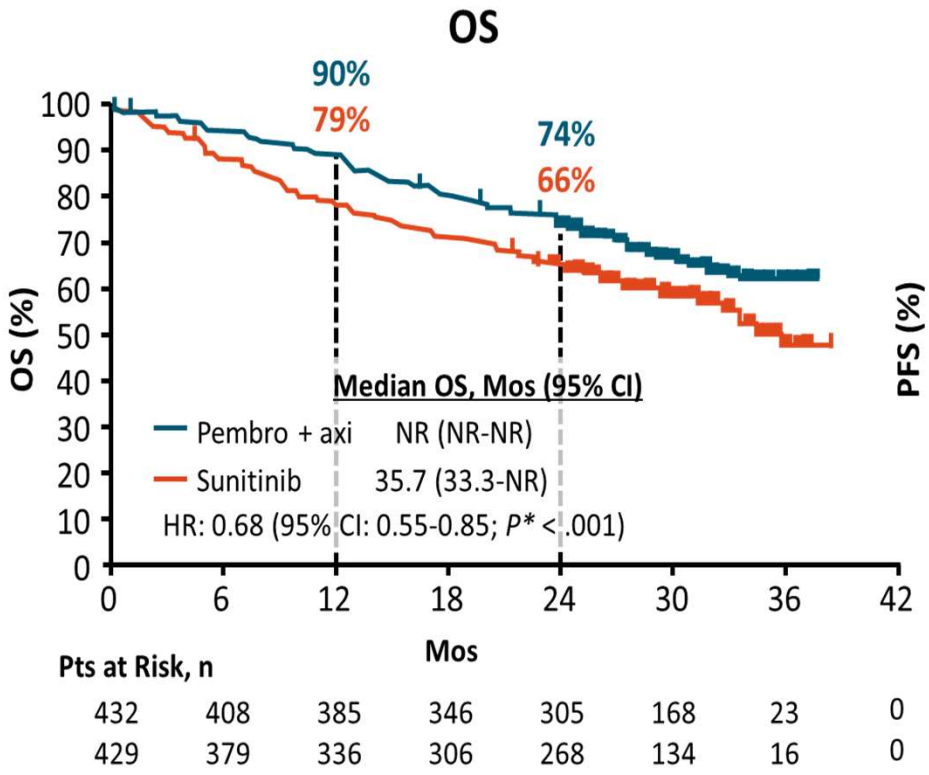
Intermediate/poor-risk population

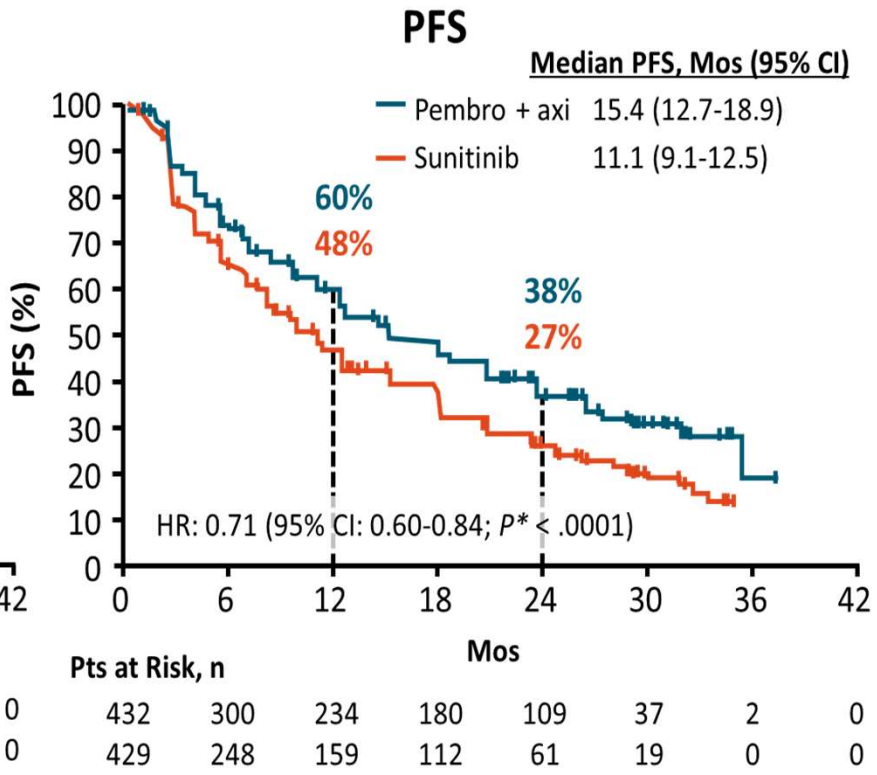




Albiges et al. ESMO 2020

First-line Pembrolizumab + Axitinib: 30 month follow up



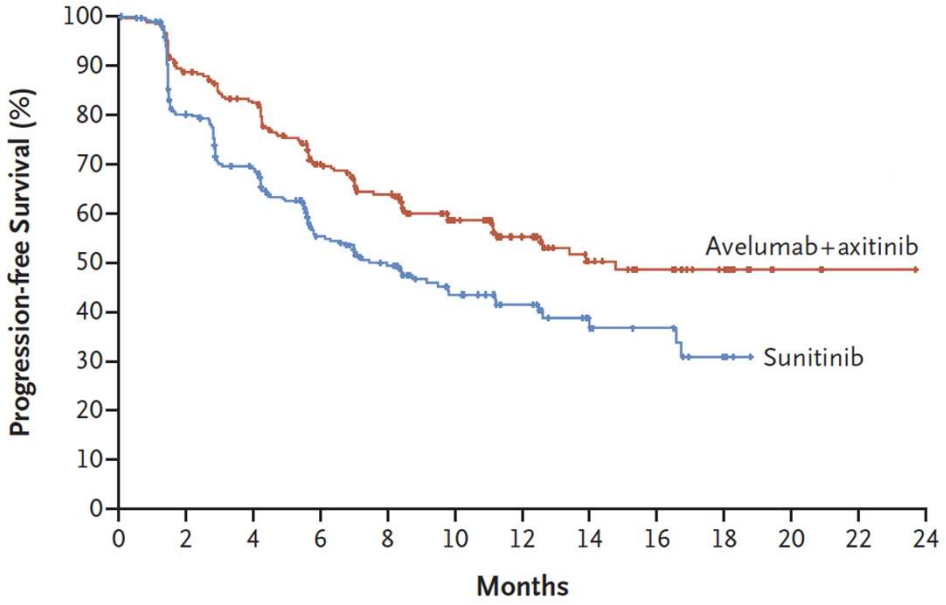


Rini, ASCO 2019; Plimack, ASCO 2020

First-line Avelumab + Axitinib in mRCC: progression-free survival

- Primary Endpoint: PFS and OS in PD-L1+
- Median PFS – 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR: 61.9% vs 29.7
- OS data: immature

JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019.

CheckMate 9ER: Study design

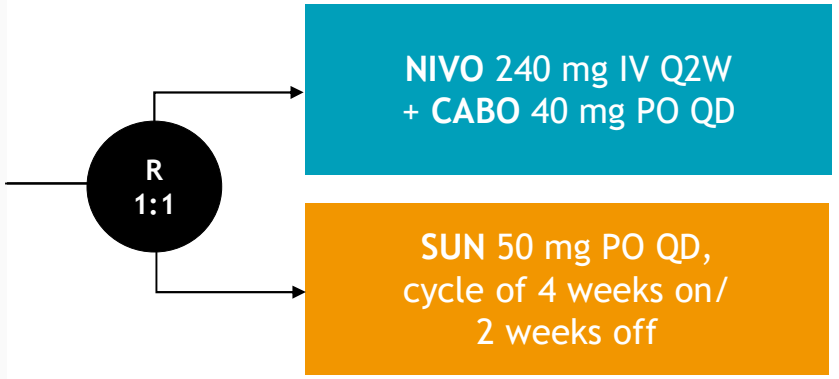
N = 651

Key inclusion criteria[1,2]

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

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1-defined progression or unacceptable toxicity[b]

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

Primary endpoint: PFS (BICR)

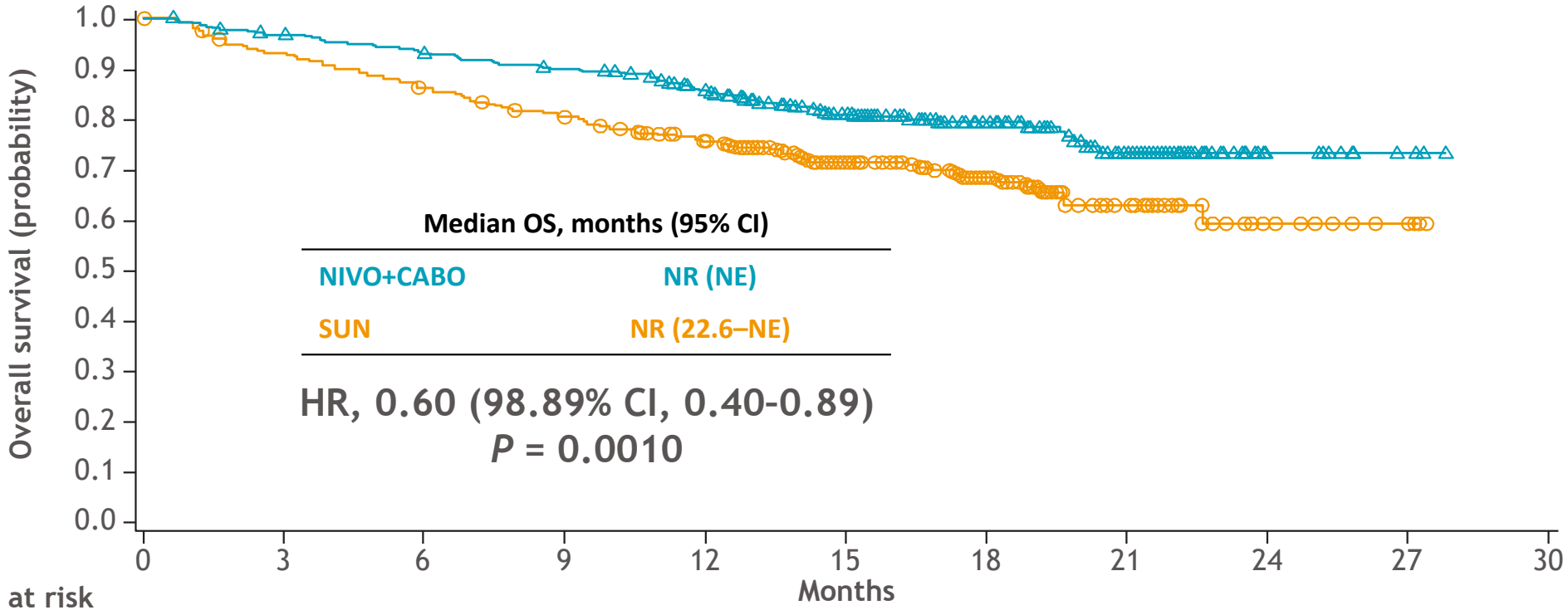
Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

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.

Choueiri TK, ESMO 2020

Overall survival



No. at risk											
NIVO+CABO	323	308	295	283	259	184	106	55	11	3	0
SUN	328	296	273	253	223	154	83	36	10	3	0

Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

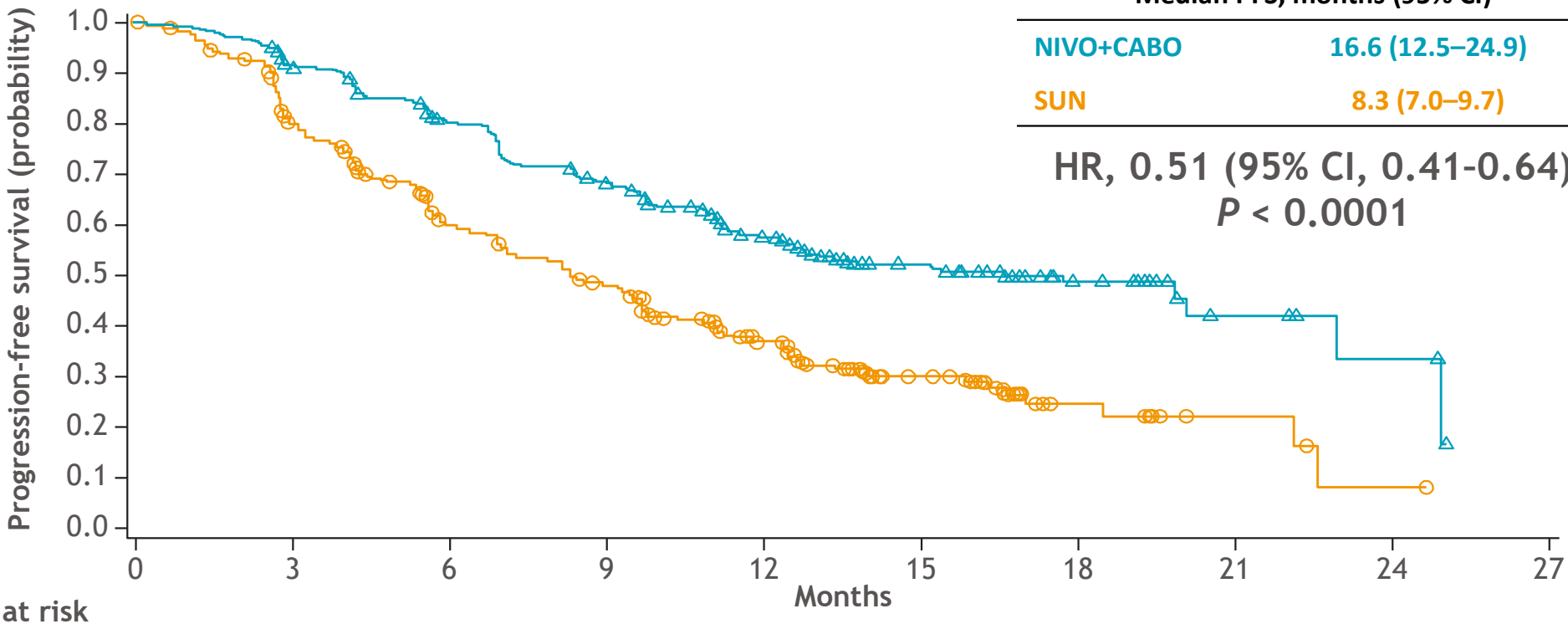
Choueiri TK, ESMO 2020

- CheckMate 9ER

Progression-free survival per BICR

Median PFS, months (95% CI)	
NIVO+CABO	16.6 (12.5–24.9)
SUN	8.3 (7.0–9.7)

HR, 0.51 (95% CI, 0.41-0.64)
P < 0.0001



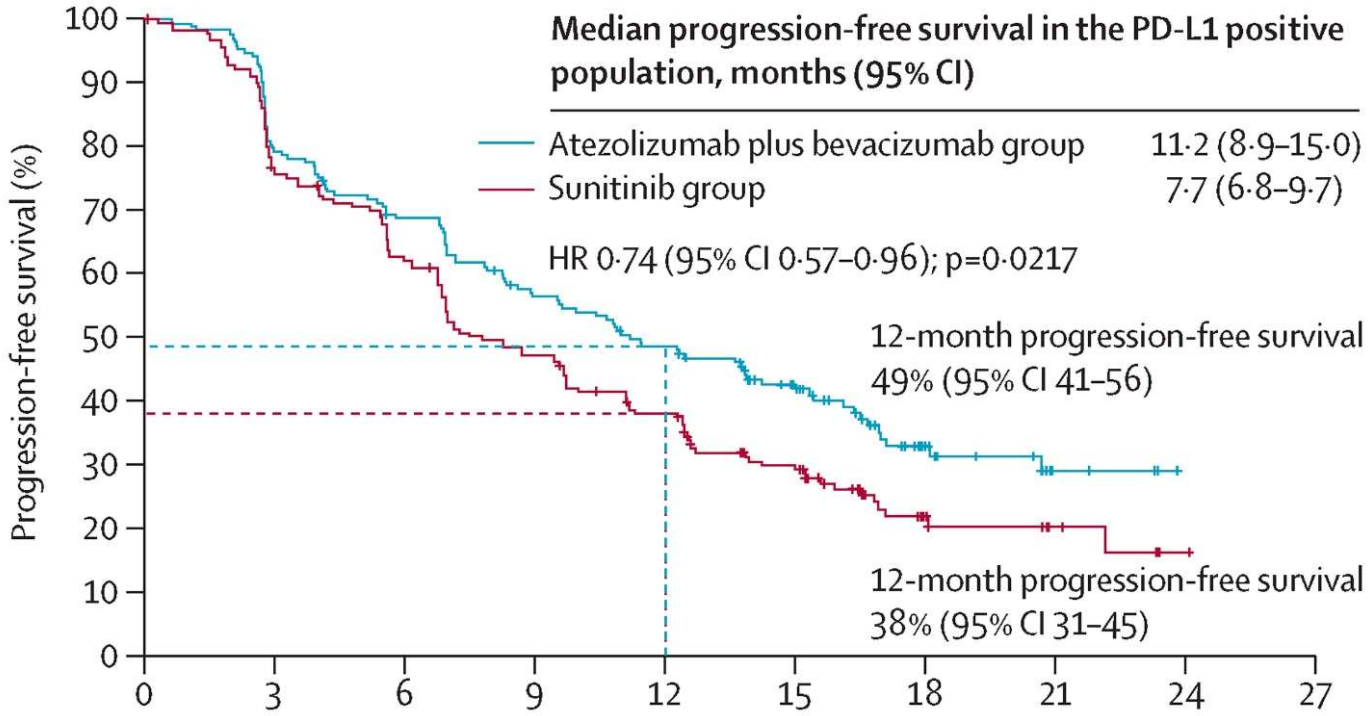
No. at risk										
NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Minimum study follow-up, 10.6 months.

Choueiri TK, ESMO 2020

First-line atezolizumab + bevacizumab in PD-L1+ mRCC

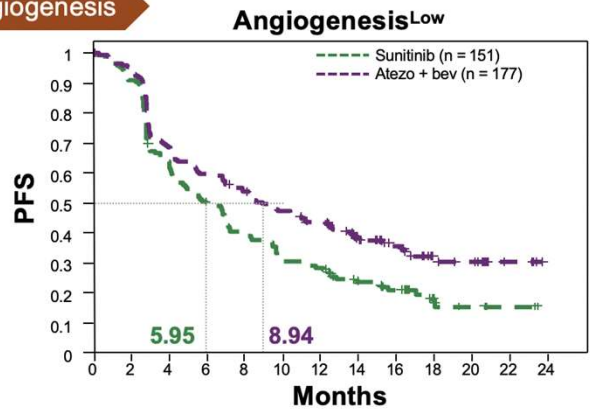
Immotion151

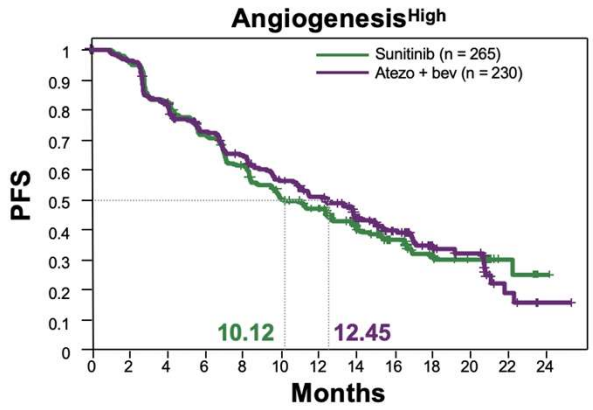


Rini, The Lancet 2019.

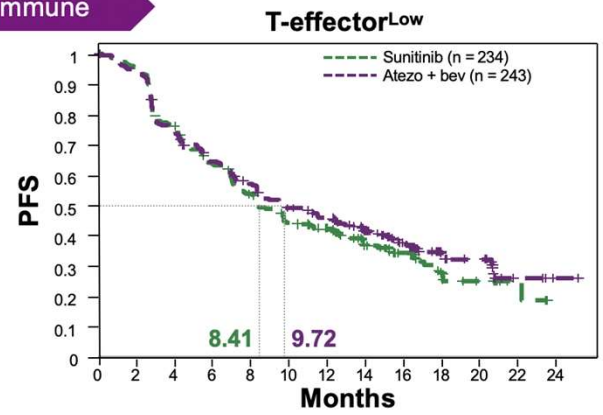
In Development: First-line atezolizumab + bevacizumab: molecular signatures

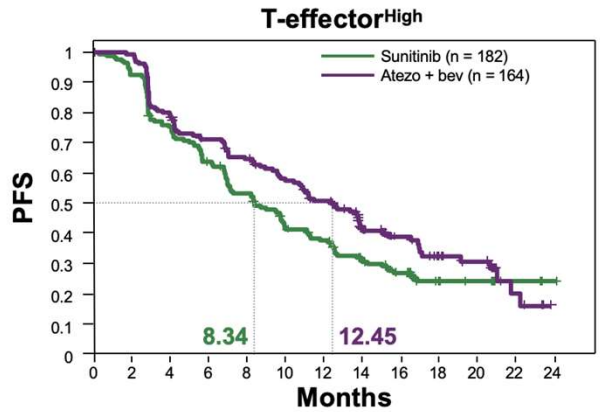
Angiogenesis





Immune





Rini et al, ESMO 2018

Front-line phase 3 trials with immunotherapy (efficacy summary)

Treatment	Follow-up OS	Risk groups	OS	PFS	ORR
Nivolumab + Ipilimumab (Int/Poor risk)	48 mos	Int 61% Poor 17%	HR 0.65 (0.54-0.78)	HR 0.74 (0.62-0.88)	42 vs 27% CR: 10 vs 1%
Nivolumab + Cabozantinib (ITT)	18 mos	Good 23% Int 58% Poor 19%	HR 0.60 (0.40-0.89)	HR 0.51 (0.41-0.64)	56 vs 27% CR: 8 vs 5%
Pembrolizumab + Axitinib (ITT)	30 mos	Good 32% Int 55% Poor 13%	HR 0.68 (0.55-0.85)	HR 0.71 (0.60-0.84)	60 vs 40% CR: 9 vs 3%
Avelumab + Axitinib (ITT)	19 mos	Good 21% Int 61% Poor 16%	HR 0.80 (0.62-1.02)	HR 0.69 (0.57-0.82)	52 vs 27% CR: 4 vs 2%
Atezolizumab + Bevacizumab (ITT)	24 mos	Good 20% Int 69% Poor 11%	HR 0.93 (0.76-1.14)	HR 0.83 (0.70-0.97)	37 vs 33% CR: 5 vs 2%

IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019
Choueiri, ESMO 2020

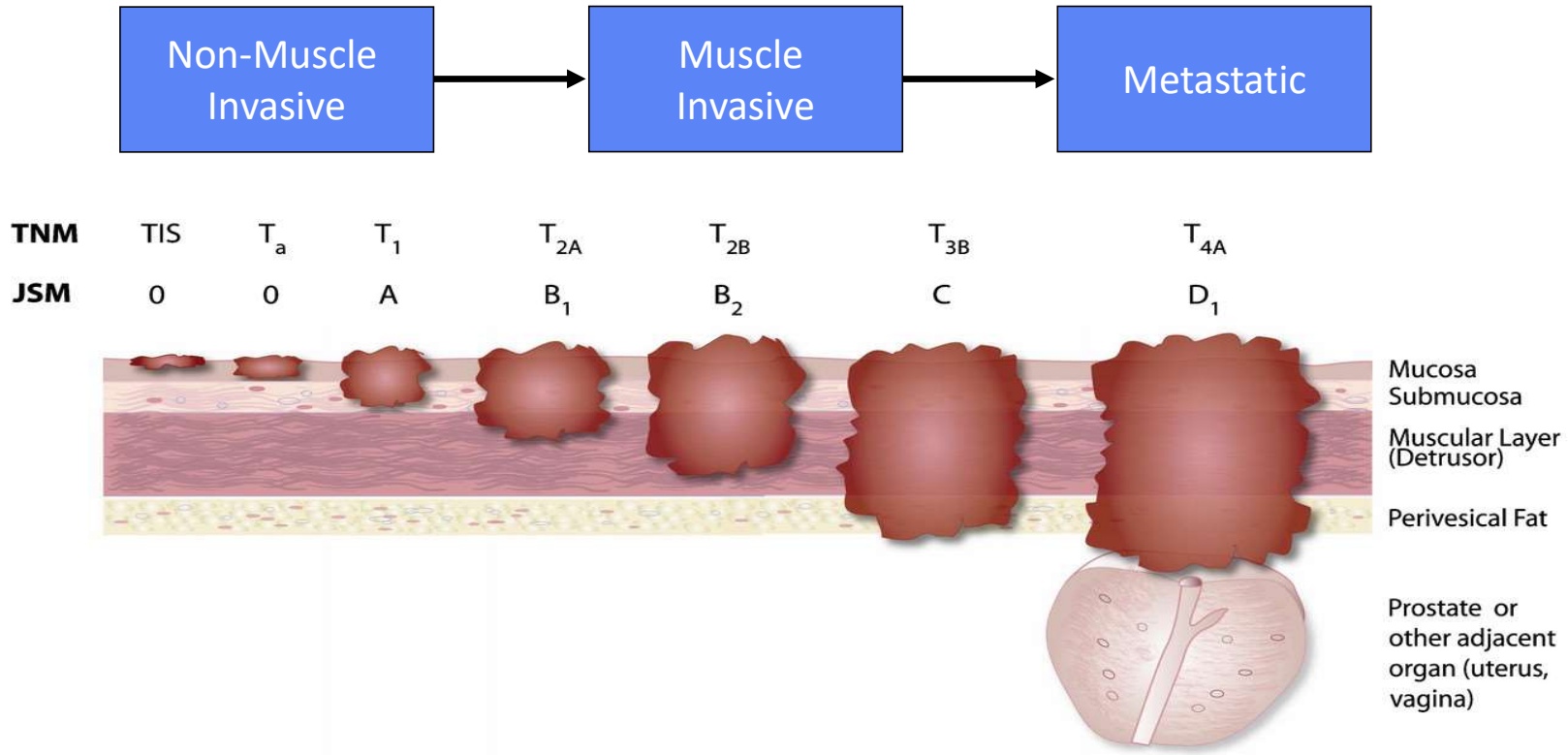
Courtesy: @LalaniMD

Ongoing front-line phase 3 trials with immunotherapy agents for front-line ccRCC

Trial number	Trial Name	Treatment Arm	Comparator Arm	Population Size	Primary End Point
NCT02811861	CLEAR	Lenvatinib + Pembrolizumab or Everolimus	Sunitinib	1050	PFS
NCT03729245	CA045002	NKTR-214 + Nivolumab	Sunitinib	600	ORR, OS
NCT03937219	COSMIC-313	Cabozantinib + Ipilimumab + Nivolumab	Sunitinib	676	PFS

PFS: progression-free survival; ORR: overall response rate; OS: overall survival

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



Approved checkpoint inhibitor for non-muscle invasive bladder cancer

Drug	Approved	Indication	Dose
Pembrolizumab	January 2020	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.

Checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC	1200 mg Q3W
Avelumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Durvalumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	2017	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab**	2017 (2018)	Advanced/metastatic UC	200 mg Q3W or 400 mg Q6W

- **Phase III trial demonstrating OS benefit (Keynote-045), Health Canada approved and reimbursed agent

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

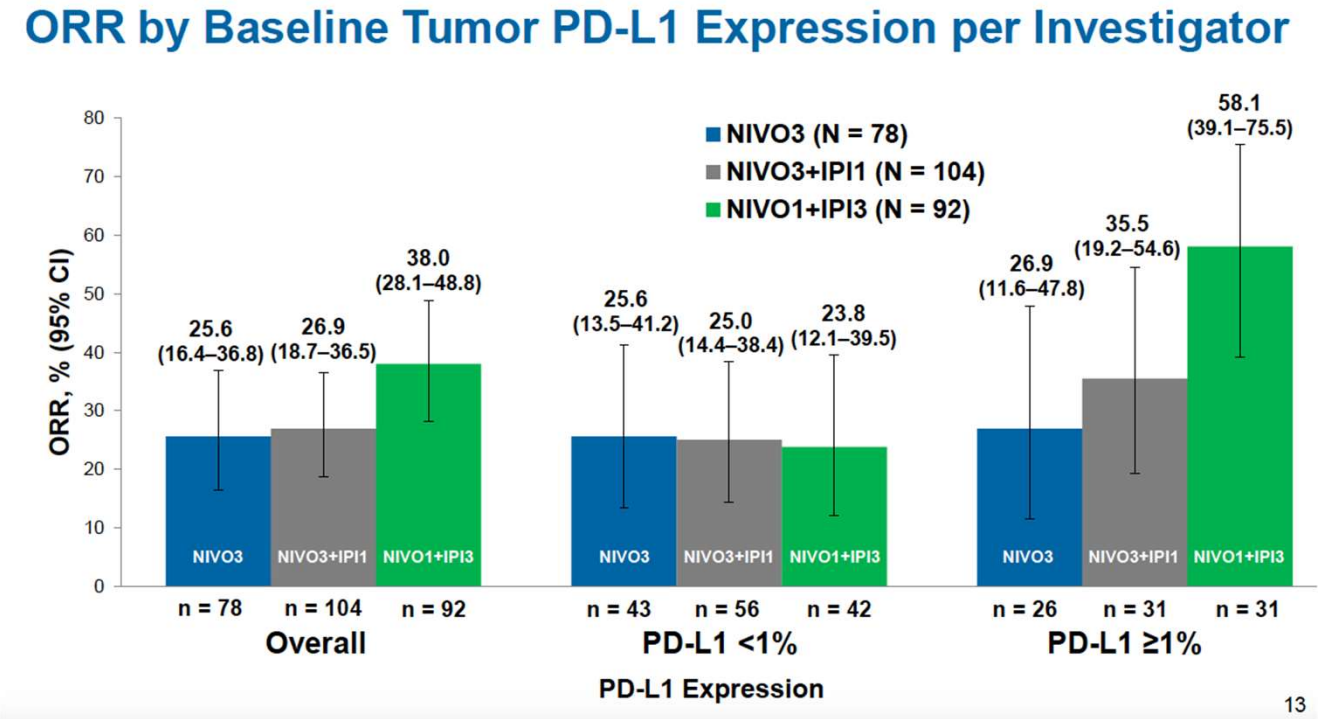
Drug	Approved	Indication	Dose
Atezolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W or 400 mg Q6W

June 2018

FDA limits the use of Atezolizumab and Pembrolizumab for some urothelial cancer patients

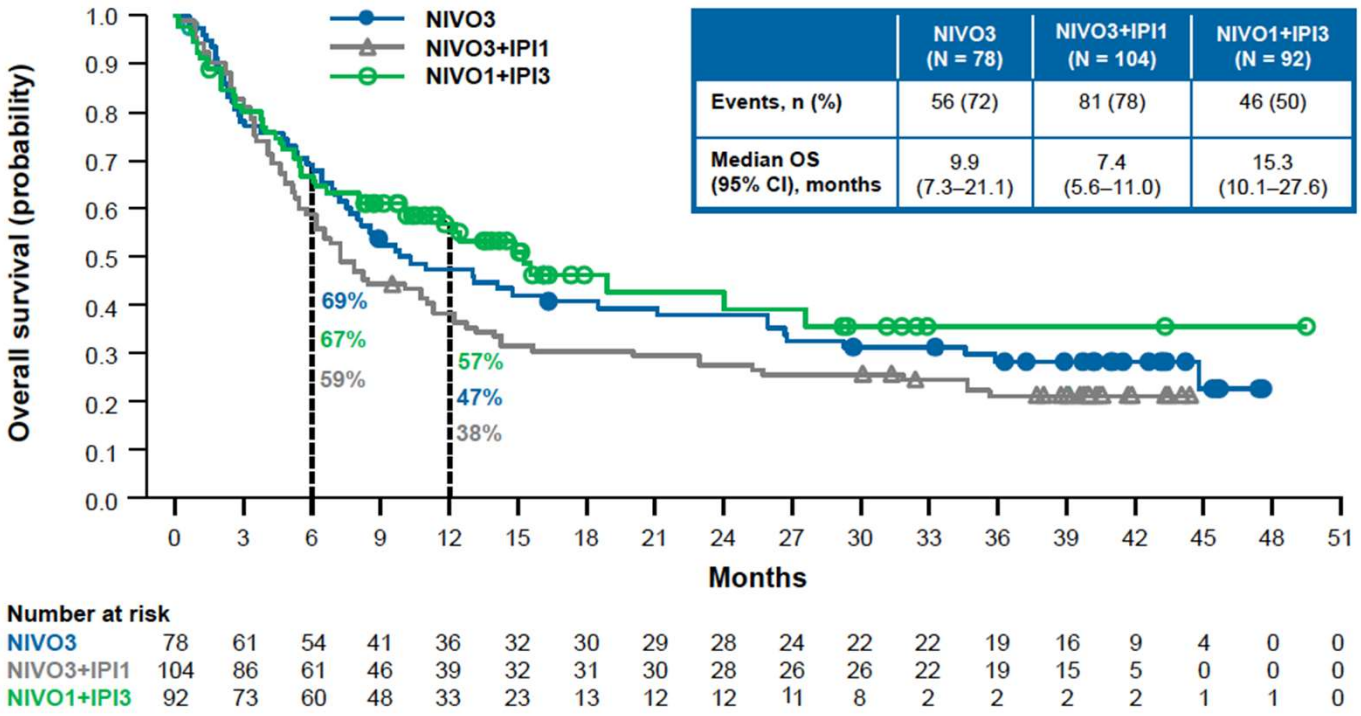
- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and tumor PD-L1 (CPS ≥ 10, pembro; IC ≥ 5% tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status
- **NOTE:** Health Canada approved, not reimbursed

In development: Ipilimumab + Nivolumab CheckMate 032



Rosenberg, ESMO 2018

In development: Ipilimumab + Nivolumab CheckMate 032

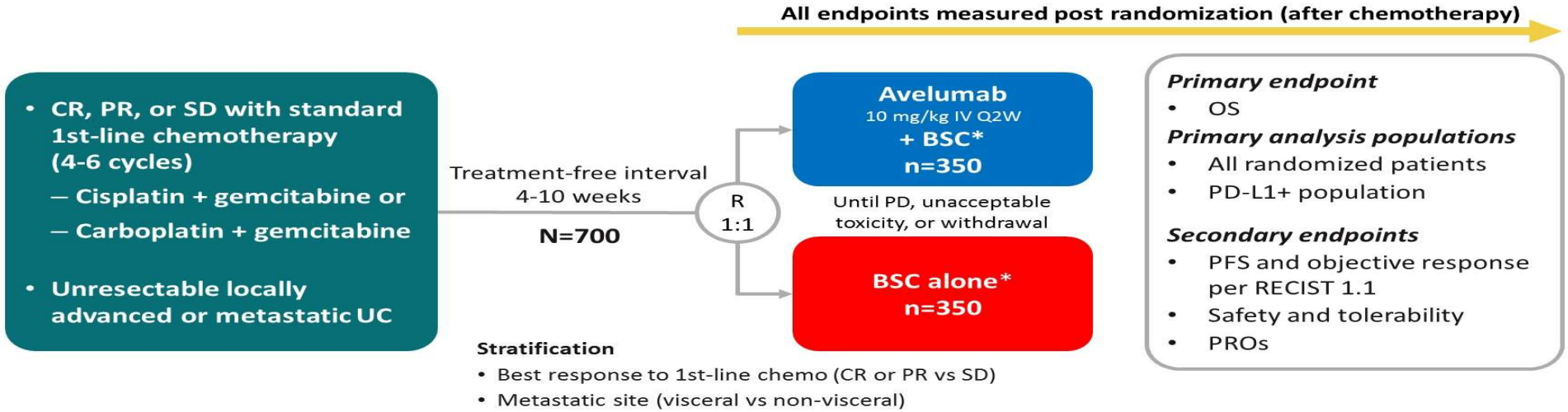


	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Rosenberg, ESMO 2018

New data: checkpoint inhibitor for maintenance treatment, first line

JAVELIN Bladder 100 study design (NCT02603432)



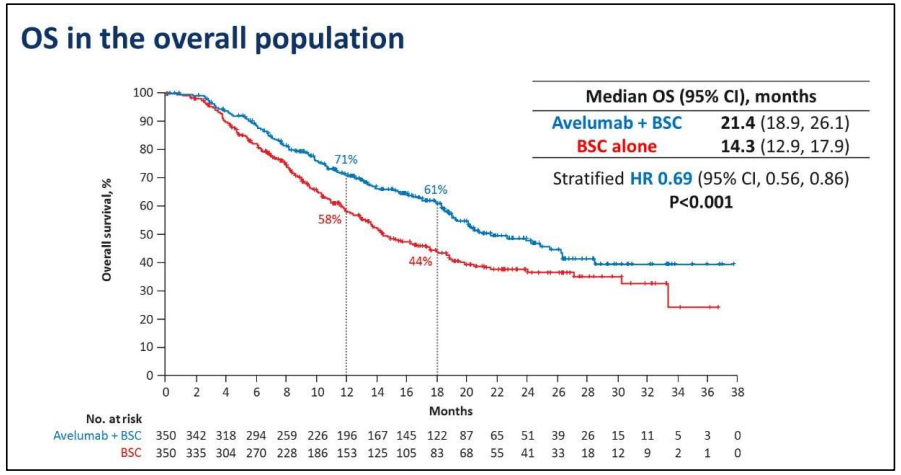
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

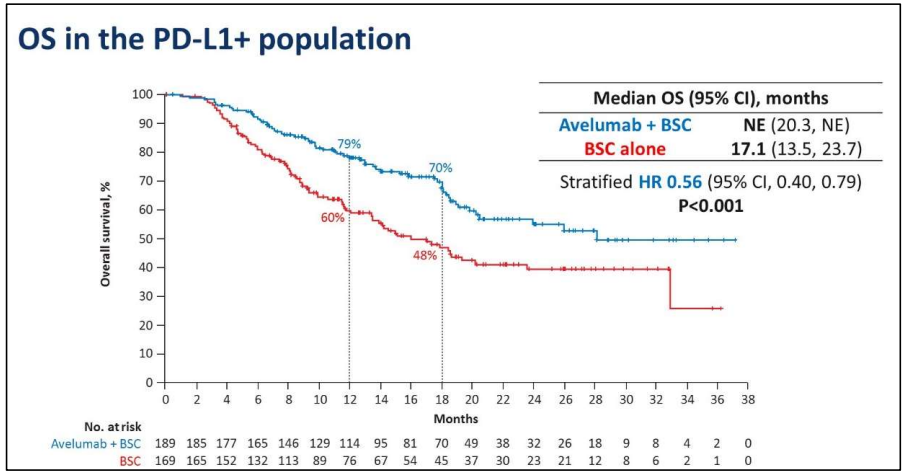
BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

New data: checkpoint inhibitor for maintenance treatment, first line

Drug	Indication	Dose
Avelumab	Maintenance of locally advanced/metastatic UC without progression on first-line platinum chemotherapy	10 mg/kg Q2W



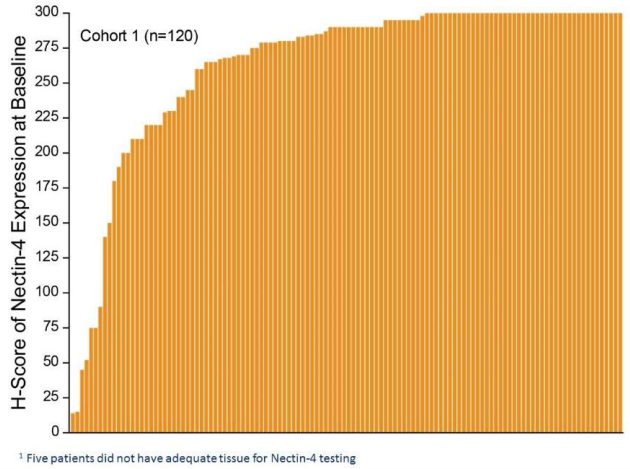


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

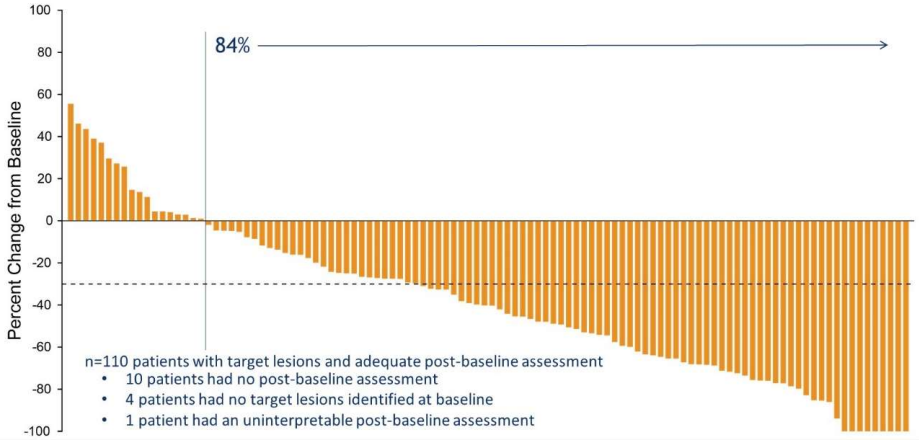
Drug	US FDA Approved	Indication	Dose
Enfortumab vedotin	December 2019 (Pending Health Canada)	Locally advanced/metatstatic UC with previous PD-1/PD-L1 and Platinum-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



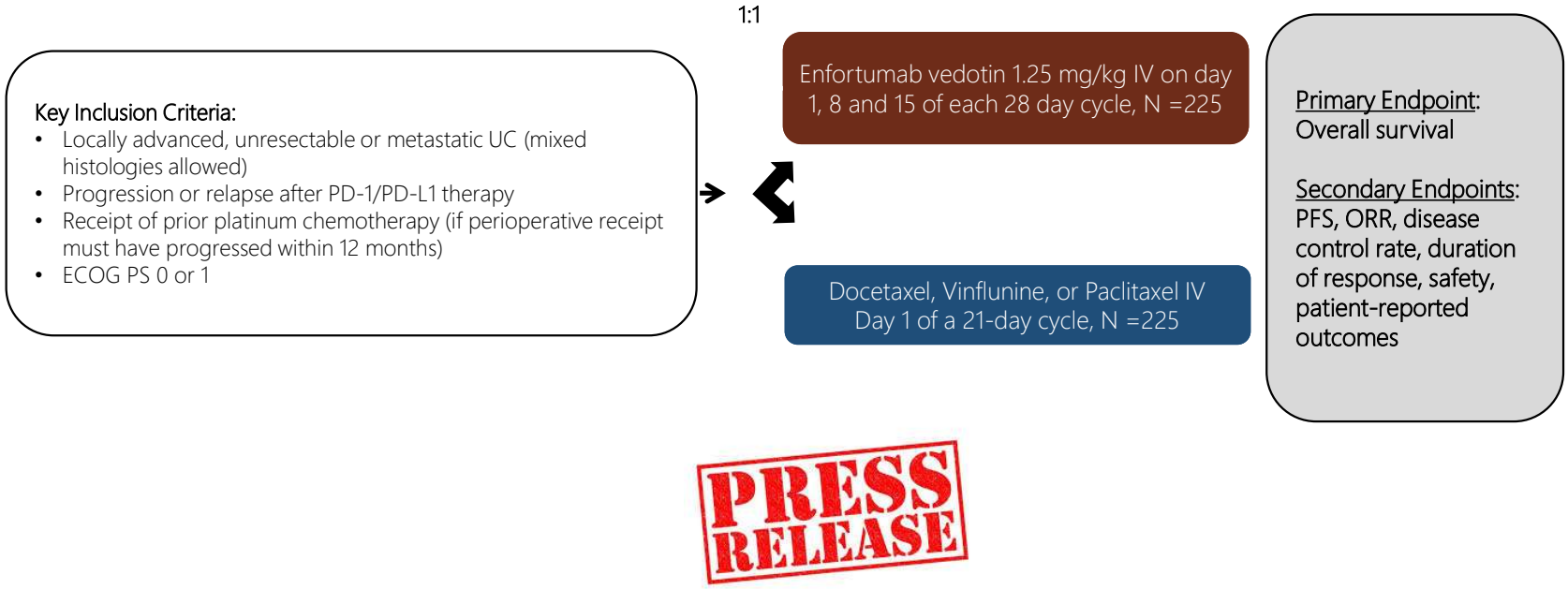
[1] Five patients did not have adequate tissue for Nectin-4 testing

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



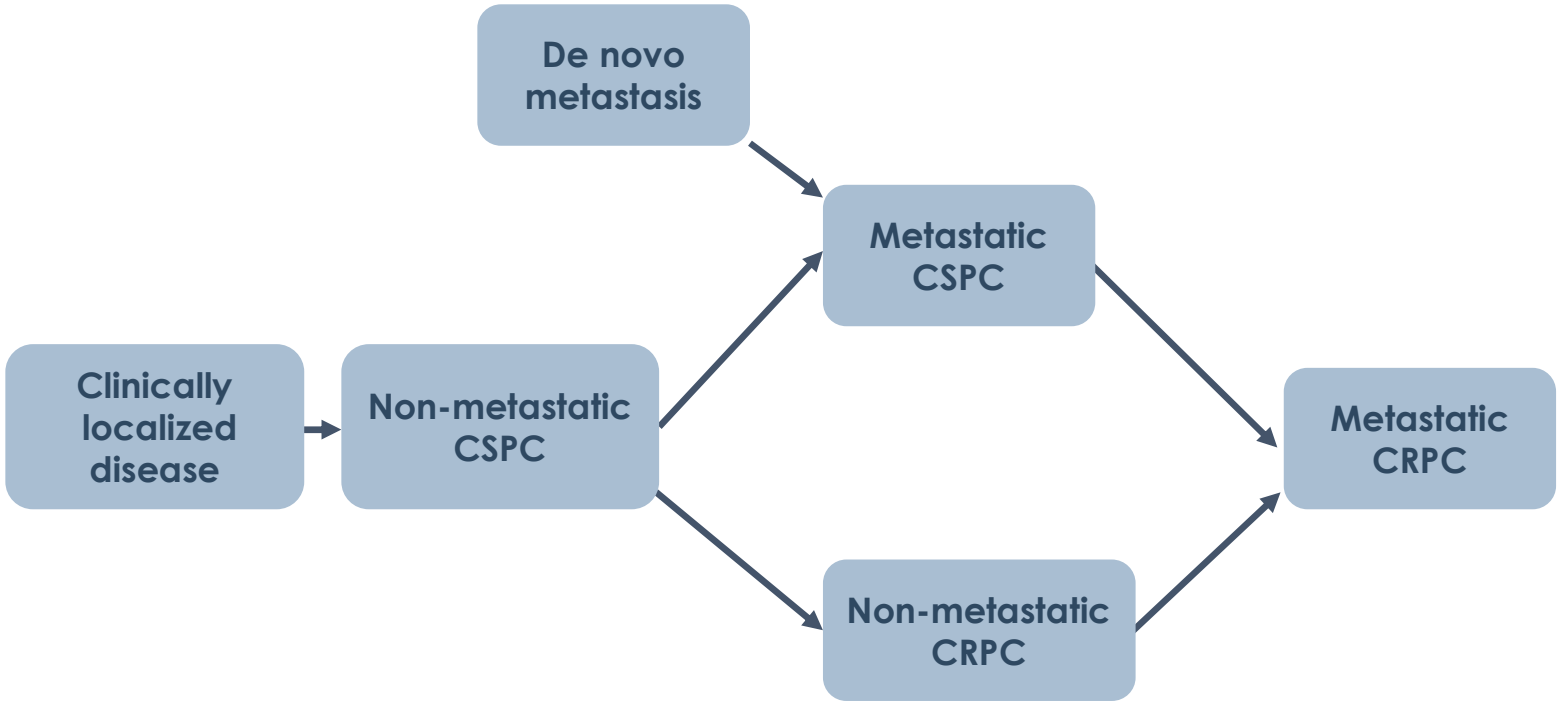
Petrylak, ASCO 2019.

EV 301 Phase 3 Study Design



SEPT 2020: Seattle Genetics and Astellas Announce PADCEV® (enfortumab vedotin) Significantly Improved Overall Survival in Phase 3 Trial in Previously Treated Locally Advanced / Metastatic Urothelial Cancer (HR OS = 0.70, HR PFS = 0.61)

The Spectrum of Prostate Cancer

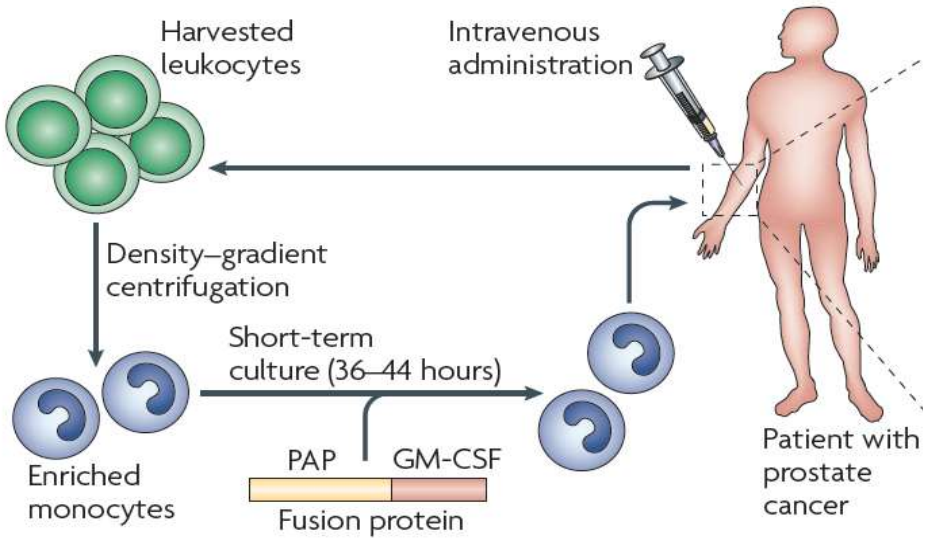


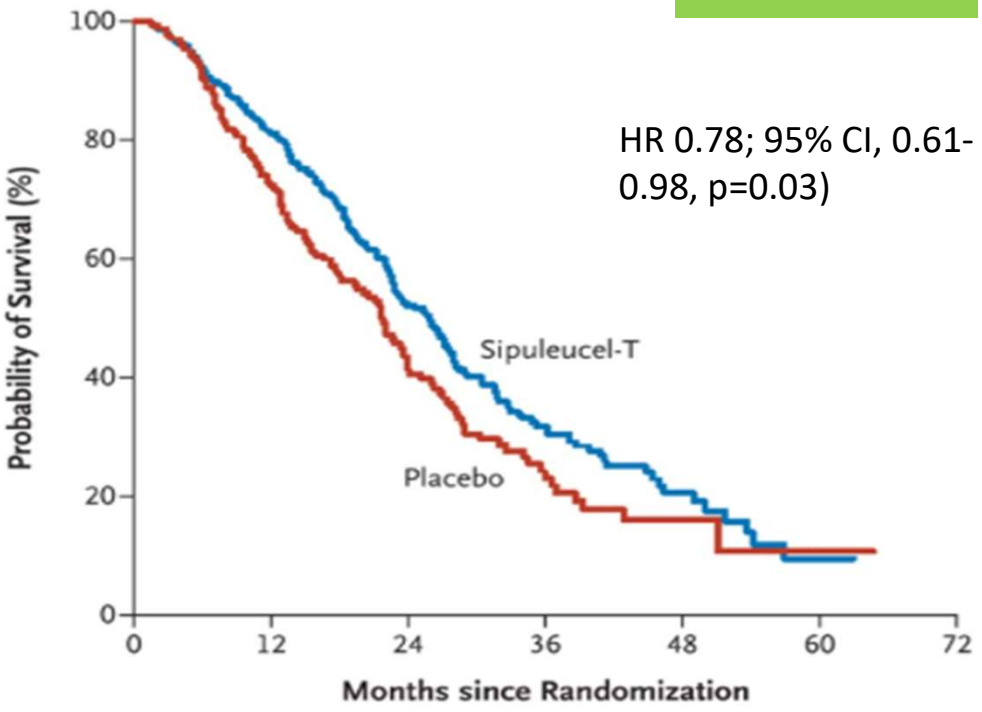
CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer; mCRPC, metastatic castrate-resistant prostate cancer
Figure adapted from Aggarwal RR et al. Oncology (Williston Park) 2017;31(6):467-474; Armstrong AJ et al. J Clin Oncol 2019;37(32):2974-2986; Chi KN et al. N Engl J Med 2019;381(1):13-24; Davis ID et al. N Engl J Med 2019;381(2):121-131; Smith MR et al. N Engl J Med 2018;378(15):1408-1418; Hussain M et al. N Engl J Med 2018;378(26):2465-2474.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine





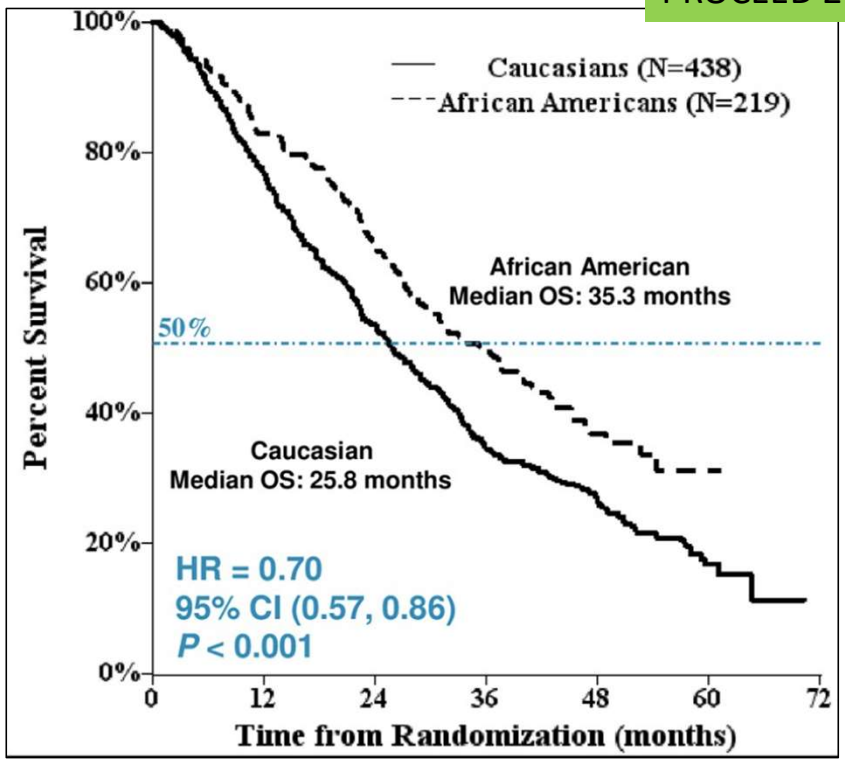
HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

Sipuleucel-T in mCRPC

PROCEED 2019

- Post-hoc analysis of Phase 3 trial PROCEED (N = 1902 mCRPC patients)
- African-Americans (AA) = 438; Caucasians (CAU) = 219
- Median OS = 35.2 (AA) vs 29.9 mo (CAU); HR 0.81, 95% CI 0.68–0.97; p = 0.03.
- AA race was independently associated with prolonged OS on multivariate analysis (HR 0.60, 95% CI 0.48–0.74; p < 0.001)

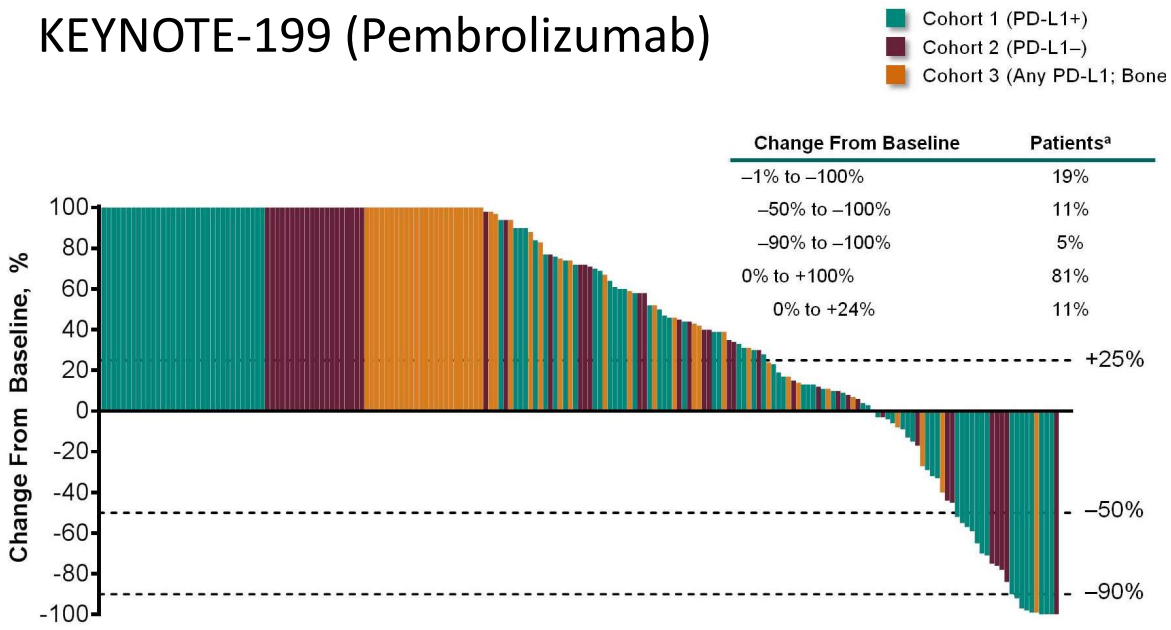


Sartor et al. ASCO 2019

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

KEYNOTE-199 (Pembrolizumab)



- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

DeBono et al. ASCO 2018

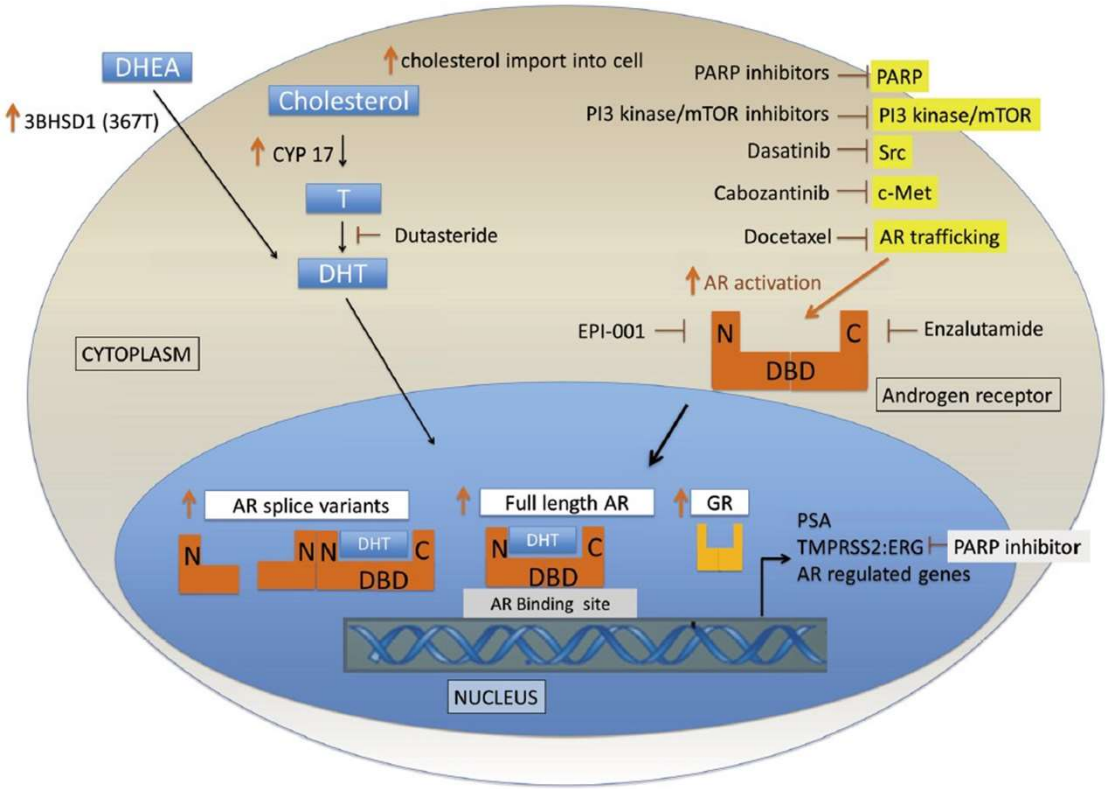
In development: nivolumab + ipilimumab in mCRPC

- Checkmate 650
- Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 doses, then Nivo 480 mg Q4W
- Progressed after 2nd-gen hormonal: 26% response @ 11.9 mo, 2 CR
- Progressed after chemo+hormonal: 10% response @ 13.5 mo, 2 CR
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Future Combinations in mCRPC to Engage Immune System

- Hormonal therapy
- Radiation
- Radium-223
- PARP inhibitors
- Chemotherapy
- New targets



Stein et al. Asian J Andrology 2014

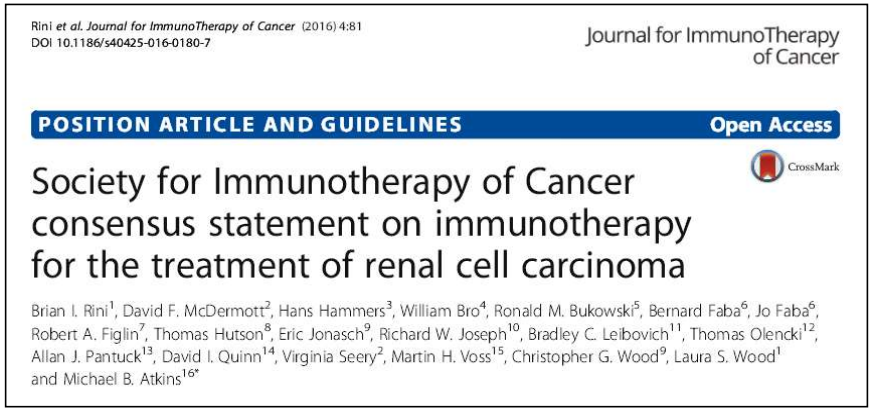
Conclusions

- The role of immunotherapy in GU malignancies is increasing
- In RCC, many front-line checkpoint inhibitor options are approved
  - Stay tuned for various adjuvant trials due to read out
- Multiple checkpoint inhibitors FDA approved for advanced/metastatic urothelial carcinoma
  - Maintenance therapy, with stable disease on platinum, will become standard of care
  - Combination immunotherapy plus chemotherapy has not proven successful yet
- Low immune engagement in prostate cancer has limited the application of immunotherapy in this disease at this time

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Additional Resources

Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES



Rini et al. Journal for ImmunoTherapy of Cancer (2016) 4:81
DOI 10.1186/s40425-016-0180-7

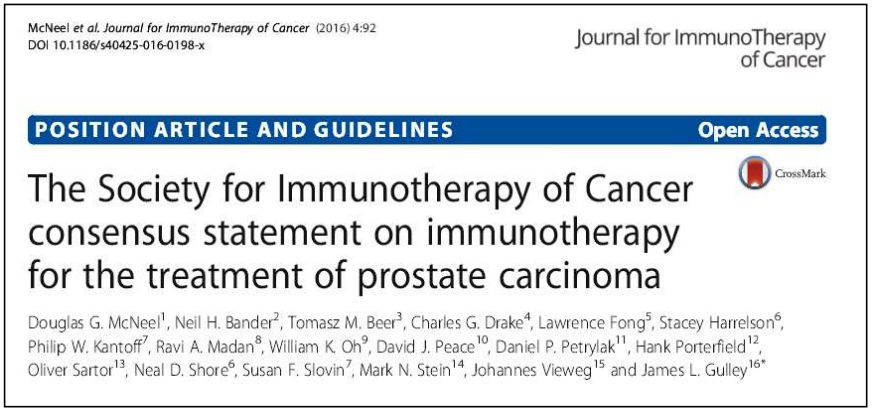
Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

CrossMark

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma

Brian I. Rini[1], David F. McDermott[2], Hans Hammers[3], William Bro[4], Ronald M. Bukowski[5], Bernard Faba[6], Jo Faba[6], Robert A. Figlin[7], Thomas Hutson[8], Eric Jonasch[9], Richard W. Joseph[10], Bradley C. Leibovich[11], Thomas Olencki[12], Allan J. Pantuck[13], David I. Quinn[14], Virginia Seery[2], Martin H. Voss[15], Christopher G. Wood[9], Laura S. Wood[1] and Michael B. Atkins[16*]



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

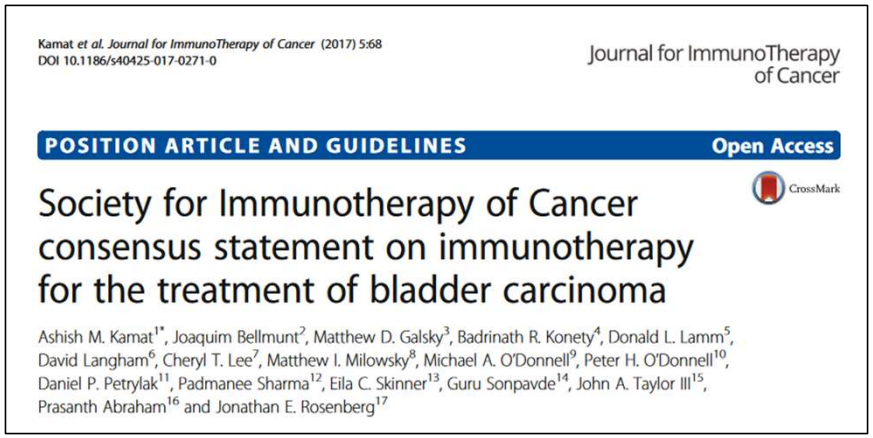
Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

CrossMark

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

CrossMark

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]

AAEM American Academy of Emergency Medicine · ACCC Association of Community Cancer Centers · HOPA Hematology/Oncology Pharmacy Association · sitc Society for Immunotherapy of Cancer

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Case Studies

Case Study 1

A 65-year-old male patient with de novo metastatic RCC presents for his first consultation. He has biopsy-proven clear cell RCC with sarcomatoid features. CT and bone scan demonstrate an 8x8 cm left renal mass, 2 pulmonary nodules (both <2 cm), one lytic bone metastasis on the sternum and another on the pelvis. His performance status is good with no functional limitations. Today, his blood work is notable for hemoglobin at 10 g/dL (lab normal 14-18) and platelet count of 500 (lab normal 150-400).

Which of the following is the most appropriate next step:

A. Consideration for cytoreductive nephrectomy followed by sunitinib, given IMDC=2 (intermediate risk)

B. Consideration for active surveillance

C. Consideration for sunitinib first, given IMDC=3 (poor risk) and limited benefit of combination immunotherapy in patients with sarcomatoid features

D. Consideration for combination immunotherapy upfront, given superiority over sunitinib and would defer cytoreductive nephrectomy given IMDC=3

Case Study 1

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Which of the following is the most appropriate next step:

A. Consideration for cytoreductive nephrectomy followed by sunitinib, given IMDC=2 (intermediate risk)

Incorrect: IMDC=3, surgery would not be preferred over systemic therapy

B. Consideration for active surveillance

Incorrect: This de novo presentation displays visceral and bone involvement and in general should proceed with upfront systemic therapy

C. Consideration for sunitinib first, given IMDC=3 (poor risk) and limited benefit of combination immunotherapy in patients with sarcomatoid features

Incorrect: combination immunotherapy (either ICI/ICI or ICI/TKI) has been shown to be superior to sunitinib and benefits are even greater in patients with sarcomatoid features

D. Consideration for combination immunotherapy upfront, given superiority over sunitinib and would defer cytoreductive nephrectomy given IMDC=3

Correct: combination IO/IO or IO/TKI would be the most appropriate upfront systemic therapy as there is no medical history precluding immunotherapy in this scenario. Patient elected for systemic combination therapy instead of cytoreductive nephrectomy and continues on therapies with improved quality of life from baseline at 12 months.

Case Study 2

A 67-year-old female patient presents with metastatic RCC. She previously had a right nephrectomy 5 years ago for localized clear-cell RCC, Fuhrman grade 4. Repeat imaging demonstrates recurrence in the nephrectomy bed, multi focal lesions in the opposite kidney, retroperitoneal and thoracic lymphadenopathy, with multiple pulmonary and 3 liver metastasis. Liver biopsy confirms recurrent clear cell RCC.

Which of the following statements is true:

A. Atezolizumab plus bevacizumab can be considered as first-line systemic therapy

B. Single agent Nivolumab could be considered as a standard first-line therapy

C. Consideration can be made for IL-2 given the potential liver toxicity from contemporary immunotherapy

D. Nivolumab plus ipilimumab has clearly demonstrated OS, PFS, and ORR benefits in this patient

Case Study 2

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Which of the following statements is true:

A. Atezolizumab plus bevacizumab can be considered as first-line systemic therapy

Incorrect: This combination has not been shown to improve overall survival compared to sunitinib and is not approved by regulatory agencies

B. Single agent Nivolumab could be considered as a standard first-line therapy

Incorrect: Currently, data dose not support the standard use of Nivolumab monotherapy as first-line option, outside of a clinical trial

C. Consideration can be made for IL-2 given the potential liver toxicity from contemporary immunotherapy

Incorrect: combination immunotherapy (either ICI/ICI or ICI/TKI) has been shown to be superior to sunitinib and has supplanted historic cytokines (IL-2, IFN) as the standard first-line approach for mRCC

D. Nivolumab plus ipilimumab has clearly demonstrated OS, PFS, and ORR benefits in this patient

***Correct*:** The CheckMate-214 study demonstrated superiority of Nivolumab/ipilimumab combination in intermediate/poor risk patients. Patient elected for this option, and remains progression free at 2 years.