

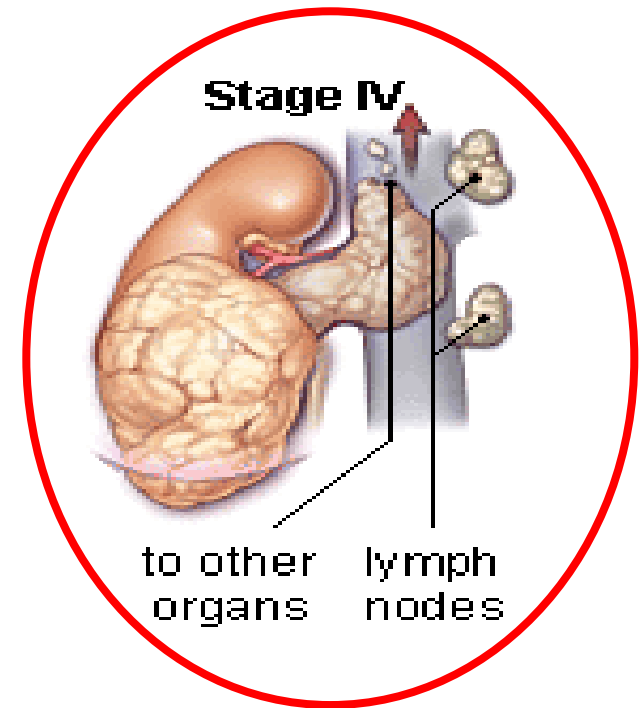
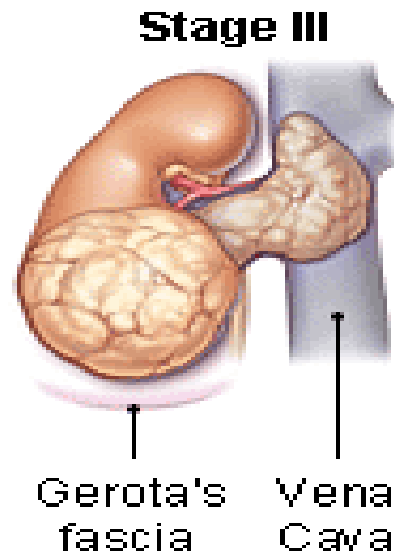
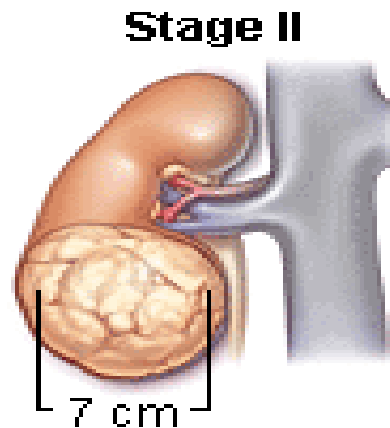
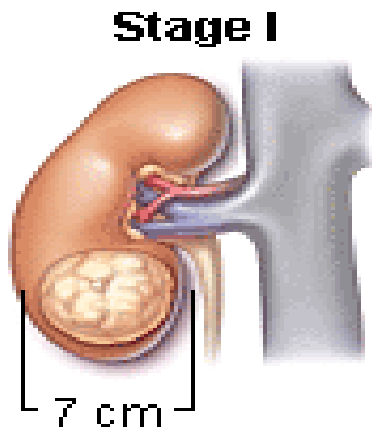
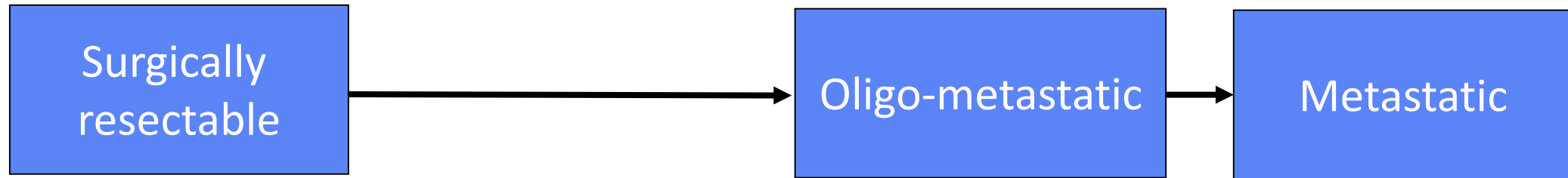
Immunotherapy for the Treatment of Genitourinary Malignancies

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Chief, Genitourinary Oncology Section
Levine Cancer Institute
Atrium Health

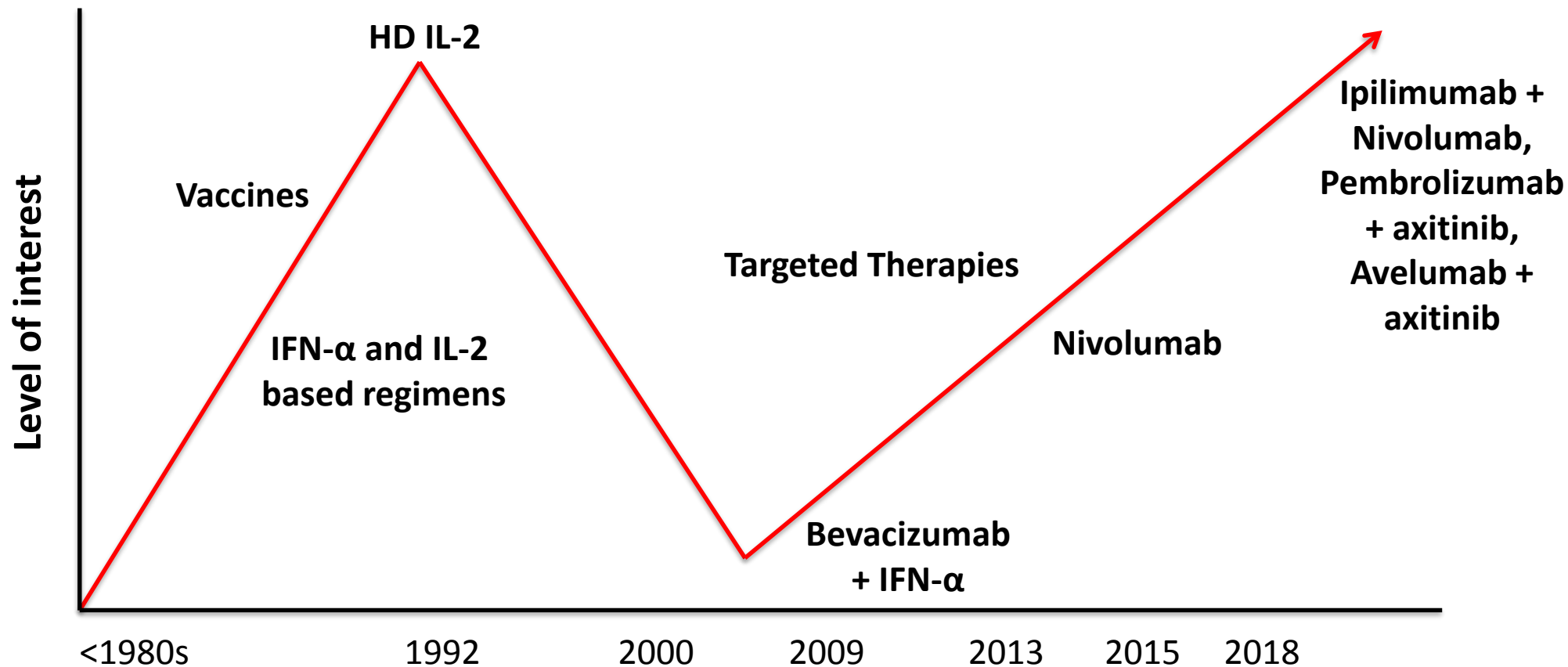
Disclosures

- Consulting: Bayer, Exelixis, Janssen
 - Research Funding: Pfizer
 - Ownership Interest: Exelixis, Gilead
-
- I will be discussing non-FDA approved indications during my presentation.

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



History of Immunotherapy in mRCC



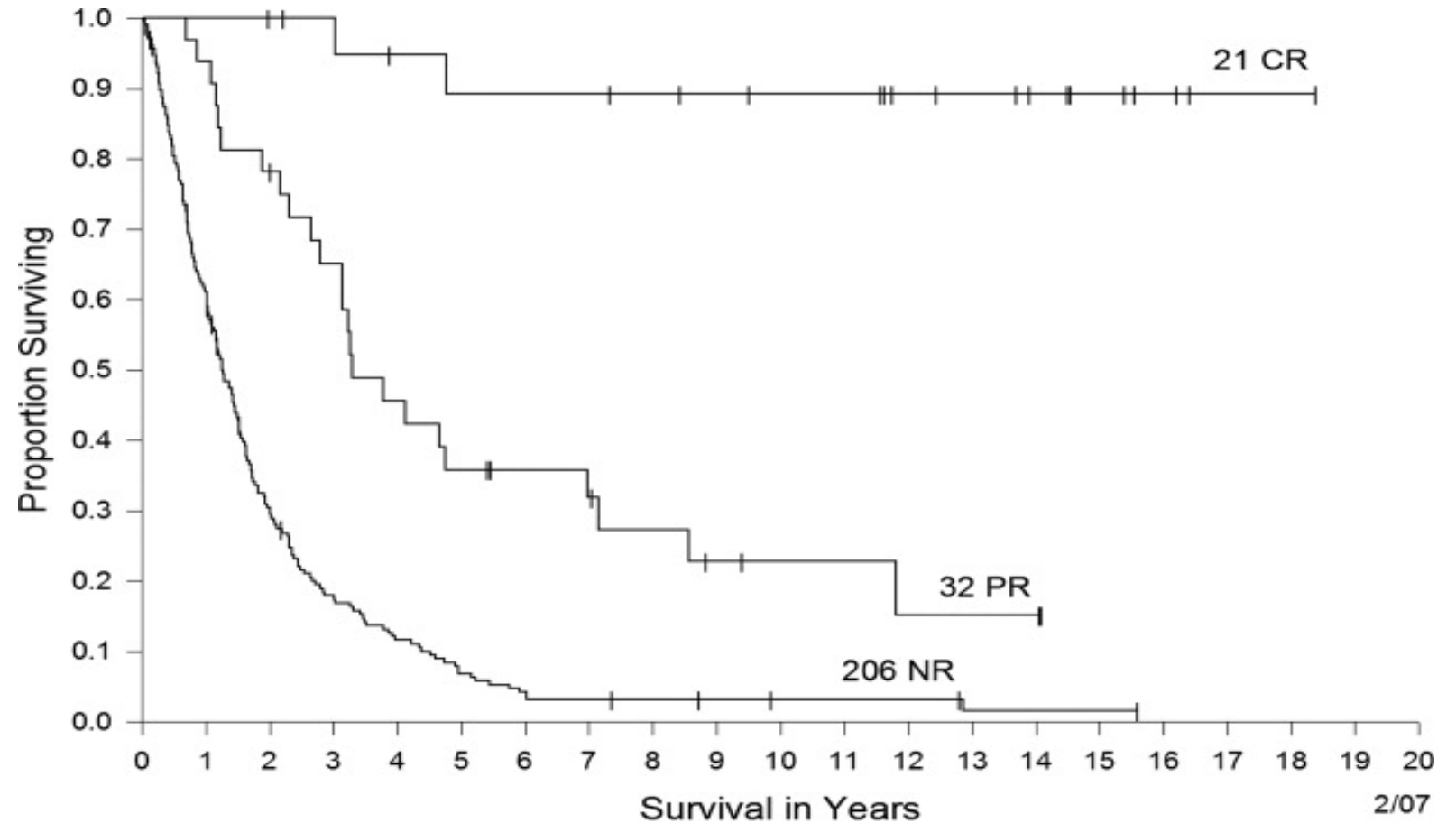
Resurgence of interest in immunotherapy

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-α + 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

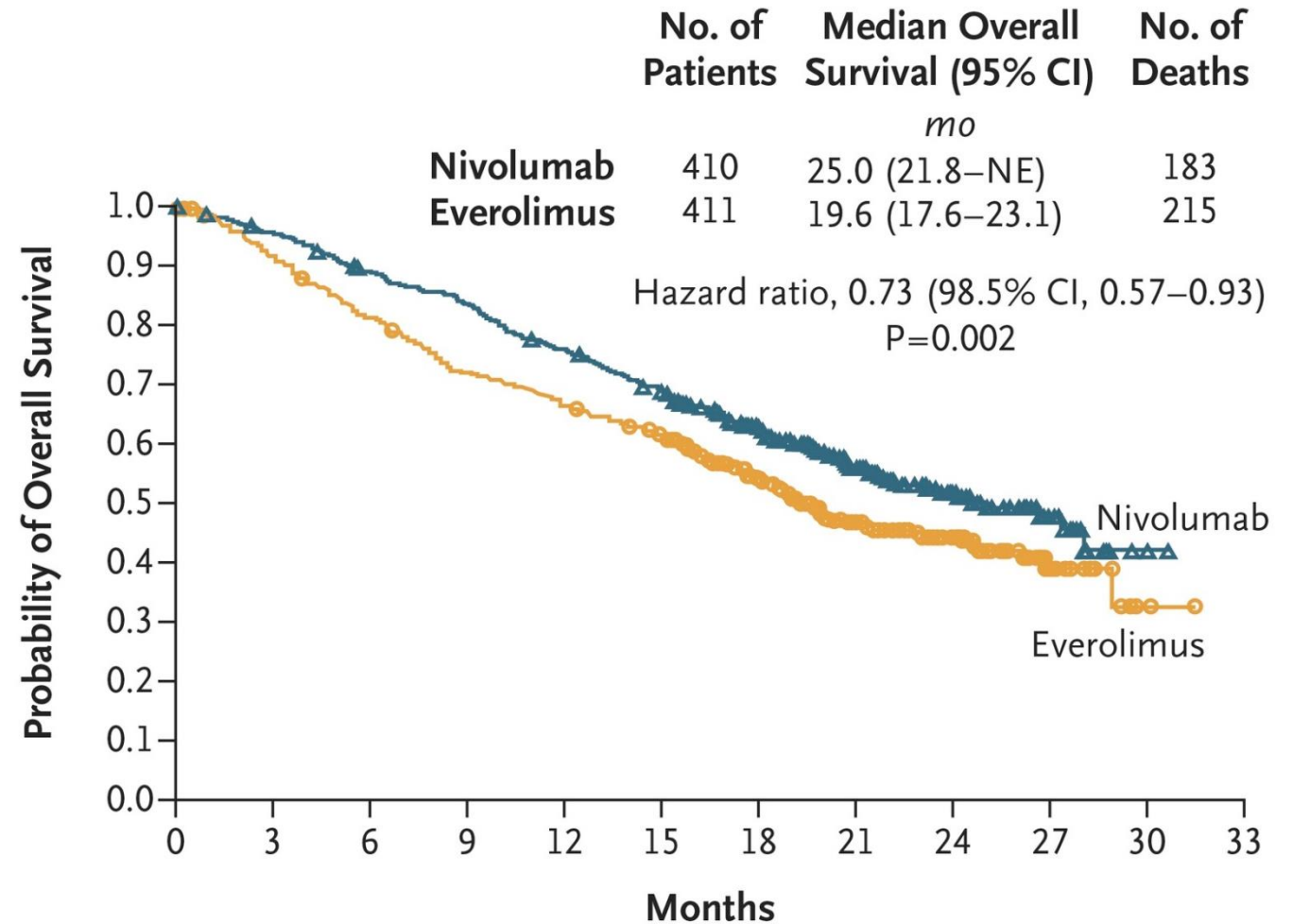
High Dose IL-2 in mRCC

- 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



Second-Line Nivolumab in mRCC

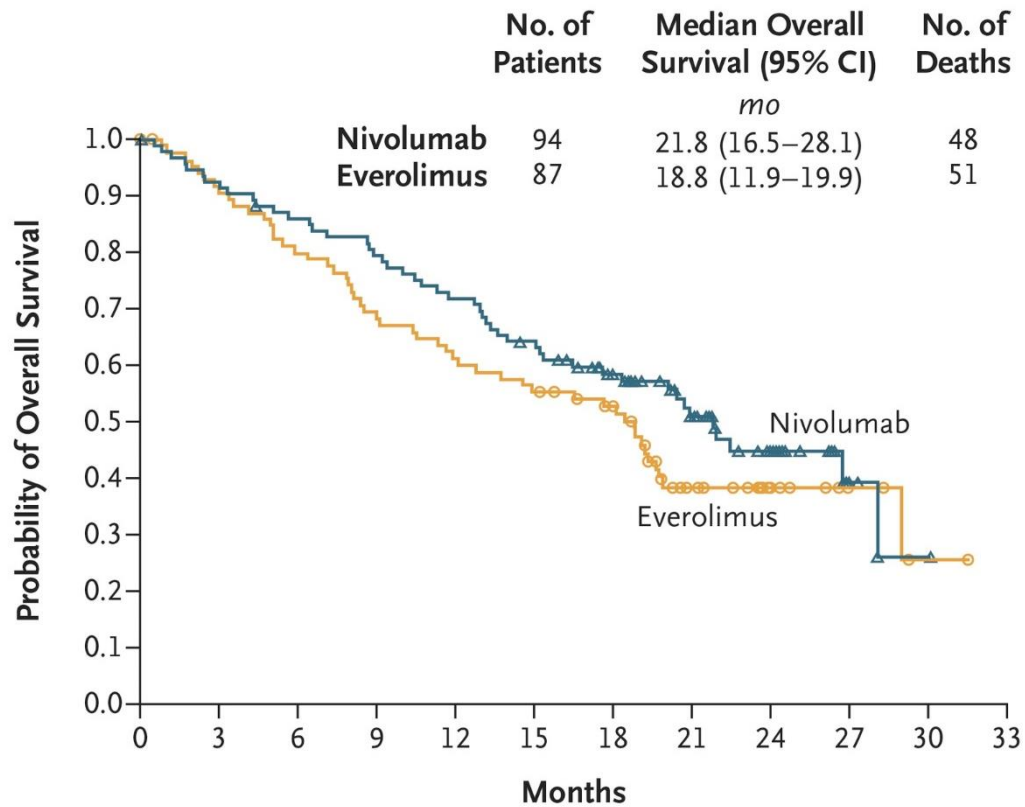
- CheckMate 025 Phase III trial
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)



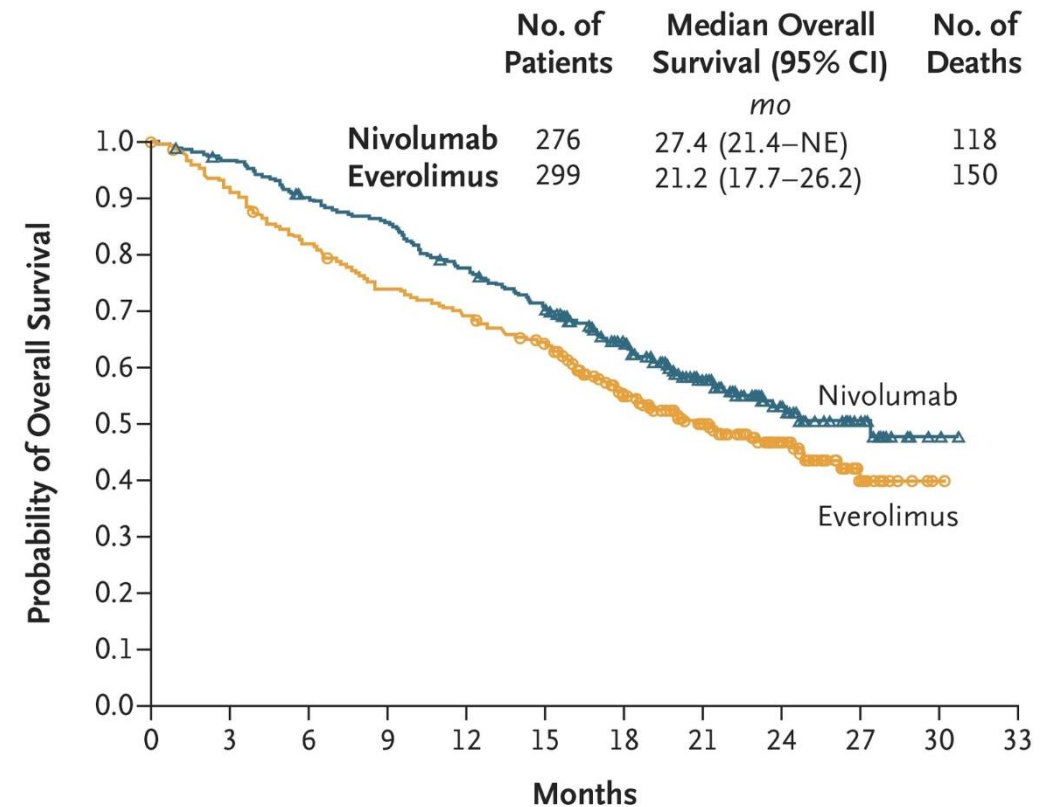
Second-Line Nivolumab in mRCC

PD-L1 subgroups

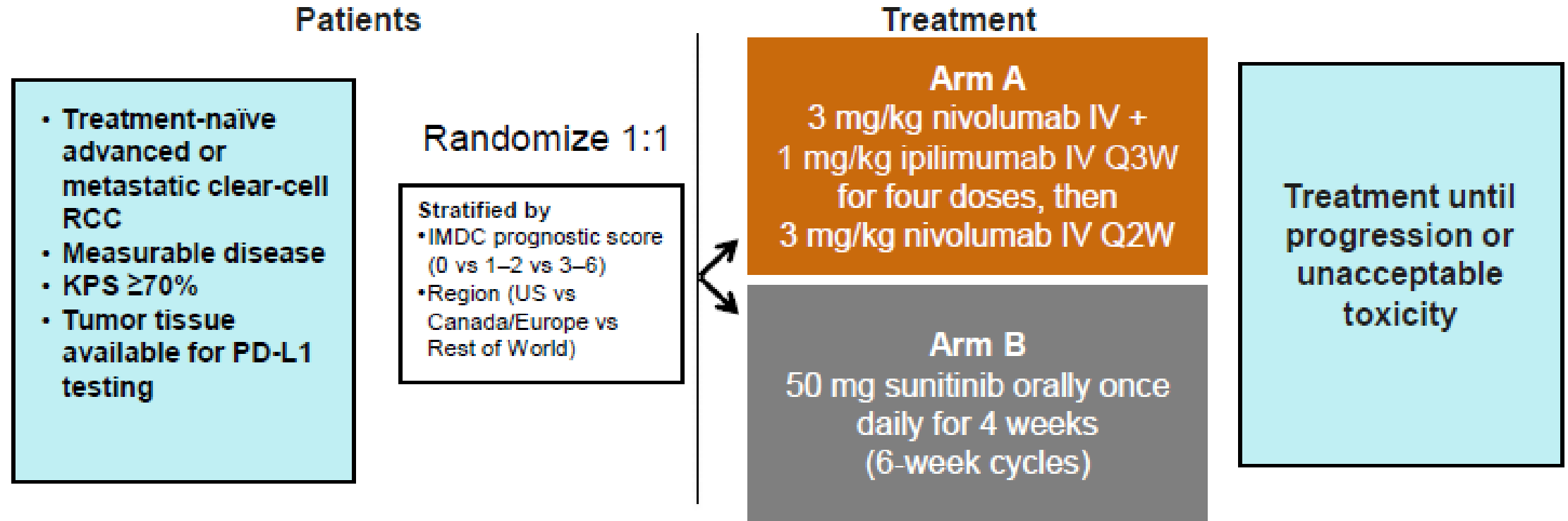
PD-L1 $\geq 1\%$



PD-L1 $< 1\%$



First-line Nivolumab + Ipilimumab in mRCC



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

IMDC = International Metastatic RCC Database Consortium

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

CheckMate 214

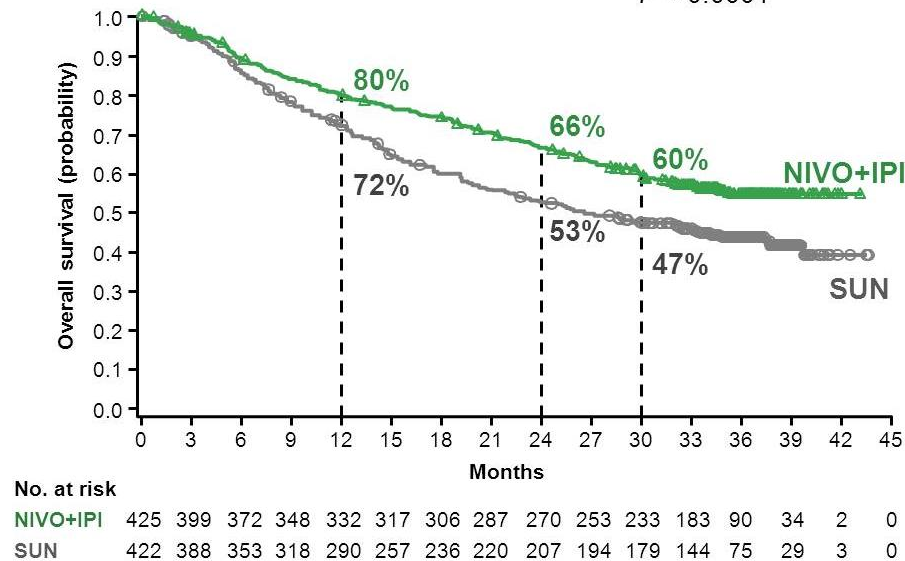
Follow-up
= 30 months

Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI NR (35.6–NE)
SUN 26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
 $P < 0.0001$

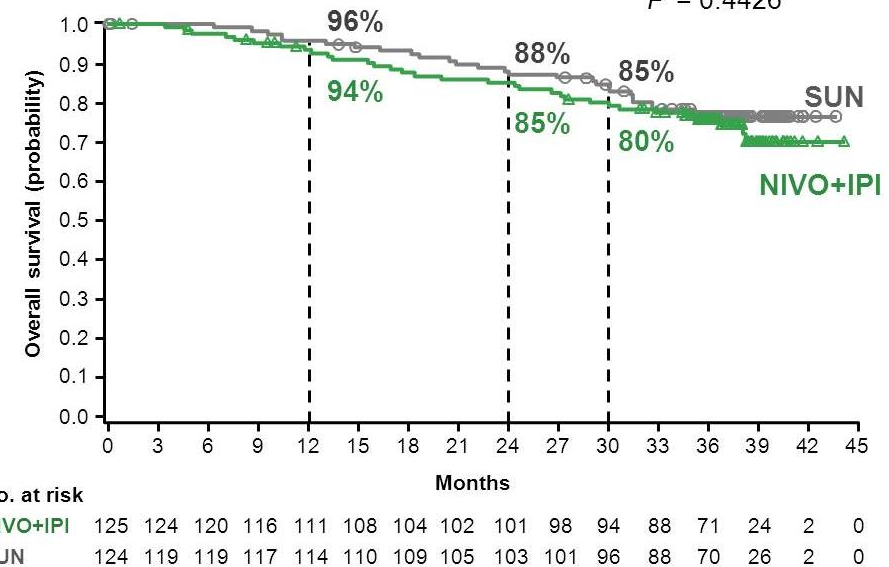


Favorable risk

Median OS, months (95% CI)

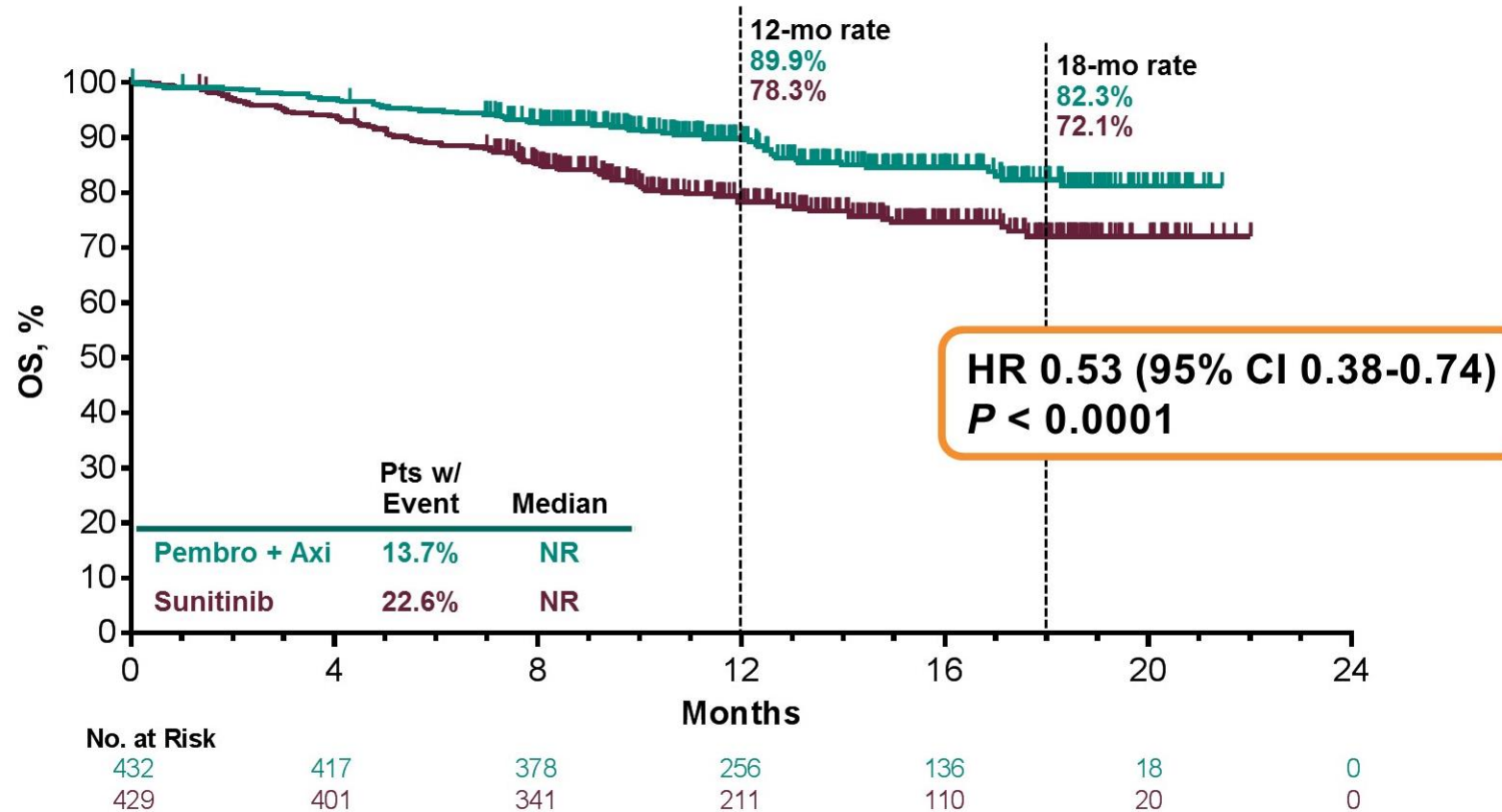
NIVO+IPI NR (NE)
SUN NR (NE)

HR (95% CI), 1.22 (0.73–2.04)
 $P = 0.4426$



First-line Pembrolizumab + axitinib in advanced RCC: overall survival

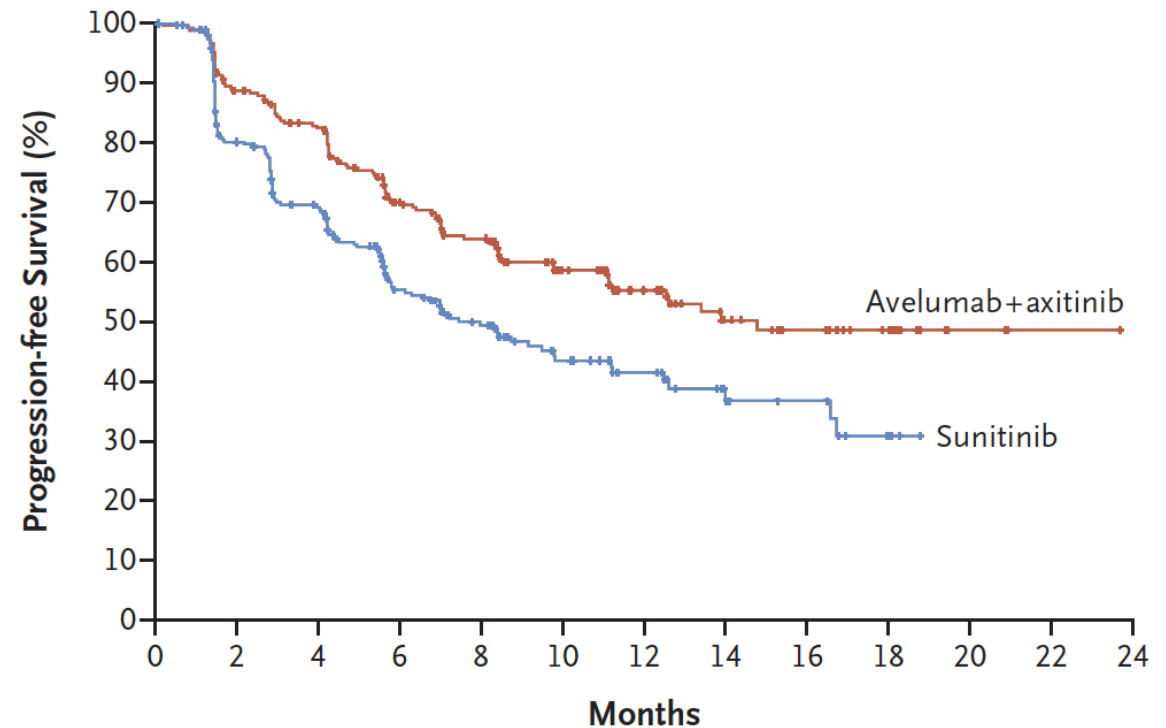
KEYNOTE-426: OS in the ITT Population



First-line avelumab + axitinib in mRCC: progression-free survival

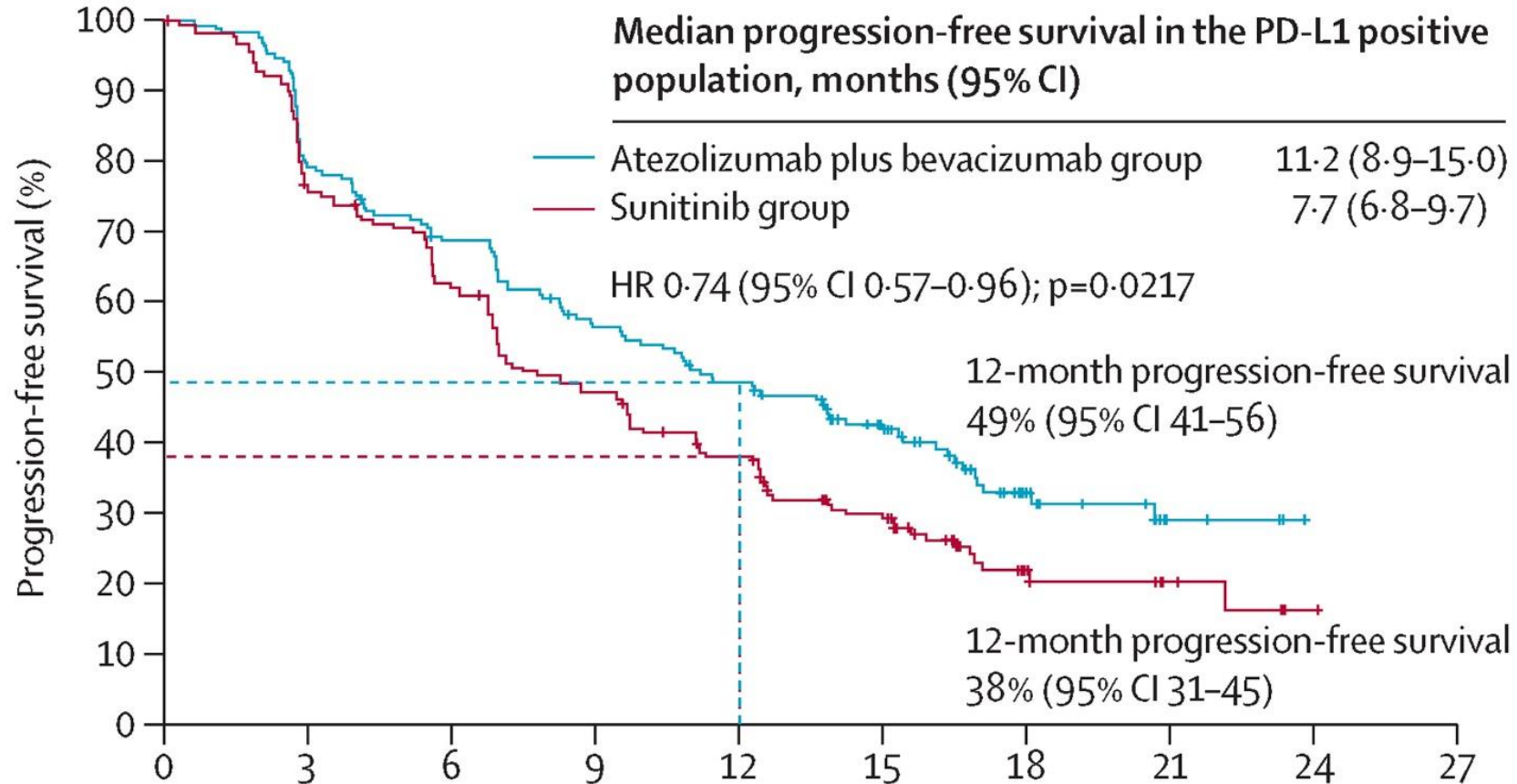
- Primary Endpoint: PFS and OS in PD-L1+
- Median PFS – 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR: 61.9% vs 29.7
- OS data: immature

JAVELIN 101 : PFS in the PD-L1+ Population

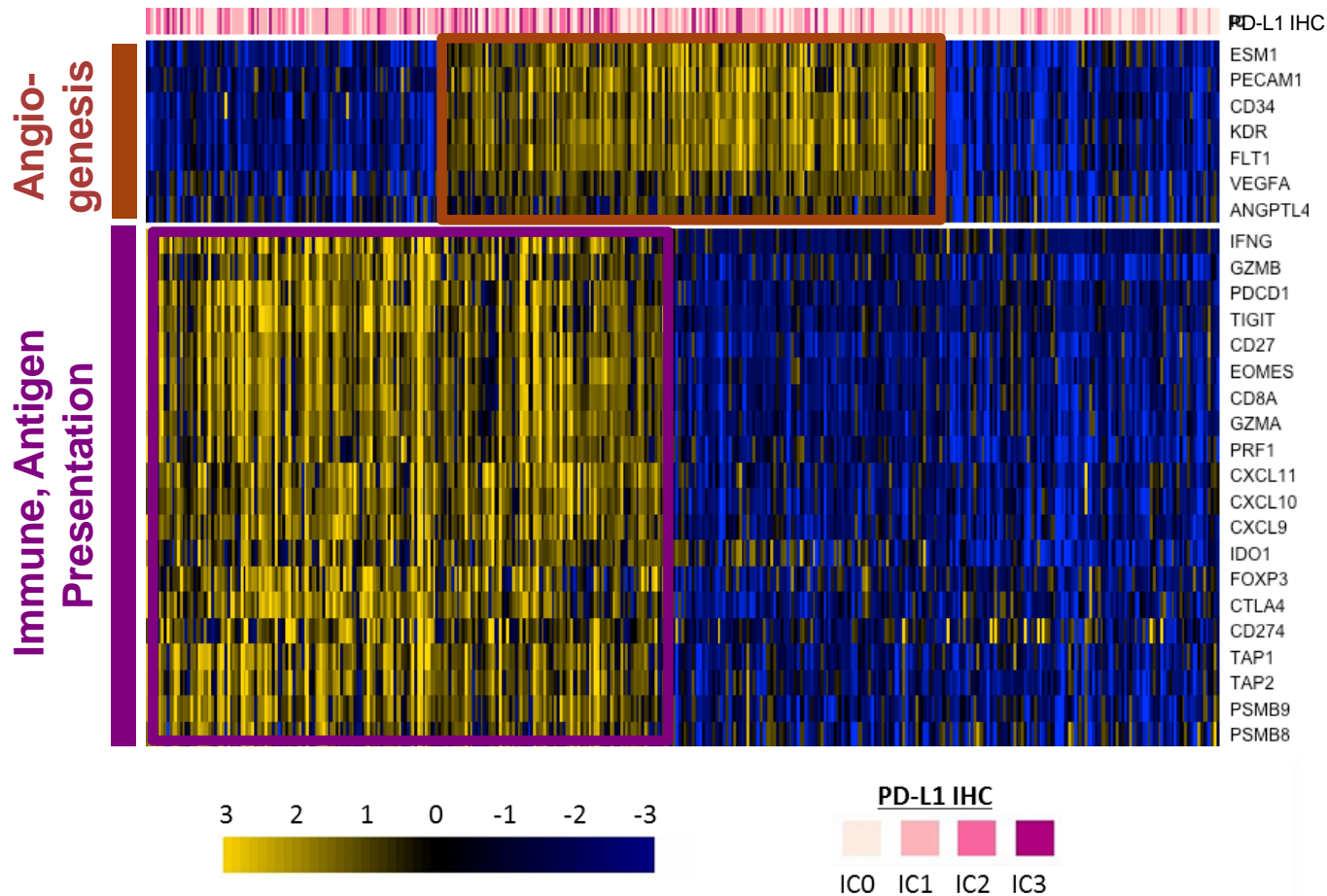


In Development: First-line atezolizumab + bevacizumab in PD-L1+ mRCC

Immotion151



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

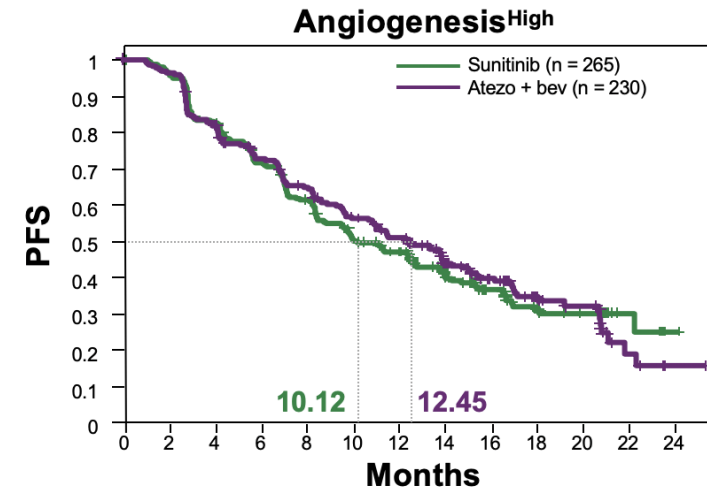
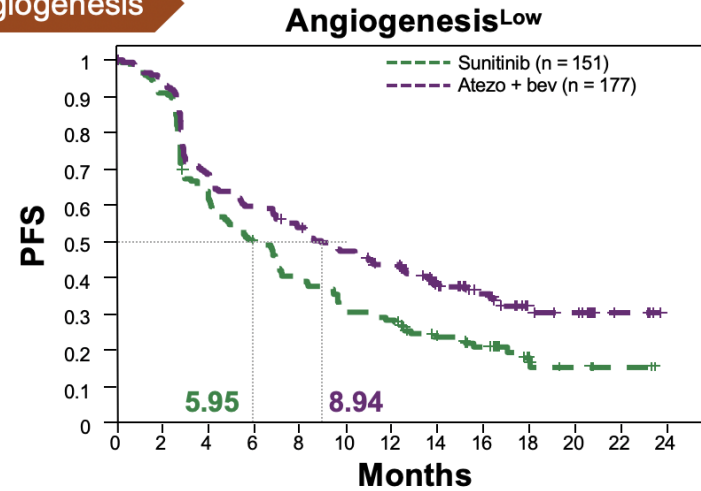


Identification of gene signatures based on association with clinical outcome

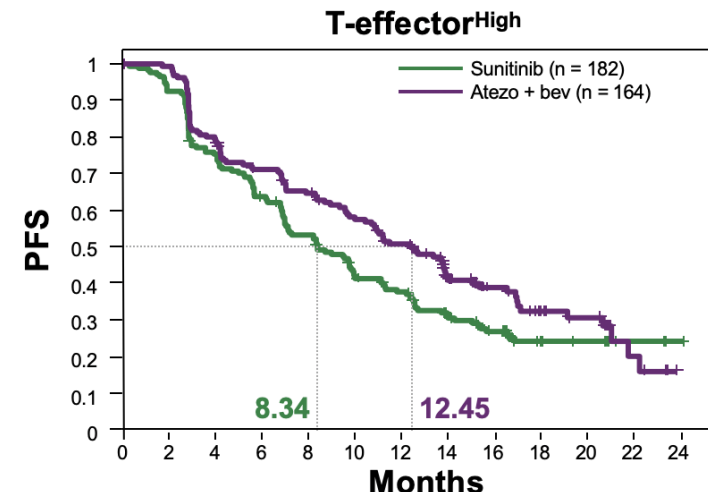
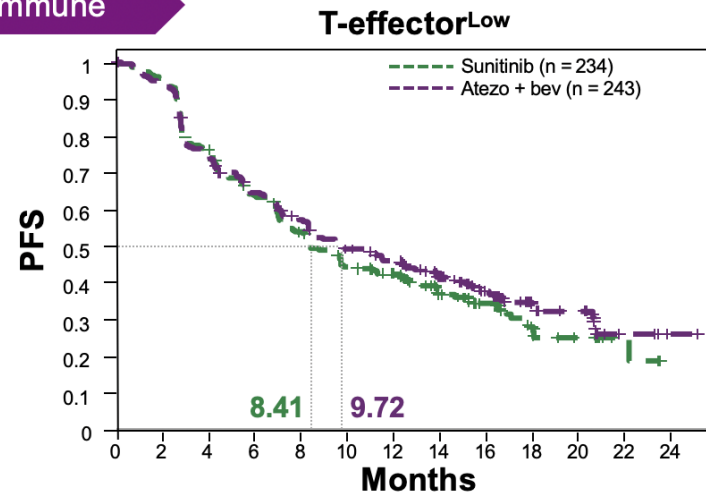
- T_{eff} : *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

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

Angiogenesis



Immune



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

	CheckMate 214	KEYNOTE-426	JAVELIN 101	IMmotion151
Intervention	Ipilimumab + Nivolumab	Pembrolizumab + Axitinib	Avelumab + Axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+	PFS in PD-L1+; OS
mOS, months	NR vs 37.9 (30 mo min followup)	NR vs NR (median 12.8 mo followup)	Not reported	33.6 vs 34.9 (median 24 mo followup)
PFS, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 7.2	11.2 vs 7.7
ORR (ITT), %	41% vs 34%	59.3% vs 35.7%	51.4% vs 25.7%	37% vs 33%
CR rate (ITT)	10.5% vs 1.8%	5.8% vs 1.9%	3.4% vs 1.8%	5% vs 2%
IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival				

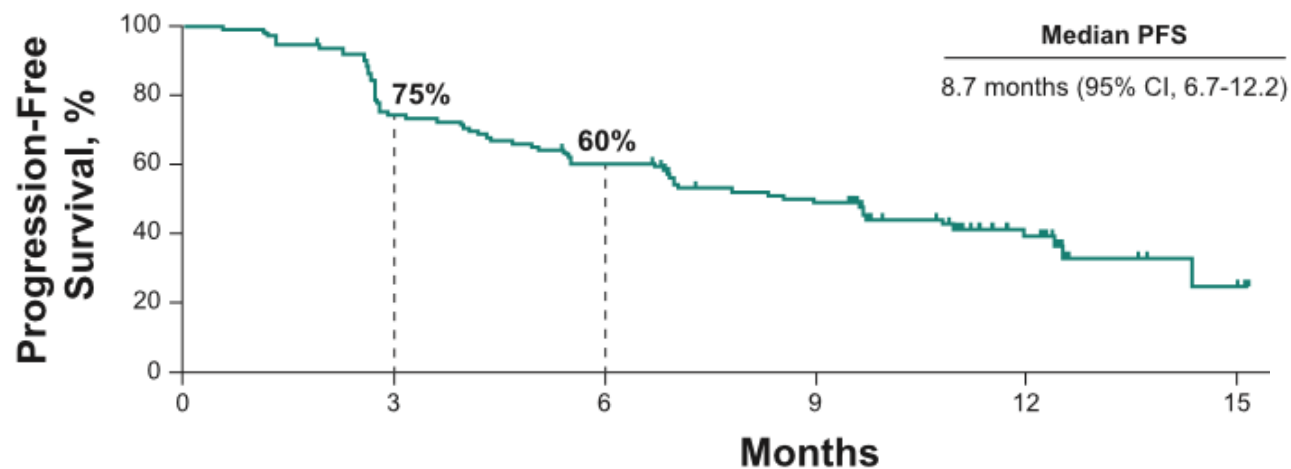
Tannir, ASCO GU 2019.
 Rini, NEJM 2019.
 Motzer, NEJM 2019.
 Rini, Lancet 2019.

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
NCT03141177	CheckMate 9ER	Cabozantinib + Nivolumab	Sunitinib	630	PFS
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					

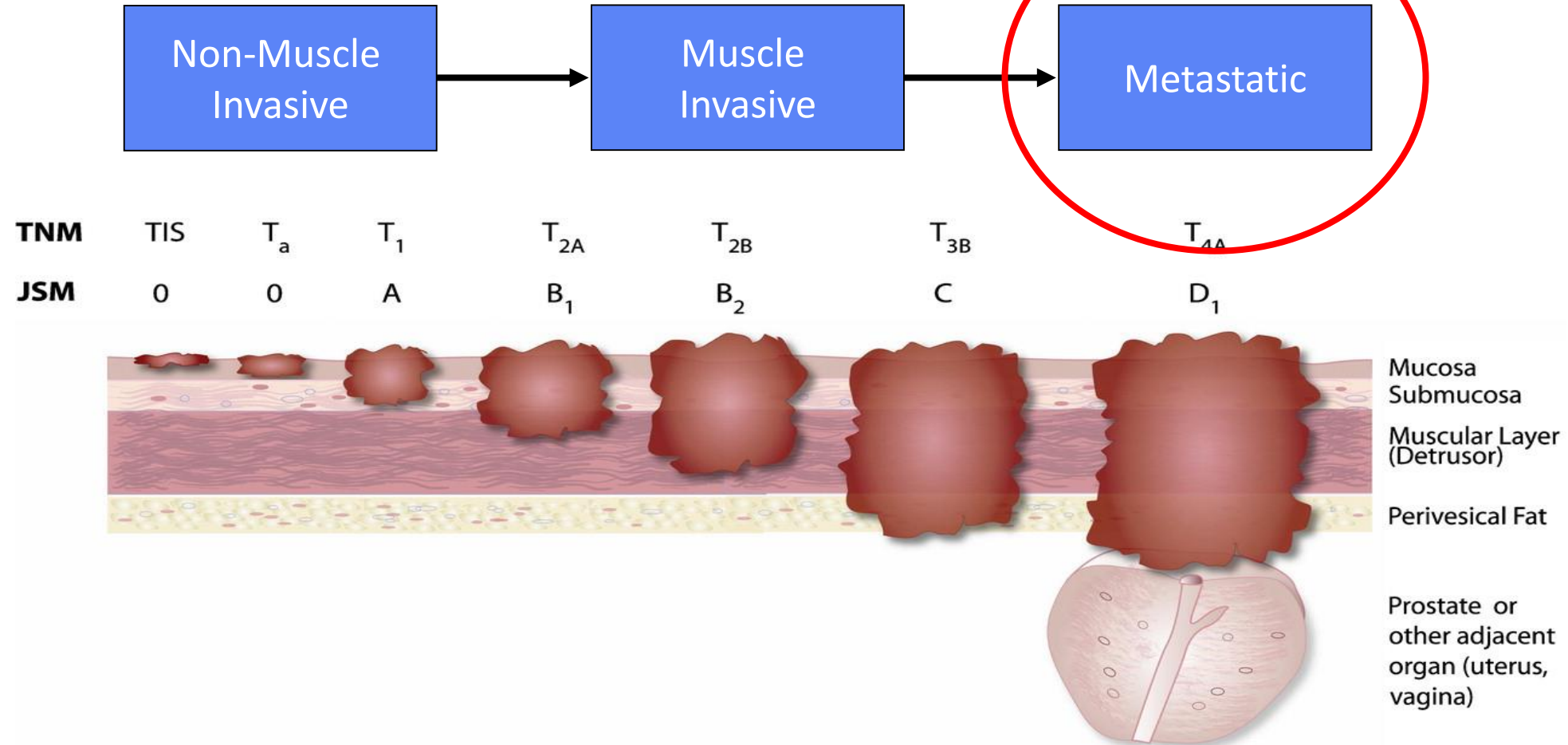
In Development: First-line pembrolizumab monotherapy in mRCC

KEYNOTE - 427



	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



Approved 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

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

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

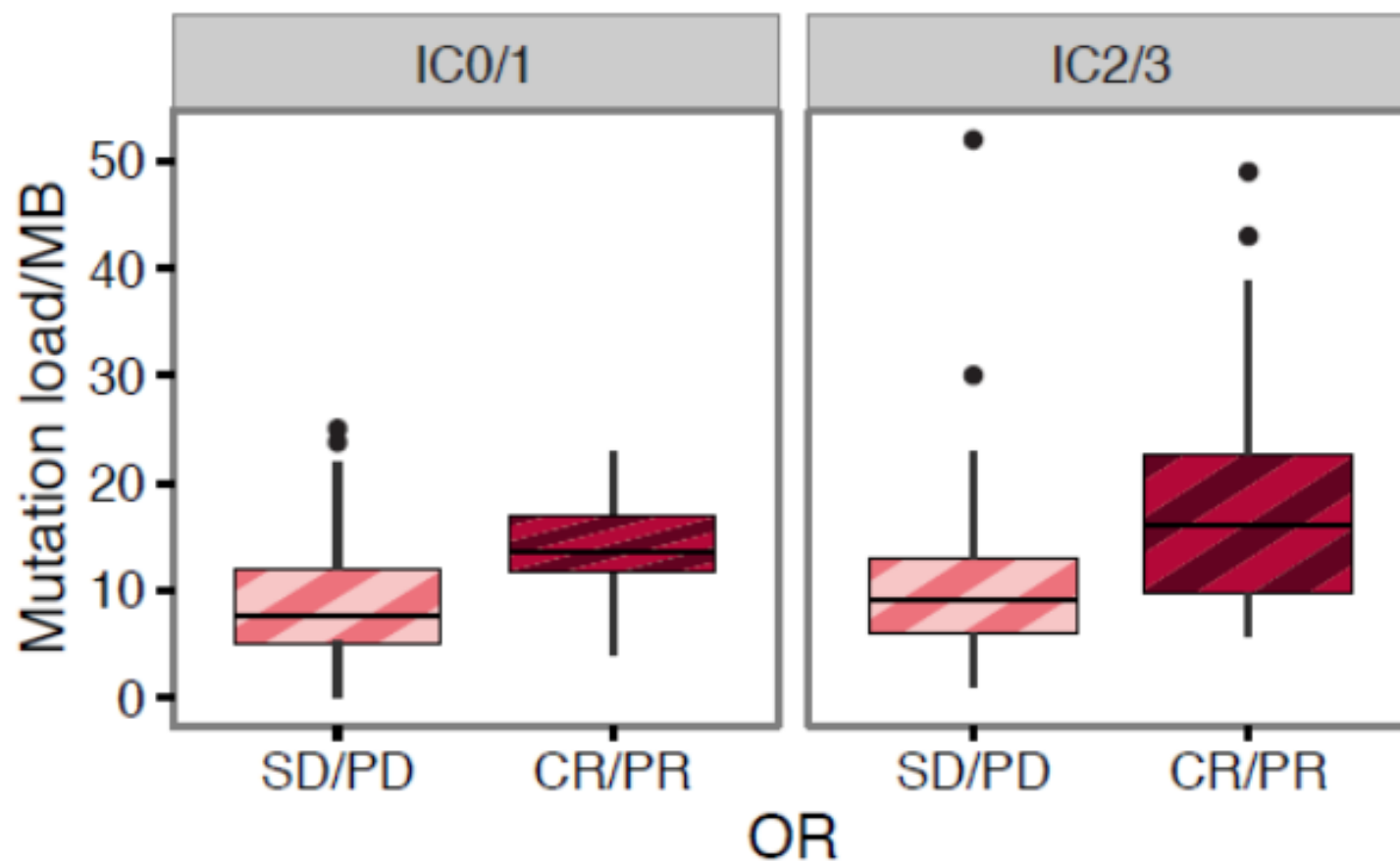
June 2018

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 $\geq 5\%$ tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status

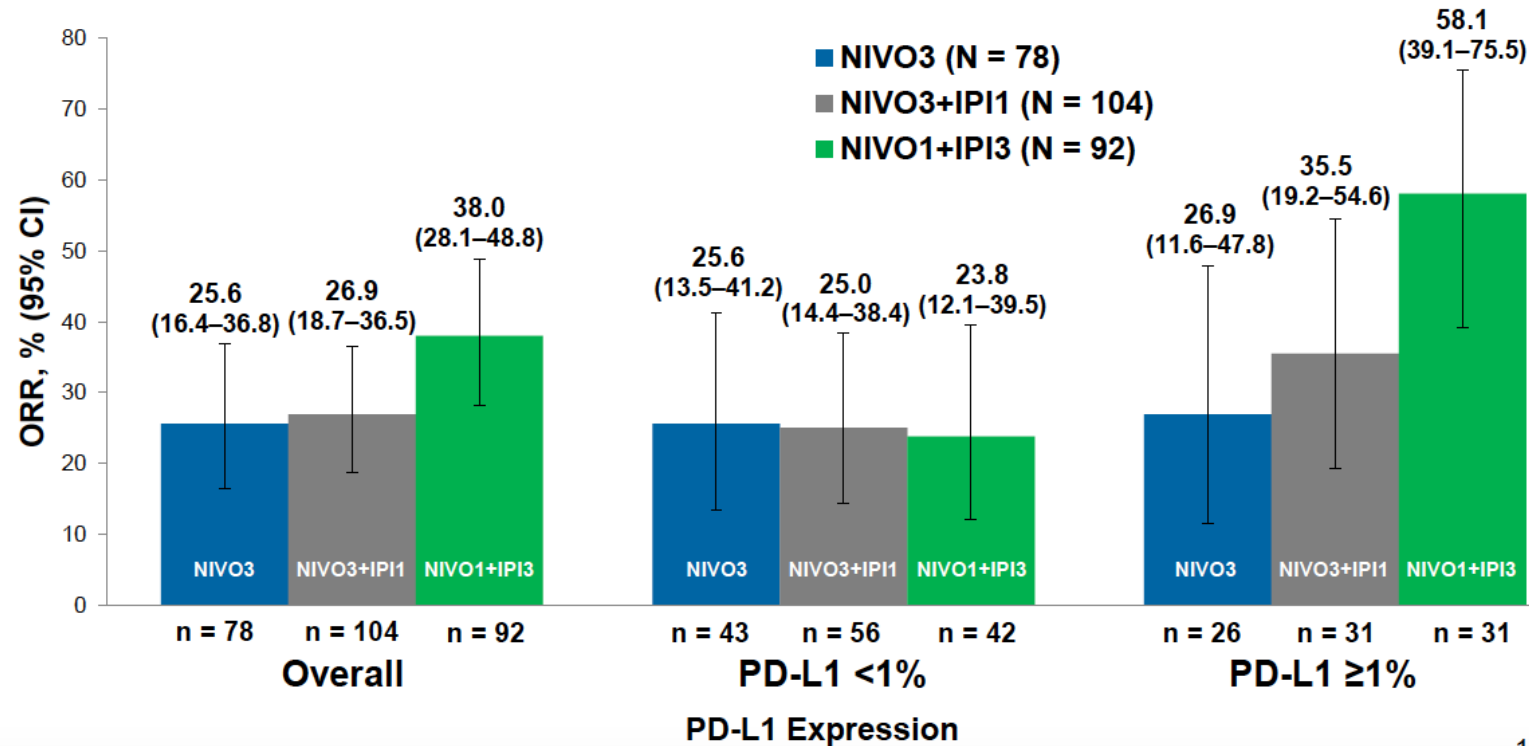
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



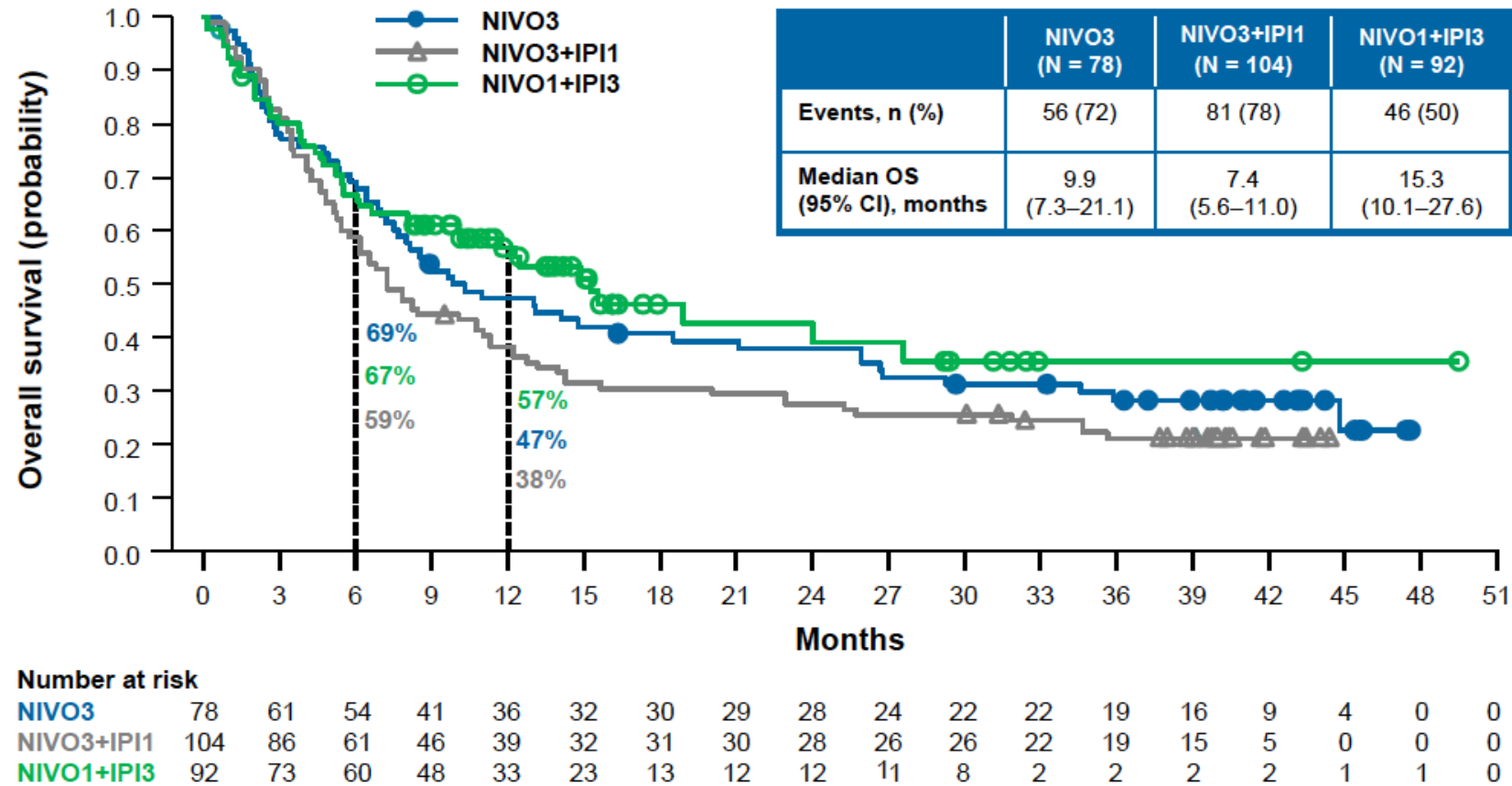
In development: Ipilimumab + Nivolumab CheckMate 032

ORR by Baseline Tumor PD-L1 Expression per Investigator



13

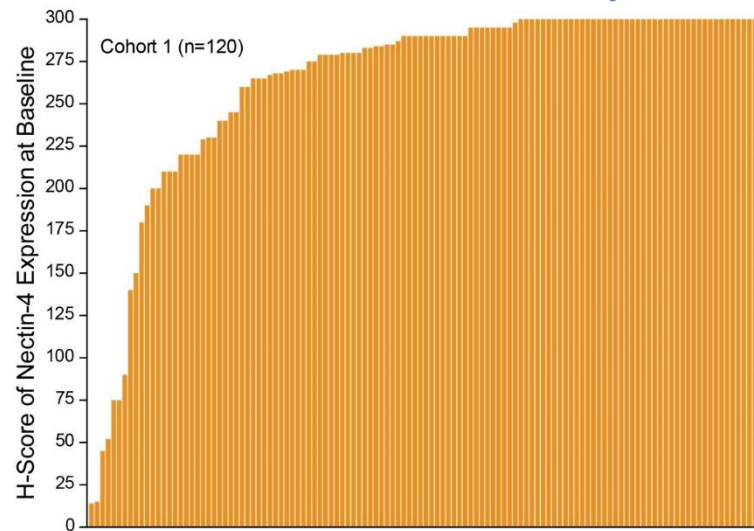
In development: Ipilimumab + Nivolumab CheckMate 032



Approved antibody-drug conjugate for mUC

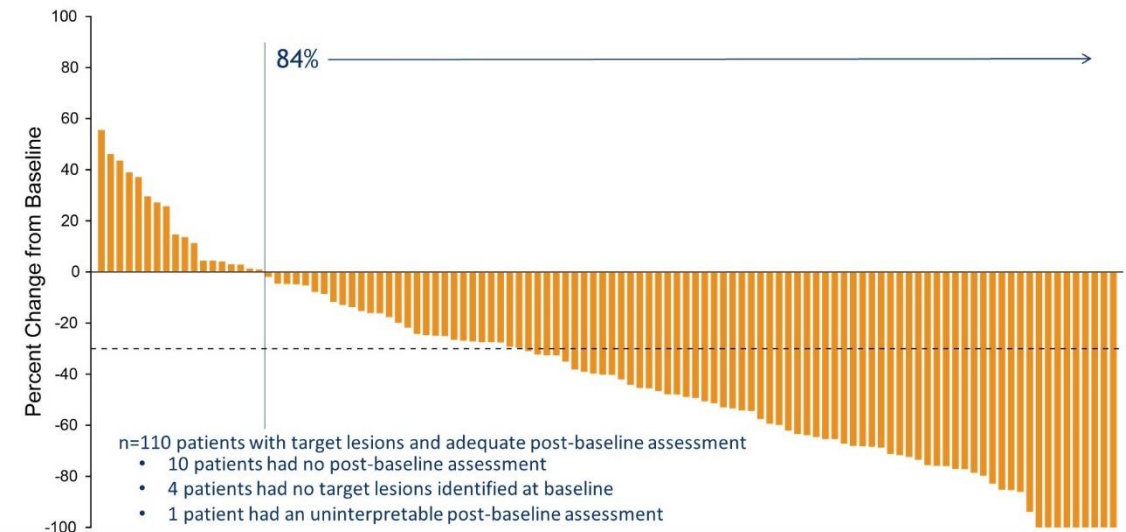
Drug	Approved	Indication	Dose
Enfortumab vedotin	December 2019	Locally advanced/metastatic UC with previous α PD-1/PD-L1 and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression

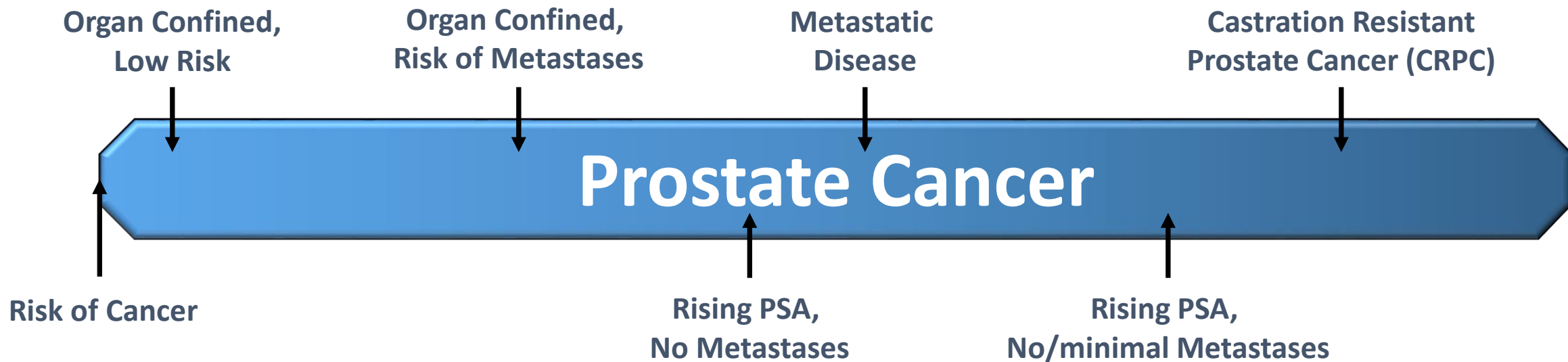


¹ Five patients did not have adequate tissue for Nectin-4 testing

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



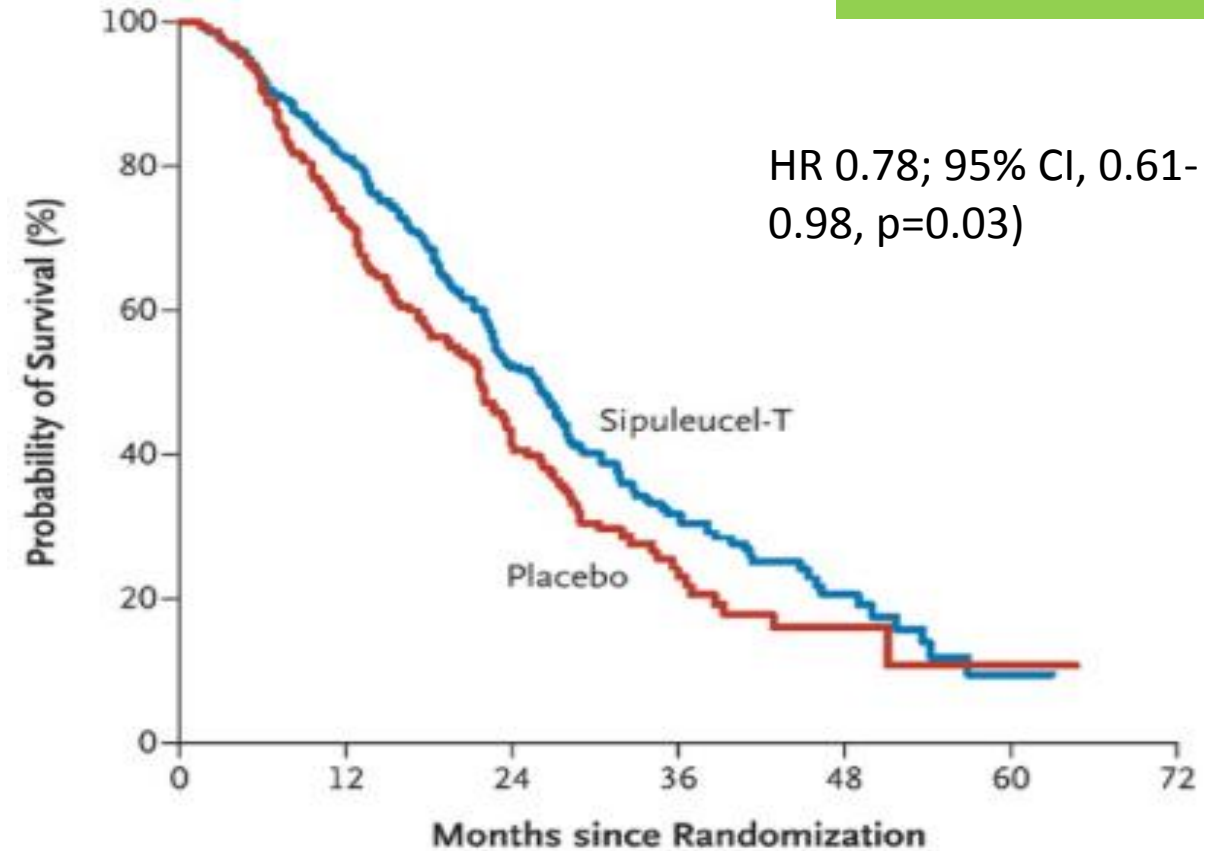
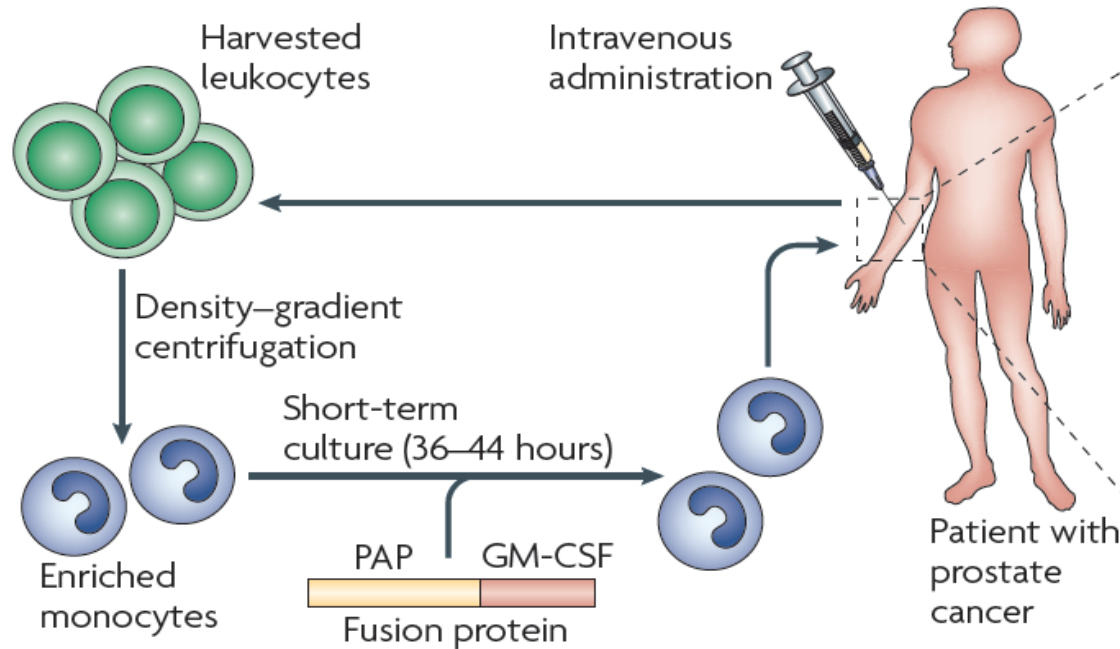
The Spectrum of Prostate Cancer



Sipuleucel-T in mCRPC

PROVENGE 2010

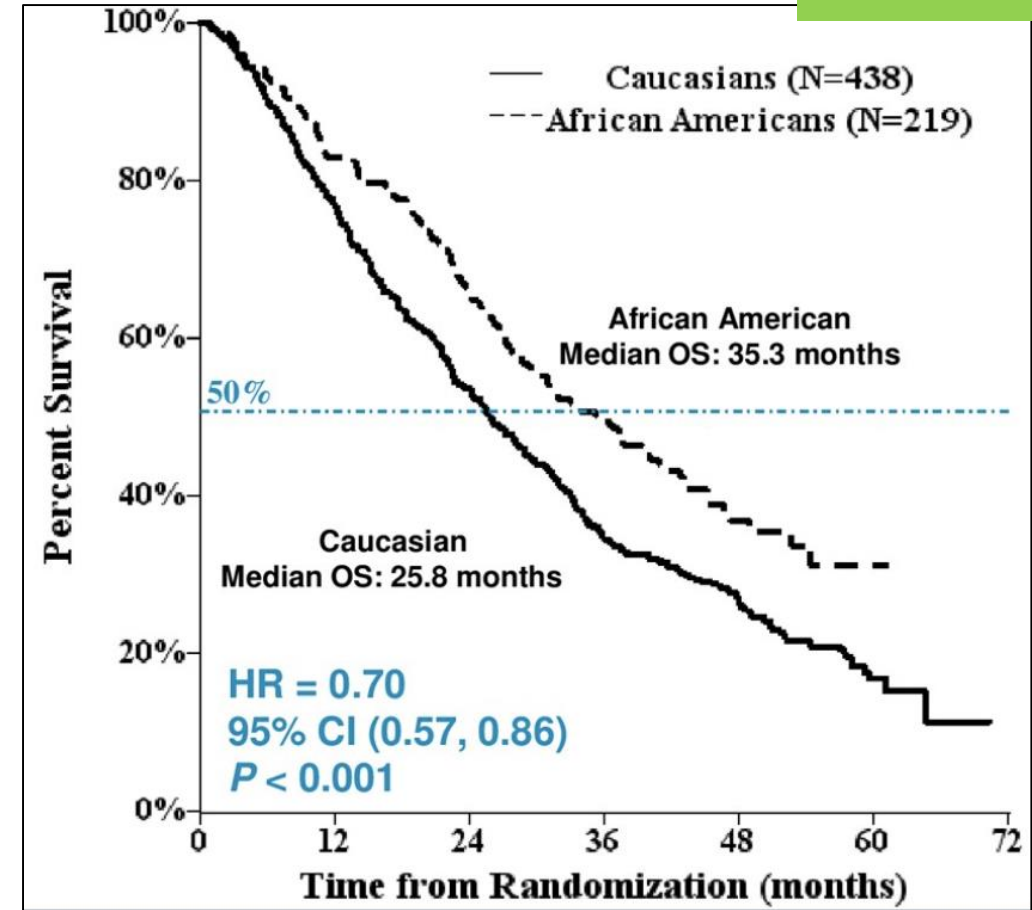
First anti-cancer therapeutic vaccine



Sipuleucel-T in mCRPC

PROCEED 2019

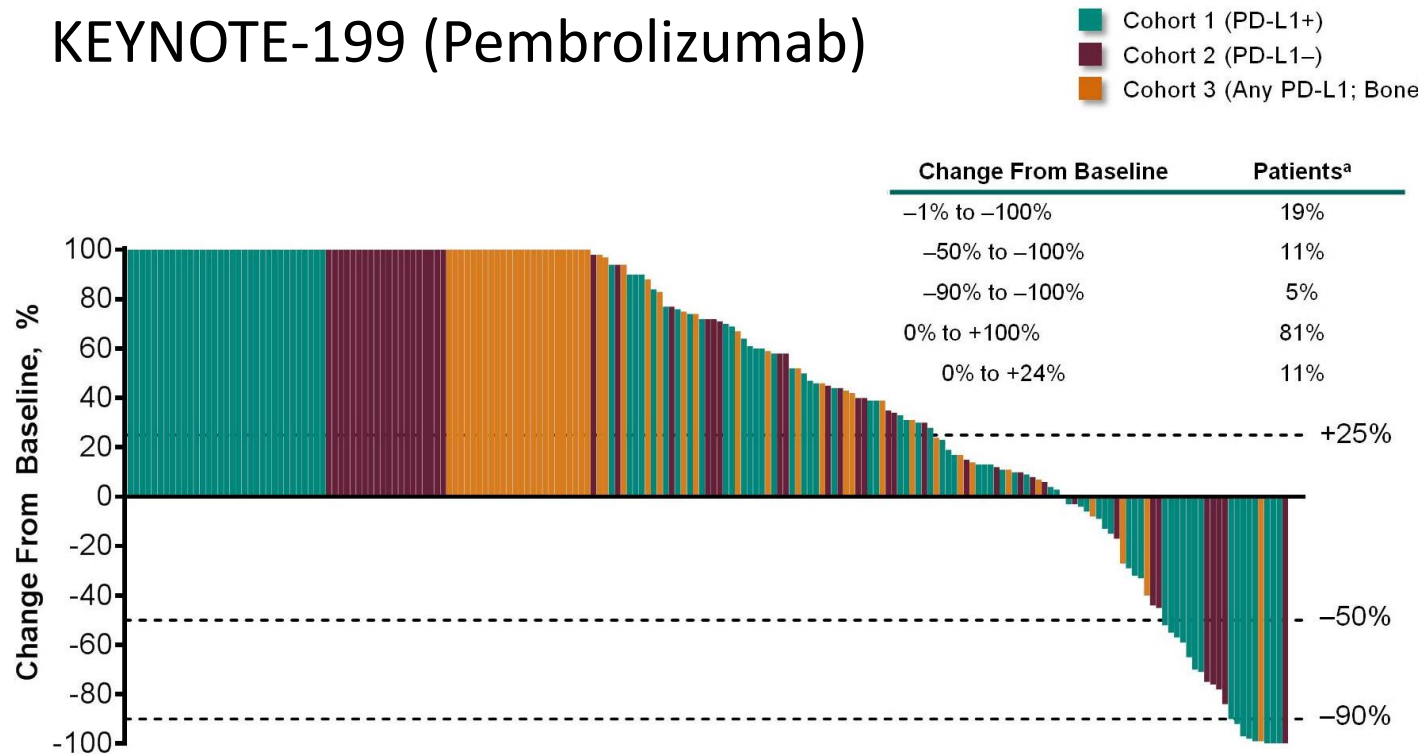
- Post-hoc analysis of Phase 3 trial PROCEED (N = 1902 mCRPC patients)
- African-Americans (AA) = 438; Caucasians (CAU) = 219
- Median OS = 35.2 (AA) vs 29.9 mo (CAU); HR 0.81, 95% CI 0.68–0.97; $p = 0.03$.
- AA race was independently associated with prolonged OS on multivariate analysis (HR 0.60, 95%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



Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

KEYNOTE-199 (Pembrolizumab)



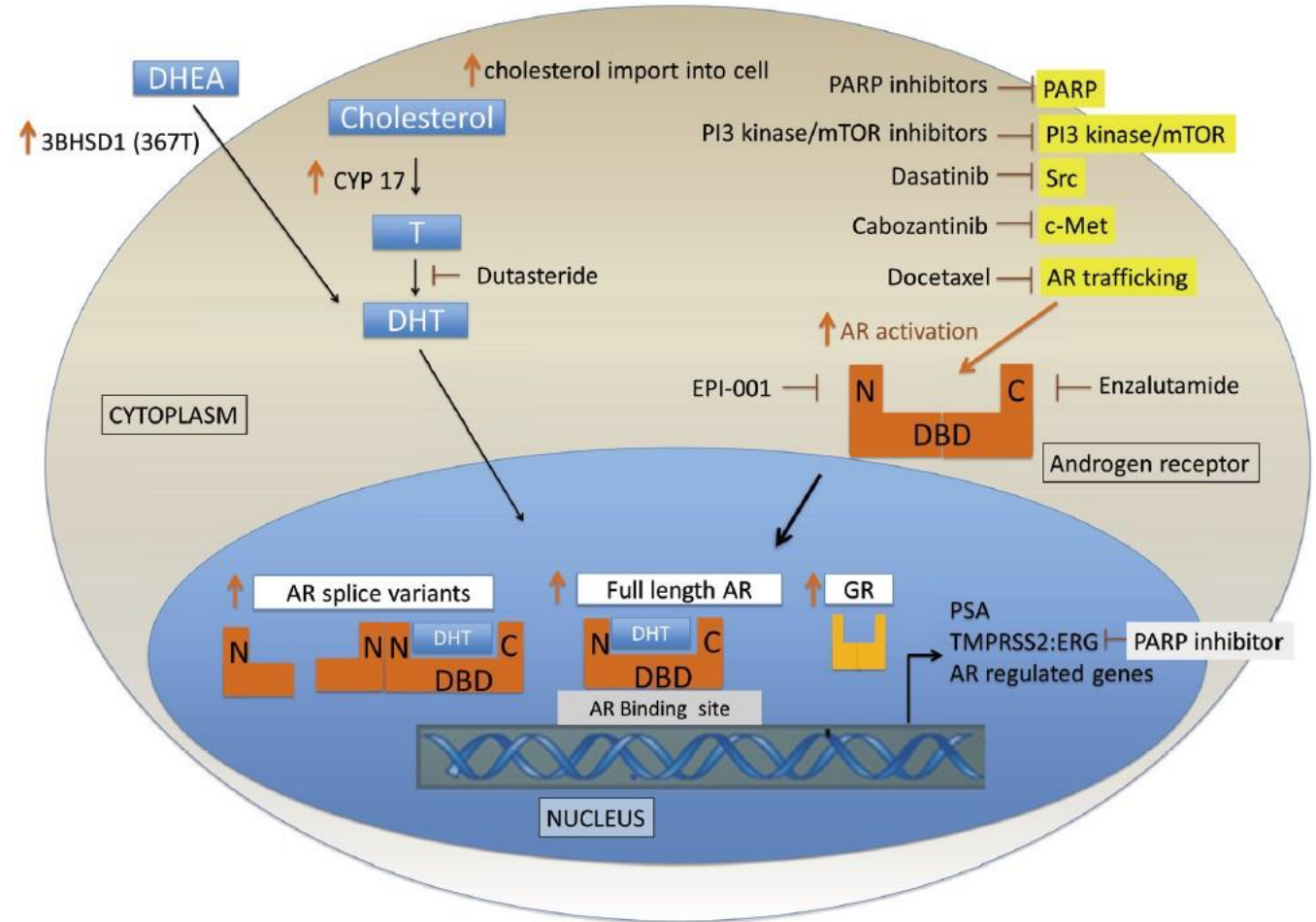
- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
 - Localized PC ~2%
 - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

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

Future Combinations in mCRPC to Engage Immune System

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



irAEs with Immune Checkpoint Inhibitors in GU Cancers - Meta-analysis of 8 studies

Similar
incidence
overall

Adverse event	Incidence, any grade (GU only trials) (%)	Incidence, grades 3–5 (GU only trials) (%)	Incidence any grade (non-GU clinical trials) (%)	Incidence, grades 3–5 (non-GU clinical trials) (%)
Hypothyroid/thyroiditis	0.8–9	0–0.6	3.9–12	0–0.1
Diabetes/DKA	0–1.5	0–0.7	0.8–0.8	0.4–0.7
LFT changes/hepatitis	1.5–5.4	1–3.8	0.3–3.4	0.3–2.7
Pneumonitis	2–4.4	0–2	1.8–3.5	0.25–1.9
Encephalitis	NR	NR	0.2–0.8	0.0–0.2
Colitis/diarrhea	1–10	1–10	2.4–4.1	1.0–2.5
Hypophysitis	0–0.5	0–0.2	0.2–0.9	0.2–0.4
Renal Dysfunction/nephritis	0.3–1.6	0–1.6	0.3–4.9	0.0–0.5
Myositis	0.8–5	0–0.8	NR	NR

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
- 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* (2016) 4:81
DOI 10.1186/s40425-016-0180-7

Journal for Immunotherapy
of Cancer

POSITION ARTICLE AND GUIDELINES

Open Access



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

Brian I. Rini¹, David F. McDermott², Hans Hammers³, William Bro⁴, Ronald M. Bukowski⁵, Bernard Faba⁶, Jo Faba⁶, Robert A. Figlin⁷, Thomas Hutson⁸, Eric Jonasch⁹, Richard W. Joseph¹⁰, Bradley C. Leibovich¹¹, Thomas Olencki¹², Allan J. Pantuck¹³, David I. Quinn¹⁴, Virginia Seery², Martin H. Voss¹⁵, Christopher G. Wood⁹, Laura S. Wood¹ 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



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*}

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

Case Studies

Case Study 1

55 yo female presented with 3 week history of progressive, severe right flank pain.

- CT urogram: 17cm right renal mass, soft tissue peritoneal nodules, possible right adnexal mass.
- CT chest: multiple sub-centimeter pulmonary nodules.
- MRI Abd: right renal vein occlusion, mass invades right adrenal gland and right/caudate hepatic lobes
- Hb 10.4 g/dL; otherwise, CBC, CMP within normal limits. ECOG PS 1.

Case Study 1



- CT guided biopsy of:
 - Peritoneal nodule: metastatic carcinoma consistent with renal primary; IHC: PAX-8, cam5.2, CK AE1/AE3 +, ER -
 - Right renal mass: renal cell carcinoma, clear cell type, PAX-8 + by IHC

Case Study 1

Diagnosis: Metastatic renal cell clear cell carcinoma, IMDC intermediate risk

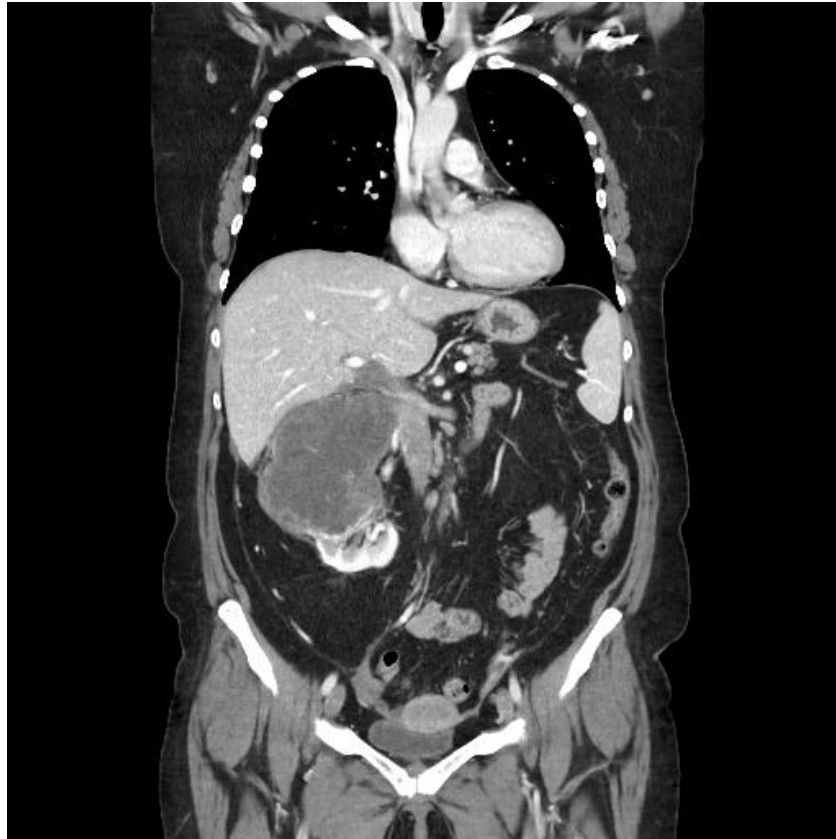
- What is preferred initial therapeutic intervention?
 - A. Cytoreductive nephrectomy
 - B. Cabozantinib
 - C. Axitinib + pembrolizumab
 - D. Ipilimumab + nivolumab

Case Study 1

- What is preferred initial therapeutic intervention?
 - A. Cytoreductive nephrectomy
 - B. Cabozantinib
 - C. Axitinib + pembrolizumab
 - D. Ipilimumab + nivolumab
- A. Unresectable, no data with modern IO regimens
- B. Less robust trial data
- D. May have lower response rate, higher serious irAE rate

Case Study 1

After 6 months of therapy, significant partial response noted, including resolution of peritoneal and pulmonary metastatic sites.



Case Study 1

- What is the next step in her care?
 - A. Cytoreductive nephrectomy
 - B. Continue axitinib + pembrolizumab
 - C. Discontinue axitinib and continue pembrolizumab
 - D. Switch to ipilimumab + nivolumab

Case Study 1

- Underwent attempted cytoreductive nephrectomy, which was aborted due to intra-operative finding of multiple, persistent peritoneal nodules.
- 4 peritoneal nodules were biopsied, final path:

DENSE SCLEROTIC TISSUE WITH SCATTERED CHRONIC INFLAMMATION, NO MALIGNANCY IDENTIFIED.
- Continues on axitinib + pembrolizumab at this time.

Case Study 2

64 yo male originally presented with gross hematuria. Diagnostic evaluation identified urothelial carcinoma of the right ureter, s/p right nephroU. Developed pulmonary recurrence 1 year later.

- Previously received: gemcitabine + carboplatin, weekly paclitaxel followed by progression.
- Tissue NGS analysis did not identify an actionable molecular aberration.
- Minimal dyspnea on exertion, fatigue. ECOG PS 1. Desires aggressive therapy.

Case Study 2

Diagnosis: Platinum refractory metastatic urothelial carcinoma of the bladder

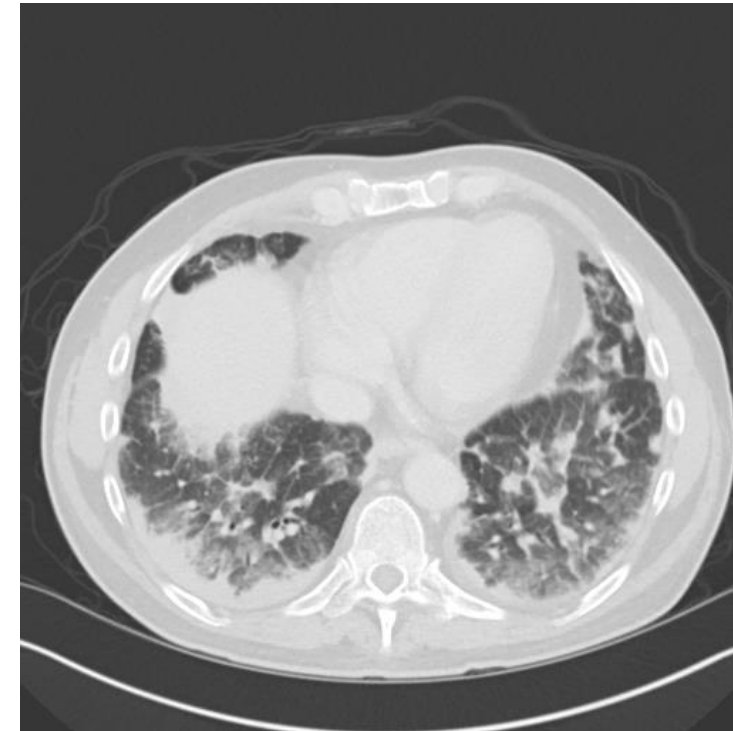
- What is preferred next therapeutic intervention?
 - A. Pembrolizumab
 - B. Best supportive care
 - C. Clinical trial enrollment with ipilimumab + nivolumab
 - D. Enfortumab vedotin
- A. Appropriate
B. Appropriate but pt declines
D. Accelerated approval for post-chemo and post-IO pts

Case Study 2

Received 2 doses of ipilimumab + nivolumab and presented with cough and shortness of breath.



Pre-treatment



Current

Case Study 2

- What is the next step in his care?
 - A. Continue ipi/nivo, add prednisone 10mg daily
 - B. Hold ipi/nivo, begin empiric azithromycin
 - C. Hold ipi/nivo, begin high dose corticosteroids
 - D. Transition to best supportive care

Case Study 2

- Admitted to ICU, received high dose corticosteroids followed by prolonged taper.
- Subsequently developed steroid refractory colitis, requiring single dose of infliximab, followed by full recovery.
- Withdrawn from clinical trial for irAE. Post-recovery imaging demonstrated a radiographic complete response.
- No additional systemic therapy in over 4 years.

Thank you!

Earle Burgess, MD

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