

ADVANCES IN  
**Cancer**  
IMMUNOTHERAPY™



# Immunotherapy for the Treatment of Genitourinary Cancers

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Society for Immunotherapy of Cancer

# Disclosures

- Madison Vaccines Inc. (ownership, intellectual property, contracted research, consulting)
- Dendreon, Janssen, Novartis, Medivation – clinical research support to my institution for trials for which I serve as PI
- I *will* be discussing non-FDA approved indications during my presentation.

## Learning Objectives:

- ***Describe the rationale for common approaches to cancer immunotherapy, particularly with respect to prostate cancer and bladder cancer***
- ***Familiarize the learner with clinical data on the efficacy of approved therapies***
- ***Recognize patient selection criteria for approved therapies***
- ***Select appropriate sequencing of approved therapies***



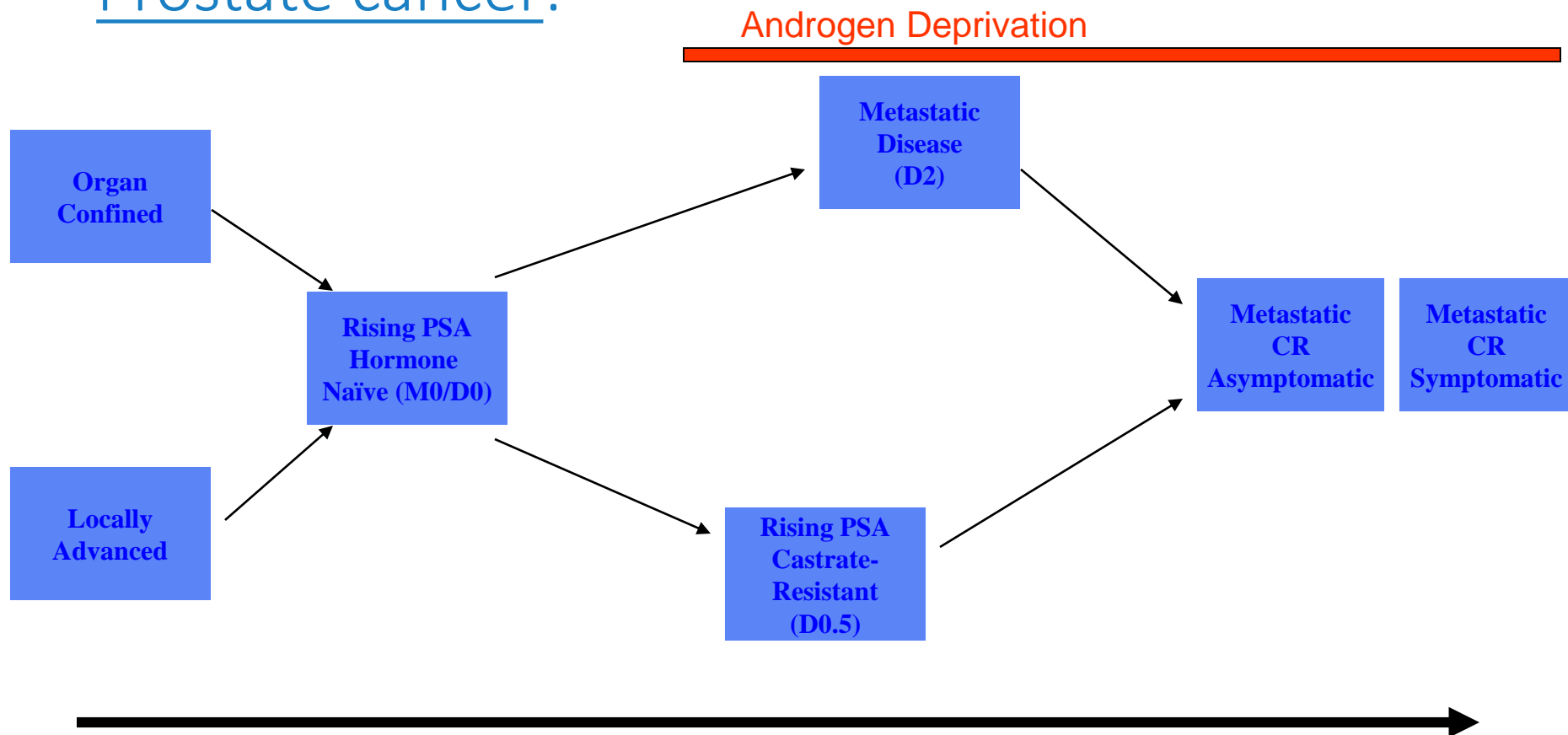
## Prostate Cancer – Case #1:

You are seeing a 68 y/o man who was diagnosed with a Gleason 5+4 prostate cancer 5 years ago. He had evidence of metastases to the bone and retroperitoneal lymph nodes, and was started on treatment with leuprolide and bicalutamide. His PSA initially declined, but then began rising two years ago, and the bicalutamide was discontinued. His PSA continued to rise, and is currently 5 ng/mL. Bone scan shows new metastases, but he remains asymptomatic. What are appropriate immunotherapy treatment options for him?

- A) Nivolumab
- B) Sipuleucel-T
- C) Pembrolizumab
- D) B or C



## Prostate cancer:



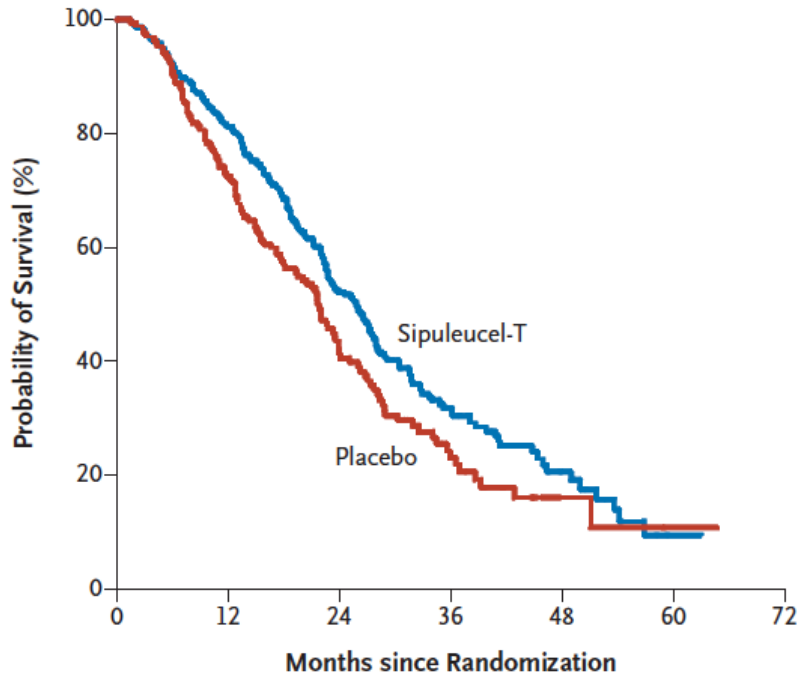
## Lessons learned:

### Prostate cancer immunotherapy trials

- Prostate *not* an “inflamed” solid tumor like melanoma, renal, lung, bladder
- *Not* significantly hyper-mutated
- For vaccines ↑ doses of vaccine ≠ augmentation of immunity
- *Limited efficacy* of checkpoint inhibitors, anti-CTLA-4, anti-PD1
- No evidence of disease pseudoprogression before response
- No abscopal effects

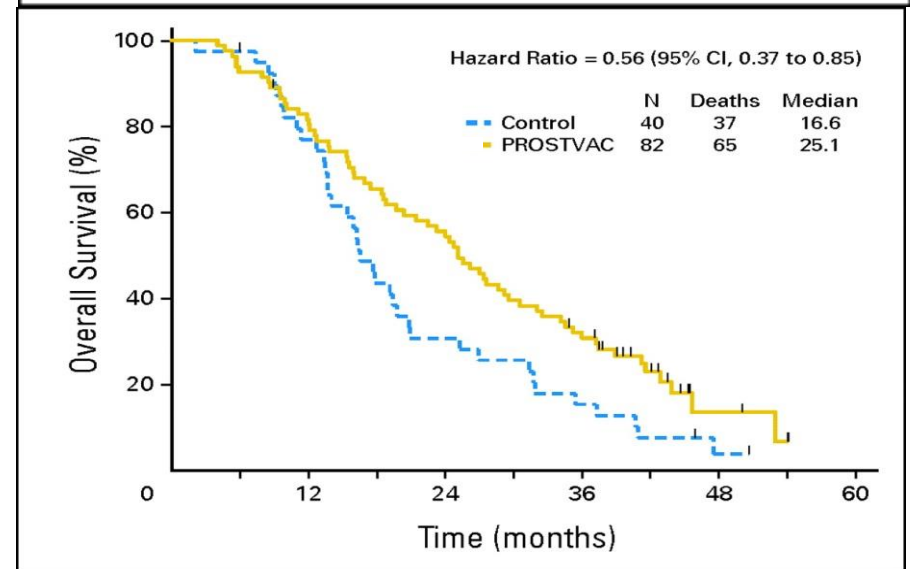
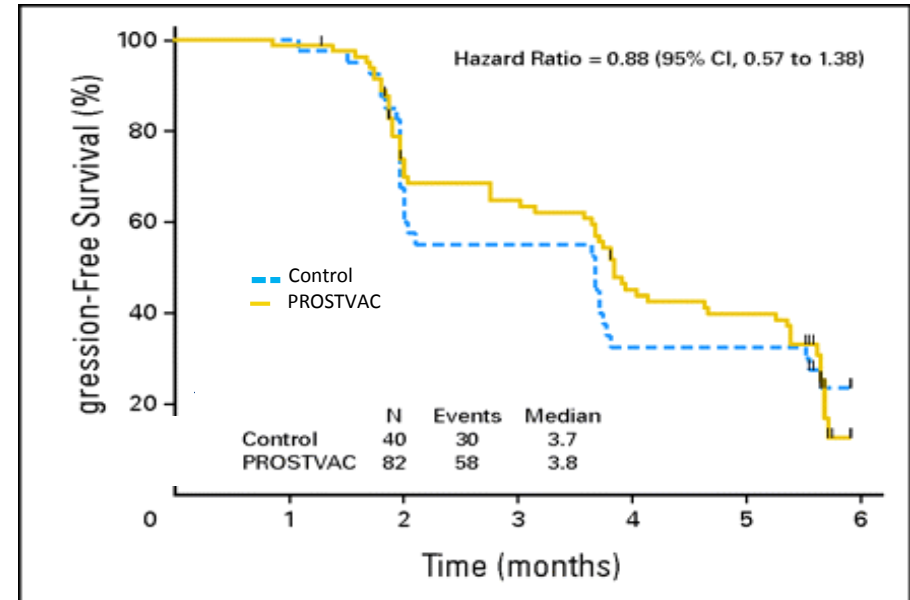
# Vaccines in Prostate Cancer

## A Primary Efficacy



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

Kantoff, et al, NEJM 2010.



Kantoff, et al, JCO 2010



## Sipuleucel-T:

### Approval indications:

Patients with asymptomatic to minimally symptomatic castration-resistant metastatic prostate cancer

Dosing: Collection and infusion every 2 weeks x 3

### Common adverse reactions:

Chills, fatigue, fever, back pain, nausea, joint aches, headache

### Warnings:

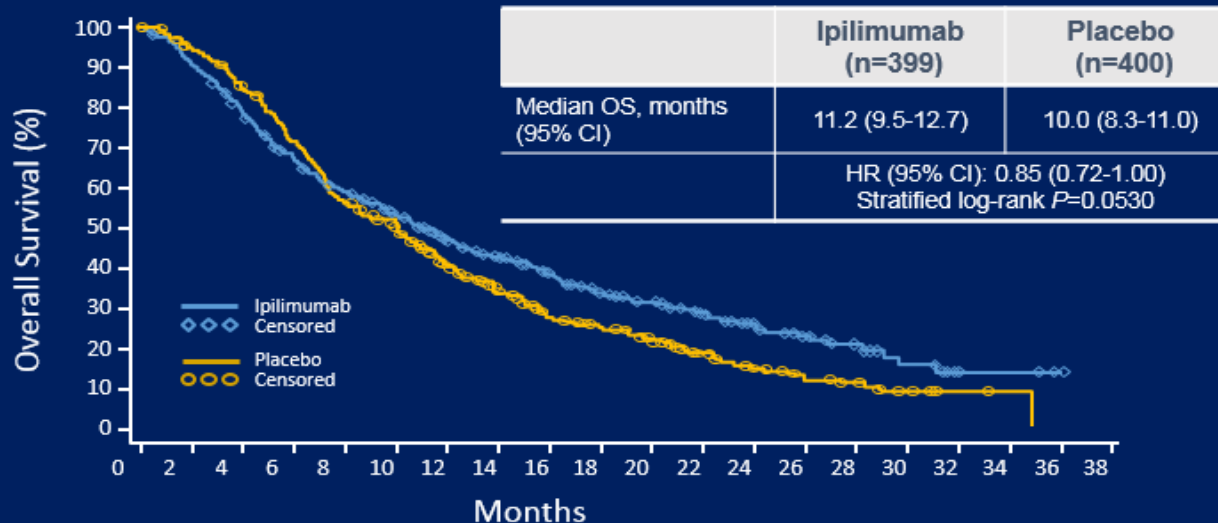
Infusion reactions, not tested for transmissible infectious diseases, syncope/hypotension, myocardial infarction, thromboembolic events





# Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)<sup>1</sup>

Primary Endpoint: OS (Intent to Treat [ITT] Population)



## Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab\*  
– The most frequent severe immune-related AEs were diarrhea and colitis

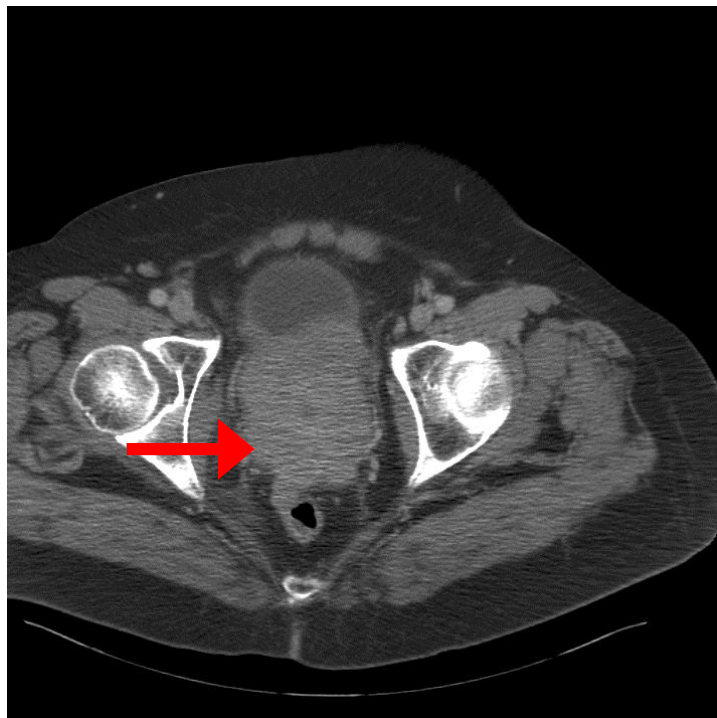
\*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

<sup>1</sup>Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

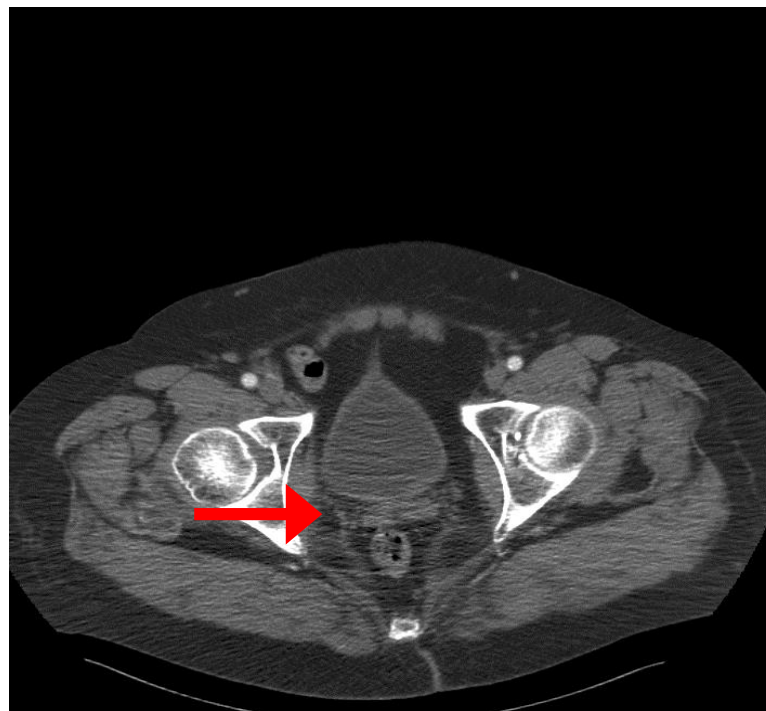


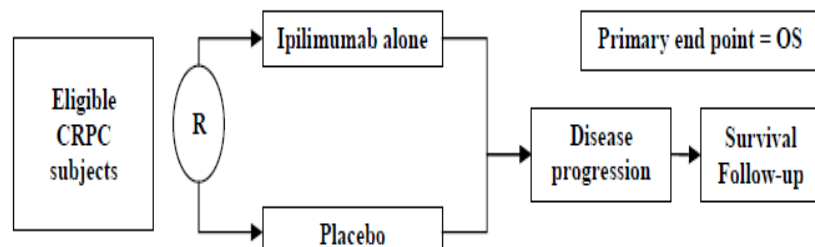
## Resolution of Prostate Mass

Screening



14 months

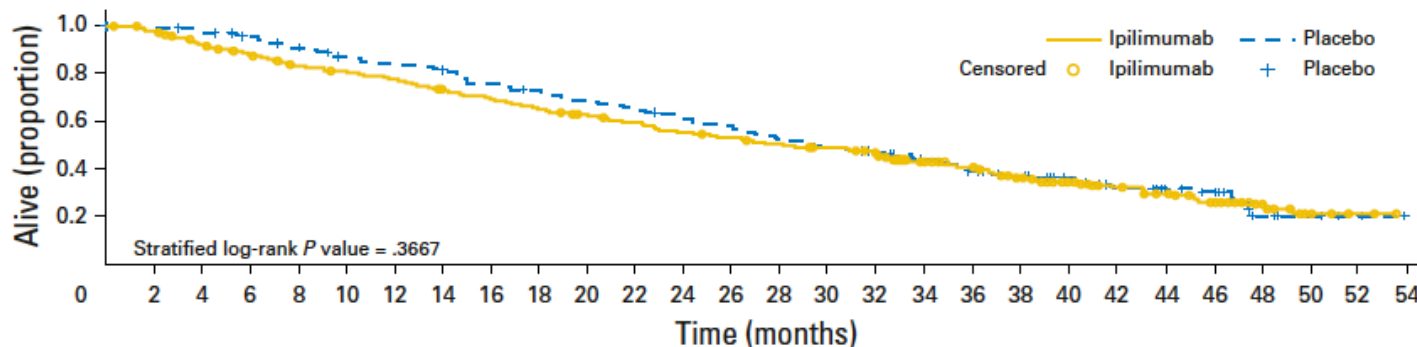




## Patients:

- Asymptomatic/minimally symptomatic, chemotherapy-naïve castration resistant prostate carcinoma (CRPC)
- No visceral metastases

**A**



No. at risk

Ipilimumab	400	389	364	342	320	310	298	279	265	250	236	223	208	197	186	179	166	136	116	94	78	64	46	32	18	7	3	0
Placebo	202	198	195	186	175	166	161	155	142	136	128	122	113	108	98	92	85	74	59	53	41	33	25	19	6	4	2	0

mOS 28.7 vs. 29.7 mos (HR 1.11; 0.88 – 1.39)



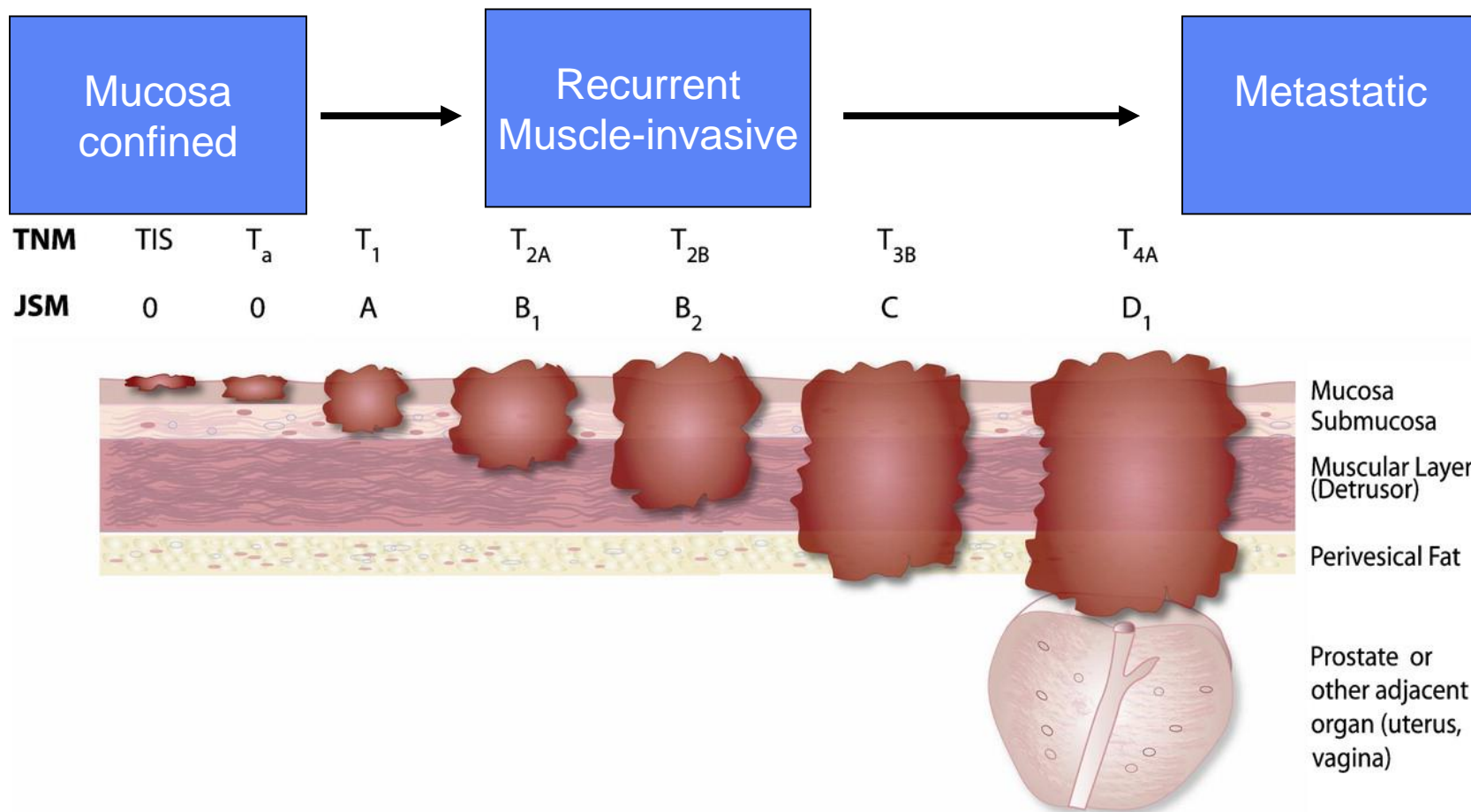
## PD-1/PD-L1 blockade in mCRPC

- Phase I trials with nivolumab
  - No evidence of single-agent activity in mCRPC
- Phase I trials with pembrolizumab
  - Small percentage response rate in patients with advanced mCRPC
  - Pembrolizumab now approved (May 2017) for MSI-high and mismatch repair deficient tumors – hence data exists to support this in the small percentage of prostate cancer that are MSI<sup>high</sup>
- Multiple combinations are underway with ipilimumab or PD-pathway inhibitors with vaccines (including sipuleucel-T), chemotherapy, androgen deprivation, and radiation therapy



## Cancer:

## Bladder



[www.cancersymptoms.xyz](http://www.cancersymptoms.xyz)

## Bladder Cancer – Case #2:

You are seeing a 60 y/o man who was diagnosed with superficial bladder cancer 5 years ago. After several courses of resection and intravesical BCG therapy, he developed muscle-invasive disease 2 years ago and underwent radical cystoprostatectomy. He then did well until 4 months ago when he was found to have lung and liver metastases. He started treatment with gemcitabine and cisplatin chemotherapy, but unfortunately had progressive disease after 3 cycles of therapy. What is the best immunotherapy treatment option for him?

- A) IL-2
- B) Atezolizumab
- C) Pembrolizumab



# The new bladder landscape: new drug approvals

- Durvalumab – anti-PDL1
- Atezolizumab – anti-PDL1
- Avelumab – anti-PDL1
- Nivolumab – anti-PD1
- Pembrolizumab – anti-PD1



## Atezolizumab – IMvigor 210 Study

- Open-label, multilabel, two cohort Phase II Study
  - Cohort 1: cisplatin-ineligible (N=119)
  - Cohort 2: progression after platinum-containing chemo (N=310)
    - Assessed PD-L1 expression on tumor infiltrating immune cells

	<u>PD-L1 Expression</u>	<u>ORR</u>
ORR all patients 15%	≥ 5%	26%
	1 – 5%	10%
Median OS 7.9 months	< 1%	8%



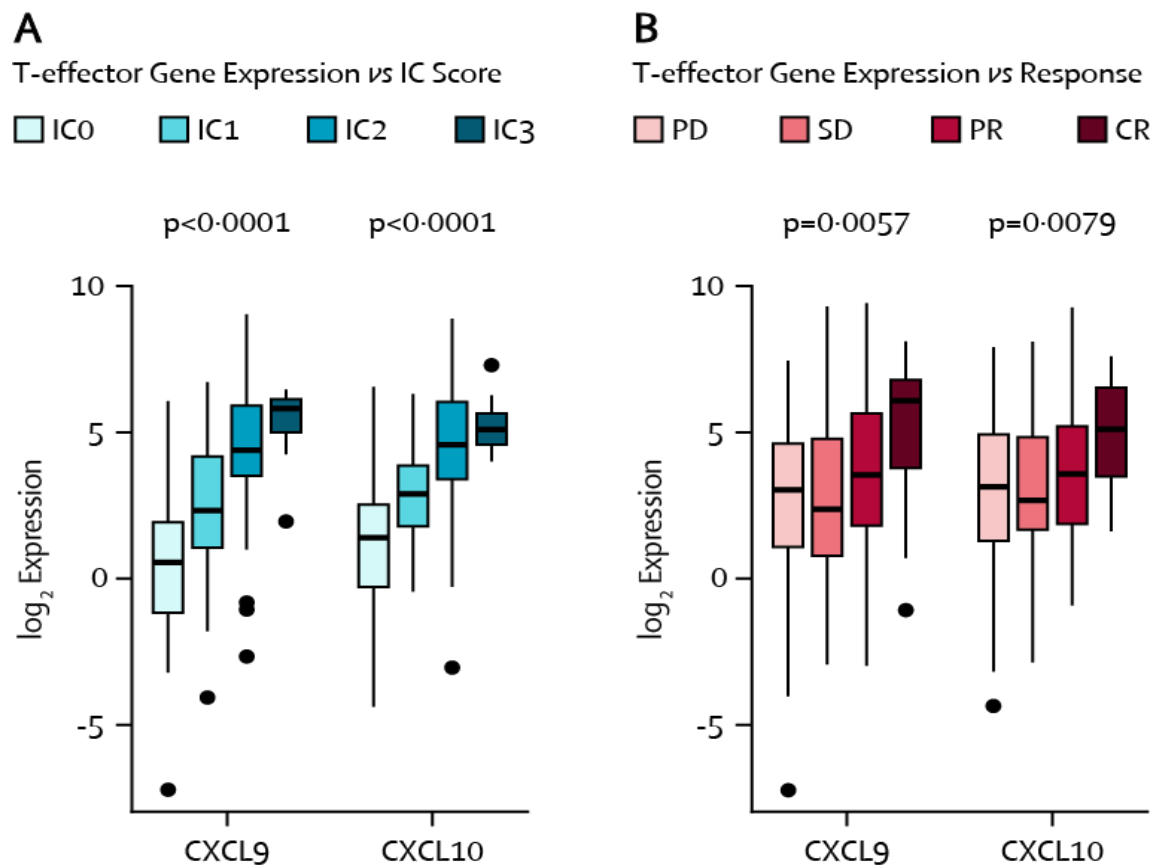


## Atezolizumab – IMvigor 210 Study

- May 2016: Accelerated approval for patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-based chemotherapy (or whose disease has worsened within 12 months of receiving platinum-based neoadjuvant or adjuvant chemotherapy).
- Expanded approval as a first-line treatment in cisplatin-ineligible patients (IMvigor 210 Cohort 1).
  - ORR 23.5% (CR in 6.7%, PR in 16.8%)
- Approved regardless of PD-L1 status



# High levels of immune response genes are associated with both PD-L1 staining and treatment response





## IMvigor 211 trial

- Open-label, multicenter, randomized Phase III study (atezolizumab vs. physician's choice)
- 931 patients
- Primary endpoint: Overall survival
- **Primary endpoint not met**
- ORR 14.8%, 26% in patients with high PD-L1 expression
- mPFS 2.7 months
- OS 15.9 months



# Nivolumab – Checkmate 275 Study

- Phase II Study in locally advanced/metastatic disease following platinum chemotherapy (N=270)
  - Stratified by PD-L1 expression  $\geq 5\%$  or  $< 5\%$

ORR all patients 19.6%

Median OS 8.7 months

PD-L1 Expression

$\geq 5\%$

$< 5\%$

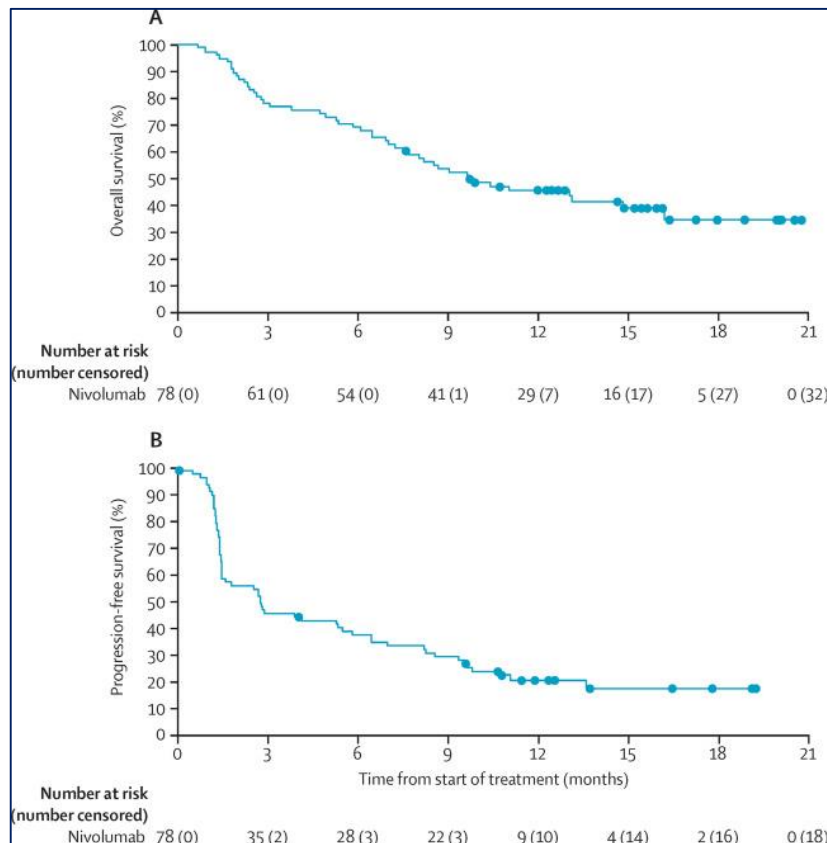
ORR

28.4%

15.8%



# Checkmate 032 Study



Kaplan-Meier curves of overall survival (A) and progression-free survival (B); circles are censored patients.

Sharma, et al., Lancet Onc , 17: 1590-1598, 2016

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	Nivolumab (n=78)	PD-L1 <1% (n=42)	PD-L1 ≥1% (n=25)
Confirmed objective response	19 (24.4%, 15.3–35.4)	11 (26.2%, 13.9– 42.0)	6 (24.0%, 9.4–45.1)
Best overall response			
Complete response	5 (6%)	1 (2%)	4 (16%)
Partial response	14 (18%)	10 (24%)	2 (8%)
Stable disease	22 (28%)	11 (26%)	8 (32%)
Progressive disease	30 (38%)	18 (43%)	8 (32%)
Unable to establish	7 (9%)	2 (5%)	3 (12%)

**Antitumour activity**





# Nivolumab

- February 2017: FDA approval for patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-based chemotherapy (or whose disease has worsened within 12 months of receiving platinum-based neoadjuvant or adjuvant chemotherapy).
- Approved regardless of PD-L1 status

## Avelumab/Durvalumab

- Locally advanced or metastatic bladder cancer whose disease has progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy.
- Approval based on single-arm, open-label JAVELIN trial in which ORR was 13.3% among 226 patients. Median duration of response not reached (1.4+ to 17.4+ months)
- **VENTANA PD-L1 (SP263) Assay** (Ventana Medical Systems, Inc.) as a complementary diagnostic for the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded urothelial carcinoma tissue.



# Pembrolizumab

- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; accelerated approval for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
- Based on **Trial KEYNOTE-045**, a multicenter, randomized, active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy.
- Accelerated approval for the first-line indication was based on data from **KEYNOTE-052**, a single-arm, open-label trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab 200 mg every 3 weeks. With a median follow-up time of 7.8 months, the ORR was 28.6% (95% CI 24, 34) and the median response duration was not reached (range 1.4+, 17.8+ months).





## KEYNOTE-045

**OS:** Median 10.3 months versus 7.4 months

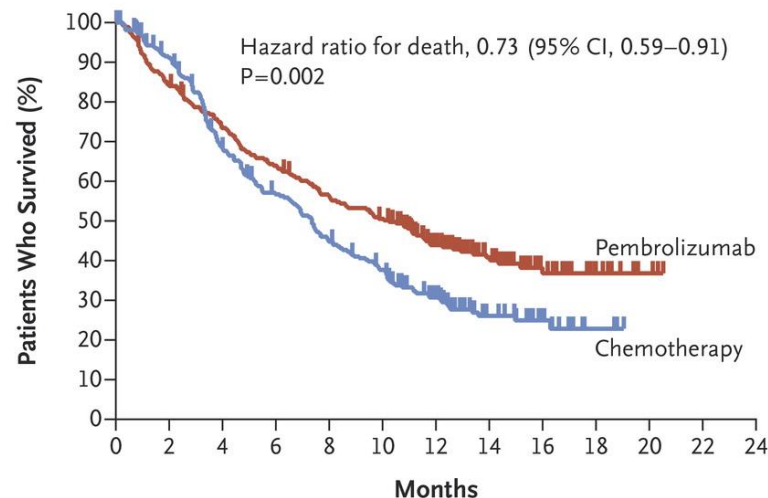
**PFS:** Not significantly different

**AE:** Fewer TRAE of any grade in the pembrolizumab group (60.9% versus 90.2%)

Bellmunt, et al., NEJM, 376: 1015-1026, 2017

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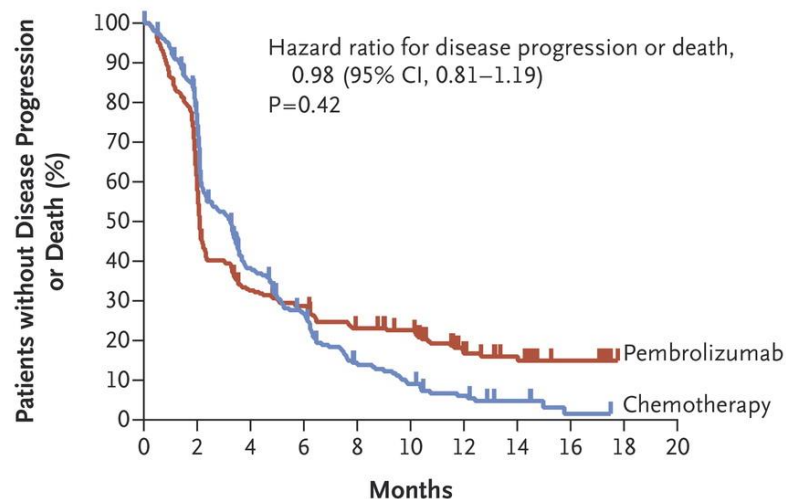
### A Overall Survival



#### No. at Risk

Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

### B Progression-free Survival



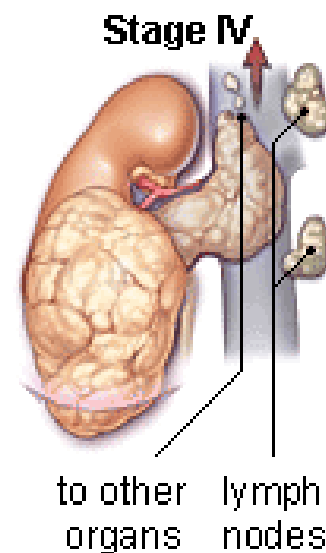
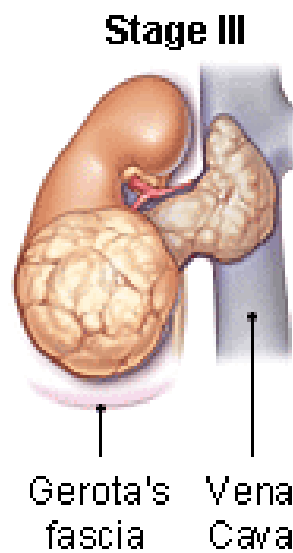
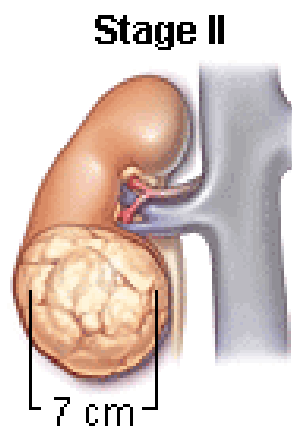
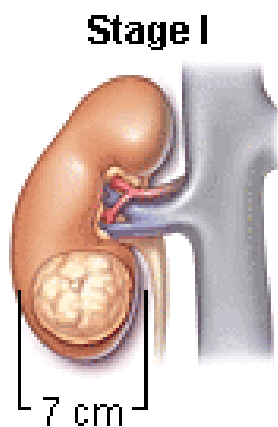
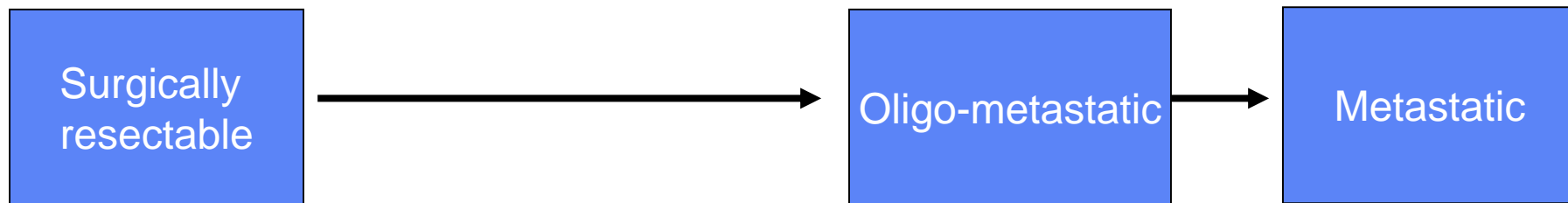
#### No. at Risk

Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0



## Cancer:

## Kidney



reemakeup.blogspot.com

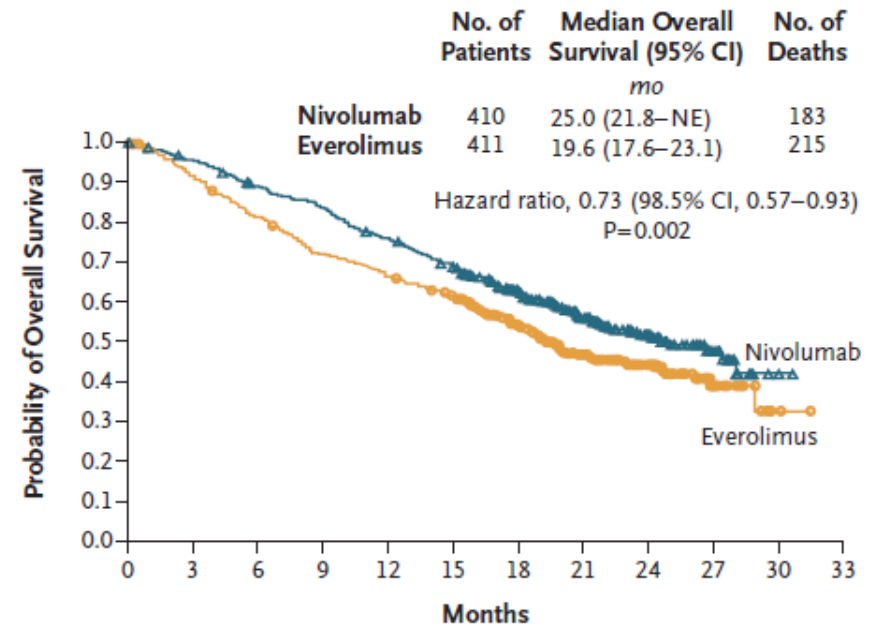


# Nivolumab

- Phase III CheckMate 025 trial – 821 patients with previously treated mRCC (1-2 VEGF TKI):  
Nivolumab (anti-PD-1) 3 mg/kg q 2 wk  
versus everolimus 10 mg per day

- Median OS: 25m vs 19.6m
- ORR: 25% vs 5%
- Median PFS: 4.6m vs 4.4m
- Median duration: 23m vs 13.7m
- Grade 3/4 AE: 19% vs 37%
- Most common AE with nivolumab was fatigue (2%)

Approved by FDA in 2015



Motzer (2015) N Engl J Med 373:1803



## Nivolumab:

### Approval indications:

Patients with metastatic renal cell cancer who have received prior anti-angiogenic therapy

Dosing: 240 mg IV every 2 weeks

### Common adverse reactions:

Asthenia, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, arthralgia

### Warnings:

Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, encephalitis, others



## Other PD-1/PD-L1 Inhibitors:

- Phase III – Nivolumab + Ipilimumab vs. Sunitinib  
Previously untreated mRCC (CheckMate 214)
- Phase III – Atezolizumab (anti-PD-L1) + Bevacizumab vs. Sunitinib  
Previously untreated mRCC
- Phase II – Nivolumab pre-surgical resection for mRCC (ADAPTeR)
- Phase I – Nivolumab + Sunitinib or Pazopanib or Ipilimumab  
Previously untreated mRCC (CheckMate 016)
- Different combinations with chemotherapy, IFN $\alpha$ , etc
- Multiple combinations with pembolizumab



# Resources

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<sup>1</sup>, Neil H. Bander<sup>2</sup>, Tomasz M. Beer<sup>3</sup>, Charles G. Drake<sup>4</sup>, Lawrence Fong<sup>5</sup>, Stacey Harrelson<sup>6</sup>, Philip W. Kantoff<sup>7</sup>, Ravi A. Madan<sup>8</sup>, William K. Oh<sup>9</sup>, David J. Peace<sup>10</sup>, Daniel P. Petrylak<sup>11</sup>, Hank Porterfield<sup>12</sup>, Oliver Sartor<sup>13</sup>, Neal D. Shore<sup>6</sup>, Susan F. Slovin<sup>7</sup>, Mark N. Stein<sup>14</sup>, Johannes Vieweg<sup>15</sup> and James L. Gulley<sup>16\*</sup>

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

Look for:

**SITC Consensus Statement on  
Immunotherapy for the  
treatment of Bladder  
Carcinoma COMING SOON  
(2017)!!!!!!!**

