ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Cancers

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City of Hope

AMERICAN ACADEMY OF EMERGENCY MEDICINE

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Disclosures

- Eisai Co., Ltd., Genentech, Inc., Novartis AG, Pfizer, Consulting Fees
- I *will* be discussing non-FDA approved indications during my presentation.

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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***

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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

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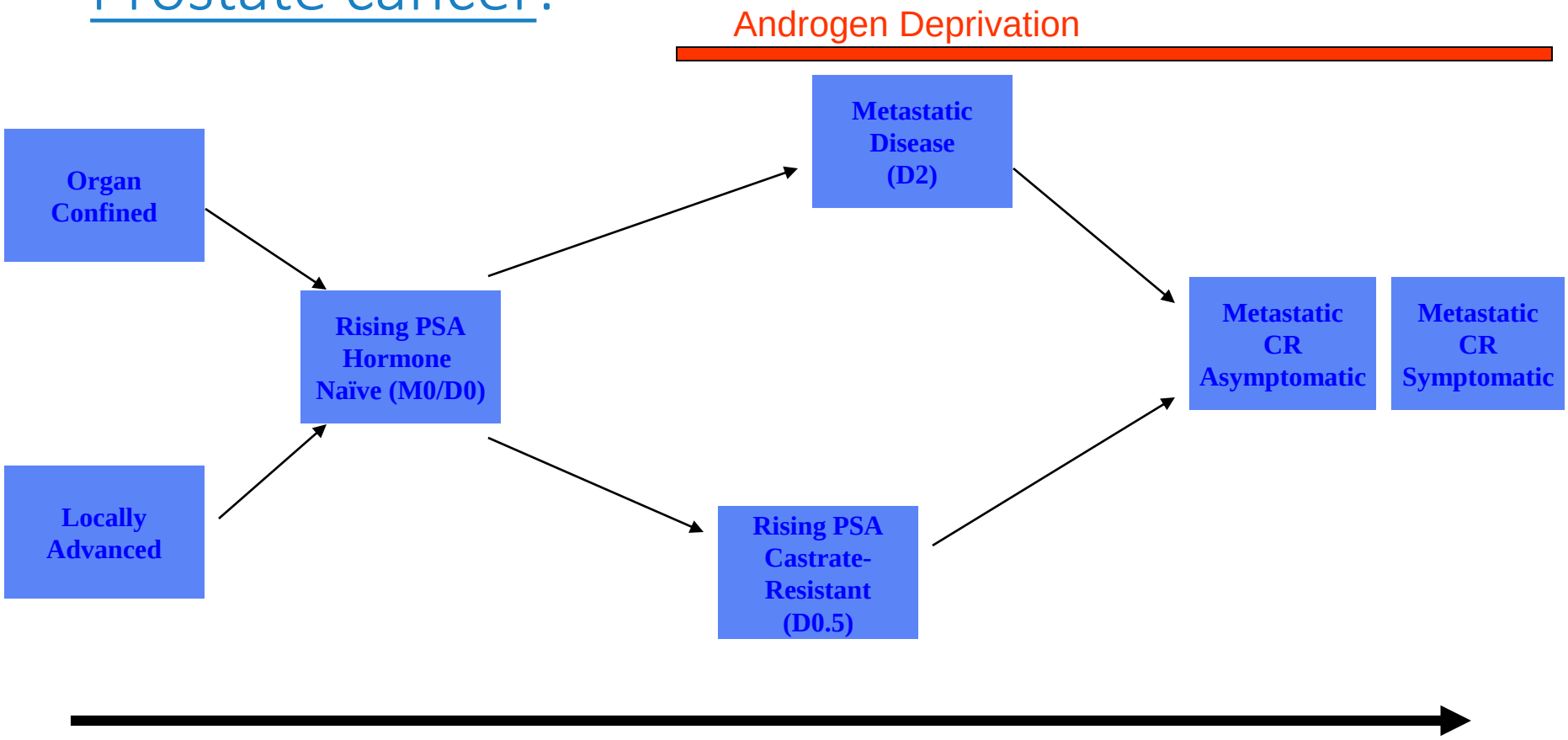
Prostate cancer:



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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

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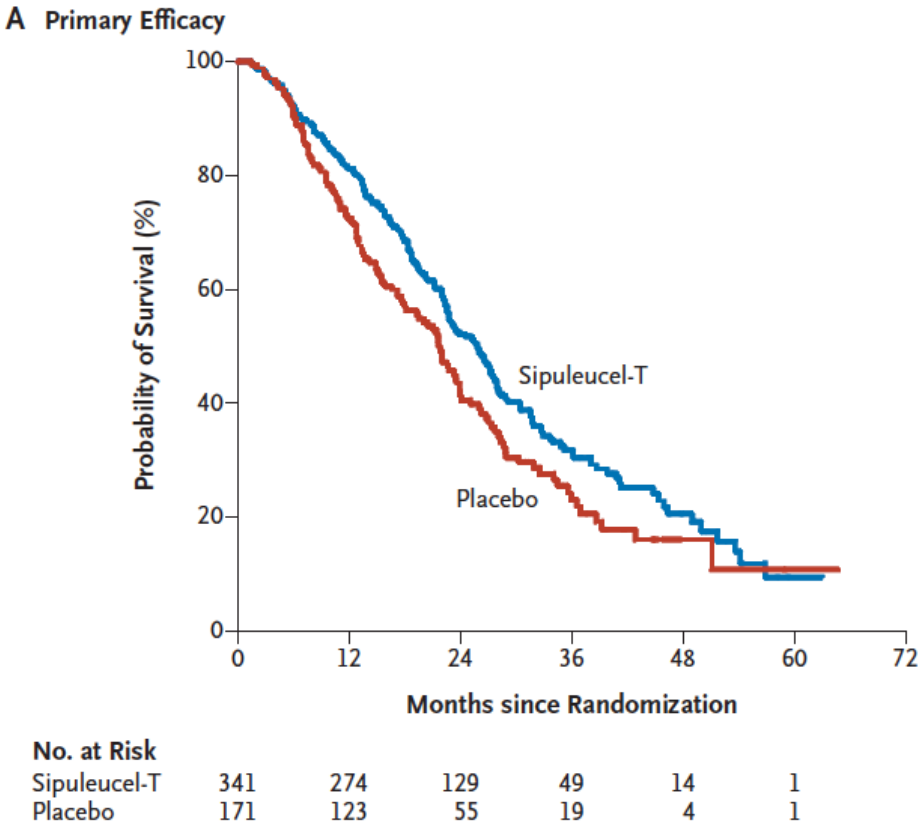
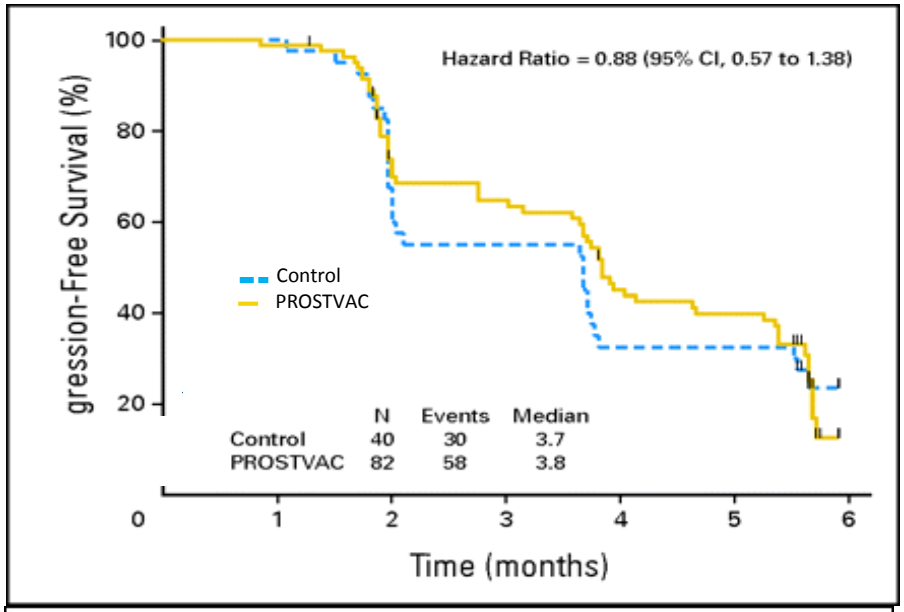
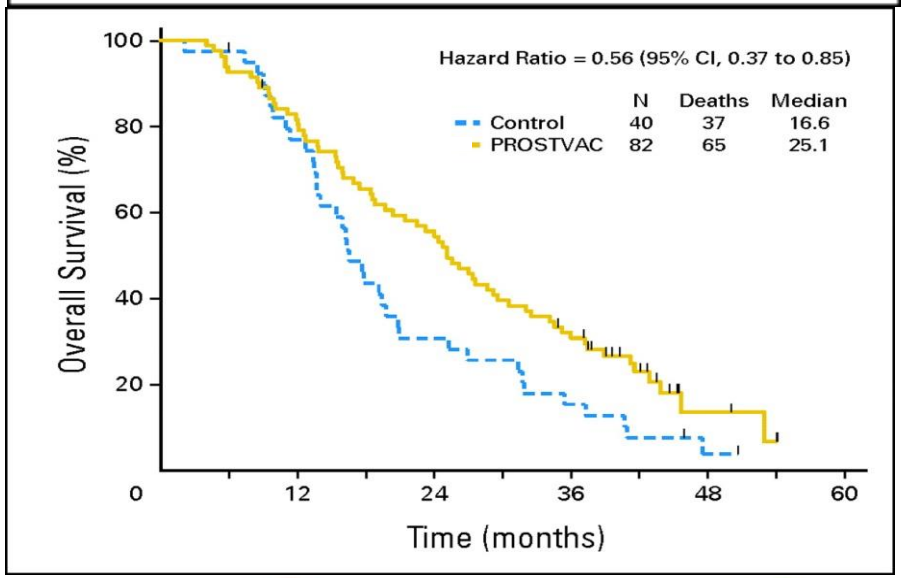
Vaccines in Prostate Cancer



Kantoff, et al, NEJM 2010.





Kantoff, el al, JCO 2010

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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

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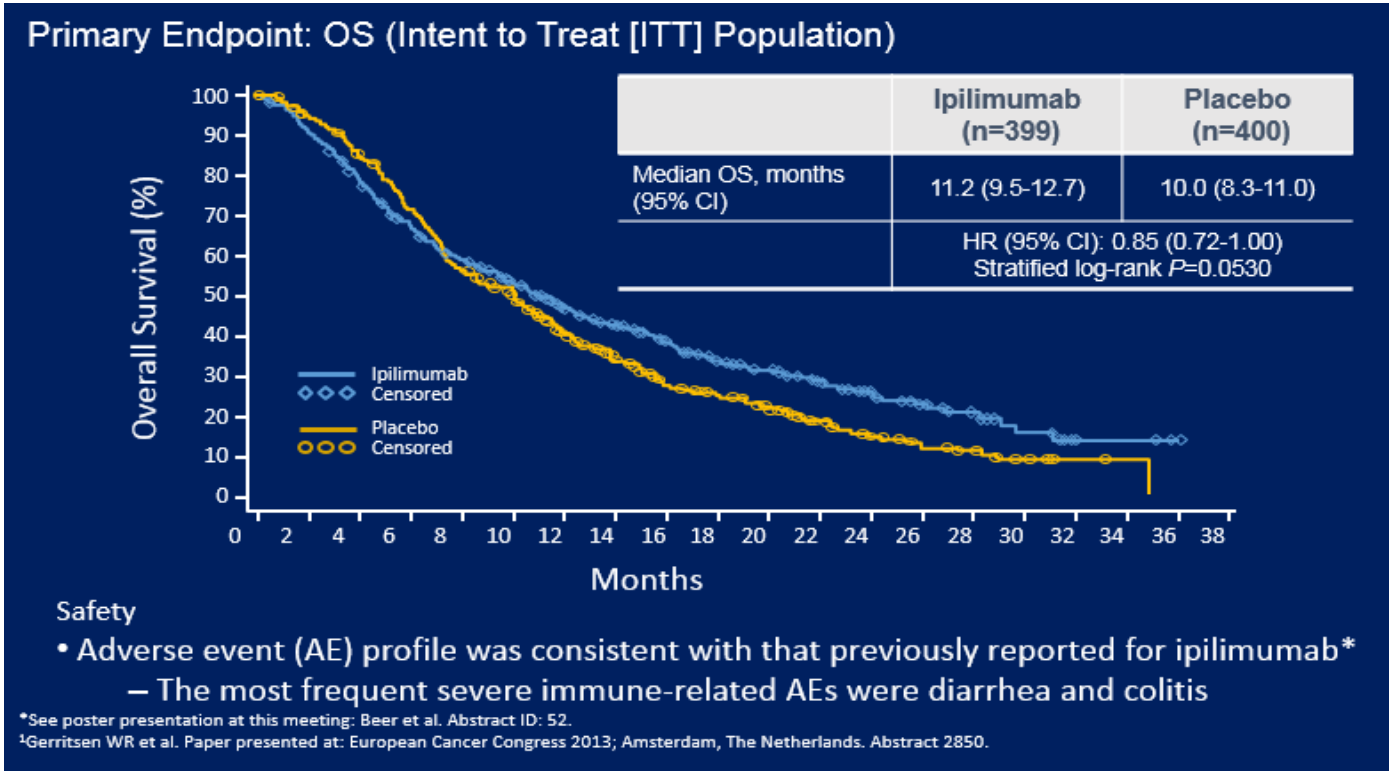
Ipilimumab CTLA-4

Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)1



Kwon et al Lancet Onc 2014 15:700

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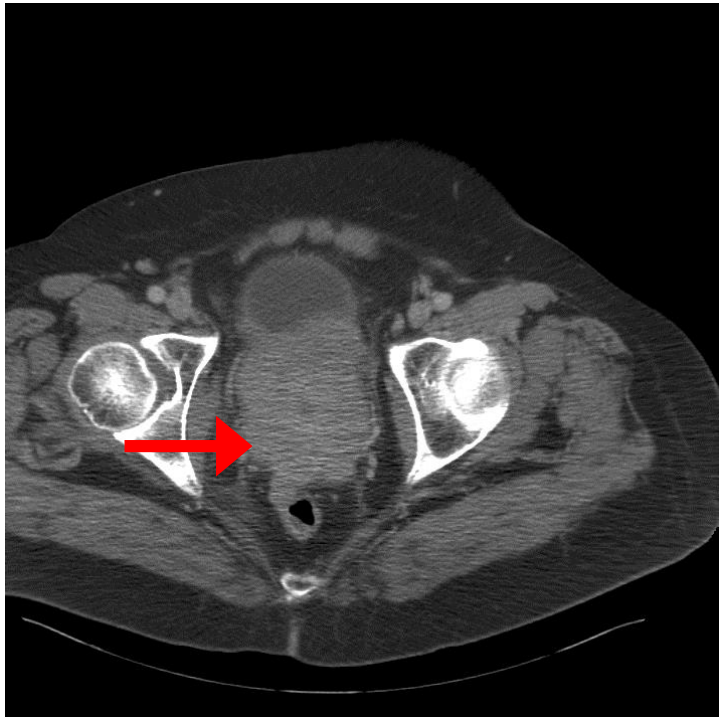
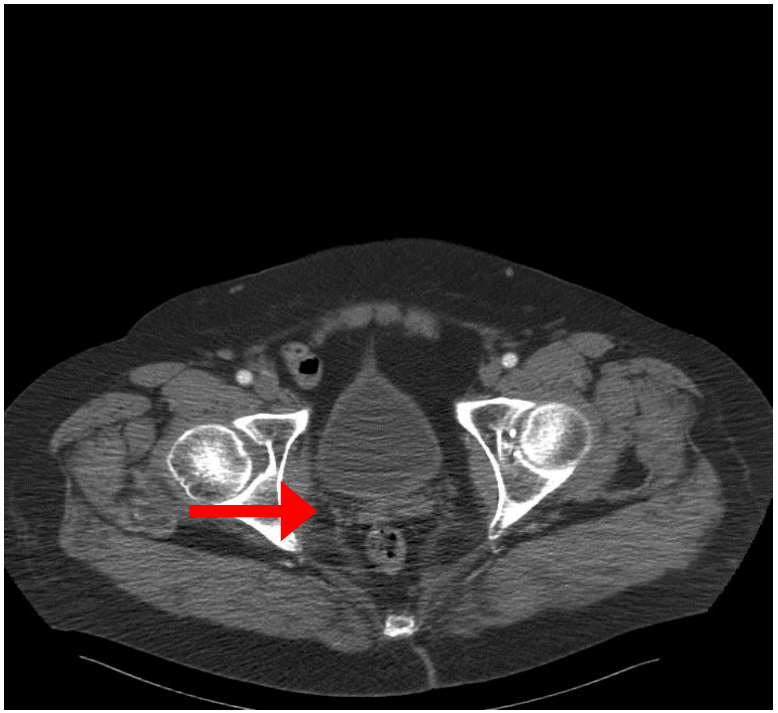
Resolution of Prostate Mass

Screening



14 months



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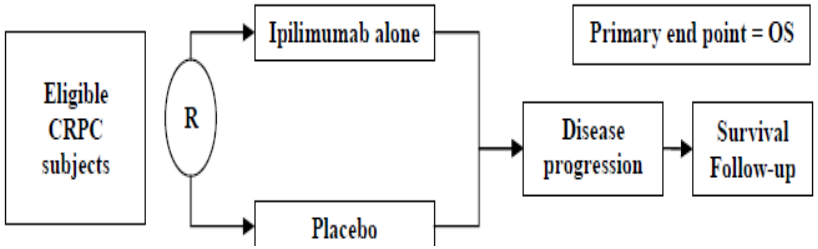
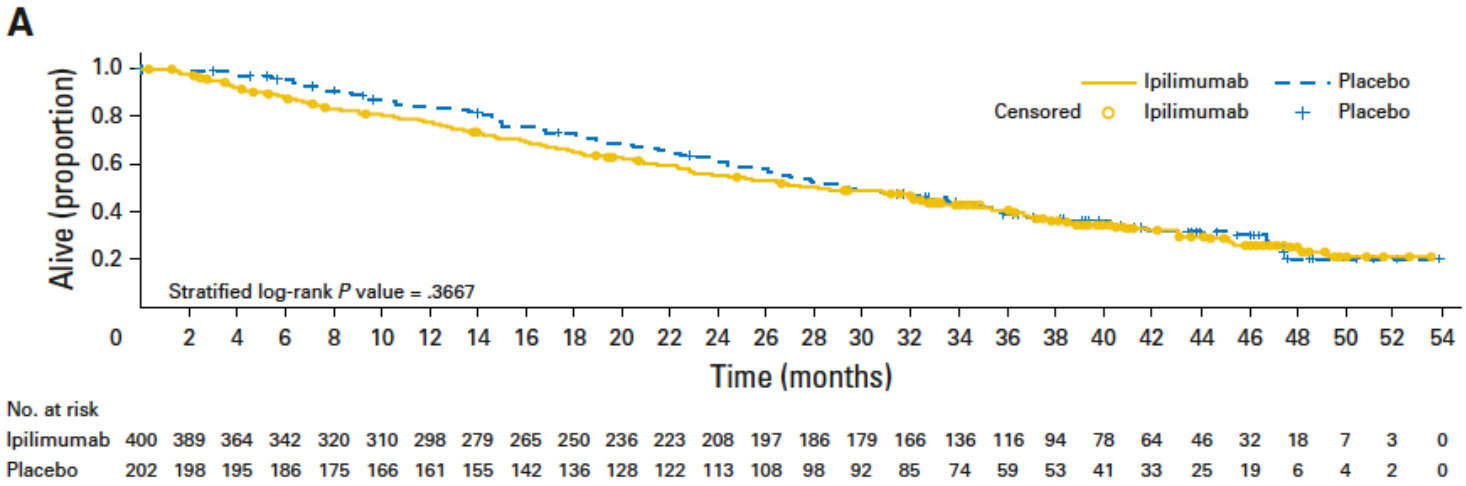


Patients:

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



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

Beer et al JCO 2016

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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 mCRCP
  - 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^{high}
- Multiple combinations are underway with ipilimumab or PD-pathway inhibitors with vaccines (including sipuleucel-T), chemotherapy, androgen deprivation, and radiation therapy

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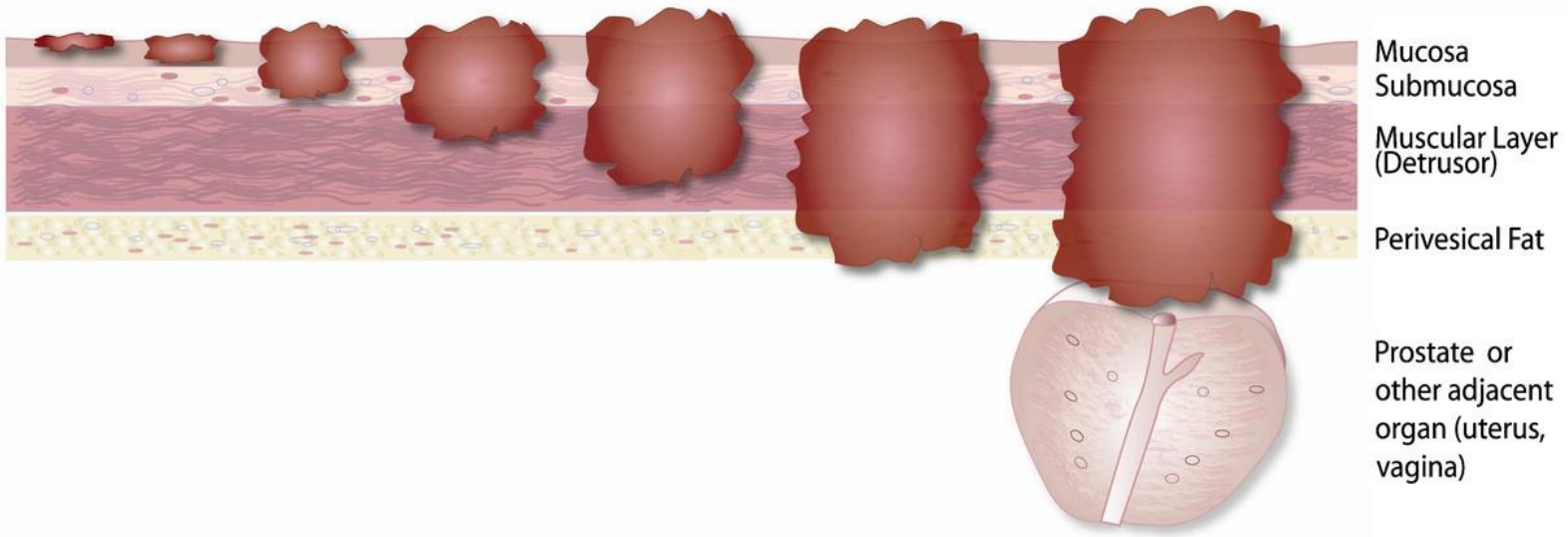
Bladder Cancer:

Mucosa confined	→	Recurrent Muscle-invasive	→	Metastatic

TNM	TIS	T_a	T_1	T_{2A}	T_{2B}	T_{3B}	T_{4A}
JSM	0	0	A	B_1	B_2	C	D_1



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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

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The new bladder landscape: new drug approvals

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

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Atezolizumab:

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

ORR all patients 15%

Median OS 7.9 months

PD-L1 Expression	ORR
≥ 5%	26%
1 – 5%	10%
< 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

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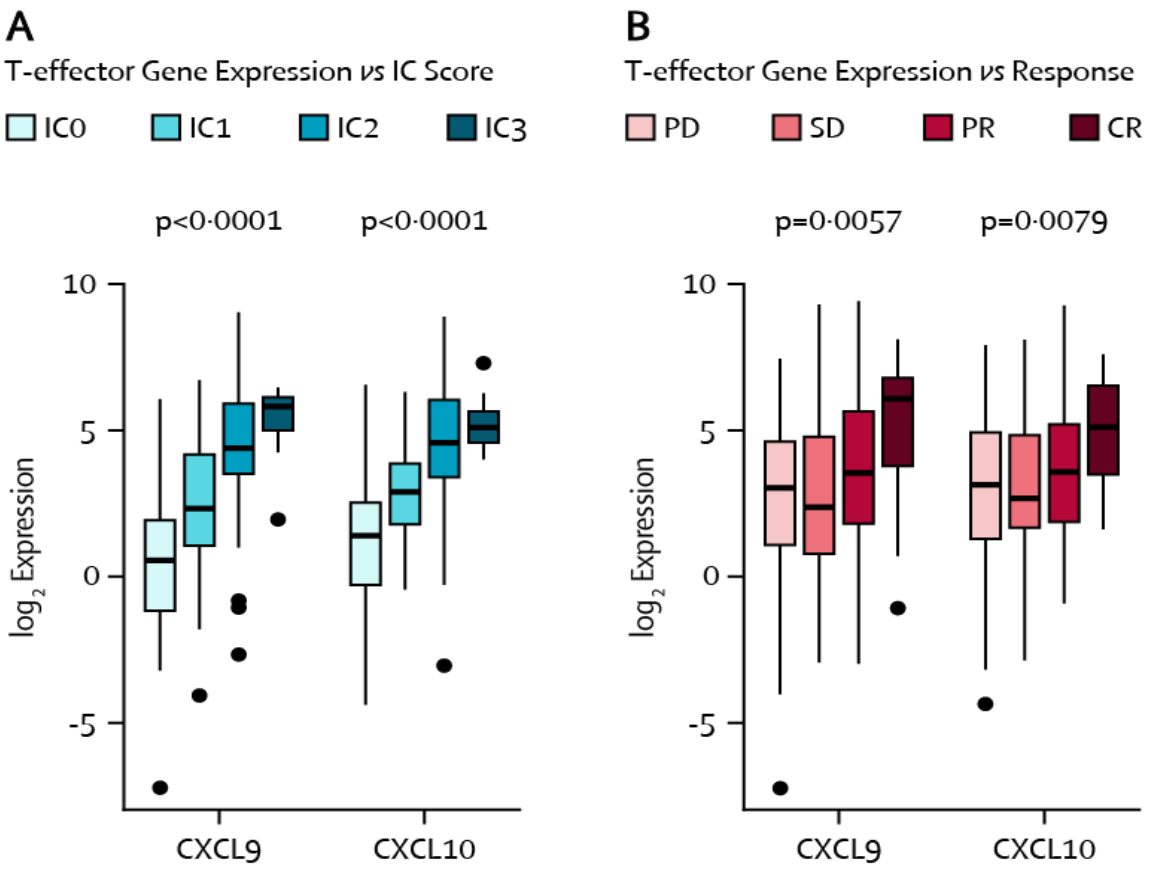
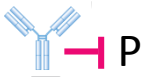
High levels of immune response genes are associated with both PD-L1 staining and treatment response



Atezolizumab:



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 ≥ 5% or < 5%

ORR all patients 19.6%

Median OS 8.7 months

PD-L1 Expression	ORR
≥ 5%	28.4%
< 5%	15.8%

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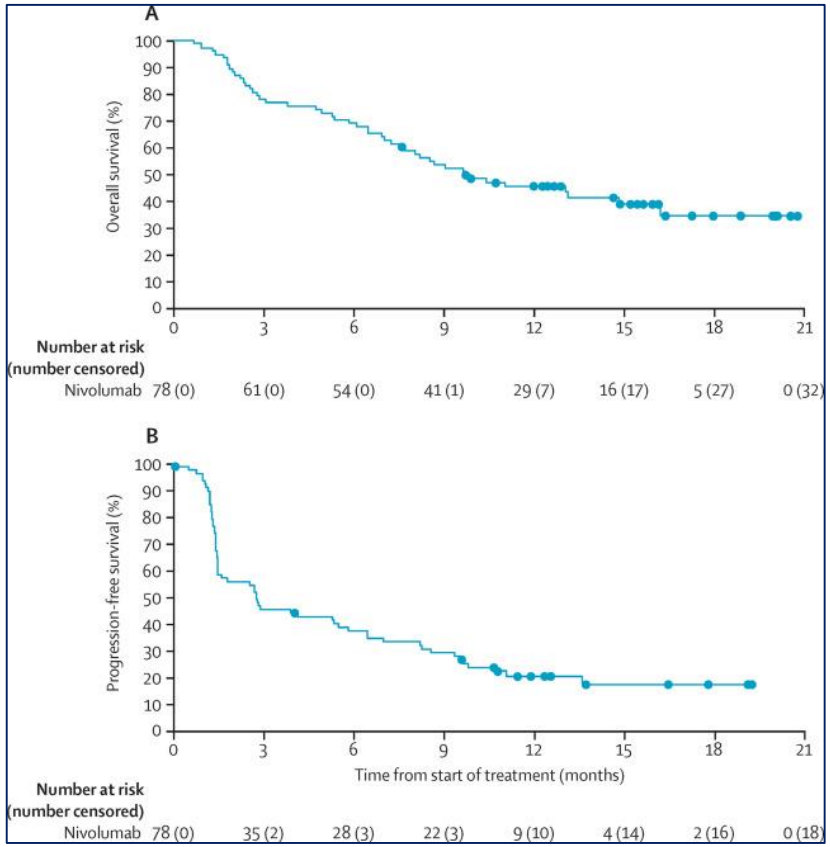
Checkmate 032 Study



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

	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

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

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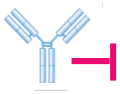
Nivolumab:



PD-1

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

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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.

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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).

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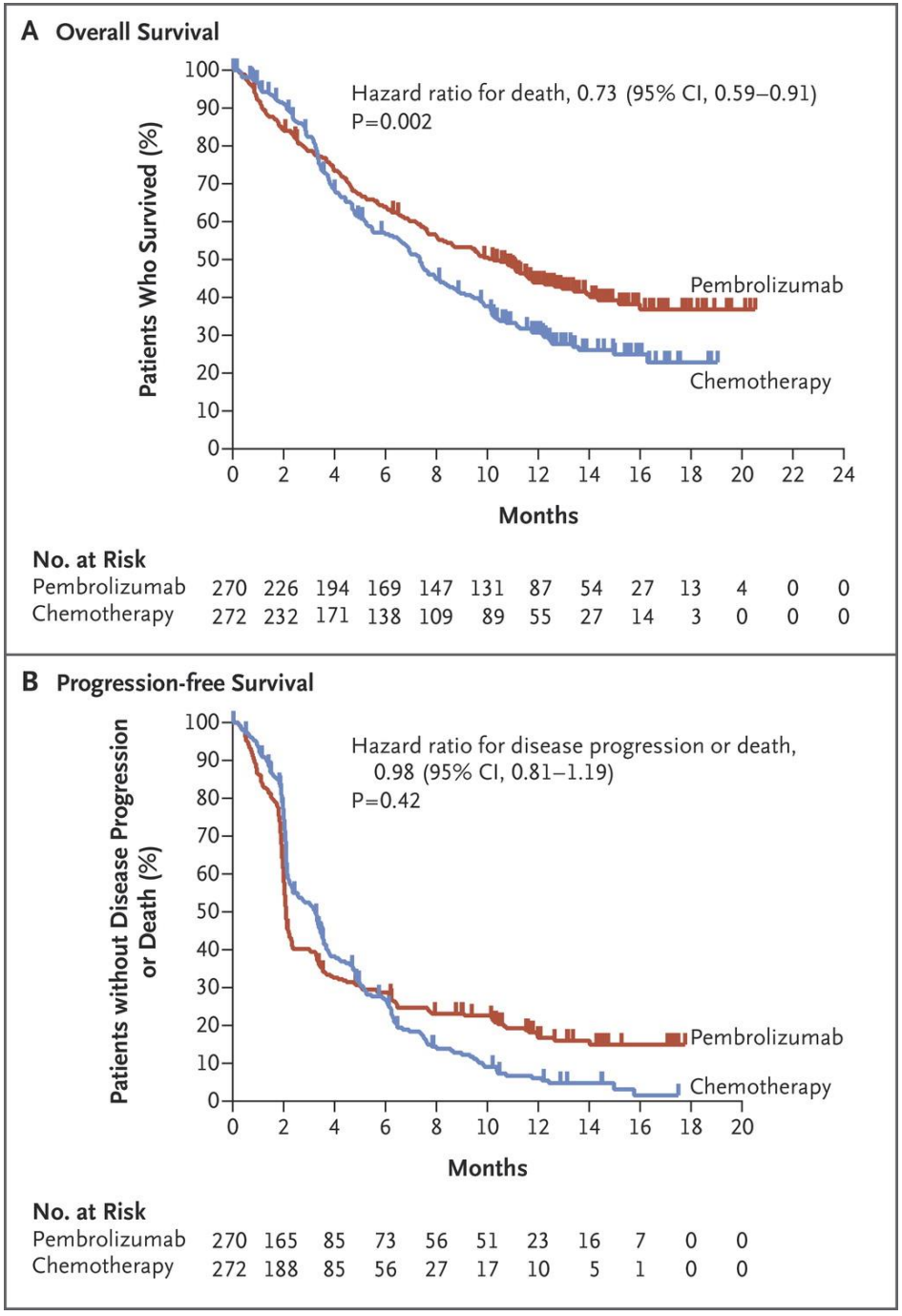
KEYNOTE-045

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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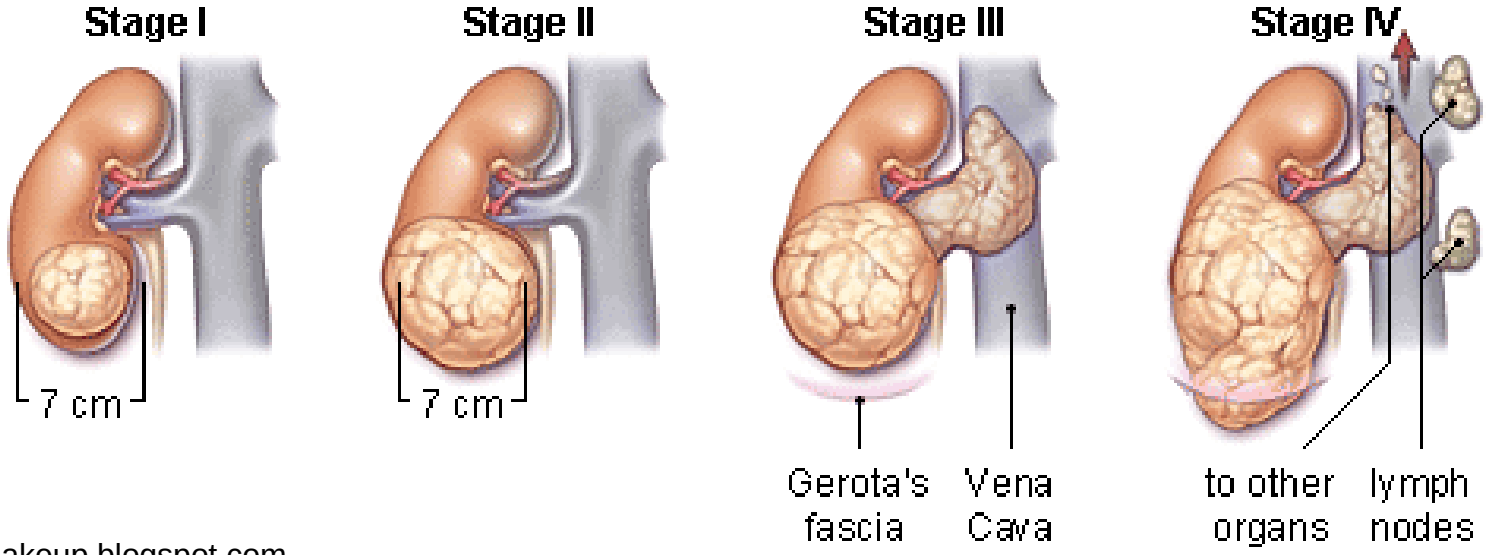
Kidney Cancer:

Surgically resectable → Oligo-metastatic → Metastatic

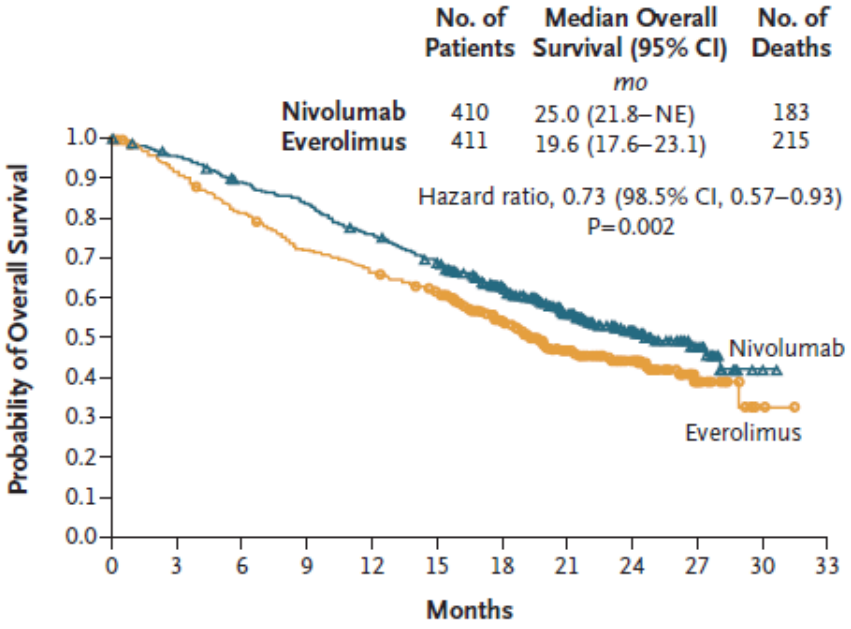


reemakeup.blogspot.com

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

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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

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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, IFNα, etc
- Multiple combinations with pembolizumab

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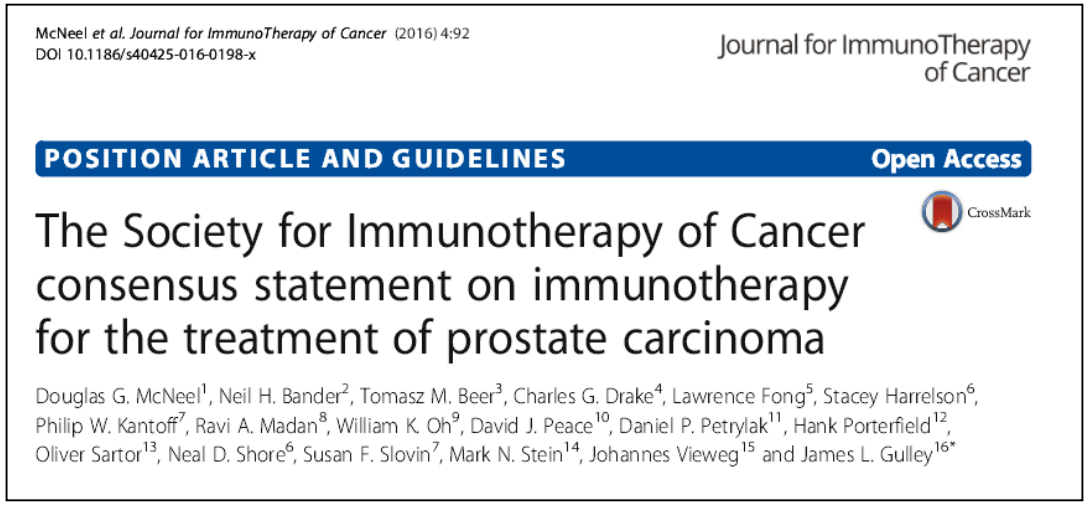
Resources



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

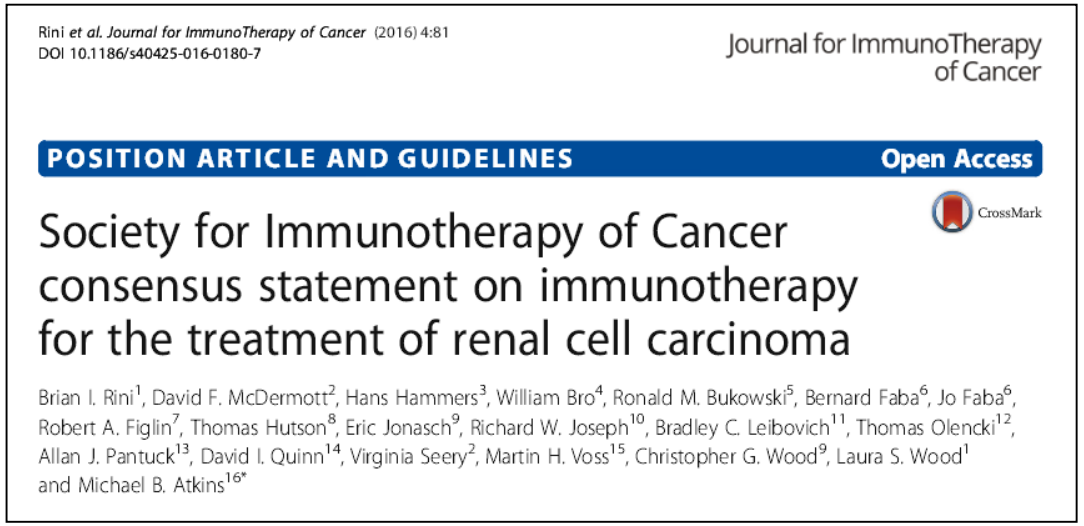
Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

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*]



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*]

Look for:

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

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