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# Immunotherapy for the Treatment of Genitourinary Cancers

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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# Disclosures

- No relevant financial relationships to disclose
- I may be discussing non-FDA approved indications during my presentation.

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# Learning Objectives:

- ***Describe the rationale for common approaches to cancer immunotherapy, with respect to prostate, bladder and renal 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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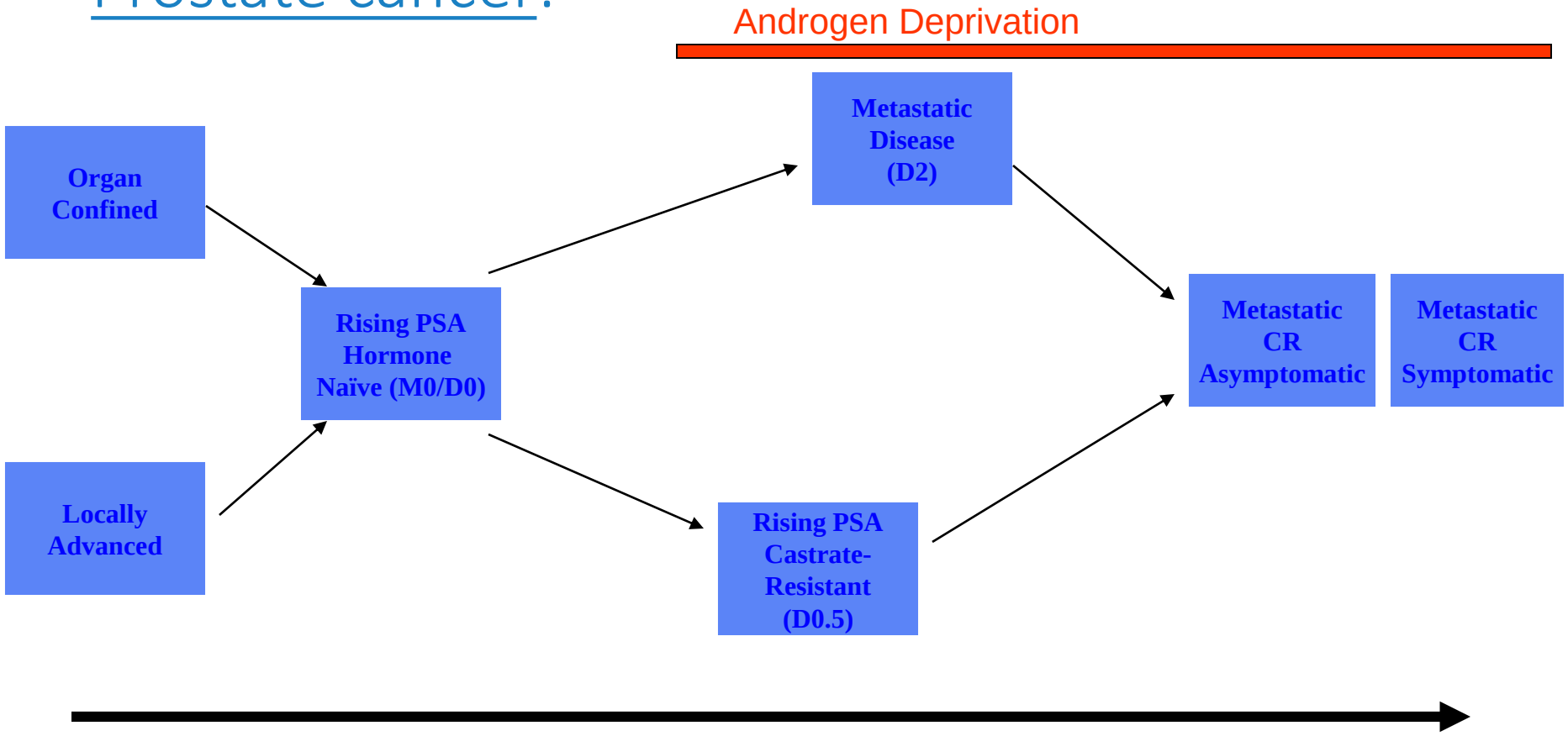
# Prostate cancer:

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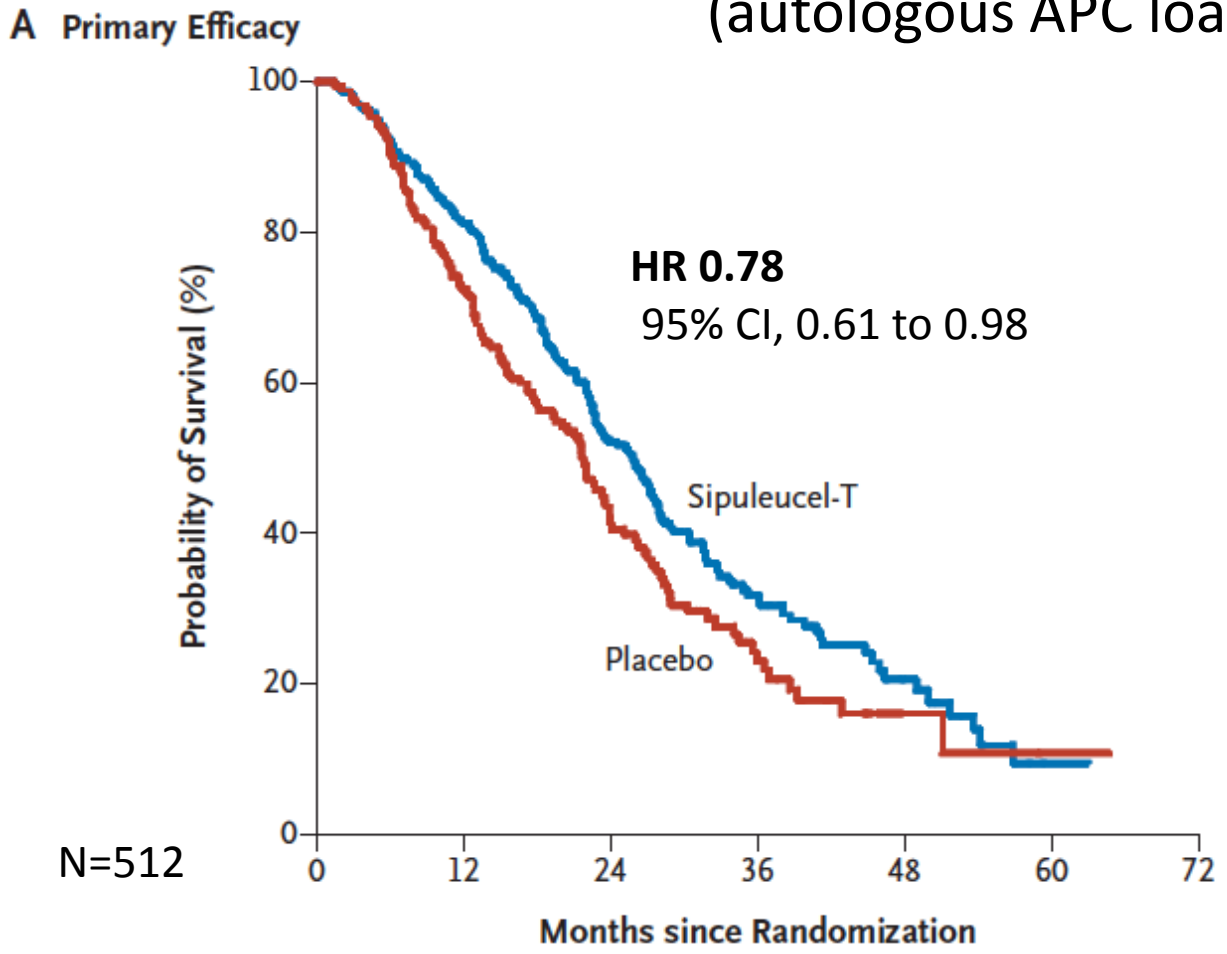
# Vaccines in Prostate Cancer

**Sipuleucel-T**

(autologous APC loaded with PAP-GM-CSF fusion protein




Kantoff, et al, NEJM 2010.

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# Sipuleucel-T:

Approval indications: **APRIL 2010**

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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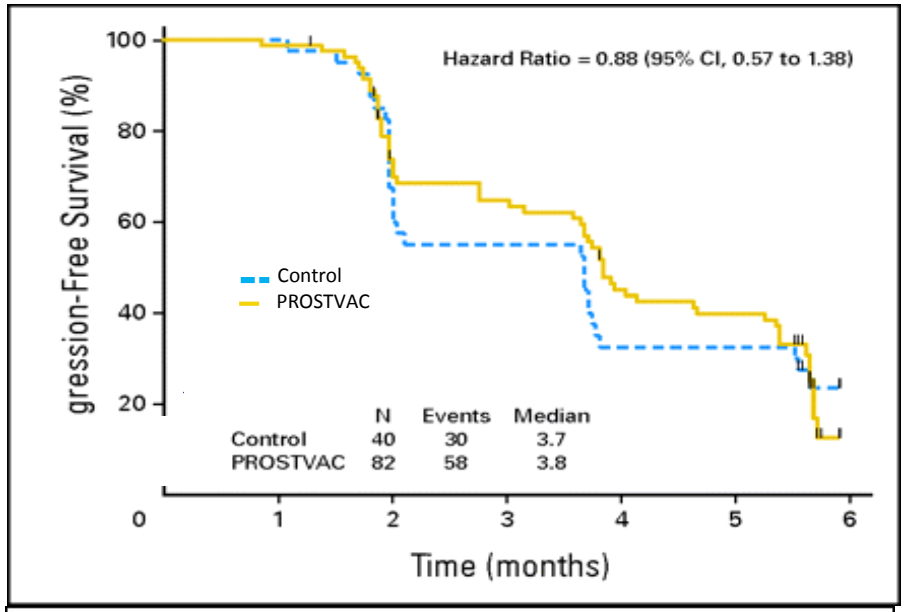
# Vaccines in Prostate Cancer

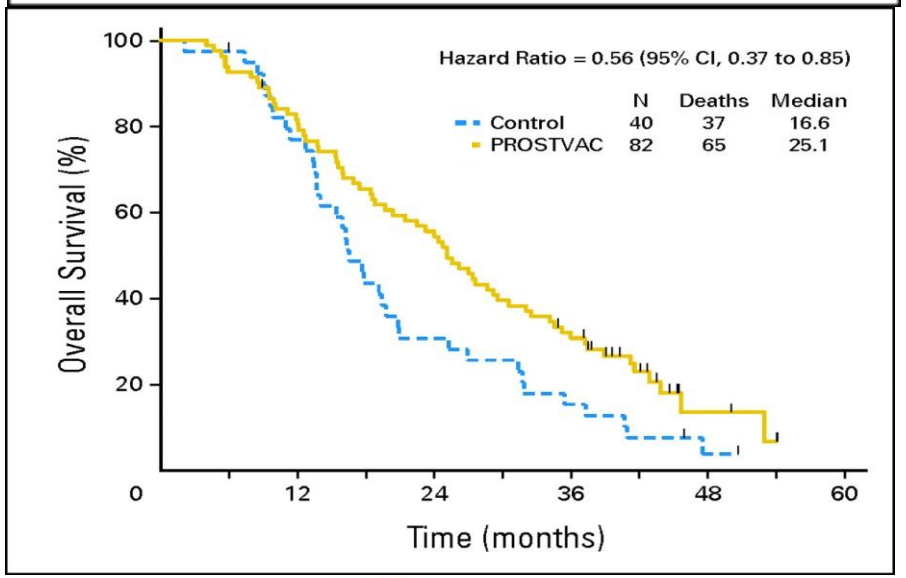
## Prostvac

**Poxvirus expressing PSA/B7-1/ICAM-1/LFA-3 Plus GM-CSF**

NCT01322490: Phase III study: N=1200 pts.

Prostvac+GM-CSF
Prostvac+placebo
Placebo
Chemo-naïve, pox-experienced min-Sx CRPC




Kantoff, el al, JCO 2010

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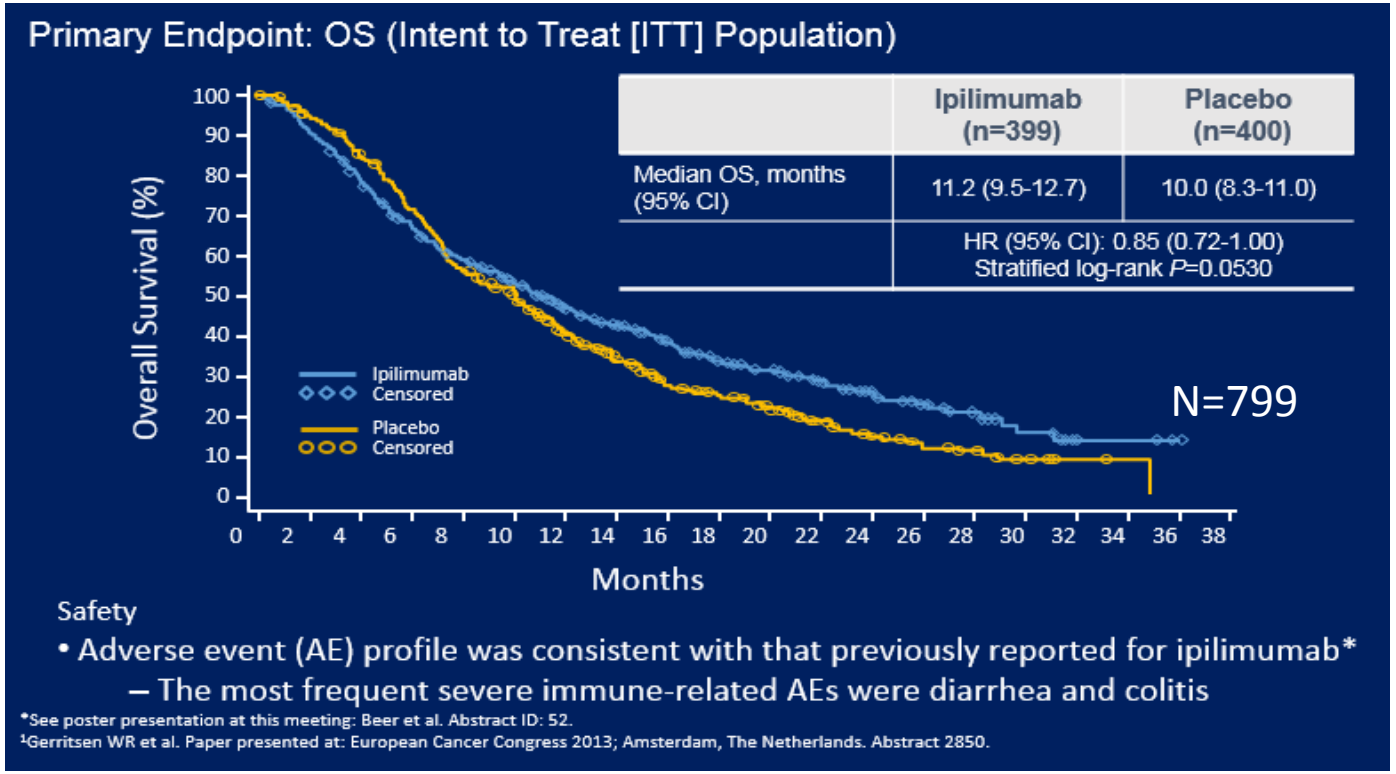
Ipilimumab CTLA-4

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




Kwon et al Lancet Onc 2014 15:700

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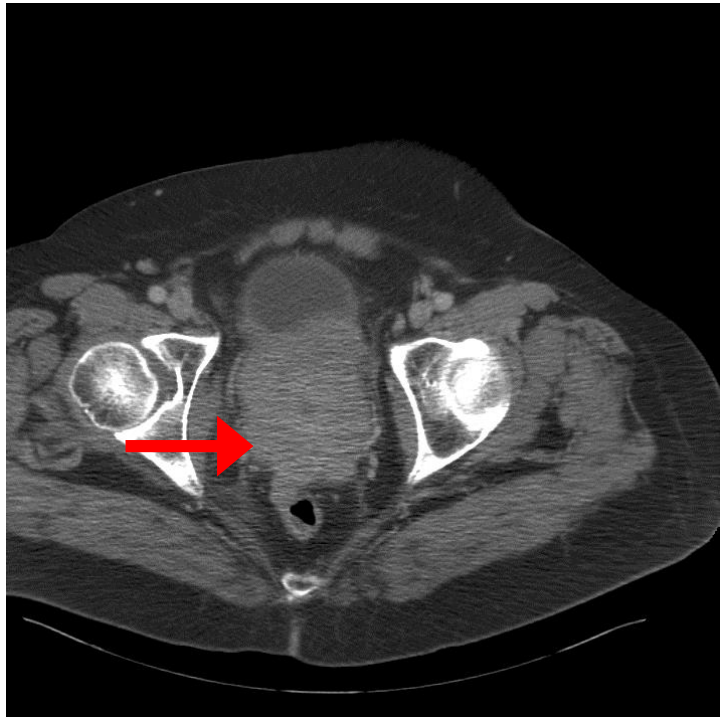
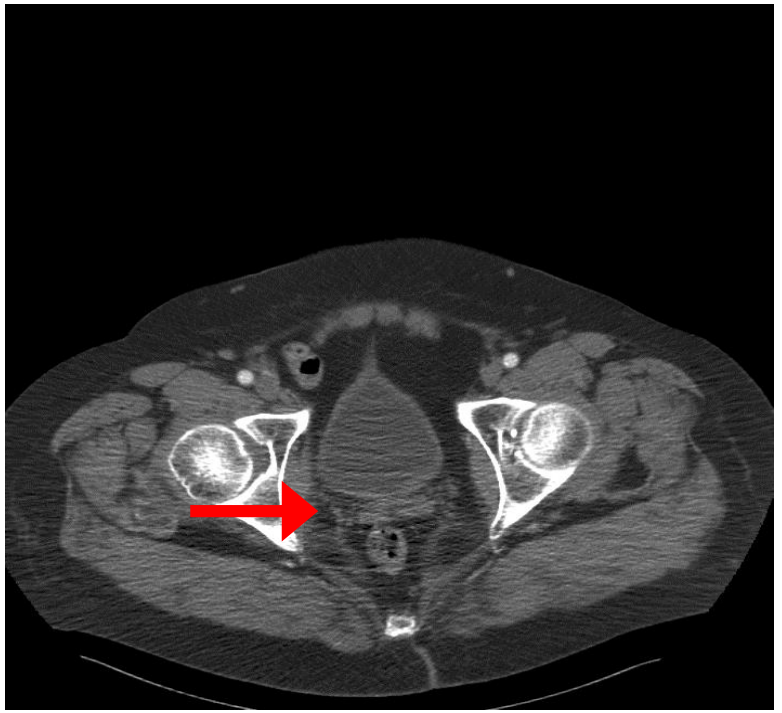
# Resolution of Prostate Mass

Screening



14 months



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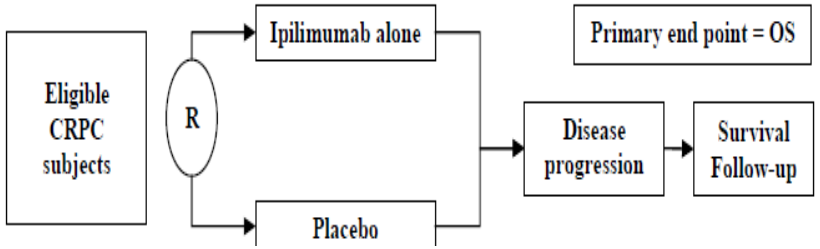
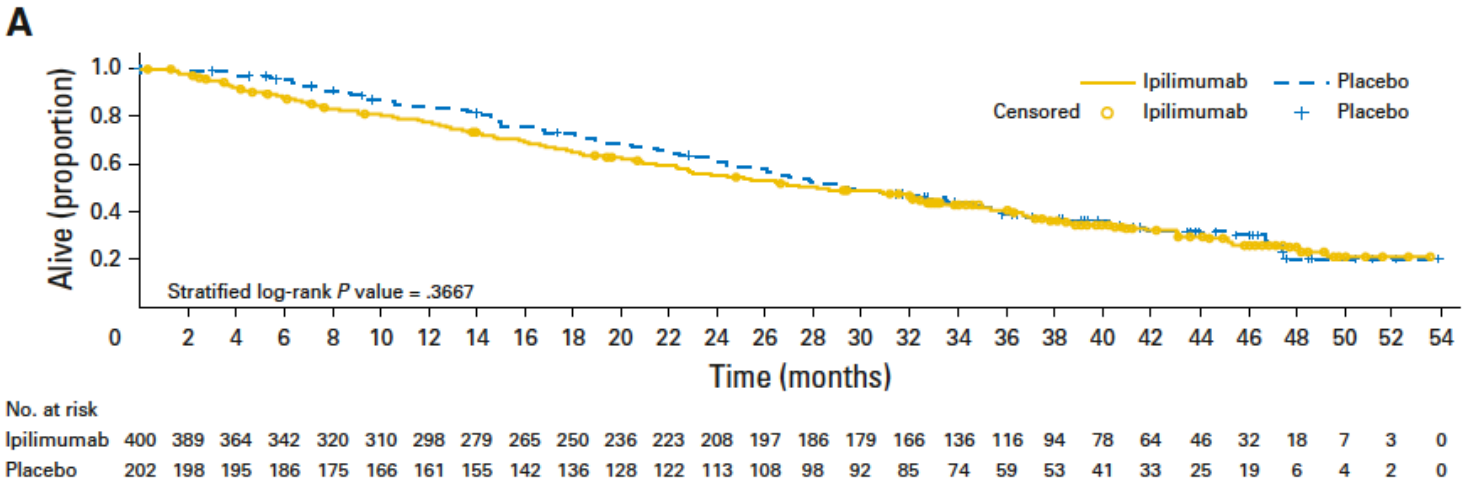
Ipilimumab CTLA-4




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)

PFS: (HR, 0.67; 95.87% CI, 0.55 to 0.81)

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 (3/10 Graff, Beer et al Oncotargets May 2016)**
  - 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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# Lessons learned: Prostate cancer immunotherapy trials

- Prostate *not* an "inflamed" solid tumor like melanoma, lung, bladder
- *Not* significantly hyper-mutated
- For vaccines ↑ doses of vaccine ≠ augmentation of immunity
- *Limited efficacy* of checkpoint inhibitors, anti-CTLA-4, anti-PD1 **as single agents**

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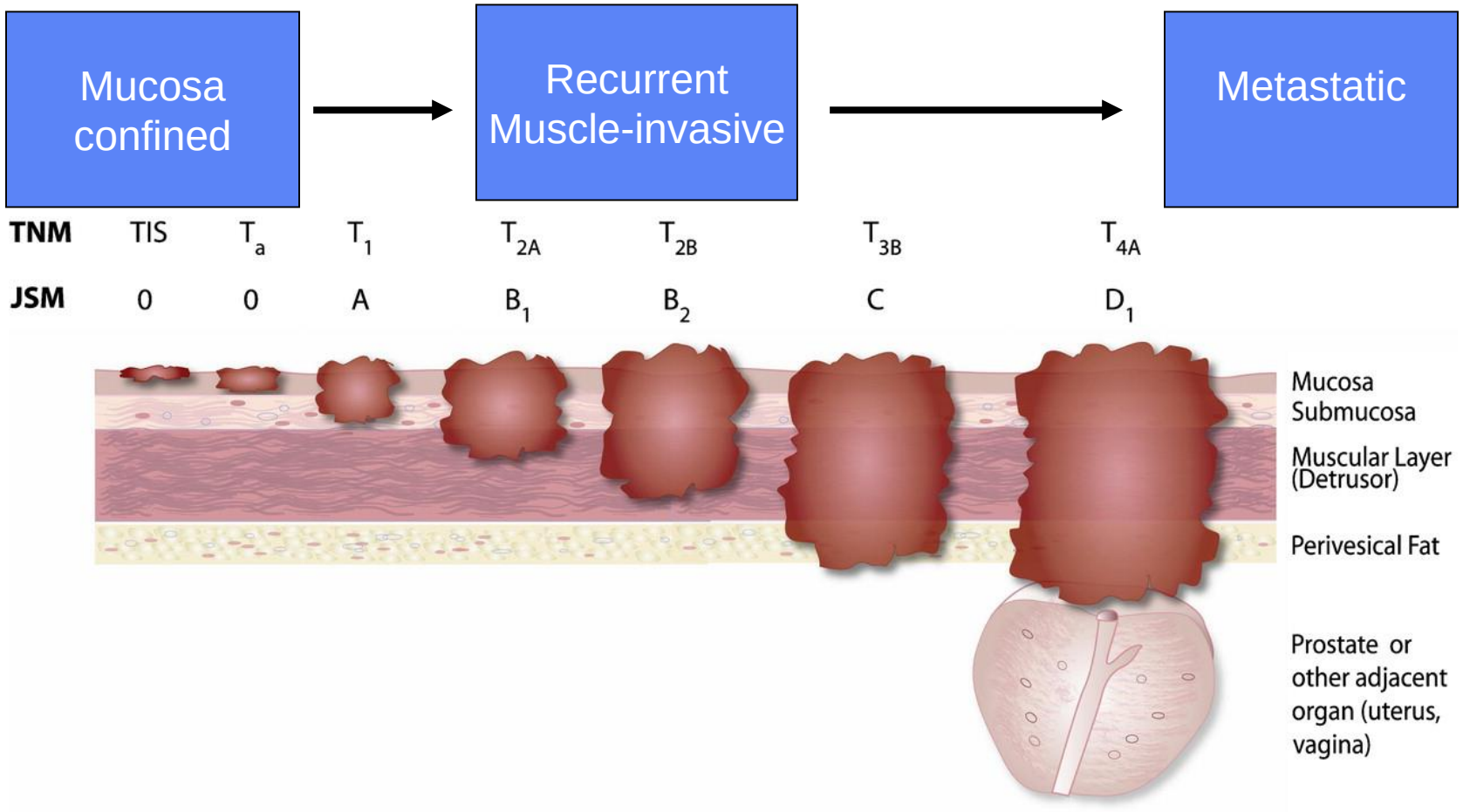
# Bladder Cancer:




www.cancersymptoms.xyz

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# Bladder Cancer:

## TREATMENT OF METASTATIC BLADDER CANCER

Gemcitabine+cisplatin chemotherapy

MVAC: methotrexate vinblastine adriamycin cisplatin

No 2nd line treatment approved in the USA

paclitaxel, docetaxel, pemetrexed, eribulin have shown modest activity

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# BLADDER CANCER 2013 UPDATE

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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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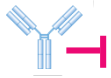
Atezolizumab:



PD-L1

# Atezolizumab – IMvigor 210 Study

- PD-L1 mAb
- 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% |

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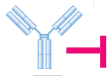
Atezolizumab:



PD-L1

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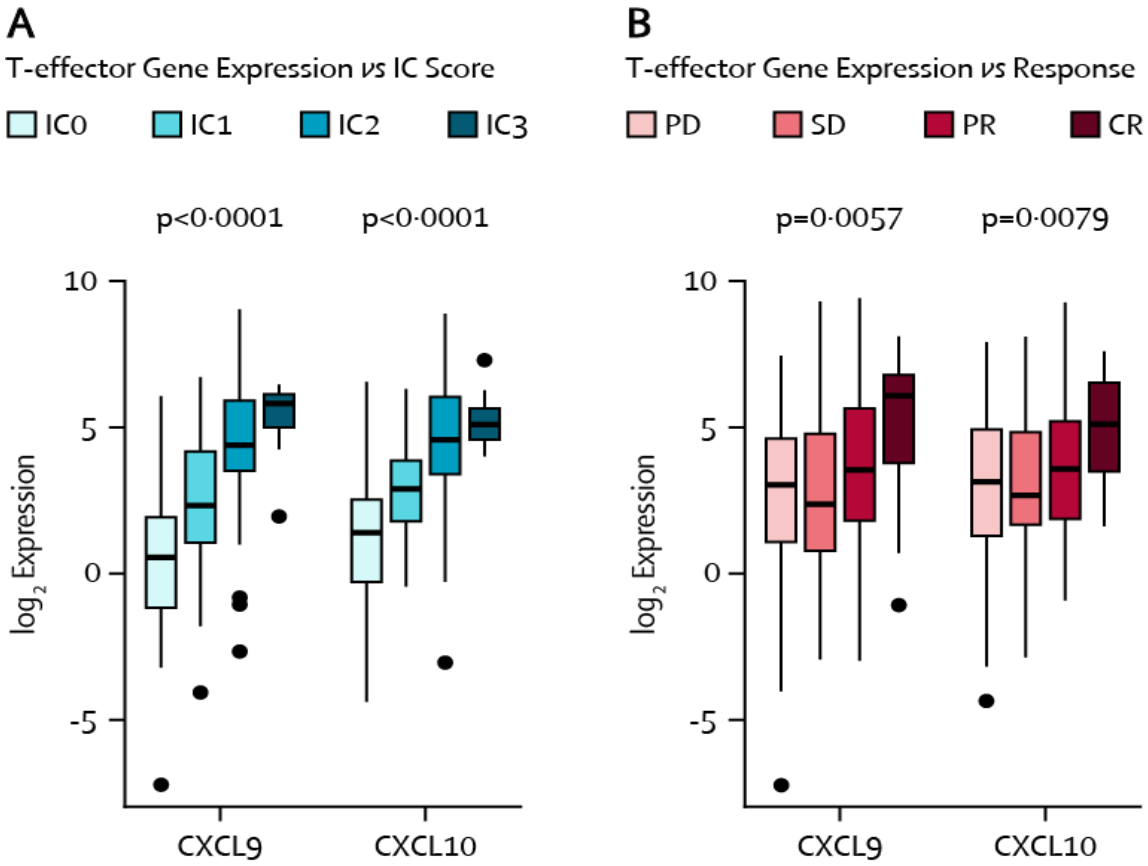
# High levels of immune response genes are associated with both PD-L1 staining and treatment response

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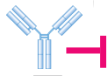
Atezolizumab:



PD-L1

# IMvigor 211 trial

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

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# 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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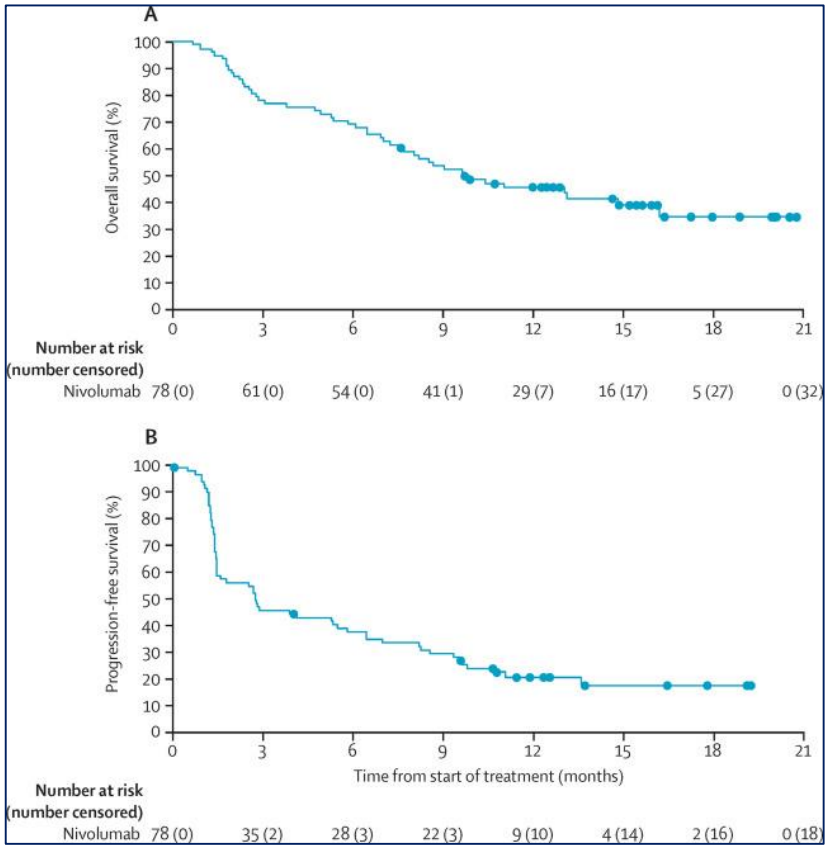
# Checkmate 032 Study




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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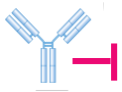
Nivolumab:



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

- 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).

- 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. **Control: investigator choice docetaxel, paclitaxel or vinflunine.**

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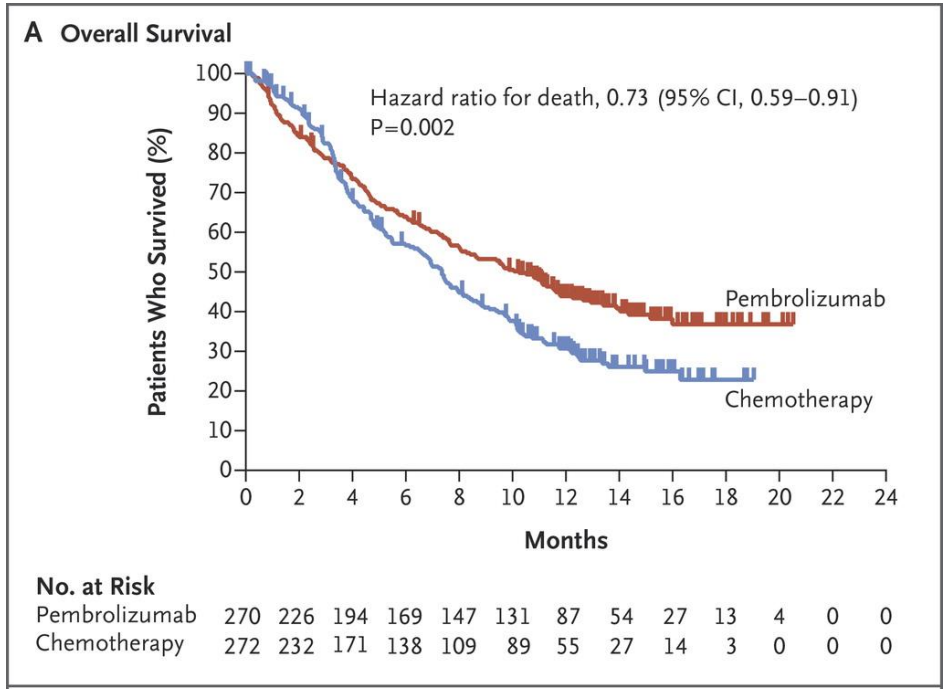
# KEYNOTE-045

**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%)




ESMO 2017 Update: HR 0.70

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

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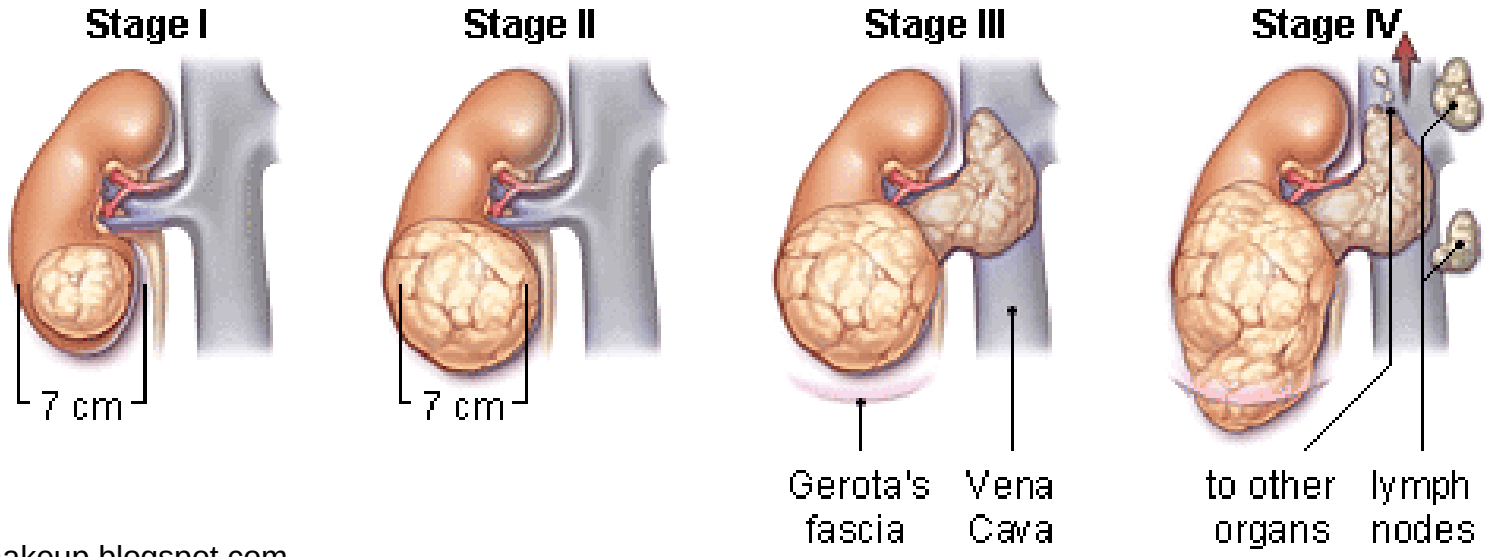
# Kidney Cancer

Surgically resectable → Oligo-metastatic → Metastatic




reemakeup.blogspot.com

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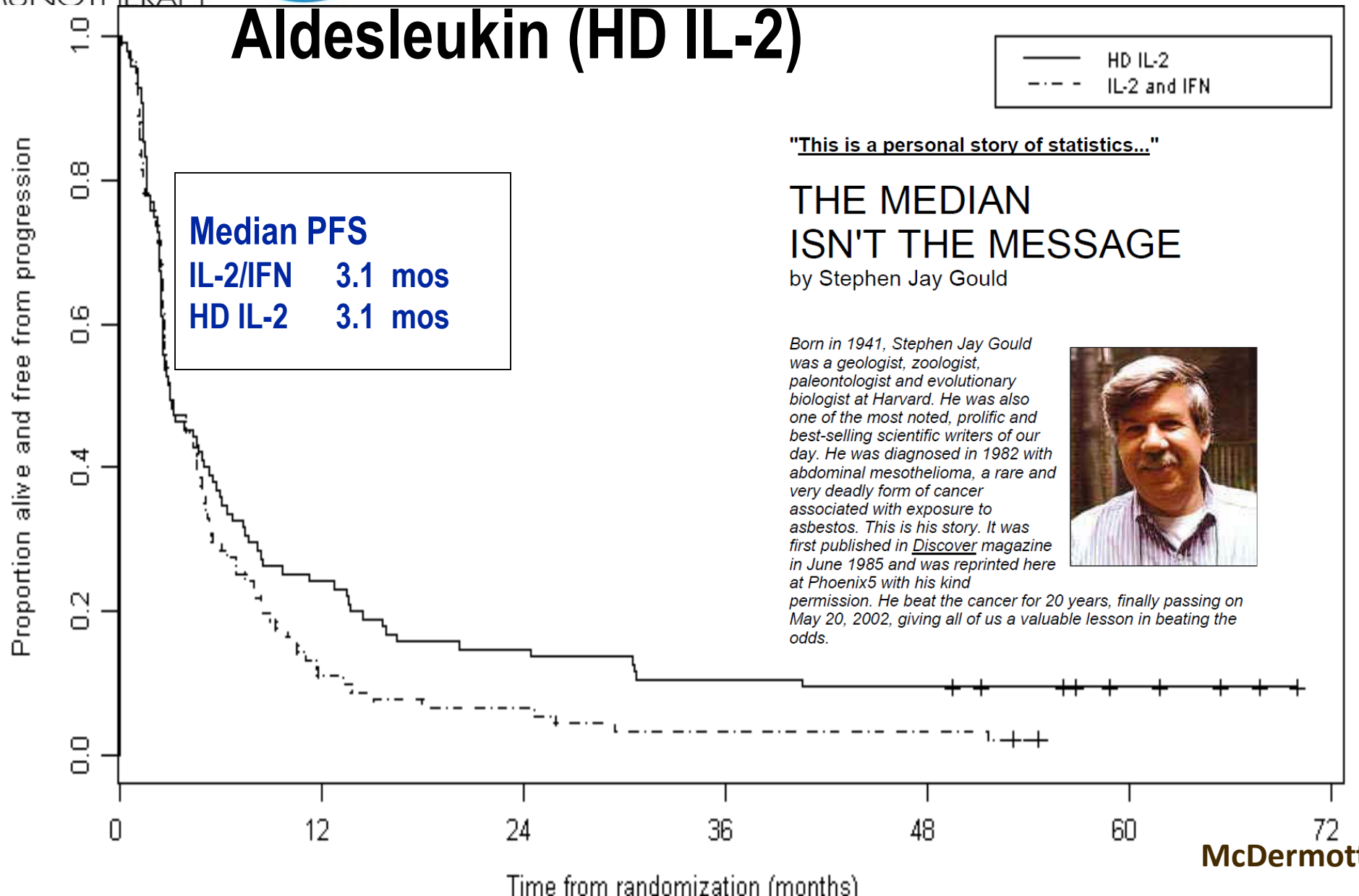
# Aldesleukin (HD IL-2)




McDermott JCO 2005

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# Renal Cell Carcinoma: Approved Agents 2017


**VEGFR TKI**

**VEGFR/MET TKI**

**mTOR inhibitor**

**Immune therapy**

**Neutralizing anti-VEGF mAb**

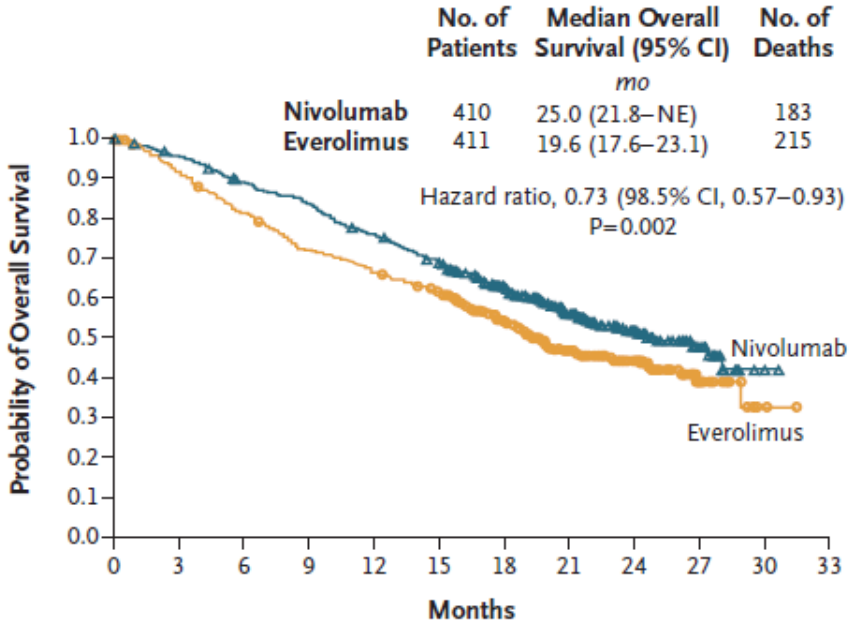
# Nivolumab

- 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

- **<u>Median OS: 25m vs 19.6m</u>**
- 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

# PD-L1 Expression is prognostic for poor survival in RCC but did not predict for response to nivolumab

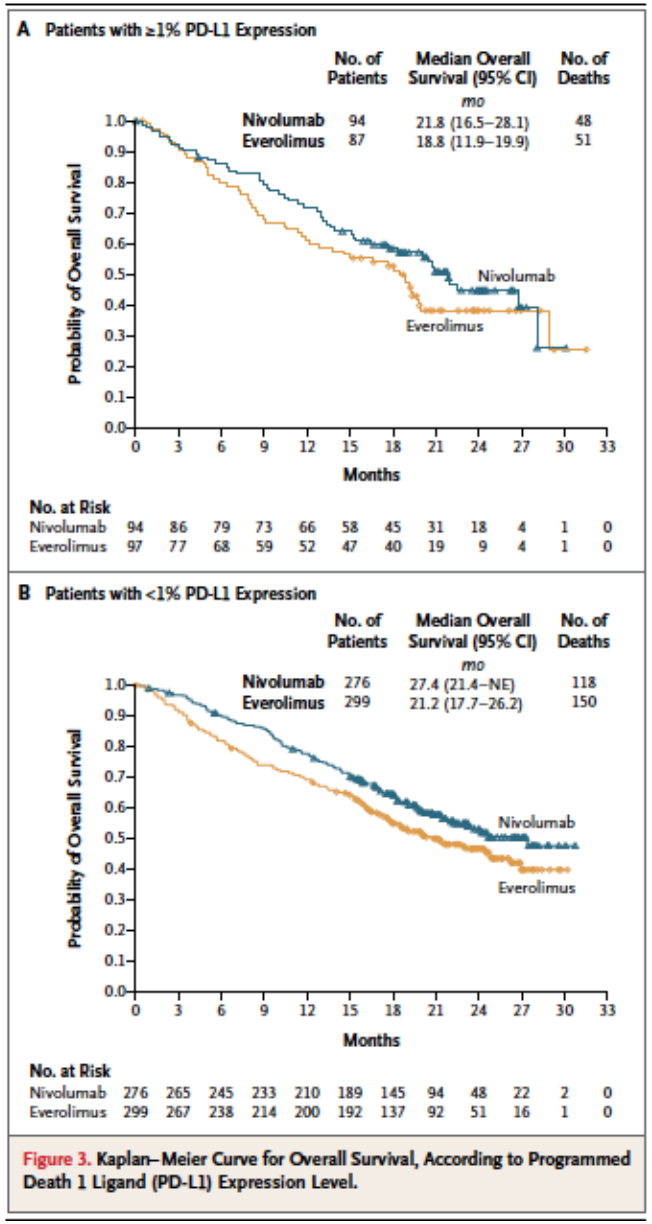



Figure 3. Kaplan–Meier Curve for Overall Survival, According to Programmed Death 1 Ligand (PD-L1) Expression Level.

MOTZER NEJM 2016

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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, IFN$\alpha$, etc
- Multiple combinations with pembolizumab

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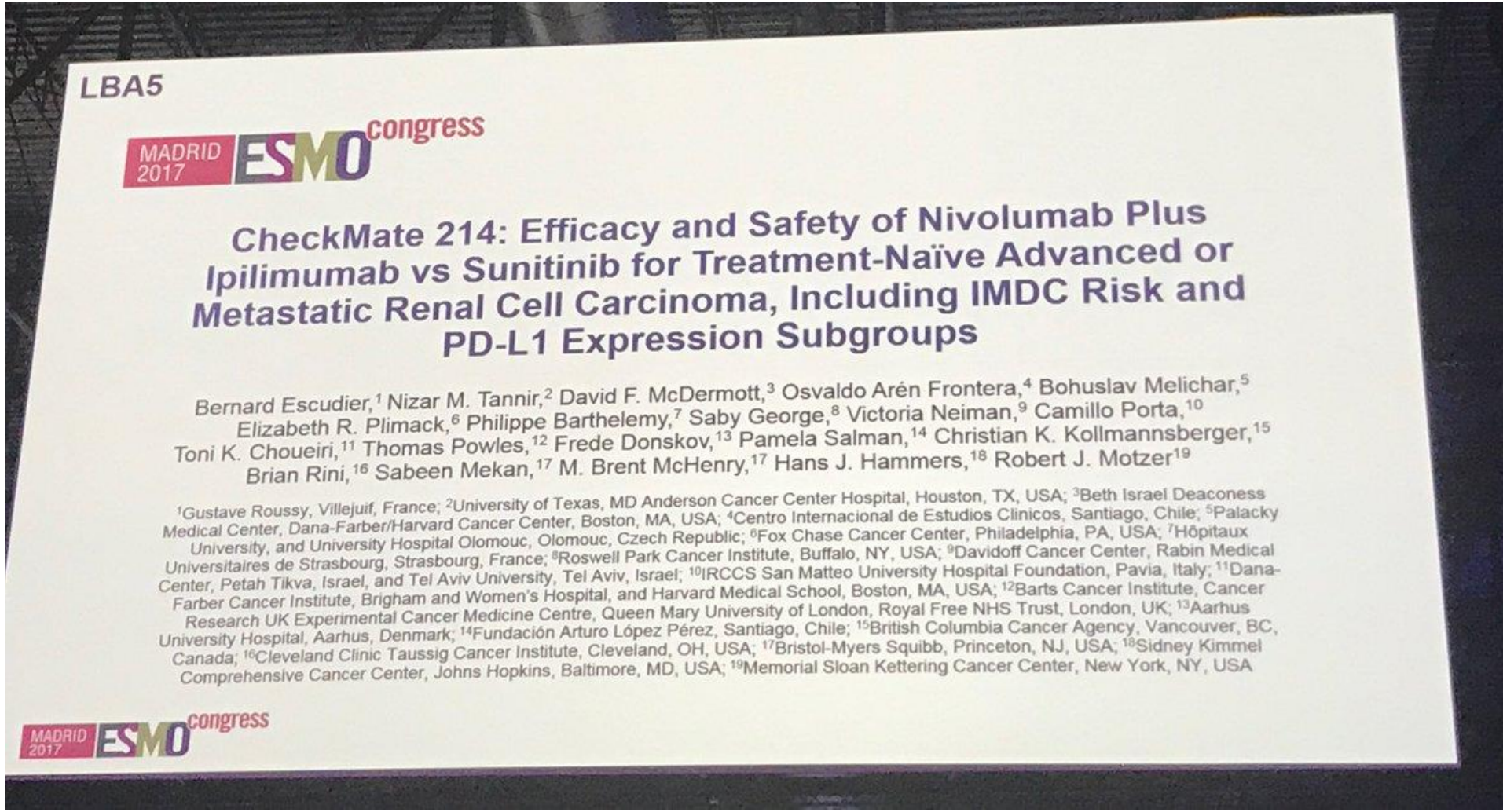


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# CheckMate 214: Study design

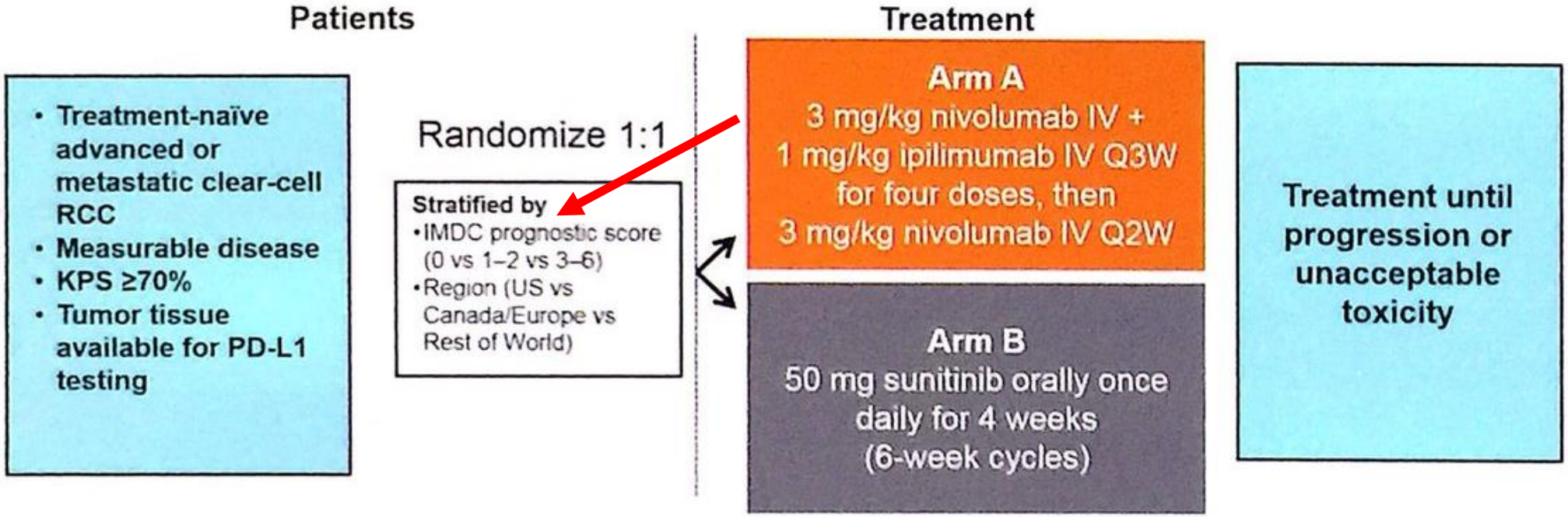
3 co-primary endpoints (Int and poor risk)

OS

PFS

ORR

**N=1000**

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IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

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**Table 3. Multivariable Analysis and Final Model**

| Parameter | Parameter Estimate ± SE | Hazard Ratio | 95% CI | P |
|---|---|---|---|---|
| Clinical | | | | |
| KPS < 80% | 0.92 ± 0.14 | 2.51 | 1.92 to 3.29 | < .0001 |
| Time from diagnosis to treatment < 1 year | 0.35 ± 0.13 | 1.42 | 1.09 to 1.84 | .0088 |
| Laboratory | | | | |
| Hemoglobin < LLN | 0.54 ± 0.14 | 1.72 | 1.31 to 2.26 | .0001 |
| Calcium > ULN | 0.59 ± 0.17 | 1.81 | 1.29 to 2.53 | .0006 |
| Neutrophil count > ULN | 0.88 ± 0.17 | 2.42 | 1.72 to 3.39 | < .0001 |
| Platelet count > ULN | 0.40 ± 0.16 | 1.49 | 1.09 to 2.03 | .0121 |

NOTE. Total number of patients = 564.

Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.

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Co-primary endpoint: ORR

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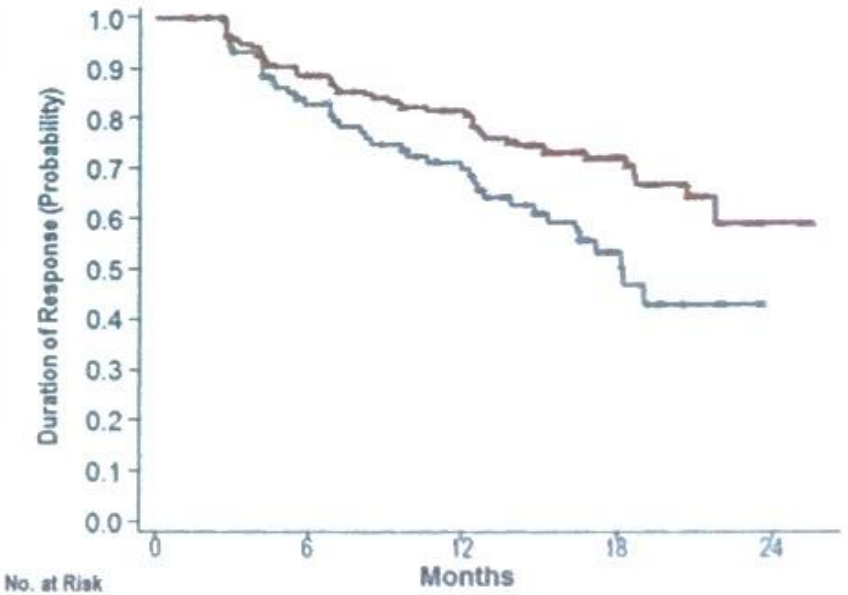
# ORR AND DOR: IMDC INTERMEDIATE/POOR RISK

| Outcome | N = 847 | |
|---|---|---|
| | NIVO + IPI N = 425 | SUN N = 422 |
| Confirmed ORR,[a] % (95% CI) | 42 (37–47) | 27 (22–31) |
| | *P* < 0.0001 | |
| **Confirmed BOR,[a] %** | | |
| Complete response | 9[b] | 1[b] |
| Partial response | 32 | 25 |
| Stable disease | 31 | 45 |
| Progressive disease | 20 | 17 |
| Unable to determine/not reported | 8 | 12 |

[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

| | Median duration of response, months (95% CI) | Patients with ongoing response, % |
|---|---|---|
| NIVO + IPI | NR (21.8–NE) | 72 |
| SUN | 18.2 (14.8–NE) | 63 |

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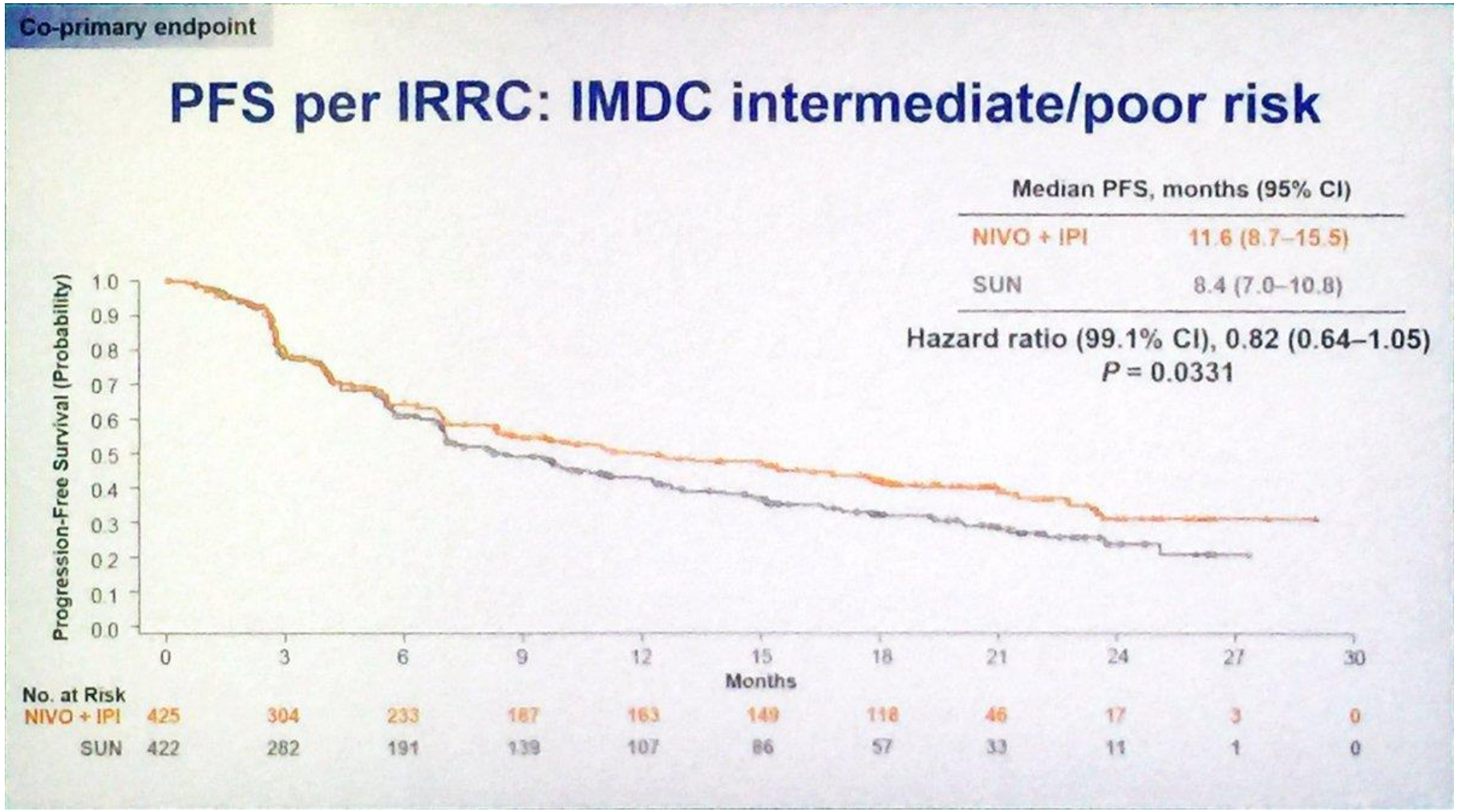


Overall population:
12 months vs 12 months
HR 0.98

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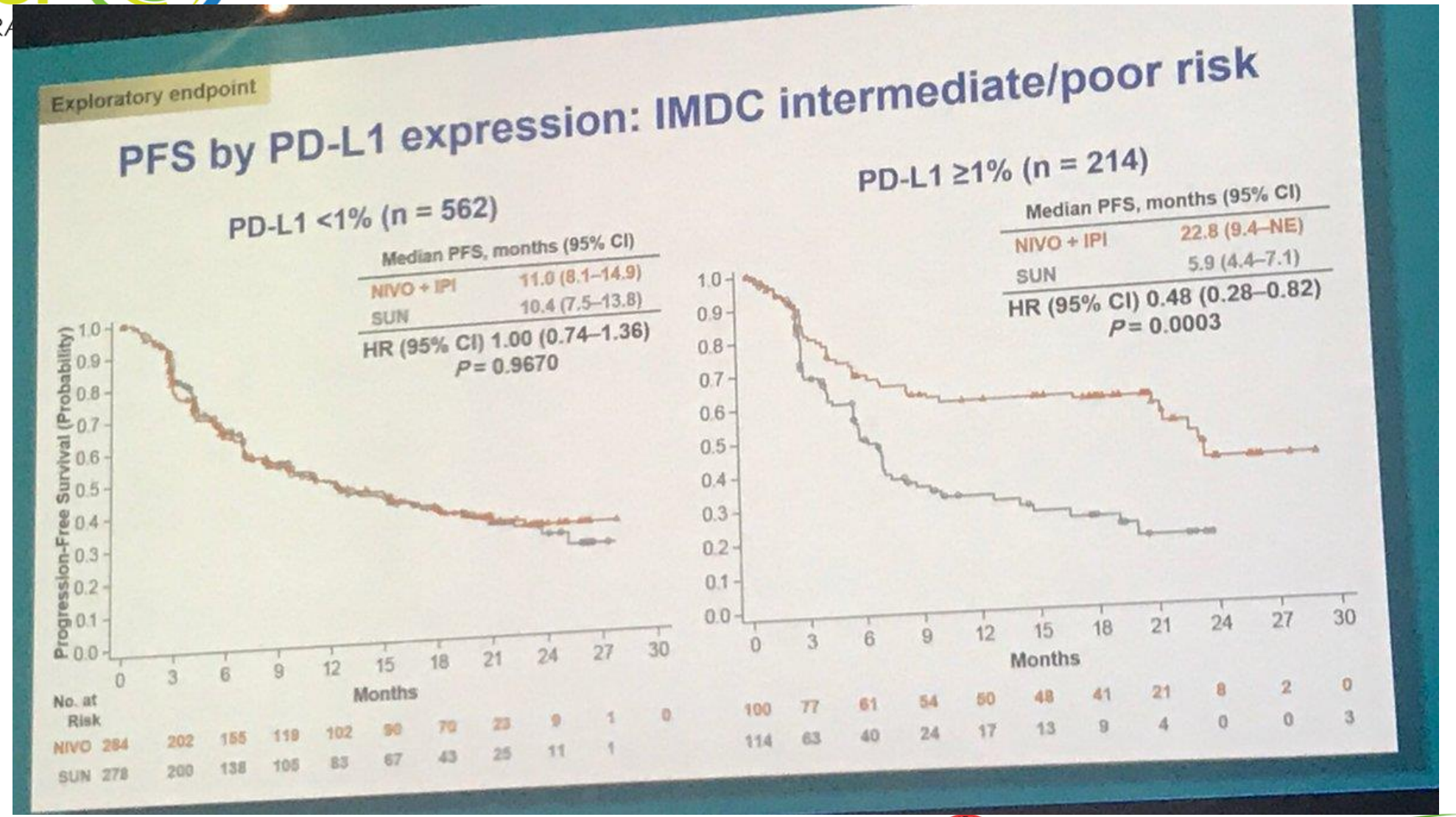


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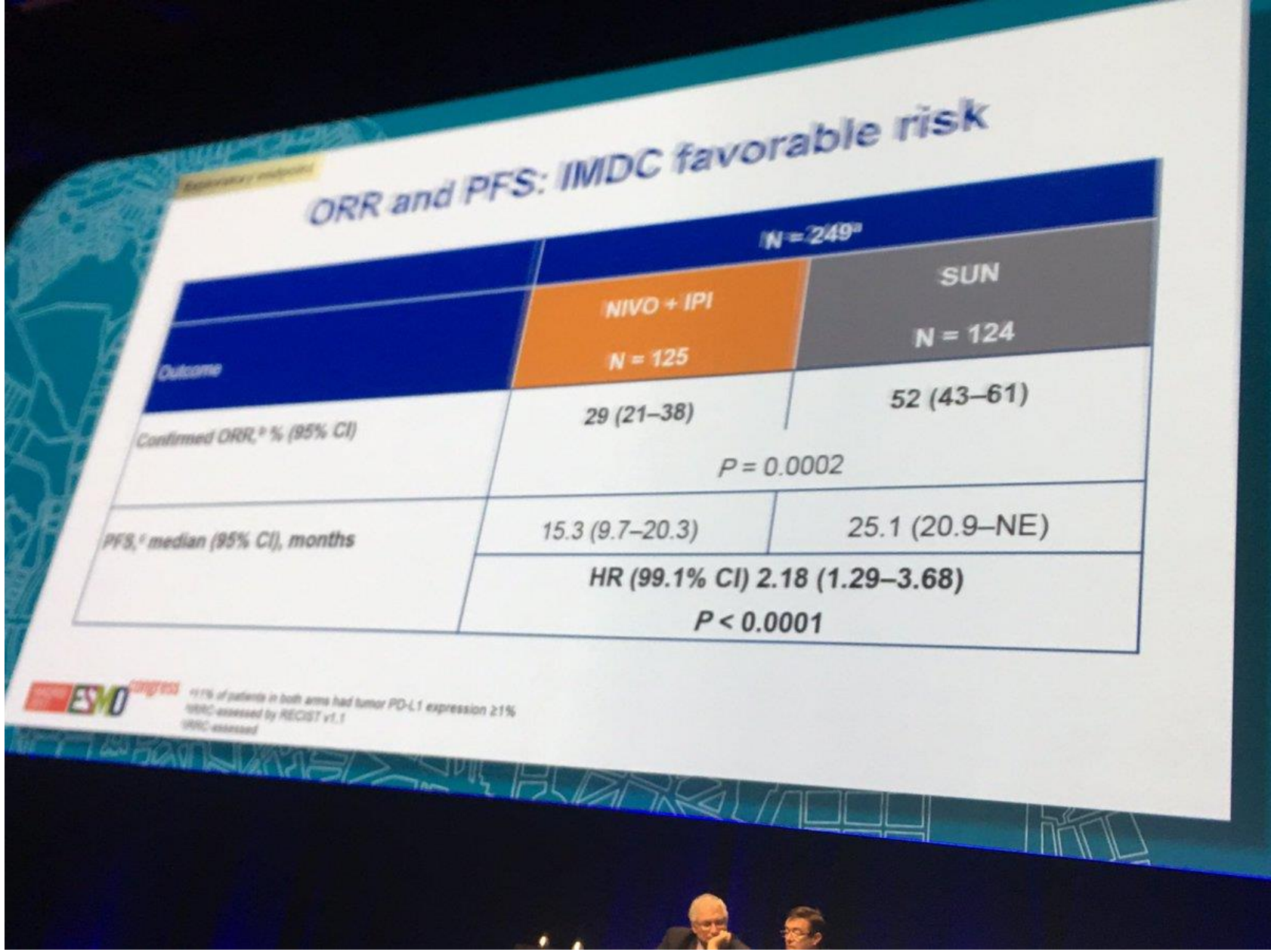


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Neeraj Agarwal and 2 others follow

**Swati Tyagi** @swatityagi · Aug 16

#Opdivo+#Yeryoy fails to achieve stats signif PFS in **CHECKMATE-214** for adv/mets RCC. Mature OS data key for 1L entry

**Bristol-Myers Squibb Announces Topline Results fr...**

Co-Primary Endpoint of Objective Response Rate was met for the combination of Opdivo and Yervoy Co-Primary Endpoint of Progression-Free Survival Favore...

investors.bms.com

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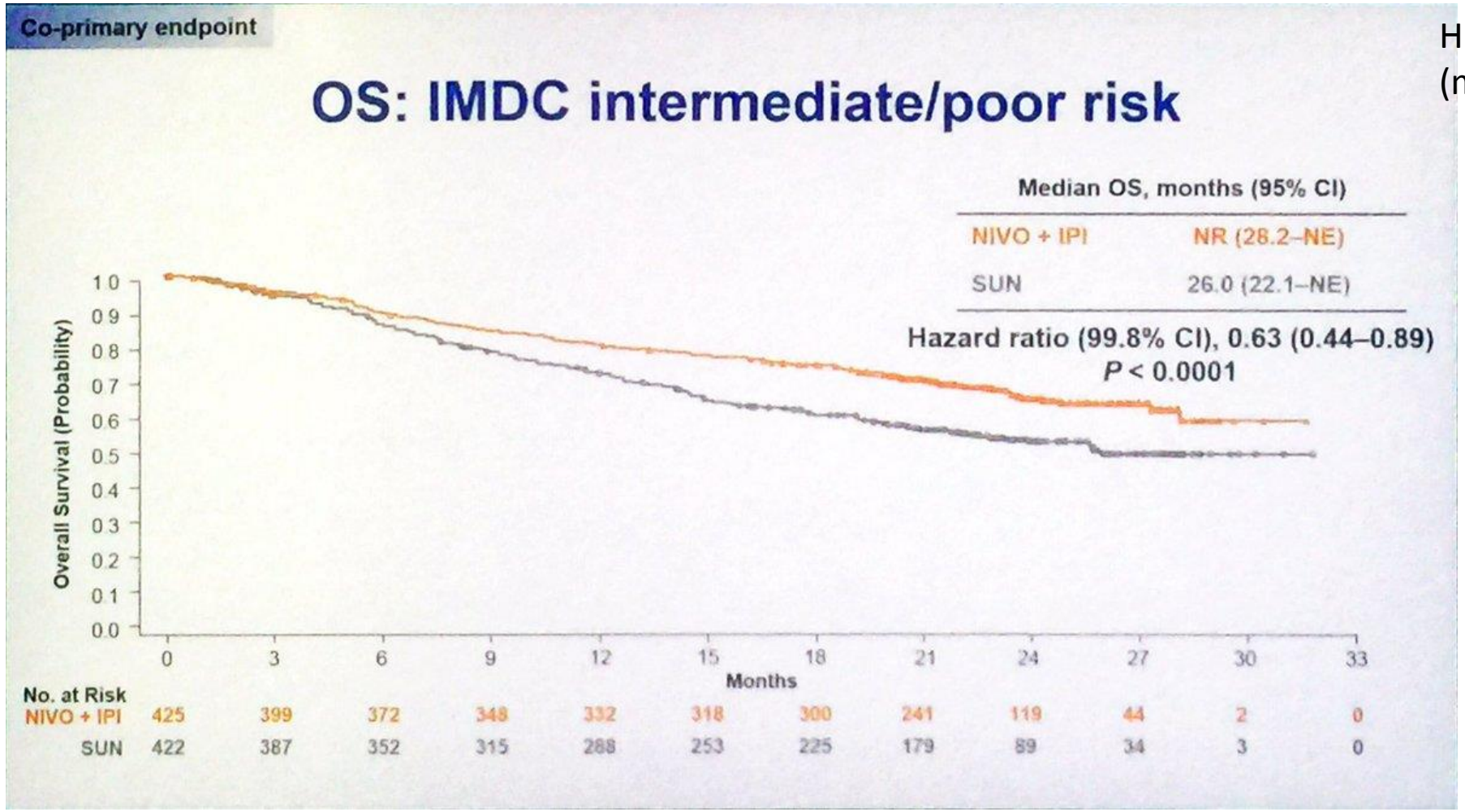


HR for all patients 0.68 (p<0.003)
(median OS NR vs 33 mo)

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| Checkmate-214 results reported at Esmo | | | |
|---|---|---|---|
| | **Intermediate/poor-risk (~75% of pts)** | **Good risk (~25% of pts)** | **All patients (ITT)** |
| **PFS** | 11.6 vs 8.4 mos. HR=0.82; p=0.0331. | 15.9 vs 25.1 mos. HR=2.18, p<0.0001 in favour of Sutent. | 12.4 vs 12.3 mos, HR=0.98, p=0.8499. |
| *PD-L1 negative* | *PFS=11.0 vs 10.4 mos. HR=1.00, p=0.9670.* | *PFS not disclosed, but HR likely to be >1.0. (ORR estimated to ~33% vs 56%.)** | *PFS not disclosed. (ORR 36% vs 35%, p=0.8799.)* |
| *PD-L1 positive* | *22.0 vs 5.9 mos. HR=0.48, p= 0.0003.* | *PFS not disclosed.* | *PFS not disclosed. (ORR=53% vs 22%, p<0.0001.)* |
| **OS** | NR vs 26.0 mos. HR 0.63, p<0.0001. | Not disclosed. Likely to favour Sutent. | NR vs 32.9 mos. HR=0.68 p=0.0003. |

*All comparisons Opdivo/Yervoy vs Sutent. NR: not reached.*by EPVantage.*

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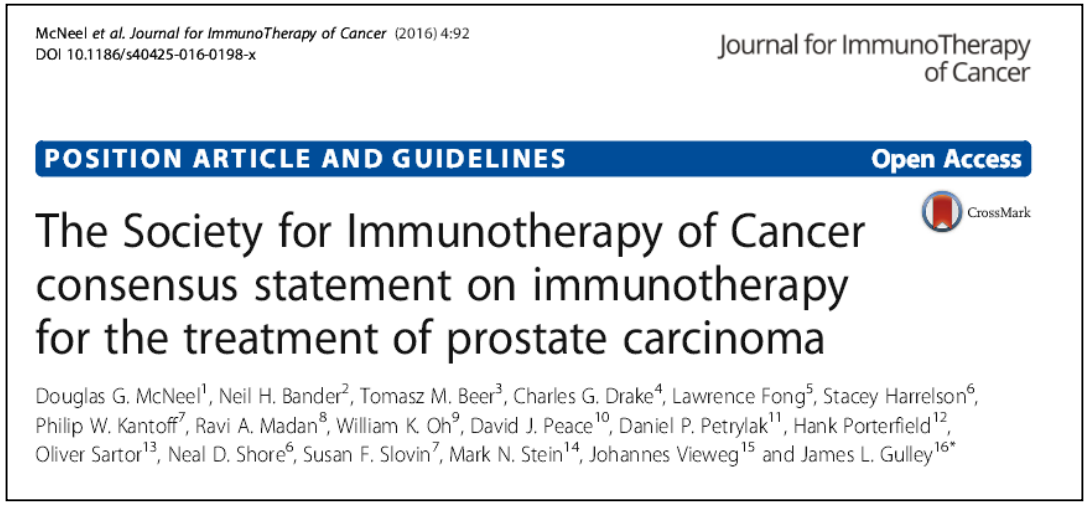
# Resources



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

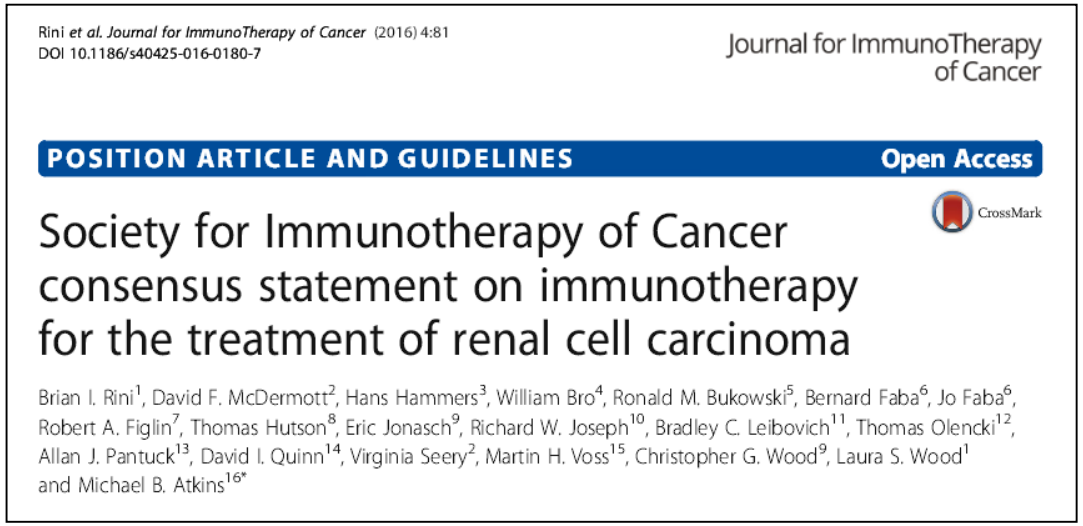
Journal for ImmunoTherapy of Cancer

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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