ADVANCES IN Cancer IMMUNOTHERAPY™

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

- I currently receive honoraria from Genentech, Astellas-Medivation
- I will be discussing approved and non-FDA approved indications during my presentation.

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Key Takeaways:

- ***Describe the rationale for common approaches to cancer immunotherapy, particularly with respect to prostate cancer, bladder cancer 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 – 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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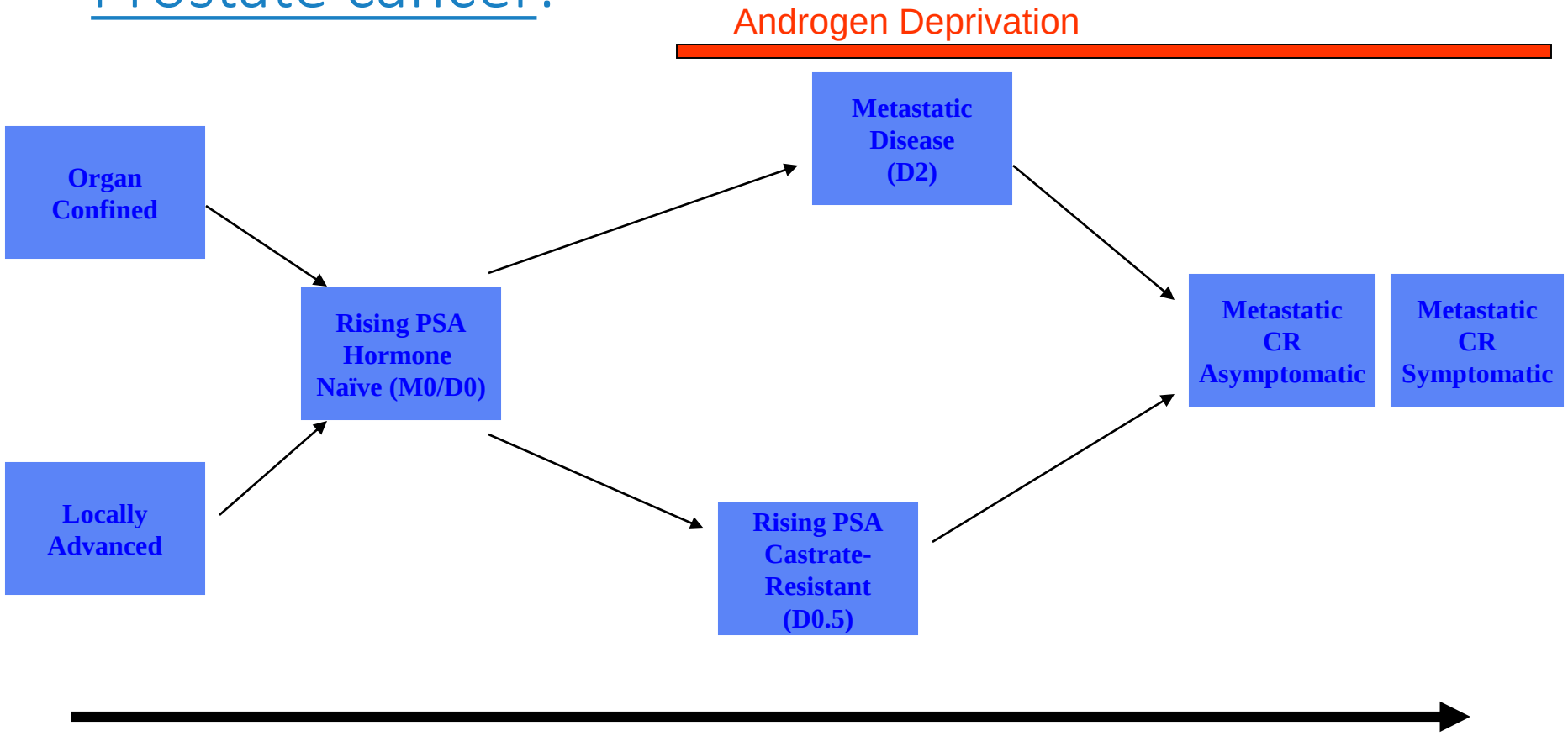
Prostate cancer:



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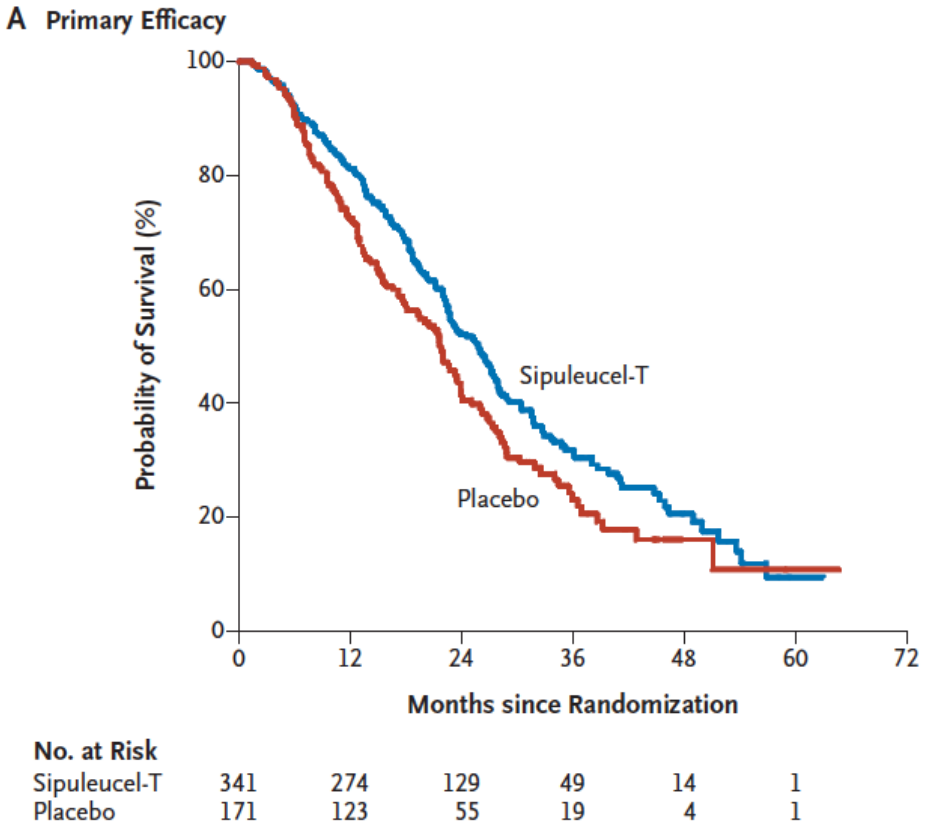
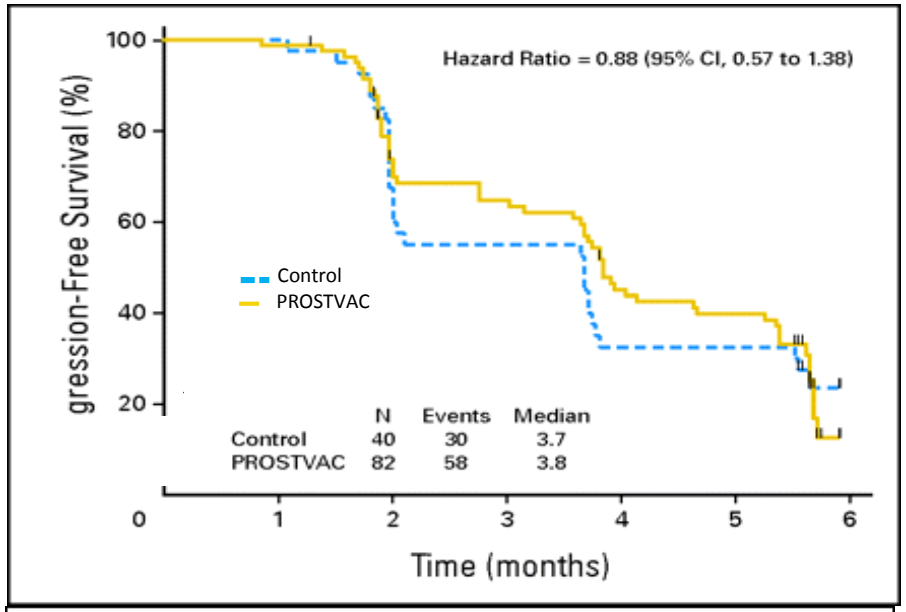
Lessons learned: Prostate cancer immunotherapy trials

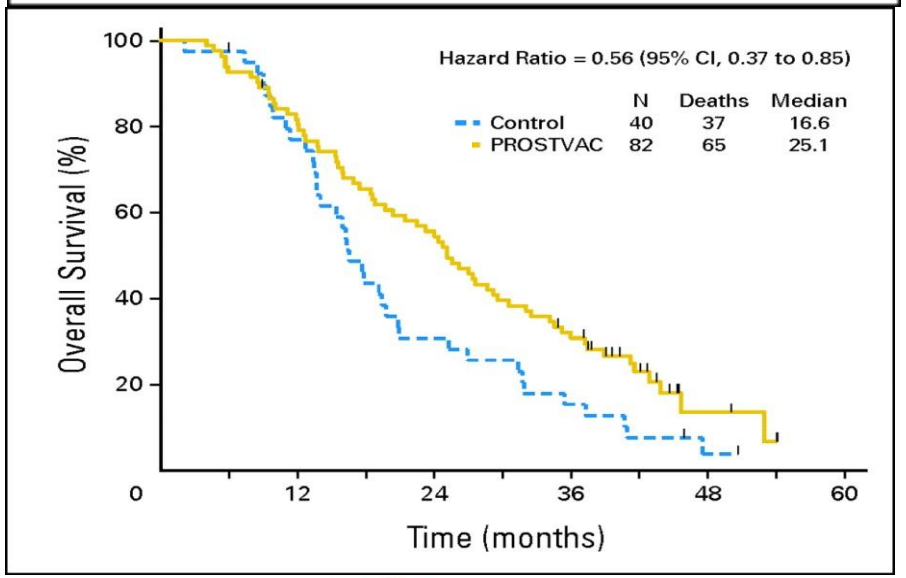
- Prostate *not* an "inflamed" solid tumor like melanoma, renal, lung, bladder
- *Not* significantly hyper-mutated
- For vaccines ↑ doses of vaccine ≠ augmentation of immunity
- *Limited efficacy* of checkpoint inhibitors, anti-CTLA-4, anti-PD1
- No evidence of disease pseudoprogression before response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

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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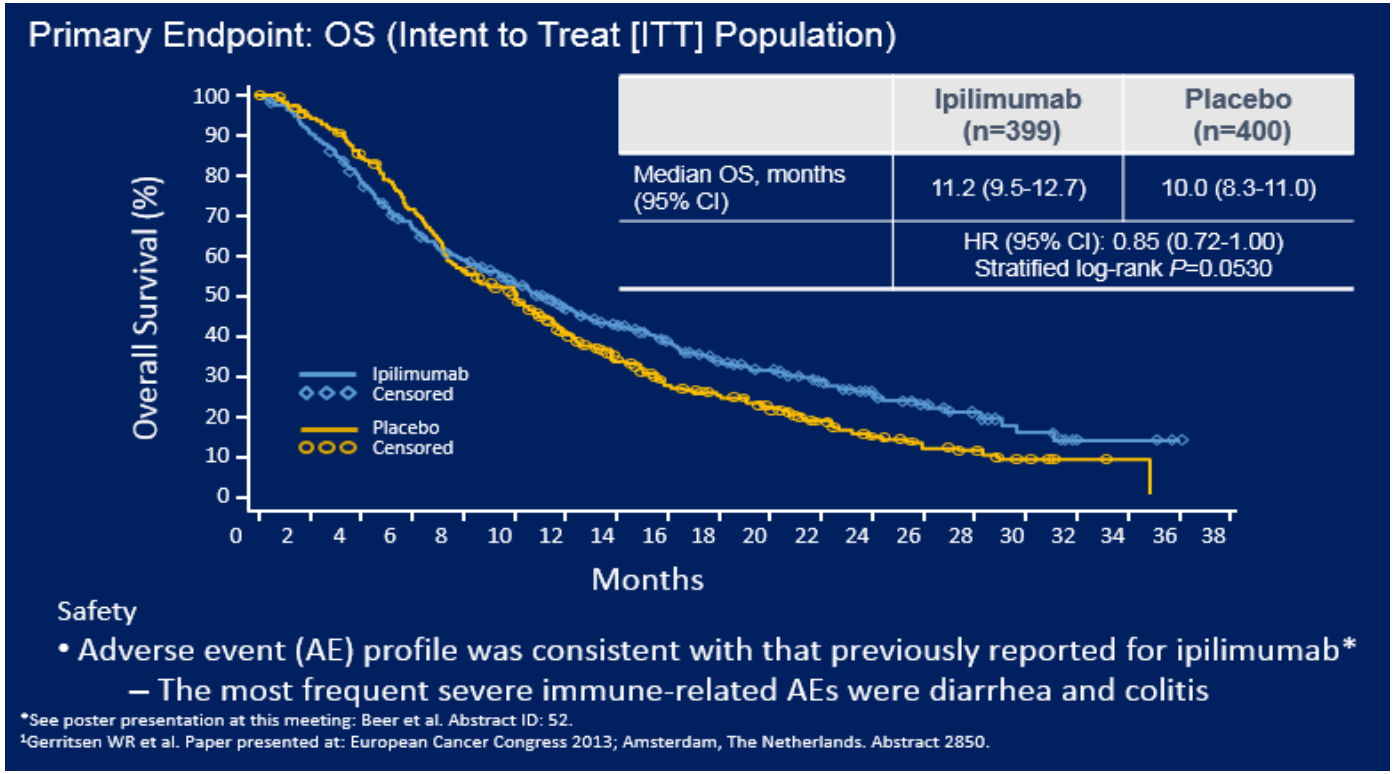
Ipilimumab CTLA-4

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



Kwon et al Lancet Onc 2014 15:700

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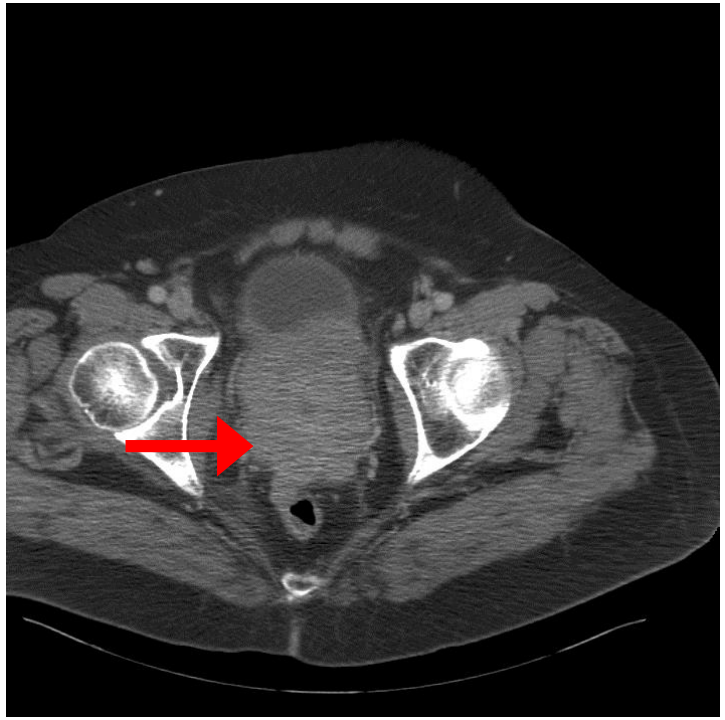
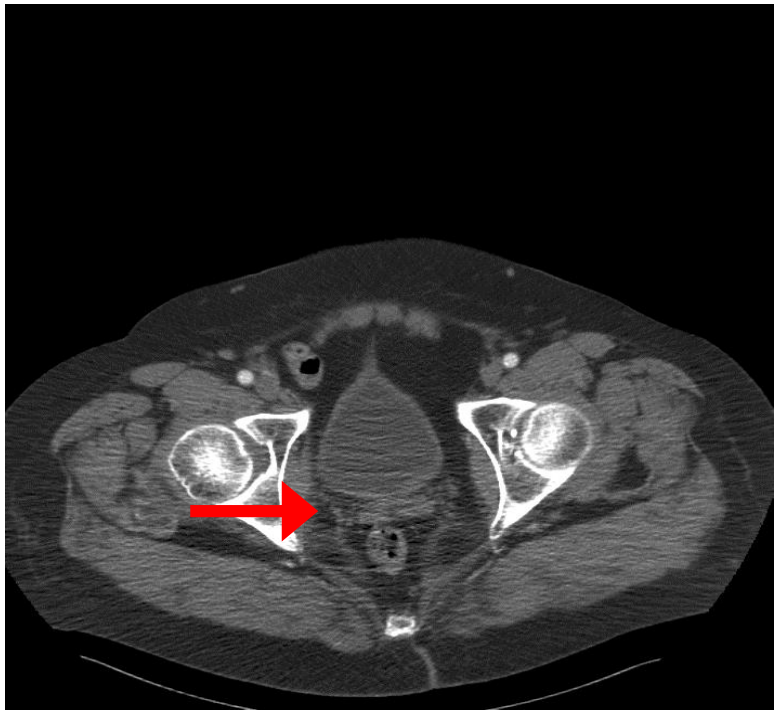
Resolution of Prostate Mass

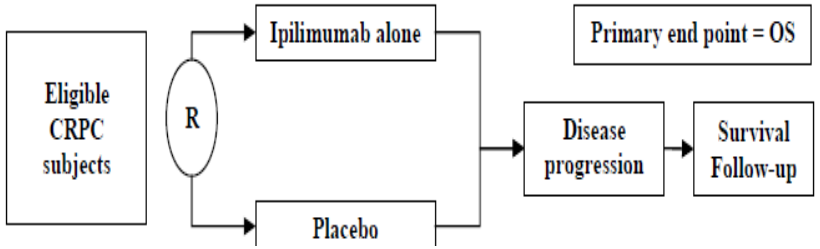
Screening



14 months

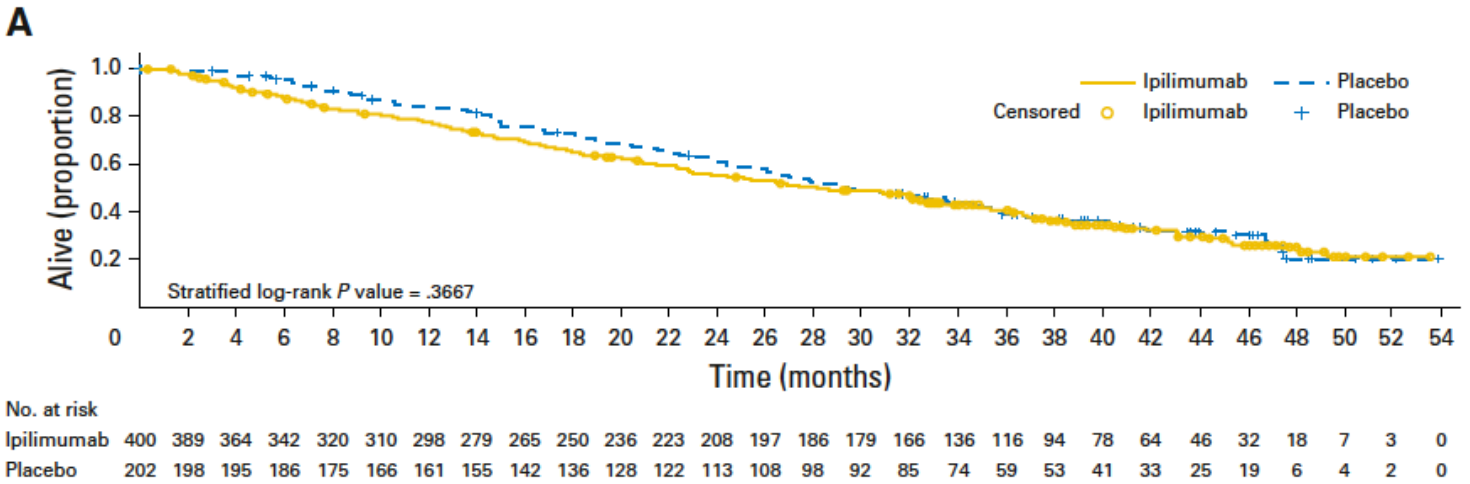


Ipilimumab CTLA-4



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)

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** – (small percentage of prostate cancers are MSI^{high})
- Multiple combinations are underway:
  - PD-pathway inhibitors +/- Ipilimumab & vaccines (including sipuleucel-T), in combination with chemotherapy, androgen deprivation, and radiation therapy.

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CTLA-4 blockade + Ipilimumab=SIPPI

- Poster ASCO GU 2018
- Small trial using ipilimumab 1mg/kg + SIP-T
- Only 9 docetaxel naïve men studied
- Median survival has surpassed 4 years
- 6/9 men remain alive with a mean PSA of 5.5
- One patient remains in durable remission.

Ku et al, abstract #368 ASCO GU 2018

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A phase 2 study of olaparib and durvalumab in metastatic castrate-resistant prostate cancer (mCRPC) in an unselected population

- Durvalumab 1500 mg q28 days + Olaparib 300mg PO q24
- All patients received previous enzalutamide or abiraterone
- Of the first 17 patients:
  - 8/17 had PSA responses
  - 12 month PFS 51.5%

Karzai et al, Abstract #163 ASCO GU 2018

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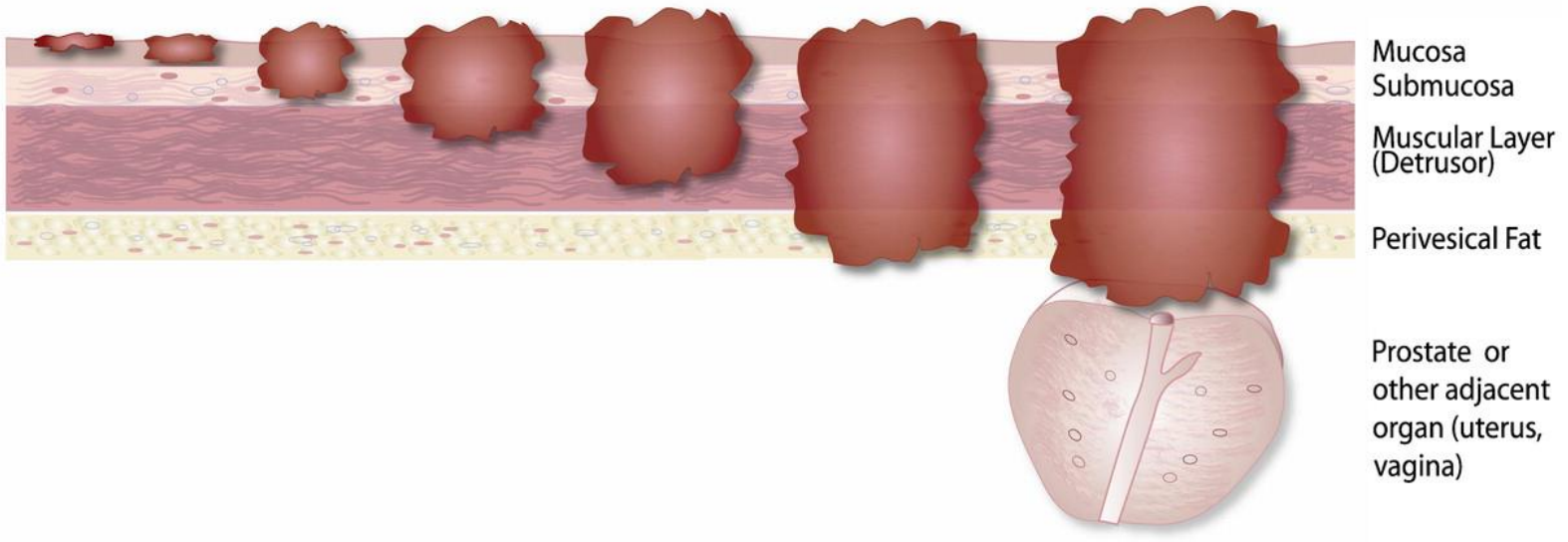
Bladder Cancer:

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

- Second-line:
  - Durvalumab – anti-PDL1
  - Atezolizumab – anti-PDL1
  - Avelumab – anti-PDL1
  - Nivolumab – anti-PD1
  - Pembrolizumab – anti-PD1 → Only one that has shown improved OS thus far.
- Front-line in "Cisplatin-ineligible":
  - Atezolizumab
  - Pembrolizumab

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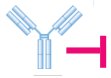
Atezolizumab:



PD-L1

Atezolizumab – IMvigor 210 Study

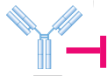
- Open-label, single arm, two cohort Phase II Study
  - Cohort 1: cisplatin-ineligible (N=119)
  - Cohort 2: progression after platinum-containing chemo (N=310)
    - Assessed PD-L1 expression on tumor infiltrating immune cells

ORR all patients 15%

Median OS 7.9 months

PD-L1 Expression	ORR
≥ 5%	26%
1 – 5%	10%
< 1%	8%

Atezolizumab:



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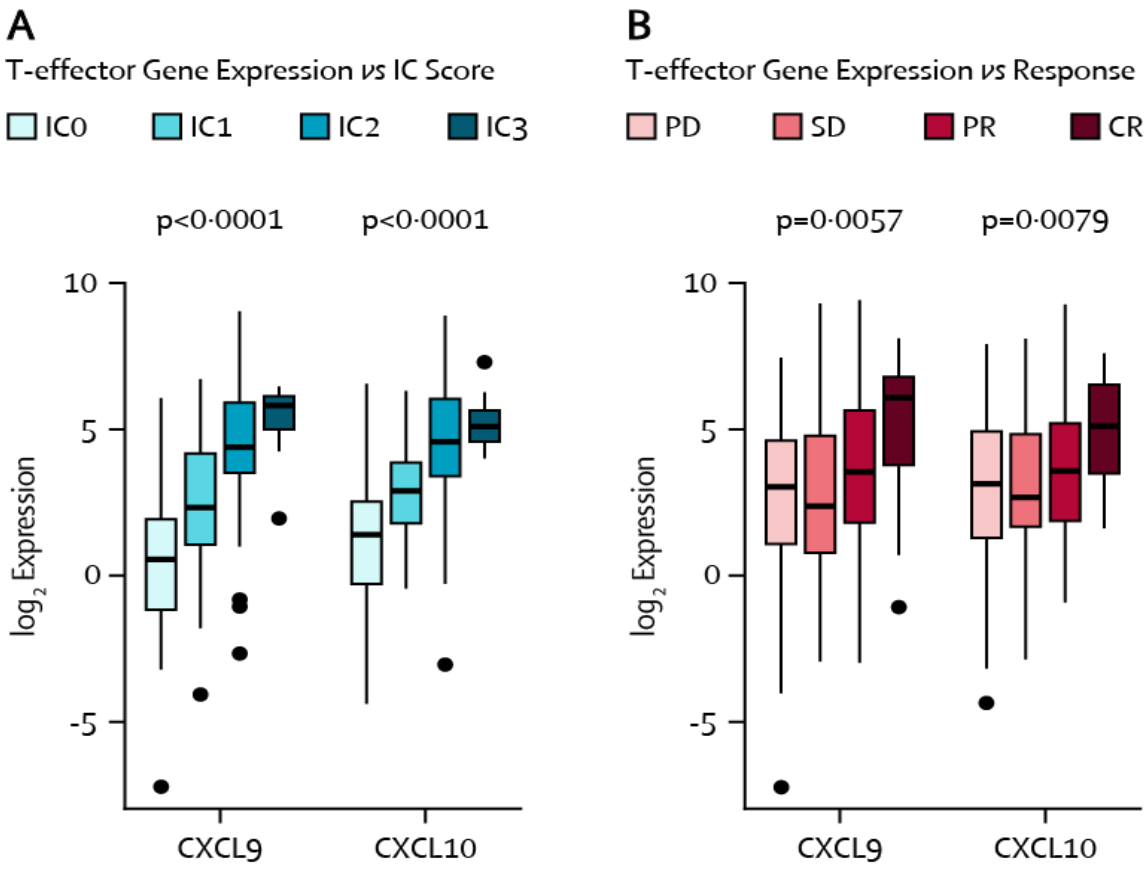
High levels of immune response genes are associated with both PD-L1 staining and treatment response



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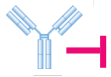
Atezolizumab:



PD-L1

IMvigor 211 trial

- Open-label, multicenter, randomized Phase III study (atezolizumab vs. physician's choice (vinflunine, docetaxel or paclitaxel)
- 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

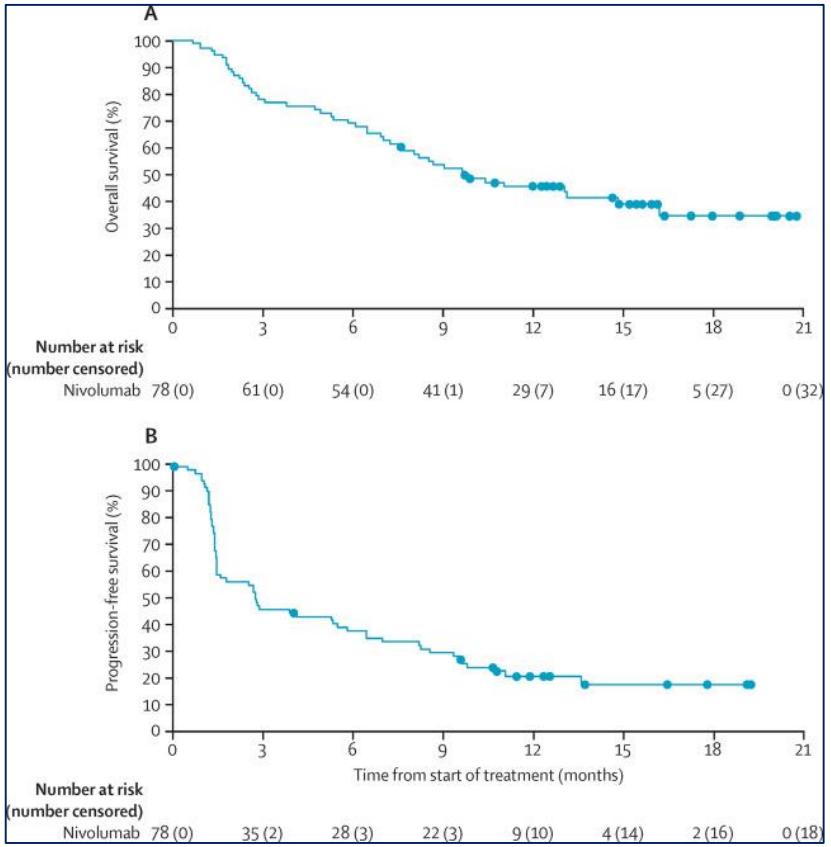
- Phase II Study in locally advanced/metastatic disease following platinum chemotherapy (N=270)
  - Stratified by PD-L1 expression ≥ 5% or < 5%

ORR all patients 19.6%

Median OS 8.7 months

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

Checkmate 032 Study – Phase I/II



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%)

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

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Checkmate 032 study- ASCO GU 2018 update

Investigator-Assessed Response

	All Patients (n = 78)	PD-L1 <1% (n = 42)	PD-L1 ≥1% (n = 26)
ORR, % 95% CI	25.6 16.4–36.8	26.2 13.9–42.0	26.9 11.6–47.8
Best overall response, %			
Complete response	7.7	4.8	15.4
Partial response	17.9	21.4	11.5
Stable disease	26.9	26.2	26.9
Progressive disease	38.5	42.9	34.6
Unable to determine	9.0	4.8	11.5

- One additional complete response was reported since the 2016 primary study publication[1]

1. Sharma P, et al. *Lancet Oncol* 2016;17:1590–8.

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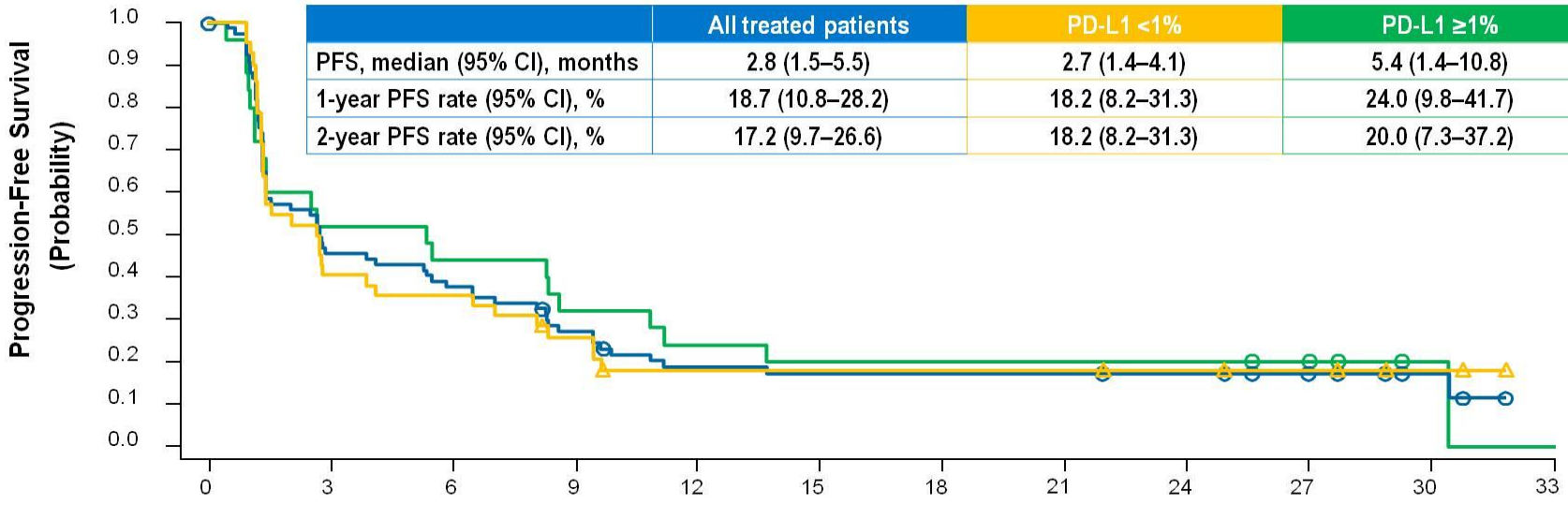
Checkmate 032 study- ASCO GU 2018 update

Progression-Free Survival

	All treated patients	PD-L1 <1%	PD-L1 ≥1%
PFS, median (95% CI), months	2.8 (1.5–5.5)	2.7 (1.4–4.1)	5.4 (1.4–10.8)
1-year PFS rate (95% CI), %	18.7 (10.8–28.2)	18.2 (8.2–31.3)	24.0 (9.8–41.7)
2-year PFS rate (95% CI), %	17.2 (9.7–26.6)	18.2 (8.2–31.3)	20.0 (7.3–37.2)



No. at Risk												
All treated patients	78	35	29	20	13	12	12	12	11	7	3	0
PD-L1 ≥1%	26	13	11	8	6	5	5	5	5	3	1	0
PD-L1 <1%	42	17	15	10	6	6	6	6	5	4	2	0

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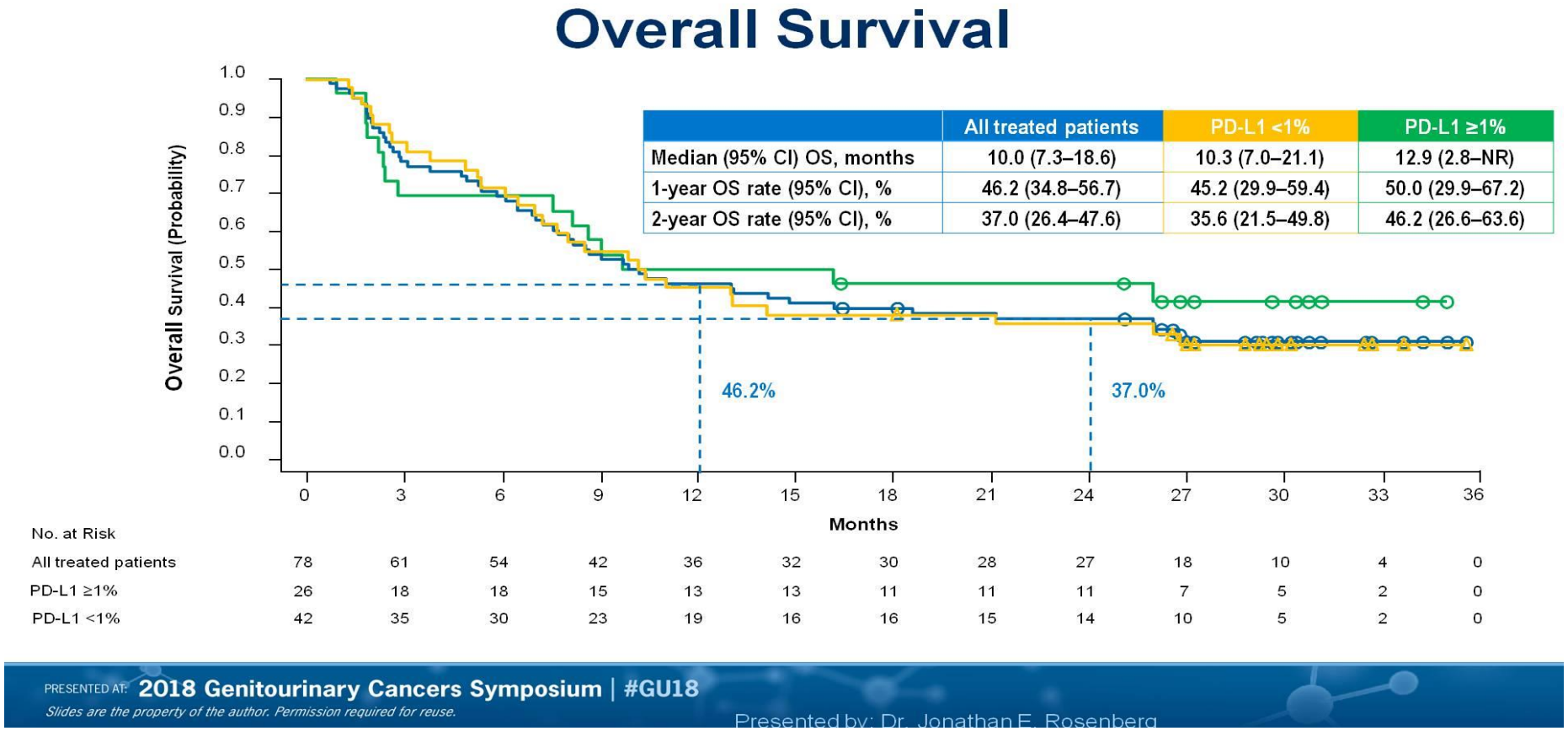
Presented By Padmanee Sharma at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Checkmate 032 study- ASCO GU 2018 update



	All treated patients	PD-L1 <1%	PD-L1 ≥1%
Median (95% CI) OS, months	10.0 (7.3–18.6)	10.3 (7.0–21.1)	12.9 (2.8–NR)
1-year OS rate (95% CI), %	46.2 (34.8–56.7)	45.2 (29.9–59.4)	50.0 (29.9–67.2)
2-year OS rate (95% CI), %	37.0 (26.4–47.6)	35.6 (21.5–49.8)	46.2 (26.6–63.6)

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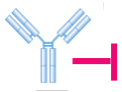
Nivolumab:



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
- Updated Survival Data ASCO GU 2018

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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.
- **Avelumab:**

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)

- **Durvalumab:**

Phase I/II trial evaluated the safety and efficacy of durvalumab in patients with locally advanced or metastatic urothelial carcinoma of the bladder (2nd line). N=191; ORR was 17.8%; with 27.6% and 5.1% in PD-L1 high and low group, respectively.

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Pembrolizumab

- Locally advanced/metastatic urothelial carcinoma with progression on or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy.
- Accelerated approval for patients with locally advanced or metastatic urothelial carcinoma who are “cisplatin-ineligible”.
- Only IO agent showing improved OS in bladder cancer thus far.
- Based on Trial **KEYNOTE-045 (2nd line):**
  - Multicenter, randomized, phase III trial.
  - Patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy.
  - **Significantly Improved OS** compared to taxane-based chemotherapy.
  - GU ASCO 2018 Update : 27.7 month follow up: 10.3 vs 7.3 months.
- Accelerated approval for the **1st line** indication based on data from **KEYNOTE-052:**
  - Single-arm, phase II trial
  - 370 patients with locally advanced or metastatic urothelial carcinoma who were “cisplatin-ineligible”
  - Received pembrolizumab 200 mg every 3 weeks
  - Median follow-up time of 7.8 months
  - ORR was 28.6% (95% CI 24, 34)
  - Median response duration not reached (1.4+ - 17.8+ m).

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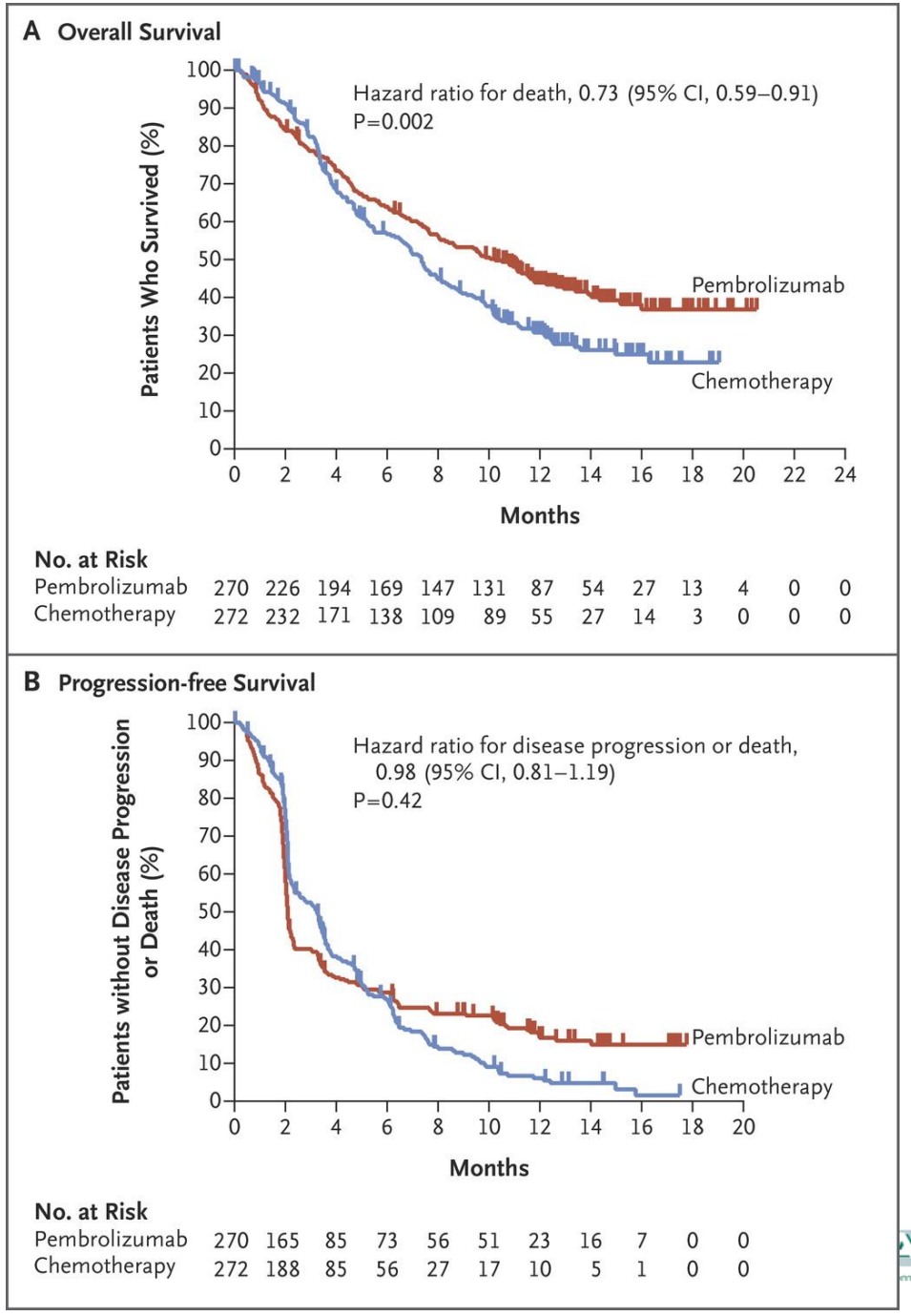
KEYNOTE-045
(Phase III) 2nd line

OS: Median 10.3 m vs 7.4 m compared to taxane-based chemotherapy.

PFS: Not significantly different

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



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

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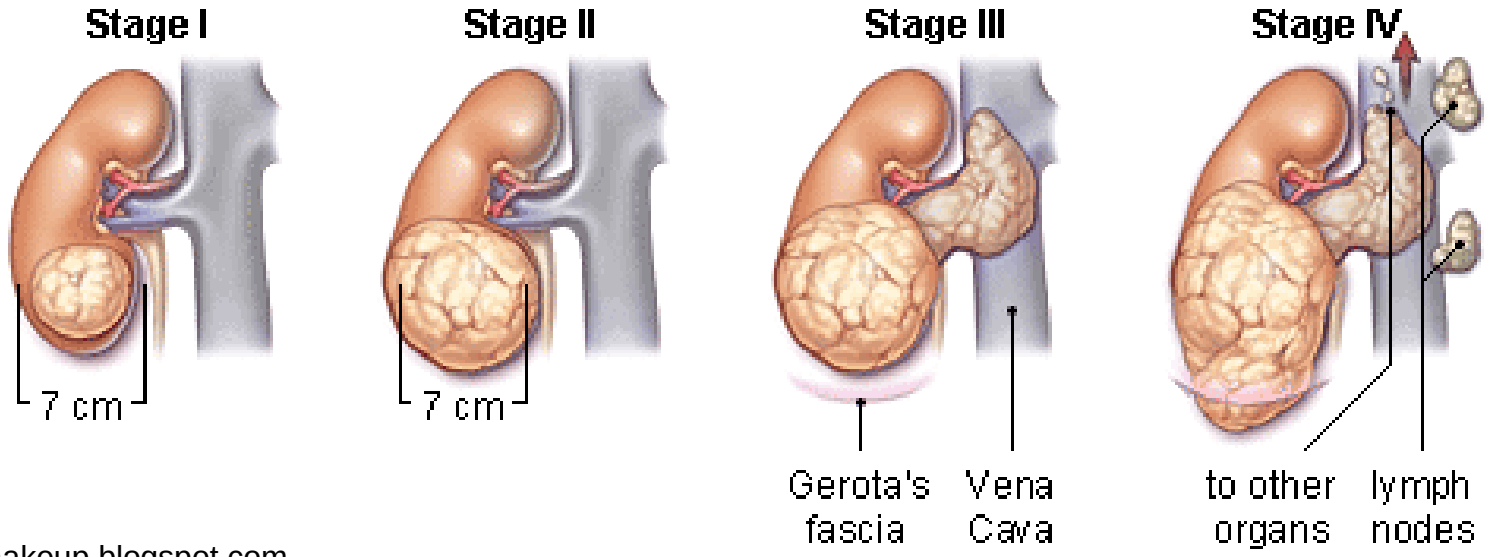
Kidney Cancer:

Surgically resectable → Oligo-metastatic → Metastatic



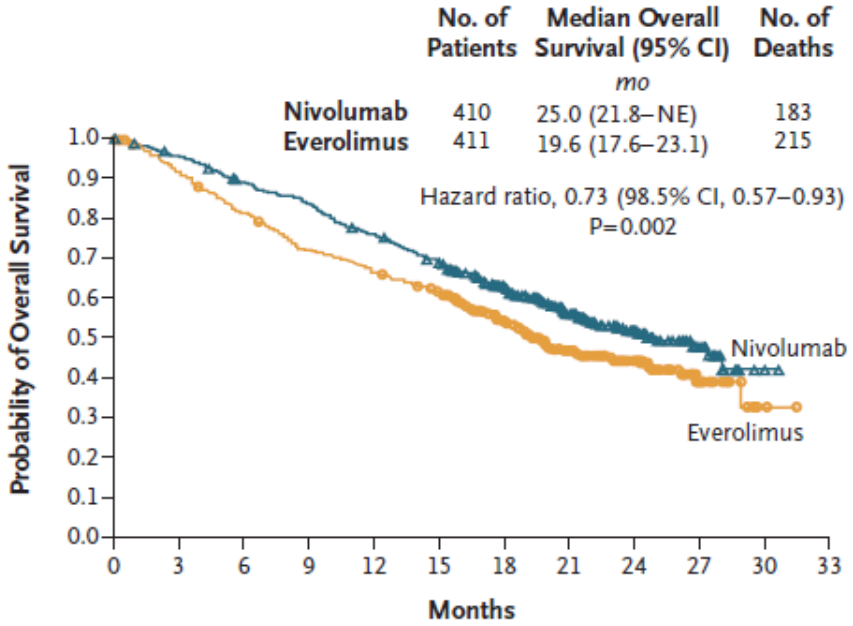
reemakeup.blogspot.com

Nivolumab

- Phase III CheckMate 025 trial:
  - 821 patients
  - Previously treated mRCC (1-2 VEGF TKI)
  - Nivolumab 3 mg/kg q2 wks vs Everolimus 10 mg/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

CheckMate 025

The present of Immuno Oncology in RCC (5)

- But impressive responses only occurs in 25% of patients

	Nivolumab (n=410)	Everolimus (n=411)
ORR, %	25	5
Best overall response, % CR PR SD	 1 24 34	 1 5 55

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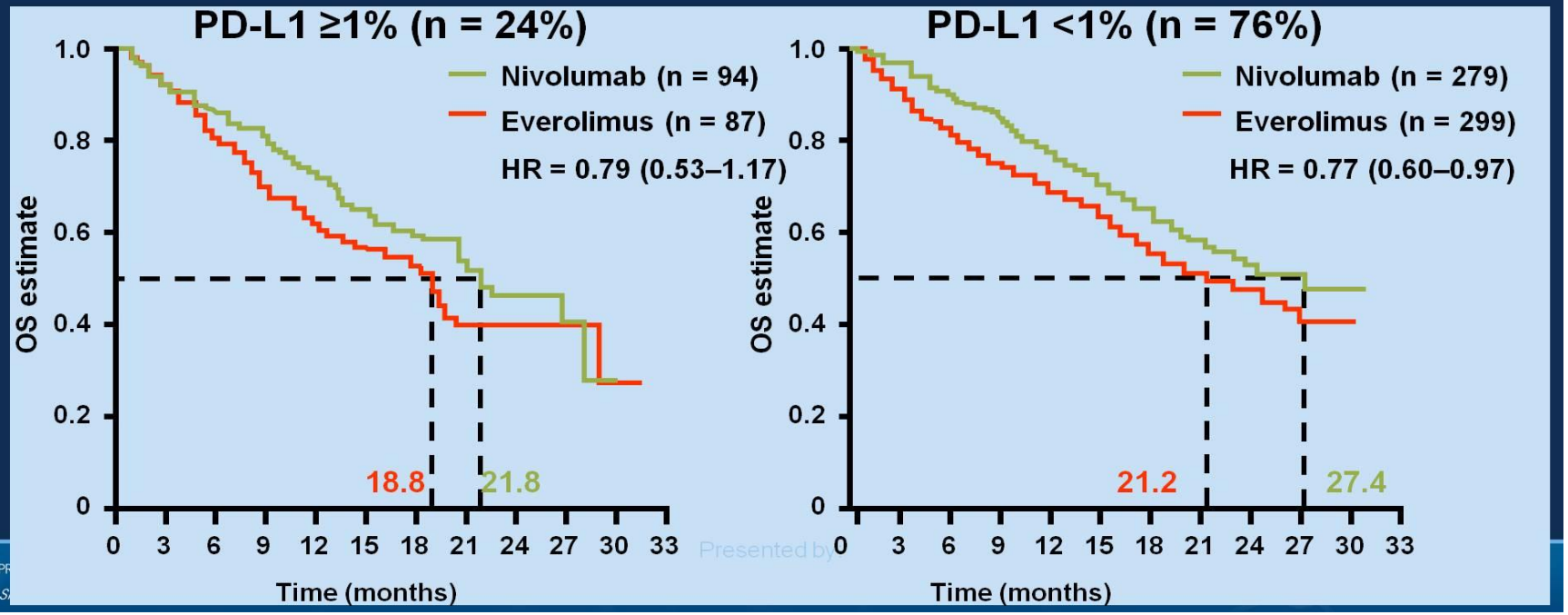
CheckMate 025

The present of Immuno Oncology in RCC (6)

- We still don't know how to predict efficacy



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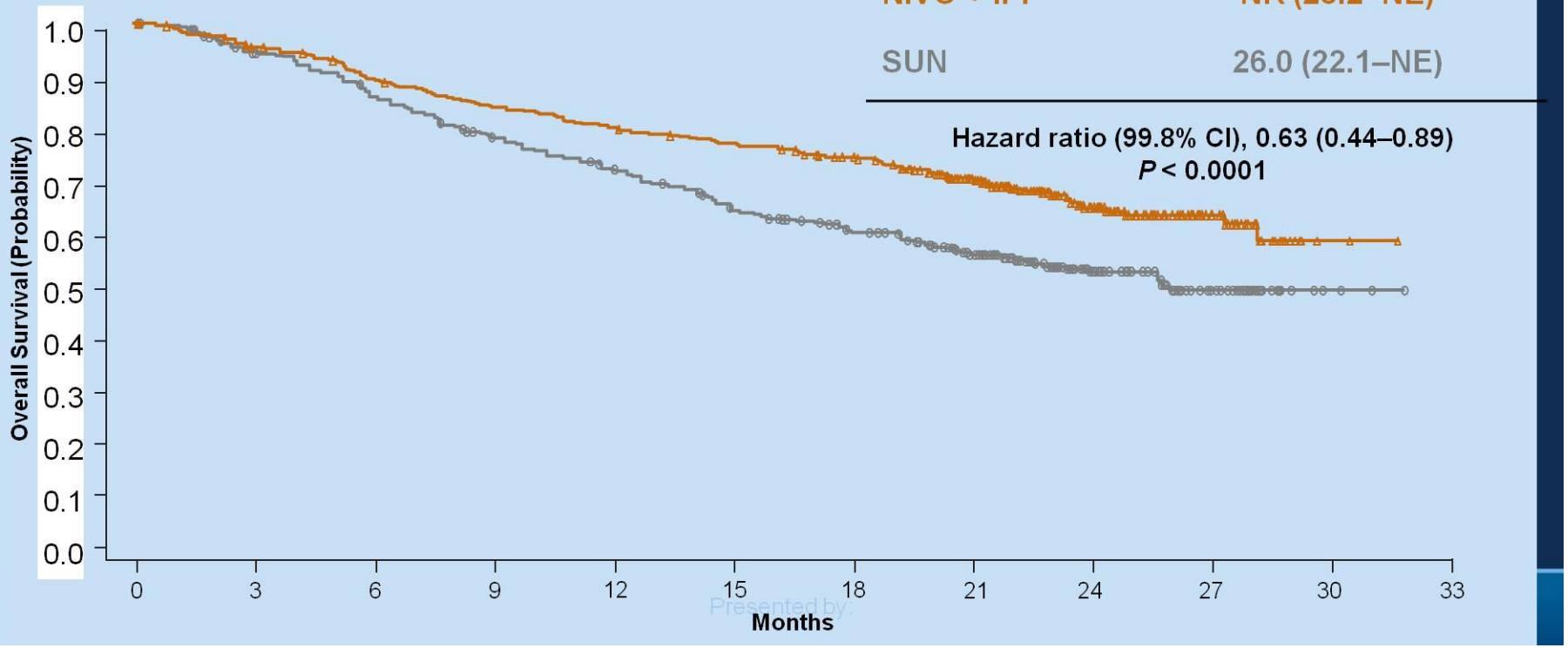
PD1 + CTLA4 BLOCKADE

Nivolumab + Ipilimumab improves OS



Nivolumab + Ipilimumab induces high RR

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

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Nivolumab + Ipilimumab induces high CR

	N = 847	
Outcome	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

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But efficacy is mostly seen in intermediate and poor risk patients, **not in good risk ones**

	N = 249[a]	
Outcome	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

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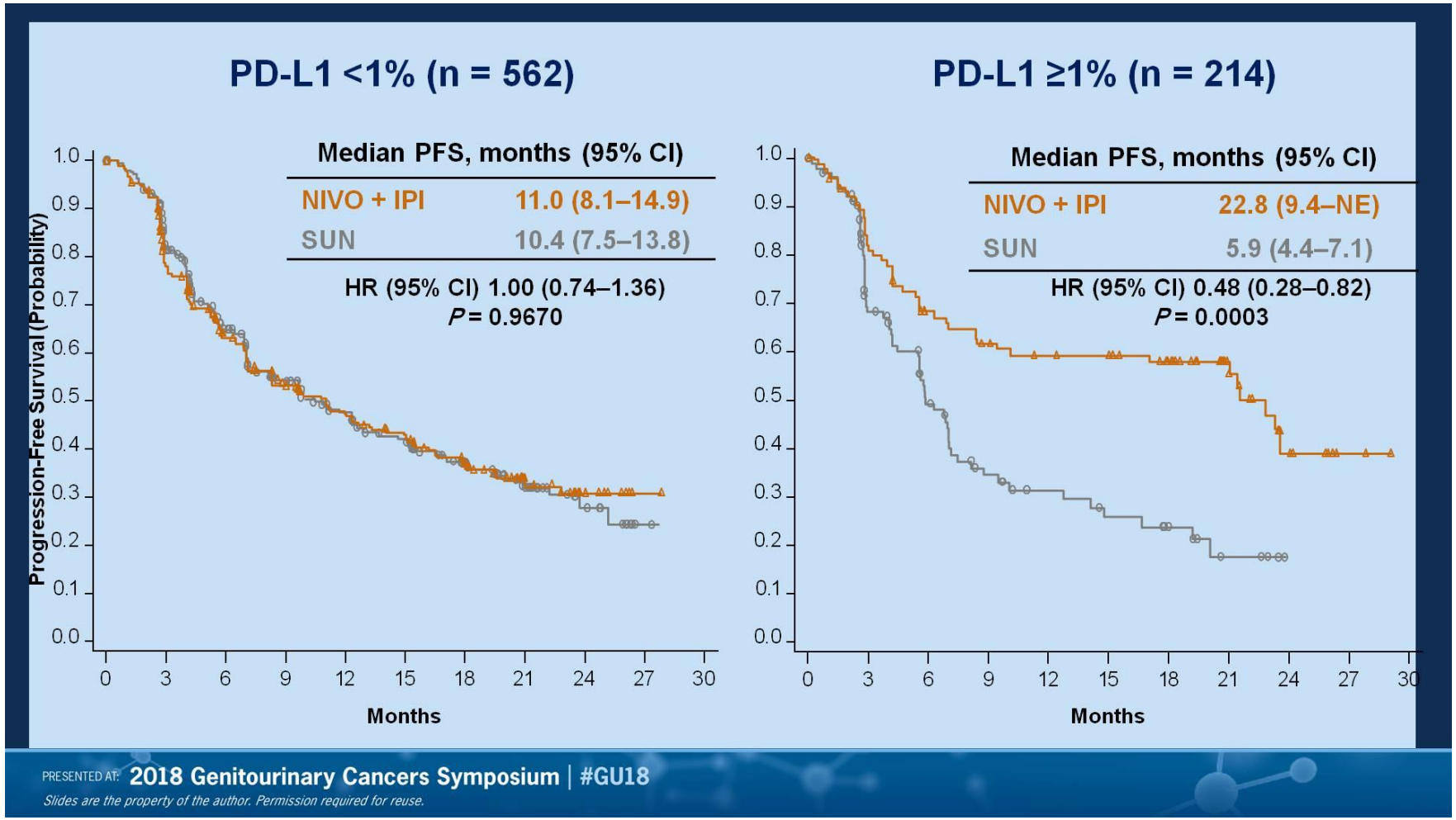
And PDL 1 expression has some predictive value

	IMDC intermediate/poor risk			
	PD-L1 <1%		PD-L1 ≥1%	
Outcome	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	**58 (48–68)**	**22 (15–31)**
	P = 0.0252		*P* < 0.0001	
BOR,[a] %				
Complete response	7	1	**16**	1
Partial response	30	27	42	21


PD-L1 <1% (n = 562)
Median PFS, months (95% CI)
NIVO + IPI 11.0 (8.1–14.9)
SUN 10.4 (7.5–13.8)
HR (95% CI) 1.00 (0.74–1.36)
P = 0.9670
PD-L1 ≥1% (n = 214)
Median PFS, months (95% CI)
NIVO + IPI 22.8 (9.4–NE)
SUN 5.9 (4.4–7.1)
HR (95% CI) 0.48 (0.28–0.82)
P = 0.0003
Progression-Free Survival (Probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 3 6 9 12 15 18 21 24 27 30
Months
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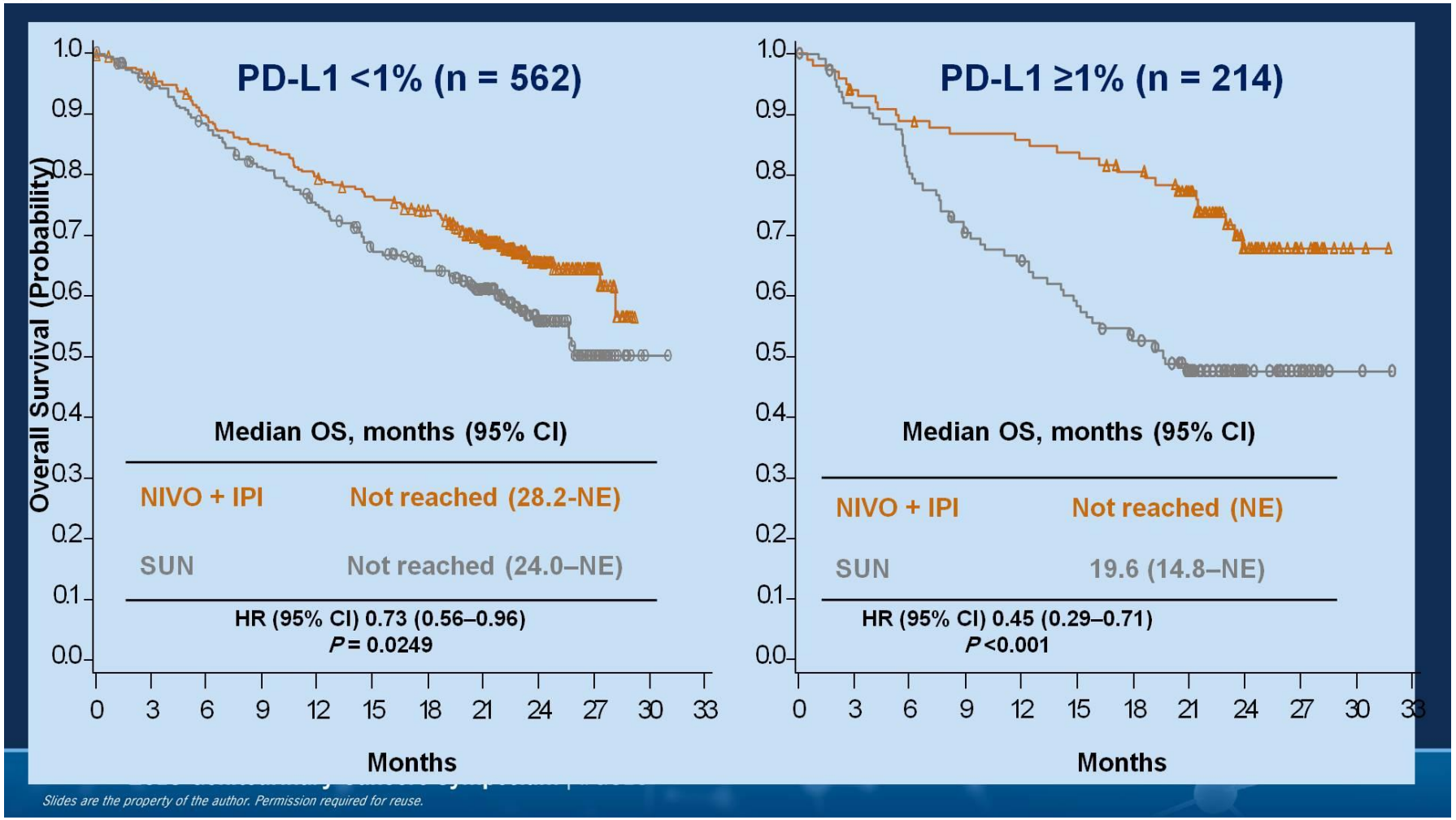

Other PD-1/PD-L1 Inhibitors/COMBOS:

PD1/PDL1 + VEGF inhibition is promising

	Pembro + axitinib	Avelumab + axitinib	Pembro + lenvatinib	Atezo + bevacizumab	Nivo + Tivozanib
n	52	45	30	101	14
CR	5.8%	5.5%	0	7%	0
PR	65.4%	52.7%	63%	25%	64.3%
ORR	71.2% (73.1%)*	58.2%	63%	32%	64.3%

*ASCO GU 2018 update

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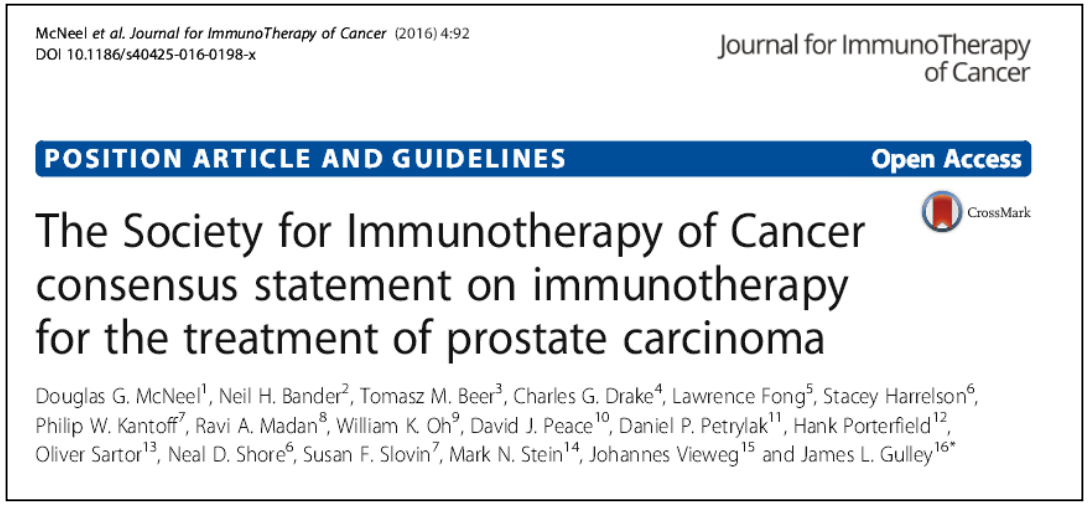

McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Journal for ImmunoTherapy of Cancer

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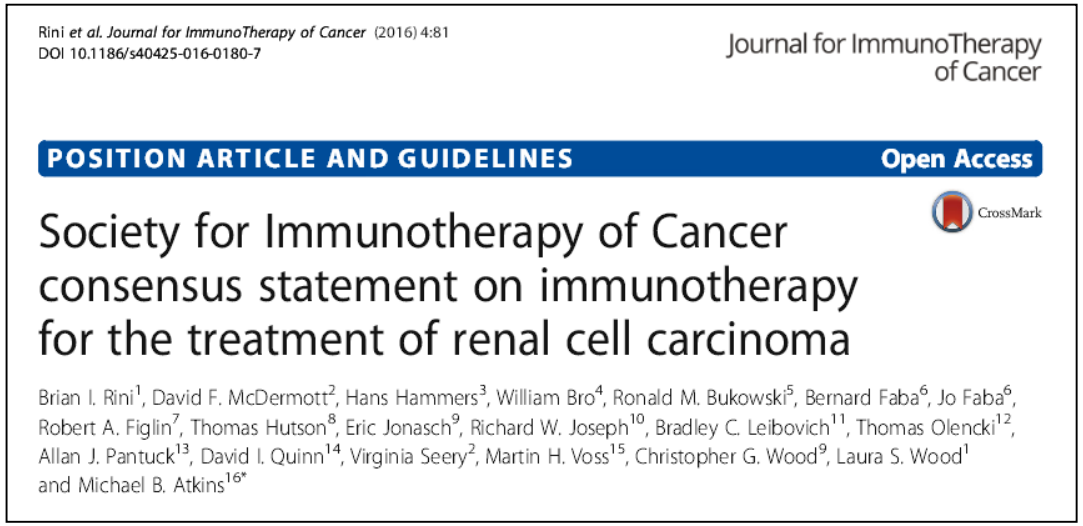
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

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

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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*]

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

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Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

Journal for ImmunoTherapy of Cancer

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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]