Immunotherapy for Genitourinary Malignancies

Society of Immunotherapy of Cancer

December 5th, 2015

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Potential Conflict of Interests

Clinical Trial Support

- BMS, Merck, Roche, Amgen

Advisory Board

- BMS, Nektar, Castle Biosciences, Eisai

NCCN Melanoma Committee Member

- **This presentation will discuss products under development in clinical trials.**

Outline

Prostate Cancer

- Sipuleucel T
- Ipilimumab

Kidney Cancer

- CTLA4 Antibody
- Anti-PD1/PD-L1
- Combinations with anti-VEGF/VEGFR

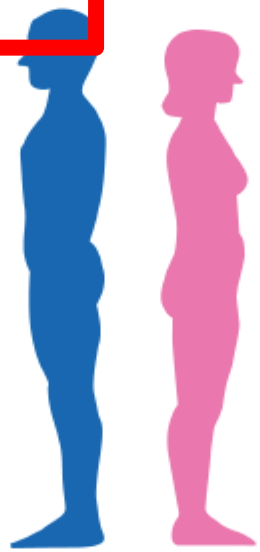
Bladder Cancer

- Anti-PD1/PDL1

Prostate cancer

Estimated New Cases*

Males			Females		
Prostate	233,000	27%	Breast	232,670	29%
Lung & bronchus	116,000	14%	Lung & bronchus	108,210	13%
Colorectum	71,830	8%	Colorectum	65,000	8%
Urinary bladder	56,390	7%	Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%	Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%	Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%	Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%	Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%	Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%	Leukemia	22,280	3%
All Sites	**855,220**	**100%**	**All Sites**	**810,320**	**100%**



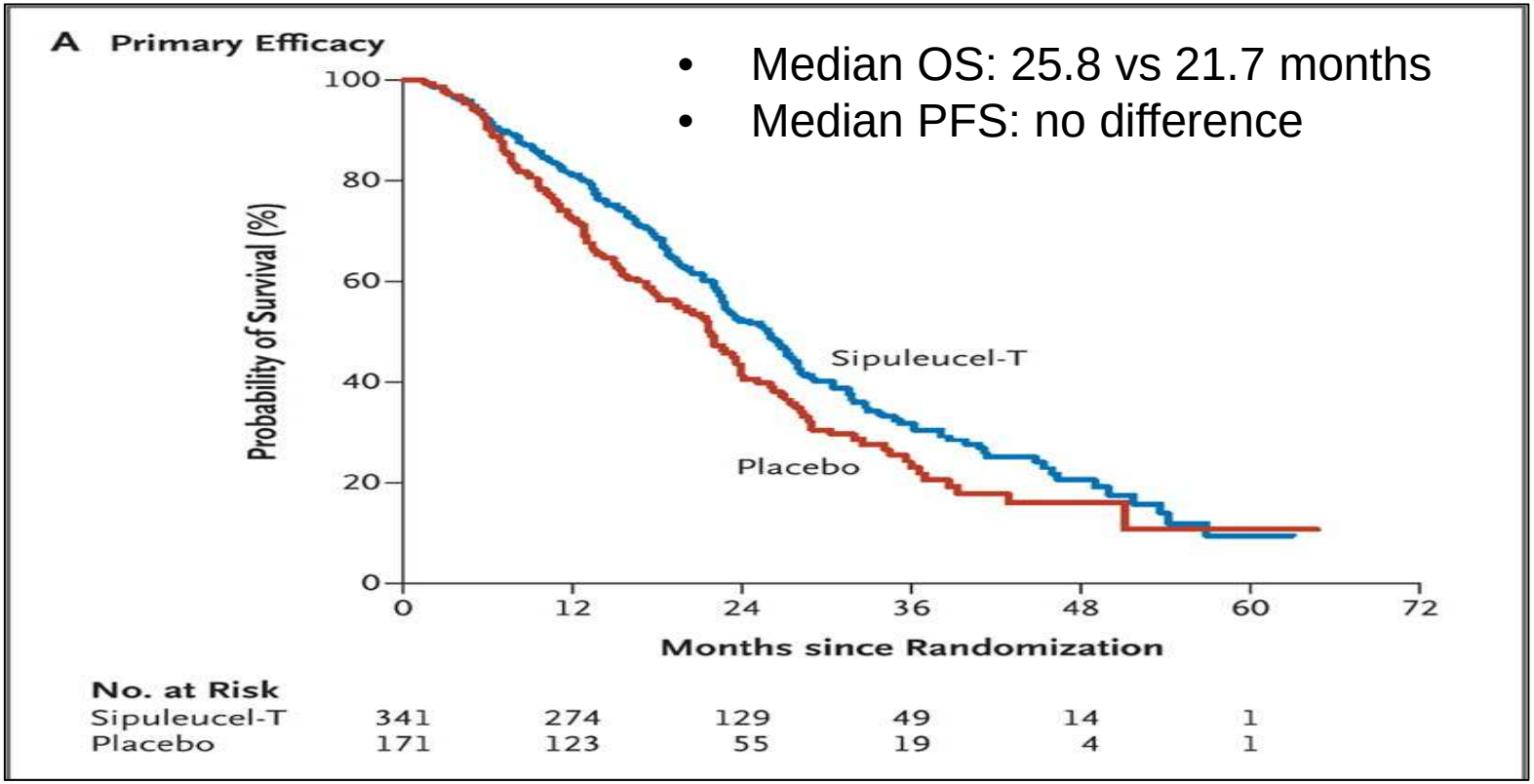
Siegel et al. CA, 2014

Sipuleucel-T

- Immunotherapy
- Dendritic cell vaccine
- Targets prostatic acid phosphatase (PAP)
- Remove peripheral blood cells, expose to PAP-GMCSF, reinfuse
- Phase 3 study vs placebo

Overall Survival

- Median OS: 25.8 vs 21.7 months
- Median PFS: no difference



Kantoff PW et al. N Engl J Med 2010;363:411-422.

Sipuleucel T-Remaining Questions

- When is the best time to use it?
- How to measure success?
- Role of adding of checkpoint inhibitors?

Ipilimumab in Prostate Cancer

- Randomized Phase 3 vs placebo
- 799 patients
- Progressed on taxotere
- 4 doses at 10 mg/kg

Lancet

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Kwon et al, 2014

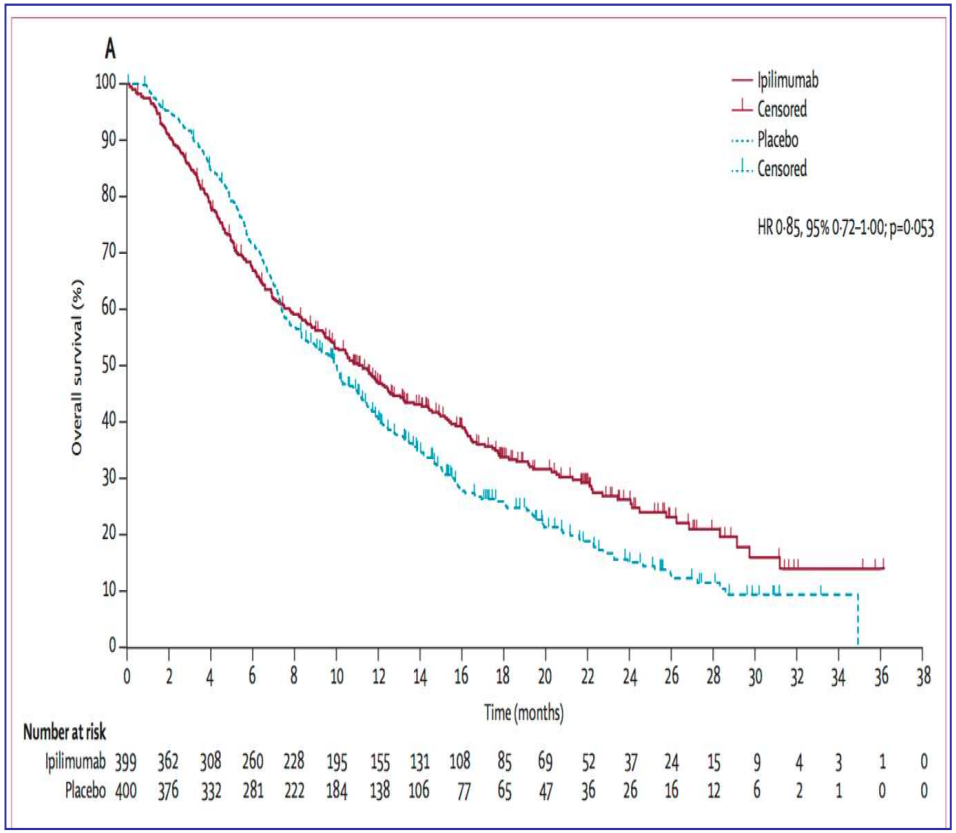
Overall Survival

Median OS

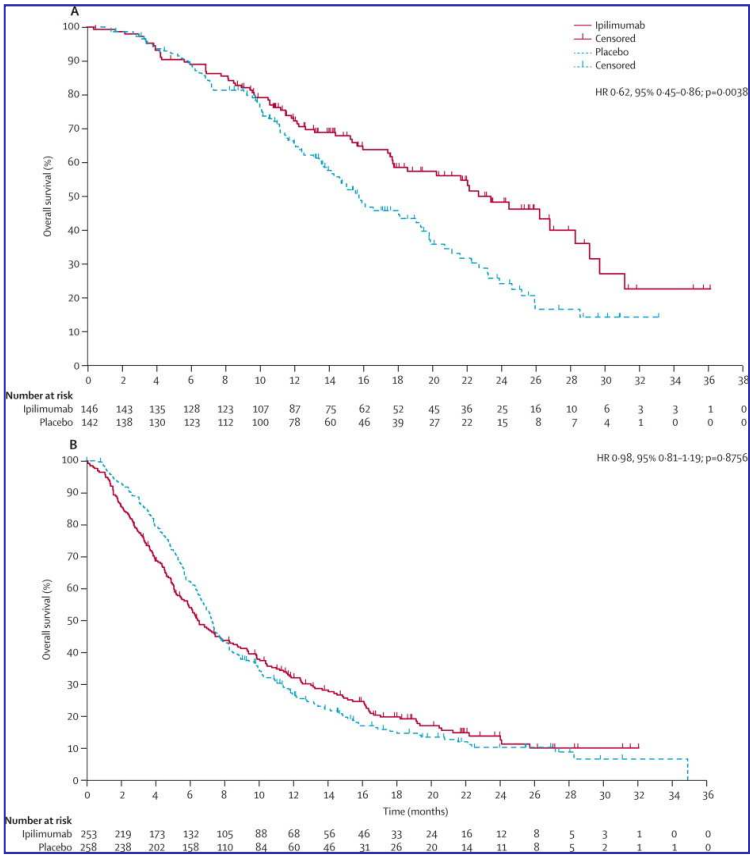
11.2 vs 10.0 months

p=0.053

Kwon et al, 2014



Subset Analysis



Good Prognostic Group

- OS: 22.7 vs 15.8 months, p=0.003

Poor Prognostic Group

- OS: 6.5 vs 7.3 months, p=0.003

Kwon et al, 2014

Conclusions-Prostate

- Proof of principle is there for immunotherapy in prostate
- More work necessary to better understand patient selection, timing, agents, and combinations

Kidney cancer

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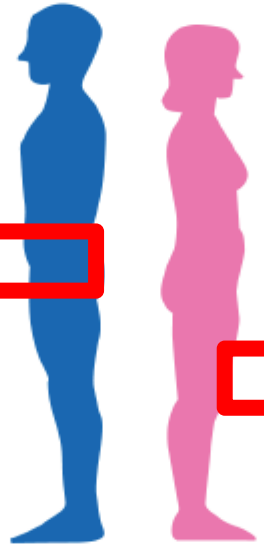


Siegel et al. CA, 2014

RCC Landscape

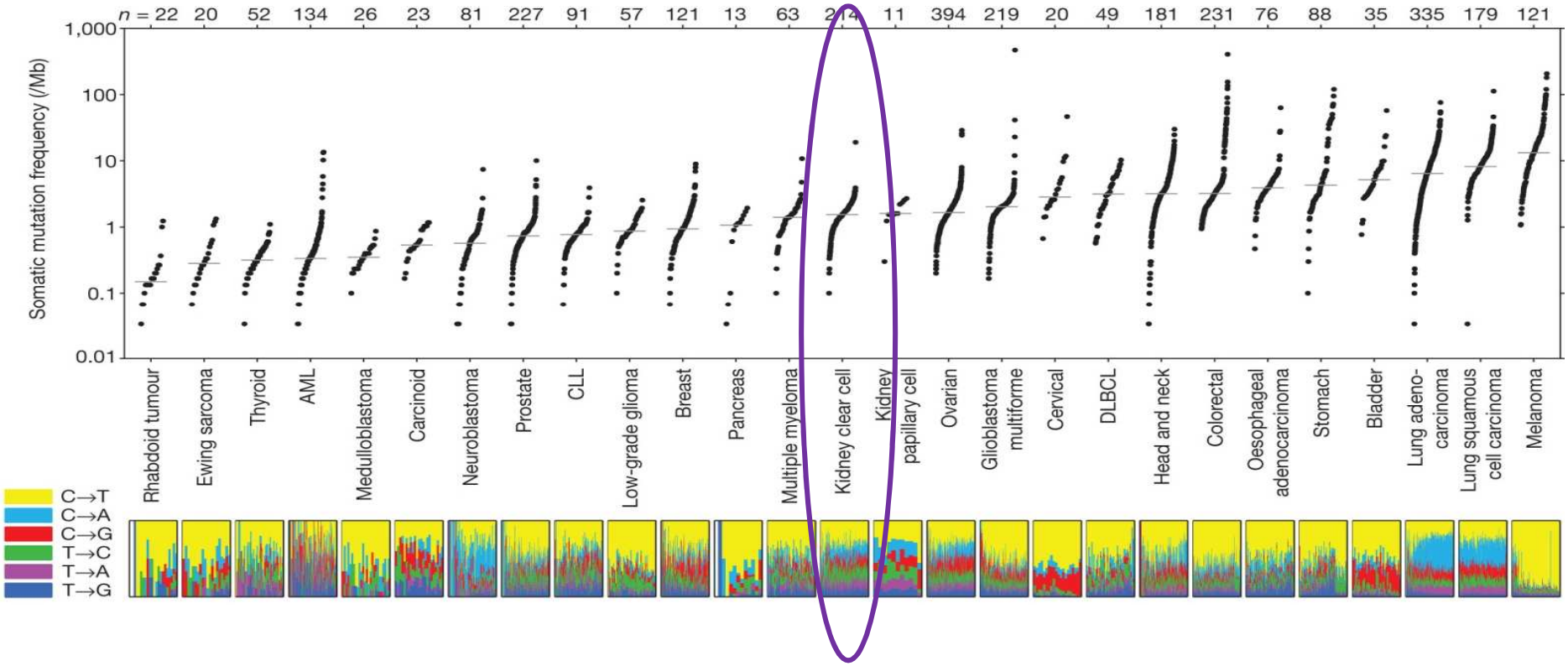
Setting		Phase III	Alternative
1st-Line Therapy	Good or intermediate risk*	Sunitinib Pazopanib	**HD IL-2**
		Bevacizumab + IFNα	
	Poor risk*	Temsirolimus	Sunitinib
2nd-Line Therapy	Prior cytokine	Sorafenib	Sunitinib or bevacizumab
	Prior VEGFR inhibitor	Everolimus Axitinib	Clinical Trials
	Prior mTOR inhibitor	Clinical Trials	

Role for Immunotherapy?

Renal Cell Carcinoma

- High dose IL-2/IFN with proof of principle of success of immunotherapy
- Both limited by increased toxicity

Somatic mutations by tumor type



MS Lawrence *et al. Nature* **2013**

CTLA-4 Blockade in mRCC

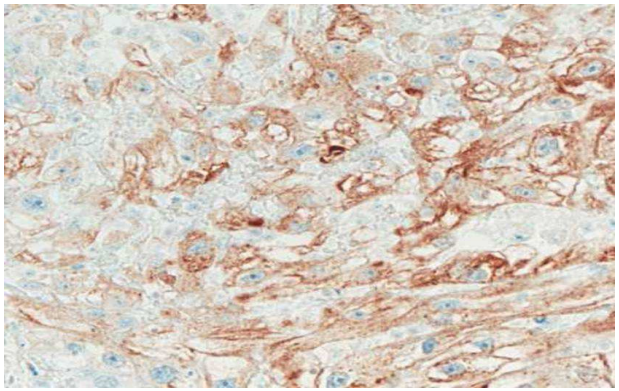
- Ipilimumab Phase II trial
  - 61 patients
  - Major response rate ~10%
- Similar ORR as in melanoma

Journal of Immunotherapy

Ipilimumab (Anti-CTLA4 Antibody) Causes Regression of Metastatic Renal Cell Cancer Associated With Enteritis and Hypophysitis

Yang et al, 2007

PD-L1 Expression is Lower in RCC



Positive PD-L1 staining in RCC (PD-L1 IHC)

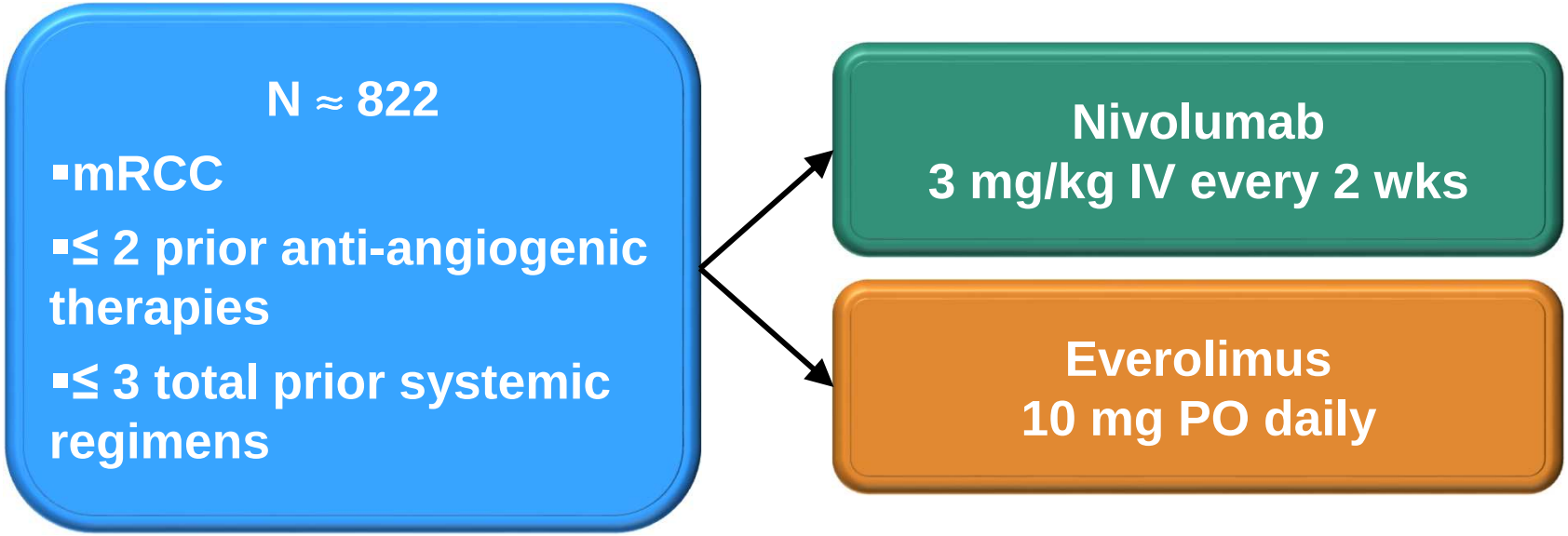
High sensitivity and specificity in FFPE samples

Tumor Type	Estimated PD-L1 Prevalence, ≈ %*
NSCLC (SCC)	50%
NSCLC (adeno)	45%
Colon	45%
Melanoma	40%
RCC	**20%**

- PD-L1 not expressed in normal human kidney cells but is aberrantly expressed in primary and metastatic RCC
- Tumor expression of PD-L1 is associated with poor prognosis

* Based on staining of archival tumor tissue from patients with metastatic cancer.
Thompson RH et al. *Cancer Res*. 2006;66(7):3381-3385.

Nivolumab Phase 3 Trial



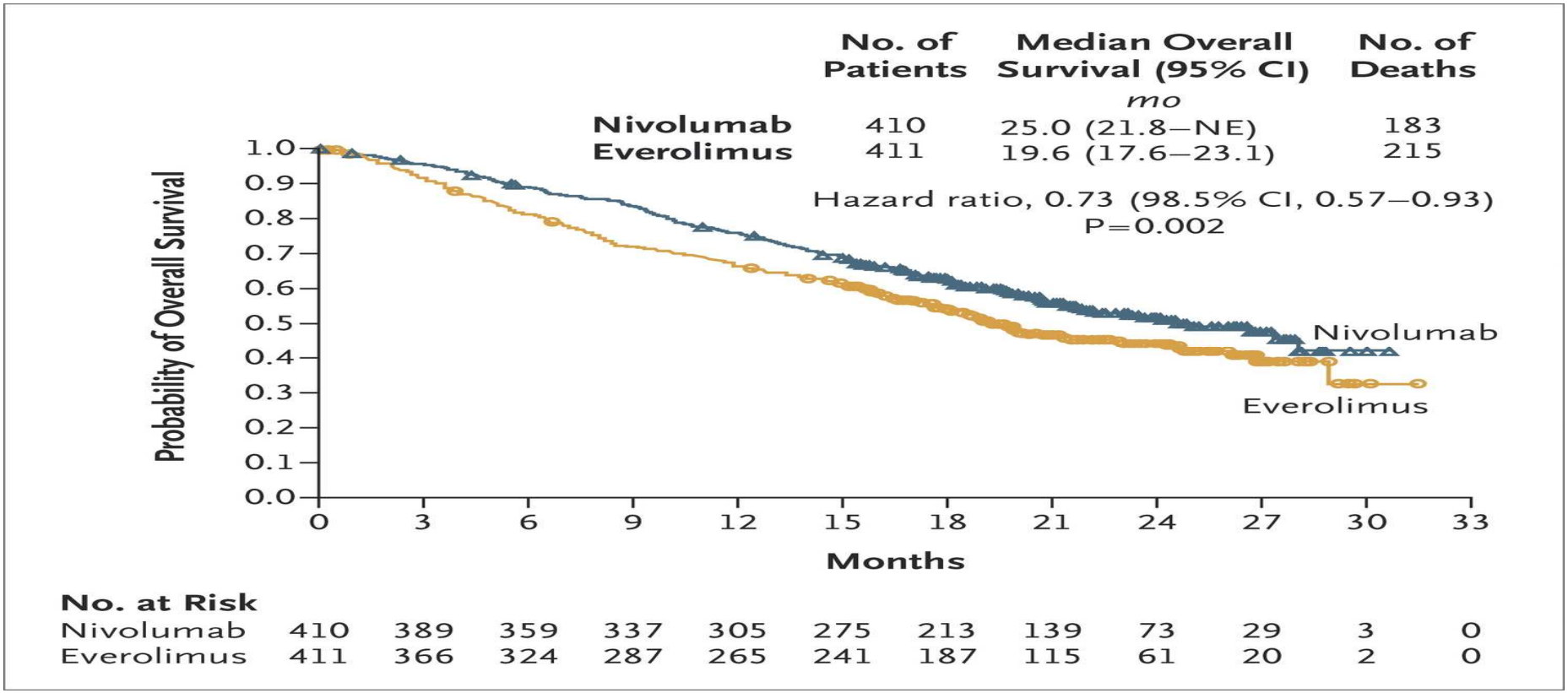
Primary endpoint: OS

Secondary endpoints: PFS, ORR, OR duration, Safety

Accrual completed early 2014; July 2015- primary endpoint reached

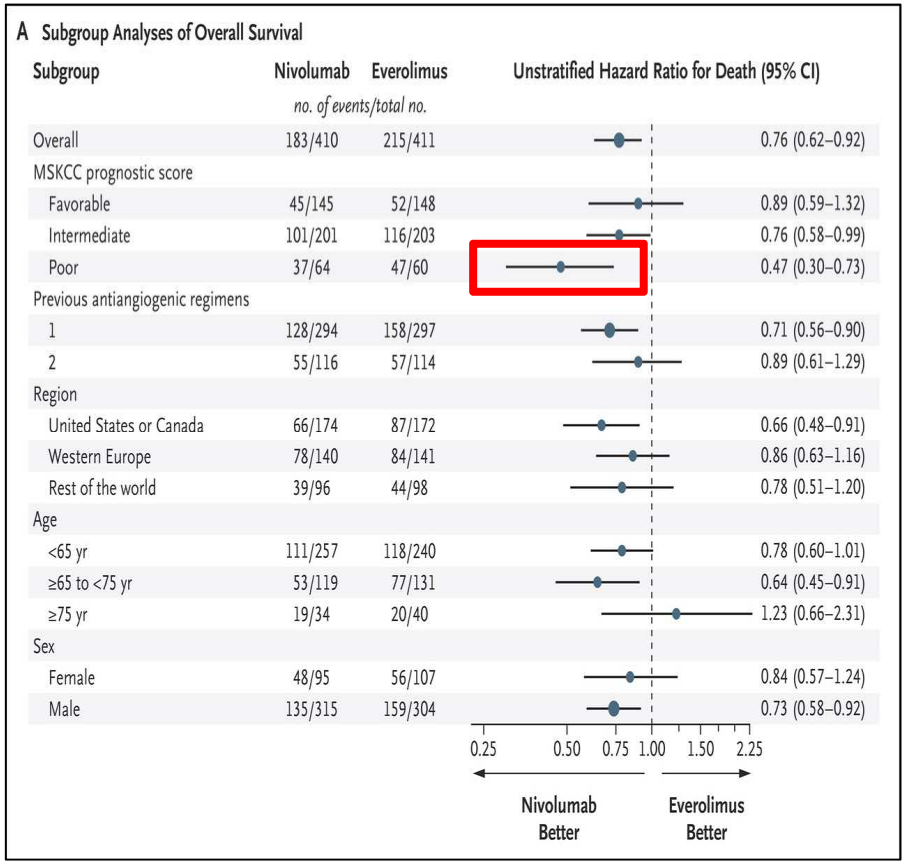
Motzer R, et al. ASCO 2013. Abstract TPS4592.

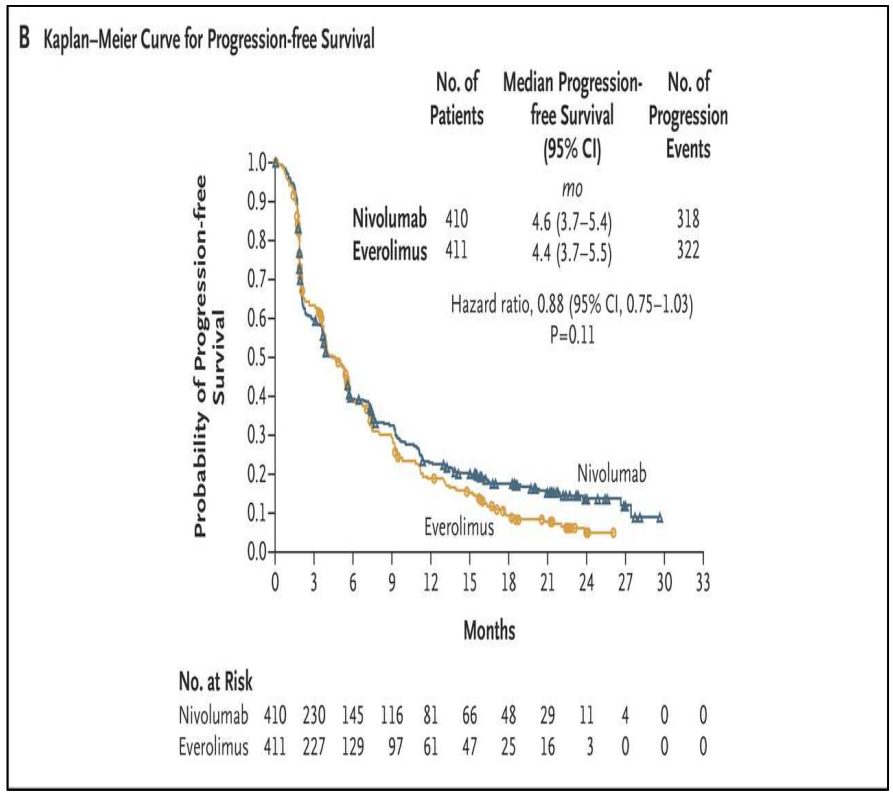
Overall Survival



Motzer RJ et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1510665

Subgroup Analyses and PFS

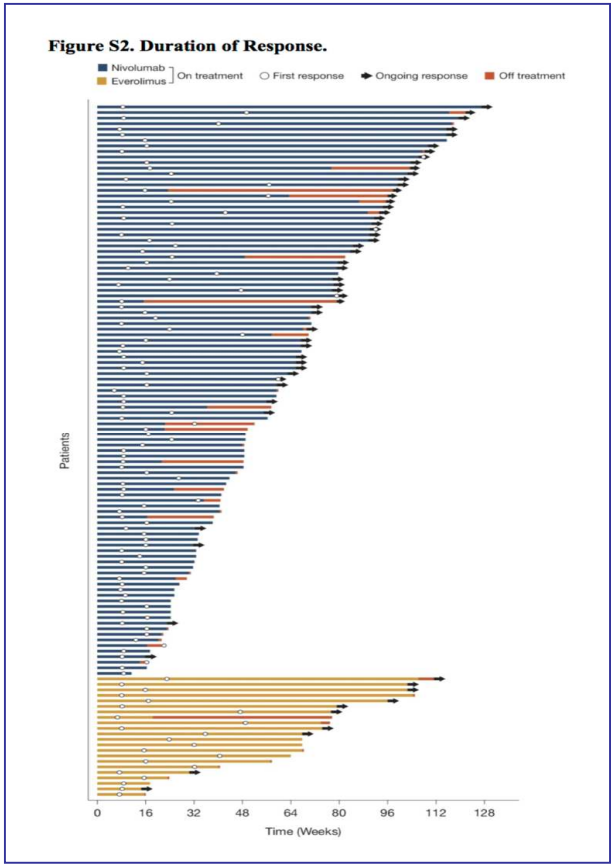




PFS: 4.6 vs 4.4 months

Motzer RJ et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1510665

Duration of Response



Nivolumab

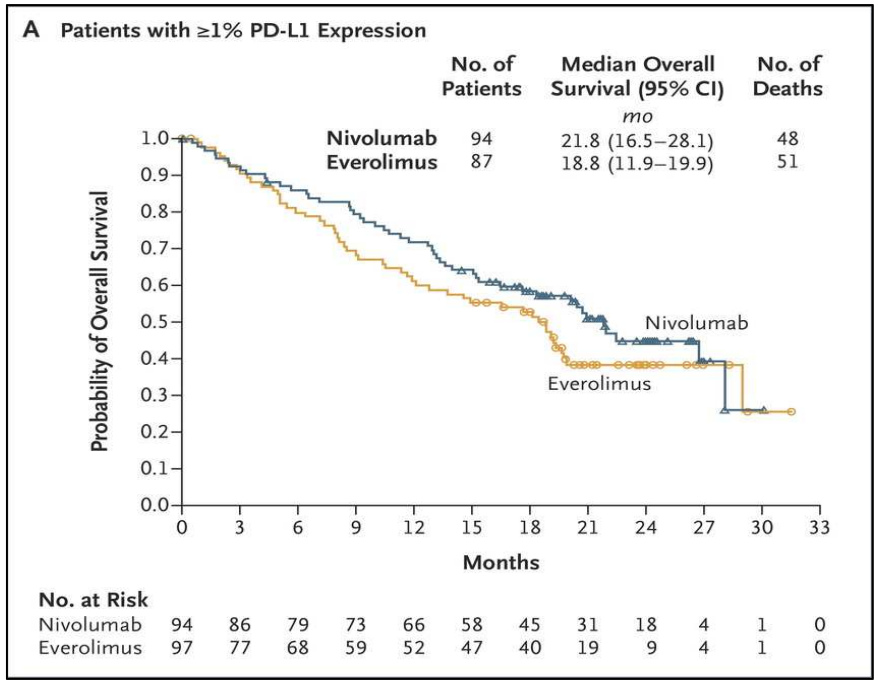
- 25% ORR
- 12 months median duration

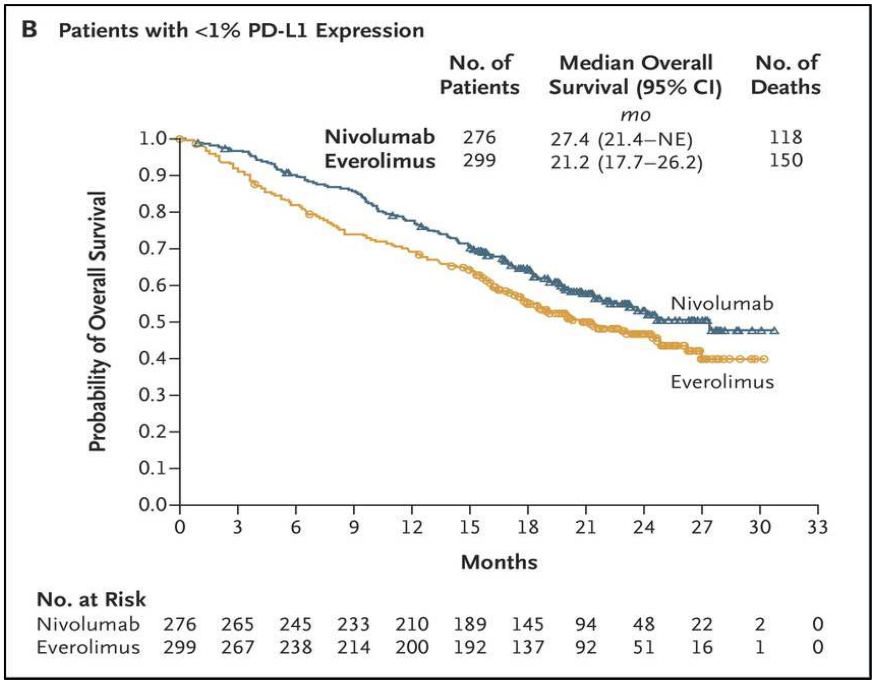
Everolimus

- 5% ORR
- 12 months median duration

Motzer RJ et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1510665

Overall Survival By PD-L1 Expression





24% with PDL1+ tumors

OS: 21.8 vs 18.8 months

76% with PDL1- tumors

OS: 27.4 vs 21.2 months

Motzer RJ et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1510665

Atezolizumab (Anti-PDL1) Phase 1a Efficacy: *Investigator Assessed*

	RECIST 1.1 Response Rate (ORR)	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	21%	16%	45%
RCC* (n = 47)	13%	32%	53%
Clear cell (n = 40)	13%	35%	57%
Non-clear cell (n = 6)	17%	0	20%

* 1 patient with unknown histology. Includes sarcomatoid and papillary RCC.
All patients first dosed prior to August 1, 2012; data cutoff February 1, 2013.
ORR includes unconfirmed PR/CR and confirmed PR/CR.

Cho et al, ASCO 2013

Atezolizumab: PD-L1 and Tumor Grade on Efficacy in RCC

PD-L1 IHC (IC)[a] n = 62	ORR (95% CI), %
IHC 3 (n = 8)	38% (11-71)
IHC 2 (n = 12)	8% (0.4-35)
IHC 1 (n = 15)	20% (6-45)
IHC 0 (n = 21)	10% (2-30)

McDermott et al. ESMO, 2014.
IC, tumor-infiltrating immune cell.
[a] A PD-L1+ cohort of patients was enrolled. 6 patients had unknown PD-L1 IHC (IC) status.
Investigator-assessed confirmed ORRs per RECIST v1.1.
Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% are PD-L1+.

PD-L1 expression is a weak predictive biomarker

Agent(s)	Tumor Type	n	RR (%) PD-L1 pos	RR(%) PD-L1 neg
Nivolumab[1]	Multiple Solid Tumors	42	36%	0%
MPDL3280A[2]	Kidney Cancer	47	20%	10%
Nivolumab[4]	Kidney Cancer	107	31%	18%
Nivo/Ipi[4]	Melanoma	27	40%	47%

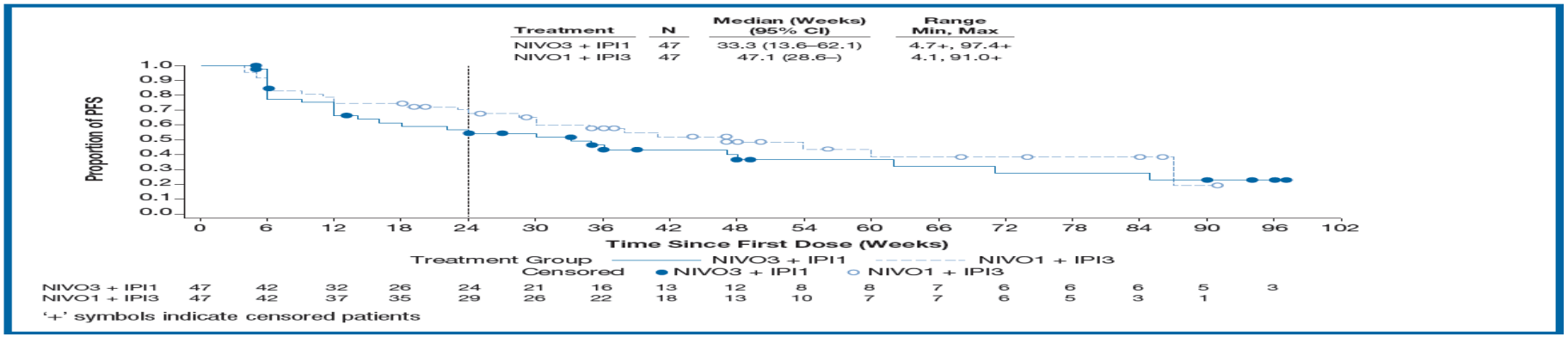
[1]Topalian et al, NEJM, 2012, [2]Cho et al ASCO 2013, [3]Grosso et al ASCO 2013, [4]Wolchok et al, NEJM 2013

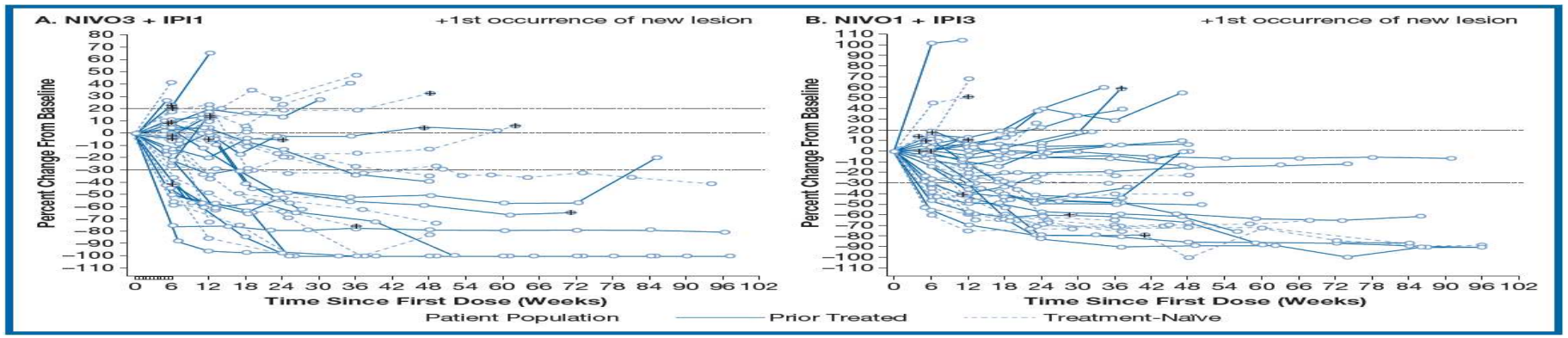
Nivolumab/Ipilimumab in mRCC

	NIVO3 + IPI1 N = 47	NIVO1 + IPI3 N =47	NIVO3 + IPI3 N = 6
Confirmed ORR, n (%)	18 (38.3)	19 (40.4)	0
Best OR, n (%)			
Complete response	4 (8.5)	1 (2.1)	0
Partial response	14 (29.8)	18 (38.3)	0
Stable disease	17 (36.2)	17 (36.2)	5 (83.3)
Progressive disease	10 (21.3)	7 (14.9)	1 (16.7)

Hammers et al ASCO 2014/2015

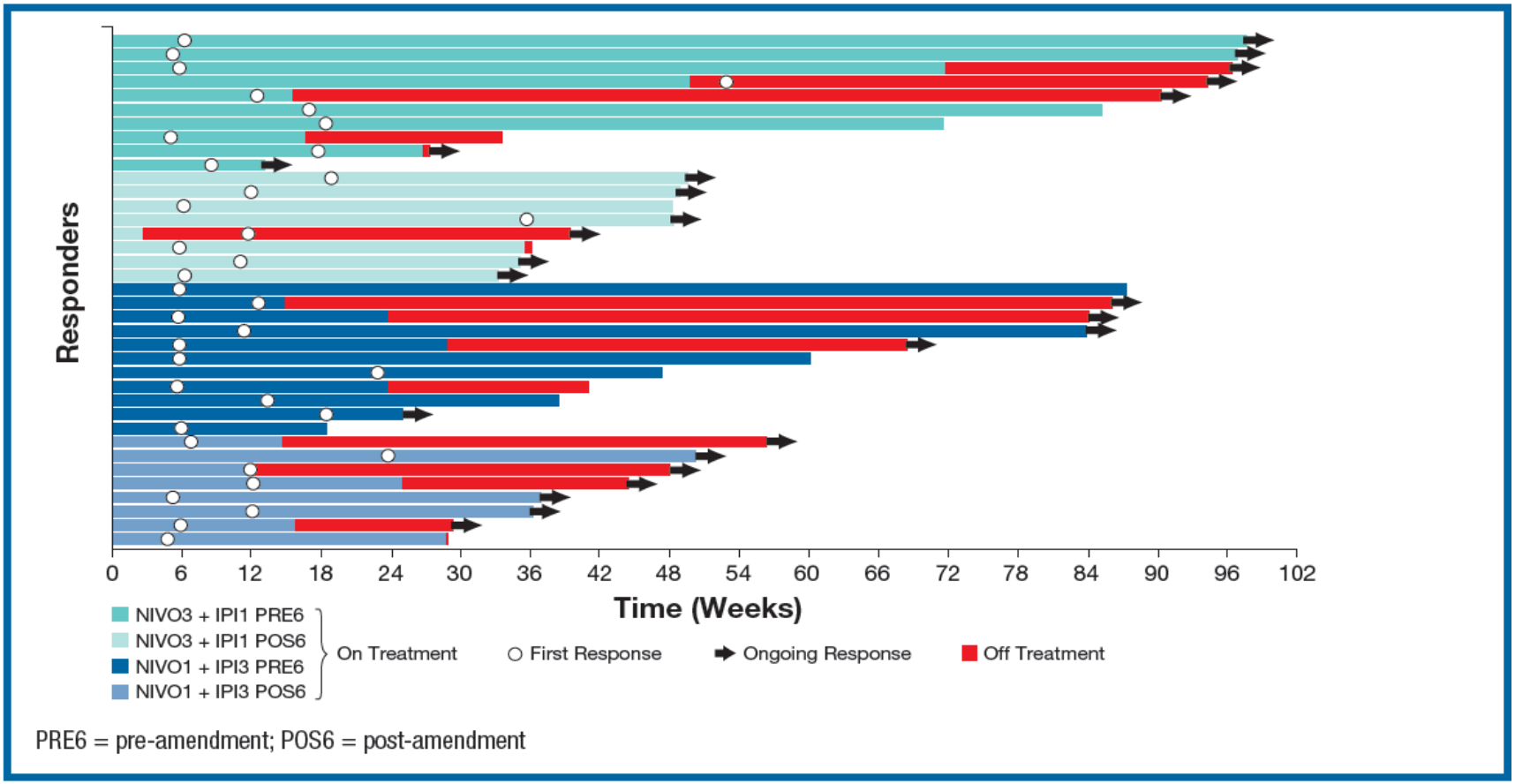
Ipilimumab and Nivolumab





McDermott et al. ESMO, 2014.

Ipilimumab and Nivolumab

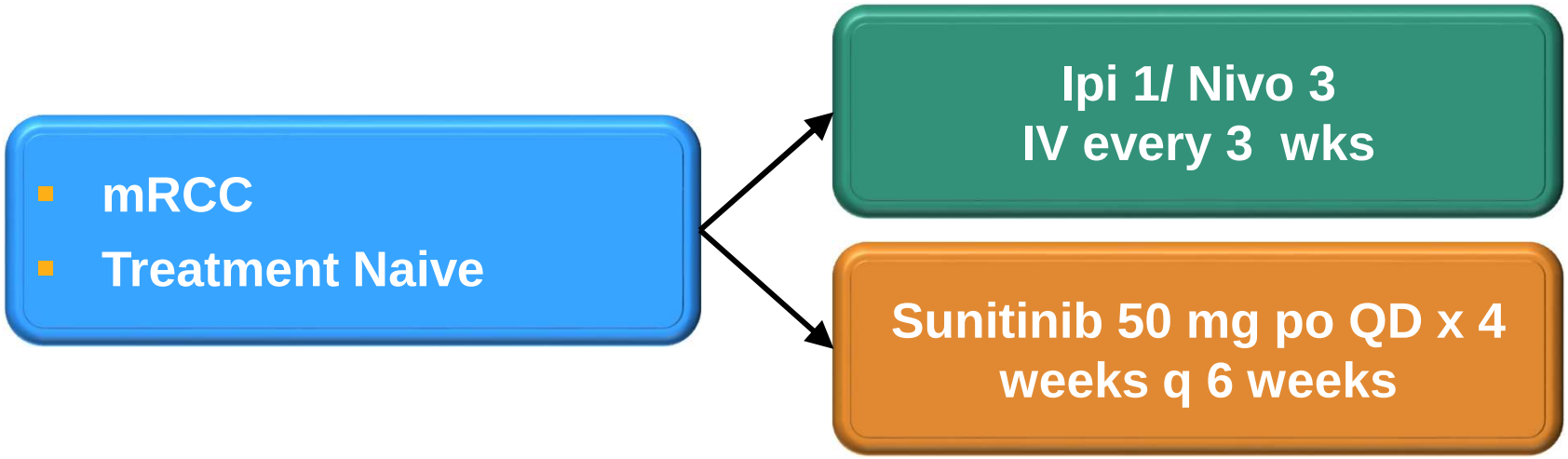


[1]Topalian et al, NEJM, 2012, [2]Cho et al, ASCO 2013, [3]Grosso et al, ASCO 2013, [4]Wolchok et al, NEJM 2013

Ipilimumab/Nivolumab AE's By Dose

	NIVO3 + IPI1 N = 47		NIVO1 + IPI3 N = 47	
AE, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Total patients	39 (83.0)	16 (34.0)	44 (93.6)	30 (63.8)
Fatigue	23 (48.9)	0	30 (63.8)	3 (6.4)
Rash	12 (25.5)	0	10 (21.3)	0
Pruritus	12 (25.5)	0	13 (27.7)	0
Nausea	11 (23.4)	0	20 (42.6)	0
Diarrhea	11 (23.4)	1 (2.1)	20 (42.6)	7 (14.9)
Colitis	1 (2.1)	0 (0)	6 (12.8)	6 (12.8)
Chills	10 (21.3)	0	4 (8.5)	0
Hypothyroidism	9 (19.1)	0	13 (27.7)	0
Pyrexia	9 (19.1)	2 (4.3)	7 (14.9)	0
Arthralgia	9 (19.1)	0	10 (21.3)	0

Front Line Phase 3 Trial



Began accrual late 2014; US sites completed accrual fall 2015

What about anti-VEGF and immune combos?

Two choices of anti-VEGF classes

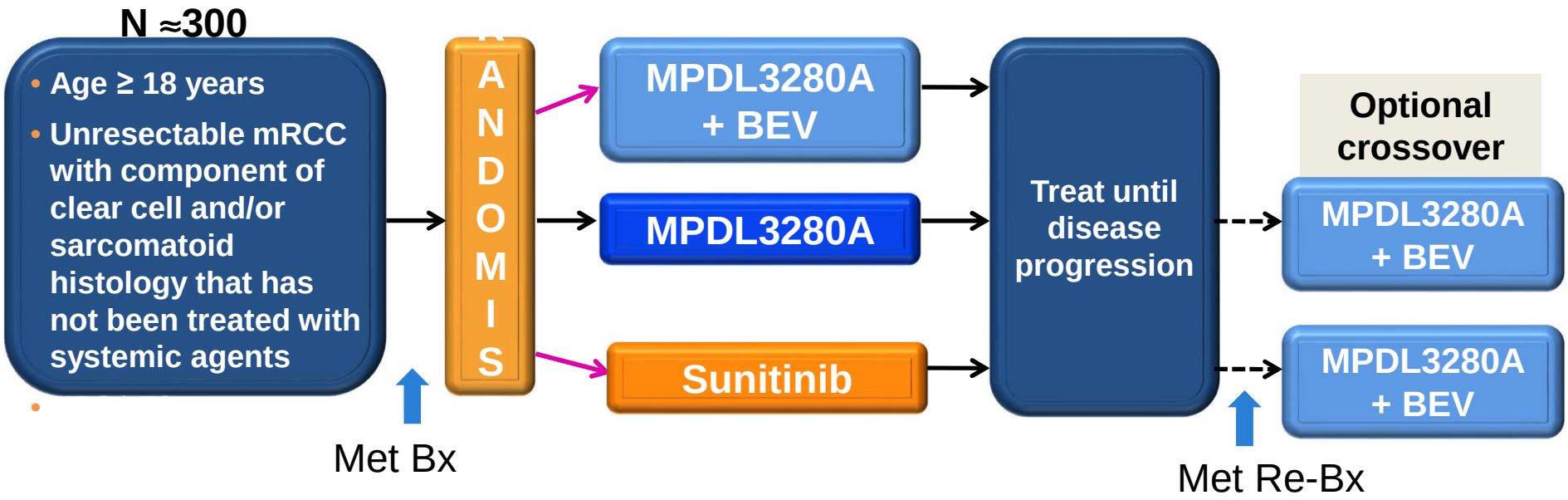
1. Anti-VEGF agents (bevacizumab)
2. Anti-VEGFR tyrosine kinase inhibitors

Phase I: Nivolumab + VEGFR TKI

	Sunitinib 50 mg (4/2) + nivolumab 2mg/kg Q3W (N2) or 5mg/kg Q3W (N5)	Pazopanib 800 mg QD + nivolumab 2mg/kg Q3W (N2)
Prior therapy	42%	100%
Nb.	n=33	n=20
MSKCC risk	Favorable/Intermediate (94%)	
ORR (%)	52%	45%
Median DOR range (wks)	54 18.1-80+	30 12.1-90.1+
Median PFS (wks) ~estimated (mo)	48.9 ~11.4	31.4 ~7.3
Gr. 3/4 Toxicity (%)	81.8%	70%
	ALT elevation 18% Hypertension 18% Hyponatremia 15%	4 DLTs (stopped) (LFTs n=3, 20%)

ASCO 2014 #5010 AMIN (Nivo+VEGF TKI)

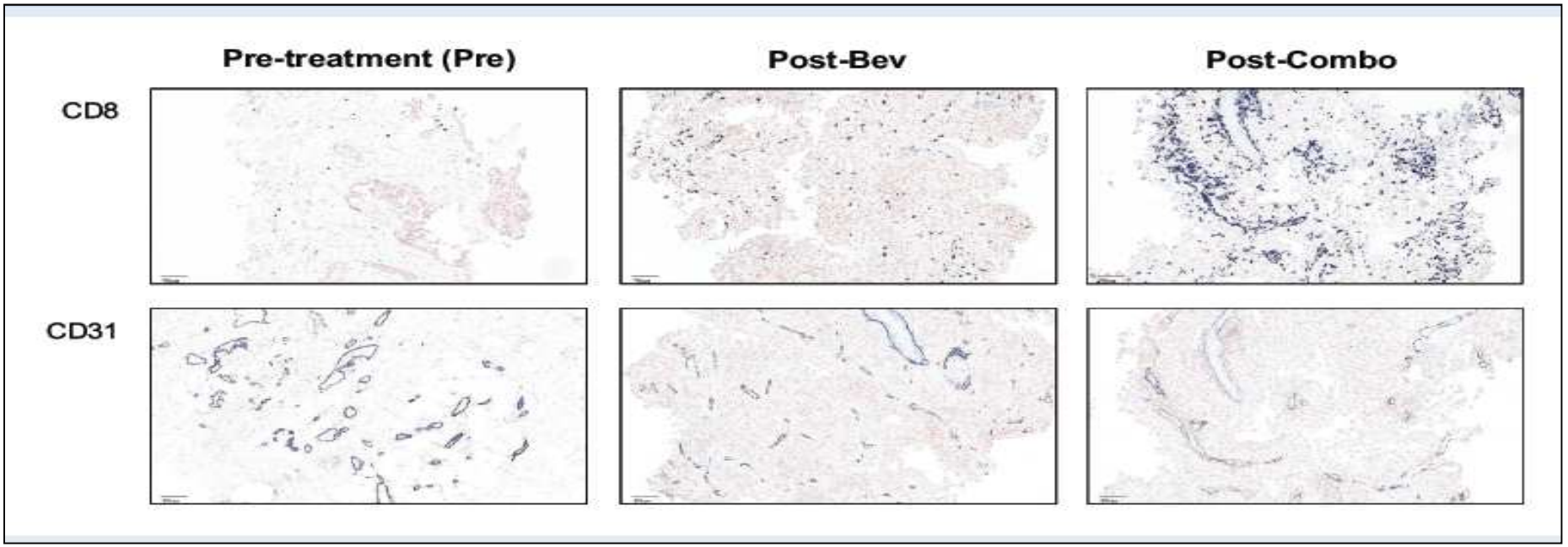
Atezo + BEV: Randomized Phase II Study



Primary endpoint: PFS (central)

Secondary endpoints: OS, ORR, DoR, OS, safety (original treatment group)
PFS, OS, ORR, DoR (crossover groups)

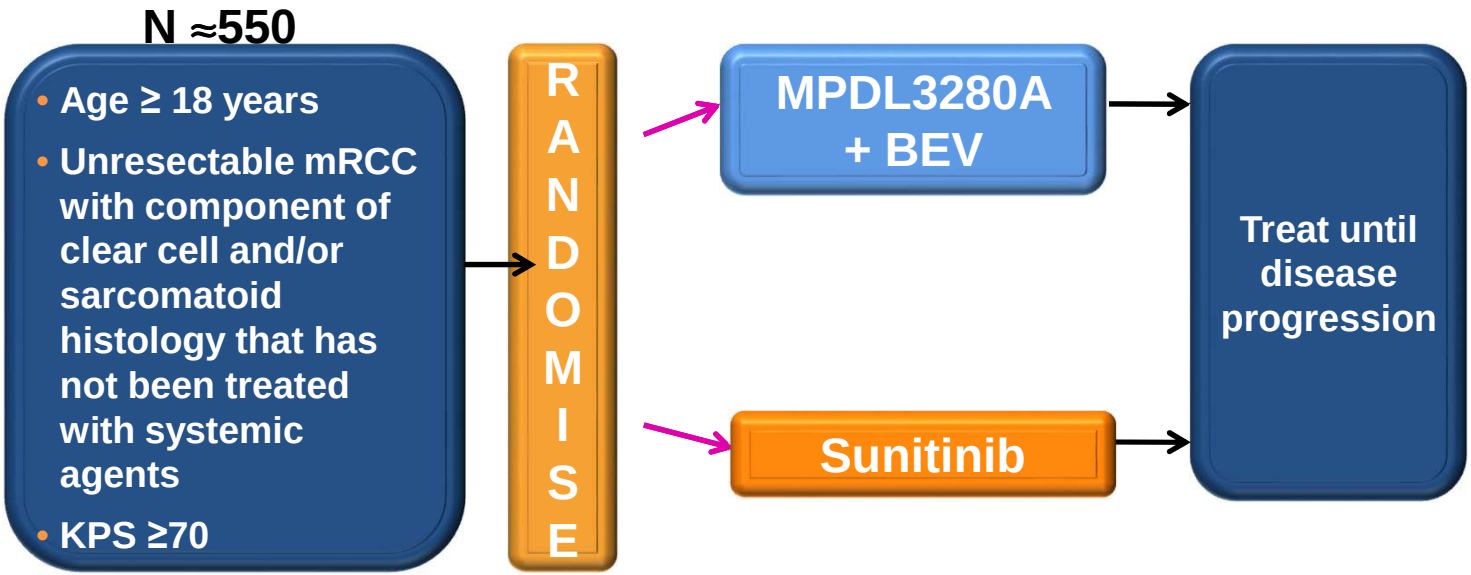
Impact on CD8 and CD31



Increases in CD8+ cell infiltration and decreases in CD31 expression were seen after Bev + Atezolizumab treatment

Sznol et al GU ASCO 2015

Randomized Phase III Study



Primary endpoint: PFS (central)

Secondary endpoints: OS, RR

Anti-PD1/PDL1 in RCC Summary-Future Directions

- Anti-PD1/PDL1 agents with clinical activity in 25-50%
- Combination of Ipilimumab/Nivolumab and Atezolizumab/Bevacizumab are promising
- What line of use is optimal?
- Can we identify biomarkers to better identify patients likely to benefit?

Urothelial cancer

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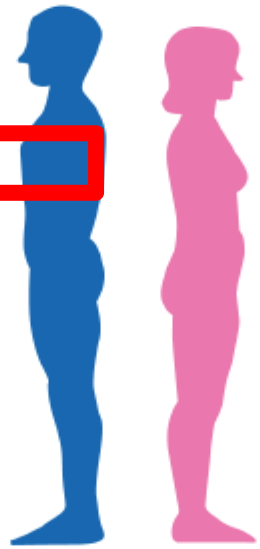
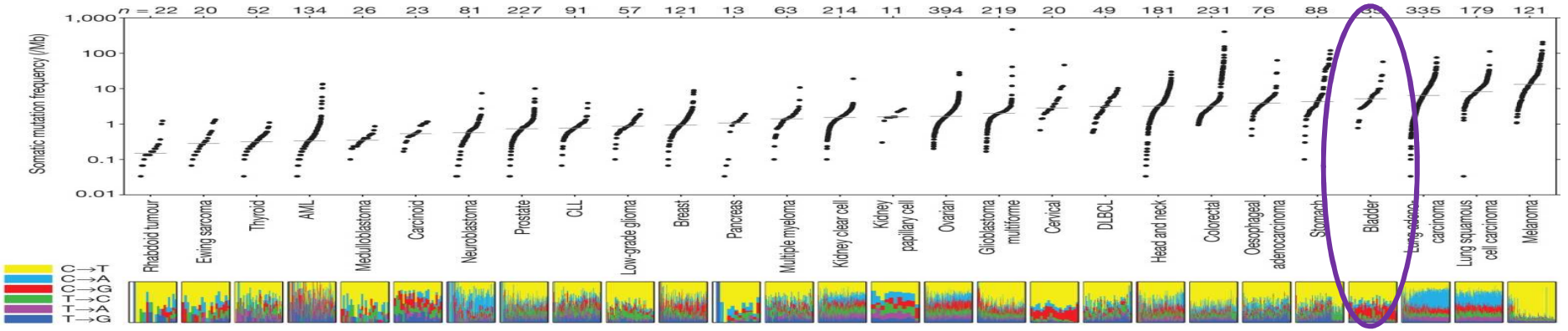


Siegel et al. CA, 2014

Metastatic Urothelial Cancer

- Advanced UC is a uniformly fatal disease after failure of platinum chemotherapy
- Median survival is short
- Durable responses are not routinely observed in this patient population
- Grade 3-4 toxicities are high with 2L chemotherapy
- Difficult to treat patient population with multiple comorbidities

Somatic mutations Bladder



- High mutational complexity rates similar to tobacco/environmental carcinogen exposure
- Potential for many neo-antigens to be seen as foreign by host immune system

MS Lawrence *et al. Nature* **2013**

IMvigor 210: Phase II Study

- **Locally advanced or metastatic cancer of the bladder, renal pelvis, ureter or urethra**
- **Progression during or following platinum**
  - **No restriction on number of prior lines of therapy**
- **Creatinine clearance ≥ 30 mL/min**
- **ECOG PS 0-1**
- **Tumor tissue evaluable for PD-L1 testing[a]**

→ **Atezolizumab 1200 mg IV** q3 weeks until loss of clinical benefit

→ **Response assessment** q9 weeks (q12 weeks after 54 weeks)

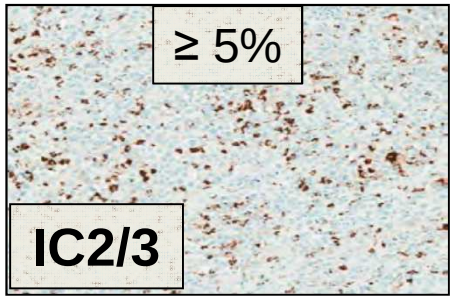
- **Co-primary Endpoints**
  - ORR (confirmed) per RECIST v.1.1 (central independent review)
  - Investigator-assessed ORR per modified RECIST
  - Primary endpoints met if null hypothesis (ORR of 10%) rejected at significance level (α) of 5%
- **Key Secondary Endpoints**
  - PFS, DOR, OS, Safety

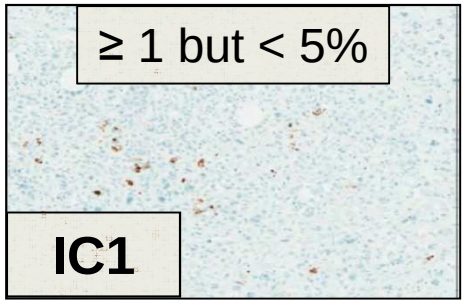
[a]PD-L1 prospectively assessed by central laboratory. Patients and investigators blinded to PD-L1 IHC status. Trial Identifier: NCT02108652.

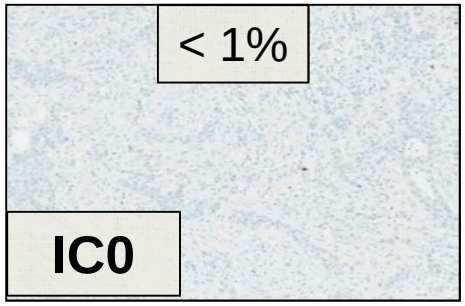
Rosenberg et al, ESMO 2015

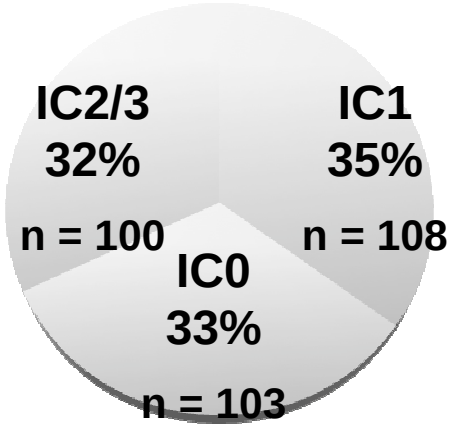
PD-L1 IHC

IHC Status of Treated Patients in IMvigor 210 Study (N = 311)









Images at 10x magnification.

- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating immune cell (IC) PD-L1 expression based on 3 IHC scoring levels

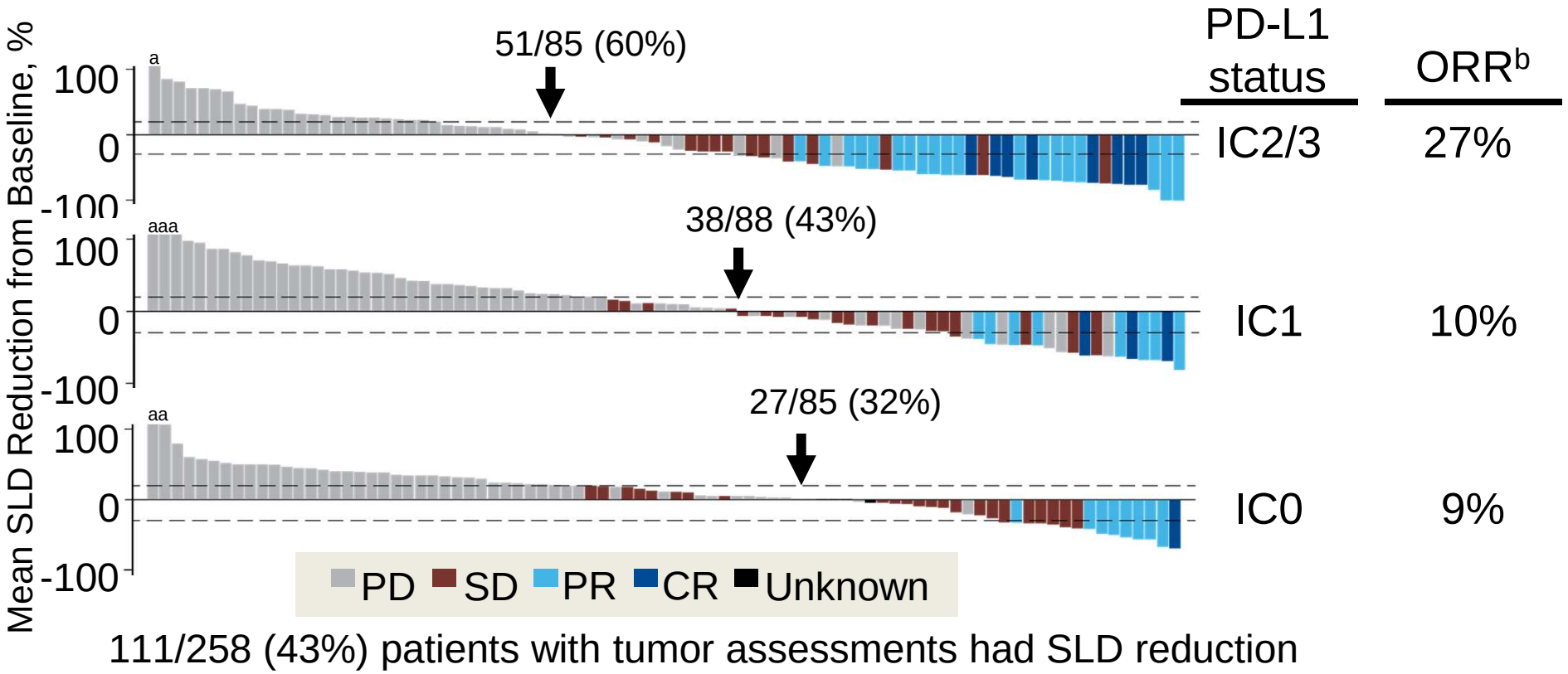
RECIST v1.1 Criteria by Independent Review

PD-L1 subgroup	n	CR (%)	ORR (%)	95% CI	P value[b]
IC2/3	100	8%	27%	19, 37	< .0001
IC1/2/3	208	5%	18%	13, 24	.0004
All	311	4%	15%	11, 20	.0058
IC1	108	3%	10%	5, 18	N/A[c]
IC0	103	1%	9%	4, 16	N/A[c]

- IMvigor 210 met its co-primary endpoints in all subgroups tested
- ORR by independent review (RECIST v1.1) and investigator (mRECIST) were concordant
- Early response data are likely to mature in subsequent analyses

[a]Objective response evaluable population: all treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. [b]*P*-value for H_o: ORR = 10% versus H_a: ORR ≠ 10%, where 10% ORR is historical control, α = 0.05. [c]No formal hypothesis testing conducted. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Changes in Target Lesions by PD-L1 Subgroup

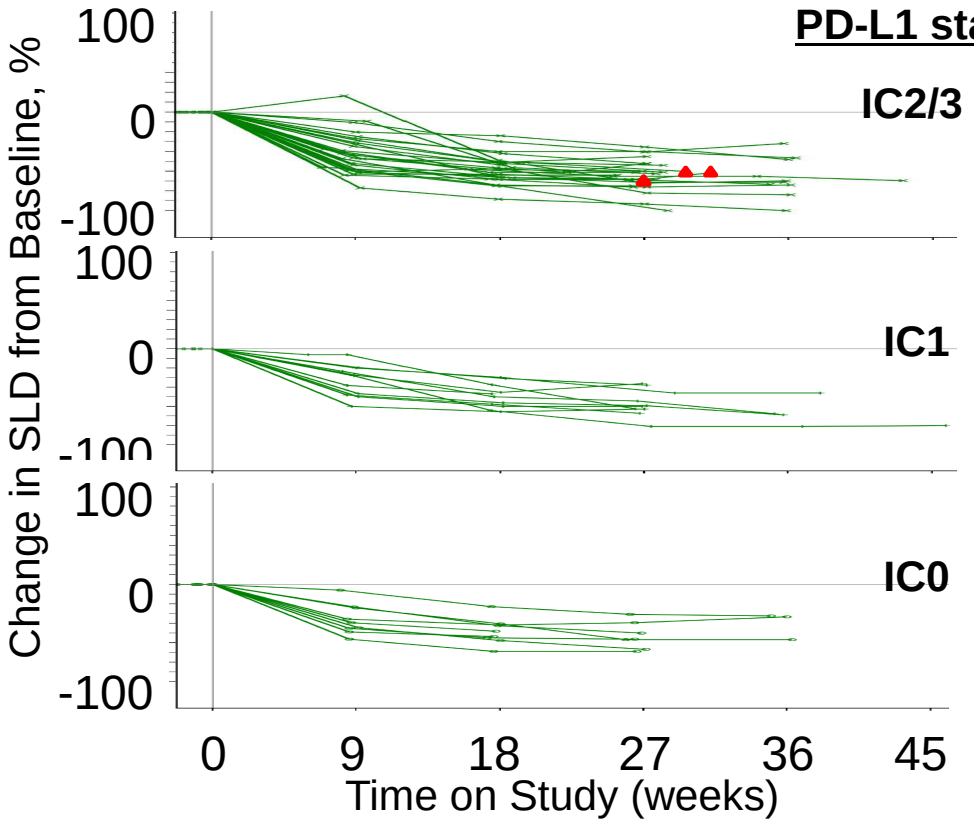


PD-L1 status	ORR[b]
IC2/3	27%
IC1	10%
IC0	9%

111/258 (43%) patients with tumor assessments had SLD reduction

SLD, sum of longest diameters. [a]> 100% increase. [b]Per confirmed RECIST v1.1 (independent review).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.
Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

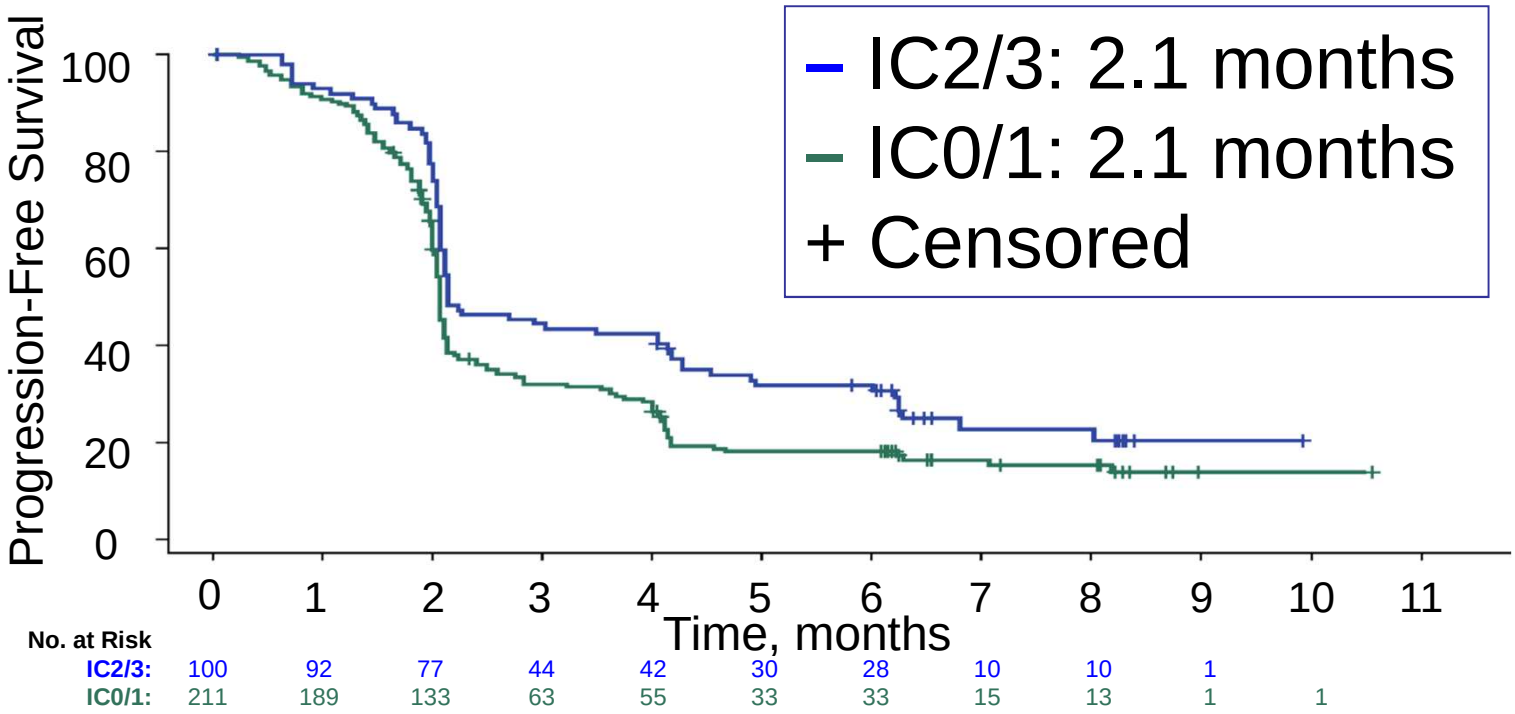
Duration of Response



- Responses were durable, with median DOR not reached in any subgroup
- Ongoing responses seen in 43/47 patients (92%)
- Median follow-up time is 7 mo (range, 0-11 mo)

SLD, sum of longest diameters. Per RECIST v1.1 (independent review). Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

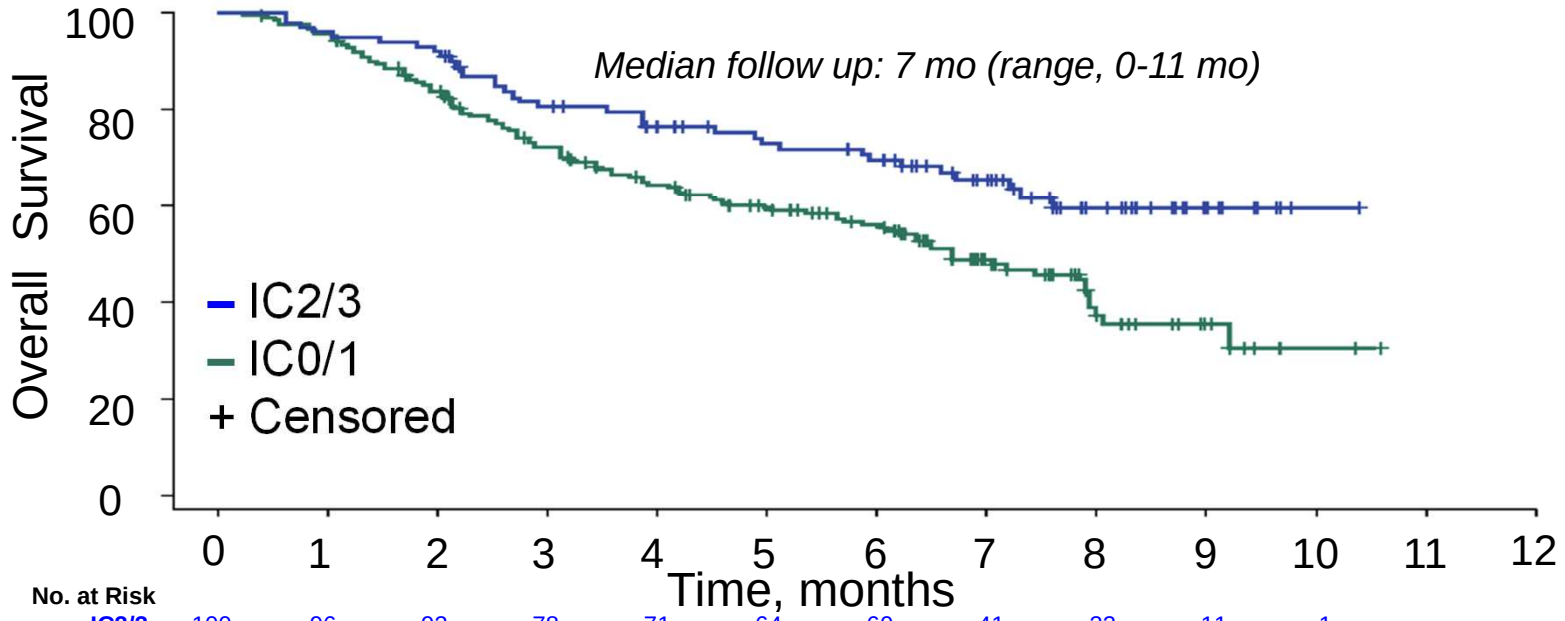
Median progression-free Survival



[a]Per RECIST v1.1 (independent review). Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Overall Survival

Survival	IC2/3 n = 100	IC0/1 n = 211	All N = 311
Median OS, mo (95% CI)	NR (7.6, NE)	6.7 (5.7, 8.0)	7.9 (6.7, NE)



No. at Risk											
IC2/3:	100	96	92	78	71	64	60	41	22	11	1
IC0/1:	211	201	173	143	123	107	90	50	23	10	2

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Subgroup Analysis

Subgroup	ORR, % (95% CI)[a] IC2/3	All
Prior systemic regimens, metastatic setting[b]		
1	26% (12, 43)	12% (7, 19)
2	39% (17, 64)	18% (9, 30)
≥ 3	20% (6, 44)	13% (6, 24)
Metastatic sites at baseline		
Visceral	17% (9, 28)	10% (6, 14)
Liver	15% (4, 34)	6% (2, 13)
Lymph node only	38% (19, 59)	33% (20, 49)
ECOG PS 1	19% (10, 31)	10% (6, 15)
Hemoglobin < 10 g/dL	21% (7, 42)	9% (3,18)

- Median DOR not yet reached in any of the subgroup populations

[a]Per RECIST v1.1 (independent review).
[b]In patients with 0 prior regimens, ORR (95% CI) was 26% (11, 46) in IC2/3 patients (n = 27) and 20% (11, 31) in all-comer patients (n = 70).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Conclusions: Atezolizumab

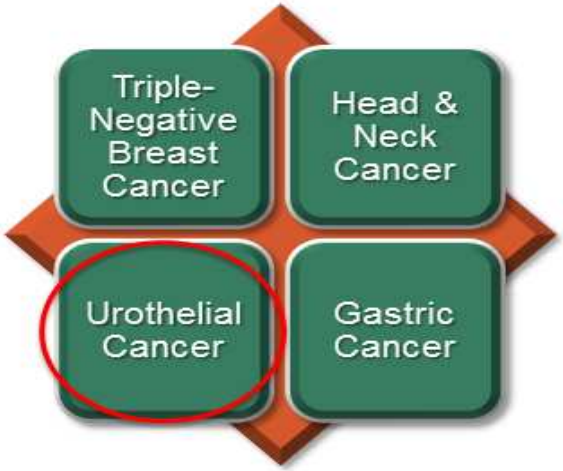
- ORR of ~20%
- Responses were durable with median not reached
- Higher PD-L1 IC status was associated with higher ORR
- Well tolerated with a low rate of treatment-related Grade 3-4 toxicities and no treatment-related renal toxicity

Pembrolizumab in UBC

E. Plimack, June 1, 2015

KEYNOTE-012 (NCT01848834)

Phase Ib Multi-Cohort Study of Pembrolizumab in Patients With PD-L1 Positive Advanced Solid Tumors



Chow LQM et al. *Ann Oncol*. 2014;25(suppl 4):abstr LBA31; Nanda R et al. Presented at: SABCS 2014; December 9-13, 2014; San Antonio, TX. Abstr 1349; Muro K et al. *J Clin Oncol*. 2015;33(suppl 3):abstr 3; Plimack E et al. *J Clin Oncol* 2015;33 (suppl 7) abstr 2967.

Baseline Characteristics

Characteristic	Total (N = 33) N (%)
Age, yr, median (range)	70 (44–85)
Male	23 (69.7)
ECOG performance status	
0	9 (27.3)
1	24 (72.7)
Histology	
Transitional cell	30 (91)
Non-transitional cell/mixed	3 (9)
Location of metastasis	
Any liver	8 (24)
Lymph node only	3 (9)

Characteristic	Total (N = 33) N (%)
No. of prior therapies for advanced disease	
0	8 (24.2)
1	8 (24.2)
2	6 (18.2)
≥3	11 (33.3)
Prior adjuvant/neoadjuvant therapy	
Yes	20 (60.6)

Analysis cutoff date: Mar 23, 2015.

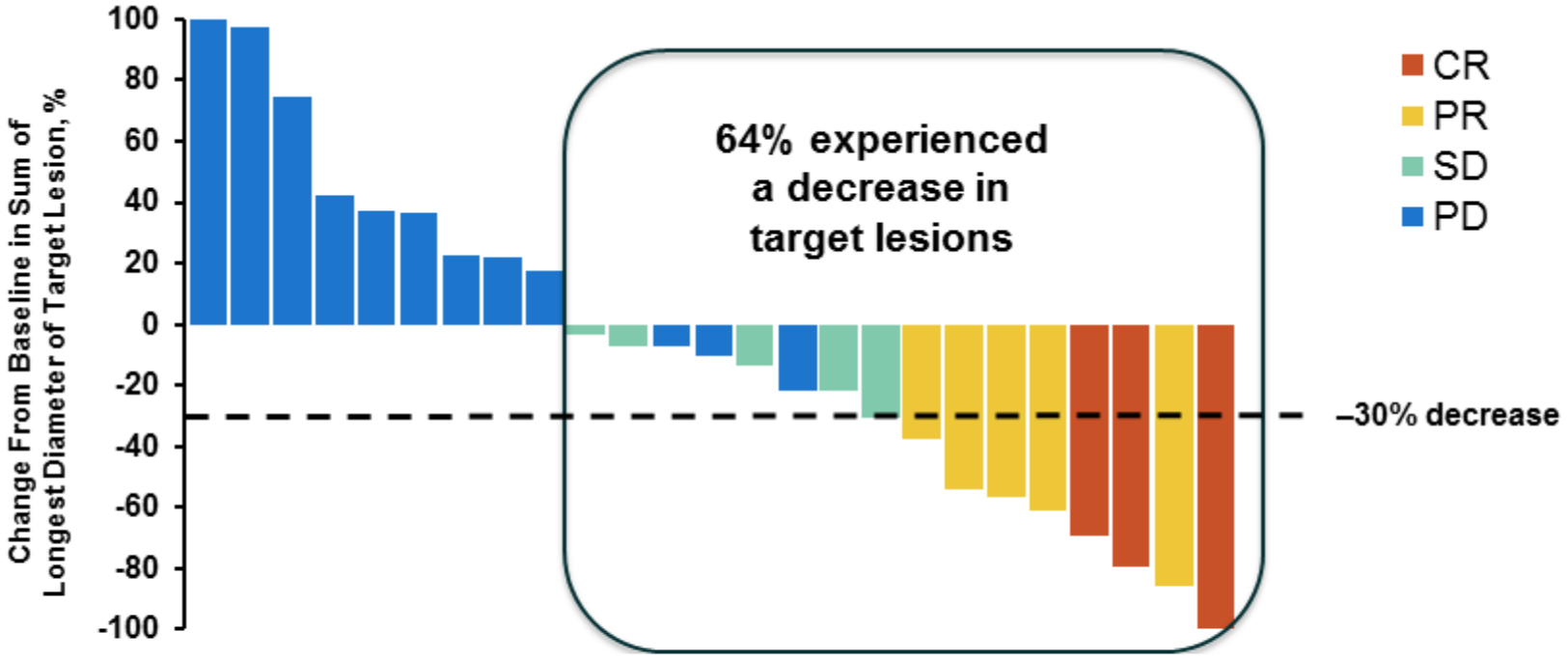
ORR: Pembrolizumab

	Patients Evaluable For Response* (N = 29)		
	n	%	95% CI
Overall response rate†	8	27.6	12.7–47.2
Best overall response			
Complete response	3	10.3	2.2–27.4
Partial response	5	17.2	5.8–35.8
Stable disease	3	10.3	2.2–27.4
Progressive disease	14	48.3	29.4–67.5
Disease Control Rate	11	37.9	20.6–57.7
No assessment	4	13.8	3.9–31.7

RECIST v1.1, Central Review.

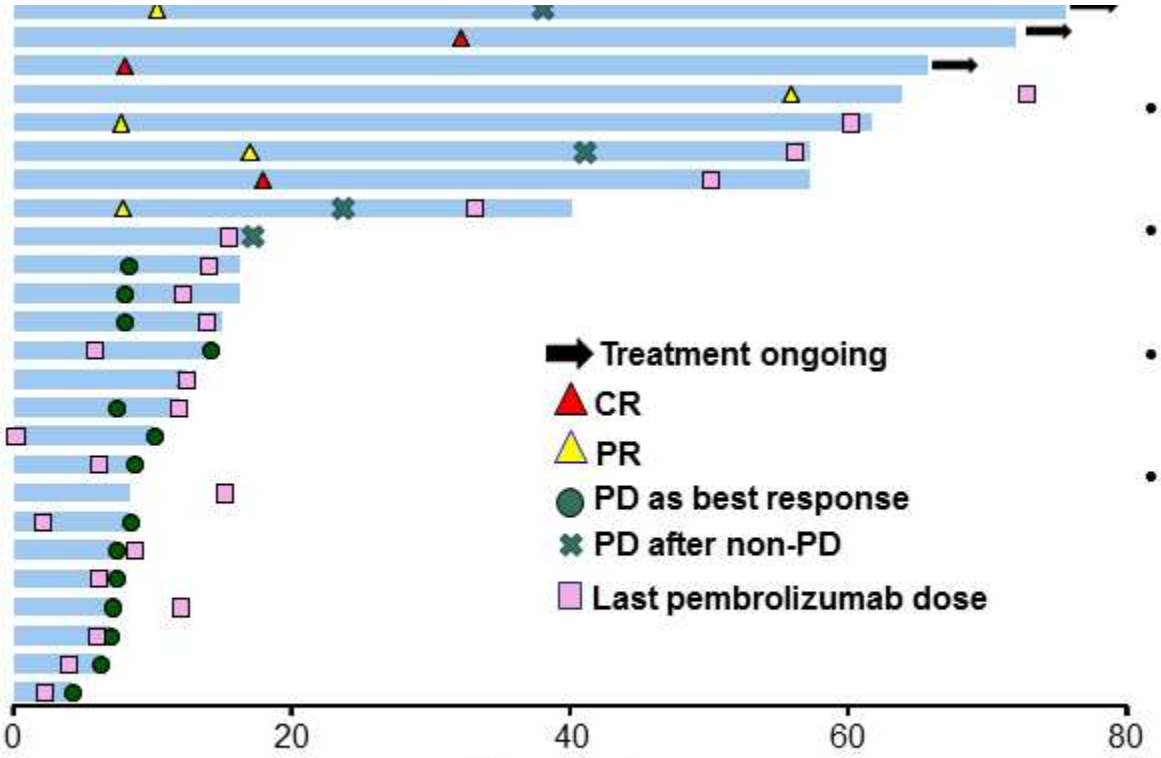
*Patients evaluable for response were those with measurable disease by central review at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. "No assessment" signifies patients who discontinued therapy before the first scan.
†Only confirmed responses are included.
Analysis cutoff date: March 23, 2015.

Maximum Change in Target Lesions



Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline tumor assessment (n = 25).
RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

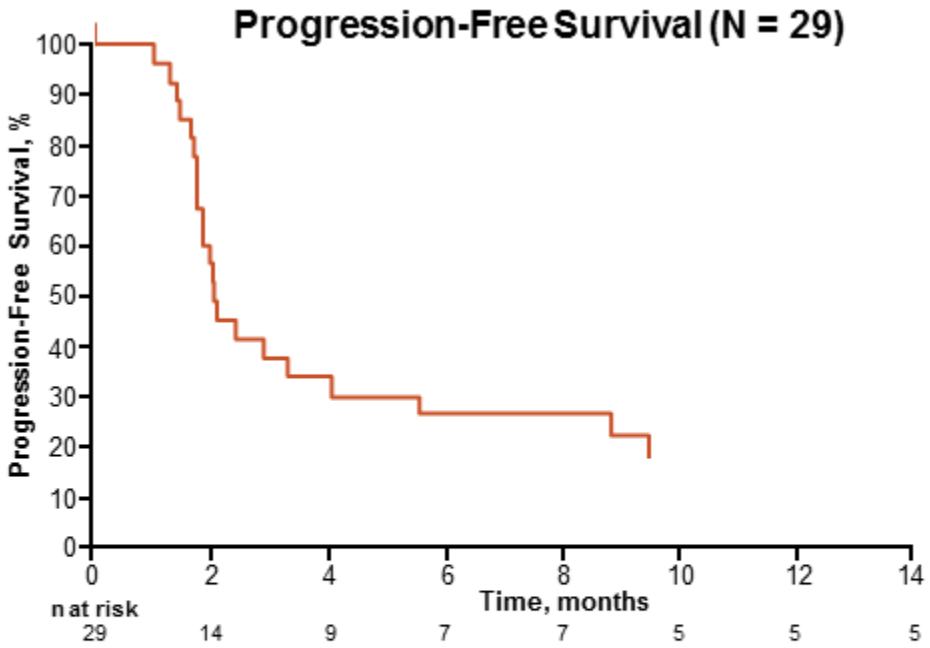
Response Duration

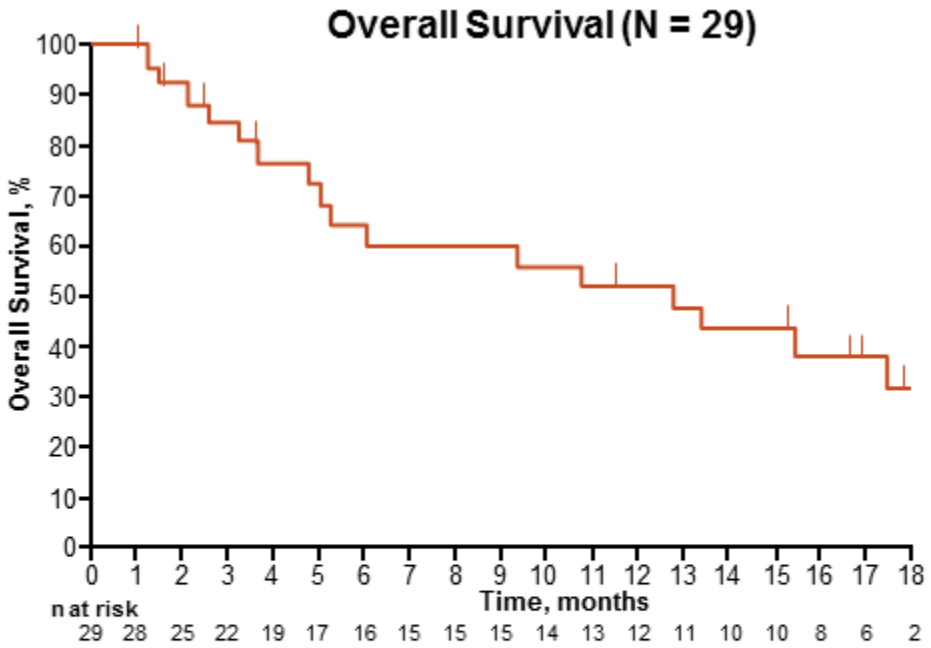


RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

- Median follow-up duration:
  - 15 (0.6-20) months
- Median time to response:
  - 9 (7.7−55.9) weeks
- Response duration:
  - 8.1 to 64.1+ weeks
- 3 patients remain on therapy

PFS and OS





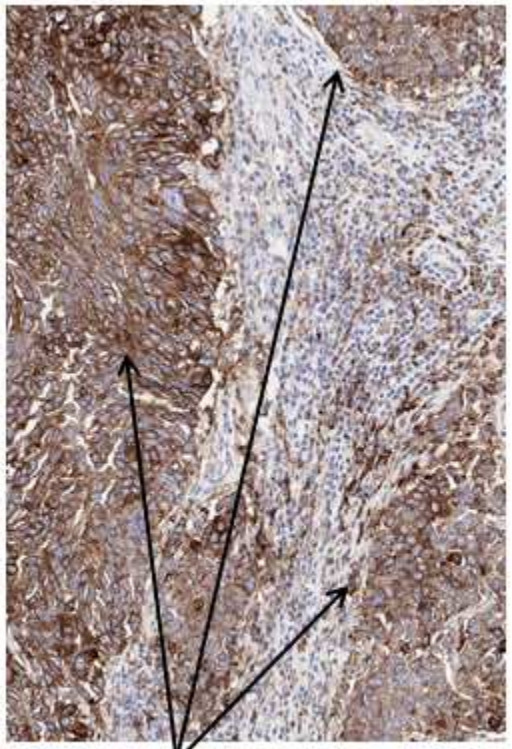
- Median PFS: 2 months (95% CI, 1.7−4.0)
- PFS rate at 12 months: 19.1%

- Median OS:12.7 months (95% CI, 5.0−NR)
- OS rate at 12 months: 52.9%

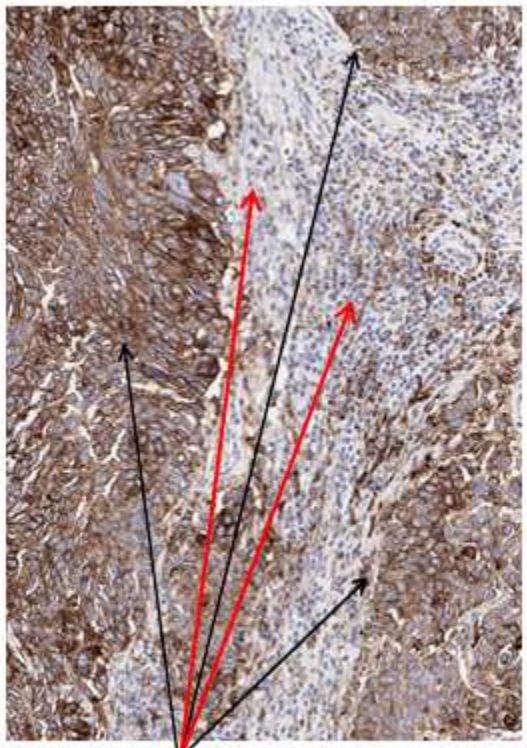
Analysis cutoff date: March 23, 2015.

PRESENTED AT: ASCO Annual '15 Meeting

PDL1 Staining



Tumor cells



Tumor + inflammatory cells

Exploration of PDL1 Predictive Capacity

Tumor Cells Only (N = 29 evaluable)		Tumor and Tumor Associated Inflammatory Cells (N = 28 evaluable)	
	ORR (95%CI)		ORR (95%CI)
Negative (N = 11)	9% (0%–41%)	Negative (N = 4)	0% (0%–60%)
Positive (N = 18)	33% (13%–59%)	Positive (N = 24)	29% (13%–51%)

- In order to maximize detecting responders while minimizing the false negative rate, scoring needs to take into account both PD-L1 positive tumor cells and PD-L1 positive tumor associated inflammatory cells

Conclusions: Pembrolizumab

- Response rate of 33% with complete response in 10%
- Response duration ranged from 8.1 to 64+ weeks
- 50% alive at 12 months
- Well tolerated with 85% with grade 1-2 or less

Anti-PD1/PDL1 Conclusions in Urotheilal

- ORR of ~25% with complete response in ~10%
- Responses appear durable
- Well tolerated
- PDL1 positive expression appears to enrich for benefit but PDL1 negative patients also benefit
- What is the efficacy in the front line or earlier stages?

GU Immunotherapy Conclusions

Prostate Cancer

- Sipuluecel T and Ipilimumab with some evidence of proof of principle for immunotherapy in prostate cancer

RCC

- Nivolumab improved OS in second line
- Awaiting results of front line combinations with ipilimumab/nivolumab and atezolizumab/bevacizumab

Urothelial Carcinoma

- Atezolizumab with promising results in large phase 2 and with breakthrough designation by FDA

GU Immunotherapy: Future Directions

Prostate Cancer

- Combinations to be tested
- Earlier in metastatic process might be beneficial

RCC

- Improvement in patient selection
- Efficacy of combinations

Urothelial Carcinoma

- Improve patient selection
- Duration of therapy, combinations

Thank you!

Questions

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