Immunotherapy for GU Cancers

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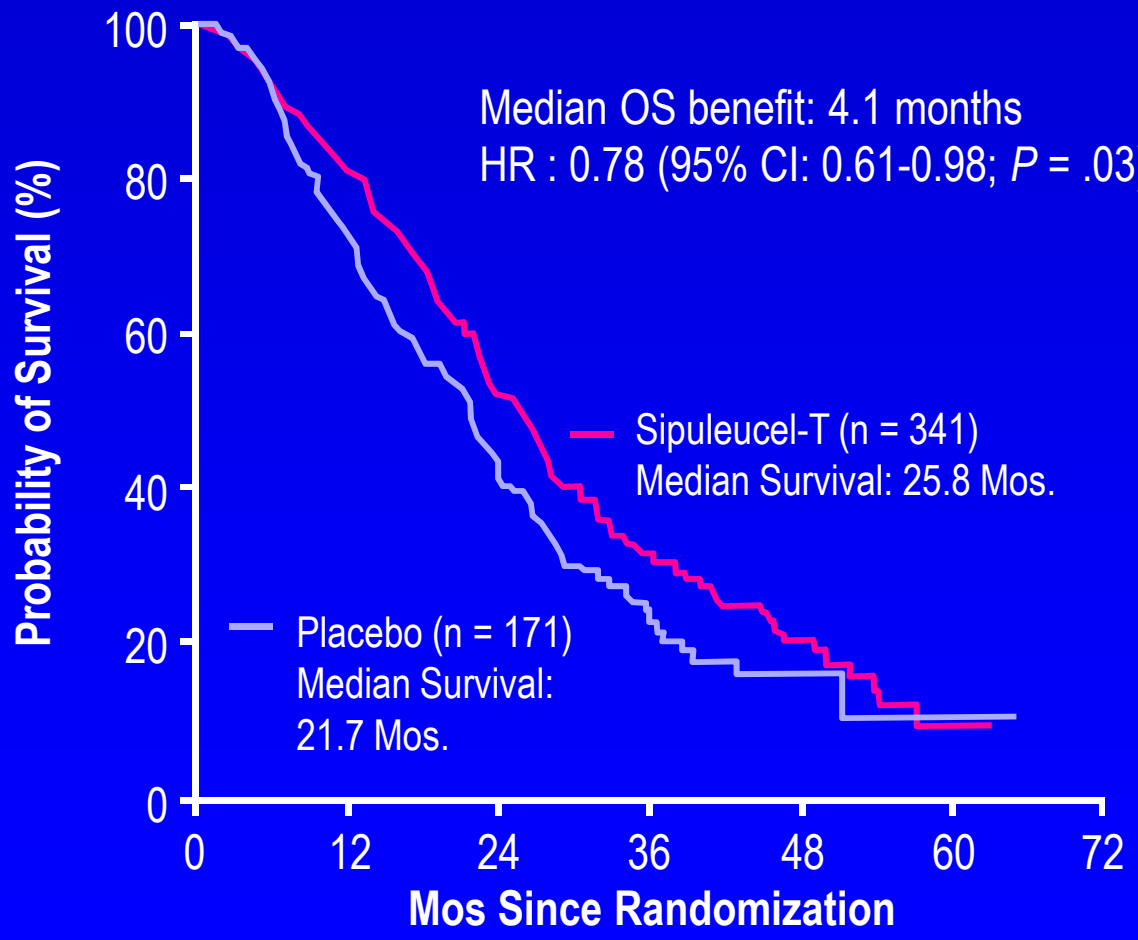
Disclosure

- Consulting Fees
  - Bristol Myers Squibb
  - Amgen
  - Novartis
  - Alkermes
  - Infinity

Agenda

- Prostate Cancer
  - Sipuleucel T
- Kidney Cancer
  - IFN, IL-2 (from earlier presentation)
  - CTLA4 Antibody
  - Anti-PD1
  - Combinations
- Bladder Cancer

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): OS



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

Sipuleucel T: Issues

- Adoption has been slow
  - Cumbersome, Expensive, No measure of efficacy
- Even though vaccine involves autologous tumors (tumor specific epitopes:
  - Even if vaccine enhances antitumor immunity, cells likely to be stymied in the tumor microenvironment
- Conclusion: Vaccines are unlikely to have a major effect in the absence of immune checkpoint blockade

RCC: Eight Years of Impressive Progress

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	

Is there a role for Immunotherapy?

CTLA-4 Blockade in mRCC

- **Ipilimumab Phase II trial**
  - **Single institution (NCI) ***
  - **Major response rate = 9%**
  - **Max dose tested 3 mg/kg**
    - **(dose response in melanoma)**
- **Survival effect in melanoma despite low response rate**
- **Additional studies warranted**
  - **CTLA-4 Blockade + Bev**

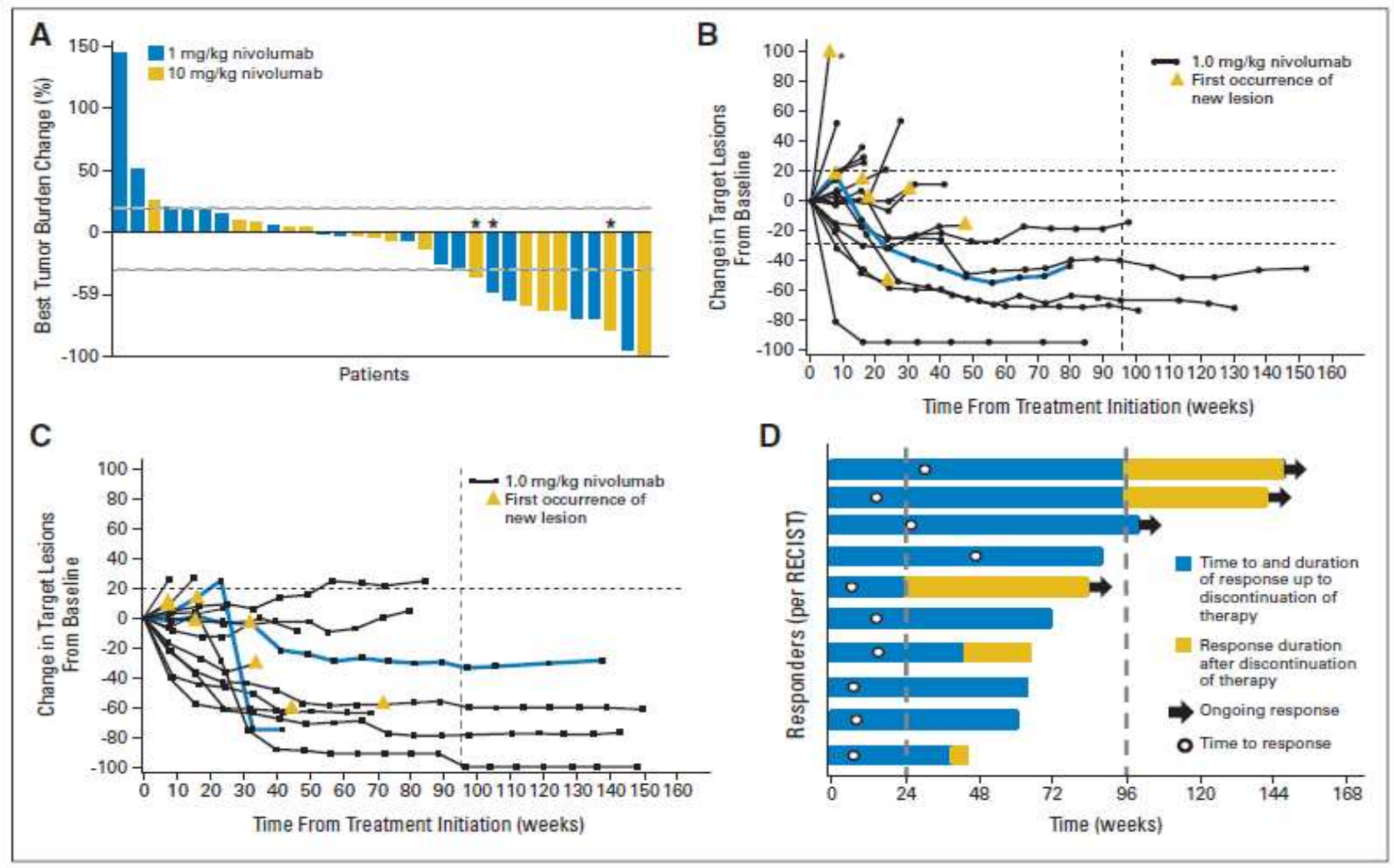
  (Hodi et al, DFHCC Melanoma Phase I, Ca Immunol Res 2014)
  - **Ipi + Nivo**

*Yang, JIT 2007

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage (RCC)
PD-1	Nivolumab	Fully human IgG4	Bristol-Myers Squibb	Phase III
	Pidilizumab	Humanized IgG1	CureTech (Medivation)	Phase I-II
	Pembrolizumab	Humanized IgG4	Merck	Phase I-II
PD-L1	BMS-936559	Fully human IgG4	Bristol-Myers Squibb	Phase I
	MedI-4736 (Durvalumab)	Engineered human IgG1	MedImmune	Phase I
	MPDL-3280A (Atezolizumab)	Engineered human IgG1	Genentech	Phase II-III
	MSB0010718C (Avelumab)		EMD Serono (Pfizer)	Phase I

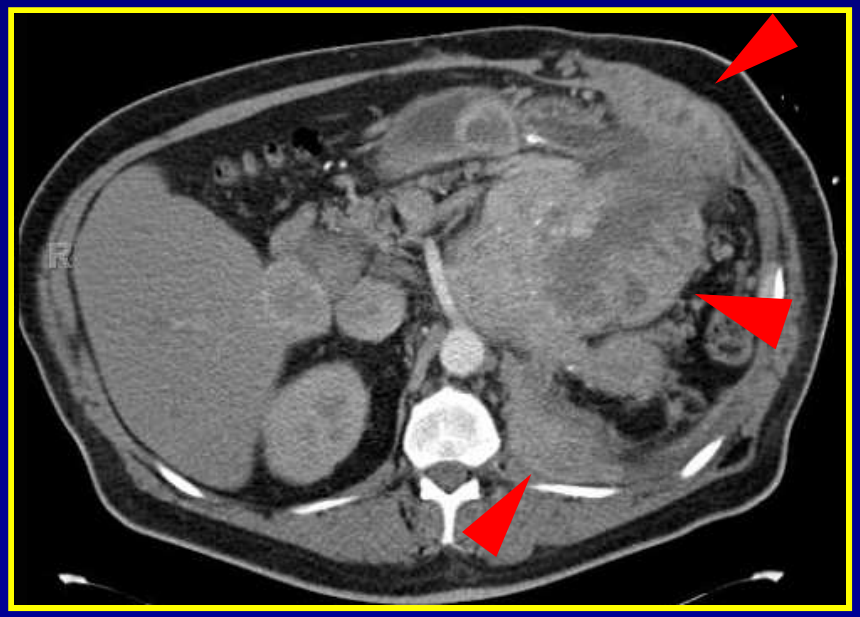
Phase I trial of Nivolumab in Metastatic RCC



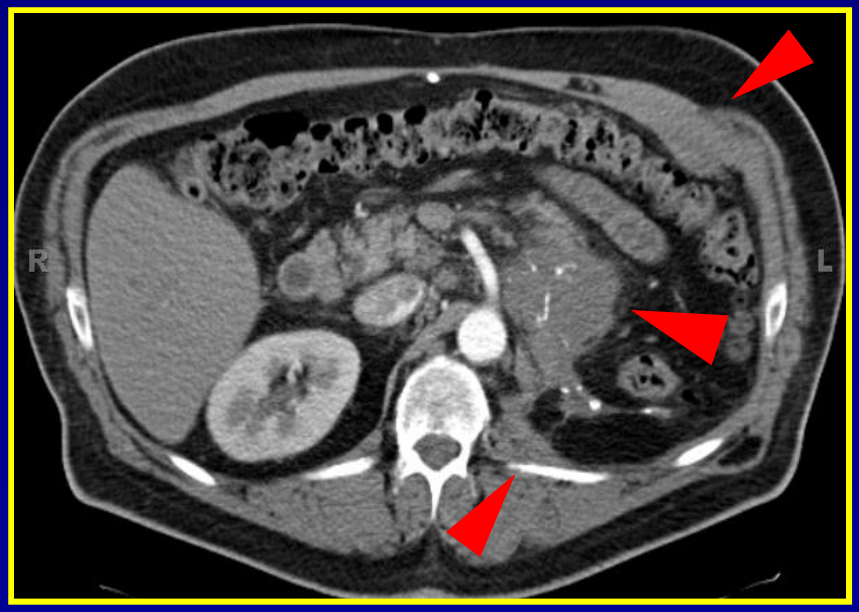
McDermott et al, JCO 2015

Partial Regression of Metastatic RCC in a Patient Treated with 1 mg/kg Nivolumab

Pretreatment



6 months

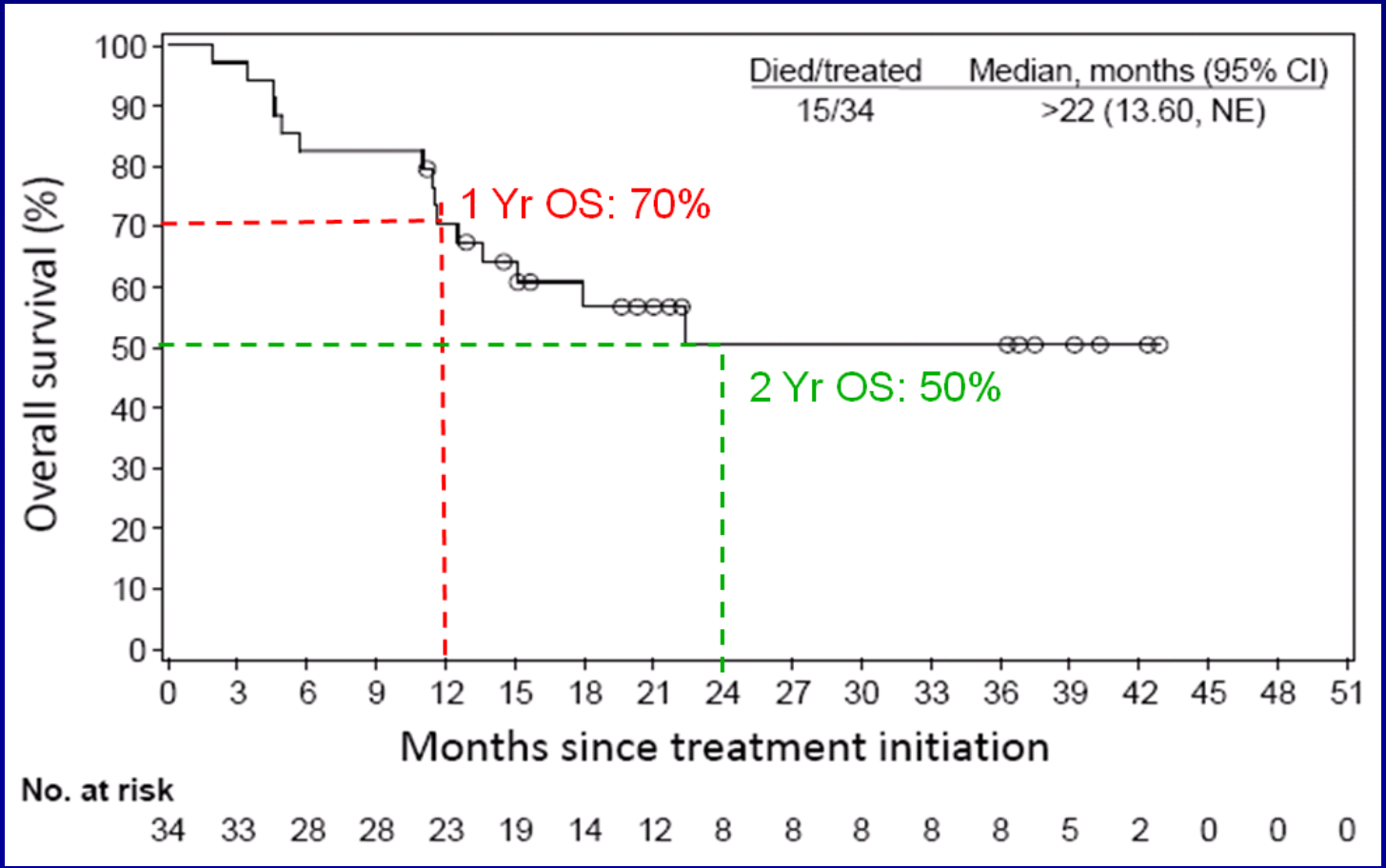


- 57-year-old patient had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib

Courtesy of C. Drake, Johns Hopkins Univ

Nivolumab in mRCC: Phase I Trial

- **44% of patients had ≥ 3 prior therapies**
- **Median OS not yet reached**



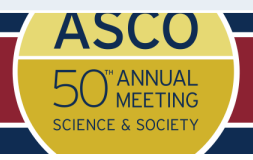
McDermott, Drake… Atkins et al J Clin Oncol 2015

ASCO 2014:Nivo RCC Update

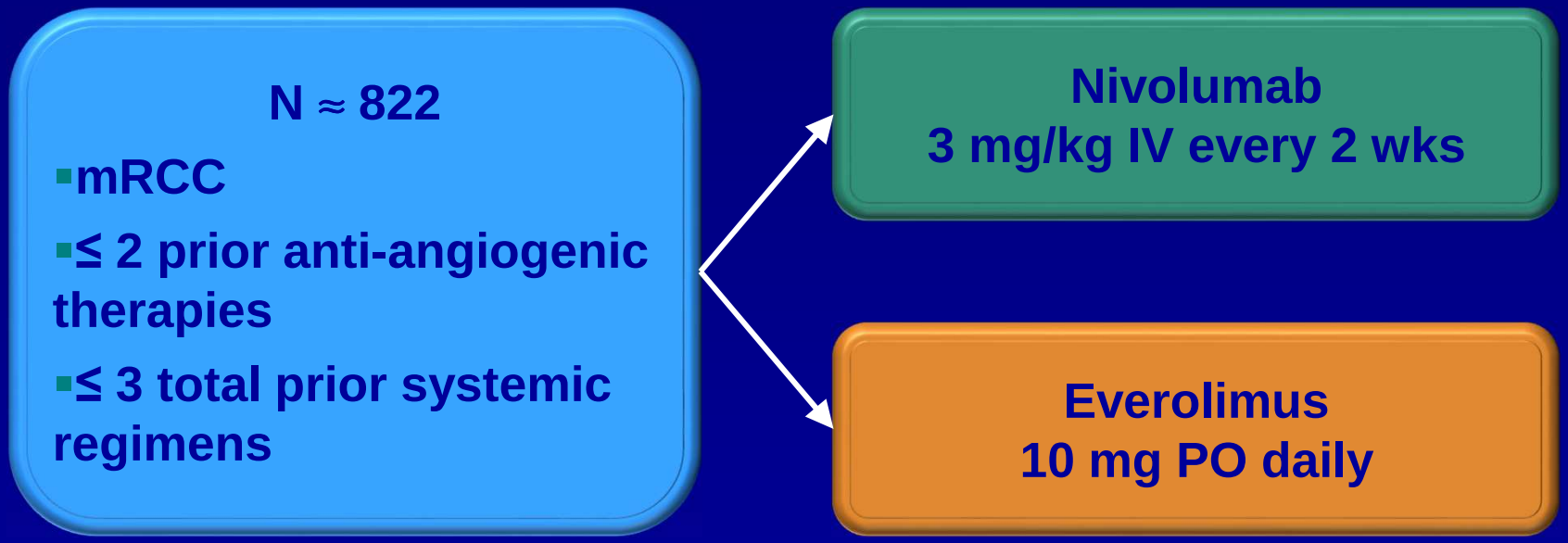
Single agent Nivolumab in mRCC

	# 5009 MOTZER			#5012 CHOUEIRI			
Design	Randomized, dose-ranging phase II (N=168)			Biomarker-based randomized clinical trial (N=91) *(Baseline and on-therapy fresh tumor biopsies)*			
Dose IV Q3W	0.3mg/kg n =60	2 mg/kg n=54	10 mg/kg n=54	0.3mg/kg n =22	2 mg/kg n=22	10 mg/kg n=23	10 mg/kg n=24 (naïve)
Prior Tx	70% ≥ 2 prior therapies No treatment-naïve pts			74% (1-3) prior therapies 24 (16%) treatment-naïve pts			
ORR (%)	20%	22%	20%	9%	23%	22%	13%
mPFS (m) *1º endpoint*	**2.7**	**4.0**	**4.2**	PFS at 24 weeks: 36%			
mOS (m)	18.2	25.5	24.7	Not Reported			
G3/4 TOX	5%	17%	13%	18%			
Biomarker	None reported			•Increased T-cell tumor infiltrates after nivolumab •Increased serum chemokines post-nivolumab •Numerically higher (22% vs. 8%) ORR in PD-L1 (+) pts			

PRESENTED AT:



Nivolumab Phase 3 Trial



Primary endpoint: OS

Secondary endpoints: PFS, ORR, OR duration, Safety

Accrual completed early 2014; Results likely imminent

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

MPDL3280A Phase 1a Efficacy Summary

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

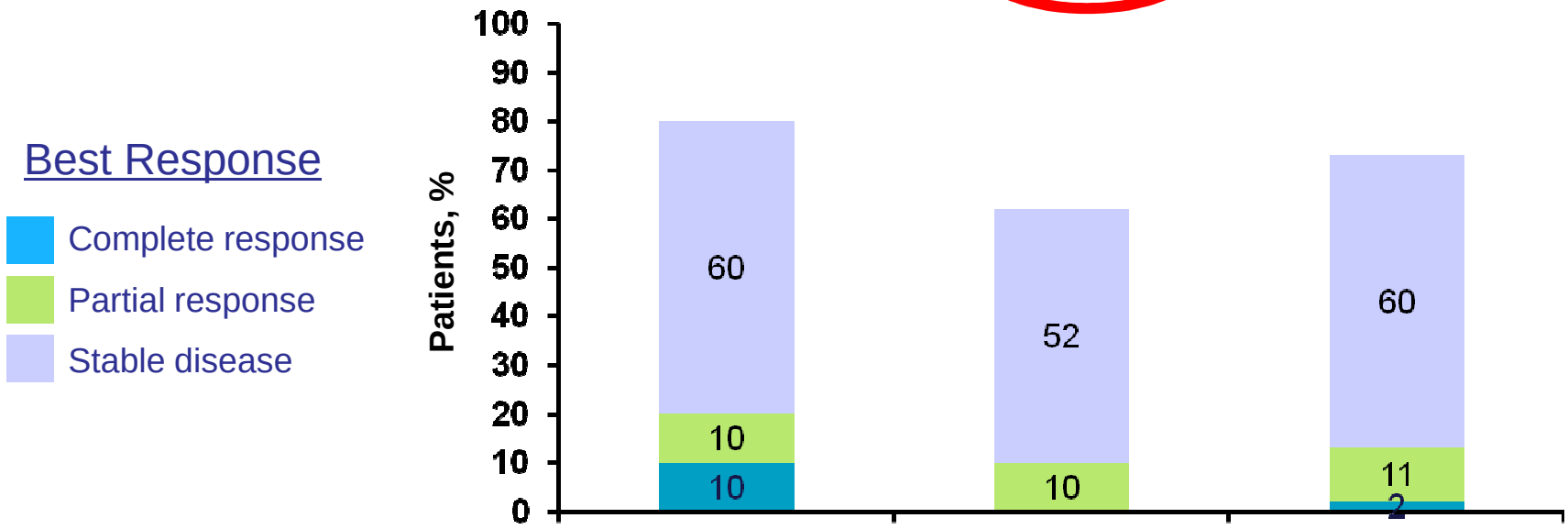
PD-L1 expression is a weak predictive biomarker

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

MPDL3280A Phase 1a in RCC: Summary of Response by PD-L1 IHC Status

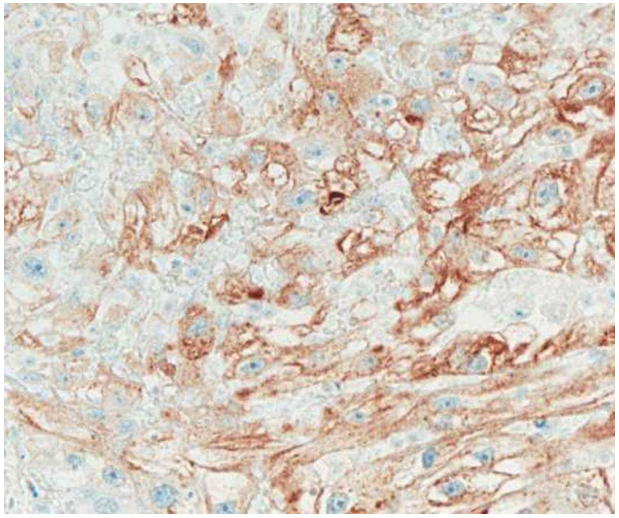
Investigator-Assessed Best Overall Response Rate (ORR*), % (n/n)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)
RCC (N = 47)	**20% (2/10)**	**10% (2/21)**	**13% (6/47)**



* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1.
† 16 patients with RCC were of unknown status.
Patients first dosed at 3-20 mg/kg prior to August 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

Cho et al, ASCO 2013

PD-L1 Expression is Lower in RCC



Positive PD-L1 staining in RCC (proprietary Genentech/Roche PD-L1 IHC)

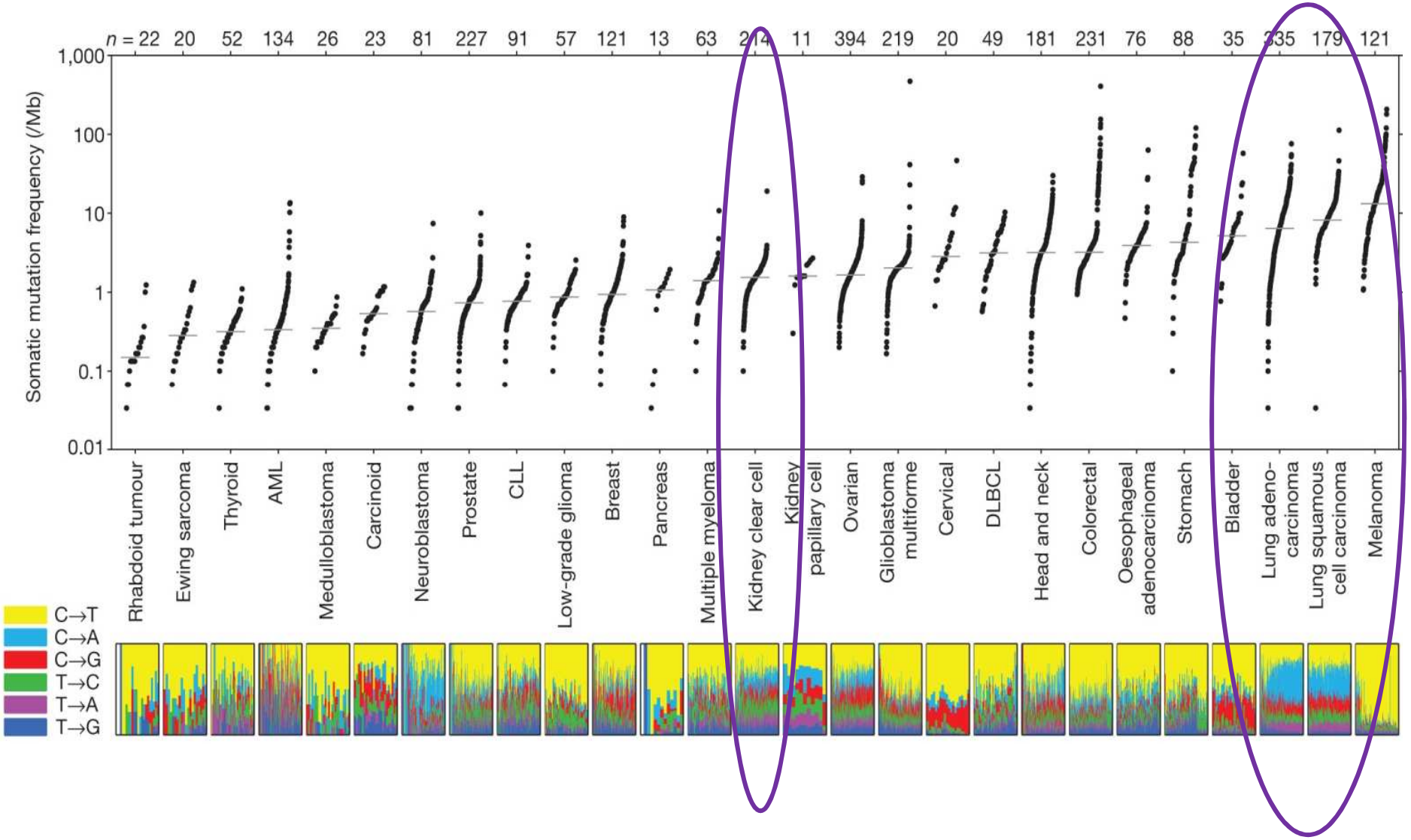
High sensitivity and specificity in FFPE samples

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 (Genentech data).
Thompson RH et al. *Cancer Res*. 2006;66(7):3381-3385.

Somatic mutations by tumor type



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

MPDL3280A: Impact of PD-L1 (IC) and Tumor Grade on Efficacy

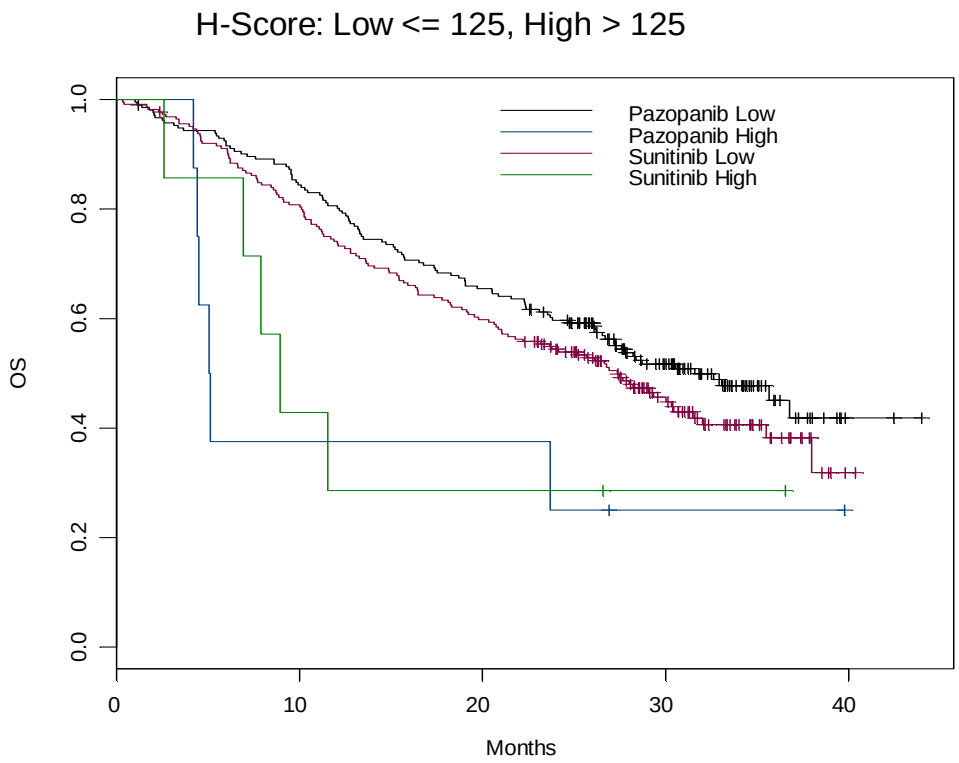
Efficacy-evaluable population with clear cell RCC

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)

- 24-week PFS rate was 51% (95% CI: 38-63)
- 1 CR (IHC [IC] 3)
- ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22% (95% CI: 8, 47)

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 is a negative prognostic marker of OS in RCC patients treated with VEGR TKI



Group (N)	Median OS months (95% CI)
Pazopanib Low (213)	31.6 (26.5, NR)
Pazopanib High (8)	5.1 (4.2, NR)
Sunitinib Low (225)	27.4 (21.4, 30.5)
Sunitinib High (7)	8.9 (2.6, NR)
P=0.017	

Front-line Trial Impact?

Choueiri et al Comparz Data ASCO 2013,

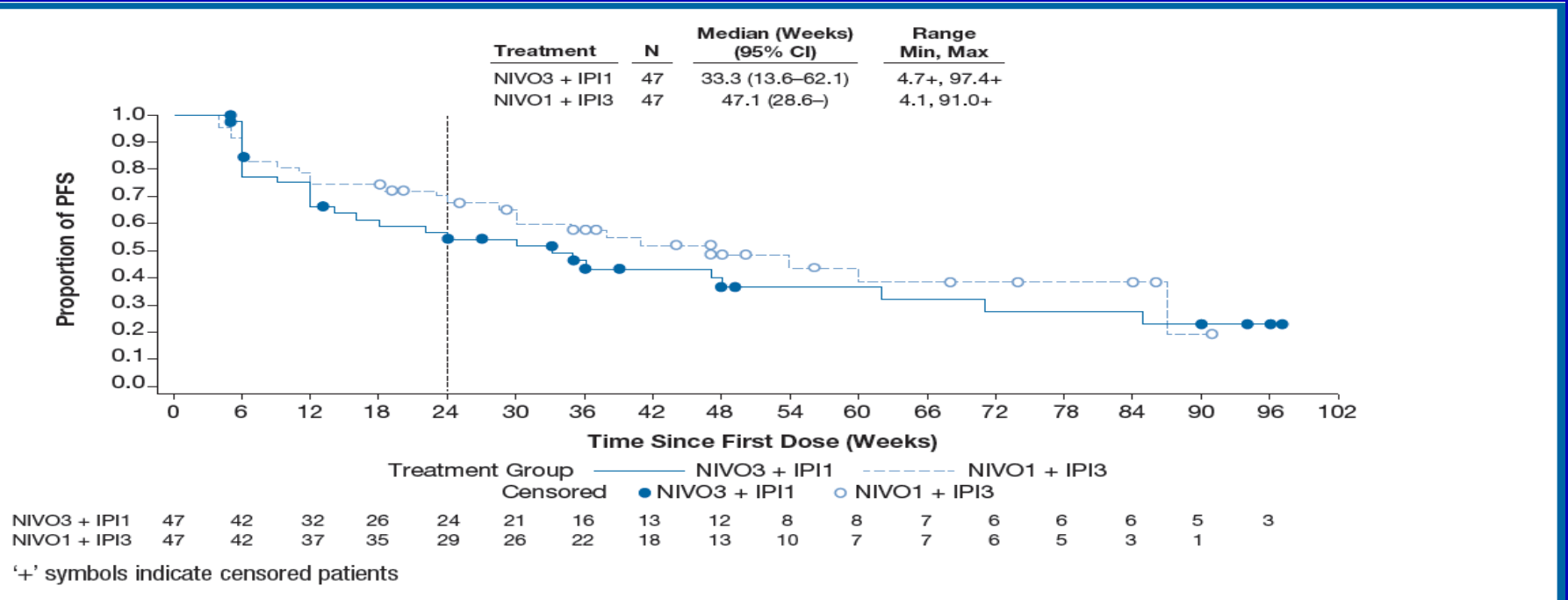
Anti-PD1/PDL1 Immunotherapy: Commentary

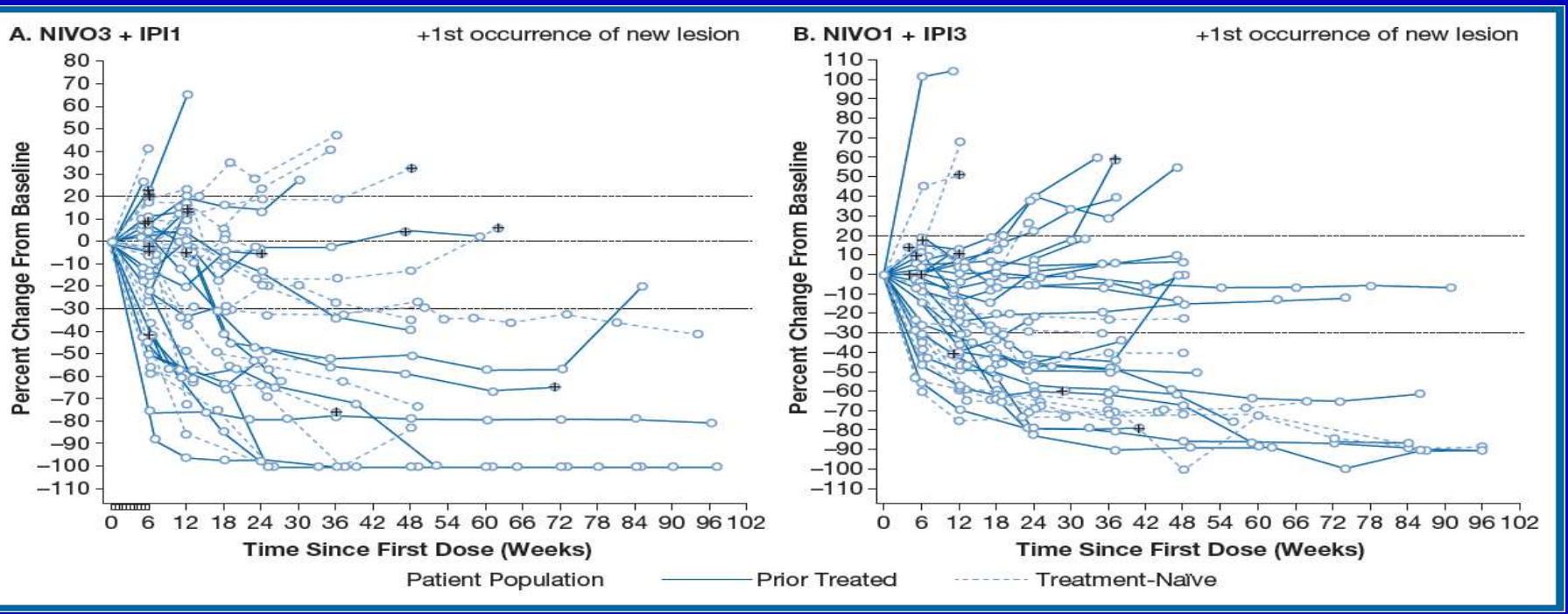
- PD1 blockade shows considerable activity in VEGFR TKI resistant RCC
  - OS data suggests the phase III trial of nivolumab vs everolimus will be positive
  - PFS does not appear sufficient to justify single agent trials vs TKI in treatment naïve patients
  - Will biomarkers enrich population enough for study?
- Tolerability supports their use as backbone in combination studies
  - These combinations might enable frontline testing

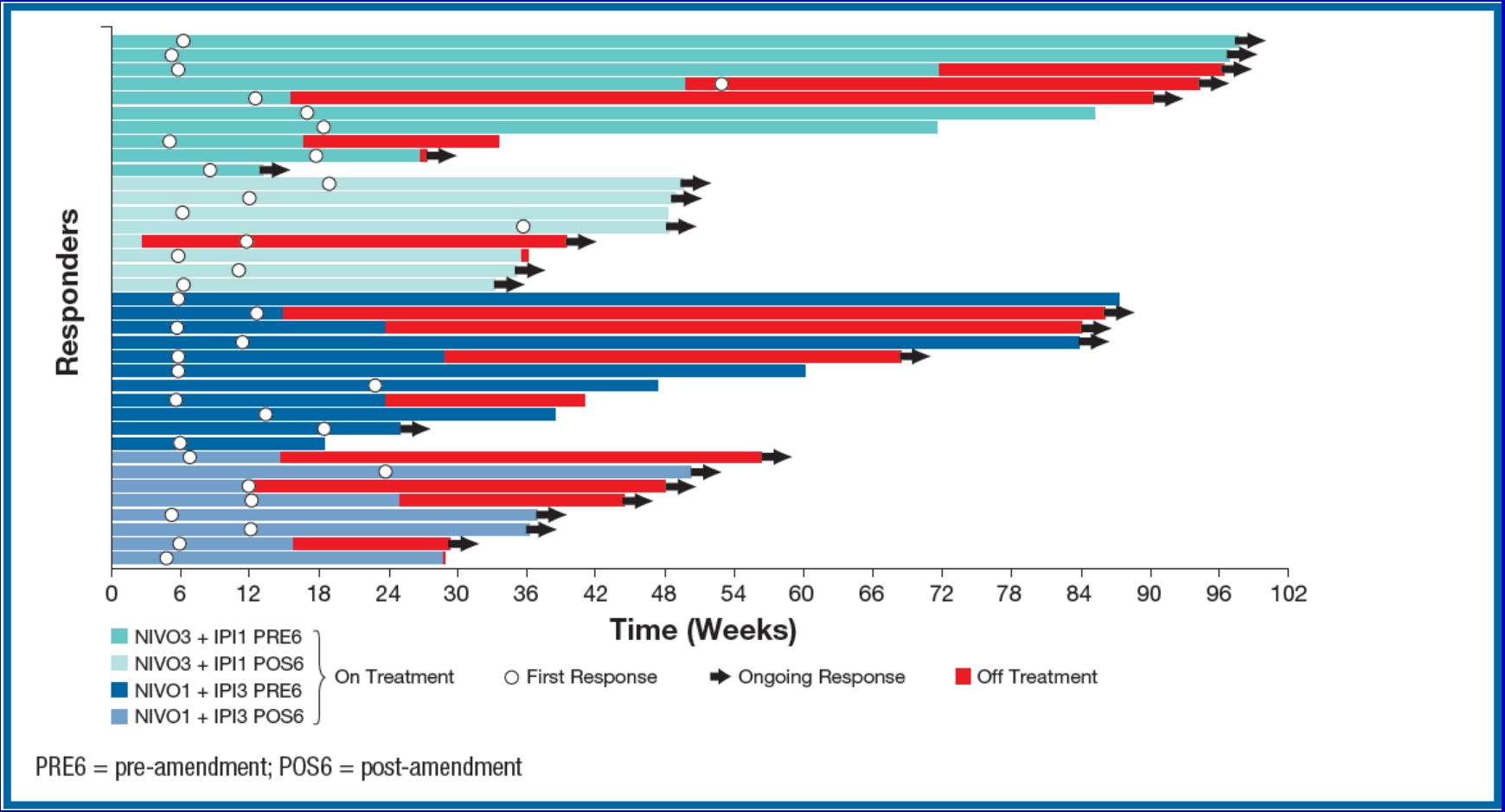
Nivo + IPI Antitumor activity in mRCC

	NIVO3 + IPI1	NIVO1 + IPI3	NIVO3 + IPI3
	N = 47	N =47	N = 6
Confirmed ORR[a], n (%) 95% CI	18 (**38.3**) 24.5–53.6	19 (**40.4**) 26.4–55.7	0
Best OR, n (%) Complete response Partial response Stable disease Progressive disease	 **4 (8.5)** 14 (29.8) 17 (36.2) 10 (21.3)	 1 (2.1) 18 (38.3) 17 (36.2) 7 (14.9)	 0 0 5 (83.3) 1 (16.7)

Hammers et al ASCO 2014/2015


Treatment | N | Median (Weeks) (95% CI) | Range Min, Max
NIVO3 + IPI1 | 47 | 33.3 (13.6–62.1) | 4.7+, 97.4+
NIVO1 + IPI3 | 47 | 47.1 (28.6–) | 4.1, 91.0+
Proportion of PFS
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102
Time Since First Dose (Weeks)
Treatment Group NIVO3 + IPI1 NIVO1 + IPI3
Censored NIVO3 + IPI1 NIVO1 + IPI3
NIVO3 + IPI1 47 42 32 26 24 21 16 13 12 8 8 7 6 6 6 5 3
NIVO1 + IPI3 47 42 37 35 29 26 22 18 13 10 7 7 6 5 3 1
'+' symbols indicate censored patients


A. NIVO3 + IPI1
+1st occurrence of new lesion
Percent Change From Baseline
80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102
Time Since First Dose (Weeks)
B. NIVO1 + IPI3
+1st occurrence of new lesion
Percent Change From Baseline
110 100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102
Time Since First Dose (Weeks)
Patient Population Prior Treated Treatment-Naïve

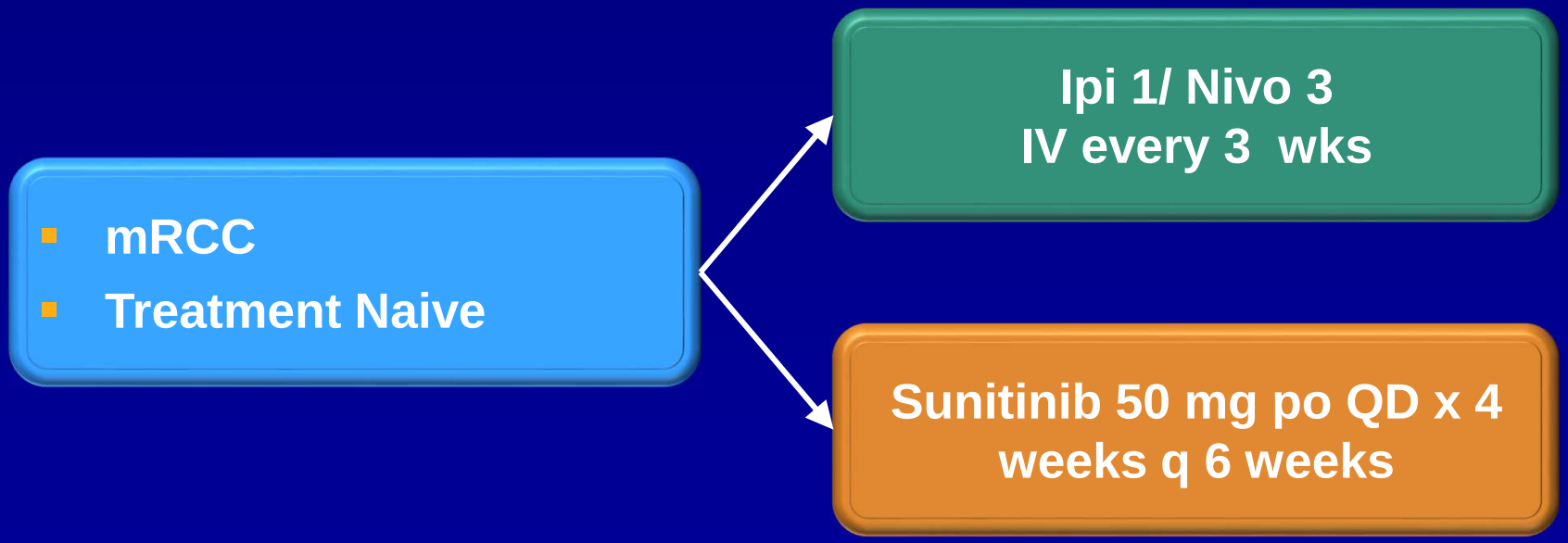


- Of those who responded, 72.2% (13/18) of pts in the nivolumab 3 + ipilimumab 1 arm and 63.2% (12/19) of pts in the nivolumab 1 + ipilimumab 3 arm had ongoing responses
- Median DOR was 67.7 weeks (range 4.1+ to 91.1+) in the nivolumab 3 + ipilimumab 1 arm and 81.1 weeks (range 6.1+ to 81.1+) in the nivolumab 1 + ipilimumab 3 arm

Treatment-related AEs[a] (≥20% of patients)

	NIVO3 + IPI1		NIVO1 + IPI3	
	N = 47		N = 47	
Preferred term, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Total patients with an event	**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
Increased amylase	**2 (4.3)**	**2 (4.3)**	**8 (17.0)**	**4 (8.5)**
Increased lipase	**8 (17.0)**	**6 (12.8)**	**16 (34.0)**	**12 (25.5)**
Myalgia	7 (14.9)	0	9 (19.1)	1 (2.1)
Headache	6 (12.8)	0	9 (19.1)	1 (2.1)
Increased alanine aminotransferase (ALT)	**6 (12.8)**	**2 (4.3)**	**13 (27.7)**	**9 (19.1)**
Increased aspartate aminotransferase (AST)	**5 (10.6)**	**2 (4.3)**	**13 (27.7)**	**4 (8.5)**
Decreased appetite	5 (10.6)	0	14 (29.8)	0
Increased blood creatinine	4 (8.5)	0	6 (12.8)	0
Dyspnea	4 (8.5)	0	4 (8.5)	0
Hyperthyroidism	3 (6.4)	1 (2.1)	8 (17.0)	0

Nivolumab Front Line Phase 3 Trial



Began accrual late 2014

VEGF Targeted Therapy + Immunotherapy

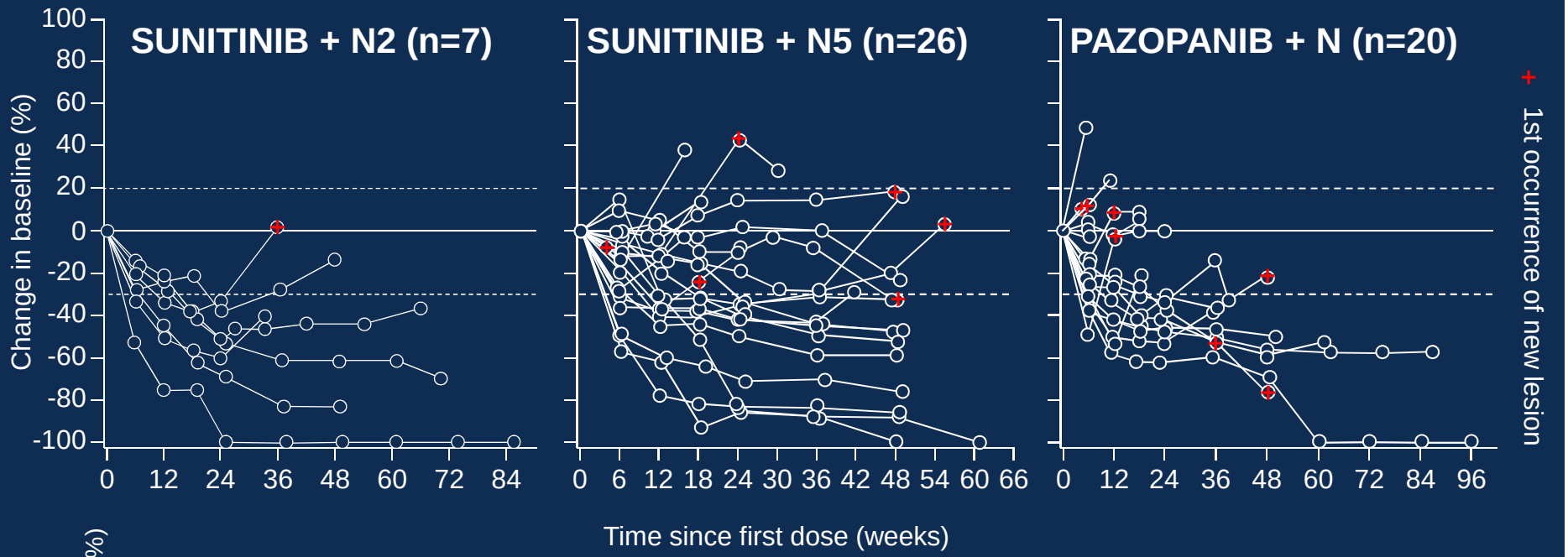
- Bevacizumab + IFN
  - Two randomized phase 3 trials prove superior PFS - FDA approval
  - Additive but not synergistic toxicity
  - Confirmed in Phase II trial by Escudier et al.
- Sunitinib + IFN: excessive toxicity
- Bevacizumab + high-dose IL2
  - Additive activity, no more CRS

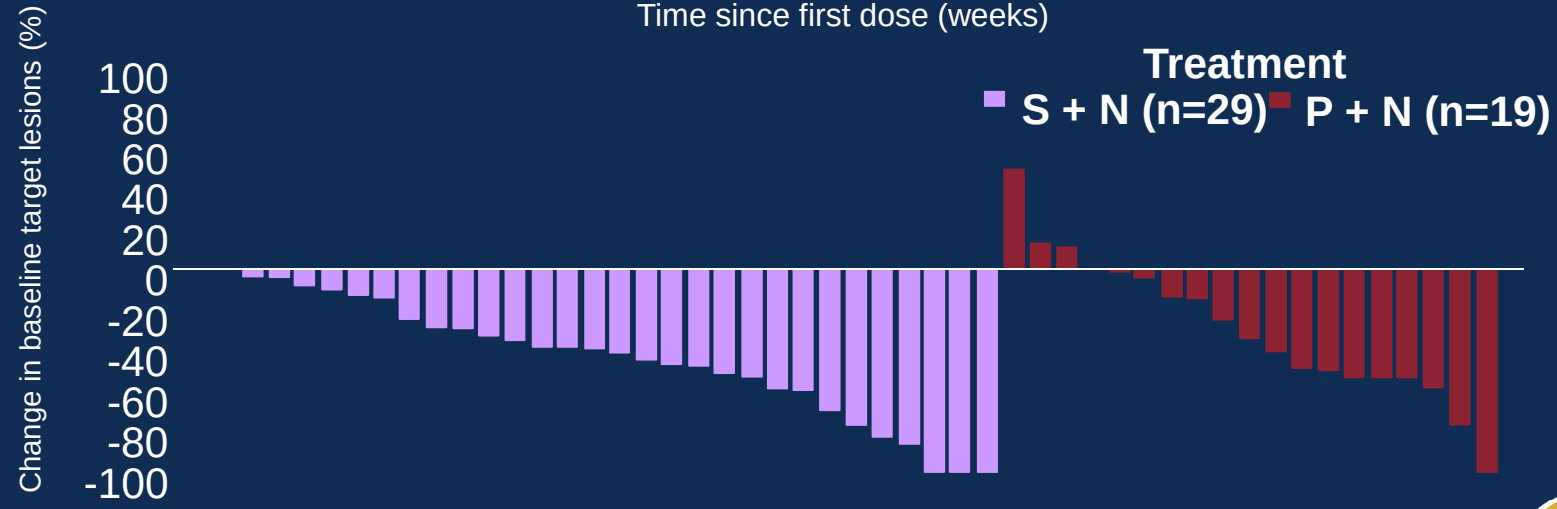
Phase I Nivolumab-+ VEGFR TKI combination studies

#5010
AMIN (Nivo+VEGF TKI)

	Arm S **Sunitinib** 50 mg (4/2) + nivolumab 2mg/kg Q3W (**N2**) or 5mg/kg Q3W (**N5**)	**Arm P** **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%)

Amin #5010 | New combination studies in mRCC : VEGFR-TKI + Nivolumab





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ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

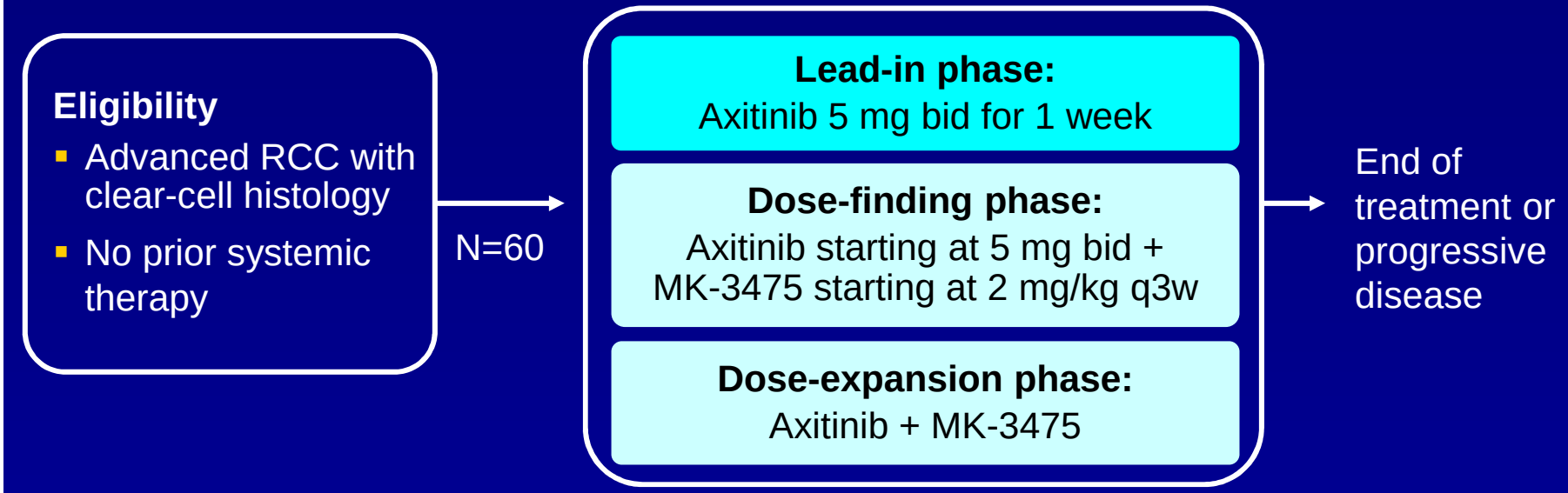
Combination anti-VEGF and anti-PD1 therapy: Commentary

- Anti-tumor activity appears to be additive
- Toxicity appears to be synergistic, but may relate to off target effects of TKIs

Can a more selective VEGF pathway inhibitor improve combination tolerability?

- Axitinib
- Bevacizumab

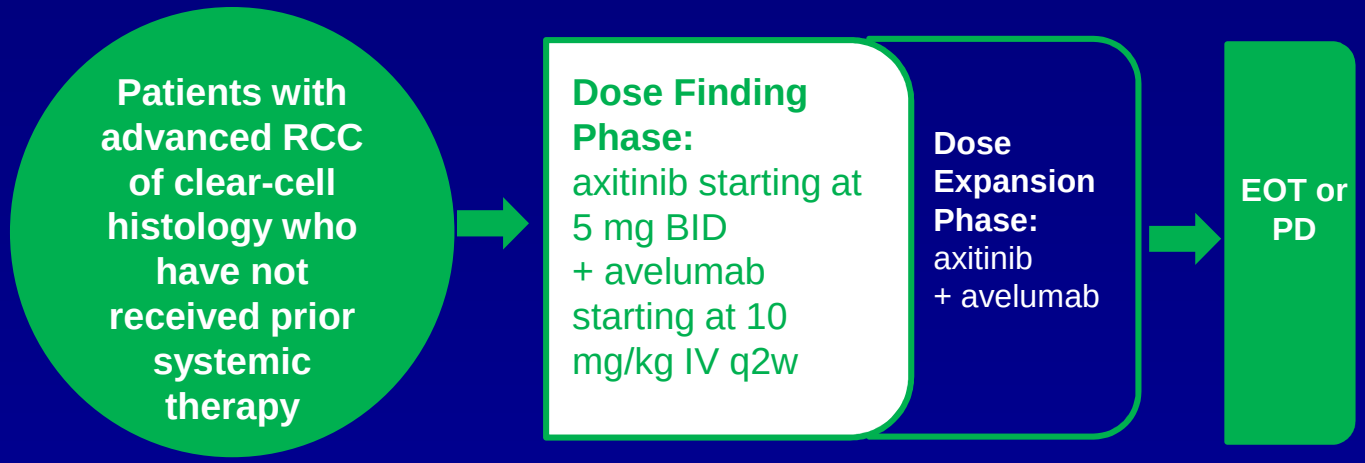
Axitinib Plus Pembrolizumab (MK-3475)



- **Primary endpoint: Safety, maximum tolerated dose (dose-limiting toxicities through Week 6 of dose-finding phase, 2 cycles)**
- **Select secondary endpoints: ORR, TTP, PFS (median, 1 year, 18 months), OS, biomarkers including PD-L1**
- **Sponsor: Pfizer (collaborator: Merck)**
- **Estimated primary/study completion date: April 2016**

PI: Atkins et al

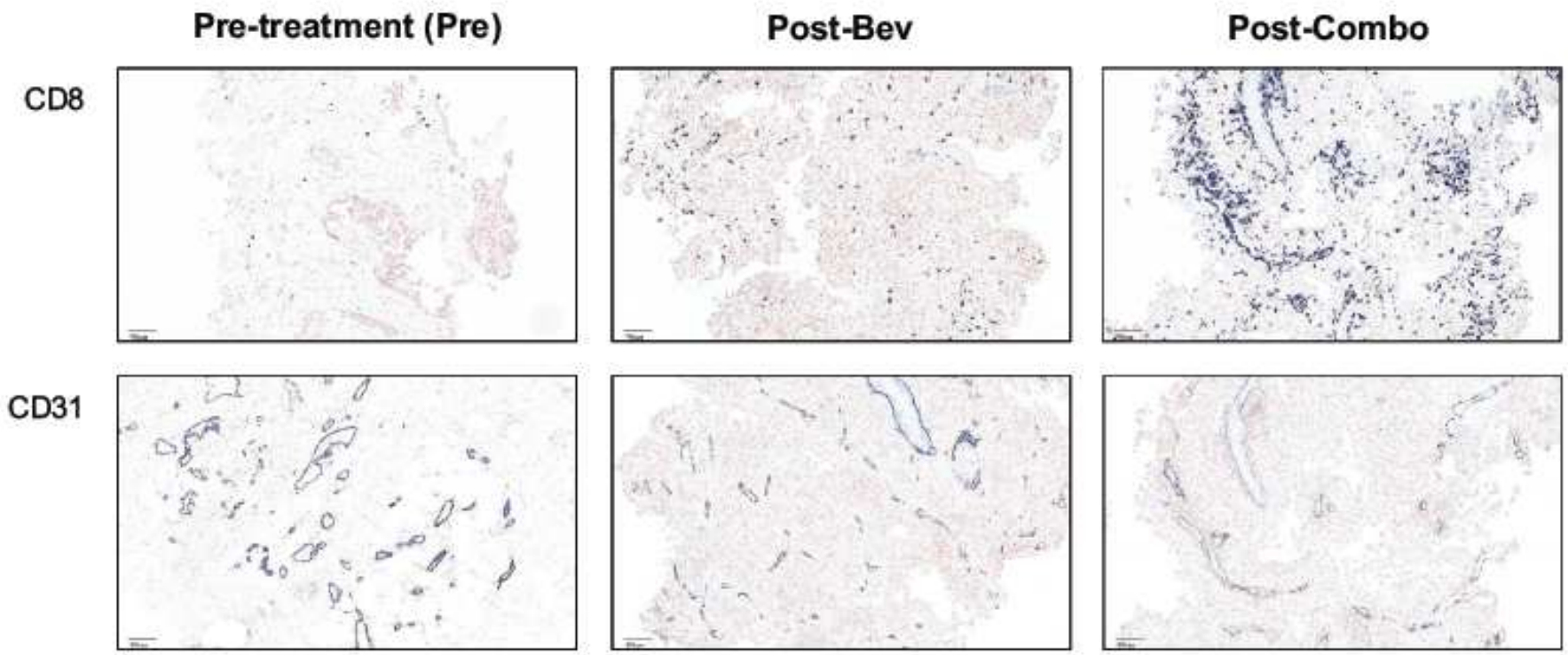
Avelumab in combination with axitinib



- **Dose Finding Phase:** All pts will have Lead-In Period (7 days, only axitinib administration) prior to Cycle 1 (before avelumab in combination with axitinib) Three potential dose levels will be evaluated.

- **Dose Expansion Phase:** At least 8 pts will have Lead-In Period (7 days, only axitinib administration) prior to Cycle 1 (before avelumab in combination with axitinib)

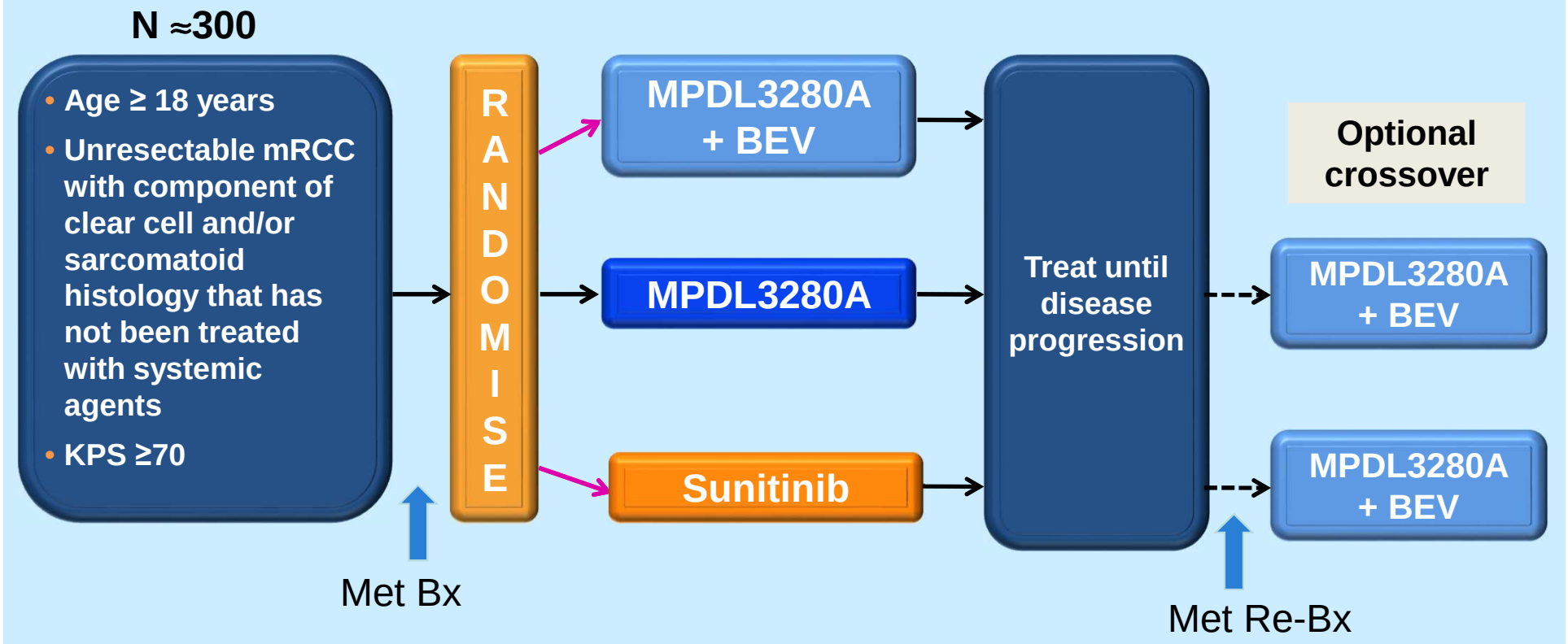
CD8 T cell prevalence in a patient with RCC following Bev and Bev + MPDL3280A



Increases in CD8+ cell infiltration and decreases in CD31 expression were seen after Bev + MPDL3280A treatment

Sznol et al GU ASCO 2015

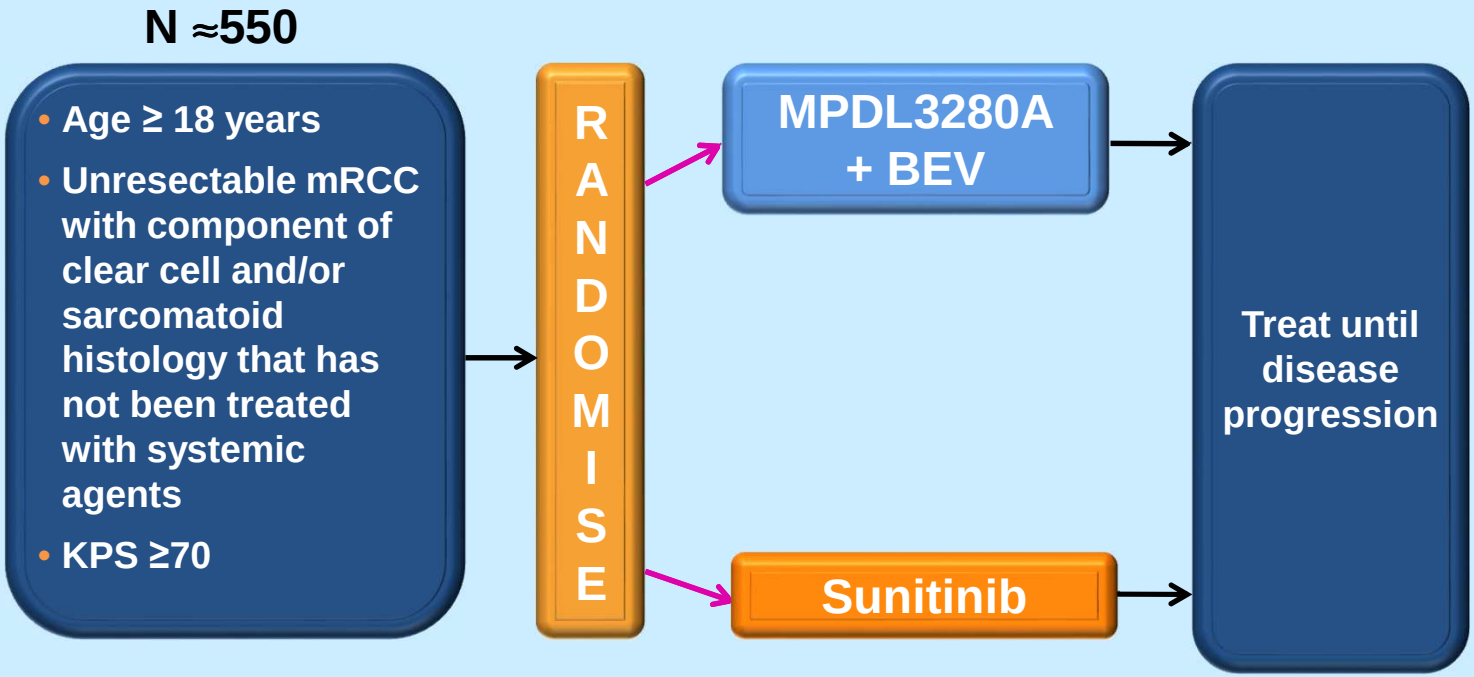
MPDL3280A: Randomized Phase II Study



Primary endpoint: PFS (central)

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

MPDL3280A: Randomized Phase III Study



Primary endpoint: PFS (central)

Secondary endpoints: OS, RR

RCC Landscape: 2020

Assumes: Phase III Trials of ipi/Nivo vs sunitinib and MPDL3280 + Bev vs sunitinb are positive

RCC Landscape: 2020

Assumes: Phase III Trials of ipi/Nivo vs sunitinib and MPDL3280 + Bev vs sunitinb are positive

- Both will become first line therapies
  - Ipi/Nivo for academic medical centers and those who can tolerate toxicity
  - MPDL3280A + bev for community oncologists and frailer patients

- Axitinib +/- “X” (dalantercept, etc) will be 2nd line therapy

- Reduced role for sunitinib, pazopanib and HD IL-2

- Future advances will come from improved immunotherapy combinations

Immunotherapy Combinations: RCC

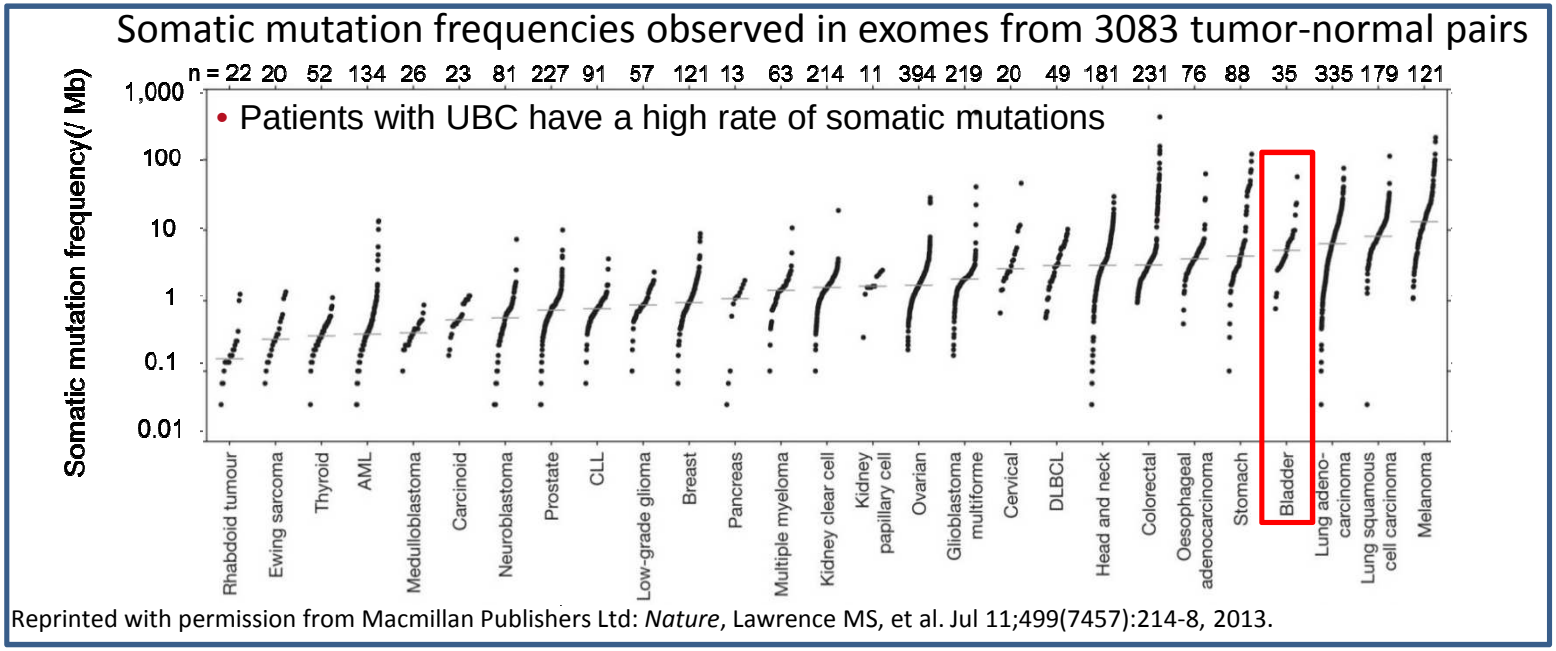
- **Immunoregulatory blockers**
  - **LAG-3, TIM-3, IDO, CCR4, CXCR4 etc**
- **Immunostimulatory molecules**
  - **Modified IL-2, IL-15, 41BB, OX40, CD27, GITR, etc**
- **Other**
  - **RT, vaccines, etc**

PD1 Therapy of RCC: Key Translational Research Questions

- Is combination VEGF and PD1-based blockade better than use of approaches in sequence? What sequence?
  - Does giving an immune therapy work optimally at the time of anti-VEGF induced tumor hypoxia?

- Biomarkers/Immunotherapy Combinations
  - Can a better biomarker for immunotherapy response be developed?
  - What is the mechanism of resistance to PD1- based blockade?
  - Can these be used to design better upfront immunotherapy combinations? Target these to specific patients?

Metastatic UBC



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- High unmet need with no FDA-approved therapies for relapse after platinum chemo
  - Vinflunine approved in EU with no significant OS benefit in ITT population
- Median OS ≈ 7 months, PFS ≈ 3 months for 2L UBC[1]
- Patients tend to be elderly with impaired renal function
- High mutational complexity rates similar to tobacco/environmental carcinogen exposure[2-4]
- Potential for many neo-antigens to be seen as foreign by host immune system[2-4]

1. Bellmunt. *Ann Oncol.* 2013; 2. TCGA. *Nature.* 2014; 3. Lawrence. *Nature.* 2013; 4. Kandoth. *Nature.* 2013.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint (UBC)

Target	Antibody	Molecule	Company	Development stage (RCC)
PD-1	Nivolumab	Fully human IgG4	Bristol-Myers Squibb	Phase III
	Pidilizumab	Humanized IgG1	CureTech (Medivation)	Phase I-II
	Pembrolizumab	Humanized IgG4	Merck	Phase I-II
PD-L1	BMS-936559	Fully human IgG4	Bristol-Myers Squibb	Phase I
	MedI-4736 (Durvalumab)	Engineered human IgG1	MedImmune	Phase I
	MPDL-3280A (Atezolizumab)	Engineered human IgG1	Genentech	Phase II-III
	MSB0010718C (Avelumab)		EMD Serono (Pfizer)	Phase I

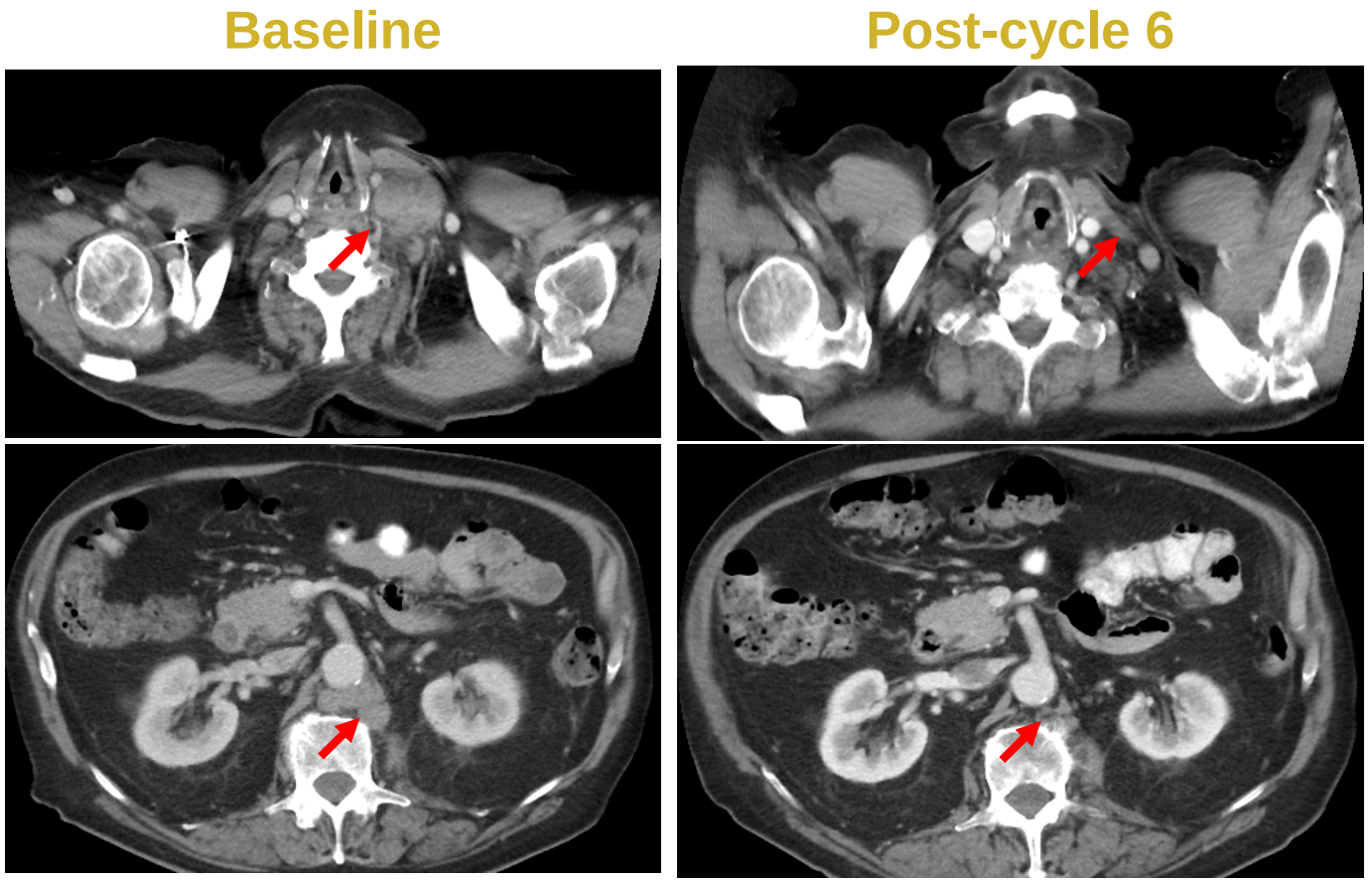
Atezolizumab (MPDL3280A): ORR in UBC by IC Status

PD-L1 IHC n = 87[b]	ORR (95% CI), %[a]		CR, n (%)		PR, n (%)	
IC3 (n = 12)	**67%** (35%-90%)	**50%** (35, 65)	4 (33%)	9 (20%)	4 (33%)	14 (30%)
IC2 (n = 34)	**44%** (27%-62%)		5 (15%)		10 (29%)	
IC1 (n = 26)	19% (7%-39%)	17% (7, 32)	-	-	5 (19%)	7 (17%)
IC0 (n = 15)	13% (2%-40%)		-		2 (13%)	

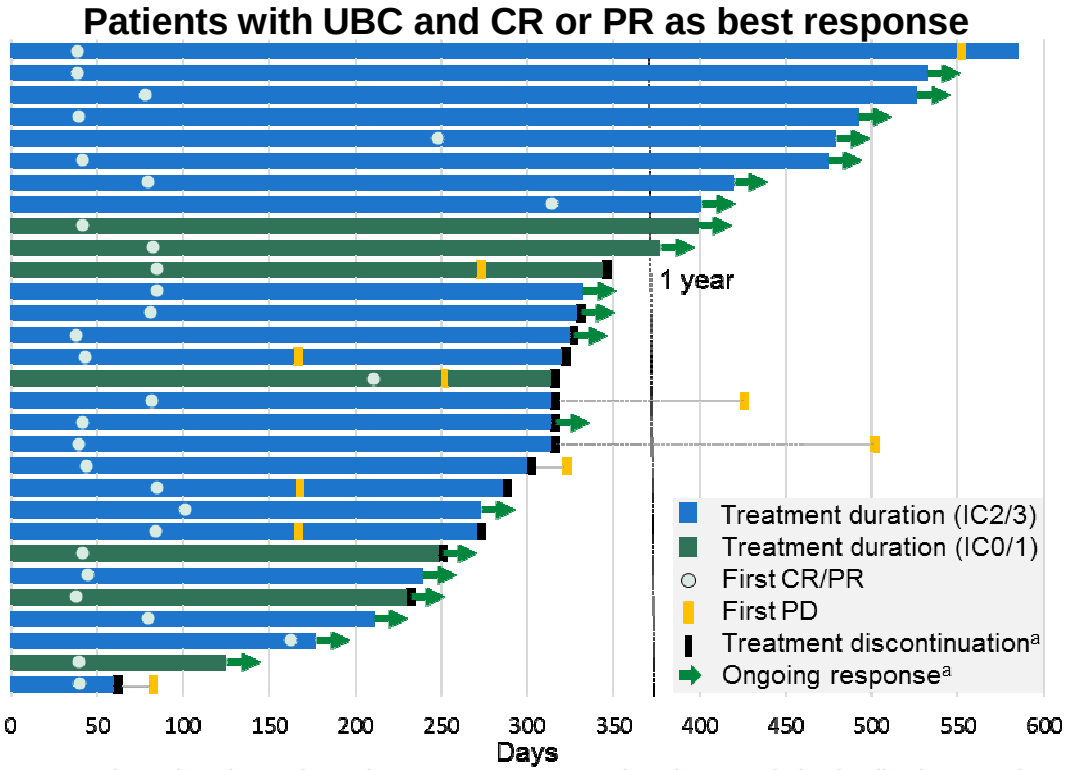
- Responses were observed all PD-L1 subgroups, with higher ORRs associated with higher PD-L1 expression in IC
- Responders also included patients with visceral metastases at baseline: 38% ORR (95% CI, 21%-56%) in 32 IC2/3 patients and 14% (95% CI, 5%-30%) ORR in 36 IC0/1 patients

[a] Efficacy-evaluable patients with measurable disease at baseline per RECIST v1.1. Responses are investigator assessed (unconfirmed); of 30 unconfirmed responses, 24 have been confirmed by the cutoff date. [b] 4 IC2/3 patients and 7 IC0/1 patients missing or unevaluable. Data cutoff, Dec 2, 2014.

MPDL3280A: Response in Patient with UBC



Atezolizumab (MPDL3280A): Duration of Treatment and Response in UBC

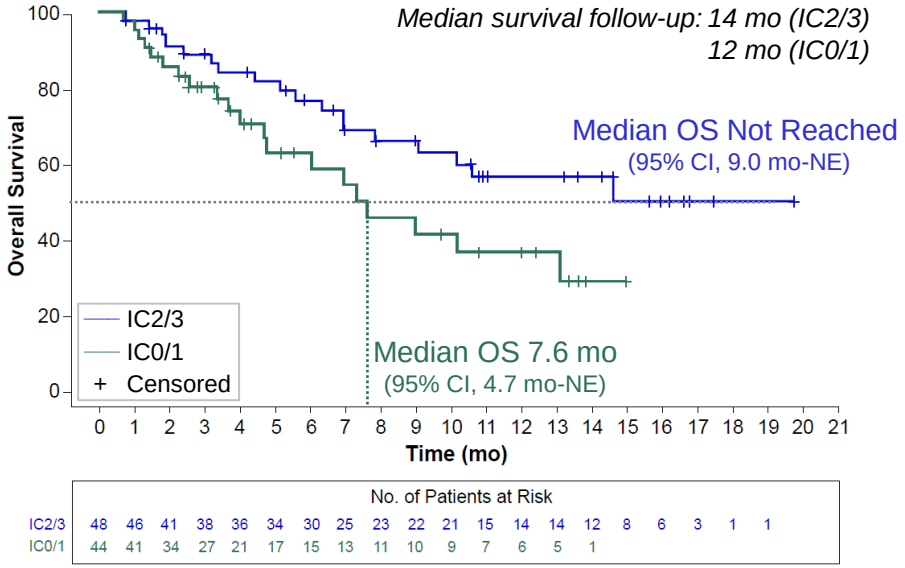


- Median duration of response has not yet been reached in either IC group (range, 0+ to 43 mo)
- Median time to response was 62 days
  - IC2/3 patients: range, 1+ to 10+ mo
  - IC0/1 patients: range, 1+ to 7+ mo
- 20 of 30 responding patients had ongoing responses at the time of data cutoff
- 10 patients have been treated for over 1 year, including 3 retreated following protocol amendment

[a] Discontinuation and ongoing response status markers have no timing implication. 4 patients discontinued treatment after cycle 16 prior to 1 year per original protocol. Responses plotted are investigator assessed and have not all been confirmed by the data cutoff (Dec 2, 2014).

Atezolizumab (MPDL3280A): Survival in UBC

Survival[a] N = 92	IC2/3 n = 48	IC0/1 n = 44
PFS		
Median PFS (range)	6 mo (0+ to 18)	1 mo (0+ to 14+)
1-y PFS (95% CI)	39% (24-54)	10% (0-21)
OS		
Median OS (range)	Not reached (1 to 20+ mo)	8 mo (1 to 15+ mo)
1-y survival (95% CI)	57% (41-73)	38% (19-56)

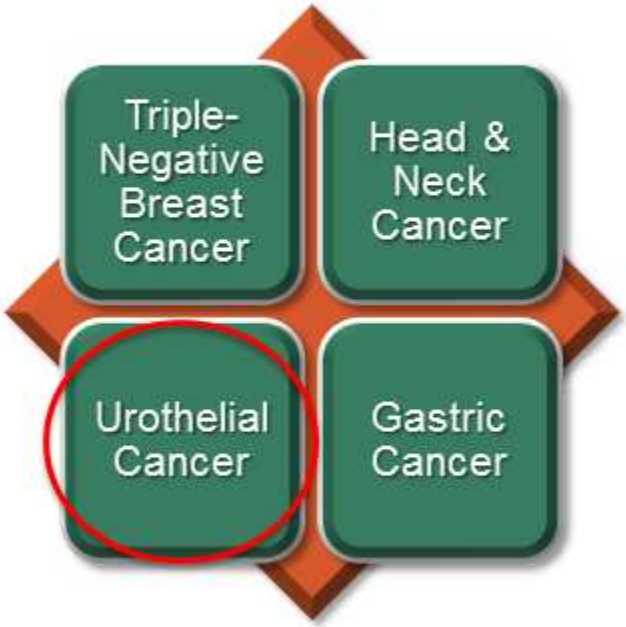


- PD-L1 IC status appeared to be predictive of benefit from atezolizumab treatment
  - mPFS and 1-year PFS rates were higher in atezolizumab-treated patients with higher PD-L1 IC expression
  - The same association was observed for 1-year OS rates, and mOS for IC2/3 patients was not yet reached
- Preliminary analysis using SP142 from an independent sample set (n = 110) suggests that PD-L1 IC status is not *prognostic* for OS in UBC[1]

Data cutoff, Dec 2, 2014. **Reference: 1.** Genentech, unpublished data.

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.

Antitumor Activity

	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.

Exploratory Predictive Value of PD-L1 Scoring

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

PD1 Pathway Blockade in UBC

- Atezolizumab- Phase II and III 2nd line studies ongoing [IMvigor 210-211]; Phase II data expected later this year

- KEYNOTE 45: Phase III trial of Pembro vs IC (paclitaxel, docetaxel or vinflunine) in chemoRx failures
- Nivolumab 2nd line trial single arm trial - PDL1+ cohort assignment (+, -, indeterminate)

Take Home Message

- PCA: Sipuluecel T limited uptake. Future rests with combination with checkpoint inhibitors
- RCC
  - Nivolumab likely to be approved in second line
  - Combinations (ipi, selective VEGF blocker, other) likely necessary for first line use
- UBC
  - Pembro and Atezo with promising activity in CDDP treated disease.
  - Phase II and III trials are ongoing in second line
  - earlier disease studies contemplated