Immunotherapy for Metastatic Renal Cell Carcinoma

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- I currently have or have the following relevant financial relationships to disclose:
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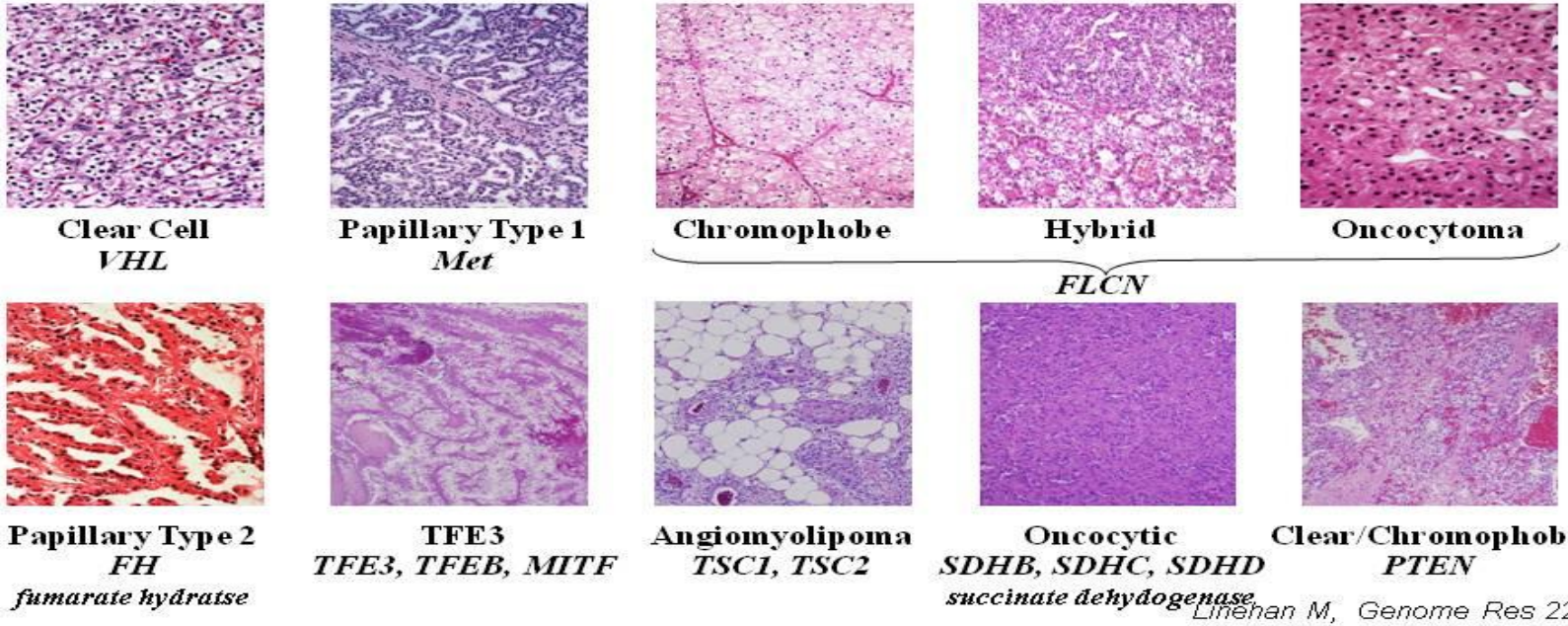
- I **do intend** to discuss off-label uses of products during this activity.

Kidney Cancer is Not a Single Disease



Linehan M, Genome Res 22: 2012

Presented By Cora Sternberg at 2015 ASCO Annual Meeting

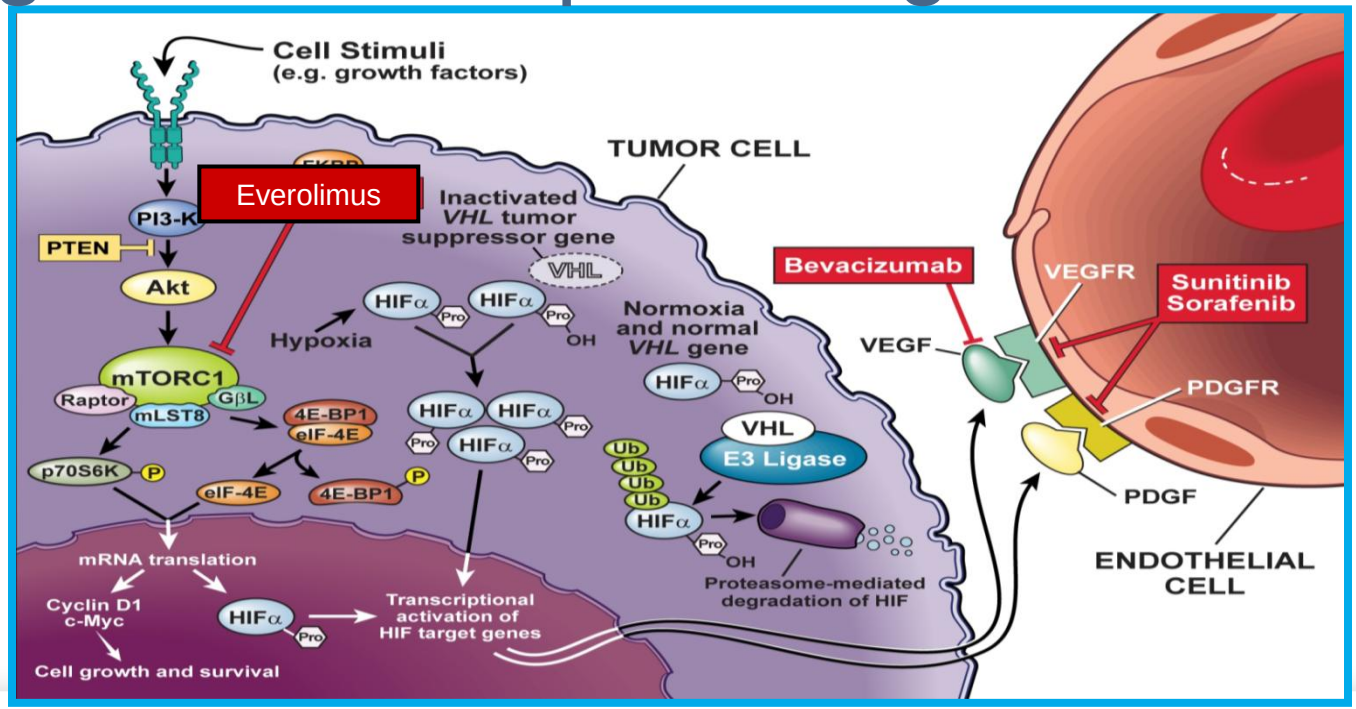
Case presentation

- **58 year old Caucasian female developed anemia in November 2011.**
- **Evaluation with CT revealed a 9.5 cm right renal mass**
- **Resection confirmed Fuhrman Grade 4 clear cell renal cell carcinoma staining positive for CA-IX**
- **No adjuvant therapy delivered**

Case Presentation (Continued)

- She returned in Nov 2013 with 20 lb wt loss (unintentional and left sided chest discomfort)
- CT imaging was obtained revealing pleural involvement by extensive tumor and several pulmonary nodules
- Her PMHx was unremarkable except for the prior anemia and an asymptomatic pulmonary embolism during her nephrectomy
- Her Physical examination was remarkable for decreased breath sounds in the left lung/KPS was 80.
- Laboratories revealed a normal LDH and calcium
- Options for therapy-?

Biological Pathways in RCC and Targets of Therapeutic Agents



Metastatic RCC: Treatment Results Prior to the Targeted Therapy Era

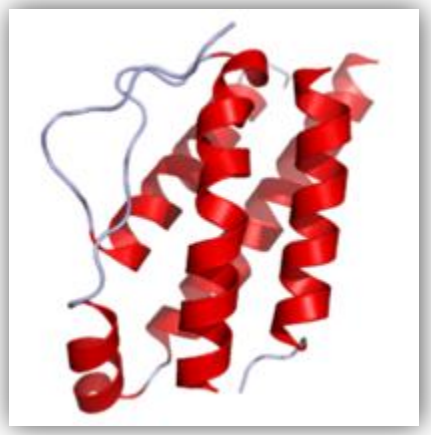
Therapy	Trials (N)	Patients (N)	ORR (%)	Survival Median (Months)
Observation	7	1139	0.3	6
Hormonal	68	754	6-10	6
Chemotherapy	83	4093	5-10	< 9
INF* INF + Nephrectomy	1	123 123		8.1 12.5
INF INF + Nephrectomy	1	42 41	12 20	7 17

*Off label

Yagoda et al. *Semin Oncol* 1993; Amato RJ. *Semin Oncol* 2000; Flanigan, *NEJM* 2001; Mickisch, *Lancet* 2001.

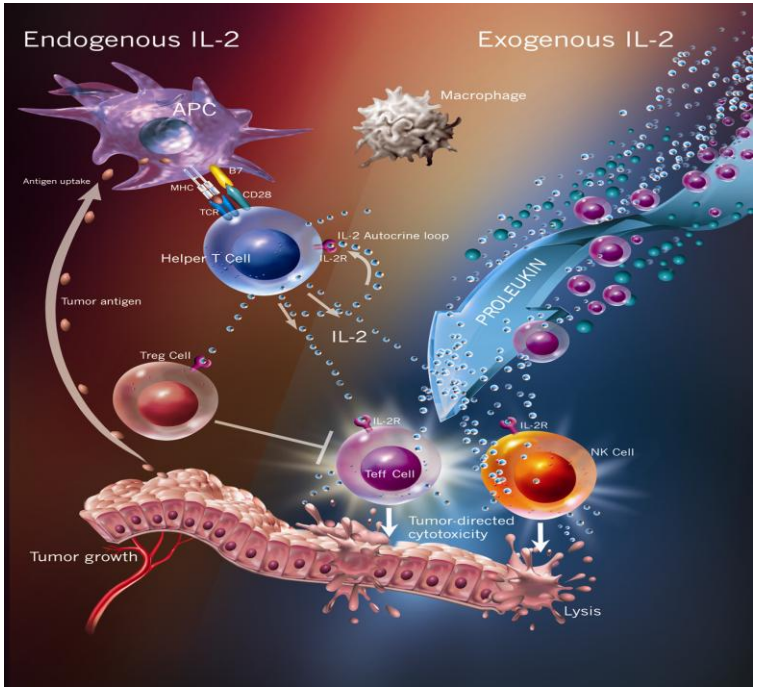
Interleukin-2 : Background

- Discovered in 1976 and described as a protein that stimulates growth of T cells.[1]
- Recombinant (r) IL-2 first cloned in 1983.[1]
- First given to cancer patients in 1983.[2]
- First phase I studies of rIL-2 in malignant disease in 1984.[4]
- Jurkat cell line-derived IL-2 first used to treat cancer patients in 1985.[3]
- Phase II clinical trials began in 1985.[1]
- FDA approval in 1992.



1. Atkins MB, et al. *J Clin Oncol* 1999; 17:2105-2116.
2. Bindon C, et al. *Br J Cancer* 1983; 47:123-133.
3. Lotze MT, et al. *J Immunol* 1985; 134:157-166.
4. Atkins MB, et al. *J Clin Oncol* 1986; 4:1380-1391.

Interleukin-2: Immunologic Background



Abbas AK and Lichtman AH. *Cellular and Molecular*

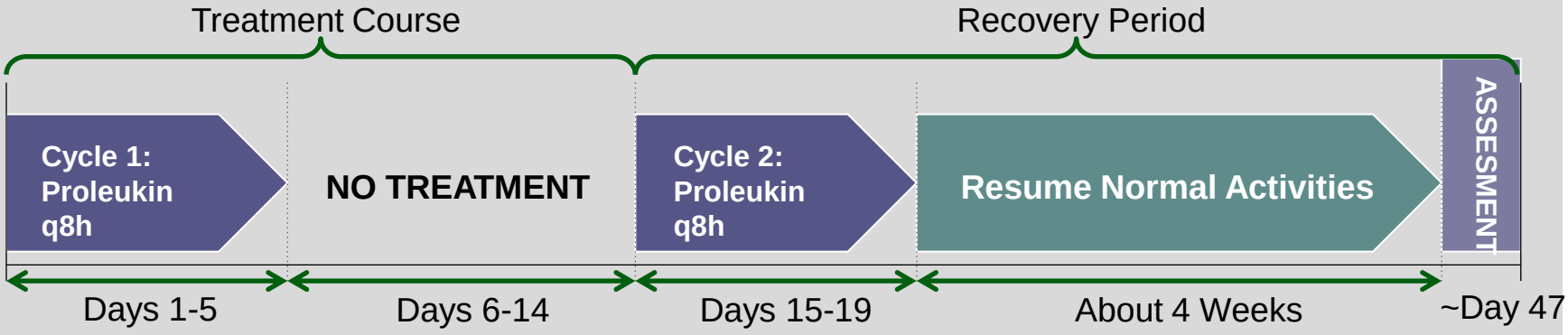
- **Natural biologic immunomodulatory agent**
- **Autocrine T-cell growth factor**
  - **Produced exclusively by activated T cells**
  - **Predominantly CD-4+ (T-helper) lymphocytes**
- **Immunomodulatory actions:**
  - **Proliferation and activation of T cells**
  - **Immune response amplification**
  - **Enhanced antibody production by B cells**
  - **NK cell expansion and activation**
- **Stimulates T-cell secretion**
  - **Tumor necrosis factor (TNF)**
  - **Other cytokines (ie, IL-4, interferon-gamma)**
- **Stimulates proliferation and activation of:**
  - **All T cells, including cytotoxic T lymphocytes (CTLs) but also Regulatory T cell (Tregs)**
  - **Natural killer and Lymphokine-activated Killer (LAK) cells**

Schedule for HD-Interleukin-2 Therapy

High-dose IL-2 (HD IL-2) has the potential to induce durable complete responses in a small number of patients

- 600,000 IU/kg (0.037 mg/kg) delivered by 15-min bolus i.v. infusion q8h for 14 doses
- 720,000 IU/kg delivered by 15-min bolus i. v. infusion q8h for 12 doses

Typical Proleukin® Treatment Schedule



- Additional courses of treatment are given if there is some shrinkage following the last course.
- Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

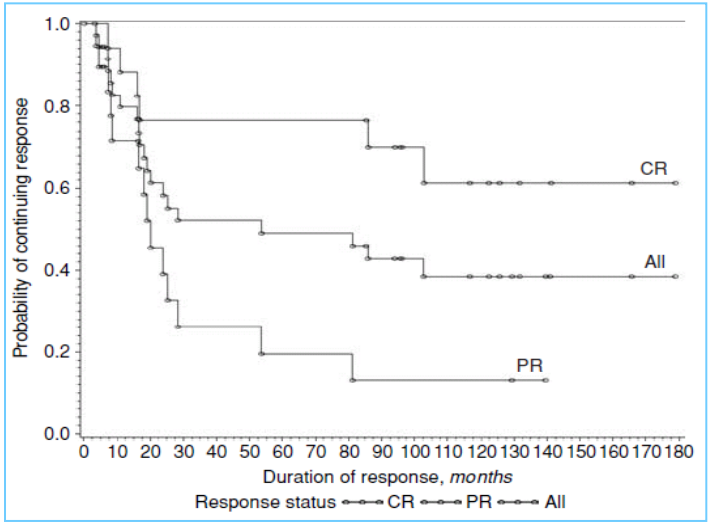
Interleukin-2: Treatment Results in Metastatic RCC

Therapy	Trials N	Patients N	ORR (CR), %	Survival Median, Months	Trial Phase
Observation	7	1139	0.3	6	
LD IL-2 + IFN HD IL-2	1	91 95	10 (3) 23 (8)	13 17	III
HD IL-2	7	255	14 (7)	16	II
HD IL-2 LD IL-2	1	156 150	21 (7) 13 (4)	17 18	III
HD IL-2 IV LD IL-2 IV LD IL-2 SC	1	96 92 93	21 (7) 11 (1) 10 (2)	17 17 17	III

Yagoda, *Semin Oncol* 1993; McDermott, *J Clin Oncol* 2005;
Fisher, *Cancer J* 2000; Yang, *J Clin Oncol* 2003

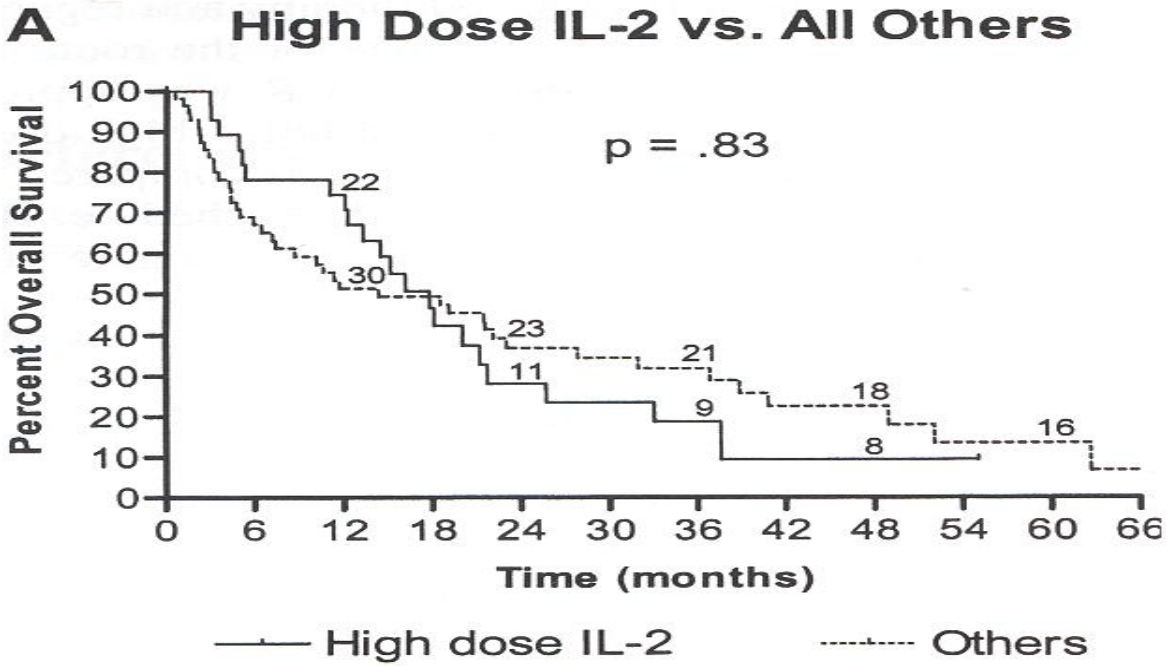
Response in metastatic RCC to High Dose Interleukin-2

- 15% response rate (7% CR, 8% PR).[1]
- Median duration of response was 54 months for all responders, 20 months for partial responders, and has not yet been reached for complete responders.[1]
- 38% of responders began therapy with tumor burdens > 50 cm^2 on pretreatment scans.
- 60% of partial responders had > 90% regression of all measurable disease.[1]
- 60% of complete responders remain in remission after 30 months.
- Residual disease from some partial responders could be resected.
  - Patients remain alive and disease-free at a minimum of 65+ months



Response Duration for Patients receiving HD IL-2[2]

Renal Cell Cancer
Northwestern Experience with Various Regimens



Pamar S,et al. Medical Oncology 22:399, 2005

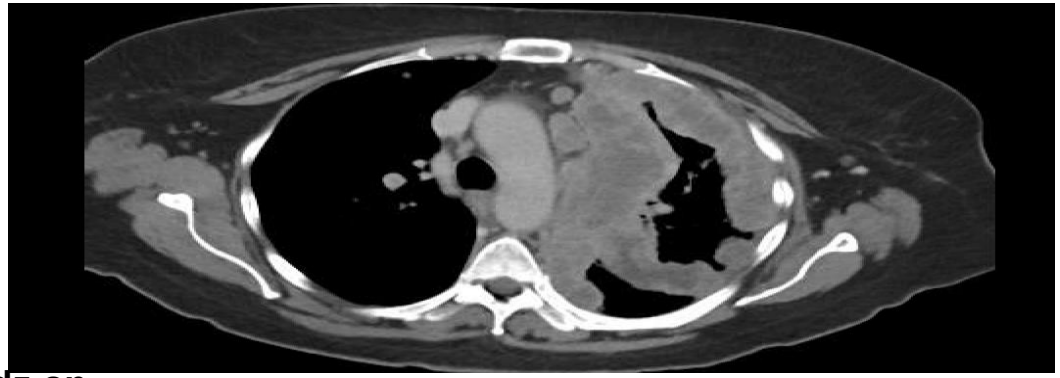
Response by Baseline Characteristics-Select Study Mcdermott D, et al

Baseline Characteristics	RR (95% CI)	*P* Value*
All Patients (n = 120)	28% (20%-37%)	0.0016
Tumor Type		
Clear Cell (n = 115)	30% (21%-39%)	0.31
Non-Clear Cell (n = 5)	0% (0%-52%)	
MSKCC Risk Group		
Favorable (n = 31)	32% (17%-51%)	0.08
Intermediate (n = 83)	24% (15%-35%)	
Poor (n = 6)	67% (22%-96%)	
UCLA Risk Group		
Low (n = 10)	30% (7%-65%)	0.22
Intermediate (n = 101)	30% (21%-40%)	
High (n = 8)	0% (0%-37%)	

Case Presentation (Con't)

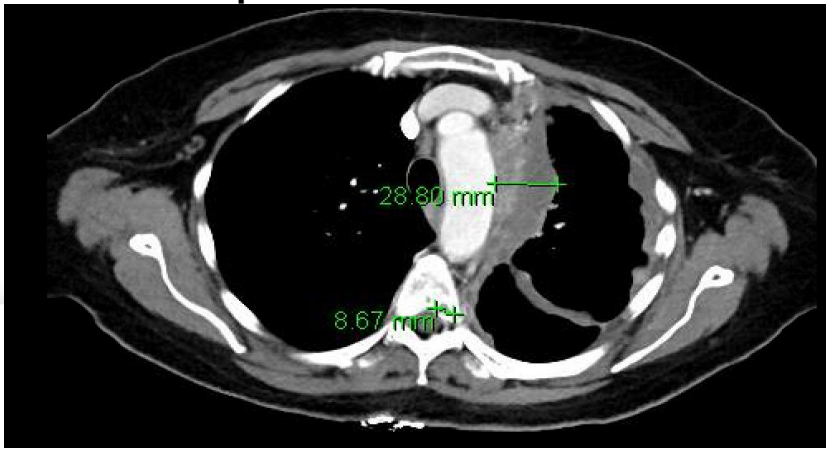
- **She was treated with standard Sunitinib x 4 cycles thru May 2014, then due to progression, was changed to Everolimus from May 2014-October 2014**
- **In October her CT showed soft tissue stability, but several new bone lesions c/w mets. Therefore she was changed to Axitinib thru May 2015 when further progression was noted**
- **Her examination remained stable, and her Performance Status was judged ECOG 1.**

Case Presentation (Con't)
Imaging

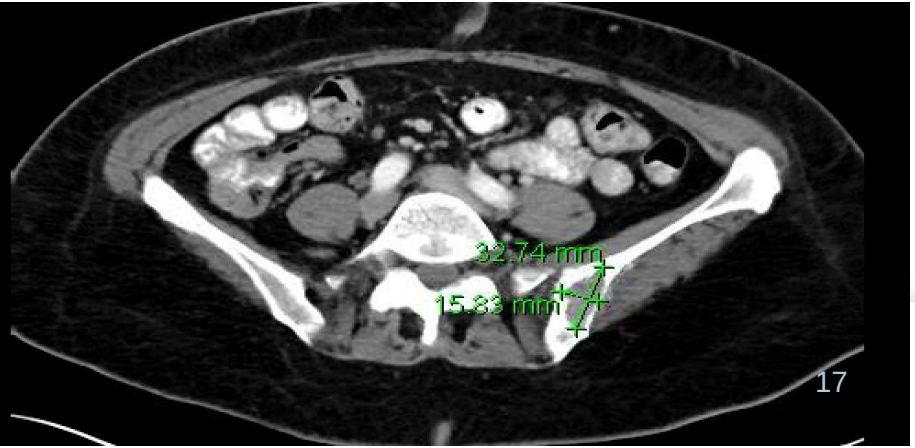


Oct 2014 after Sunitinib

May 2015 stable chest dz on Axitinib from prior Everolimus



May 2015 new bone lesion



Case Presentation (Con’t)

- **What therapy would you offer next?**
  - **Alternative TKI**
  - **Temsirolimus**
  - **Anti CTLA-4 antibody Ipilimumab**
  - **Anti PD-1 Antibody Nivolumab**

Newer Immunotherapy Approaches in Development

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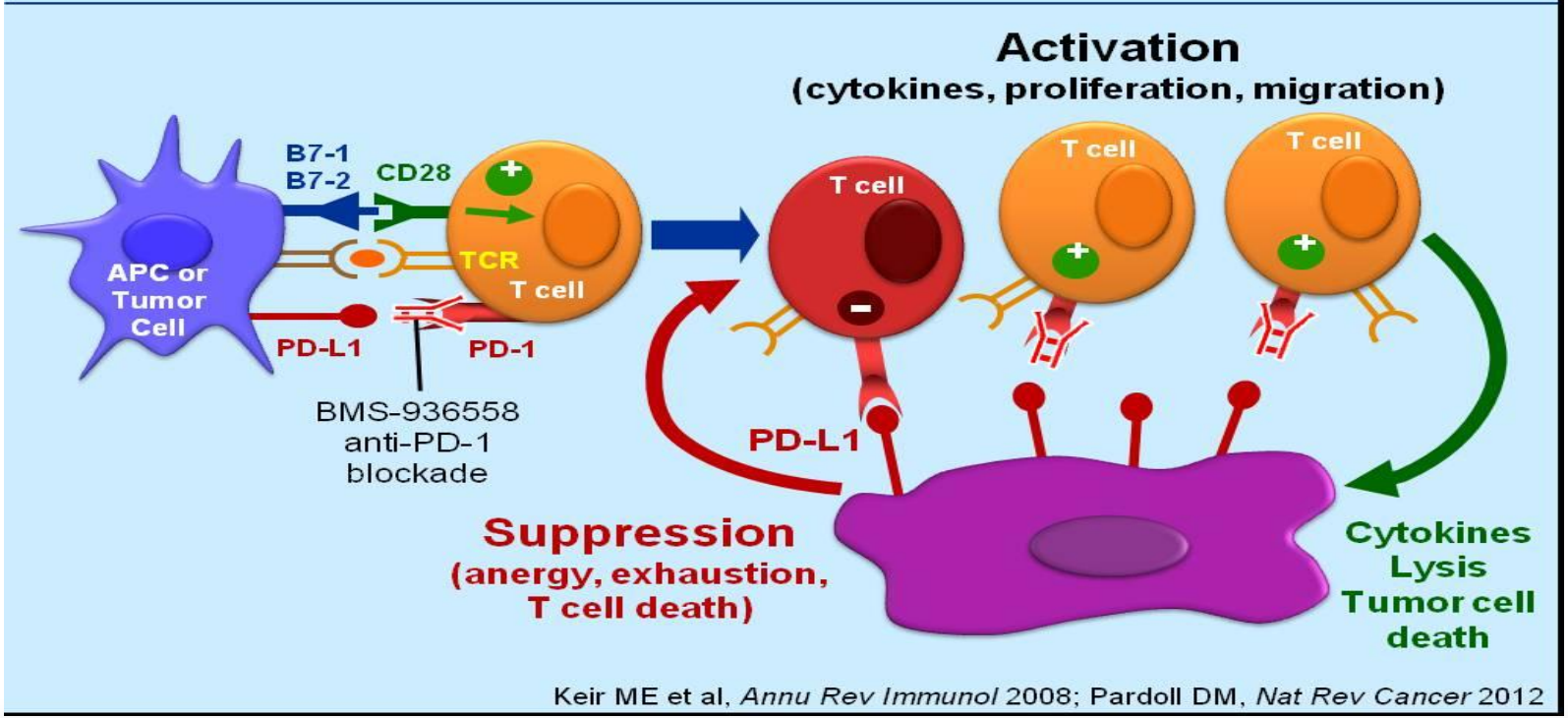
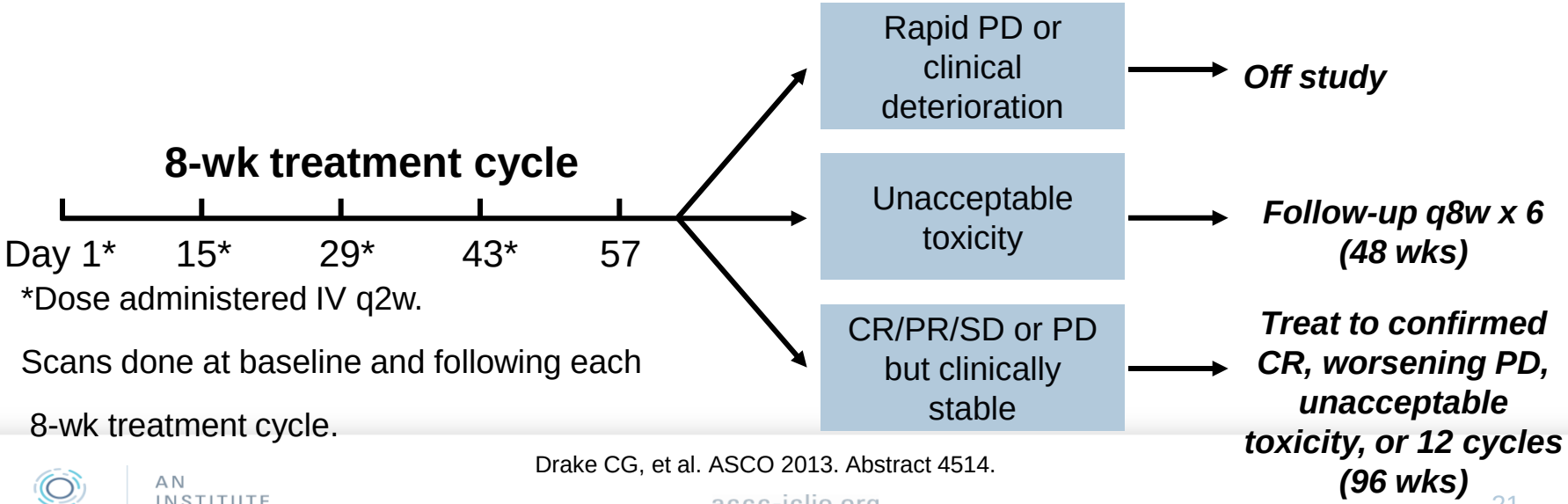
Anti-PD-1: Blocking T cell Suppression



Keir ME et al, *Annu Rev Immunol* 2008; Pardoll DM, *Nat Rev Cancer* 2012

Phase I Nivolumab Multidose Regimen

- **Eligibility: advanced melanoma, NSCLC, RCC, CRC, or CRPC with PD after 1-5 systemic therapies**



Drake CG, et al. ASCO 2013. Abstract 4514.

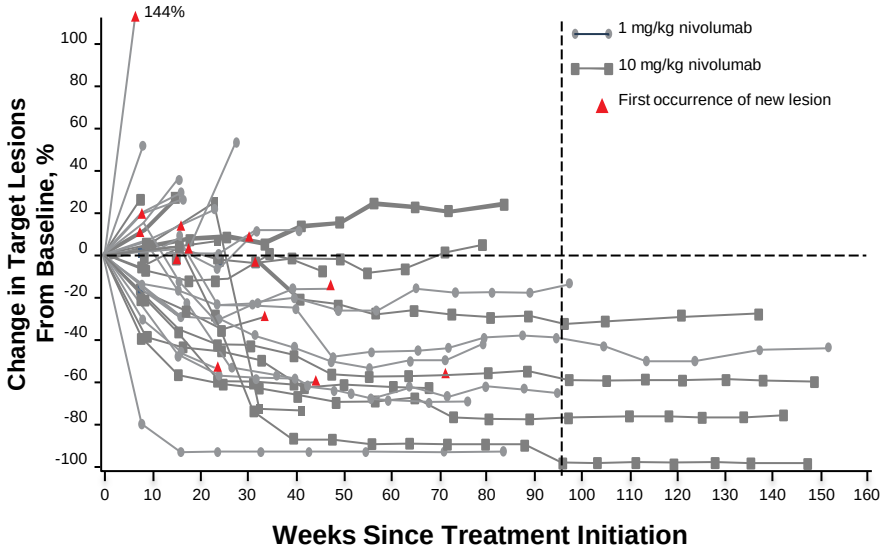
Nivolumab: Outcomes in Patients With Metastatic RCC

Dose, mg/kg	Objective Response Rate, % (n/N)	Median DoR, Wks (Range)	SD Rate, % (n/N)	
			≥ 24 Wks	≥ 48 Wks
All doses	29.4 (10/34)	56.1 (36.6-126.7+)	26.5 (9/34)	5.9 (2/34)
1	27.8 (5/18)	56.1 (40.1-76.1+)	22.2 (4/18)	5.6 (1/18)
10	31.3 (5/16)	56.1 (36.6-126.7+)	31.3 (5/16)	6.3 (1/16)

Drake CG, et al. ASCO 2013. Abstract 4514.

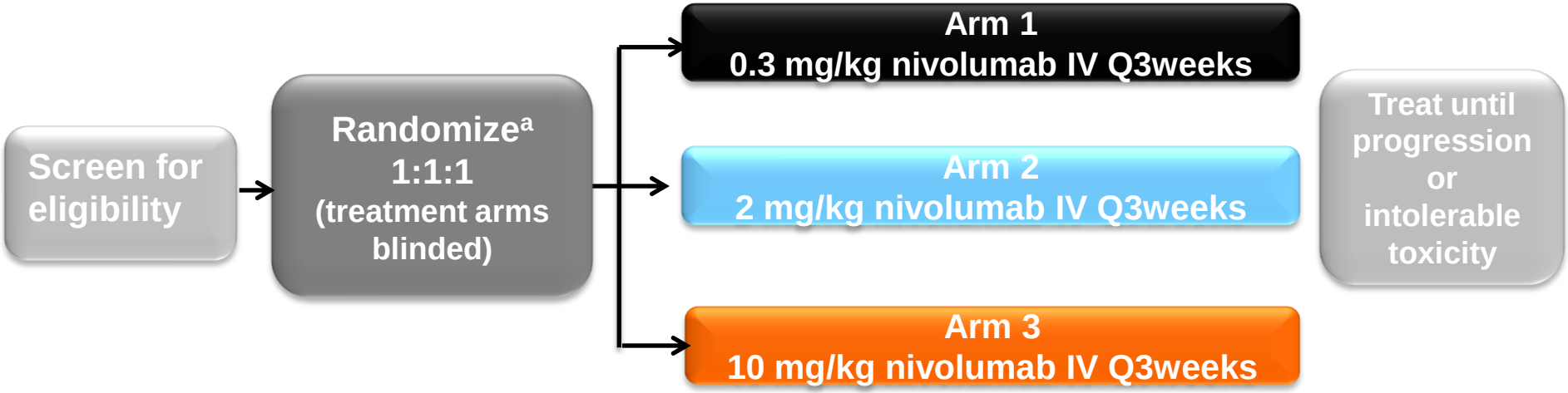
Change in Target Lesions From Baseline After Nivolumab Therapy

Patients with mRCC treated with nivolumab 1 or 10 mg/kg



Hodi FS, et al. 12th International Congress on Targeted Anticancer Therapies. Abstract O2.3.

Phase II study design



ClinTrials.gov NCT01354431

[a]Stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior lines of therapy in the metastatic setting (1 vs >1).

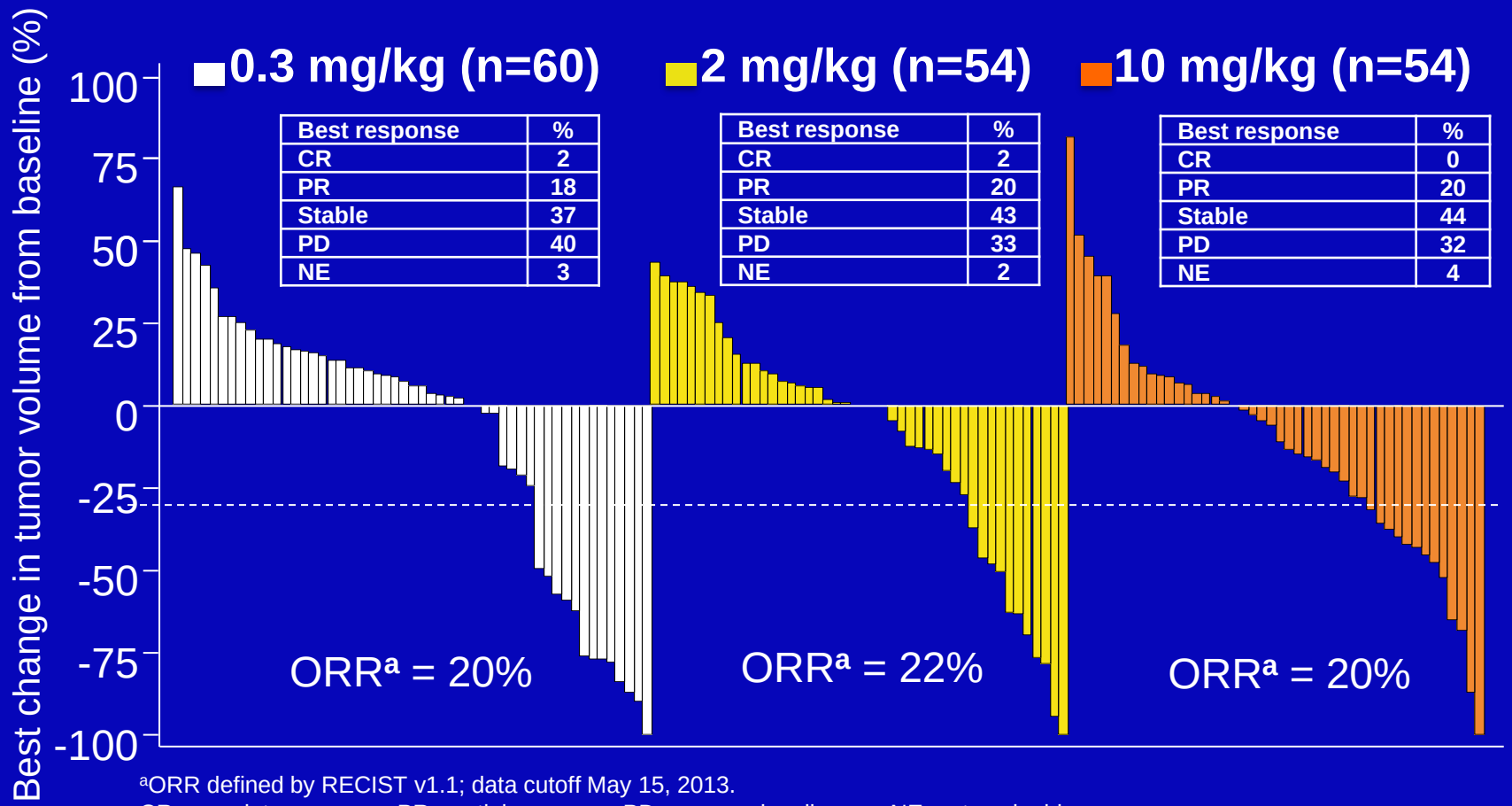
Patient demographics

	Nivolumab, mg/kg			
	0.3 (n=60)	2.0 (n=54)	10 (n=54)	Total (N=168)
MSKCC risk factors, %[a]				
0	33	33	33	33
1	43	41	41	42
2-3	23	26	26	25
Number of metastatic sites, %				
1	22	9	22	18
≥2	78	91	78	82
Prior antiangiogenic regimens, %[a]				
1	57	65	65	62
2	37	30	33	33
3	7	6	2	5

Prior treatment in metastatic setting

	Nivolumab, mg/kg			
	0.3 (n=60)	2.0 (n=54)	10 (n=54)	Total (N=168)
Prior lines of therapy, %				
1	27	30	33	30
2	33	35	43	37
3	40[a]	35	24	33
Common prior agents[b], %				
Sunitinib	77	78	69	74
Everolimus	35	33	33	34
Pazopanib	25	33	24	27
Interleukin-2	25	20	22	23

Objective responses



Best response	%
CR	2
PR	18
Stable	37
PD	40
NE	3

Best response	%
CR	2
PR	20
Stable	43
PD	33
NE	2

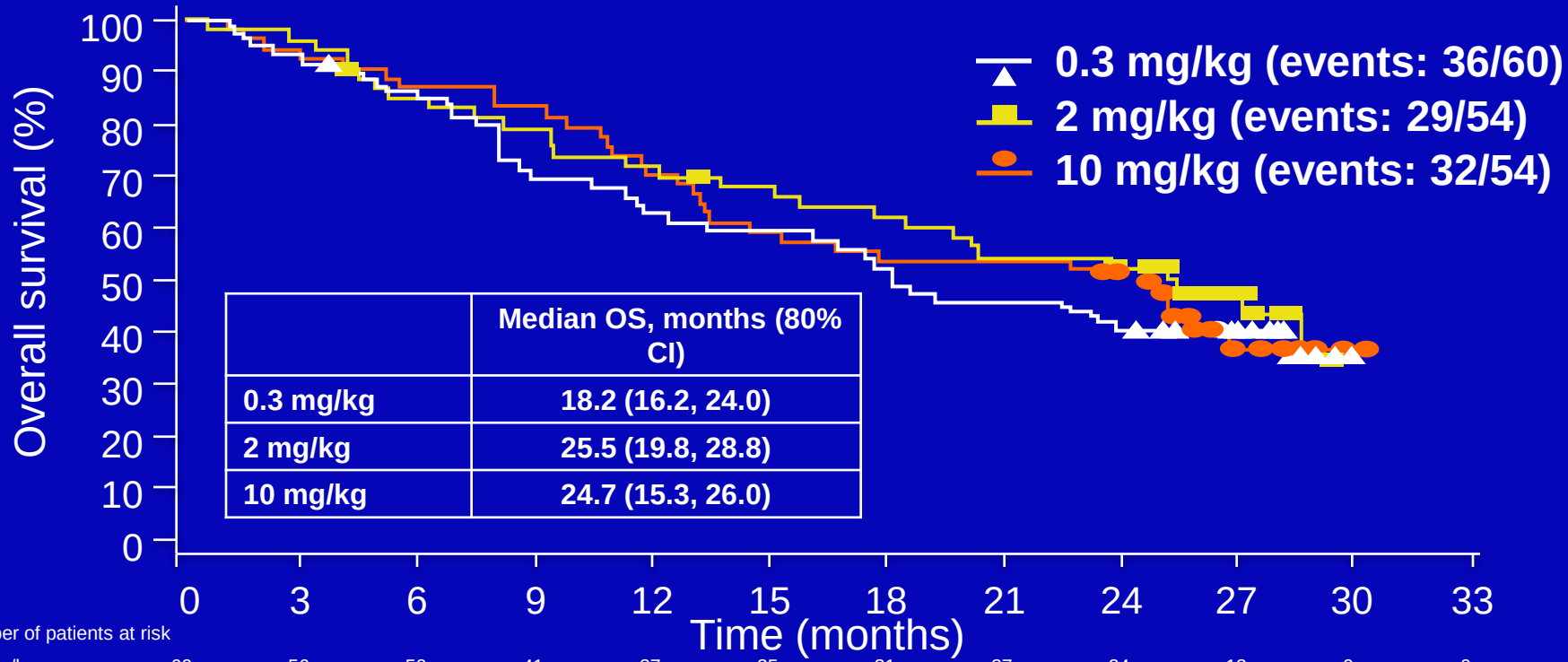
Best response	%
CR	0
PR	20
Stable	44
PD	32
NE	4

[a]ORR defined by RECIST v1.1; data cutoff May 15, 2013.
CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable.

Treatment-related adverse events (≥10% of patients in any arm)

	Nivolumab, mg/kg					
	0.3 (n=59)		2.0 (n=54)		10 (n=54)	
Patients with event, %	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any event	75	5	67	17	78	13
Fatigue	24	0	22	0	35	0
Nausea	10	2	13	2	13	0
Pruritus	10	0	9	2	11	0
Rash	9	0	7	0	13	0
Diarrhea	3	0	11	0	15	0
Appetite decreased	3	0	13	0	4	0
Dry mouth	3	0	6	0	11	0
Dry skin	2	0	6	0	13	0
Hypersensitivity	2	0	2	0	17	0
Arthralgia	2	0	7	0	15	2

Overall survival



	Median OS, months (80% CI)
0.3 mg/kg	18.2 (16.2, 24.0)
2 mg/kg	25.5 (19.8, 28.8)
10 mg/kg	24.7 (15.3, 26.0)

Number of patients at risk

0.3 mg/kg	60	56	50	41	37	35	31	27	24	13	0	0
2 mg/kg	54	52	45	42	38	35	32	28	26	12	0	0
10 mg/kg	54	50	47	45	38	32	29	29	26	8	1	0

Based on data cutoff of March 5, 2014; Symbols represent censored observations.

Overall survival in phase III trials and nivolumab phase II study

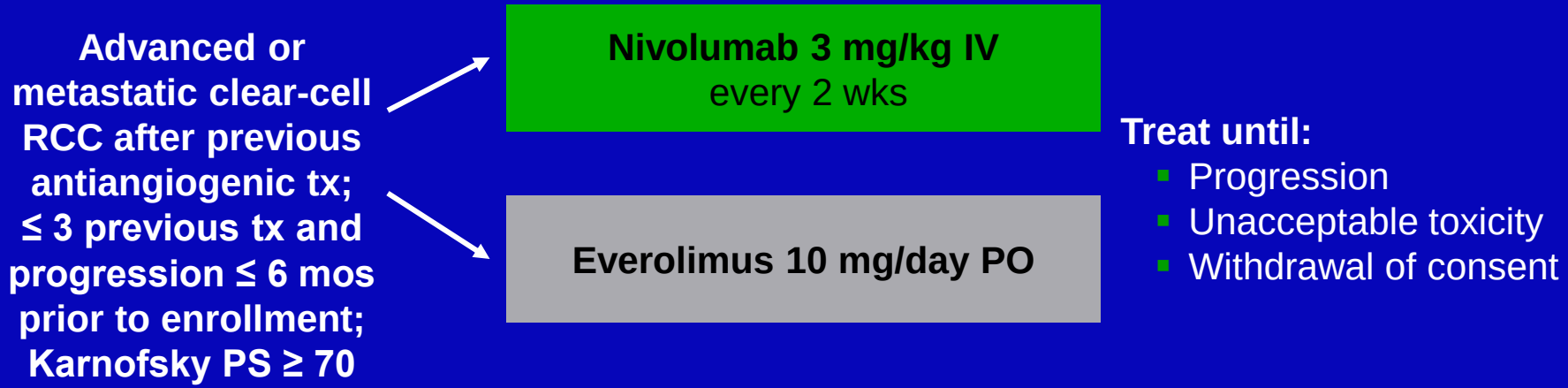
	AXIS[1,a]	INTORSECT[2]	RECORD-1[3]	GOLD[4]	Nivolumab study
Drug	Axitinib; sorafenib	Temsirolimus; sorafenib	Everolimus; placebo	Dovitinib; sorafenib	**Nivolumab; 0.3; 2; 10 mg/kg**
Patients, n	389	512	416	570	168
Risk group, %[b]					
Favorable	Not stated	19	29	20	33
Intermediate		69	56	58	42
Poor		12	14	22	25
Prior therapy	Sunitinib	Sunitinib	VEGF	VEGF + mTOR	VEGF ± mTOR
Line of therapy	2nd	2nd	2nd or higher	3rd or higher	2nd to 4th
Median OS, months	15.2; 16.5	12.3; 16.6	14.8; 14.4	11.1; 11.0	**18.2; 25.5; 24.7**
CI	12.8, 18.3[c] 13.7, 19.2[c]	10.1,14.8[c] 13.6, 18.7[c]	Not stated	9.5, 13.4[c] 8.6, 13.5[c]	16.2, 24.0[d] 19.8, 28.8[d] 15.3, 26.0[d]

[a]Post TKI subset; [b]Total ≠100% due to rounding; [c]95% CI; [d]80% CI.

1. Motzer R, et al. *Lancet Oncol.* 2013;14:552-62; 2. Hutson TE, et al. *J Clin Oncol.* 2014;32:760-7; 3. Motzer R, et al. *Cancer.* 2010;116:4256-65; 4. Motzer R, et al. *Lancet Oncol.* 2014;15:286-96.

Phase III Study of Nivolumab vs Everolimus in Pts With mRCC

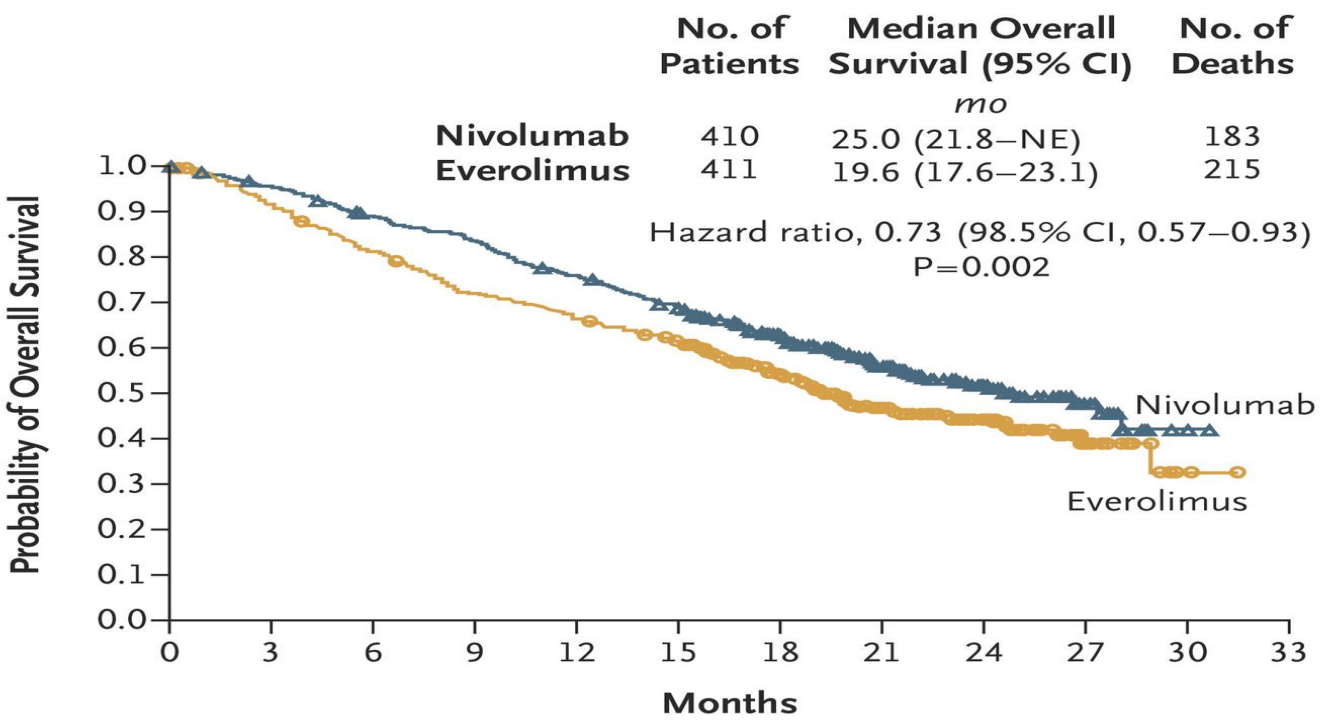
- **A randomized, open-label phase III trial**



ClinicalTrials.gov NCT01668784.

- **Primary endpoint: OS**
- **Secondary endpoints: PFS, ORR, DoR, OS in PD-L1 subgroup, safety**

Kaplan–Meier Curve for Overall Survival



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

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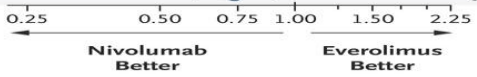
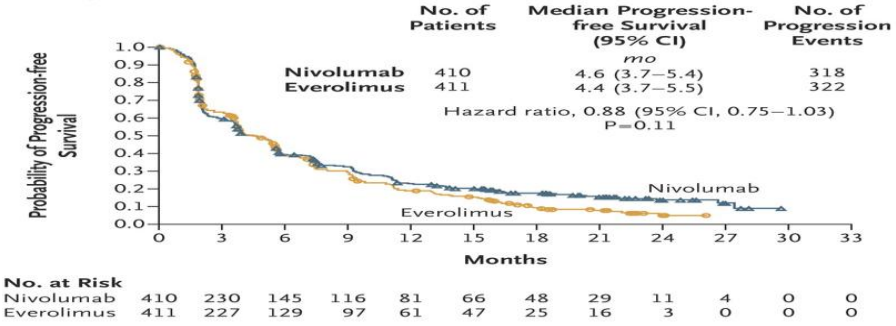
Overall Survival in Subgroup Analyses and Kaplan–Meier Curve for Progression-free Survival.

A Subgroup Analyses of Overall Survival

Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic regimens			
1	128/294	158/297	0.71 (0.56–0.90)
2	55/116	57/114	0.89 (0.61–1.29)
Region			
United States or Canada	66/174	87/172	0.66 (0.48–0.91)
Western Europe	78/140	84/141	0.86 (0.63–1.16)
Rest of the world	39/96	44/98	0.78 (0.51–1.20)
Age			
<65 yr	111/257	118/240	0.78 (0.60–1.01)
≥65 to <75 yr	53/119	77/131	0.64 (0.45–0.91)
≥75 yr	19/34	20/40	1.23 (0.66–2.31)
Sex			
Female	48/95	56/107	0.84 (0.57–1.24)
Male	135/315	159/304	0.73 (0.58–0.92)



B Kaplan–Meier Curve for Progression-free Survival



RR favored Nivo
25% vs 5%

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

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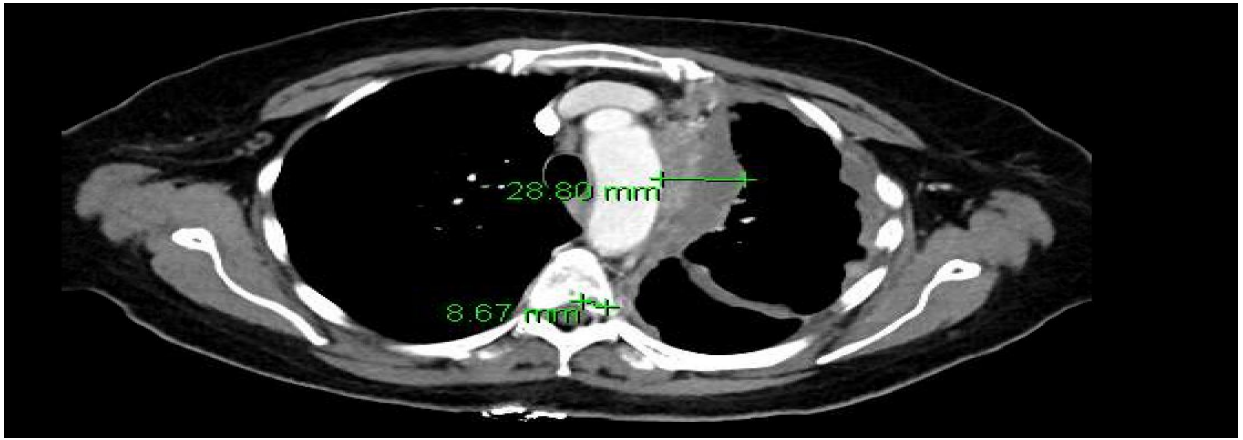
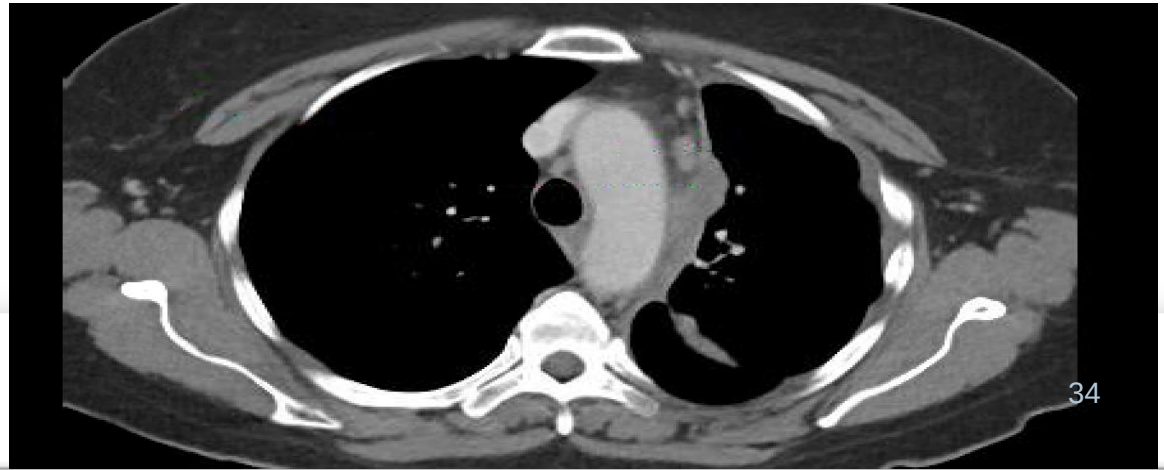
Case Presentation (Con't)
Imaging



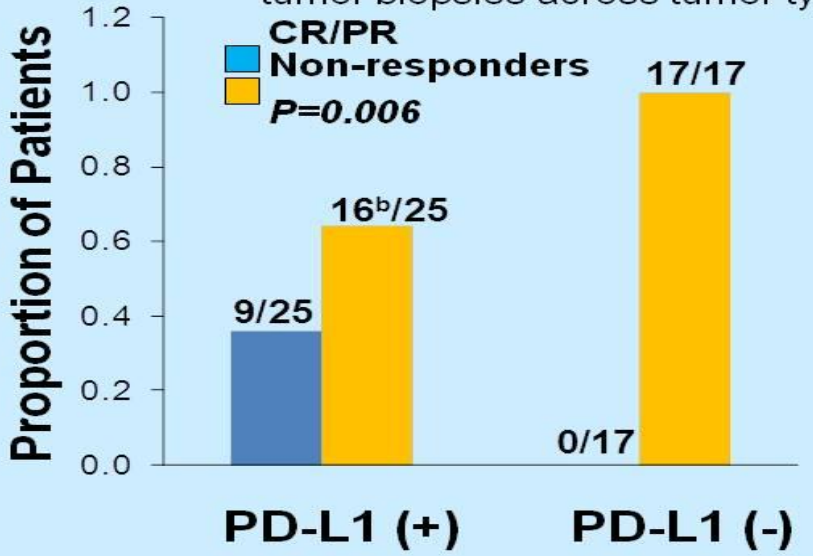
May 2015-pre Nivo

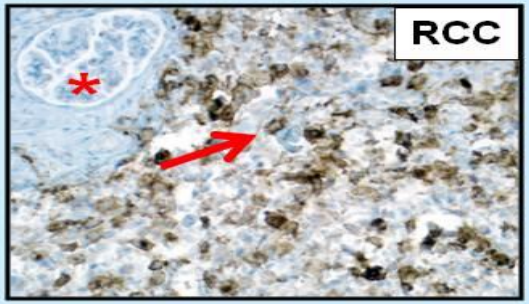
Dec 2015 s/p 5 months of nivolumab



Correlation of PD-L1 expression in pre-treatment tumor biopsies with clinical outcomes

PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 patients[a]





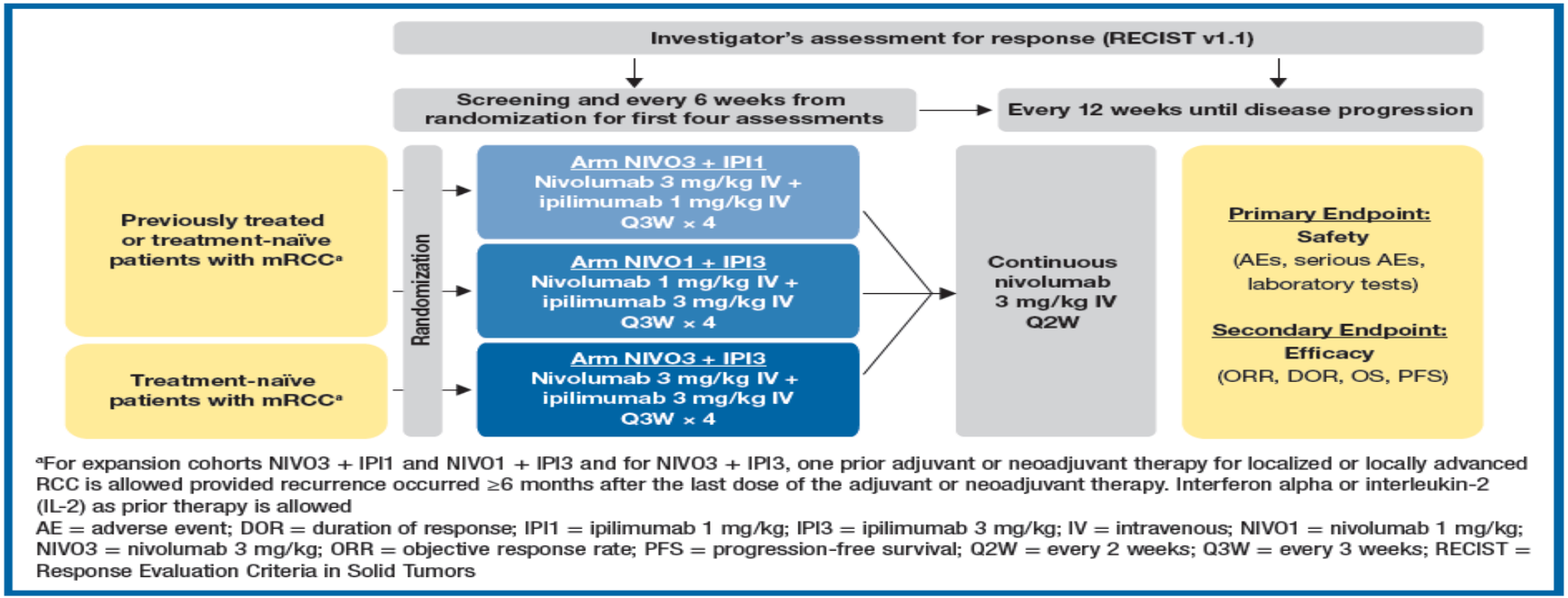
Patient samples: 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

[a]Analysis was not pre-planned and based on a subset of patients
[b]2 patients still under evaluation

Topalian et al NEJM, 2012

RCC Immunotherapy Trial

Figure 1. Study design



[a]For expansion cohorts NIVO3 + IPI1 and NIVO1 + IPI3 and for NIVO3 + IPI3, one prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred ≥6 months after the last dose of the adjuvant or neoadjuvant therapy. Interferon alpha or interleukin-2 (IL-2) as prior therapy is allowed

AE = adverse event; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; IV = intravenous; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; ORR = objective response rate; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

- At induction visits, patients received two infusions. The first infusion was always nivolumab (1 or 3 mg/kg), and the second was always ipilimumab, which was started ≥30 minutes after completion of the nivolumab infusion (Figure 2)

Ipilimumab/Nivolumab in RCC Efficacy

Efficacy

- ORR and best overall response are shown in Table 6

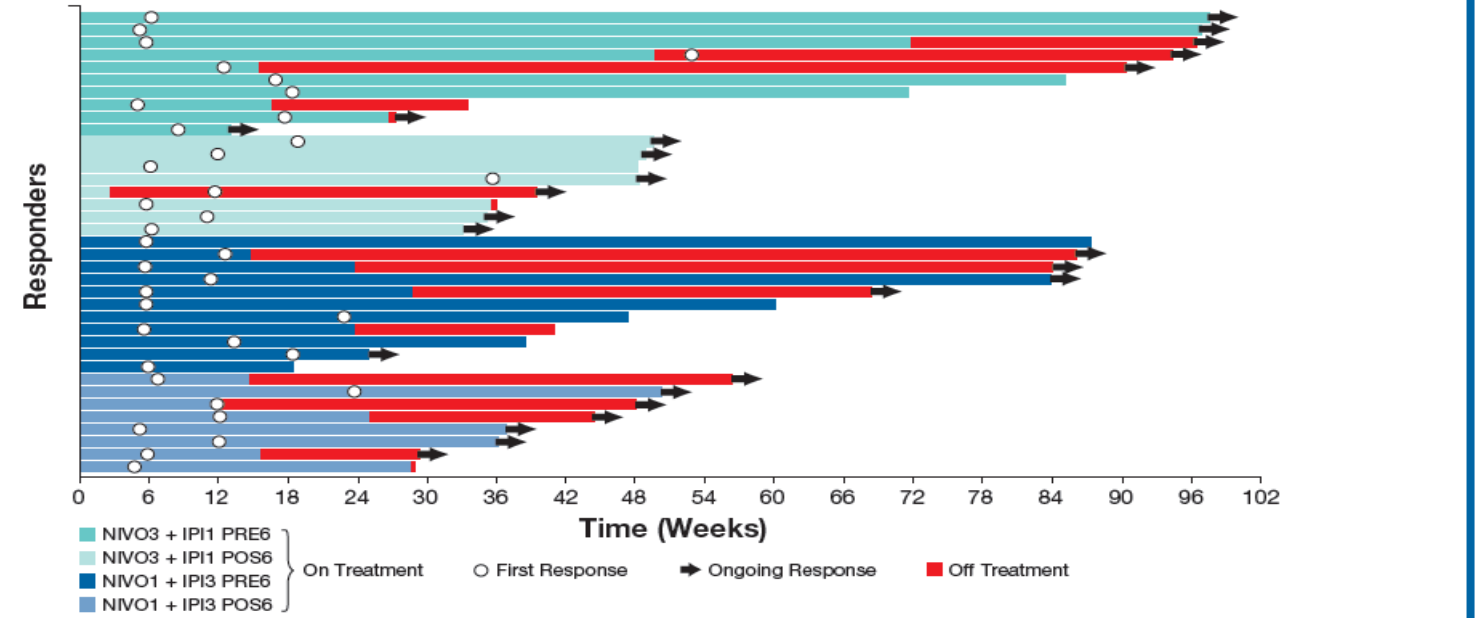
Table 6. Antitumor activity

	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 overall response[b], 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)

[a]Confirmed response only; [b]No unconfirmed complete responses were reported in either arm; unconfirmed partial responses were reported in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm. Best overall response was not determinable in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm

- The median DOR is shown in Figure 3
- Of those who responded to treatment, 72.2% (13/18) of patients in the nivolumab 3 + ipilimumab 1 arm and 63.2% (12/19) of patients 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
  - DOR was defined as the time between date of first response and date of disease progression or death (whichever occurred first)

Duration of Responses



- The PFS rate (95% CI) at 24 weeks was 54% (39–68) in the nivolumab 3 + ipilimumab 1 arm (N = 47) and 68% (52–79) in the nivolumab 1 + ipilimumab 3 arm (N = 47) (Figure 4)

Toxicity of Ipi/Nivo Rx in RCC

Table 5. Treatment-related select AEs[a,b]

Category, n (%)	NIVO3 + IPI1 N = 47		NIVO1 + IPI3 N = 47		NIVO3 + IPI3 N = 6	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin disorder	18 (38.3)	0	24 (51.1)	1 (2.1)	3 (50.0)	0
GI disorder	11 (23.4)	1 (2.1)	21 (44.7)	11 (23.4)	3 (50.0)	2 (33.3)
Endocrinopathy	11 (23.4)	1 (2.1)	20 (42.6)	0	5 (83.3)	0
Hepatic	7 (14.9)	2 (4.3)	15 (31.9)	10 (21.3)	3 (50.0)	0
Renal disorder	5 (10.6)	1 (2.1)	7 (14.9)	1 (2.1)	2 (33.3)	0
Infusion reaction	4 (8.5)	0	3 (6.4)	0	1 (16.7)	0
Pulmonary	2 (4.3)	0	3 (6.4)	0	0	0

[a]Select AEs were defined as AEs with potential immune-mediated etiology that may require special monitoring and specific unique interventions
[b]Treatment-related select AEs are ordered by decreasing frequency in the NIVO3 + IPI1 arm

Conclusions of Immunotherapy Approaches to mRCC

- **High Dose Interleukin-2 offers for pts with clear cell mRCC high objective response rates and opportunities for durable remissions**
- **Single agent anti PD-1 therapy shows activity in relapsed setting with improved median OS compared to historical controls- randomized trial completed and reported positive in press release**
- **Combination CTLA-4 inhibition and anti PD-1 inhibition associated with impressive response rates, with significant 60% ongoing responses**
- **Toxicity appears consistent with prior reports of these combinations**
- **Phase III trial of combination vs sunitinib underway**

Audience Questions

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