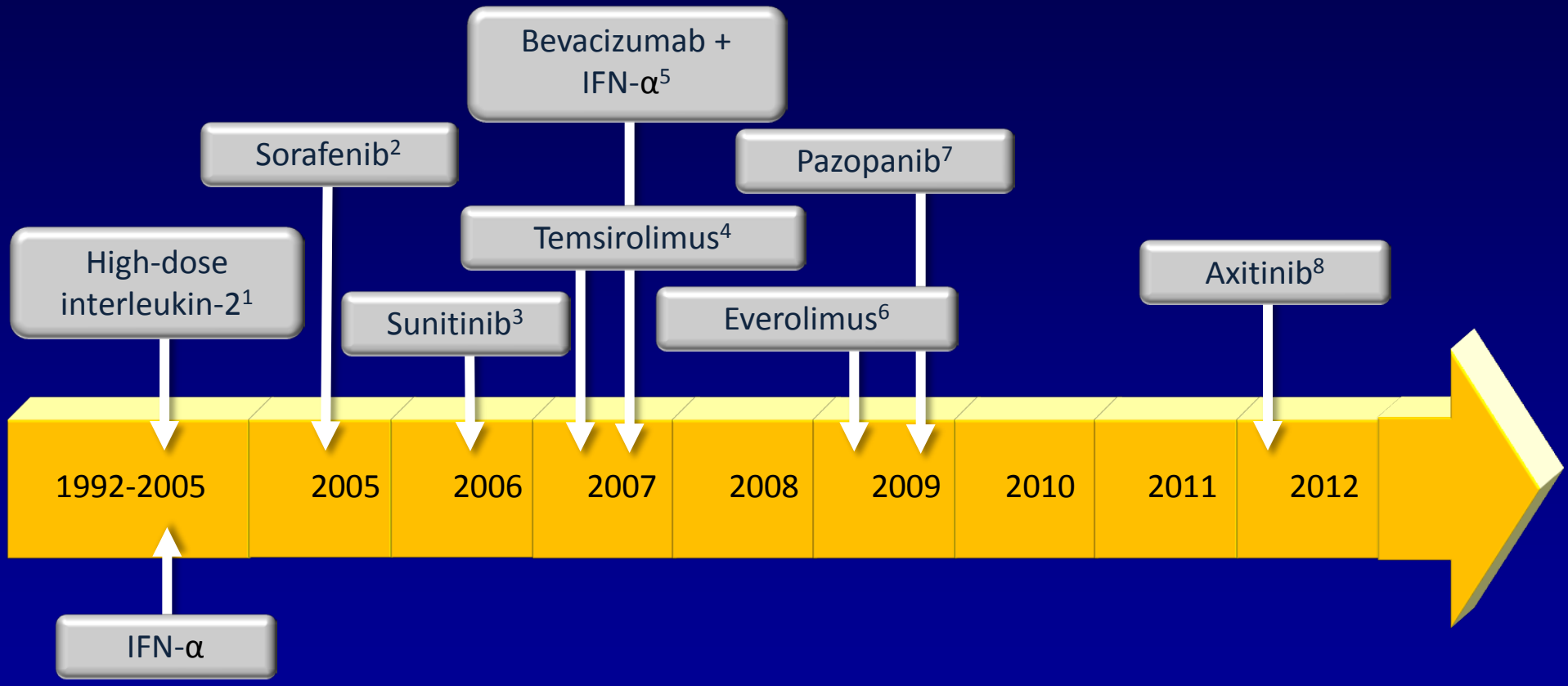
2014 Best of ASCO: Novel Immunotherapy for Kidney (and Bladder) Cancer

Robert J. Motzer, MD

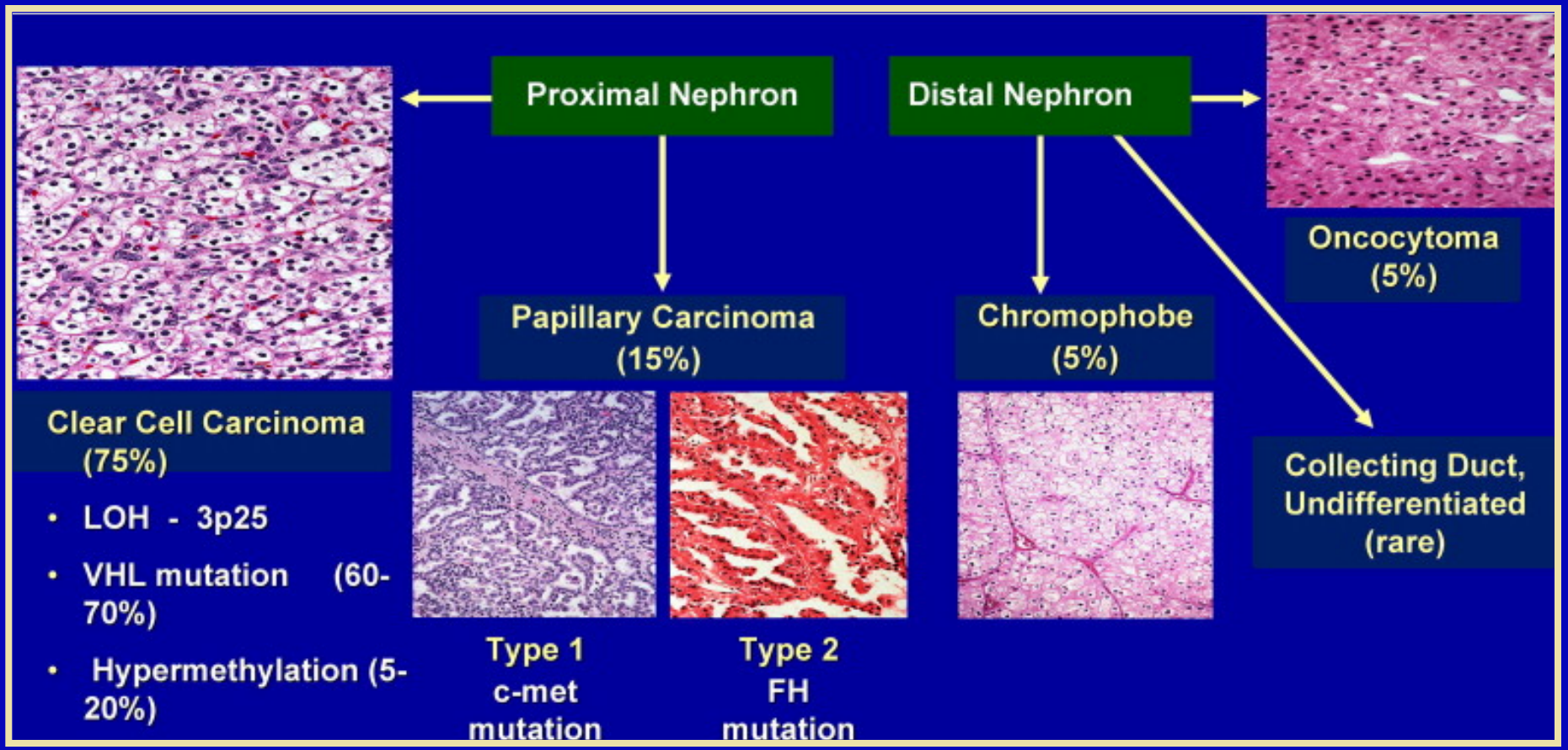
Memorial Sloan-Kettering Cancer Center

Treatment options for patients with mRCC have been revolutionised in a short period of time…

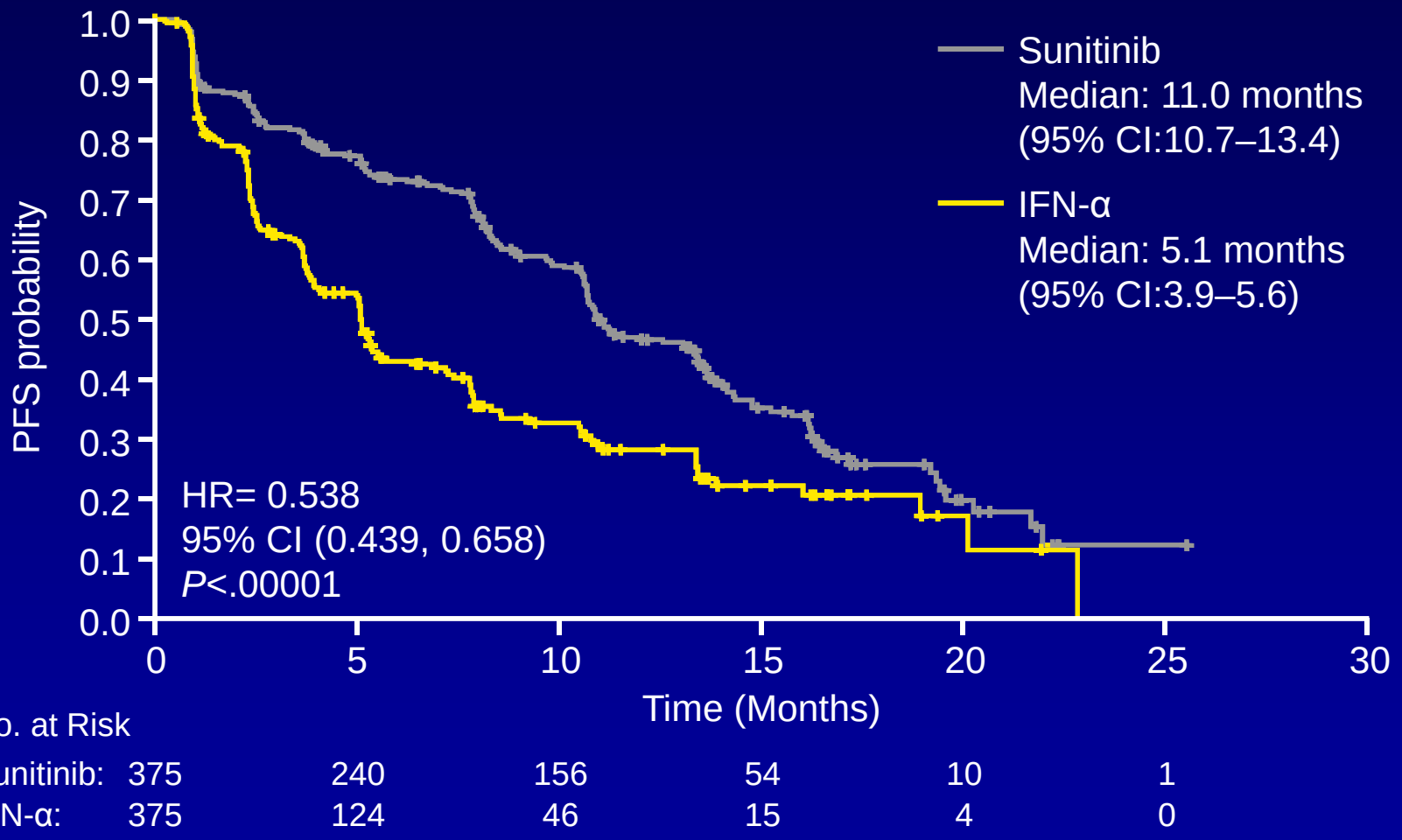


1. Fyfe G, *et al. J Clin Oncol* 1995;13:688-696.
2. Escudier B, *et al. N Engl J Med* 2007;356:125-134.
3. Motzer RJ, *et al. N Engl J Med* 2007;356:115-124.
4. Hudes G, *et al. N Engl J Med* 2007;356:2271-2281.
5. Escudier B, *et al. Lancet* 2007;370:2103-2111.
6. Motzer RJ, *et al. Lancet* 2008;372:449-456.
7. Sternberg CN, *et al. J Clin Oncol* 2010;28:1061-1068.
8. Rini BI, *et al. Lancet* 2011;378:1931-1939.

Renal Cell Carcinoma



Phase III Trial Sunitinib vs IFN-α: Progression-free Survival



No. at Risk

Sunitinib:	375	240	156	54	10	1
IFN-α:	375	124	46	15	4	0

Motzer RJ, et al. *N Engl J Med.* 2007;356:115–124; Motzer RJ, et al. *J Clin* Oncol. 2007;20(Suppl. 18S):5024 (Abstract).

Treatments for Clear-cell mRCC

Setting	Patients	Level 1*	≥ Level 2*
First-line	Good- or intermediate-risk	**Sunitinib** Bevacizumab + IFN-α Pazopanib	High-dose IL-2
	Poor-risk	Temsirolimus **Sunitinib**	
Second-line	Prior VEGF TKI	Everolimus Axitinib	Sorafenib

*Guide to clinical preventive services: National Library of Medicine (Web site). http//www.ncbi.nlm.nih.gov.
Molina AM, Motzer RJ. *Clin GU Cancer*. 2008;6:S7–S12.

Challenges in Clinical Outcome With Targeted Drugs

- Few complete responses
- Plateau in efficacy
- Primary treatment refractory
- Acquired resistance
- Survival benefit elusive in trials
- Chronic toxicities

Challenges in Clinical Outcome With Targeted Drugs

- Few complete responses
- [illegible]
- [illegible]
- Acquired resistance
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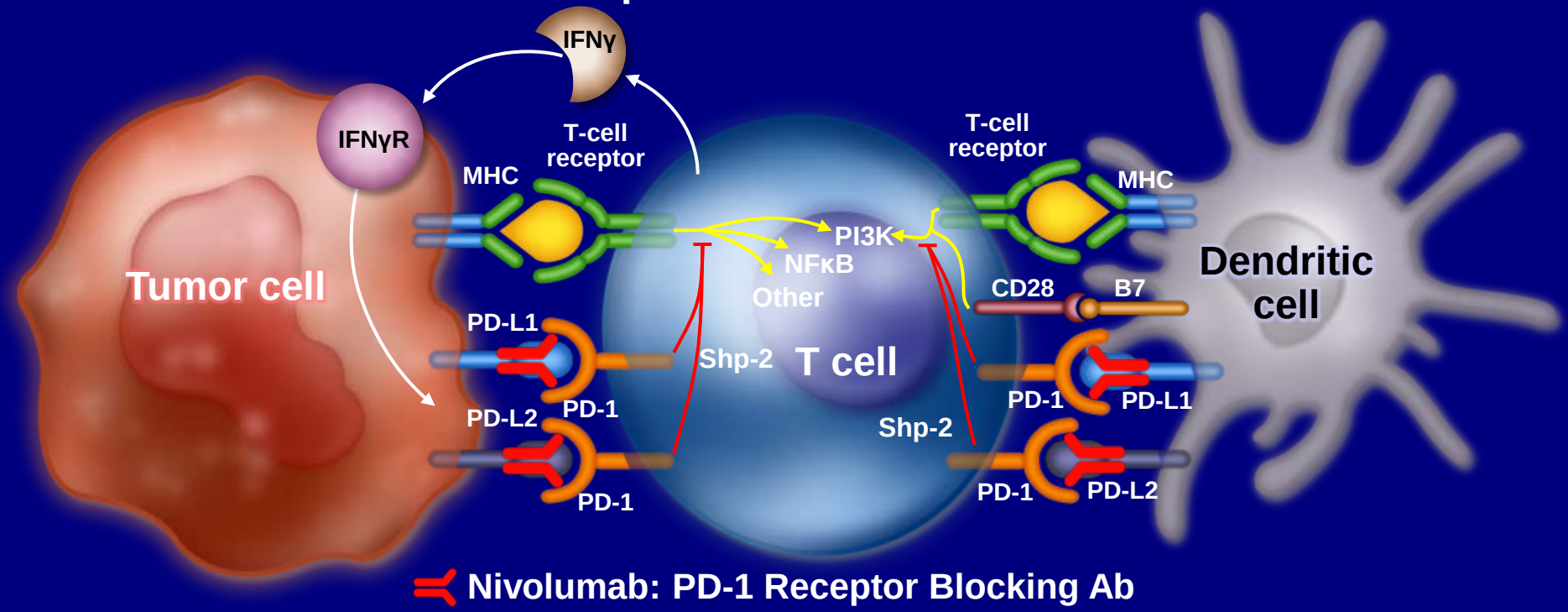
NEW DRUGS ARE NEEDED WITH A NOVEL MECHANSIM OF ACTION

Nivolumab: Mechanism of Action

- Binding of PD-1 to its ligands PD-L1 and PD-L2 leads to downregulation of the antitumor immune response[1]



- Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor
- Nivolumab selectively blocks the PD-1 and PD-L1/PD-L2 interaction, restoring antitumor T-cell function[1–4]

IFNγ, interferon gamma; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-ligand

1. Hamid O, et al. *Exp Opin Biol Ther.* 2013;13:847–61; 2. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167–75; 3. Nurieva RI, et al. *Immunol Rev.* 2011;241:133–44; 4. Hamanishi J, et al. *Proc Natl Acad Sci U S A.* 2007;104:3360–5.

ASCO 2014 Abstracts

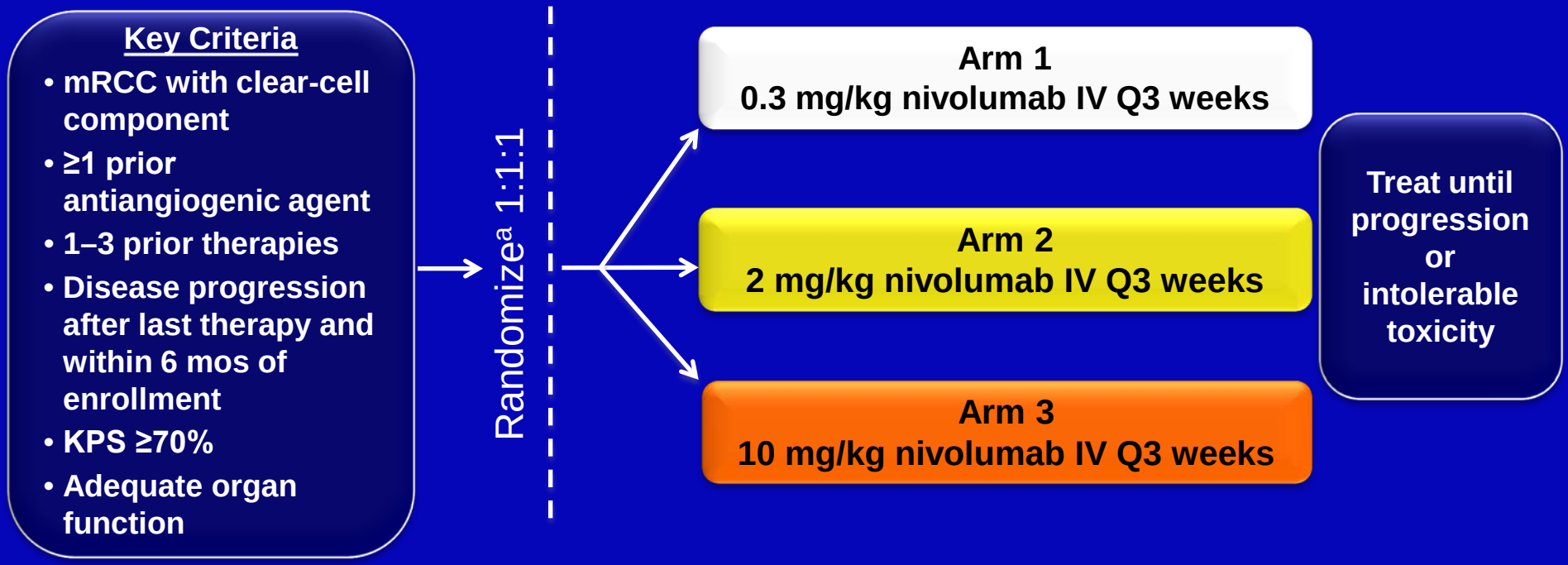
- Abstract 5009: Nivolumab for metastatic renal cell carcinoma: results of a randomized, dose-ranging phase II trial
- Abstract 5012: Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma: biomarker-based results from a randomized clinical trial
- Abstract 5010: Nivolumab in combination with sunitinib or pazopanib in patients with metastatic renal cell carcinoma
- Abstract 4504: Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma

Abstract 5009

Nivolumab for metastatic renal cell carcinoma (mRCC): results of a randomized, dose-ranging phase II trial

R. Motzer, B. Rini, D. McDermott, B. Redman, T. Kuzel, M. Harrison, U. Vaishampayan, H. Drabkin, S. George, T. Logan, K. Margolin, E. R. Plimack, I. Waxman, A. Lambert, H. Hammers

Phase II study design



Primary Objective: To assess whether a dose–response relationship exists in the 0.3, 2, and 10 mg/kg arms as measured by PFS (RECIST v1.1)

Secondary Objectives: Estimation of PFS, ORR, OS, and adverse event rate

Exploratory Objectives: Pharmacokinetics, PD-L1 expression (prototype assay)

ClinTrials.gov NCT01354431

[a]Treatment arms blinded. 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).

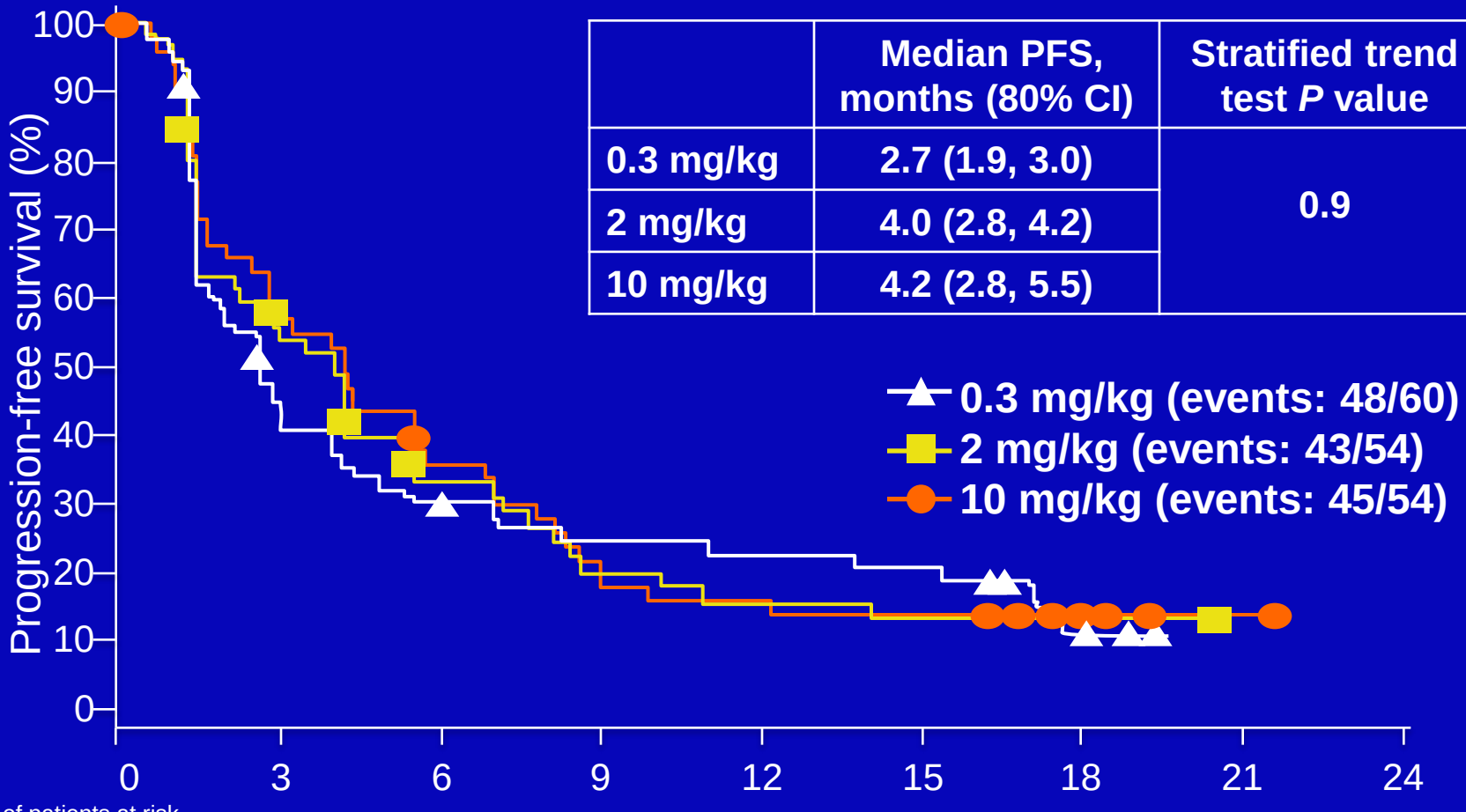
Prior therapy in metastatic setting

	Nivolumab, mg/kg			
	0.3 (n = 60)	2.0 (n = 54)	10 (n = 54)	Total (N = 168)
Prior nephrectomy, %	90	91	94	92
Prior systemic regimens, %				
1	27	30	33	30
2	33	35	43	37
3	40[a]	35	24	33
Common prior systemic therapies, %[b]				
Sunitinib	77	78	69	74
Everolimus	35	33	33	34
Pazopanib	25	33	24	27
Interleukin-2	25	20	22	23
Sorafenib	22	15	19	19

[a]1 patient (2%) in the 0.3 mg/kg group received >3 prior systemic therapies in the metastatic setting. [b]>20% of patients in any group.

Progression-free survival

	Median PFS, months (80% CI)	Stratified trend test *P* value
0.3 mg/kg	2.7 (1.9, 3.0)	0.9
2 mg/kg	4.0 (2.8, 4.2)	
10 mg/kg	4.2 (2.8, 5.5)	



Number of patients at risk

0.3 mg/kg	60	24	17	13	12	11	3	0	0
2 mg/kg	54	27	15	9	7	6	1	0	0
10 mg/kg	54	30	18	10	8	7	3	1	0

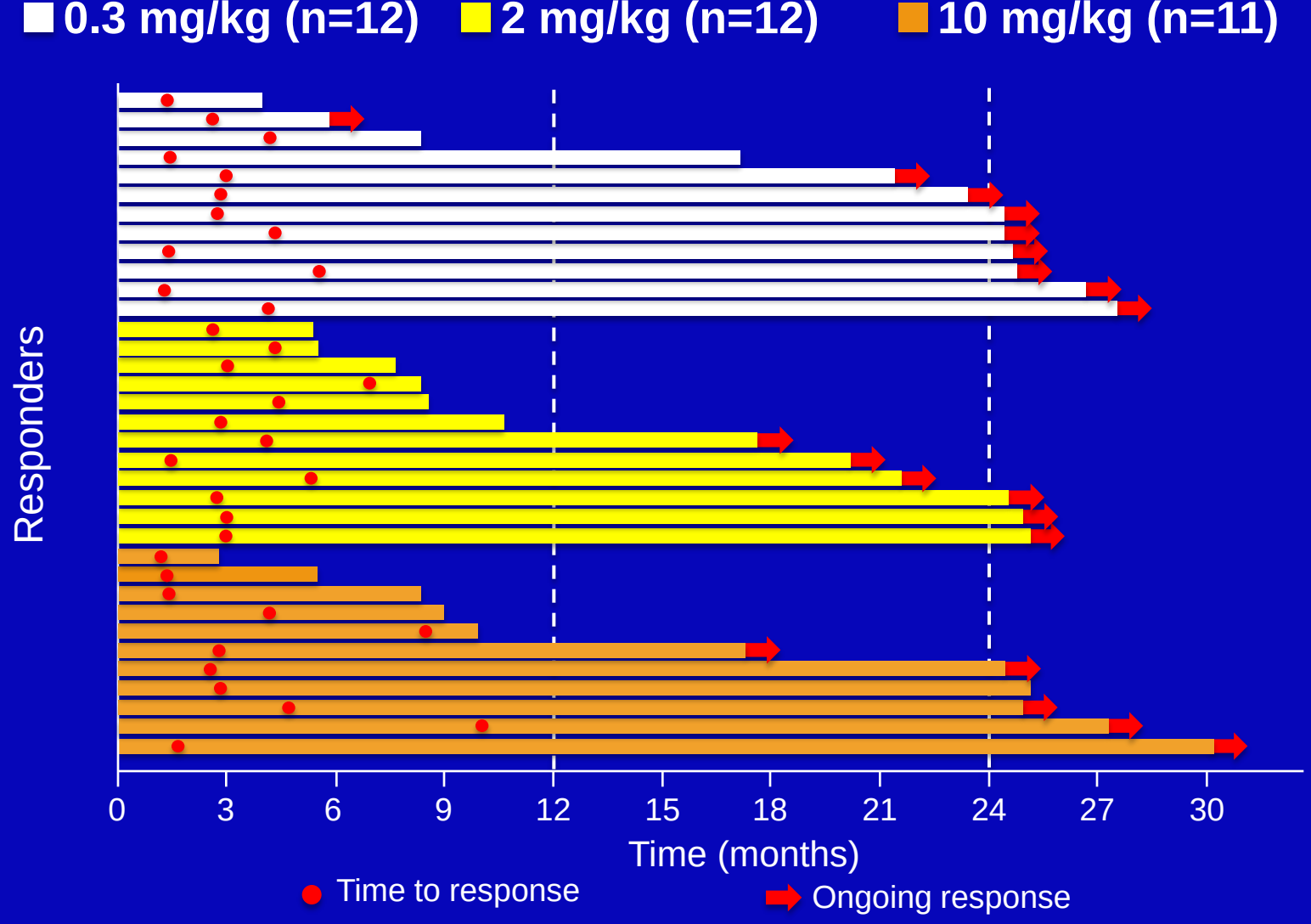
Symbols represent censored observations.

Objective responses

	Nivolumab, mg/kg		
	0.3 (n = 60)	2.0 (n = 54)	10 (n = 54)
ORR, n (%)[a]	12 (20)	12 (22)	11 (20)
(80% CI)	(13.4, 28.2)	(15.0, 31.1)	(13.4, 29.1)
Duration of response, median (80% CI), months[b]	NR (NR, NR)	NR (4.2, NR)	22.3 (4.8, NR)
Best overall response, %			
Complete response	2	2	0
Partial response	18	20	20
Stable disease	37	43	44
Progression	40	33	32
Not evaluable	3	2	4

[a]ORR defined by RECIST v1.1; data cutoff May 15, 2013. [b]Derived from the Kaplan–Meier estimate; data cutoff March 5, 2014.
NR, not reached.

Duration of response



Based on data cutoff of March 5, 2014.

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

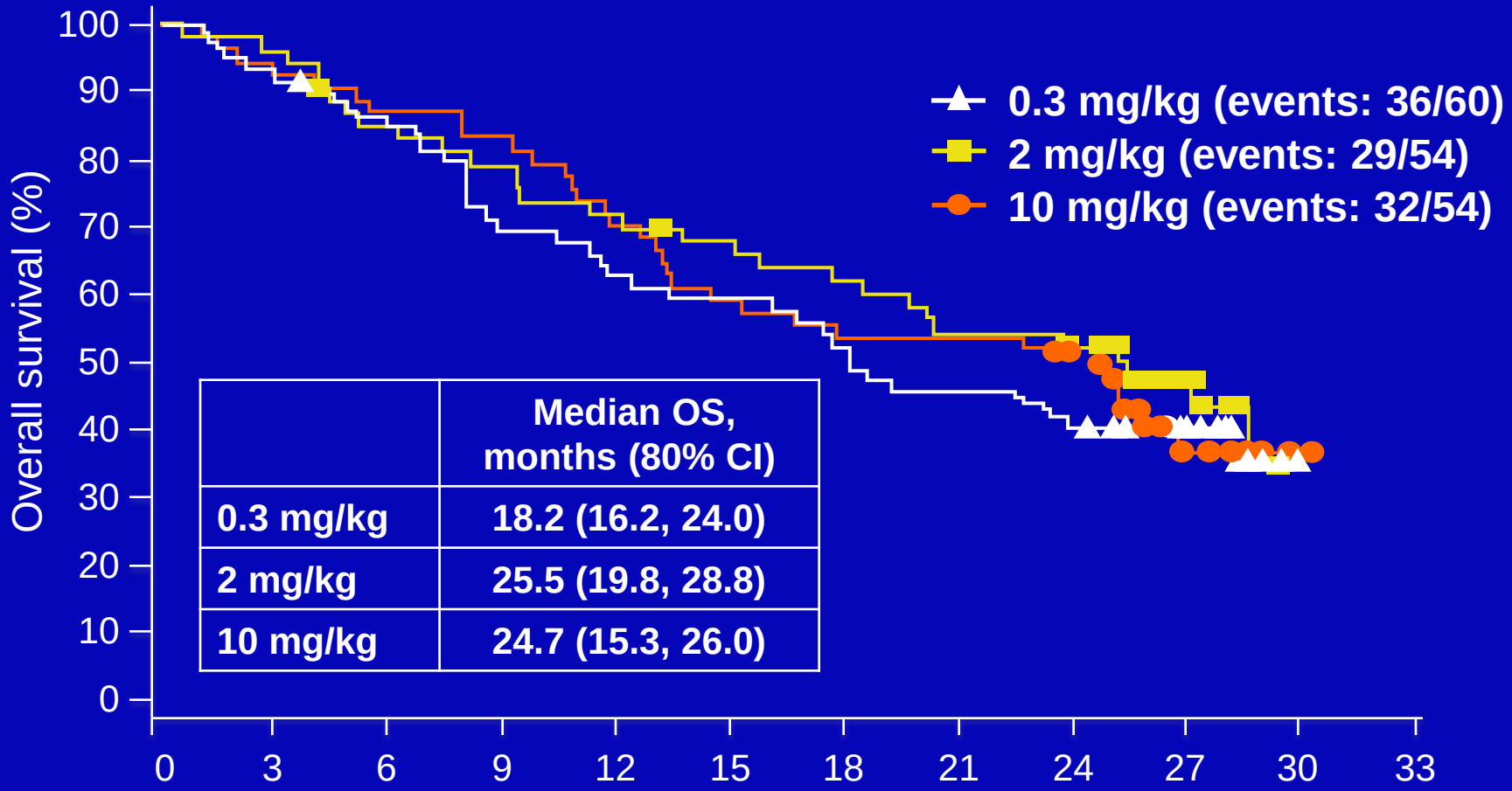
	Nivolumab, mg/kg					
	0.3 (n=59)		2.0 (n=54)		10 (n=54)	
Patients with event, %	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any event	75	5	67	17	78	13
Fatigue	24	0	22	0	35	0
Nausea	10	2	13	2	13	0
Pruritus	10	0	9	2	11	0
Rash	9	0	7	0	13	0
Diarrhea	3	0	11	0	15	0
Appetite decreased	3	0	13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

Treatment-related select adverse events

	Nivolumab, mg/kg					
	0.3 (n = 59)		2.0 (n = 54)		10 (n = 54)	
Category, %	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin	22	0	22	4	28	0
Gastrointestinal	5	0	11	2	15	0
Endocrine	5	0	11	4	11	0
Hepatic	3	2	7	4	6	0
Pulmonary	5	0	4	0	7	0
Hypersensitivity/infusion reaction	2	0	4	0	19	0
Renal	2	0	0	0	2	0

- **No treatment-related grade 3/4 pneumonitis events or grade 5 events were reported**

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

[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.

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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.

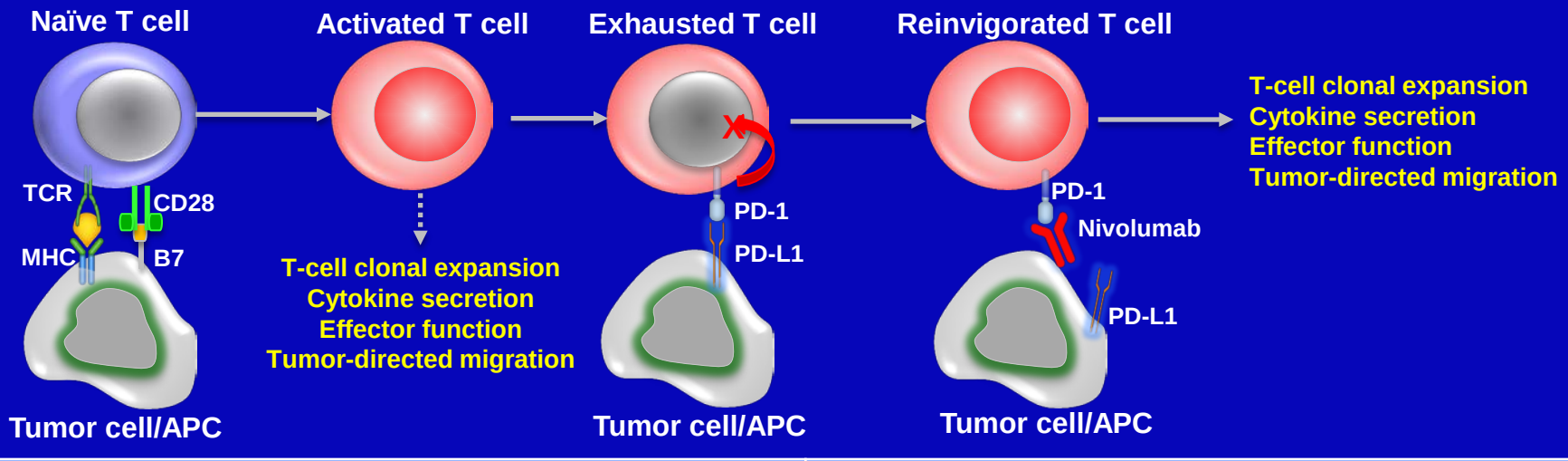
Abstract 5012

Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma (mRCC): biomarker-based results from a randomized clinical trial

Toni K. Choueiri,[1] Mayer N. Fishman,[2] Bernard Escudier,[3] Jenny J. Kim,[4] Harriet Kluger,[5] Walter M. Stadler,[6] Jose Luis Perez-Gracia,[7] Douglas McNeel,[8] Brendan Curti,[9] Michael Harrison,[10] Elizabeth R. Plimack,[11] Leonard Appleman,[12] Lawrence Fong,[13] Charles G. Drake,[4] Lewis Cohen,[14] Shivani Srivastava,[14] Maria Jure-Kunkel,[14] Quan Hong,[14] John F. Kurland,[14] Mario Sznol[5]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [5]Yale Cancer Center, New Haven, CT, USA; [6]University of Chicago Medicine, Chicago, IL, USA; [7]University Clinic of Navarra, Pamplona, Spain; [8]University of Wisconsin-Madison, Department of Medicine, Madison, WI, USA; [9]Providence Cancer Center, Providence Portland Medical Center, Portland, OR, USA; [10]Duke University Medical Center, Durham, NC, USA; [11]Fox Chase Cancer Center, Philadelphia, PA, USA; [12]University of Pittsburgh Medical Center (UPMC) Cancer Pavilion, Pittsburgh, PA, USA; [13]University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [14]Bristol-Myers Squibb, Princeton, NJ, USA

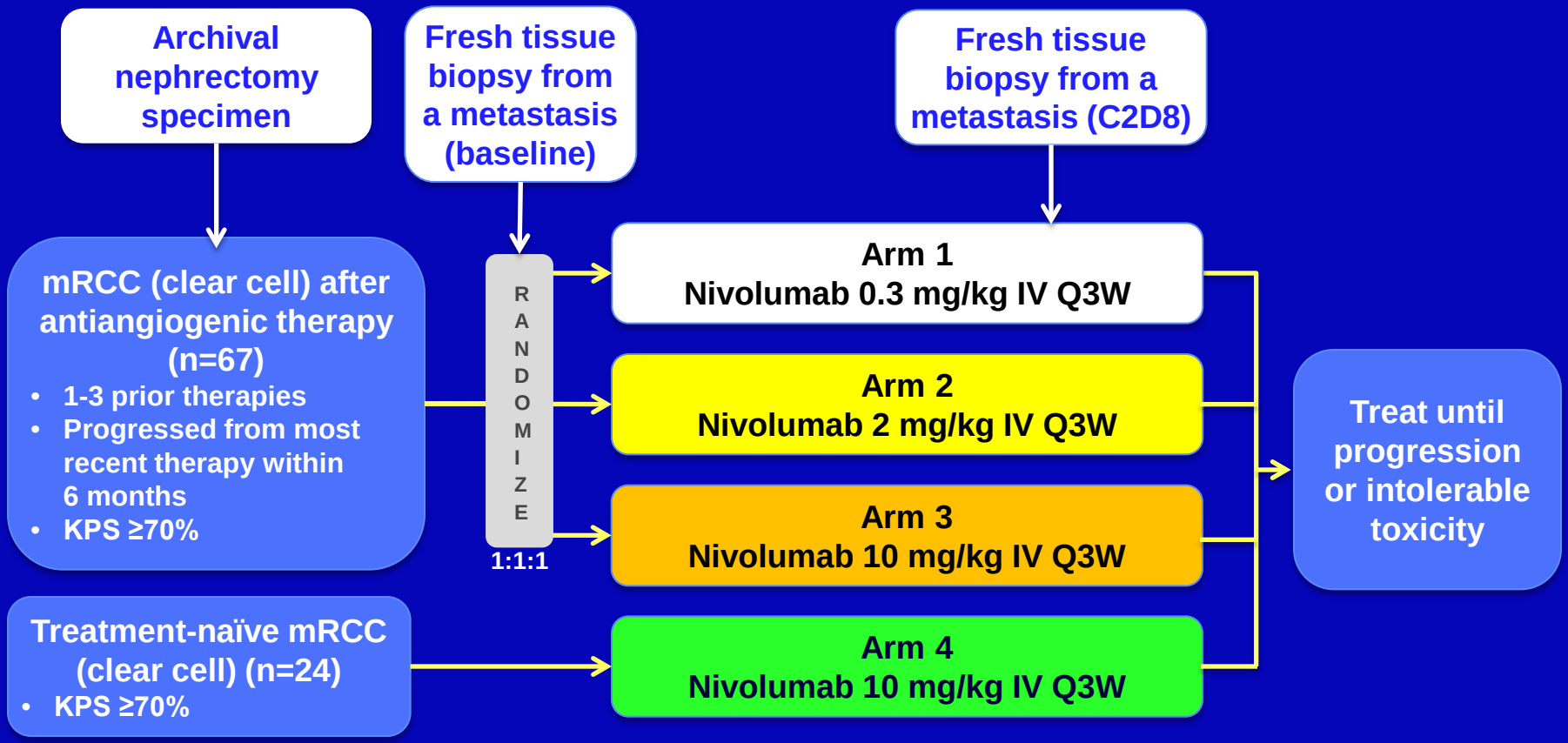
Nivolumab mechanism of action: seeking pharmacodynamic and correlative evidence



Hypothesis	Expected observation
Nivolumab reactivates T cells, resulting in expansion and tumor-directed migration	↑ in CD3+ and CD8+ cells and transcripts in tumor biopsies
Cytokines associated with T-cell expansion and migration will be released	↑ in IFNγ signaling in tumor microenvironment and serum (CXCL9[a], CXCL10[b])
Pretreatment measures of exhaustion represent a T-cell response that may be stimulated by nivolumab, resulting in antitumor activity	Pretreatment PD-L1 expression on tumor associates with clinical response
Changes in tumor-directed migration of T cells associates with antitumor activity	↑ in CD3+ and/or CD8+ cells associates with clinical response

[a]Monokine induced by gamma interferon (MIG). [b]IFNγ-induced protein 10 (IP-10). APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

Study design



- Serum and whole blood sampled at baseline and throughout study period

CR, complete response; C2D8, cycle 2, day 8.

Clinical activity

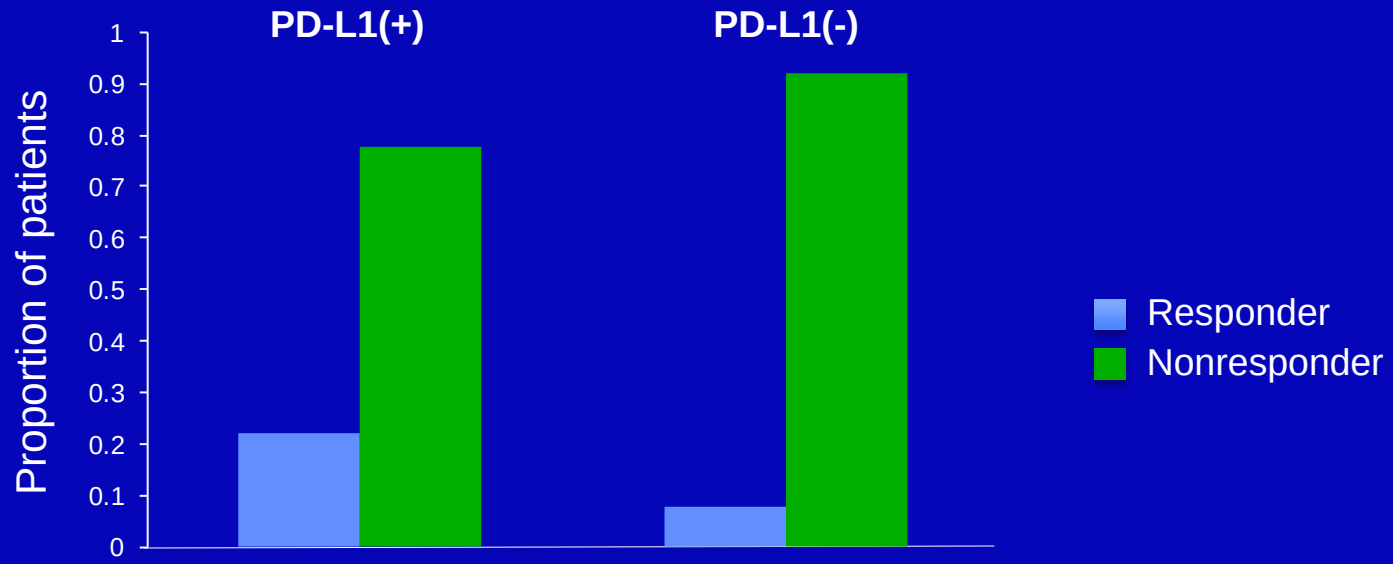
	Previously treated (n=67)			Treatment-naïve (n=23)	All (N=90)[b]
	Nivolumab 0.3 mg/kg (n=22)	**Nivolumab 2.0 mg/kg (n=22)**	**Nivolumab 10 mg/kg (n=23)**	**Nivolumab 10 mg/kg (n=23)**	
Objective response rate, n (%); (95% CI)[a]	2 (9) (1.1-29.2)	5 (23) (7.8-45.4)	5 (22) (7.5-43.7)	3 (13) (2.8-33.6)	**15 (17) (9.6-26.0)**
Best response, n (%)					
Partial response (PR)	2 (9)	5 (23)	4 (17)	3 (13)	**14 (16)**
Unconfirmed PR	0	0	1 (4)	0	**1 (1)**
Stable disease (SD)	5 (23)	6 (27)	8 (35)	10 (43)	**29 (32)**
Progression-free survival rate, % (95% CI)					
24 weeks	18 (6-36)	32 (14-51)	49 (27-68)	45 (24-64)	**36 (26-46)**

- Secondary endpoints: tumor response for all subjects determined as defined by RECIST v1.1 criteria

[a]CR, PR, unconfirmed CR, unconfirmed PR; [b]90 pts were evaluable for response.

Response according to PD-L1 status by IHC

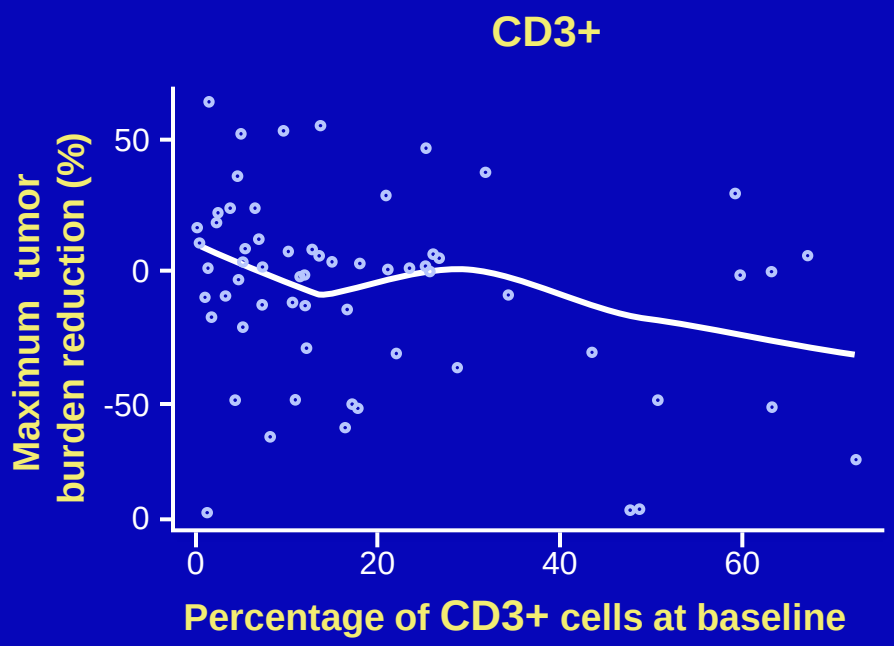
- **56 evaluable fresh pretreatment biopsies:**
  - **Minimum of 100 tumor cells (DAKO assay; antibody 28-8)**
  - **PD-L1+ specimens defined by plasma membrane staining on ≥5% of tumor cells**
  - **18 of 56 (32%) samples were PD-L1+**

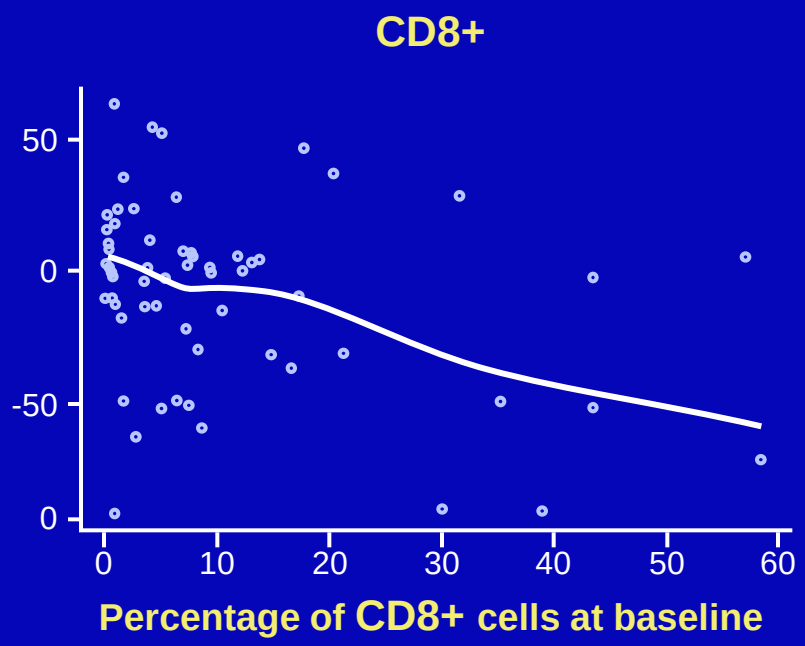


Response rate: 4/18 (22%) 3/38 (8%)

- **81% (22/27) of matched fresh specimens showed a <5% increase in tumor membrane PD-L1 expression from baseline to C2D8**

Tumor T-cell infiltrates at baseline correlate with tumor burden decrease



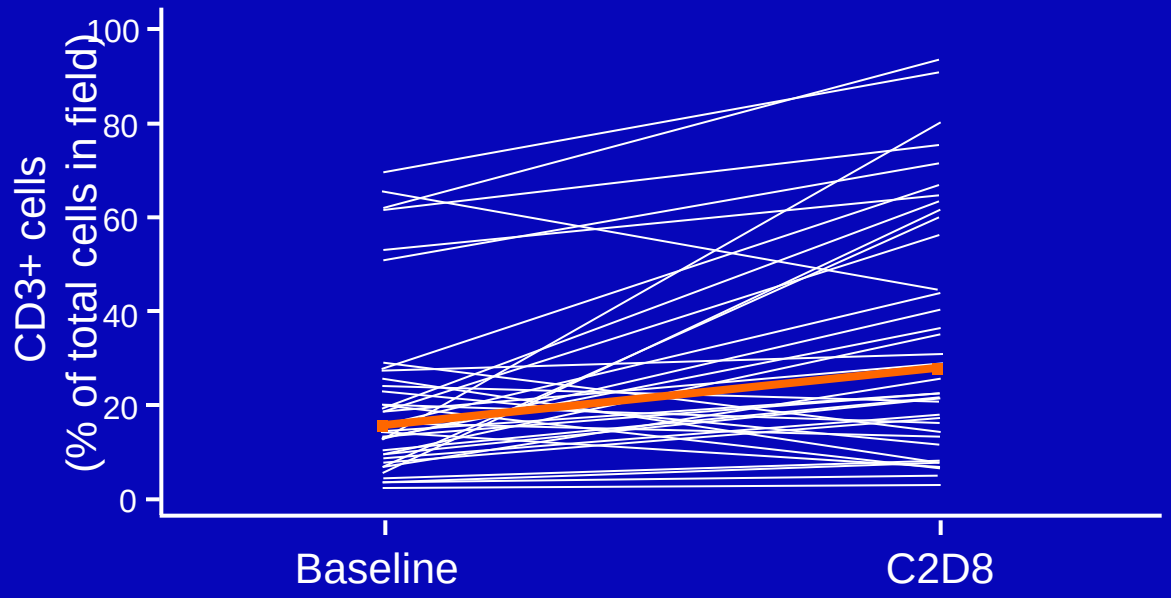


Moving average; NOT linear regression.

CD3/CD8 multiplexed IHC and tumor T-cell infiltrates

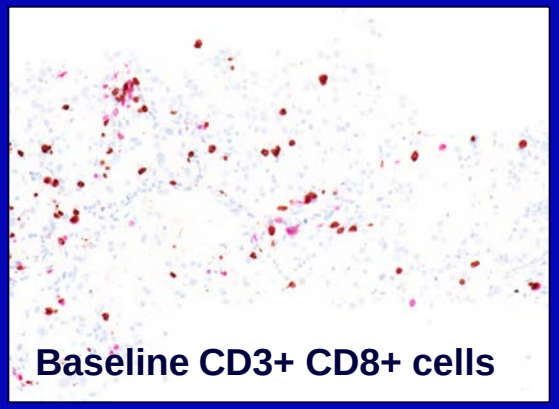
Median increase in T cell infiltrates (CD3/CD8 multiplexed IHC), baseline to C2D8 (%)	All	0.3 mg/kg	2 mg/kg	10 mg/kg	10 mg/kg (naïve)
CD3+	78%	115%	140%	80%	62%
CD8+	88%	257%	162%	139%	61%

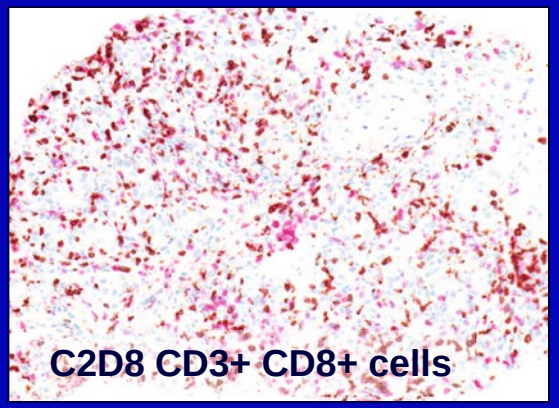
- Increase in TILs seen in previously treated & treatment-naïve patients, independent of dose levels



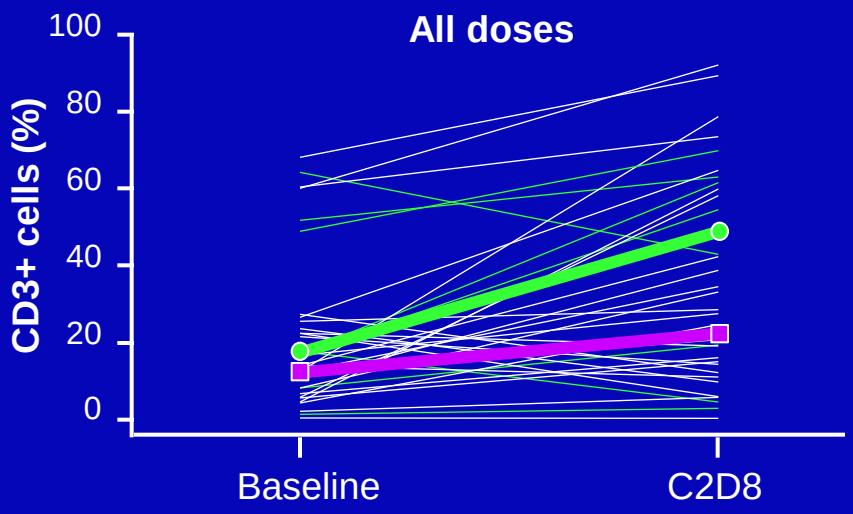
Total number of cells counted in region chosen by pathologist (automated software assessment)

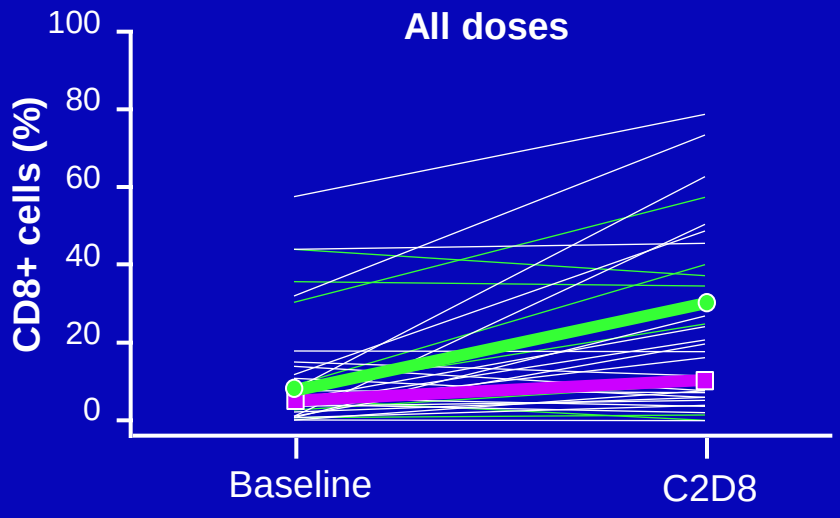
Percentage of CD3+, CD8+ and CD3/8+ determined





Baseline and on-treatment tumor T-cell infiltrates (CD3 and CD8): association with response





N=33

Individual responder

Individual nonresponder

Responder median

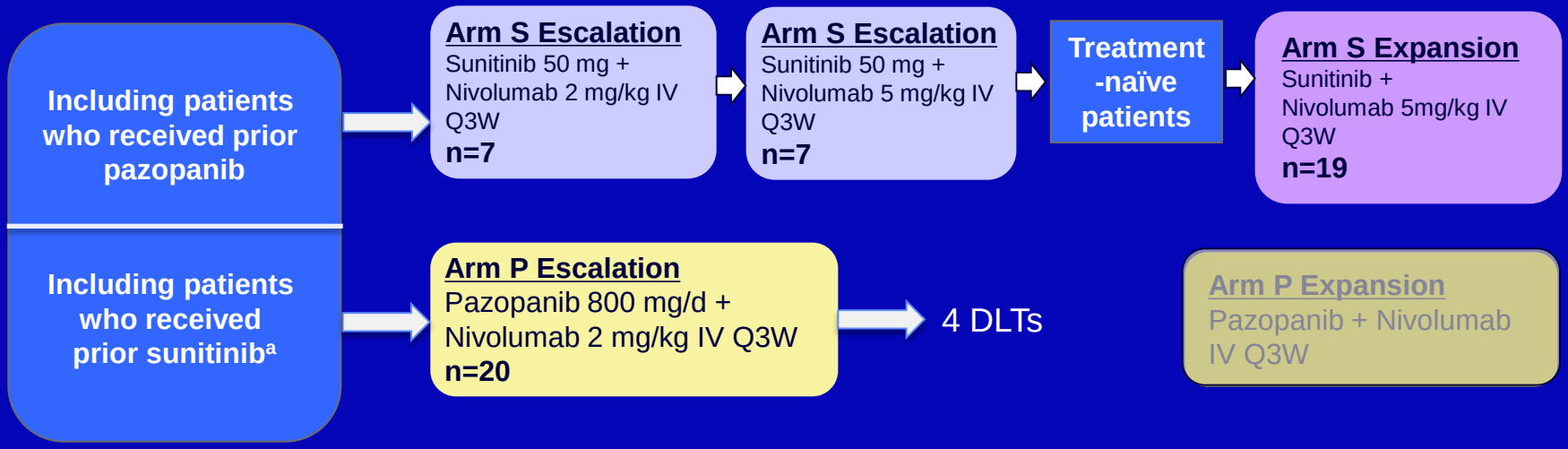
Nonresponder median

Abstract 5010

Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC)

A. Amin, E.R. Plimack, J.R. Infante, M.S. Ernstoff, B. Rini, D.F. McDermott, J. Knox, S.K. Pal, M.H. Voss, P. Sharma, C. Kollmannsberger, D. Heng, J. Spratlin, Y. Shen, J. Kurland, P. Gagnier, H. Hammers

Dose escalation



S + N arm

- S + N2: n=7 pretreated patients
- S + N5: n=7 pretreated patients
- S + N5 expansion: n=19 treatment-naïve patients

P + N arm

- P + N2: n=20 pretreated patients

Baseline patient characteristics

Characteristic	S + N (n=33)	P + N (n=20)
Age, years, mean (SD)	58.0 (9.1)	56.3 (8.5)
Sex, n (%) Male Female	 26 (78.8) 7 (21.2)	 18 (90.0) 2 (10.0)
MSKCC risk category, n (%) Favorable Intermediate Poor	 8 (24.2) 24 (72.7) 1 (3.0)	 4 (20.0) 14 (70.0) 2 (10.0)
Surgery, n (%)	33 (100)	20 (100)
Radiotherapy, n (%)	5 (15.2)	10 (50)
Systemic therapy, n (%) VEGF-TKI Bevacizumab Cytokine mTOR inhibitor	14 (42.4) 5 (15.2) 2 (6.1) 9 (27.3) 0	20 (100) 17 (85.0) 0 10 (50.0) 3 (15.0)
Prior lines of therapy, n (%) 1 ≥2	 14 (42.4) 0	 14 (70.0) 6 (30.0)

Antitumor activity (per RECIST 1.1)

	S + N (n=33)	P + N (n=20)
Confirmed ORR, n (%) 95% CI	17 (52) 33.5-69.2	9 (45) 23.1-68.5
Median duration of response, weeks (range)	37.1 (18.1-80+)[a]	30.1 (12.1-90.1+)[b]
Ongoing responses, % (n/N)	59 (10/17)	33 (3/9)
Best overall response, n (%)		
Complete response	1 (3)	0
Partial response	16 (48)	9 (45)
Stable disease	10 (30)	7 (35)
Progressive disease	1 (3)	4 (20)
Unable to determine	4 (12)	0

[a]Median follow-up 54.7 weeks; [b]Median follow-up 76.5 weeks.
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).
ORR, objective response rate.

Grade 3-4 treatment-related AEs in ≥ 10% of patients

	S + N (n=33)		P + N2 (n=20)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event, n (%)	33 (100)	27 (81.8)	20 (100)	14 (70.0)
Hypertension	16 (48.5)	6 (18.2)	5 (25.0)	2 (10.0)
Increased ALT	13 (39.4)	6 (18.2)	5 (25.0)	4 (20.0)
Hyponatremia	6 (18.2)	5 (15.2)	0	0
Increased lymphocyte count	6 (18.2)	5 (15.2)	1 (5.0)	1 (5.0)
Diarrhea	20 (60.6)	3 (9.1)	12 (60.0)	4 (20.0)
Increased AST	12 (36.4)	3 (9.1)	6 (30.0)	4 (20.0)
Fatigue	27 (81.8)	3 (9.1)	12 (60.0)	3 (15.0)

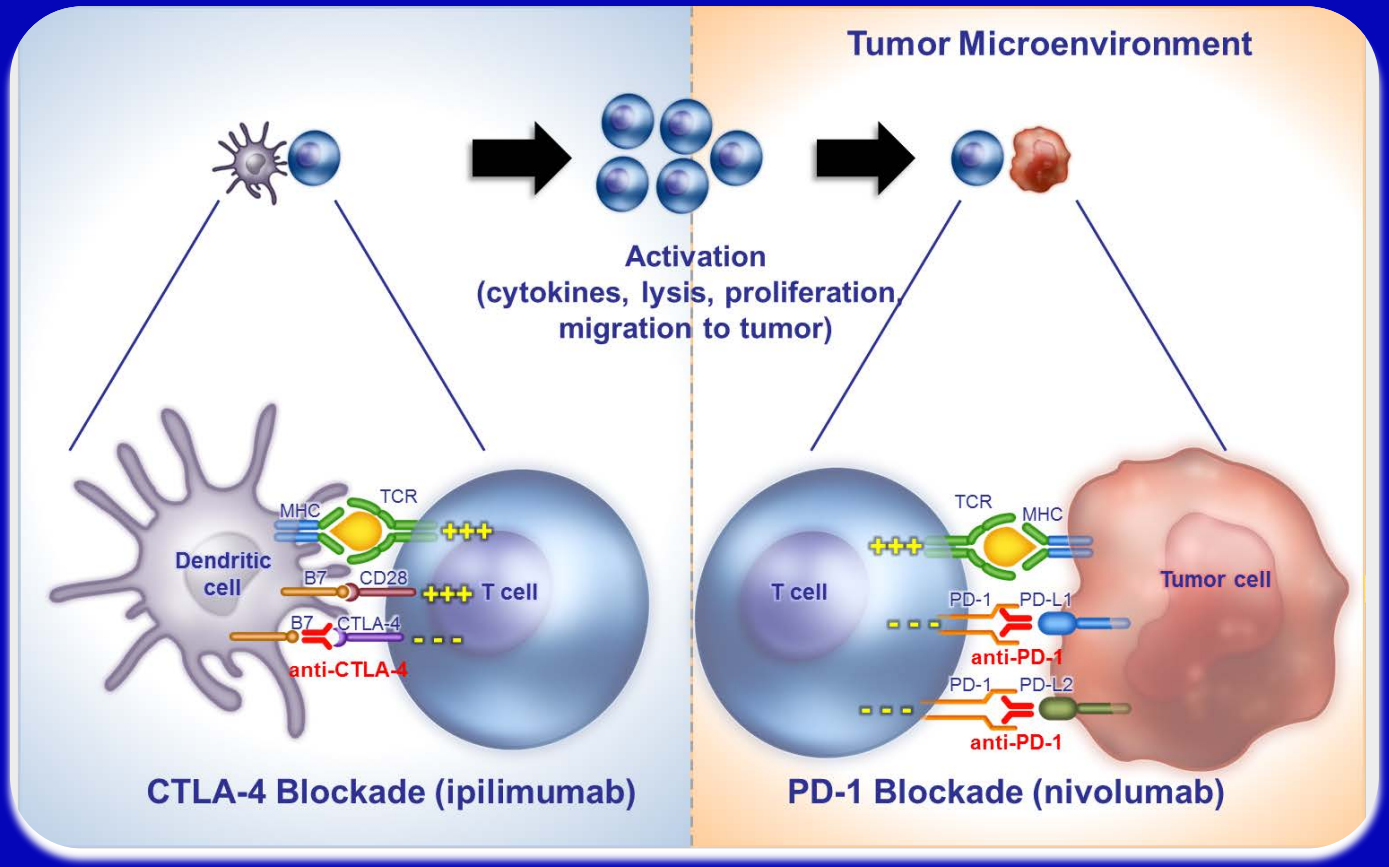
- **Patients with any event (any grade): 53 (100%)**
- **No grade 5 treatment-related AEs were observed**
- **Most toxicities were consistent with the known profile of TKIs**

Abstract 4504

Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC)

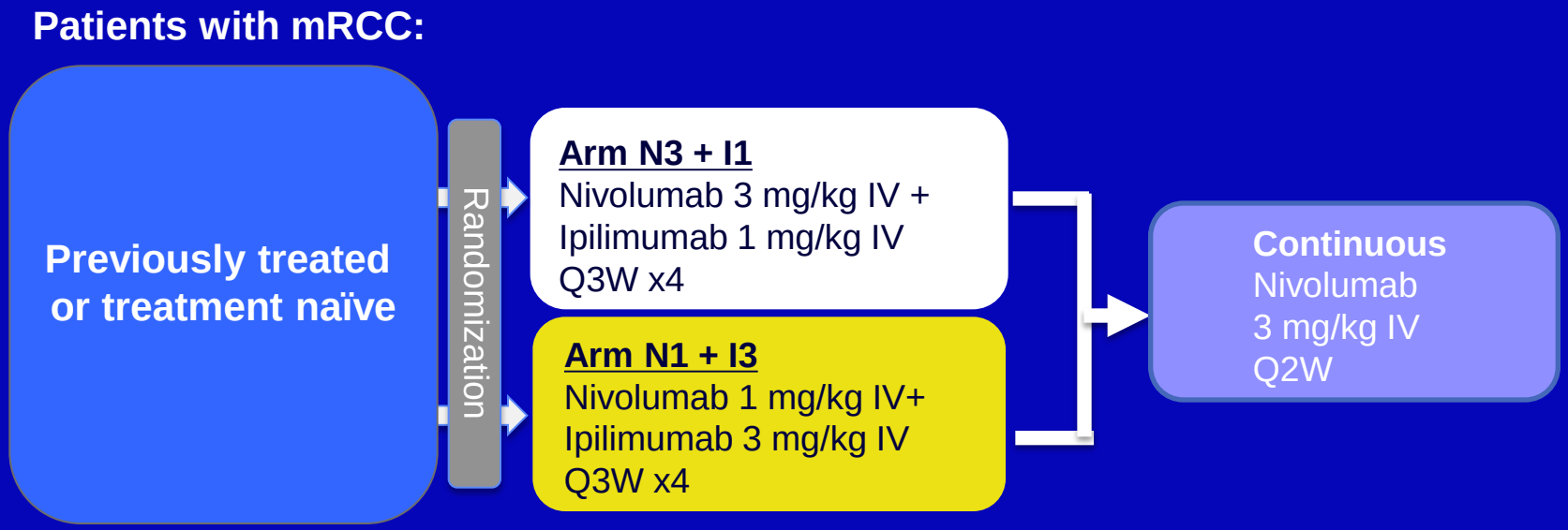
H. Hammers, E.R. Plimack, J.R. Infante, M.S. Ernstoff, B. Rini, D.F. McDermott, A. Razak, S.K. Pal, M.H. Voss, P. Sharma, C. Kollmannsberger, D. Heng, J. Spratlin, Y. Shen, J.F. Kurland, P. Gagnier, A. Amin

Mechanism of action



MHC, major histocompatibility complex; TCR, T-cell receptor.

CA209-016 (NCT01472081): phase I study design (N + I cohort)

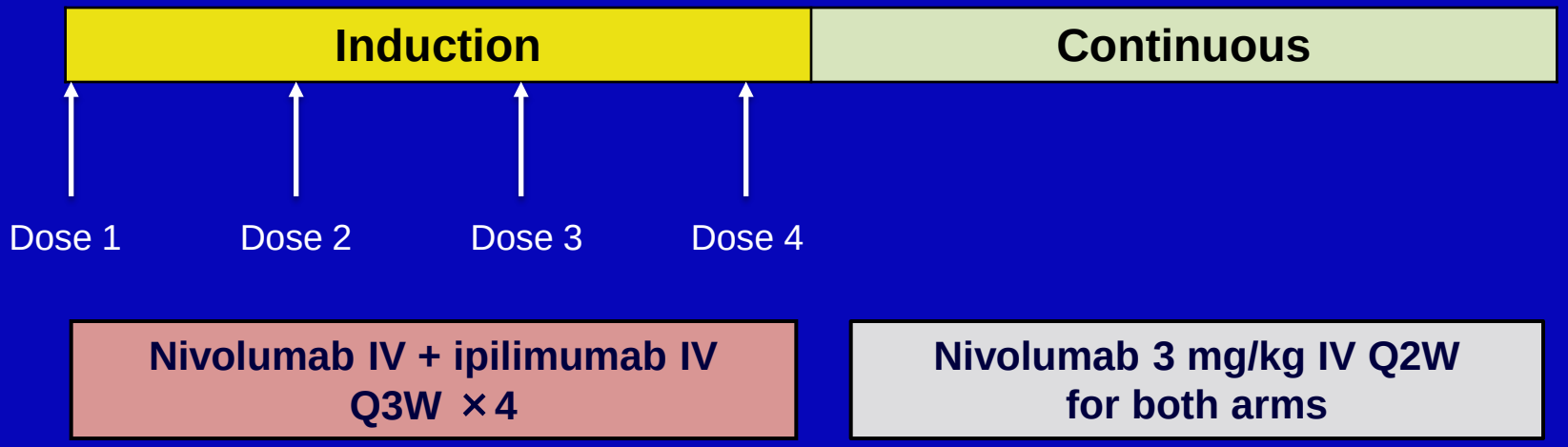


- **Primary endpoint: Safety (AEs, laboratory tests)**
- **Secondary endpoint: Efficacy (ORR, duration of response, PFS)**
- **Exploratory endpoint: Response by tumor PD-L1 status**
- **Study assessments: Tumor response (RECIST v1.1) evaluated at screening, every 6 weeks (first 4 assessments), then every 12 weeks until disease progression**

ORR, objective response rate.
TKI cohort presented by Amin A *et al.* ASCO 2014, Abstract 5010

Nivolumab plus Ipilimumab Treatment administration

- **Dosing schedule:**



- **At induction visits, patients received 2 infusions**
  - **1st infusion was always nivolumab (1 or 3 mg/kg)**
  - **Ipilimumab (1 or 3 mg/kg) infusion was started ≥30 min after completion of nivolumab infusion**

Baseline patient characteristics

Characteristic	N3 + I1 (n=21)	N1 + I3 (n=23)
Age, y, mean (SD)	53.2 (8.26)	53.5 (11.24)
Sex, male, n (%)	17 (81.0)	21 (91.3)
MSKCC risk category, n (%) Favorable Intermediate Poor	 5 (23.8) 16 (76.2) 0	 5 (21.7) 18 (78.3) 0
Radiotherapy, n (%)	7 (33.3)	8 (34.8)
Systemic treatments, n (%) Antiangiogenic Cytokine mTOR inhibitor	17 (81.0) 10 (47.6) 12 (57.1) 5 (23.8)	18 (78.3) 15 (65.2) 6 (26.1) 7 (30.4)
Prior lines of therapy, n (%) 0 1 2 >2	 4 (19.0) 11 (52.4) 3 (14.3) 3 (14.3)	 5 (21.7) 11 (47.8) 1 (4.3) 6 (26.1)

- **All patients had prior nephrectomy except for 1 in the N3 + I1 arm, and 2 in N1 + I3 arm**

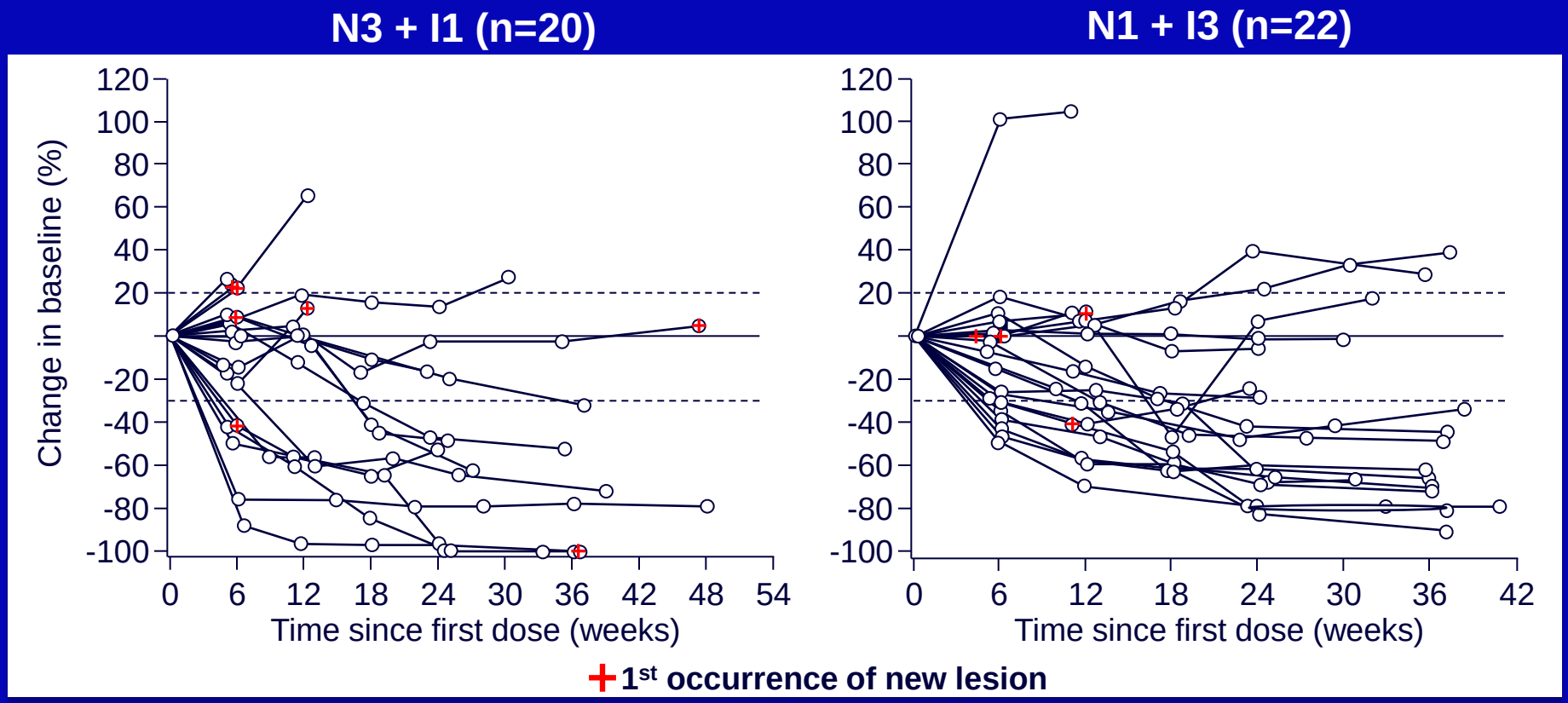
Antitumor activity

	N3 + I1 (n=21)	N1 + I3 (n=23)
Confirmed ORR, n (%) 95% CI	9 (43) 21.8-66.0	11 (48) 26.8-69.4
Median duration of response, weeks (range)[a]	31.1 (4.1+-42.1+)[b]	NR (12.1+-35.1+)[c]
Ongoing responses, % (n/N)	78 (7/9)	82 (9/11)
Best objective response, n (%) Complete response Partial response Stable disease Progressive disease Unable to determine	 0 9 (43) 5 (24) 5 (24) 1 (5)	 1 (4) 10 (43) 8 (35) 3 (13) 1 (4)
24-week PFS, % (95% CI)	65 (40-82)	64 (41-80)

[a]Due to the high percentage of ongoing responses, median duration of response may be misleading; [b]Median follow-up 36.1 weeks; [c]Median follow-up 40.1 weeks

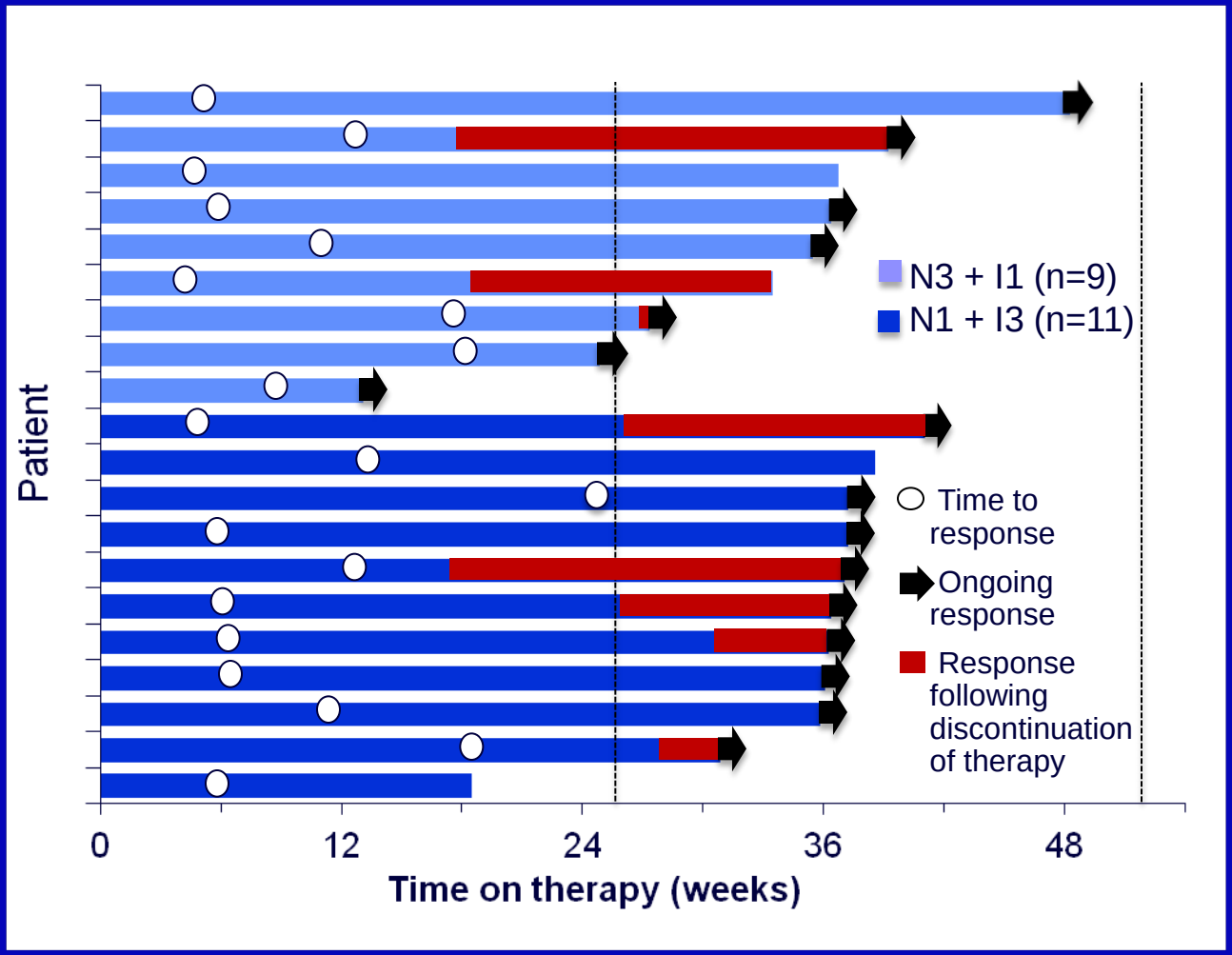
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).

Change from baseline in target tumor burden



Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.

Time to response and duration of response



Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

Ongoing responders:
N3 + I1 = 7/9 (77.8%)
N1 + I3 = 9/11 (81.8%)

Patients discontinuing treatment (not due to progression) who continued to respond:
N3 + I1 = 3/9 (33.3%)
N1 + I3 = 5/11 (45.5%)

- **Median duration of response (DOR) for N3 + I1 was 31 weeks**
- **Median DOR was not reached in the N1 + I3 arm at 40.1 weeks follow-up**

Nivolumab plus Ipilimumab Treatment-related AEs

	N3 + I1 (n=21)		N1 + I3 (n=23)	
	All	Grade 3-4	All	Grade 3-4
Total patients with an event, n (%)	16 (76.2)	6 (28.6)	23 (100)	14 (60.9)
Fatigue	11 (52.4)	0	16 (69.6)	2 (8.7)
Rash	8 (38.1)	0	4 (17.4)	0
Pruritus	6 (28.6)	0	5 (21.7)	0
Diarrhea	6 (28.6)	1 (4.8)	8 (34.8)	3 (13.0)
Dry skin	4 (19.0)	0	3 (13.0)	0
Nausea	4 (19.0)	0	9 (39.1)	0
Pyrexia	4 (19.0)	0	4 (17.4)	0
Chills	3 (14.3)	0	2 (8.7)	0
Constipation	3 (14.3)	0	2 (8.7)	0
Hypothyroidism	3 (14.3)	0	6 (26.1)	0
Lipase increased	3 (14.3)	3 (14.3)	6 (26.1)	6 (26.1)
Amylase increased	1 (4.8)	1 (4.8)	3 (13.0)	1 (4.3)
ALT increased	1 (4.8)	0	9 (39.1)	6 (26.1)
AST increased	0	0	9 (39.1)	3 (13.0)

- **No grade 5 treatment-related AEs were reported.**

Hammers et al. JCO 32S; Abstr 4504,2014

Nivolumab plus Ipilimumab
Treatment-related select AE categories

Category, n (%)	N3 + I1 (n=21)		N1 + I3 (n=23)	
	All	Grade 3-4	All	Grade 3-4
Endocrinopathy	3 (14.3)	0	8 (34.8)	0
Gastrointestinal disorder	6 (28.6)	1 (4.8)	9 (39.1)	4 (17.4)
Hepatic	1 (4.8)	0	9 (39.1)	6 (26.1)
Infusion reaction	2 (9.5)	0	2 (8.7)	0
Pulmonary	1 (4.8)	0	2 (8.7)	0
Renal disorder	2 (9.5)	0	3 (13.0)	0
Skin disorder	8 (38.1)	0	9 (39.1)	0

- **No high-grade pulmonary AEs, including pneumonitis, were observed**

Hammers et al. JCO 32S; Abstr 4504,2014

Nivolumab Next Steps

- Nivolumab is being compared with everolimus in a phase III trial for patients who progressed on VEGF targeted therapy with an overall survival endpoint

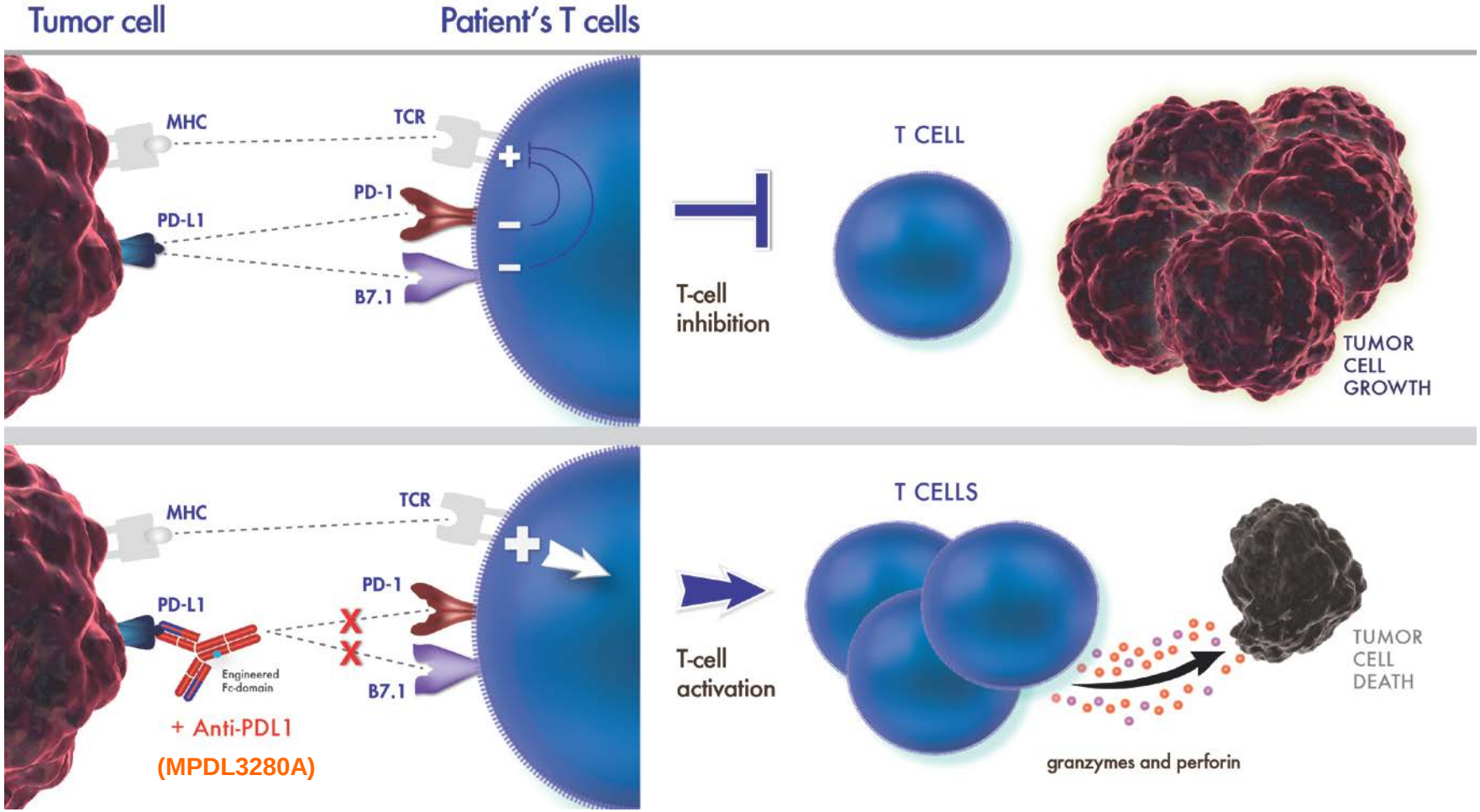
- A phase III trial is planned in the first-line setting for nivolumab plus ipilimumab versus sunitinib

Trials to Watch with Other Checkpoint Inhibitors

- A phase II trial is underway for MPDL3280A plus bevacizumab versus MPDL3280A monotherapy versus sunitinib in first line therapy for metastatic RCC (Genentech)

- Phase I trial of MK-3475 plus pazopanib (Merck/GSK) is underway and for MK-3475 plus axitinib (Merck/Pfizer) is planned

MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1



- Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
- Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety

Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic urothelial bladder cancer (UBC)

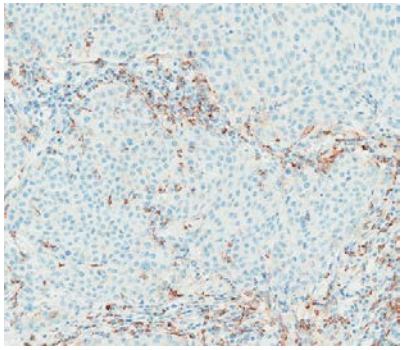
Thomas Powles,[1] Nicholas J. Vogelzang,[2] Gregg Fine,[3] Joseph Paul Eder,[4] Fadi Braiteh,[5] Yohann Loriot,[6] Cristina Cruz,[7] Joaquim Bellmunt,[8] Howard Burris,[9] Siew-leng Melinda Teng,[3] Xiaodong Shen,[3] Hartmut Koeppen,[3] Priti S. Hegde,[3] Daniel S. Chen,[3] Daniel P. Petrylak[4]

[1]Barts Cancer Institute, Queen Mary University of London; [2]University of Nevada School of Medicine and US Oncology/Comprehensive Cancer Centers of Nevada; [3]Genentech, Inc.; [4]Yale Cancer Center; [5]Comprehensive Cancer Centers of Nevada; [6]Gustave Roussy, University of Paris-Sud; [7]Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital; [8]Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School; [9]Sarah Cannon Research Institute

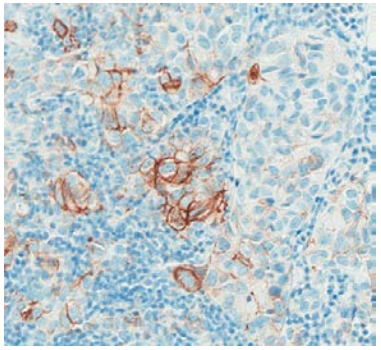
PD-L1 Prevalence in Solid Tumors

Indication	PD-L1+ (IC)	PD-L1+ (TC)
NSCLC (n = 184)	26%	24%
UBC (n = 205)	**27%**	**11%**
RCC (n = 88)	25%	10%
Melanoma (n = 59)	36%	5%
HNSCC (n = 101)	28%	19%
Gastric cancer (n = 141)	18%	5%
CRC (n = 77)	35%	1%
Pancreatic cancer (n = 83)	12%	4%

ICs; tumor-infiltrating immune cells.
TCs; tumor cells.
PD-L1+ if ≥ 5% ICs or TCs were positive for PD-L1 staining (Genentech/Roche PD-L1 IHC).



UBC IHC (ICs)



UBC IHC (TCs)

MPDL3280A: Treatment-Related AEs

Safety-evaluable population with UBC in Phase I expansion

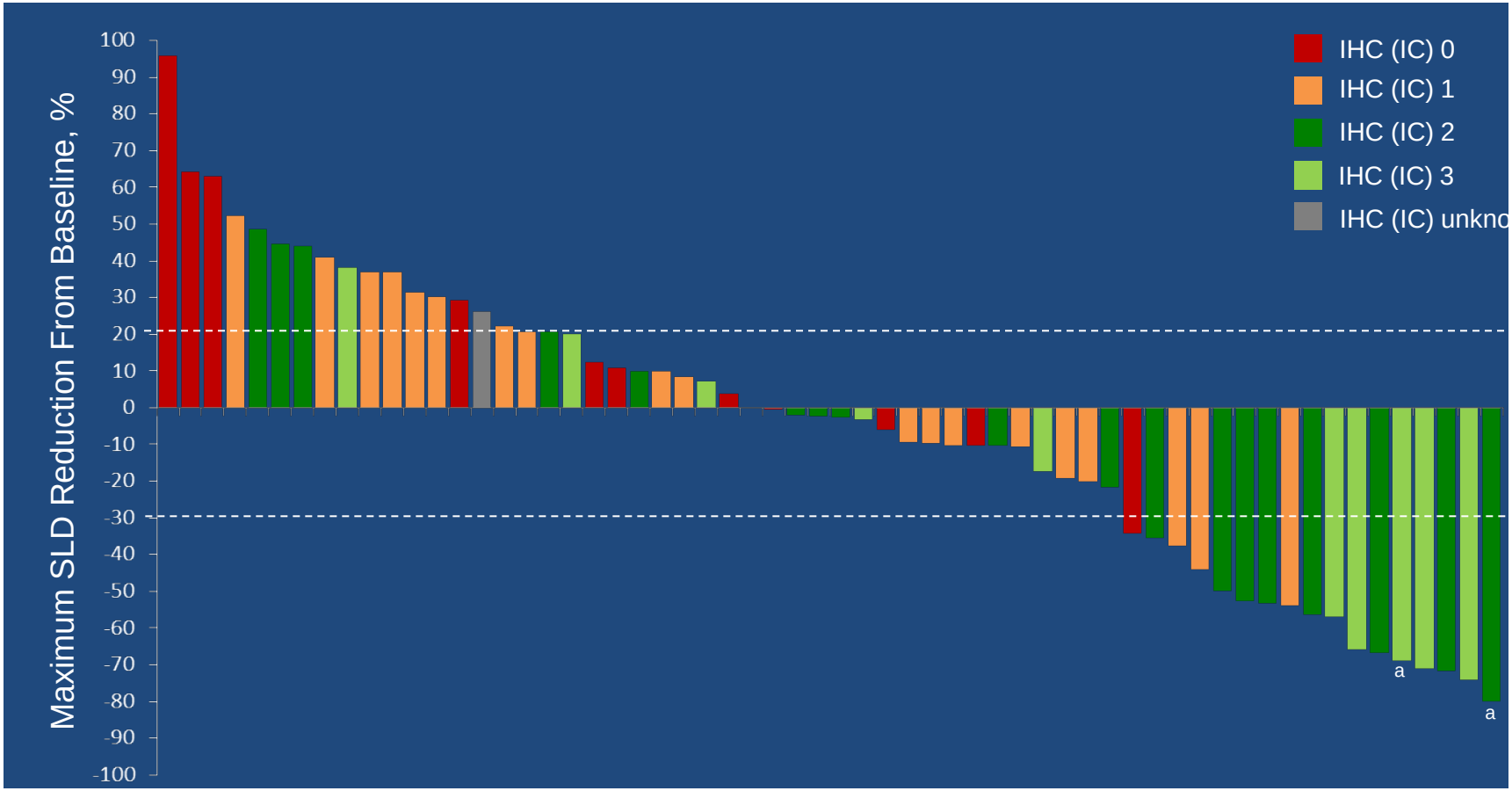
Patients With UBC N = 68	**All Grade n (%)**	**Grade 3-4[a] n (%)**
All	39 (57%)	3 (4%)
Decreased appetite	8 (12%)	0
Fatigue	8 (12%)	0
Nausea	8 (12%)	0
Pyrexia	6 (9%)	0
Asthenia	5 (7%)	1 (2%)
Chills	3 (4%)	0
Influenza-like illness	3 (4%)	0
Lethargy	3 (4%)	0

- MPDL3280A was well tolerated in patients with UBC, including the elderly and patients with impaired renal function
- No treatment-related grade 4 or 5 AEs
- No investigator-assessed immune-related toxicities were reported as of the clinical cutoff

[a] Additional treatment-related Grade 3/4 AEs: thrombocytopenia and decrease in blood phosphorus (1 each).
Clinical data cutoff was Jan 1, 2014.
Includes events occurring in ≥ 3 patients.

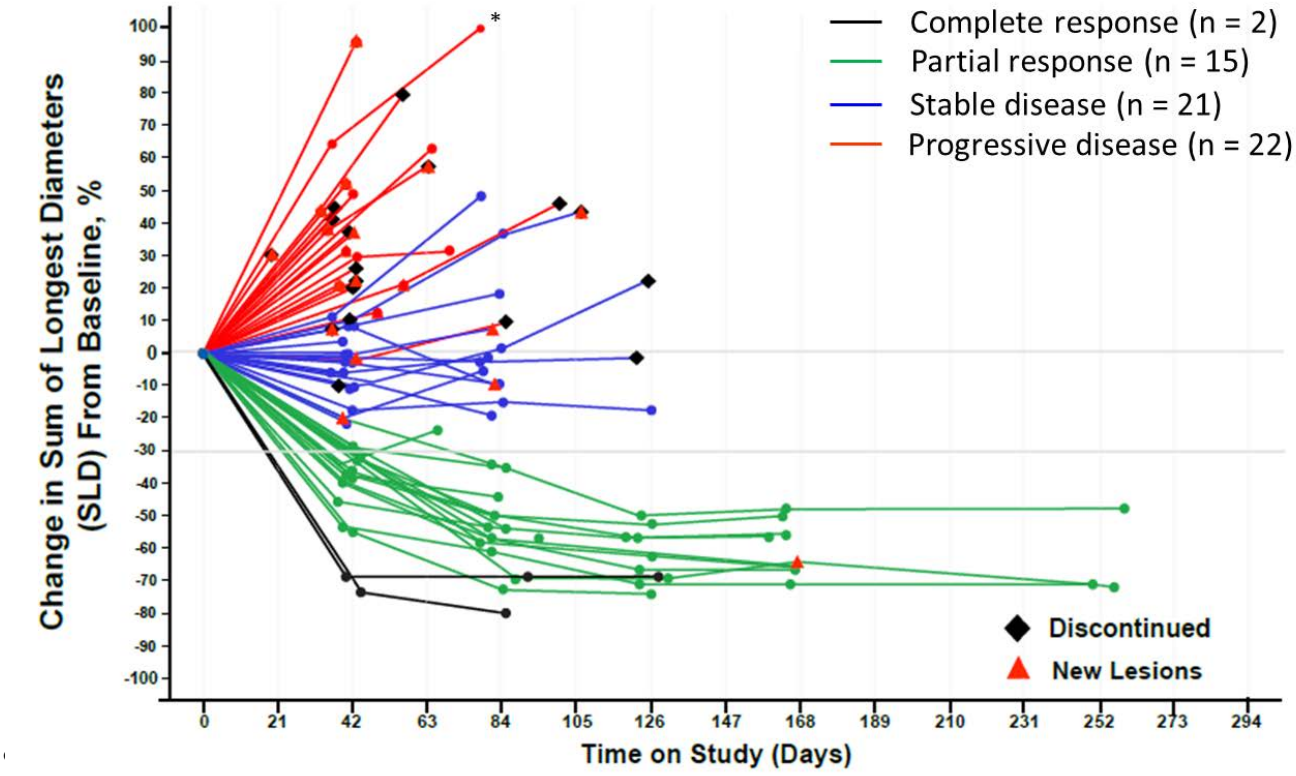
MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion



[a] Patients with complete responses. Patients with a CR had < 100% reduction of the target lesions due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.
IC; tumor-infiltrating immune cells.
Responses are investigator assessed, Best response is not known for 7 patients.
Diagnostic/(Dx) PD-L1 positive: IHC 3 (≥ 10% of ICs PD-L1+) and IHC 2 (≥ 5% but < 10% of ICs PD-L1+).
Diagnostic/(Dx) PD-L1 negative: IHC 1 (≥ 1% but < 5% ICs PD-L1+) and IHC 0 (<1% ICs PD-L1+).
Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline. Clinical data cutoff was Jan 1, 2014.

MPDL3280A: Tumor Burden Over Time in UBC



days)

- Median duration of response has not been reached
  - 0.1+ to 30.3+ weeks IHC (IC) 2 or 3 and 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1

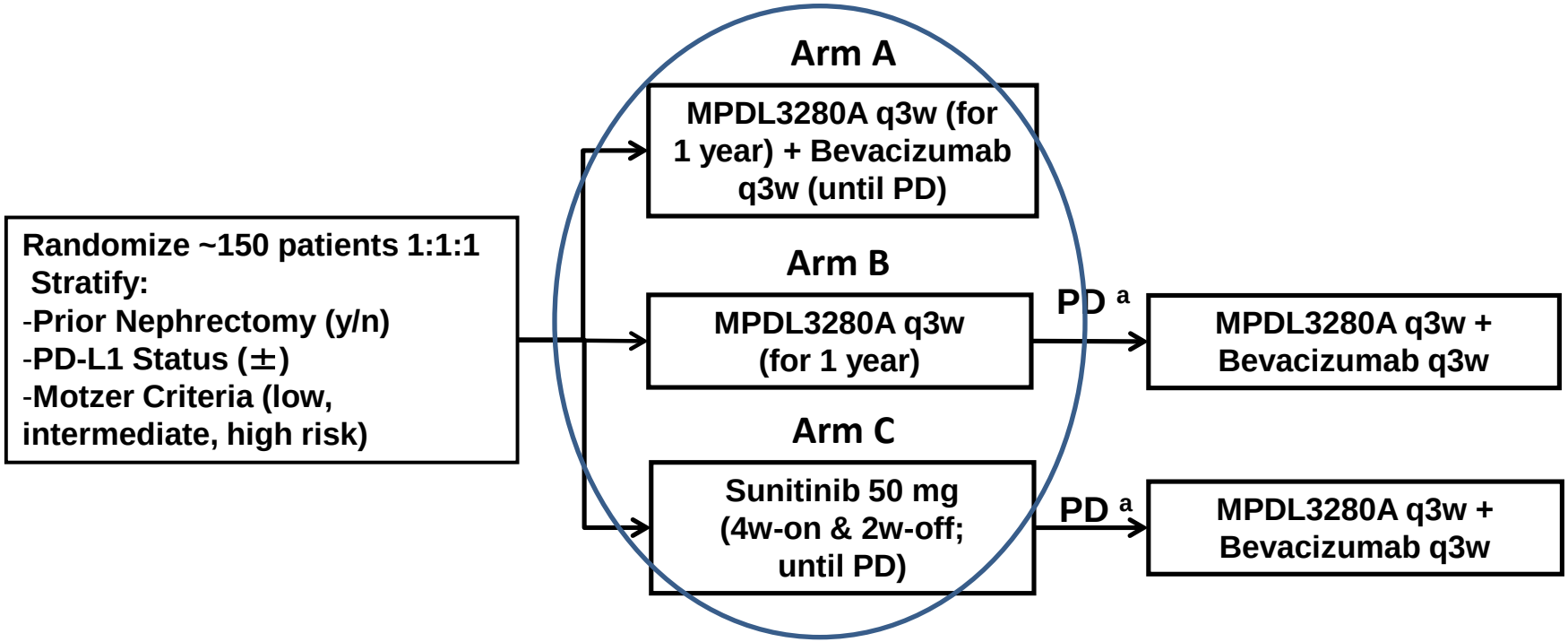
Best response is not known for 7 patients.
Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline and at least 1 post-baseline measurement.
Clinical data cutoff was Jan 1, 2014.

MPDL3280A in urothelial carcinoma

- Low toxicity even in elderly patients
  - No grade 4-5 events
- High efficacy in PDL1 positive patients
  - Primarily related to infiltrating immune cells
- Activity in PDL1 negative patients similar to our standard salvage chemotherapies
- 94% of responders still responding at data cutoff
- Further development is ongoing
  - Large single arm phase II study recruiting at MSK and other centers

Genentech Randomized Phase II trial Study Design

Study Schema



PD = progressive disease; PD – L1 = programmed cell death–1 ligand 1; q3w = every 3 weeks.

[a] Mandatory biopsy at progressive disease to be eligible for crossover.