Presentation 810O
Abstract 8020

Randomized, dose-ranging phase II trial of nivolumab for metastatic renal cell carcinoma (mRCC)

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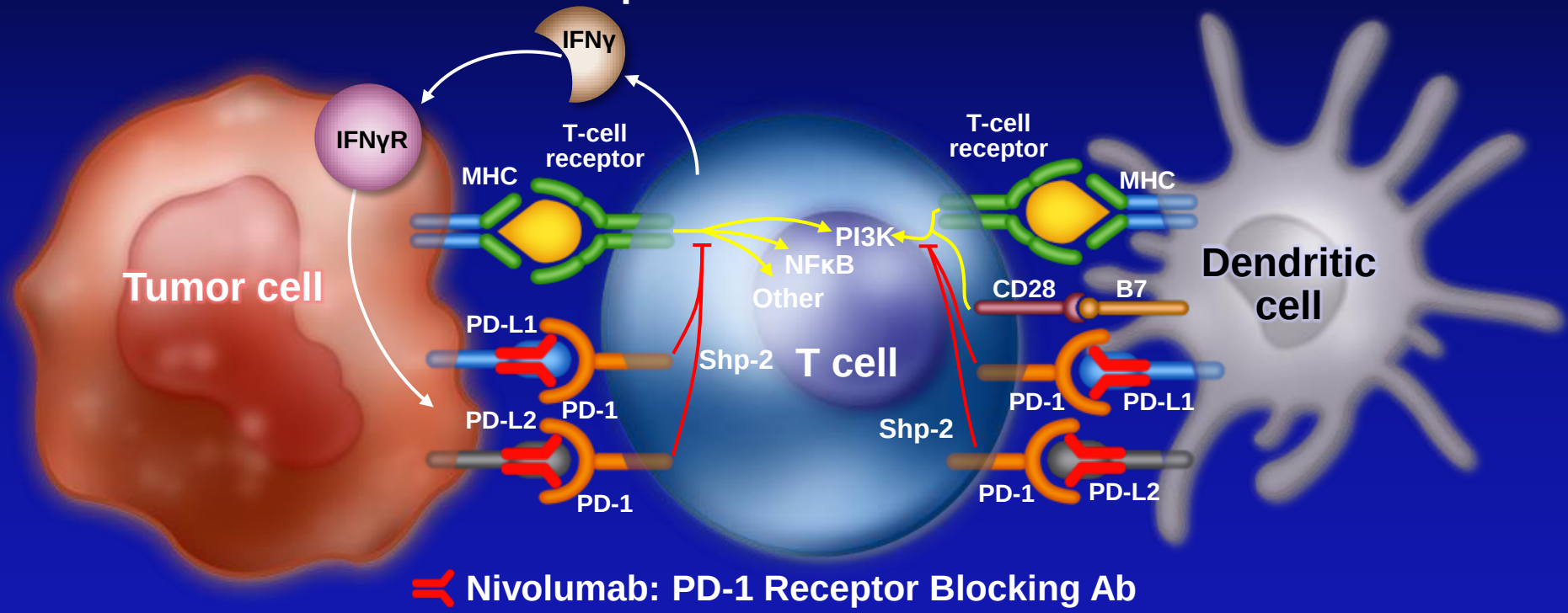
Disclosures

- R. Motzer has been a consultant for Pfizer, Merck, Genentech, and Aveo Oncology, and has received research funding from Novartis, GlaxoSmithKline, Aveo, and Bristol-Myers Squibb

- Study sponsored by Bristol-Myers Squibb

Introduction

- 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

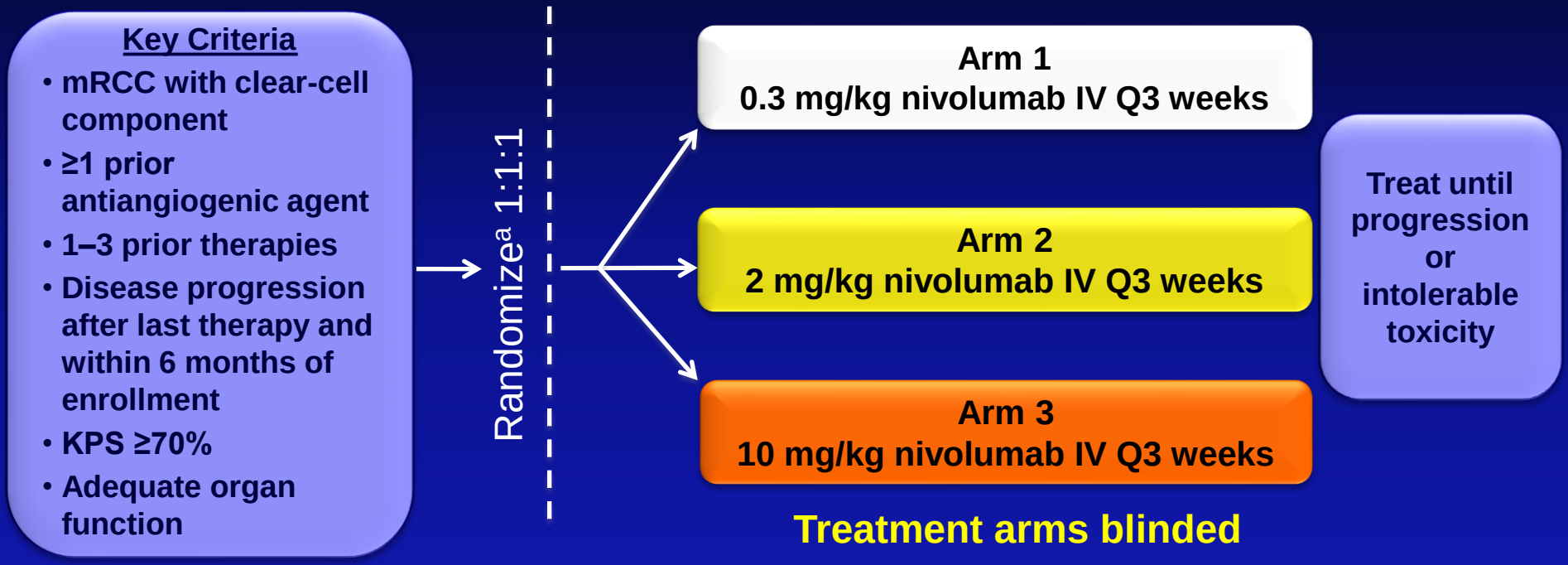
1. Hamid O, et al. Exp Opin Biol Ther. 2013;13:847–61. 2. Brahmer JR, et al. J Clin Oncol. 2010;28:3167–75. 3. Nurieva RI, et al. Immunol Rev. 2011;241:133–44. 4. Hamanishi J, et al. Proc Natl Acad Sci U S A. 2007;104:3360–5.

Introduction

- Nivolumab showed encouraging efficacy in patients with previously treated mRCC in a phase I study[1]
- Phase I results in varied malignancies showed no dose–toxicity relationship (0.1–10 mg/kg)[1]
- A randomized phase II trial evaluating different doses was warranted to assess dose–response relationship and activity of nivolumab in patients with mRCC

1. Topalian SL, et al. N Engl J Med. 2012;366:2443–54.

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: To assess PFS, ORR, OS, and safety

Exploratory Objectives: To assess efficacy by PD-L1 expression

ClinTrials.gov NCT01354431

[a]Treatment arms 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).

Study assessments

Measure	Frequency
Efficacy	• Every 6 weeks for first 12 months • Every 12 weeks thereafter until progression or treatment discontinuation, whichever occurred later
Safety[a]	• Every clinic visit

[a]Adverse events assessed by the Common Terminology Criteria for Adverse Events v4.0.

- **Treatment until progression or intolerance**
  - **Treatment beyond progression was allowed if clinical benefit noted**

Statistical analysis

- **Primary endpoint**
  - PFS evaluated using a two-sided 20% level stratified log-rank trend test
  - Planned sample size: 150 patients (116 events)
  - 90% power to detect a dose–response relationship (assuming median PFS by dose of 4.0, 5.7, and 8.1 months)
- **Data cutoff**
  - Primary PFS analysis: May 15, 2013
  - ORR and safety analyses: May 15, 2013
  - OS and duration of response analyses: March 5, 2014

Patient demographics

	Nivolumab, mg/kg			
	0.3 (n = 60)	2.0 (n = 54)	10 (n = 54)	Total (N = 168)
Mean age, y	61	61	61	61
Sex, male, %	68	74	74	72
MSKCC risk factors, %[a]				
0	33	33	33	33
1	43	41	41	42
2–3	23	26	26	25
KPS, %[b]				
70 or 80	37	56	46	46
90 or 100	63	44	52	54
Site of metastasis, %				
Lung	77	72	72	74
Lymph node	48	65	63	58
Liver	25	24	35	28

[a]Total ≠100% due to rounding. [b]1 patient (2%) in the 10 mg/kg group had a worsening of KPS score to <70.

Prior therapy 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 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

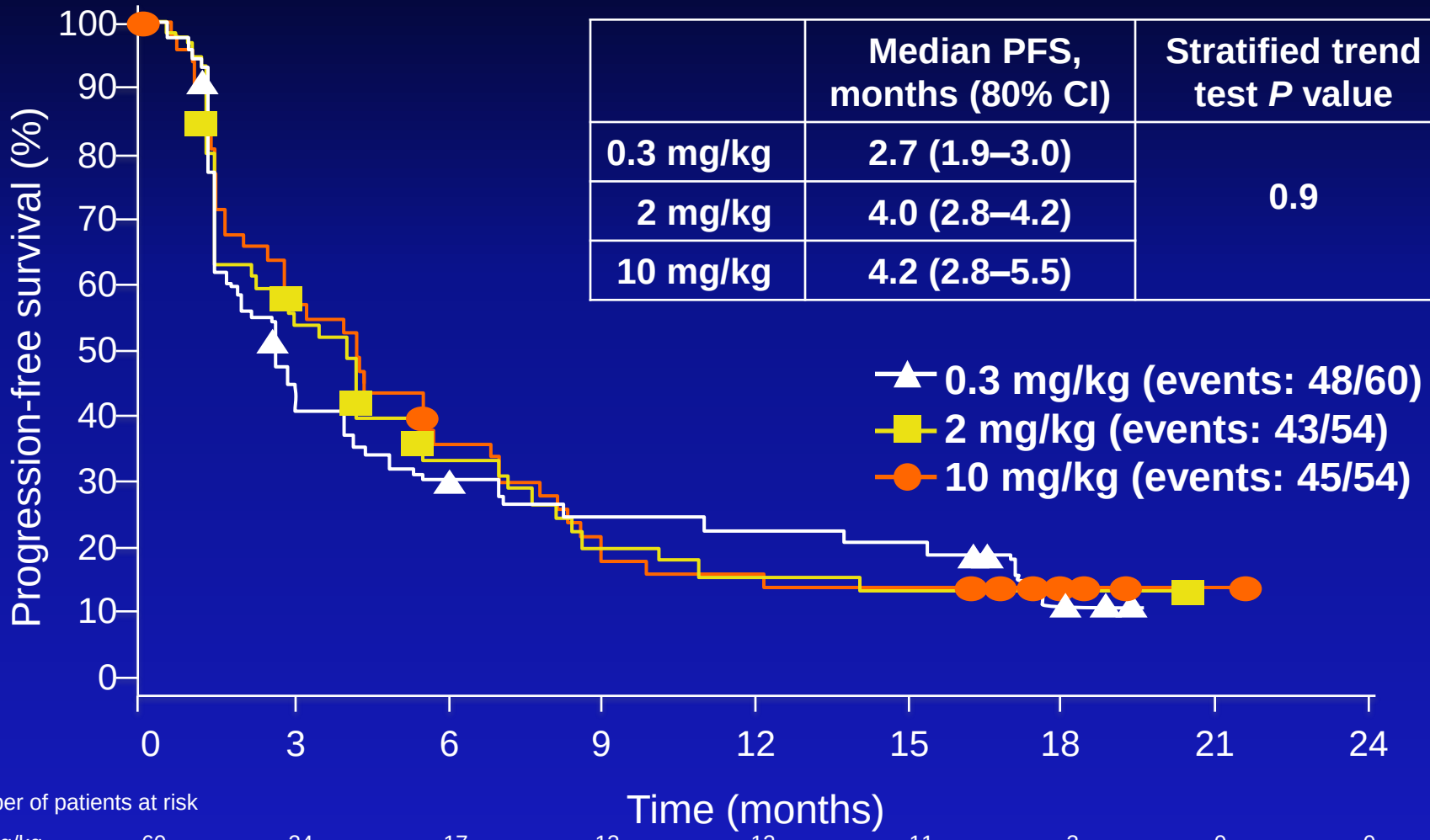
[a]1 patient (2%) in the 0.3 mg/kg group received >3 prior systemic regimens in the metastatic setting. [b]>20% of patients in any group.

Patient disposition

	Nivolumab, mg/kg			
	0.3 (n = 60)	2.0 (n = 54)	10 (n = 54)	Total (N = 168)
Patients treated, n	59	54	54	167
Doses per patient, median (range)	6 (1–29)	8 (1–32)	8 (1–31)	--
Patients discontinued, %	85	91	82	86
Primary reason for discontinuation, %				
Disease progression	81	74	69	75
Drug-related toxicity	2	9	7	6
Other	2	7	6	5

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

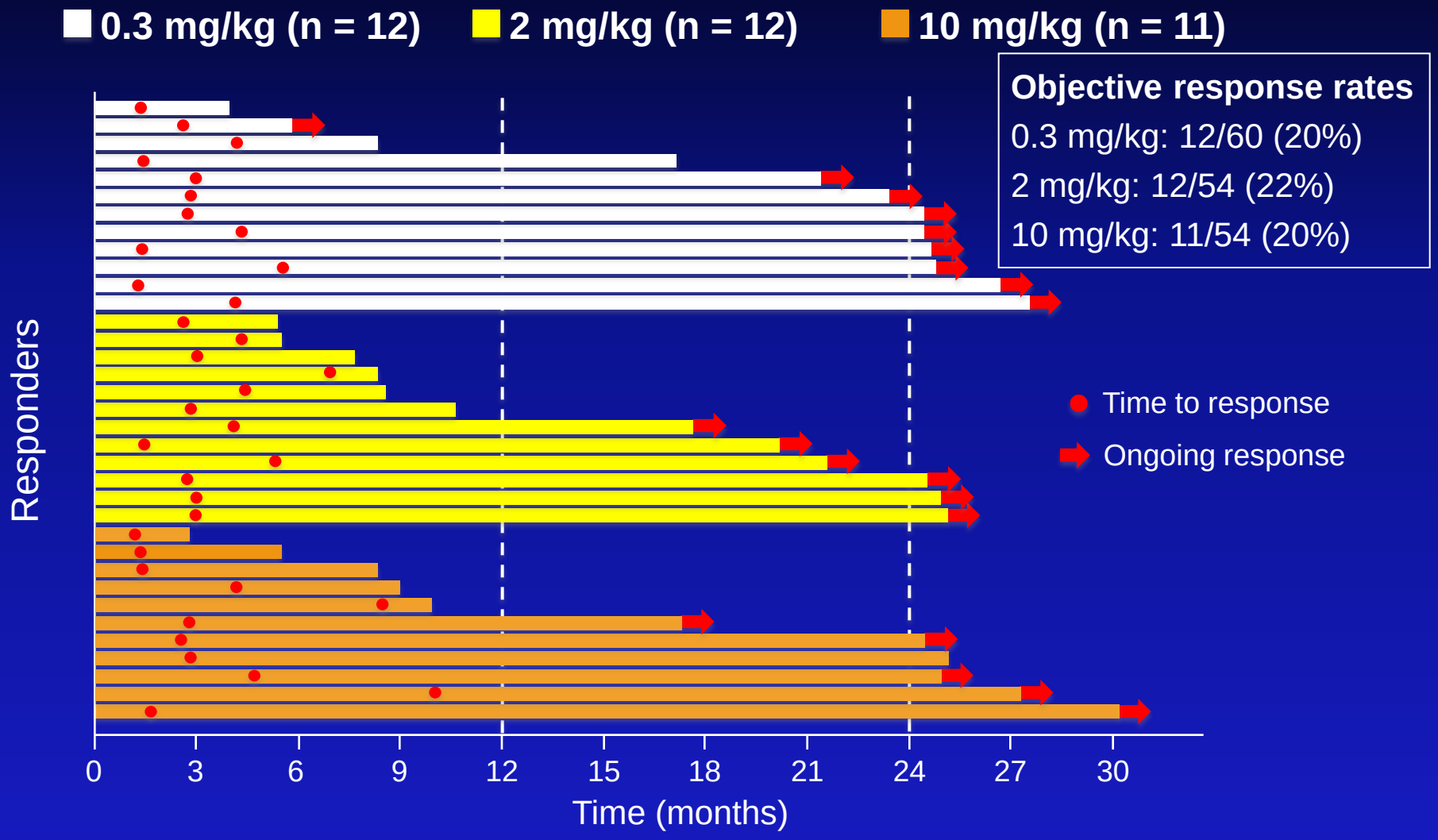
Symbols represent censored observations.

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

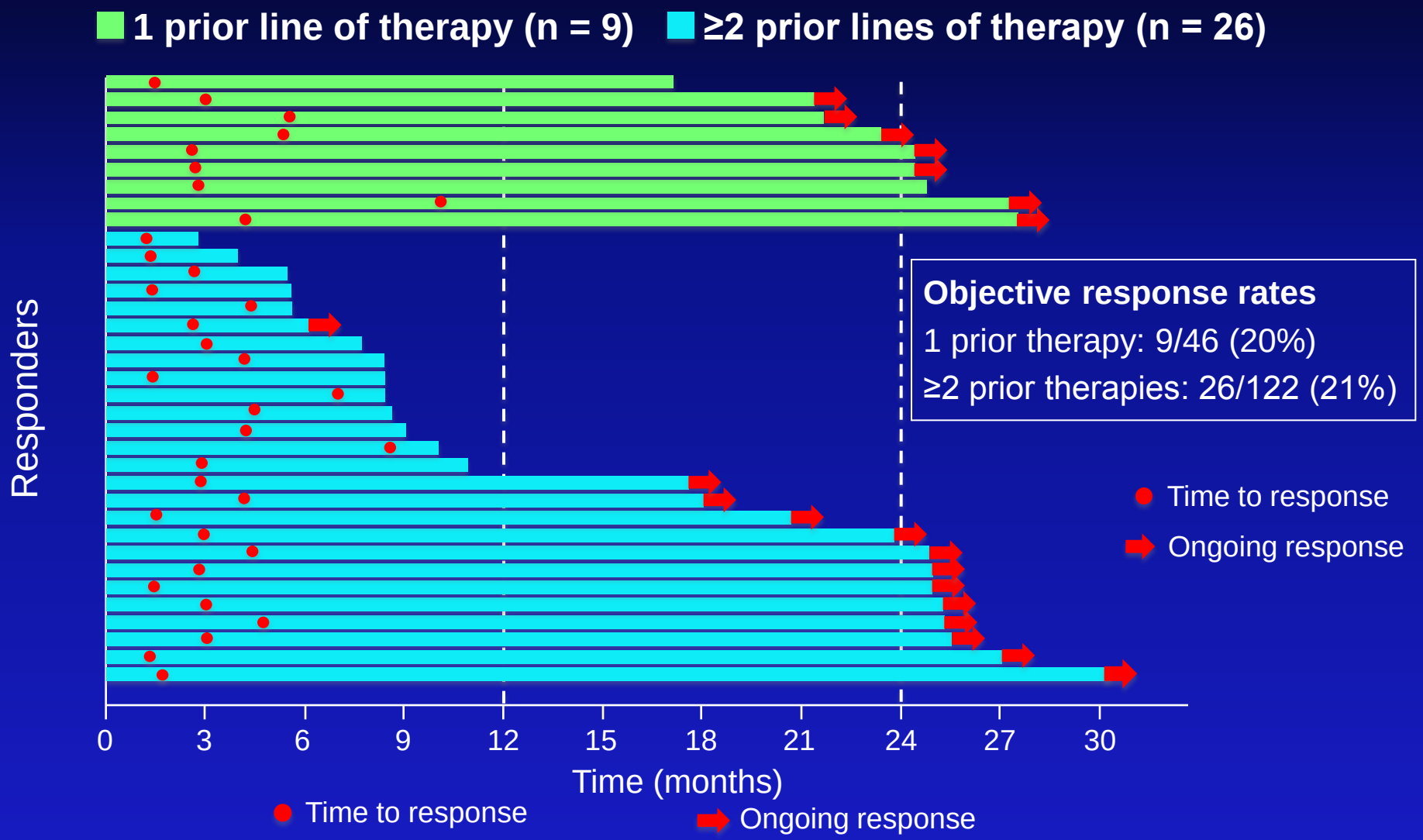
[a]ORR defined by RECIST v1.1; data cutoff May 15, 2013. [b]Derived from the Kaplan–Meier estimate; data cutoff March 5, 2014.
NR, not reached.

Duration of response by dose



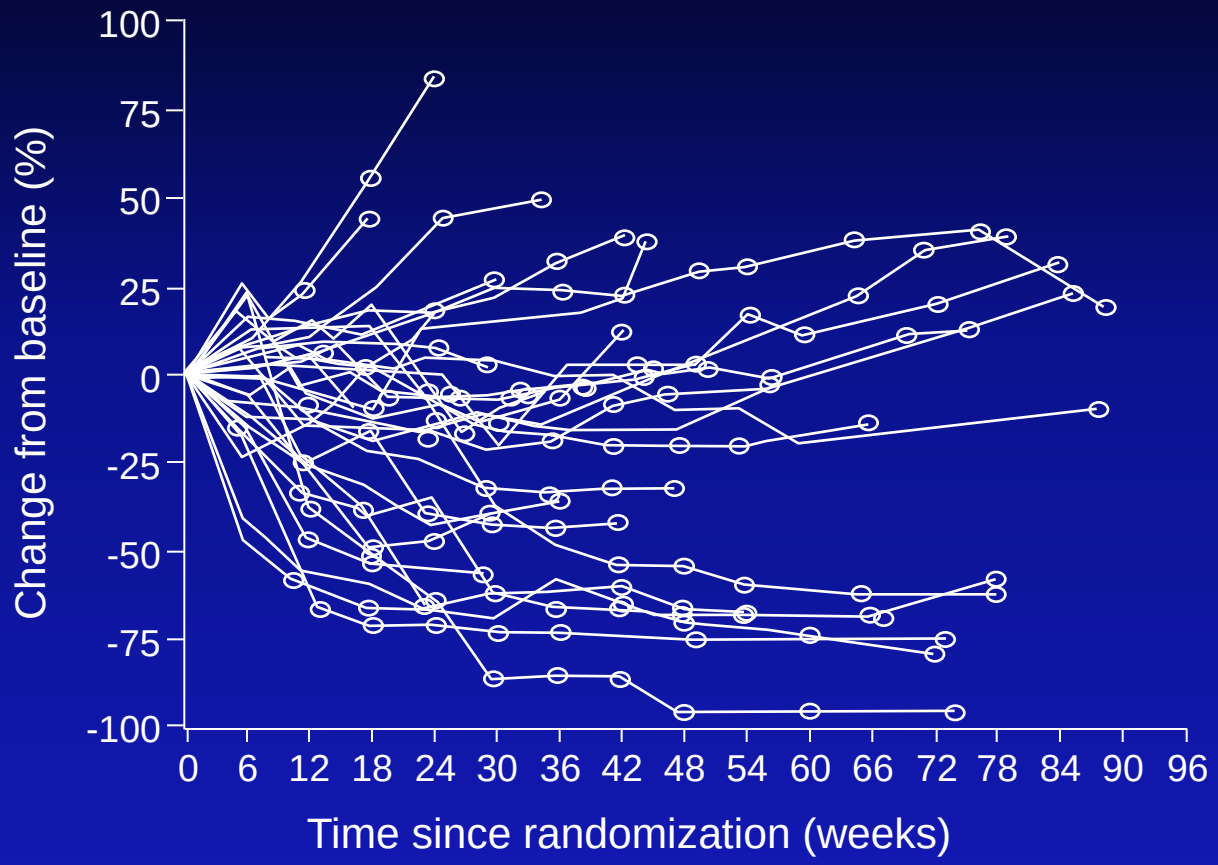
Based on data cutoff of March 5, 2014.

Duration of response by prior lines of therapy



Based on data cutoff of March 5, 2014.

Changes in measurable lesions from baseline in patients treated beyond progression



Circles represent assessments that occurred after initial progression

Nivolumab, mg/kg	0.3	2.0	10
Patients treated, n (%)[a]	10 (17)	12 (22)	14 (26)

[a]Patients with last available dose >6 weeks after progression date.

Treatment-related adverse events*

	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

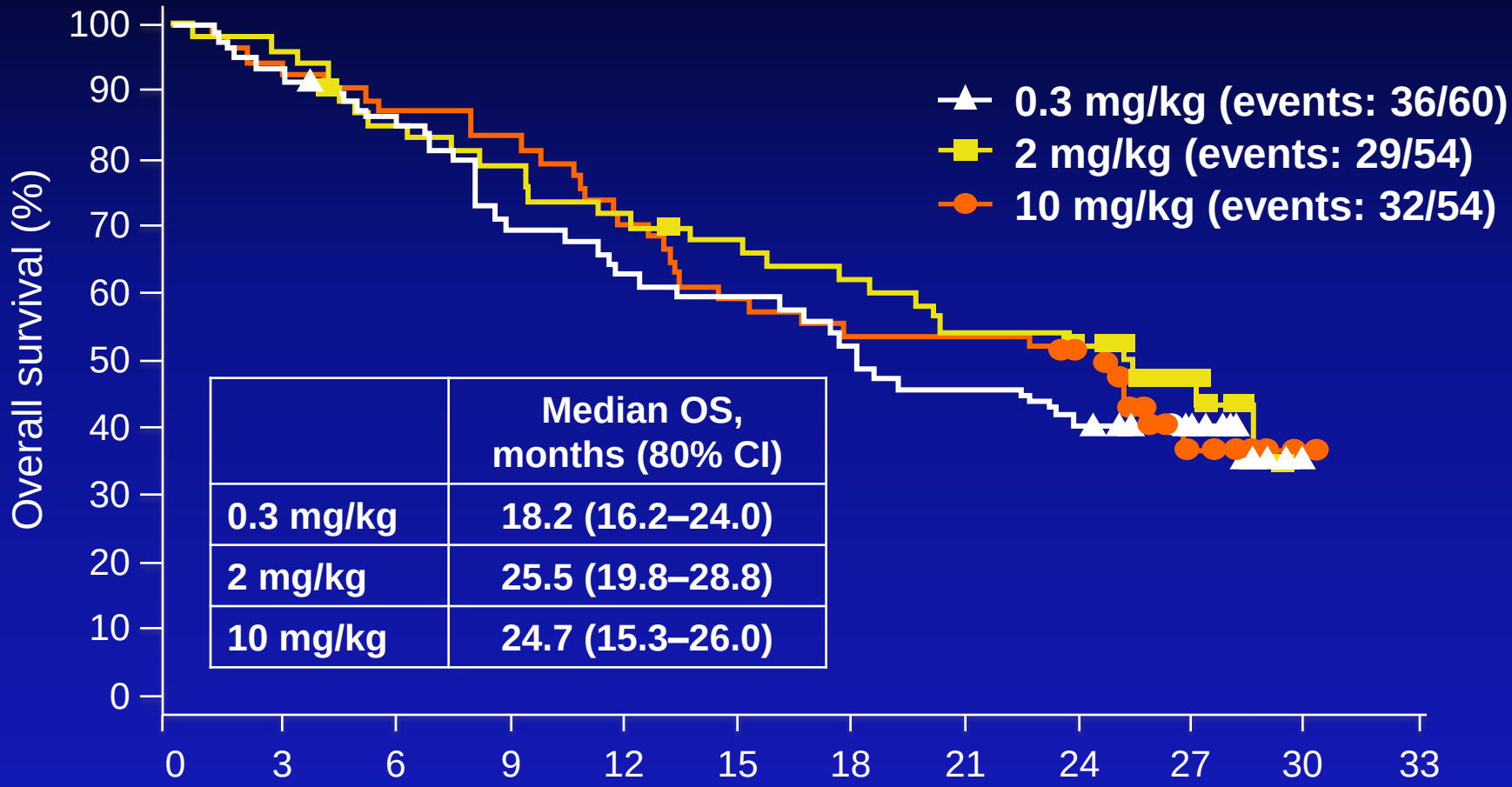
- **No patients experienced a Grade 4 or 5 treatment-related event**

*≥10% of patients in any arm.

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	7	0	11	4	15	0
Hepatic	3	2	7	4	6	0
Pulmonary	5	0	4	0	7	0
Renal	2	0	0	0	2	0

Overall survival



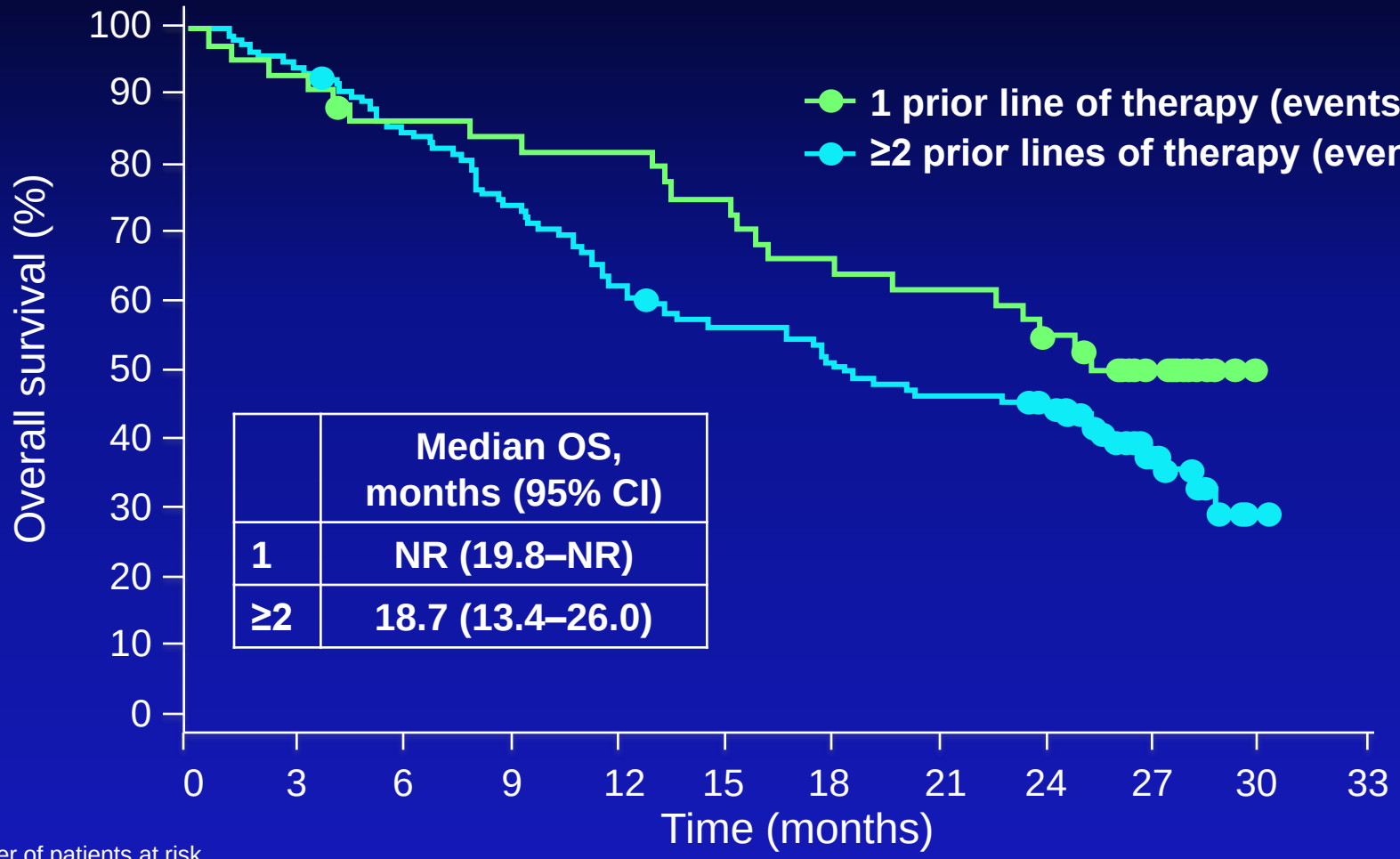
	Median OS, months (80% CI)
0.3 mg/kg	18.2 (16.2–24.0)
2 mg/kg	25.5 (19.8–28.8)
10 mg/kg	24.7 (15.3–26.0)

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 by number of prior lines of therapy



	Median OS, months (95% CI)
1	NR (19.8–NR)
≥2	18.7 (13.4–26.0)

Number of patients at risk

1 prior therapy	46	43	39	38	37	34	30	28	24	13	0	0
>1 prior therapy	122	115	103	90	76	68	62	56	52	20	1	0

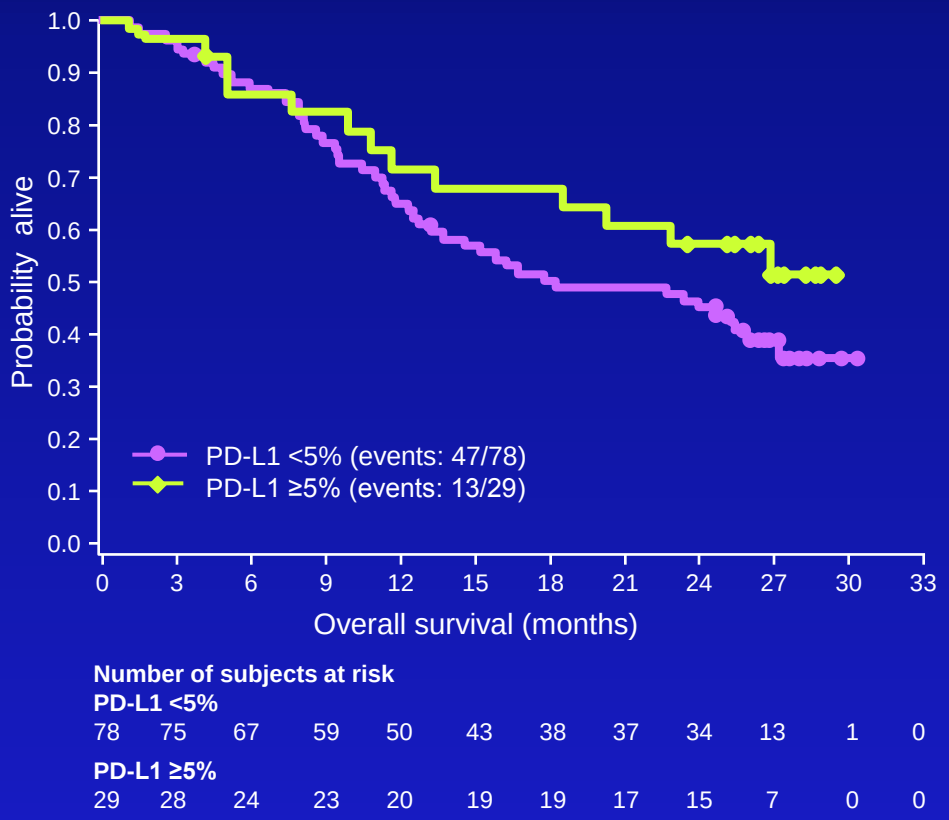
NR, not reached; Symbols represent censored observations.

Outcomes by PD-L1 expression

- 107/168 (64%) patients were PD-L1 quantifiable
- 78/107 (73%) had PD-L1 expression <5%; 29/107 (27%) had expression ≥5%

Efficacy parameter	PD-L1 <5% (n = 78)	PD-L1 ≥5% (n = 29)
PFS, median (95% CI) months	2.9 (2.1–4.2)	4.9 (1.4–7.8)
ORR, % (95% CI)	18.0 (10.2–28.3)	31.0 (15.3–50.8)
OS, median (95% CI) months	18.2 (12.7–26.0)	NR (13.4–NR)

Overall survival by PD-L1 status subgroup



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.

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- This randomized phase II trial demonstrates antitumor activity for nivolumab, including durable responses
- No dose-response relationship was observed for progression-free survival across the 3 doses studied
- The safety profile was manageable, with 11% of patients experiencing a treatment-related Grade 3 event and no Grade 4 events reported
- Encouraging overall survival results were demonstrated in this pretreated mRCC patient population

Next steps

- Nivolumab is being compared with everolimus in a phase III trial with a similar population and an overall survival endpoint

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- **Nivolumab is being compared with everolimus in a phase III trial with a similar population and an overall survival endpoint**

- **A phase III trial is planned in the first-line setting for nivolumab plus ipilimumab based on demonstrated efficacy[1]**

1. Hammers H, et al. European Society for Medical Oncology (ESMO) 2014, 26–30 September, Madrid, Spain. 1050O/Abstract 7843.

Acknowledgments

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