Supplement 2: Online Content

Topalian SL, Hodi FS, Brahmer JR, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non–small cell lung cancer treated with nivolumab. *JAMA Oncol*. Published online July 25, 2019. 10.1001/jamamoncol.2019.2187

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Patient Characteristics (N = 270)

	Melanoma (n = 107)	RCC (n = 34)	NSCLC (n = 129)	All (N = 270)
Median age, years (range)	61 (29-85)	58 (35-74)	65 (38-85)	62 (29-85)
Sex, n (%)				
Male	72 (67)	26 (76)	79 (61)	177 (66)
Female	35 (33)	8 (24)	50 (39)	93 (34)
ECOG PS, n (%)				
0	68 (64)	17 (50)	27 (21)	112 (41)
≥1	39 (36)	17 (50)	102 (79)	158 (59)
No. of prior systemic therapies, n (%)				
≤2	81 (76)	19 (56)	61 (47)	161 (60)
≥3	26 (24)	15 (44)	68 (53)	109 (40)

ECOG PS indicates Eastern Cooperative Oncology Group performance status.

eTable 2. Univariate Analysis of Associations Between Baseline Demographic or Clinical Characteristics and Overall Survival at 5 Years in 270 Patients With Melanoma, RCC, or NSCLC Receiving Nivolumab[a]

Variable	N	5-Year OS, % (95% CI)	Unstratified HR (95% CI)	*P* value
Age, y				
<65	151	26.4 (19.4-33.9)	0.96 (0.73-1.27)	.7796
≥65	119	22.4 (15.1-30.7)		
Age, y				
<75	229	24.7 (19.1-30.6)	1.00 (0.68-1.49)	.9840
≥75	41	24.4 (11.7-39.6)		
Sex				
Male	177	24.7 (18.4-31.5)	1.04 (0.78-1.40)	.7716
Female	93	24.7 (16.1-34.2)		
ECOG PS				
0	112	35.7 (26.7-44.8)	0.53 (0.40-0.71)	<.0001
≥1	158	16.7 (11.1-23.3)		
Baseline tumor site (bone)[b]				
Yes	52	11.0 (4.1-21.8)	1.58 (1.13-2.20)	.0065
No	218	28.0 (22.0-34.3)		
Baseline tumor site (brain)[b]				
Yes	5	20.0 (0.8-58.2)	1.14 (0.42-3.06)	.7999
No	265	24.8 (19.6-30.4)		
Baseline tumor site (liver)[b]				
Yes	70	12.6 (5.8-22.1)	1.78 (1.31-2.41)	.0002
No	200	28.9 (22.6-35.5)		
Baseline tumor site (lung)[b]				
Yes	208	21.8 (16.2-27.9)	1.42 (1.00-2.01)	.0470
No	62	33.8 (22.2-45.8)		
Baseline tumor site (lymph node)[b]				
Yes	185	21.4 (15.6-27.8)	1.14 (0.84-1.56)	.3906
No	85	32.5 (22.5-42.9)		
Baseline tumor site (visceral)[b]				
Yes	233	22.5 (17.1-28.2)	1.78 (1.13-2.79)	.0118
No	37	39.0 (22.8-54.8)		
No. of prior systemic therapies				
≤2	161	27.9 (21.0-35.2)	0.84 (0.63-1.11)	.2221
≥3	109	20.0 (12.8-28.5)		

[a] Analysis is based on a Cox Model using data from 55 patients alive and 215 patients not alive at 5 years.
[b] Patients could be included in more than 1 tumor site category if they had metastases in more than 1 location.
ECOG PS indicates Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival.

eTable 3. Association Between Baseline Sum of Target Lesion Diameters and 5-Year Survival in All Patients Receiving Nivolumab (N = 270)[a]

Sum of Target Lesion Diameters (mm)	5-Year Survivors	All Other Patients	*P* value
Melanoma Median (IQR) Range	n = 30 75 (48-134) 22-374	n = 77 111 (69-189) 10-377	.0427
RCC Median (IQR) Range	n = 9 98 (89-110) 42-236	n = 25 139 (88-191) 43-615	.0542
NSCLC Median (IQR) Range	n = 16 83 (62.5-117) 11-291	n = 113 95 (59-147) 10-292	.5084
All 3 tumor types Median (IQR) Range	n = 55 88 (52-116) 11-374	n = 215 109 (65-165) 10-615	.0244

[a] Analysis is based on *t* tests for comparing the 2 subsets of baseline sum of target lesion diameters.
IQR indicates interquartile range.

eTable 4. Association Between Objective Response[a] and 5-Year Survival in Patients With Melanoma, RCC, or NSCLC Receiving Nivolumab

Tumor Type	5-Year Survivors	All Other Patients
Melanoma	n = 30	n = 77
Objective response, n (%)	23 (76.7)	11 (14.3)
Complete response, n	2	0
Partial response, n	21	11
Stable disease, n	5	18
RCC	n = 9	n = 25
Objective response, n (%)	6 (66.7)	4 (16.0)
Complete response, n	1	0
Partial response, n	5	4
Stable disease, n	3	11
NSCLC	n = 16	n = 113
Objective response, n (%)	12 (75.0)	10 (8.8)
Complete response, n	0	0
Partial response, n	12	10
Stable disease, n	2	30
All 3 tumor types	n = 55	n = 215
Objective response, n (%)	41 (74.5)[b]	25 (11.6)

[a] Complete response and partial response
[b] Odds ratio (95% CI), 22.3 (10.7-46.5), *P* <.0001 vs. "All Other Patients" as determined by a logistic regression model fitting rate of objective response with 5-year survival as a binary covariate (*P* value based on Wald statistics).

eTable 5. Association Between Objective Response and 5-Year Survival in All Patients Receiving Nivolumab (N = 270)[a]

Objective Response Status, n (%)[b]	5-Year Survivors	All Other Patients	Odds Ratio (95% CI)	*P* value
At any time after treatment initiation Responders Nonresponders	n = 55 41 (74.5) 14 (25.5)	n = 215 25 (11.6) 190 (88.4)	22.3 (10.7-46.5)	<.0001
Within 6 months of treatment initiation Responders Nonresponders	n = 55 35 (63.6) 20 (36.4)	n = 141 23 (16.3) 118 (83.7)	9.0 (4.4-18.2)	<.0001
Within 12 months of treatment initiation Responders Nonresponders	n = 55 41 (74.5) 14 (25.5)	n = 83 22 (26.5) 61 (73.5)	8.1 (3.7-17.7)	<.0001
Within 18 months of treatment initiation Responders Nonresponders	n = 55 41 (74.5) 14 (25.5)	n = 50 18 (36.0) 32 (64.0)	5.2 (2.3-12.0)	.0001

[a] Analysis is based on a logistic regression model fitting objective response rate with 5-year survival as a binary covariate with *P* values based on Wald statistics. For the landmark analyses, the response status is defined at the landmark; ie, a patient is considered a responder if the response occurred up to the landmark inclusive. Patients censored or who died before the landmark are not included.

[b] A "responder" refers to a patient achieving a complete or partial response as their best overall response; a "nonresponder" refers to a patient achieving stable disease or progressive disease as their best overall response or a patient in whom the best overall response was indeterminate.

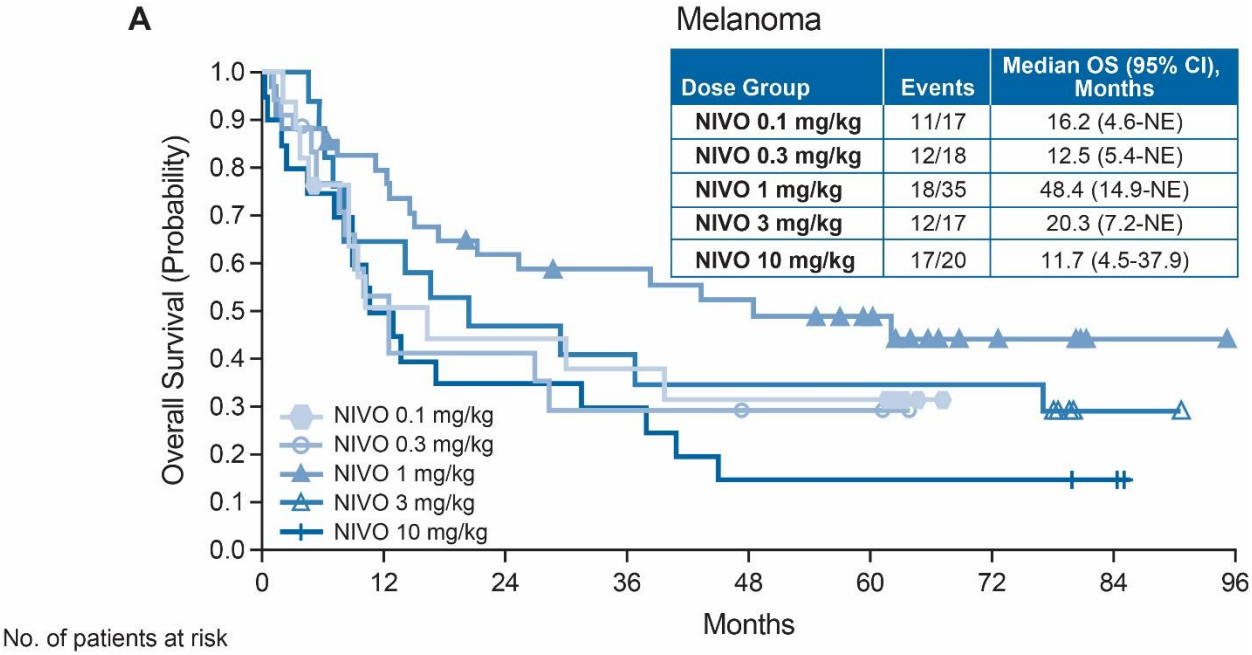
eTable 6. Summary of Treatment-Related Adverse Events in All Patients Receiving Nivolumab (N = 270)

	All Patients (N = 270)	
	Any Grade	**Grade ≥3**
All treatment-related AEs, n (%)[a]	210 (77.8)	53 (19.6)
Fatigue	79 (29.3)	6 (2.2)
Rash	44 (16.3)	0
Diarrhea	40 (14.8)	3 (1.1)
Pruritus	31 (11.5)	1 (0.4)
Decreased appetite	26 (9.6)	1 (0.4)
Nausea	24 (8.9)	2 (0.7)
Decreased hemoglobin	20 (7.4)	1 (0.4)
Pyrexia	16 (5.9)	0
Arthralgia	15 (5.6)	0
Abdominal pain	14 (5.2)	3 (1.1)
Pneumonitis	14 (5.2)	4 (1.5)
Treatment-related select AEs, n (%)[b]	136 (50.4)	17 (6.3)
Skin	76 (28.1)	1 (0.4)
Rash	44 (16.3)	0
Pruritus	31 (11.5)	1 (0.4)
Vitiligo	10 (3.7)	0
Gastrointestinal	43 (15.9)	3 (1.1)
Diarrhea	40 (14.8)	3 (1.1)
Endocrine	29 (10.7)	2 (0.7)
Hypothyroidism	12 (4.4)	1 (0.4)
Increased blood thyroid-stimulating hormone	11 (4.1)	1 (0.4)
Hepatic	19 (7.0)	5 (1.9)
Increased ALT	12 (4.4)	2 (0.7)
Increased AST	10 (3.7)	1 (0.4)
Pulmonary	18 (6.7)	5 (1.9)
Pneumonitis	14 (5.2)	4 (1.5)
Renal	6 (2.2)	1 (0.4)
Hypersensitivity	15 (5.6)	1 (0.4)
Infusion-related reaction	11 (4.1)	0

[a] Includes individual any-grade AEs occurring in >5% of patients.
[b] Includes category totals and individual any-grade treatment-related select (immune-mediated) AEs occurring in >2% of patients.
AE indicates adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

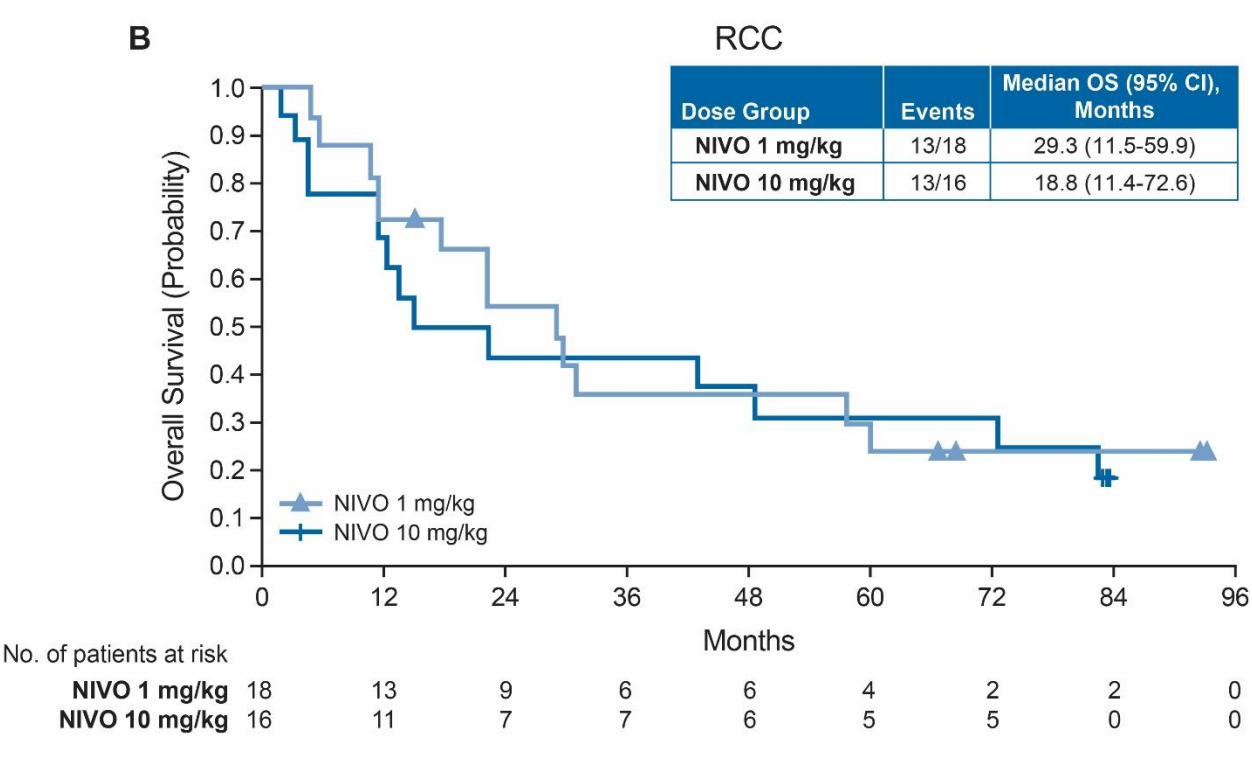
eFigure 1. Overall Survival In Patients With Melanoma, RCC, or NSCLC Based on Nivolumab Dose Received.

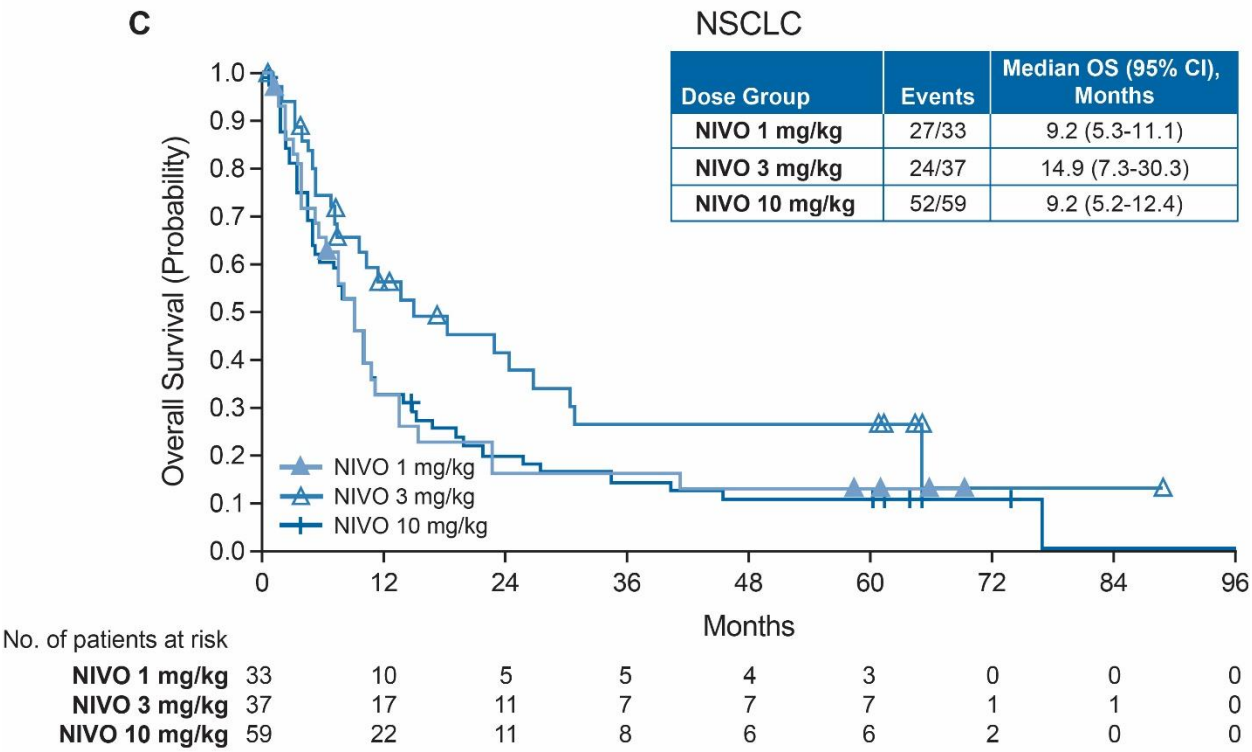
Kaplan–Meier estimates of overall survival in 270 patients. The longest median OS was seen with nivolumab 1 mg/kg in melanoma (48.4 months) and RCC (29.3 months), and 3 mg/kg in NSCLC (14.9 months). NE indicates not estimable; NIVO, nivolumab.



No. of patients at risk

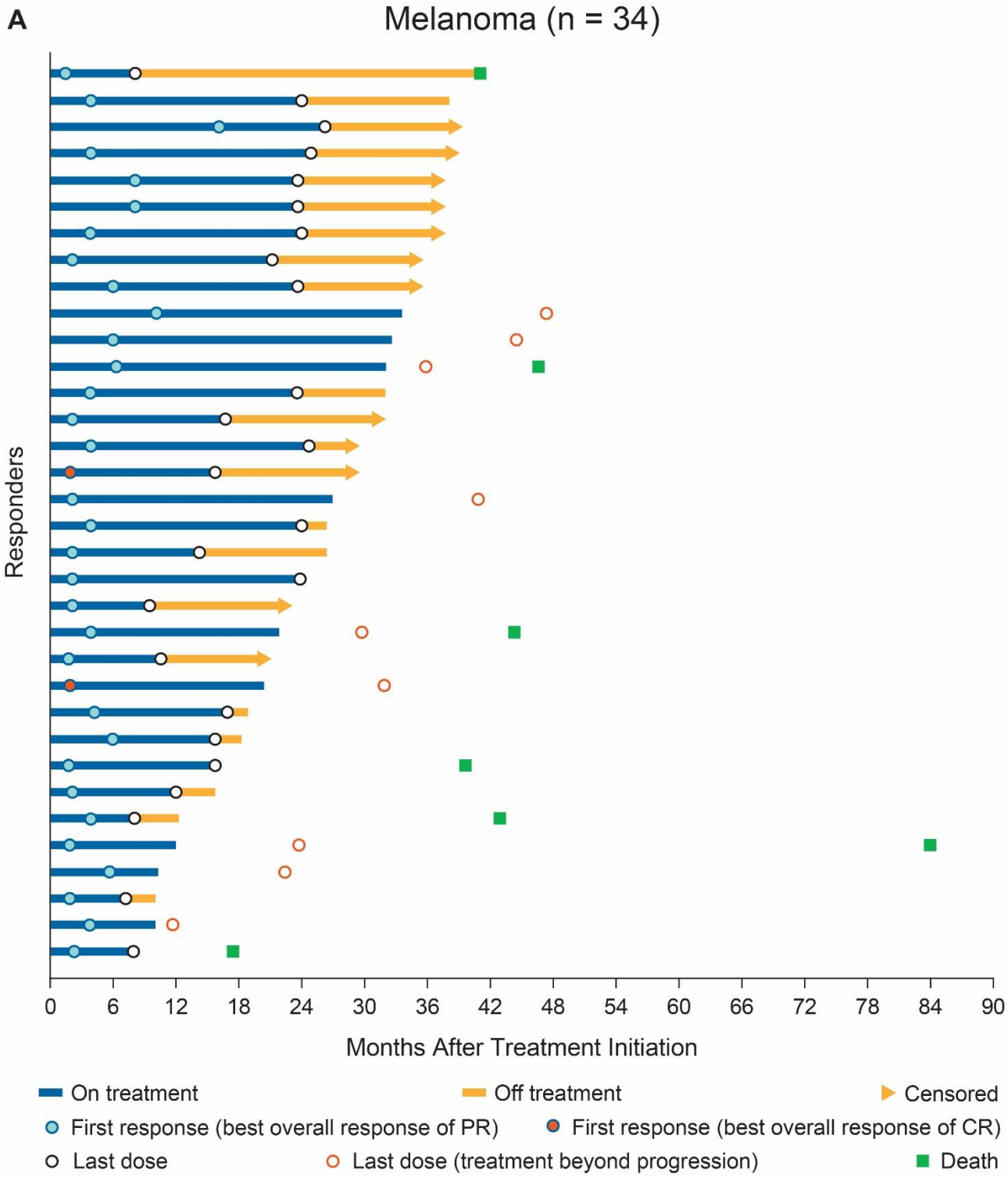
NIVO 0.1 mg/kg	17	8	7	6	5	5	0	0	0
NIVO 0.3 mg/kg	18	9	7	5	4	4	0	0	0
NIVO 1 mg/kg	35	27	20	18	16	12	5	1	0
NIVO 3 mg/kg	17	11	8	7	6	6	6	1	0
NIVO 10 mg/kg	20	10	7	6	3	3	3	2	0

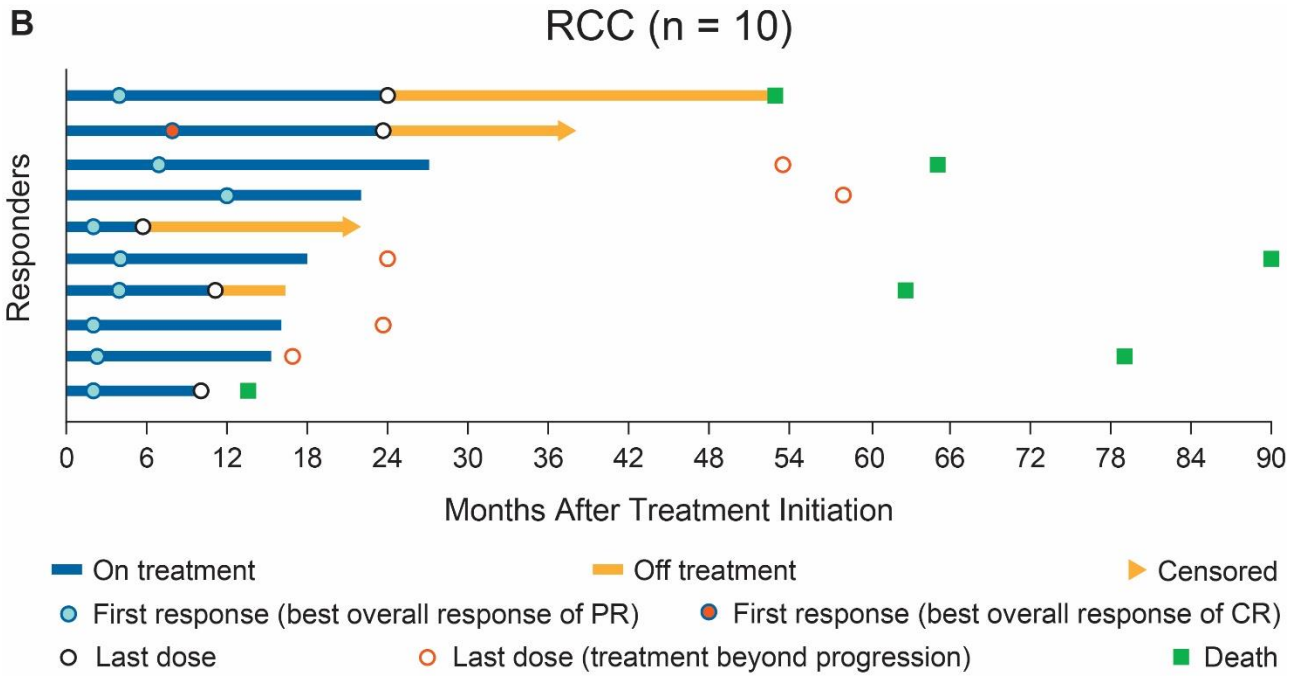


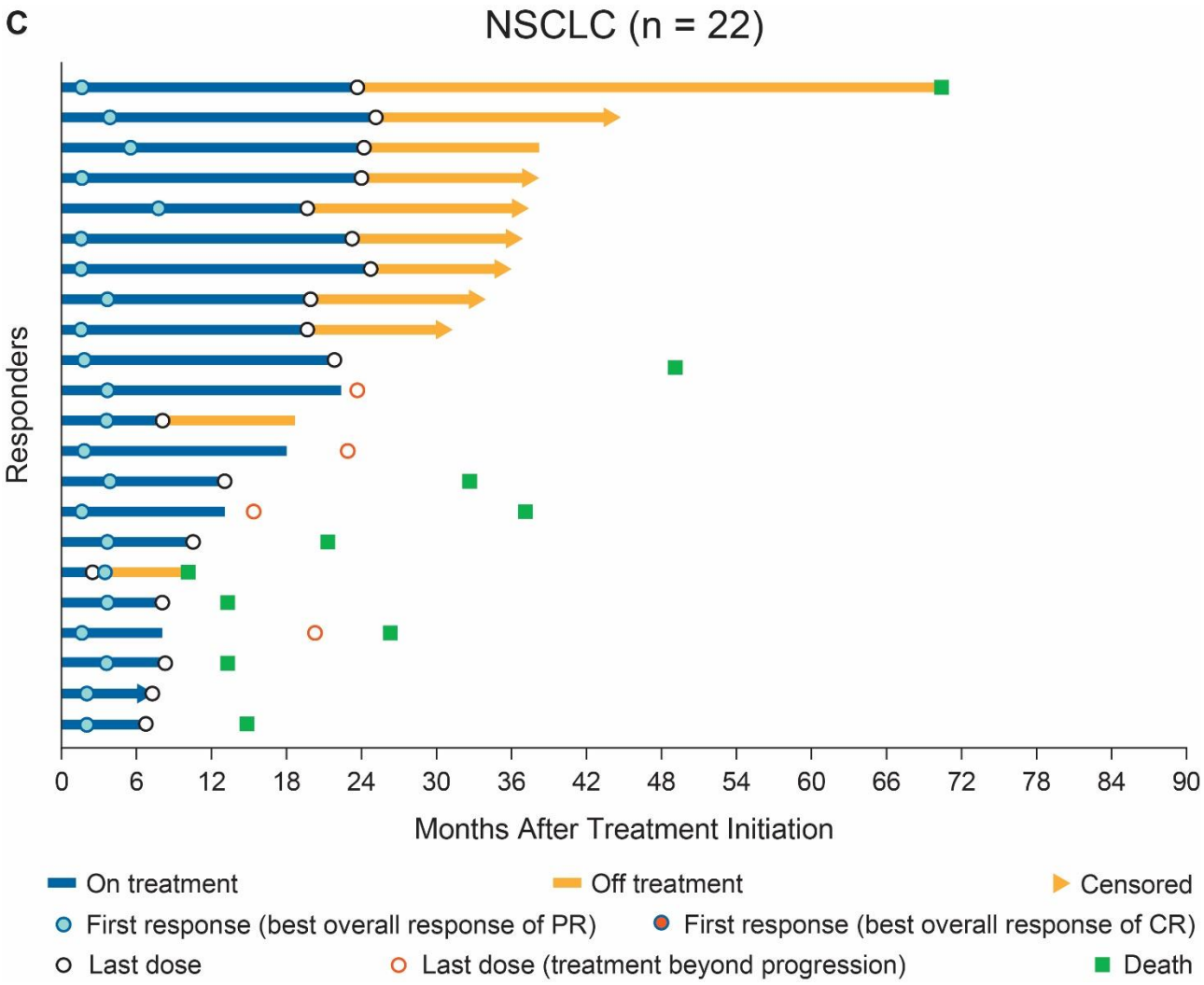


eFigure 2. Swimmer Plots for Responders With Advanced Melanoma, RCC, or NSCLC.

In the absence of censoring or death, the end of the colored horizontal bar indicates the point of disease progression for each respective patient. CR indicates complete response; PR, partial response.

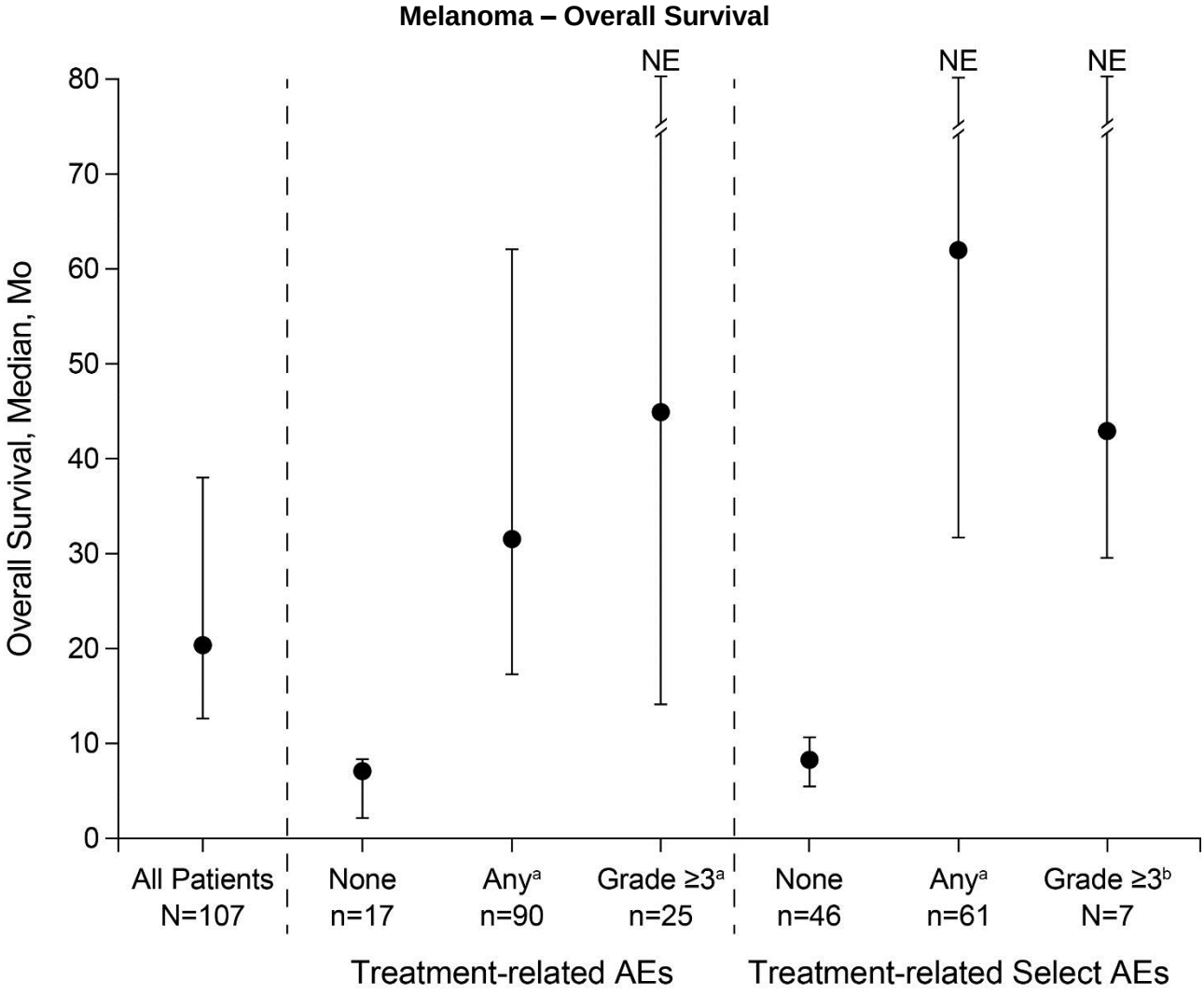




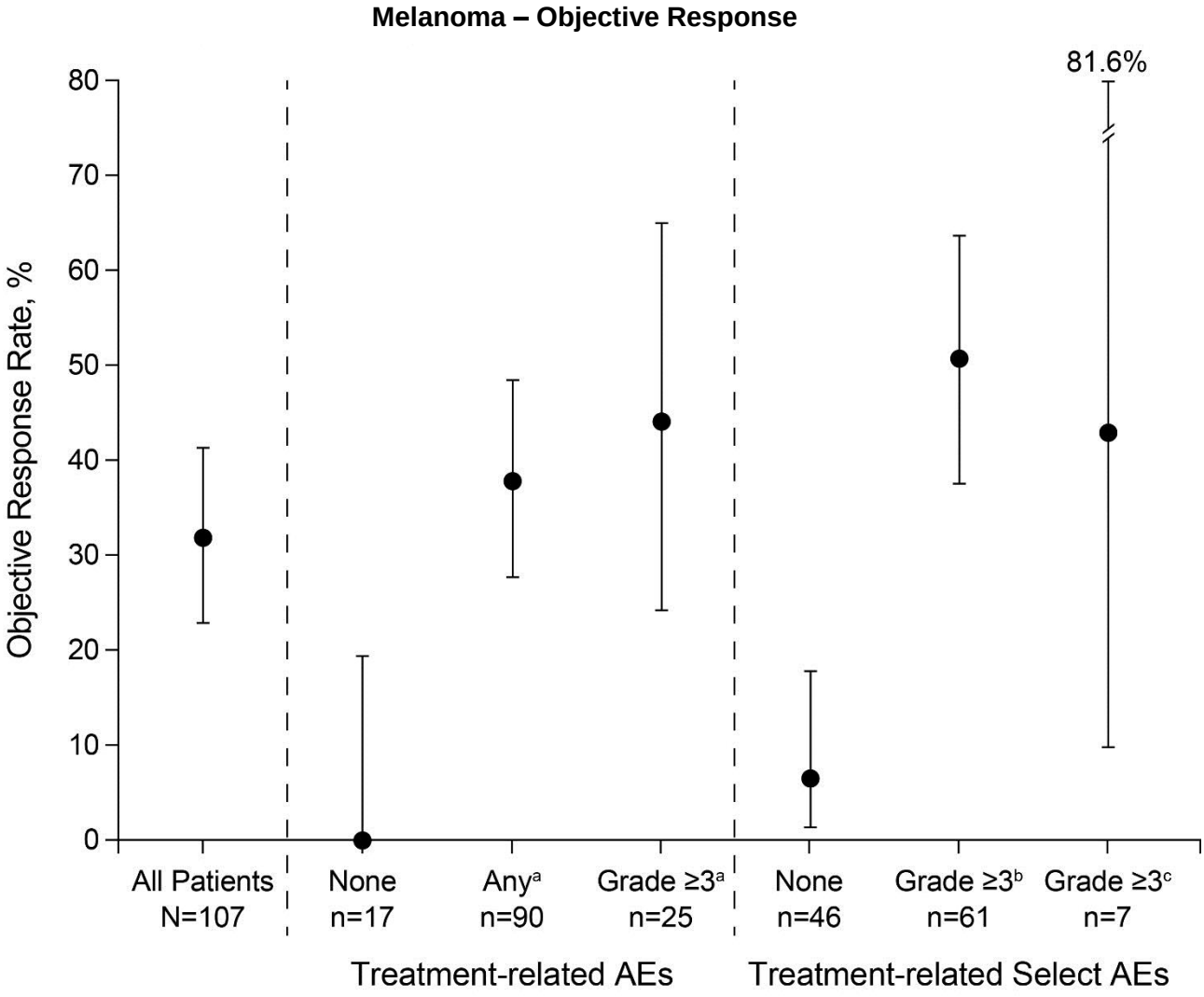


eFigure 3. Association Between Incidence of Treatment-Related Adverse Events and Clinical Outcomes in Patients With Melanoma, RCC, or NSCLC Receiving Nivolumab.

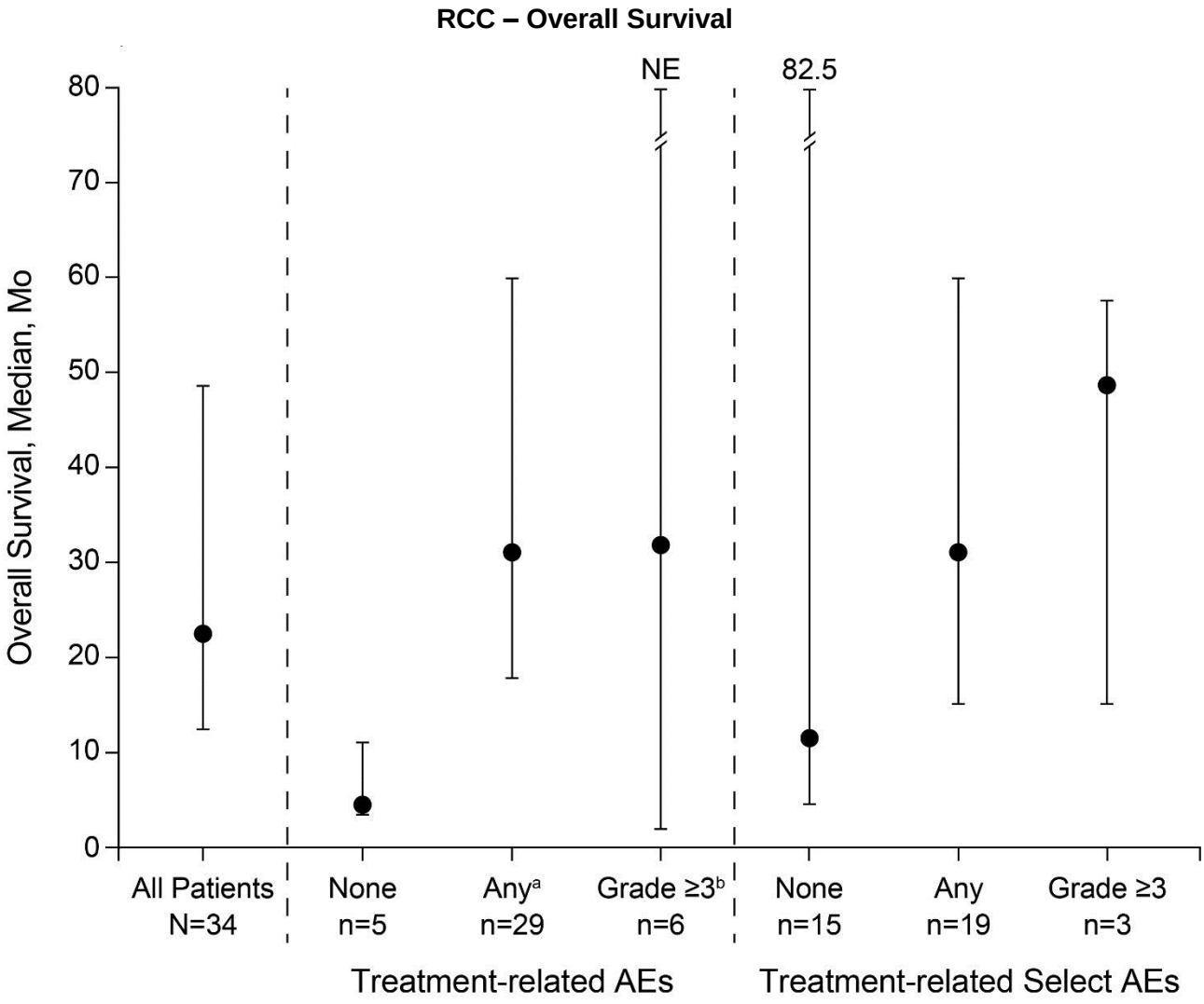
Association between treatment-related adverse event (TRAE) occurrence and overall survival or rate of objective response (complete response or partial response). Analysis includes all TRAEs occurring between administration of the first dose of nivolumab and 30 days after the last dose. Incidence of TRAEs was not controlled for drug exposure. Treatment-related select AEs are defined as those with a potential immune-mediated etiology. *P* values were determined using a Cox proportional hazards model and are based on the hazard ratio for survival between the respective categories. Error bars represent 95% confidence intervals around the OS medians and objective response rates.



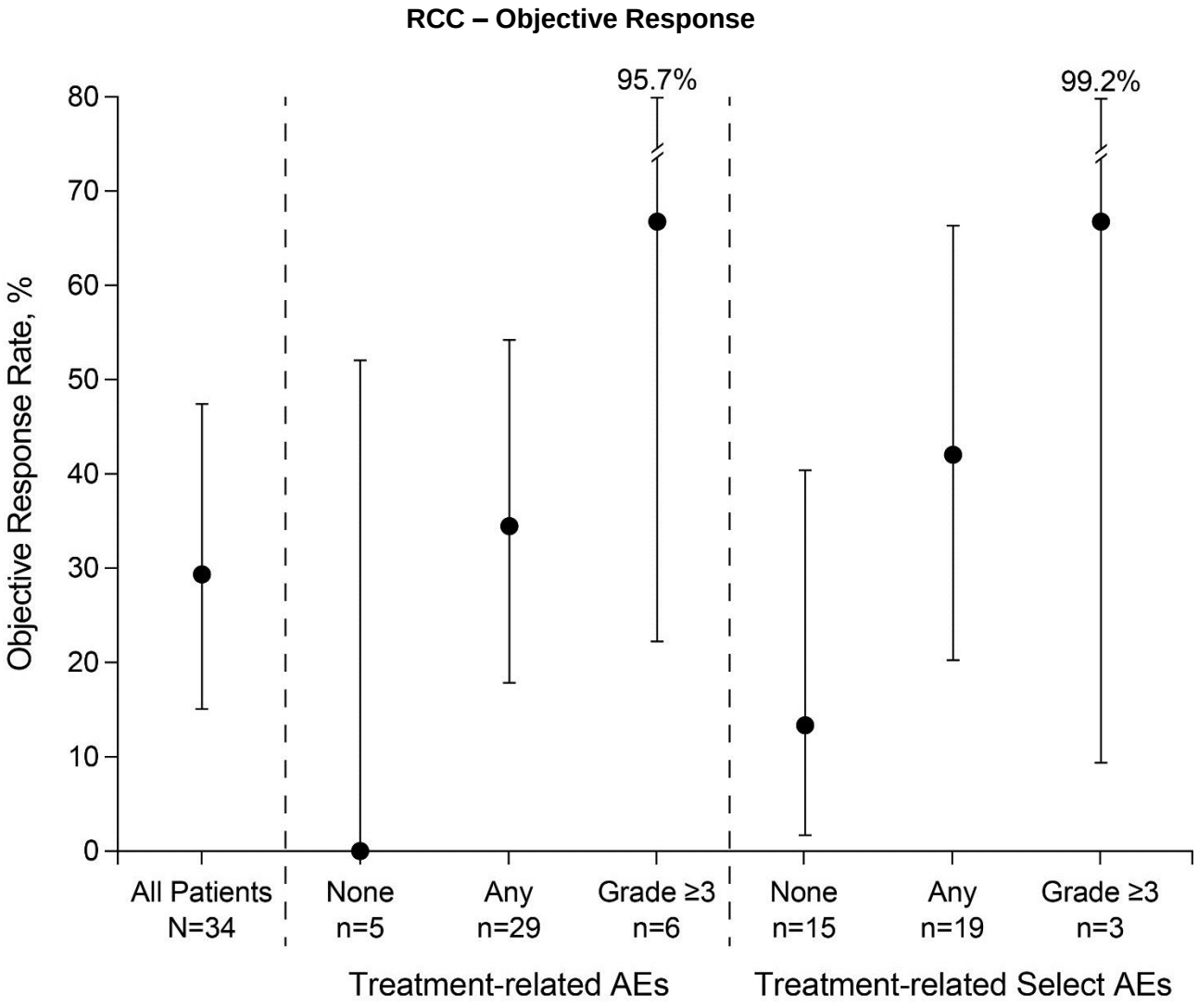
[a] *P* < .0001; [b] *P* < .05 (based on hazard ratio) vs "none" in the respective AE category.
NE indicates that the upper 95% confidence interval was not estimable.

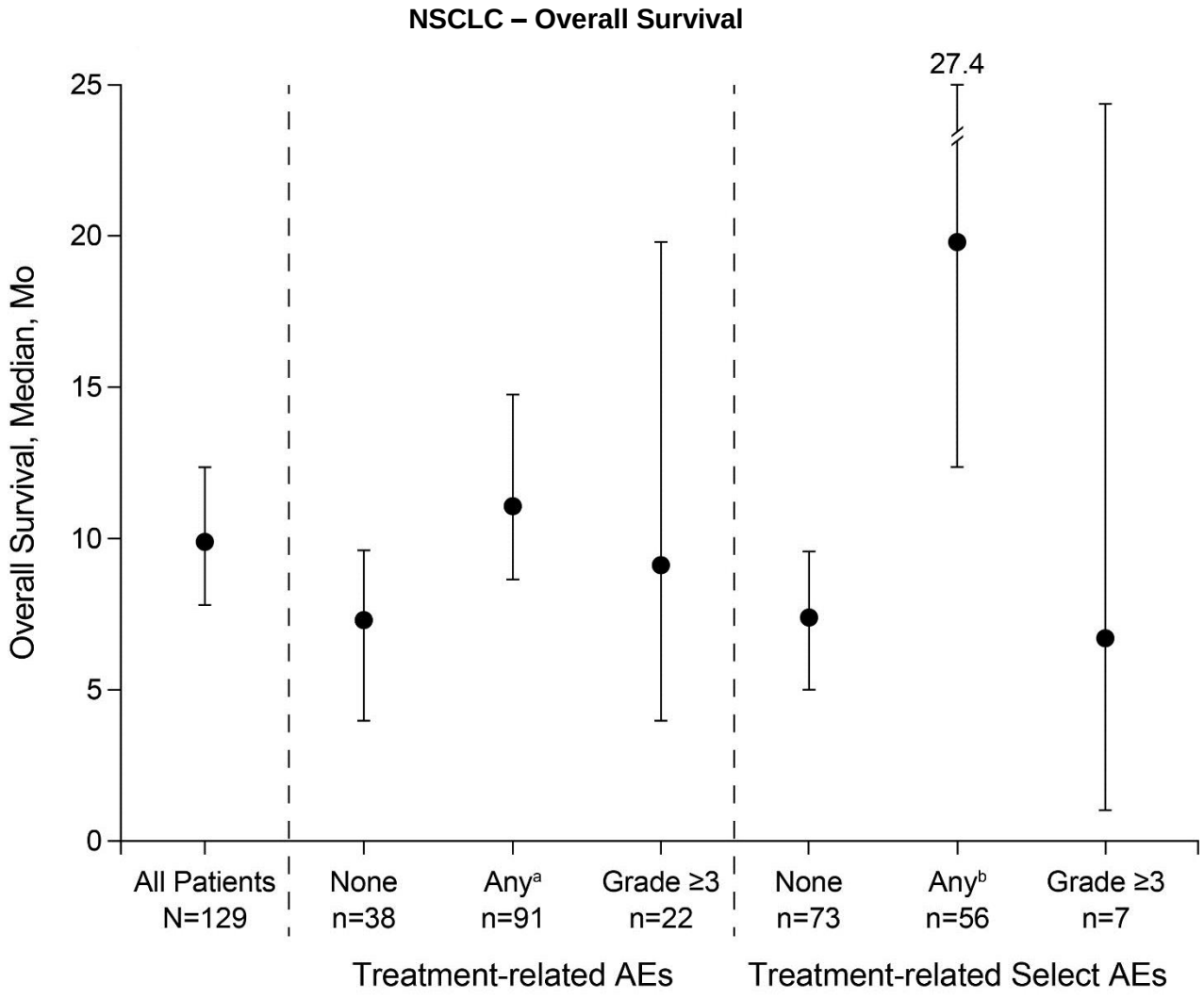


[a] $P < .01$; [b] $P < .0001$; [c] $P < .05$ (based on hazard ratio) vs "none" in the respective AE category.

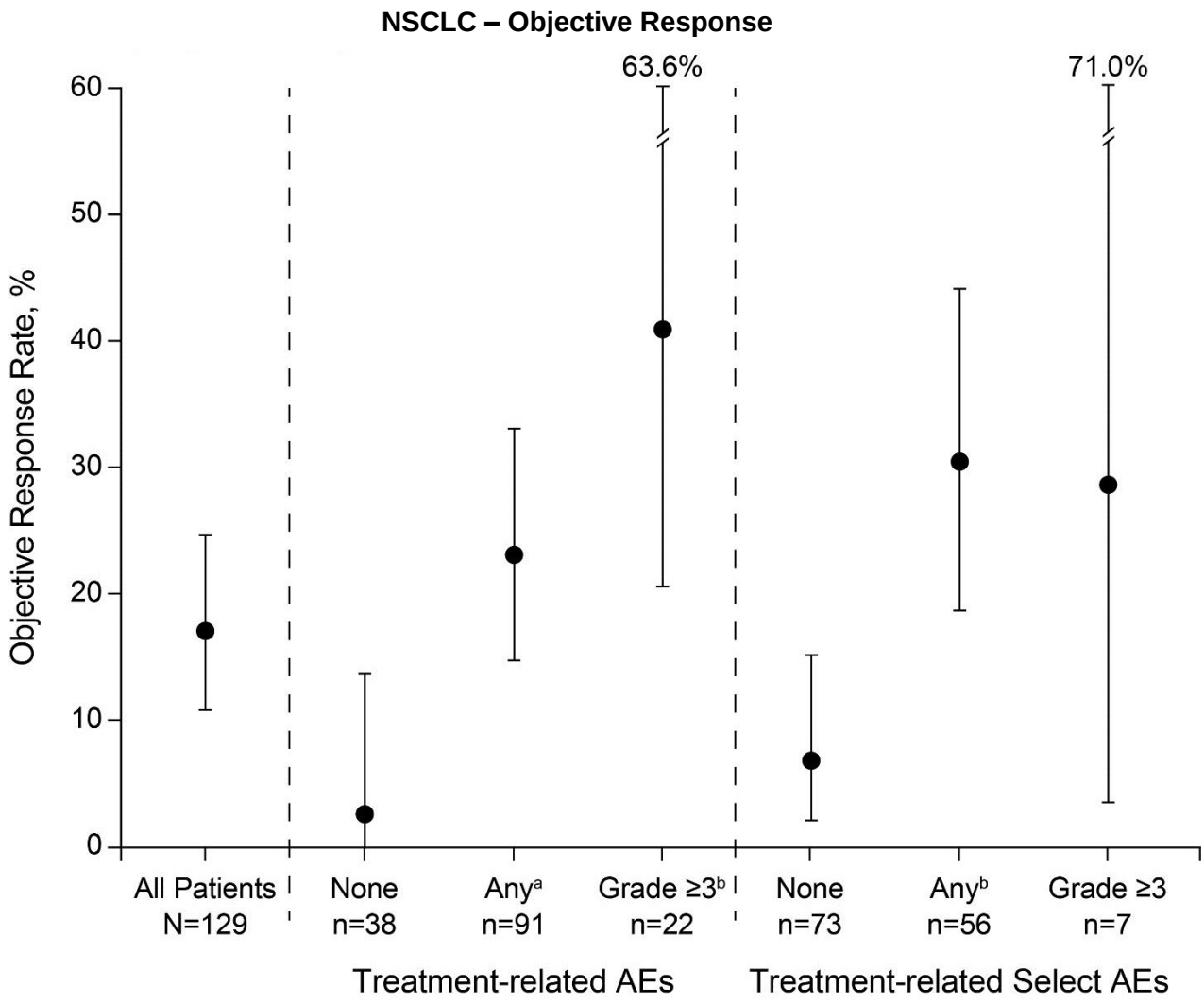


[a] $P = .0001$; [b] $P < .05$ (based on hazard ratio) vs "none" in the respective AE category.
NE indicates that the upper 95% confidence interval was not estimable.





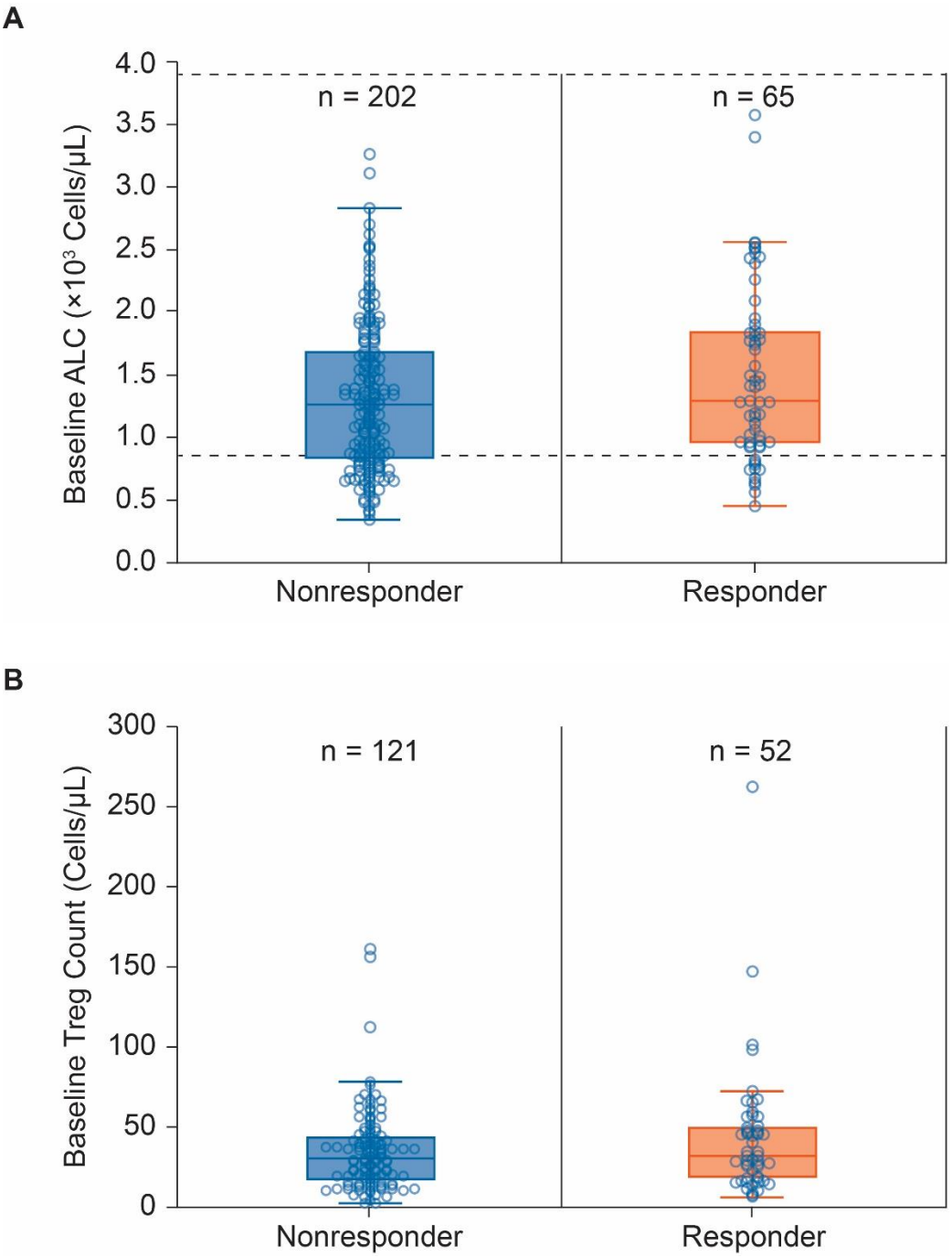
[a] $P < .01$; [b] $P < .0001$ (based on hazard ratio) vs "none" in the respective AE category.



[a] $P < .01$; [b] $P < .001$ (based on hazard ratio) vs "none" in the respective AE category.

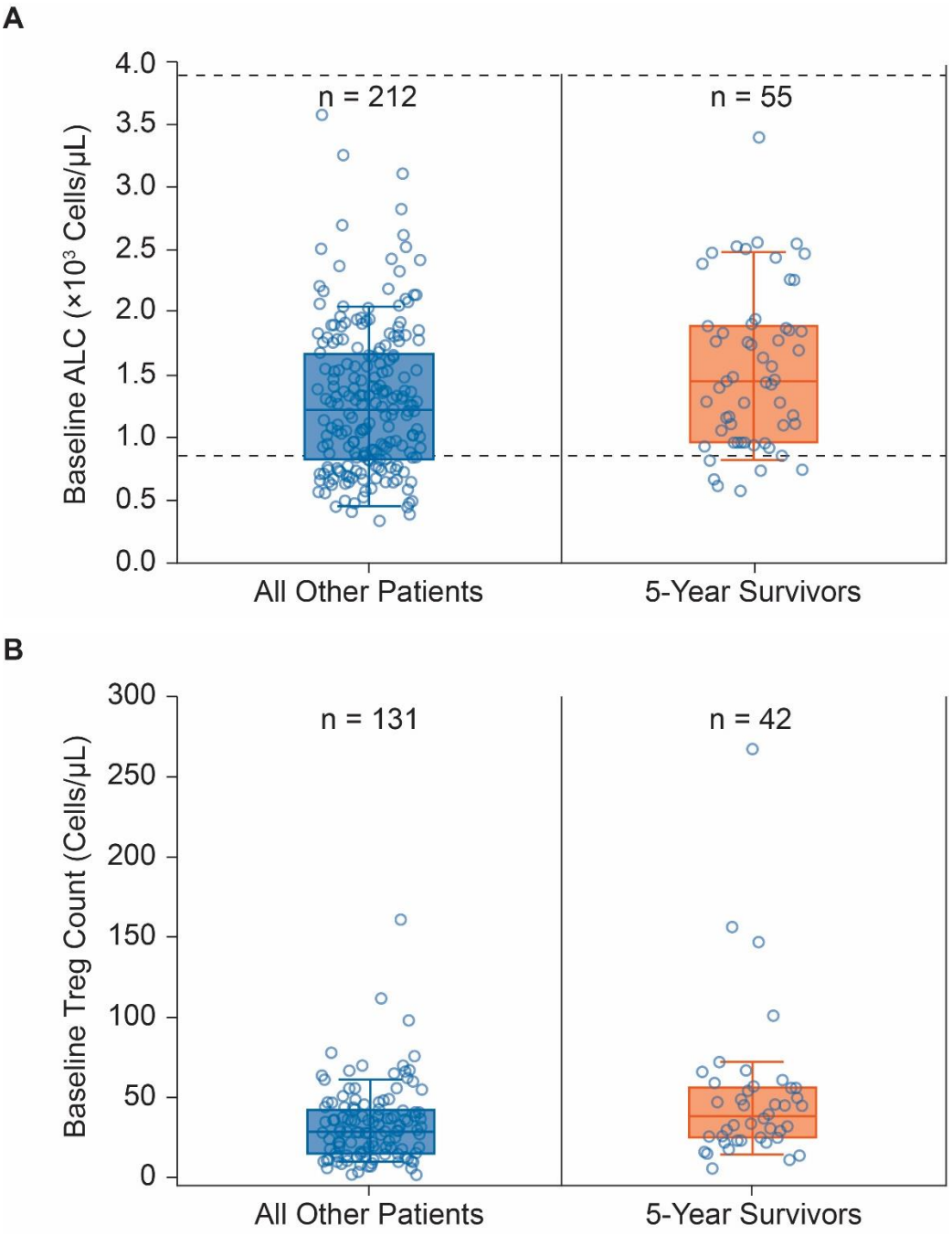
eFigure 4. Association Between Baseline Immune Cell Counts and Objective Response in Patients With Melanoma, RCC, or NSCLC Receiving Nivolumab.

ALC and Treg counts were determined on peripheral whole blood samples, as detailed in Methods. Normal range of values for ALC is 850 to 3900 cells/μL (indicated by horizontal dotted lines). **A** Baseline ALC in 65 patients with an objective response (CR + PR) was significantly higher than in 202 nonresponders (mean 1480 vs 1300 cells/μL, respectively; *P* = .036). **B** Baseline Treg counts were not significantly different between 52 patients with an objective response and 121 nonresponders (mean 42.2 vs 34.2 cells/μL, respectively; *P* = .184). The colored rectangles represent the second and third quartiles with the internal horizontal line showing the median value; boxplot whiskers represent 10th and 90th percentiles. ALC indicates absolute lymphocyte count; CR, complete response; PR, partial response.



eFigure 5. Association Between Baseline Immune Cell Counts and 5-Year Survival in Patients With Melanoma, RCC, or NSCLC Receiving Nivolumab.

ALC and Treg counts were determined on peripheral whole blood samples, as detailed in Methods. Normal range of values for ALC is 850 to 3900 cells/µL (indicated by horizontal dotted lines). **A** Baseline ALC in 55 patients alive at 5 years was higher than in 212 patients not alive at 5 years (mean 1546 vs 1290 cells/µL, respectively; *P* = .0079). **B** Baseline Treg counts were higher between 42 patients alive at 5 years and 131 patients not alive at 5 years (mean 49.5 vs 32.6 cells/µL, respectively; *P* = .0254). The colored rectangles represent the second and third quartiles with the internal horizontal line showing the median value; boxplot whiskers represent 10th and 90th percentiles. ALC indicates absolute lymphocyte count.



eFigure 6. Maximum Change in Tumor Burden in 23 Patients With Melanoma, RCC, or NSCLC Who Were Treated With Nivolumab Beyond Tumor Progression.

Among 43 patients who continued to receive nivolumab after experiencing progressive disease in the first 2 cycles of treatment, 23 had at least 1 post-progression radiologic assessment and are depicted here. Values indicate best reduction in the sum of target lesion measurements for each patient, compared with maximum tumor measurements at progression. Horizontal dotted lines indicate a 20% increase and 30% reduction in target lesion measurement. Four patients showed evidence of response (tumor burden reduction of ≥30%), another 4 showed a tumor burden reduction of <30%, and 13 showed tumor burden increases of <20%. The median change (interquartile range) in tumor burden was +3.77% (–11.1 to 11.1).