Overall Survival and Long-Term Safety of Nivolumab (Anti-PD-1 Antibody, BMS-936558, ONO-4538) in Patients with Previously Treated Advanced Non-Small-Cell Lung Cancer

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RESULTS S1. Description of Patients With Non-Small-Cell Lung Cancer With Treatment-Related Deaths

Three non-small-cell lung cancer (NSCLC) patients had treatment-related deaths, all were associated with pneumonitis.

i. A 62-year-old man with NSCLC (adenocarcinoma) in the 1 mg/kg treatment group who developed grade 4 pneumonitis died due to sepsis in July 2011. He was an ex-smoker (25 pack year history, quitting 6 ½ years prior to initiation of trial therapy) previously treated with chemotherapy (cisplatin/ pemetrexed) and bevacizumab for advanced NSCLC. Sepsis and pneumonitis were considered related to nivolumab.

ii. A 40-year-old woman with NSCLC (adenocarcinoma) in the 1 mg/kg treatment group developed grade 4 pneumonitis and tumor progression and died due to respiratory failure in November 2011. She was a never smoker previously treated with chemotherapy (cisplatin/ pemetrexed), an experimental pan-HER tyrosine kinase inhibitor, and erlotinib for advanced NSCLC. Respiratory failure and pneumonitis were considered related to nivolumab.

iii. A 72-year old man with NSCLC (squamous histology) in the 3 mg/kg treatment group developed grade 5 pneumonitis considered related to nivolumab in the setting of disease progression in May 2013. He was an ex-smoker (50 pack year history, quitting 10 months prior to initiation of trial therapy) previously treated with concurrent thoracic chemoradiation (carboplatin/ paclitaxel) followed by a randomized maintenance trial of an experimental vaccine versus placebo for locally advanced NSCLC. This patient died after the March 2013 safety analysis.

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Table S1. Progression-free survival rates by histology and dose for patients treated with nivolumab.

NSCLC Histology	Dose (mg/kg)	Time*	Patients at risk, n	PFS Rate, % (95% CI)
All Histologies				
	ALL	6 months	34	33 (25, 42)
		1 Year	21	22 (15, 30)
		2 Year	7	9 (4, 15)
	1	6 months	5	26 (11, 43)
		1 Year	3	19 (6, 38)
		2 Year	0	0
	3	6 months	13	40 (24, 55)
		1 Year	9	30 (16, 46)
		2 Year	3	11 (3, 26)
	10	6 months	16	33 (21, 46)
		1 Year	9	19 (9, 30)
		2 Year	4	10 (4, 20)
Non Squamous				
	ALL	6 months	17	29 (18, 40)
		1 Year	11	18 (10, 29)
		2 Year	3	6 (2, 41)
	1	6 months	2	18 (3, 41)
		1 Year	2	18 (3, 41)
		2 Year	0	0
	3	6 months	7	42 (20, 62)
		1 Year	5	30 (12, 51)
		2 Year	0	0
	10	6 months	8	26 (13, 41)
		1 Year	4	13 (4, 27)
		2 Year	3	10 (3, 23)
Squamous				
	ALL	6 months	17	41 (27, 55)
		1 Year	10	27 (15, 41)
		2 Year	4	13 (5, 26)
	1	6 months	3	33 (10, 59)
		1 Year	1	17 (1, 48)
		2 Year	0	0
	3	6 months	6	38 (15, 60)
		1 Year	4	30 (10, 53)
		2 Year	3	23 (6, 46)
	10	6 months	8	50 (25, 70)
		1 Year	5	31 (12, 53)
		2 Year	1	9 (1, 32)

*The 6 month, 1- and 2-year time values correspond to the 24 wk, 48wk, and 96 wk tumor assessment visits

Table S2. Treatment-Related Adverse Events That Occurred in at Least 3% of All Treated Patients in the Non-Small-Cell Lung Cancer Population[*]

Treatment-Related Adverse Event	Nivolumab Dose, mg/kg												Total Patients (n=129)			
	1 (n=33)				3 (n=37)				10 (n=59)							
	All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any adverse event[‡]	21	63.6	5	15.2	25	67.6	5	13.5	45	76.3	8	13.6	91	70.5	18	14.0
General disorders																
Fatigue	8	24.2	3	9.1	7	18.9	0	0	16	27.1	1	1.7	31	24.0	4	3.1
Pyrexia	3	9.1	0	0	2	5.4	0	0	3	5.1	0	0	8	6.2	0	0
Chills	0	0	0	0	1	2.7	0	0	3	5.1	0	0	4	3.1	0	0
Mucosal inflammation	0	0	0	0	0	0	0	0	4	6.8	0	0	4	3.1	0	0
Investigations																
Hemoglobin decreased	3	9.1	0	0	3	8.1	0	0	6	10.2	0	0	12	9.3	0	0
CD4 lymphocytes decreased	0	0	0	0	1	2.7	0	0	3	5.1	3	5.1	4	3.1	3	2.3
White blood cell count decreased	2	6.1	0	0	1	2.7	0	0	1	1.7	0	0	4	3.1	0	0
Gastrointestinal disorders																
Diarrhea	4	12.1	0	0	4	10.8	0	0	5	8.5	1	1.7	13	10.1	1	0.8
Nausea	3	9.1	1	3.0	5	13.5	0	0	4	6.8	0	0	12	9.3	1	0.8
Abdominal pain	1	3.0	0	0	2	5.4	0	0	1	1.7	1	1.7	4	3.1	1	0.8
Vomiting	0	0	0	0	2	5.4	0	0	2	3.4	0	0	4	3.1	0	0
Metabolism and nutrition disorders																
Decreased appetite	4	12.1	1	3.0	4	10.8	0	0	8	13.6	0	0	16	12.4	1	0.8
Hypophosphatemia	2	6.1	0	0	1	2.7	0	0	2	3.4	0	0	5	3.9	0	0
Hypocalcemia	2	6.1	0	0	1	2.7	0	0	1	1.7	0	0	4	3.1	0	0
Skin and subcutaneous tissue disorders																
Pruritus	3	9.1	0	0	0	0	0	0	8	13.6	0	0	11	8.5	0	0

Treatment-Related Adverse Event	Nivolumab Dose, mg/kg												Total Patients (n=129)			
	1 (n=33)				3 (n=37)				10 (n=59)							
	All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4		All Grades[†]		Grades 3-4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Rash	0	0	0	0	3	8.1	0	0	6	10.2	0	0	9	7.0	0	0
Respiratory disorders[§]																
Pneumonitis	3	9.1	2	6.1	1	2.7	0	0	4	6.8	1	1.7	8[¶]	6.2[¶]	3	2.3
Dyspnea	0	0	0	0	3	8.1	0	0	3	5.1	0	0	6	4.7	0	0
Cough	1	3.0	0	0	2	5.4	0	0	2	3.4	0	0	5	3.9	0	0
Musculoskeletal disorders																
Arthralgia	1	3.0	0	0	2	5.4	0	0	2	3.4	0	0	5	3.9	0	0
Musculoskeletal pain	2	6.1	1	3.0	1	2.7	0	0	1	1.7	0	0	4	3.1	1	0.8
Myalgia	3	9.1	1	3.0	1	2.7	0	0	0	0	0	0	4	3.1	1	0.8
Pain in extremity	2	6.1	0	0	0	0	0	0	2	3.4	0	0	4	3.1	0	0
Nervous system disorders																
Dizziness	0	0	0	0	0	0	0	0	7	11.9	0	0	7	5.4	0	0
Dysgeusia	1	3.0	0	0	1	2.7	0	0	2	3.4	0	0	4	3.1	0	0
Blood and lymphatic system disorders																
Lymphopenia	1	3.0	0	0	1	2.7	1	2.7	3	5.1	0	0	5	3.9	1	0.8
Procedural complications																
Infusion-related reaction	1	3.0	0	0	0	0	0	0	3	5.1	0	0	4	3.1	0	0

[*]March 2013 safety analysis.

[†]Grades 1-5. Three grade 5 treatment-related events occurred in non-small-cell lung cancer patients: A 62-year-old man in the 1mg/kg treatment group had grade 5 sepsis and a 40-year-old woman in the 1mg/kg treatment group had grade 5 respiratory failure. A 72-year-old man in the 3

mg/kg treatment group had grade 5 pneumonitis but is not included in this table because the event occurred after the date of the safety analysis. These patients are described in detail in this Data Supplement, Results S1.

‡The numbers reported within a column may not add up to the total number reported under "any adverse event" because patients who had more than one adverse event were counted for each event but were counted only once for "any adverse event", and data for only those events that were reported in at least 3% of the treated patient population are presented in this table.

§ Treatment–related respiratory adverse events that were reported in <3% of the total NSCLC population included hypoxia, respiratory tract inflammation, and wheezing (2 patients each, 1.6%) and interstitial lung disease, oropharyngeal pain, pleural effusion, pulmonary fibrosis, sinus congestion, and sneezing (1 patient each, 0.8%).

¶Two additional patients had treatment-related grade 2 pneumonitis, which occurred prior to the date of the safety analysis, but are not included in this table because these data were not available until after this analysis. A third patient had treatment-related grade 5 pneumonitis but is not included in this table because the event occurred after the date of the safety analysis.

Table S3. Clinical activity presented by tumor PD-L1 expression[ref]

PD-L1 status[a,b]	**N**	**ORR, % (n/N)**	**Median PFS, mo (95% CI)**	**Median OS, mo (95% CI)**
Positive	33	15 (5/33)	3.3 (1.8, 7.5)	7.8 (5.6, 21.7)
Negative	35	14 (3/35)	1.8 (1.7, 2.3)	10.5 (5.2, 14.8)

[a] There were a total of 68 samples evaluable for PD-L1 expression

[b] Positivity is defined as tumor cell membrane staining at any intensity with ≥5% PD-L1 expression in a minimum number of 100 evaluable cells

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Figure S1. Kaplan-Meier curves of overall survival of patients with squamous cell histology (n=54) and non-squamous cell histology (n=74). Symbols indicate censored events, defined for overall survival as the time to the last known alive date before the date of data analysis, for patients without a death. OS, overall survival.

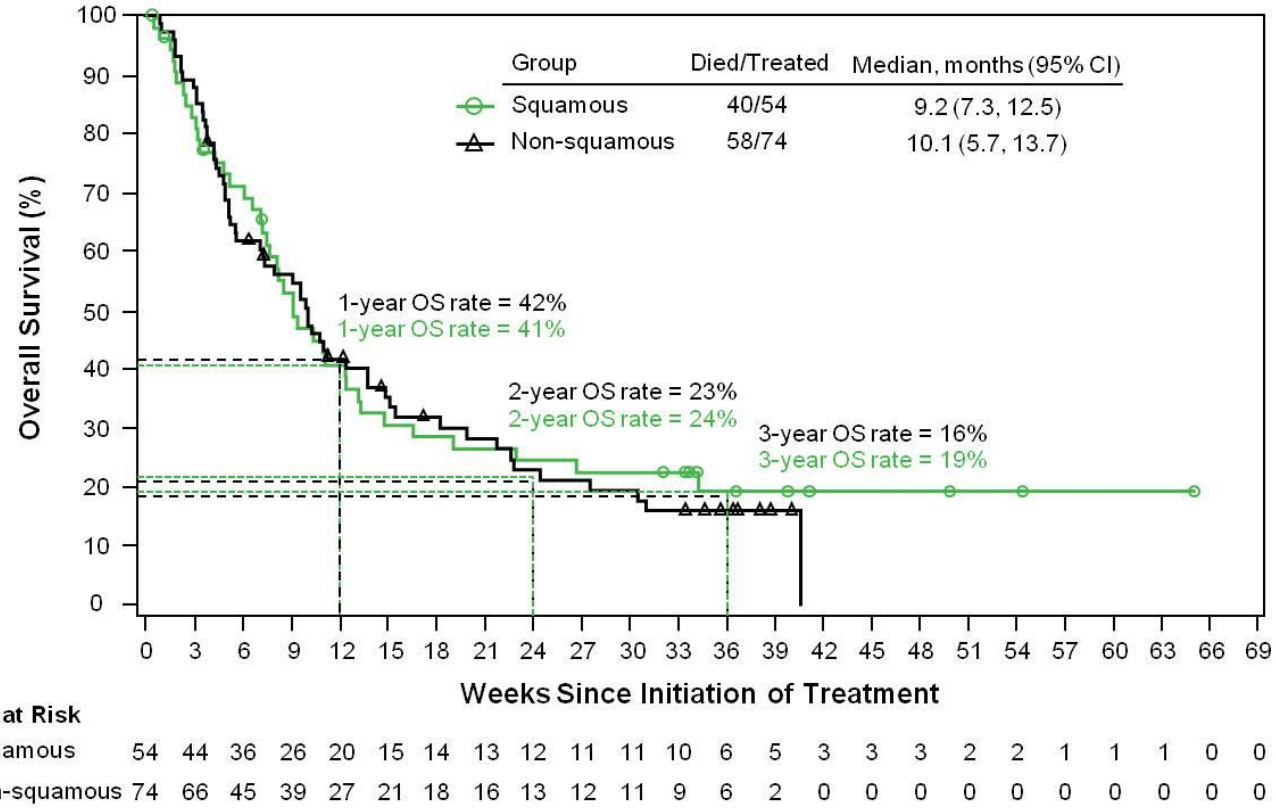
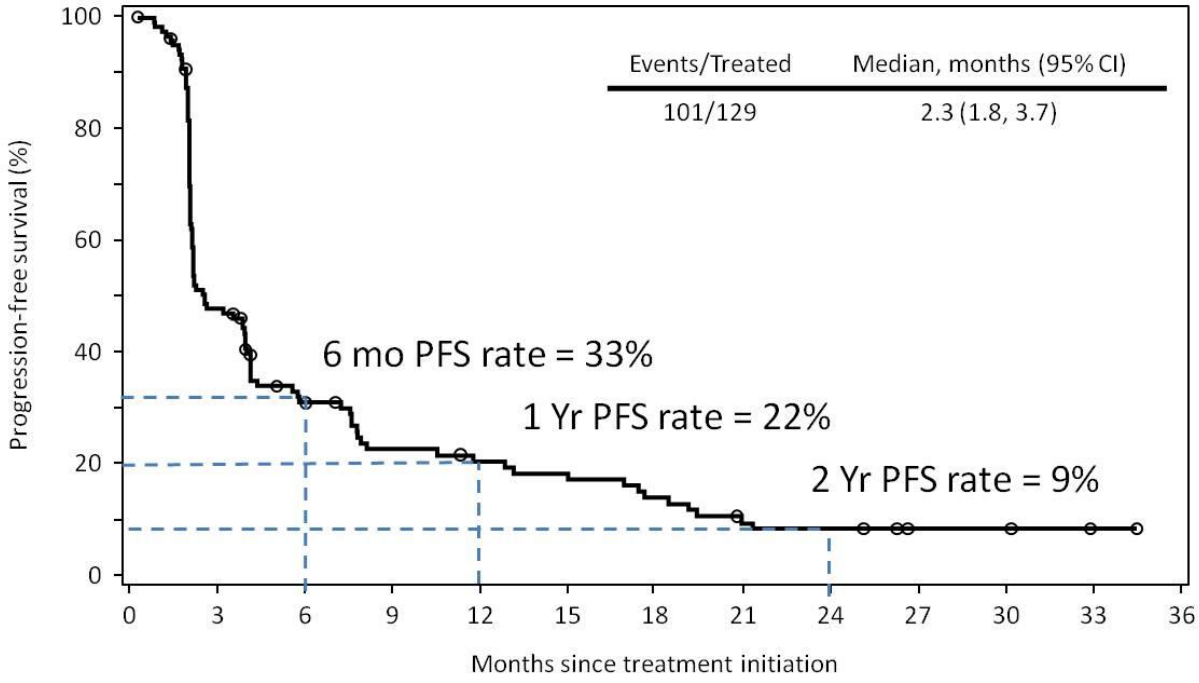
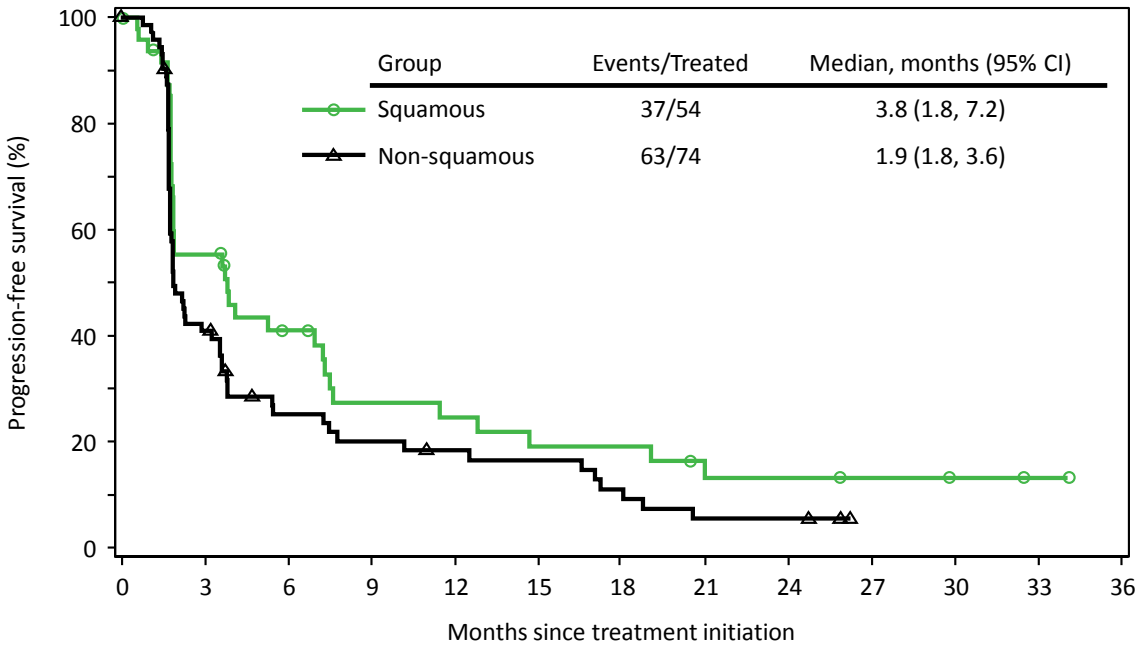


Figure S2-A. Kaplan-Meier curve of progression-free survival of nivolumab-treated patients with non-small-cell-lung cancer (n=129). Open circles indicate censored events, defined for progression-free survival as the time to the last tumor assessment before the date of data analysis, for patients without disease progression or death (during the treatment and clinical follow-up periods).



No. at risk	129	56	31	22	19	16	13	7	7	3	2	1	0

Figure S2-B. Kaplan-Meier curves of progression-free survival of nivolumab-treated patients with squamous (n=54) and non-squamous (n=74) non-small-cell-lung cancer. Symbols indicate censored events, defined for progression-free survival as the time to the last tumor assessment before the date of data analysis, for patients without disease progression or death (during the treatment and clinical follow-up periods).



No. at risk

Squamous	54	26	16	10	9	7	7	4	4	3	2	1	0
Non-squamous	74	29	15	12	10	9	6	3	3	0	0	0	0

Figure S3. Tumor kinetics in non-small-cell lung cancer patients with unconventional responses (e.g., persistent reduction in target lesions in the presence of new lesions or regression following initial progression) with nivolumab treatment (n=6). Baseline tumor measurements are standardized to zero. Tumor burden was measured as the sum of the longest diameters of target lesions compared with baseline. Red triangles indicate first occurrence of a new lesion. The horizontal line at −30% indicates the threshold for defining objective response (partial tumor regression) in the absence of new lesions or non-target disease progression, according to RECIST v1.0.

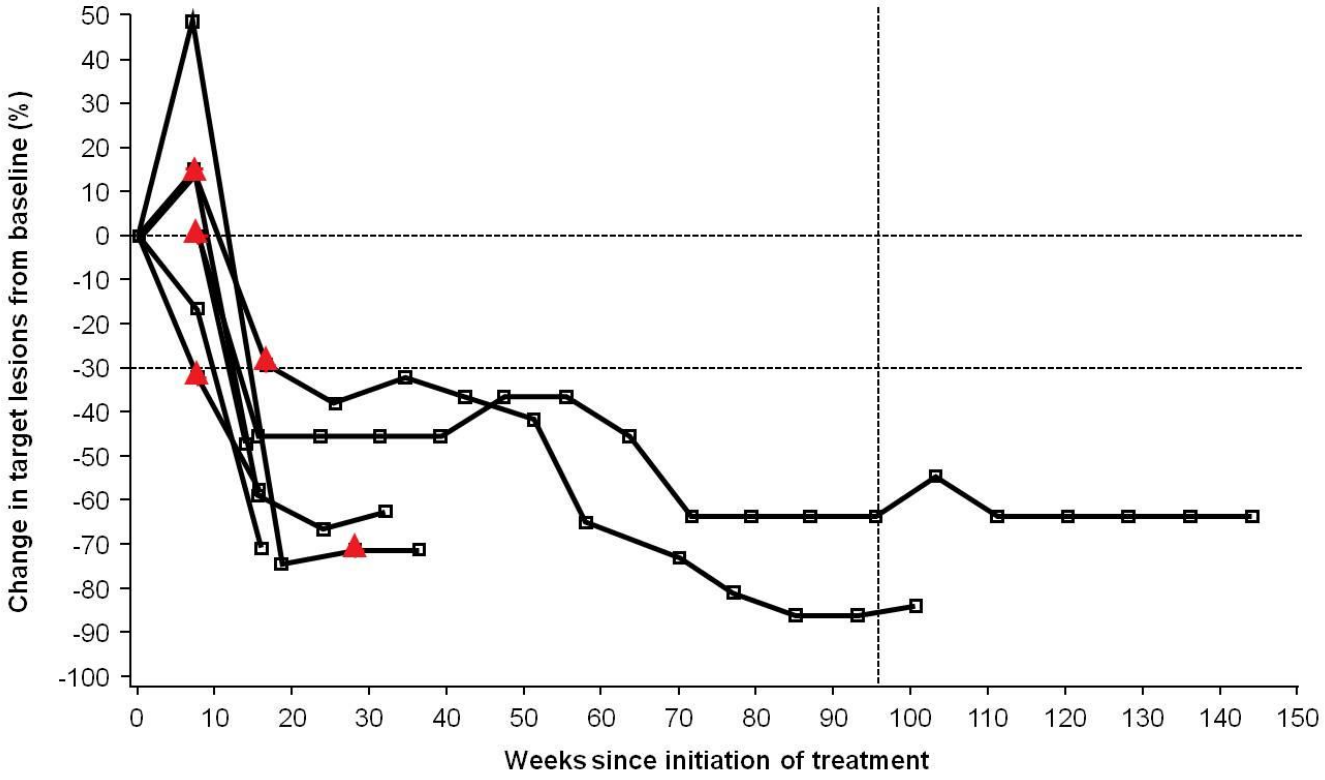


Figure S4. Kaplan-Meier curve of response duration in the 22 patients with objective responses. NE, not estimable.

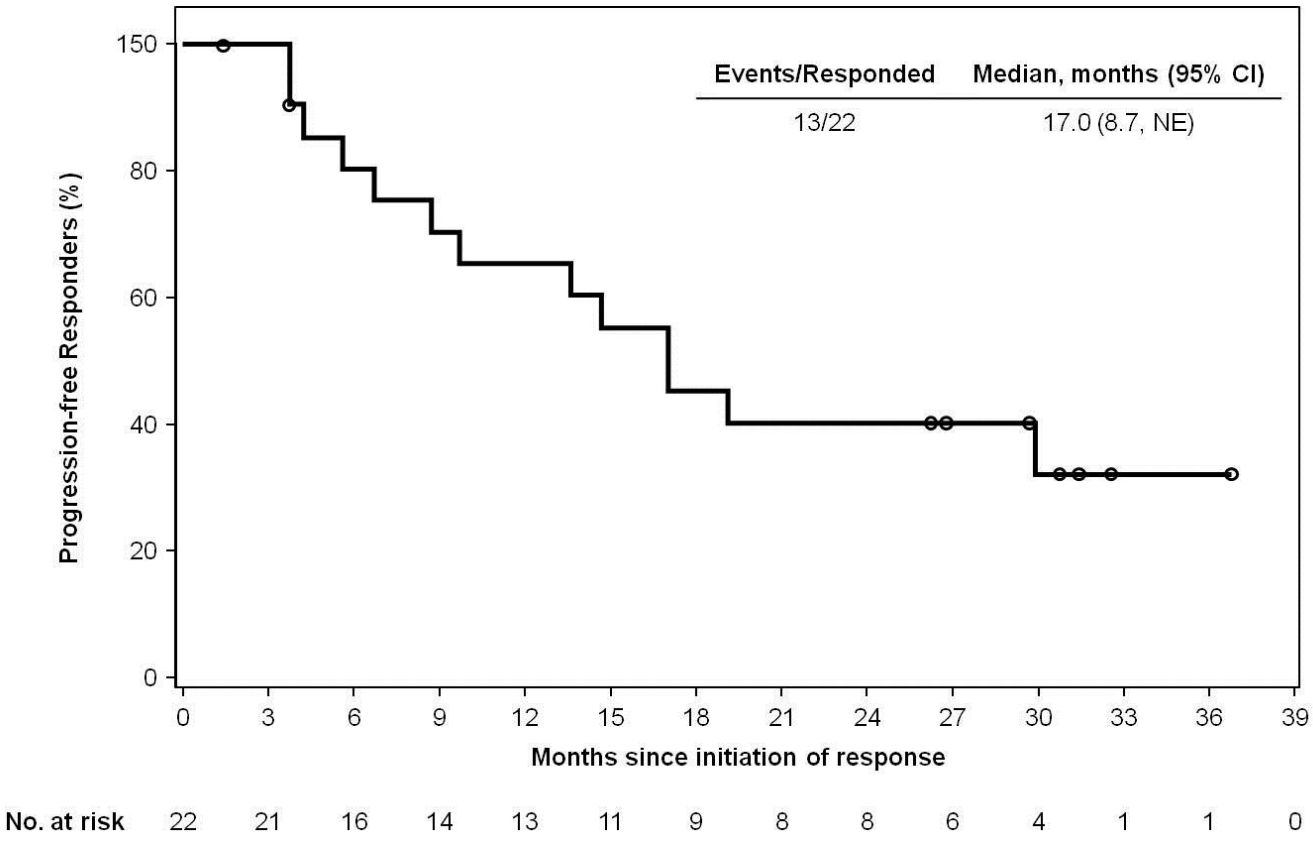


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Figure S5-A. Characteristics of tumor regression in patients with non-small-cell lung cancer who received less than or at least 3 prior therapies. (A) Best change in overall tumor burden in all patients with tumor measurements during treatment (n=115). (B) Tumor kinetics in NSCLC patients treated with 3 mg/kg nivolumab and with at least one post-baseline tumor assessment (n=33). Baseline tumor measurements are standardized to zero. Overall tumor burden was measured as the sum of the longest diameters of target lesions compared with baseline. The horizontal line at −30% indicates the threshold for defining objective response (partial tumor regression) in the absence of new lesions or non-target disease progression, according to RECIST v1.0. The vertical line at 96 weeks indicates the protocol-defined maximum duration of continuous nivolumab therapy.

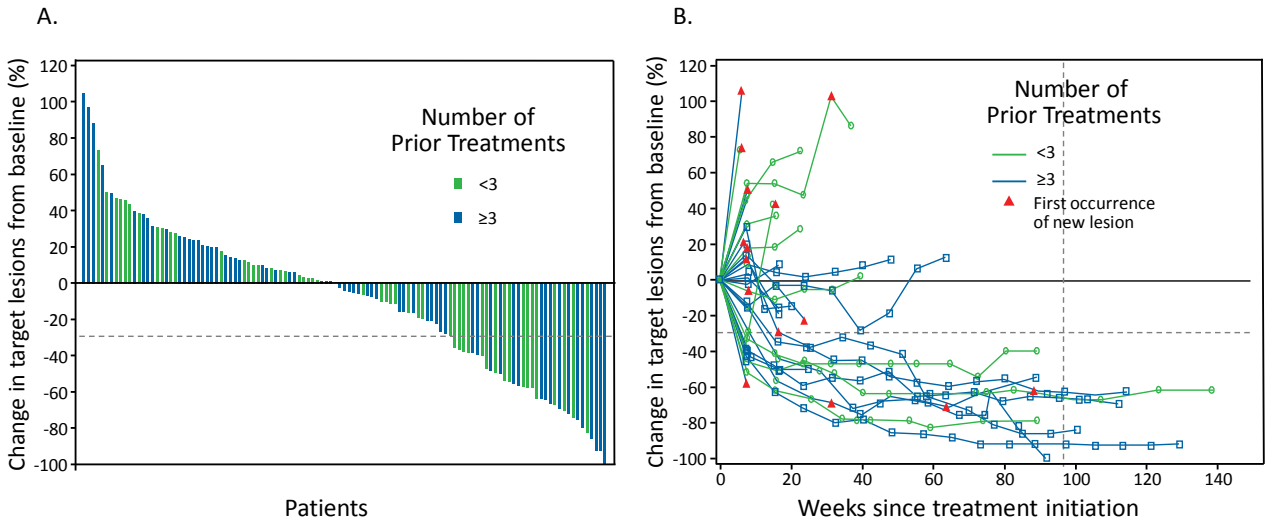

Figure S5-B. Best change in overall tumor burden among non-small-cell lung cancer patients treated with nivolumab based on (A) *EGFR* and (B) *KRAS* tumor mutation status. Patients with tumor measurements during nivolumab treatment were included (n=115). Overall tumor burden was measured as the sum of the longest diameters of target lesions compared with baseline. The horizontal line at −30% indicates the threshold for defining objective response (partial tumor regression) in the absence of new lesions or non-target disease progression, according to RECIST v1.0.