

Supplementary Appendix

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

Supplement to: Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33. DOI: 10.1056/NEJMoa1302369

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Methods S1. Definition of Tumor Response Terms.

Tumor Responses as Defined by WHO and Immune-Related Response Criteria¹

	WHO	Immune-Related Response Criteria
New, measurable lesions (ie, $\geq 5 \times 5$ mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (ie, $< 5 \times 5$ mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best overall response of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 wk apart	Disappearance of all lesions in 2 consecutive observations not less than 4 wk apart
PR	$\geq 50\%$ decrease in SPD of all index lesions compared with baseline in 2 observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	$\geq 50\%$ decrease in tumor burden compared with baseline in 2 observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 wk apart

PD denotes progressive disease, irCR immune-related complete response, CR complete response, PR partial response, SD stable disease, SPD the sum of the products of the 2 largest perpendicular diameters of all index lesions.

Deep tumor response: A response in target lesions that was characterized by a reduction of $\geq 80\%$ from baseline measurements by radiographic assessment.

Figure S1. Study Design.

Treatment Scheme for Concurrent Regimen *

		Ipilimumab once every 3 weeks (4 doses)								Ipilimumab once every 12 weeks (8 doses)							
Weeks		↓	↓	↓	↓					↓	↓	↓	↓	↓	↓	↓	↓
	0	3	6	9	12	15	18	21	24	36	48	60	72	84	96	108	
		↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
		Nivolumab once every 3 weeks (8 doses)								Nivolumab once every 12 weeks (8 doses)							

Planned Dose Levels for Concurrent- and Sequenced-Regimens

Cohort	Nivolumab (mg/kg)	Ipilimumab (mg/kg)
Concurrent regimen		
1	0.3	3
2	1	3
2a	3	1
3	3	3
4	10	3
5	10	10
Sequenced regimen [†]		
6	1	Prior
7	3	Prior

*Patients were to be treated with nivolumab and ipilimumab as shown (cohorts 1-5). When both drugs were administered together, nivolumab was administered first. Within a cohort, nivolumab and ipilimumab doses were kept constant during induction and maintenance. The dose-limiting-toxicity evaluation period was through week 9. Tumor assessments were at weeks 12, 18, 24, 30, and 36 and then every 12 weeks thereafter. Tumor responses were adjudicated using mWHO and immune-related mWHO criteria for both regimens.

[†]Patients in cohorts 6 and 7 were to be treated with nivolumab every 2 weeks for up to 48 doses. Nivolumab therapy was initiated within 4-12 weeks after ipilimumab monotherapy. Patients received ipilimumab monotherapy prior to study entry. Tumor assessments were at week 8 and then every 8 weeks thereafter.

Figure S2. Clinical Activity of Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

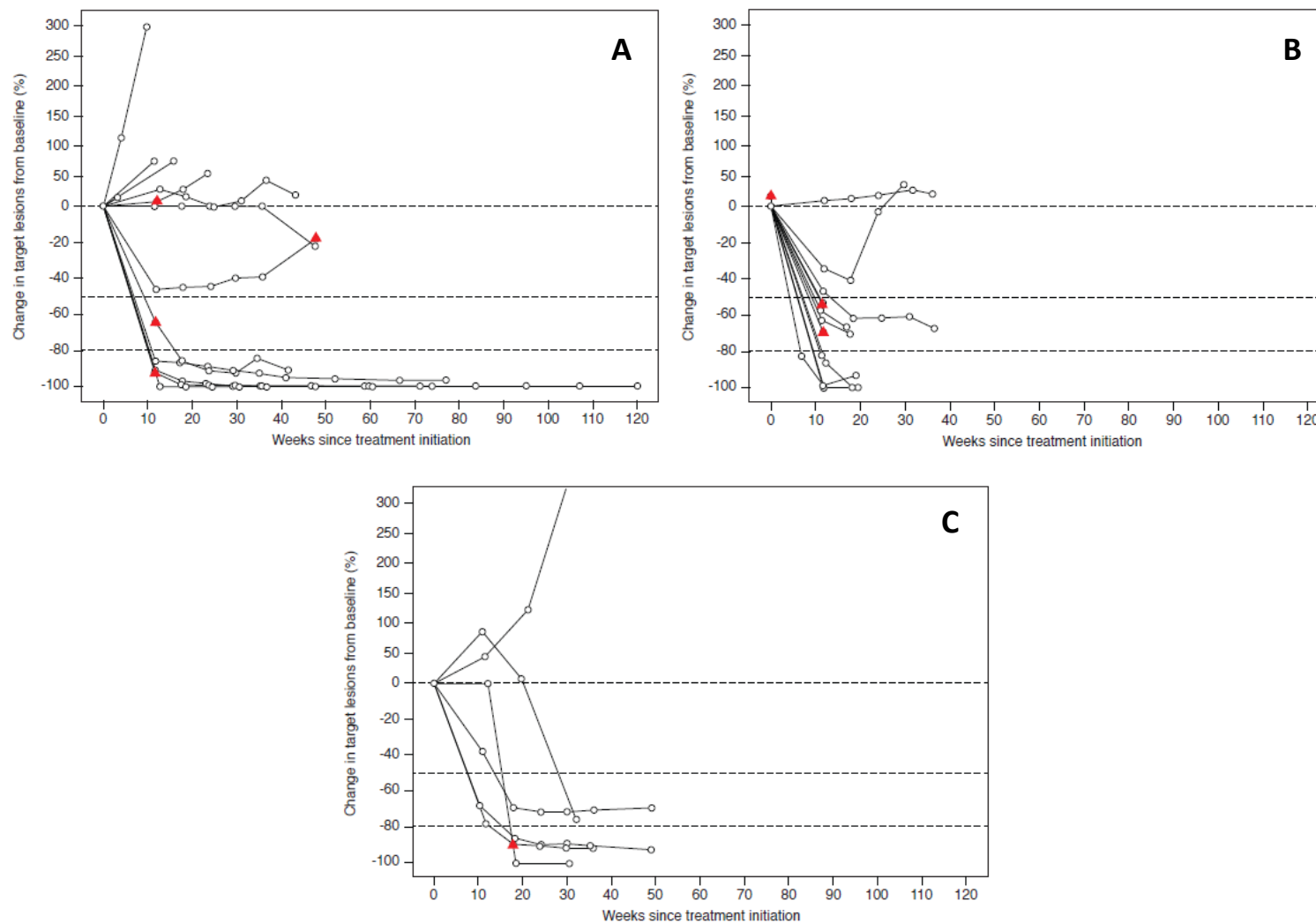


Figure S2. Clinical Activity of Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab. Representative spider plots show changes from baseline in the tumor burden, measured as the sum of products of perpendicular diameters of all target lesions, in patients who received the concurrent regimen of 0.3 mg/kg nivolumab + 3 mg/kg ipilimumab (panel A), 3 mg/kg nivolumab + 1 mg/kg ipilimumab (panel B), or 3 mg/kg nivolumab + 3 mg/kg ipilimumab (panel C). Red triangles indicate the first occurrence of a new lesion. Dashed lines indicate 50% and 80% improvement from baseline as assessed by means of modified World Health Organization criteria.

Figure S3. Tumor Regression of a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

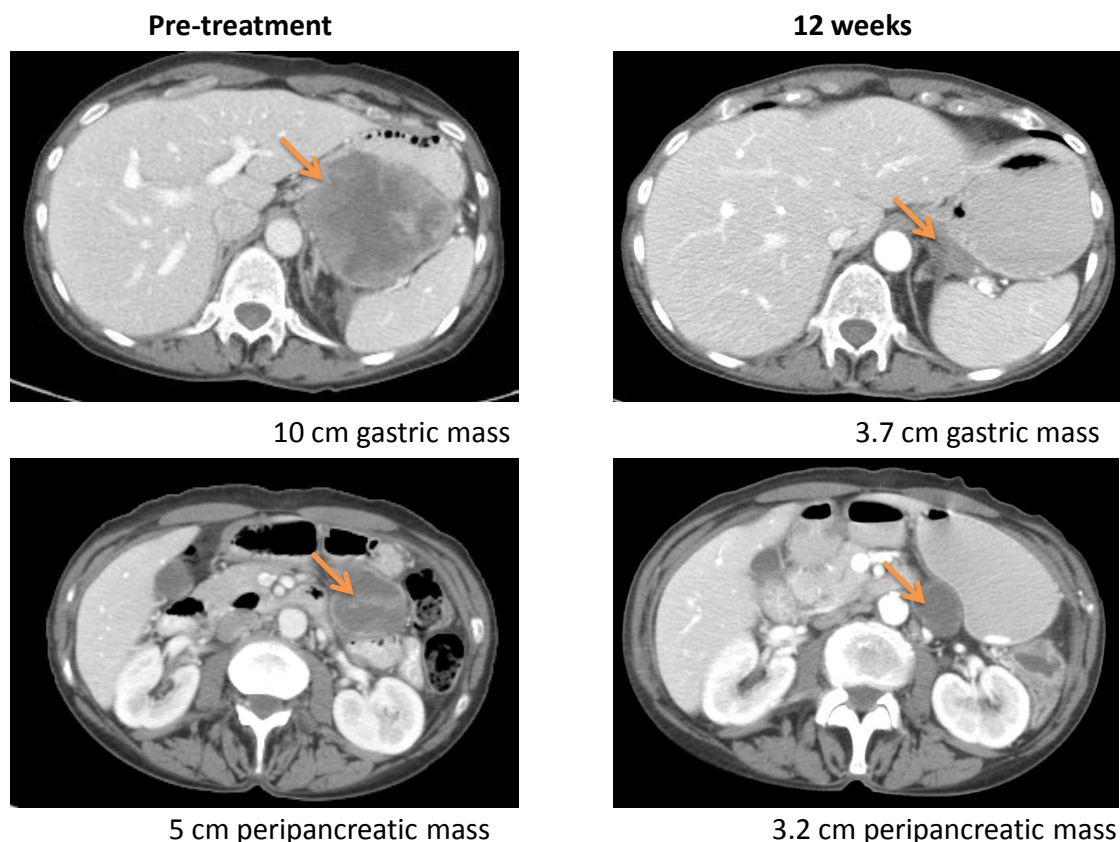


Figure S3. Tumor Regression of a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab. Regression of tumors in a 61-year-old patient who received 0.3 mg/kg nivolumab + 3 mg/kg ipilimumab. The patient presented with stage IV (M1c) melanoma of an unknown primary site, metastatic to the stomach and the mesentery. Lactate dehydrogenase was 225 and hemoglobin was 9.6 g/dL after a recent transfusion. Twelve weeks after the initiation of study treatment, a computed tomographic scan showed an 86% reduction in the bulky disease burden.

Figure S4. Clinical Activity of Patients Who Received the Sequenced Regimen of Nivolumab and Ipilimumab.

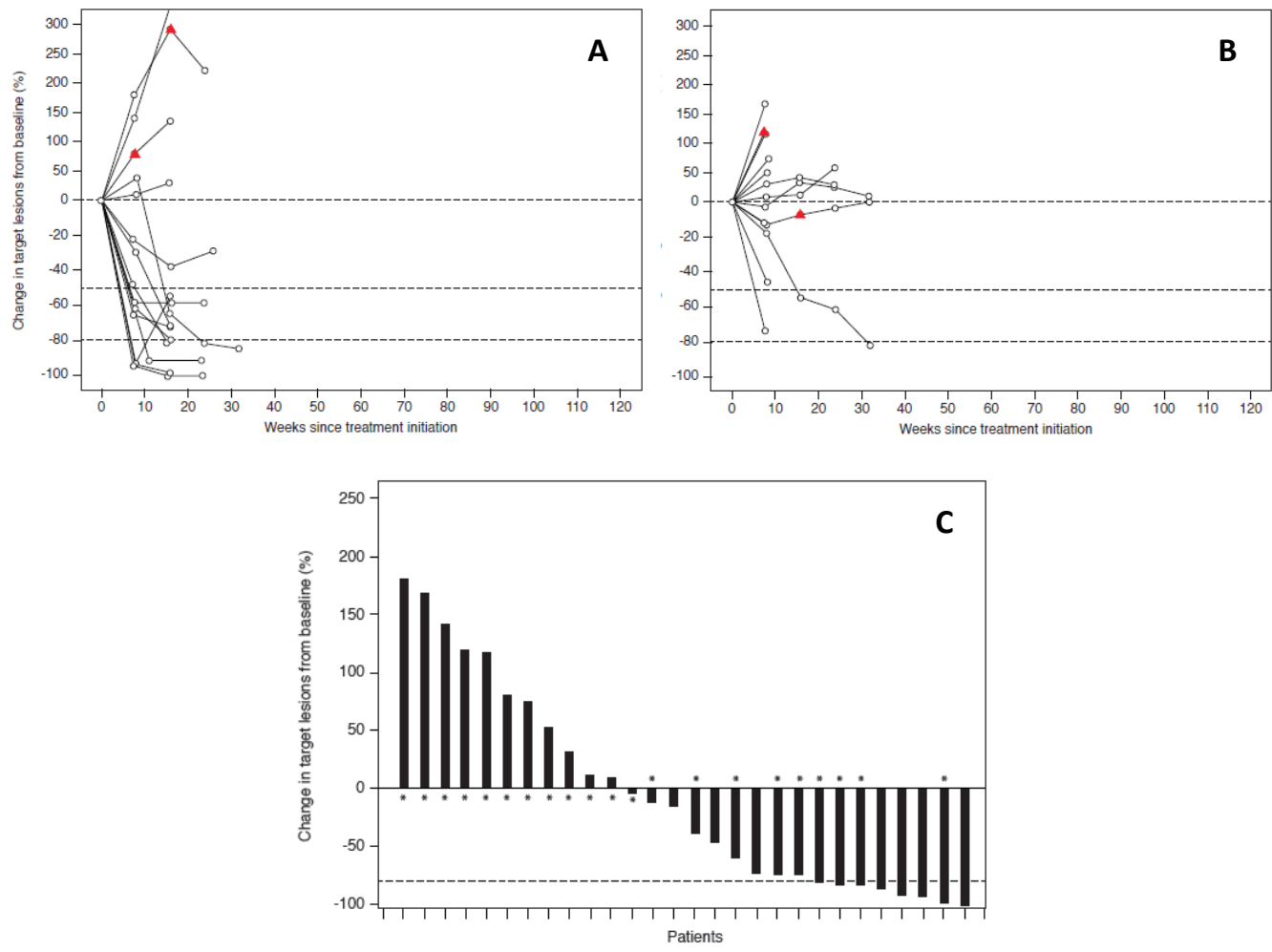


Figure S4. Clinical Activity of Patients Who Received the Sequenced Regimen of Nivolumab and Ipilimumab.

Representative spider plots show changes from baseline in the tumor burden, measured as the sum of products of perpendicular diameters of all target lesions, in patients who received the sequenced regimen of 1 mg/kg nivolumab (panel A) or 3 mg/kg nivolumab (panel B) after prior ipilimumab therapy. Red triangles indicate the first occurrence of a new lesion. Dashed lines indicate 50% and 80% improvement from baseline as assessed by means of modified World Health Organization criteria. A representative waterfall plot shows maximum percentage response in baseline target lesions in patients who received the sequenced regimen (panel C); “*” denotes patients who had radiographic progression with prior ipilimumab treatment. The dashed line denotes 80% tumor reduction in target lesions from baseline.

Figure S5. PD-L1 Expression Patterns in Melanoma Tumor Lesions as Assessed by Immunohistochemistry.

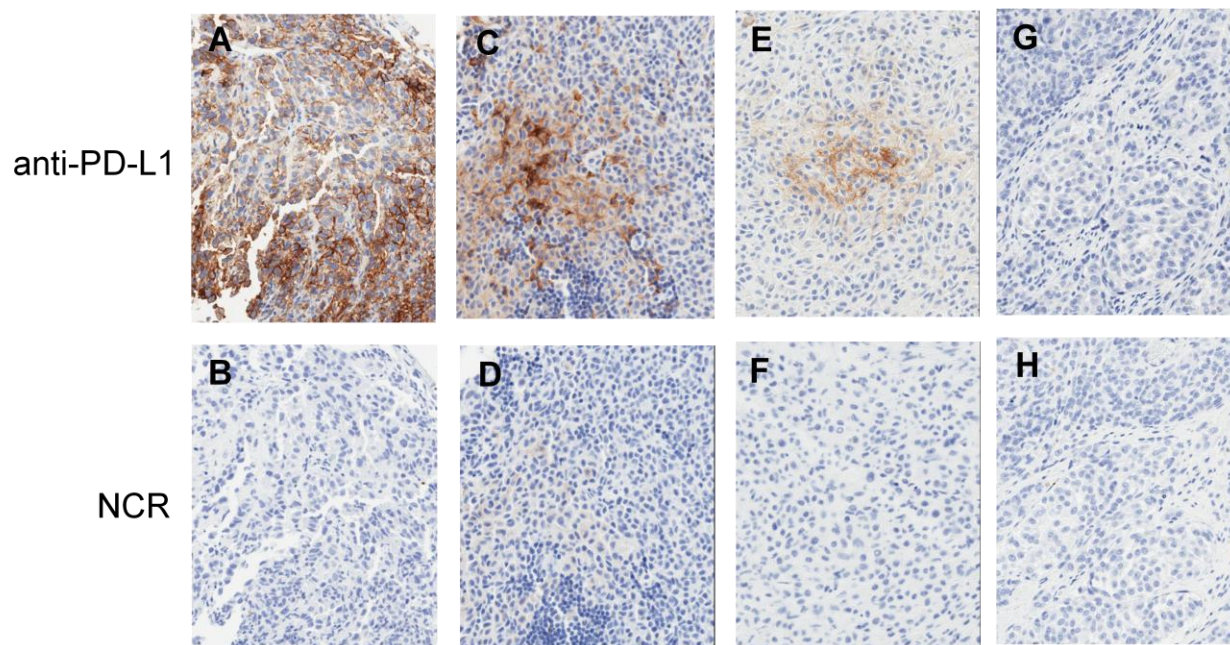


Figure S5. PD-L1 Expression Patterns in Melanoma Tumor Lesions as Assessed by

Immunohistochemistry. Following deparaffinization, rehydration, and epitope retrieval on the Dako PT Link Pre-Treatment Module, formalin-fixed, paraffin-embedded tissue sections were incubated with the rabbit monoclonal anti-PD-L1 antibody (clone 28-8) and stained using the Dako EnVision™ FlexHRP detection system on the Dako Automated Link Platform. Consecutive sections were stained with a negative-control reagent (NCR). Exogenous controls, both positive- and negative-control cell lines and a positive-control tonsil section, were included in all staining runs. Photomicrographs of regions of tumor tissue sections stained with anti-PD-L1 (panels A, C, E, G) and their respective NCR-stained areas (panels B, D, F, H) at 200 X original magnification are shown. Homogenous staining pattern of membrane PD-L1 in 80% of tumor cells within the entire tissue area (panel A). Heterogeneous staining pattern of membrane PD-L1 in 5% of tumor cells within the entire tissue area (panel C). Focal region of a tumor tissue section with membrane PD-L1 staining in 3% of tumor cells within the entire tissue area (panel E). Area of tumor from a sample with no membrane PD-L1 staining in melanoma cells (panel G).

Supplementary appendix for “Nivolumab plus Ipilimumab in Advanced Melanoma” by Wolchok et al.

Table S1-A. Adverse Events, Regardless of Causality, Highest Grade, That Occurred in at Least 10% of All Treated Patients*

Adverse Event	0.3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=14)		1 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=17)		3 mg/kg Nivolumab + 1 mg/kg Ipilimumab (n=16)		3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=6)		Concurrent Treatment, All (n=53)		1 mg/kg Nivolumab + Prior Ipilimumab (n=17)		3 mg/kg Nivolumab + Prior Ipilimumab (n=16)		Sequenced Treatment, All (n=33)	
	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4
	number of patients (percent)															
Any adverse event [†]	14 (100)	9 (64)	17 (100)	14 (82)	15 (94)	11 (69)	6 (100)	4 (67)	52 (98)	38 (72)	17 (100)	6 (35)	12 (75)	5 (31)	29 (88)	11 (33)
General disorders																
Fatigue	9 (64)	0	11 (65)	0	7 (44)	0	4 (67)	0	31 (58)	0	7 (41)	0	5 (31)	0	12 (36)	0
Pyrexia	5 (36)	0	7 (41)	0	4 (25)	0	2 (33)	0	18 (34)	0	3 (18)	0	3 (19)	0	6 (18)	0
Chills	3 (21)	0	5 (29)	0	1 (6)	0	0	0	9 (17)	0	1 (6)	0	1 (6)	0	2 (6)	0
Gastrointestinal disorders																
Diarrhea	5 (36)	0	5 (29)	1 (6)	8 (50)	2 (13)	4 (67)	0	22 (42)	3 (6)	2 (12)	0	2 (13)	0	4 (12)	0
Nausea	7 (50)	1 (7)	5 (29)	0	4 (25)	0	3 (50)	0	19 (36)	1 (2)	3 (18)	0	3 (19)	0	6 (18)	0
Constipation	4 (29)	0	2 (12)	0	3 (19)	0	1 (17)	0	10 (19)	0	1 (6)	0	3 (19)	0	4 (12)	0
Vomiting	5 (36)	2 (14)	4 (24)	1 (6)	3 (19)	0	1 (17)	0	13 (25)	3 (6)	0	0	1 (6)	0	1 (3)	0
Abdominal pain	3 (21)	0	3 (18)	0	4 (25)	0	1 (17)	0	11 (21)	0	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Skin and subcutaneous tissue disorders																
Rash	9 (64)	2 (14)	11 (65)	0	9 (56)	1 (6)	3 (50)	0	32 (60)	3 (6)	6 (35)	0	1 (6)	0	7 (21)	0
Pruritus	7 (50)	1 (7)	11 (65)	0	9 (56)	0	1 (17)	0	28 (53)	1 (2)	2 (12)	0	4 (25)	0	6 (18)	0
Respiratory, thoracic, and mediastinal disorders																
Cough	5 (36)	0	6 (35)	0	7 (44)	0	1 (17)	0	19 (36)	0	5 (29)	0	3 (19)	0	8 (24)	0

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Dyspnea	5 (36)	1 (7)	2 (12)	0	2 (13)	0	0	0	9 (17)	1 (2)	3 (18)	1 (6)	0	0	3 (9)	1 (3)
Investigations																
Lipase increased	2 (14)	2 (14)	3 (18)	2 (12)	2 (13)	2 (13)	4 (67)	3 (50)	11 (21)	9 (17)	2 (12)	1 (6)	2 (13)	1 (6)	4 (12)	2 (6)
Aspartate amino- transferase increased	4 (29)	3 (21)	4 (24)	2 (12)	3 (19)	1 (6)	2 (33)	2 (33)	13 (25)	8 (15)	1 (6)	0	0	0	1 (3)	0
Alanine amino- transferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (13)	0	2 (33)	2 (33)	12 (23)	7 (13)	0	0	1 (6)	0	1 (3)	0
Amylase increased	2 (14)	0	3 (18)	2 (12)	1 (6)	0	3 (50)	1 (17)	9 (17)	3 (6)	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Musculoskeletal and connective tissue disorders																
Arthralgia	4 (29)	0	3 (18)	0	3 (19)	0	1 (17)	0	11 (21)	0	3 (18)	1 (6)	4 (25)	0	7 (21)	1 (3)
Back pain	3 (21)	0	1 (6)	0	3 (19)	0	2 (33)	0	9 (17)	0	3 (18)	0	1 (6)	0	4 (12)	0
Pain in extremity	5 (36)	0	0	0	2 (13)	0	0	0	7 (13)	0	2 (12)	0	0	0	2 (6)	0
Nervous system disorders																
Headache	2 (14)	0	9 (53)	0	4 (25)	0	3 (50)	0	18 (34)	0	1 (6)	0	2 (13)	0	3 (9)	0
Metabolism and nutrition disorders																
Decreased appetite	3 (21)	0	3 (18)	0	3 (19)	0	0	0	9 (17)	0	2 (12)	0	1 (6)	0	3 (9)	0

*Only the highest grade of event was counted for each patient. Gr denotes grade.

†The numbers reported within a column may not add up to the total number reported under “any adverse event” because (i) patients who had more than one adverse event were counted for each event but were counted only once for “any adverse event” and (ii) data for only those events that were reported in at least 10% of the all-treated patient population are presented in this table.

Supplementary appendix for “Nivolumab plus Ipilimumab in Advanced Melanoma” by Wolchok et al.

Table S1-B. Treatment-Related Adverse Events, Highest Grade, That Occurred in at Least 3% of All Treated Patients*

Treatment-Related Adverse Event	0.3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=14)		1 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=17)		3 mg/kg Nivolumab + 1 mg/kg Ipilimumab (n=16)		3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=6)		Concurrent Treatment, All (n=53)		1 mg/kg Nivolumab + Prior Ipilimumab (n=17)		3 mg/kg Nivolumab + Prior Ipilimumab (n=16)		Sequenced Treatment, All (n=33)	
	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4
	number of patients (percent)															
Any adverse event [†]	13 (93)	6 (43)	17 (100)	11 (65)	13 (81)	7 (44)	6 (100)	4 (67)	49 (93)	28 (53)	14 (82)	4 (24)	10 (63)	2 (13)	24 (73)	6 (18)
<i>Skin and subcutaneous tissue disorders</i>																
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)	3 (18)	0	0	0	3 (9)	0
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0	2 (12)	0	4 (25)	0	6 (18)	0
Vitiligo	2 (14)	0	3 (18)	0	1 (6)	0	0	0	6 (11)	0	0	0	0	0	0	0
Night sweats	1 (7)	0	2 (12)	0	0	0	0	0	3 (6)	0	0	0	0	0	0	0
<i>Gastrointestinal disorders</i>																
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)	2 (12)	0	1 (6)	0	3 (9)	0
Nausea	3 (21)	0	3 (18)	0	4 (25)	0	1 (17)	0	11 (21)	0	1 (6)	0	0	0	1 (3)	0
Vomiting	1 (7)	0	2 (12)	1 (6)	3 (19)	0	0	0	6 (11)	1 (2)	0	0	0	0	0	0
Abdominal pain	2 (14)	0	1 (6)	0	2 (13)	0	0	0	5 (9)	0	0	0	0	0	0	0
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)	0	0	0	0	0	0
Dry mouth	1 (7)	0	0	0	1 (6)	0	0		2 (4)	0	2 (12)	0	1 (6)	0	3 (9)	0
Flatulence	1 (7)	0	1 (6)	0	1 (6)	0	1 (17)	0	4 (8)	0	0	0	0	0	0	0
<i>General disorders</i>																
Fatigue	5 (36)	0	7 (41)	0	5 (31)	0	3 (50)	0	20 (38)	0	1 (6)	0	2 (13)	0	3 (9)	0
Pyrexia	3	0	3	0	4	0	1	0	11	0	0	0	1	0	1	0

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	(21)		(18)		(25)		(17)		(21)				(6)		(3)	
Chills	1 (7)	0	1 (6)	0	1 (6)	0	0	0	3 (6)	0	0	0	0	0	0	0
Investigations																
Lipase increased	2 (14)	2 (14)	3 (18)	1 (6)	1 (6)	1 (6)	4 (67)	3 (50)	10 (19)	7 (13)	2 (12)	1 (6)	2 (13)	1 (6)	4 (12)	2 (6)
Alanine amino- transferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (13)	0	1 (17)	1 (17)	11 (21)	6 (11)	0	0	1 (6)	0	1 (3)	0
Aspartate amino- transferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (13)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)	0	0	0	0	0	0
Amylase increased	2 (14)	0	3 (18)	2 (12)	0	0	3 (50)	1 (17)	8 (15)	3 (6)	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)	0	0	0	0	0	0
γ-Glutamyl transferase increased	2 (14)	1 (7)	1 (6)	0	0	0	0	0	3 (6)	1 (2)	0	0	0	0	0	0
Weight decreased	1 (7)	0	0	0	2 (13)	0	0	0	3 (6)	0	0	0	0	0	0	0
Nervous system disorders																
Headache	0	0	4 (24)	0	2 (13)	0	0	0	6 (11)	0	0	0	0	0	0	0
Dysgeusia	0	0	2 (12)	0	2 (13)	0	0	0	4 (8)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders																
Cough	2 (14)	0	2 (12)	0	2 (13)	0	1 (17)	0	7 (13)	0	2 (12)	0	0	0	2 (6)	0
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)	0	0	1 (6)	0	1 (3)	0
Dyspnea	1 (7)	0	1 (6)	0	1 (6)	0	0	0	3 (6)	0	0	0	0	0	0	0
Metabolism and nutrition disorders																
Decreased appetite	0	0	2 (12)	0	3 (19)	0	0	0	5 (9)	0	0	0	1 (6)	0	1 (3)	0
Musculoskeletal and connective tissue disorders																
Arthralgia	0	0	2	0	1	0	1	0	4	0	0	0	3	0	3	0

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			(12)		(6)		(17)		(8)				(19)		(9)	
Endocrine disorders																
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0	1 (6)	0	0	0	1 (3)	0
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0	0	0	0	0	0	0
Eye disorders																
Uveitis	0	0	3 (18)	2 (12)	0	0	0	0	3 (6)	2 (4)	0	0	0	0	0	0

*Only the highest grade of event was counted for each patient. Gr denotes grade.

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

Table S1-C. Treatment-Related Serious Adverse Events, Highest Grade, That Occurred in at Least Two of All Treated Patients*

Serious Adverse Event [†]	0.3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=14)		1 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=17)		3 mg/kg Nivolumab + 1 mg/kg Ipilimumab (n=16)		3 mg/kg Nivolumab + 3 mg/kg Ipilimumab (n=6)		Concurrent Treatment, All (n=53)		1 mg/kg Nivolumab + Prior Ipilimumab (n=17)		3 mg/kg Nivolumab + Prior Ipilimumab (n=16)		Sequenced Treatment, All (n=33)	
	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4	All Gr	Gr 3-4
	number of patients (percent)															
Any adverse event [†]	5 (36)	4 (29)	11 (65)	10 (59)	7 (44)	5 (31)	3 (50)	3 (50)	26 (49)	22 (42)	4 (24)	4 (24)	3 (19)	2 (13)	7 (21)	6 (18)
Investigations																
Alanine amino-transferase increased	3 (21)	2 (14)	3 (18)	3 (18)	2 (13)	0	1 (17)	1 (17)	9 (17)	6 (11)	0	0	0	0	0	0
Aspartate amino-transferase increased	3 (21)	3 (21)	3 (18)	2 (12)	2 (13)	1 (6)	1 (17)	1 (17)	9 (17)	7 (13)	0	0	0	0	0	0
Lipase increased	0	0	1 (6)	1 (6)	1 (6)	1 (6)	1 (17)	1 (17)	3 (6)	3 (6)	1 (6)	1 (6)	1 (6)	1 (6)	2 (6)	2 (6)
Amylase increased	0	0	0	0	0	0	1 (17)	1 (17)	1 (2)	1 (2)	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Blood creatinine increased	1 (7)	0	0	0	1 (6)	1 (6)	0	0	2 (4)	1 (2)	0	0	0	0	0	0
Gastrointestinal disorders																
Diarrhea	0	0	2 (12)	1 (6)	3 (19)	1 (6)	0	0	5 (9)	2 (4)	0	0	0	0	0	0
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	0	0	4 (8)	2 (4)	0	0	0	0	0	0
Abdominal pain	0	0	1 (6)	0	1 (6)	0	0	0	2 (4)	0	0	0	0	0	0	0
Pancreatitis	1 (7)	1 (7)	0	0	0	0	1 (17)	0	2 (4)	1 (2)	0	0	0	0	0	0
Endocrine disorders																
Adrenal	0	0	1	0	0	0	0	0	1	0	1	1	0	0	1	1

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insufficiency			(6)						(2)		(6)	(6)			(3)	(3)
Hyper-thyroidism	0	0	1 (6)	0	0	0	1 (17) [§]		2 (4) [¶]	0	0	0	0	0	0	0
Hypophysitis	0	0	0	0	0	0	1 (17)	1 (17)	1 (2)	1 (2)	1 (6)	1 (6)	0	0	1 (3)	1 (3)
General disorders																
Pyrexia	0	0	1 (6)	0	2 (13)	0	0	0	3 (6)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders																
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)	0	0	1 (6)	0	1 (3)	0
Eye disorders																
Uveitis	0	0	2 (12)	2 (12)	0	0	0	0	2 (4)	2 (4)	0	0	0	0	0	0
Renal and urinary disorders																
Renal failure, acute	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)	0	0	0	0	0	0

*Only the highest grade of event was counted for each patient. Gr denotes grade.

†Serious adverse event was defined as an adverse event that was fatal or life threatening, required hospitalization, or resulted in persistent or significant disability/incapacity and/or required medical or surgical intervention to prevent one of the outcomes listed above.

‡The numbers reported within a column may not add up to the total number reported under “any adverse event” because (i) patients who had more than one adverse event were counted for each event but were counted only once for “any adverse event” and (ii) data for only those events that were reported in at least 2 patients of all treated patients are presented in this table.

§The specific grade is unknown.

¶One patient with grade 2 and one patient with unknown grade.

Table S1-D. Treatment-Related Selected Adverse Events, Highest Grade, That Occurred in at Least One of All Treated Patients Who Received the Sequenced Regimen of Nivolumab and Ipilimumab *

Selected Adverse Event [†]	1 mg/kg Nivolumab + Prior Ipilimumab (n=17)		3 mg/kg Nivolumab + Prior Ipilimumab (n=16)		Sequenced Treatment, All (n=33)	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
<i>Category</i>	number of patients (percent)					
<i>Pulmonary</i>[‡]	0	0	1 (6)	0	1 (3)	0
Pneumonitis	0	0	1 (6)	0	1 (3)	0
<i>Endocrinopathies</i>[‡]	3 (18)	2 (12)	0	0	3 (9)	2 (6)
Hypothyroidism	1 (6)	0	0	0	1 (3)	0
Hypophysitis	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Thyroiditis	0	0	0	0	0	0
Adrenal insufficiency	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Hyperthyroidism	0	0	0	0	0	0
Thyroid function test abnormal	0	0	0	0	0	0
<i>Hepatic</i>[‡]	0	0	1 (6)	0	1 (3)	0
Aspartate aminotransferase increased	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	1 (6)	0	1 (3)	0
<i>Gastrointestinal</i>[‡]	2 (12)	0	1 (6)	0	3 (9)	0

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Diarrhea	2 (12)	0	1 (6)	0	3 (9)	0
Colitis	0	0	0	0	0	0
Renal[‡]	0	0	0	0	0	0
Blood creatinine increased	0	0	0	0	0	0
Renal failure, acute	0	0	0	0	0	0
Renal failure	0	0	0	0	0	0
Tubulointerstitial nephritis	0	0	0	0	0	0
Skin[‡]	4 (24)	0	4 (25)	0	8 (24)	0
Rash	3 (18)	0	0	0	3 (9)	0
Pruritus	2 (12)	0	4 (25)	0	6 (18)	0
Urticaria	0	0	0	0	0	0
Blister	0	0	0	0	0	0
Infusion reaction[‡]	0	0	0	0	0	0
Infusion-related reaction	0	0	0	0	0	0

*Only the highest grade of event was counted for each patient.

[†]Adverse events that require more frequent monitoring and/or intervention with immune suppression or hormone replacement, based on a prespecified list of MedDRA terms.

[‡]The numbers reported for the specific adverse events within an organ category may be greater than the number reported for the organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.

Table S2. Summary of Patient Disposition, All Treated Patients

Patient Disposition	0.3 mg/kg Nivolumab + 3 mg/kg Ipilimumab	1 mg/kg Nivolumab + 3 mg/kg Ipilimumab	3 mg/kg Nivolumab + 1 mg/kg Ipilimumab	3 mg/kg Nivolumab + 3 mg/kg Ipilimumab	Concurrent Treatment, All	1 mg/kg Nivolumab + Prior Ipilimumab	3 mg/kg Nivolumab + Prior Ipilimumab	Sequenced Treatment, All
	number of patients (percent)							
All treated patient population	14	17	16	6	53	17	16	33
Efficacy population	14	17	15	6	52	16	14	30
Study status								
Completed study	2 (14)	5 (29)	2 (13)	3 (50)	12 (23)	0	0	0
Off study	12 (86)	12 (71)	5 (31)	3 (50)	32 (60)	9 (53)	6 (38)	15 (46)
Key reasons for discontinuation from study								
Disease progression	5 (36)	1 (6)	2 (13)	0	8 (15)	3 (18)	5 (31)	8 (24)
Adverse event related to study drug	2 (14)	4 (24)	3 (19)	2 (33)	11 (21)	3 (18)	0	3 (9)
Adverse event unrelated to study drug	0	1 (6)	0	0	1 (2)	0	0	0
Death	4 (29)	1 (6)	0	0	5 (9)	2 (12)	1 (6)	3 (9)

Table S3. Duration of Confirmed Objective Responses of Individual Patients

Cohort	Dose	Response	Duration of Response, weeks
1	0.3 mg/kg nivolumab + 3 mg/kg ipilimumab	CR	48.0+
		PR	72.1+, 65.4+
2	1 mg/kg nivolumab + 3 mg/kg ipilimumab	CR	36.1+, 28.9+, 24.7+
		PR	54.4+, 52.6, 23+, 18.4+, 14.0 +, 11.1+
2a	3 mg/kg nivolumab + 1 mg/kg ipilimumab	CR	7.7+
		PR	18.1+, 12.3, 6.6+, 6.4+, 6.1+
3	3 mg/kg nivolumab + 3 mg/kg ipilimumab	PR	38.7+, 31.3+, 12.1+
6	1 mg/kg nivolumab + prior ipilimumab	CR	24.1+
		PR	16.1+, 12.1+, 8.7+, 8.4+, 8.1+
7	3 mg/kg nivolumab + prior ipilimumab	CR	NA*
		PR	NA*

* Not available; as of the date of this analysis, no confirmed objective responses had been reported.

Table S4. Clinical Activity of Patients Who Received the Sequenced Regimen of Nivolumab and Ipilimumab*

Cohort	Dose	Response-Evaluable Patients[†] n	CR n	PR n	uPR[‡] n	irPR[§] n	SD ≥24 wk n	irSD[§] ≥24 wk n	Objective Response Rate[¶] % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 8 wk n (%)
6	1 mg/kg nivolumab + prior ipilimumab	16	1	5	2	2	1 (6)	0	38 [15-65]	69 [41-89]	4 (25)
7	3 mg/kg nivolumab + prior ipilimumab	14	0	0	1	1	0	0	0	14 [2-43]	0
All	Sequenced treatment	30	1	5	3	3	1 (3)	0	20 [8-39]	43 [26-63]	4 (13)

*CR denotes complete response, PR partial response, uPR unconfirmed partial response, irPR immune-related partial response, SD stable disease, irSD immune-related stable disease.

[†]Response-evaluable patients were those who received at least one dose of study therapy, had measurable disease at baseline, and one of the following: 1) at least one on-treatment tumor evaluation, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.

[‡]Patients who had a PR after one tumor assessment but did not have sufficient follow-up time for confirmation of the initial PR.

[§]Patients who had target tumor-lesion reduction in the presence of new lesions, consistent with immune-related PR or SD.¹

[¶] $[(CR + PR) / \text{no. response-evaluable patients}] \times 100$. Confidence intervals were estimated by the Clopper-Pearson method.

^{||} $[(CR + PR + uCR + uPR + irPR + SD \geq 24 \text{ wk} + irSD \geq 24 \text{ wk}) / \text{no. response-evaluable patients}] \times 100$.

Table S5. Association between Pretreatment Tumor PD-L1 Expression and Objective Response

Cohorts	Response Status	Objective Response n (%)	No Objective Response n (%)	Total n
1, 2, 2a, 3	PD-L1 positive*	6 (46)	7 (54)	13
	PD-L1 negative	9 (41)	13 (59)	22
	All	15 (43)	20 (57)	35
6, 7	PD-L1 positive*	4 (50)	4 (50)	8
	PD-L1 negative	1 (8)	12 (92)	13
	All	5 (24)	16 (76)	21
All		20	36	56

*Positive is defined as a tumor sample with $\geq 5\%$ tumor cell membrane expression in ≥ 100 evaluable cells. The choice of cut off for positivity is the subject of ongoing investigations and will be explored in future studies.

Table S6. Changes in ALC (Absolute Lymphocyte Count) from Baseline

Cohorts	Weeks Since Initiation of Treatment	n	Mean Change in ALC (x10³ cells/μL) from Baseline (+/- SD)
1, 2, 2a, 3	0 - 2	52	-0.10 (+/- 0.47)
	3 - 5	53	0.02 (+/- 0.43)
	6 - 8	49	-0.01 (+/- 0.63)
	9	42	0.29 (+/- 0.97)
	12	38	0.11 (+/- 0.55)
6, 7	0 (Cycle 1)	30	-0.06 (+/- 0.24)
	10 (Cycle 2)	24	-0.12 (+/- 0.31)
	20 (Cycle 3)	16	-0.19 (+/- 0.32)

Table S7. Association between ALC (Absolute Lymphocyte Count) at Weeks 5-7 and Objective Response

Cohorts	ALC ($\times 10^3$ cells/μL at weeks 5-7)	Objective Response n (%)	No Objective Response n (%)	Total n
1, 2, 2a, 3	<1.0	6 (43)	8 (57)	14
	≥ 1.0	15 (40)	23 (61)	38
	All	21 (40)	31 (60)	52
6, 7	<1.0	1 (17)	5 (83)	6
	≥ 1.0	5 (23)	17 (77)	22
	All	6 (21)	22 (79)	28
All		27	53	80

Reference

1. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.