Supplementary Appendix

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

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Supplementary Appendix

Nivolumab versus Docetaxel in Advanced Squamous Non-small Cell Lung Cancer

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Supplemental Text

Safety narratives of patients who discontinued nivolumab treatment due to pneumonitis

Patient 1 was a 72-year-old male with stage IV SQ NSCLC. Relevant medical history included pleural effusion, radiation pneumonitis and tobacco use. On study Day 45, 14 days after his 3rd nivolumab dose, the patient's computed tomography (CT) scan showed interval development of patchy consolidation and ground glass opacity in a predominately upper lobe distribution. The investigator reported non-serious, grade 2 treatment-related adverse events of dyspnea and pneumonitis. Accordingly, nivolumab was delayed and the patient was started on treatment with oral prednisone 40 mg per day which was decreased to 20 mg per day on Day 59 and increased back to 60 mg per day on Day 64 following a chest x-ray that showed bilateral upper lobe fibrosis and volume loss, with left upper lobe ground glass opacities similar to the prior exam (Day 50). On Day 69, 38 days after his 3rd nivolumab dose, the patient's dyspnea and pneumonitis worsened to grade 3 and study therapy continued to be delayed. On Day 78, a CT scan showed a right-sided loculated pleural effusion and associated atelectasis of the right upper lobe, slightly improved compared to the previous CT scan.

Sulfamethoxazole/trimethoprim therapy was started. On Day 85, a chest x-ray showed unchanged right upper lobe atelectasis with ipsilateral apical loculated fluid, and the patient's dyspnea was reported resolved. Nivolumab was permanently discontinued that same day due to the pneumonitis, with the last dose received on Day 31. On Day 99, a chest x-ray showed right upper lobe atelectasis with significant volume loss, and the dose of prednisone was tapered to 50 mg/day. On Day 106, the patient presented with an oxygen saturation of 80% on room air (baseline: 97%) and was diagnosed with grade 4 pulmonary embolism unrelated to study therapy. On Day 110 the pulmonary embolism was resolved, and on Day 113 the pneumonitis was resolved. Prednisone was tapered to 20 mg/day by Day 160. On Day 177, the patient died due to disease progression.

Patient 2 was a 53-year-old male with stage IIIB SQ NSCLC and metastases to the pleura, lymph nodes and liver. Relevant medical history included emphysema and chronic obstructive pulmonary disease, and he was a former smoker. Risk factors included respiratory failure for which the patient required prior hospitalization. On Day 195, 9 days post the 14th infusion day, the patient was hospitalized and treated for post-obstructive pneumonia. A chest x-ray showed stable opacification of the left lung. The event was resolved on Day 199. On Day 230, 2 days after his 16th nivolumab dose, the patient presented with grade 3 dyspnea and grade 3 hypoxia, and was hospitalized. The investigator reported a serious adverse event of grade 3 pneumonitis and a non-serious adverse event of grade 2 pneumonia both of which were initially reported to be not related to the study therapy; however, following database lock, the investigator changed the relationship of the pneumonitis to be related to study therapy. A chest x-ray showed ground glass opacities in the right lung. A CT angiography scan showed left upper pleural effusion and collapse of the left upper and lower lobes. Blood cultures showed no growth. The patient was treated with piperacillin/tazobactam, levofloxacin, and prednisone 60 mg daily, and his condition improved. Nivolumab was delayed due to the pneumonia, which subsequently resolved on Day 235. On Day 251, the patient presented again with dyspnea and was re-hospitalized. A CT scan of the chest showed extensive patchy infiltrates throughout the right lung, consolidation in the left lung with a left pleural effusion and volume loss in the left thorax, and no evidence of pulmonary emboli. The patient received oxygen therapy, nebulizer treatments, and steroids, and his condition gradually improved. On Day 255, he was discharged from the hospital on amoxicillin/clavulanic acid and prednisone 40 mg daily. On Day 259, the patient was seen in the clinic and prednisone was increased to 60 mg daily with a tapering schedule. Nivolumab was discontinued due to the event of pneumonitis, with the last dose of study therapy on Day 228. On Day 304, he received his last dose of prednisone and the pneumonitis was resolved.

Patient 3 was a 60-year-old male with stage IV SQ NSCLC with metastases to the skin/soft tissue, pleura and pericardium. He was also a former smoker. On Day 190, 7 days after his 13th infusion, the patient's CT scan of the thorax showed a possible infection; the investigator reported a non-serious adverse event of grade 2 pneumonitis, which was considered to be related to the study therapy. The patient was treated with amoxicillin/clavulanic acid and prednisolone 60 mg. Study therapy was delayed due to the pneumonitis. On Day 204, prednisolone was decreased to 20 mg. On Day 211, the pneumonitis was reported resolved and study therapy was resumed. On Day 274, 7 days post the 18th infusion day, the CT scan of the thorax showed probable infection and 2 lymph nodes; the investigator reported a non-serious adverse event of grade 2 pneumonitis, which was considered to be related to the study therapy. A chest x-ray showed 2 growing lymph nodes and stable index lesions. The patient was treated with trimethoprim/sulfamethoxazole and the dose of prednisolone was increased to 30 mg daily. Study therapy was discontinued due to the pneumonitis, with the last dose received on Day 267. On Day 281, 14 days post the 18th infusion day, the pneumonitis improved to grade 1. On Day 306, prednisolone was tapered to 10 mg and the patient was noted with grade 1 hypothyroidism, considered by the investigator to be related to the study therapy. On Day 317, prednisolone was further tapered to 5 mg, which continued until Day 323. On Day 358, the patient's pneumonitis worsened again to grade 2. He was treated with trimethoprim/sulfamethoxazole and prednisolone 40 mg daily. Prednisolone was tapered to 30 mg daily on Day 372, 20 mg daily on Day 390, and 10 mg daily on Day 400. The dose of prednisolone was then increased to 20 mg daily on Day 449, and was continuing at the time of database lock. The event of pneumonitis was ongoing at the time of database lock.

Patient 4 was a 61-year-old male with stage IIIB SQ NSCLC with metastases to right hilar and pre-carinal lymph nodes. The patient's relevant history included penicillin allergy and prior tobacco use (cigarettes). On Day 141, the patient began to experience dyspnea. On Day 148, 7 days after his 11th infusion, a CT scan showed newly developed, very limited basal interstitial

disease, without evidence of pulmonary embolism. The investigator reported a serious adverse event of grade 2 pneumonitis, considered to be related to the study therapy. Study therapy was discontinued due to the pneumonitis, with the last dose of study therapy received on Day 141. On Day 154, the patient's cough worsened to grade 2, and he was started on treatment with oral methylprednisolone 40 mg daily, which was continued until Day 195. On Day 169, his cough improved to grade 1. On Day 176, the patient was reported to have radiographic evidence of disease progression with a CT scan showing multiple new lung lesions; the pneumonitis was reported resolved that same day. On Day 191, the patient began alternate systemic therapy with docetaxel, and methylprednisolone 100 mg daily was initiated. On Day 218 (07-Jan-2014), the subject was again reported with a non-serious adverse event of grade 1 dyspnea, which was considered by the investigator to be not related to the study therapy. The second cycle of docetaxel was administered that day. On Day 241, the investigator considered the event of asthenia to be not related to the study therapy. Oral methylprednisolone 100 mg was continued until Day 311. On Day 336, radiotherapy to the thorax was started. On Day 361, the patient died due to disease progression. The events of grade 1 cough, grade 1 dyspnea, and grade 1 asthenia were ongoing at the time of death.

Table S1. Baseline Characteristics, Stratification Factors and Prior Therapy[a].

	Nivolumab n = 135	Docetaxel n = 137	Total N = 272
Median age, years (range)	62 (39–85)	64 (42–84)	63 (39–85)
Age categorization, n (%)			
<65	79 (59)	73 (53)	152 (56)
≥65 and <75	45 (33)	46 (34)	91 (33)
≥75	11 (8.1)	18 (13)	29 (11)
Gender, n (%)			
Male	111 (82)	97 (71)	208 (76)
Female	24 (18)	40 (29)	64 (24)
Race,[b] n (%)			
White	122 (90)	130 (95)	252 (93)
Black/African American	6 (4)	2 (1)	8 (3)
Asian	4 (3)	2 (1)	6 (2)
Other	1 (1)	2 (1)	3 (1)
Not reported	2 (1)	1 (1)	3 (1)
Disease stage, n (%)			
Stage IIIB	29 (21)	24 (18)	53 (19)
Stage IV	105 (78)	112 (82)	217 (80)
Not reported	1 (1)	1 (1)	2 (1)

ECOG performance status,[c] n (%)			
0	27 (20)	37 (27)	64 (24)
1	106 (79)	100 (73)	206 (76)
Not reported	2 (1)	0	2 (1)
CNS metastasis, n (%)			
Yes	9 (7)	8 (6)	17 (6)
No	126 (93)	129 (94)	255 (94)
Smoking status, n (%)			
Current/former	121 (90)	129 (94)	250 (92)
Never	10 (7)	7 (5)	17 (6)
Unknown	4 (3)	1 (1)	5 (2)
Region, n (%)			
United States/Canada	43 (32)	43 (31)	86 (32)
Europe	77 (57)	78 (57)	155 (57)
Rest of world[d]	15 (11)	16 (12)	31 (11)
Prior surgery, n (%)	69 (51)	76 (56)	145 (53)
Prior radiotherapy, n (%)	71 (53)	73 (53)	144 (53)
Number of prior systemic regimens, n (%)			
1	134 (99)	137 (100)	271 (100)
2	1 (1)	0	1 (<1)
Type of prior systemic therapy, n (%)			
Prior platinum-based therapy	135 (100)	137 (100)	272 (100)
Prior EGFR-TKI[e]	0	3 (2)	3 (1)

Other prior chemotherapy	135 (100)	136 (99)	271 (100)
Other prior experimental therapy	9 (7)	2 (1)	11 (4)
Other systemic cancer therapy (chemotherapy),[f] n (%)			
Bevacizumab	1 (1)	1 (1)	2 (1)
Cetuximab	0	2 (1)	2 (1)
Etoposide	17 (13)	11 (8)	28 (10)
Fluorouracil	1 (1)	0	1 (<1)
Gemcitabine	60 (44)	71 (52)	131 (48)
Paclitaxel	46 (34)	46 (34)	92 (34)
Pemetrexed	3 (2)	3 (2)	6 (2)
Vinorelbine	20 (15)	24 (18)	44 (16)
Most recent prior platinum therapy, n (%)			
Cisplatin	54 (40)	36 (26)	90 (33)
Carboplatin	81 (60)	101 (74)	182 (67)
Best response to most recent prior systemic regimen (per investigator),[g] n (%)			
Complete or partial response	48 (36)	43 (31)	91 (33)
Stable disease	33 (24)	47 (34)	80 (29)
Progressive disease	44 (33)	41 (30)	85 (31)
Unknown/not reported	10 (7)	6 (4)	16 (6)
Time from completion of most recent prior systemic regimen, n (%)			
<3 months	64 (47)	59 (43)	123 (45)
3–6 months	35 (26)	40 (29)	75 (28)

>6 months	35 (26)	37 (27)	72 (27)

[a] Data from all patients who underwent randomization are included. There were no significant differences between the study groups at baseline.

[b] Race was self-reported.

[c] ECOG performance status scores range from 0 to 5, with higher numbers indicating greater disability; a score of 0 indicates no symptoms, and 1 mild symptoms.

[d] The countries in the rest-of-the-world geographic region were Argentina, Australia, Chile, Mexico, and Peru.

[e] No patient from either arm received prior anaplastic lymphoma kinase inhibitor treatment.

[f] Other systemic cancer therapy includes chemotherapy as part of prior first-line therapy.

[g] All but one patient received only one line of prior cancer therapy, which could include multiple agents or a switch of agents within the first-line regimen.

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

Table S2. Patient Disposition.

	Nivolumab N = 131	**Docetaxel N = 129**
Patients continuing in treatment period, n (%)	21 (16)	2 (1.6)
Reason for not continuing in the treatment period, n (%)		
Disease Progression	88 (67)	80 (62)
Study Drug Toxicity	5 (4)	13 (10)
Death	1 (1)[a]	0
Adverse event unrelated to study drug	6 (5)	13 (10)
Patient request to discontinue study treatment	2 (2)	4 (3)
Patient withdrew consent	3 (2)	5 (4)

[a] Unrelated to treatment.

Table S3. Subsequent Cancer Therapy.[a]

	Nivolumab N = 135	Docetaxel N = 137
Subsequent radiotherapy, n (%)	27 (27)	24 (18)
Subsequent systemic therapy,[b] n (%)	49 (36)	41 (30)
Chemotherapy, n (%)	48 (36)	33 (24)
Platinum agents	11 (8)	12 (9)
Taxanes	39 (29)[c]	7 (5)
Antimetabolites	16 (12)	22 (16)
Vinca alkaloids	7 (5)	9 (7)
Topoisomerase inhibitors	2 (1)	1 (1)
EGFR inhibitors, n (%)	6 (4)	8 (6)
Erlotinib	5 (4)	8 (6)
Dacomitinib	0	1 (1)
Cetuximab	1 (1)	0
Immunotherapy, n (%)	1 (1)	3 (2)
Filgrastim	1 (1)	0
MEDI4736	0	2 (1)[d]
Tremelimumab	0	1 (1)[d]
MPDL3280A	0	1 (1)
Experimental therapy,[e] n (%)	3 (2)	6 (4)

[a] Subsequent therapy was defined as therapy started on or after first dosing date or date of randomization if patient was never treated.

[b] Patients may have received more than one type of subsequent therapy.

[c] Of these patients, 24% received subsequent docetaxel.

[d] One patient received combination MEDI4736 plus tremelimumab.

[e] Non-immunotherapy experimental agents.

EGFR = epidermal growth factor receptor.

Table S4. Treatment Course and Overall Survival in Patients Treated After Initial RECIST v1.1-defined Progression.

Patient	Duration of treatment (months)	Number of doses received after initial progressive disease	Duration of treatment after initial progressive disease (months)	Overall survival (months)	Meets non-conventional benefit criteria[a]
1	5.9	7	3.8	14+	Y
2	4.5	2	0.8	11+	Y
3	7.5	2	1.4	13+	Y
4	8.4	13	6.5	9.6	Y
5[b]	6.3	8	4.3	17+	
6	1.1	2	0.9	7.3	
7	5.1	1	0.4	8.9	
8[b]	21.2+	33	16.3+	21.2+	
9	3.3	3	1.3	14+	
10	3.5	1	0.0	8.4	
11	12.5	1	0.2	17.1	
12	10.2	3	1.2	13.9+	
13[b]	5.9	9	4.6	16.0	
14	16.9	3	1.1	21.9+	
15	3.3	3	1.3	16.7	Y
16	10.6	1	0.3	13.2+	
17	11.0	8	4.3	12.7+	Y
18	7.0	2	0.7	9.2	
19[b]	20.4+	32	16.0+	21.4+	
20[b]	10.8	7	3.2	12.1+	

21	18.7	9	5.1	22.8+	Y
22	2.6	3	1.3	6.3	Y
23	2.1	1	0.2	4.8	
24	2.4	2	0.6	3.7	
25	3.7	5	2.0	7.5	
26	8.8	6	2.8	9.5	Y
27	2.3	1	0.4	2.8	
28	5.7	2	1.0	9.2	

[a] Defined as patients who had not experienced a best overall response of partial or complete response prior to initial RECIST v1.1-defined progression, and met at least one of the following: 1) appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions or 2) initial increase from nadir ≥20% in sum of target lesions followed by reduction from baseline of at least 30% or 3) initial increase from nadir ≥20% in sum of target lesions followed by at least 2 tumor assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions.

[b] Patient had extended nivolumab treatment (defined as >3 doses received after initial progression) and overall survival (defined as >median overall survival in the nivolumab group) after initial RECIST v1.1-defined progression, but did not meet the pre-defined criteria for non-conventional benefit.

Table S5. Clinical Activity of Nivolumab versus Docetaxel by PD-L1 Expression Level.

	PD-L1 expression level						
	<1%	**≥1%**	**<5%**	**≥5%**	**<10%**	**≥10%**	**Not evaluable[a]**
Nivolumab (N = 135)							
PD-L1 expression,[b] n (%)	54 (40)	63 (47)	75 (56)	42 (31)	81 (60)	36 (27)	18 (13)
Objective response rate,[c] n (%) [95% CI]	9 (17) [8, 29]	11 (17) [9, 29]	11 (15) [8, 25]	9 (21) [10, 37]	13 (16) [9, 26]	7 (19) [8, 36]	7 (39) [17, 64]
Docetaxel (N = 137)							
PD-L1 expression,[b] n (%)	52 (38)	56 (41)	69 (50)	39 (29)	75 (55)	33 (24)	29 (21)
Objective response rate,[c] n (%) [95% CI]	5 (10) [3, 21]	6 (11) [4, 22]	8 (12) [5, 22]	3 (8) [2, 21]	8 (11) [5, 20]	3 (9) [2, 24]	1 (3) [<0.1, 18]

[a] No quantifiable PD-L1 expression.

[b] Percent membranous staining in ≥100 tumor cells.

[c] Confirmed complete and partial responses per RECIST v1.1 criteria, as assessed by the investigator. CI based on the Clopper-Pearson method.

CI = confidence interval.

Table S6. Predictive Relationship of PD-L1 Expression Level for Efficacy of Nivolumab.

Efficacy endpoint	PD-L1 expression level[a]		
	1%	**5%**	**10%**
Overall survival[b]			
Treatment by PD-L1 expression interaction P-value	0.5556	0.4747	0.4062
Progression-free survival[b]			
Treatment by PD-L1 expression interaction P-value	0.6982	0.1591	0.3473
Objective response rate[c,d]			
Treatment by PD-L1 expression interaction P-value	0.9364	0.2908	0.6411

[a] PD-L1^{+}: patients with baseline PD-L1 expression ≥ cut-point value; PD-L1^{-}: patients with baseline PD-L1 expression < cut-point value.

[b] Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

[c] Logistic regression model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction. Responders include patients with confirmed complete or partial response.

[d] Confirmed objective response per RECIST v1.1 response criteria was required.

CI = confidence interval; HR = hazard ratio; RECIST = Response Evaluation Criteria In Solid Tumors.

Table S7. Treatment-related Adverse Events Reported in at least 5% of Patients[a].

	Nivolumab[a] N = 131		Docetaxel[b] N = 129	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
Any event	**76 (58)**	**9 (7)**	**111 (86)**	**71 (55)**
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	1 (1)	0	0

Rash	5 (4)	0	8 (6)	2 (2)
Vomiting	4 (3)	0	14 (11)	1 (1)
Mucosal inflammation	3 (2)	0	12 (9)	0
Peripheral edema	2 (2)	0	8 (6)	0
Abdominal pain	2 (2)	0	7 (5)	1 (1)
Constipation	2 (2)	0	8 (6)	0
Myalgia	2 (2)	0	13 (10)	0
Dizziness	2 (2)	0	7 (5)	0
Paresthesia	2 (2)	0	7 (5)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)

Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)
Neutrophil count decreased	0	0	8 (6.2)	6 (5)
White blood cell count decreased	0	0	7 (5.4)	5 (4)

[a] Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

Table S8. Treatment-related Serious Adverse Events Reported in Patient Treated with Nivolumab or Docetaxel.

	Nivolumab N = 131			Docetaxel N = 129		
	Any grade, n (%)	**Grade 3–4, n (%)**	**Grade 5, n (%)**	**Any grade, n (%)**	**Grade 3–4, n (%)**	**Grade 5, n (%)**
Any event	9 (7)	3 (2)	0	31 (24)	25 (19)	3 (2)
Pyrexia	2 (2)	0	0	1 (1)	1 (1)	0
Chills	1 (1)	0	0	0	0	0
Chronic obstructive pulmonary disease	1 (1)	0	0	0	0	0
Pneumonitis	2 (2)	1 (1)	0	0	0	0
Interstitial lung disease	0	0	0	1 (1)	0	1 (1)
Pulmonary hemorrhage	0	0	0	1 (1)	0	1 (1)
Hypothyroidism	1 (1)	0	0	0	0	0
Upper respiratory tract infection	1 (1)	1 (1)	0	0	0	0
Bronchopneumonia	0	0	0	1 (1)	1 (1)	0

Infection	0	0	0	1 (1)	1 (1)	0
Lung infection	0	0	0	1 (1)	1 (1)	0
Neutropenic infection	0	0	0	1 (1)	1 (1)	0
Pneumonia	0	0	0	1 (1)	1 (1)	0
Sepsis	0	0	0	1 (1)	0	1 (1)
Myasthenic syndrome	1 (1)	1 (1)	0	0	0	0
Peripheral sensory neuropathy	0	0	0	1 (1)	0	0
Tubulointerstitial nephritis	1 (1)	1 (1)	0	0	0	0
Febrile bone marrow aplasia	0	0	0	1 (1)	1 (1)	0
Febrile neutropenia	0	0	0	13 (10)	13 (10)	0
Neutropenia	0	0	0	4 (3)	4 (3)	0
Pancytopenia	0	0	0	1 (1)	1 (1)	0
Abdominal pain	0	0	0	1 (1)	0	0
Constipation	0	0	0	1 (1)	0	0

Diarrhea	0	0	0	1 (1)	0	0
Intestinal perforation	0	0	0	1 (1)	1 (1)	0
Nausea	0	0	0	1 (1)	1 (1)	0
Vomiting	0	0	0	1 (1)	1 (1)	0
Dehydration	0	0	0	2 (2)	2 (2)	0
Musculoskeletal pain	0	0	0	1 (1)	1 (1)	0

Table S9. Treatment-related Select Adverse Events Reported in Patients Treated with Nivolumab or Docetaxel.

Select adverse event category	Nivolumab N = 131		Docetaxel N = 129	
	Any Grade, n (%)	Grade 3-4, n (%)	Any Grade, n (%)	Grade 3-4, n (%)
Endocrine	5 (4)	0	0	0
Hypothyroidism	5 (4)	0	0	0
Gastrointestinal	11 (8)	1 (1)	26 (20)	3 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Colitis	1 (1)	1 (1)	0	0
Hepatic	2 (2)	0	2 (2)	1 (1)
Alanine aminotransferase increased	2 (2)	0	1 (1)	1 (1)
Aspartate aminotransferase increased	2 (2)	0	1 (1)	1 (1)
Blood bilirubin increased	0	0	1 (1)	0
Pulmonary	7 (5)	1 (1)	1 (1)[a]	0
Pneumonitis	6 (5)	1 (1)	0	0
Lung infiltration	1 (1)	0	0	0

Interstitial lung disease	0	0	1 (1)[a]	0
Renal	4 (3)	1 (1)	3 (2)	0
Blood creatinine increased	4 (3)	0	2 (2)	0
Tubulointerstitial nephritis	1 (1)	1 (1)	0	0
Renal failure acute	0	0	1 (1)	0
Skin	12 (9)	0	11 (9)	2 (2)
Rash	5 (4)	0	8 (6)	2 (2)
Pruritus	3 (2)	0	0	0
Erythema	1 (1)	0	2 (2)	0
Rash maculopapular	1 (1)	0	0	0
Skin exfoliation	1 (1)	0	2 (2)	0
Urticaria	1 (1)	0	0	0
Palmar-Plantar erythrodysasthesia syndrome	0	0	1 (1)	0
Hypersensitivity/Infusion reaction	1 (1)	0	3 (2)	1 (1)
Infusion-related reaction	1 (1)	0	1 (1)	0

Hypersensitivity	0	0	2 (2)	1 (1)

[a] Grade 5 event.

Table S10. Median Time to Onset and Resolution of Treatment-related Select Adverse Events in Nivolumab and Docetaxel-treated Patients.

	Nivolumab		Docetaxel	
Select adverse event category	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Endocrine				
Number of patients with event	5	0	0	0
Median TTO, weeks (range)	7.4 (6.3–18.1)	NA (NA–NA)	NA (NA–NA)	NA (NA–NA)
Patients who resolved, n (%)	2 (40)			
Median TTR, weeks (range)	NA (0.4–47.6+)			
Patients using immune-modulating medication, n (%)	1 (20)			
Gastrointestinal				
Number of patients with event	11	1	26	3
Median TTO, weeks (range)	3.0 (0.1–91.0)	91.0 (91.0–91.0)	1.0 (0.3–9.7)	1.1 (0.9–6.6)
Patients who resolved, n (%)	9 (82)	0	24 (96)[a]	3 (100)
Median TTR, weeks (range)	1.7 (0.1–31.0)	NA (2.0+ to 2.0+)	0.7 (0.1–51.0+)	0.7 (0.1–1.9)
Patients using immune-modulating medication, n (%)	2 (18)	1 (100)	0	0
Hepatic				
Number of patients with event	2	0	2	1

Median TTO, weeks (range)	17.6 (4.1–31.1)	NA (NA–NA)	5.5 (1.1–9.9)	9.9 (9.9–9.9)
Patients who resolved, n (%)	1 (50)		2 (100)	1 (100)
Median TTR, weeks (range)	NA (2.9–22.3+)		5.6 (2.1–9.0)	9.0 (9.0–9.0)
Patients using immune-modulating medication, n (%)	0		0	0
Pulmonary				
Number of patients with event	6[b]	0[b]	1	1
Median TTO, weeks (range)	15.1 (2.6–85.1)[b]	NA (NA–NA)[b]	17.7 (17.7–17.7)	17.7 (17.7–17.7)
Patients who resolved, n (%)	6 (100)[b,c]		0	0
Median TTR, weeks (range)	5.0 (0.6–12.1)[b]		NA (3.7+ to 3.7+)	NA (3.7+ to 3.7+)
Patients using immune-modulating medication, n (%)	5 (83)[b]		1 (100)	1 (100)
Renal				
Number of patients with event	4	1	3	0
Median TTO, weeks (range)	10.5 (3.9–16.6)	24.1 (24.1–24.1)	3.1 (1.1–6.1)	NA (NA–NA)
Patients who resolved, n (%)	2 (50)	1 (100)	3 (100)	
Median TTR, weeks (range)	NA (0.7–37.6+)	7.9 (7.9–7.9)	1.1 (1.0–2.9)	
Patients using immune-modulating medication, n (%)	2 (50)	1 (100)	0	
Skin				
Number of patients with event	12	0	11	2

Median TTO, weeks (range)	7.3 (0.3–51.9)	NA (NA–NA)	1.1 (0.6–36.9)	1.4 (1.1–1.7)
Patients who resolved, n (%)	11 (92)		9 (82)	2 (100)
Median TTR, weeks (range)	2.5 (0.1–46.9+)		2.1 (0.7–54.4)	1.8 (1.7–1.9)
Patients using immune-modulating medication, n (%)	3 (25)		4 (36)	0
Hypersensitivity/infusion reaction				
Number of patients with event	1	0	3	1
Median TTO, weeks (range)	0.3 (0.3–0.3)	NA (NA–NA)	3.1 (0.1–4.0)	4.0 (4.0–4.0)
Patients who resolved, n (%)	1 (100)		3 (100)	1 (100)
Median TTR, weeks (range)	0.3 (0.3–0.3)		0.1 (0.1–0.3)	0.1 (0.1–0.1)
Patients using immune-modulating medication, n (%)	0		1 (33)	1 (100)

Includes events reported between first dose and 30 days after last dose of study drug. Median TTR calculated from Kaplan-Meier estimate.

[a] Patients who experienced a select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

[b] Not included here is one additional grade 3 event of pneumonitis that was changed from not treatment-related to treatment-related after the database lock. The event was reported with onset on 25-Jun-2014 and resolution on 07-Sept-2014.

[c] One patient who had resolution of pneumonitis at 30 days follow-up experienced recurrence of pneumonitis during the period of extended follow-up (between 30–100 days post last nivolumab dose), which was ongoing at time of database lock.

Symbol + indicates a censored value. NA = not applicable (when there is 0 frequency) or not achieved (when there is non-zero frequency); TTO = time to onset; TTR = time to resolution.

Table S11. Treatment-related Adverse Events Leading to Discontinuation of Nivolumab.

	Nivolumab[a] N = 131	
	Any grade, n (%)	**Grade 3-4, n (%)**
Total patients who discontinued	4 (3)	2 (2)
Alanine aminotransferase increased	1 (1)	0
Aspartate aminotransferase increased	1 (1)	0
Lipase increased	1 (1)	1 (1)
Pneumonitis[b]	2 (2)	0
Myasthenic syndrome	1 (1)	1 (1)
Rash	1 (1)	0

[a] No grade 5 treatment-related events occurred in patients treated with nivolumab.

[b] Two additional nivolumab patients were discontinued due to pneumonitis (one for whom the relationship was changed from not related to treatment-related after database lock, and one who was discontinued >30 days after the most recent nivolumab dose).

Table S12. Treatment-related Adverse Events Leading to Discontinuation of Docetaxel.

	Docetaxel N = 129	
	Any Grade, n (%)	**Grade 3-4, n (%)**
Total patients who discontinued	13 (10)	8 (6.2)
Peripheral neuropathy	4 (3)	2 (2)
Dysgeusia	1 (1)	0
Neurotoxicity	1 (1)	1 (1)
Fatigue	2 (2)	0
Asthenia	1 (1)	1 (1)
Interstitial lung disease	1 (1)	1 (1)
Pulmonary hemorrhage	1 (1)[a]	0
Febrile bone marrow aplasia	1 (1)	1 (1)
Intestinal perforation	1 (1)	1 (1)

Hypersensitivity	1 (1)	1 (1)
Sepsis	1 (1)	1 (1)
Decreased appetite	1 (1)	1 (1)
Onycholysis	1 (1)	1 (1)

[a] Grade 5 event.

Figure S1A. CONSORT Diagram for Patient Disposition.

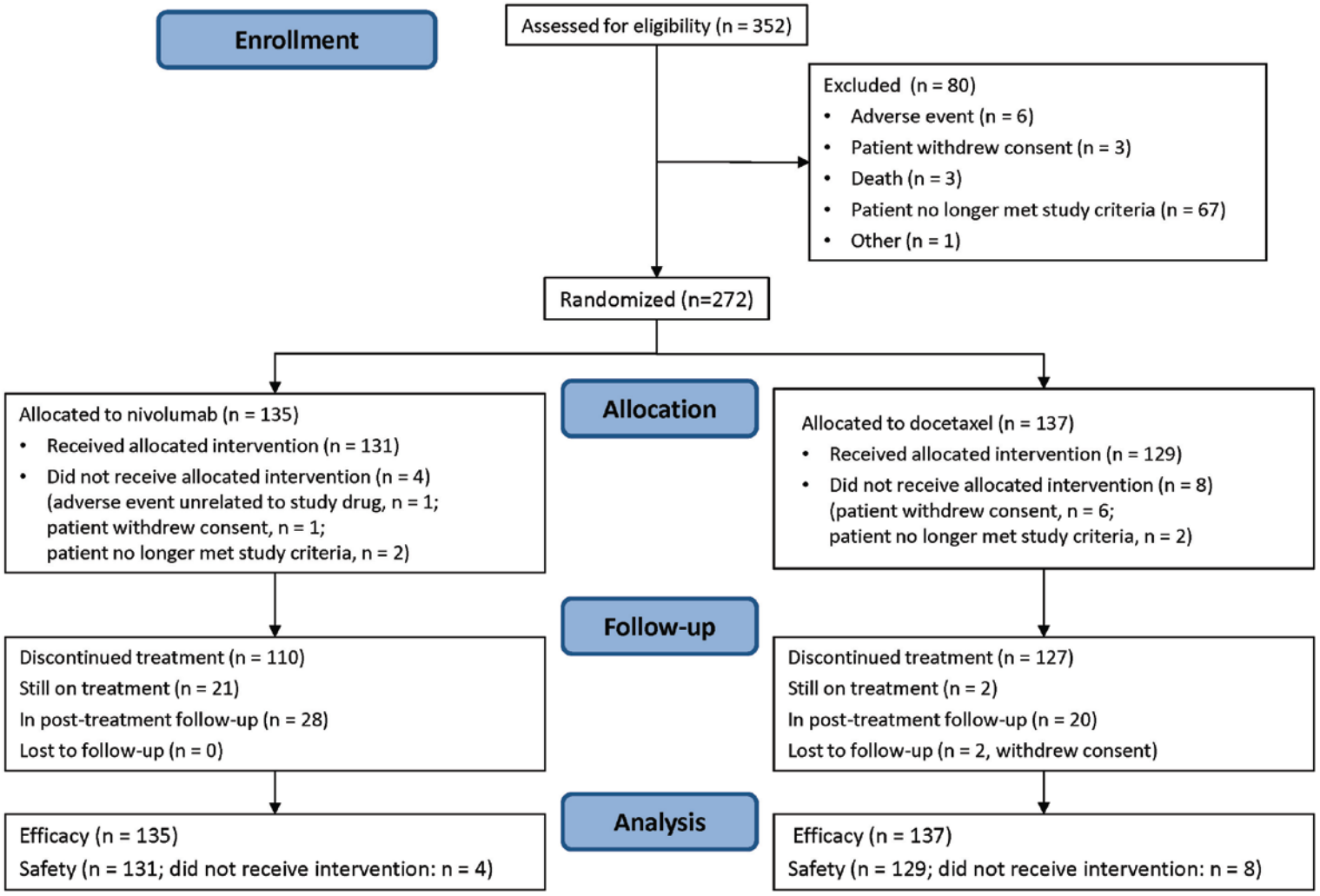
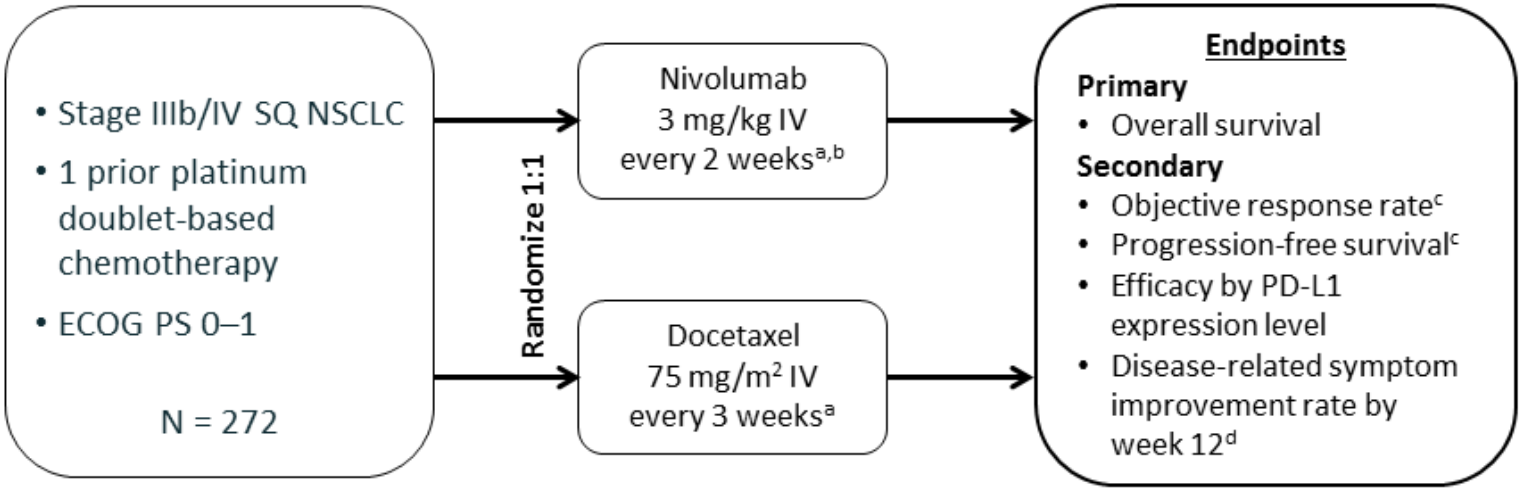


Figure S1B. Study Design.



[a] Treatment continued until disease progression or discontinuation due to toxicity or other protocol-defined reasons.

[b] Treatment with nivolumab after initial disease progression was allowed per protocol.

[c] Per RECIST v1.1 criteria as determined by the investigator.

[d] Disease-related symptoms were measured using the Lung Cancer Symptom Scale questionnaire on Day 1 of every other cycle for nivolumab and every cycle for docetaxel for the first 6 months on study then every 6 weeks thereafter for the remainder of the study, and at follow-up visits 1 and 2. Improvement by week 12 was defined as a 10 point or greater decrease from baseline in average symptom burden index score at any time between randomization and week 12. Analyses of PROs are ongoing.

ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PD-L1 = programmed cell death ligand 1; PS = performance status; RECIST = response evaluation criteria in solid tumors; SQ = squamous.

Figure S2. Treatment Effect on Overall Survival in Pre-defined Subsets.

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)

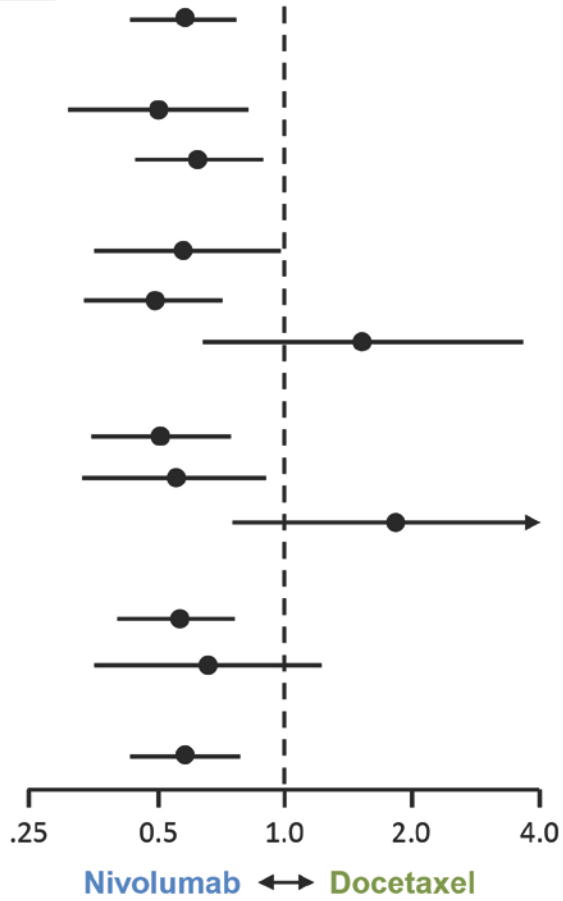
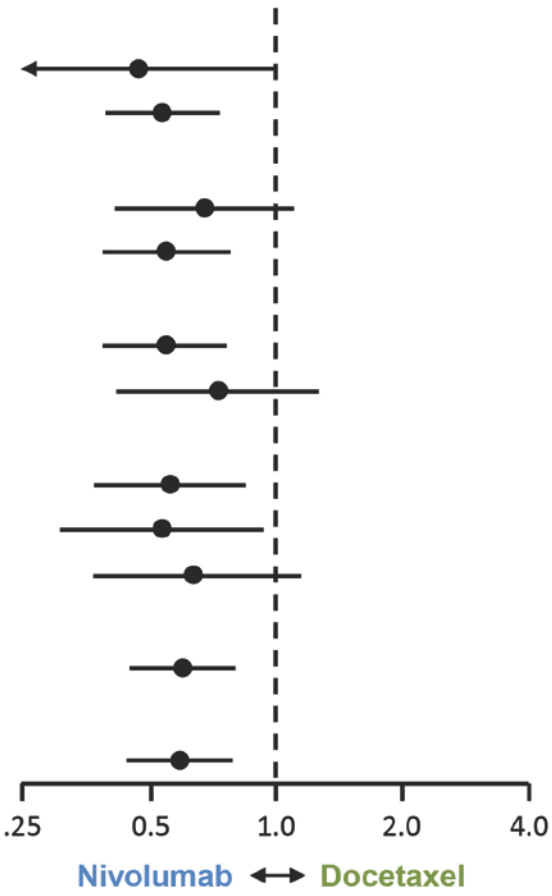


Figure S2.Treatment Effect on Overall Survival in Pre-defined Subsets (Cont'd).

	N	Unstratified HR (95% CI)
ECOG PS		
0	64	0.48 (0.24, 0.99)
1	206	0.54 (0.39, 0.74)
Type of prior patient regimen		
Cisplatin	90	0.67 (0.41, 1.10)
Carboplatin	182	0.55 (0.39, 0.78)
Time from diagnosis to randomization		
<1 year	193	0.55 (0.39, 0.77)
Other	79	0.73 (0.42, 1.26)
Time from completion of most recent regimen to randomization		
<3 months	123	0.56 (0.37, 0.85)
3–6 months	75	0.54 (0.31, 0.95)
>6 months	72	0.64 (0.37, 1.13)
CNS metastases		
No	255	0.60 (0.45, 0.80)
Smoking status		
Current/former smoker	250	0.59 (0.44, 0.80)



All randomized patients (nivolumab, n = 135; docetaxel, n = 137). HR was not computed for other subsets with less than 10 patients per treatment group.

HR = hazard ratio.

Figure S3. Best Change in Baseline Target Tumor Lesions in Nivolumab and Docetaxel Patients.

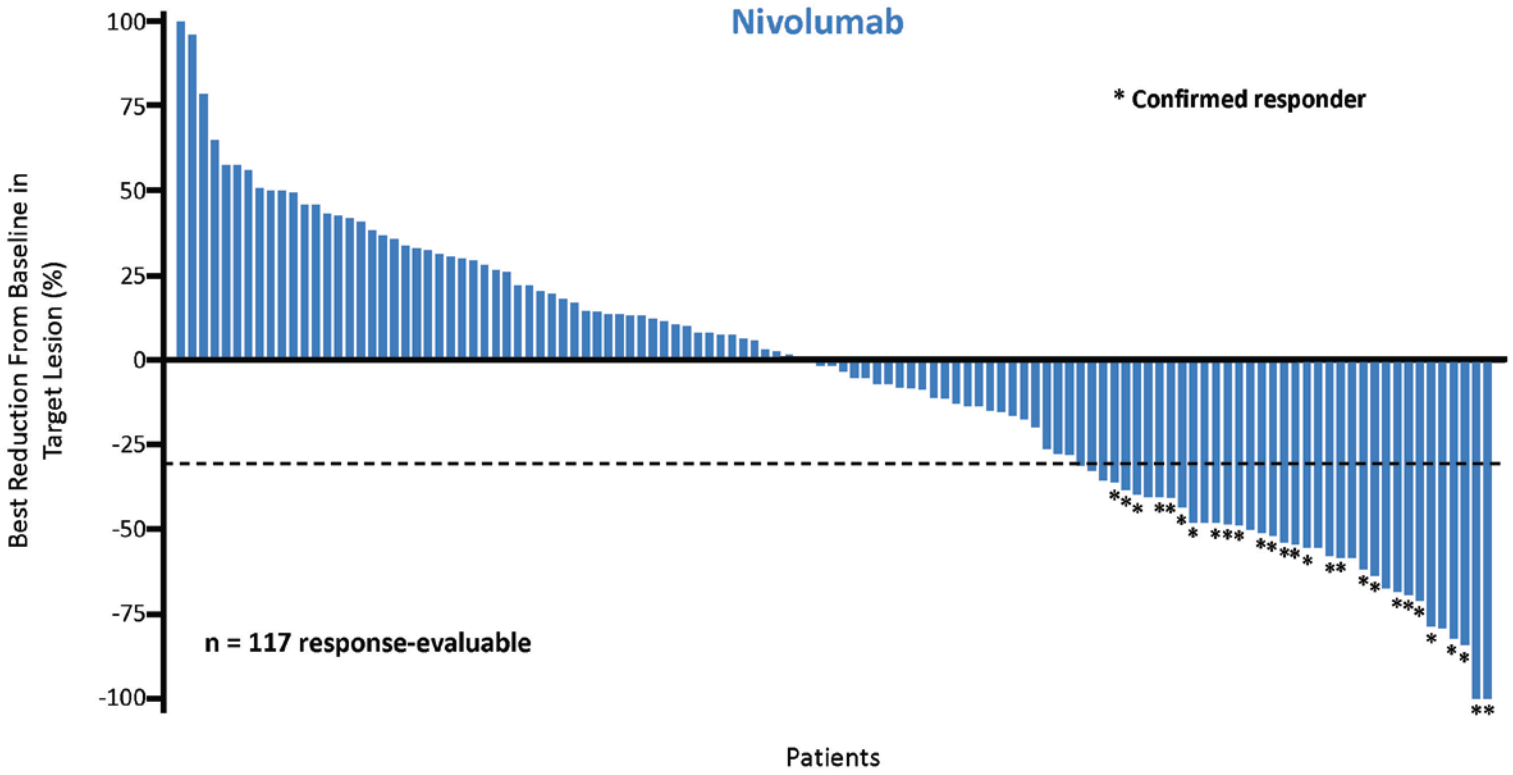
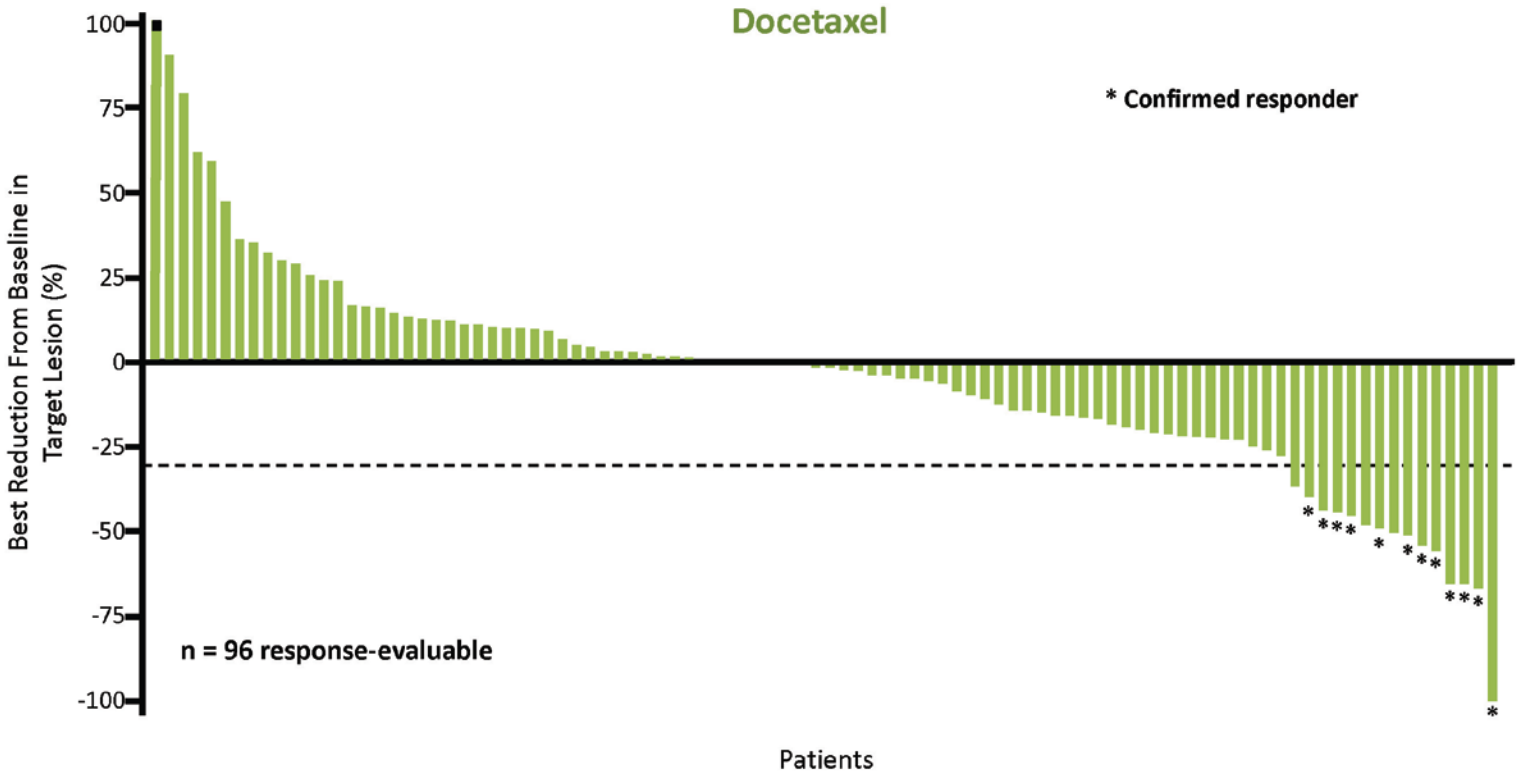


Figure S3. Best Change in Baseline Target Tumor Lesions in Nivolumab-treated and Docetaxel Patients (Cont'd).



Response-evaluable patients had a baseline assessment and at least one on-treatment tumor assessment. Negative and positive values indicate maximum tumor reduction and minimum tumor increase, respectively. Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy date, excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions. Dashed horizontal reference line at -30% indicates the threshold for a RECIST v.1.1-defined objective response. Symbol square represents percent change truncated to 100%.

CNS = central nervous system; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S4. Treatment Effect on Progression-free Survival in Pre-defined Subsets.

	N	Unstratified HR (95% CI)
Overall	**272**	**0.63 (0.48, 0.82)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.61 (0.39, 0.96)
Another agent	180	0.62 (0.44, 0.86)
Region		
US/Canada	86	0.68 (0.42, 1.09)
Europe	155	0.57 (0.40, 0.81)
Rest of world	31	0.82 (0.37, 1.83)
Age		
<65 years	152	0.62 (0.44, 0.89)
≥65 and <75 years	91	0.51 (0.32, 0.82)
≥75 years	29	1.76 (0.77, 4.05)
Gender		
Male	208	0.63 (0.46, 0.85)
Female	64	0.71 (0.40, 1.26)
Race		
White	252	0.62 (0.47, 0.82)

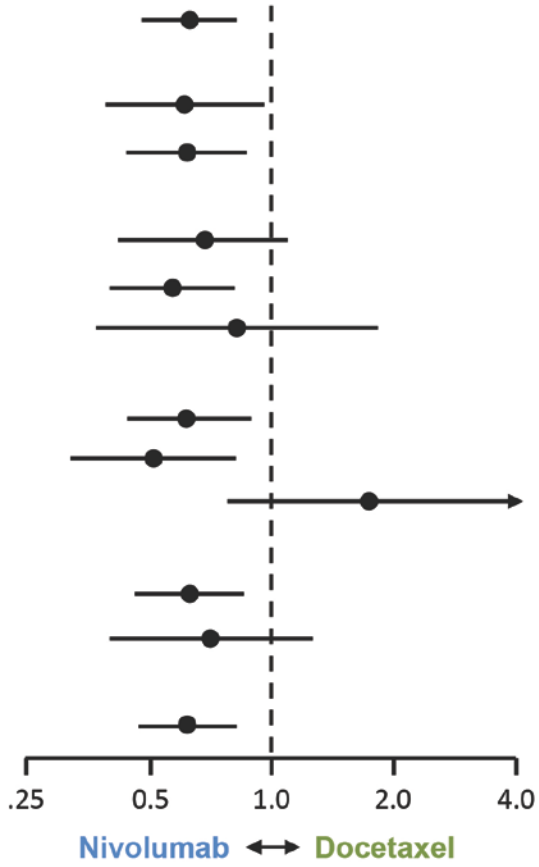
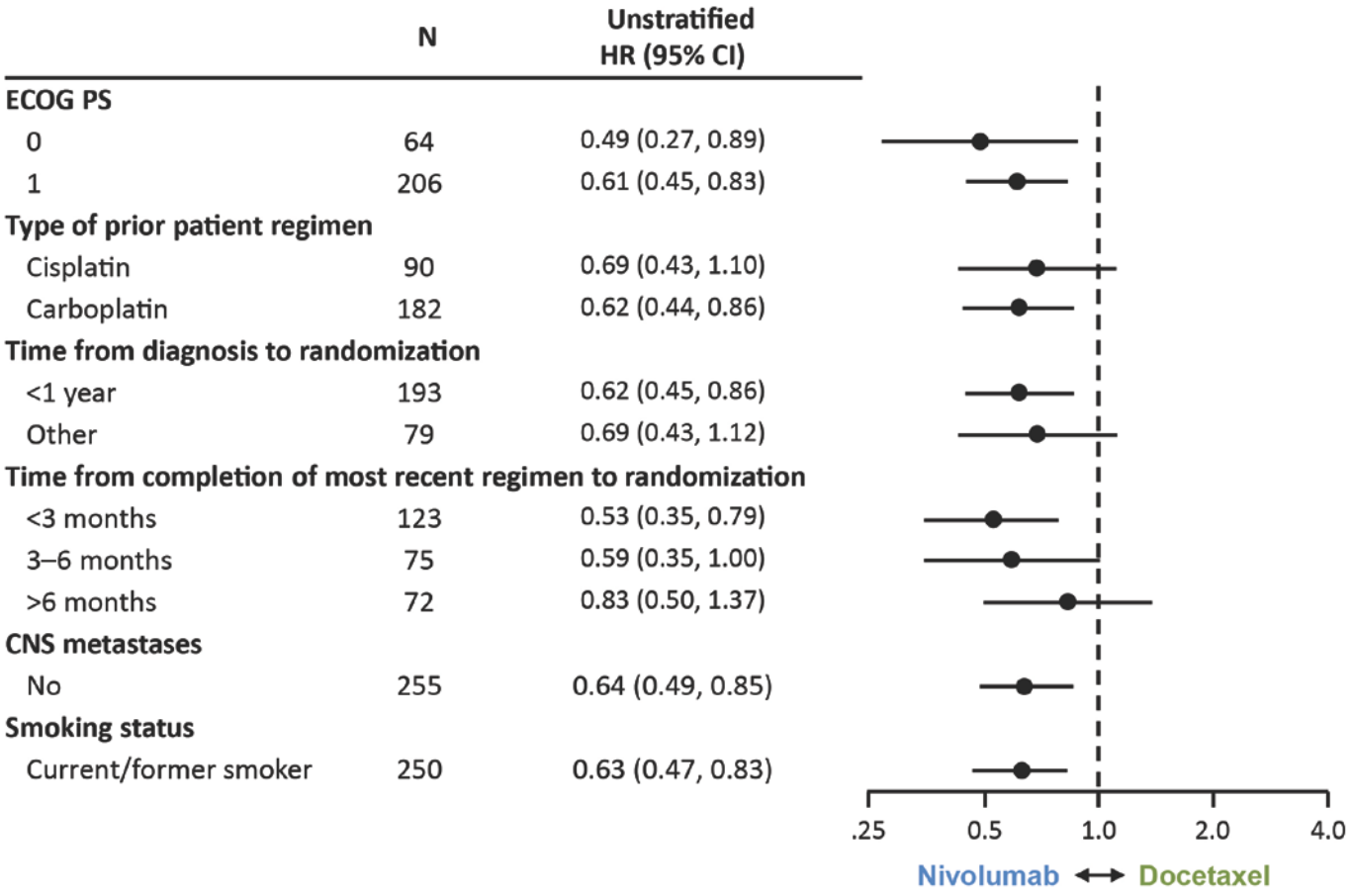


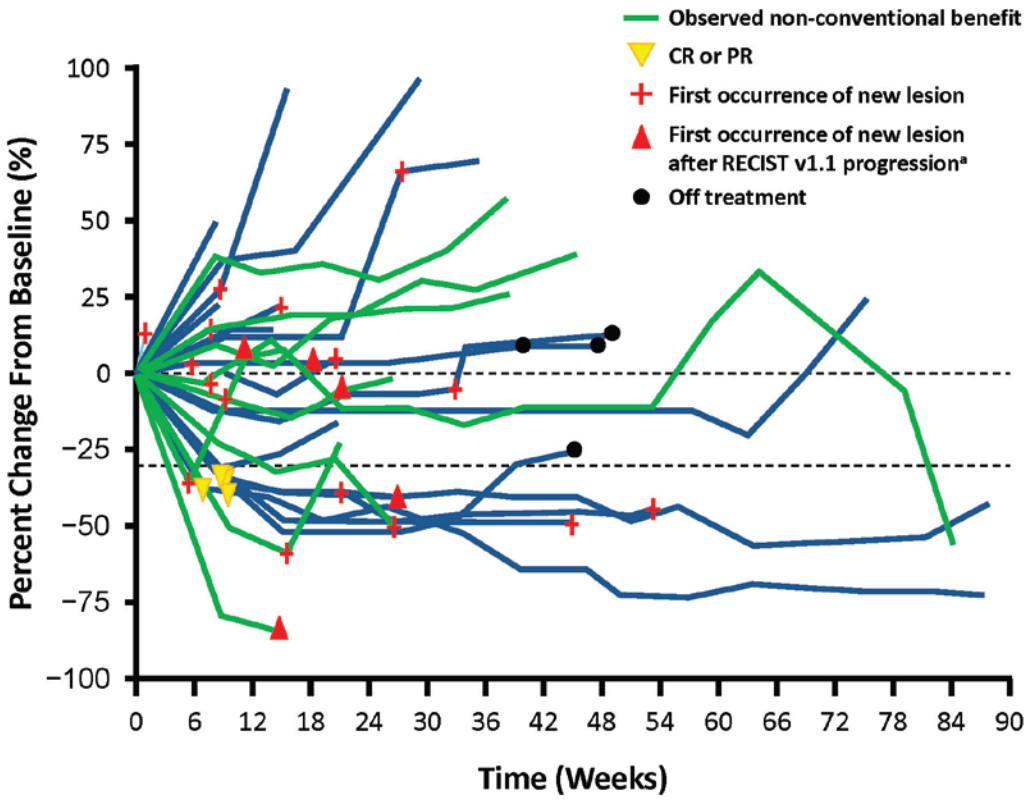
Figure S4. Treatment Effect on Progression-free Survival in Pre-defined Subsets (Cont'd).



All randomized patients (nivolumab, n = 135; docetaxel, n = 137). HR was not computed for other subsets with less than 10 patients per treatment group.

HR = hazard ratio.

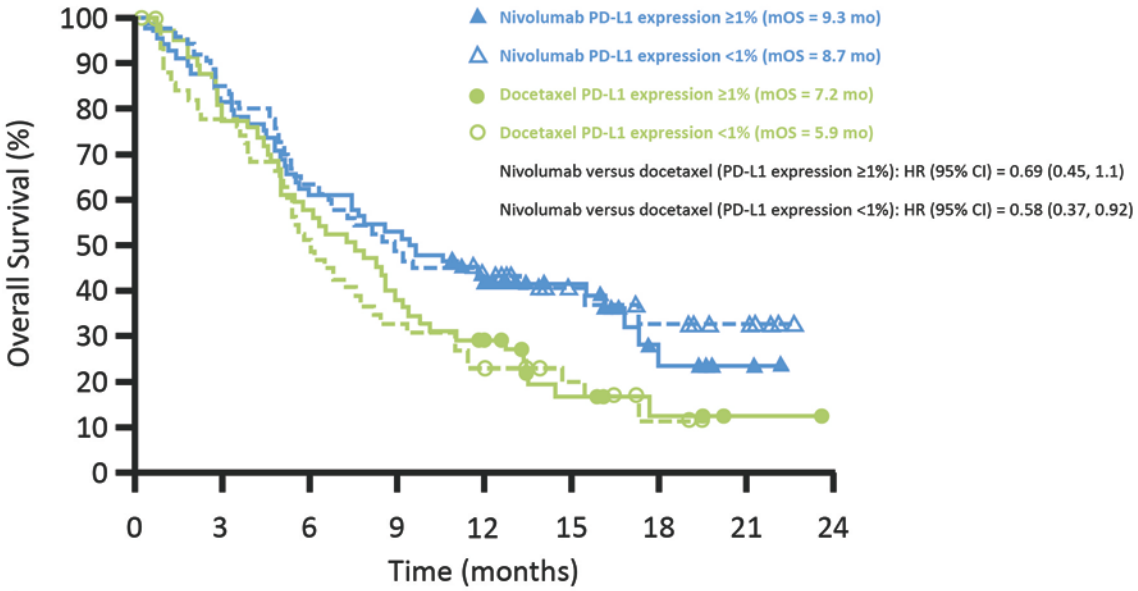
Figure S5. Change in Target Lesions from Baseline in Patients Treated with Nivolumab After Initial RECIST v1.1-defined Progression.



[a] Assessments are per Investigator using RECIST v1.1 criteria, with confirmation of response required. Patients treated beyond progression are defined as patients with last available dose date after RECIST v1.1 progression date.

RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S6A. Kaplan-Meier Curve of Overall Survival by 1% PD-L1 Expression Level.

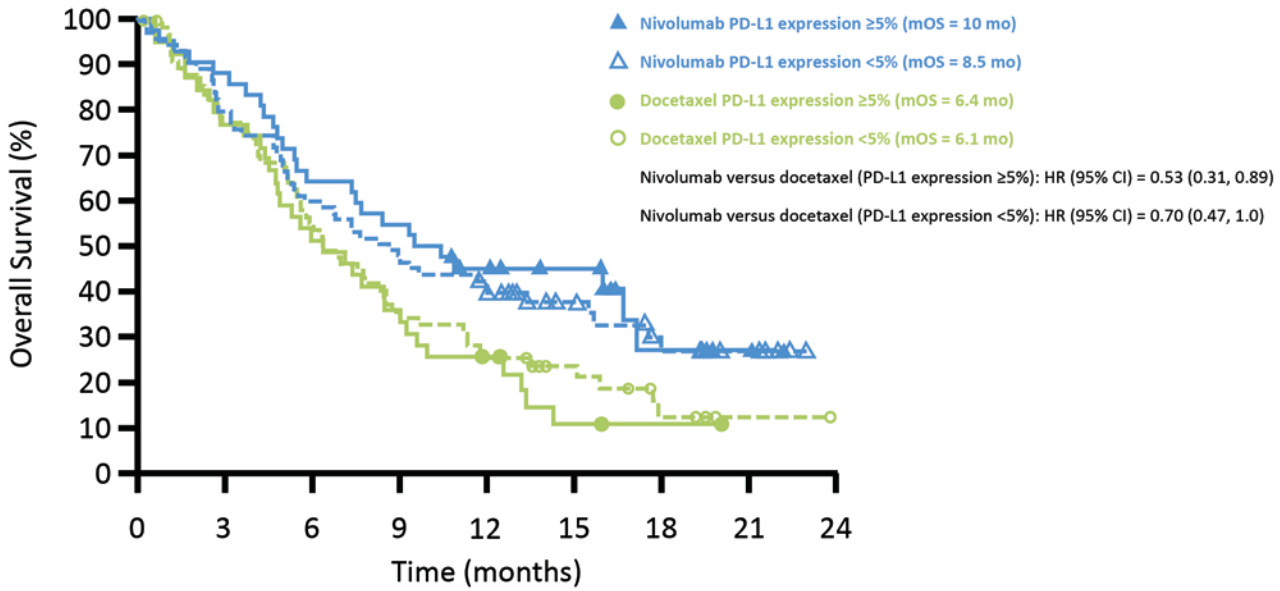


Number of patients at risk

Nivolumab PD-L1 expression ≥1%	63	51	38	32	23	15	5	2	0
Nivolumab PD-L1 expression <1%	54	46	34	26	21	11	8	5	0
Docetaxel PD-L1 expression ≥1%	56	43	31	21	14	6	3	1	0
Docetaxel PD-L1 expression <1%	52	39	25	16	11	6	2	0	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S6B. Kaplan-Meier Curve of Overall Survival by 5% PD-L1 Expression Level.

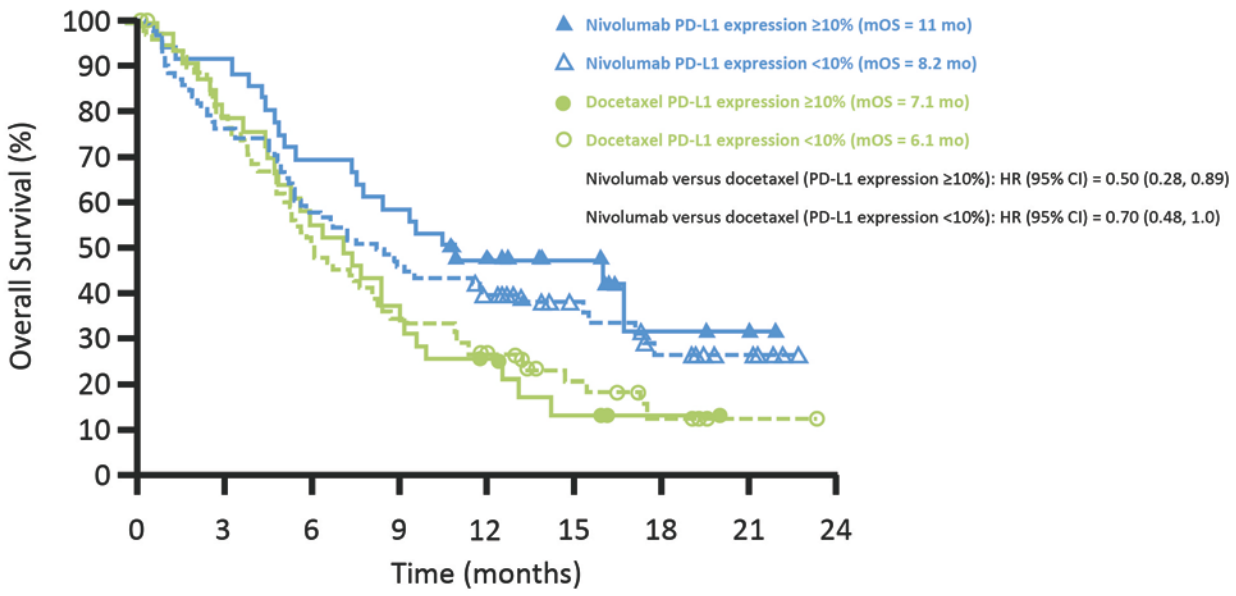


Number of patients at risk

Nivolumab PD-L1 expression ≥5%	42	37	27	23	17	11	4	2	0
Nivolumab PD-L1 expression <5%	75	60	45	35	27	15	9	5	0
Docetaxel PD-L1 expression ≥5%	39	30	20	14	8	3	1	0	0
Docetaxel PD-L1 expression <5%	69	52	36	23	17	9	4	1	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S6C. Kaplan-Meier Curve of Overall Survival by 10% PD-L1 Expression Level.

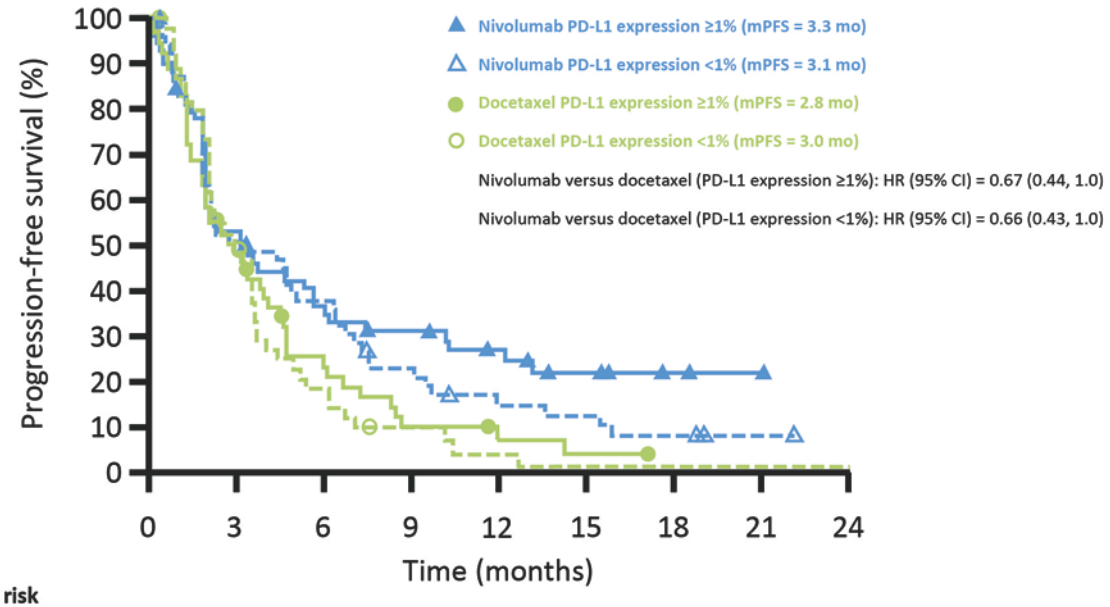


Number of patients at risk

Nivolumab PD-L1 expression ≥10%	36	33	25	21	15	9	3	2	0
Nivolumab PD-L1 expression <10%	81	64	47	37	29	17	10	5	0
Docetaxel PD-L1 expression ≥10%	33	26	18	12	7	3	1	0	0
Docetaxel PD-L1 expression <10%	75	56	38	25	18	9	4	1	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S7A. Kaplan-Meier Curve of Progression-free Survival by 1% PD-L1 Expression Level.

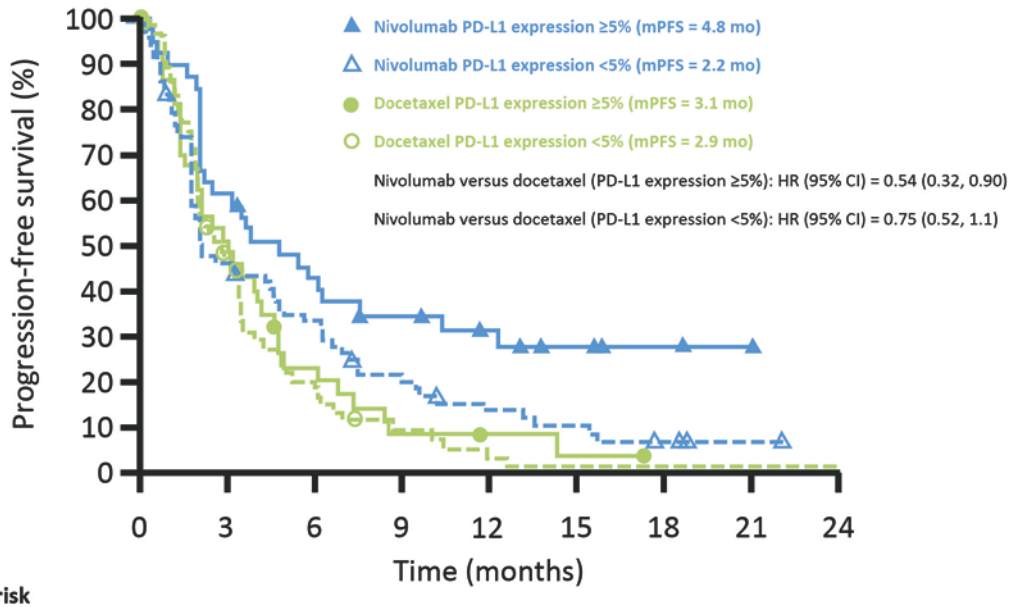


Number of patients at risk

Nivolumab PD-L1 expression ≥1%	63	30	19	15	11	7	3	1	0
Nivolumab PD-L1 expression <1%	54	27	20	11	6	5	3	1	0
Docetaxel PD-L1 expression ≥1%	56	26	11	4	3	1	0	0	0
Docetaxel PD-L1 expression <1%	52	23	8	3	1	0	0	0	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S7B. Kaplan-Meier Curve of Progression-free Survival by 5% PD-L1 Expression Level.

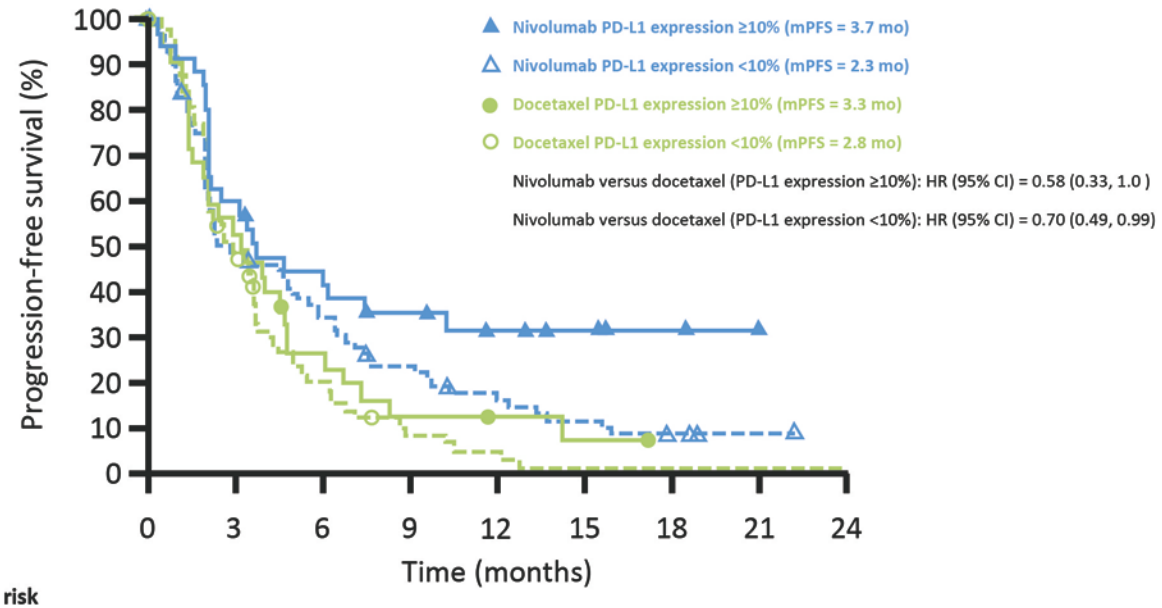


Number of patients at risk

Nivolumab PD-L1 expression ≥5%	42	24	16	12	9	6	3	1	0
Nivolumab PD-L1 expression <5%	75	33	23	14	8	6	3	1	0
Docetaxel PD-L1 expression ≥5%	39	19	8	3	2	1	0	0	0
Docetaxel PD-L1 expression <5%	69	30	11	4	2	0	0	0	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure S7C. Kaplan-Meier Curve of Progression-free Survival by 10% PD-L1 Expression Level.



Number of patients at risk

Nivolumab PD-L1 expression ≥10%	36	20	14	10	7	5	2	1	0
Nivolumab PD-L1 expression <10%	81	37	25	16	10	7	4	1	0
Docetaxel PD-L1 expression ≥10%	33	17	7	3	2	1	0	0	0
Docetaxel PD-L1 expression <10%	75	32	12	4	2	0	0	0	0

CI = confidence interval; HR = hazard ratio; mo = months; mPFS = median progression-free survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.