THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015; published online Feb 20. http://dx.doi.org/10.1016/S1470-2045(15)70054-9.

Supplementary Appendix

This appendix is a supplement to: Rizvi N, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small cell lung cancer (CheckMate 063): a phase 2, single-arm clinical trial. *Lancet Oncol* 2015.

Supplemental Methods

Supplemental Data

Supplemental Text

Supplemental Methods

Exclusion Criteria

1. **Target Disease Exceptions**

    a. Patients with untreated central nervous system (CNS) metastases are excluded. Patients are eligible if CNS metastases are treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, patients must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

    b. Patients with carcinomatous meningitis.

2. **Medical History and Concurrent Diseases**

    a. Patients with active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

    b. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Corticosteroids with minimal systemic absorption (ie, topical, ocular, intra-articular, intranasal, and inhalational), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

    c. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

    d. Prior treatment on either arm of nivolumab study CA209-017 (NCT01642004) or ipilimumab study CA184-104 (NCT01285609).

    e. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

    f. Other active malignancy requiring concurrent intervention.

    g. Patients with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.

    h. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4) or baseline before administration of study drug.

    i. Patients must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

    j. Prohibited Treatments and/or Restricted Therapies

        i. Ongoing or planned administration of anti-cancer therapies other than those specified in this study.

        ii. Use of corticosteroids or other immunosuppressive medications as per Exclusion Criteria 2b.

        iii. Anti-cancer therapy, including an investigational agent, less than 14 days prior to the first dose of study drug.

3. **Physical and Laboratory Test Findings**

    a. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

    b. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

4. **Allergies and Adverse Drug Reaction**

    a. History of severe hypersensitivity reactions to other monoclonal antibodies.

    b. History of allergy or intolerance (unacceptable adverse event [AE]) to study drug components or Polysorbate-80-containing infusions.

5. **Sex and Reproductive Status**

    a. Woman of child bearing potential who are pregnant or breastfeeding.

    b. Women with a positive pregnancy test at enrollment or prior to administration of study medication.

6. **Other Exclusion Criteria**

    a. Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a patient's ability to comply with the study requirements, substantially increase risk to the patient, or impact the interpretability of study results.

    b. Prisoners or patients who are involuntarily incarcerated.

    c. Patients who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Dose Delay Criteria

Tumor assessments for all patients were continued as per protocol even if dosing was delayed. Nivolumab administration was delayed for the following:

- Any grade ≥2 non-skin, treatment-related AE, with the following exceptions:
    - Grade 2 treatment-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any grade 3 skin, treatment-related AE.
- Any grade 3 treatment-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin:
    - Grade 3 lymphopenia or leukopenia does not require dose delay.
    - If a patient has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for treatment-related grade ≥2 toxicity.
    - If a patient has baseline AST, ALT, or total bilirubin within the grade 1 toxicity range, delay dosing for treatment-related grade ≥3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Criteria to Resume Treatment with Nivolumab

Patients were allowed to resume treatment with nivolumab when the treatment-related AE(s) resolve(s) to grade ≤1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of grade 2 fatigue.
- Patients who have not experienced a grade 3 treatment-related skin AE may resume treatment in the presence of grade 2 skin toxicity.

- Patients with baseline AST/ALT or total bilirubin in the grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of grade 2 AST/ALT OR total bilirubin.
- Patients with combined grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (as described under procedures of methods section) should have treatment permanently discontinued.
- Treatment-related pulmonary toxicity, diarrhea, colitis or nephritis must have resolved to baseline before treatment is resumed. Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If treatment is delayed > 6 weeks, the patient must be permanently discontinued from study therapy, with the following exceptions
    - Dosing interruptions to allow for prolonged steroid tapers to manage treatment-related AEs are allowed. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, the Bristol-Myers Squibb medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
    - Dosing interruptions > 6 weeks that occur for non-treatment-related reasons may be allowed if approved by the Bristol-Myers Squibb medical monitor. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, the Bristol-Myers Squibb medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

Supplemental Data

Table S1. Limits of clinical laboratory parameters required for study enrollment

Clinical laboratory parameter	Criteria for enrollment
WBCs	≥2000/μL
Neutrophils	≥1500/μL
Platelets	≥100 x 10^3/μL
Hemoglobin	≥9·0 g/dL
Serum creatinine or CrCl	≤1·5 X ULN or >40 mL/minute*
AST	≤3X ULN
ALT	≤3X ULN
Total bilirubin	≤1·5 X ULN†

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; ULN = upper limit of normal; WBC = white blood cell.

*Using Cockcroft/Gault formula. Female CrCl = [(140 – age in years) x weight in kg x 0·85]/72 x serum creatinine in mg/dL; Male CrCl = [(140 – age in years) x weight in kg x 1·0]/72 x serum creatinine in mg/dL.

†Except in patients with Gilbert Syndrome who must have total bilirubin <3·0 mg/dL.

Table S2. Best overall response by PD-L1 expression status using 1%, 5%, and 10% cut-offs for PD-L1 positivity[*]

PD-L1 Expression Cut-Off[*]	BOR					
	PR		SD		PD	
	n/N	%	n/N	%	n/N	%
<1% (n=31)	4/31	13	6/31	19	15/31	48
≥1% (n=45)	9/45	20	10/45	22	21/45	47
<5% (n=51)	7/51	14	10/51	20	25/51	49
≥5% (n=25)	6/25	24	6/25	24	11/25	44
<10% (n=51)	7/51	14	10/51	20	25/51	49
≥10% (n=25)	6/25	24	6/25	24	11/25	44
Unevaluable (n=10)	3/10	30	4/10	40	2/10	20

BOR = best overall response; PR = partial response; PD = progressive disease SD = stable disease.

[*]BOR at 1% and 10% tumor cells demonstrating membrane staining is shown for purposes of comparison. PD-L1 expression in patients with BOR of unable to determine (n=7), and in patients with BOR of not reported by the IRC (n=5) is not shown in this table. PD-L1 expression was evaluable in all of these patients, except for one patient with BOR of not reported.

Table S3. Enrollment by country and site

Country, Site number, % (n/N)	Principal investigator	Enrolled (N = 140)	Treated (N = 117)
France		**29 (40/140)**	**31 (36/117)**
0019	David Planchard	8 (11/140)	8 (9/117)
0014	Julien Mazières	7 (10/140)	9 (10/117)
0028	Lena Herve	4 (6/140)	4 (5/117)
0020	Bertrand Mennecier	3 (4/140)	3 (4/117)
0015	Gerard Zalcman	2 (3/140)	3 (3/117)
0018	Pierre-Jean Souquet	2 (3/140)	3 (3/117)
0027	Christos Chouaid	2 (3/140)	2 (2/117)
Germany		**4 (5/140)**	**4 (5/117)**
0035	Jürgen Wolf	2 (3/140)	2 (3/117)
0036	Christian Grohe	1 (1/140)	1 (1/117)
0037	Rudolf Huber	1 (1/140)	1 (1/117)
Italy		**7 (10/140)**	**8 (9/117)**
0033	Roila Fausto	4 (6/140)	4 (5/117)
0034	Editta Baldini	1 (2/140)	2 (2/117)
0042	Federico Cappuzzo	1 (2/140)	2 (2/117)
United States		**61 (85/140)**	**57 (67/117)**
0012	Grace K. Dy	8 (11/140)	6 (7/117)
0017	Naiyer A. Rizvi	8 (11/140)	9 (10/117)
0009	Thomas E. Stinchcombe	7 (10/140)	7 (8 /117)
0007	Leora Horn	6 (9/140)	5 (6/117)
0013	Suresh S. Ramalingam	6 (9/140)	8 (9/117)
0032	Scott J. Antonia	6 (8/140)	5 (6/117)
0002	Gregory A. Otterson	4 (5/140)	3 (4/117)
0010	Suresh Nair	3 (4/140)	3 (3/117)
0021	Afshin Dowlati	3 (4/140)	2 (2/117)
0001	Luis A. Campos	2 (3/140)	3 (3/117)
0005	Rachel E. Sanborn	2 (3/140)	2 (2/117)
0022	Benjamin P. Levy	2 (3/140)	3 (3/117)
0030	David Gandara	2 (3/140)	3 (3/117)
0023	Jeremy Cetnar	1 (1/140)	1 (1/117)
0039	Michael Kraut	1 (1/140)	0 (0/117)

*Of the 140 enrolled patients, 23 were not treated for the following reasons: no longer met study criteria (n=20), death (n=2), and lost to follow-up (n=1)

Table S4. Frequencies of disease sites (≥10% of patients) at study entry (investigator-assessed)

	Nivolumab 3 mg/kg (N=117) % (n/N)
Patients with at least one lesion	**117 (100·0)**
Site of lesion[*†]	
Lung	86 (100/117)
Lymph node	46 (54/117)
Liver	25 (29/117)
Mediastinum	20 (23/117)
Bone	18 (21/117)
Kidney	10 (12/117)
Number of sites with at least one lesion[†]	
1	18 (21/117)
2	33 (38/117)
3	30 (35/117)
4	15 (17/117)
≥5	5 (6/117)

[*]Patients may have lesions at more than one site. [†]Includes both target and non-target lesions.

Table S5. Patient disposition

	Nivolumab 3 mg/kg (N=117) % (n/N)
Patients continuing in treatment period*	13 (15/117)
Reason for not continuing in the treatment period	
Disease progression	67 (78/117)
Study drug toxicity	12 (14/117)
Death	0 (0/117)
AE unrelated to study drug	8 (9/117)
Patient request to discontinue study treatment	1 (1/117)

AE = adverse event.

*Patients continuing in the treatment period at the time of database lock (July 23 2014).

Table S6. Efficacy of nivolumab monotherapy in patients with advanced refractory SQ NSCLC

Efficacy Parameter	IRC Assessment
Objective responses*	
No. of patients/total no. of treated patients	17/117
Rate, % (95% CI) [†]	15 (8·7–22·2)
BOR[‡] – % (n/N) [95% CI]	
Confirmed CR	0 (0/117) [NA]
Confirmed PR	15 (17/117) [8·7–22·2]
SD	26 (30/117) [18·0–34·5]
Progressive disease	44 (51/117) [34·4–53·1]
Unable to determine	6 (7/117) [2·4–11·9]
Not reported	10 (12/117) [5·4–17·2]
Time to event, months[¶]	
Time to response – median	3·3
Range	1·7–8·8
DOR – median (95% CI)[§]	NR (8·3–NA)
Range	1·9+ to 11·5+
Duration of SD – median (95% CI)	6·0 (4·7–10·9)
Progression-free survival – median (95% CI)[‖]	1·9 (1·8–3.2)
6-mo PFS rate – % (95% CI) [no. at risk]	26 (18·0–34·6) [25]
1-year PFS rate – % (95% CI) [no. at risk]	20 (12·7–28·5) [9]
OS, median (95% CI)[**]	8·2 (6·1–10·9)
No. of deaths (%)	72 (61·5%)
1-year OS rate – % (95% CI) [no. at risk]	41 (31·6–49·7) [28]

BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent radiology review committee; NSCLC = non-small cell lung cancer; NA = not applicable; OS = overall survival; PR = partial response; SD = stable disease; SQ = squamous.

*Patients with confirmed CRs or PRs.

[†]ORRs ([{confirmed CRs + confirmed PRs} ÷ total no. of treated patients] ×100) were summarized by binomial response rates and two-sided 95% exact CIs using the Clopper-Pearson method.

[‡]BOR was defined as the best response designation recorded between the date of first dose and the date of initial objectively documented tumor progression per RECIST v1.1, or the date of subsequent therapy, whichever occurred first. Patients who were not evaluable for imaging plus clinical BOR assessment were listed as having BOR of unable to determine. Patients without on-study scans were listed as having BOR of not reported with the reasons including: death prior to disease assessment (n=6), investigator-assessed progressive disease (n=3), early discontinuation due to toxicity (n=1), clinical progression without CT scan (n=1), no subsequent scan taken after cycle 1, day 1 (n=1).

[§]Time-to-event endpoints were estimated using the Kaplan-Meier product-limit method with two-sided 95% CIs for the medians calculated using the Brookmeyer Crowley method. For survival rates, 95% CIs were calculated using Greenwood's formula.

[¶]DOR was defined as the date from first confirmed CR or PR to the date of the initial documented tumor progression, death, or for censored patients who neither progressed nor died (denoted by "+"), the date of last evaluable tumor assessment. NA denotes not available.

[‖]PFS was defined as the time from the first dose of nivolumab to the date of first documented tumor progression or death due to any cause. Patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who neither progressed nor died were censored on the date of their last tumor assessment. Patients who received subsequent anticancer therapy without a prior reported progression were censored at the date of the last tumor assessment prior to initiation of further therapy. Patients who did not have any on-study tumor assessments and did not die were censored on the date of the first dose of nivolumab.

[**]OS was defined as the time from the date of first dose to the date of death from any cause or last known date alive for patients who were alive at the date of data analysis.

Table S7. Objective response rate by patient subgroups as assessed by the IRC

	Nivolumab 3 mg/kg (N=117)
Characteristic	**ORR, % (n/N) [95% CI]***
Age	
<65	12 (7/58) [5·0–23·3]
≥65	17 (10/59) [8·4–29·0]
≥65 and <75	21 (9/43) [10·0–36·0]
<75	16 (16/101) [9·3–24·4]
≥75	6 (1/16) [0·2–30·2]
Gender	
Male	19 (16/85) [11·2–28·8]
Female	3 (1/32) [0·1–16·2]
ECOG PS	
0	15 (4/26) [4·4–34·9]
1	14 (13/91) [7·8–23·2]
Region	
United States	18 (12/67) [9·6–29·2]
Europe	10 (5/50) [3·3–21·8]
Race	
Caucasian	15 (15/99) [8·7–23·8]
Black or African American	18 (2/11) [2·3–51·8]
Asian	0 (0/2) [0·0–84·2]
Other	0 (0/5) [0·0–52·2]
Number of prior therapies	
2	10 (4/41) [2·7–23·1]
3	17 (9/52) [8·2–30·3]
≥4	17 (4/24) [4·7–37·4]

ECOG PS = Eastern Cooperative Oncology Group performance status.

*Based on a July 23 2014 database lock.

Table S8. Clinical activity of nivolumab by investigator assessment

	Nivolumab 3 mg/kg (N=117)
	Investigator-assessed (secondary endpoint)*
ORR, % (n/N) [95% CI]	13 (15/117) [7·4–20·3]
Confirmed BOR, % (n/N)	
CR	1 (1/117)
PR	12 (14/117)
SD	32 (37/117)
PD	44 (52/117)
Unable to determine	11 (13/117)
Not reported	0 (0/117)
Median duration of response, months (95% CI)	NR (7·0 to NR)
Median time to response, months (range)	2·2 (1·3–6·0)

BOR = best overall response; CR = complete response; NR = not reached; ORR = objective response rate; PR = partial response; PD = progressive disease SD = stable disease.

*Based on a March 6 2014 database lock.

Table S9. OS in patients treated after initial RECIST v1.1-defined progression

Patient	Duration of treatment (months)	Number of doses received after progression	Duration of treatment after progression (months)	OS (months)	Death (Y/N)
1	1·9	1	0·1	2·6	Y
2	2·3	2	0·5	4·7	N
3	2·8	3	1·1	3·7	N
4	7·0	3	1·1	11·5	N
5	6·7	6	4·7	12·9	N
6	2·8	3	1·0	9·0	N
7	2·9	2	0·9	7·7	Y
8	6·2	6	2·9	13·5	N
9	12·4+	22	11·3+	12·4	N
10	4·0	5	2·2	8·0	Y
11	4·2	6	2·5	6·6	Y
12	8·4	15	6·6	11·6	N
13	7·0	3	1·1	14·1	N
14	1·0	1	0·5	1·7	Y
15	2·3	1	0·5	3·4	Y
16	6·9	8	3·7	8·0	Y
17	3·0	3	1·2	12·0	N
18	2·3	2	0·6	8·9	N
19	6·0	3	1·2	12·7	Y
20	2·8	2	0·9	10·9	Y
21	2·8	2	0·9	12·0	N
22	4·3	2	1·1	10·9	Y

Table S10. Characteristics of patients treated after initial RECIST v1.1-defined progression

Patient	Investigator best response	No. of prior systemic therapies	Sum of target lesions (mm)			Reason for initial progression	No. of doses received after progression	Treatment duration after progression (months)[*]	OS (months)[*]
			BL	Pre-progression (Max % change from BL)	Post-discontinuation (Max % change from BL)				
1	PD	3	32	46 (↑ 43·8)[†]	NA[‡]	Progression in target and non-target lesions	1	0·1	2·6
2	PD	3	27	39 (↑ 44·4)[†]	42 (↑ 55·6)	Progression in target and non-target lesions; new lesion	2	0·5	4·7+
3	PD	2	29	50 (↑ 72·4)	54 (↑ 86·2)	Progression in target lesions	3	1·1	3·7+
4	SD	3	80	66 (↓ 17·5)	91 (↑ 13·8)	New lesion	3	1·1	11·5+
5[§]	PD	2	182	148 (↓18·7%)[†]	119 (↓ 34·6%)	Progression in non-target lesions	6	4·7	12·9+
6	PD	2	47	66 (↑ 40.4)	86 (↑ 83·0)	Progression in target lesions	3	1·0	9·0+
7	PD	4	70	81 (↑ 15·7)[†]	68 (↓ 2·9)	Progression in non-target lesion	2	0·9	7·7
8[§]	SD	2	19	19 (0·0%)	21 (↑ 10·5%)	Progression in non-target lesions	6	2·9	13·5+
9[‖]	PD	3	103	NA[¶]	44 (↓ 57·3)	See footnote	22	11·3+	12·4+
10	PD	5	80	85 (↑ 6·3)	84 (↑ 5·0)	New lesion	5	2·2	8·0
11[§]	PD	3	59	NE[#]	45 (↓ 23·7%)	New lesion	6	2·5	6·6
12[§]	PD	2	114	128 (↑ 12·3%)[†]	133 (↑ 16·7%)	Progression in non-target lesions; new lesion	15	6·6	11·6+
13	SD	3	115	84 (↓ 27·0)	135 (↑ 17·4)	Progression in target lesions	3	1·1	14·1+

14	PD	3	106	NA[¶]	NA[‡]	NA[**]	1	0·5	1·7
15	PD	2	30	30 (0·0)[†]	NA[§]	New lesion	1	0·5	3·4
16	SD	3	49	49 (0·0)	51 (↑ 4·1)	New lesion	8	3·7	8·0
17	PD	4	34	46 (↑ 35·3)[†]	57 (↑ 67·6)	Progression in target lesions	3	1·2	12·0+
18	PD	2	44	54 (↑ 22·7)[†]	62 (↑ 40·9)	Progression in target lesions	2	0·6	8·9+
19	SD	2	90	90 (0·0)	120 (↑ 33·3)	Progression in non-target lesion; new lesion	3	1·2	12·7
20	PD	2	91	122 (↑ 34·1)[†]	132 (↑ 45·1)	Progression in target and non-target lesions; new lesion	2	0·9	10·9
21	PD	3	91	112 (↑ 23·1)[†]	113 (↑ 24·2)	Progression in target lesions	2	0·9	12·0+
22	SD	5	48	52 (↑ 8·3)	50 (↑ 4·2)	New lesion	2	1·1	10·9

BL = baseline; Max = maximum; mm = millimeter; NA = not available; NE = not evaluable; No. = number; OS = overall survival; PD = progressive disease; SD = stable disease.

[*]"+" symbol indicates ongoing at the time of analysis.

[†]Target lesion measurements at the time of first on-treatment scan, at which time progression was noted.

[‡]No additional scans were performed post-progression.

[§]Indicates patient met criteria for non-conventional benefit (experienced either a tumor burden reduction, or no further progression for at least 2 tumor assessments, after initial RECIST v1.1-defined PD).

[‖]Patient received palliative brain radiotherapy for a symptomatic brain metastasis, and per protocol was assigned a BOR of PD. Otherwise, the patient did not meet criteria for non-conventional benefit.

[¶]Progression prior to first scheduled scan.

[#]Unable to determine - lesion obscured.

[**]Disease progression documented on CT angiogram; measurements not provided.

Table S11. Treatment-related immune-mediated AEs

Immune-mediated AE category*	Any grade, % (n/N)	Grade 3–4, % (n/N)
Skin	**15 (18/117)**	**2 (2/117)**
Rash	11 (13/117)	1 (1/117)
Pruritus	6 (7/117)	1 (1/117)
Rash maculo-papular	2 (2/117)	0 (0/117)
Gastrointestinal	**10 (12/117)**	**3 (3/117)**
Diarrhea	10 (12/117)	3 (3/117)
Endocrine	**6 (7/117)**	**1 (1/117)**
Thyroid disorder	**5 (6/117)**	**0 (0/117)**
Hypothyroidism	3 (3/117)	0 (0/117)
Blood TSH decreased	1 (1/117)	0 (0/117)
Blood TSH increased	1 (1/117)	0 (0/117)
Thyroiditis	1 (1/117)	0 (0/117)
Adrenal disorder	**1 (1/117)**	**1 (1/117)**
Adrenal insufficiency	1 (1/117)	1 (1/117)
Pulmonary	**5 (6/117)**	**3 (4/117)**
Pneumonitis	5 (6/117)	3 (4/117)
Renal	**3 (4/117)**	**0 (0/117)**
Blood creatinine increased	2 (2/117)	0 (0/117)
Renal failure	1 (1/117)	0 (0/117)
Renal failure acute	1 (1/117)	0 (0/117)
Hepatic	**1 (1/117)**	**0 (0/117)**
ALT increased	1 (1/117)	0 (0/117)

AEs = adverse events; ALT = alanine aminotransferase; TSH = thyroid stimulating hormone.

*Based on a July 23 2014 database lock. There were no immune-mediated AEs of grade 5 reported. Includes events reported between first dose and 30 days after last dose of study therapy.

Supplemental Figure Legends

Figure S1. CA209-063 (NCT01721759; CheckMate 063) study design. DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent radiology review committee; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PD = progressive disease; Q2W = every two weeks; SQ = squamous

*Further characterized by DOR. †Based on July 23 2014 database lock. ‡Based on March 6 2014 database lock.

Figure S2. Waterfall plot of response to nivolumab in patients with progressive disease as their best overall response to the most recent prior treatment, and who started nivolumab within three months of completion of prior treatment. Twelve (12) of 55 patients who met criteria for inclusion in this plot are not displayed due to lack of evaluable on-study assessments.

Figure S3. Best reduction in baseline target tumor lesions of patients with tumor PD-L1 expression that was negative (n=40), positive (n=25), or unevaluable (n=9) using a 5% cut-off of tumor cell membrane staining to define PD-L1 positivity. Patients with complete target lesion data, a baseline assessment, and at least one on-treatment assessment before progression or start of subsequent therapy were included. Patients for whom PD-L1 expression was evaluable but who had a BOR of unable to determine or not reported (n=11), as assessed by the IRC, are not shown here. Reduction in tumor lesions was assessed by the IRC.

Figure S1. CA209-063 (CheckMate 063) study design

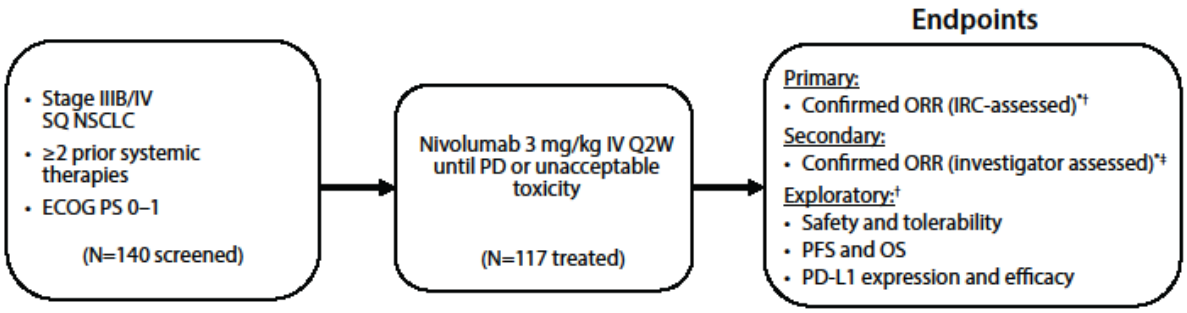


Figure S2. Best reduction in target lesion in patients rapidly progressing on prior therapy (IRC-assessed)

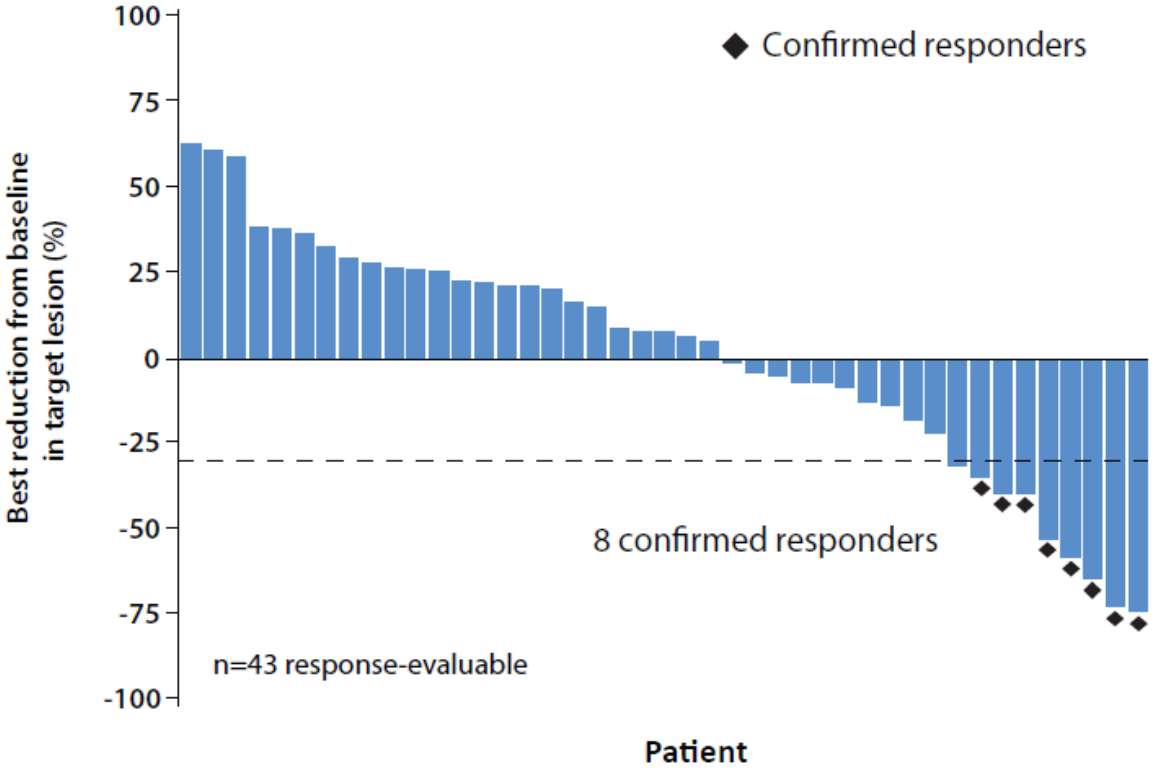
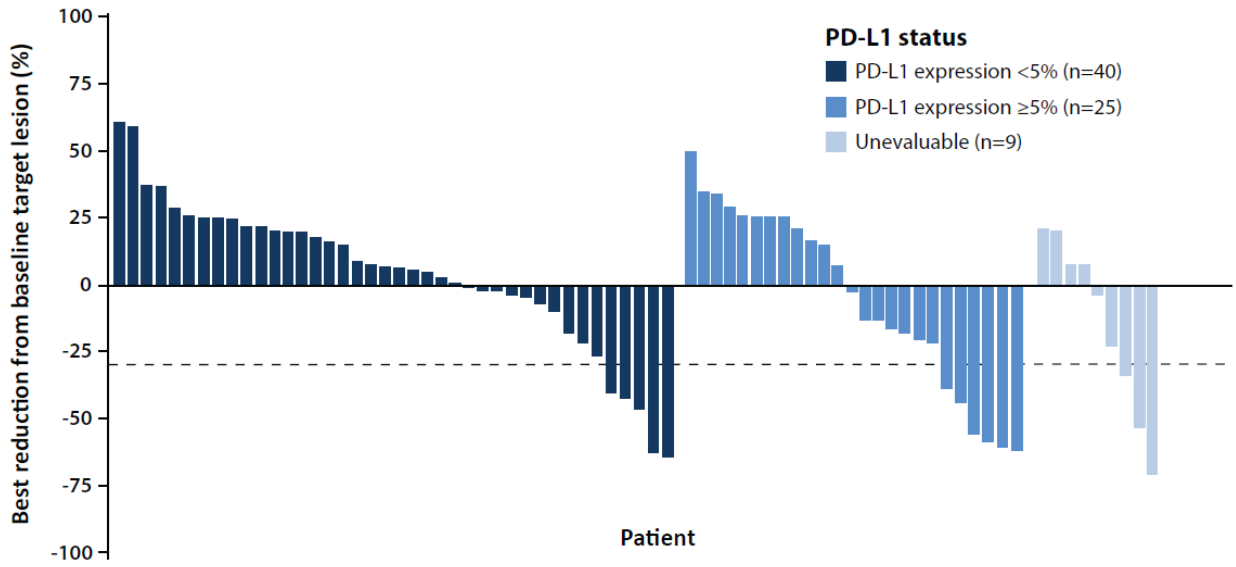


Figure S3. Best reduction in baseline target tumor lesions by tumor PD-L1 expression



Supplemental Text

Narrative summaries of treatment-related deaths

Patient 1 was a 45-year old male with squamous (SQ) non-small cell lung cancer (NSCLC) and metastases in bone, mediastinum, and pleura. Relevant medical history included hemopneumothorax and prior thoracic radiotherapy, and he was a current smoker. On Study Day 56, 13 days after his 4th and final dose of nivolumab, the patient's computer tomography (CT) scan showed unequivocal disease progression in bone and pleural lesions. The study therapy was discontinued due to disease progression with the last dose received on Study Day 43. On Study Day 65, 22 days post the last dose of nivolumab, the subject presented with a 3-day history of pyrexia (temperature of 37°–38° Celsius and dyspnea. His oxygen saturation was 88% (baseline 97%). Chest x−ray showed new bilateral infiltrates with consolidation and diffuse opacity in half of the left lung. A CT scan showed an interstitial syndrome predominant in the posterior segments of the upper right and lower right lobes. Laboratory test results showed elevated C-reactive protein. A bronchoscopy and bronchoalveolar lavage was not performed due to his clinical status. The patient received treatment with ceftriaxone, levofloxacin, albuterol, oxygen, sulfamethoxazole/trimethoprim, and methylprednisolone. On Study Day 67 he underwent a single radiotherapy treatment for T11 rib and vertebra lesions. On Study Day 71 he experienced acute respiratory failure and died. The cause of death was reported by the investigator as hypoxic pneumonia considered related to nivolumab. No autopsy was performed.

Patient 2 was a 74-year old female with SQ NSCLC and metastases in lymph nodes, vertebrae, and adrenal glands. Relevant medical history included hypertension, heart attack, pulmonary embolism, carotid artery thrombosis, history of radiation therapy to the thoracic spine, history of percutaneous kyphoplasty and vertebrectomy with fixation, and temporal central nervous system bleeding 2 months prior to enrolling in the trial. The subject was a former smoker. Beginning on approximately Study Day 11, 10 days post the 1st and only dose of nivolumab, she developed lower extremity paresis, rash, venous thrombosis/pulmonary embolus and renal insufficiency, in the setting of progressive disease. The patient underwent an extensive rheumatological evaluation suggestive of immune complex vasculitis or light-chain associated neuritis, but without confirmatory evidence (eg - negative autoantibody and cold agglutinin testing, skin biopsy negative for vasculitis). She received treatment with dexamethasone, moxifloxacin, piperacillin/tazobactam, intravenous immunoglobulin, plasmapheresis, cyclophosphamide, certoparin, and enoxaparin. While hospitalized for the paresis 41 days following her only nivolumab dose, the patient experienced a grade 5 ischemic stroke that was considered treatment-related by the investigator. No autopsy was performed.