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APPENDIX

Supplementary Methods

Overall survival was defined as time from first dosing date to date of death. Progression-free survival was defined as time from first dosing date to date of first documented tumor progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause, whichever occurred first. Objective response rate was defined as the proportion of patients with confirmed complete or partial response per RECIST v1.1. Duration of response among responders was defined as time between date of first confirmed response to date of first documented tumor progression per RECIST v1.1, or death due to any cause, whichever occurred first.

Radiographic tumor assessments occurred every 6 weeks until week 48, and every 12 weeks thereafter until disease progression. Patients with known brain metastases underwent magnetic resonance imaging or computed tomography assessment at least every 12 weeks. Before initiation of study treatment, tumor programmed death ligand 1 (PD-L1) expression was assessed at a central laboratory in fresh or archival tumor tissue using the PD-L1 immunohistochemistry 28-8 pharmDx kit (Dako/Agilent Technologies; Dako. PD-L1 IHC 28-8 pharmDx. 2016 [https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150027c.pdf]).

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Supplementary Table S1. Eligibility criteria

	Cohort A	Cohort A1
Key eligibility criteria	• ECOG PS 0–1 • Absence of untreated brain metastases • No known history of positive HIV status • Serum creatinine ≤1.5 × ULN (unless creatinine clearance ≥40 mL/min as measured or calculated using the Cockroft-Gault formula) • AST/ALT ≤3.0 × ULN • Total bilirubin ≤1.5 × ULN (except patients with Gilbert Syndrome who must have a total bilirubin level of <3.0 × ULN)	• ECOG PS 2, or 0–1 with one of the following: asymptomatic untreated brain metastases, renal impairment, hepatic impairment, or positive HIV status ○ Renal impairment: creatinine clearance 20–39 mL/min ○ Hepatic impairment: AST/ALT 3.0–5.0 × ULN and/or total bilirubin 1.5–3.0 × ULN
	Cohorts A and A1	
Key inclusion criteria	• ≥18 years of age • Histologically confirmed stage IV or recurrent NSCLC (squamous or non-squamous), per the 7th International Association for the Study of Lung Cancer Classification • No prior systemic anticancer therapy, including EGFR inhibitors, ALK inhibitors, or other immuno-oncology agents, given as primary therapy for advanced or metastatic disease • Prior adjuvant/neoadjuvant chemotherapy or definitive chemoradiation (for locally advanced disease) were permitted if the last administration occurred at least 6 months before study enrollment • Prior palliative radiotherapy to non-central nervous system lesions was permitted if completed at least 2 weeks before treatment assignment • Evaluable disease by computed tomography or magnetic resonance imaging, with radiographic tumor assessment performed within 28 days of study treatment start • Tumor tissue was obtained by core needle, excisional, or incisional biopsy for PD-L1 testing prior to treatment assignment, unless expression levels were available from another Bristol Myers Squibb–sponsored study or diagnostics tools using acceptable antibodies (ie, 28-8, 22C3, SP263)	
Key exclusion criteria	• Patients with *EGFR* or *ALK* mutations known to be sensitive to available targeted inhibitor therapy • Patients with non-squamous histology and unknown or indeterminate *EGFR* mutation status ○ Patients with unknown or indeterminate *ALK* mutation status could be enrolled • Prior treatment with an anti–PD-1, anti–PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody/drug specifically targeting T-cell costimulation or checkpoint pathways • Treatment with botanical preparations within 2 weeks of treatment assignment • Allergy/hypersensitivity to the study drug components • White blood cells <2000/μL, neutrophils <1500/μL, platelets <100,000/μL, hemoglobin <9.0 g/dL • Presence of carcinomatous meningitis or active malignancy requiring concurrent intervention • Active, known, or suspected autoimmune disease (except type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, psoriasis, or alopecia not requiring systemic treatment, and conditions not expected to recur in the absence of an external trigger) • Condition requiring systemic treatment with corticosteroids (>10 mg daily of prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment	

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	• Interstitial lung disease that was symptomatic or may have interfered with detection or management of suspected treatment-related pulmonary toxicity • Presence of acquired immunodeficiency syndrome • Any positive test for hepatitis B or C virus indicating acute or chronic infection, respectively • Any known medical condition that, in the investigator's opinion, would have increased the risk associated with study participation/drug administration or interfered with safety data interpretation

ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA, cytotoxic T-lymphocyte-associated protein; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HIV, human immunodeficiency virus; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; PD-L2, programmed cell death ligand 2; ULN, upper limit of normal.

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Supplementary Table S2. Dose delay criteria for nivolumab and ipilimumab administration[a]

Patients in cohorts A and A1 without hepatic and renal impairment	**Patients in cohort A1 with hepatic and renal impairment**
• Grade 2 treatment-related creatinine, AST, ALT, and/or total bilirubin abnormalities • Grade ≥3 treatment-related laboratory abnormality, with the following exceptions: - Grade 3 lymphopenia or asymptomatic amylase or lipase do not require a dose delay - Grade ≥3 AST, ALT, or total bilirubin require dose discontinuation	• For patients with grade 2 baseline AST or ALT elevation (>3.0–5.0 × ULN), dose delay required for a two-fold increase in AST or ALT, or for AST/ALT values 8 × ULN • For patients with grade 2 baseline total bilirubin (>1.5–3.0 × ULN), dose delay required for treatment-related elevation >5.0 × ULN • For patients with grade 4 CrCl (CrCl <15 mL/min), dose delay required until CrCl >20 mL/min
All patients in cohorts A and A1	
• Grade 2 non-skin, treatment-related AE, except for fatigue • Grade 3 skin, treatment-related AE • Any AE, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants dose delay	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ULN, upper limit normal.

[a]Patients with treatment-related toxicities that meet the criteria for dose delay should have both ipilimumab and nivolumab delayed until retreatment criteria are met. Patients who require delay should be re-evaluated at least weekly and resume study medication dosing when retreatment criteria are met.

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Supplementary Table S3. Patient disposition in cohort A and cohort A1

		Cohort A1[a]		
	Cohort A (N=391)	**Overall (N=198[b])**	**ECOG PS 2 (n=139[c])**	**Asymptomatic untreated brain metastases (n=49[d])**
Patients continuing in the treatment period, n (%)[e]	0	0	0	0
Patients not continuing in the treatment period, n (%)[e]	391 (100)	198 (100)	139 (100)	49 (100)
Reason for treatment discontinuation, n (%)				
Disease progression	184 (47.1)	109 (55.1)	76 (54.7)	32 (65.3)
Study drug toxicity	90 (23.0)	31 (15.7)	19 (13.7)	10 (20.4)
Completed treatment	56 (14.3)	16 (8.1)	12 (8.6)	2 (4.1)
Adverse event unrelated to study drug	29 (7.4)	18 (9.1)	12 (8.6)	2 (4.1)
Patient request	10 (2.6)	5 (2.5)	3 (2.2)	1 (2.0)
Death	7 (1.8)	3 (1.5)	3 (2.2)	0
Consent withdrawn	5 (1.3)	2 (1.0)	2 (1.4)	0
Maximum clinical benefit	5 (1.3)	2 (1.0)	2 (1.4)	0
Poor / non-compliance	-	2 (1.0)	2 (1.4)	0
Patient no longer meets the eligibility criteria	-	1 (0.5)	1 (0.7)	0
Other	5 (1.3)	9 (4.5)	7 (5.0)	2 (4.1)
Patients continuing in the study, n (%)	319 (81.6)	147 (74.2)	98 (70.5)	41 (83.7)
Patients not continuing in the study, n (%)	72 (18.4)	51 (25.8)	41 (29.5)	8 (16.3)
Reason for study discontinuation, n (%)				
Death	56 (14.3)	41 (20.7)	33 (23.7)	5 (10.2)
Consent withdrawn	10 (2.6)	4 (2.0)	3 (2.2)	1 (2.0)
Lost to follow-up	3 (0.8)	1 (0.5)	1 (0.7)	0
Other	3 (0.8)	5 (2.5)	4 (2.9)	2 (4.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus.

[a]Patients belonging to multiple subgroups are included in each of the subgroups.

[b]Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.

[c]Includes 5 patients with untreated brain metastases, 1 with renal impairment, and 3 with hepatic impairment.

[d]Includes 5 patients with ECOG PS 2 and 1 patient with positive HIV status.

[e]Refers to treatment with flat-dose nivolumab plus weight-based ipilimumab.

Supplementary Table S4. Treatment exposure

		Cohort A1[a]		
Treatment	**Cohort A (N=391)**	**Overall (N=198[b])**	**ECOG PS 2 (n=139[c])**	**Asymptomatic untreated brain metastases (n=49[d])**
Duration of treatment, median (95% CI), months	4.0 (3.7–4.9)	2.8 (2.3–3.8)	2.8 (1.9–3.8)	2.5 (1.4–4.0)
On treatment, n (%)				
>3 months	235 (60.1)	95 (48.0)	67 (48.2)	21 (42.9)
>6 months	159 (40.7)	64 (32.3)	47 (33.8)	13 (26.5)
>9 months	116 (29.7)	45 (22.7)	34 (24.5)	7 (14.3)
>12 months	98 (25.1)	36 (18.2)	28 (20.1)	6 (12.2)
Number of nivolumab doses, median (range)	9.0 (1–54)	6.0 (1–54)	6.0 (1–54)	5.0 (1–50)
Number of ipilimumab doses, median (range)	3.0 (1–18)	2.0 (1–18)	2.0 (1–18)	2.0 (1–17)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus.

[a]Patients belonging to multiple subgroups are included in each of the subgroups.

[b]Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.

[c]Includes 5 patients with untreated brain metastases, 1 with renal impairment, and 3 with hepatic impairment.

[d]Includes 5 patients with ECOG PS 2 and 1 patient with positive HIV status.

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Supplementary Table S5. Subsequent therapies in all patients treated with nivolumab plus ipilimumab

		Cohort A1[a]		
Subsequent therapy, n (%)	**Cohort A (N=391)**	**Overall (N=198[b])**	**ECOG PS 2 (n=139[c])**	**Asymptomatic untreated brain metastases (n=49[d])**
Any	178 (45.5)	73 (36.9)	45 (32.4)	22 (44.9)
Radiotherapy	76 (19.4)	37 (18.7)	24 (17.3)	12 (24.5)
Curative	6 (1.5)	10 (5.1)	7 (5.0)	3 (6.1)
Palliative	72 (18.4)	28 (14.1)	17 (12.2)	10 (20.4)
Surgery	7 (1.8)	1 (0.5)	0	1 (2.0)
Tumor resection, palliative	5 (1.3)	1 (0.5)	0	1 (2.0)
Other	2 (0.5)	0	0	0
Systemic therapy	139 (35.5)	53 (26.8)	31 (22.3)	17 (34.7)
Immunotherapy	32 (8.2)	14 (7.1)	9 (6.5)	3 (6.1)
Nivolumab	13 (3.3)	7 (3.5)	4 (2.9)	2 (4.1)
Pembrolizumab	17 (4.3)	6 (3.0)	4 (2.9)	1 (2.0)
Atezolizumab	3 (0.8)	1 (0.5)	1 (0.7)	0
Investigational AB928	1 (0.3)	0	0	0
Targeted therapy	11 (2.8)	5 (2.5)	3 (2.2)	2 (4.1)
Bevacizumab	4 (1.0)	3 (1.5)	2 (1.4)	1 (2.0)
Erlotinib	4 (1.0)	1 (0.5)	1 (0.7)	0
Nintedanib	4 (1.0)	0	0	0
Afatinib	1 (0.3)	0	0	0
Alectinib	1 (0.3)	0	0	0
Crizotinib	2 (0.5)	1 (0.5)	0	1 (2.0)
Daratumumab	1 (0.3)	0	0	0
Gefitinib	1 (0.3)	0	0	0
Ramucirumab	1 (0.3)	0	0	0
Trastuzumab	0	1 (0.5)	0	1 (2.0)
Chemotherapy	120 (30.7)	43 (21.7)	27 (19.4)	13 (26.5)
Carboplatin	87 (22.3)	35 (17.7)	23 (16.5)	9 (18.4)
Pemetrexed	60 (15.3)	16 (8.1)	8 (5.8)	9 (18.4)
Paclitaxel	29 (7.4)	19 (9.6)	13 (9.4)	4 (8.2)
Gemcitabine	25 (6.4)	5 (2.5)	4 (2.9)	1 (2.0)
Cisplatin	23 (5.9)	6 (3.0)	4 (2.9)	3 (6.1)
Docetaxel	18 (4.6)	5 (2.5)	4 (2.9)	2 (4.1)
Vinorelbine	10 (2.6)	5 (2.5)	3 (2.2)	0
Etoposide	4 (1.0)	1 (0.5)	1 (0.7)	0
Capecitabine	0	1 (0.5)	1 (0.7)	0
Antibody-drug conjugate including chemotherapy	1 (0.3)	1 (0.5)	0	1 (2.0)
Trastuzumab emtansine	1 (0.3)	0	0	0
Unassigned				
Dexamethasone	0	1 (0.5)	1 (0.7)	0
Experimental drugs	3 (0.8)	3 (1.5)	3 (2.2)	1 (2.0)
BP29435	1 (0.3)	0	0	0
BP29889	1 (0.3)	0	0	0
BP40234	1 (0.3)	0	0	0
CPI 444	1 (0.3)	0	0	0
MSC-01	1 (0.3)	0	0	0

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Sitravatinib	1 (0.3)	0	0	0
ICOS agonist	0	1 (0.5)	1 (0.7)	0
GSK3359609	0	1 (0.5)	1 (0.7)	1 (2.0)
LOXO-292	0	1 (0.5)	1 (0.7)	0

ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus.

[a]Patients belonging to multiple subgroups are included in each of the subgroups.

[b]Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.

[c]Includes 5 patients with untreated brain metastases, 1 with renal impairment, and 3 with hepatic impairment.

[d]Includes 5 patients with ECOG PS 2 and 1 patient with positive HIV status.

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Supplementary Table S6. Summary of patients treated with systemic corticosteroid (≥40 mg) and other immune-modulating medication for IMAE management in patients treated with nivolumab plus ipilimumab in cohorts A and A1

Patients receiving indicated treatment / patients who had an IMAE of any grade, n/N (%)[a]	Cohort A (N=391)			Cohort A1 (N=198[b])		
	Corticosteroid ≥40 mg	Corticosteroid + IMM	Duration of corticosteroid ≥40 mg, median (months)	Corticosteroid ≥40 mg	Corticosteroid + IMM	Duration of corticosteroid ≥40 mg, median (months)
Pneumonitis	33/39 (84.6)	1/39 (2.6)	0.8	6/6 (100.0)	1/6 (16.7)	1.2
Diarrhea/colitis	27/40 (67.5)	1/40 (2.5)	0.8	17/18 (94.4)	3/18 (16.7)	0.8
Hepatitis	19/22 (86.4)	2/22 (9.1)	1.0	10/10 (100.0)	1/10 (10.0)	0.5
Adrenal insufficiency	1/10 (10.0)	0/10 (0.0)	1.5	3/5 (60.0)	0/5 (0.0)	0.5
Hypothyroidism/thyroiditis	1/55 (1.8)	0/55 (0.0)	0.2	1/14 (7.1)	0/14 (0.0)	20.2
Hypothyroidism	0/52 (0.0)	0/52 (0.0)	0	1/14 (7.1)	0/14 (0.0)	20.2
Thyroiditis	1/6 (16.7)	0/6 (0.0)	0.2	0/1 (0.0)	0/1 (0.0)	0
Diabetes mellitus	0/3 (0.0)	0/3 (0.0)	0	0/1 (0.0)	0/1 (0.0)	0
Nephritis and renal dysfunction	2/3 (66.7)	0/3 (0.0)	1.0	3/3 (100.0)	0/3 (0.0)	0.6
Rash	17/52 (32.7)	0/52 (0.0)	0.5	7/20 (35.0)	0/20 (0.0)	0.3
Hypersensitivity	4/11 (36.4)	0/11 (0.0)	<0.1	2/2 (100.0)	0/2 (0.0)	<0.1
Hyperthyroidism	4/28 (14.3)	0/28 (0.0)	0.3	1/17 (5.9)	0/17 (0.0)	1.2
Hypophysitis	3/7 (42.9)	0/7 (0.0)	<0.1	2/4 (50.0)	0/4 (0.0)	1.0

ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; IMAE, immune-mediated adverse event; IMM, immune-modulating medication.

[a]Data are n/N (%) unless otherwise stated.

[b]Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.

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Supplementary Table S7. Tumor response to treatment in cohort A

		Cohort A by tumor PD-L1 expression[a]		
	Cohort A overall (N=391)	**PD-L1 ≥1% (n=176)**	**PD-L1 <1% (n=181)**	**PD-L1 ≥50% (n=65)**
Objective response rate, n (%)[b] **95% CI**	146 (37.3) 32.5–42.3	77 (43.8) 36.3–51.4	56 (30.9) 24.3–38.2	35 (53.8) 41.0–66.3
Complete response, n (%)	16 (4.1)	8 (4.5)	6 (3.3)	3 (4.6)
Partial response, n (%)	130 (33.2)	69 (39.2)	50 (27.6)	32 (49.2)
Stable disease, n (%)	131 (33.5)	56 (31.8)	61 (33.7)	16 (24.6)
Progressive disease, n (%)	84 (21.5)	31 (17.6)	47 (26.0)	7 (10.8)
Not evaluable, n (%)	30 (7.7)	12 (6.8)	17 (9.4)	7 (10.8)
Time to objective response, median (range), months	2.6 (1.1–28.8)	2.5 (1.1–28.8)	2.6 (1.2–22.8)	1.7 (1.1–28.8)
Duration of response, median (95% CI), months	27.6 (20.4–34.3)	29.9 (15.2–39.8)	25.8 (16.8–34.3)	18.3 (8.3–NR)
Patients with duration of response of at least, % (95% CI)				
6 months	84 (77–89)	85 (74–91)	81 (68–89)	76 (58–87)
1 year	73 (64–79)	70 (58–79)	71 (57–82)	58 (39–73)
2 years	55 (46–63)	57 (44–68)	51 (37–64)	48 (30–64)
3 years	41 (32–50)	45 (32–56)	35 (22–49)	40 (23–57)

CI, confidence interval; NR, not reached; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Tumor PD-L1 expression was not evaluable in 34 patients in cohort A.

[b]Defined as the sum of complete and partial responses per RECIST v 1.1.

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Supplementary Table S8. Tumor response to treatment in cohort A1 by tumor PD-L1 expression ≥50%[a]

Cohort A1	**PD-L1 ≥50% (n=32)**
Objective response rate, n (%)[b] **95% CI**	13 (40.6) 23.7–59.4
Complete response, n (%)	0
Partial response, n (%)	13 (40.6)
Stable disease, n (%)	10 (31.3)
Progressive disease, n (%)	5 (15.6)
Not evaluable, n (%)	4 (12.5)
Time to objective response, median (range), months	1.4 (1.2–5.4)
Duration of objective response, median (95% CI), months	24.8 (10.0–NR)
Patients with duration of response of at least, % (95% CI)	
6 months	100 (100–100)
1 year	73 (37–90)
2 years	55 (23–78)
3 years	45 (17–71)

CI, confidence interval; NR, not reached; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Tumor PD-L1 expression was not evaluable in 27 patients in cohort A1.

[b]Defined as the sum of complete and partial responses per RECIST v 1.1.

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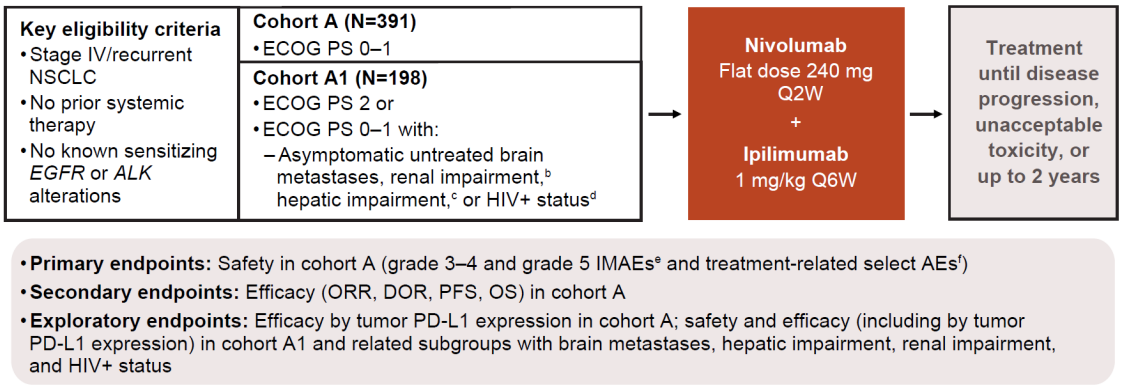
Supplementary Figure S1. Study design[a]



AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, once every 2 weeks; Q6W, once every 6 weeks; TRAE, treatment-related adverse event.

[a]The study included 2 additional cohorts that are not discussed in this manuscript: cohort B, in which patients had ECOG PS 0–1 and stage IIIb/IV NSCLC treated with 1 prior platinum-doublet chemotherapy regimen, and cohort C, in which patients had ECOG PS 0–1 and a tumor mutation burden ≥10 mutations/megabase.

[b]Renal impairment was defined as creatinine clearance 20–39 mL/min (Cockcroft-Gault formula).

[c]Hepatic impairment was defined as AST/ALT = 3.0–5.0 × ULN and/or total bilirubin = 1.5–3.0 × ULN.

[d]Patients with a diagnosis of acquired immunodeficiency syndrome were excluded.

[e]Specific AEs considered by the investigators as potential immune-mediated events occurring within 100 days of the last dose of study drug, regardless of causality, and treated with immune-modulating medication (except for endocrine events, which are included regardless of treatment).

[f]TRAEs with a potential immunological etiology that require frequent monitoring/intervention, and reported between the first dose and 30 days of last dose of study drug.

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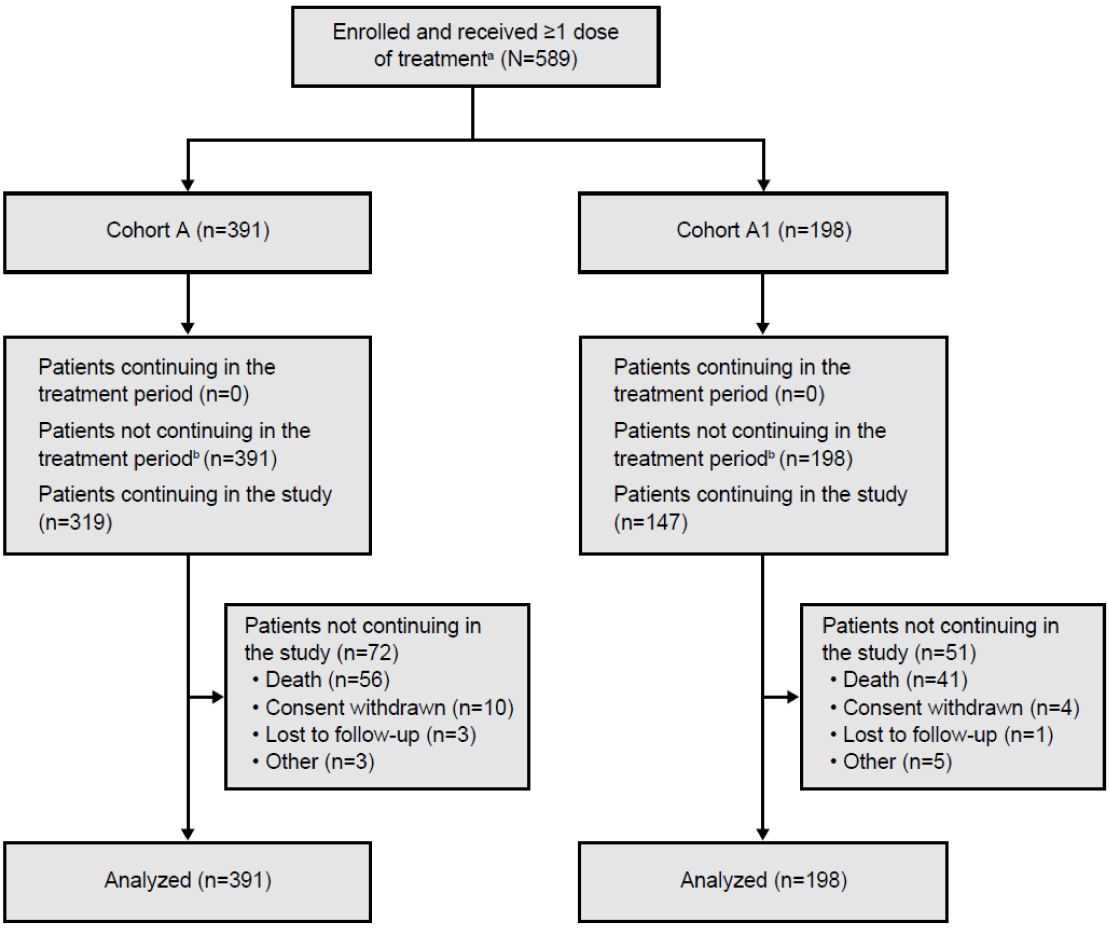
Supplementary Figure S2. CheckMate 817 trial profile and patient flow



[a]Additional cohorts from CheckMate817 not included in this total; actual enrollment was N=1034.
[b]For reasons for not continuing in the treatment period, please see Supplementary Table S3.