Supplementary Appendix

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

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Supplementary Appendix

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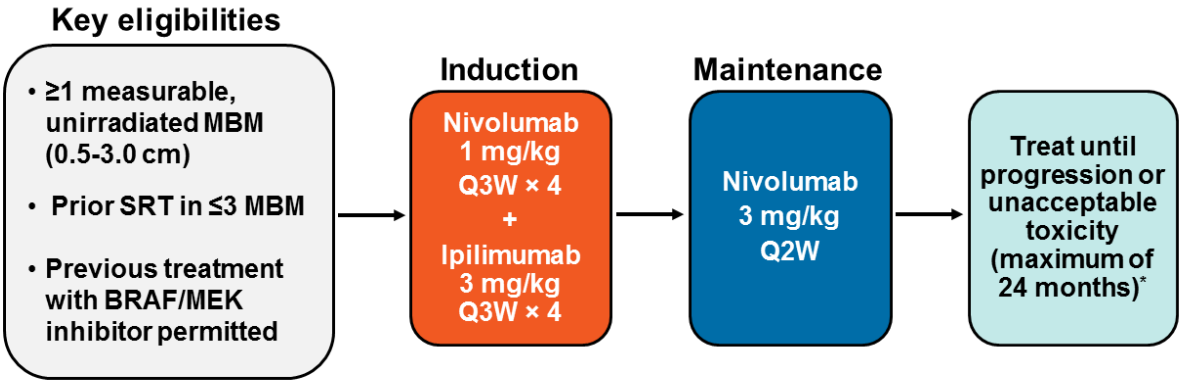
Collaborators

In addition to the authors, the following investigators participated in the CheckMate 204 trial: Sanjiv S. Agarwala (St. Luke's University Health Network, Easton, PA); Diwakar Davar (Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA); Tara C. Gangadhar (Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA); John A. Glaspy (Jonsson Comprehensive Cancer Center, UCLA Medical Center, Santa Monica, CA); Sekwon Jang (Inova Melanoma and Skin Cancer Center, Fairfax, VA); Jose Lutzky (Mount Sinai Comprehensive Cancer Center, Miami, FL); April K. Salama (Duke University Medical Center, Durham, NC); Amy Weise (Karmanos Cancer Institute, Wayne State University, Detroit, MI).

Figure S1. CheckMate 204 Study Design.



MBM denotes melanoma brain metastasis, Q2W every 2 weeks, Q3W every 3 weeks, and SRT stereotactic radiotherapy.

*Patients with grade 3 or 4 adverse events during nivolumab plus ipilimumab induction could resume nivolumab monotherapy when the adverse event resolved; all patients who discontinued study treatment proceeded to the follow-up phase.

Figure S2. Patient Disposition.

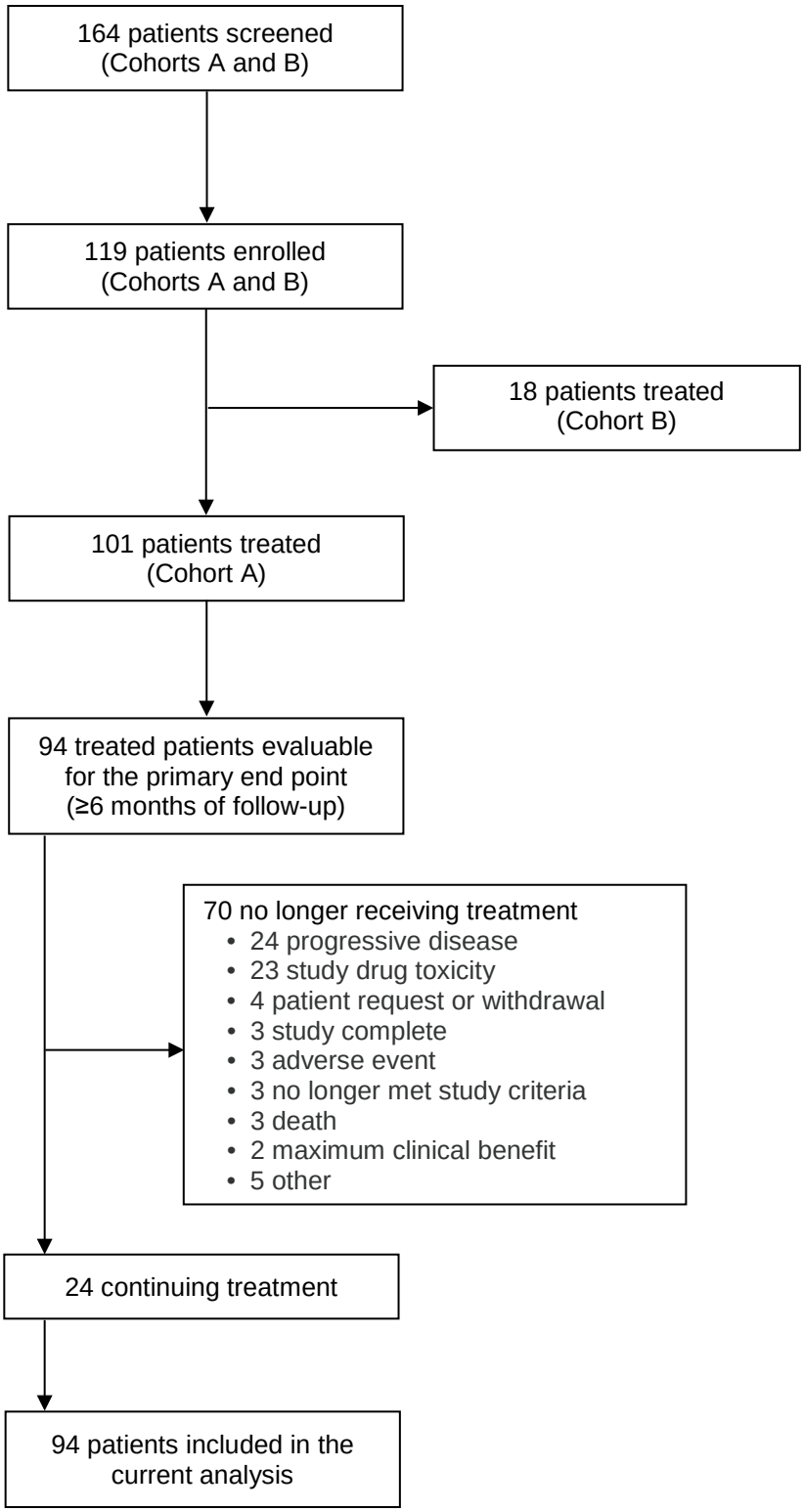


Figure S3. Time to and Duration of Extracranial Response.

Plot shows the onset and durability of extracranial objective responses to the combination of nivolumab and ipilimumab, according to modified RECIST version 1.1 criteria. Open circles indicate the first evidence of objective response and arrows indicate an ongoing response; 43 of 47 responses (91%) were ongoing at the time of the current analysis. Median time to response was 2.1 months (range, 1.1 to 15.0). The median duration of extracranial response has not been reached.

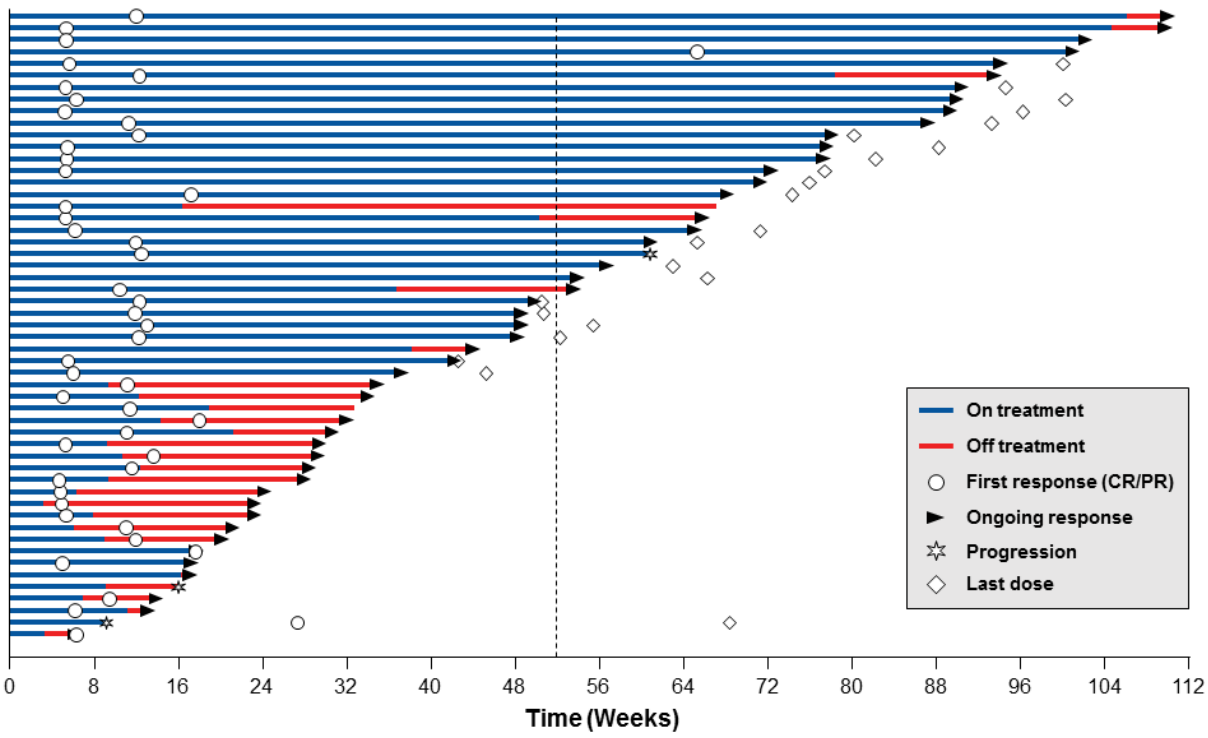


Table S1. Subsequent Anti-cancer Therapies.

	Nivolumab plus ipilimumab (N=94)
Patients who received any subsequent therapy	25 (26.6)
Radiotherapy	15 (16.0)
Stereotactic radiotherapy	4 (4.3)
Systemic therapy	13 (13.8)
Anti-CTLA-4 agent (ipilimumab)	2 (2.1)
Anti-PD-1 agent	8 (8.5)
Nivolumab	7 (7.4)
Pembrolizumab	1 (1.1)
BRAF inhibitor (dabrafenib)	7 (7.4)
MEK/NRAS inhibitor (trametinib)	6 (6.4)

Table S2. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Nivolumab plus Ipilimumab (N=94)
Age – yr	
Median (range)	59 (22–81)
Age category – no. (%)	
<65 yr	62 (66.0)
≥65 yr	32 (34.0)
Sex – no. (%)	
Male	65 (69.1)
Female	29 (30.9)
Lactate dehydrogenase – no. (%)	
≤ULN	55 (58.5)
>ULN	39 (41.5)
≤2x ULN	83 (88.3)
>2x ULN	11 (11.7)
BRAF status – no. (%)	
Mutation	54 (57.4)
No mutation	25 (26.6)
Unknown	15 (16.0)
NRAS status – no. (%)	
Mutation	6 (6.4)
No mutation	17 (18.1)
Unknown	71 (75.5)
PD-L1 status – no. (%)	
1% cutoff	
≥1%	41 (43.6)
<1%	34 (36.2)
5% cutoff	
≥5%	25 (26.6)
<5%	50 (53.2)
Could not be determined or not reported	19 (20.2)
SRT prior to study entry – no. (%)	
Yes	8 (8.5)

No	86 (91.5)
Prior systemic cancer therapy – no. (%)	16 (17.0)
Dabrafenib	8 (8.5)
Trametinib	8 (8.5)
Vemurafenib	2 (2.1)
Pre-treatment tumor assessment – intracranial	
Target lesions – no. (%)	
0	1 (1.1)*
1	49 (52.1)
2	23 (24.5)
≥3	21 (22.3)
Largest individual target lesion – no. (%)	
<1 cm	33 (35.1)
≥1–<2 cm	49 (52.1)
≥2–<3 cm	10 (10.6)
≥3 cm	2 (2.1)*

*Protocol deviation. SRT denotes stereotactic radiotherapy.

Table S3. Number of Target and Non-target Lesions at Baseline.

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Target lesions – no. (%)			
0	1 (1.1)*	15 (16.0)	0
1	49 (52.1)	16 (17.0)	10 (10.6)
2	23 (24.5)	20 (21.3)	12 (12.8)
3	8 (8.5)	14 (14.9)	13 (13.8)
4	6 (6.4)	14 (14.9)	14 (14.9)
≥5	7 (7.4)	15 (16.0)	45 (47.9)
Non-target lesions – no. (%)			
0	52 (55.3)	26 (27.7)	18 (19.1)
1	26 (27.7)	22 (23.4)	20 (21.3)
2	6 (6.4)	13 (13.8)	15 (16.0)
3	3 (3.2)	15 (16.0)	9 (9.6)
4	3 (3.2)	6 (6.4)	7 (7.4)
≥5	4 (4.3)	12 (12.8)	25 (26.6)
Sum of reference diameters of target lesions (mm) – median (range)	15.0 (5–91)	65.2 (12–361)	76.7 (5–381)

*Protocol deviation.

Table S4. Intracranial Response by Number of Baseline Target Lesions.

No. of target lesions	No. of patients (N=94)	BOR – no.			ORR, % (n/N)
		CR	PR	SD ≥6 months	
0	1*	0	0	0	0
1	49	15	11	2	53.1 (26/49)
2	23	6	10	0	69.6 (16/23)
3	8	1	1	0	25.0 (2/8)
4	6	1	3	0	66.7 (4/6)
≥5	7	1	3	0	57.1 (4/7)

*Protocol deviation.

Table S5. Subgroup Analyses of Intracranial Objective Response Rate and Clinical Benefit Rate.

Subgroup	N	Objective Response Rate		Clinical Benefit Rate	
		n	% (95% CI)	n	% (95% CI)
All patients	94	52	55.3 (44.7–65.6)	54	57.4 (46.8–67.6)
Age					
<65 yr	62	37	59.7 (46.4–71.9)	38	61.3 (48.1–73.4)
≥65 yr	32	15	46.9 (29.1–65.3)	16	50.0 (31.9–68.1)
Sex					
Male	65	35	53.8 (41.0–66.3)	37	56.9 (44.0–69.2)
Female	29	17	58.6 (38.9–76.5)	17	58.6 (38.9–76.5)
Lactate dehydrogenase					
≤ULN	55	26	47.3 (33.7–61.2)	28	50.9 (37.1–64.6)
>ULN	39	26	66.7 (49.8–80.9)	26	66.7 (49.8–80.9)
≤2x ULN	83	47	56.6 (45.3–67.5)	49	59.0 (47.7–69.7)
>2x ULN	11	5	45.5 (16.7–76.6)	5	45.5 (16.7–76.6)
BRAF status					
Mutation	54	31	57.4 (43.2–70.8)	32	59.3 (45.0–72.4)
No mutation	25	10	40.0 (21.1–61.3)	11	44.0 (24.4–65.1)
Unknown	15	11	73.3 (44.9–92.2)	11	73.3 (44.9–92.2)
NRAS status					
Mutation	6	3	50.0 (11.8–88.2)	4	66.7 (22.3–95.7)
No mutation	17	7	41.2 (18.4–67.1)	7	41.2 (18.4–67.1)
Unknown	71	42	59.2 (46.8–70.7)	43	60.6 (48.3–72.0)
PD-L1 status*					

1% cutoff					
≥1%	41	24	58.5 (42.1–73.7)	25	61.0 (44.5–75.8)
<1%	34	17	50.0 (32.4–67.6)	18	52.9 (35.1–70.2)
5% cutoff					
≥5%	25	18	72.0 (50.6–87.9)	19	76.0 (54.9–90.6)
<5%	50	23	46.0 (31.8–60.7)	24	48.0 (33.7–62.6)
SRT prior to study entry					
Yes	8	4	50.0 (15.7–84.3)	4	50.0 (15.7–84.3)
No	86	48	55.8 (44.7–66.5)	50	58.1 (47.0–68.7)
No. of target lesions					
1–2	72	42	58.3 (46.1–69.8)	44	61.1 (48.9–72.4)
≥3	21	10	47.6 (25.7–70.2)	10	47.6 (25.7–70.2)
Largest individual target lesion					
<1 cm	33	19	57.6 (39.2–74.5)	21	63.6 (45.1–79.6)
≥1–<2 cm	49	27	55.1 (40.2–69.3)	27	55.1 (40.2–69.3)
≥2–<3 cm	10	5	50.0 (18.7–81.3)	5	50.0 (18.7–81.3)
≥3 cm**	2	1	50.0 (1.3–98.7)	1	50.0 (1.3–98.7)

*PD-L1 expression was assessed in extracranial tumor tissue using a validated immunohistochemical assay and a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8) as described previously.[11]

**Protocol deviation.

SRT denotes stereotactic radiotherapy.

Table S6. Treatment-related Adverse Events.*

Event	Nivolumab plus ipilimumab† (N=94)	
	Any Grade	Grade 3-4
	number of patients with event (percent)	
Treatment-related adverse event	90 (95.7)	52 (55.3)
Fatigue	45 (47.9)	4 (4.3)
Increase in ALT level	35 (37.2)	15 (16.0)
Maculopapular rash	34 (36.2)	7 (7.4)
Diarrhea	33 (35.1)	6 (6.4)
Increased AST level	32 (34.0)	14 (14.9)
Pruritus	28 (29.8)	0
Nausea	26 (27.7)	2 (2.1)
Headache	21 (22.3)	3 (3.2)
Hypothyroidism	20 (21.3)	1 (1.1)
Arthralgia	19 (20.2)	0
Decreased appetite	16 (17.0)	1 (1.1)
Pyrexia	16 (17.0)	0
Increased lipase level	14 (14.9)	8 (8.5)
Hyperthyroidism	12 (12.8)	3 (3.2)
Vomiting	12 (12.8)	2 (2.1)
Increased amylase level	11 (11.7)	6 (6.4)
Hypophysitis	11 (11.7)	5 (5.3)
Myalgia	19 (10.6)	0
Generalized pruritus	9 (9.6)	0
Pneumonitis	8 (8.5)	2 (2.1)
Rash	8 (8.5)	2 (2.1)
Anemia	8 (8.5)	1 (1.1)
Increased blood alkaline phosphatase level	8 (8.5)	0

Cough	8 (8.5)	0
Colitis	7 (7.4)	7 (7.4)
Abdominal pain	7 (7.4)	1 (1.1)
Adrenal insufficiency	6 (6.4)	1 (1.1)
Increased blood bilirubin level	6 (6.4)	1 (1.1)
Decreased platelet count	6 (6.4)	0
Decreased weight	6 (6.4)	0
Night sweats	6 (6.4)	0
Skin hypopigmentation	6 (6.4)	0
Hyponatremia	5 (5.3)	1 (1.1)
Blurred vision	5 (5.3)	0
Hypokalemia	5 (5.3)	0
Chills	5 (5.3)	0
Vitiligo	5 (5.3)	0
Decreased lymphocyte count	4 (4.3)	1 (1.1)
Influenza-like illness	4 (4.3)	1 (1.1)
Hypotension	3 (3.2)	2 (2.1)
Macular rash	3 (3.2)	1 (1.1)
Increased transaminases	2 (2.1)	2 (2.1)
Brain edema	2 (2.1)	2 (2.1)
Dehydration	2 (2.1)	2 (2.1)
Intracranial hemorrhage	2 (2.1)	1 (1.1)
Myositis	2 (2.1)	1 (1.1)
Pancreatitis	2 (2.1)	1 (1.1)
Acute hepatitis	1 (1.1)	1 (1.1)
Acute kidney injury	1 (1.1)	1 (1.1)
Autoimmune hepatitis	1 (1.1)	1 (1.1)
Autoimmune pancreatitis	1 (1.1)	1 (1.1)
Cytokine release syndrome	1 (1.1)	1 (1.1)

Decreased blood phosphorus level	1 (1.1)	1 (1.1)
Duodenitis	1 (1.1)	1 (1.1)
Gastritis	1 (1.1)	1 (1.1)
Rhabdomyolysis	1 (1.1)	1 (1.1)
Syncope	1 (1.1)	1 (1.1)
Type I diabetes mellitus	1 (1.1)	1 (1.1)
Uveitis	1 (1.1)	1 (1.1)
Treatment-related adverse events leading to discontinuation	25 (26.6)	19 (20.2)

*Shown are treatment-related adverse events of any grade that occurred in at least 5% of the patients and treatment-related adverse events of grade 3 or 4 that occurred in at least one patient who received nivolumab plus ipilimumab. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

[†]One patient died due to grade 5 myocarditis.

Table S7. Adverse Events in the Central Nervous System.*

Event	Nivolumab plus ipilimumab (N=94)	
	Any Grade	Grade 3-4
	number of patients with event (percent)	
Any treatment-related adverse event	34 (36.2)	7 (7.4)
Headache	21 (22.3)	3 (3.2)
Paraesthesia	4 (4.3)	0
Dysgeusia	3 (3.2)	0
Brain edema	2 (2.1)	2 (2.1)
Intracranial hemorrhage	2 (2.1)	1 (1.1)
Aphasia	2 (2.1)	0
Seizure	2 (2.1)	0
Syncope	1 (1.1)	1 (1.1)
Dizziness	1 (1.1)	0
Tremor	1 (1.1)	0

*The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.