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: Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol* 2021; published online Nov 10. http://dx.doi.org/10.1016/S1470-2045(21)00545-3.

Supplementary Appendix

Supplement to: Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab: final results of CheckMate 204

Contents

Table S1. Subsequent anti-cancer therapies

	Asymptomatic (n=101)	Symptomatic (n=18)
Patients who received any subsequent therapy*	34 (33·7)	7 (38·9)
Radiotherapy	17 (16·8)	4 (22·2)
Surgery	13 (12·9)	3 (16·7)
Systemic therapy	19 (18·8)	4 (22·2)
Anti-CTLA-4 agent (ipilimumab)	2 (2·0)	0
Anti-PD-1 agent	12 (11·9)	2 (11·1)
Nivolumab	9 (8·9)	0
Pembrolizumab	4 (4·0)	2 (11·1)
BRAF inhibitor	12 (11·9)	2 (11·1)
Dabrafenib	12 (11·9)	1 (5·6)
Vemurafenib	1 (1·0)	2 (11·1)
MEK/NRAS inhibitor (trametinib)	10 (9·9)	0
Other approved agent	3 (3·0)	2 (11·1)
Investigational agent	1 (1·0)	0
Stereotactic radiation therapy	8 (7·9)	0
Median time to subsequent therapy, months (IQR)	4·5 (2·2–6·2)	1·7 (1·0–2·1)

Data are n (%) unless specified.
CTLA-4=cytotoxic T lymphocyte antigen-4; IQR=interquartile range; PD-1=programmed death-1.
*Patients may have received more than one type of subsequent therapy, and more than one agent within each type.

Table S2. Response to treatment in patients with asymptomatic disease by BICR assessment

	Patients (n=101 [95 available for BICR])		
	Intracranial	**Extracranial**	**Global**
Best overall response, n (%)*			
Complete response	26 (25·7)	14 (13·9)	11 (10·9)
Partial response	24 (23·8)	36 (35·6)	38 (37·6)
Stable disease ≥6 months	4 (4·0)	5 (5·0)	3 (3·0)
Progressive disease	30 (29·7)	14 (13·9)	31 (30·7)
Not evaluable†	11 (10·9)	26 (25·7)	12 (11·9)
Objective response rate,‡ n/N (% [95% CI])	50/101 (49·5 [39·4–59·6]) §	50/101 (49·5 [39·4–59·6])	49/101 (48·5 [38·4–58·7])
Clinical benefit rate,‖ n/N (% [95% CI])	54/101 (53·5 [43·3–63·5])¶	55/101 (54·5 [44·2–64·4])	52/101 (51·5 [41·3–61·6])
Duration of response			
Ongoing responders/patients with objective response (%)	42/50 (84·0)	41/50 (82·0)	38/49 (77·6)
Median (95% CI), months	38·4 (NR–NR)	NR (NR–NR)	NR (34·5–NR)

CI=confidence interval; BICR= blinded independent central review; NR=not reached.

*Best overall response was assessed by BICR in accordance with Response Evaluation Criteria in Solid Tumors, version 1·1 (modified criteria were used for intracranial response). Best response and response rates were calculated based on cohort intention-to-treat populations; data for six patients were not available for BICR analysis because the patients died, progressed, or withdrew consent before they had the requisite scans to be evaluated for response.

†Reasons for patients being not evaluable for BICR-assessed responses were not captured in the clinical database.

‡Data include patients with a complete response or partial response; confidence interval based on Clopper-Pearson method.

§50/95 (52·6%) based on the 95 patients available for BICR.

‖Data include patients with a complete response, partial response or stable disease for 6 months or longer; confidence interval based on Clopper-Pearson method.

¶54/95 (56·8%) based on the 95 patients available for BICR.

Table S3. Subgroup analyses of intracranial objective response rate and clinical benefit rate in patients with asymptomatic melanoma brain metastases

Subgroup	N	Objective response rate		Clinical benefit rate	
		n	% (95% CI)	n	% (95% CI)
All patients	101	54	53·5 (43·3–63·5)	58	57·4 (47·2–67·2)
Age					
<65 years	68	39	57·4 (44·8–69·3)	42	61·8 (49·2–73·3)
≥65 years	33	15	45·5 (28·1–63·6)	16	48·5 (30·8–66·5)
Sex					
Male	68	35	51·5 (39·0–63·8)	38	55·9 (43·3–67·9)
Female	33	19	57·6 (39·2–74·5)	20	60·6 (42·1–77·1)
Baseline ECOG performance status					
0	77	37	48·1 (36·5–59·7)	41	53·2 (41·5–64·7)
1	24	17	70·8 (48·9–87·4)	17	70·8 (48·9–87·4)
Lactate dehydrogenase					
≤ULN	60	27	45·0 (32·1–58·4)	30	50·0 (36·8–63·2)
>ULN	41	27	65·9 (49·4–79·9)	28	68·3 (51·9–81·9)
≤2×ULN	90	49	54·4 (43·6–65·0)	53	58·9 (48·0–69·2)
>2×ULN	11	5	45·5 (16·7–76·6)	5	45·5 (16·7–76·6)
BRAF status					
Mutation	66	39	59·1 (46·3–71·0)	41	62·1 (49·3–73·8)
No mutation	33	14	42·4 (25·5–60·8)	16	48·5 (30·8–66·5)
Unknown	2	1	NE	1	NE
NRAS status					
Mutation	7	3	NE	5	NE
No mutation	19	8	42·1 (20·3–66·5)	8	42·1 (20·3–66·5)
Unknown	75	43	57·3 (45·4–68·7)	45	60·0 (48·0–71·1)
PD–L1 status					
1% cutoff					
≥1%	46	27	58·7 (43·2–73·0)	28	60·9 (45·4–74·9)
<1%	37	18	48·6 (31·9–65·6)	20	54·1 (36·9–70·5)
5% cutoff					
≥5%	30	21	70·0 (50·6–85·3)	22	73·3 (54·1–87·7)
<5%	53	24	45·3 (31·6–59·6)	26	49·1 (35·1–63·2)
SRT prior to study entry					

Subgroup	N	Objective response rate		Clinical benefit rate	
		n	% (95% CI)	n	% (95% CI)
Yes	9	4	NE	4	NE
No	92	50	54·3 (43·6–64·8)	54	58·7 (47·9–68·9)
No· of intracranial target lesions					
1–2	78	43	55·1 (43·4–66·4)	47	60·3 (48·5–71·2)
≥3	22	10	45·5 (24·4–67·8)	10	45·5 (24·4–67·8)

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; NE=not evaluable; PD-L1=programmed ligand-1; SRT=stereotactic radiotherapy; ULN=upper limit of normal.

Table S4. Survival rates in asymptomatic patients

	Investigator		BICR	
	24-months	**36-months**	**24-months**	**36-months**
Progression-free survival				
Intracranial	54·1 (42·7–64.1)	54·1 (42·7–64.1)	52·5 (41·4–62.4)	52·5 (41·4–62.4)
Extracranial	59·1 (46·5–69.7)	53·2 (39·4–65.3)	62·5 (49·9–72.8)	62·5 (49·9–72.8)
Global	50·2 (38·9–60.4)	45·4 (33·5–56.6)	48·5 (37·4–58.8)	48·5 (37·4–58.8)
Overall survival	74·1 (64·1–81·7)	71·9 (61·8–79·8)	NA	NA

Data are % (95% CI). NA=not available.

Table S5. Response to treatment in patients with symptomatic disease by BICR assessment

	Patients (n=18 [17 available for BICR])		
	Intracranial	**Extracranial**	**Global**
Best overall response, n (%)*			
Complete response	3 (16·7)	2 (11·1)	2 (11·1)
Partial response	1 (5·6)	2 (11·1)	2 (11·1)
Stable disease ≥6 months	0	0	*0*
Progressive disease	10 (55·6)	6 (33·3)	10 (55·6)
Not evaluable[†]	3 (16·7)	7 (38·9)	3 (16·7)
Objective response rate,[‡] n/N (% [95% CI])	4/18 (22·2 [6·4–47·6]) [§]	4/18 (22·2 [6·4–47·6])	4/18 (22·2 [6·4–47·6])
Clinical benefit rate,[‖] n/N (% [95% CI])	4/18 (22·2 [6·4–47·6]) [§]	4/18 (22·2 [6·4–47·6])	4/18 (22·2 [6·4–47·6])
Duration of response			
Ongoing responders/patients with objective response	4/4 (100)	4/4 (100)	4/4 (100)
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)

CI=confidence interval; BICR= blinded independent central review; NR=not reached.

[*]Best overall response was assessed by BICR in accordance with Response Evaluation Criteria in Solid Tumors, version 1·1 (modified criteria were used for intracranial response). Best response and response rates were calculated based on cohort intention-to-treat populations; data for one patient was not available for BICR analysis because the patient died before they had the requisite scans to be evaluated for response.

[†]Reasons for patients being not evaluable for BICR-assessed responses were not captured in the clinical database.

[‡]Data include patients with a complete response or partial response; confidence interval based on Clopper-Pearson method.

[§]4/17 (23·5%) based on the 17 patients available for BICR.

[‖]Data include patients with a complete response, partial response, or stable disease for 6 months or longer; confidence interval based on Clopper-Pearson method.

Table S6. Survival rates in symptomatic patients

	Investigator		BICR	
	24 months	**36 months**	**24 months**	**36 months**
Progression-free survival				
Intracranial	18·9 (4·6–40.5)	18·9 (4·6–40.5)	28·2 (9·6–50.5)	28·2 (9·6–50.5)
Extracranial	28·2 (8·9–51.5)	28·2 (8·9–51.5)	36·3 (12·3–61.2)	36·3 (12·3–61.2)
Global	23·9 (7·5–45.5)	23·9 (7·5–45.5)	25·9 (8·1–48.3)	25·9 (8·1–48.3)
Overall survival	43·9 (19·2–66·3)	36·6 (14·0–59·8)	NA	NA

Data are % (95%, CI). NA=not available.

Table S7. Concordance between investigator-assessed and BICR-assessed response in patients with asymptomatic disease (cohort A n=95 with data available for both investigator and BICR)

	Intracranial					Extracranial					Global				
	Best objective response per BICR					Best objective response per BICR					Best objective response per BICR				
Best objective response per investigator	CR	PR	SD	PD	Not evaluable	CR	PR	SD	PD	Not evaluable	CR	PR	SD	PD	Not evaluable
CR	24 (25·3)	7 (7·4)	0	2 (2·1)	0	11 (11·6)	1 (1·1)	1 (1·1)	0	3 (3·2)	10 (10·5)	6 (6·3)	0	1 (1·1)	0
PR	1 (1·1)	13 (13·7)	2 (2·1)	4 (4·2)	1 (1·1)	2 (2·1)	30 (31·6)	0	0	1 (1·1)	1 (1·1)	30 (31·6)	0	3 (3·2)	1 (1·1)
SD	0	1 (1·1)	2 (2·1)	1 (1·1)	0	0	1 (1·1)	4 (4·2)	0	0	0	0	3 (3·2)	1 (1·1)	0
PD	1 (1·1)	3 (3·2)	0	22 (23·2)	4 (4·2)	0	2 (2·1)	0	10 (10·5)	5 (5·3)	0	2 (2·1)	0	21 (22·1)	3 (3·2)
Not evaluable	0	0	0	1 (1·1)	6 (6·3)	1 (1·1)	2 (2·1)	0	4 (4·2)	17 (17·9)	0	0	0	5 (5·3)	8 (8·4)
Concordance between BICR and investigator for each response category, n (%)*	67/95 (70·5)					72/95 (75·8)					72/95 (75·8)				

BICR=blinded independent central review; CR=complete response; PD = progressive disease; PR = partial response.

*Number and proportion of patients with same best objective response as per BICR and investigator based on total number of patients with assessments by both the investigator and BICR (n=95).

Table S8. Concordance between investigator-assessed and BICR-assessed response in patients with symptomatic disease (cohort B; n = 17 with data available for both investigator and BICR)

	Intracranial					Extracranial					Global				
	Best objective response per BICR					Best objective response per BICR					Best objective response per BICR				
Best objective response per investigator	CR	PR	SD	PD	Not evaluable	CR	PR	SD	PD	Not evaluable	CR	PR	SD	PD	Not evaluable
CR	3 (17·6)	0	0	0	0	1 (5·9)	0	0	0	0	1 (5·9)	0	0	0	0
PR	0	0	0	0	0	1 (5·9)	2 (11·8)	0	0	0	1 (5·9)	2 (11·8)	0	0	0
SD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PD	0	1 (5·9)	0	9 (52·9)	1 (5·9)	0	0	0	4 (23·5)	3 (17·6)	0	0	0	7 (41·2)	3 (17·6)
Not evaluable	0	0	0	1 (5·9)	2 (11·8)	0	0	0	2 (11·8)	4 (23·5)	0	0	0	3 (17·6)	0
Agreement between BICR and investigator for each response category,[†] n (%)	14/17 (82·4)					11/17 (64·7)					10/17 (58·8)				

BICR=blinded independent central review; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

[†]Number and proportion of patients with same best objective response as per BICR and investigator based on total number of patients with assessments by both the investigator and BICR (n=17).

Table S9. Treatment-related adverse events in the central nervous system

	Asymptomatic Patients (n=101)			Symptomatic Patients (n=18)		
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 1–2**	**Grade 3**	**Grade 4**
Treatment-related neurologic adverse events*	28 (27·7)	5 (5·0)	2 (2·0)	0	3 (16·7)	0
Headache	17 (16·8)	3 (3·0)	0	0	1 (5·6)	0
Parasthesia	4 (4·0)	0	0	0	0	0
Dysgeusia	3 (3·0)	0	0	0	0	0
Peripheral sensory neuropathy	3 (3·0)	0	0	0	0	0
Aphasia	2 (2·0)	0	0	0	0	0
Seizure	2 (2·0)	0	0	0	0	0
Autoimmune neuropathy	1 (1·0)	0	0	0	0	0
Carpal tunnel syndrome	1 (1·0)	0	0	0	0	0
Dizzines	1 (1·0)	0	0	0	0	0
Facial paralysis	1 (1·0)	0	0	0	0	0
Intracranial hemorrhage	1 (1·0)	0	1 (1·0)	0	0	0
Postural dizziness	1 (1·0)	0	0	0	0	0
Tremor	1 (1·0)	0	0	0	0	0
Amnesia	0	0	0	0	1 (5·6)	0
Brain edema	0	0	2 (2·0)	0	0	0
Dysarthria	0	0	0	0	1 (5·6)	0
Lethargy	0	0	0	1 (5·6)	0	0
Partial seizures	0	0	0	0	1 (5·6)	0
Peripheral motor neuropathy	0	1 (1·0)	0	0	0	0
Syncope	0	1 (1·0)	0	0	1 (5·6)	0

Data are n (%). *All treatment-related nervous system adverse events are shown. Listed are events that were reported between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0.

Table S10. Immune-mediated adverse events*

	Asymptomatic (n=101)		Symptomatic (n=18)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Non-endocrine immune-related adverse event				
Pneumonitis	8 (7·9)	3 (3·0)	2 (11·1)	1 (5·6)
Pneumonitis	8 (7·9)	3 (3·0)	2 (11·1)	1 (5·6)
Diarrhoea/colitis	17 (16·8)	9 (8·9)	1 (5·6)	1 (5·6)
Diarrhoea	14 (13·9)	4 (4·0)	1 (5·6)	1 (5·6)
Colitis	6 (5·9)	6 (5·9)	1 (5·6)	1 (5·6)
Hepatitis	23 (22·8)	18 (17·8)	1 (5·6)	1 (5·6)
Increased alanine aminotransferase	17 (16·8)	15 (14·9)	1 (5·6)	1 (5·6)
Increased aspartate aminotransferase	18 (17·8)	10 (9·9)	1 (5·6)	1 (5·6)
Hepatitis acute	1 (1·0)	1 (1·0)	0	0
Immune-mediated hepatitis	2 (2·0)	2 (2·0)	0	0
Hepatotoxicity	1 (1·0)	0	0	0
Hyperbilirubinemia	1 (1·0)	0	0	0
Increased transaminases	1 (1·0)	0	0	0
Increased blood bilirubin	1 (1·0)	0	0	0
Nephritis and renal dysfunction	2 (2·0)	1 (1·0)	1 (5·6)	1 (5·6)
Nephritis	0	0	1 (5·6)	1 (5·6)
Acute kidney injury	1 (0·1)	1 (0·1)	0	0
Immune-mediated nephritis	1 (1·0)	0	0	0
Rash	36 (35·6)	9 (8·9)	7 (38·9)	2 (11·1)
Rash	7 (6·9)	2 (2·0)	2 (11·1)	0
Maculopapular rash	24 (23·8)	7 (6·9)	2 (11·1)	1 (5·6)
Pruritic rash	3 (3·0)	0	2 (11·1)	1 (5·6)
Macular rash	2 (2·0)	1 (1·0)	0	0
Dermatitis acneiform	1 (1·0)	0	1 (5·6)	0
Papular rash	1 (1·0)	0	0	0
Rash Pustular	0	0	1 (5·6)	0
Hypersensitivity	2 (2·0)	0	1 (5·6)	1 (5·6)
Hypersensitivity	2 (2·0)	0	1 (5·6)	1 (5·6)
Endocrine immune-related adverse event				
Adrenal insufficiency	10 (9·9)	4 (4·0)	0	0
Adrenal insufficiency	10 (9·9)	4 (4·0)	0	0
Hypothyroidism/thyroiditis	29 (28·7)	1 (1·0)	2 (11·1)	0
Hypothyroidism	26 (25·7)	1 (1·0)	1 (5·6)	0
Thyroiditis	4 (4·0))	0	1 (5·6)	0
Diabetes mellitus	2 (2·0)	1 (1·0)	0	0
Diabetes mellitus	1 (1·0)	0	0	0
Type 1 diabetes mellitus	1 (1·0)	1 (1·0)	0	0
Hyperthyroidism	14 (13·9)	3 (3·0)	0	0
Hyperthyroidism	14 (13·9)	3 (3·0)	0	0
Hypophysitis	13 (12·9)	7 (6·9)	2 (11·1)	0
Hypophysitis	12 (11·9)	6 (5·9)	2 (11·1)	0
Lymphocytic hypophysitis	1 (1·0)	1 (1·0)	0	0

Data are n (%).*All immune-related adverse events are shown. Listed are events that were reported between the first dose and 100 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0.

Table S11. Treatment-related serious adverse events

	Asymptomatic (n=101)		Symptomatic (n=18)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Treatment-related serious adverse events	34 (33·7)	29 (28·7)	5 (27·8)	4 (22·2)
Colitis	5 (5·0)	5 (5·0)	1 (5·6)	1 (5·6)
Diarrhoea	5 (5·0)	4 (4·0)	1 (5·6)	1 (5·6)
Hypophysitis	5 (5·0)	5 (5·0)	0	0
Increased alanine aminotransferase	5 (5·0)	4 (4·0)	0	0
Increased aspartate aminotransferase	4 (4·0)	4 (4·0)	0	0
Hyperthyroidism	3 (3·0)	3 (3·0)	0	0
Acute kidney injury	2 (2·0)	2 (2·0)	0	0
Adrenal insufficiency	2 (2·0)	2 (2·0)	0	0
Brain oedema	2 (2·0)	2 (2·0)	0	0
Intracranial haemorrhage	2 (2·0)	1 (1·0)	0	0
Nausea	2 (2·0)	2 (2·0)	0	0
Peripheral sensory neuropathy	2 (2·0)	0	0	0
Pneumonitis	2 (2·0)	2 (2·0)	1 (5·6)	0
Pyrexia	2 (2·0)	0	0	0
Vomiting	2 (2·0)	2 (2·0)	0	0
Acute hepatitis	1 (1·0)	1 (1·0)	0	0
Blurred vision	1 (1·0)	0	0	0
Cytokine release syndrome	1 (1·0)	0	0	0
Dehydration	1 (1·0)	1 (1·0)	0	0
Duodenitis	1 (1·0)	1 (1·0)	0	0
Gastritis	1 (1·0)	1 (1·0)	0	0
Headache	1 (1·0)	1 (1·0)	0	0
Hyponatraemia	1 (1·0)	1 (1·0)	0	0
Immune-mediated pancreatitis	1 (1·0)	1 (1·0)	0	0
Increased amylase	1 (1·0)	1 (1·0)	0	0
Increased lipase	1 (1·0)	1 (1·0)	0	0
Influenza like illness	1 (1·0)	1 (1·0)	0	0
Maculopapular rash	1 (1·0)	1 (1·0)	0	0
Myocarditis*	1 (1·0)	0	0	0
Myositis	1 (1·0)	1 (1·0)	0	0
Nephritis	1 (1·0)	0	0	0
Pancreatitis	1 (1·0)	1 (1·0)	0	0
Peripheral motor neuropathy	1 (1·0)	1 (1·0)	0	0
Rhabdomyolysis	1 (1·0)	1 (1·0)	0	0
Seizure	1 (1·0)	0	0	0
Syncope	1 (1·0)	1 (1·0)	0	0
Type 1 diabetes mellitus	1 (1·0)	1 (1·0)	0	0
Warm-type haemolytic anaemia	1 (1·0)	1 (1·0)	0	0
Gastroenteritis	0	0	1 (5·6)	1 (5·6)
Mucosal inflammation	0	0	1 (5·6)	1 (5·6)
Partial seizure	0	0	1 (5·6)	1 (5·6)
Pustular rash	0	0	1 (5·6)	0
Stomatitis	0	0	1 (5·6)	1 (5·6)
Tumour pseudoprogression	0	0	1 (5·6)	1 (5·6)
Upper respiratory tract infection	0	0	1 (5·6)	1 (5·6)

Data are n (%). *All treatment-related serious adverse events are shown. Listed are events that were reported between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0.

Table S12. Late emergent treatment-related adverse events voluntarily reported

	Asymptomatic (n=101)		Symptomatic (n=18)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Late emergent treatment-related adverse events*	4 (4·0)	3 (3·0)	0	0
Increased alanine aminotransferase	1 (1·0)	0	0	0
Increased lipase	1 (1·0)	1 (1·0)	0	0
Drug-induced liver injury	1 (1·0)	1 (1·0)	0	0
Pulmonary embolism	1 (1·0)	1 (1·0)	0	0

Data are n (%). *Listed are events that were voluntarily reported beyond 100 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0.

Figure S1. Patient disposition

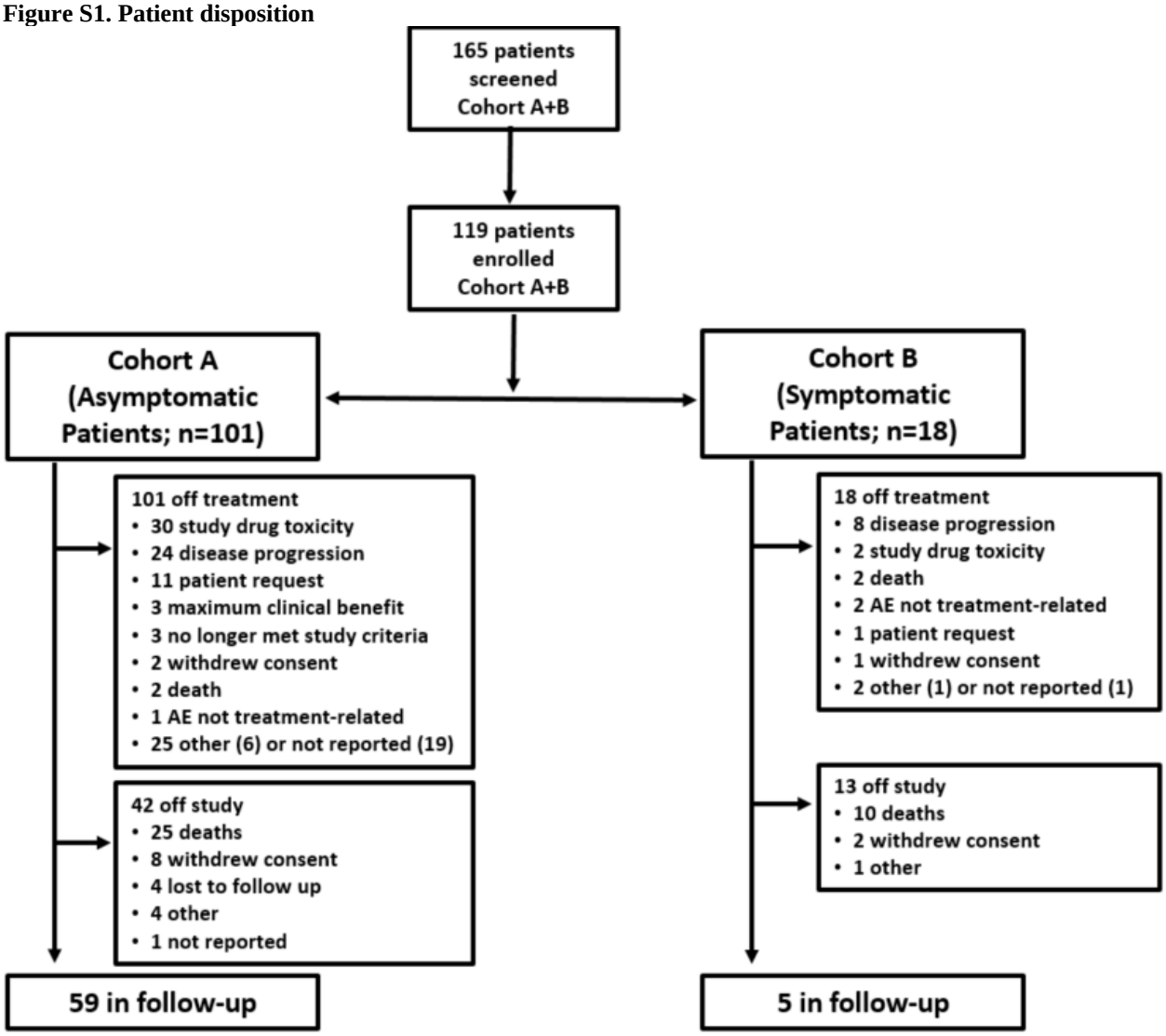


Figure S2. Intracranial tumour burden change from baseline in target lesions from asymptomatic patients per BICR response

BICR=blinded independent central review; IQR=interquartile range. Horizontal dashed line indicates the threshold for a response (30% reduction in tumour burden) by Response Evaluation Criteria in Solid Tumors, version v1.1. Asterisk symbol represents responder; square symbol represents percentage change truncated to 100%. Results obtained in evaluable patients with target lesions at baseline and at least one on-treatment or post-baseline intracranial tumor assessment are shown.

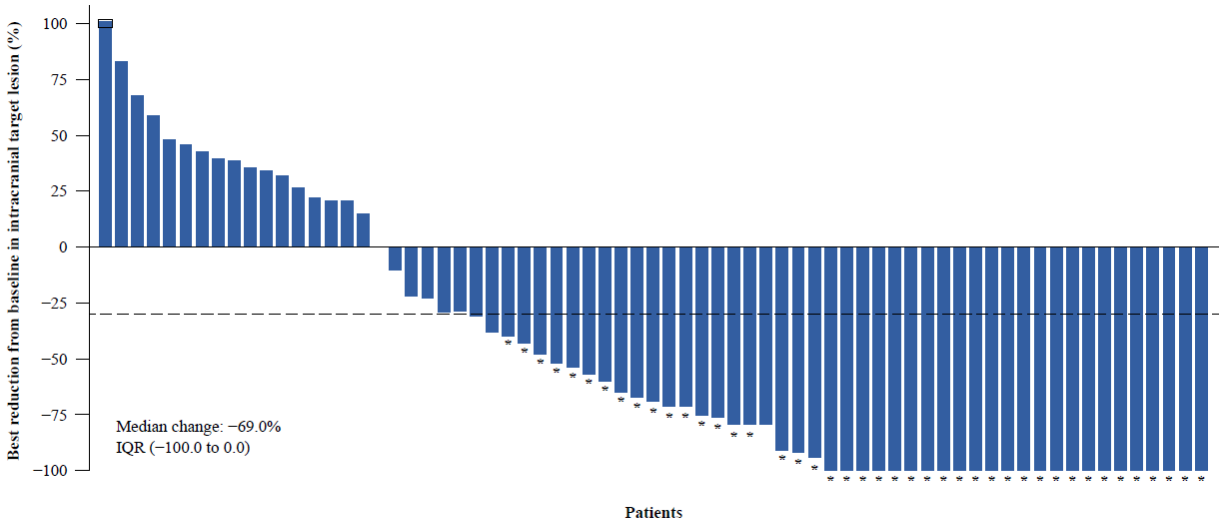


Figure S3. Time to and duration of intracranial response in asymptomatic patients by BICR assessment
BICR=blinded independent central review; CR=complete response; PFS=progression-free survival; PR=partial response· Onset and durability of intracranial objective responses (in patients with these responses) according to modifed Response Evaluation Criteria in Solid Tumors, version 1.1 are shown.

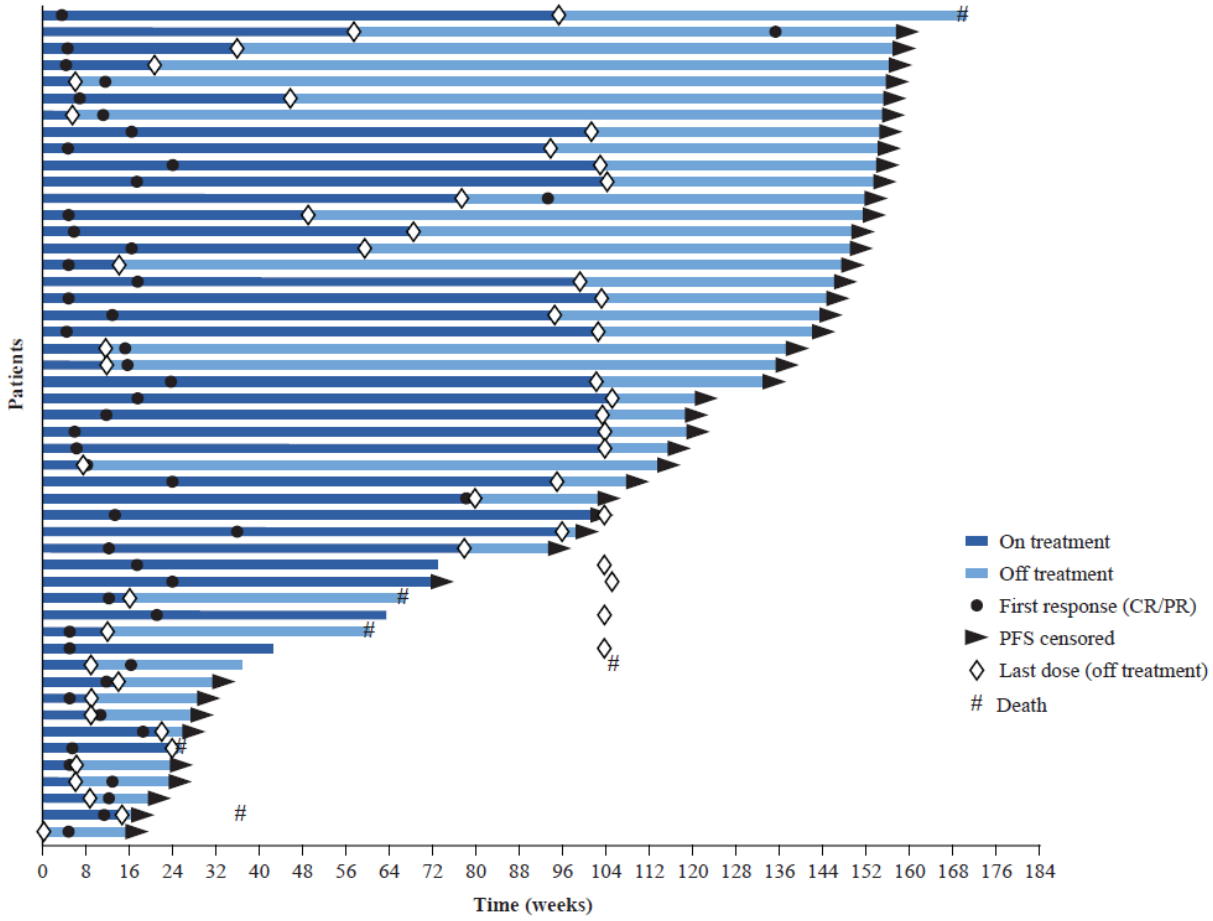


Figure S4. Kaplan-Meier estimates of overall survival in patients with asymptomatic melanoma brain metastases by *BRAF* mutation status

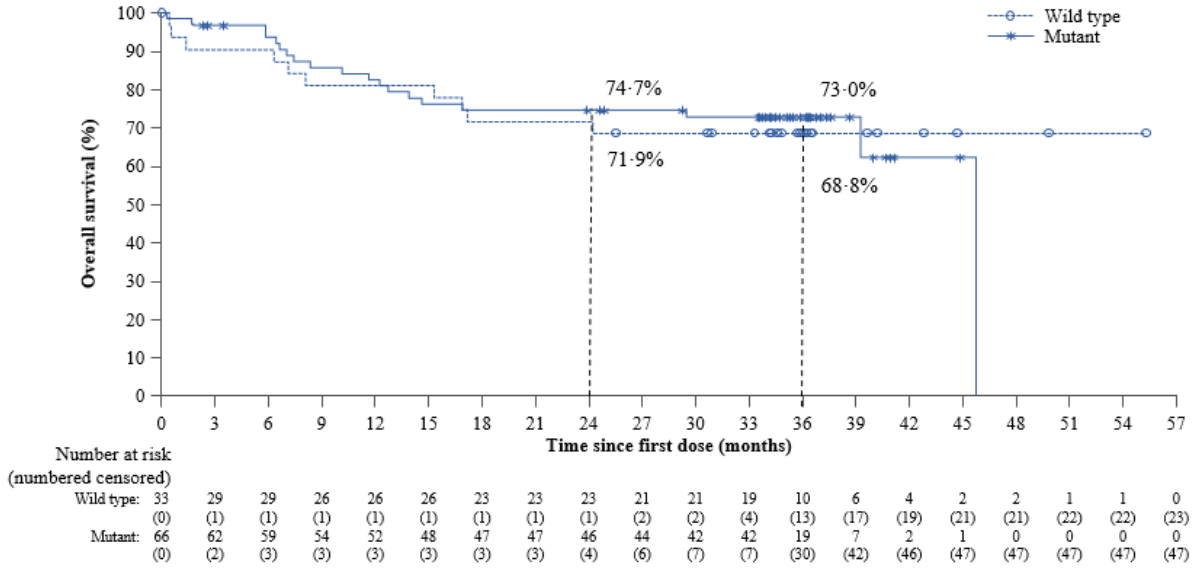
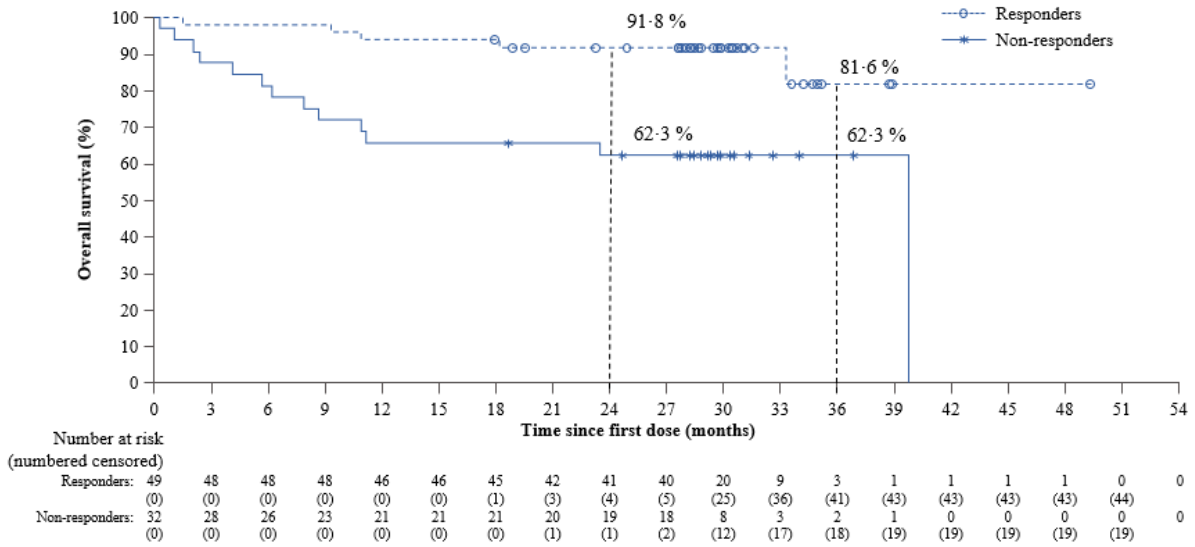


Figure S5. Kaplan-Meier estimates of overall survival in patients with asymptomatic melanoma brain metastases by response status as a 6-month landmark analysis (A) and a 12-week landmark analysis (B)

A. 6-month landmark analysis



B. 12-week landmark analysis

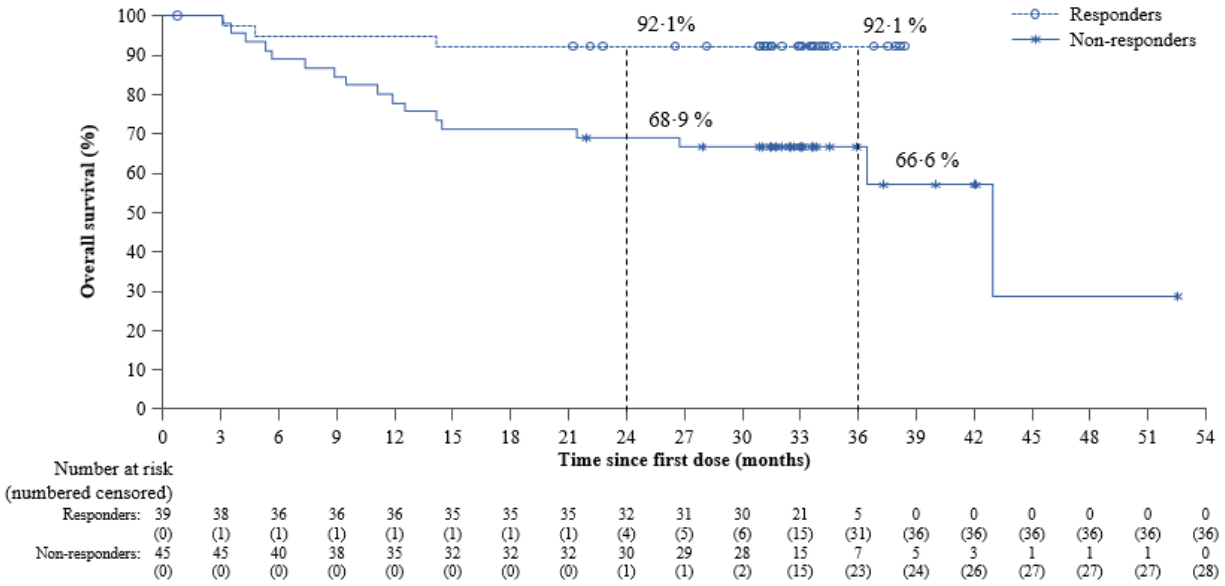


Figure S6. Intracranial tumour burden change from baseline in target lesions from symptomatic patients per BICR assessment

BICR=blinded independent central review; IQR=interquartile range· Horizontal dashed line indicates the threshold for a response (30% reduction in tumour burden) by Response Evaluation Criteria In Solid Tumors, version 1.1. Asterisk symbol represents responder. Results obtained in evaluable patients with target lesions at baseline and at least one on-treatment or post-baseline intracranial tumor assessment are shown.

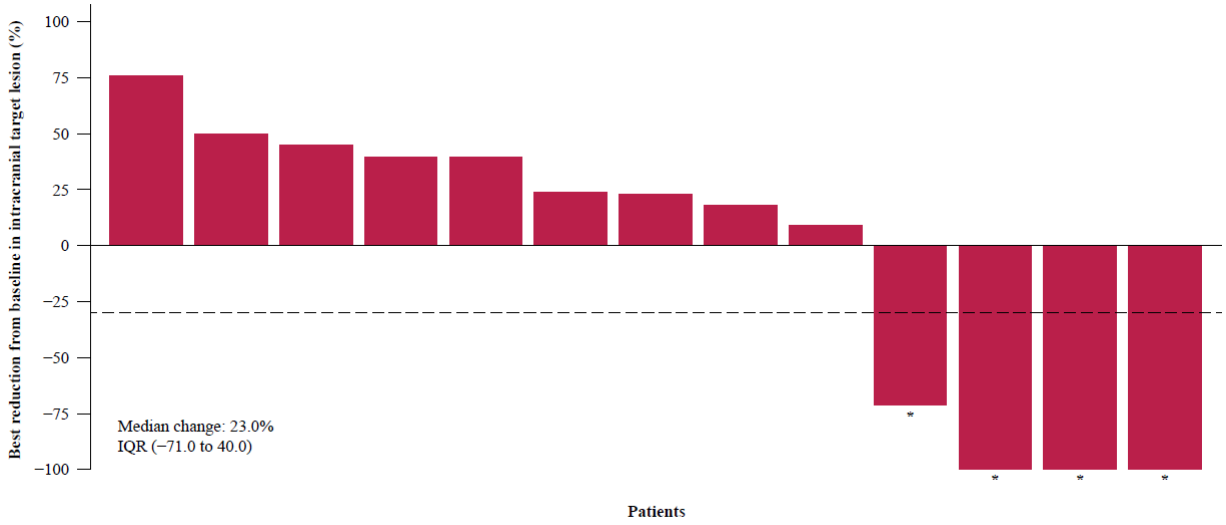


Figure S7. Time to and duration of intracranial response in symptomatic patients by BICR assessment
BICR=blinded independent central review; CR=complete response; PFS=progression-free survival; PR=partial response. Onset and durability of intracranial objective responses (in patients with these responses) according to modifed Response Evaluation Criteria in Solid Tumors, version 1·1 (RECIST v1.1) is shown.

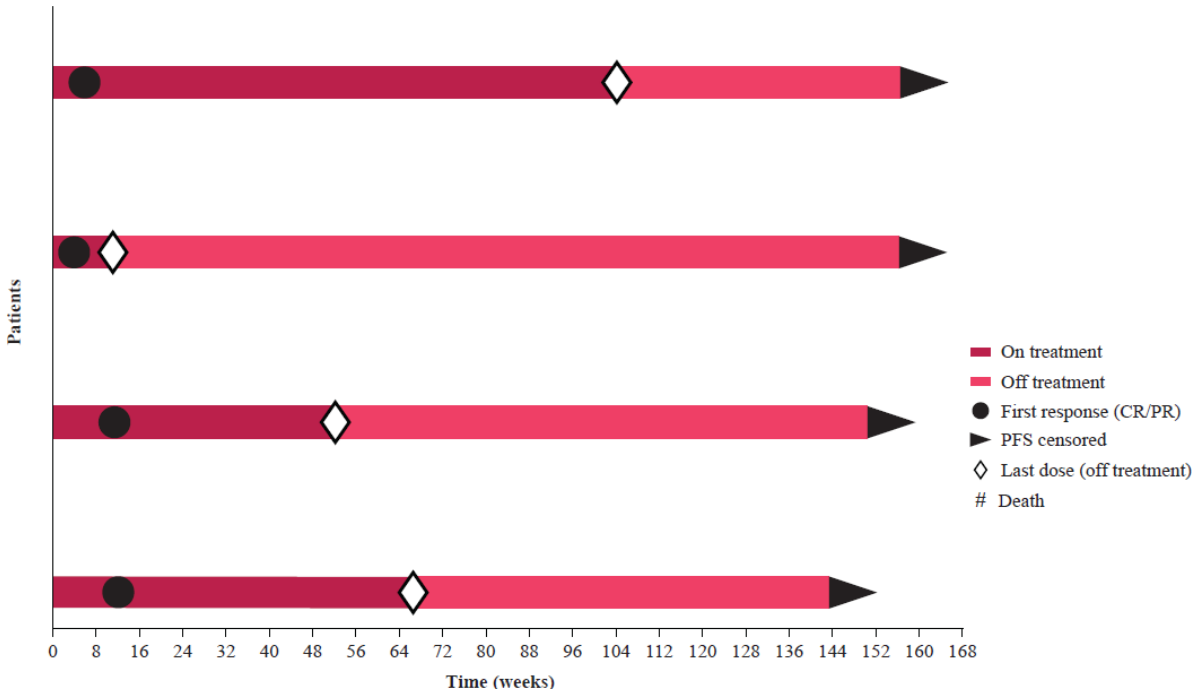
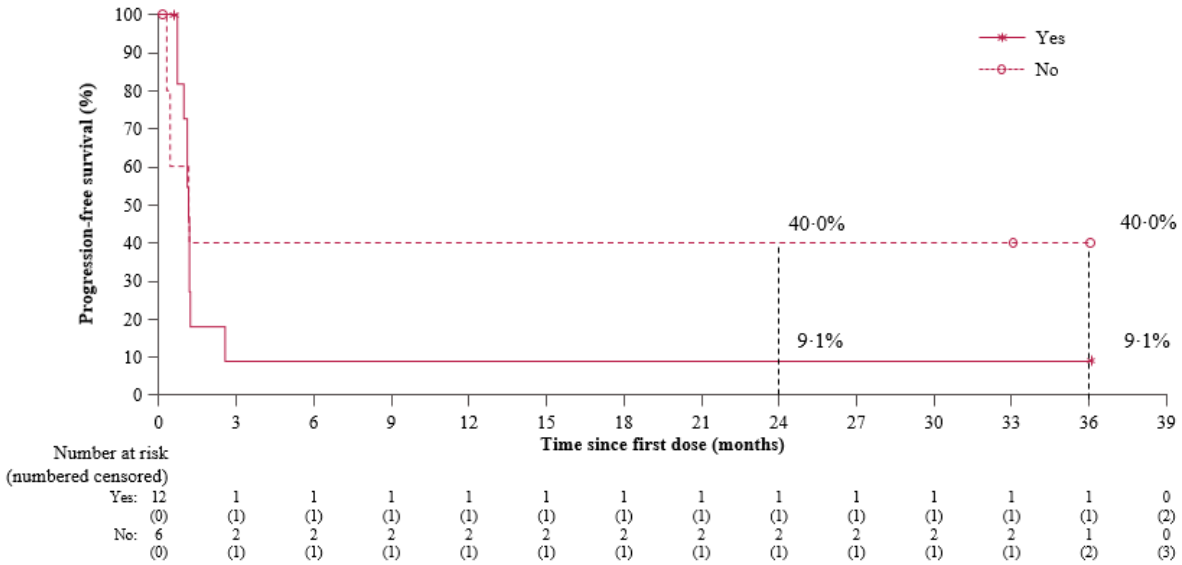
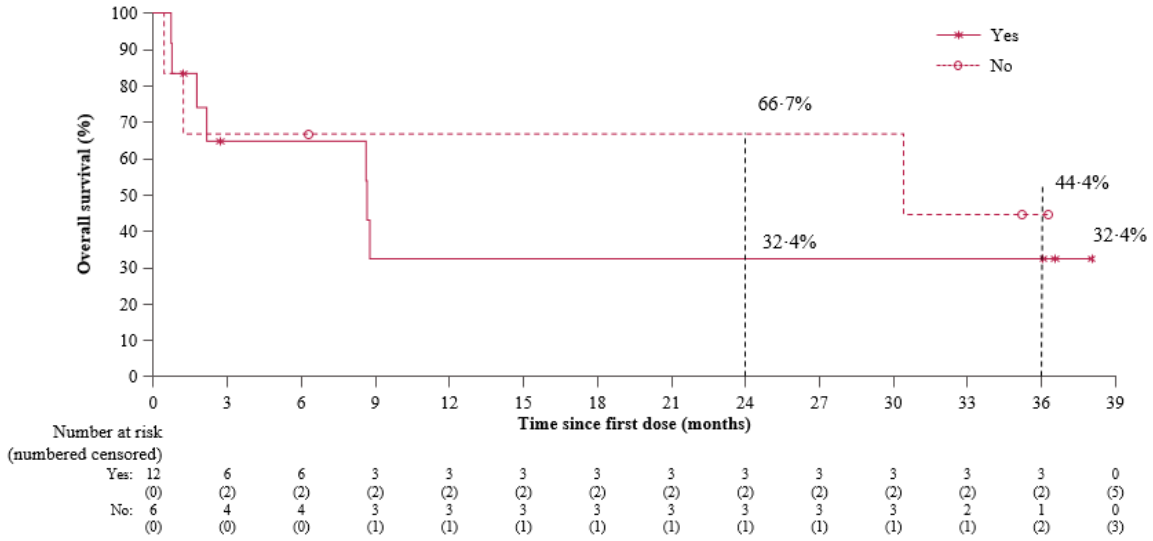


Figure S8. Kaplan-Meier estimates of intracranial progression-free survival (A) and overall survival (B) in patients with symptomatic melanoma brain metastases by baseline dexamethasone use

A. Progression-free survival



B. Overall survival



List of participating investigators

Principal investigator	Study site (study number)	Number of patients enrolled
Peter Forsyth	H· Lee Moffitt Cancer Center and Research Institute - Parent Account, Tampa, FL, USA (13)	18
Hussein Tawbi	MD Anderson Cancer Center-Parent Account, Houston, TX, USA (39)	13
Alain Algazi	University of California - San Francisco-Parent Account, San Francisco, CA, USA (2)	12
Omid Hamid	The Angeles Clinic & Research Institute-Parent Account, Los Angeles, CA, USA (6)	8
Christopher Lao	University of Michigan-Parent Account, Ann Arbor, MI, USA (20)	8
Stergios Moschos	University of North Carolina, Chapel Hill, NC, USA (32)	7
F· Stephen Hodi	Massachusetts General Hospital-Parent Account, Boston, MA, USA (24)	6
Michael Atkins	Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA (3)	5
Karl Lewis	University of Colorado Cancer Center, Aurora, CO, USA (22)	5
F ·Stephen Hodi	Dana-Farber Cancer Institute, Boston, MA, USA (7)	4
Reena Thomas	University of Washington - Seattle Cancer Care Alliance, Seattle, WA, USA (10)	3
Janice Mehnert	Nyu Clinical Cancer Institute, New York, NY, USA (31)	3
Michael Postow	Memorial Sloan-Kettering Cancer Center-Parent Account, New York, NY, USA (33)	3
Warren Chow	City of Hope, Duarte, CA, USA (40)	3
Sekwon Jang	Washington Cancer Inst at MedStar Washington Hospital Center, Washington, DC, USA (8)	2
Kristin Ancell	Vanderbilt University Medical Center - Parent Account, Nashville, TN, USA (12)	2
Asim Ali	St· Luke's Hospital & Health Network, Quakertown, PA, USA (14)	2
Diwakar Davar	University of Pittsburgh Medical Center, Pittsburgh, PA, USA (15)	2
Oleg Gilgich	Mount Sinai Medical Center, Miami Beach, FL, USA (17)	2
F· Stepehn Hodi	Beth Israel Deaconess Medical Center-Parent Account, Boston, MA, USA (23)	2
April Salama	Duke University—Parent Account, Durham, NC, USA (30)	2
Ragini Kudchadkar	Emory University—Parent Account, Atlanta, GA, USA (34)	2
John Glaspy	University of California - Los Angeles-Parent Account, Los Angeles, CA, USA (37)	2
Tara Mitchell	University of Pennsylvania-Parent Account, Philadelphia, PA, USA (38)	2
Ankit Mangla	University Hospitals, Cleveland, OH, USA (21)	1
Manmeet Ahluwalia	Cleveland Clinic, Cleveland, OH, USA (1)	0
Joseph Clark	Loyola University Medical Center, Maywood, IL, USA (4)	0
Amy Weise	Karmanos Cancer Institute, Detroit, MI, USA (16)	0
Suresh Nair	Lehigh Valley Health Network - Parent Account, Allentown, PA, USA (18)	0
Ann Silk	The Cancer Institute of New Jersey, New Brunswick, NJ, USA (25)	0

Principal investigator	Study site (study number)	Number of patients enrolled
Jason Luke	University of Chicago-Parent Account, Chicago, IL, USA (27)	0
Kevin Kim	California Pacific Medical Center, San Francisco, CA, USA (28)	0
Michael Atkins	Weinberg Cancer Institute at Franklin Square, Baltimore, MD, USA (35)	0
Michael Atkins	Washington Cancer Inst at MedStar Washington Hospital Ctr, Washington, DC, USA (36)	0
Kenneth Grossmann	Huntsman Cancer Institute at The Univ· of Utah, Salt Lake City, UT, USA (41)	0
Igor Puzanov	Roswell Park Cancer Institute—Parent Account, Buffalo, NY, USA (42)	0

Protocol Number: CA209204
IND Number: 104,225
Ex-US Non-IND
EUDRACT Number N/A
Date: 22-Sep-2014
Revised Date 13-Nov-2017

Clinical Protocol CA209204

A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy

CheckMate 204: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 204

Revised Protocol Number: 03
Incorporates Administrative Letters 03 and 04

Study Director/Medical Monitor

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390
PPD Safety Hotlines: 1-888-483-7729; 1-800-201-8725

Bristol-Myers Squibb Research and Development
777 Scudders Mill Road
Plainsboro, NJ 08536

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	13-Nov-2017	Major Changes • Addition of progression free survival (PFS) as a secondary objective to align with nivolumab program-wide objectives. • Expansion of secondary and exploratory objectives to align with data reported for this study. • All radiologic images will be transmitted to a centralized imaging core laboratory. Details of the review conducted by an Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter. • Intracranial and extracranial replace brain and systemic, respectively, for protocol-specific references throughout the document.
Administrative Letter 04	10-Jan-2017	Clarification of dosing in study design figure: nivolumab and ipilimumab should be dosed every 3 weeks (Q3) during the Induction Phase of protocol treatment.
Administrative Letter 03	28-Oct-2016	Administrative change: study personnel.
Revised Protocol 02	15-Aug-2016	Incorporates Global Amendment 02
Global Amendment 02	15-Aug-2016	Major Amendment 02 Changes • Eligibility criteria modified to allow a second cohort of symptomatic subjects with melanoma metastatic to the brain as defined in the revised Inclusion/Exclusion Criteria. • Efficacy objectives will be based on Investigator review at the study sites rather than on review at a central facility. All radiologic images will be sent to a centralized imaging core laboratory for storage and potential future central reading. • Exploratory objective to evaluate association between exposure to corticosteroid treatment and efficacy and safety in symptomatic patients in Cohort B. • The second interim analysis has been removed from the study design. • Treatment for all enrolled patients who continue to show response is permitted for up to a maximum of 24 months. • Follow-up period has been extended to 5 years from the date of first treatment. • Clarification added that 1 un-irradiated lesion must remain post stereotactic treatment (SRT) for subjects to remain on study. • Subjects must be re-consented to receive treatment beyond progression • Guideline added for subjects to discontinue treatment beyond progression. • Inclusion criteria updated to include criteria for symptomatic patients. • Minor changes within inclusion criteria for reproduction to comply with study-drug program-wide standard. • Alignment of on-study laboratory assessments. • Statistical section now includes additional analyses by cohort:

Document	Date of Issue	Summary of Change
		Cohort A: asymptomatic subjects (approximate cap of 90) Cohort B: symptomatic subjects who may be on steroids (approximate cap of 20). • Appendix 1, Management Algorithms has been updated. Changes have been made to the Renal, Pulmonary, Hepatic, and Skin Management Algorithms.
Revised Protocol 01	28-Aug-2015	Incorporates Global Amendment and Administrative Letters 01 and 02.
Global Amendment 01	28-Aug-2015	Major Amendment 01 Changes: • Subjects with melanoma metastatic to the brain with and without systemic lesions are now eligible for the study • Prior treatment allowed: BRAF and/or MEK inhibitors for advanced disease • Prior treatment allowed: patients who received ipilimumab as adjuvant therapy must have a 6 month washout before receiving dosing on this study • Modifications to the tumor sample requirements for biomarker analyses in the eligibility criteria, flow chart, and biomarker • Enrolled subjects may receive stereotactic radiation therapy (SRT) (single episode) for progression of up to 3 brain lesions • Brain edema or post SRT steroid treatment specified as ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks • Two interim analyses incorporated into the study design • Steering Committee replaces safety committee • Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) incorporated in response algorithm for brain tumors • Immune-related Response Criteria and the Protocol-defined response criteria have been removed from the study • Subsections in Section 5.4 Efficacy Assessments that also appear in Appendix 3 are now deleted from protocol body • Neurologic Assessment in Neuro-Oncology (NANO) scale added as an assessment of efficacy (exploratory) • Appendix 3 modified to reflect changes made for brain lesions.
Administrative Letter 02	15-Jul-2015	Modified the requirements for pre-treatment tumor tissue within the eligibility criteria. This change allows for submission of archival tumor tissue when an extracranial metastasis tissue specimen collected after the most recent prior systemic therapy is not available or cannot be obtained by biopsy.
Administrative Letter 01	13-Mar-2015	Corrects IND Number for Protocol CA209-204
Original Protocol	22-Sep-2014	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 03

The revisions incorporated into Revised Protocol 03 were made to align the study objectives with those of the Sponsor's nivolumab program by the addition of progression-free survival (PFS) as a secondary objective and to align the secondary and exploratory objectives with data reported for this study. An adjustment to 3 years from 5 years has been incorporated for the time subjects will be followed after the date of first treatment. In addition, all radiologic images will be transmitted to a centralized imaging core laboratory; the details of the independent review performed by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

Revisions to the tumor assessment text of the Time Events schedules were incorporated for clarification only. Throughout the document, intracranial and extracranial replace brain and systemic, respectively, for protocol-specific references.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Title Page	Update of study personnel	Change in Medical Monitor/Study Director
Throughout the protocol	• Intracranial and extracranial replace brain and systemic, respectively, for protocol-specific references throughout the document.	Align with therapeutic area standard nomenclature.
• Synopsis, Objectives, Primary, Secondary, Exploratory • Synopsis, Study Assessments • Synopsis, Statistical Considerations, Efficacy Analyses • Section 1.3.2 Secondary Objectives • Section 1.3.3 Exploratory Objectives • Section 8.3.1.1 Best Overall Response (BOR) per Subject. Endpoint Definitions	• Addition of progression-free survival (PFS) as a secondary objective • Secondary and exploratory efficacy objectives have been expanded. Definitions for new objectives have been included. • Sensitivity analyses using IRRC-assessed Clinical Benefit Rate (CBR) and Overall Response Rate (ORR) will also be performed.	To align the objectives of study CA209204 with nivolumab program-wide objectives and with data reported for this study

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 8.4.2 Secondary Endpoints • Section 8.4.3 Exploratory Endpoints (s) • Section 8.5.2 Primary Efficacy Analyses • Section 8.5.3 Secondary Efficacy Analyses • Section 8.5.4 Exploratory Efficacy Analyses		
• Synopsis, Study Design and Figure; • Section 3.1 Study Design and Duration; Figure 3.1-1 CA209204 Study Design	• Subjects will be followed for 3 years after first treatment rather than for 5 years	Alignment with nivolumab program standard.
• Synopsis, Study Assessments • Section 3.1 Study Design and Duration • Section 5.8 Results of Central Assessments	• Central review of all images will be conducted by an Independent Radiologic Review Committee (IRRC) specified in the Imaging Review Charter.	Central review by an IRRC will be conducted as part of this study.
• Section 3.1 Study Design	• The following three sections were added: Section 3.1.1, Screening Phase; Section 3.1.2, Treatment Phase; Section 3.1.3 Follow-up Phase.	Added sections align text with Time and Events Schedule.
• Section 4.5.2, Dose Delay Criteria	• Sentence added to specify that tumor assessments are to be conducted per protocol even if a dose is delayed	Clarification for the sites: a dose delay should not preclude subjects from tumor assessment per protocol.
• Section 4.5.7 Treatment Beyond Initial Radiological Assessment of Disease Progression	• Revision of description of treatment beyond progression. • Progression of disease should be verified in cases where progression is	Clarification: Due to the delayed kinetics of response with immunotherapy, an increase in tumor size may be due to T-lymphocyte infiltration.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 5.4.3 Confirmation of Scans	equivocal.	
• Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-2 On-study Assessments Cycles 1 and 2 (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-3 On-study Assessments Cycles 1 and 2 (CA209204)	• A note in the table header now specifies that tumor assessments are to be conducted per protocol even if a dose is delayed. The footnote regarding dose delay and study assessments has been removed.	Clarification for the sites: a dose delay should not preclude subjects from tumor assessment per protocol.
• Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-1 Screening Assessments (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-1 On-study Assessments Cycles 1 and 2 (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-3 On-study Assessments Cycle 3 and Beyond (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-4 Follow-up Assessments (CA209204)	• Presentation of Tumor Assessment aligned to program-wide standards. No content change.	Clarification only
• Section 5.4 Efficacy Assessments	• Revised to align with Schedule of Activities. No content change.	Clarification only.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 8.5.9, Interim Analyses	• Revised based on results of interim analyses.	Updated to reflect current study status.
Appendix 3: Image Assessment Criteria 1.1: Measurability of tumor	Required thickness of MRI scan slice for intracranial lesions ≤10 mm LD and >10 mm LD are now specified in second bullet.	Revised to include specifications for all intracranial lesions.
Throughout the document.	Minor editorial or formatting changes/corrections	Minor, no content change.

SYNOPSIS

Clinical Protocol CA209204

Protocol Title: A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy CheckMate 204: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 204

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Nivolumab administered IV over 60 minutes at 1 mg/kg and ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses (combination regimen) followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or discontinuation due to toxicity

Study Phase: Phase 2

Research Hypothesis: Treatment with nivolumab combined with ipilimumab followed by nivolumab monotherapy will provide clinical benefit to subjects with melanoma metastatic to the brain.

Objectives:

Study objectives will be applied for all treated subjects (Cohort A and Cohort B).

Primary, secondary, and exploratory efficacy endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Primary Objective: To assess intracranial clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD]) $\geq$ 6 months in subjects with melanoma metastatic to the brain per modified RECIST 1.1 criteria.

Secondary Objectives:

- To assess the extracranial clinical benefit rate defined as CR+PR+SD $\geq$ 6 months (per RECIST 1.1 criteria)
- To assess intracranial objective response rate (ORR), intracranial progression-free survival (PFS) per modified RECIST 1.1 criteria
- To assess extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- To assess global CBR, global ORR, global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess overall survival (OS)
- To evaluate the intracranial-specific safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry, or on study.

Exploratory Objectives

- To assess intracranial time to objective response (TTR) and intracranial duration of response (DOR) per investigator per modified RECIST 1.1 criteria
- To assess extracranial TTR and DOR per modified RECIST 1.1 criteria
- To assess global TTR and DOR per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess efficacy using Neurologic Assessment in Neuro-Oncology (NANO) scale
- To evaluate the overall safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry, or on study
- To evaluate association between dexamethasone (or equivalent) exposure and treatment effects in symptomatic patients treated with corticosteroids (Cohort B patients).

- To evaluate association between baseline pathologic features of primary cutaneous melanoma (eg, regression, ulceration, pattern and components of immune infiltrate) and CBR endpoints
- To explore potential biomarkers associated with clinical response to nivolumab combined with ipilimumab by analyzing tumor tissue specimens for proteins including, but not limited to PD-1, PD-L1, and other markers related to immune cell populations involved in regulating immune responses in comparison to clinical outcomes
- To evaluate association between BRAF/NRAS mutation status and response endpoints
- To compare tissue biomarker profiles between paired tissues from extracranial and intracranial metastases from individual patients, where available; if possible this analysis will also be applied for sample sets that include a primary, a extracranial metastasis and a intracranial metastasis from the same patient
- To assess peripheral blood immune cell subpopulations (which may include but is not limited to CD4+ T-cell, CD8+ T-cell, Treg, NK, B-cell, MDSC, activated T-cells, memory/exhausted T-cells) and serum soluble factors with changes in post-treatment profiles as they relate to clinical endpoints and/or the occurrence of adverse events
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the occurrence of adverse events
- To estimate the incidence of MRI-defined intracranial edema, hemorrhage and increase in tumor size before regression (pseudoprogression) in the intracranial metastases and to evaluate any association with the onset and/or clinical benefit rate (CR+ PR+SD $\geq$6 mo.) observed in the intracranial or non-CNS
- To compare computer-assisted tumor volume from three dimensional (3D) MRI to bi-dimensional measures with respect to absolute values and percent change from baseline.

Study Design: This is an open-label, multi-site, Phase 2 study of nivolumab combined with ipilimumab followed by nivolumab monotherapy for the treatment of subjects with melanoma metastatic to the brain.

Cohort A comprises subjects with histologically-confirmed malignant melanoma with asymptomatic intracranial metastases with or without measurable extracranial disease. Per Amendment 02, August 2016, the patient population was expanded to include Cohort B, which will enroll approximately 20 patients with symptomatic intracranial metastases who may be on steroids per protocol specifications. Symptomatic patients who are not on steroids are also eligible for Cohort B.

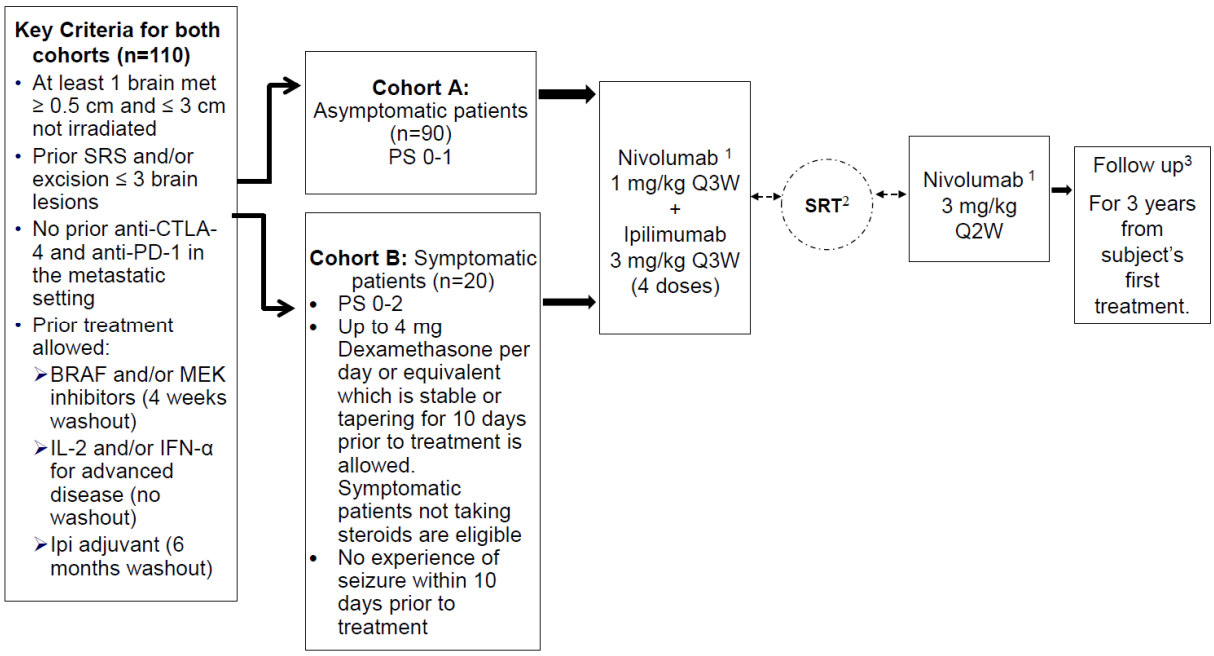
Asymptomatic subject who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.

All patients will be treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W (4 doses), followed by nivolumab monotherapy (3 mg/kg Q2W) for a maximum of 24 months, or until progression or unacceptable toxicity. The study will close after the last enrolled subject completes 3 years of follow up from the date of first treatment or the study is discontinued by the sponsor.

At any time, if the safety profile of an enrolled subject suggests an unfavorable risk/benefit profile, a decision will be made by the sponsor in conjunction with the investigators whether to pause or continue enrollment. The steering committee will be informed if a safety signal emerges and will be informed of the results of the planned interim analysis.

The use of SRT (single episode) for disease progression of $\leq$ 3 intracranial lesions is permitted in this study per protocol-defined guidelines. Any subject who receives SRT while on study will be observed for a protocol-defined period before treatment with the study drug(s) can be resumed. The length of the observation period is determined by when in the course of treatment the subject receives SRT - during induction (nivolumab plus ipilimumab) or during maintenance treatment (nivolumab monotherapy). NOTE: To continue on-study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

Any subject who meets criteria for discontinuation following SRT will proceed to follow-up. All subjects who have completed 24 months of treatment with study drugs, or have been discontinued from treatment will continue to be followed for safety, progression, and overall survival for up to 3 years from the date of the subject's first treatment.



SRT = stereotactic radiotherapy

[1] Subjects may continue to receive on study treatment for a maximum of 24 months or until confirmed progression or unacceptable toxicity or patient withdrawal of consent. After discontinuation from treatment with study drug(s) subjects will proceed to follow-up. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply or under appropriate care per investigator.

[2] Use of SRT for progression of ≤ 3 intracranial lesions will be allowed per protocol-specific guidelines. Subjects who require SRT for a second episode of disease progression will be discontinued from treatment and proceed to follow-up.

[3] All subjects who are discontinued from treatment with study drug(s) or have received the maximum of 24 months of treatment will proceed to follow-up.

Study Population:

Cohort A (asymptomatic) Patients with histologically confirmed metastatic melanoma presenting with intracranial metastases and at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

Approximate enrollment in Cohort A is 90 patients.

Cohort B (symptomatic): Patients with histologically confirmed metastatic melanoma presenting with symptomatic intracranial metastases who may be on steroids with doses no higher than a total daily dose of 4 mg of dexamethasone or equivalent that is stable or tapering within 10 days prior to treatment. Patients who are symptomatic and are not being treated with steroids are also eligible. Patients enrolled in Cohort B must have at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated, must not require immediate local therapy (SRT or surgery within 3 weeks prior to first treatment), performance status must be 0-2, and no experience of seizure within 10 days prior to first treatment.

Subjects with a history of whole brain irradiation are not eligible for this study.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drugs for CA209204		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP

Study Assessments: Response to treatment will be assessed in the intracranial and extracranial compartments and will be evaluated by serial radiographic assessment every 6 weeks for the first year and every 12 weeks thereafter until documented progression, withdrawal of consent, or the end of the study.

All efficacy objectives, including the primary efficacy objective, intracranial clinical benefit rate (CBR), defined as CR + PR + SD $\geq$ 6 months per the modified RECIST 1.1 criteria, will be based on Investigator assessment. Extracranial response will be based on RECIST 1.1. Global (intracranial plus extracranial) tumor burden response assessment will be assessed per a combination of modified RECIST 1.1 for intracranial lesions and RECIST 1.1 for extracranial disease per the modified RECIST 1.1 criteria, also Investigator evaluated. Secondary and exploratory objectives include responses in all compartments as specified above. In addition, 3-D MRI will be conducted and may be evaluated for exploratory study. All images will be evaluated at the site. As an exploratory objective, efficacy will also be assessed with the NANO scale for neurologic function.

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review performed by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 4.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. Clinical decisions to continue or hold/discontinue therapy will be based on the judgment of the treating physician/principal investigator.

Exploratory biomarker assessments are included to evaluate associations with clinical endpoints, safety and tolerability, as well as for the identification of potential predictive markers for future studies or practice.

Statistical Considerations:

Sample Size: The sample size for the combination treatment of nivolumab plus ipilimumab is 110 subjects:

Cohort A: 90 patients (asymptomatic as defined under Study Population)
Cohort B: 20 patients (symptomatic as defined under Study Population)

All treated patients in Cohort A and Cohort B will contribute to the efficacy assessments. The planned sample size ensures that the maximum width of the exact 90% CI for any given CBR estimate does not exceed 18%.

A sample size of 110 achieves 80.4% power to detect an improvement of about 12% over the estimated CBR for non-investigational immunotherapies in similar patients, estimated to be about 40% or lower.

Endpoints: The primary efficacy endpoint is the intracranial clinical benefit rate (CBR, defined as CR + PR + SD $\geq$ 6 months) in subjects with malignant melanoma metastatic to the brain, treated with nivolumab combined with ipilimumab therapy.

Analyses: The analyses of primary, secondary, and exploratory efficacy endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Demographics and Baseline Characteristics: Demographic and baseline characteristics will be summarized using descriptive statistics for all treated subjects. Patients will be categorized into 4 subgroups according to their SRT status (prior to study with or without SRT and on study with or without SRT) and by cohorts (asymptomatic and symptomatic). The number of enrolled subjects will be summarized. Summarization will be provided for treated

subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Efficacy Analyses: All of the efficacy analyses will be summarized for the 4 subgroups (prior to study - with or without SRT and on study with or without SRT), for the overall group and by cohorts (asymptomatic and symptomatic).

The primary endpoint of intracranial CBR for the overall population, with its corresponding 90% exact confidence interval (CI) will be calculated by the Clopper-Pearson method. A sensitivity analysis using IRRC-assessed intracranial CBR will also be performed.

Secondary endpoints are as follows:

- Intracranial ORR and intracranial PFS per modified RECIST 1.1 criteria;
- Extracranial CBR, extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- Global (intracranial +extracranial) CBR, global ORR, and global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- Overall survival (OS).
- Safety and tolerability will be measured by the incidence of adverse events (AE), serious adverse events (SAE), deaths, and laboratory abnormalities.

Progression-free survival (PFS) is defined as the time between the date of first dose of study drug and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose of study drug. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Overall response rate (ORR) is defined as the number of subjects who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects.

The BOR is defined as the best response designation recorded between the date of first study dosing date and the date of progression, or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. In this study, BOR is specified for the intracranial, extracranial, and global compartments based on the (1) modified RECIST 1.1 criteria (intracranial), (2) RECIST 1.1 criteria (extracranial), (3) combination of modified RECIST 1.1 criteria and RECIST 1.1 criteria (global). The BOR for each patient as determined by the IRRC is determined from a predefined set of rules specified within the Image Review Charter.

Median overall survival (OS) will be estimated using the Kaplan-Meier product-limit method. Overall survival curves will be plotted using the Kaplan-Meier method. The incidence of MRI-defined intracranial edema, hemorrhage, and increase in size before achievement of clinical benefit (pseudoprogression) in the intracranial metastases and any association with efficacy endpoints observed in the intracranial or extracranial compartment will be summarized by MRI-defined group (eg, edema, hemorrhage, pseudoprogression). If necessary, a comparison will be made between the MRI-defined event group and non-event group (eg presence of edema vs no edema).

Data for exploratory objectives will be summarized.

The exploratory endpoints include:

- intracranial time to objective response (TTR) and intracranial duration of response (DOR) per investigator per modified RECIST 1.1 criteria;
- extracranial TTR and DOR per modified RECIST 1.1 criteria;
- global TTR and DOR per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease

Duration of response (DOR) is defined as the time between the date of first response to the date of first documented tumor progression (per modified RECIST 1.1 and/or RECISIT 1.1) or death due to any cause. Subjects who neither progress nor die are censored on the date of their last tumor assessment.

Time to response (TTR) is defined as the time from the first study dose date to the date of the first documented CR or PR.

DOR and TTR are evaluated for responders (CR or PR) only.

Detailed analysis plans will be described in the statistical analysis plan in a separate document.

For the secondary and exploratory efficacy analyses - CBR (extracranial and global) and ORR (intracranial, extracranial, and global) and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method. BOR will be tabulated. Time to event distributions (ie, PFS, OS, TTR, and DOR) will be estimated using Kaplan Meier methodology. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (eg, OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

In addition, sensitivity analyses using IRRC-assessed CBR (extracranial and global) and ORR (intracranial, extracranial, and global) will also be performed.

Exploratory analysis will be conducted to assess potential association between dexamethasone exposure and treatment effect in symptomatic subjects treated with corticosteroids. Intracranial CBR, extracranial CBR, and global CBR will be summarized descriptively by subjects on study with or without receipt of dexamethasone.

Safety Analyses: Safety analyses will be summarized in all treated subjects by subgroup (prior to study with or without SRT and on study with or without SRT), overall and by cohorts (asymptomatic and symptomatic subjects). Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All treatment-emergent adverse events (AEs), drug-related AEs, serious adverse events (SAEs) and drug-related SAEs will be tabulated using worst grade per NCI CTCAE by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE criteria.

Biomarker Analyses: In general, for the exploratory analysis of biomarkers, a logistic model will be used to explore its predicting effect for CBR. If the marker(s) is assessed for its impact on the outcome of OS, a Cox proportional hazards model will be used. For example, to evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model will be used to compare PD-L1 expression (positive vs negative) for effect on the OS endpoint. Additionally, OS will be analyzed within each PD-L1 expression subgroup (positive and negative) including log-rank tests and hazard ratios with corresponding confidence intervals. OS curves and medians will be estimated using Kaplan-Meier methodology. These analyses will be descriptive and not adjusted for multiplicity.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

This is a Phase 2, multi-site, open-label study of nivolumab in combination with ipilimumab followed by nivolumab monotherapy in subjects with melanoma metastatic to the brain who are asymptomatic. As of Amendment 02 [August 2016] subjects with symptomatic melanoma metastatic to the brain per protocol defined inclusion guidelines (Section 3.3) are also eligible for enrollment.

This is the first trial to evaluate the safety and efficacy of nivolumab and ipilimumab as a combination treatment followed by nivolumab monotherapy in this patient population. Current standard of care for progressing melanoma intracranial metastases includes the use of stereotactic radiotherapy (SRT), and it is anticipated that ~50% of patients who are eligible for this study will have had prior treatment with SRT. Planned ongoing safety assessments will regularly monitor all patients for neurologic safety while on study treatment.

The doses and schedule proposed for this study are in alignment with those used for the registrational Phase 3, randomized, double-blind study (CA209067) in subjects with previously untreated unresectable or metastatic melanoma. Immunologic and molecular features of the tumor and host will be explored in the correlative analyses to this trial, in anticipation of identifying biomarkers predictive of benefit for future patient selection and management. This will include an analysis of PD-L1 expression using the Sponsor's assay as well as a number of other biomarkers potentially associated with clinical benefit from these immunotherapies.

The study will evaluate the combination treatment of nivolumab plus ipilimumab followed by nivolumab monotherapy in asymptomatic patients and symptomatic patients who cannot be cured with surgery, stereotactic radiotherapy or other systemic therapy and will provide essential information on the use of SRT concurrent with the combination regimen in this patient population. Subjects who have received prior treatment with BRAF inhibitors and/or MEK inhibitors or ipilimumab in the adjuvant setting are eligible for the study. Results of this study will impact the treatment of patients with melanoma metastatic to the brain and define characteristics of these patients overall, as well as those associated with their brain metastasis management.

1.1 Study Rationale

1.1.1 Disease Background

Cutaneous malignant melanoma is the most aggressive form of skin cancer, accounting for the large majority of skin cancer-related deaths. The global incidence continues to rise, with current estimates of 132,000 new diagnoses/year and 37,000 deaths.[1] Melanoma accounts for ~5% of all new cases of cancer in the United States (US). The incidence of melanoma continues to rise by almost 3% per year in the US, with 2014 estimates of 76,100 new diagnoses and 9,710 deaths. According to NCI Surveillance Epidemiology and End Results (SEER) data from 1975-2007, the five-year survival rate is 15% for late-stage disease.[2] The lifetime risk of developing invasive melanoma has been dramatically increasing, and the overall mortality from melanoma continues to rise.[3,4,5]

Brain metastasis develops in ~50% of subjects with metastatic melanoma; in 10 - 40% of these subjects, the brain is the first site of relapse. Progressive disease in the brain is the major cause of tumor-related death in subjects with melanoma who develop metastases in this site.[6] The median survival is 4 months after diagnosis.[7] The limited activity of available agents, along with relative resistance to radiotherapy and poor central nervous system (CNS) penetration of most chemotherapeutic agents, make this one of the most daunting problems in oncology.[8]

There is no optimal systemic or local therapy for melanoma metastatic to the brain. Therapy for small, single lesions or a limited number of metastases consists of surgery or stereotactic radiotherapy (SRT), with a moderate local control rate but a high incidence of new lesions that are neither prevented by nor responsive to whole brain radiation. Temozolomide, a drug with very high CNS penetration, has been studied in this setting but has a response rate of <10% in both the CNS and overall, so it contributes little benefit and has no apparent synergy with radiotherapy.[6,9,10,11] Combining any of these approaches with whole brain irradiation has been of little value in the management of these subjects.[12] While antibodies are not believed to cross an intact blood-brain barrier, activated T-cells may be able to penetrate the blood brain barrier, providing a rationale for testing immunomodulatory therapies in this setting.[13,14] Previously reported results from the Phase 2 study (CA184042) of ipilimumab monotherapy (presented in detail in Section 1.4.4) showed similar clinical benefit in the brain and systemically, with durable disease control of 24% (CNS) and 27% (extra-cranial) of these patients, providing a rationale for further study of promising immunotherapies in melanoma patients with brain metastases.[15] Similarly, ipilimumab combined with fotemustine was associated with a disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) of 50% (10/20) in patients with asymptomatic brain metastases in a Phase 2 trial (NIBIT-M1).[16] In a Phase 1 dose escalation study (CA209004), the combination of nivolumab and ipilimumab was studied in subjects with unresectable or metastatic melanoma. An objective response rate of 53% was observed when patients were treated with the combination regimen (ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks x 4); an additional benefit of prolonged stable disease or minor response occurred in another ~20% of patients.[17] Since brain metastases in melanoma are the most frequent cause of death from this disease and the brain is a frequent site of failure even in subjects who achieve control of extra-cranial disease with systemic therapy, it is essential to discover whether the combination of ipilimumab plus nivolumab can provide similar promise to patients whose melanoma has metastasized to the brain.

1.1.2 Overall Study Design

Given the limited survival of patients with melanoma metastatic to the brain, the primary goal of this study is to evaluate clinical benefit defined in a similar fashion as has been described in other studies of immune checkpoint blockade using a modified form of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for intracranial lesions (considered measurable disease if the longest diameters of up to 5 intracranial lesions is each at least 5mm), and RECIST 1.1 for extracranial disease (10 mm for measurable non-nodal lesions and 15 mm SA for nodal lesion). (Appendix 3).

Stereotactic radiation therapy (SRT) for clinically-significant, definitively-progressing lesions is standard of care in this patient population. Patients with a single episode of disease progression may receive SRT (single episode) to treat up to 3 lesions, per protocol-defined guidelines (Section 3.4.2.2). Treatment with the study drugs can resume after a protocol defined period, which includes the completion of a steroid taper (≤ 16 mg dexamethasone PO daily tapered over ≤ 4 weeks). Subjects treated with SRT are to be observed for neurotoxicity for a recommended period of time after treatment is resumed (Section 3.4.2.2).

The Steering Committee was created and is composed of a core group of study investigators who are experts in treating patients with melanoma brain metastases along with sponsor physicians/ study staff (Section 7). After review of the available safety and tolerability data from the interim analyses, the Steering Committee can recommend continuation, modification or termination of the study.

The combination induction regimen of nivolumab and ipilimumab followed by nivolumab maintenance monotherapy proposed for this study is based on safety and tolerability data from the use of nivolumab and ipilimumab in systemic metastatic melanoma and other tumor types (Section 1.4.3), and the proposed treatment regimen is expected to be tolerable in subjects with melanoma metastatic to the brain. To assess safety and tolerability as well as efficacy, an interim analyses was conducted after 20 subjects completed induction treatment or were discontinued due to an AE or progression after treatment with at least 1 dose of combination treatment.

After the interim safety analysis was conducted by the steering committee, the combination was determined to be safe in patients with asymptomatic untreated melanoma intracranial metastases. Per Amendment 02 (August 2016), the patient population was expanded to include Cohort B which will enroll approximately 20 patients with symptomatic intracranial metastases who may be on steroids at a total daily dose of no higher than 4 mg of dexamethasone or equivalent that is stable or tapering for 10 days prior to first treatment, have no immediate need for SRT or surgery (within 3 week prior to first treatment), have a performance status of 0-2, and have had no experience of seizure within 10 days prior to first treatment. Symptomatic patients who are not being treated with steroids for CNS symptoms are eligible for Cohort B.

1.1.2.1 Rationale for Cohort B: Addition of Symptomatic Patients

The purpose of including this population is to explore the safety of the combination of nivolumab and ipilimumab in a real-world clinical setting, as a significant number of patients present with central nervous system symptoms that may not preclude benefit from the combination. Of note, the use of steroids can theoretically impede the benefit of immunotherapy, but this therapy is often required in this patient population. A low dose of steroids may be necessary at the time of initiation of therapy but may be low enough not to impact the efficacy of this potent immunotherapy combination. Symptomatic patients who are not being treated with steroids for CNS symptoms are eligible for Cohort B.

1.1.2.2 Rationale for Clinical Benefit Rate as Primary Endpoint

Approximately 50% of patients with metastatic melanoma will develop brain metastases. The median OS in these patients is short, at approximately 4 months. Cytotoxic therapies have been

associated with low response rates in the brain (~6 %).[18] A recent trial of ipilimumab (CA184042) showed a CNS disease control rate (CR + PR + SD > 3 months) of 24%, a rate similar to that observed in systemic disease.[15] The observed extended 24-month survival of 26% supported clinical benefit of this immunotherapy in the brain metastases melanoma population, as has been demonstrated in patients with systemic disease.

For the present study, the primary endpoint of clinical benefit rate (CBR) (CR + PR + SD ≥ 6 months) was selected based on its clinical relevance in this patient population and as such, its potential to inform medical practice. Given the potential for disease control with immunotherapy as demonstrated with ipilimumab monotherapy and the increased response rate observed with combined nivolumab and ipilimumab in Phase 1 data, an optimal primary endpoint would capture both objective response and durable stable disease that is meaningfully longer than the median OS of 7-10 months that is characteristic of the asymptomatic brain metastasis population to be studied in this trial. The CBR as defined for this protocol meets these criteria. Durable stable disease of 6 months is clinically meaningful in these patients.

1.1.2.3 Rationale for Response Algorithms and NANO Scale

Subjects with multiple small brain metastases are representative of the metastatic melanoma population. To ensure meaningful response assessment to these small, frequently sub-centimeter, lesions and to allow data generated from this study to be evaluated within the growing body of data for immuno-oncology agents[19] a modified RECIST assessment will be used to assess intracranial lesions. This modified assessment criteria will allow measurement for ≤ five intracranial target lesions (between 5 mm and 30 mm in diameter), in addition to five extracranial target lesions as per RECIST 1.1. The CA209204 Imaging Manual contains information on gadolinium-enhanced MRI; MRI scan slice thickness of 1 mm is necessary for intracranial metastases 5 mm or larger but less than 10 mm. Extracranial response assessments will utilize RECIST 1.1[20] as this response algorithm for extracranial disease assessment for solid tumors is the currently accepted assessment algorithm and has been used in clinical trials using immunotherapy agents.

Neurologic Assessment in Neuro-Oncology (NANO) scale: To create an overall response assessment for intracranial tumors, a standardized metric is needed to assess disease progression but also to measure neurologic function.[21] While the Macdonald and RANO (response assessment in neuro-oncology) criteria defined radiologic parameters to characterize clinical outcomes in primary tumors, neither criterion provided an objective and quantifiable metric of neurologic function. The NANO scale evaluates and quantifies eight relevant neurologic domains based on direct observation/testing that may be conducted in a routine office visit. The score defines criteria for domain-specific and overall scores of response, progression, stable disease, and not assessed. The NANO scale provides a more detailed and objective measure of neurologic function than currently exists for brain tumor patients.

As an exploratory aim, global tumor response assessments will combine modified RECIST 1.1 criteria (5 mm longest dimension [LD]) for intracranial lesions and standard RECIST 1.1 (10 mm

LD) in extracranial tumors. In addition, volumetric imaging will be performed to evaluate response in the brain to gain experience and generate data using this newer modality. Increasing evidence supports the hypothesis that volumetric estimates of tumor burden are more accurate than 1D/2D measurement of tumor extent. In general, a relatively higher inter-observer variability has been noted using 1D/2D measurements, presumably due to difficulty defining the exact margins and identifying the largest diameter or perpendicular diameter[22,23,24,17]

1.1.2.4 Rationale for Continued Treatment in Cases of Suspected Progressive Disease.

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab[57] and has also been reported for ipilimumab monotherapy.[23] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects initially meeting radiologic criteria for disease progression will be allowed to continue study therapy until a second radiologic confirmation of progression performed approximately 4 weeks later, as long as the following criteria are met: 1) the subject is experiencing investigator-assessed clinical benefit and 2) the subject is tolerating the study treatment. Clinical treatment decisions regarding continuation/discontinuation of study treatment will be determined by the treating physician/local protocol primary investigator using RECIST 1.1 criteria for extracranial tumors and modified RECIST 1.1 for intracranial metastases.

1.1.3 Radiation Therapy with Ipilimumab

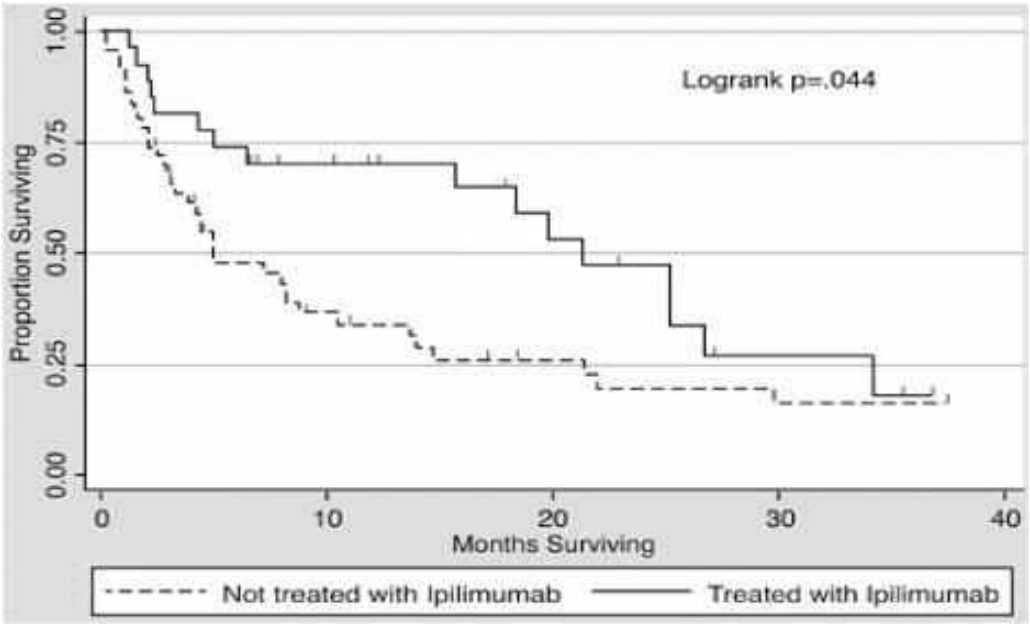
The combination of immune checkpoint therapy and radiotherapy has not been prospectively studied in melanoma subjects with brain metastases. Retrospective analyses, chart reviews, and case studies have been performed to evaluate the safety and efficacy of ipilimumab and radiotherapy.

Shoukat et al evaluated whether stereotactic radiosurgery (SRS) in combination with ipilimumab is safe and can improve overall survival (OS).[25] Patients with melanoma brain metastases who had SRS treatment (n = 176) were compared to patients with similar SRS treatment and disease characteristics who also received ipilimumab therapy (n = 38). The primary endpoint was median OS from time of SRS; secondary endpoints were local control, intra-cranial failure, repeat SRS, and toxicity. Median OS for the cohort was 9.0 months and median follow up was 41.2 months. Patients in the ipilimumab group had median OS of 28.0 versus 7.0 months in the non- ipilimumab group ($p < 0.001$). No difference was noted in local control or any intracranial failures. No increased toxicity was reported, as evidenced by radio-necrosis, hemorrhage, patient-reported

memory deficits or need for repeated SRS in the ipilimumab group. The authors concluded that the use of SRS with ipilimumab appears to be safe and associated with an increase in OS in patients with melanoma brain metastases and warrants additional investigation.

Knisely et al conducted a retrospective analysis of patients who received any form of brain radiotherapy to treat metastatic melanoma and reported the outcomes by any treatment with ipilimumab. The demographic data included radiosurgery timing in relation to ipilimumab treatment, number of metastases treated, whole-intracranial radiation therapy use, follow-up duration, and survival at the last follow-up.[26] A cohort of 77 patients was evaluated, with 35% of these patients having received ipilimumab. The authors concluded that ipilimumab treatment in some patients in combination with radiosurgery for intracranial metastases was associated with an increased median survival from 4.9 (95% CI 3.3 - 10.4 months) to 21.3 (95% CI 6.43 - 26.7 months) months, with a 2-year survival rate of 19.7% versus 47.2% (Figure 1.1.3-1). Of course, the results of retrospective analyses such as these two reports, which do not represent prospectively designed, uniform treatment approaches or provide sufficient patients for multivariate analyses of the factors contributing to different outcomes, can only provide a groundwork for trials such as the present one.

Figure 1.1.3-1: Kaplan-Meier survival curve [26]



The Kaplan-Meier survival curve shows a median survival of 4.9 months (95% CI 3.3–10.4 months) for patients not receiving ipilimumab and 21.3 months (95% CI 6.43–26.7 months) in those receiving the drug. Two-year survival was 47.2% (95% CI 24.8%–66.8%) in the ipilimumab group compared with 19.7% (95% CI 9.0%–33.5%) in the non-ipilimumab group.

In a case study, a 63-year-old female patient was diagnosed with melanoma metastatic to the brain prompting surgical resection of one lesion and SRS to remaining 3 lesions.[27] The patient later received compassionate use ipilimumab 3 mg/kg once every 3 weeks for 4 doses with maintenance dosing every 12 weeks. The patient experienced stable disease for 7 months after starting ipilimumab, after which she progressed in the brain requiring surgical excision of the progressed lesion. The pathological changes in the resected melanoma metastasis (following treatment with ipilimumab) showed marked infiltration with CD8+ T-cells, and a paucity of T-regs, indicating pathologic evidence of an activated immune response in brain metastases, despite the inability of monoclonal antibodies to penetrate an intact blood–brain barrier.

Also of note is a case report of a patient with systemic metastatic melanoma who, after progression on ipilimumab, received palliative radiotherapy to a paraspinal mass. The patient experienced marked regression of the paraspinal lesion as well as regression of additional lesions not targeted by the radiotherapy, suggesting a potential synergy between immunotherapy and radiotherapy in activation of the immune system and tumor regression (abscopal effect).[28] Whether this phenomenon will be observed in patients with untreated intracranial metastases is not known, but the knowledge that immunotherapy can generate an inflammatory response in CNS metastatic disease, together with the preliminary evidence of abscopal effect provide the impetus for further characterizing the interaction of immunotherapy and radiotherapy in metastatic melanoma.

1.1.4 Rationale for Exploratory Biomarker Assessments

This study aims to evaluate the association of several biomarkers within the tumor and peripheral blood with response to nivolumab treatment in combination with ipilimumab in subjects with melanoma. The study also will assess immunomodulatory pharmacodynamic effects of nivolumab treatment in combination with ipilimumab. The goal is to gain an understanding of nivolumab in combination with ipilimumab can modulate the immune system to affect an anti-tumor response. This will be accomplished through assessments of tumor cells and the tumor stroma including the immune infiltrate, peripheral blood immunophenotyping, measurement of serum soluble factors, as well as measures of T-cell function.

Genomic analyses including BRAF/NRAS mutation status (or any other genomic characterization that has been performed on the patient's tumor) as well as single nucleotide polymorphisms (SNPs) in immune-related genes will also be analyzed for association with response or adverse events. The data collected and analyzed in this study will be used to inform the development of nivolumab treatment in combination with ipilimumab for asymptomatic patients and symptomatic patients as well as for the design of future clinical trials. The study is an important contribution towards optimizing treatment approaches for patients with brain metastases.

Initial data from the Phase 1 nivolumab protocol (CA209003) showed a positive correlation between PD-L1 expression in tumor cells and drug response when the "highest ever" PD-L1 expressing tumor was use for correlation.[29] This association has held up in a recently published follow-up analysis from this study in which a single specimen obtained closest to the time of study entry was utilized for analysis and in which correlations to objective response and clinical benefit were found to be statistically significant.[30] Given that the relationship between PD-L1 expression

in systemic vs brain metastases in individual patients is unknown, the present study plans to address whether the response prediction in the brain is linked to systemic PD-L1 status. Additionally, inhibition of the enzyme indoleamine dioxygenase (IDO), which restores tryptophan and thus overcomes an important immunosuppressive phenomenon in the tumor microenvironment, has enhanced anti-tumor effects pre-clinically and is now being studied in the clinic. IDO immunohistochemistry (IHC) may be performed to assess association with drug response. Features of the immune infiltrate including Tregs, CD4/CD8 ratio, presence of tumor associated macrophages (TAMs) with or without PD-L1 expression, and pattern of immune infiltrate relative to tumor will be assessed as well. Finally, classical histopathologic features of primary cutaneous melanoma may provide insight into the presence or absence of an initial immune response to the melanoma that was thwarted (eg, adaptive resistance). It has long been known that the presence of tumor infiltrating lymphocytes (TILs) is a positive prognostic variable and the presence of regression is a negative prognostic variable: a seemingly paradoxical observation that has been explained by postulating that lesions showing regression may have started out with a higher T stage and were falsely down staged rather than favorably impacted by the apparent immune cell infiltrate. Other explanations include the likelihood that the lymphocytic infiltrate may be functionally impaired[31]or polarized toward a suppressive or regulatory lymphocyte rather than immune effector CD8+ T- cells.[32] These features of the primary lesion have not previously been correlated with response to nivolumab with ipilimumab. Where primary lesions are available, this information will be captured and correlated with response in the present study.

Although PD-1 and CTLA-4 are both co-inhibitory molecules, evidence suggests that they utilize distinct mechanisms to limit T-cell activation. Based on peripheral assessments, anti-CTLA4 blockade with ipilimumab increases the total number of lymphocytes and the frequency of activated CD4+ and CD8+ lymphocytes.[33,34,35,36,37,38,39,40] Nevertheless, these increases alone are not sufficient for anti-tumor activity, as there is no relationship between the increase in activated CD4+ and CD8+ T-cells and survival. Immunosuppressive mechanisms within the tumor microenvironment may limit the anti-tumor activity of ipilimumab as an active proinflammatory, interferon-gamma signature is observed in tumor biopsies of patients who have received a single dose of ipilimumab and specifically in patients who have derived clinical benefit in study CA184004. These immunosuppressive mechanisms may include suppressive cell types, such as regulatory T-cells or myeloid derived suppressor cells (MDSC) and/or T-cell expression of other checkpoint inhibitors, such as PD-1, Lag-3, and Tim-3.

Currently, the information regarding the mechanism of action of nivolumab in the clinic is limited. Initial data from CA209003 (Phase 1 nivolumab monotherapy) and CA209006 (Phase 1 study combining nivolumab with a peptide vaccine) have suggested key differences in the action of nivolumab from ipilimumab on peripheral T-cells. Specifically, nivolumab treatment does not appear to increase absolute lymphocyte counts, nor increase the frequency of activated CD4+ and CD8+ T-cells.[41] Both agents may be associated with an increase in tumor antigen specific T-cells. Nevertheless, nivolumab appears more active in subjects with lower baseline peripheral levels of NY-ESO1 and MART-1 specific CD8+ T-cells.[42]

Initial efforts in CA209004 (Phase 1b study of nivolumab and ipilimumab combination) have revealed that the concurrent administration of nivolumab and ipilimumab may have different molecular effects than either agent alone. While increases in activated and proliferating CD4+ and CD8+ T-cells are evident with the combination, a consistent rise in absolute lymphocytes is not observed, as has been observed with ipilimumab alone.[43] The increased frequency of activated CD4+ and CD8+ T-cells may be more profound than ipilimumab monotherapy, but this is difficult to conclude since the collection time points and the methods of assessment were slightly different between CA209004 and the ipilimumab studies.

There is a need to understand the kinetics and mechanism of action of concurrent nivolumab and ipilimumab. Based on preliminary data from CA209004, peak increases in activated CD4+ and CD8+ T-cells are observed between Days 8 and 15 in the periphery in a majority of patients.[43] A comprehensive assessment of T-cell subsets and other immune cells in the periphery for T-cell checkpoint proteins and other relevant markers will offer insights into how nivolumab in combination with ipilimumab impact T-cell function and antitumor activity.

1.2 Research Hypothesis

Treatment with nivolumab combined with ipilimumab, followed by nivolumab monotherapy, will provide clinical benefit to subjects with melanoma metastatic to the brain.

1.3 Objectives

Study objectives will be applied for all treated subjects (Cohort A and Cohort B).

Primary, secondary, and exploratory efficacy endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

1.3.1 Primary Objective

Primary Objective: To assess intracranial clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] $\geq$ 6 months) in subjects with melanoma metastatic to the brain per modified RECIST 1.1 criteria.

1.3.2 Secondary Objectives

- To assess the extracranial clinical benefit rate defined as CR+PR+SD > 6 months (per RECIST 1.1 criteria)
- To assess intracranial objective response rate (ORR), intracranial progression-free survival (PFS) per modified RECIST 1.1 criteria
- To assess extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- To assess global CBR, global ORR, global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess OS
- To evaluate the intracranial-specific safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry, or while on study.

1.3.3 Exploratory Objectives

- To assess intracranial time to objective response (TTR) and intracranial duration of response (DOR) per investigator per modified RECIST 1.1 criteria
- To assess extracranial TTR and DOR per modified RECIST 1.1 criteria
- To assess global TTR and DOR per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess efficacy using NANO criteria
- To evaluate the overall safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry or on study
- To evaluate association between dexamethasone (or equivalent) exposure and treatment effects in symptomatic patients treated with corticosteroids (Cohort B patients).
- To evaluate association between baseline pathologic features of primary cutaneous melanoma (eg, regression, ulceration, pattern and components of immune infiltrate) and CBR endpoints
- To explore potential biomarkers associated with clinical response to nivolumab combined with ipilimumab by analyzing tumor tissue specimens for proteins including, but not limited to, PD-1, PD-L1, and other markers related to immune cell populations involved in regulating immune responses in comparison to clinical outcomes
- To evaluate association between BRAF/NRAS mutation status and response endpoints
- To compare tissue biomarker profiles between paired tissues from extracranial and intracranial metastases from individual patients, where available; if possible this analysis will also be applied for sample sets that include a primary, an extracranial metastasis and a intracranial metastasis from the same patient
- To assess peripheral blood immune cell subpopulations (which may include but is not limited to CD4+ T-cell, CD8+ T-cell, Treg, NK, B-cell, MDSC, activated T-cells, memory/exhausted T cells) and serum soluble factors with changes in post-treatment profiles as they relate to clinical endpoints and/or the occurrence of adverse events
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the occurrence of adverse events
- To estimate the incidence of MRI-defined intracranial edema, hemorrhage, and increase in tumor size before regression (pseudoprogression) in the intracranial metastases and to evaluate any association with the onset and/or CBR observed in the intracranial or extracranial compartment
- To compare computer-assisted tumor volume from three-dimensional (3D) MRI to bi-dimensional measures with respect to absolute values and percent change from baseline.

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with solid tumors and hematological malignancies. In addition to the present study, two ongoing studies (CA209067 and CA209069) are being conducted to evaluate the efficacy and safety of nivolumab and ipilimumab combination therapy in subjects with advanced or metastatic melanoma.

As of June 2015, approximately 8,600 subjects have been treated with nivolumab in completed and ongoing studies assessing pharmacokinetics (PK), clinical activity, and safety. Nivolumab is currently being studied in Phase 3 studies in squamous and non-squamous non-small cell lung cancer (NSCLC), malignant melanoma, renal (clear) cell carcinoma (RCC), and other indications.[44] Nivolumab is being investigated both as monotherapy and in combination with chemotherapies and other immunotherapies.

CA209066 is a Phase 3, randomized, double-blind study of nivolumab plus placebo versus dacarbazine plus placebo in subjects with previously untreated, unresectable or metastatic melanoma. In June 2014, this study for nivolumab in first-line melanoma was stopped early because an analysis conducted by the independent Data Monitoring Committee showed clear evidence of superior overall survival benefit in patients receiving nivolumab compared to patients in the control arm who received the chemotherapy DTIC. The decision to stop the blinded comparative portion of the trial will allow patients to continue or start treatment with nivolumab in an open-label extension as part of the study.

Yervoy (ipilimumab) is an approved therapy for metastatic melanoma and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine. An extensive clinical development program for ipilimumab that encompasses more than 13,800 subjects in several cancer types in completed and ongoing studies, as well as a compassionate use program has been conducted. Ipilimumab continues to be investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

In the proposed study, the combination treatment of nivolumab and ipilimumab followed by nivolumab monotherapy in the treatment of melanoma brain metastases continues the work of exploring immune based therapies in this patient population that was begun in the Phase 2 study CA184042 trial. Previously reported results from that study of ipilimumab monotherapy showed similar clinical benefit rates in the brain and systemic disease, providing rationale for further study of immunotherapies in melanoma patients with brain metastases.

1.4.1 Summary of Investigational Agents

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology, and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptor are two important cellular targets that play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.[45]

OPDIVO™ (nivolumab) is approved in the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic squamous NSCLC, the EU for treatment of previously treated, unresectable or metastatic melanoma, and Japan for treatment of

unresectable melanoma. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promote immune responses and antigen-specific T cell responses to both foreign and self antigens. PD-1 receptor blockade by nivolumab is a new approach for immunotherapy of tumors. Results from a Phase 1/2 study (CA209003)[46] indicate that nivolumab is active in multiple tumor types. Nivolumab 3 mg/kg monotherapy is currently being studied in advanced melanoma, renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC).

Ipilimumab is a fully humanized IgG1 monoclonal antibody (mAb) binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for unresectable or metastatic melanoma[47] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[48,49] Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.[50] Phase 3 studies are ongoing in NSCLC, small cell lung carcinoma (SCLC), and prostate carcinoma.

In the Phase 1 dose escalation study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma. In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. An objective response rate of 53% (9/17) was observed for patients treated with 3 mg/kg ipilimumab plus 1 mg/kg nivolumab administered every 3 weeks for four doses (induction) and subsequently continued every 12 weeks for up to eight doses.[17] The induction regimen is currently being studied in ongoing global, randomized Phase 2 and 3 studies in advanced melanoma, CA209069 and CA209067.[51] The combination of nivolumab with ipilimumab is also currently being investigated in NSCLC (study CA209012)[52], metastatic (clear cell) renal cell carcinoma (mRCC) (study CA209016)[53] and other indications.

1.4.2 Summary of Results from the Ipilimumab and Nivolumab Programs

1.4.2.1 Preclinical Summary of Nivolumab Combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[54]

A 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

1.4.2.2 Clinical Pharmacology Summary

Ipilimumab Monotherapy

Ipilimumab has a terminal half-life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies into small peptides and amino acids occurs via biochemical pathways that are independent of cytochrome P450 enzymes. The population pharmacokinetics (PPK) of ipilimumab was studied with 785 subjects and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from population PK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with an increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen. Additional details are provided in the ipilimumab Investigator Brochure (IB).

Nivolumab Monotherapy

Single-dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in MD1106-01 whereas multiple dose PK was evaluated in subjects in CA209003. In addition, a PPK model has been developed with data from ± 350 subjects from MDX1106-01, MDX1106-02 and CA209003.

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is

linear in the range of 0.3 to 10 mg/kg with dose proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while the mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the nivolumab IB.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body.

1.4.3 Summary of Safety

Ipilimumab Monotherapy

In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug-related adverse events, with 21% assessed as Grade 3/4 and 3/131 (2%) assessed at Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

In study CA184042, CNS adverse events that were assessed as at least possibly related to drug are summarized as follows. Three CNS SAEs were reported in two subjects, and these events were assessed by the investigator as possibly drug-related. A single event of Grade 2 seizure occurred in one subject, one month after completion of ipilimumab induction regimen. This subject had received multiple SRT treatments that ended 2.5 months prior to the first dose of ipilimumab. A second subject experienced two events of Grade 4 CNS hemorrhage that occurred 3 and 17 days after the first dose of ipilimumab induction. This subject did not receive prior radiation to the brain. Seven additional subjects experienced a total of 12 non-serious Grade 1-2 events that were assessed by the investigator as possibly (11/12) or probably (1/12) related. These events included: headache (4), light-headedness/dizziness (2), decreased mental activity/memory difficulty (2), balance difficulty (1), R. hand shaking (1), parasthesia in fingers (1) and toes (1).

Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the BMS734016 (ipilimumab) IB.

Nivolumab Monotherapy

One study has contributed most to the clinical experience with nivolumab monotherapy in subjects with melanoma and other solid malignancies. CA209003 (MDX1106-03) is a completed Phase 1 open label, multiple dose-escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously

every 2 weeks, up to a maximum of 2 years of total therapy. As of November 2013, a total of 107 melanoma subjects were treated with nivolumab in the dose range of 0.1-10 mg/kg.

No maximum tolerated dose was identified in CA209003 with doses tested up to 10 mg/kg. The nature, frequency, and severity of any causality and treatment-related safety events were generally similar across dose levels and tumor types. These AEs were generally manageable and reversible with the use of immunosuppressants.

Nivolumab treatment-related SAEs of any grade were reported in 13.7% of subjects. The most frequent nivolumab treatment related SAE was pneumonitis (7 subjects, 2.3%). Of these events, pneumonitis reported in 4 (1.3%) subjects was Grade 3-4. The most frequently reported any grade select AEs were fatigue (25.7%), diarrhea (34.3%), rash (24.2%), and pruritis (18.3%). The most frequently-reported Grade 3 to 4 select AEs were renal failure acute (2.3%), ALT increased (1.6%), AST increased (1.6%) and pneumonitis (1.3%).

The most frequently reported Grade 3 to 4 treatment-related select AEs were pneumonitis (1.3%) and diarrhea (1.0%). A total of 230 patients (75.2%) experienced treatment-related select AEs; fifty-two of these 230 subjects (23%) required management with systemic glucocorticoids and/or other immunosuppressive agents. Twenty-one (40%) resumed nivolumab therapy after toxicity resolved, while others discontinued therapy due to treatment-related select AEs.

There was no apparent relationship between the incidence of select AEs and the dose of nivolumab. Although there was numerically more treatment-related Grade 3 to 4 select AEs in subjects receiving 10 mg/kg, no single category of select AE seemed to drive that finding. Similarly, there was no apparent relationship between the incidence of select AEs and the underlying tumor type. As the numbers of reported AEs were small, the possibility of a true difference in the incidence of categories of select AEs by tumor type cannot be eliminated.[46]

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[55] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.[44]

Nivolumab Combined with Ipilimumab

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at Week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The 3 initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated

nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16) and Cohort 8 that represents an additional cohort of patients treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg The maintenance regimen for Cohorts 1-3 consisted of nivolumab q3 weeks x 4 then nivolumab plus ipilimumab q12 weeks x 8, while the maintenance regimen for Cohort 8 consisted of nivolumab 3 mg/kg q2 weeks until progression. The following dose limiting toxicities (DLTs) were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 subject); in Cohort 2 - Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject) and in Cohort 3 - Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD. Among the 53 patients in the concurrent-regimen group, adverse events of any grade, regardless of whether they were attributed to the therapy, were observed in 98% of patients.

Treatment-related adverse events of any grade were reported in 96.2% of patients, in pooled Cohorts 1-3 and 95.1% of Cohort 8. The drug-related skin select AE category was the most frequently reported category in all cohorts; rash and pruritus were the most frequently reported drug-related AEs in all cohorts. The most frequently reported drug-related AEs of any grade were rash (62.3%, Cohorts 1-3; 58.5%, Cohort 8), pruritus (56.6%, Cohorts 1-3; 46.3% Cohort 8), diarrhea (41.5%, Cohorts 1-3; 31.7%, Cohort 8), fatigue (41.5%, Cohorts 1-3; 41.5%, Cohort 8), lipase increased (26.4%, Cohorts 1-3; 14.6%, Cohort 8), AST increased (24.5%, Cohorts 1-3; 9.8%, Cohort 8), ALT increased (22.6%, Cohorts 1-3; 12.2%, Cohort 8), nausea (22.6%, Cohorts 1-3; 24.4%, Cohort 8), pyrexia (22.6%, Cohorts 1-3; 22.0%, Cohort 8), amylase increased (20.8%, Cohorts 1-3; 12.2%, Cohort 8). The only reported drug-related AE belonging to the pulmonary select AE category was pneumonitis; 3 (5.7%) subjects in Cohorts 1 to 3 and 1 (2.4%) subject in Cohort 8. Grade 3-4 events were reported in 1 subject each in Cohort 2a and Cohort 8. Treatment-related SAEs of any grade were reported in 58.5% of patients on pooled Cohorts 1-3 and 41.5 % of Cohort 8. The most frequently reported SAE in ≥ 5% subjects included: ALT increased, AST increased, lipase increased, colitis, diarrhea, amylase increased, pneumonitis, and pyrexia.

A total of 13 subjects (24.5%) in Cohorts 1-3 and 9 subjects (22.0%) in Cohort 8 discontinued therapy due to treatment-related adverse events.

The majority of the deaths were due to disease progression in CA209004. One subject died due to drug-related enterocolitis.

The only CNS treatment-related AE reported in >10% of subjects was headache [11.3% Cohorts 1-3 (Grade 1-2); 12.2% Cohort 8 with 1 Grade 3-4 event (2.4%)]. A single case of radiation necrosis was observed in a subject who received SRT for progression in the brain while on nivolumab monotherapy maintenance dosing. The subject had completed 4 doses of induction with combination ipilimumab and nivolumab, and 3 doses of nivolumab monotherapy maintenance. He received SRT for progression between dose #3 and dose #4 of nivolumab maintenance. He subsequently received a single dose of combination maintenance. Approximately 5-6 weeks after the dose of combination maintenance, radionecrosis was diagnosed. Attribution was assessed as related to SRT and unrelated to study drug. Three subjects experienced drug-related CNS adverse events that led to discontinuation - one subject with blurred vision (Grade 1) and headache (Grade 2) , one subject with presyncope (Grade 3) and one subject with ageusia

(Grade 1). A single subject experienced CNS adverse events assessed as not related, that led to discontinuation: muscular weakness (Grade 3), dizziness (Grade 2), headache (Grade 2), confusion (Grade 2). None of these subjects had received prior brain radiotherapy. Of the 11 subjects who did receive prior radiotherapy to the brain, only 1 subject experienced a CNS adverse event which was the case of radiation necrosis described above.[17]

Adverse Event Management Algorithms

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity. Prompt interventions are recommended according to the management algorithms included in Appendix 1.

In order to standardize the management of the overlapping adverse event management algorithms presented in both the nivolumab and ipilimumab IB (GI, hepatic, and endocrine algorithms), the recommendations are to follow the BMS-936558 (nivolumab) IB adverse event algorithms and not the ipilimumab IB algorithms. The algorithms recommended for utilization in CA209204 are contained in the nivolumab (BMS-936558) IB and in Appendix 1 of this Protocol.

As of June, 2015, 3 subjects out of approximately 4000 patients on nivolumab clinical trials have developed opportunistic infections (2 cases of Aspergillus pneumonia, and 1 case of Pneumocystis jiroveci pneumonia) after receiving prolonged treatment with high dose steroids for nivolumab-related adverse events.[44] Details of these cases are available in the nivolumab IB. Because of the potential for opportunistic infections with prolonged high dose corticosteroids administration, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the IB.[44]

1.4.4 Summary of Clinical Activity

Ipilimumab Monotherapy

In melanoma, two completed Phase 3 studies have demonstrated clinically meaningful and statistically significant survival benefit in advanced melanoma. The completed Phase 3 study, MDX010-20, demonstrated improved survival in pre-treated advanced melanoma. The study

compared the overall survival (OS) of ipilimumab (3 mg/kg) plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS ($p = 0.0004$ and 0.0026, respectively). The median OS was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively. The objective response rate was 5.7% (95% CI: 3.7, 8.4), 10.9% (95% CI: 6.3, 17.4), and 1.5% (95% CI: 0.2, 5.2) on the ipilimumab arm, the ipilimumab plus gp100 arm, and the gp100 arm, respectively.

The completed Phase 3 study CA184024 demonstrated improved survival in treatment-naive melanoma. The study compared the OS of ipilimumab (10 mg/kg) plus dacarbazine vs dacarbazine plus placebo. OS was improved in the ipilimumab plus dacarbazine group compared to the dacarbazine plus placebo group (11.2 months vs 9.1 months, respectively, HR 0.72, $p < 0.001$). The objective response rate was 15.2% on the ipilimumab plus dacarbazine arm compared to 10.3% on the dacarbazine plus placebo arm.

Summary of Clinical Activity of Ipilimumab in Brain Metastases

The CA184042 clinical trial evaluated the efficacy and safety of ipilimumab in patients with advanced Stage IV melanoma and active brain metastases. Patients in Cohort A were neurologically asymptomatic with no systemic glucocorticosteroid therapy in the 10 days prior to the start of ipilimumab therapy. Patients receiving concurrent systemic corticosteroids for control of neurological signs and symptoms related to brain metastases were enrolled in Cohort B. Study treatment consisted of an induction phase consisting of 10 mg/kg intravenous ipilimumab, every 3 weeks for 4 treatments followed at 24 weeks by maintenance therapy using the same dose every 12 weeks. Subjects remained on treatment if they were medically stable and without severe toxicity. The primary endpoint was disease control rate (DCR), defined as an objective response or stable disease after the 12-week time point, on the basis of modified WHO (mWHO) criteria. Immune-related response criteria (irRC) were applied with new lesions incorporated into the measurement of tumor burden rather than themselves constituting progression. Median OS (mOS) was 7 months (range 0.4 – 31+) for Cohort A and 4 months (0.5 – 25+) for Cohort B. Survival rates at 6-, 12-, 18-, and 24 months were 55%, 31%, 26%, and 26% for Cohort A and 38%, 19%, 19%, and 10% for cohort B. Importantly, the disease control rate (DCR) was similar in the CNS and systemic compartments, supporting the fact that ipilimumab provides therapeutic benefit in CNS disease. The most common adverse effects were fatigue, diarrhea, nausea, headache, rash, and pruritus, with immune-related adverse effects clearly attributable to ipilimumab occurring in the reported and expected frequency. Similarly, data generated in the NIBIT-M1 trial (ipilimumab + fotemustine) was associated with a DCR of 50% (10/20) and with a 1 year median OS of 54% in patients with asymptomatic brain metastases.[16] Lastly, a retrospective analysis of patients with asymptomatic brain metastases treated on the ipilimumab EAP showed a mOS of 20 months.[56] Collectively, these data with ipilimumab treatment support the role of immunotherapy for melanoma brain metastases.

Nivolumab Monotherapy

In CA209003 (MDX1106-03), the clinical activity of nivolumab was demonstrated in a variety of tumor types and across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). As of the clinical cut-off date of 05-Mar-2013, a total of 306 subjects with melanoma, RCC, and NSCLC have been treated with nivolumab. All subjects initiated treatment at least one year prior to analysis. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.0, has been reported at all dose levels.

Among 107 patients with advanced melanoma who received nivolumab, the objective response rate was 33/107 (31% [95% CI 22, 41]). Responses occurred at each dose level, with 6/17 (35%), 5/18 (28%), 11/35 (31%), 7/17 (41%), and 4/20 (20%) melanoma subjects responding at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.[46] One additional subject was reported as a responder after 05-Mar-2013.[57]

Updated MDX1106-03 efficacy results (based on 17-Sep-2013 data cut-off), showed induced sustained activity in subjects with advanced melanoma. The 1-, 2-, and 3-year survival rates were 63%, 48%, and 41%, respectively, based on Kaplan Meier estimates. The mOS was 17.3 months (95% CI: 12.5, 36.7). Overall survival at 3 mg/kg dose was 20.3 months (95% CI: 7.2, NE [not estimable].[57,58]

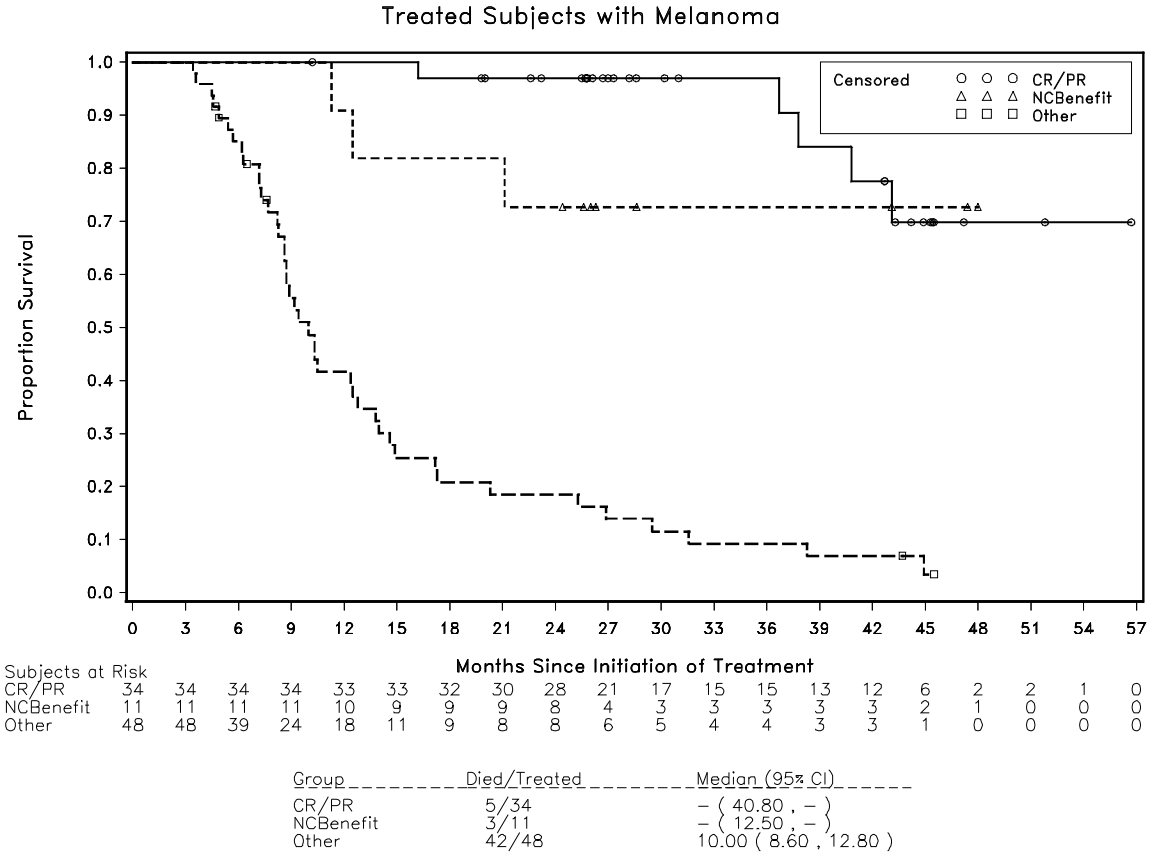
Updated analyses of other efficacy endpoints (progression-free survival [PFS] and duration of response) continue to support the durable clinical effect and survival obtained with nivolumab treatment.

The PFS rate in subjects with melanoma at 48 weeks was 38% [95% CI: 28, 47]) and at 96 weeks 29% [95% CI: 20, 39]. Median PFS was 3.7 months in all melanoma subjects (95% CI: 1.9, 9.3) and 9.7 months (95% CI:1.8, 16.4) for subjects treated at the 3 mg/kg dose level.

In the 34 responders, duration of response ranges were 24.1 to 80.1+, 18.4 to 93.3+, 32.4 to 108.1+, 40.1+ to 115.4+, and 73.9 to 117.0+ months in subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. The median duration of response was 22.9 (range: 3.9+ - 26.9+) months. Responses were still ongoing in 19 of the 34 responders (56%) as of 17 Sep-2013. Of these 19 subjects, 5 were receiving active study therapy and 14 had discontinued treatment. Among the 14 subjects who had discontinued, response was maintained in 11 subjects for at least 2 to 56 weeks with 8 subjects maintaining response for at least 16.6 weeks after discontinuation.

Of the 107 melanoma subjects treated in MDX1106-03, 12 (11%) subjects were identified as non-conventional clinical benefiters. Of those, 4 were previously reported as non-conventional responders (05-Mar-2013)[46] and 8 more were identified after being followed with at least 3 scans with PD. The pattern of OS in non-conventional benefiters (Figure 1.4.4-1) was similar to that observed in subjects with conventional RECIST responses.[57]

Figure 1.4.4-1: Survival Analysis by Response or Non-Conventional Benefit in Melanoma Subjects



CA209066 is a Phase 3, randomized, double-blind study of nivolumab plus placebo versus dacarbazine plus placebo in subjects with previously untreated, unresectable or metastatic melanoma. This study allowed for direct comparison of the clinical benefit, as measured by overall survival, provided by nivolumab vs dacarbazine (DTIC). This study for nivolumab in first-line melanoma was stopped early because an analysis conducted by the independent Data Monitoring Committee showed clear evidence of superior overall survival benefit in patients receiving nivolumab compared to patients in the control arm who received the chemotherapy DTIC. The results of this controlled, randomized Phase 3 trial of an investigational PD-1 checkpoint inhibitor are the first to demonstrate an overall survival benefit. The decision to stop the blinded comparative portion of the trial will allow patients to continue or start treatment with nivolumab in an open-label extension as part of the study. A full evaluation of the final CA209066 data will characterize help long-term survival.

Nivolumab Combined with Ipilimumab

In the ongoing Phase 1b study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm of this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at Week 24,

ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16).

In the concurrent-regimen cohorts, across all dose levels, confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% CI, 27, 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective response rates.

After noting several patients had major responses (approaching complete response), a post hoc analysis of the number of patients with tumor reduction of 80% or more was conducted. This depth of response was uncommon in published studies of checkpoint blockade.[48,59] A total of 16/52 patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response. Among patients treated in Cohort 2, 9/17 (53%) objective responses were observed, all 9 with ≥ 80% tumor reduction.

In the concurrent-regimen group, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients (95% CI, 51 to 78). Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis.[17]

In April 2013, an additional treatment cohort (Cohort 8) was added to this study, and 40 subjects were enrolled and treated on a concurrent dose regimen of 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab every 3 weeks for 4 doses followed by 3 mg/kg of nivolumab (as monotherapy every 2 weeks for up to a maximum of 48 doses (16 cycles).

For the 53 subjects who received concurrent therapy with nivolumab + ipilimumab and the 40 subjects in the expansion treatment group updated efficacy data (05-April-2014 cut-off date) has been reported. The overall response rate (ORR [modified World Health Organization criteria]) for all subjects in the concurrent-regimen group and concurrent expansion group was 22/53 (42% [95% CI: 28, 56]) and 17/40 (43% [95% CI: 27, 59]), respectively.

Median OS at 1 year was 85% (95% CI: 75, 95) for the concurrent treatment group. Median OS was not calculated for subjects treated in the expansion group because too few subjects had died by the database lock. At the ASCO 2014 Annual Meeting, Sznol et al reported 2-year overall survival rates of 79% in cohorts receiving concurrent treatment with nivolumab and ipilimumab (n=53). For subjects in the Cohort 2, receiving nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n=17), 1- and 2-year overall survival rates were 94% and 88%, respectively. A ≥ 80% reduction in tumor volume was observed in most responding patients. The majority of objective responses were ongoing; the median duration of response was not reached.[60]

1.5 Overall Risk/Benefit Assessment

There continues to be a significant unmet need for patients with melanoma brain metastases.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced prior treated melanoma, with an overall objective response rate of 33% (95% CI: 22 - 41) in 107 melanoma subjects treated at various dose levels in CA209003. Nivolumab has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. Preliminary analysis of the evaluable CA209004 subjects revealed that approximately 33% of the subjects had > 80% tumor reductions in index lesions by week 12. This compares favorably to < 2% for 3 mg/kg ipilimumab monotherapy based on the CA184020 (n = 540) and < 3% for nivolumab monotherapy based on the CA209003. However, the combination of nivolumab and ipilimumab also has the potential for increased frequencies of adverse events. The most commonly reported treatment-related AEs were rash, pruritus, diarrhea, fatigue, lipase increased, AST increased, ALT increased, nausea, pyrexia, and amylase increased. Although the data show an increase in adverse event frequency of nivolumab combined with ipilimumab compared to ipilimumab monotherapy or nivolumab monotherapy, there were no unexpected adverse events noted in the combination of nivolumab and ipilimumab. In addition, many of the Grade 3-4 adverse events associated with the nivolumab combined with ipilimumab were laboratory toxicities without clinical sequelae, and adverse events have been manageable and reversible following intervention dose delays or with systemic steroid treatment. In the CNS, the only treatment-related adverse event that occurred in > 10% of patients that was reported as related was headache (N=12; 13%) with 11/12 events being Grade 1-2. This supports a safe/tolerable CNS profile in this study population for which the only patients with brain metastases who were study-eligible must have been previously treated and stable without corticosteroids. The data from CA209004 do not suggest that there is an added risk of CNS events in patients who received radiotherapy to the brain prior to study entry (see Section 1.4.3). The single case of radiation necrosis in the brain occurred in a patient treated with the concurrent regimen on CA209004 who progressed in the brain while on study (during nivolumab maintenance dosing) and received SRT. This SAE was assessed as unrelated to study drug but related to SRT, and should be considered in the context of the ~2-15% baseline rate of radionecrosis observed with SRT.[61] Nonetheless, this occurrence supports the incorporation of an SRT safety assessment and regular ongoing safety assessments in the current protocol study design.

Since brain metastases in melanoma are the most frequent cause of death from this disease and the brain is a frequent site of failure even in subjects who achieve control of systemic disease with systemic therapy, successful treatment of this complication remains a serious challenge. New therapeutic approaches are desperately needed and could have an enormous impact on outcome. Current standards of care include stereotactic radiotherapy that may control limited metastases in the brain for prolonged periods of time, but are often followed by the development of new disease that is not amenable to that approach.

Evaluating the combination of nivolumab and ipilimumab therapy followed by nivolumab monotherapy will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The robust clinical activity demonstrated by

nivolumab monotherapy and the substantial clinical activity of nivolumab combined with ipilimumab in subjects with advanced melanoma together with the manageable safety profile and the lack of approved survival-prolonging agents for a large segment of the previously untreated population supports the further development of nivolumab combined with ipilimumab therapy in subjects with melanoma metastatic to the brain.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, multi-site Phase 2 study of nivolumab combined with ipilimumab followed by nivolumab monotherapy for the treatment of subjects with melanoma metastatic to the brain. Per Amendment 02 (August 2106), both asymptomatic and symptomatic patients are eligible for enrollment as described below:

Cohort A (asymptomatic) Patients with histologically confirmed metastatic melanoma presenting with intracranial metastases and at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

Approximate enrollment in Cohort A is 90 patients.

Cohort B (symptomatic): Patients with histologically confirmed metastatic melanoma presenting with symptomatic intracranial metastases who may be on steroids with doses no higher than a total daily dose of 4 mg of dexamethasone or equivalent that is stable or tapering within 10 days prior to treatment. Patients who are symptomatic and are not being treated with steroids are also eligible. Patients enrolled in Cohort B must have at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated, must not require immediate local therapy (SRT or surgery within 3 weeks prior to first treatment), have a performance status 0-2, and no experience of seizure within 10 days prior to first treatment.

Approximate enrollment in Cohort B is 20 patients.

Asymptomatic subject who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.

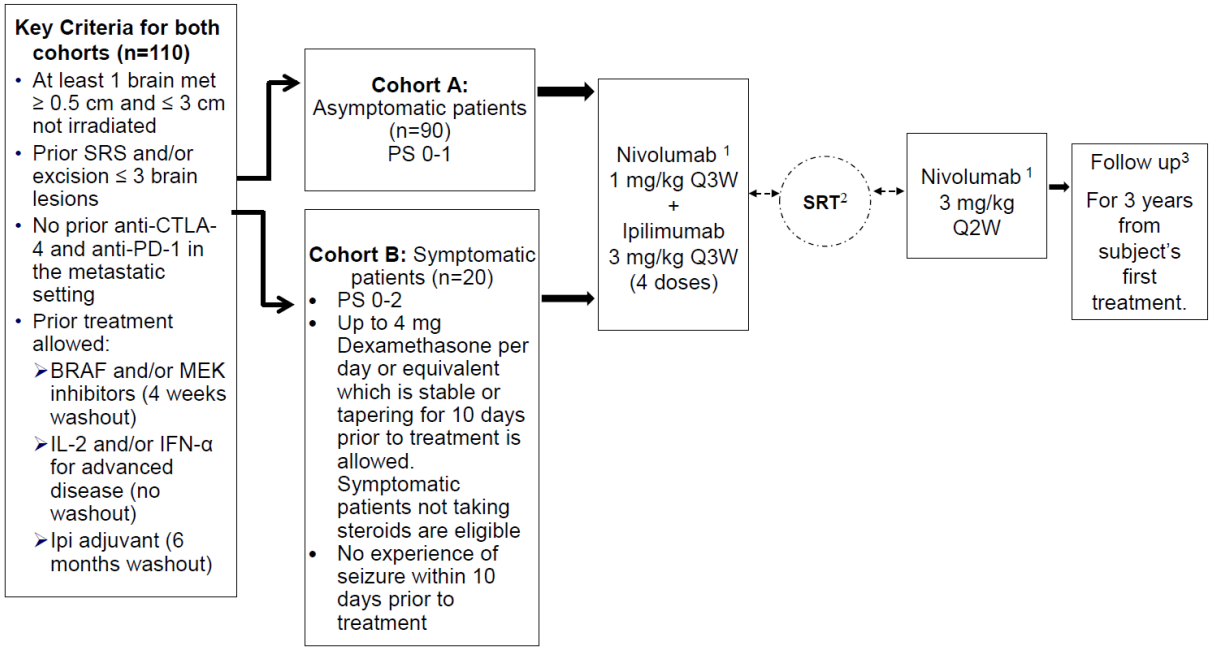
Subjects who have received prior treatment with BRAF inhibitors and/or MEK inhibitors, and subjects who have been treated with ipilimumab in an adjuvant setting are eligible for the study.

All patients will be treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W (4 doses), followed by nivolumab monotherapy (3 mg/kg Q2W) for a maximum of 24 months, or until disease progression or unacceptable toxicity. The use of SRT (single episode) for disease progression for ≤ 3 intracranial lesions is permitted. (Section 3.4.2.2) Recommended intervals between treatment with study drug and use of SRT, dose delay after SRT, allowable steroid use (≤ 16 mg dexamethasone PO QD), and tapered over no more than 4 weeks), and observation of patients post SRT when treatment is resumed are also specified in Section 3.4.2.2. Any subject who meets criteria for discontinuation following SRT (Section 4.5.5) will proceed to follow-up for safety, progression, and overall survival after discontinuation of study medication based on the assessment schedules presented in Section 5. NOTE: To continue on-study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

A follow-up period of 3 years from the date of first treatment with study drugs is available for all subjects. The study will close after the last enrolled subject completes 3 years of follow up from

the date of first treatment or the study is discontinued by the Sponsor. The study design is presented in Figure 3.1-1:

Figure 3.1-1: CA209204 Study Design



1 Subjects may continue to receive treatment for a maximum or 24 months, or until confirmed progression or unacceptable toxicity. After discontinuation from treatment with study drug(s) subjects will proceed to follow-up. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply or appropriate care per investigator.

2 Use of SRT for progression of ≤ 3 intracranial lesions will be allowed per protocol-specific guidelines (See Section 3.4.2.2). Subjects who require SRT after second episode of disease progression will be discontinued from treatment and proceed to follow-up.

3 All subjects who are discontinued from treatment with study drug(s) will proceed to follow-up. See Table 5.1-4 for schedule of follow up assessments.

SRT = stereotactic radiotherapy

Enrolled subjects will be evaluated for safety and efficacy throughout the study and during follow up at the time points indicated on the time and events schedules presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4. Response to treatment will be assessed in the intracranial and extracranial compartments and will be evaluated by serial radiographic assessment every 6 weeks for the first year and every 12 weeks thereafter until documented progression, withdrawal of consent, or the end of the study.

Follow-Up Phase for each enrolled subject begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Subjects will be followed for efficacy and OS.

Treatment decisions will be based on local imaging evaluations using modified RECIST 1.1 for intracranial lesions (at least 5mm LD) and RECIST 1.1 for extracranial lesions (Appendix 3).

Additional imaging may be performed for patient care at the discretion of the investigator. All efficacy objectives will be based on Investigator assessment at the study site.

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review performed by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 4.0. Safety assessments will be based on medical review of AE reports, vital sign measurement results, physical examinations, and clinical laboratory tests. In addition, a designated Steering Committee composed of a core group of study investigators who are experts in treating patients with melanoma intracranial metastases and sponsor physicians/staff will evaluate safety and efficacy throughout the trial as described in Section 7.

The exploratory efficacy objective of global (intracranial and extracranial) tumor burden response assessment will use modified RECIST 1.1. Additionally, exploratory analyses will be conducted on volumetric measurements using 3-D MRI.

Safety and Tolerability Assessment Evaluation of Risk/Benefit

An interim analysis was conducted when 20 subjects completed induction or discontinued treatment for any reason. At the completion of the interim analysis by the steering committee, the combination was determined to be safe in patients with asymptomatic untreated melanoma intracranial metastases. Per Amendment 02 (August 2016), the patient population will be expanded to include Cohort B, which will enroll approximately 20 patients with symptomatic intracranial metastases who may be on steroids provided there is no immediate need for SRT or surgery (within 3 weeks prior to first treatment, performance status is 0-2, the patient has not experienced seizure within 10 days prior to first treatment, and does not require steroid therapy at a total daily dose of higher than 4 mg of dexamethasone or equivalent, which is stable or tapering for 10 days prior to first treatment. Patients who are symptomatic and are not being treated with steroids for CNS symptoms are eligible for enrollment.

In the event unfavorable safety/tolerability event occurs in the interim analyses, the Steering Committee and the Sponsor will review the available data. Upon review of the risk/benefit profile, the Sponsor and the Steering Committee will recommend continuation, modification, or termination of the study.

The most frequent severe drug related AEs for the combination of nivolumab and ipilimumab in melanoma have been asymptomatic and reversible (eg, laboratory testing of liver function tests (LFT) and lipase levels) and preliminary evidence shows deep and durable responses in advanced melanoma (CA209004) despite these events. In particular, any assessment of the risk/benefit will be examined if the following criteria are met:

- A majority of subjects have at least stable disease or a partial tumor response

- All treatment-related AEs leading to discontinuation are non-fatal, reversible, and without severe sequelae
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable by routine blood draws.

If a decision is made to continue because of a favorable risk/benefit profile (ie, non-fatal AEs in subjects with at least stable disease or a partial tumor response) and despite meeting the safety signals for 'not tolerable' criteria, the EC/IRBs must be notified, Informed Consent forms updated if necessary to add new information, and discussion of the risk/benefit, if determined to be different than at the outset of the study, must be documented with all current and future subjects who are enrolled into the study.

3.1.1 Screening Phase

- Screening begins by establishing the subject's initial eligibility and signing of the ICF.
- Subject is enrolled using the IRT. Subjects will be enrolled into either Cohort A (asymptomatic) or Cohort B (symptomatic). Asymptomatic subjects who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.
- Subject is assessed for study eligibility as described in Section 3.3.1 and Section 3.3.2.
- Pre-treatment tumor tissue is required from all patients and should be from an excisional, incisional, (preferred), punch, or core needle biopsy. Tissue representing an extracranial metastasis collected after prior therapies is preferred, but archival primary or metastatic tumor tissue specimens are acceptable. A tumor tissue block or minimum of 15 slides should be submitted.

3.1.2 Treatment Phase

- A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
- On study laboratory assessments should be drawn within 72 hours prior to dosing.
- Study assessments are to be collected as outlined in Table 5.1-2 (Cycles 1 and 2) and Table 5.1-3 (Cycles 3 and beyond).
- Adverse event assessments should be documented at each clinic visit.
- Outcomes Research Assessment (Healthcare Resources Utilization (HCRU) will be conducted prior to Cycle 1 dosing and at the time of progression.
- Exploratory Biomarker Testing will be conducted according to Table 5.6.1.3-1.
- All enrolled participants will be treated with nivolumab IV over 60 minutes ± 10 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes ± 10 minutes at 3 mg/kg every 3 weeks for a total of 4 doses of the combination therapy followed by nivolumab administered IV over 60 minutes ± 10 minutes at 3mg/kg every 2 weeks for a maximum of 24 months or until progression or unacceptable toxicity.

- Study drug dose may be delayed for toxicity. Tumor assessment should be continued as per protocol even if dosing is delayed.
- Response to treatment will be evaluated by serial radiographic assessment every 6 weeks (± 7 days) for the first 12 months and every 12 weeks (± 7 days) thereafter until documented progression.
- NANO Scale evaluation to be conducted weekly during Cycle 1, prior to dosing on Weeks 1 and 4 in Cycle 1 and Cycle 2; and on Weeks 1, 3, and 5 during Cycle 3 and thereafter during the treatment phase. See Section 8.4.3.1.
- The treatment phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation see Section 3.5.

3.1.3 Follow-Up Phase

- Begins when the decision to discontinue a subject from treatment is made (no further treatment with study therapy).
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.
- Follow-up assessments are to be collected as outlined in Table 5.1-4.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 6 weeks (± 7 days) from the first dose of study drug for the first 12 months, and every 12 weeks (± 7 days) thereafter until documented tumor progression.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.

3.2 Post Study Access to Study Drug

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate care to treat the condition under study. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply.

3.3 Study Population.

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent
   a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
   b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2. Target Population

   a) Histologically confirmed malignant melanoma with measurable metastases in the brain

   b) **Cohort A**: At least 1 measurable intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in longest diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

      Cohort B: Per Amendment 02 (August 2016) Subjects with neurologic signs and symptoms related to metastatic intracranial lesions are eligible per Amendment 02. Subjects must have at least 1 measurable intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in longest diameter that has not been previously irradiated. No immediate requirement (within 3 weeks prior to first treatment) for local intervention (surgery, radiosurgery, corticosteroid therapy). Steroid use is permitted as defined in inclusion criterion 2e).

   c) Prior stereotactic radiotherapy (SRT) and prior excision of up to 3 melanoma intracranial metastases is permitted if there has been complete recovery, with no neurologic sequelae, and measurable lesions remain. Growth or change in a lesion previously irradiated will not be considered measurable. Regrowth in cavity of previously excised lesion will not be considered measurable. Any prior SRT to intracranial lesions or prior excision must have occurred ≥ 3 weeks before the start of dosing for this study.

   d) Must have tumor tissue available for biomarker analysis. Biopsy should be excisional, incisional, punch, or core needle. Fine needle aspirates or other cytology samples are not allowable.

   e) **Cohort A** (asymptomatic): Subjects must be free of neurologic signs and symptoms related to metastatic intracranial lesions and must not have required or received systemic corticosteroid therapy within 10 days prior to first treatment.

      Cohort B (symptomatic): Subjects with neurologic signs and symptoms related to metastatic intracranial lesions are eligible per Amendment 02. Subjects with neurologic signs and symptoms may be treated with a total daily dose of no more than 4 mg of dexamethasone that is stable or tapering for 10 days prior to first treatment. Subjects with neurologic signs and symptoms who are not being treated with steroids are eligible for Cohort B. No experience of seizure within 10 days prior to first treatment.

   f) Allowable prior therapy

      i) Approved adjuvant therapies, which may include molecularly-targeted agents, IFN-α, and ipilimumab. Patients who received ipilimumab as adjuvant therapy must have a 6 month washout before receiving any dosing on this study

      ii) For advanced disease, interleukin-2 at any dose and/or IFN-α (any formulation, no washout required); MEK and BRAF inhibitors: washout for at least 4 weeks prior to the start of dosing in this study

      iii) Steroids for physiological replacement are allowed.

   g) Cohort A (asymptomatic): ECOG performance status ≤ 1.
      Cohort B: (symptomatic): ECOG performance status ≤ 2

h) Screening laboratory values must meet the following criteria (using CTCAE v4):

- WBC ≥ 2000/uL
- Neutrophils ≥ 1500/uL
- ANC ≥ 1000/uL
- Platelets ≥ 100 x 10^3/uL
- Hemoglobin ≥ 9 g/dL
- Serum Creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 40 mL/min (using the Cockcroft-Gault formula)

  Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$

  Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$
- AST ≤ 3.0 x ULN
- ALT ≤ 3.0 x ULN
- Total Bilirubin ≤ 1.5 x ULN, (except subjects with Gilbert's syndrome who must have a total bilirubin < 3.0 x ULN).

i) Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, has not been treated) if the reason for pre-treatment failure is related to the size of potential index lesions. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, ≥18 years.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half lives.

WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half lives.

Males who receive nivolumab who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Sexual Abstinence
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - WOCBP participants who choose complete abstinence must continue to have pregnancy tests.
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

* A male and female condom must not be used together

3.3.2 Exclusion Criteria

1) Target Disease Exceptions
   a) History of known leptomeningeal involvement (lumbar puncture not required).
   b) Previous stereotactic or highly conformal radiotherapy within 3 weeks before the start of dosing for this study. Note the stereotactic radiotherapy field must not have included the intracranial index lesion(s).
   c) Subjects previously treated with SRT > 3 lesions in the brain
   d) Intracranial lesion size > 3cm
2) Medical History and Concurrent Diseases
   a) History of whole brain irradiation.
   b) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitis, 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.
   c) Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled.
   d) Any concurrent malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix. For any prior invasive malignancy, at least 5 years must have elapsed since curative therapy and patients must have no residual sequelae of prior therapy.
   e) **Cohort A**: (asymptomatic): The use of corticosteroids is not allowed within 10 days prior to first treatment (based upon 5 times the expected half-life of dexamethasone) except patients who are taking steroids for physiological replacement. If alternative corticosteroid therapy has been used, consultation with the sponsor Medical Monitor is required to determine the washout period prior to initiating study treatment.
   Cohort B: (symptomatic): Subjects with neurologic sign and symptoms related to intracranial metastases who are being treated with a total daily dose of **higher** than 4 mg dexamethasone or equivalent within 10 prior to the start of treatment with study drug are excluded.
   f) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
   g) Subjects with history of life-threatening toxicity related to prior ipilimumab adjuvant therapy except those that are unlikely to re-occur with standard countermeasures (eg. hormone replacement after adrenal crisis).
3) Physical and Laboratory Test Findings
   g) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
   h) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) even if fully immunocompetent on ART—

due to the unknown effects of HIV on the immune response to combined nivolumab plus ipilimumab or the unique toxicity spectrum of these drugs in patients with HIV.

4) Allergies and Adverse Drug Reaction
   a) History of allergy to study drug components.
   b) History of severe hypersensitivity reaction to any monoclonal antibody.
5) Other Exclusion Criteria
   i) Prisoners or subjects who are involuntarily incarcerated.
   j) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products.

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2) Does not apply to symptomatic subjects in Cohort B who are being treated with CST for CNS symptoms.

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of melanoma)

3.4.2 Other Restrictions and Precautions

Cohort A: Asymptomatic subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.4.2.1 Magnetic Resonance Imaging

Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and principal investigator should determine the appropriate precautions or guidelines that should be instituted for subjects with tattoos, body piercings or other body art. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

3.4.2.2 Permitted Therapies: SRT

If a subject demonstrates clinical benefit, but disease progression in ≤ 3 intracranial metastases occurs, the investigator may prescribe SRT (single episode), and 2 scenarios are permitted as detailed below.

- If the patient is clinically stable, progression should be confirmed by follow-up imaging after 4 weeks. If progression is confirmed, the patient may undergo SRT treatment (single episode) for ≤ 3 lesions and may receive ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks. Treatment with the study drugs can be resumed after taper completion as long as the patient does not demonstrate criteria for discontinuation (see Section 3.5, Section 4.5.5, Section 4.5.5.1)
- If the patient is symptomatic as a result of the disease progression, and clinical assessment indicates a requirement for SRT without the delay imposed by the 4 week confirmatory scan, the patient may undergo SRT and may receive ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks. Treatment with the study drugs can be resumed after the completion of the taper as long as the patient does not demonstrate criteria for discontinuation (see Section 3.5, Section 4.5.5, and Section 4.5.5.1).

As a general guide, efforts should be made to avoid radiotherapy within 2 weeks after a treatment of either nivolumab + ipilimumab combination therapy or nivolumab monotherapy and avoid treatment resumption until at least 1 treatment-cycle length after radiotherapy.

NOTE: To continue on study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

Recommended Observation Period after On-Study SRT

Subjects should be evaluated for neurologic toxicity during the post-SRT treatment window as defined below:

- Subjects receiving SRT during induction (nivolumab combined with ipilimumab) should be followed for 3 weeks following the next nivolumab with ipilimumab dose. The resumption of treatment with study drugs after SRT is specified in Section 4.5.2.1 and Section 4.5.2.2.
- Subjects receiving SRT during maintenance (nivolumab monotherapy) should be followed for a period of 2 weeks following the next nivolumab monotherapy dose. The resumption of treatment with study drugs after SRT is specified in Section 4.5.2.1 and Section 4.5.2.2.

Criteria for discontinuation include steroid dependency and/or maintenance of/ development of neurological symptoms (see Sections 3.5, Section4.5.5, and Section 4.5.5.1). See Section 4.5.2.1for dose interruptions due to SRT.

3.4.2.3 Permitted Therapy for Brain Edema

Steroid treatment ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks is allowed only for the treatment of brain edema (single episode). If a second episode of brain edema requires steroid treatment, the BMS medical monitor and overall study primary investigator must be consulted.

3.4.2.4 Permitted Therapy: Brain Surgery

If a subject has disease progression in the brain and qualifies as a medical emergency, a single surgical intervention is permitted with the approval of the Medical Monitor. To remain on-study, the subject must have remaining measurable disease in the brain.

3.5 Discontinuation of Subjects from Treatment with Study Drugs

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation including the development of treatment-emergent, treatment-related unacceptable toxicity including neurological toxicity (see Section 4.5.5 and Section 4.5.5.1)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study, clinical benefit rate is the primary endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained

third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following (Table 4-1):

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4-1: Study Drugs for CA209204

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light, freezing and shaking.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are nivolumab and ipilimumab.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Please refer to the current version of the nivolumab and ipilimumab IBs and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and BMS-734016 (ipilimumab).

Nivolumab

Nivolumab vials must be stored at a temperature of 2° C to 8° C and should be protected from light, freezing, and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab IB section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60-minute IV infusion ± 10 minutes using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets. Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab is to be administered as a 90-minute IV infusion ± 10 minutes, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

4.4 Method of Assigning Subject Identification

CA209204 study is an open-label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

4.5 Selection and Timing of Dose for Each Subject.

All enrolled subjects will be treated in an open-label fashion as described below:

- Nivolumab administered IV over 60 minutes ± 10 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes ± 10 minutes at 3 mg/kg every 3 weeks for a total of 4 doses of the combination therapy followed by nivolumab administered IV over 60 minutes ± 10 minutes at 3mg/kg every 2 weeks for a maximum of 24 months or until progression or unacceptable toxicity.

Dosing schedule is detailed in Table 4.5-1 and Table 4.5-2 .

.

Table 4.5-1: CA209204: Dosing Schedule for Cycle 1 and Cycle 2

1 Cycle = 6 weeks						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
All Enrolled Subjects Combination Treatment (Nivolumab 1mg/kg + Ipilimumab 3 mg/kg)	1 mg/kg Nivolumab + 3 mg/kg Ipilimumab			1 mg/kg Nivolumab + 3 mg/kg Ipilimumab		

Table 4.5-2: CA209204 Dosing Schedule Cycle 3 and Beyond

Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treament with Nivolumab +Ipilimumab. **1 Cycle = 6 weeks**						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
All Enrolled Subjects Nivolumab monotherapy	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 4.5.6 for premedication recommendations following either a nivolumab- or an ipilimumab-related infusion reaction.

4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume. See Section 4.5.4.

Ipilimumab and / or nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The BMS Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of ipilimumab or nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume ipilimumab or nivolumab dosing when re-treatment criteria are met.

Tumor assessments should continue as per protocol even if dosing is delayed.

4.5.2.1 SRT and Dose interruptions

If a patient requires SRT for a single episode of intracranial progression in ≤ 3 intracranial metastases, treatment with study drug will be interrupted as specified in Section 3.4.2.2. The protocol specified steroid treatment and taper (≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks four week steroid) must be completed before treatment with the study drugs is resumed.

The length of dose delay/dose interruptions for patients receiving SRT is counted from the date of the last dose of study drug. As specified in Section 4.5.5, patients may resume treatment with study drug after the protocol allowed limit of 6 weeks, if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks for any reason including on study treatment with SRT, the BMS Medical Monitor must be consulted.

If the patient is unable to resume treatment due to corticosteroid dependence or neurologic symptoms, the patient will discontinue study drug treatment and go to follow-up.

4.5.2.2 Resumption of Treatment after Dose Delay

If there is a delay in treatment due to AEs associated with study medication, when the patient resumes treatment, he/she will receive the next dose, rather than the missed dose. If the dose delay occurs during the combination treatment (induction), the patient will receive less than 4 doses of the combination treatment.

If there is a delay due to SRT or AEs not associated with study medication, when the patient resumes treatment, he/she will receive the missed dose. If the dose delay occurs during the combination treatment (induction), the patient has the opportunity to receive all four doses of the combination treatment.

4.5.2.3 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration from adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrine
- Dermatologic
- Neurologic

While the ipilimumab IB contains safety management algorithms for similar adverse events, the recommendations are to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management.[62] Therefore, the algorithms recommended for utilization in CA209204 are included in Appendix 1.

4.5.3 Dose modifications

Dose reductions or dose escalations are not permitted.

4.5.4 Criteria to Resume Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- Subjects with baseline Grade 1 AST/ALT or total bilirubin 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
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor

Dose delay of treatment that results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.5.2.1 and Section 4.5.5

There will be no dose reductions for study medications.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.2.1 and Section 4.5.5.

4.5.5 Discontinuation of Study Drug

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies::
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN

  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Note: If a subject experiences a severe adverse event during induction treatment (ie, the combination of nivolumab and ipilimumab) that requires discontinuation from further treatment with the combination, continuing treatment with nivolumab monotherapy may be considered contingent on discussion with and approval by the BMS Medical Monitor.

<u>Exceptions to Permanent Discontinuation of study drug dosing under the following situations</u>:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Subjects with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.

4.5.5.1 Discontinuation of Treatment with Study Drug due to Neurotoxicity

Treatment-related neurologic adverse events, ≥ Grade 3 define unacceptable neurotoxicity and require permanent discontinuation of study drug. Any neurologic adverse event that occurs at increased frequency or severity, or is unexpected in nature, should be considered potentially related to study treatment.

4.5.6 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For **Grade 2** symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.5.7 Treatment Beyond Initial Radiological Assessment of Disease Progression

As previously described in Section 1.1.2.4, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[23] This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy.

Subjects receiving treatment in this study will be permitted to continue treatment beyond initial PD (intracranial metastases using modified RECIST 1.1 criteria; extracranial disease by RECIST 1.1) as long as they meet the following criteria:

- Investigator assesses clinical benefit AND
- Subject is tolerating study drug.

If a patient has disease progression of ≤ 3 intracranial lesions, the patient may receive SRT (single episode) as clinically appropriate and then resume study treatment as outlined in Section 3.4.2.2.

Subjects with confirmed progression (confirmation assessment will occur approximately 4 weeks after initially assessed progression) will be assessed radiographically and by clinical judgment as to whether the subject is deriving clinical benefit from treatment and should continue study treatment or discontinue and enter the follow up/survival phase of the study according to the time and events schedule presented in Section 5. If progression is confirmed, then the date of disease progression will be the first date the subject met the criteria for progression.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. Subject must provide written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent

including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply

For subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Treatment with study medication should be discontinued permanently upon documentation of further progression.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not applicable to this study.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209204)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening.
Medical History	X	
Tumor Tissue Samples	X	• Pre-treatment tumor tissue is required from all patients and should be from an excisional, incisional, (preferred), punch, or core needle biopsy. Tissue representing an extracranial metastasis collected after prior therapies is preferred, but archival primary or metastatic tumor tissue specimens are acceptable. A tumor tissue block or minimum of 15 slides should be submitted. • The following are optional: -H&E of primary cutaneous melanoma with accompanying pathology report; where available but strongly recommended (can be submitted at later date) -Intracranial metastasis: Any biopsy specimen acceptable (block or minimum of 15 slides); where available • -Submit a copy of the original pathology reports that correspond to submitted specimens if available.
Safety Assessments		
Complete Physical Examination	X	
Vital Signs and oxygen saturation	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion. Obtain vital signs at the screening visit and within 72 hours prior to first dose
Physical Measurements	X	Height and weight
Performance Status	X	
ECOG	X	Within 14 days prior to dosing
Assessment of Signs and Symptoms	X	Within 14 days prior to dosing

Table 5.1-1: Screening Assessments (CA209204)		
Procedure	**Screening Visit**	**Notes**
Concomitant Medication Collection	X	Within 14 days prior to dosing Cohort B: CST treatment for CNS symptoms must be recorded.
Laboratory Tests	X	CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C (HBV sAG, HCV antibody, or HCV RNA) within 14 days prior to dosing
Pregnancy Test (WOCBP Only)	X	Serum or urine must be performed.
Efficacy Assessments		
Tumor Assessment	X	Section 5.4 CT/MRI Chest, abdomen, pelvis and all known or suspected sites of disease within the prior 28 days. Brain MRI is required within the prior 14 days. Scans must follow sponsor-supplied Imaging Manual.

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes • **Tumor assessment should be continued as per protocol even if dosing is delayed**
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**	
Safety Assessments							
Targeted Physical Examination Cycle 1	X	X	X	X	X	X	**Cycle 1**: **Weekly** for first 6 weeks: conducted by study physician; Within 72 hours prior to dosing on Weeks 1 and 4.
Cycle 2	X			X			**Cycle 2**: **Weeks 1 and 4**: conducted by study physician within 72 hours prior to dosing.
Phone assessment with study medical staff: Cycle 2 only.		X	X		X	X	**Cycle 2**: **Weeks 2,3,5,6** * Phone assessment with study medical staff required
Vital Signs and Oxygen Saturation Cycle 1	X	X	X	X	X	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing. **Cycle 1**: Weekly for first 6 weeks.
Cycle 2	X			X			**Cycle 2**: Weeks 1 and 4 only
Physical Measurements (including performance status) Cycle 1	X	X	X	X	X	X	Weight and ECOG status within 72 hours prior to dosing. **Cycle 1**: Weekly for first 6 weeks.
Cycle 2	X			X			**Cycle 2**: Weeks 1 and 4 only
Adverse Events Assessment	Continuously						
Review of Concomitant Medications Cycle 1	X	X	X	X	X	X	**Cycle 1**: **Every week** during study visit. **Cohort B**: CST treatment for CNS symptoms must be recorded.
Cycle 2	X	X*	X*	X	X*	X*	**Cycle 2: Weeks 1 and 4** during study visit. *Phone check in with study medical staff required **Cohort B**: CST treatment for CNS symptoms must be recorded.

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes • Tumor assessment should be continued as per protocol even if dosing is delayed
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Laboratory Tests	X			X			Within 72 hrs prior to dosing to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test (WOCBP Only)	X			X			Within 24 hours prior to administration of study drug. Serum or Urine
Outcome Research Assessment Healthcare Resources Utilization (HCRU)	X						Only Cycle 1 prior to dosing and at the time of progression
Exploratory Biomarker Testing							At progression: Samples from subjects that have progressed are optional. Refer to Table 5.6.1.3-1
Myeloid-derived Suppressor Cells	Refer to Table 5.6.1.3-1						To be collected pre-dose
Exploratory Serum Biomarkers	Refer to Table 5.6.1.3-1						To be collected pre-dose.
Peripheral Blood RNA	Refer to Table 5.6.1.3-1						To be collected pre-dose
Peripheral Blood Mononuclear Cells (PBMCs) for Immunophenotyping / Functional Assessment	Refer to Table 5.6.1.3-1						To be collected pre-dose
Whole Blood Samples (DNA for SNPs and Exome Sequencing)	Refer to Table 5.6.1.3-1						To be collected pre-dose.

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes • **Tumor assessment should be continued as per protocol even if dosing is delayed**
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**	
Efficacy Assessments							
Tumor Assessment	Section 5.4 **CT/MRI of chest, abdomen, pelvis, and brain (MRI).** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.						
NANO Scale Cycle 1	X	X	X	X	X	X	**Cycle 1**: **Weekly** for first 6 weeks: conducted by study physician; Within 72 hours prior to dosing on Weeks 1 and 4.
Cycle 2	X			X			**Cycle 2**: **Weeks 1 and 4**: conducted by study physician within 72 hours prior to dosing.
Administer Study Treatment							
Nivolumab 1mg/kg + Ipilimumab 3 mg/kg	X			X			Dose will remain the same as long as current patient weight is within 10% of the Cycle 1/Day 1/enrollment weight Doses may be administered within 2 days after the scheduled date if necessary. See Section 4.5.2.1 for dose interruption specific for SRT.

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• **Tumor assessment should be continued as per protocol even if dosing is delayed.** • **Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.**
Safety Assessments							
Targeted Physical Examination	X		X*		X		Week 1 and Week 5: conducted by study physician. *Week 3: conducted by study medical staff. May be performed more frequently as clinically indicated
Vital Signs and Oxygen Saturation	X		X		X		Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing.
Physical Measurements and Performance Status	X		X		X		Weight and ECOG status within 72 hours prior to dosing.
Adverse Event Assessment	Continuously						
Review of Concomitant Medications	X		X		X		**Cohort B**: CST treatment for CNS symptoms must be recorded
Laboratory Tests	X				X		Within 72 hrs prior to dosing to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test (WOCBP Only)	X				X		Within 24 hours prior to administration of study drug. Serum or Urine
Outcomes Research Assessment Healthcare Resource Utilization	X						From Cycle 3 and beyond, prior to dosing, every 12 weeks for a maximum of 24 months of treatment or at the time of progression

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**	• **Tumor assessment should be continued as per protocol even if dosing is delayed.** • **Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.**
Exploratory Biomarker Testing							At progression, Samples from subjects that have progressed are optional. Refer to Table 5.6.1.3-1
Exploratory Serum Biomarkers	Refer to Table 5.6.1.3-1						To be collected pre-dose.
Peripheral Blood Mononuclear Cells (PBMCs) for Immunophenotyping / Functional Assessment	Refer to Table 5.6.1.3-1						To be collected pre-dose
Efficacy Assessments							
Tumor Assessments	Section 5.4 **CT/MRI of chest, abdomen, pelvis, and brain (MRI).** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.						
NANO Scale	X		X*		X		Week 1 and Week 5: conducted by study physician. *Week 3: conducted by study medical staff May be performed more frequently as clinically indicated.

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• **Tumor assessment should be continued as per protocol even if dosing is delayed.** • **Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.**
Administer Study Treatment							
Nivolumab 3 mg/kg	X		X		X		Dose will remain the same as long as current patient weight is within 10% of the Cycle 1/Day 1/enrollment weight Doses may be administered within 2 days after the scheduled date if necessary. Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab

Table 5.1-4: Follow-up Assessments (CA209204)			
Procedure	**Follow-Up[a] Visits 1 and 2**	**Survival[b] Follow-up Visits**	**Notes Follow up is 3 years from start of treatment.**
Safety Assessments			
Complete Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	All SAEs must be collected that occur within 100 days of the last dose of study drug(s). All nonserious adverse events (not only those deemed to be treatment-related) should be collected for a minimum of 100 days following discontinuation of study treatment. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form.
Laboratory Tests	X		Perform Lab tests for Follow-up Visit 1 and repeat at Follow-up Visit 2, if any study drug toxicity persists. CBC w/differential, LFTs, BUN or serum urea level, creatinine, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3).
Pregnancy Test (WOCBP Only)	X		Serum or urine
Review of Concomitant Medication	X		**Cohort B**: CST treatment for CNS symptoms must be recorded
Document any current treatment regimen	X	X	To include immuno-therapy, chemotherapy, targeted therapy, radiotherapy, surgery, and all interventions to treat metastatic melanoma.
Survival Status		X	
Subject Status	X	X	Every 3 months, may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy
Exploratory Biomarker Testing	X		At progression only: Samples from subjects that have progressed are optional. Refer to Table 5.6.1.3-1

Table 5.1-4: Follow-up Assessments (CA209204)			
Procedure	**Follow-Up[a] Visits 1 and 2**	**Survival[b] Follow-up Visits**	**Notes Follow up is 3 years from start of treatment.**
Efficacy Assessments			
Tumor Assessments	X		Only for subjects who have not progressed on study therapy or who have discontinued study treatment for reasons other than documented disease progression. Section 5.4 **CT/MRI of chest, abdomen, pelvis and brain (MRI)** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.
NANO Scale	X		
Outcomes research assessment (HCRU)	X	X	To be conducted at progression and at survival follow ups

[a] Follow-up Visit 1 = 30 days from the last dose +/- 7 days or coincide with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 37 days after last dose, Follow-up visit 2 = 84 days (+/- 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from Follow-up Visit 2 +/- 7 days

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will not be permitted (this does not include parameters that require a confirmatory result) unless there was a technical error in performance of the lab test and the first result is invalid.

Any new result will override the previous result (ie, the most current result prior to dosing) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- CA209204 Imaging Manual

5.3 Safety Assessments

5.3.1 Medical History, Physical Exam, Physical Measurements

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be performed within 28 days prior to first dose.

Baseline local laboratory assessments should be done within 14 day prior to first dose and are to include: CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C (HBV sAG, HCV antibody, or HCV RNA).

While on-study and during follow-up, local laboratory assessments are to be conducted as specified on Table 5.1-2 to Table 5.1-4. Thyroid function testing is to be done every 6 weeks (every 3 cycles) for subjects receiving nivolumab.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During study treatment and nivolumab Follow-Up Visits 1 and 2, toxicity assessments should be done in person. Once subjects reach the survival follow-up, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as specified in Section 5.1 and as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments are to be completed within 72 hours prior to dosing.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) IB.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.3.2 Vital Signs

Vital signs consist of blood pressure, heart rate, respiratory rate and temperature measurements. Vital signs will be obtained as outlined in Table 5.1-1 to Table 5.1-3.

5.3.3 Imaging Assessment for the Study

All subjects will undergo CT scanning and volumetric MRI of the brain at the time points specified in Table 5.1-1 to Table 5.1-4.

CT and MRI scans will be assessed locally per the modified RECIST 1.1 criteria outlined in Appendix 3. Up to 5 extracranial and 5 intracranial lesions will be followed for efficacy per the criteria. Please refer to Appendix 3 for guidelines regarding images, target lesion selection and response criteria.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Clinically significant radiologic findings or changes from baseline scans will be coded as adverse events or serious adverse events according to the criteria described in Section 6.

5.3.4 Pregnancy Testing

WOCBP are required to have several pregnancy tests performed as presented in Table 5.1-1 to Table 5.1-4. A negative serum or urine pregnancy test must be documented at the screening visit as per Table 5.1-1. Additionally WOCBP must exhibit a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug; therefore the screening pregnancy test may need to be repeated prior to the start of study drug dosing. A serum or urine pregnancy test will also be conducted at End of Treatment Visit.

5.3.5 ECOG Status

ECOG performance status will be evaluated at the screening evaluation and at each visit as outlined in Time and E. An outline of the ECOG performance status is provided in Appendix 2.

5.3.6 Adverse Event Monitoring

Adverse Events (AEs) will be evaluated according to the NCI CTCAE Version 4.0 on a continuous basis starting from when the subject takes the first dose of study administration, up to and including Follow-Up and End of Treatment visits (at minimum, for 100 days following last dose of study drug). Serious Adverse Events (SAEs) must be collected from the time period following written consent to participate in the study up to and including follow-up.

5.3.7 Laboratory Test Assessments

Results of all safety laboratory collections must be obtained and reviewed in advance of study drug dosing, as applicable. Amylase and lipase should be collected with the chemistry collection, but these lab results do not require review prior to dosing.

Serum Chemistry is to be obtained as specified in Table 5.1-1 to Table 5.1-4. A free-T4 and free-T3 will be performed reflexively for out of range TSH values. A CBC with differential is to be obtained. The CBC with differential includes hemoglobin, hematocrit, white blood cells, platelets (direct platelet count), erythrocyte sedimentation rate, WBC differential enumeration of total and percentage of neutrophils, lymphocytes, eosinophils, basophils and monocytes.

5.4 Efficacy Assessments

Assessment of extracranial disease (by CT scan or other approved modalities and intracranial disease (by MRI scan) will be performed per the schedule in Table 5.1-1 to Table 5.1-4. Investigators may obtain more frequent follow-up MRI scans as medically indicated.

Baseline assessments should be performed within 28 days prior to first dose of study drug utilizing CT or MRI for systemic lesions and within 14 days for brain lesions (MRI only). In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, brain, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning at 6 weeks (± 7 days) from the first dose of study drugs for the first 12 months and every 12 weeks (± 7 days) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing

study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria for all systemic lesions and modified RECIST 1.1 for brain lesions (Appendix 3).

Radiographic images will be collected and sent to a centralized imaging core laboratory for storage and potential future central reading.

All radiologic imaging from this study will be assessed at the study site by the Investigator. Sites will be trained in image acquisition parameters, image analyses, and submission process, prior to scanning the first study subject. These guidelines will be outlined in a separate CA209204 Site Imaging Manual.

For extracranial disease assessment, contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis and other areas of disease are to be performed for tumor assessments per Table 5.1-1 to Table 5.1-4. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of $\leq$ 5 mm with no gap (contiguous).

Use of CT component of a PET/CT scanner: Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MRI scans: Bi-dimensional and three-dimensional contrast enhanced MRI of the brain will be acquired per the CA209204 Imaging Manual requirements. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points. Cases of suspected radiologic disease progression will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment of progression.

5.4.1 Computed Tomography Imaging (CT)

Baseline CT assessments should be performed within 28 days prior to enrollment. In addition to chest, abdomen, pelvis, all known sites of disease should be assessed at baseline.

Subsequent CT assessments should occur at +/- 7 days per scheduled visits and should include chest, abdomen, and pelvis, and all known sites of disease. The same imaging method used at baseline should be used for all CT assessments. Subjects will be evaluated for tumor response every 6 weeks for Year 1 and every 12 weeks thereafter until progression or discontinuation, whichever is later.

5.4.2 Brain Magnetic Resonance Imaging (MRI)

All subjects will receive efficacy assessments with brain MRI at time points specified in Table 5.1-1 to Table 5.1-4. Baseline brain MRI should be performed with 14 days prior to enrollment.

All MRIs should occur at ± 7 days per scheduled visits. Investigators may obtain more frequent follow-up MRI scans as medically indicated.

5.4.3 Confirmation of Scans

Verification of Response: Confirmation of intracranial response will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment. If repeat scans confirm overall response (OR), then response should be declared using the date of the initial scan. If repeat scans do not confirm OR, then the subject is considered not to have had an OR.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal and will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment of progression. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease.

5.4.4 Algorithms for Response Assessments

5.4.4.1 Primary Efficacy Assessment

The primary endpoint of the study is intracranial CBR $\geq$ 6 months in subjects with malignant melanoma with intracranial metastases treated with nivolumab combined with ipilimumab therapy. Tumor response will be based on Investigator assessment using modified RECIST 1.1.

5.4.4.2 Secondary Efficacy Assessments

The secondary efficacy endpoints include extracranial CBR $\geq$ 6 months using RECIST 1.1 and will be based on Investigator assessment.

Additional secondary endpoints are specified in Section 8.4.2.

5.4.4.3 Exploratory Efficacy Assessment

An exploratory efficacy endpoint will compare computer-assisted tumor volume from three-dimensional (3D) MRI to bi-dimensional measures with respect to absolute values and percent change from baseline in CNS lesions. Three-dimensional MRI images will be evaluated.

NANO assessment will be performed to determine change in neurologic function.

Additional exploratory endpoints are specified in Section 8.4.3.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

5.6.1 Rationale and Aims for Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab and/or nivolumab in combination with ipilimumab will be investigated in peripheral blood and in tumor specimens acquired from all subjects prior to treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with melanoma or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

The major questions that will be addressed by the biomarker plan for CA209204 are:

- Is there an association between baseline pathologic features of primary cutaneous melanoma (eg, regression, ulceration, pattern and components of immune infiltrate) and CBR endpoints?
- Does expression of PD-L1 on tumor cells prior to therapy correlate with clinical efficacy to combination therapy?
- Does the composition and phenotype of the tumor microenvironment at baseline (including immune infiltrates) correlate with clinical efficacy?
- Does the mutational status of tumor cells (eg BRAF, NRAS) correlate with clinical efficacy to nivolumab and ipilimumab combination therapy?
- Are baseline levels or changes in peripheral blood immune cell subpopulations and serum soluble factors associated with clinical endpoints and/or the occurrence of adverse events?
- How does combination therapy alter the activating and negative costimulatory molecules on immune cells in the periphery? Are there distinct mechanisms of resistance to combination therapy?
- Does natural genetic variation (SNPs) in select immune-related genes associate with clinical endpoints and/or on the occurrence of adverse events?
- Are the tissue biomarker profiles of paired extracranial and intracranial metastases within individual patients (where available) similar such that an extracranial tumor can act as a surrogate for predicting drug response when an intracranial metastatic sample is unavailable for testing?

Pre-treatment tumor tissue should be collected on all patients. Where feasible, baseline tumor tissue representative of a extracranial metastasis collected after prior therapies should be submitted for biomarker analysis. In cases where no extracranial metastatic sample is amenable to biopsy and there is no archival metastatic tumor tissue available, then an archival primary cutaneous lesion will suffice. In cases where an archival sample exists and is available, but acquisition of the sample will result in delay of initiation of treatment, the patient may begin study treatment prior to sample receipt. Peripheral blood will be collected prior to therapy. Peripheral blood samples will also be collected at selected time points on treatment and optional tumor biopsies are encouraged at any time point on study. If a biopsy or surgical resection is performed on treatment or at the time of

progression, tumor sample (block or slides and frozen tissue where available) should be submitted for analysis. If biomarker samples are collected but study drug(s) is not administered, samples will be retained. A detailed description of each assay system is described below and a schedule of pharmacodynamic evaluations is provided in Table 5.6.1.3-1.

Tumor-Based Biomarkers

Tumor biopsy specimens representative of baseline extracranial metastatic disease or primary cutaneous disease if metastatic tumor tissue is not available will be obtained from consenting subjects enrolled on the study to characterize immune cell populations, expression of selected tumor markers, and to measure genomic characteristics of the tumor including BRAF/NRAS mutation status. Either archived material or a newly acquired biopsy representing a extracranial metastasis, or primary cutaneous disease submitted as blocks or slides, is required for all patients. Newly acquired biopsies of baseline extracranial disease, are encouraged for patients with accessible lesions where this additional biopsy is deemed safe by the investigator. These newly acquired biopsies will be used to generate fixed tissue (for provision of blocks/slide sections) and frozen tissue, to support biomarker analyses. Newly acquired biopsies should be prioritized over archival material where clinically appropriate. An archived biopsy prior to therapy is acceptable if the fresh biopsy cannot be obtained and if the archived tissue meets the defined criteria as stated below:

- An archived specimen (block or slides) should contain abundant tumor tissue (~50%) and adjacent stroma suitable to support biomarker objectives
- If an archived block is not available, 15 or more slides containing tumor can be generated for exploratory use
- Whenever possible the archival tumor sample should be obtained from a time point after the subject has completed other systemic therapy and prior to study treatment.

While on-treatment biopsy samples are optional, they are encouraged to evaluate the effect of nivolumab in combination with ipilimumab in the tumor microenvironment, which is expected to be the site where restoration of T-cell function occurs. It is important to study immune events at the tumor microenvironment level to understand possible associations with responses and to identify markers that can be measured peripherally in future trials. Pre-treatment and on-treatment biopsies will generate data to further the understanding of the mechanism of action of nivolumab in combination with ipilimumab and to further refine the combinability of these regimens in future trials.

5.6.1.1 Tumor-Based Biomarker Measurements

Tumor samples may be used for the following assessments:

Characterization of tumor infiltrating lymphocytes (TILs) and tumor antigens:

- Immunohistochemistry (IHC) will be used to assess the tumor microenvironment including the pattern and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before exposure to therapy (and after therapy when tumors are available). Tumor and immune cell markers that

will be assessed by IHC may include, but not necessarily be limited to, CD3, CD4, CD8, FOXP3, CD68, MHC-II, PD-1, PD-L1, PD-L2 and IDO.

- BRAF/NRAS mutation assessment: BRAF and NRAS mutation testing will be centrally performed, regardless of prior testing. If available, the archival tumor tissues specimens will be used for this assessment, but in the event that archival tissue is not available, fresh biopsy specimens may be used for this purpose. Most importantly, this assay should **only** be performed on fresh tumor tissue if there is adequate tissue available for all other studies.

Other exploratory tumor-based biomarker measures:

- Tumor tissue or derived RNA/DNA may also be evaluated by fluorescent *in situ* hybridization (FISH), genetic mutation, DNA sequencing (eg T cell receptor sequencing), rearrangement detection methods, such as whole exome and transcriptome sequencing, and/or quantitative PCR or RT-PCR as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance to therapeutics used in the treatment of melanoma. Such analyses will be completed retrospectively and within the scope of informed consent. Additionally, residual tumor tissue samples from all mandatory and optional collections will also be retained by the BMS Biobank for medical research purposes. No additional sampling is required for residual collections. Medical research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations.

5.6.1.2 Tumor Sample Collection Details

Newly acquired Biopsy:

- Newly acquired biopsies at baseline should be prioritized over archived samples and are also encouraged on treatment. The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be performed with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional/incisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

- Biopsy samples should be excisional, incisional (strongly encouraged), punch biopsies or core needle biopsies, using a gauge needle that is utilized within the institution. In general, a 16 or 18 gauge needle is used for core biopsies. For core needle biopsies, up to 4 cores are recommended. An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided two ways in the following priority order: 1) into formalin for fixation and paraffin embedding, 2) in RNAzole for RNA/DNA extraction.

- Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any case where

the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

- Samples should be fixed in 10% Neutral-buffered formalin for 24 – 48 hours. Tumor tissue samples should not be shipped in formalin as the temperature and length of fixation cannot be controlled during shipping.
- If slides are submitted, the recommended tissue section thickness is 4 microns and the **slides must be positively charged**. Freshly cut slides sections should be submitted, and slides should be shipped refrigerated at 2-8 ^{0} C.
- Sample shipments should include a completed requisition form containing collection date, collection method, primary/met, site, fixation conditions, and a copy of Pathology report, if available.

Archived Specimens (Primary diagnostic melanoma biopsy (cutaneous or other), extracranial metastasis and intracranial metastasis):

For the primary diagnostic biopsy, an H&E should be submitted for review of pathologic features. For metastatic lesions (extracranial +/- intracranial), and primary cutaneous lesions a minimum of 1 formalin-fixed paraffin embedded (FFPE) tumor tissue block (preferred) OR minimum of 15 FFPE unstained slide sections, freshly cut, are required for assessment of PD-L1 status and other biomarker evaluations. Complete instructions on the collection, processing, handling, and shipment of archival tumor tissue and tumor biopsy samples will be provided in a separate procedure manual.

5.6.1.3 Peripheral Blood Biomarkers

Peripheral blood samples will be taken prior to initiation of study therapy and at designated time points post-treatment (see Table 5.6.1.3-1 for additional details on the blood sample collection schedule). These samples will be analyzed for the following measures:

Exploratory Serum Biomarkers: Baseline and post- treatment modulation of serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include, but are not limited to ELISA, or other multiplex-based assay methods. Analysis of these factors may identify potential biomarkers with prognostic and predictive value for outcomes (response, progression-free survival, overall survival, and toxicity). Analytes to be assayed may include but are not limited to soluble PD-1, IL-10, IL-6, IL-8, MIP-1 alpha, MCP-1, TNF alpha, ICAM-1, IL-1r alpha, MMP-3, IP-10, MCP-2, MIG, IL-2R alpha, MICA, AAT, CRP, vWF, RANTES, TIMP-1, TNFR2, IL-18, MIP-1 beta, Haptoglobin, B2M, and VCAM-1. Serum samples will be collected as specified in Table 5.6.1.3-1 and processed as detailed in the Laboratory Manual.

PBMC Flow Cytometry (Immunophenotyping) and Functional Analyses: To explore the immunomodulatory effects of nivolumab in combination with ipilimumab over the course of treatment on peripheral blood leukocytes, exploratory flow cytometric analyses will be conducted. T cell subsets to be analyzed may include, but are not limited to CD4/CD25/FoxP3, CD4/CD8/CD45RA/CCR7, CD4/CD8/LAG3/PD-1/PD-L1 and CD4/CD8/CD137. CD14 and PD-

L1 may be utilized to measure a subset of monocytes. To explore whether blockade of PD-1 and/or combination PD-1 and CTLA-4 blockade will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells may be performed, including but not limited to, assays for interferon-gamma (IFN-γ), CD107 and granzyme B. This assay will use a non-specific stimulus, including but not limited to anti-CD3, and would allow for comparison of the effect of nivolumab in combination with ipilimumab on T cell function across multiple indications where more specific assays are not available. By using a non-specific stimulus, it allows for determination of the full effector function potential that can be achieved.

Myeloid-Derived Suppressor Cells (MDSCs): Baseline and on-treatment samples will be collected for measurement of myeloid-derived suppressor cells (MDSCs), a cell population of myelogenous origin that suppresses T cell activation/proliferation and thus may be associated with worse outcome in patients treated with immunotherapy. MDSC measures will be associated with efficacy. Blood samples will be collected as specified in Table 5.6.1.3-1 and processed as detailed in the Laboratory Manual. Blood will be submitted to a location specified by the Sponsor.

Whole Blood Samples (DNA for SNPs and Exome Sequencing): In order to identify potential polymorphisms associated with the safety and efficacy of nivolumab in combination with ipilimumab, selected genes will be evaluated for single nucleotide polymorphisms (SNPs). A next generation sequencing platform will be used to examine a panel of immune-related genes. These genes were selected due to their potential association with response or resistance to immunotherapies, immune-related adverse events, and auto-immune diseases. Genes may include but are not limited to immune cell receptors or ligands, immunotherapeutic targets, and/ or immune cell functional markers or regulators. Blood samples will be collected during the study from consenting subjects to explore SNPs in specific genes. Data from this study will be combined with SNP results from other studies to explore possible associations of SNPs and clinical activity or adverse events associated with nivolumab and ipilimumab therapies. This sample may also be used for whole exome sequencing in order to support identification of somatic mutations present within the tumor tissue specimens.

Other exploratory peripheral biomarker measures: PBMCs, serum, peripheral blood RNA or whole bloos DNA may be used for future exploratory biomarker analyses relevant to melanoma or immunotherapy including but not limited to antitumor antibodies, TCR sequencing, gene expression or immune cell populations including but not limited to MDSC. Additionally, residual PBMCs, serum, whole blood or RNA/DNA derived from whole blood from all mandatory and optional collections will be retained by the BMS Biobank for medical research purposes. No additional sampling is required for residual collections. Medical research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations.

Table 5.6.1.3-1: CA209204 Biomarker Sample Schedule[a]

Collection Timing	Tumor	PBMC		Serum	Whole blood			
Study Day	Tumor biopsy	Immuno-phenotyping	Functional assessment	Exploratory Serum Biomarkers	Whole Blood Samples (DNA for SNPs and Exome Sequencing)		Peripheral Blood RNA	MDSC
Screening	X[b]							
C1D1W1	X[c]	X	X	X	X	X	X	X
C1D1W2		X	X					
C1D1W4		X	X	X				
C2D1W1		X	X	X			X	X
C3D1W1		X	X	X				
Upon progression[d]		X	X	X			X	X

[a] Biomarker sampling occurs prior to dosing of study drug(s). Sample collection time points must be aligned with dosing and imaging time points.

[b] Submission of a tumor sample prior to therapy is mandatory. If a fresh biopsy is not feasible, then an archived tumor sample must be submitted.

[c] Optional biopsies on-treatment (any visit) and upon progression and may be taken at the discretion of the investigator.

[d] Samples from subjects that have confirmed progression are optional.

5.7 Other Assessments

Healthcare resource utilization (HCRU) data will be collected in subjects with melanoma metastatic to the brain treated with nivolumab combined with ipilimumab followed by nivolumab monotherapy. HCRU is evaluated based on inpatient, outpatient office visits, emergency department and other ancillary services (such as home health, hospice and other) and reasons for these resource utilizations.

An HCRU questionnaire, part of the electronic case report form, will be administered at the start of Cycle 1 (Day 1, Week 1), every 12 weeks, at progression, and during follow up (Table 5.1-2, Table 5.1-3, and Table 5.1-4).

5.8 Results of Central Assessments

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review conducted by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

All efficacy objectives will be evaluated by Investigator assessment based on local radiologic tumor measurements using a modified RECIST 1.1 for intracranial and RESCIST 1.1 for extracranial (Appendix 3).

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs

must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause

interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1 .

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, X-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee external to BMS will not be used in this study. A Steering Committee will be created and composed of a core group of study investigators who are experts in treating patients with melanoma brain metastases with sponsor physicians/ study staff. The steering committee will be informed if a safety signal emerges and will be informed of the results of the interim analyses. After review of the available safety and tolerability data from the interim analysis, the Steering Committee will recommend continuation, modification or termination of the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The total sample size for the treatment of nivolumab combined with ipilimumab is 110 subjects. All patients will contribute to the primary efficacy assessment.

Cohort A will enroll asymptomatic subjects (n ~ 90), and Cohort B will enroll symptomatic subjects (defined in Section 3.3.1).

Table 8.1-1 presents the clinical benefit rates (CBRs) that would have to be observed to yield clinically meaningful results with respect to the lower bounds of the Clopper-Pearson exact two sided 90% and 95% CI. The planned sample size ensures that the maximum width of the exact 90% CI for any given CBR estimate does not exceed 18% and the maximum width of the exact 95% CI for any given CBR estimate does not exceed 20%.

Table 8.1-1: CA209204: Clinical Benefit Rates – two sided 90% confidence interval (Clopper-Pearson)

		Nivolumab + Ipilimumab (n=110)		
	Clinically meaningful CBR	Observed CBR	Clopper-Pearson exact two-side 90% CI	Clopper-Pearson exact two-side 95% CI
Brain (intracranial)	40%	53/110 (48.2%)	(40.0%, 56.4%)	(38.5%, 57.9%)
		57/110 (51.8%)	(43.6%, 60.0%)	(42.1%, 61.5%)
Systemic (extracranial)/ Global (intracranial +extracranial)	50%	65/110 (59.1%)	(50.8%, 67.0%)	(49.3%, 68.4%)

CBR = Clinical Benefit Rate

If the observed intracranial CBR rate is 51.8%, the sample size of 110 will achieve 80.4% power to detect a difference of 11.8% (51.8% versus 40% historical intracranial CBR rate) with a type I error rate of 0.10 for the two-sided binomial test.

8.2 Populations for Analysis

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- All Biomarker Subjects: All treated subjects with available biomarker data.

8.3 Endpoint Definitions

8.3.1 Tumor Assessment Endpoints

8.3.1.1 Best Overall Response (BOR) per Subject

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of first dose of study drug and the date of objectively documented progression or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.

In this study, BOR is specified for the intracranial, extracranial, and global compartments based on the (1) modified RECIST 1.1 criteria (intracranial), (2) RECIST 1.1 criteria (extracranial), (3) combination of modified RECIST 1.1 criteria and RECIST 1.1 criteria (global). Image assessment criteria (modified RECIST 1.1 and RECIST 1.1) are presented in Appendix 3.

For the assessment of BOR, all available assessments per subject are considered.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules, listed in order of priority:

- CR = At least two determinations of CR at least 4 weeks apart before progression.
- PR = At least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = At least one SD assessment ≥ 6 months after start of treatment.
- PD = At least two determinations of PD at least 4 weeks apart after start of treatment (and not qualifying for CR, PR or SD).

The BOR for each patient will also be determined by the IRRC as specified within the CA209204 Imaging Review Charter.

8.3.1.2 Overall Survival

Overall Survival (OS) is defined as the time from the date of the start of treatment until the date of death. For those subjects who have not died, OS will be censored at the recorded last date of subject contact, and subjects with a missing recorded last date of contact will be censored at the last date the subject was known to be alive.

8.4 Endpoints

8.4.1 Primary Endpoint

Intracranial clinical benefit rate (CBR) defined as the proportion of patients, whose best overall response according to modified RECIST1.1, is either complete response (CR), a partial response (PR) or stable disease (SD).

The primary endpoint is intracranial CBR. It is defined as the proportion of all treated subjects whose best overall response is either a CR or PR or whose best overall response was SD with duration of ≥6 months, as determined by modified RECIST 1.1 criteria for index intracranial lesions based on investigator review.

8.4.2 Secondary Endpoint(s)

Secondary endpoints are as follows:

- Intracranial ORR and intracranial PFS per modified RECIST 1.1 criteria;
- Extracranial CBR, extracranial ORR, extracranial PFS per RECIST 1.1 criteria

- Global (intracranial + extracranial) CBR, global ORR, and global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- OS
- Safety and tolerability will be measured by the incidence of AE adverse events, serious adverse events (SAE), deaths, and laboratory abnormalities.

Overall survival (OS) is defined as the time from first dosing date to the date of death, will be estimated using the Kaplan-Meier product-limit method, with subjects censored at their last known date alive.

Progression-free survival (PFS) is defined as the time between the date of first dose of study drug and the first date of documented confirmed progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose of study drug. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Overall response rate (ORR) is defined as the number of subjects who achieve a best overall response of complete response (CR) or partial response (PR) divided by the number of treated subjects. The best overall response is defined as the best response designation recorded between the date of first study dosing date and the date of progression, or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first.

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

8.4.3 Exploratory Endpoint(s)

The exploratory endpoints include:

- Intracranial time to objective response (TTR) and intracranial duration of response (DOR) per investigator per modified RECIST 1.1 criteria;
- Extracranial TTR and DOR per modified RECIST 1.1 criteria;
- Global TTR and DOR per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease.

Duration of response (DOR) is defined as the time between the date of first response to the date of first documented tumor progression (per modified RECIST 1.1 and/or RECISIT 1.1) or death due to any cause. Subjects who neither progress nor die are censored on the date of their last tumor assessment.

Time to response (TTR) is defined as the time from the first study dose date to the date of the first documented CR or PR.

DOR and TTR are evaluated for responders (CR or PR) only.

8.4.3.1 Neurologic Assessment in Neuro-Oncology (NANO)

Neurologic functioning will be evaluated using NANO. This objective and quantifiable assessment will evaluate nine major domains for subjects with intracranial tumors. The domains include: gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, behavior and overall. Each domain is rated on a scale of 0 to 3 where 0 represents normal and 3 represents the worst severity. A given domain should be scored non-evaluable if it cannot be accurately assessed due to preexisting conditions, co-morbid events and/or concurrent medications. The evaluation is based on direct observation/testing performed during routine office visits. The NANO scale will be completed by the investigator or designated study physician prior to dosing Day 1 Week 1 (baseline) and then at the time points indicated in on the schedule of events.

Additional exploratory endpoints for biomarkers and pharmacogenomics are described below.

8.4.3.2 Bi-dimensional and Three-dimensional MRI Imaging

Bi-dimensional (2D) and three-dimensional (3D) MRI will used to estimate intracranial tumor volume. The absolute values and percent change from baseline will be measured by computer-assisted software. MRI will also be used to define intracranial edema, hemorrhage, and increase in tumor size prior to regression (pseudoprogression) in the intracranial metastases.

8.4.3.3 Pathological Evaluation of Primary Tumors

A pathologist will evaluate the primary cutaneous melanomas for features including but not necessarily limited to, regression, ulceration, pattern and components of the immune infiltrate.

8.4.3.4 Characterization of Tumor Immune Infiltrates and Expression of Tumor Markers

Baseline levels and changes from baseline, where applicable, will be analyzed for the following biomarkers measured by immunohistochemical techniques: the number and composition of immune infiltrates in tumor biopsies, with selected markers including but not limited to, CD3+, CD4+, CD8+, FoxP3+, PDL1+, PD-1+, CD68, and MHCII. Tumor cell expression of markers including but not limited to, PD-L1 and PD-L2 may also be measured.

8.4.3.5 Genomic characterization of Tumor and Non-tumor DNA and RNA

Tumor DNA will be analyzed for BRAF and NRAS mutation status if this information is unknown at the time of enrollment. Next generation sequencing will be used to identify single nucleotide polymorphisms (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4. Gene expression analysis of whole blood may be performed. Sequencing of T cell receptors may also be performed.

8.4.3.6 Phenotypic and Functional Characterization of Peripheral Immune Cells

Flow cytometry will be used to measure the change from baseline of various populations of immune cells in the periphery including but not limited to MDSC, B cells, NK cells, T cell subsets including effector, memory, exhausted and regulator. The functional status of T cell subsets may also be assessed.

8.4.3.7 Measurement of Soluble Factors

Changes from baseline will be analyzed for the analytes that may include but are not limited to, soluble PD-1, IL-10, IL-6, IL-8, MIP-1 alpha, MCP-1, TNF alpha, ICAM-1, IL-1r alpha, MMP-3, IP-10, MCP-2, MIG, IL-2R alpha, MICA, AAT, CRP, vWF, RANTES, TIMP-1, TNFR2, IL-18, MIP-1 beta, haptoglobin, B2M, and VCAM-1.

8.5 Analyses

The analyses of primary, secondary, and exploratory endpoints will be reported for the treated subjects, and by cohorts (asymptomatic and symptomatic).

8.5.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics for all treated subjects. Patients will be categorized into 4 groups according to their SRT status (prior to study with or without SRT and on study with or without SRT). Number of enrolled subjects will be summarized. Summarization will be provided for the overall group. by cohort (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

8.5.2 Primary Efficacy Analyses

The primary endpoint of intracranial CBR will be calculated for the overall population and by cohorts (asymptomatic and symptomatic) with its corresponding two sided 90% exact CI using the Clopper-Pearson method. The two-sided 95% CI will also be calculated. A sensitivity analysis using IRRC-assessed intracranial CBR will also be performed.

In addition, a sensitivity analysis will also be conducted to evaluate the impact of SRT on intracranial CBR by excluding the patients who received on-study SRT.

8.5.3 Secondary Efficacy Analyses

For all the secondary efficacy analysis endpoints for the overall population and by cohorts (asymptomatic and symptomatic), a two-sided type I error rate 0.05 will be applied (including calculation of the confidence interval).

The secondary endpoints CBR (extracranial and global) and ORR (intracranial, extracranial and global) and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method. BOR will be tabulated.

Time to event distributions (PFS [intracranial, extracranial and global] and OS,) will be estimated using Kaplan Meier methodology. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[63] (using log-log transformation for

constructing the confidence intervals). Rates at fixed time points (eg, OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

In addition, sensitivity analyses using IRRC-assessed CBR (extracranial and global) and ORR (intracranial, extracranial, and global) will also be performed.

To estimate the incidence of MRI-defined intracranial edema, hemorrhage, and increase before regression (pseudoprogression) in the intracranial metastases and evaluate any association with the onset and/or duration of tumor response observed in the intracranial or system, efficacy results (CBR, OS, etc) will be summarized by MRI-defined groups. If necessary, comparisons will be made between MRI- defined event groups and non-event groups.

8.5.4 Exploratory Efficacy Analyses

The exploratory endpoints include intracranial TTR and DOR, extracranial TTR and DOR, and global TTR and DOR.

Exploratory objectives will be summarized.

Time to event distributions (ie, TTR and DOR) will be estimated using Kaplan Meier methodology. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[63] (using log-log transformation for constructing the confidence intervals). Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

DOR curve is estimated using the KM product-limit method for subjects with a BOR of CR or PR. Median DOR, corresponding two-sided 95% CI, and range is to be reported.

Summary statistics of TTR is provided for subjects with a BOR of CR or PR. TTR curve is estimated using the KM product-limit method in treated subjects and represents the cumulative rate of response over time.

For the volumetric imaging exploratory endpoint that will compare computer-assisted tumor volume from three dimensional (3D) MRI to bi-dimensional (2D) measures with respect to absolute values and percent change from baseline, summary statistics for the overall population and by cohorts (asymptomatic and symptomatic) will be provided for the measurements by the 2 approaches. A comparison can be performed for the paired data analysis.

Potential association between dexamethasone exposure and treatment effect in symptomatic subjects treated with corticosteroids will be assessed. Intracranial CBR, extracranial CBR, and global CBR will be summarized descriptively by subjects on study with or without receipt of dexamethasone.

8.5.5 Safety Analyses

Subjects will be evaluated for safety if they have received any treatment for the overall population and by cohorts (asymptomatic and symptomatic). Adverse events and other symptoms will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events

version 4.0 (CTCAE v4). Additionally, serious adverse events (SAE) will be reported from the time of consent forward for all subjects. The analysis of safety will be based on the frequency of AEs and their severity for all treated subjects. Worst toxicity grades per subject will be used in the summary for AEs and laboratory measurements by using the CTCAE v4.

Safety analyses will be summarized in all treated subjects by subgroup (prior to study with or without SRT and on study with or without SRT) and for the overall population. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE criteria.

8.5.6 Pharmacokinetic Analyses

Not applicable

8.5.7 Biomarker Analyses

In general, for the exploratory analysis of biomarker(s), analyses will be descriptive and not adjusted for multiplicity. Details of the analysis plan will be provided in the Statistical Analysis Plan developed for this protocol.

8.5.8 Other Analyses

Healthcare Resource Utilization (HCRU), the impact of AEs, and its association with clinical outcomes (CBR, survival, AEs) will be evaluated using ANCOVA (for continuous variables), and chi-square (for categorical variables).

8.5.9 Interim Analyses

To assess safety and tolerability, an interim analysis was conducted after 20 subjects completed induction treatment or discontinued treatment for any reason. At the completion of the interim analysis by the steering committee, the study drug treatment was deemed safe in asymptomatic patients. Per Amendment 02 (August 2016), the patient population was expanded to include Cohort B which will enroll approximately 20 symptomatic patients as specified in Section 3.3.1.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): ipilimumab. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated

or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. Expanded definition Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
CBC	complete blood count
CBR	Clinical benefit ratio
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLR	renal clearance
CLT	total body clearance

Term	Definition
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy

Term	Definition
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K+	potassium
kg	kilogram
L	liter
LD	longest dimension
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug

Term	Definition
OS	Overall survival
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TID, tid	ter in die, three times a day
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

12 REFERENCES

1 Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available at http://globocan.iarc.fr. Accessed 23-May-2012.

2 Cancer Facts and Figures 2012. American Cancer Society. Atlanta, GA. 2012.

3 Kopf AW, Rigel DS, Friedman RJ. The rising incidence and mortality rate of malignant melanoma. J Dermatol Surg Oncol. 1982; 8(9): 760.

4 Rigel DS, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer J Clin. 2010; 60(5): 301.

5 Gellar AC, Miller DR, Annas GD, et al. Melanoma incidence and mortality among US whites, 1969-1999. JAMA 2002; 288(14): 1719.

6 Margolin K. et al., Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of Cytokine Working Group. J Cancer Res Clin Oncol. 2002, 128: 214-218

7 Fife KM, Colman MH, Stevens GN, et al. Determinants of Outcome in Melanoma Patients With Cerebral Metastases. J Clin Oncol. 2004;22:1293-1300

8 Bafaloukos D, Gogas H; The treatment of brain metastases in melanoma subjects. Cancer Treat Rev. 2004 Oct;30(6):515-20).

9 Atkins MB, Sosman JA, Agarwala S, Logan T, Clark JI, Ernstoff MS, et al. Temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma: a phase II Cytokine Working Group study. Cancer 2008;113:2139–45.

10 Agarwala SS: Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: cytotoxic T-lymphocyte antigen-4 blockade in advanced melanoma. Melanoma Res, 20: 1-10, 2010.

11 Agarwala SS et al, Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. Journal of Clinical Oncology, Vol 22, No 11 (June 1), 2004: pp. 2101-2107

12 Atkins MB. et al., A Cytokine Working Group phase II study of temozolomide (TMZ), thalidomide (THAL) and whole brain radiation therapy (WBRT) for subjects with brain metastases from melanoma. Proc. Am Soc Clin Oncol 2005, 23: 723S

13 Prins RM, Vo DD, Khan-Farooqi H, Yang MY, Soto H, Economou JS, et al. NK and CD4 cells collaborate to protect against melanoma tumor formation in the brain. J Immunol. 2006;177:8448–55

14 Wilson EH, Weninger W, Hunter CA. Trafficking of immune cells in the central nervous system. J Clin Invest. 2010;120:1368–79. doi: 10.1172/JCI41911

15 Margolin, K, Ernstoff MS , Hamid O. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. The Lancet 2012: 13: 459–465.

[16] Di Giacomo AM1, Ascierto PA, Pilla L, Santinami M. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol. 2012 Sep;13(9):879-86

[17] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med; June 2, 2013, DOI: 10.1056/NEJMoa1302369 Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med; June 2, 2013, DOI: 10.1056/NEJMoa1302369

[18] Long et al. Multidisciplinary Approach to Brain metastasis from Melanoma….", ASCO Educational Book, 2013 ASCO Annual Meeting.

[19] Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov;13(11):1087-95. doi: 10.1016/S1470-2045(12)70431-X. Epub 2012 Oct 8.

[20] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

[21] Nayak,L: DeAngelis, L, Wen, P; Brandes, A; Soffietti, R; Lin, N; Peereboom, D; Chamberlain, M; Macdonald, D; Galanis, Perry, J; Jaeckle, K; Mehta, M; Stupp, R; Van Den Bent, M; Reardon, D. The Neurologic Assessment in Neuro-Oncology (NANO) Scale: A Tool to Assess Neurologic Function for Integration in the Radiologic Assessment in Neuro-Oncology (RANO) Criteria (S22.005), Neurology April 8, 2014 vol. 82 no. 10 Supplement S22.005

[22] Yung A et al, Imaging Endpoints in Brain Tumor Clinical Trials: Proceedings of the January 30, 2014 Workshop Neuro-Oncology (2014) 16, (suppl 7)

[23] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–7420.

[24] Wen P, Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group, JCO, vol 28 no. 11, Apr 10, 2010

[25] Shoukat S, Marcus D, Rizzo M, et al. Outcome with stereotactic radiosurgery (SRS) and ipilimumab (Ipi) for malignant melanoma brain metastases (mets). J Clin Oncol 32:5s, 2014

[26] Knisely J, Yu J, Flanigan J, Sznol M, Kluger H, Chiang H. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival Journal of NeurosurgeryAug 2012; 117;227-233.

[27] Hodi, S; Oble, D; Drappatz, J; Velazquez, E; Ramaiya, N; Ramakrishna, N; Day, A; Kruse, A; Rae, S; Hoos, A and Mihm, M. CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS Nature Clinical Practice Oncology (2008) 5, 557-561

[28] Postow M, Callahan MK, Barker CA, etal. Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma. NEJM (2012): , 366;(10) 925-931,

[29] Taube JM, Anders RA, Young GD et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med. 2012 Mar 28;4(127):127ra37. doi: 10.1126/scitranslmed.3003689

[30] Taube JM, Klein AP, Brahmer JR et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res. 2014 Apr 8. [Epub ahead of print] PMID:24714771.

[31] Ahmadzadeh M, Johnson LA, Heemskerk B, et al. Tumor antigen–specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood, 20 August 2009, vol. 114, no. 8, 1537-1544.

[32] Spranger S, Science Translational Medicine, 28 August 2013, vol 5, issue 200, 1-10.

[33] Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advancedmelanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. Cancer 2010; 116: 1767-75.

[34] Berman D, Wolchok JD, Weber J, et al. Association of peripheral blood absolute lymphocyte count (ALC) and clinical activity in patients (pts) with advanced melanoma treated with ipilimumab. J Clin Oncol 2009; 27 (suppl; abstr 3020).

[35] Yang A, Kendle R, Ginsberg B, et al. CTLA-4 blockade with ipilimumab increases peripheral CD8+ T cells: Correlation with clinical outcomes. J Clin Oncol 2010; 28 (suppl; abstr 2555).

[36] Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical trial. Clin Cancer Res 2010; 16: 2861-71.

[37] Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci USA 2003; 100: 8372-8377.

[38] Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol 2005; 23: 6043-6053.

[39] Maker AV, Phan GQ, Attia P, et al. Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: a phase I/II study. Ann Surg Oncol 2005: 1005-1016.

[40] Maker AV, Yang JC, Sherry RM, et al. Intrapatient dose escalation of anti-CTLA-4 antibody in patients with metastatic melanoma. J Immunotherapy 2006; 29: 455-63.

[41] Grosso JG, Horak CE, Inzunza D, et al. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). J. Clin. Oncol. 2013; 31 (suppl abstr3016)

[42] Weber JS, Kudchadkar RR, Yu B et al. Safety, Efficacy, and Biomarkers of Nivolumab With VAccine in ipilimumab-Refractory or 0Naive Melanoma. J Clin Oncol 2013; 51:4802.

[43] Callahan MK, Horak CE, Curran MA, et al. Peripheral and tumor immune correlates in patients with advanced melanoma treated with combination nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab. J Clin Oncol 2013; 31 (suppl abstr 3003)

[44] Investigator Brochure Nivolumab BMS-936558 Version no.: 14 Version date: 30-Jun-2015

[45] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010; 107: 4275-80

[46] Clinical Study Report: Study No. MDX1106-03. A Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 (MDX1106) in subjects with selected advanced or recurrent malignancies. Bristol-Myers Squibb Company; 2013.Document Control No. 930044417.

[47] Yervoy, Prescribing Information, Bristol-Myers Squibb, 03/2015

[48] Hodi FS, O'Day SJ, McDermott DF, et al. , Improved Survival with Ipilimumab in Patients with Metastatic Melanoma; N Engl J Med. 2010 Aug 19;363(8):711-23

[49] Robert C, Thomas L, Bondarenko et al.NEJM, 2011, Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26

[50] Ipilimumab Investigator Brochure Version 16. 13-Mar-2013.

[51] CA209067: Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate-067). NCT01844505

[52] CA209012: Study of Nivolumab (BMS-936558) in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in First-Line or in Switch Maintenance in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (CheckMate 012). NCT01454102

[53] CA209016: Nivolumab (BMS-936558; MDX-1106) in Combination With Sunitinib, Pazopanib, or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma (RCC) (CheckMate016). NCT01472081

[54] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010; 107: 4275-80.

[55] Non-Clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1); BMS DCN 930067627 1.0

[56] Heller KN et al, Safety and Survival Analysis of Ipilimumab Therapy in Patients with Stable Asymptomatic Brain Mets, JCO, June 9, 2011, 8581.

[57] Addendum 1 to Final Clinical Study Report for MDX1106-03 (CA209003): Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 (MDX1106) in subjects with selected advanced or recurrent malignancies. Bristol-Myers Squibb Company; 2014. Document Control No. 930078197.

[58] Hodi S, Sznol M, Kluger H et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial. J Clin Oncol 32:5s, 2014 (suppl; abstr 9002).

[59] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54

[60] Sznol M, Kluger H, Callahan MK. et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9003).

[61] Minniti G, D'Angelillo RM, Scaringi C, et al. Fractionated stereotactic radiosurgery for patientswith brain metastases. J Neurooncol (2014) 117:295–301.

[62] BMS-936558 Nivolumab Investigator Brochure, v.12 July 21, 2013, DCN 930038243

[63] Brookmeyer R, Crowley JA. A confidence interval for the median survival time. Biometrics1982; 38:29-41.

APPENDIX 1 MANAGEMENT ALGORITHMS

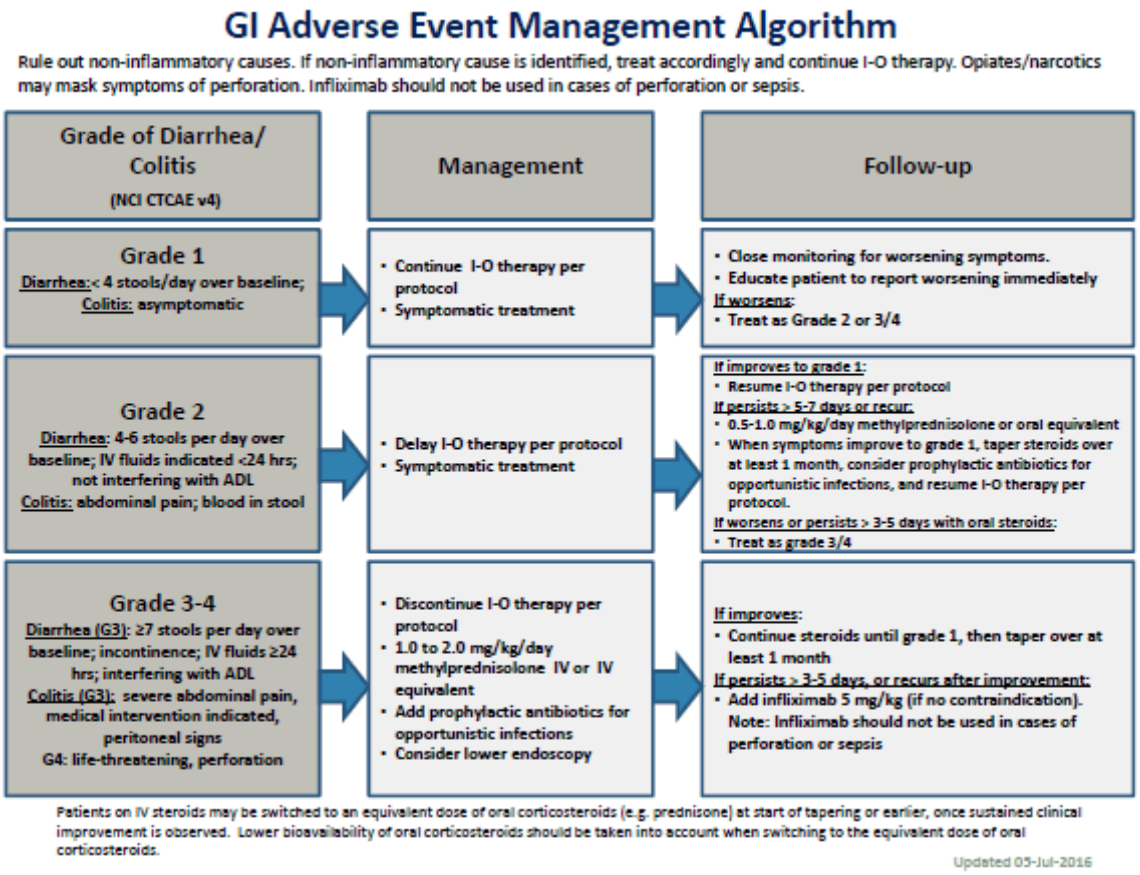
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

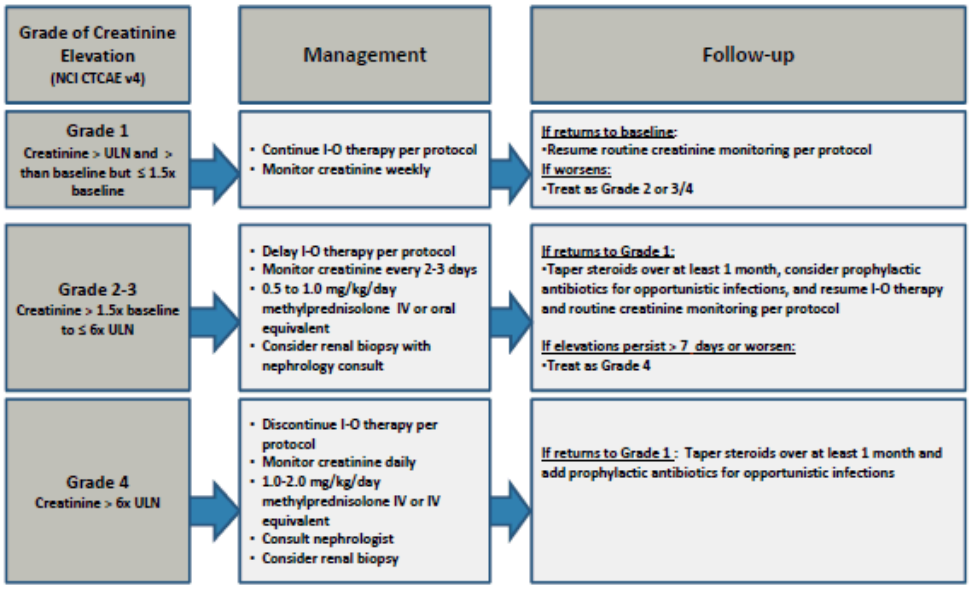
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.



Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

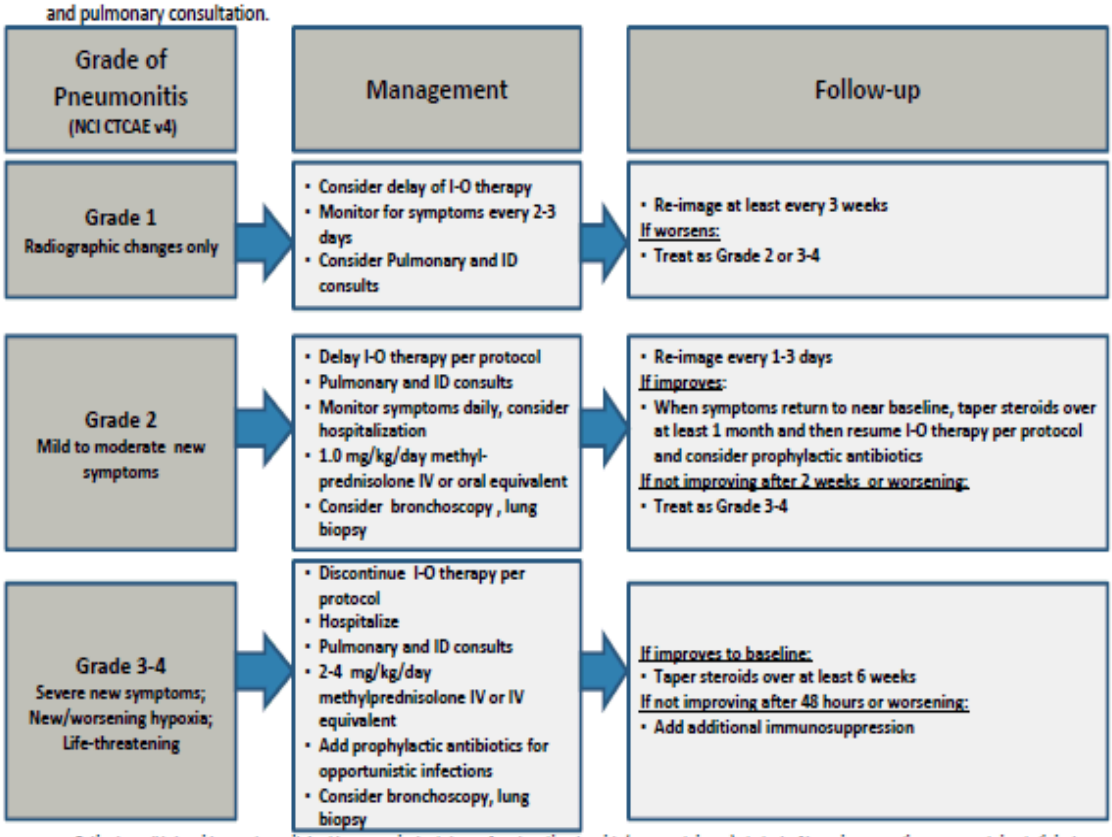


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

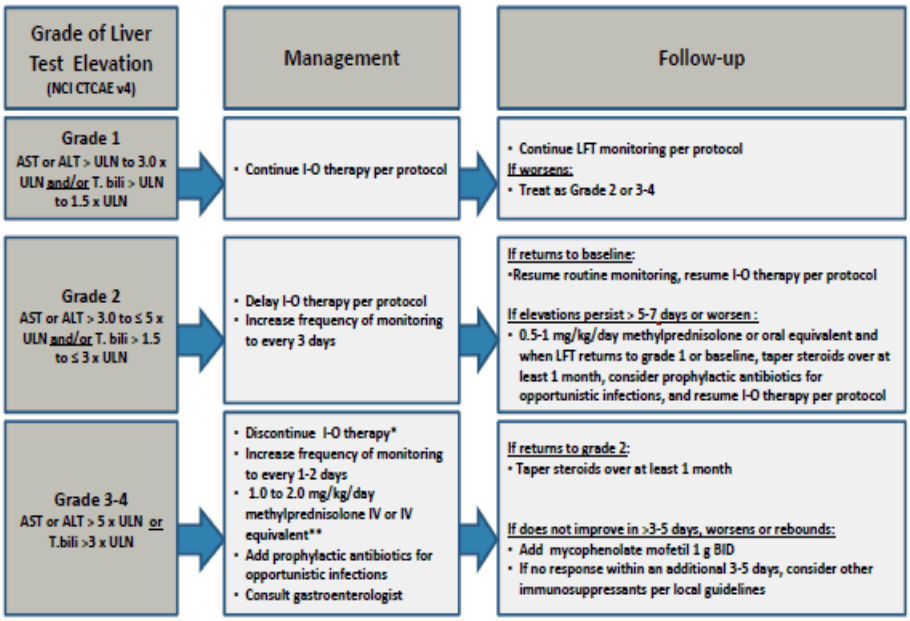


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

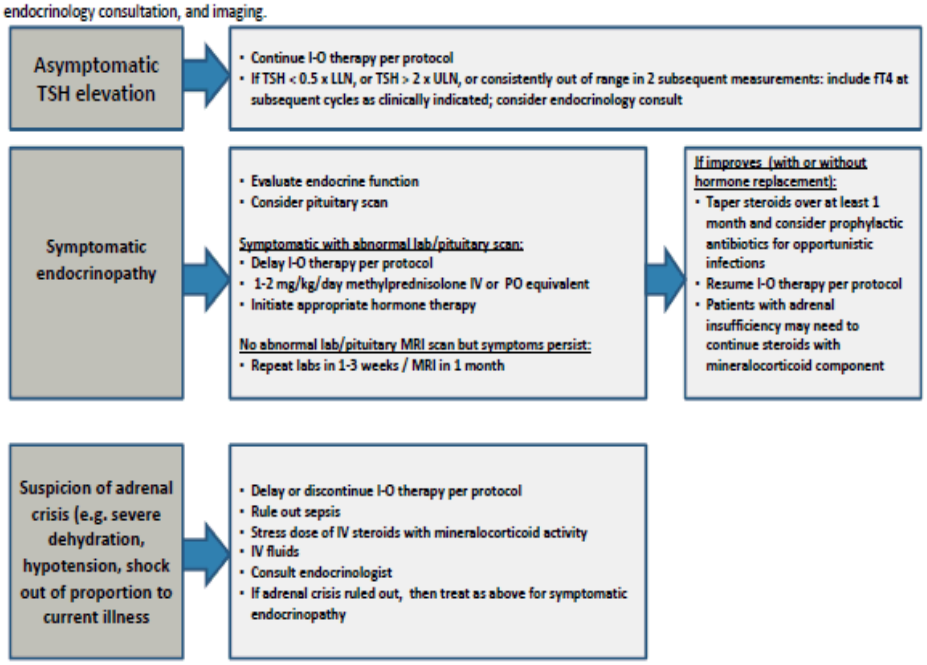


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

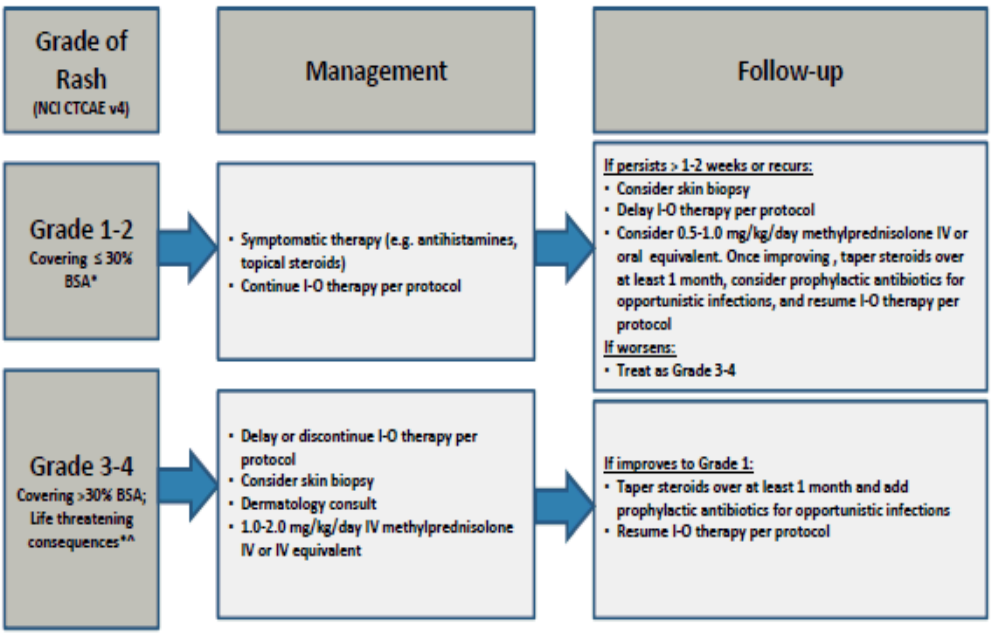


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

APPENDIX 2 ECOG

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 3 IMAGE ASSESMENT CRITERIA

RECIST 1.1 CRITERIA [SYSTEMIC: NON BRAIN] WITH MODIFIED RECIST 1.1 [BRAIN]

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

This Appendix contains an additional section modified from RECIST 1.1 to address intracranial lesions that measure less than 10 mm but no less than 5 mm in LD.

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- **Brain lesions:** Intracranial lesions can be measured only by gadolinium-enhanced MRI. For brain metastases less than or equal to 10 mm LD, an MRI scan slice thickness of 1 mm is necessary. Lesions greater than 10 mm LD may use a slice thickness of 5 mm.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be

considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not beconsidered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions.

However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of 10 lesions total (a maximum of 2 lesions per organ systemically and up to 5 brain lesions) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements. **Brain lesions are** considered target lesions if the lesion is ≥ 0.5 cm and ≤ 3 cm in longest diameter.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should not be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

1. if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
2. if an extracranial lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:

- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease:* To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Appendix Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Appendix Table 1 -Summary of the Overall Response Status Calculation [Time point response -patients with target (+/-) non-target disease]

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=inevaluable

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best overall response: all timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix 3 Table 2.

Table 2: Appendix Table 2 -Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix 3 Table 1 and Table 2.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance.

In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.

1. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.