GEM 1202:

A MULTICENTER, SINGLE ARM, PHASE 2 CLINICAL STUDY ON THE COMBINATION OF RADIATION THERAPY AND IPILIMUMAB, FOR THE TREATMENT OF PATIENTS WITH MELANOMA AND BRAIN METASTASES.

SHORT TITLE: **GRAY-B**

(**G**EM STUDY: **R**ADIATION **A**ND **Y**ERVOY IN PATIENTS WITH MELANOMA AND **B**RAIN METASTASES)

EUDRACT STUDY NUMBER: 2013-001132-22

Sponsor: GE**M** (Spanish Multidisciplinary Melanoma Group) Study Coordinator: [redacted]

Version 1.0 / 28 Nov 2013

PROTOCOL SIGNATURE PAGE

Protocol Number: GEM 1202/GRAY-B

Protocol Version: 1.0 November 28th 2013

I have read this protocol and I agree to conduct this clinical study in accordance with the specific provisions of this protocol, GCPs and Helsinki Declaration.

Clinical Trial Chief Investigator	Principal Investigator
Dr. [redacted]	Name:
Signature:	Signature:

Sponsor
Dr. [redacted]
Chairman of GEM
Signature:.

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PROTOCOL SYNOPSIS

Protocol Title:	GEM 1202 A MULTICENTER, SINGLE ARM, PHASE 2 CLINICAL STUDY ON THE COMBINATION OF RADIATION THERAPY AND IPILIMUMAB, FOR THE TREATMENT OF PATIENTS WITH MELANOMA AND BRAIN METASTASES.
Short Title	GRAY-B (GEM STUDY RADIATION AND YERVOY IN PATIENTS WITH MELANOMA AND BRAIN METASTASES
EUDRACT STUDY NUMBER	2013-001132-2
Country (ies) and Site Numbers.	Spain, 12 sites (Appendix 3)
Research Hypothesis:	Ipilimumab adds a clinical benefit to radiation therapy in patients with melanoma metastatic to the brain. • Melanoma is the third most common cancer causing brain metastases, after cancers of the lung and breast, which appears to reflect the relative propensity of melanoma to metastasize to the central nervous system (CNS). Brain metastases are responsible for 20 to 54 percent of deaths in patients with melanoma, and among those with documented brain metastases, these lesions contribute to death in up to 95 percent of cases, with an estimated median overall survival ranging between 1.8 and 10.5 months, depending upon other prognostic factors. • Ipilimumab is an anti-CTLA4 monoclonal antibody that has demonstrated a clinically relevant and statistically significant improvement in overall survival, either alone (second line) or in combination with DTIC (1st line). • Ipilimumab has shown activity against brain metastases • According to the EMA-approved label for Yervoy®, the use of glucocorticoids at baseline (commonly prescribed when brain metastases are diagnosed) should be avoided before the administration of ipilimumab. Data show that the use of even high doses of glucocorticoids for the management of immune-related adverse events do not decrease the efficacy of Yervoy®. There is no documented experience on the efficacy of Yervoy® when given concomitantly with radiation therapy and glucocorticoids. • In experimental models, radiation therapy is synergistic to anti-CTLA-4 strategies (abscopal effect) • There are no published results from clinical trials on the interaction between radiation therapy and ipilimumab.
Study Schema: **Drugs / Doses /** **Length of Treatment)**	● Ipilimumab 3mg/Kg iv q 3 weeks for 4 cycles ● WBRT 30 Gy in 10 fractions (or radiobiological equivalent schedule, after Sponsor approval), starting between C1D2 and C2D1
Study Objectives: **Primary:** **Secondary:**	**Primary Objective** ● Efficacy - Primary endpoint: 1-year survival rate **Secondary Objectives** ● Efficacy – Endpoints: o Progression-Free survival-PFS (median, 6-month PFS rate) ▪ Intracranial PFS (median, 6-month PFS rate)

	▪ Extracranial PFS (median, 6-month PFS rate) o Overall survival (median) o Response rate: (global, intracranial, extracranial) ("Immune-related response criteria") ● Safety: Adverse Event rates ● Feasibility: dose delays/reductions, treatment exposure
Study Design:	Multicenter, single arm, phase 2 clinical study on the combination of radiation therapy and ipilimumab
Accrual Goal: **(Total number of patients)**	56 patients treated 66 included
Accrual Rate: **(Number of patients expected per month)**	3 to 4 patients per month
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	**03/2014** **10/2015** **10/2016**
Correlative Studies: **(PK/PD, etc.)**	**Exploratory Objectives.** o Potential baseline predictors of efficacy (in tumor tissue and peripheral blood) Potential early surrogates for response: intrapatient variation of quantitative apparent diffusion coefficients of serial diffusion-weighted magnetic resonance imaging
Inclusion Criteria:	1) Willing and able to give written informed consent. 2) Histologic diagnosis of melanoma. 3) First episode of radiological evidence of brain metastases 4) Age>18 years. 5) RTOG-RPA class 2 (Appendix 1) 6) Karnofsky performance status (PS) > 70%.(Appendix 2) 7) Barthel Index of Activities of Daily Living > 10 (Appendix 3) 8) Measurable disease (mWHO criteria). 9) Adequate organ function as determine by the following criteria: a. WBC ≥ 2000/uL b. Absolute neutrophil count (ANC) >1.5 x 10^9/L. c. Platelet count >75 x 10^9/L. d. Hemoglobin >9 g/dL. If the patient received a RBC transfusion, the required value of hemoglobin should be met at least 1 week after the most recent transfusion. e. Serum creatinine ≤ 2.0 x ULN. f. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤ 2.5 x ULN for patients without liver metastasis, or ≤ 5 times for liver metastases. g. Total bilirubin ≤ 2.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL) 10) Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 26 weeks after ipilimumab is stopped: (see definitions in protocol text)
Exclusion Criteria:	1) Patients with melanoma and brain metastases with any of the following disease-specific characteristics:

	a. Documented evidence of prior progression of melanoma to an ipilimumab-containing regimen (i.e. received at least 2 doses of ipilimumab for either advanced disease or in the adjuvant setting and the disease progressed/relapsed -according to mWHO criteria- within 24 weeks since the first dose of ipilimumab) b. Prior radiation therapy to the brain c. Other prior antineoplastic therapies for brain metastases. d. Patients with cerebral metastases as the only location of the disease, for which local therapy (neurosurgery, radiosurgery) could achieve a disease-free status e. Patients with a rapid clinical deterioration, or with risk of herniation, or who require unstable ascending dosing of supportive medication in the last week -including anti-convulsivants, steroids and analgesics-, or who require dexamethasone > 16 mg/d (or other glucocorticoid at an equipotent dose), or with a high LDH (> 2 x ULN). 2) Any other malignancy form which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, or incidental prostate cancer. 3) Uncontrolled diabetes mellitus (HbA1c > 9%) 4) Autoimmune disease other than vitiligo or past thyroiditis under substitutive hormone therapy: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis). 5) Other chronic intestinal diseases associated with diarrhea. 6) Active infection or other serious illness or medical condition. 7) Known active or chronic infection with HIV, Hepatitis B, or Hepatitis C. 8) Concomitant therapy with any of the following: IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; target molecular inhibitors (BRAF, MEK, KIT); or chronic use of systemic corticosteroids (used for the management of non-cancer related illnesses), either concomitantly or during the last 3 weeks prior to the beginning of the treatment. 9) Any experimental therapy administered in the past 30 days prior to the beginning of the treatment. 10) Any non-oncology vaccine therapy used for the prevention of infectious diseases (for up to 4 weeks prior to or after any dose of blinded study drug) (see definitions in protocol text) 11) Women of childbearing potential (WOCBP), as defined above in "Inclusion criteria", who: a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire

	study period and for at least 26 weeks after cessation of study drug, or b. have a positive pregnancy test at baseline, or c. are pregnant or breastfeeding. 12) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness. 13) Any other general, medical or psychological conditions which in the opinion of the investigator will make the administration of ipilimumab hazardous, or that would preclude appropriate informed consent or compliance with the protocol, or obscure the interpretation of eventual AEs.
Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	**Efficacy Assessments** Survival status will be assessed after 1 year since the start of therapy, and will constitute the primary endpoint. Tumor response evaluations will be based on immune related response criteria (irRC) and they will be performed during the induction period at week 12, 17 $\pm$ 1, and every 9 $\pm$ 1weeks until progression. **Safety Assessments** Will be evaluated for all treated subjects using the NCI CTC (Common Toxicity Criteria) version 4.0
Statistics:	A one-stage Fleming design has been adopted. Assuming a historical 1-year survival rate of 20% (with radiation therapy + best supportive care) for the selected population, a sample size of 56 evaluable patients would be needed to show that the addition of ipilimumab to radiotherapy generates a 1-year survival rate of 35%, reaching 80% power at the 0.05 significance level. A total of 56 evaluable patients would need to be included. In case that at least 17 out of these 56 evaluable patients would survive for at least one year, the conclusion of the trial would be that the higher 1-year survival rate of 35% is more likely for the combination than the historical 20% survival rate.

List of Abbreviations

Abbreviation	Term
ANC	Absolute Neutrophil Count
ALC	Absolute Lymphocyte Count
APC	Antigen-presenting cell
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
BORR	Best Objective Response Rate
CTLA4	cytotoxic T lymphocyte antigen 4
CT scan	Computed Axial Tomography scan
CBC	Complete Blood Count
CR	Complete Response
CRP	C Reactive Protein
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
IRAE	Immune-related adverse events
HIPAA	Health Insurance Portability and Accountability Act
IMAE	Immune-mediated adverse events
IRB	Institutional Review Board
irRC	Immune-related response criteria
IRCR	Immune-related complete response
IRPD	Immune-related progressive dose
FPFV	First patient first visit
LPFV	Last patient first visit
MRI	Magnetic Resonance Imaging
OS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
WBRT	Whole Brain Radiotherapy

1 INTRODUCTION

1.1 Research Hypothesis

Among patients with melanoma and brain metastases, Ipilimumab adds a clinically relevant benefit to radiation therapy.

1.2 Product Development Rationale

Ipilimumab is approved for use in the US (metastatic melanoma) and in the EU (for previously treated metastatic melanoma). The currently approved dose is 3 mg/kg every 3 weeks for up to 4 doses. The current label specifies that the use of systemic corticosteroids at baseline, before starting Ipilimumab, should be avoided because of their potential interference with the pharmacodynamics and, therefore, with the efficacy of Ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting Ipilimumab, to treat immune-related adverse reactions. The use of systemic corticosteroids after starting Ipilimumab treatment does not appear to impair the efficacy of Ipilimumab.

Several studies have been designed that included patients with cerebral metastases. However, patients with active brain metastases with symptoms or requiring corticosteroid treatment, as well as those who had to receive concomitant radiation therapy, were almost universally excluded from these protocols. An open label phase 2 study on Ipilimumab in patients with brain metastases was recently published. However, although this trial explored the activity of the compound as a single agent for patients with or without concomitant glucocorticoids, the completion of previous radiotherapy had to be done at least 2 weeks before the start of Ipilimumab.[1]

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. In experimental models, radiation therapy is synergistic to anti-CTLA-4 strategies.

1.2.1. Melanoma and brain metastases: clinical relevance of the condition.

Melanoma is the third most common cancer causing brain metastases, after cancers of the lung and breast,[2] which appears to reflect the relative propensity of melanoma to metastasize to the central nervous system (CNS).[3] Brain metastases are responsible for 20 to 54 percent of deaths in patients with melanoma,[4] and among those with documented brain metastases, these lesions contribute to death in up to 95 percent of cases.[5]

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1 Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13: 459–65

2 Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am. 1996;7(3):337

3 Sawaya R, Bindal RK. Metastatic brain tumors. In: Brain Tumors, Kaye AH, Laws ER Jr (Eds), Churchill Livingstone, New York 1995. p.923.

4 Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. Ann Surg Oncol. 1996;3(2):118.

5 Sampson JH, Carter JH Jr, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg. 1998;88(1):11.

As with other primary tumors, patients with melanoma metastatic to brain typically present with symptoms of increased intracranial pressure (e.g. headache), focal neurologic deficits, and/or seizures. Brain metastases from melanoma may have a particularly high propensity for spontaneous hemorrhage.

Melanoma patients with brain metastases in general have a poor prognosis. In a combined analysis of two series totaling almost 1400 patients, the median survival was four months, and one year survival rates were 9 and 19 percent, respectively.[5,6]

Despite the general poor prognosis, occasional patients do well. Favorable prognostic signs include the presence of a single brain metastasis without other visceral metastatic disease, and an initial presentation with a metastasis to the brain.[5] In contrast, multiple brain lesions, extensive visceral metastases, or a primary lesion of the head and neck region carry an unfavorable prognosis.[5]

In patients with brain metastases from other primary tumors, good performance status and limited intra- and extracranial disease are associated with a favorable prognosis. The Radiation Therapy Oncology Group (RTOG) used recursive partitioning analysis (RPA) to analyze over 1200 patients with brain metastases and develop a prognostic index to predict the outcome following palliative whole brain radiation therapy (WBRT) (Table 1).[7] When RPA was applied to 74 patients with brain metastases from melanoma, the median survival durations for patients in RPA classes I, II, and III were 10.5, 5.9, and 1.8 months, respectively (Figure 1).[8]

Table 1.

Prognostic groups for outcome after palliative treatment of brain metastases by recursive partitioning analysis.[7]

Class	Prognostic factors	Median survival, months
I	KPS ≥70 percent	7.1
	Age <65 years	
	Controlled primary site	
	No extracranial metastases	
III	KPS <70	2.3
II	All others	4.2

KPS: Karnofsky performance status.

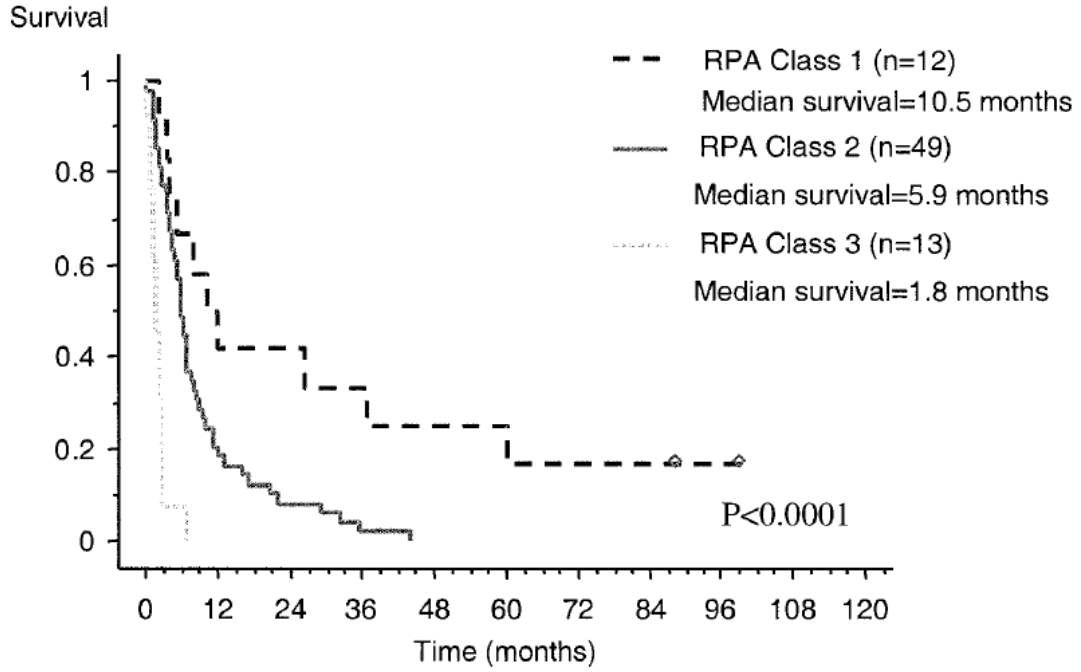
6 Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol. 2004;22(7):1293.

7 Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys. 2000;47(4):1001.

8 Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer. 2002;94(8):2265.

Figure 1.

Overall survival in RPA prognostic groups in patients with metastatic melanoma.[8]



More recently, a diagnosis-specific graded prognostic assessment tool has been developed to estimate prognosis in patients with brain metastases.[9] When a multivariate analysis was applied to 481 patients with melanoma and brain metastases, the only statistically significant factors were the Karnofsky performance status (<70, 70 to 80, versus 90 to 100) and the number of brain metastases (>3, 2 to 3, or 1) (Table 2). Median survival based upon these parameters ranged from 3.4 to 13.2 months.[10]

Table 2.

Graded prognostic assessment for brain metastases from melanoma.[10]

Prognostic factor	Scoring criteria			Median survival (months) by score:
	0	**1.0**	**2.0**	
Karnofsky PS	<7	70-8	90-10	0-1.0 = 3.4
	0	0	0	1.5-2.0 = 4.7
Number of brain metastases	>3	2-3	1	2.5-3.0 = 8.8 3.5-4.0 = 13.2

[9] Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastases in solid-tumor patients: natural history and results of treatment. Cancer. 1981;48(2):384.

[10] Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012 Feb 1;30(4):419-25.

1.2.2. Management of patients with melanoma metastatic to the brain with favorable prognosis.

In favorable prognosis patients (i.e., limited or no extracranial disease, a good performance status, and a single or limited number of brain metastases), aggressive treatment to eradicate metastases in the brain is associated with an improved outcome. Surgery traditionally was used to treat patients with a single or limited number of lesions, often supplemented with WBRT. Subsequent advances have made stereotactic radiosurgery (SRS) an alternative, particularly when lesions are not surgically accessible or when multiple lesions are present.

1.2.3. Management of patients with melanoma metastatic to the brain with intermediate and poor prognosis.

Patients with less favorable prognosis (Table 1) are generally treated with WBRT rather than surgery or SRS. However, surgery might be occasionally performed to resect a large symptomatic or life-threatening lesion.

WBRT is widely used as the treatment for intermediate/poor prognosis patients with melanoma metastatic to the brain. Even with treatment, the prognosis for these patients is poor. In the Melanoma Institute Australia study, 234 patients treated with WBRT alone had a median survival of 3.4 months, compared to 2.1 months in 210 who received supportive care only.[11]

The Radiation Therapy Oncology Group (RTOG) conducted a series of randomized trials to determine the optimal dose and fractionation schedule for WBRT in patients with brain metastases. Patients were assigned to 40 Gy in four weeks, 40 Gy in three weeks, 30 Gy in three weeks, 30 Gy in two weeks, or 20 Gy in one week. The overall response rate (75 to 80 percent for symptom palliation) and median survival (15 to 18 weeks) were equivalent in all arms of these studies. Patients treated with larger fractions over a shorter time responded more quickly, but the duration of the clinical response and the time to progression were similar in all treatment arms. Brain metastases caused death in 40 percent of patients.[12,13,14]

Subsequent RTOG trials exploring the use of ultra-rapid fractionation schedules, dose escalation in favorable prognosis subgroups, accelerated fractionation, and the use of radio sensitizers, failed to show any benefit over conventional radiation therapy.[15]

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[11] Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol. 2004;22(7):1293.

[12] Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, Perez CA, Hendrickson FR. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1980;6(1):1.

[13] Vermeulen SS. Whole brain radiotherapy in the treatment of metastatic brain tumors. Semin Surg Oncol. 1998;14(1):64.

[14] Berk L. An overview of radiotherapy trials for the treatment of brain metastases. Oncology (Williston Park). 1995;9(11):1205.

[15] Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2012;4:CD003869.

1.2.4. Systemic therapy for melanoma patients with brain metastases.

Clinical results from the development of immunotherapy agents such as ipilimumab and targeted therapies such as dabrafenib and vemurafenib suggest that systemic therapy may have a role in carefully selected patients with brain metastases not amenable to surgery and/or radiation therapy.

Nevertheless, more studies are required to define the role of immunotherapy and targeted therapy in patients with melanoma brain metastases.

Immunotherapy both with high-dose interleukin-2 and the anti-CTLA4 monoclonal antibody ipilimumab have clinically useful activity in the treatment of disseminated melanoma. Both ipilimumab and IL-2 in the context of adoptive cell therapy may have clinically useful activity against brain metastases.

In phase II studies and case reports, ipilimumab, a human monoclonal antibody that blocks CTLA-4, has demonstrated activity against brain metastases in patients with advanced melanoma. In the largest experience, 12 of 51 patients (24 percent) with asymptomatic brain metastases not on steroids had either a partial response or stable disease for their brain lesions.[1,16] In a cohort of 21 patients with minimally symptomatic brain metastases on a stable dose of steroids, one patient had a complete response and another had stable disease (overall rate of disease control 10 percent) during treatment. Results from that study and from other phase II studies indicate that the safety profile and level of activity against brain metastases is similar to that seen at non-CNS sites.[17] Adoptive cell therapy using autologous antitumor lymphocytes plus interleukin-2 following a lymphocyte-depleting preparative regimen has antitumor activity in carefully selected patients with metastatic melanoma. An analysis of the experience at the National Cancer Institute found 7 of 17 evaluable patients (44 percent) with brain metastases had a complete response in the brain.[18]

Advances in understanding the pathogenesis of melanoma have identified the MAPK pathway as a target for treatment in many patients with metastatic melanoma. Dabrafenib and vemurafenib target mutations in BRAF.

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[16] Heller KN, et al. Safety and survival analysis of ipilimumab therapy in patients with stable asymptomatic brain metastases. J Clin Oncol 29: 2011 (suppl; abstr 8581).

[17] Weber JS, Amin A, Minor D, Siegel J, Berman D, O'Day SJ. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. Melanoma Res. 2011;21(6):530

[18] Hong JJ, Rosenberg SA, Dudley ME, Yang JC, White DE, Butman JA, Sherry RM. Successful treatment of melanoma brain metastases with adoptive cell therapy. Clin Cancer Res. 2010;16(19):4892.

Dabrafenib has activity in melanoma patients with brain metastases.[19,20,21] In a multicenter phase II study, 172 patients with asymptomatic brain metastases containing either the V600E or V600K mutation were treated with dabrafenib. In the 139 patients whose tumor contained a V600E mutation, objective responses were observed in 29 of 74 patients (39 percent) in those whose brain metastases were treatment naïve and 20 of 65 (31 percent) in those who had received prior local treatment. Objective responses were observed in 5 of 33 patients (15 percent) with a V600K mutation.

Case reports indicate that vemurafenib, another small molecule inhibitor of BRAF, also has activity in patients with multiple brain metastases who received prior temozolomide and/or whole brain radiation therapy.[22,23] A phase 2 trial with this molecule in this setting is in progress.

Neither vemurafenib nor dabrafenib has been compared directly with radiation for treatment of brain metastases.

Systemic chemotherapy for patients with metastatic melanoma has generally had only limited activity, and this approach has been replaced by immunotherapy and targeted therapy for the initial treatment of metastatic disease. Although chemotherapy agents such as fotemustine and temozolomide have shown evidence of some activity against brain metastases,[24,25,26] cytotoxic chemotherapy does not have an established role in the management of patients with melanoma brain metastases.

1.2.5. Glucocorticoids in brain metastases

Most patients with brain tumors and peritumoral edema can be adequately managed with glucocorticoids. Reduction of intracranial pressure and improvement in neurologic symptoms usually begins within hours.

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[19] Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012 May;379(9829):1893-901.

[20] Long GV, Kefford RF, Carr PJ, et al. Phase 1/2 study of GSK2118436, a selective inhibitor of V600E mutatn BRAF kinase: evidence of activity melanoma brain metastases. Ann Oncol. 2010;21 (#LBA27)

[21] Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patietns with VAl600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;

[22] Dummer R, et al. An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases. J Clin Oncol. 2011;29:537s.

[23] Rochet NM, Kottschade LA, Markovic SN. Vemurafenib for melanoma metastases to the brain. N Engl J Med. 2011 Dec;365(25):2439-41.

[24] Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol. 2004;22(6):1118.

[25] Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol. 2004;22(11):2101.

[26] Schadendorf D, Hauschild A, Ugurel S, et al. Dose-intensified bi-weekly temozolomide in patients with asymptomatic brain metastases from malignant melanoma: a phase II DeCOG/ADO study. Ann Oncol. 2006;17(10):1592.

[27] A decrease in capillary permeability (ie, improvement in blood-brain barrier function) can be identified within six hours,[28] and changes of diffusion-weighted MRI indicating decreased edema are identifiable within 48 to 72 hours.[29] However, adequate reduction in elevated ICP resulting from peritumoral edema may take several days with glucocorticoid therapy alone, and additional treatment may be required in the initial management of these patients.

Systemic glucocorticoids are indicated in all patients who have symptomatic peritumoral edema.[30] Dexamethasone is the standard agent, because its relative lack of mineralocorticoid activity reduces the potential for fluid retention.[31] In addition, dexamethasone may be associated with a lower risk of infection and cognitive impairment compared to other glucocorticoids.[32]

The mechanism of action of glucocorticoids for control of vasogenic edema is not fully understood. Dexamethasone has recently been shown to upregulate Ang-1, a strong BBB-stabilizing factor, whereas it downregulates VEGF, a strong permeabilizing factor, in astrocytes and pericytes.[33] Glucocorticoids may also increase the clearance of peritumoral edema by facilitating the transport of fluid into the ventricular system, from which it is cleared by cerebrospinal fluid (CSF) bulk flow.[34]

In patients with severe symptoms, the usual dexamethasone regimen consists of a 10 mg loading dose, followed by 4 mg four times per day or 8 mg twice daily. There is some evidence that lower doses (1 to 2 mg four times per day) may be as effective and less toxic in patients without impending herniation.[35] Although dexamethasone is typically administered in four divided daily doses, its biological half-life is sufficiently long to allow twice daily dosing and this approach is often used for maintenance therapy.[36] To

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[27] Alberti E, Hartmann A, Schütz HJ, Schreckenberger F. The effect of large doses of dexamethasone on the cerebrospinal fluid pressure in patients with supratentorial tumors. J Neurol 1978; 217:173.

[28] Jarden JO, Dhawan V, Moeller JR, et al. The time course of steroid action on blood-to-brain and blood-to-tumor transport of 82Rb: a positron emission tomographic study. Ann Neurol 1989; 25:239.

[29] Sinha S, Bastin ME, Wardlaw JM, et al. Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. J Neurol Neurosurg Psychiatry 2004; 75:1632.

[30] Koehler PJ. Use of corticosteroids in neuro-oncology. Anticancer Drugs 1995; 6:19.

[31] Galicich JH, French LA, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. J Lancet 1961; 81:46.

[32] Batchelor T, DeAngelis LM. Medical management of cerebral metastases. Neurosurg Clin N Am 1996; 7:435.

[33] Kim H, Lee JM, Park JS, et al. Dexamethasone coordinately regulates angiopoietin-1 and VEGF: a mechanism of glucocorticoid-induced stabilization of blood-brain barrier. Biochem Biophys Res Commun 2008; 372:243.

[34] Neurological effects of steroid treatment. In: Neurological Complications of Cancer Treatment, Butterworth-Heinemann, Boston p.173.

[35] Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994; 44:675.

[36] Use of glucocorticoids in neuro-oncology. In: Neurological complications of cancer, Marcel Dekker, New York 1995. p.199.

minimize complications, subsequent dosing should be modified to use the lowest possible dose necessary to control peritumoral edema.

Absorption of oral glucocorticoids is excellent and is complete within 30 minutes of administration.[37] Intravenous dosing may be necessary if oral absorption cannot be assured, or if mentation is altered.

Most patients begin to improve symptomatically within hours and achieve a maximum benefit from a given dose of glucocorticoids within 24 to 72 hours, although standard neuroimaging studies may not reveal decreased edema for at least a week.[36] In general, headaches tend to respond better than focal deficits. If a dose of 16 mg/day of dexamethasone per day is insufficient, the dose may be increased up to 100 mg/day.[38]

Once patients have responded, glucocorticoids should be gradually withdrawn if possible.[39] Because dexamethasone is the most commonly used corticosteroid for brain edema, has a long duration of action, the drug should be tapered about every four days. For patients in good clinical condition, this may entail a reduction in dose of up to 50 percent every four days. However, for those not tolerating glucocorticoid withdrawal, a more protracted course and chronic treatment may be required.

These recommendations are consistent with a systematic review and evidence-based clinical guidelines for the use of steroids in brain metastases.[40] Those guidelines recommended a dose of dexamethasone of 16 mg per day or more for patients with severe symptoms due to increased intracranial pressure and edema due to brain metastases. For patients with milder symptoms, a starting dose of 4 to 8 mg of dexamethasone daily was recommended; steroids are not recommended for asymptomatic patients. Based upon this review the drug should be tapered slowly over two week time period or longer in symptomatic patients.

1.2.6. Abscopal effect of radiation therapy.

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. Ipilimumab is a monoclonal antibody that inhibits an immunologic checkpoint on T cells, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). In experimental models, radiation therapy is synergistic to anti-CTLA-4 strategies.[41,42]

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[37] Kehlet H, Binder C, Blichert-Toft M. Glucocorticoid maintenance therapy following adrenalectomy: assessment of dosage and preparation. Clin Endocrinol (Oxf) 1976; 5:37.

[38] Vick NA, Wilson CB. Total care of the patient with a brain tumor with consideration of some ethical issues. Neurol Clin 1985; 3:705.

[39] Kaal EC, Vecht CJ. The management of brain edema in brain tumors. Curr Opin Oncol 2004; 16:593.

[40] Ryken TC, McDermott M, Robinson PD, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:103.

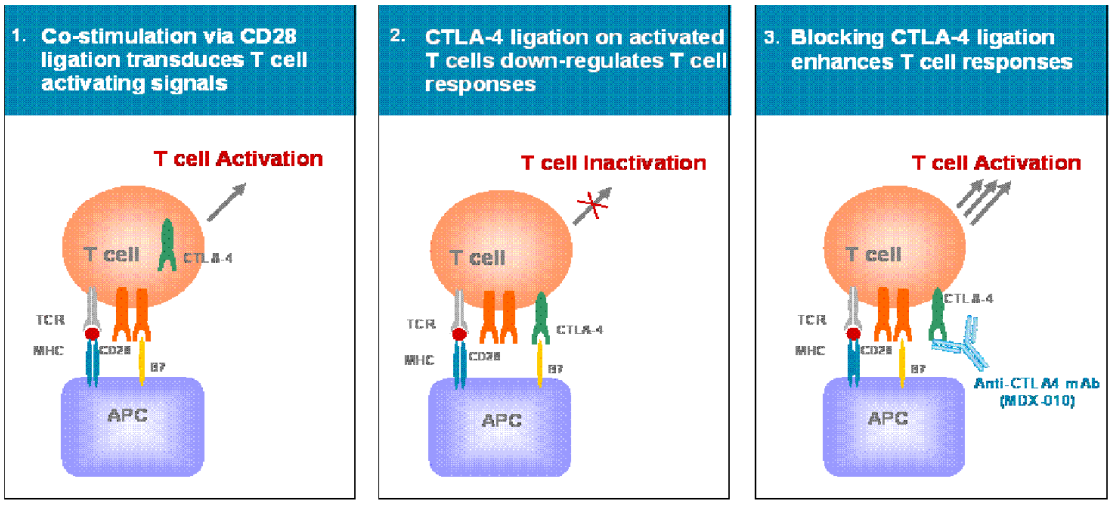
[41] Dewan MZ, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009 Sep 1;15(17):5379-88.

[42] Demaria S, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res. 2005 Jan 15;11(2 Pt 1):728-34.

In the clinical setting this effect has been recently reported,[43] although no published results from clinical trials exploring this interaction between radiation therapy and ipilimumab are yet available.

1.2.7. CTLA-4 and T Cell Activation

Figure 2 Mechanism of Action



Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this costimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC).[44] (Figure 2.)

Expression of B7 has been shown to be limited to "professional" antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be

[43] Postow MA, Callahan MK, Barker CA, et al. Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma. N Engl J Med 2012; 366:925-93

[44] Lenschow D.J., et al., CD28/B7 system of T cell costimulation. Ann Rev Immunol, 1996. 14:233-258.

stimulated by appropriate APCs.[45] The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.[46,47]

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product.[48,49]

In the past few years it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28.[50] Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses.[51]

This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses; (2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune

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45 Schwartz R.H. Costimulation of T lymphoctyes: the role of CD28, CTLA4, and B7/BB1 in interleukin-2 production and immunotherapy. Cell, 1992. 71(7): 1065-1068.

46 Chen L.S., et al., Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. Cell, 1992. 71(7):1093-1102.

47 Townsend S.E., et al., Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells. Science, 1993. 259(5093):368-370.

48 Townsend S.E., et al., Specificity and longevity of antitumor immune responses induced by B7-transfected tumors. Cancer Res, 1994. 54(24):6477-6483.

49 Allison J.P., et al., Manipulation of costimulatory signals to enhance antitumor t cell responses. Curr Opin Immunol, 1995. 7(5):682-686.

50 Linsley P.S., et al., CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med, 1991. 174(3):561-569.

51 Thompson C.B., and Allison J.P. The emerging role of CTLA-4 as an immune attenuator. Immunity, 1997. 7(4): p.445-450.

response to peptide antigens or superantigens in mice.[52,53,54,55] Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro[53]

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation.[56,57,58] CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.[55]

1.3 Summary of Results of Investigational Program

1.3.1 *Pharmacology of Ipilimumab*

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). *In vitro* studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

1.3.2 *Animal Toxicology of Ipilimumab*

The effects of ipilimumab on prenatal and postnatal development in monkeys have not been fully investigated. Preliminary results are available from an ongoing study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters

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[52] Walunas T.L., et al., CTLA-4 can function as a negative regulator of T cell activation. Immunity, 1994. 1(5): p. 405-413.

[53] Kearney E.R., et al., Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. J Immunol, 1995. 155(3): 1032-1036.

[54] Krummel M.F. and Allison J.P. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995; 182(2): 459-465.

[55] Krummel M.F., et al., Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. Int Immunol, 1996. 8(4): 519-523.

[56] Tivol E.A., et al., Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity, 1995. 3(5): 541-547.

[57] Waterhouse P. et al., Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science, 1995. 270(5238): 985-988.

[58] Chambers C.A., et al., Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. Immunity, 1997, 7(6): 885-895.

of pregnancy. Beginning in the third trimester, the ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/-), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/- heterozygous offspring. Mated CTLA-4+/- heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4-/-). The CTLA-4-/- homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3–4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included *in vitro* evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The *in vitro* studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub-chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

1.3.3 *Clinical Pharmacology*

1.3.3.a *Mechanism of Action*

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

1.3.3.b *Pharmacokinetics*

The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C max), trough concentration (Cmin), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of

variation) parameters were generated through population pharmacokinetic analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab Cmin achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. Mean plasma concentrations of ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of ipilimumab. There was moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC(0-21d), 20% to 59% in CL, and 17% to 46% in Vss.

Ipilimumab was originally produced and purified from a hybridoma clone. Ipilimumab drug substance is currently manufactured using Process B. A new drug substance manufacturing process (Process C) has been developed utilizing a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps. The new drug substance manufacturing process is intended to replace the current drug substance manufacturing process. The biocomparability of Process C relative to Process B was assessed in Study CA184087.

PK in Phase 1 Study CA184087 (Process B and Process C)

The PK of ipilimumab was assessed when manufactured by a newer process C relative to current process B as an IV infusion (1.5-hr), in subjects with advanced melanoma (CA184087). Upon meeting eligibility criteria, subjects were randomized (1:1) to receive either ipilimumab Process B (Arm A, reference) or ipilimumab Process C (Arm B, test) at a dose of 10 mg/kg IV administered over 90 minutes every 3 weeks on Days 1, 22, 43, and 64 (Weeks 1, 4, 7, and 10) during induction therapy. Randomization was

stratified by baseline body weight (BW) and LDH values since both were identified as potential covariates in a population PK assessment.

The primary endpoint of PK data at week 4 demonstrated that the PK of Process B and Process C are biocomparable as the 90% CIs for the ratio of geometric means of AUC(0-21d) and Cmax - both adjusted or not adjusted for covariates - were entirely contained with the pre-specified equivalence interval (80 - 125%).

Population Pharmacokinetics

The population pharmacokinetics (PPK) of ipilimumab was developed with 420 subjects (1767 serum concentrations) with advanced melanoma in phase 2 studies (CA184007, CA184008, and CA184022).[16,17,18] Subsequently, the final PPK model was evaluated by an external model validation dataset from CA184004 (79 subjects with 328 serum concentration data). The PPK analysis 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. The ipilimumab CL of 15.3 mL/h from PPK analysis is consistent with that determined by PK analysis as assessed in MDX010-15 as 12.8 mL/h for a dose of 2.8 mg/kg and 15.7 mL/h for a dose of 10 mg/kg. The terminal half-life and Vss of ipilimumab calculated from the model were 14.7 days, and 7.21 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central and peripheral compartment were found to be 4.16 and 3.22 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab was found to increase with increase in body weight, supporting dosing of ipilimumab based on a weight normalized regimen. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance.

1.3.4 *Clinical Safety with Ipilimumab*

1.3.4.a *Overview of Clinical Trials Experience*

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to ipilimumab 3 mg/kg for four doses given by intravenous infusion in previously treated patients with unresectable or metastatic melanoma was assessed in a randomized, double-blind clinical study (MDX010-20). One hundred thirty-one patients (median age 57 years, 60% male) received ipilimumab as a single agent, 380 patients (median age 56 years, 61% male) received ipilimumab with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range 1 to 4 doses). Ipilimumab was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions (≥5%) in patients who received ipilimumab at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 3 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the ipilimumab-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events.

Table 3: Selected Adverse Reactions in MDX010-20

	Percentage (%) of Patients[a]

	YERVOY 3 mg/kg n = 131		YERVOY 3mg/kg + gp100 n = 380		gp100 n = 132	
System Organ Class/Preferred Term	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorders						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

[a] Incidences presented in this table are based on reports of adverse events regardless of causality.

Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

Table 4 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from MDX010-20.

Table 4: Severe to Fatal Immune-mediated Adverse Reactions in MDX010-20

	Percentage (%) of Patients	
	YERVOY 3 mg/kg n = 131	YERVOY 3 mg/kg + gp100 n = 380
Any Immune-mediated Adverse Reaction	15	12
Enterocolitis [a,b]	7	7
Hepatotoxicity [a]	1	2
Dermatitis [a]	2	3
Neuropathy [a]	1	< 1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	< 1
Meningitis	0	< 1
Nephritis	1	0
Eosinophilia [c]	1	0
Pericarditis [a,c]	0	< 1

[a] Including fatal outcome

[b] Including intestinal perforation

[c] Underlying etiology not established

Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg or placebo for cycles 1-4 and as maintenance after completion of chemotherapy. Ipilimumab AEs were consistent with previous studies and predominately affected skin, I tract, liver, and the endocrine system. Events were managed with established guidelines and were generally responsive to dose interruption/discontinuation, corticosteroids and/or other immunosuppresants. Select adverse events associated with the mechanism of action of ipilimumab, regardless of attribution by the investigator) are shown in Table 5.

Table 5: CA184024 Select Adverse Events

	Ipilimumab + DTIC n = 247		Placebo + DTIC n = 251	
	Total	Grade 3 - 4	Total	Grade 3 - 4
	% Patients			
Dermatologic				
Pruritis	29.6	2.0	8.8	0
Rash	24.7	1.2	6.8	0
Gastrointestinal (GI)				
Diarrhea	36.4	4.0	24.7	0
Colitis	4.5	2.0	0.4	0
GI perforation	0	0	0	0
Hepatic				
Increased ALT	33.2	21.9	5.6	0.8
Increased AST	29.1	18.2	5.6	1.2
Endocrine				
Hypothyroidism	1.6	0	0.4	0
Autoimmune thyroiditis	0.8	0	0	0
Hyperthyroidism	0.4	0	0.4	0
Hypophysitis[a]	0	0	0	0

[a] 1 (0.4%) hypophysitis was reported on Day 364.

Safety Profile of Ipilimumab at a Dose of 10 mg/kg (Phase 2 data)

The safety profile of ipilimumab at a dose of 10 mg/kg was characterized in a total of 325 subjects who received multiple doses of 10 mg/kg ipilimumab as monotherapy in the 4 completed melanoma studies (CA184004, -007, -008, and -022). Overall, the incidence of Grade 3/4 AEs attributable to study drug was 31%. The target organ system, the incidence and the severity of the most commonly observed irAEs are displayed in Table 6.

Table 6: Summary of irAE Safety Data for 10 mg/kg in Melanoma

	Total	Low-grade (Grade 1 - 2) (%)	High-grade (Grade 3 - 4) (%)	Median Time to Resolution of Grade 2 - 4 irAEs (weeks)
All irAEs	72.3	46.2	25.2	-
Skin (eg, rash, pruritus)	52.0	49.2	2.8	6.14
GI (eg, colitis, diarrhea)	37.2	24.9	12.3	2.29
Liver (eg, LFT elevations)	8.0	0.9	6.8	4.0
Endocrine (eg, hypophysitis, hypothyroid)	6.2	3.7	2.5	20.1

Overall, the 10 mg/kg had an acceptable safety regimen, while being the most active dose. The study drug related deaths across the program are inthe SMPC.

Across clinical studies that utilized ipilimumab doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

1.3.4.b *Immunogenicity*

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ipilimumab with the incidences of antibodies to other products may be misleading.

1.3.4.c *Pregnancy Outcomes*

Based on animal data, ipilimumab may cause fetal harm. The use of ipilimumab during human pregnancy has not been formally studied in clinical trials. There have been 7 known pregnancies during ipilimumab treatment: in 3 female subjects and in the partners of 4 male study subjects. Two of the 3 female pregnancies ended with elected terminations. The third female subject had a history of seizures and delivered the baby at 36 weeks gestation. The baby had respiratory complications that resolved by birth week 16. Three of the 4 partners of male study subjects had full term, normal babies. The fourth baby had small ureters, which are expected to grow as the baby matures. Although these outcomes do not indicate that stillbirths or other severe abnormalities will occur, pregnancy should be avoided during treatment with ipilimumab.

1.3.4.d *Immune-mediated Adverse Reactions with Ipilimumab.*

Ipilimumab can result in severe and fatal immune-mediated reactions due to T-cell activation and proliferation.

Immune-related Gastrointestinal Events

The clinical presentation of GI immune-related AEs included diarrhea, increase in the frequency of bowel movements, abdominal pain, or hematochezia, with or without fever. Fatalities due to GI perforation have

been reported in clinical trials of ipilimumab. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea, or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Immune-related Hepatotoxicity

Hepatic immune-related AEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis. Elevations in liver function tests (LFTs) may develop in the absence of clinical symptoms. Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

Immune-related Skin Toxicity

Skin immune-related AEs presented mostly as a rash and/or pruritus. Some subjects reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

Immune-related Endocrinopathy

Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, and adrenal insufficiency and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy. It is possible that long-term hormone replacement therapy will be required for subjects developing hypophysitis/hypopituitarism after treatment with ipilimumab.

Immune-related Neurological Events

Neurological manifestations included muscle weakness and sensory neuropathy. Fatal Guillain-Barré syndrome has been reported in clinical trials of ipilimumab. Patients may present with muscle weakness. Sensory neuropathy may also occur. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, and medications should be excluded.

Other Immune-related AEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed immune-related AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for < 1% of subjects.

Overall, immune-related AEs commonly started within 3 to 10 weeks from first dose, were successfully managed in most instances by omitting doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned above and detailed in Section 7. Immune-related AEs generally resolved within days to weeks in the majority of subjects.

1.3.5 *Clinical Efficacy: Melanoma Program*

The clinical efficacy of ipilimumab as a single agent at a dose of 3 mg/kg administered every 3 weeks for 4 doses has been established in MDX010-20 (a randomized, controlled study in second line, locally advanced/metastatic melanoma), which led to approval of ipilimumab by the FDA for the treatment of unresectable or metastatic melanoma. In study CA184024, the addition of 10 mg/kg ipilimumab to dacarbazine led to a prolongation of overall survival in patients with previously untreated melanoma and was feasible with an acceptable safety profile.

Overall survival and other efficacy endpoints were assessed in ipilimumab studies.

Overall Survival: Prolongs survival in patients with metastatic melanoma who have failed prior treatment.

Best Objective Response Rate (BORR): By the conventional mWHO criteria confirmed objective responses have been observed in subjects receiving ipilimumab. These responses tend to be durable with the majority of subjects who achieve objective responses progression-free at the end of long observation periods.

Disease Control Rate (DCR): Disease stabilization in subjects receiving ipilimumab is a key characteristic of anti-tumor activity. Stable disease, sometimes of long duration, or slow steady decline of tumor lesion size over long periods of time, has been observed. Consequently, SD as well as objective responses (both captured in DCR) are important for completely characterizing anti-tumor activity of ipilimumab

Progression-Free Survival (PFS): Some subjects demonstrate initial tumor volume increase before response, possibly due to T-cell infiltration as shown by biopsies. Consequently, PFS incompletely captures all patterns of activity and may underestimate the clinical activity of ipilimumab.

1.3.5.a *Rationale for Using Immune-Related Tumor Assessment Criteria (irRC)*

Ipilimumab is an immuno-stimulating antibody with evidence of anti-cancer activity (durable objective response and stable disease) in subjects with advanced melanoma, including subjects with established brain disease. Observations of clinical activity defined by tumor response endpoints defined by conventional criteria (eg, mWHO) may be inadequate to realize the kinetics and magnitude of clinical benefit achieved with ipilimumab.

Histopathologic evidence has demonstrated ipilimumab can produce an influx or expansion of tumor infiltrating lymphocytes. Therefore, early increases in lesion size detected radiologically or upon gross examination could be misinterpreted as progressive tumor growth and precede objective tumor shrinkage. In addition the appearance of new lesions may have categorized a subject to have progressive disease using conventional tumor assessment criteria despite the concurrent observation of objective tumor responses in pre-existing lesions and a net reduction in global tumor burden that includes the new lesions.

Hence the appearance of new lesions in and of themselves may not necessarily constitute progressive disease. The immune-related response criteria (irRC) were developed as a tool to gauge tumor response using the changes in global tumor burden. In addition, the irRC may be useful to inform a physician's decision to continue dosing in subjects who may receive benefit from additional ipilimumab therapy. The ir-response assessment is based solely on objective measurements (SPD) of index and new lesions. Non-index lesions are not considered.

1.3.5.b *MDX010-20 (Phase 3, 3 mg/kg, previously treated melanoma)*

MDX010-20, a randomized (3:1:1), double-blind, double-dummy study included 676 randomized subjects with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 subjects, 403 were randomized to receive ipilimumab at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded subjects with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Ipilimumab/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. Assessment of tumor response was conducted at Weeks 12 and 24, and every 3 months thereafter. Subjects with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the ipilimumab + gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the ipilimumab + gp100 arm compared to the ipilimumab arm, OS in the ipilimumab arm compared to the gp100 arm, best overall response rate (BORR) at Week 24 between each of the study arms, and duration of response.

Of the randomized subjects, 61%, 59%, and 54% in the ipilimumab + gp100, ipilimumab, and gp100 arms, respectively, were men. Twenty-nine (29%) percent were ≥ 65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin and 38% had elevated LDH level. Sixty-one (61%) percent of subjects randomized to either ipilimumab -containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

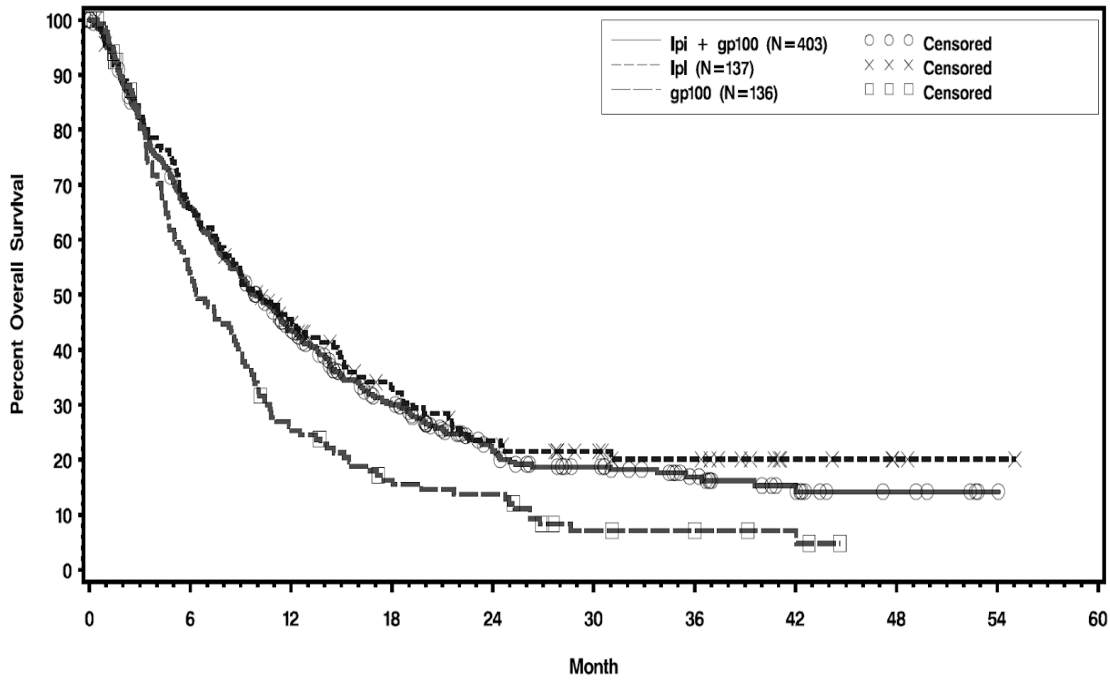
The OS results are shown in Table 7 and Figure 3.

Table 7: MDX010-20 Overall Survival Results

	Ipilimumab n = 137	Ipilimumab + gp100 n = 403	gp100 n = 136
Hazard Ratio (vs gp100)	0.66	0.68	
(95% CI)	(0.51, 0.87)	(0.55, 0.85)	
p-value	p = 0.0026[a]	p = 0.0004	
Hazard Ratio (vs ipilimumab)		1.04	
(95% CI)		(0.83, 1.30)	
Median (months)	10	10	6
(95% CI)	(8.0, 13.8)	(8.5, 11.5)	(5.5, 8.7)

[a] Not adjusted for multiple comparisons.

Figure 3: MDX010-20 - Overall Survival by Treatment (ITT Population)



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the ipilimumab + gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the ipilimumab arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the ipilimumab + gp100 arm and has not been reached in the ipilimumab or gp100 arm.

1.3.5.c *CA184024 (Phase 3, previously untreated melanoma, 10 mg/kg)*

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg/kg or placebo cycles 1-4, and as maintenance after completion of chemotherapy.

The two arms were well balanced regarding most baseline characteristics, as shown in Table 8.

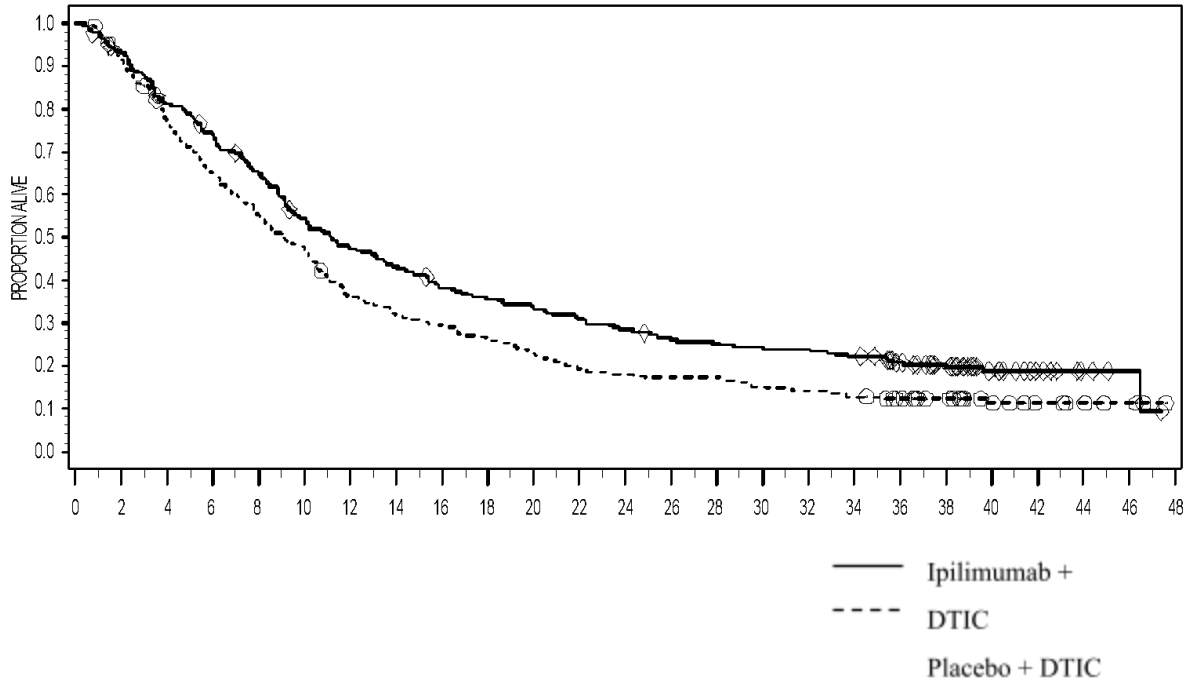
Table 8: CA184024 Baseline Characteristics

	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Age (years)		
Mean	57.5	56.4
Gender (%)		
Male	60.8	59.1
Female	39.2	40.9
M Stage (%)		
M0	2.4	3.2
M1a	14.8	17.1
M1b	25.6	24.6
M1c	57.2	55.2
ECOG PS (%)		
0	70.8	71.0
1	29.2	29.0
LDH (%)		
≤ ULN	62.8	55.6
> ULN	37.2	43.7
≤ 2x ULN	86.4	85.3
> 2x ULN	13.6	13.9
Prior adjuvant therapy (%)	26.4	26.6
Prior therapy for advanced disease (%)	0	0

Patients on the ipilimumab arm received a median of 3 ipilimumab induction doses, versus 4 placebo induction doses on the placebo arm. A total of 17.4% and 21.1% of patients continued to receive maintenance ipilimumab or placebo, for a median of 4 and 2 doses, respectively. The number of patients who received all 8 dacarbazine doses was 12.2% in the ipilimumab arm, and 21.5% in the placebo arm.

The study met its primary end-point of prolonging overall survival in patients treated with ipilimumab (HR 0.72 (95% CI, 0.59 – 0.87), median OS 11.2 vs 9.1 months, p = 0.0009). The OS Kaplan-Meier curve is presented in Figure 4.

Figure 4: CA184024 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects



One, two and three year survival rates were 47.3%, 28.5% and 20.8% in the ipilimumab arm, and 36.3%, 17.9% and 12.2% in the placebo arm.

PFS, a secondary end-point, was also prolonged by the addition ipilimumab, HR 0.76 (95% CI, 0.63 - 0.93). The median PFS was 2.8 months in the ipilimumab and vs 2.6 months in the placebo arm, p = 0.006.

BORR was increased from 10.3% in the placebo arm to 15.2% in the ipilimumab arm (Table 9). More importantly, duration of response was more than twice as long in the ipilimumab arm (19.3 months) than in the placebo arm (8.1 months).

Table 9: CA184024 Tumor Response

	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)

BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

1.3.5.d *10 mg/kg Dosing with Ipilimumab*

In melanoma, Phase 3 studies show improved survival at both 3 mg/kg (study MDX010-20) as well as with 10 mg/kg (study CA184024). Several additional conducted trials studied the efficacy and safety of 10 mg/kg dosing, and additional information gained from these trials is listed below:

- A dose of 10 mg/kg is necessary to ensure a blockade of the CTLA-4 pathway: *in vitro* a concentration of 20 μg/mL of ipilimumab was the minimal concentration able to fully abrogate the binding of CTLA-4 to B7.1 and B7.2. With a dose of 3 mg/kg q3w 30% achieved a trough concentration of ipilimumab greater than 20 μg/mL, compared to 95% of subjects treated at 10 mg/kg q3w.
- In addition, in all ipilimumab trials examined to date, mean Absolute Lymphocyte Count (ALC) increased after ipilimumab treatment throughout the 12-week induction-dosing period, in a dose-dependent manner. In an analysis of ipilimumab at 0.3, 3, or 10 mg/kg in melanoma studies CA184007, CA184008, and CA184022 combined, the rate of change in ALC after ipilimumab treatment was significantly associated with dose ($p = 0.0003$), with the largest rate at 10 mg/kg ipilimumab. Moreover, the rate of change in ALC over the first half of the induction-dosing period was significantly associated with clinical activity in these studies ($p = 0.009$), where clinical activity was defined as CR, PR, or prolonged SD (ie, SD lasting at least 6 months from first dose). Although these analyses alone could not determine whether the rate of change in ALC was specifically associated with clinical activity in response to ipilimumab treatment, as opposed to being generally prognostic, these results do suggest a potential benefit to higher rates of ALC increase after ipilimumab treatment. Among the 3 doses evaluated, 10 mg/kg ipilimumab led to the greatest such rates.
- In the 3 primary studies conducted in advanced melanoma (CA184007, CA184008, and CA184022), subjects treated with 10 mg/kg during the induction period had the highest response, disease control rates, median OS as well as 1-year and 2-year survival rates compared to other doses. The CA184022 data are summarized in Table 10.

Table 10: Summary of Phase 2 Response Data in Melanoma (CA184022)

	10 mg/kg (n = 72)	**3 mg/kg (n = 72)**	**0.3 mg/kg (n = 73)**
BORR (mWHO) – %	11.1	4.2	0
(95% CI)	(4.9 - 20.7)	(0.9 - 11.7)	(0.0 - 4.9)
DCR (mWHO) – %	29.2	26.4	13.7
(95% CI)	(19.0 - 41.1)	(16.7 - 38.1)	(6.8 - 23.8)
Survival rate at 1 year - %	48.64	39.32	39.58
%, 95% CI	(36.84, 60.36)	(27.97, 50.87)	(28.20, 51.19)

Survival rate at 2 year - %	29.81	24.20	18.43
%, 95% CI	(19.13, 41.14)	(14.42, 34.75)	(9.62, 28.22)
Overall median survival	11.43	8.74	8.57
95%CI (months)	(6.90, 16.10)	(6.87, 12.12)	(7.69, 12.71)

Finally, the dose and schedule in study CA184156 is the one that was evaluated in the signal finding study CA184041, with an acceptable safety profile and improvement of irPFS and OS.

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma.

1.3.5.e *Advanced Melanoma*

Ipilimumab prolonged survival in subjects with pre-treated advanced melanoma are based on results from MDX010-20 (Phase 3) supported by data from Phase 2 studies; the primary efficacy and safety studies are

summarized in Table 11.[59,60,61,62,63,64,65,66] The primary endpoint in MDX010-20 was OS, which was also a key secondary endpoint in Phase 2 studies.

Table 11: Studies Supporting the Efficacy and Safety of Ipilimumab in Subjects with Advanced Melanoma

				# Randomized or Enrolled/Treated		
Study No. (Phase)	**Populations**	**Primary Efficacy Endpoint**	**Doses Studies**	**3 mg/kg**	**10 mg/kg**	**Total**
MDX010-20 (Phase 3)	HLA-A2*0201-positive, previou	OS	3 mg/kg q3 wk x 4 ± gp100 (induction)	540/512	--/--	676/643[a]

[59] Randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesoride (Entocort EC) in patients with unresectable stage III or IV malignant melanoma (Protocol CA184007). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043852.

[60] A multicenter, single arm Phase 2 study of MDX-010 (BMS-734016) monotherapy in patients with previously treated unresectable stage III or IV melanoma (Protocol CA184008). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043858.

[61] A randomized, double-blind, multicenter, Phase 2, fixed study of multiple dose of ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma (Protocol CA184022). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 9.0043860.

[62] A randomized, double-blind multicenter study comparing MDX010-10 monotherapy, MDX-010 in combination with a melanoma peptide vaccine and melanoma vaccine monotherapy in HLA-A*201-postive patients with previously treated unresectable stage III or IV melanoma (Protocol MDX0102). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043837.

[63] An exploratory study to determine potential predicitve markers of response and/or toxicity in patients with unresectable stage III or IV malignant melanoma randomized and treated with ipilimumab (MDX-010/BMS-734016) at two dose levels (Protocol CA184004). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043855.

[64] A randomized study comparing MDX-010 alone or in combination with DTIC in the treatment of patients with chemotherapy naive metastatic melanoma (Protocol MDX01008). Bristol-Myers Squibb Research and Development; 3008. Document Control No. 930023182.

[65] Interim report of a multicenter Phase 2 study to evaluate response to ipilimumab (BMS-734016) monotherapy in subjects with melanoma brain metastases (Protocol CA184042). Bristol-Myers Squibb Research and Development.

[66] Collection of long-term outcome data for subjects who have previously participated in selected ipilimumab (MDX-010) studies in metastatic melanoma (Protocol MDX01028). Bristol-Myers Squibb Research and Development; 2009. Document Control No. 9300038451.

	sly treated, unresectable Stage III or IV melanoma		followed by re-induction			
CA184022 (Phase 2)	Previously treated, unresectable Stage III or IV melanoma	BORR	0.3, 3, or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	72/71	72/71	217/214
CA184004 (Phase 2) Biomarker Study	Unresectable Stage III or IV melanoma	BORR	3 or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	40/40	42/42	82/82
CA184008 (Phase 2)	Previously treated unresectable State III or IV melanoma	BORR	10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	--/--	155/155	155/155
CA184007	Unresectable Stage III or IV melanoma	BORR	10 mg/kg q3 wk x 4 ± budesonide (induction) followed by maintenance dosing q12 wk	--/--	115/115	115/115
Additional Studies						
MDX010-08(Phase 2)	Chemotherapy-naive advanced melanoma	ORR	3 mg/kg q4 wk x 4 ± DTIC (induction)	78/74	--/--	78/74
CA184042 (Phase 2)	Stage IV melanoma with	DCR	10 mg/kg q3 wk x 4 (inducti	--/--	28/28[b]	28/28[b]

	brain metastases		on) followed by maintenance dosing q12 wk			
MDX010-28 (Phase 2) Survival Follow-up Study	Subjects enrolled in earlier Medarex studies, including MDX010-08 and MDX010-15[c]	OS	N/A	--/N/A	--/NA	--/N/A

BORR = best overall response rate; DCR = disease control rate; DTIC = dacarbazine; N/A = not applicable; ORR = overall response rate; OS = overall survival; PK = pharmacokinetics.

[a] Total includes 136 randomized/131 treated subjects in the gp100 treatment group.

[b] Information is presented only for subjects enrolled in MDX010-20, Arm A.

[c] MDX010-15 was primarily a PK study that evaluated ipilimumab at single and multiple doses.

Source: References: 59-66

1.4 Overall Risk/Benefit Assessment

Ipilimumab has been the first drug to demonstrate prolonged survival in subjects with pre-treated advanced melanoma, based on a large, multinational, double-blind, pivotal, Phase 3 study [67] supported by a comprehensive Phase 2 program.

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab impacts tumor cells indirectly, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in subjects who are not experiencing rapid clinical deterioration, confirmation of progression is recommended, at the

[67] Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26.

investigator's discretion, to better understand the prognosis as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefitting from treatment. Immune-related (ir) response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response, and in some instances is associated with slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses. Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its improvement in OS.

The immune-based mechanism of action is also reflected in the safety profile. The most common drug-related AEs are immune-mediated, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. As previously discussed, the immune-mediated adverse reactions primarily involve the GI tract, skin, liver, endocrine glands, and nervous system.

The early diagnosis of immune-mediated adverse reactions is important to initiate therapy and minimize complications. Immune-mediated adverse reactions are generally manageable using symptomatic or immunosuppressive therapy as recommended through detailed diagnosis and management guidelines, as described fully in the current IB. The management guidelines for general immune-mediated adverse reactions and ipilimumab-related GI toxicities, hepatotoxicity, endocrinopathy, and neuropathy are provided in the appendices of the current IB.

In summary, ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with pre-treated advanced melanoma and evidence of clinical activity in randomized studies in other tumor types. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-mediated toxicities, suggest an acceptable benefit to risk ratio.

This clinical study will focus on patients with melanoma and brain metastases of intermediate prognosis (RPA class 2). As described earlier, the estimated prognosis of these patients is dismal. All patients are to receive the standard therapy for this condition, that is, WBRT. Ipilimumab as a single agent has shown to be active in these patients. There are biological grounds for potential synergistic efficacy. The safety of the proposed dose of Ipilimumab is well known, and there is no major concern on its use in this patient population. The safety of the combination of ipilimumab and WBRT has not been described. Given the fact that a safety data monitoring group will be defined for this study, and that the patients have a condition which clearly represents an unmet medical need, the overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and potentially better than alternative options.

1.5 Study Rationale

- Melanoma is the third most common cancer causing brain metastases, after cancers of the lung and breast, which appears to reflect the relative propensity of melanoma to metastasize to the central nervous system (CNS). Brain metastases are responsible for 20 to 54 percent of deaths in patients with melanoma, and among those with documented brain metastases, these lesions contribute to death in up to 95 percent of cases, with an estimated median overall survival ranging between 1.8 and 10.5 months, depending upon other prognostic factors. [2,3,5,6,7,8,9,11]

- Ipilimumab is an anti-CTLA4 monoclonal antibody that has demonstrated a clinically relevant and statistically significant improvement in overall survival, either alone (second line)[67] or in combination with DTIC (1st line).[68]
- Ipilimumab has shown activity against brain metastases.[1,16,17]
- According to the EMA-approved label for Yervoy®, the use of glucocorticoids at baseline (commonly prescribed when brain metastases are diagnosed) should be avoided before the administration of ipilimumab. Data show that the use of even high doses of glucocorticoids for the management of immune-related adverse events do not decrease the efficacy of Yervoy®. There is no documented experience on the efficacy of Yervoy® when given concomitantly with radiation therapy and glucocorticoids.[69]
- In experimental models, radiation therapy is synergistic to anti-CTLA-4 strategies (abscopal effect).[41,42,43]
- There are no published results from clinical trials on the interaction between radiation therapy and ipilimumab.

2 STUDY OBJECTIVES

2.1 Primary Objective.

- Efficacy - Primary endpoint: 1-year survival rate

2.2 Secondary Objectives

- Efficacy – Endpoints:
  - Progression-Free survival-PFS (median, 6-month PFS rate)
    - Intracranial PFS (median, 6-month PFS rate)
    - Extracranial PFS (median, 6-month PFS rate)
  - Overall survival (median)
  - Response rate: (global, intracranial, extracranial) (“Immune-related response criteria”)
- Safety: Adverse Event rates
- Feasibility: dose delays/reductions, treatment exposure

2.3. Exploratory Objectives.

- Potential baseline predictors of efficacy (in tumour tissue and peripheral blood – see 6.4.3.)
- Potential early surrogates for response: intrapatient variation of quantitative apparent diffusion coefficients of serial diffussion-weighted magnetic resonance imaging

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[68] 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.

[69] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf

3 STUDY DESIGN

This is a non-controlled, single stage, multicenter phase 2 clinical study. A total of 56 evaluable patients will be treated in this study.

- Main elegibility criteria are: patients with melanoma and brain metastases, adequately fit (ECOG PS 0 to 1; Barthel Index > 10/20) and of intermediate prognosis according to the RPA classification (Table 1).These patients must not have cerebral metastases for which local therapy (neurosurgery, radiosurgery) might achieve a disease-free status; they must not be experiencing a rapid clinical deterioration, risk of herniation; patients must not require unstable ascending dosing of supportive medication in the last week -including anti-convulsivants, steroids and analgesics-, or dexamethasone > 16 mg/day (or other glucocorticoid at an equivalent dose); patients must not have a high LDH (> 2 x ULN), they must not have an uncontrolled diabetes mellitus(HbA1c > 9%) and must be suitable for receiving an anti CTLA4 (i.e. not having any autoimmune-mediated co-morbidities). Patients must have not received prior therapy for brain metastases. Screening stage:Once the ICF is signed by the patient and investigator, patients will be sequentially registered at the Spanish Melanoma Group Datacenter or delegated CRO, by submitting a “registration form”. A Patient Identification Number will be provided by the Sponsor. A second form, the “eligibility checklist”, will be sent by the investigational site once the screening phase has been completed, either if the patient becomes elegible or if he/she results in a screening failure. No protocol exceptions will be permitted by the sponsor.

Patient inclusion:

After confirming that a patient is a candidate for inclusion in this study (inclusion / exclusion), the subject will be assigned a code of patient centralized (registration or inclusion of patients).

The process of enrolling patients described below:

1. Complete and sign the inclusion of the patient (the registration form must be signed by a clinical Principal Investigator or designated appropriately identified in the list of signatures and recording studio delegation of responsibilities).

2. Send the completed and signed form to:

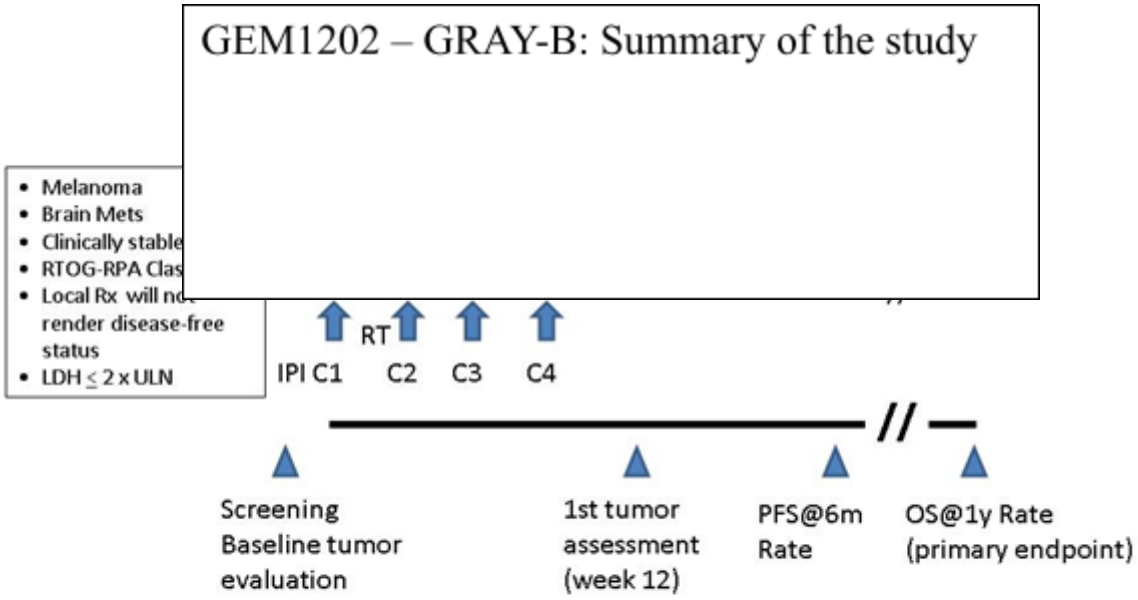
[redacted]

3. [redacted] will register the patient and

4. will send the inclusion confirmation form to the site, both by fax and email. Confirmation of patient inclusion will contain the patient number, which identifies subjects in the trial.

5. Once the site has received the confirmation of inclusion for the patient, the patient can begin receiving protocol treatment.

- The trial schema is represented in the following figure:



All individual patient registered into the trial should undergo the screening phase of the study. Patients consenting, registered and eligible will subsequently proceed through the treatment and follow up phases of the trial.

- **Screening Phase**
  - It initiates after the written informed consent is obtained and the patients is registered. In this phase the assessment of the subject's eligibility to participate will be done, as determined by the inclusion/exclusion criteria.
- **Treatment Phase**
  - Treatment will consist in the administration of ipilimumab and WBRT. The dose of ipilimumab will be 3 mg/kg, administered intravenously over a 90-minute period every 3 weeks, for a total of four doses. Standard WBRT should be initiated between the first and second dose of ipilimumab. The dose of radiation therapy will be 30 Gy over 10 fractions. Radiobiologically equivalent doses might be acceptable, but require discussion and approval of the Sponsor.
  - Laboratory evaluations should be performed and the results examined before administration of each ipilimumab dose, with the exception of hormone results. For these latter parameters it is required that at least the results of the tests performed within the last 3 weeks are available and normal.
  - As durable disease stabilization and/or objective tumor response can be seen after early progression before Week 12, it is recommended that, in the absence of dose-limiting toxicities

(eg, serious immune-mediated adverse reactions), all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.

- All subjects who enter the treatment period, including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression during the induction period, should obtain a 12-week tumor assessment.
- Based on clinical experience in the ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the Week 12 or later tumor assessments:
  - The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
  - As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up, even in the presence of new lesions.
  - Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

- **Follow-up** (duration of study).
  - Subjects who are no longer receiving ipilimumab because of unacceptable toxicity (refractory Grade > 3 immune-mediated adverse reactions) or due to investigator judgment are managed in follow-up. Efficacy assessments for these subjects during follow-up are as per the standard of care. Date of death is recorded.
  - Subjects who discontinue ipilimumab treatments should be followed until death or the closure of the study (whichever is first).
  - Subjects who are no longer receiving ipilimumab because of clinical progression and who have switched to alternative treatment are not followed formally except to record the date of death.

Study duration:

- For each individual patient, the maximal duration of the treatment period is 4 cycles of ipilimumab. Patients will be followed up until death or trial termination (whatever comes first), for a maximum of 36 months. The study will be terminated 18 months after the last patient received the first dose of ipilimumab.

4 SUBJECT SELECTION CRITERIA

For entry into the study, the following criteria MUST be met. No exceptions from the protocol-specific selection criteria will be approved.

4.1 Inclusion Criteria

1) Willing and able to give written informed consent.
2) Histologic diagnosis of melanoma.
3) First episode of radiological evidence of brain metastases
4) Age>18 years.
5) RTOG-RPA class 2 (Table 1)
6) Karnofsky performance status (PS) > 70%.(Appendix 1)
7) Barthel Index of Activities of Daily Living > 10 (Appendix 2)
8) Measurable disease (mWHO criteria).
9) Adequate organ function as determine by the following criteria:
    a. WBC ≥ 2000/uL
    b. Absolute neutrophil count (ANC) >1.5 x 10^9/L.
    c. Platelet count >75 x 10^9/L.
    d. Hemoglobin >9 g/dL. If the patient received a RBC transfusion, the required value of hemoglobin should be met at least 1 week after the most recent transfusion.
    e. Serum creatinine ≤ 2.0 x ULN.
    f. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤ 2.5 x ULN for patients without liver metastasis, or ≤ 5 times for liver metastases.
    g. Total bilirubin ≤ 2.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
    h. Albumin > 2.5 g/dL
10) Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 26 weeks after ipilimumab is stopped:
    a. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab. If the pregnancy test is positive, the patient must not receive ipilimumab and must not be enrolled in the study. Before study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. WOCBP must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate

methods to prevent pregnancy should be determined by discussions between the investigator and the study subject.

- Post-menopause is defined as:
    i. Amenorrhea ≥ 12 consecutive months without another cause, or
    ii. For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥ 35 mIU/mL.
- Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

b. Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study, and for up to 26 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized.

4.2 Exclusion Criteria

1) Patients with melanoma and brain metastases with any of the following disease-specific characteristics:
    a. Documented evidence of prior progression of melanoma to an ipilimumab-containing regimen (i.e. received at least 2 doses of ipilimumab for either advanced disease or in the adjuvant setting and the disease progressed/relapsed -according to mWHO criteria- within 24 weeks since the first dose of ipilimumab)
    b. Prior radiation therapy to the brain
    c. Other prior antineoplastic therapies for brain metastases.
    d. Patients with cerebral metastases as the only location of the disease, for which local therapy (neurosurgery, radiosurgery) could achieve a disease-free status
    e. Patients with a rapid clinical deterioration, or with risk of herniation, or who require unstable ascending dosing of supportive medication in the last week -including anti-convulsivants, steroids and analgesics-, or who require dexamethasone > 16 mg/d (or other glucocorticoid at an equipotent dose), or with a high LDH (> 2 x ULN).
2) Any other malignancy form which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, or incidental prostate cancer.
3) Uncontrolled diabetes mellitus (HbA1c > 9%)
4) Autoimmune disease other than vitiligo or past thyroiditis under substitutive hormone therapy: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis).

5) Other chronic intestinal diseases associated with diarrhea.
6) Active infection or other serious illness or medical condition.
7) Known active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
8) Therapy with any of the following: IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; target molecular inhibitors (BRAF, MEK, KIT); or chronic use of systemic corticosteroids (used for the management of non-cancer related illnesses), either concomitantly or during the last 3 weeks prior to the beginning of the treatment.
9) Any experimental therapy administered in the past 30 days prior to the beginning of the treatment.
10) Any non-oncology vaccine therapy used for the prevention of infectious diseases (for up to 4 weeks prior to or after any dose of blinded study drug)
11) Women of childbearing potential (WOCBP), as defined above in "Inclusion criteria", who:
    a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 26 weeks after cessation of study drug, or
    b. have a positive pregnancy test at baseline, or
    c. are pregnant or breastfeeding.
12) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness.
13) Any other general, medical or psychological conditions which in the opinion of the investigator will make the administration of ipilimumab hazardous, or that would preclude appropriate informed consent or compliance with the protocol, or obscure the interpretation of eventual AEs.

4.3 Data Safety Monitoring Plan

A Data Safety Monitoring Committee (DSMC) will be designated prior to the initiation of the study, and chaired by the coordinating principal investigator. The DSMC will meet approximately every 4 months to ensure that subject safety is carefully monitored. The DSMC might also be consulted on an *ad-hoc* basis should a safety signal emerge, and may also convene an *ad-hoc* meeting on its own initiative. Following the review, the DSMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities.

The DSMC will have access to reports of study data including analyses addressing population characteristics, dosing, safety, and efficacy updated as available prior to each of its meetings.

5. STUDY THERAPY

5.1. Ipilimumab

5.1.1. Dose Calculations

Each patient will receive ipilimumab 3 mg/Kg every 3 weeks, for a total of 4 administration. Infusions should be given over 90 minutes (not bolus or IV push).

Calculate **Total Dose** as follows:

Patient body weight in kg x (x) mg = total dose in mg

Calculate **Total Infusion Volume** as follows:

Total dose in mg ÷ 5 mg/mL = infusion volume in mL

Calculate **Rate of Infusion** as follows:

Infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min.

For example, a patient weighing 75 kg would be administered 225 mg of ipilimumab (75 kg x 3 mg/kg = 225 mg) with an infusion volume of 45 mL (225 mg ÷ 5 mg/mL = 45 mL) at a rate of approximately 0.5 mL/min (45 mL ÷ 90 minutes) in 90 minutes.

The total dose must be calculated using the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion).

The maximum dose of ipilimumab per cycle is 400 mg. Therefore, patients ≥ 133 kg should not receive a dose > 400 mg per cycle.

5.1.2. Storage, Preparation, and Administration

Ipilimumab injection must not 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.

- Do not shake product.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of ipilimumab.

Administration Instructions

- Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.

- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 0.5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

See the current Summary of product characteristics (SMPC)Brochure for additional information on allowable filter types. The infusion must be completed in 90 minutes with an 10 ml normal saline flush at the end.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only.

5.1.3. Dose Modification

Ipilimumab Dose Skipping Rule

Decisions to skip an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be skipped or discontinued if the subject experiences at least one adverse event, specified below, considered by the investigator to be **"possibly," probably," or "certainly" related to ipilimumab treatment.** The investigator should contact the Sponsor for any adverse event that will prompt a skipped dose or discontinuation of ipilimumab.

The following criteria will be used to determine dose skipping, restarting doses, or discontinuing ipilimumab.

It may be necessary to skip study drug dosing for the following related adverse event(s):

- Any ≥ Grade 2 non-skin related adverse event (including immune-mediated adverse reactions), except for laboratory abnormalities
- Any ≥ Grade 3 laboratory abnormality
- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.

It is necessary to skip study drug dosing for the following adverse events:

- Any ≥ Grade 3 skin related adverse event regardless of causality.

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 2 weeks of initial dose administration:

- If the adverse event has resolved, restart ipilimumab dosing at the next scheduled timepoint per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (3 weeks [±3 days]), the next scheduled dose will be skipped and dosing will be resumed at the subsequently scheduled dose.
- If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

5.1.4. Discontinuation of Study Therapy

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy
  - All WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify the Sponsor in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by the Sponsor.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

5.1.5. Permanent Discontinuation of Ipilimumab

5.1.5.a Permanent Discontinuation for Related Adverse Events

Permanently discontinue ipilimumab for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day (due to an AE).
- Failure to complete full treatment course within 18 weeks from administration of first dose.
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- The development of progression (irPD) in the global tumor burden confirmed by serial imaging 4-6 weeks later and/or clinical deterioration of subject's condition such that further benefit from ipilimumab dosing is unlikely or requires a change of therapy.

Please refer to the IB for specific treatment algorithms.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity >/= Grade 3 regardless of causality
- Any >/= Grade 3 treatment related sensory neurologic toxicity

Please refer to the IB for specific treatment algorithms.

5.1.5.b Exceptions to Permanent Discontinuation

- 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.
- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy.
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated for this toxicity with systemic corticosteroids, except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

5.1.6. Immune-Related Adverse Events (irAEs)Reactions and Immune-mediated Adverse Reactions: Definition, Monitoring, and Treatment

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed immune-mediated adverse reactions, noted in previous ipilimumab studies.

For the purposes of this study, an immune-related adverse reaction is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an immune-related adverse reactions. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form. Another term for an irAE is an

immune-mediate adverse reaction, as it is termed in both FDA and EMA approved Prescribing Information. Both terms may be used in this protocol document.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-mediated adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment.

Specific treatment algorithms for immune-mediated adverse reactions adverse events are included as appendices in the IB.

5.1.7. Other Guidance

In patients experiencing neurological deterioration due to an increase of either the tumor mass or the peritumoral edema, the decision to maintain or not ipilimumab will be done case by case on the basis of clinical judgement and discussion with the Sponsor.

5.1.8. Treatment of Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the ipilimumab infusion at the initial planned rate.
  - Diphenhydramine 50 mg IV, Dexchlorpheniramine maleate 5 mg IV, or an equivalent antihistaminic agent may be administered at the discretion of the treating physician; patients may receive additional doses with close monitoring.
  - Premedication with diphenhydramine or dexchlorpheniramine maleate may be given at the discretion of the investigator for subsequent doses of ipilimumab.
- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
  - Interrupt ipilimumab.
  - Administer diphenhydramine 50 mg IV, dexchlorpheniramine maleate 5 mg IV, or an equivalent antihistaminic agent

- Monitor patient closely until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
- Resume ipilimumab infusion after recovery of symptoms.
- At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*
- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure •80 mm Hg, or angioedema):
  - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV (or dexchlorpheniramine maleate 5 mg, or an equivalent antihistaminic agent), with methylprednisolone 100 mg IV, as needed.
  - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
  - No further ipilimumab will be administered.
- In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.1.9. Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.1.10. Monitoring and Management of Immune-mediated Adverse Reactions

Immune-mediated Enterocolitis

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In

symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue ipilimumab in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Withhold ipilimumab dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than one week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent.

Immune-mediated Hepatitis

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of ipilimumab. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue ipilimumab in patients with Grade 3–5 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold ipilimumab in patients with Grade 2 hepatotoxicity.

Immune-mediated Dermatitis

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue ipilimumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold ipilimumab dosing in patients with moderate to severe signs and symptoms.

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

Immune-mediated Neuropathies

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold ipilimumab dosing in patients with moderate neuropathy (not interfering with daily activities).

Immune-mediated Endocrinopathies

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble

other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Withhold ipilimumab dosing in symptomatic patients. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in Study 1: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue ipilimumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.1.11. Liver Function Test (LFT) Assessments Required Before Administration of Ipilimumab

Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed at local or central labs within 3 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: $\leq$ 2.5 x ULN for AST, ALT and $\leq$ 1.5 x ULN for T. bilirubin unless liver metastases are present in which case LFT $\leq$ 5 x ULN for AST, ALT and T. bilirubin $\leq$ 3.0 x ULN) prior to dosing.

If, during the course of treatment abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm section of the ipilimumab Investigators.

5.2. Radiation therapy

The selected dose and regimen for WBRT is a total dose of 30 Gy in 10 daily fractions of 3 Gy. Radio biologically equivalent doses might be discussed, but require the approval of the sponsor.

5.3. Glucocorticoid therapy

The following guidelines are consistent with a systematic review and evidence-based clinical guidelines for the use of steroids in brain metastases.[40]

Those guidelines recommended a dose of dexamethasone of 16 mg per day or more for patients with severe symptoms due to increased intracranial pressure and edema due to brain metastases. However, these patients are formally excluded from the protocol.
For patients with milder symptoms, a starting dose of 4 to 8 mg of dexamethasone daily is recommended; steroids are not recommended for asymptomatic patients.
Based upon this review the drug should be tapered slowly over two week time period or longer in symptomatic patients.

5.4. Prohibited and Restricted Therapies During the Study

5.4.1. Prohibited Therapies

Patients in this study may not use vaccines for the treatment or prevention of cancer for up to one month pre and post dosing with ipilimumab.

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments, with the exception of WBRT.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other CTLA-4 inhibitors or agonists
- CD137 agonists
- Anti-PD1 agents
- Immunosuppressive agents
- Chronic systemic corticosteroids for other conditions not related to the disease or to the managements of ipilimumab adverse events.
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

5.4.2. Restricted Therapies

Not applicable
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6. STUDY PROCEDURES AND OBSERVATIONS

6.1. Time and Events Schedule (Table 12)

Visit	*Visit 1 Registration* (Day -28 to day -1)	*Visit 2 Eligibility* (Day -7 to day -1)	*Visit 3.* C1D 1	Visits R.1 to R.x Starting Between C1D2 and C2D1	*Visit 4* C2D 1	*Visit 5* C3D 1	*Visit 6* C4D 1	*End of treatment C4D30(±2)*	*Follow-up Tumor Assesment (every 9 weeks +/- 1)*	*Follow up visits Months 6, 9, 12, 15, 18, 21, 24, 27, 30 (+/- 1 week)*
Informed Consent Form	X									
Central registration	X									
Medical History		X(1)								
Concomitant diseases		X(1)	X	X	X	X	X	X		X
Symptoms		X	X	X	X	X	X	X		X
Karnofsky PS,Barthel Index, Physical exam, vital constants, body weight		X	X	X	X	X	X	X		X
Neurological exam		X	X	X	X	X	X	X		X
Concomitant medications		X	X	X	X	X	X	X		X
RPA class		X								
Inclusion/Exclusion checklist		X								
Eligibility communication		X								
Blood Workup										
Hematology		X		X	X	X	X	X		X
Biochemistry		X		X	X	X	X	X		X
Pregnancy test		X(2)			X	X	X	X		
Auto-immunity panel		X(1)								
Hormones (morning cortisol and ACTH, free T4, T3, TSH, prolactin)		X(1)			X	X	X	X		X
Efficacy evaluation										

Chest-Abdomen-pelvis CT scan		X(1)						X(5)	X	X
Craneal CT scan/MRI		X(1)						X(5)	X	X
Safety evaluation										
Adverse events /SAEs	Throughout the study									
Dose reductions					Throughout the study, when applicable					
Dose delays					Throughout the study, when applicable					
Biomarker evaluation (optional)										
Archived tumour tissue		X(1)								
Peripheral blood (serum + whole blood)			X		X	X	X	X		
DW-MRI (optional)		X(3)				X(4)		X		
Intervention										
Ipilimumab infusion			C1		C2	C3	C4			
Initiation of radiation therapy				X						

(1) Can be performed between d-28 and d-1.
(2) All WOCBP MUST have a negative pregnancy test within 72 hours before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.
(3) If done, it should be performed up to 2 weeks prior to C1D1
(4) If applicable, 4 weeks (± 1) after the end of WBRT
(5) Should be done on week 12±1

6.2. Procedures by Visit

The Time and Events Schedule summarizes the frequency and timing of various measurements. (Table 12)

6.2.1. Study Procedures by Visit and Treatment Cycle

Note that results of all safety laboratory tests (that is, all chemistry and all hematology results) must be obtained and reviewed before ipilimumab administration, as applicable. All laboratory results must be within the established range before ipilimumab is administered. All treatment-period laboratory samples must be collected within a window of up to 1 days before administration of ipilimumab. Laboratory evaluations using a local laboratory must be performed and the result examined by the investigator before administration of each dose of ipilimumab. The only exception might be the hormonal tests, for which is acceptable a delay of up to 3 weeks in reporting the results.

6.2.1.a Registration visit.

Explanation of the study to the patient. Completion and signature of the informed consent form. Submission of the registration form to the Sponsor. Assignation of a patient number.

6.2.1.b Screening/Baseline Visit

Initiation of study specific procedures to assess eligibility: medical history, concomitant medications, rule out forbidden therapies, record baseline symptoms, physical exam (including basic neurologic exam), lab workout, assessment of the disease. Cathegorization of RPA class (table 1), and Karnofsky and Barthel scales.

6.2.1.c Treatment Visits

Patients will be assessed at least once before each administration of ipilimumab. Patients will also be evaluated before the first dose of WBRT, and at least weekly during the administration of WBRT. These assessments will record patient's symptoms, performance status, Barthel index, vital constants, physical examination (including basic neurological examination), lab tests and concomitant medications. Once treatment has started, evaluation of eventual adverse events and deviations from dosing regimen will also be documented, with mention of their potential relation with the study therapy. The disease will be evaluated morphologically as detailed in section 6.4.2.

Patient's weight will be measured at each treatment visit (or the day before). The dose of ipilimumab will be based on that measurement.

6.2.1.d End of Treatment visit.

End of treatment visit (EOT) will take place 30 + 2 days after the last dose of ipilimumab. This visit will require a complete evaluation of patient's symptoms, Karnofsky/Barthel scores, physical exam (including weight, vital constants and neurological exam), lab tests, collection of AEs and of concomitant medication. If the disease was not evaluated before, EOT visit should include a body and craneal CTscan/MRI.

6.2.1.e Follow-up visits.

Per protocol, the disease should be evaluated until death or confirmed progression (mWHO/immune response criteria). Tumor assessment will be performed with CT/MRI of brain, chest, abdomen and pelvis at baseline, at weeks 12 and 17 $\pm$ 1 and then, every 9 $\pm$ 1 weeks. The same method of assessment (CT or MRI) should be used throughout the patient's time on study for consistent evaluation of response.

After EOT visit, the occurrence of new SAEs and irAEs will be reported up to 90 days after last ipilimumab administration. Ongoing SAEs/irAEs will be followed up until recovery.

Survival status will be checked at week 12, 16-18 and then, every 8-10 weeks.

6.2.2. Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

6.2.3. Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

6.3. Details of Procedures

6.3.1. Study Materials

The Sponsor will provide ipilimumab at no cost for this study.
In-line infusion filters will be obtained locally by the site.
The sponsor (or designee) will also supply:

- Study document file binder
- SMPC
- Drug Preparation Guidelines
- Laboratory Manuals
- CRFs
- NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

6.3.2. Safety Assessments

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of non-SAE or SAE from time of consent forward, up to and including follow-up visits, will be reported. See Section 8: Adverse Event Reporting.

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

6.4. Criteria for Evaluation

6.4.1. Safety Evaluation

6.4.1.a Medical History, Physical Exam, Physical Measurements

Medical history will be obtained at the Elegibility Visit. Medical history must include date of diagnosis of melanoma, including histological documentation of malignancy and current staging. B-Raf mutation status will be recorded.

Pre-treatment events present within 2 weeks of starting study therapy, whether or not related to current disease, will be captured prior to study start. Any changes from baseline will be documented as an AE in the CRF.

The Screening Visit Physical Examination should include weight, height, Karnofsky PS (Appendix 1), Barthel Index (Appendix 2), RPA class of brain metastases (Table 1), blood pressure, heart rate and temperature and should be performed within 7 days of starting study therapy.

Subsequent targeted physical examinations, including weight, will be performed at each dosing visit and at the End of Treatment Visit. Targeted physical examinations are a focused assessment of body areas relevant at the time of the visit. Only physical examination findings that qualify as an AE or SAE will be documented on the appropriate CRF pages.

6.4.1.b Vital Signs

Vital signs to include: blood pressure (BP), heart rate, and temperature. During study drug infusions, vital sign measurements must be collected prior to dosing and every 30 minutes for the duration of the infusion. Vital signs are to be captured in the subject record. Findings should be reported only if they meet AE/SAE criteria.

6.4.1.c Pregnancy Testing

WOCBP are required to have pregnancy tests performed. A negative pregnancy test must be documented at the eligibility visit. Additionally, WOCBP must exhibit a *negative serum or urine pregnancy* (minimum sensitivity 25 IU/L or equivalent units of HCG) *within 72 hours prior to the start of study drug*. The Screening pregnancy test may need to be repeated prior to the start of study drug dosing.
A urine pregnancy test must be performed prior to dosing at every study drug administration visit.

6.4.1.d Performance Status and Barthel Index

Karnofsky Performance Status and Barthel Index will be evaluated and documented at Screening, at each dosing visit, and at the End of Treatment visit. See Appendix 1 and 2 for description of the respective scoring systems.

6.4.1.e Laboratory Testing

Laboratory tests are obtained as part of screening and to determine eligibility. Results of safety laboratory collections (ie, Chemistry and Hematology) must be obtained and reviewed in advance of study drug dosing.

• The following lab parameters must be collected within a window of up to 1 day prior to dosing: CBC/diff (includes ANC and ALC), AST, ALT, total bilirubin, CRP, sodium, chloride, bicarbonate, BUN

or urea, creatinine, and glucose. Baseline values up to 7 days before the first dose are acceptable prior to C1.These lab tests will also be performed at week 12, EOT, and 90 days after last dose administration of ipilimumab (+/-1 week).

• CBC/diff, AST, ALT, total bilirubin, sodium, chloride, BUN or urea, creatinine, and glucose will also be collected weekly during WBRT

All protocol-specified laboratory tests will be analyzed and reported by a local lab.

Importantly, **LFT results (AST, ALT, and total bilirubin) must be reviewed within 24 h prior to dosing**. If abnormal LFTs are detected, the subject must be managed using the hepatoxicity algorithm in the SMPC. (Additional draws must be incorporated when monitoring recovery from any non-hematologic AE (eg, elevations in ALT, AST).

6.4.1.f Endocrine Tests

The following endocrine tests should be performed at Screening and prior to each dosing visit: TSH, free T4 and T3, morning ACTH and cortisol, and prolactin.
Other hormones might be tested as well as clinically indicated.

During treatment, if patient is asymptomatic, it will be adequate to confirm at least the normality of the results of the tests performed within the last 3 weeks. If the patient is symptomatic (e.g. asthenia, cephalea) it will be mandatory to check the results of the pre-dose testing (at least 72 h prior to dose administration)

6.4.1.g HIV and Hepatitis Panel

At screening, testing for HIV, hepatitis C antibody, and hepatitis B surface antigen (HBsAg) should be performed for clinically suspected HIV, HBV, and HCV. If positive results at Screening are not indicative of true active or chronic infection, the subject may enter the study after discussion and agreement between the Investigator and the Medical Monitor. These tests will be repeated during the course of the study if clinically indicated.

6.4.2. Efficacy Evaluation

The primary endpoint will be 1-year survival. Secondary endpoints require the assessment of disease progression or response to therapy.

Secondary response-based endpoints (PFS, BORR, DCR, and duration of response) will be captured using two distinct but related criteria:

- Modified WHO (mWHO) criteria.
- Immune-related Response Criteria (irRC)

The mWHO criteria will be used to define response-based secondary endpoints. The irRC will be used to a) define exploratory endpoints and to b) define confirmed disease progression for the purpose of discontinuing ipilimumab treatment in order to permit physicians to continue treating with ipilimumab in spite of the appearance of small new lesions and/or transient increases in tumor burden that may signal anti-cancer inflammation. The irRC criteria will be used for exploratory analyses. Tumor response will be based on investigator assessment.

Tumor assessment of the disease will be performed with CT/MRI of brain, chest, abdomen and pelvis at baseline, at weeks 12 and 16-18 and then, every 8-10 weeks. The same method of assessment (CT or MRI) should be used throughout the patient's time on study for consistent evaluation of response.

6.4.2.a Radiological Assessment of Tumor Lesions

CT/MRI imaging of the brain, chest and abdomen-pelvis is required at Screening (ie, Baseline) and at each tumor assessment visit, regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans, in subjects where there is clinical suspicion for deep soft tissue metastases (eg, lesions in the thigh). Such additional CT/MRIs will be required at Screening only when deep soft tissue disease is suspected during Screening and must be consistently repeated at all tumor assessment visits if a deep soft tissue lesion is identified during Screening. In cases without suspicion for deep soft tissue disease, no such CT/MRIs are required.

Obviously, brain scans are required at Screening and at each disease evaluation visit. MRIs are preferred, contrast-enhanced CTs are a second choice.

Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at Screening during the treatment evaluation phases. Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of chest and abdomen are preferred. If not available, conventional (nonhelical, non-spiral CT) should be used. If not contraindicated, IV contrast should be used for all studies. If IV contrast is contraindicated, MRI should be used at the Screening exam and at all tumor assessment time points. Oral contrast should be used for all applicable imaging unless contraindicated.

A reference measurement ruler must be printed on every image for scale determination. Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (eg, from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease.

Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

Screening bone scans are not mandatory, and should be performed as clinically indicated. Abnormal findings on Screening bone scans, consistent with malignant disease, require follow-up bone scans in specified intervals. Normal bone scans at Screening do not require follow-up bone scans, except when clinically indicated. Abnormal bone scans should be confirmed with radiographic plain films, CT or MRI. Similarly, progressive disease based only on new lesion(s) found on bone scans must be supported with plain films, CT or MRI imaging studies of the bone lesion(s) to confirm their malignant nature. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless the lesions seen on the correlative imaging studies confirm the finding of disease progression. New areas of abnormal uptake on a bone scan represent disease progression.

Any subject who develops an objective tumor response (CR or PR) is required to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding.

6.4.2.b Non-radiographic Assessments

Visible cutaneous lesions must be measured clinically. Digital and standardized photographic images including a ruler for scale as part of the image are recommended for documentation. All clinical assessments must be performed within close proximity (± 7 days) of any protocol specified radiographic assessments

6.4.2.c Definition of Measurable/Non-measurable Lesions

Definitions of lesions are based on modified WHO criteria in this study.

- Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.
- Non-measurable (evaluable) lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm).
- The definition of measurable and non-measurable lesions also applies to new lesions to be included in the assessments for irRC

Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.

All measurable and non-measurable lesions should be assessed at Screening and at the defined time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression. The Investigator will base tumor evaluations on the modified form of the WHO criteria or irRC as specified in the subsequent sections.

6.4.2.d Definition of Index/Non-index Lesions

All measurable lesions, up to a maximum of **five lesions per organ and fifteen lesions in total**, should be identified as index lesions to be measured and recorded on the CRF at Screening. The index lesions should be representative of all involved organs. No more than five index lesions can be identified among skin lesions. No more than ten index lesions can be identified among all sites other than skin. In addition, index lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a sum of the products of diameters for all index lesions will be calculated and considered the baseline sum of the products of diameters. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions.

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be recorded on the CRF and should be evaluated at the same assessment time points as the index lesions. In subsequent assessments, non-index lesions will be recorded as "stable or decreased disease", "absent", or "progression".

6.4.2.e Definition of Tumor Response per mWHO

mWHO tumor response will be based on the following criteria: **Index Lesions**

- Complete Response (CR): Complete disappearance of all index lesions.
- Partial Response (PR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index lesions.

- Stable Disease (SD): Does not meet criteria for complete or partial response, in the absence of progressive disease.
- Progressive Disease (PD): At least 25% increase in the sum of the products of all index lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of any new lesion(s).

Non-Index Lesions

- Complete Response (CR): Complete disappearance of all non-index lesions.
- Incomplete Response (IR) / Stable Disease (SD): No change or any change with persistence of one or more non-index lesions.
- Progressive Disease (PD): Appearance of any new lesion(s) and/or unequivocal progression of non-index lesion(s) (eg, an increase in pleural effusions, or other fluid collections defined as an approximate doubling of the volume which was present at baseline or nadir, unless there is radiographic evidence of a benign cause for the fluid collection or the effusion is cytologically negative for malignant cells).

6.4.2.f Response per Time Point

OR is determined as the combination of assessments of index and non-index lesions using the following criteria presented in Table 13

Table 13: Overall Response per mWHO

Index Lesions	Non-index Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	IR/SD	No	**PR**
PR	CR or IR/SD	No	**PR**
SD	CR or IR/SD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

6.4.2.g Best Overall Response (BOR)per Subject (Including all TimePoints)

BOR is the best confirmed response designation over the study as a whole, recorded between the date of first dose until the last tumor assessment prior to subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. The assessment of response at 12 weeks has particular emphasis due to the mechanism of action of ipilimumab inducing immune responses as basis for clinical responses. For the assessment of BOR, all available assessments per subject are considered. CR or PR determinations included in the BOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Consistent with the definition of BOR in this study, the date of disease progression is defined for each subject based on post-Week 12 time points, in cases where a subject had an OR of CR, PR or SD at Week 12. BOR assessment of SD requires an OR of SD (or unconfirmed PR or CR) at Week 12, in the absence of BOR of CR, PR or PD.

The following criteria (Table 14) summarize the combination of assessments of OR at different time points throughout the study to establish BOR for the individual subject with emphasis on the 12 week time point due to the mechanism of action of ipilimumab:

Table 14. Assessment of Best Overall Response

Overall Response At Time Points Before Week 12	Overall Response At Week 12	Overall Response At Time Points After Week 12	Best Overall Response For All Time Points
CR* or PR*	Any	Any	**CR or PR (at time point before Week 12)**
PD, SD, or no data	CR* or PR*	Any	**CR or PR (at 12 weeks)**
PD, SD, CR**, PR** or no data	SD, CR**, PR**	CR* or PR*	**CR or PR (at time point after Week 12)**
PD, SD, PR**, CR** or no data	SD, PR**, CR**	PD, SD, PR**, CR** or no data	**SD**
SD, PR**, CR** or no data	PD	Any	**PD (at Week 12)**
PD	PD	Any	**PD (at time point before Week 12)**

* Initial OR of PR or CR confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.
** OR of PR or CR not confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

6.4.2.h Local Radiotherapy for Symptomatic Bone Lesions

Local radiation treatment to the site of bone metastasis will be permitted for palliative pain management at any time during the study but it is encouraged that the Investigator perform this local radiotherapy following consultation with the Medical Monitor and the Week 12 following re-staging assessments (ie, Week 16, confirmatory assessments).

6.4.2.i Response Kinetics and Immune-related Endpoints

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to become evident. Some subjects with advanced melanoma may have objective volume increase of tumor lesions within 12 weeks following start of ipilimumab dosing. These subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. Therefore, in this study, subjects with tumor volume increase detected prior to Week 12 but without rapid clinical deterioration will continue to be treated with ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response until progression is confirmed at the subsequent timepoint. Such assessments will be using identical criteria, considering

index and non-index lesions. Best overall response assessments will therefore include responses occurring at any time before disease progression and after early progression within the first twelve weeks of the study. This will improve the overall assessment of the clinical activity of ipilimumab and more likely capture its true potential to induce clinical responses.

In this study, disease progression using irRC as determined by the investigator will serve to determine discontinuation from study treatment. New lesions will be measured and incorporated into the tumor assessment. Tumor volume will be treated as a continuous variable and new lesion volume will be added to the volume of existing index lesions. Response as well as progression will require confirmation through a subsequent scan at least 4 weeks apart.

6.4.2.j Definition of Tumor Response Using irRC

Calculation of Immune-Related Sum of Products of Diameters (irSPD)

The immune-related sum of products of diameters (irSPD) incorporates measurable new lesions that may have developed on-study, providing an assessment that includes both index and new lesions. The tumor assessment performed during Screening will serve as the baseline for determination of tumor response using irRC.

irSPD at Baseline: The sum of the product of the diameters for all index lesions identified prior to randomization. At baseline, irSPD and SPD are the same.

irSPD at Tumor Assessment (TA): For every post-treatment TA collected, per protocol or as clinically indicated, the irSPD at TA will be calculated using tumor imaging scans. Both index lesions and any measurable new lesions that have developed on study will be included.

irSPD Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the irSPD (irSPD Baseline or irSPD at TA) is used to classify subsequent TAs for each subject. Because ipilimumab treatment may result in complex tumor dynamics in which index lesions may shrink while new lesions appear, the irSPD nadir may be different from the SPD nadir, and may occur either before or after the SPD nadir.

At baseline, the irSPD is measured and recorded.

At each subsequent assessment timepoint, a separate assessment of timepoint overall response will be obtained for that timepoint. The sum of products of perpendicular diameters calculated and recorded at each post-baseline timepoint for immune-related response purposes (irSPD) include measurements of index lesions and also include measurable new lesions which are not too small to measure at this timepoint. A value of 25 mm2 (5 mm x 5 mm) is imputed for each index and previously measurable new lesion which is present but too small to measure.

Timepoint Overall Response using irRC

The overall assessment of immune-related response reported at each timepoint will be based on the following criteria:

- **Immune-related Complete Response (irCR)**: Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions).
- **Immune-related Partial Response (irPR):** A decrease, relative to baseline of the irSPD (as defined above) of 50% or greater is considered an irPR.
- **Immune-related Stable Disease (irSD):** irSD is defined as an evaluable response that fails to meet criteria for immune-related complete response or immune-related partial response, in the absence of immune-related progressive disease.
- **Immune-related Progressive Disease (irPD):** At least a 25% increase in the irSPD (based on irSPD of all index lesions and any measurable new lesions, as defined above) over the nadir irSPD, or the occurrence of any new measurable lesions if the SPD nadir is “0”.

- **Immune-related Unknown Response (irUN):** Tumor assessments which cannot be evaluated (eg, due to image quality, inability to assess all relevant lesions, etc) will be reported as irUN.

Immune-related Response Criteria Definitions are summarized in Table 15.

Table 15. Immune-related Response Criteria Definitions

Index Lesions	Non-index Lesions	New Lesions	% Change in Tumor Burden (including new lesions)	Overall irRC Response
CR	CR	No	- 100%	irCR
CR	Any	Any	>-100% to ≤ -50%	irPR
			> -50% to < +25%	irSD
			≥ +25%	irPD
PR	Any	Any	> -100% to ≤ -50%	irPR
			> -50% to < +25%	irSD
			≥ +25%	irPD
SD	Any	Any	> -50% to < +25%	irSD
			≥ +25%	irPD
PD	Any	Any	≥ +25%	irPD
U	Any	Any	U	irUN

Note: Both immune-related response and progression require confirmation through a subsequent scan at least 4 weeks apart from first detection.

6.4.2.k Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

6.4.3. Exploratory endpoints: predictive biomarkers

6.4.3.a Background for Biomarker Research in Melanoma

Despite advances in our knowledge of the disease, malignant melanoma remains an unpredictable entity. Biomarkers are playing an increasing role in the development of new cancer treatments. Predictive biomarkers can be used to improve response rate, by subject stratification and support treatment discontinuation decision in case of severe adverse events. Biomarkers also add to the knowledge on the mechanism of action of drugs, supporting rationale for different combination therapies and dosing schedules.

An area of unmet need in melanoma drug development is the identification of biomarkers that can be used to reliably predict or assess whether systemic therapies would provide benefit to subjects. The revolution in molecular biological techniques, such as DNA sequencing and gene-expression profiling, has

uncovered many potential protein targets and biomarkers relevant to melanoma progression. The elucidation of biomarkers in melanoma, both diagnostic and prognostic, is an important area for investigation.

Previous Ipilimumab studies have explored a variety of predictive and pharmacodynamic biomarkers in melanoma subjects and resulted in the identification of a number of potential biomarker candidates that might be used to better understand the mechanism of action of Ipilimumab and to predict or early predict (by measuring changes within few weeks after the start of the treatment) response to this agent. These include peripheral blood biomarkers such as Absolute Lymphocyte Count (ALC), activated and memory T cells, and some serum biomarkers such as C-reactive protein (CRP). An apparent association was detected between low baseline serum levels of CRP and longer overall survival in metastatic melanoma subjects treated with 10 mg/kg ipilimumab in CA184007 Phase 2 trial. Gene polymorphisms of CD86 and CTLA-4 have been associated with a number of autoimmune diseases. Previously, the association of some of these genetic markers with efficacy or safety of ipilimumab has been explored. However, data from limited number of subjects from Phase 2 trials with ipilimumab have not yet resulted in the discovery of any genetic biomarkers that might predict efficacy or immune-mediated adverse events caused by this agent.

The aim of this optional study is to determine whether a correlation between the proposed biomarkers and disease behavior (progression, overall survival, treatment response) exist in patients with melanoma metastatic to the brain, that have specifically consented for the participation in this part of the study.

The present biomarker plan proposes assessment of such biomarkers to investigate their associations with immune-mediated adverse events when ipilimumab is administered with radiation therapy:

- To evaluate tumor biomarkers pathways by IHC and their correlation with prognosis as well as their role as predictive factors to treatment with ipilimumab+radiotherapy in 29 patients participating on GEM 12-02 clinical trial.
- To evaluate serum levels of several cytoquines (by means of cytoquines panel) at baseline, and before each ipilimumab administration (expected 4-5 samples per patient, 29 patients).
- To evaluate Peripheral Blood Mononuclear Cells (PBMCs), with true counts for absolute numbers and percentage at baseline, and before each ipilimumab administration (expected 4-5 samples per patient, 29 patients).

6.4.3.b Biomarker Measures

- ALC will be assessed as a part of standard hematology panel.
- CRP will be obtained as a component of the serum chemistry lab test.
- Tumor Samples: at least 29 tumor samples (biopsies) will be collected and histology and IHC will be carried out to evaluate a panel of biomarkers that includes: CD3, CD4, CD8, CD31, PD-1, PD-L1, CD45RO, CD68, NK, DC, CD80, CD86, ICAM, VCAM, HLA-A,B,C, HLA-DR, PTEN.
- Serum Samples will be evaluated in at least 29 patients at 4-5 timepoints (116 refrigerated serum samples). For each sample, 10 ml of serum will be collected and a cytokine panel will be carried out, including:

Cytokines			
IFN-γ	TNF-α	IL-1β	IL-2
IL-4	IL-6	IL-7	IL-8

IL-10	IL-12	IL-15	IL-17
Adhesion molecules			
sICAM-1	sVCAM-1	sCD25	

- Peripheral Blood immune cells will be evaluated in at least 29 patients at 4-5 timepoints (116 refrigerated periferal blood samples). For each sample, 10 ml of heparin blood will be collected for flow citometry to evaluate a panel of cells that include:

T cells			
CD3	CD4	CD8	CD56
CD45RA	CD45RO	CD62L	LFA-1 (activated conformation)
NK cells			
NKp46	CD16	CD56	
T reg			
CD4	CD25	FoxP3	
MDSC			
CD14	CD15	CD33	HLA-DR
DC			
BDCA-1	BDCA-2	BDCA-3	
T cell activation (with PMA + ionomycin)			
CD69	CD25	IFN-	IL-4
IL-17	LFA-1(active conformation)		

If consented by the patient, the remaining biological materials (tissue blocks or its derivatives, serum alliquots and frozen pellets) will be stored for future studies.

Biological samples for the these exploratory studies will be collected by

[redacted]

The molecular substudy coordinator is Dr. [redacted]

Samples will be analyzed and stored in

[redacted]

An additional document will be provided in the Investigator Site File with detailed instructions for biological sample collection and shipment.

6.4.3.c. Blood/Lab Biomarkers timepoints

Except for ALC and RCP, which will be determined with every routine blood tests as per section 6.4.1.e and Table 12, the other biomarkers will be sampled at baseline (i.e. up to 28 days prior to C1D1), at C1D21, C2D21, C3D21 (+/- 3 days),and at the EOT visit.

6.4.3.d Archival Tumor Tissue

When available, paraffin-embedded tumor tissue will be submitted for each subject for immunoscoring. The tumor tissue does not have to be submitted prior to the start of treatment and is not required for eligibility. Separate instructions for submission of archival tumor samples will be provided.

6.4.4. DIFUSSION-WEIGHTED MRI (DW-MRI).[70]

DW Imaging (DWI) explores the random motion of water molecules in the body. Water molecules held in a container outside the body are in constant random brownian motion. This uninhibited motion of water molecules is free diffusion. By contrast, the movement of water molecules in biologic tissues is restricted because their motion is modified and limited by interactions with cell membranes and macromolecules.

In biologic tissue, the DWI signal is derived from the motion of water molecules in the extracellular space, the intracellular space, and the intravascular space. Not surprisingly, given a unit time, water molecules in the intravascular space will have a greater diffusion distance because of blood flow than those in the extracellular and intracellular spaces. Clearly, the contribution of intravascular water diffusion to the measured DWI signal can vary among tissues. In tumors showing increased vascularity, the contribution of intravascular water diffusion to the MR signal may account for a significant proportion.

The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in tissues with a high cellular density associated with numerous intact cell membranes (e.g., tumor tissue). The lipophilic cell membranes act as barriers to motion of water molecules in both the extracellular and intracellular spaces. By contrast, in areas of low cellularity or where the cellular membrane has been breached, the motion of water molecules is less restricted. A less cellular environment provides a larger extracellular space for diffusion of water molecules, and these molecules may also freely transgress defective cell membranes to move from the extracellular into the intracellular compartment.

DWI yields qualitative and quantitative information that provides unique insight into tumor characteristics, and there is growing evidence for its use in the assessment of the patient with cancer.

Tumors are frequently more cellular than the tissue from which they originate and thus appear to be of relatively high signal intensity (restricted diffusion) at DWI. Tumors differ in their cellularity, and this difference may reflect their histologic composition and biologic aggressiveness. The use of DWI for tumor characterization was first shown in brain tumors.

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[70] Provenzale JM, Mukundan S,P. Barboriak DP. Diffusion-weighted and Perfusion MR Imaging for Brain Tumor Characterization and Assessment of Treatment Response. Radiology 2006; 239: 632-649

Perhaps one of the most exciting potential applications of DW MRI imaging has been in measurement of the response of solid tumors to therapy. The results of several studies, usually of animal models, have suggested that substantial changes in water diffusion evolving in the first few weeks after initiation of treatment may be helpful in predicting response to therapy. If this application is validated in human studies, it could lead to important changes in clinical practice by allowing much earlier changes in therapy.

Studies of patients with brain tumors have shown that increases in water diffusion generally indicate a positive response to therapy. It appears likely, at least for some antineoplastic agents, that measurement of tumoral ADC shortly after the start of therapy might be an early marker of good response to therapy.

DW-MRI will be optional and will be done in two timepoints: at baseline (up to 2 weeks prior to therapy) and 1 month after the end of WBRT.

7. INVESTIGATIONAL PRODUCT: IPILIMUMAB

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study, whether blinded or unblinded. In this study, the investigational product is ipilimumab.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, a noninvestigational product is dexamethasone or equivalent glucocorticoid.

7.1. Identification

Ipilimumab is available in concentrations of 5 mg/mL (50 mg/10 mL and 200 mg/40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

7.2. Packaging and Labeling

The Sponsor will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement.

7.3. Storage, Handling, and Dispensing

7.3.1. Storage

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature $\geq 2°C$ and $\leq 8°C$.

7.3.2. Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

7.3.3. Dispensing

It is the responsibility of the investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

7.4. Drug Ordering and Accountability

7.4.1. Initial Orders

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from the site's Pharmacy by completing a Drug Request Form. The first request may take place at site opening.

Ipilimumab vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from the receipt of the Drug Request Form by the Sponsor (or designated third party vendor). Drug is protocol specific, but not patient specific. All product will be shipped by courier in a temperature-controlled container. Shipments will be made from a third party vendor. There will be no weekend or holiday delivery of drugs.

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be used for this study.

7.4.2. Re-Supply

Drug re-supply request form should be submitted electronically or by fax to a Sponsor-designated third party vendor, at least 5 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 5 business days from the Sponsor designated third party vendor receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

7.5. Ipilimumab Accountability

It is the responsibility of the investigator to ensure that a current record of ipilimumab disposition is maintained at each study site where ipilimumab is inventoried and disposed. 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 ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

7.6. Ipilimumab Destruction

If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained. Provide a certificate of destruction to the Sponsor upon disposal.

8. ADVERSE EVENT REPORTING

8.1. Collection of Safety Information

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

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.)

8.1.1. Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose:</u>

- 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.)
- Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.4 for reporting pregnancies.)

<u>**NOTE**</u>: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)

- elective surgery planned before 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 for purpose other than remedying ill health state that was planned before study entry. 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).

8.1.2. Nonserious Adverse Events

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

8.2. Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.
The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression “reasonable causal relationship” is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

8.3. Collection and Reporting

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.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.

The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

8.3.1. Serious Adverse Events

The following information is provided to investigators for either inclusion in protocol documents or other related study documents. It will also be contained in the Study Agreement:

Following the subject’s written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur

within 90 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify the Sponsor of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to the Sponsor or delegated CRO (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be immediately reported to CRO:

Suspected Unexpected Serious Adverse Reactions (SUSAR) will be reported by the study Sponsor to the relevant Authorities and into the Eudravigilance database. The Sponsor will be provided with a simultaneous copy of all adverse events filed with the Authorities.

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to the Sponsor (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. 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.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product, 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 page.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

8.3.2. Handling of Expedited Safety Reports

In accordance with local regulations, the Sponsor will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in theSMPC). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, a SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from the Sponsor, the investigator must review and retain the ESR with theSMPC. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by the Sponsor to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

8.3.3. Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. In general, the collection period will last for 30 days after the last treatment administration. The exceptions are the immune-related AEs that occur within 90 days of discontinuation of dosing of the investigational product, which should also be collected.

If an ongoing nonserious AE worsens in its intensity, or if its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described in the medical record.

8.3.4. Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify the Sponsor of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to the Sponsor, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to the Sponsor according to SAE reporting procedures.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the Sponsor, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

8.3.5. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

9. STATISTICAL METHODOLOGY

9.1. Sample size.

The primary endpoint in this study is the 1-year actual survival rate. A one-stage Fleming design has been adopted. Assuming a historical 1-year survival rate of 20% (with radiation therapy + best supportive care) for the selected population, a sample size of 56 evaluable patients would be needed to show that the addition of ipilimumab to radiotherapy generates a 1-year survival rate of 35%, reaching 80% power at the 0.05 significance level.

A total of 56 evaluable patients would need to be included. In case that at least 17 out of these 56 evaluable patients would survive for at least one year, the conclusion of the trial would be that the higher 1-year survival rate of 35% is more likely for the combination than the historical 20% survival rate.

9.2 Populations for Analyses

- Enrolled Subjects: All subjects who signed and informed consent form and were registered.
- Treated Subjects (Safety Population): Includes all subjects in the study who receive at least one dose of ipilimumab. Unless otherwise indicated, analyses of drug exposure and safety will be performed on this population as treated.

- Evaluable Subjects: Includes all subjects who received at least 1 dose of ipilimumab and the full WBRT therapy.
- Biomarker Subjects: Includes all treated subjects with at least baseline biomarker studies.

9.3 Endpoint Definitions

9.3.1 Primary Endpoint

Actuar survival rate at 1 year since the first dose. Overall survival status will be ascertained, at a minimum, every 12 weeks from first ipilimumab dose.

9.3.1.1 Overall Survival (OS)

OS is defined for each subject as the time between the date of the first dose of ipilimumab and death. If a subject has not died, the subject will be censored at the time of last contact (last known alive date).

9.3.2 Secondary and Exploratory Endpoints

The secondary endpoints will be based upon tumor assessments which are performed as described in section 6.2. until progression by irRC, intolerable toxicity, or withdrawal of consent. Response based endpoints will be evaluated based on mWHO criteria for secondary endpoints and irRC for exploratory endpoints (see Section 6.2 for definitions).

9.3.2.1 Progression Free Survival (PFS)

PFS is defined for each subject as the time between the date of the first dose of ipilimumab and the date of progression or death, whichever occurs first. A subject who dies without reported prior progression will be considered to have progressed on the date of death. For a subject who undergoes tumor resection on study, PFS will be censored on the date of the last tumor assessment prior to resection. For those who remain alive and have not progressed, PFS will be censored on the date of last tumor assessment. For subjects who have PD prior to Week 12 and a subsequent assessment of SD, PR or CR, the date of PD following response (where available) will be used in the analysis of PFS; otherwise these subjects will be censored on the date of their last tumor assessment.

9.3.2.2 Best Overall Response Rate (BORR)

BORR is defined by population subset as the total number of treated subjects in the subset whose BOR is CR or PR, divided by the total number of treated subjects in the subset.

9.3.2.3 Disease Control Rate (DCR)

DCR is as the total number of treated subjects in each population subset with BOR of CR, PR or SD, divided by the total number of treated subjects in the subset.

9.3.2.4 Duration of Response

A subject's duration of response is defined as the time between the date measurement criteria are first met for overall response of PR or CR (whichever status is recorded first, and if subsequently confirmed) and the date of disease progression or death, whichever occurs first. For subjects who undergo tumor resection on study, duration of response will be censored on the date of last tumor assessment prior to resection. For those subjects who remain alive and have not progressed, duration of response will be censored on the date of last tumor assessment.

9.3.2.5 Duration of Stable Disease

Duration of stable disease is defined for subjects whose BOR is SD as the time between when SD is first docuemtned and the date of PD or death (whichever occurs first). For a subject who undergoes tumor resection following Week 12 but prior to disease progression, duration of stable disease will be censored on the date of the last evaluable tumor assessment prior to resection. For subjects who have BOR of SD at Week 12, the date of PD following thereafter (where available) will be used in the analysis of duration of stable disease. For subjects with BOR of SD who have not subsequently progressed and who remain alive, duration of stable disease will be censored on the date of last evaluable tumor assessment.

9.4 Analyses

9.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized by population subset using descriptive statistics.

9.4.2 Efficacy Analyses

9.4.2.1 Methods for Time to Event Primary Endpoint

The yearly rate of survivors will be the actual proportion of patients alive after 1 year of the first administration of ipilimumab.

9.4.2.2 Methods for Time to Event Secondary Endpoints

The overall survival and event-free survival probabilities will be estimated and plotted using the Kaplan-Meier product-limit method.

Additionally, 1 and 2 year rates will be also based upon Kaplan-Meier estimates along with their corresponding log-log transformed 95% confidence intervals.

The progression-free survival probabilities will also be estimated and plotted using the Kaplan-Meier product-limit method. Duration of response, duration of stable disease, and overall survival in subjects with brain metastasis will also be described using these same Kaplan-Meier methods.

A differential analysis will be done with intracranial and extracranial disease.

9.4.2.3 Methods for Proportion Based Rates Secondary Endpoints

For BORR and DCR, descriptive summary statistics (e.g., total number of patients, number and percent responders, 95% confidence interval)will be used.. An exact two-sided 95% CI for these rates will be computed. A differential analysis will be done with intracranial and extracranial disease.

9.4.3 Safety Analyses

Descriptive statistics of safety will be presented for all treated subjects using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related AEs, immune-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade

per NCI CTCAE v4.0 criteria by system organ class and by preferred term. The listings by subject will be produced for all deaths, all SAEs, and all AEs leading to discontinuation of study drug. On-study laboratory parameters, including hematology, serum chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria. The reporting period for safety data will be from the first dose of study medication to 90 days (> 5 half lives) after the last dose is received.

Immune-related Adverse Events (irAEs)

Immune-related adverse events (irAEs) are AEs of unknown etiology, which are consistent with an immune phenomenon and identified by the investigator as study treatment related. The irAEs will be defined using a predefined list of MedDRA highlevel group terms, high-level terms and preferred terms; changes may be made to this list with each new version of MedDRA. Six (6) subcategories of irAEs will be reported: GI, liver, skin, endocrine, neurological, and other. Immune-related AE summaries will also be produced on diarrhea as a separate grouped term. Analysis of irAEs will be based on all treated subjects who received at least one dose of study therapy, and the reporting period will be from the first dose of after the last dose is received.

Immune-mediated Adverse Reactions (imARs)

This study will also describe immune-mediated adverse reactions (imARs) using the same adjudication algorithm and predefined list of AEs of special interest (enterocolitis, hepatitis, dermatitis, endocrinopathies, neuropathies, and other) used for the USPI. Specifically, the determination of imAR will take into account available clinical evidence through ruling out non-inflammatory etiologies such as infection or tumor progression, and consideration of evidence of inflammation such as tumor biopsies or responsiveness to steroids, but not the causality assessment of the investigator. imARs are likely to be

inflammatory events associated with ipilimumab treatment. Documentation of surveillance, intervention and outcomes are to be documented in the CRFs for inclusion of the imAR assessment. Analysis of imARs will be based on all treated subjects who received at least one dose of ipilimumab. The reporting period will be from the first dose of study therapy to 90 days after the last dose is received.

9.4.5 Exploratory Analyses

Two types of ALC analyses will be done: pharmacodynamic and predictive. Both analyses will include all treated subjects with known date of first dose of ipilimumab. Pharmacodynamic analyses will examine the patterns of change in ALC over time, and how these patterns might differ between treatment arms. Predictive analyses will examine potential relationships between ALC and measures of response such as overall survival.

The proposed biomarker study includes analysis of tumor tissue at diagnosis and serum/peripheral blood at different phases within the treatment schedule. All analysed parameters will be correlated with progression-free survival (PFS), overall survival and histopathological parameters.

For the statistical analysis, it will be used binary variables, reflecting the positivity status of the measures (yes or no; presence/absence). Association with histopathological parambles. The significance level will be set at 5%. To study the impact of the histological, immunohistochemical and molecular factors on progression-free survival (PFS) and overall survival (OS), the Kaplan-Meier proportional risk test (log rank) will be used. Evidence of the relative risk for each patient will be also provided by means of a Cox proportional hazards model using stepwise selection to identify the independent predictors of poor outcome.

For the kinetic profile of the serum/blood biomarkers, each variable will be considered as continuous. A correlation at different points of the treatment schedule will be considered and the slope value will be used in order to distinguish those cases with no change, negative or positive trend. The threshold will be calculated after considering the behavior of the whole series.

9.5 Interim Analyses

There will not be a planned interim analysis. The DSMC will have access to periodic interim reports of safety to allow them to conduct a risk-to-benefit assessment.

10. ADMINISTRATIVE SECTION

10.1. Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the EC/HA must be sent to the Sponsor’s protocol manager.

All revisions (protocol amendments, administrative letters, and changes to the informed consent) must be submitted to the Sponsor’s protocol manager. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the EC/HA of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

10.2. Informed Consent

Two different PIS and CF have been developed for this trial. One for clinical trial, that is mandatory, and another for the biomarker study, that is optional.

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

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

10.3. Records and Reports

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 (e.g. medical record) on each individual treated with Ipilimumab or entered as a control in the investigation. The investigator is required to retain, in a confidential manner, the data pertinent to the study.

10.4. 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 the Sponsor 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.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). 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).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

10.5. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

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/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the SMPCor product labeling, information to be provided to subjects and any updates.

The investigator 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

10.6. Records Retention

The investigator must retain Ipilimumab disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. medical record) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Documentation of such transfer must be provided to the Sponsor.

11. REFERENCES

APPENDIX 1 **KARNOFSKY PERFORMANCE STATUS SCALE**

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance, but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death.

References:

1. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980 Apr 15;45(8):2220-4. [Medline]
2. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984 Mar;2(3):187-93. [Medline]

APPENDIX 2 **BARTHEL INDEX OF ACTIVITIES OF DAILY LIVING**

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident (once/week)
2 = continent
Patient's Score:

Bladder
0 = incontinent, or catheterized and unable to manage
1 = occasional accident (max. once per 24 hours)
2 = continent (for over 7 days)
Patient's Score:

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving (implements provided)
Patient's Score:

Toilet use
0 = dependent
1 = needs some help, but can do something alone
2 = independent (on and off, dressing, wiping)
Patient's Score:

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent (food provided within reach)
Patient's Score:

Transfer
0 = unable – no sitting balance
1 = major help (one or two people, physical), can sit
2 = minor help (verbal or physical)
3 = independent
Patient's Score:

Mobility
0 = immobile
1 = wheelchair independent, including corners, etc.
2 = walks with help of one person (verbal or physical)
3 = independent (but may use any aid, e.g., stick)
Patient's Score:

Dressing
0 = dependent
1 = needs help, but can do about half unaided
2 = independent (including buttons, zips, laces, etc.)
Patient's Score:

Stairs
0 = unable
1 = needs help (verbal, physical, carrying aid)
2 = independent up and down
Patient's Score:

Bathing
0 = dependent
1 = independent (or in shower)
Patient's Score:

Total Score:

Scoring:

Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

Guidelines for the Barthel Index of Activities of Daily Living

General

- The Index should be used as a record of what a patient ***does***, NOT as a record of what a patient ***could do***.
- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
- The need for supervision renders the patient not independent.
- A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses will be the usual source, but direct observation and common sense are also important. However, direct testing is not needed.
- Usually the performance over the preceding 24 – 48 hours is important, but occasionally longer periods will be relevant.
- Unconscious patients should score '0' throughout, even if not yet incontinent.
- Middle categories imply that the patient supplies over 50% of the effort.
- Use of aids to be independent is allowed.

Bowels (preceding week)

- If needs enema from nurse, then 'incontinent.'
- 'Occasional' = once a week.

Bladder (preceding week)

- 'Occasional' = less than once a day.
- A catheterized patient who can completely manage the catheter alone is registered as 'continent.'

Grooming (preceding 24 – 48 hours)

- Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.

Toilet use

- Should be able to reach toilet/commode, undress sufficiently, clean self, dress, and leave.
- 'With help' = can wipe self and do some other of above.

Feeding

- Able to eat any normal food (not only soft food). Food cooked and served by others, but not cut up.

- 'Help' = food cut up, patient feeds self.

Transfer

- From bed to chair and back.
- 'Dependent' = NO sitting balance (unable to sit); two people to lift.
- 'Major help' = one strong/skilled, or two normal people. Can sit up.
- 'Minor help' = one person easily, OR needs any supervision for safety.

Mobility

- Refers to mobility about house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided.
- 'Help' = by one untrained person, including supervision/moral support.

Dressing

- Should be able to select and put on all clothes, which may be adapted.
- 'Half' = help with buttons, zips, etc. (*check!*), but can put on some garments alone.

Stairs

- Must carry any walking aid used to be independent.

Bathing

- Usually the most difficult activity.
- Must get in and out unsupervised, and wash self.
- Independent in shower = 'independent' if unsupervised/unaided.

References:

- Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud*. 1988;10(2):61-63.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.
- Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? Int Disabil Stud. 1988;10(2):64-67.