A Phase III Randomized Clinical Trial Comparing Tremelimumab With Standard-of-Care Chemotherapy in Patients With Advanced Melanoma

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CLINICAL PROTOCOL

A PHASE 3, OPEN LABEL, RANDOMIZED, COMPARATIVE STUDY OF CP-675,206 AND EITHER DACARBAZINE OR TEMOZOLOMIDE IN PATIENTS WITH ADVANCED MELANOMA

Compound:	CP-675,206
Compound Name (if applicable):	
Description:	anti-CTLA4 human monoclonal antibody
US IND Number (if applicable):	BB-10096
Protocol Number:	A3671009
Phase:	3
Version and Date:	Amendment #1 11 September 2006 Original Protocol 20 September 2005

SUMMARY

Indication:

First line therapy for surgically incurable advanced melanoma

Rationale:

CP-675,206 is a fully human monoclonal antibody. It binds to the CTLA4 molecule, which is expressed on the surface of activated T lymphocytes. CP-675,206 is thought to stimulate patients' immune systems to attack their tumors. CP-675,206 has been shown to induce durable tumor responses in patients with metastatic melanoma in Phase 1 and Phase 2 clinical studies.

Objectives:

Primary Objectives

- To compare overall survival for patients with advanced melanoma who are randomized to receive CP-675,206 with that of patients who are randomized to receive either dacarbazine or temozolomide

Secondary Objectives

- To compare durable response rate (responses present at or after 6 months post randomization) for patients in the 2 treatment arms
- To compare 6-month progression-free survival (proportion of patients who are alive and who have not progressed at 6 months or more post randomization) for patients in the 2 treatment arms
- To assess objective response rate for patients in each treatment arm
- To assess duration of response for patients in each treatment arm
- To assess time to worsening of ECOG performance status for patients in each treatment arm
- To further characterize the safety profile and toleration of CP-675,206
- To characterize any human antihuman antibody (HAHA) response to CP-675,206
- To compare health related quality of life (HQoL) outcomes in the 2 treatment arms
- To compare patient reported healthcare resource utilization and loss of productivity in the 2 treatment arms
- To explore any relationship between CP-675,206 exposure, measured as C_{max} and C_{4wk}, and clinical response in this population
- To explore whether the CTLA4, FcgammaRIIa, and IgG2a genotypes influence the safety and/or efficacy of patients treated with CP-675,206
- To explore relationships between clinical response (efficacy or toxicity) and tumor or blood genomics

Trial Design:

This is a Phase 3, multi-national, open-label, 2-arm randomized study in patients with surgically incurable metastatic melanoma who have received no prior chemotherapy, immunotherapy or biological therapy for the treatment of unresectable metastatic disease. Approximately 630 patients will be enrolled. Randomization will be stratified by disease stage (IIIC versus IV M1a, M1b versus IV M1c) and presence of measurable lesions (measurable disease versus no measurable disease).

Patients randomized to Arm A will receive CP-675,206 15 mg/kg administered intravenously on Day 1 of every 90-day cycle for up to 4 cycles. Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. Overall survival is the primary endpoint. For patients in Arm A, tumor assessments will be done every 3 months. For patients in Arm B, tumor assessments will be done every 2 cycles. For patients in either arm, additional scans will be done if clinically indicated. Patients in the control arm who progress will not be allowed to cross over to receive CP-675,206.

A blood sample will be obtained from all subjects to evaluate genetic polymorphisms of CTLA4, FcgammaRIIa and IgG2a, in order to determine whether polymorphisms in these genes are associated with drug response (efficacy and/or toxicity) to CP-675,206. Additional blood samples will be analyzed for expression of RNA (genomics blood samples). This clinical study has an additional research component to request an optional blood sample for genetic analysis and/or accessible tumor sample for RNA expression analysis, subject to IRB/IEC approval. Separate informed consent will be required. Patients who do not elect to donate these samples may still participate in the study. The optional blood specimen will be anonymized and analyzed for the genetic database.

Endpoints:

Primary Endpoints

- Overall survival

Secondary Endpoints

Efficacy Endpoints:

- Durable response, defined as an objective tumor response that is present at 6 or more months after randomization
- Progression-free survival at 6 months post randomization
- Objective tumor response
- Duration of tumor response

Safety Endpoints

- Adverse Events
- Human antihuman antibody (HAHA) response to CP-675,206 for patients on Arm A

Pharmacokinetics Endpoints for Patients in Arm A Only

- Cycle 1: plasma concentration of CP-675,206 1 hour after the end of infusion (C_{max}) and plasma concentration of CP-675,206 28 days after administration of CP-675,206 (C_{4wk})
- Cycle 2-4: plasma concentration of CP-675,206 prior to infusion (C_{trough}) and C_{max}

Pharmacogenomics Endpoints

- Genotyping of CTLA4, FcgammaRIIa and IgG2a will be determined by the frequency of SNP (Single Nucleotide Polymorphisms)
- Tumor and blood genomics will be determined by relative RNA expression levels

Patient Reported Outcomes Endpoints

- HQoL data will be collected using the EORTC QLQ-C30 questionnaire.
- Healthcare resource utilization and loss of productivity assessment using the Healthcare Resource Utilization Questionnaire (HCRUQ)

Trial Treatments:

Arm A: CP-675,206

Patients randomized to Arm A will receive intravenous administration of CP-675,206 at a dose of 15 mg/kg on Day 1 of every 90-day cycle for up to 4 cycles. No dose reduction of CP-675,206 is permitted in this study. The initiation of a subsequent cycle may be delayed to allow recovery from treatment-related toxicity, according to specific guidelines in Section 5.1.2.

Arm B: Dacarbazine or Temozolomide

Patients randomized to Arm B will receive either dacarbazine or temozolomide at the discretion of the investigator. Dacarbazine will be administered intravenously at a dose of 1000 mg/m^2 on Day 1 of each 21-day cycle until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent. Doses of dacarbazine may be decreased or delayed depending upon individual patient tolerance, according to specific guidelines in Section 5.2.1 and Section 5.2.2. Temozolomide will be administered orally at a dose of 200 mg/m^2 (starting dose) on Days 1-5 of each 28-day cycle for up to 12 cycles. Doses of temozolomide may be decreased or delayed depending upon individual patient tolerance, according to specific guidelines in Section 5.3.1 and Section 5.3.2.

Statistical Methods:

Sample Size Determination

It is assumed that the median survival for patients in the control arm treated with either dacarbazine or temozolomide is approximately 7 months. It is assumed that the true hazard ratio is 1.33 (control arm over CP-675,206 arm). This represents a 33% improvement in true median overall survival from 7 months to 9.33 months. A total of 537 events (deaths) is required to enable an unstratified log-rank test with an overall 2-sided significance level of 0.045 and power 0.90. This number of events is based on two equally spaced interim analyses before the

final analysis with group sequential design to reject either the null or the alternative hypothesis using the alpha and beat spending approach to an O'Brien-Fleming boundary.

Applying a 1:1 randomization and a planned accrual period of 21 months, a total of 630 patients are to be enrolled in order to achieve the expected number of events by the end of the minimum follow-up period. It is expected that the maximum study duration will be 35 months.

Interim Analysis

Two interim analyses of overall survival will occur when approximately one third and two thirds of the events (deaths) have been observed, with the objective of stopping early for efficacy or for futility; both outcomes will be based on an O'Brien-Fleming boundary.

Final Analysis

In case the study failed to stop for efficacy or futility in the previous 2 interim looks, the final analysis of overall survival will occur when all 537 deaths are observed.

The primary comparison of the 2 arms of the trial will be by an unstratified log-rank test using Kaplan-Meier methods. A secondary comparison of the arms will be performed by a stratified log-rank test accounting for the specified stratification factors. A secondary analysis of overall survival will also be performed for the As Treated patient population.

A stratified Cox regression model will be used to assess the impact of prognostic factors on overall survival. The prognostic factors will include age, gender, geographical region, site of the disease, and HLA class 1 type.

Table 1. Schedule of Activities for Both Arms: Screening Period

Protocol Activities	Days Prior to Randomization	
	≤28 days	≤14 days
Informed Consent [1]	X	
Contraception Counseling [2]	X	
Medical/Oncologic History	X	
Review of Visual Symptoms [3]	X	
Tumor Assessment (Imaging/Clinical) [4]	X	
Brain CT scan with contrast or MRI	X	
ECG, 12 lead, resting [5]	X	
Performance Status (ECOG)		X
Weight and Height		X
Physical Exam / Vital Signs [6]		X
Pregnancy Test [7]		X
Hematology labs [8]		X
Chemistry labs [9]		X
Thyroid Function [10]		X
Urinalysis		X
Optional Genetics (blood) [11]		X
Optional Genomics (tumor biopsy) [12]		X
EORTC QLQ-C30 [13]		X
HCRUQ[14]		X

Footnotes to Schedule of Activities: Screening Period
1. **Informed Consent**: All patients must sign an informed consent document prior to any study-related procedures that are not considered standard of care. Patients may be asked to sign an additional informed consent document for optional blood draws or tumor procurement if such procedures have been approved by the IRB/IEC
2. **Contraceptive Counseling**: All patients must agree to practice a form of effective contraception prior to entry into the study and for 6 months (males) or 12 months (females) following the last dose of study drug.
3. **Review of Visual Symptoms**: Any patient who is experiencing symptoms suggestive of uveitis or melanoma-associated retinopathy should be evaluated by an ophthalmologist to rule out these conditions.
4. **Tumor Assessments (Imaging/Clinical):** Scans should include CT with contrast or MRI of chest, abdomen, and pelvis. Outside radiographic studies must be repeated to establish baseline on the equipment that will be used throughout the study. Documentation of skin lesions that can be clearly visualized must be established by color photography, including a ruler to document size.
5. **ECG, 12 lead, resting**: Any abnormalities should be noted and any workup should be completed before the patient is randomized.
6. **Vital Signs**: temperature, blood pressure (sitting), and heart rate
7. **Pregnancy test**: for women of childbearing potential. Urine or serum.
8. **Hematology labs**: WBC with differential count and absolute neutrophil count (ANC), RBC count, hemoglobin, hematocrit, platelet count
9. **Chemistry labs**: calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen (BUN), creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase (GGT), lactic acid dehydrogenase (LDH), amylase, lipase, albumin, total bilirubin
10.**Thyroid Function**: thyroid stimulating hormone (TSH), T3, T4
11. **Optional Genetics (blood)**: Separate informed consent required.
12. **Optional Genomics (tumor biopsy)**: Separate informed consent required.
13. **EORTC QLQ-C30**: Should be self-administered when the patient is in clinic preferably before clinical assessments/treatments. May be administered via telephone interview by personnel who have received appropriate training.
14. **HCRUQ**: Healthcare resource utilization questionnaire

Table 2. Schedule of Activities: Arm A (CP-675,206) Randomization through Cycle 2

ARM A: CP-675,206 A3671009	CYCLE[1] 1						CYCLE 2				
Protocol Activities	Day 1 or up to 72 hours before dose	Day 1	Day 15	Day 30	Day 60	Within 10 days prior to C2D1	Day 1[17]	Day 15	Day 30	Day 60	Within 10 days prior to C3D1
Time Windows			14-16	28-32	56-64			14-16	28-32	56-64	
EORTC QLQ-C30[2]				X	X		Pre-dose				
HCRUQ[3]				X	X		Pre-dose				
Baseline Signs & Symptoms[4]		Pre-dose									
Adverse Event Assessment[5]		Post - dose	X	X	X		X	X	X	X	
Concomitant Medications[6]	X		X	X	X		X	X	X	X	
ECOG Performance Status	X			X	X		Pre-dose		X	X	
Weight	X			X	X		Pre-dose		X	X	
Physical Exam/Vital Signs[7]	X		X	X	X		Pre-dose	X	X	X	
ECG[8]											
Pregnancy Test[9]	X						Pre-dose				
Safety Labs/Thyroid Function[10]	X		X	X	X	X		X	X	X	X
Urinalysis	X					X					X
HAHA[11]	X						Pre-dose				
Pharmacokinetics	X	1 hour Post-End of infusion		X			Pre-dose and 1 hour Post-End of infusion				
Serum Storage for Auto-antibodies[12]	X					X					X
HLA Class 1 Typing	X										
Total IgG	X										
Pharmacogenetics (blood)	X										
Pharmacogenomics (blood)	X			X							
Optional Genomics (tumor biopsy)[13]											
CP-675,206 Administration		X					X				
Tumor Assessment (Imaging/Clinical)[14]						X					X
Biopsy of Skin In-Transit Target Lesions (if indicated)[15]						X					X

Table 2 (continued): Schedule of Events Arm A (CP-675,206) Cycle 3 through Follow-Up

CP-675,206: Arm A A3671009	[1]CYCLE 3 and CYCLE 4[19]				EOT [18]	Follow-Up [16]
Protocol Activities [1]	Day 1[17]	Day 30	Day 60	Within 10 days prior to C4D1	90 Days post-dose 4 or 30 days post final dose if <4 doses	Every 3 Months
Window		28-32	56-64			
Patient Reported Outcomes						
EORTC QLQ-C30 [2]	Pre-dose				X	
HCRUQ[3]	Pre-dose				X	
Safety Assessments						
Baseline Signs & Symptoms [4]						
Adverse Event Assessment [5]	X	X	X		X	X[5]
Concomitant Medications [6]	X	X	X		X	
ECOG Performance Status	Pre-dose	X	X		X	
Weight	Pre-dose	X	X		X	
Physical Exam / Vital Signs [7]	Pre-dose	X	X		X	
ECG[8]					X	
Pregnancy Test [9]	Pre-dose					
Safety Labs/Thyroid Function [10]		X	X	X	X	
Urinalysis				X	X	
HAHA [11]	Pre-dose				X	Month 3 Only
Pharmacokinetics	Pre-dose and 1 hour post-end of infusion				X	Month 3 Only
Serum Storage for Auto-antibodies [12]				X	X	
HLA Class 1 Typing						
Total IgG						
PHARMACOGENOMICS / PHARMACOGENETICS						
Genetics (blood)						
Genomics (blood)						
Optional Genomics (tumor biopsy) [13]					X	
STUDY TREATMENTS						
CP-675,206 Administration	X					
EFFICACY ASSESSMENTS						
Tumor Assessment (Imaging/Clinical) [14]				X	X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[15]				X	X	
FU for survival and subsequent treatment [16]						X

Footnotes to Schedule of Activities: (Arm A: CP-675,206)
1. **Cycle:** Each cycle is 90 days (86-94 days).
2. **EORTC QLQ-C30:** Should be self-administered when the patient is in clinic and prior to any clinical assessments, treatments or procedures. May be administered via telephone interview by personnel who have received appropriate training. Do not administer after patient begins new systemic therapy for melanoma.
3. **HCRUQ:** Healthcare resource utilization questionnaire
4. **Baseline Signs and Symptoms**: The investigator should describe all abnormal findings that have occurred within 14 days prior to starting study drug on the Baseline Signs and Symptoms CRF.
5. **Adverse Event Assessment:** Following the first dose, adverse events should be continuously assessed and documented during the study reporting period (Section 8.2). All study drug-related adverse events must be followed until the event has resolved, returned to baseline or has been deemed irreversible, or until the patient dies.
6. **Concomitant Medications:** All medications that have been taken within 14 days prior to starting study drug and on study treatment should be continuously documented. Start and stop dates and dose should be provided. Generic names should be used whenever available.
7. **Physical Exam/Vital Signs:** Vital signs, including temperature, blood pressure (sitting), and heart rate. Only clinically significant abnormalities should be reported as adverse events in the CRF.
8. **ECG:** 12 lead, resting
9. **Pregnancy Test:** For women of childbearing potential. Serum or urine. Results must be available prior to dosing. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations.
10. **Safety Labs: (Hematology)** WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet count. **(Blood Chemistry)** Calcium, Chloride, Total protein, Potassium, Random glucose, Sodium, BUN, Creatinine, AST (SGOT), ALT (SGPT), Alkaline Phosphatase (ALP), Gamma-Glutamine Transferase (GGT), lactic acid dehydrogenase (LDH), Amylase, Lipase, Albumin, Total Bilirubin, CRP, **Thyroid Function** (TSH, T3. T4)
11. **HAHA: Human-anti-Human Antibody:** Note that a blood sample for Pharmacokinetics must be drawn at the same time as each blood sample for HAHA.
12. **Serum Storage for Autoantibodies:** An additional blood sample should be drawn for a 3.0 mL serum sample to be stored at a central lab for potential future analysis of autoantibodies.
13. **Optional Genomics (tumor biopsy):** An optional tumor sample for RNA expression analysis may be obtained anytime within 14 days prior to first dose of study drug and at EOT. Separate informed consent is required. Baseline tumor sample should be obtained from a lesion that is NOT designated as a target lesion.
14. **Tumor Assessment (Imaging/Clinical):** Scans should include CT with contrast or MRI scans of chest, abdomen and pelvis. All patients with objective tumor response should have additional scans scheduled 4-6 weeks after the criteria for response are first met in order to confirm the response. EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.
15. **Biopsy of Skin In-Transit Target Lesions (if indicated):** If the appearance of in-transit skin lesions has changed substantially, a biopsy should be performed in order to confirm a suspected tumor response. To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.
16. **Follow-Up:** Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on date of death, cause of death, and any new therapy for melanoma. If there is evidence of continuing study drug-related toxicity, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. All patients who have stable disease or objective response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the duration of response can be determined. This information may be obtained by telephone interview.
17. **Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of safety labs must be available before the patient receives the dose.
18. **End of Treatment (EOT) Assessment:** For patients who complete a total of 4 doses, the EOT visit should be 90 days (84-96 days) after dose 4. For others, it should be scheduled approximately 30 days after the last dose of study drug, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.2.3.
19. Note that additional cycles may be administered under certain circumstances; see Section 6.2.5.

Table 3. Schedule of Activities: Arm B (Dacarbazine)

Protocol Activities	Post Randomiza-tion	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [17]	Follow-Up [15]
	Day 1 or within 72 hrs before	Day 1	Day 8	Day 15	Day 1[16]	Day 15	≤7 Days before next dose	Day 1[16]	Day 15	30 days post final dose	Every 3 Months
Patient Reported Outcomes											
EORTC QLQ-C30 [2]			X	X	Pre-dose			Pre-dose		X	
HCRUQ[3]					Pre-dose			Pre-dose		X	
SAFETY ASSESSMENTS											
Baseline Signs & Symptoms [4]		Pre-dose									
Adverse Event Assessment [5]		Post - dose	X	X	X	X		X	X	X	X[5]
Concomitant Medications [6]	X		X	X	X	X		X	X	X	
Performance Status (ECOG) / Weight	X				Pre-dose			Pre-dose		X	
Physical Exam/Vital Signs [7]	X			X	Pre-dose	Opt[7]		Pre-dose	Opt[7]	X	
ECG[8]										X	
Pregnancy Test [9]	X										
Safety Labs [10]		Pre-dose	X	X	Pre-dose	X		Pre-dose	X	X	
HLA Class 1 Typing		X									
PHARMACOGENOMICS / PHARMACOGENETICS											
Genetics (blood)		Pre-dose									
Optional Genomics (tumor biopsy) [11]										X	
STUDY TREATMENTS											
Premedication		X			X			x			
Dacarbazine IV [12]		X			X			X			
EFFICACY ASSESSMENTS											
Tumor Assessment (Imaging/Clinical) [13]							X			X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[14]							X			X	
FU for survival and subsequent treatment [15]											X

Footnotes to Schedule of Activities: (Arm B: Dacarbazine)	
1.	**Cycle:** A Cycle may be longer than 21 days if a dose of dacarbazine must be delayed due to toxicity.
2.	**EORTC QLQ-C30:** Should be self-administered when the patient is in clinic and prior to any clinical assessments, treatments or procedures. May be administered via telephone interview by personnel who have received appropriate training. Do not administer after patient begins new systemic therapy for melanoma.
3.	**HCRUQ:** Healthcare resource utilization questionnaire
4.	**Baseline Signs and Symptoms**: The investigator should describe all abnormal findings that have occurred within 14 days prior to starting study drug on the Baseline Signs and Symptoms CRF.
5.	**Adverse Event Assessment:** Following the first dose, adverse events should be continuously assessed and documented during the study reporting period (Section 8.2). All drug-related adverse events must be followed until the event has resolved, returned to baseline or has been deemed irreversible, or until the patient dies.
6.	**Concomitant Medications:** All medications that have been taken within 14 days prior to starting study drug and on study should be continuously documented. Start and Stop dates and Dose should be provided. Generic names should be used whenever available.
7.	**Physical Exam/Vital Signs:** Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. After the first cycle, physical exams on Day 15 are optional.
8.	**ECG:** 12 lead, resting
9.	**Pregnancy Test:** Urine or serum test. Pregnancy tests should be repeated during the study according to the investigator's usual practice for patients on dacarbazine. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations
10.	**Safety Labs: (Hematology)** WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet count. (**Blood Chemistry)** Calcium, Chloride, Total protein, Potassium, Random glucose, Sodium, BUN, Creatinine, AST (SGOT), ALT (SGPT), Alkaline Phosphatase (ALP), Gamma-Glutamine Transferase (GGT), lactic acid dehydrogenase (LDH), Amylase, Lipase, Albumin, Total Bilirubin, CRP
11.	**Optional Genomics (tumor biopsy):** An optional tumor sample for RNA expression may be obtained within 14 days prior to administration of study drug on Cycle 1, Day 1 and at EOT. Separate informed consent is required. Tumor sample should be obtained from a lesion that is NOT designated as a target lesion.
12.	**Dacarbazine Administration:** Patients receive intravenous administration of dacarbazine 1000 mg/m^2 to be repeated every 21 days. The initiation of subsequent cycles may be delayed to allow recovery from treatment-related toxicities.
13.	**Tumor Assessments (Imaging/Clinical):** Scans should include CT with contrast of chest, abdomen and pelvis. EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.
14.	**Biopsy of Skin In-Transit Target Lesions (if indicated):** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.
15.	**Follow-Up:** Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on date of death, cause of death, and any new therapy for melanoma. If there is evidence of continuing study drug-related toxicity, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. All patients who have stable disease or objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the duration of response can be determined. This information may be obtained by telephone interview.
16.	**Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of hematology laboratories must be available before the patient receives the dose.
17.	**End of Treatment (EOT) Assessment:** The EOT visit should be scheduled approximately 30 days after the last dose of dacarbazine, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.3.3.

Table 4. Schedule of Activities: Arm B (Temozolomide)

Protocol Activities	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [18]	Follow-Up [16]
	Day 1 or up to 72 hours before	Day 15	Day 22	Day 1[17]	Day 22	≤7 Days before next dose	Day 1[17]	Day 22	Day 30	Every 3 Months
Patient Reported Outcomes										
EORTC QLQ-C30 [2]		X	X	X			X		X	
HCRUQ[3]				X			X		X	
SAFETY ASSESSMENTS										
Baseline Signs & Symptoms [4]	X									
Adverse Event Assessment [5]		X	X	X	X		X	X	X	X[5]
Concomitant Medications [6]	X	X	X	X	X		X	X	X	
Performance Status (ECOG)	X			X			X		X	
Weight	X		X	X			X		X	
Physical Exam/Vital Signs [7]	X		X	X	opt[7]		X	opt[7]	X	
ECG [8]									X	
Pregnancy Test [9]	X									
Hematology Labs [10]	X	X	X	X	X		X	X	X	
Chemistry Labs[11]	X			X			X		X	
HLA Class 1 Typing	X									
PHARMACOGENOMICS / PHARMACOGENETICS										
Genetics (blood)	X									
Optional Genomics (tumor biopsy) [12]									X	
STUDY TREATMENTS										
Antiemetics	Days 1-5			Days 1-5			Days 1-5			
Temozolomide [13]	Days 1-5			Days 1-5			Days 1-5			
EFFICACY ASSESSMENTS										
Tumor Assessment (Imaging/Clinical) [14]						X			X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[15]						X			X	
FU for survival and subsequent treatment [16]										X

Footnotes to Schedule of Activities: (Arm B: Temozolomide)
1. **Cycle:** A Cycle may be longer than 28 days if a dose of temozolomide must be delayed due to toxicity.
2. **EORTC QLQ-C30:** Should be self-administered when the patient is in clinic and prior to any clinical assessments, treatments or procedures. May be administered via telephone interview by personnel who have received appropriate training. Do not administer after patient begins new systemic therapy for melanoma.
3. **HCRUQ:** Healthcare resource utilization questionnaire
4. **Baseline Signs and Symptoms**: The investigator should describe all abnormal findings that have occurred within 14 days prior to starting study drug on the Baseline Signs and Symptoms CRF.
5. **Adverse Event Assessment:** Following the first dose, adverse events should be continuously assessed and documented during the study reporting period (Section 8.2). All drug-related adverse events must be followed until the event has resolved, returned to baseline or has been deemed irreversible, or until the patient dies.
6. **Concomitant Medications:** All medications that have been taken within 14 days prior to starting study drug and on study should be continuously documented. Start and Stop dates and Dose should be provided. Generic names should be used whenever available.
7. **Physical Exam/Vital Signs:** Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. After the first cycle, physical exams on Day 22 are optional.
8. **ECG:** A 12-lead, resting electrocardiogram
9. **Pregnancy Test:** Pregnancy tests should be repeated during the study according to the investigator's usual practice for patients on temozolomide. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations.
10. **Hematology Labs:** WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet count.
11. **Blood Chemistry:** Calcium, Chloride, Total protein, Potassium, Random glucose, Sodium, BUN, Creatinine, AST (SGOT), ALT (SGPT), Alkaline Phosphatase (ALP), Gamma-Glutamine Transferase (GGT), lactic acid dehydrogenase (LDH), Amylase, Lipase, Albumin, Total Bilirubin, CRP
12. **Optional Genomics (tumor biopsy):** Separate informed consent is required. Tumor sample should be obtained from a lesion that is **not** designated as a target lesion.
13. **Temozolomide:** Patients should take temozolomide orally on Days 1-5 of each 28-day cycle.
14. **Tumor Assessments (Imaging/Clinical):** Scans should include CT with contrast of chest, abdomen and pelvis. EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.
15. **Biopsy of Skin In-Transit Target Lesions (if indicated):** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.
16. **Follow-Up:** Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on date of death, cause of death, and any new therapy for melanoma. If there is evidence of continuing study drug-related toxicity, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. All patients who have experienced objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the duration of response can be determined. This information may be obtained by telephone interview.
17. **Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of hematology laboratories must be available before the patient receives the next dose.
18. **End of Treatment (EOT) Assessment:** The EOT visit should be scheduled approximately 30 days after the start of the last cycle of temozolomide, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.4.3.

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1.7. Rationale for Efficacy Endpoints

Overall survival was chosen as the primary endpoint of this study because it is a direct measure of clinical benefit. Secondary endpoints were selected to provide additional proof of activity or to demonstrate what clinical effects could be expected when CP-675,206 is used for first line treatment of metastatic melanoma.

The schedule of treatments and assessments for the 2 arms of this study are different. The values assigned to endpoints such as progression free survival and duration of response depend on the time points at which these endpoints are assessed. Therefore, direct comparisons of these endpoints between the 2 arms may be biased.

Progression-free survival (PFS) will be compared between the 2 arms only at 6 months, when both arms have a scheduled assessment. Similarly, the percent of patients with tumor response present at or after 6 months will be compared between the 2 arms. Tumor responses of 6-month duration are presumed to be evidence of benefit to the patient.

1.8. Rationale for Comparator Drugs

Dacarbazine is the only chemotherapeutic agent approved for metastatic melanoma. Its approval was based on tumor responses. No randomized trial has been conducted comparing dacarbazine to observation, so it is not known how big an effect, if any, dacarbazine has on survival. When dacarbazine was approved in the 1970s, it was given at a lower dose spread out over 5 days. However, the use of newer anti-emetic drugs has allowed for the administration of a higher dose on Day 1 of each cycle. Dacarbazine, at a dose of 850 to 1000 mg/m^2 once every 3 weeks, is the current standard reference therapy for patients with metastatic melanoma.[2]

Temozolomide is an orally administered drug with the same active moiety as dacarbazine, monomethyl triazenoimidazole carboxamide (MTIC). It is not approved for treatment of metastatic melanoma but is commonly used for this indication in some countries, including the United States of America. Temozolomide was compared to dacarbazine, in terms of overall survival, progression-free survival, objective response and safety, in a randomized Phase 3 trial of 305 patients with advanced melanoma.[3] Patients received temozolomide 200 mg/m^2/day orally for 5 consecutive days every 4 weeks, or dacarbazine 250 mg/m^2/day intravenously for 5 consecutive days every 3 weeks. There were no statistically significant differences in overall survival or response rate. There was a significant difference in PFS (1.9 months vs 1.5 months) in favor of temozolomide, but this could be attributed at least in part to the difference in assessment schedule between the 2 arms.

In this trial, temozolomide is included as an option for investigators who are experienced with this drug in their standard practice for melanoma. In the analysis of this trial, the CP-675,206 arm will be compared to the comparator arm as a whole, because the 2 comparator drugs are assumed to be not significantly different in terms of the primary endpoint of this study.

1.9. Rationale for Pharmacogenomics Research

There are several well-characterized polymorphisms within the CTLA4 gene. A C-318T polymorphism within the promoter region has been associated with increased CTLA4 expression on the cell surface. An A49G polymorphism within the leader peptide sequence has been associated with several autoimmune disorders. More recently, a G to A polymorphism 6.1 kb 3' of the CLTA4 has been strongly associated with autoimmune disease and results in lower levels of the soluble form of CTLA4 mRNA. A common polymorphism in the FcgammaRIIa gene results in a His 131 Arg substitution. It occurs at a frequency of 44% in Caucasians, 56% in African Americans, and 8% in Japanese. The Arg variant has a significantly lower affinity for human IgG2 and may influence response to cellular activation by CP-675,206. Characterizing the effects of these variants on response to CP-675,206 would enable a better understanding of interpatient variability in toxicity and tumor response rates.

The tumor and peripheral blood samples will be used to analyze the expression of RNA as they may relate to clinical response (tumor regression and/or toxicity) to CP-675,206. Exploratory analyses will be performed to detect potential changes in gene expression that distinguish tumors that respond, or at least regress, from those that are stable or progressing.

2. TRIAL OBJECTIVES

2.1. Primary Objective

- To compare overall survival for patients with advanced melanoma who are randomized to receive CP-675,206 with that of patients who are randomized to receive either dacarbazine or temozolomide

2.2. Secondary Objectives

- To compare durable response rate (responses present at or after 6 months post randomization) for patients in the 2 treatment arms
- To compare 6-month progression-free survival (proportion of patients who are alive and who have not progressed at 6 months or more post randomization) for patients in the 2 treatment arms
- To assess objective response rate for patients in each treatment arm
- To assess duration of response for patients in each treatment arm
- To assess time to worsening of ECOG performance status for patients in each treatment arm
- To further characterize the safety profile and toleration of CP-675,206
- To characterize any human antihuman antibody (HAHA) response to CP-675,206
- To compare health related quality of life (HQoL) outcomes in the 2 treatment arms
- To compare patient reported healthcare resource utilization and loss of productivity in the 2 treatment arms

- To explore any relationship between CP-675,206 exposure, measured as C_{max} and C_{4wk}, and clinical response in this population
- To explore whether the CTLA4, FcgammaRIIa, and IgG2a genotypes influence the safety, and/or efficacy of patients treated with CP-675,206
- To explore relationships between clinical response (efficacy or toxicity) and tumor or blood genomics

3. TRIAL DESIGN

This is a Phase 3, multi-national, open-label, 2-arm randomized study in patients with unresectable metastatic melanoma who have received no prior chemotherapy, immunotherapy or biological therapy for the treatment of metastatic disease. Approximately 630 patients will be enrolled. Randomization will be 1:1 and will be stratified by disease stage (IIIC versus IV M1a, M1b versus IV M1c) and presence of measurable lesions (measurable disease versus no measurable disease). Patients randomized to Arm A will receive intravenous administration of CP-675,206 at a dose of 15 mg/kg on Day 1 of every 90-day cycle, for up to 4 cycles. Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. Overall survival is the primary endpoint. For patients in Arm A, tumor assessments will be done every 3 months. For patients in Arm B, tumor assessments will be done every 2 cycles. For patients in either arm, additional scans will be done if clinically indicated. Patients in the control arm who progress will not be allowed to cross over to receive treatment with CP-675,206.

Patients in Arm A who complete treatment without disease progression and who subsequently experience disease progression may receive 2 additional doses of CP-675,206 provided that they have not received other systemic therapy for their melanoma.

A blood sample will be obtained from all subjects to evaluate genetic polymorphisms of CTLA4, FcgammaRIIa and IgG2a, in order to determine whether polymorphisms in these genes are associated with drug response (efficacy and/or toxicity) to CP-675,206. Additional blood samples will be analyzed for expression of RNA (genomics blood samples). This clinical study has an additional research component to request an optional genetics blood sample and/or accessible tumor sample for genetic analysis, subject to IRB/IEC approval. Separate informed consent will be required. Patients who do not elect to donate these samples may still participate in the study. The optional blood specimen will be anonymized and analyzed for the genetic database. The Clinical Pharmacogenomics Supplement provides details on this additional research.

4. PATIENT SELECTION

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Histologically confirmed melanoma that is not surgically curable and is either:
   - Stage IV (AJCC 6th edition) OR
   - Stage IIIC (AJCC 6th edition) with N3 status for regional lymph nodes and in-transit or satellite lesions

   NOTE: Patients with mucosal melanoma will not be excluded. All HLA types are eligible.

2. Patients must either have measurable disease or have non-measurable disease which can be evaluated for objective response, as defined here:
   - Measurable Disease. Patient has at least one lesion that meets the following criteria: Measurable lesions can be accurately measured in at least one dimension. Lesions on CT scan must have longest diameter ≥2.0 cm using conventional techniques or ≥1.0 cm with spiral CT scan. Skin lesions documented by photography must have longest diameter at least 1.0 cm. Clinically detected lesions must be superficial (eg, skin nodules), and the longest diameter must be ≥2.0 cm. Palpable lymph nodes >2.0 cm should be demonstrable by CT scan. If the measurable disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology or histology. Tumor lesions that are situated in a previously irradiated area will be considered measurable only if progression is documented following completion of radiation therapy.
   - Non-Measurable Disease. Patients with non-measurable disease (ie, without lesions that meet the above criteria for measurability) must have evidence of disease confirmed by pathology (ie, needle aspirate/biopsy). Patients with previously irradiated lesions must have documented progression or disease outside the radiation port.
3. ECOG performance status of 0 or 1
4. Age ≥18 years or older
5. Adequate bone marrow, hepatic, and renal function determined within 14 days prior to randomization, defined as:
   - Absolute neutrophil count ≥1.5 x 10^9 cells/L
   - Platelets ≥100 x 10^9/L
   - Hemoglobin ≥10 g/dL
   - Aspartate and alanine aminotransferases (AST, ALT) ≤2.5 x Upper Limit of Normal (ULN), or ≤5 x ULN, if documented liver metastases are present

- Total serum bilirubin ≤2 x ULN (except patients with documented Gilbert's syndrome)
- Serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥60 mL/min

6. Serum lactic acid dehydrogenase (LDH) ≤2 x ULN
7. CT scan of the brain with contrast or MRI of the brain within 28 days of enrollment showing no evidence of brain metastases
8. Patients must have recovered from all prior surgical or adjuvant treatment-related toxicities, to baseline status, or a CTC Grade of 0 or 1, except for toxicities not considered a safety risk, such as alopecia. Post-surgical pain will not be considered a basis for exclusion.
9. Females of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to randomization. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.
10. Females of childbearing potential and males who have not undergone surgical sterilization must agree to practice a form of effective contraception prior to entry into the study and for 12 months (females) or 6 months (males) following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.
11. Patient must be willing and able to provide written informed consent.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the trial:

1. Melanoma of ocular origin (uveal melanoma)
2. Received any systemic therapy for metastatic melanoma except post-surgical adjuvant treatment with cytokines (eg, alfa-interferon or GM-CSF) or with vaccines after complete resection of melanoma. Patients who received adjuvant cytokine therapy must be at least 30 days from the last dose. Patients who received adjuvant vaccine therapy must be at least 6 months from the last dose. (See Appendix F for a list of cancer vaccines). All patients who received adjuvant therapy must have documented tumor progression since the last dose. **Note:** Prior chemotherapy or biochemotherapy, including isolated limb perfusion therapy is not allowed. Prior resection for Stage III or Stage IV disease is allowed as long as the patient has unresectable lesions at the time of randomization. Patients who received intradermal BCG for adjuvant therapy for Stage III or IV melanoma are not excluded.
3. History of brain metastases
4. Received any prior CTLA4 inhibiting agent (eg MDX-010)
5. Patients previously randomized on this protocol

6. History of chronic autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, hypophysitis, etc.). **Note:** Active vitiligo or a history of vitiligo will not be a basis for exclusion.
7. History of uveitis or melanoma-associated retinopathy
8. History of inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis), celiac disease, or other chronic gastrointestinal conditions associated with diarrhea, or current acute colitis of any origin
9. Known active or chronic viral hepatitis
10. Any serious uncontrolled medical disorder or active infection that would impair the patient's ability to receive study treatment. **Note**: Patients with Acquired Immunodeficiency Syndrome (AIDS) are excluded.
11. Received an immunosuppressive dose of corticosteroids or other immunosuppressive medication (eg, methotrexate, rapamycin) within 30 days of randomization. **Note:** Patients with adrenal insufficiency may take up to 5 mg of prednisone or equivalent daily. Topical and inhaled corticosteroids in standard doses are allowed.
12. History of other malignancy, except for adequately treated basal cell carcinoma or squamous cell skin cancer or carcinoma in situ of the cervix, unless the patient has been disease-free for at least 5 years
13. Breast-feeding
14. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol

4.3. Randomization Criteria

Following full assessment and determination that a patient meets all eligibility criteria and has given written informed consent for study participation, the investigator or designee may enroll the patient. Patients will be assigned individual study numbers and randomized to treatment arm as described in the Study Manual. Randomization will be stratified by disease stage (IIIC versus IV M1a, M1b versus IV M1c) and presence of measurable lesions (measurable disease versus no measurable disease).

No patient shall receive study drug therapy until the entire registration process has been completed.

5. TRIAL TREATMENTS

5.1. Arm A: CP-675,206

Patients randomized to Arm A will receive intravenous administration of CP-675,206 at a dose of 15 mg/kg on Day 1 of every 90-day cycle for up to 4 cycles. For purposes of treatment visits and scheduling, each cycle is defined as a 90 (± 4 day) period. To allow for possible change in

body weight over time, patients should be weighed within 10 days prior to each cycle and the administered dose of CP-675,206 should be recalculated.

Patients in Arm A who discontinue treatment without disease progression and who subsequently experience disease progression may receive 2 additional doses of CP-675,206 provided that they have not received other systemic therapy for their melanoma.

5.1.1. Dose Reduction of CP-675,206

No dose reduction of CP-675,206 is permitted in this study.

5.1.2. Dose Delays and Re-Dosing Criteria for CP-675,206

The initiation of a cycle may be delayed for up to 12 weeks to allow recovery from treatment-related toxicity. All patients must meet the following criteria for laboratory parameters by the day of dosing, as detailed in Table 6, in order to be treated with subsequent doses of CP-675,206.

Table 6. Re-Dosing Criteria for CP-675,206: Laboratory Parameters

Laboratory Parameter	Re-Dosing Criteria
Hepatic Function (within 10 days)	AST, ALT ≤2.5 x ULN (≤5 x ULN if liver metastases are present) bilirubin ≤2 x ULN (except in patient with Gilbert's syndrome)
Renal Function (within 10 days)	serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥60 mL/min
Amylase and Lipase (within 10 days)	≤1.5 x ULN or baseline

For all patients, treatment-related adverse events must have resolved at least to CTCAE Grade 1 or baseline and be considered tolerable by the day of dosing, in order to be treated with subsequent doses of CP-675,206 except as noted in Table 7 and in Section 5.1.3 (Stopping Rules for Adverse Events).

Table 7. Re-Dosing Criteria for CP-675,206: Treatment-Related Adverse Events.

Adverse Event	Re-Dosing Criteria
Thyroiditis	Asymptomatic or stable on thyroid replacement therapy
Rash	Tolerable and ≤ Grade 2
Vitiligo	May be re-dosed regardless of severity
All other treatment-related adverse events	Tolerable and ≤ Grade 1 or baseline

NOTE: If a patient has a hypersensitivity reaction to CP-675,206 or a Grade 3 treatment-related toxicity at any time during a cycle, the investigator must notify the Pfizer Clinician.

The mechanism of action of CP-675,206 is thought to involve infiltration of tumor by lymphocytes, which may lead to a transient apparent increase in tumor size. In addition, CP-675,206 treatment has been observed to have a delayed effect on tumors. Therefore, an objective response may be observed after an initial increase in tumor size. Given this possibility, a patient may receive subsequent doses of CP-675,206 despite evidence of progression during the first 3 months of treatment, at the discretion of the investigator and the patient.

After 2 doses of CP-675,206, if there is no evidence that the patient is deriving any benefit from treatment, the patient must discontinue treatment. Evidence of benefit includes objective responses, mixed responses, or stable disease.

5.1.3. Stopping Rules for Adverse Events

Patients who experience the following adverse events at any time during the previous cycle must not receive further dosing with CP-675,206 and will be considered off-study.

- Any Grade 4 CP-675,206-related adverse event
- Hypersensitivity to CP-675,206, Grade 3 (see Section 5.1.4.2)
- Hypersensitivity to CP-675,206, Grade 2, and symptoms reappear after infusion restarted
- Melanoma associated retinopathy, Grade 2 or above
- Uveitis, Grade 2 or above
- Hepatitis, Grade 3
- Diarrhea, Grade 3, requiring treatment with systemic steroids for more than 10 days in any one cycle

5.1.4. Management of Toxicity of CP-675,206

CP-675,206 is an immune modulator, so investigators should be alert for the development of immune mediated side effects.

Possible immune-mediated disorders that have been observed in patients who received CP-675,206 in early phase trials involved the skin (vitiligo and cutaneous leukocytoclastic vasculitis), the thyroid gland (autoimmune thyroiditis), the liver (autoimmune hepatitis) and the pituitary (hypophysitis). Abnormal lab results, which may be immune-mediated, include elevations of serum lipase and amylase and liver function tests.

If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for appropriate autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of those autoantibodies. Doses of CP-675,206 should be held until the etiology of the event is established. Continuation of CP-675,206 in the presence of immune-mediated events should be done by the investigator only after discussion with the patient on a case-by-case basis with consideration to risk-benefit analysis.

5.1.4.1. Management of Diarrhea

Available information suggests that diarrhea is an expected clinically significant adverse event when treating patients with anti-CTLA4 experimental drugs.[4] Intestinal perforation has been reported with CP-675,206, as well as for another investigational agent that targets CTLA4. The following algorithm is recommended for the treatment of patients who develop diarrhea while on

study. (See CP-675,206 Treatment-Emergent Diarrhea Management Guidelines, Appendix A, for additional details.)

Table 8. Diarrhea Algorithm

Diarrhea Severity and Duration	Recommendation
Grade 1 less than or equal to 14 days	• Consider use of probiotics • Follow Diarrhea Management Guidelines including *C. difficile* titer, empiric loperamide, oral fluid replacement • Consider mesalamine
Grade 1 more than 14 days or Grade 2 of any duration not responsive to loperamide	• Consider use of probiotics • Evaluation of severity by clinician familiar with CP-675,206-related diarrhea • Follow Diarrhea Management Guidelines • Consider IV fluids if indicated • Consider use of mesalamine or steroids*
Grade 3 or Grade 4 for any duration Or Any grade & duration associated with evidence of severe enterocolitis including bleeding, fever, pain or other signs/symptoms	• Consider use of probiotics • Evaluation by clinician familiar with CP-675,206-related diarrhea • Consider inpatient hospitalization for IV fluids, monitoring • Consider use of steroids* • Consider use of octreotide, budesonide, olsalazine, or mesalamine (See Appendix A.) • Consider infliximab if not responsive to steroids • Notify the Pfizer Clinician
* Response of diarrhea to steroids has been reported for a similar experimental drug that targets CTLA4. Example: oral or intravenous dexamethasone up to 4 mg every 4 hours	

5.1.4.2. Management of Hypersensitivity Reactions to CP-675,206

In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate and notify the Pfizer Clinician of the event. The following treatment recommendations may be applicable and can be adopted at investigator's judgment:[5,6]

- CTCAE v.3.0 Grade 1 Allergy (transient flushing or rash, drug fever <38°C):
  - Supervise at the bedside.
- CTCAE v.3.0 Grade 2 Allergy (urticaria, drug fever ≥38°C, and/or asymptomatic bronchospasm):
  - Interrupt the infusion of CP-675,206 and disconnect infusion tubing from patient
  - Administer IV antihistamines (diphenhydramine 25-50 mg and ranitidine 50 mg or cimetidine 300 mg).
  - After recovery of symptoms, resume the infusion at half the initial infusion rate. If no further symptoms appear, complete the administration of the dose. If symptoms reappear, stop infusion and discontinue patient from the study.

- CTCAE v.3.0 Grade 3 or 4 Allergy (symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related edema/angioedema; hypotension; anaphylaxis):
  - Stop the infusion of CP-675,206 and disconnect infusion tubing from patient.
  - Administer epinephrine (1:10,000) in 3.5 to 5 mL IV boluses (no more than 6 doses).
  - Administer IV antihistamine (diphenhydramine 50 mg IV push).
  - If wheezing persists: 0.35 mL of inhaled albuterol or other bronchodilators.
  - Consider methylprednisolone 30 to 60 mg IV push, which may prevent recurrent or ongoing reactions.
  - Patient must be taken off study.

5.1.5. Drug Supply: CP-675,206

CP-675,206 will be supplied as a 5 mg/mL sterile solution in 10 mL vials, therefore containing 50 mg per vial.

5.1.6. Formulation and Packaging of CP-675,206

CP-675,206 is supplied as a sterile solution, packaged in 10 mL clear glass vials with a rubber stopper and an aluminum seal. Each vial contains 5 mg/mL of CP-675,206 (with a nominal fill of 50 mg per vial), sodium chloride, sodium acetate, and polysorbate 80 at ph 5.5.

The standard supply of CP-675,206 is delivered to the investigator site in a white carton with 100 vials of CP-675,206 within foam inserts.

The vial and carton labels identify CP-675,206 as "CP-675,206 (clonal), IV Vial Solution 5 mg/mL". The study number listed on the vial and carton labels is "A367PSOF_____" which is a code for pooled clinical supplies that includes A3671009.

5.1.7. Preparation and Dispensing of CP-675,206

Specific preparation instructions are provided in the most current version of the Dosage and Administration Instructions. A member of the Pharmacy or Clinical Research Unit staff with appropriate training and experience must prepare all supplies.

5.1.8. Administration of CP-675,206

CP-675,206 is diluted with sterile normal saline (supplied by the investigator) prior to administration according to specific instructions in the Dosage and Administration Instructions. CP-675,206 should be administered open-label as an intravenous solution at a rate of 100 mL/hr, followed by observation. Specific dosing and administration instructions are provided in the most current version of the Dosage and Administration Instructions.

Although CP-675,206 is a fully human monoclonal antibody, immunogenicity remains a possibility, and thus acute hypersensitivity reactions such as urticaria, pruritus, laryngeal edema, angioedema, bronchospasm, respiratory distress, nausea, vomiting, crampy abdominal pain, acute back pain, fever, diarrhea, hypotension and fatal anaphylactic shock, as well as subacute reactions, are also possible. The patients' blood pressure, heart rate, and temperature should be recorded prior to treatment and monitored as needed during drug infusion and for approximately 1 hour post-infusion.

Medications to treat hypersensitivity reactions should be available, such as IV saline, acetaminophen, and emergency drugs, including subcutaneous epinephrine, diphenhydramine, methylprednisolone, and inhaled albuterol. See Section 5.1.4.2 for guidelines on management of hypersensitivity reactions. If a hypersensitivity reaction attributed to CP-675,206 occurs, the investigator must report this to the Pfizer Clinician.

5.1.9. Premedication

To date, one patient has had a reported hypersensitivity reaction to CP-675,206. Premedication for CP-675,206 will not be required unless the patient has experienced a hypersensitivity reaction with a prior dose. If a hypersensitivity reaction attributed to CP-675,206 occurs, the investigator must report this to the Pfizer Clinician. The investigator and Pfizer Clinician will decide whether premedication should be implemented for that patient or whether the patient should be withdrawn from further treatment. Premedication with diphenhydramine, at least one half hour prior to the infusion of CP-675,206, would be recommended.[7]

5.1.10. CP-675,206 Storage and Drug Accountability

CP-675,206 must be stored at 2°C to 8°C (36°F to 46°F). It is important that the formulation is not frozen. The investigator or an approved representative (eg, pharmacist) must ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

To ensure adequate records, all study drug must be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the patients must be returned to Pfizer or its appointed agent.

5.1.11. Concomitant Medications for Patients on CP-675,206

Concomitant medications used by patients during their participation in this study should be recorded on the Concomitant Medication CRF.

During the study, patients may require immunosuppressive drugs such as corticosteroids for management of underlying disease, treatment-related toxicity, or unrelated conditions. Patients who receive a systemic immunosuppressive drug for any reason must not receive CP-675,206 for 30 days after the last dose. Topical and inhaled corticosteroids in standard doses are allowed. Patients with adrenal insufficiency may take up to 5 mg of prednisone or equivalent daily.

Patients who receive systemic corticosteroids for more than 10 days in the previous cycle for Grade 3 diarrhea must be withdrawn from the study. Patients who receive immunosuppressive drugs for more than 30 days in the previous cycle must be withdrawn from the study.

It is highly recommended that patients not be exposed to anti-infective vaccinations while participating in the study, given that the effect of the vaccination has not been explored under conditions of CTLA4 blockade. Any such vaccinations should be recorded on the Concomitant Medication CRF.

Patients who begin new investigational therapy, chemotherapy, cytokine therapy, or immunotherapy (including vaccines) for melanoma must not receive further treatment in this study.

5.2. Arm B: Dacarbazine

Patients randomized to Arm B will receive either dacarbazine or temozolomide at the discretion of the investigator. Dacarbazine will be administered at a dose of 1000 mg/m^2 administered intravenously on Day 1 of each 21-day cycle. Patients in Arm B who are treated with dacarbazine will receive treatment until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent.

5.2.1. Dose Reduction of Dacarbazine

Doses of dacarbazine may be adjusted depending upon individual patient tolerance. Table 9 indicates potential dose levels for dacarbazine.

Table 9. Dacarbazine Dose Levels

Dacarbazine Dose Levels	
Dose Modification	**Dose Level**
Starting Dose	1000 mg/m^2
Dose Modification #1	750 mg/m^2
Dose Modification #2	500 mg/m^2
Dose Modification #3	Off study

The height measured at baseline and the weight measured up to 10 days before the beginning of each cycle should be used to calculate body surface area.

Dacarbazine doses will be adjusted at the beginning of a new cycle based upon the most severe toxicity encountered in the current cycle and upon laboratory values on the scheduled day of treatment. Doses reduced for drug-related toxicity should not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Patients whose dose has been reduced for adverse events that are subsequently not felt to be related to dacarbazine may have the dose re-escalated after completion of 1 cycle with toxicities ≤ Grade 1.

Table 10 describes the recommended dose modifications. All dose modifications are relative to the Day 1 dose of the current cycle.

Table 10. Dose Modifications for Dacarbazine

Dose Modifications
(Based On Most Severe Toxicity Observed)

NCI-CTC Toxicity Grade[a] (value) (most severe grade in previous cycle)	At Start of New Cycle
Neutropenia	
1. ≥500/mm^3	Maintain dose level
2. <500/mm^3	↓ 1 dose level
Thrombocytopenia	
1. ≥10,000/mm^3	Maintain dose level
2. <10,000/mm^3	↓ 1 dose level
Neutropenic fever or sepsis Grade 3 or 4 neutropenia (ANC <1,000/mm^3) with fever ≥38.5°C)	↓ 1 dose level
Nausea or Vomiting[b]	
1. Grade 1 or 2	Maintain dose level
2. Grade 3 or 4	↓ 1 dose level
Other nonhematologic toxicities	
1. Grade 1 or 2	Maintain dose level
2. Grade 3 or 4.	↓ 1 dose level

[a] NCI CTC, Version 3.0
[b] Dose modifications apply only if event occurs despite maximal medical treatment/prophylaxis.

5.2.2. Dose Delays for Dacarbazine

If on the expected day of re-treatment (Day 22), ANC is <1.5 x 10^9/L, and/or platelets are <100 x 10^9/L and/or any treatment related non-hematological toxicity is > Grade 1 severity (with the exclusion of alopecia), treatment must be delayed 1 week and the patient reassessed for recovery weekly. If recovery is not observed after 3 weeks of delay, the patient should be discontinued from the study. Granulocyte colony-stimulating factor is permitted for marrow recovery, if a previous cycle of therapy was associated with Grade 4 neutropenia, neutropenic fever or neutropenia that resulted in delay of dosing.

5.2.3. Drug Supply: Dacarbazine

Dacarbazine for this trial will be obtained by the investigator sites from commercial suppliers.

5.2.4. Formulation and Packaging of Dacarbazine

Formulation and packaging may vary depending on the commercial suppliers in each country of the investigator site. Please refer to package insert.

5.2.5. Preparation and Dispensing of Dacarbazine

Please refer to the package insert.

5.2.6. Administration of Dacarbazine

Dacarbazine (1000 mg/m^2) is to be administered intravenously according to instructions in the package insert, on Day 1 of every cycle.

5.2.7. Premedication for Dacarbazine

Prophylactic anti-emetic treatment should be administered before each dose of dacarbazine. A serotonin 5-HT_3 receptor antagonist such as ondansetron, dolasetron, or granisetron is recommended. Additional oral anti-emetic drugs should be considered for delayed nausea.

5.2.8. Dacarbazine Storage

Vials of dacarbazine should be protected from light and stored according to directions on the package insert. The investigator or an approved representative (eg, pharmacist) must ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

5.2.9. Concomitant Medications for Patients on Dacarbazine

Concomitant medications used by patients during their participation in this study should be recorded on the Concomitant Medication CRF.

Patients who begin new investigational therapy, chemotherapy, cytokine therapy, or immunotherapy (including vaccines) for melanoma must not receive further treatment in this study.

5.3. Arm B: Temozolomide

Patients randomized to Arm B will receive either dacarbazine or temozolomide at the discretion of the investigator. Temozolomide will be administered at a starting dose of 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle. Patients in Arm B who are treated with temozolomide will receive treatment until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent.

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

5.3.1. Dose Modification of Temozolomide

The dose of temozolomide in a new cycle may be modified based upon the most severe toxicity observed during the preceding cycle. As shown in the table below, doses may be reduced from the 200 mg/m^2 starting dose.

Table 11. Temozolomide Dose Levels

Temozolomide Levels	
Dose Modification	**Dose Level**
Starting Dose	200 mg/m^2
Dose Modification -1	150 mg/m^2
Dose Modification -2	100 mg/m^2

The height measured at baseline and the weight measured up to 10 days before the beginning of each cycle should be used to calculate body surface area.

Table 12 describes the recommended dose reductions for Day 1 in subsequent cycles of therapy. All dose modifications for the start of a new cycle should be based on the most severe toxicity observed in the previous cycle and are relative to the Day 1 dose of the previous cycle.

If the ANC falls to <1000/mm^3 and/or the platelet count falls to <50,000/mm^3 and/or the patient experiences any temozolomide-related non-hematologic toxicity ≥ Grade 3 during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose. (Patients who do not tolerate 100 mg/m^2 should discontinue treatment.) If Grade 4 hematologic toxicity occurs, the CBC should be repeated at least every other day or as dictated by the local standard of care until the Grade 4 hematologic toxicity resolves.

Doses reduced for drug-related toxicity should not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Patients whose dose has been reduced for adverse events that are subsequently considered not related to temozolomide may have the dose re-escalated after completion of 1 cycle with toxicities ≤ Grade 1 (or, at the investigator's discretion, Grade ≤2 for the following toxicities: alopecia; allergic rhinitis; fatigue; sweating; dry skin; nail changes; hot flashes/flushes; constipation; dyspepsia/heartburn; flatulence; ileus; mouth dryness; sense of smell; taste disturbance; insomnia; dry eye; tearing (watery eyes); hiccoughs; erectile impotence; libido; and vaginal dryness).

Table 12. Temozolomide Dose Modifications At Start Of A Subsequent Cycle Of Therapy
(Based On Most Severe Toxicity In The Previous Cycle)

NCI-CTC Toxicity Grade[a] (value)	Temozolomide
Neutropenia	
1.(1500 to 1999/mm^3)	Maintain dose level
2.(1000 to 1499/mm^3)	Maintain dose level
3.(500 to 999/mm^3)	↓ 1 dose level
4.(<500/mm^3)	↓ 1 dose level
Thrombocytopenia	
≥50,000/mm^3	Maintain dose level
<50,000/mm^3	↓ 1 dose level
Neutropenic fever or sepsis (Grade 3 or 4 neutropenia [ANC <1,000/mm^3] with fever ≥38.5°C)	↓ 1 dose level
Nausea or Vomiting[b]	
1.	Maintain dose level
2.	Maintain dose level
3.	↓ 1 dose level
4.	↓ 1 dose level
Other nonhematologic toxicities	
1.	Maintain dose level
2.	Maintain dose level
3.	↓ 1 dose level
4.	↓ 1 dose level

a NCI CTC, Version 3.0
b Dose reductions apply only if event occurs despite maximal medical treatment/prophylaxis.

5.3.2. Dose Delays for Temozolomide

A new cycle of treatment may begin on Day 29 when the ANC is ≥1500/mm^3 and the platelet count is ≥100,000/mm^3 and temozolomide-related non-hematologic toxicities are Grade ≤1. If these conditions have not been met, treatment should be delayed for 1 week to allow for recovery. At the investigator's discretion, patients with the following toxicities on the expected day of retreatment that are deemed to be temozolomide-related and Grade 2 severity may proceed with treatment (without delaying treatment until recovery of these toxicities to Grade ≤1): alopecia; allergic rhinitis; fatigue; sweating; dry skin; nail changes; hot flashes/flushes; constipation; dyspepsia/heartburn; flatulence; ileus; mouth dryness; sense of smell; taste disturbance; insomnia; dry eye; tearing (watery eyes); hiccoughs; erectile impotence; libido; and vaginal dryness.

If dosing is delayed due to hematologic toxicity, the CBC should be repeated at least weekly until the toxicity resolves. In addition, if Grade 4 hematologic toxicity occurs, the CBC should be repeated at least every other day or as dictated by the local standard of care until the Grade 4 hematologic toxicity resolves. If after a 1-week delay, the ANC and platelet count exceed these levels and all temozolomide-related non-hematologic toxicities are Grade ≤1, then proceed with treatment as outlined in Table 12. If after a 2-week delay, toxicities do not allow treatment, the patient should discontinue study treatment.

5.3.3. Drug Supply (Temozolomide)

Temozolomide for this trial will be obtained by the investigator sites from commercial suppliers.

5.3.4. Formulation and Packaging of Temozolomide

Formulation and packaging may vary depending on the commercial suppliers in each country. Please refer to package insert.

5.3.5. Preparation and Dispensing of Temozolomide

Please refer to the package insert.

5.3.6. Administration of Temozolomide

Temozolomide will be administered at a starting dose of 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle, according to instructions in the package insert.

5.3.7. Premedication for Temozolomide

Patients who receive temozolomide should receive prophylactic anti-emetics. The prophylactic anti-emetic regimen will be determined by the investigator based on his/her standard practice.

5.3.8. Temozolomide Storage

Vials of temozolomide should be protected from light and stored according to directions on the package insert. The investigator or an approved representative (eg, pharmacist) must ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

5.3.9. Concomitant Medications for Patients on Temozolomide

Concomitant medications used by patients during their participation in this study should be recorded on the Concomitant Medication CRF.

Patients who begin new investigational therapy, chemotherapy, cytokine therapy, or immunotherapy (including vaccines) for melanoma must not receive further treatment in this study.

5.4. Allocation to Treatment

Patients will be assigned a unique identification number by telerandomization. Patients randomized to Arm B may receive either dacarbazine or temozolomide, at the discretion of the investigator.

6. TRIAL PROCEDURES

6.1. Screening and Randomization: Arm A and Arm B

6.1.1. Informed Consent

All patients being considered for this study must sign an informed consent document prior to any study-related procedures that are not considered to be standard of care and prior to receiving study drug. Patients may be asked to sign an additional separate informed consent document for optional blood draws or tumor procurement if such procedures have been approved by the IRB/IEC.

6.1.2. Pre-Study Assessments (Screening)

The following should be performed within 28 days before randomization:

1. **Medical History**: Includes review of systems, oncologic history and general medical history of all disease processes (active or resolved), and concomitant illnesses. Oncologic baseline disease characteristics include date of diagnosis, cytology or histology, stage at time of study entry, and melanoma treatment history. Record in the medical record and in the CRF.
2. Patients should be questioned about **visual symptoms**. Any patient who is experiencing symptoms suggestive of uveitis or melanoma-associated retinopathy (eg, eye pain or redness, sensitivity to light or glare, blurred vision, floaters, night blindness, or visual field defects) should be evaluated by an ophthalmologist to rule out these conditions.
3. **Counseling on contraception:** All patients (male and female) must agree to practice a form of effective contraception prior to entry into the study and for 6 months (males) or 12 months (females) following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.
4. **Tumor Assessments** (Imaging/Clinical): Documentation of baseline target and non-target lesions by imaging techniques or by measurement of clinical lesion(s) must be performed at the institution participating in the study. Assessment must include CT scans with contrast or MRI of chest, abdomen and pelvis. Outside radiographic studies should be repeated to establish baseline on the equipment that will be used throughout the study. Documentation of skin lesions that can be clearly visualized must be established by color photography, including a ruler to document size.
5. **Radiological Assessment of the Brain**: All patients are required to have CT scan with contrast or MRI scan of the brain. Patients found to have any brain metastases are excluded from enrollment.
6. **Electrocardiogram (ECG)**: 12 lead, resting. Any abnormalities should be noted and any workup completed before the patient is randomized.

The following should be performed within 14 days before randomization. They should be fully documented in the patient's medical record and recorded in the CRF:

7. **Performance Status (ECOG)**
8. **Weight** and **Height**
9. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
10. **Physical Exam**
11. Collect urine for **Urinalysis** (blood, protein, other)
12. Collect blood for
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin)
    - **Thyroid Function** thyroid stimulating hormone (TSH) T3, T4
13. Each patient must complete baseline **EORTC QLQ-C30** and **HCRUQ questionnaires** prior to randomization.
14. All females of childbearing potential must have a negative serum or urine **Pregnancy Test** in order to be eligible for randomization. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential. Note: Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations
15. Under separate informed consent, patients can donate optional specimens within 14 days prior to initial dose of study drug; a single optional **blood specimen for pharmacogenetics** as well as an optional **tumor core biopsy for pharmacogenomics** (RNA expression). Any tumor sample should be obtained from a lesion that is not designated as a target lesion. These samples should be obtained only in patients who will be participating in the study.

6.1.3. Randomization

Patients will be assigned a unique identification number by telerandomization. Randomization will be stratified by disease stage (IIIC versus IV M1a, M1b versus IV M1c) and presence of measurable lesions (measurable disease versus no measurable disease). Patients should begin treatment within 5 working days of randomization. If extenuating circumstances prevent a patient from beginning treatment within this time, the patient may begin treatment only with written permission by the Pfizer Clinician.

6.2. Post-Randomization Procedures: Arm A (CP-675,206)

6.2.1. Cycle 1: Arm A (CP-675,206)

6.2.1.1. Cycle 1: Within 72 Hours Prior to First Dose (CP-675,206)

The following procedures may be performed on Day 1 prior to dosing or up to 72 hours prior to dosing:

1. Weight
2. **Physical Examination** and **Vital Signs**
3. Baseline **ECOG** Performance Status
4. Review of **Concomitant Medications**
5. Collect urine for **Urinalysis** (blood, protein, other)
6. Repeat **Pregnancy Test** for women of childbearing potential unless a previous pregnancy test was negative ≤7 days prior to dosing.
7. Draw blood for the following:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)
   - **HAHA**
   - **Pharmacokinetics**
   - **Serum storage for auto-antibodies**
   - **HLA class 1 typing**
   - **Total IgG**
   - **Pharmacogenetics** and **Pharmacogenomics**

6.2.1.2. Cycle 1, Day 1: Arm A (CP-675,206)

The following should be done prior to the first dose of CP-675,206:

1. Complete any assessments in the previous section that were not completed within 72 hours prior to dosing.
2. **Baseline Signs and Symptoms**
3. **Vital Signs** (temperature, blood pressure while sitting, heart rate)

After the assessments listed above are performed, if a pregnancy test within 7 days is negative or not required, the study drug may be administered.

4. **Administer CP-675,206** intravenously at a dose of 15 mg/kg.
5. Record any **Adverse Events** that occur after the beginning of the infusion.
6. One hour after the end of the infusion, draw blood for **Pharmacokinetics**.

6.2.1.3. Cycle 1, Day 15: Arm A (CP-675,206)

1. Review **Adverse Events** since previous visit.
2. Review **Concomitant Medications**.
3. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
4. **Physical Exam**
5. Draw blood for:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)

6.2.1.4. Cycle 1, Day 30: Arm A (CP-675,206)

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Weight**
6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. Draw blood for:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid

dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

- **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)
- **Pharmacokinetics**
- **Genomics** (RNA expression)

6.2.1.5. Cycle 1, Day 60: Arm A (CP-675,206)

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Weight**
6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. Draw blood for:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)

6.2.1.6. Within 10 Days Prior to Scheduled Dose 2: Arm A (CP-675,206)

1. Tumor Assessment, using the same methods and techniques that were used to assess the target lesions at baseline. Results of these assessments should be available prior to administration of the next dose of CP-675,206.
2. If the appearance of in-transit skin lesions has changed substantially, a biopsy may be performed in order to confirm a suspected tumor response.
3. Collect urine for **Urinalysis** (blood, protein, other)
4. Draw blood for:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid

dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

- **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)
- **Serum Storage for Autoantibodies**

6.2.2. Cycle 2 and Subsequent Cycles: Arm A (CP-675,206)

6.2.2.1. Day 1 of Cycle 2 and Subsequent Cycles: Arm A (CP-675,206)

The following should be done prior to the dose of CP-675,206:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires
2. Review **Adverse Events** since previous visit
3. Review **Concomitant Medications**
4. **ECOG** Performance Status
5. **Weight**
6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. **Pregnancy test** for women of childbearing potential
9. Check results of pregnancy test, hematology labs, chemistry labs, thyroid function tests, and urinalysis.
10. Blood should be drawn for the following:
    - **HAHA**
    - **Pharmacokinetics**

After the assessments listed above are performed, the study drug may be administered if the patient meets the re-dosing criteria.

1. **Administer CP-675,206** intravenously at a dose of 15 mg/kg.
2. Record any **Adverse Events** that occur during or after the infusion.
3. One hour after the end of the infusion, draw blood for **Pharmacokinetics**.

6.2.2.2. Day 15 of Cycle 2 Only: Arm A (CP-675,206)

1. Review **Adverse Events** since previous visit.
2. Review **Concomitant Medications**.
3. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
4. **Physical Exam**
5. Draw blood for:

- **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
- **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)

6.2.2.3. Day 30 and Day 60 Clinic Visits: Cycle 2 and Subsequent Cycles: Arm A (CP-675,206)

1. Review **Adverse Events** since previous visit.
2. Review **Concomitant Medications**.
3. **ECOG** Performance Status
4. **Weight**
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Physical Exam**
7. Draw blood for:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)

6.2.2.4. Within 10 Days Prior to Next Dose: Arm A (CP-675,206)

1. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline. Results of these assessments should be available prior to administration of the next dose of CP-675,206.
2. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.
3. Collect urine for **Urinalysis** (blood, protein, other)
4. Draw blood for:
   - Safety Labs, including Hematology (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), Blood Chemistry (calcium, chloride, total protein, potassium, random glucose, sodium,

blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), Serum C-Reactive Protein (CRP)

- **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)
- Serum Storage for Autoantibodies

6.2.3. End of Treatment (EOT) Visit: Arm A (CP-675,206)

For patients who complete a total of 4 doses, the EOT visit should be at the end of Cycle 4, 90 days (86-94 days) after the last dose. For others, it should be scheduled approximately 30 days after the last dose of CP-675,206, or before the patient begins new systemic therapy for melanoma.

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications. Draw blood for pharmacokinetics and human anti human antibodies only.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**
4. **ECOG** Performance Status
5. **Weight**
6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. **Electrocardiogram** (ECG) 12-lead, resting
9. Collect urine for **Urinalysis** (blood, protein, other)
10. Draw blood for:
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
    - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)

- **HAHA**
- **Pharmacokinetics**
- **Serum Storage** for autoantibodies

11. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline.
12. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.
13. **Optional tumor biopsy for genomics** (RNA expression) (only if separate informed consent has been signed)

6.2.4. Follow-up Assessments: Arm A (CP-675,206)

1. Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on **survival**, **cause of death**, and any **new therapy for melanoma**.
2. If there is evidence of continuing study **drug-related adverse events**, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. Drug related adverse events must be followed until the event has resolved, returned to baseline, or has been deemed irreversible, or until the patient dies.
3. All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the **duration of response** can be determined.
4. At the first Follow-up Visit (3 Months) draw blood for:
   - **HAHA**
   - **Pharmacokinetics**

6.2.5. Re-treatment for Progression During Follow-up

Patients in Arm A who discontinue treatment without disease progression and who subsequently experience disease progression may receive 2 additional doses of CP-675,206 provided that they have not received other systemic therapy for their melanoma. The Pfizer Clinician must be consulted before a patient in follow-up begins re-treatment.

The Cycle 3 and Cycle 4 schedule of assessments should be followed, except that Patient Reported Outcomes (EORTC QLQ-C30 and HCRUQ questionnaires) are not required, and Safety Labs and Thyroid Function Tests should be done within 10 days prior to Dose 5. An End of Cycle 6 Visit should be done, following the schedule of assessments for the End of Treatment Visit, except that Patient Reported Outcomes and tumor biopsy for blood genomics are not required.

6.3. Post-Randomization Procedures: Arm B (Dacarbazine)

6.3.1. Cycle 1: Arm B (Dacarbazine)

6.3.1.1. Within 72 Hours Prior to First Dose: Arm B (Dacarbazine)

The following procedures may be performed on Day 1 prior to dosing or up to 72 hours prior to dosing:

1. Measure **Weight** and calculate Body Surface Area (BSA) using screening Height
2. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
3. Physical Exam

   Repeat **Pregnancy Test** for women of childbearing potential unless a previous pregnancy test was negative ≤7 days prior to dosing. Note: Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations

4. Baseline **ECOG** Performance Status
5. Review of **Concomitant Medications**

6.3.1.2. Day 1 Cycle 1: Arm B (Dacarbazine)

The following should be done up to 72 hours prior to the first dose of dacarbazine:

1. Baseline Signs and Symptoms
2. Draw blood for the following:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **HLA class 1 typing**
   - **Pharmacogenetics**

After the assessments listed above are performed, if a pregnancy test within 7 days is negative or not required, the study drug may be administered.

3. **Administer prophylactic antiemetics and dacarbazine** intravenously.
4. Record any **Adverse Events** that occur after the beginning of the infusion.

6.3.1.3. Day 8 Cycle 1: Arm B (Dacarbazine)

1. Administer **EORTC QLQ-C30 Questionnaire**. (This questionnaire may be administered by telephone interview.)
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. Draw blood for:

- **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

6.3.1.4. Day 15 Cycle 1: Arm B (Dacarbazine)

1. Administer **EORTC QLQ-C30** questionnaire.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
5. **Physical Exam**
6. Draw blood for:

    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

6.3.2. Cycle 2 and Subsequent Cycles: Arm B (Dacarbazine)

6.3.2.1. Day 1 of Cycle 2 and Subsequent Cycles: Arm B (Dacarbazine)

The following may be done up to 72 hours before the dose of dacarbazine is administered:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Weight**

6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. Draw blood for:
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

After the results of these assessments have been reviewed, if the patient meets the re-dosing criteria, the study drug may be administered. Note that pregnancy tests should also be performed according to the investigator's usual practice for patients on dacarbazine. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations

9. **Administer antiemetics and dacarbazine** intravenously
10. Record any **Adverse Events** that occur during or after the infusion

6.3.2.2. Day 15 of Cycle 2 and Subsequent Cycles: Arm B (Dacarbazine)

1. Review **Adverse Events** and **Concomitant Medications** since previous visit if the patient is seen in clinic.
2. **Vital Signs** (temperature, blood pressure while sitting, heart rate) (optional)
3. **Physical Examination** (optional)
4. Draw blood for:
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

6.3.2.3. Within 7 Days of Upcoming Cycle (Even numbered Cycles Only: Arm B (Dacarbazine)

1. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline. Results of these assessments should be available prior to administration of the next dose of dacarbazine.
2. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.

The results of these tumor assessments should be reviewed before the next scheduled dose of dacarbazine.

6.3.3. End of Treatment (EOT) Visit: Arm B (Dacarbazine)

The EOT Visit should be scheduled approximately 30 days after the last dose of dacarbazine, or before the patient begins new systemic therapy for melanoma.

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Physical Exam** and **Weight**
7. **Electrocardiogram** (ECG) (12-lead, resting)
8. Draw blood for:
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
9. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline, unless scans have been performed within the previous 28 days or if progressive disease has already been documented.
10. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.
11. Under separate informed consent, patients who donated optional tumor specimens prior to the initial dose of study drug may donate an additional optional **tumor core biopsy for pharmacogenomics** (RNA expression). Any tumor sample should be obtained from a lesion that is not designated as a target lesion.

6.3.4. Follow-up Assessments: Arm B (Dacarbazine)

1. Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on **survival**, **cause of death**, and any **new therapy for melanoma**.
2. If there is evidence of continuing study **drug-related adverse events**, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. Drug related adverse events must be followed until the event has resolved, returned to baseline, or has been deemed irreversible, or until the patient dies.
3. All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the **duration of response** can be determined.

6.4. Post-Randomization Procedures: Arm B (Temozolomide)

6.4.1. Cycle 1: Arm B (Temozolomide)

6.4.1.1. Day 1 Cycle 1: Arm B (Temozolomide)

The following should be done up to 72 hours prior to the first dose of temozolomide:

1. Measure **Weight** and calculate Body Surface Area (BSA) using screening Height
2. Baseline **ECOG** Performance Status
3. Review of **Concomitant Medications**
4. **Baseline Signs and Symptoms**
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Physical Exam**
7. Repeat **Pregnancy Test** for women of childbearing potential unless a previous pregnancy test was negative ≤7 days prior to dosing.
8. Draw blood for the following:
   - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
   - **HLA class 1 typing**
   - **Pharmacogenetics**

After the assessments listed above are performed, the study drug may be provided to the patient.

9. Provide prophylactic **antiemetics and temozolomide** and instructions to patient. Temozolomide should be taken orally on Days 1-5.

6.4.1.2. Day 15 Cycle 1: Arm B (Temozolomide)

1. Administer **EORTC QLQ-C30 Questionnaire**. (This questionnaire may be administered by telephone interview.)
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. Draw blood for:

- **Hematology labs** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count)

6.4.1.3. Day 22 Cycle 1: Arm B (Temozolomide)

1. Administer **EORTC QLQ-C30** questionnaire.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **Weight**
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Physical Exam**
7. Draw blood for:

    - **Hematology labs** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count)

6.4.2. Cycle 2 and Subsequent Cycles: Arm B (Temozolomide)

6.4.2.1. Day 1 of Cycle 2 and Subsequent Cycles: Arm B (Temozolomide)

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires.
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Weight**
6. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
7. **Physical Exam**
8. Draw blood for:

    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood**

Chemistry (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**

After the results of these assessments have been reviewed, if the patient meets the re-dosing criteria, the study drug may be provided to the patient. Note that pregnancy tests should also be performed according to the investigator's usual practice for patients on temozolomide. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations.

9. Provide prophylactic **antiemetics and temozolomide** and instructions to the patient. Temozolomide should be taken orally on Days 1-5

6.4.2.2. Day 22 of Cycle 2 and Subsequent Cycles: Arm B (Temozolomide)

1. Review **Adverse Events** since previous visit if the patient is seen in clinic.
2. Review **Concomitant Medications** if the patient is seen in clinic.
3. **Vital Signs** (temperature, blood pressure while sitting, heart rate) (optional)
4. **Physical Exam** (optional)
5. Draw blood for:
   - **Hematology labs**(WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count

6.4.2.3. Within 7 Days of Upcoming Cycle (Even numbered Cycles Only: Arm B (Temozolomide)

1. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline. Results of these assessments should be available prior to administration of the next dose of temozolomide.
2. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.

The results of these tumor assessments should be reviewed before the next scheduled dose of temozolomide.

6.4.3. End of Treatment (EOT) Visit: Arm B (Temozolomide)

The EOT Visit should be scheduled approximately 30 days after the last beginning of the last cycle of temozolomide, or before the patient begins new systemic therapy for melanoma.

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Weight**
7. **Physical Exam**
8. **Electrocardiogram** (ECG) 12-lead, resting
9. Draw blood for:
    - **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
10. **Tumor Assessment**, using the same methods and techniques that were used to assess the target lesions at baseline, unless scans have been performed within the previous 28 days or if progressive disease has already been documented.
11. If the appearance of in-transit skin lesions has changed substantially, a **biopsy** may be performed in order to confirm a suspected tumor response.
12. Under separate informed consent, patients who donated optional tumor specimens prior to the initial dose of study drug may donate an additional optional **tumor core biopsy for pharmacogenomics** (RNA expression). Any tumor sample should be obtained from a lesion that is not designated as a target lesion.

6.4.4. Follow-up Assessments: Arm B (Temozolomide)

1. Patients (or their physicians) should be seen or contacted at least every 3 months to collect information on **survival**, **cause of death**, and any **new therapy for melanoma**.
2. If there is evidence of continuing study **drug-related adverse events**, the patient should continue to be followed at intervals deemed medically appropriate by the investigator. Drug related adverse events must be followed until the event has resolved, returned to baseline, or has been deemed irreversible, or until the patient dies.
3. All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the **duration of response** can be determined

6.5. Patient Withdrawal

Patients may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.6. Patient Discontinuations

A discontinuation occurs when an enrolled patient discontinues the treatment to which they were randomized. The investigator must determine the primary reason for discontinuation:

1. Completion of a course of study therapy (4 cycles of CP-675,206 for patients in Arm A or 12 cycles of dacarbazine or temozolomide for patients in Arm B).
2. Withdrawal due to adverse event. When a discontinuation is due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements and the discontinuation must be reported immediately to the Pfizer Clinician or his/her designee.
3. Patients may decide to withdraw from the study at any time. Patients who withdraw from treatment should be followed for survival, and their subsequent treatments should be recorded.
4. The investigator should withdraw the patient at any time if he/she believes it is in the patient's best interest to do so (eg, if it is in the patient's best interest to begin new chemotherapy or biological therapy for his/her disease).
5. Patients who become pregnant must not receive further treatment in this study. Pregnant patients should be followed for the duration of the pregnancy, and the outcome of the pregnancy should be recorded.
6. Patients who begin new investigational therapy, chemotherapy, cytokine therapy or immunotherapy must not receive further treatment in this study. Note that surgery or radiation therapy for melanoma lesions is allowed.
7. Patients may be discontinued from the study for poor compliance at the discretion of the investigator.

The final evaluation required by the protocol should be performed at the time of study discontinuation. The investigator should record the reason for study discontinuation and provide or arrange for appropriate follow-up (if required) for the patient. After withdrawal from study

treatment, all patients should continue to be followed for survival, and if the patient begins new treatment for melanoma, the name of the treatment should be recorded. In addition, all patients who have experienced objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new therapeutic regimen, so that the duration of response can be determined. This information may be obtained by telephone interview or from the patient's physician.

7. ASSESSMENTS

The minimum required screening, on study, and follow-up evaluations are summarized for each arm in the Schedules of Activities. Other parameters and/or increased frequency of examinations or clinical follow-up may be needed based on the findings during the study.

7.1. Safety Assessments

Laboratory safety assessments are detailed in the Schedules of Activities and include the following: hematology and chemistry labs; ECG; urinalysis; and function of endocrine organs including T3, T4, TSH, lipase, and amylase. Human antihuman antibody (HAHA) response to CP-675,206 will be monitored in patients on Arm A. Serum samples are stored at baseline for patients in Arm A for potential testing for autoantibodies. If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of the those autoantibodies.

Medical history and physical exams with ECOG performance status, vital signs, weight as well as ECGs, will be performed during the study.

7.2. Tumor Assessments

7.2.1. Schedule of Tumor Assessments

Baseline documentation of tumor sites should include imaging assessment of disease in the chest, abdomen and pelvis. A baseline brain CT scan with contrast or MRI is required. All baseline evaluations must be performed as close as possible to the first day of study treatment and never more than 28 days before enrollment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

For patients in Arm A, imaging studies and/or measurement of clinical lesions should be performed every 3 months. For patients in Arm B, tumor assessments should be performed every 2 cycles. Malignancy status (tumor assessment) must be completed within 10 days (Arm A) or 7 days (Arm B) prior to the planned start of the next cycle (dose) and should be available for clinical evaluation and disease assessment prior to administration of study drug. The same method of assessment and the same techniques used to assess the target lesions at screening should be performed. Brain scans do not need to be repeated unless clinically indicated.

All patients in Arm A who have objective tumor response should have additional scans scheduled 4 to 6 weeks after the criteria for response are first met in order to confirm response. Additional scans should be done whenever clinically indicated.

7.2.2. Assessment of Tumor Response

To be assigned a status of Partial Response (PR) or Complete Response (CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

7.2.3. Measurability of Tumor Lesions

Only measurable lesions may be selected as target lesions. Patients who do not have measurable lesions at baseline should not have target lesions assigned. These patients can still be evaluated for tumor response, as described in Section 7.2.7.

a. Measurable Lesions:

- If the patient has a solitary measurable lesion, its neoplastic nature should be confirmed by cytology/histology in order for it to be considered measurable.
- Lesions that can be accurately measured radiographically in at least 1 dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques or ≥1.0 cm with spiral CT scan.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules). Skin lesions documented by photography must be at least 1.0 cm in longest diameter in order to be considered measurable. Documentation by color photography, including a ruler to document the size of the lesions, is required.

b. Non-Measurable Lesions:

- All other lesions, including small lesions (longest diameter <2.0 cm with conventional techniques or <1.0 cm with spiral CT scan) and truly non-measurable lesions. Also, skin lesions with longest diameter <1.0 cm and other clinical lesions <2.0 cm. Lesions that are considered non-measurable include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, and abdominal masses that are not confirmed and followed by imaging techniques. Patients with non-measurable disease (ie, without lesions that meet the size criteria for measurability) must have evidence of disease confirmed by pathology (ie, needle aspirate/biopsy). Patients with previously irradiated lesions must have documented progression or disease outside the radiation port. Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

7.2.4. "Target" and "Non-Target" Lesions

a. Target Lesions:

- Up to 10 total lesions, a maximum of 5 lesions per organ, that are representative of all involved organs may be selected and recorded as target lesions at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A non-measurable lesion cannot be selected as a target. A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the disease. Previously irradiated lesions should not be selected as target lesions unless there is documented progression of the lesion since the completion of radiation therapy.

b. Non-Target Lesions:

- All other lesions (or sites of disease) should be identified as non-target lesions and recorded as non-target lesions at baseline. Non-target lesions are not required to be measured, and should be recorded as "present" at baseline. Each non-target lesion should be documented as either present, absent or new in each subsequent evaluation. Note that all in-transit skin lesions should be photographed at baseline, with a ruler to document size, regardless of size.

7.2.5. Techniques for Assessing Measurable Disease

The same method and technique of assessment used at baseline should be used to characterize each identified and reported lesion during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment. Accepted methods of tumor assessment include:

- Clinical Examination: Documentation by color photography, including a ruler to document the size of the lesion(s), is required.
- CT, magnetic resonance imaging (MRI): Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck and extremities require specific protocols as per RECIST.
- Ultrasound: Ultrasound should not be used to measure tumor lesions that are not clinically accessible. It is, however, a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

7.2.6. Objective Response Classifications

The following criteria will be the method utilized in this study for the assessment and reporting of tumor response data:

- Complete Response (CR): Disappearance of all target and non-target lesions. CR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met to qualify as CR
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Non-target lesions may persist provided there is no unequivocal progression in these lesions. PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met to qualify as PR. Note: For patients who do not have measurable disease at baseline a partial response is not defined.
- Progressive Disease (PD): At least a 20% increase in the sum LD of the target lesions from the smallest sum LD recorded since the beginning of therapy or the appearance of one or more new lesions or unequivocal progression of existing non-target lesions
- Stable Disease (SD): Measurements demonstrating neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify as PD after the start of treatment taking as reference the smallest sum LD since the treatment started. During this time, non-target lesions may persist provided there is no unequivocal progression in these lesions.

7.2.7. Evaluation of Overall Response

Determination of overall response is summarized in Table 13:

Table 13. Overall Response for Patients with Measurable Lesions at Baseline

Target Lesions	Nontarget lesions	New Lesions	Overall response
CR[a]	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR[b]	Non-PD	No	PR
SD[c]	Non-PD	No	SD
PD[d]	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

a Complete Response
b Partial Response
c Stable Disease
d Progressive Disease

For patients who do not have measurable lesions at baseline, the following criteria will be used:

Table 14. Overall Response for Patients without Measurable Lesions at Baseline

Nontarget lesions	New Lesions	Overall response
CR	No	CR
Non-PD	No	SD
PD	Yes or No	PD
Any	Yes	PD

7.2.8. Use of Clinical Data in Assessment of Tumor Response

In the case of resection of lesions or radiotherapy during the on-study or follow-up period, the anatomical site(s) of a given intervention and any pathology results must be noted in the Case Report Form. The assessment of overall tumor response may be altered after biopsy, resection, or radiotherapy of one or more lesions during the on-study or follow-up period, depending on the results of the pathology report.

If the biopsy results or other clinical data are not consistent with the radiology report, then this information will be taken into account for the determination of tumor status. For example, if a lesion that is present in a follow-up scan (new lesion consistent with progression) is found on biopsy or surgical resection to contain no living melanoma cells (eg, inflammatory cells and dead melanoma cells) then this information may be taken into consideration for the determination of tumor status (eg, will not be considered to be evidence of progression). If a baseline lesion or new lesion that is considered non-malignant in the radiology report is found on biopsy to contain melanoma cells, then this may be taken into account for tumor status determinations (eg, considered evidence of progression). Likewise, if the pathology report shows that a resected lesion does not contain live melanoma cells (eg, inflammatory cells and dead melanoma cells), the lesion should be considered to have resolved. If the results of a biopsy of a lesion that was thought to represent melanoma at baseline show that it is not consistent with melanoma (eg, sarcoidosis), then the overall response should be assigned according to remaining lesions.

7.3. Patient Reported Outcomes

The assessment of health-related quality of life and healthcare resource utilization, including productivity, are patient reported outcomes. Data from these analyses will contribute in assessing this dosing regimen, building the outcomes research knowledge base for CP-675,206 as well as provide insight into designing future patient reported outcome studies.

Health-related quality of life will be measured using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire version 3.0, (EORTC QLQ-C30).[8] This instrument is a self-administered questionnaire that has been extensively validated. The EORTC QLQ-C30 consists of 30 questions that measure functional status, symptoms, and global health. The 30 questions require approximately 10-15 minutes of the patient's time to complete and are best accomplished when the patient is in the clinic awaiting investigator follow-up and before any clinical assessments. Every effort should be made to have the patient complete the self-assessment questionnaire in the clinic. However, a study nurse/monitor can read the questions to the patient (eg, should the patient require assistance because of having forgotten their reading glasses, or being unable to write because of pain or injury to the writing arm or hand), and in

cases when the patient is unavailable for continued clinic visits, the HQoL questionnaire can be administered by telephone interview.

The HQoL questionnaire should be administered at baseline and at Day 1 of the each treatment cycle starting with Cycle 2 (prior to dosing) in each treatment arm. Additional HQoL questionnaires should be administered in the first treatment cycle of each arm. In patients receiving CP-675,206 (Arm A), these additional assessments should be done at the Day 30 and Day 60 clinic visits. For patients receiving dacarbazine, these additional assessments should be done at Day 8 and Day 15 of the first treatment cycle. For patients receiving temozolomide, these additional assessments should be done at Day 15 and Day 22 of the first treatment cycle. The questionnaire may be administered either by telephone or in person. In addition, patients will be required to complete the HQoL assessments at the time of study discontinuation (End of Treatment Assessment). However, HQoL questionnaires should not be administered after a patient begins new therapy for melanoma.

The Healthcare Resource Utilization Questionnaire will be used to assess healthcare resources used and productivity. This questionnaire consists of 3 questions regarding physician and other health professional visits, hospitalizations, and emergency room visits; and 2 questions assessing productivity. The HCRUQ is to be administered every cycle during the dosing visit for Arm B, and every month during the first cycle and then every cycle during the dosing visit for Arm A while the patient is on study. This questionnaire will also be administered at the End of Treatment Visit in both treatment arms.

7.4. CP-675,206 Pharmacokinetic Assessments

For patients in Arm A only:

- Blood specimens sufficient to provide 2.0 mL of plasma in heparinized tubes will be obtained for PK analysis will be obtained prior to administration of CP-675,206 and 1 hour after the end of infusion of CP-675,206 every treatment cycle. A blood specimen will be obtained on Day 30 of the first treatment cycle.
- Blood specimens will also be collected at the End of Treatment Visit and at the first Follow-up visit.

7.5. Human antihuman antibody (HAHA) Assessments

For patients in Arm A only:

- A blood specimen for HAHA assay will be obtained prior to administration of CP-675,206 every treatment cycle.
- Blood specimens will also be collected at the End of Treatment Visit and at the first Follow-up visit.

7.6. Pharmacogenetics

A specimen (6 mL whole blood in EDTA tube) for non-anonymous genotyping to evaluate polymorphisms in CTLA4, FcgammaRIIa and IgG2a will be obtained prior to the initial dose of study drug. This sample will be disposed of after study analyses are completed.

Optional anonymized pharmacogenetics specimens can be donated under separate informed consent per the Clinical Pharmacogenomics Supplement within 14 days prior to dosing. Patients who sign the informed consent document will be asked to provide a single additional 9 mL blood sample for Pfizer's genetic database.

Shipment of all specimens will be completed according to the information provided in a separate laboratory manual.

7.7. Pharmacogenomics (RNA Expression Analysis)

All patients in Arm A will provide a blood specimen (5 mL in Pax Gene tubes) to analyze expression of RNA as it relates to drug response (tumor regression and/or toxicity) to CP-675,206. This sample will be obtained prior to the administration of the first dose (pre-dose) and on Day 30 of the first cycle.

In patients with easily accessible tumor that is not a target lesion, optional tumor biopsies may be requested for pharmacogenomic (RNA expression) analysis as it may relate to the study drug response. Patients consenting to this optional procedure will have a tumor biopsy (core biopsy of approximately 4 x 4 x 4 mm^3) within 14 days prior to the initial dose of CP-675,206 and at the End of Treatment Visit. If no lesions are available after the last dose, the genomic analysis will be performed using the pre-dose biopsy only to evaluate molecular markers of clinical response (tumor regression) to CP-675,206. Expression of genes in the tumor may change as a result of the treatment and these changes may reflect the characteristics of tumors that respond to treatment with CP-675,206.

Shipment of all specimens will be completed according to the information provided in a separate laboratory manual.

All non-anonymized blood and tumor samples will be disposed of after study analyses are completed.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for

classification as a serious adverse event (see Section 8.5) requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.2. Reporting Period

Serious adverse events require immediate notification to Pfizer or its designated representative beginning from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including the End of Treatment visit or 28 calendar days after the last administration of the investigational product, whichever is later. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of trial treatment through the End of Treatment Visit.

If a patient begins a new anticancer therapy, the adverse event reporting period for non-fatal adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;

- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation;
- Exposure *in utero*.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the malignancy under trial should not be reported as an adverse event. However, if the malignancy has a fatal outcome during the trial or within the safety reporting period, then disease progression must be recorded as an adverse event and as a serious adverse event with CTC Grade 5 (see Section 8.7, Severity Assessment).

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse[a].

8.6. Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

[a] 21CFR 312.32

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator’s assessment of causality must be provided for all adverse events (serious and non-serious). An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator’s final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records.

In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure In Utero

For investigational products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if:

1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);

2) a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial patient or trial patient's partner becomes or is found to be pregnant during the trial patient's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.

8.10. Withdrawal Due to Adverse Events (See also Patient Withdrawal, Section 6.5)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a patient withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent

determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Pfizer.

Any hypersensitivity reaction to CP-675,206 and any CP-675,206-related adverse events of Grade 3 or higher should be reported to the Pfizer Clinician before the patient receives another dose of study drug.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

It is assumed that the median survival for patients in the control arm treated with dacarbazine or temozolomide is approximately 7 months. It is assumed that the true hazard ratio is 1.33 (control arm over CP-675,206 arm). This represents a 33% improvement in true median overall survival from 7 months to 9.33 months. A total of 537 events (deaths) is required to enable an unstratified log-rank test with an overall 2-sided significance level of 0.045 and power 0.90. This number of events is based on two equally spaced interim analyses before the final analysis with group sequential design to reject either the null or the alternative hypothesis using the alpha and beta spending approach to an O'Brien-Fleming boundary.

Applying a 1:1 randomization and a planned accrual period of 21 months a total of 630 patients are to be enrolled in order to achieve the expected number of events by the end of the minimum follow-up period. It is expected that the maximum study duration will be 35 months.

9.2. Study Populations

Four populations will be assessed:

- As-Randomized population, defined as all randomized patients with study drug assignment designated according to initial randomization, regardless of whether patients receive any study drug or receive a different drug from that to which they were randomized. This will be the primary population for evaluating all efficacy endpoints as well as patient characteristics. The primary analysis of the primary endpoint (overall survival) will be performed in this population.
- An As-Treated population, defined as all patients randomized in the study who receive at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population will be the primary population for evaluating safety.

- An Evaluable-for-PK population: This group consists of all patients who have baseline and sufficient on-study blood samples to provide interpretable PK results.
- An Evaluable-for-Patient Reported Outcomes (PRO) population: Patients who received at least one dose of study drug and have a baseline assessment on the PRO and at least one post-treatment assessment on the PRO. Patients will be analyzed according to the treatment group to which they were randomized.

9.3. Efficacy Analysis

All primary efficacy analyses will be based on the As-Randomized population. .

9.3.1. Analysis of Primary Endpoint

The primary endpoint for the study is Overall Survival (OS). OS will be measured from date of randomization to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

9.3.2. Interim Analysis

Two interim analyses of overall survival will occur before the final analysis when approximately one third and two thirds of the events (deaths) have been observed with the objective of stopping early to reject the null hypothesis or to reject the alternative hypothesis. The boundaries will be computed using the Lan-DeMets alpha and beta spending function approach to an O'Brien-Fleming type boundary. Based on two equally spaced interim analyses, the stopping boundaries for efficacy, futility and the final analysis are provided in Table 15.

Table 15. Boundaries for the Interim and Final Analyses

Analysis	Number of Events (Deaths)	Efficacy Boundary Z -Scale	Futility Boundary Z-Scale
Interim #1	179	3.783	0.011
Interim # 2	358	2.564	0.864
Final	537	2.016	

9.3.3. Final Analysis

If the study continues to its end, then the final analysis will occur when 537 deaths are observed.

The primary comparison of the 2 arms of the trial will be by an unstratified log-rank test using Kaplan-Meier methods. A secondary comparison of the arms will be performed by a stratified log-rank test accounting for the specified stratification factors. A secondary analysis of overall survival will also be performed for the As Treated patient population.

A stratified Cox regression model will be used to assess the impact of prognostic factors on overall survival. The prognostic factors will include age, gender, geographical region, site of the disease, baseline LDH, and HLA class 1 type.

9.3.4. Analysis of Secondary Efficacy Endpoints

Tumor data will be reviewed by the Pfizer internal peer review committee. The review committee will assign responses, date of response based on the CRF tumor data and scans if and when necessary. These responses will be databased as Pfizer Response and will be used in the primary analysis of tumor response and response related endpoints such as Duration of Response and 6 month PFS rate.

The following secondary efficacy endpoints will be analyzed:

- Durable Response (DR), defined as a tumor response that is present at 6 or more months after randomization.
- Duration of Objective Response (CR or PR) for responding patients will be measured from the date of randomization to the date of progression or death due to progressive disease, whichever occurs first. In addition, the Duration of Complete Response will be measured from the date that a CR was first documented to date of progression or death due to progressive disease, whichever occurs first. Patients last known to be progression-free are censored at the date they were last known to be progression free, with the following exception: 1) Patients who go off treatment prior to progression will continue to be followed for progression until a new treatment is initiated. The date of new treatment will be used as the progression date unless the patient has clearly not progressed by the time of new treatment. If the patient has clearly not progressed, censorship will be at the date of new treatment. 2) Patients who die of causes clearly not related to disease before progression, will be censored at date last known to be progression free. Otherwise date of death will be used as the progression date.
- A 6-month progression free survivor will be defined as a patient who is alive and who has not progressed at 6 months or more post randomization.
- Objective Response (OR), defined as a confirmed complete response (CR) or partial response (PR)
- Time to ECOG PS worsening will be defined from the date of randomization to the first date of ECOG PS worsening by 1 point or death due to progressive disease, whichever occurs first. Patients last known to be without ECOG PS worsening are censored at the date they were last known to be without ECOG PS worsening.
- The proportion of patients who achieve an objective tumor response, complete response, durable response, and 6-month progression –free survival will be computed for each arm and compared by means of a Chi-square test.

Duration of Objective Response and duration of Complete Response, and time to worsening of ECOG PS will be explored using Kaplan-Meier methods and compared using a log-rank test. A logistic regression method will be used to assess the impact of prognostic factors on probability of response.

9.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, clinical benefit endpoints, and PK variables. Data will also be displayed graphically, where appropriate. CP-675,206 concentration-time data from this study will be analyzed with PK data from other clinical studies using a population PK approach.

9.5. Safety Analysis

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTC Version 3.0 whenever possible.

Adverse events will be summarized by treatment and by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Adverse events will be summarized by worst NCI CTC grade. Adverse events will be summarized by cycle and by relatedness to study treatment. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTC Grade 3 or higher, study drug related events, and serious adverse events will be considered with special attention.

Hematological and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTC severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. For parameters for which an NCI CTC scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

9.6. Patient Reported Outcomes

9.6.1. Health-Related Quality of Life

The instrument will be scored according to EORTC recommendations, as described in the EORTC QLQ-C30 scoring manual.[9] The main objective of the analysis will be to determine the proportions of patients in each treatment group who "improved," "deteriorated," and remain "stable" in 3 specific domains and symptoms, including physical functioning, role functioning, and fatigue as compared with the baseline (pretreatment) scores. Other domains and symptoms will be treated descriptively.

The analyses will involve, for each treatment group, the calculation of 1) completion rates on the EORTC QLQ-C30 at each designated time assessment, 2) descriptive statistics (median, mean, SD, SE, n) at baseline and at each designated follow-up time 3) mean changes (SE, SD, n) and median changes from baseline to each designated time and across designated times, and 4) proportions of patients who improve (at least a 10-point improvement), worsen (at least a 10-point deterioration), and remain stable based on a patient's average of mean changes over the time that he or she has available measurements. Ninety-five percent confidence interval of EORTC QLQ-C30 mean scores and mean change scores within treatment group will be used to gauge the range of a true effect and will be reported at each time and across times. The limited hypothesis tests on physical functioning, role functioning, and fatigue will be based on 1) each

patient's overall mean change from baseline, 2) each patient's mean change from baseline to Week 12 and 3) each patient's mean change from baseline to Week 24 using a paired t test for analyses within group and unpaired t test between groups. For each of these three times of change from baseline each patient's overall categorical response (improved, deteriorated, stable) will be cross-classified with treatment group and analyzed using a chi-square test. A prespecified alpha adjustment of 0.02 two-tailed test will be made for multiple testing of the three HQoL domains and symptoms between groups. Supplemental analyses involving more advanced methods such as mixed effect models for a continuous outcome will be considered and may be performed.

9.6.2. Healthcare Resource Utilization

The 3 endpoints on utilization (physician and other health professional visits, hospitalizations, and emergency room visits) from the Healthcare Resource Utilization Questionnaire and the two questions on productivity will each be summarized descriptively by the observed number of events and person-months for each treatment group at each visit. The estimated rate per person month, standard errors, and descriptive *P* values and 95% confidence intervals between treatment rates (risk ratio) will be reported. Supplemental analyses involving more advanced methods such as generalized linear models or generalized linear mixed models for counts using a Poisson model will be considered and may be performed.

9.7. Study therapy

Study therapy will be described in terms of cycles of treatment administered, duration of study treatment, dose intensity, relative dose intensity, and dose delays.

9.8. Data Monitoring Committees

9.8.1. Internal Monitoring of Safety

A Pfizer Risk Management Committee will review safety data consisting of reported serious and non-serious adverse events, discontinuations and mortality on an ongoing basis during the course of the trial.

9.8.2. External Data Safety Monitoring Board

An independent Data Safety Monitoring Board will meet periodically to review safety data and will review the interim analyses of survival. The independent DSMB will make recommendations based on risk benefit analysis about conduct of the trial and any modifications thereof.

The DSMB members are independent of the sponsor, have not had previous involvement in the design of the trial, are not involved in its conduct except through their role on the DSMB, and have no significant financial interest in the sponsor or in the outcome of the trial. To avoid any possible influence of knowledge of interim results on the conduct of the trial, DSMB members are not investigators in this trial.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During trial conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the physician's patient records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, Pfizer and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all

CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, Pfizer should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

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

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, eg, advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Pfizer in writing within 5 working days after the implementation.

12.2. Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

The informed consent form must be agreed to by Pfizer and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each trial patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and Pfizer before use. The investigator will retain the original of each patient's signed consent form.

13. DEFINITION OF END OF TRIAL

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the trial as stated in the

regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the trial in that Member State.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of CP-675,206 at any time.

If a trial is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients within one month. As directed by Pfizer, all trial materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Study Agreement.

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APPENDIX A. CP-675,206 TREATMENT-EMERGENT DIARRHEA MANAGEMENT GUIDELINES

Enrollment of Appropriate Patients:

During screening and enrollment, it is important to enroll patients who have access to appropriate medical care (eg access to telephone, transportation) in case of adverse reactions, in particular diarrhea, which could lead to dehydration or other serious consequences.

- Patient should be able to receive evaluation and care by a clinician familiar with CP-675,206-associated diarrhea, and should be able to access appropriate medical care if required during study participation.

Patient Instructions:

- **Patients should be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.**

- The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.
- Instruct patient to record the number/volume of stools and report associated symptoms that could reflect severe changes in vital signs or organ dysfunction, including those listed below.

Assessment of patient: History and Physical Exam

- Onset and duration of diarrhea; number of stools per day
- Stool consistency; liquid stool measured by (approximate) volume
- Accompanying symptoms: fever, dizziness, weakness, tenesmus or urgency, abdominal pain, abdominal bloating and cramping
- Blood and/or mucus in stool
- Weight loss, anorexia
- Incontinence
- Nocturnal diarrhea
- Vital signs, signs of dehydration
- Presence or absence of perianal or peristomal skin breakdown
- Medications and dietary profiles (ie to identify diarrhea-enhancing foods or medications)
- Need for hospitalization, parenteral support or intensive care

Diagnostic Tests:

- Fecal leucocytes (baseline, f/u, CTC level)
    - Calprotectin
    - lactoferrin
- *C. difficile* x 3 (repeat *C. difficile* stool titer at future time(s) may be indicated in patients with unexplained recurrent or prolonged diarrhea)
- Fecal Occult Blood (FOB)
- Sigmoidoscopy or Colonoscopy reaching the terminal ileum with biopsies, if indicated
- Upper endoscopy with duodenal biopsies, if indicated.
- Fasting stool volumes
- Stools cytokines

Management:

For mild diarrhea (Grade 1, ≤14 days):

- Consider use of probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements). Probiotics have been shown to be effective with other types of diarrhea, including ulcerative colitis.
- Drink 1.5-2 liters of water, electrolyte-containing liquid (eg Gatorade) or both a day.
- Eat potatoes, bananas, rice, applesauce, toast, jello, plain pasta. Avoid all lactose-containing products and supplements, fruits and vegetables.
- If *C. difficile* negative: Loperamide (Imodium) 4 mg initial dose, followed by 2 mg q2h until 12 hours without diarrhea (at night, take 4 mg q4h). Titrate up.
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day. Mesalamine is an anti-inflammatory drug, and it is not immediately effective.

If Grade 2 or if Grade 1 and persists > 14 days:

- Consider use of probiotics
- In addition to above measures, patient should be evaluated by clinician familiar with CP-675,206-related diarrhea
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day

If persistent despite loperamide and/or Grade 3 or 4 or severe per investigator's judgment:

- Consider use of probiotics
- Admit to hospital if required.
- Intravenous fluid, monitoring and replacement of electrolytes. (The required duration of intravenous fluids should be recorded on the Case Report Form to align with CTC severity grade)

- Evaluation of infection
- Consider octreotide (Sandostatin) 125 mcg subcutaneously, three times a day, only if secretory.
- Consider use of steroids, eg oral or intravenous dexamethasone up to 4 mg every 4 hours or budesonide (Entocort EC) 9mg once a day in the morning up to 8 weeks
- For patients for whom steroids do not control the diarrhea, consider use of infliximab (Remicade), a monoclonal antibody indicated for Crohn's disease. Infliximab has been reported to be effective in patients with steroid-resistant diarrhea due to another anti-CTLA4 monoclonal antibody.[b]
- Consider olsalazine (Dipentum): 500 mg oral twice a day
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day

Note: Any patient with Grade 3 diarrhea requiring systemic steroids for more than 10 days in any one cycle or with Grade 4 diarrhea must be withdrawn from treatment.

Drugs and probiotics used for treatment or prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

[b] Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner D, Quezado M, Lowy I, Yellin M, Rosenberg SA, Yang JC. Enterocolitis in Patients with Cancer After Antibody Blockade of Cytotoxic T-Lymphocyte- Associated Antigen 4. J Clin Oncol 24:2283-2289 2006.

GUIDANCE: Prevention of CP-675,206 Treatment-Emergent Diarrhea

There is no data/evidence indicating effectiveness of prophylactic therapy for prevention of treatment emergent diarrhea secondary to ticilimumab. However, prophylaxis may be considered. If prophylaxis is used, one of the following drugs would be recommended:

- Probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements) have been shown to be effective with other types of diarrhea, including ulcerative colitis, in clinical trials. Probiotics might prevent diarrhea by replacing gut bacteria with more benign strains, thereby decreasing the overactive T cell response to gut flora. This approach is not expected to present a risk to the patient.
- Mesalamine (Asacol) 1.6 g PO in divided doses. Mesalamine is an anti-inflammatory drug, and it is not immediately effective. It may be considered for prophylactic use, but to date there is no data to support its use.

Loperimide treats only the symptoms of diarrhea and not the underlying cause. It should not be used prophylactically.

Steroids can be used to treat severe or prolonged diarrhea due to CP-675,206, but should not be used prophylactically.

Drugs and probiotics used for prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

APPENDIX B. ECOG PERFORMANCE STATUS

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

*As published in Am J Clin Oncol 5:649-655, 1982

APPENDIX G. CLINICAL PROTOCOL AMENDMENT #1

Current Amendment:

Amendment No.	Date	Country (ies)	Site(s)
1	11 September 2006	All	All

SUMMARY

REASON(S) FOR AMENDMENT

- In the original protocol, the only prior adjuvant therapy that was allowed was interferon alpha. Discussions with investigators revealed that there are many patients seen in the clinical setting who have received cancer vaccines and/or GM-CSF as adjuvant therapy. Pfizer decided that there is no rationale to exclude patients who received vaccines or cytokines such as GM-CSF while including patients who received nonspecific immunotherapy with interferon. Patients who received vaccine in the adjuvant setting will be eligible for the A3671009 study if at least six months have passed since they received the last dose of vaccine, so that their immune systems will not be in the process of responding to the cancer vaccine at the time that CP-6759206 is administered. Patients who received adjuvant cytokine therapy must be at least 30 days from the last dose. In addition, it has been clarified that patients who were in the placebo arm of the Canvaxin trials, who received intradermal BCG with the first 2 doses of saline, would be eligible.
- The definition of a cancer vaccine and a listing of vaccine examples are included as an appendix. Cancer vaccines are defined as specific active immunotherapy intended to elicit an immune response to destroy tumor cells. A cancer vaccine either contains tumor antigens or consists of immune adjuvant injected into tumors to induce an immune response.
- The inclusion criterion for serum bilirubin has been changed from "≤1.5 × ULN" to "≤2 × ULN", in order to make it consistent with the redosing criterion and with the eligibility criterion for A3671008.
- Several other eligibility criteria have been reworded for clarity and to ensure consistent interpretation.
- The re-dosing criteria for amylase and lipase was changed from "≤ 1.5 x ULN" to "≤ 1.5 x ULN or baseline".
- The regimen of the comparator drug dacarbazine is 1000 mg/m^2 on Day 1 of each cycle. The original protocol stated that the dacarbazine was to be administered over 60 minutes. Some investigators prefer to give it over 3 hours or to slow the infusion in some circumstances. The phrase "over 60 minutes" has been deleted in the amendment.
- Because of the possibility that CP-675,206 may be detectable in some people beyond 6 months postdose, it is recommended that women who receive CP-675,206 practice contraception for up to 1 year after their final dose. (Men must still agree to practice contraception for 6 months because they may be randomized to receive chemotherapy.)
- It was intended that patients in the comparator arm would have a physical exam on Day 15 (dacarbazine) or Day 22 (temozolomide) of the first cycle. However, the Schedule of Events inadvertently included a physical exam on these days in every cycle. This was not consistent with the text of the protocol. This caused confusion, and some investigators commented that it would be unnecessary and inconvenient for patients to have 2 physical exams in every cycle. In the amendment, this extra physical exam has been made optional.

- A rationale for the comparator drugs has been added, in response to requests from investigators and IRBs/IECs.
- It has been clarified that it is permissible for a weight taken up to 10 days before the beginning of a cycle to be used to calculate the dose of study drug.
- The A3671009 protocol states, "All patients with objective tumor response should have additional scans scheduled four to 6 weeks after the criteria for response are first met in order to confirm the response". The amendment clarifies that this statement refers to patients in Arm A, for whom scans are scheduled every 12 weeks. The scans already scheduled for patients in the comparator arm will be adequate to confirm responses.
- It has been clarified that all serious adverse events are to be collected through the End of Treatment Visit or 28 days after the last dose of drug, whichever is longer.
- The generic name, ticilimumab, was challenged internationally, and Pfizer is in the process of obtaining a new generic name for the compound. In the meantime, all references to ticilimumab were changed to the compound number, CP-675,206.
- The term “Preparation and Administration Protocol” has been replaced with the term “Dosage and Administration Instructions”.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

PROTOCOL SECTION(S) AMENDED

The protocol sections that were amended are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.
- The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Entire Protocol and Appendices

Change From

The name of the drug changed from "ticilimumab" to "CP-675,206" in entire protocol and appendices

~~Ticilimumab~~ **CP-675.206**

Change To

CP-675,206

Cover Page

Change From

Compound Name (if applicable): ~~ticilimumab~~

Change To

Compound Name (if applicable):

Summary; Trial Design

Change From

1st paragraph, 1st sentence

This is a Phase 3, multi-national, open-label, 2-arm randomized study in patients with surgically incurable metastatic melanoma who have received no prior chemotherapy, immunotherapy or biological therapy for the treatment of **unresectable** metastatic disease. . .

2nd paragraph, 2nd sentence

. . . Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously ~~over 60 minutes~~ on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. . .

Change To

1st paragraph, 1st sentence

This is a Phase 3, multi-national, open-label, 2-arm randomized study in patients with surgically incurable metastatic melanoma who have received no prior chemotherapy, immunotherapy or biological therapy for the treatment of unresectable metastatic disease. . .

2nd paragraph, 2nd sentence

. . . Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. . .

Summary; Trial Treatments; Arm B: Dacarbazine or Temozolomide

Change From

2nd sentence

. . . Dacarbazine will be administered intravenously at a dose of 1000 mg/m^2 ~~over 60 minutes~~ on Day 1 of each 21-day cycle until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent. . .

Change To

. . . Dacarbazine will be administered intravenously at a dose of 1000 mg/m^2 on Day 1 of each 21-day cycle until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent. . .

Summary; Schedule of Activities; Screening Period; Footnotes

Change From

2. Contraceptive Counseling: All patients ~~(male and female)~~ must agree to practice a form of effective contraception prior to entry into the study and for 6 months **(males) or 12 months (females)** following the last dose of study drug.

Change To

2. Contraceptive Counseling: All patients must agree to practice a form of effective contraception prior to entry into the study and for 6 months (males) or 12 months (females) following the last dose of study drug.

Summary; Schedule of Activities: Arm A (CP-675,206); Randomization through Cycle 2; Table 2

Change From

ARM A: CP-675,206 A3671009	CYCLE[1] 1						CYCLE 2				
Protocol Activities	Day 1 or up to ~~48~~ **72** hours before dose	Day 1	Day 15	Day 30	Day 60	Within 10 days prior to C2D1	Day 1[17]	Day 15	Day 30	Day 60	Within 10 days prior to C3D1
HCRUQ [3]				X	X		**Pre-dose** ~~X~~				
Physical Exam/Vital Signs [7]	**X**	~~Pre-dose~~	X	X	X		Pre-dose	X	X	X	
Pregnancy Test [9]	X						**Pre-dose** ~~X~~				
Safety Labs/**Thyroid Function** [10]	X		X	X	X	X		X	X	X	X
Biopsy of Skin In-Transit Target Lesions **(if indicated)** [15]						X					X

Change To

ARM A: CP-675,206 A3671009	**CYCLE[1] 1**						**CYCLE 2**				
Protocol Activities	**Day 1 or up to 72 hours before dose**	**Day 1**	**Day 15**	**Day 30**	**Day 60**	**Within 10 days prior to C2D1**	**Day 1[17]**	**Day 15**	**Day 30**	**Day 60**	**Within 10 days prior to C3D1**
HCRUQ [3]				X	X		Pre-dose				
Physical Exam/Vital Signs [7]	X		X	X	X		Pre-dose	X	X	X	

Pregnancy Test [9]	X						Pre-dose				
Safety Labs/Thyroid Function [10]	X		X	X	X	X		X	X	X	X

Biopsy of Skin In-Transit Target Lesions (if indicated) [15]						X					X

Summary; Schedule of Events Arm A (CP-675,206); Cycle 3 through Follow-Up; Table 2 (continued)

Change From

CP-675,206: Arm A A3671009		[1]CYCLE 3 and CYCLE 4[19]				EOT [18]	Follow-Up [16]
Protocol Activities [1]	**(**Within 10 days prior to C3D1**)**	Day 1[17]	Day 30	Day 60	Within 10 days prior to ~~next dose~~ **C4D1**	90 Days post-dose 4 or 30 days post final dose if <4 doses	Every 3 Months
HCRUQ[3]		**Pre-dose** ~~X~~				X	
~~Ticilimumab IV~~ **CP-675,206 Administration**		X					
Tumor Assessment (Imaging/Clinical) [14]	X				**X**~~Cycle 3 Only~~	X	
Biopsy of Skin In-Transit Target Lesions **(if indicated)**[15]	X				**X**~~Cycle 3 Only~~	X	

Footnotes to Schedule of Activities: (Arm A: CP-675,206)

15. Biopsy of Skin In-Transit Target Lesions **(if indicated):** If the appearance of in-transit skin lesions has changed substantially, a biopsy should be performed in order to confirm a suspected tumor response. To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for **1 or more representative** ~~the majority of~~ target skin lesions.

17. Day 1: "Pre-dose" activities may be performed up to ~~48~~ **72** hours prior to administration of the dose. Results of safety labs ~~(~~must be available before the patient receives the dose.

18. End of Treatment (EOT) Assessment: For patients who complete a total of 4 doses, the EOT visit should be 90 days (84-96 days) after dose 4. For others, it should be scheduled approximately 30 days after the last dose of study drug, or before the patient begins new

systemic therapy for melanoma. **If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.2.3.**

19. Note that additional cycles may be administered under certain circumstances; see Section 6.2.5.

Change To

CP-675,206: Arm A A3671009		[1]CYCLE 3 and CYCLE 4[19]				EOT [18]	Follow-Up [16]
Protocol Activities [1]	(Within 10 days prior to C3D1)	Day 1[17]	Day 30	Day 60	Within 10 days prior to C4D1	90 Days post-dose 4 or 30 days post final dose if <4 doses	Every 3 Months
HCRUQ[3]		Pre-dose				X	
CP-675,206 Administration		X					
Tumor Assessment (Imaging/Clinical) [14]	X				X	X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[15]	X				X	X	

Footnotes to Schedule of Activities: (Arm A: CP-675,206)

15. **Biopsy of Skin In-Transit Target Lesions** (if indicated)**:** If the appearance of in-transit skin lesions has changed substantially, a biopsy should be performed in order to confirm a suspected tumor response. To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.

17. **Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of safety labs must be available before the patient receives the dose.

18. **End of Treatment (EOT) Assessment:** For patients who complete a total of 4 doses, the EOT visit should be 90 days (84-96 days) after dose 4. For others, it should be scheduled approximately 30 days after the last dose of study drug, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.2.3.

19. Note that additional cycles may be administered under certain circumstances; see Section 6.2.5.

Summary; Schedule of Activities: Arm B (Dacarbazine); Table 3

Change From

Protocol Activities	Post Randomization	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [17]	Follow-Up [15]
	Day 1 or within ~~48~~ **72** hrs before	Day 1	Day 8	Day 15	Day 1[16]	Day 15	≤7 Days before next dose	Day 1[16]	Day 15	30 days post final dose	Every 3 Months
EORTC QLQ-C30 [2]			X	X	Pre-dose			**Pre-dose**~~X~~		X	
HCRUQ[3]					**Pre-dose**~~X~~			**Pre-dose**~~X~~		X	
Physical Exam / Vital Signs [7]	**X**	~~Pre-dose~~		X	Pre-dose	~~X~~**Opt**[7]		Pre-dose	~~X~~ **Opt**[7]	X	
Biopsy of Skin In-Transit Target Lesions **(if indicated)**[14]							X			X	

Footnotes to Schedule of Activities: (Arm B: Dacarbazine)

7. Physical Exam/Vital Signs: Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. **After the first cycle, physical exams on Day 15 are optional.**

12. Dacarbazine Administration: Patients receive intravenous administration of dacarbazine 1000 mg/m^2 ~~over 60 minutes~~ to be repeated every 21 days. The initiation of subsequent cycles may be delayed to allow recovery from treatment-related toxicities.

13. Tumor Assessments (Imaging/Clinical): Scans should include CT with contrast of chest, abdomen and pelvis. ~~All patients with objective tumor response should have additional scans scheduled 4-6 weeks after the criteria for response are first met in order to confirm the response.~~ EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.

14. Biopsy of Skin In-Transit Target Lesions **(if indicated):** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for **1 or more representative** ~~the majority of~~ target skin lesions.

16. Day 1: "Pre-dose" activities may be performed up to ~~48~~ **72** hours prior to administration of the dose. Results of hematology laboratories must be available before the patient receives the dose.

17. End of Treatment (EOT) Assessment: The EOT visit should be scheduled approximately 30 days after the last dose of dacarbazine, or before the patient begins new systemic therapy for melanoma. **If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.3.3.**

Change To

Protocol Activities	Post Randomiza-tion	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [17]	Follow-Up [15]
	Day 1 or within 72 hrs before	Day 1	Day 8	Day 15	Day 1[16]	Day 15	≤7 Days before next dose	Day 1[16]	Day 15	30 days post final dose	Every 3 Months
EORTC QLQ-C30 [2]			X	X	Pre-dose			Pre-dose		X	
HCRUQ[3]					Pre-dose			Pre-dose		X	
Physical Exam/Vital Signs [7]	X			X	Pre-dose	X		Pre-dose	X	X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[14]							X			X	

Footnotes to Schedule of Activities: (Arm B: Dacarbazine)

7. **Physical Exam/Vital Signs:** Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. After the first cycle, physical exams on Day 15 are optional.

12. **Dacarbazine Administration:** Patients receive intravenous administration of dacarbazine 1000 mg/m^2 to be repeated every 21 days. The initiation of subsequent cycles may be delayed to allow recovery from treatment-related toxicities.

13. **Tumor Assessments (Imaging/Clinical):** Scans should include CT with contrast of chest, abdomen and pelvis. EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.

14. **Biopsy of Skin In-Transit Target Lesions** (if indicated)**:** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.

16. **Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of hematology laboratories must be available before the patient receives the dose.

17. **End of Treatment (EOT) Assessment:** The EOT visit should be scheduled approximately 30 days after the last dose of dacarbazine, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.3.3.

Summary; Schedule of Activities: Arm B (Temozolomide); Table 4

Change From

Protocol Activities	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [18]	Follow-Up [16]
	Day 1 **or up to 72 hours before**	Day 15	Day 22	Day 1[17]	Day 22	≤7 Days before next dose	Day 1[17]	Day 22	Day 30	Every 3 Months
Weight	X		~~X~~	X			X		X	
Physical Exam/Vital Signs [7]	X		X	X	~~X~~**opt**[7]		X	~~X~~**opt**[7]	X	
Biopsy of Skin In-Transit Target Lesions **(if indicated)**[15]						X			X	

Footnotes to Schedule of Activities: (Arm B: Temozolomide)

7. Physical Exam/Vital Signs: Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. **After the first cycle, physical exams on Day 22 are optional.**

14. Tumor Assessments (Imaging/Clinical): Scans should include CT with contrast of chest, abdomen and pelvis. ~~All patients with objective tumor response should have additional~~

~~scans scheduled 4-6 weeks after the criteria for response are first met in order to confirm the response.~~ EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.

15. Biopsy of Skin In-Transit Target Lesions **(if indicated):** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for **1 or more representative** ~~the majority of~~ target skin lesions.

17. Day 1: **"Pre-dose" activities may be performed up to 72 hours prior to administration of the dose.** Results of hematology laboratories must be available before the patient receives the next dose.

18. End of Treatment (EOT) Assessment: The EOT visit should be scheduled approximately 30 days after the start of the last cycle of temozolomide, or before the patient begins new systemic therapy for melanoma. **If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.4.3**.

Change To

Protocol Activities	[1]CYCLE 1			CYCLE 2 & EVEN CYCLES			CYCLE 3 & ODD CYCLES		EOT [18]	Follow-Up [16]
	Day 1 or up to 72 hours before	Day 15	Day 22	Day 1[17]	Day 22	≤7 Days before next dose	Day 1[17]	Day 22	Day 30	Every 3 Months
Weight	X			X			X		X	
Physical Exam/Vital Signs [7]	X		X	X	opt[7]		X	opt[7]	X	
Biopsy of Skin In-Transit Target Lesions (if indicated)[15]						X			X	

Footnotes to Schedule of Activities: (Arm B: Temozolomide)

7. **Physical Exam/Vital Signs:** Clinical assessments include physical exam and vital signs, including temperature, blood pressure (sitting), and heart rate. All assessments should be recorded in the patient's source documentation; only clinically significant abnormalities should be reported as adverse events in the CRF. After the first cycle, physical exams on Day 22 are optional.

14. **Tumor Assessments (Imaging/Clinical):** Scans should include CT with contrast of chest, abdomen and pelvis. EOT tumor measurements are required only if the last evaluation was performed more than 28 days prior to this visit.

15. **Biopsy of Skin In-Transit Target Lesions** (if indicated)**:** To be assigned a status of complete response, confirmatory biopsies (negative for melanoma) must be performed for 1 or more representative **target** skin lesions.

17. **Day 1:** "Pre-dose" activities may be performed up to 72 hours prior to administration of the dose. Results of hematology laboratories must be available before the patient receives the next dose.

18. **End of Treatment (EOT) Assessment:** The EOT visit should be scheduled approximately 30 days after the start of the last cycle of temozolomide, or before the patient begins new systemic therapy for melanoma. If the patient has begun new therapy for melanoma before the EOT visit, only a subset of the activities should be done. See Section 6.4.3.

Section 1.3; CP-675,206 Risks and Precautions

Change From

3rd paragraph

CP-675,206 is an immune modulator, so investigators should be alert for the development of immune mediated side effects. Possible immune-mediated disorders observed have involved the skin (vitiligo and cutaneous leukocytoclastic vasculitis), the thyroid gland (autoimmune thyroiditis), the liver (autoimmune hepatitis), **the pancreas (pancreatitis),** and the pituitary (hypophysitis). Abnormal lab results which may be immune-mediated include elevations of serum lipase and amylase and liver function tests. No deaths related to CP-675,206 have been reported. ~~Furthermore, investigators have not reported infusion-related toxicities (including hypersensitivity reaction, anaphylaxis, anaphylactoid reaction) or retinal or uveal abnormalities.~~

Last 2 paragraphs

Although CP-675,206 is a fully human monoclonal antibody, immunogenicity ~~remains a possibility~~ **may occur**, and thus acute hypersensitivity reactions such as urticaria, pruritus, laryngeal edema, angioedema, bronchospasm, respiratory distress, nausea, vomiting, crampy abdominal pain, acute back pain, fever, diarrhea, hypotension and fatal anaphylactic shock, as well as subacute reactions, are also possible.

CP-675,206 is a monoclonal antibody of the IgG2a type, and it is expected that it would cross the placenta if administered to a pregnant woman and could be secreted in breast milk of a lactating woman. The effect of exposure of a fetus or newborn to CP-675,206 is unknown. ~~Patients~~ **Women of childbearing potential** must agree to use contraception during this trial and for ~~6~~ **12** months after the last dose of study drug. Patients who become pregnant must not receive further treatment in this study.

Change To

3rd paragraph

CP-675,206 is an immune modulator, so investigators should be alert for the development of immune mediated side effects. Possible immune-mediated disorders observed have involved the skin (vitiligo and cutaneous leukocytoclastic vasculitis), the thyroid gland (autoimmune thyroiditis), the liver (autoimmune hepatitis), the pancreas (pancreatitis), and the pituitary (hypophysitis). Abnormal lab results which may be immune-mediated include elevations of serum lipase and amylase and liver function tests. No deaths related to CP-675,206 have been reported.

Last 2 paragraphs

Although CP-675,206 is a fully human monoclonal antibody, immunogenicity may occur, and thus acute hypersensitivity reactions such as urticaria, pruritus, laryngeal edema, angioedema, bronchospasm, respiratory distress, nausea, vomiting, crampy abdominal pain, acute back pain, fever, diarrhea, hypotension and fatal anaphylactic shock, as well as subacute reactions, are also possible.

CP-675,206 is a monoclonal antibody of the IgG2a type, and it is expected that it would cross the placenta if administered to a pregnant woman and could be secreted in breast milk of a lactating woman. The effect of exposure of a fetus or newborn to CP-675,206 is unknown. Women of childbearing potential must agree to use contraception during this trial and for 12 months after the last dose of study drug. Patients who become pregnant must not receive further treatment in this study.

Section 1.8; Rationale for Comparator Drugs

Change From

Entire section added; following section renumbered accordingly

Change To

Dacarbazine is the only chemotherapeutic agent approved for metastatic melanoma. Its approval was based on tumor responses. No randomized trial has been conducted comparing dacarbazine to observation, so it is not known how big an effect, if any, dacarbazine has on survival. When dacarbazine was approved in the 1970s, it was given at a lower dose spread out over 5 days. However, the use of newer anti-emetic drugs has allowed for the administration of a higher dose on Day 1 of each cycle. Dacarbazine, at a dose of 850 to 1000 mg/m^2 once every 3 weeks, is the current standard reference therapy for patients with metastatic melanoma.[2]

Temozolomide is an orally administered drug with the same active moiety as dacarbazine, monomethyl triazenoimidazole carboxamide (MTIC). It is not approved for treatment of metastatic melanoma but is commonly used for this indication in some countries, including the

United States of America. Temozolomide was compared to dacarbazine, in terms of overall survival, progression-free survival, objective response and safety, in a randomized Phase 3 trial of 305 patients with advanced melanoma.[3] Patients received temozolomide 200 mg/m^2/day orally for 5 consecutive days every 4 weeks, or dacarbazine 250 mg/m^2/day intravenously for 5 consecutive days every 3 weeks. There were no statistically significant differences in overall survival or response rate. There was a significant difference in PFS (1.9 months vs 1.5 months) in favor of temozolomide, but this could be attributed at least in part to the difference in assessment schedule between the 2 arms.

In this trial, temozolomide is included as an option for investigators who are experienced with this drug in their standard practice for melanoma. In the analysis of this trial, the CP-675,206 arm will be compared to the comparator arm as a whole, because the 2 comparator drugs are assumed to be not significantly different in terms of the primary endpoint of this study.

Section 3; Trial Design

Change From

1st paragraph, 5th sentence

. . . Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously ~~over 60 minutes~~ on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. . .

Change To

. . . Patients randomized to Arm B will receive either dacarbazine 1000 mg/m^2 administered intravenously on Day 1 of every 21-day cycle for up to 12 cycles, or temozolomide 200 mg/m^2 administered orally on Days 1-5 of every 28-day cycle for up to 12 cycles. . .

Section 4.1; Inclusion Criteria

Change From

#2; 1st sub-bullet

- Measurable Disease. Patient has at least one lesion that meets the following criteria: Measurable lesions can be accurately measured in at least one dimension. Lesions on CT scan must have longest diameter ≥2.0 cm using conventional techniques or ≥1.0 cm with spiral CT scan. Skin lesions **documented by photography** must have longest diameter at least 1.0 cm. Clinically detected lesions must be superficial (eg, skin nodules), and the longest diameter must be ≥2.0 cm. Palpable lymph nodes >2.0 cm should be demonstrable by CT scan. If the measurable disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology or histology. Tumor lesions that are situated in a previously irradiated area will be considered

measurable only if progression is documented following completion of radiation therapy.

#5; 5th sub-bullet

- Total serum bilirubin ≤~~1.5~~**2** x ULN (except patients with documented Gilbert's syndrome)

. . .

8. Patients must have recovered from all prior surgical or adjuvant ~~(alpha-interferon)~~ treatment-related toxicities, to baseline status, or a CTC Grade of 0 or 1, except for toxicities not considered a safety risk, such as alopecia. Post-surgical pain will not be considered a basis for exclusion.

10. Females of childbearing potential and males who have not undergone surgical sterilization must agree to practice a form of effective contraception prior to entry into the study and for **12 months (females) or** 6 months **(males)** following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.

Change To

#2; 1st sub-bullet

- Measurable Disease. Patient has at least one lesion that meets the following criteria: Measurable lesions can be accurately measured in at least one dimension. Lesions on CT scan must have longest diameter ≥2.0 cm using conventional techniques or ≥1.0 cm with spiral CT scan. Skin lesions documented by photography must have longest diameter at least 1.0 cm. Clinically detected lesions must be superficial (eg, skin nodules), and the longest diameter must be ≥2.0 cm. Palpable lymph nodes >2.0 cm should be demonstrable by CT scan. If the measurable disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology or histology. Tumor lesions that are situated in a previously irradiated area will be considered measurable only if progression is documented following completion of radiation therapy.

#5; 5th sub-bullet

- Total serum bilirubin ≤2 x ULN (except patients with documented Gilbert's syndrome)

. . .

8. Patients must have recovered from all prior surgical or adjuvant treatment-related toxicities, to baseline status, or a CTC Grade of 0 or 1, except for toxicities not

considered a safety risk, such as alopecia. Post-surgical pain will not be considered a basis for exclusion.

10. Females of childbearing potential and males who have not undergone surgical sterilization must agree to practice a form of effective contraception prior to entry into the study and for 12 months (females) or 6 months (males) following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.

Section 4.2; Exclusion Criteria

Change From

1. Melanoma of ocular origin **(uveal melanoma)**

2. **Received any systemic therapy for metastatic melanoma except post-surgical adjuvant treatment with cytokines (eg, alfa-interferon or GM-CSF) or with vaccines after complete resection of melanoma. Patients who received adjuvant cytokine therapy must be at least 30 days from the last dose. Patients who received adjuvant vaccine therapy must be at least 6 months from the last dose. (See Appendix F for a list of cancer vaccines). All patients who received adjuvant therapy must have documented tumor progression since the last dose. Note: Prior chemotherapy or biochemotherapy, including isolated limb perfusion therapy is not allowed. Prior resection for Stage III or Stage IV disease is allowed as long as the patient has unresectable lesions at the time of randomization. Patients who received intradermal BCG for adjuvant therapy for Stage III or IV melanoma are not excluded.** ~~Received any systemic therapy for metastatic melanoma except post-surgical adjuvant treatment with alpha-interferon for resected Stage II or Stage III disease. Patients who received alpha-interferon must be at least 30 days from the last dose, and must have documented tumor progression since the last dose.~~ **Note:** ~~Prior chemotherapy, biochemotherapy, cytokine therapy (other than alpha-interferon), or vaccine therapy are not allowed. Prior intralesional injections and prior isolated limb perfusion therapy are not allowed. Prior resection for Stage III or Stage IV disease is allowed as long as the patient has unresectable lesions at the time of randomization.~~

6. History of chronic ~~inflammatory or~~ autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, hypophysitis, ~~pituitary disorders,~~ etc.). **Note:** Active vitiligo or a history of vitiligo will not be a basis for exclusion.

8. History of inflammatory bowel disease **(eg, Crohn's disease or ulcerative colitis)**, celiac disease, or other chronic gastrointestinal conditions associated with diarrhea ~~or bleeding~~, or current acute colitis of any origin

9. ~~History of hepatitis due to Hepatitis B virus~~ **Known active** or ~~Hepatitis C virus~~ **chronic viral hepatitis**

10. Any serious uncontrolled medical disorder or active infection that would impair the patient's ability to receive study treatment**. Note: Patients with Acquired Immunodeficiency Syndrome (AIDS) are excluded.**

Change To

1. Melanoma of ocular origin (uveal melanoma)

2. Received any systemic therapy for metastatic melanoma except post-surgical adjuvant treatment with cytokines (eg, alfa-interferon or GM-CSF) or with vaccines after complete resection of melanoma. Patients who received adjuvant cytokine therapy must be at least 30 days from the last dose. Patients who received adjuvant vaccine therapy must be at least 6 months from the last dose. (See Appendix F for a list of cancer vaccines). All patients who received adjuvant therapy must have documented tumor progression since the last dose. **Note:** Prior chemotherapy or biochemotherapy, including isolated limb perfusion therapy is not allowed. Prior resection for Stage III or Stage IV disease is allowed as long as the patient has unresectable lesions at the time of randomization. Patients who received intradermal BCG for adjuvant therapy for Stage III or IV melanoma are not excluded.

6. History of chronic autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, hypophysitis, etc.). **Note:** Active vitiligo or a history of vitiligo will not be a basis for exclusion.

8. History of inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis), celiac disease, or other chronic gastrointestinal conditions associated with diarrhea, or current acute colitis of any origin

9. Known active or chronic viral hepatitis

10. Any serious uncontrolled medical disorder or active infection that would impair the patient's ability to receive study treatment. **Note**: Patients with Acquired Immunodeficiency Syndrome (AIDS) are excluded.

Section 5.1; Arm A: CP-675,206

Change From

1st paragraph; last sentence

. . . To allow for possible change in body weight over time, patients should be weighed **within 10 days** prior to each cycle and the administered dose of CP-675,206 should be recalculated.

Change To

. . . To allow for possible change in body weight over time, patients should be weighed within 10 days prior to each cycle and the administered dose of CP-675,206 should be recalculated.

Section 5.1.2; Dose Delays and Re-Dosing Criteria for CP-675,206; Table 6

Change From

Table 6. Re-Dosing Criteria for CP-675,206: Laboratory Parameters

Laboratory Parameter	Re-Dosing Criteria
Amylase and Lipase (within 10 days)	≤1.5 x ULN **or baseline**

Change To

Table 6. Re-Dosing Criteria for CP-675,206: Laboratory Parameters

Laboratory Parameter	Re-Dosing Criteria
Amylase and Lipase (within 10 days)	≤1.5 x ULN or baseline

Section 5.1.2; Dose Delays and Re-Dosing Criteria for CP-675,206; Table 7

Change From

Table 7. Re-Dosing Criteria for CP-675,206: Treatment-Related Adverse Events.

~~Laboratory Parameter~~Adverse Event	Re-Dosing Criteria
~~Hyperthyroid~~**Thyroiditis**	Asymptomatic or stable on thyroid replacement therapy
Rash	Tolerable and ≤ Grade 2
Vitiligo	May be re-dosed regardless of severity
All other treatment-related adverse events	**Tolerable and ≤ Grade 1 or baseline**

Last paragraph

After 2 doses of CP-675,206, if there is no evidence that the patient is deriving any benefit from treatment~~- including objective response, mixed response or stable disease~~**,** the patient must discontinue treatment. **Evidence of benefit includes objective responses, mixed responses, or stable disease.**

Change To

Table 7. Re-Dosing Criteria for CP-675,206: Treatment-Related Adverse Events.

Adverse Event	Re-Dosing Criteria
Thyroiditis	Asymptomatic or stable on thyroid replacement therapy
Rash	Tolerable and ≤ Grade 2
Vitiligo	May be re-dosed regardless of severity
All other treatment-related adverse events	Tolerable and ≤ Grade 1 or baseline

Last paragraph

After 2 doses of CP-675,206, if there is no evidence that the patient is deriving any benefit from treatment, the patient must discontinue treatment. Evidence of benefit includes objective responses, mixed responses, or stable disease.

Section 5.1.4; Management of Toxicity of CP-675,206

Change From

3rd paragraph

~~If a patient has an adverse event that is thought to be potentially immune-mediated (other than vitiligo), the investigator should send a blood sample to the central lab for autoimmune antibody testing.~~ **If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for appropriate autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of those autoantibodies.** Doses of CP-675,206 should be held until the etiology of the event is established. Continuation of CP-675,206 in the presence of immune-mediated events should be done by the investigator only after discussion with the patient on a case-by-case basis with consideration to risk-benefit analysis.

Change To

If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for appropriate autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of those autoantibodies. Doses of CP-675,206 should be held until the etiology of the event is established. Continuation of CP-675,206 in the presence of immune-mediated events should be done by the investigator only after discussion with the patient on a case-by-case basis with consideration to risk-benefit analysis.

Section 5.1.4.1; Management of Diarrhea

Change From

1st paragraph; 2nd sentence

. . . Intestinal perforation has ~~not~~ been reported with CP-675,206, ~~but has been reported~~ **as well as** for another investigational agent that targets CTLA4 ~~(in combination with peptide vaccine)~~. . .

Table 8, Diarrhea Algorithm

Table 8. Diarrhea Algorithm

Diarrhea Severity and Duration	Recommendation
Grade 1 less than or equal to 14 days	• **Consider use of probiotics** • Follow Diarrhea Management Guidelines including *C. difficile* titer, ~~stool tests,~~ empiric loperamide, oral fluid replacement • **Consider mesalamine**
Grade 1 more than 14 days or Grade 2 of any duration not responsive to loperamide	• **Consider use of probiotics** • Evaluation of severity by clinician familiar with CP-675,206-related diarrhea • Follow Diarrhea Management Guidelines • Consider IV fluids if indicated • Consider use of **mesalamine or** steroids*
Grade 3 or Grade 4 for any duration Or Any grade & duration associated with evidence of severe enterocolitis including bleeding, fever, pain or other signs/symptoms	• **Consider use of probiotics** • Evaluation by clinician familiar with CP-675,206-related diarrhea • Consider inpatient hospitalization for IV fluids, monitoring • Consider use of steroids* • Consider use of octreotide, budesonide, olsalazine, or mesalamine (See Appendix A.) • **Consider infliximab if not responsive to steroids** • Notify the Pfizer Clinician
* Response of diarrhea to steroids has been reported for a similar experimental drug that targets CTLA4. Example: oral or intravenous dexamethasone up to 4 mg every 4 hours	

Change To

1st paragraph; 2nd sentence

. . . Intestinal perforation has been reported with CP-675,206, as well as for another investigational agent that targets CTLA4. . .

Table 8, Diarrhea Algorithm

Table 8. Diarrhea Algorithm

Diarrhea Severity and Duration	Recommendation
Grade 1 less than or equal to 14 days	• Consider use of probiotics • Follow Diarrhea Management Guidelines including *C. difficile* titer, empiric loperamide, oral fluid replacement • Consider mesalamine
Grade 1 more than 14 days or Grade 2 of any duration not responsive to loperamide	• Consider use of probiotics • Evaluation of severity by clinician familiar with CP-675,206-related diarrhea • Follow Diarrhea Management Guidelines • Consider IV fluids if indicated • Consider use of mesalamine or steroids*
Grade 3 or Grade 4 for any duration Or Any grade & duration associated with evidence of severe enterocolitis including bleeding, fever, pain or other signs/symptoms	• Consider use of probiotics • Evaluation by clinician familiar with CP-675,206-related diarrhea • Consider inpatient hospitalization for IV fluids, monitoring • Consider use of steroids* • Consider use of octreotide, budesonide, olsalazine, or mesalamine (See Appendix A.) • Consider infliximab if not responsive to steroids • Notify the Pfizer Clinician
* Response of diarrhea to steroids has been reported for a similar experimental drug that targets CTLA4. Example: oral or intravenous dexamethasone up to 4 mg every 4 hours	

Section 5.1.4.2; Management of Hypersensitivity Reactions to CP-675,206

Change From

2nd bullet, 2nd sub-bullet

- Administer IV antihistamines (diphenhydramine 25-50 mg and ranitidine **50 mg** or cimetidine **300 mg**).

3rd bullet, 4th sub-bullet

- If wheezing persists: 0.35 mL of ~~nebulized~~ **inhaled** albuterol or other bronchodilators.

Change To

2nd bullet, 2nd sub-bullet

- Administer IV antihistamines (diphenhydramine 25-50 mg and ranitidine 50 mg or cimetidine [300 mg]).

3rd bullet, 4th sub-bullet

- If wheezing persists: 0.35 mL of inhaled albuterol or other bronchodilators.

Section 5.1.7; Preparation and Dispensing of CP-675,206

Change From

Specific preparation instructions are provided in the most current version of the **Dosage and Administration Instructions** ~~Preparation and Administration Protocol~~. A member of the Pharmacy or Clinical Research Unit staff with appropriate training and experience must prepare all supplies.

Change To

Specific preparation instructions are provided in the most current version of the Dosage and Administration Instructions. A member of the Pharmacy or Clinical Research Unit staff with appropriate training and experience must prepare all supplies.

Section 5.1.8; Administration of CP-675,206

Change From

1st paragraph

CP-675,206 is diluted with sterile normal saline (supplied by the investigator) prior to administration according to specific instructions in the **Dosage and Administration Instructions** ~~Preparation and Administration Protocol~~. CP-675,206 should be administered open-label as an intravenous solution at a rate of 100 mL/hr, followed by observation. Specific dosing and administration instructions are provided in the most current version of the **Dosage and Administration Instructions** ~~Preparation and Administration Protocol~~.

Last paragraph, 1st sentence

Medications to treat hypersensitivity reactions should be available, such as IV saline, acetaminophen, and emergency drugs, including subcutaneous epinephrine, diphenhydramine, methylprednisolone, and ~~nebulized~~ **inhaled** albuterol. . .

Change To

1st paragraph

CP-675,206 is diluted with sterile normal saline (supplied by the investigator) prior to administration according to specific instructions in the Dosage and Administration Instructions. CP-675,206 should be administered open-label as an intravenous solution at a rate of 100 mL/hr,

followed by observation. Specific dosing and administration instructions are provided in the most current version of the Dosage and Administration Instructions.

Last paragraph, 1st sentence

Medications to treat hypersensitivity reactions should be available, such as IV saline, acetaminophen, and emergency drugs, including subcutaneous epinephrine, diphenhydramine, methylprednisolone, and inhaled albuterol. . .

Section 5.1.9; Premedication

Change From

1st sentence

~~No hypersensitivity reactions have been reported to date with ticilimumab.~~ **To date, one patient has had a reported hypersensitivity reaction to CP-675,206**. . .

Change To

To date, one patient has had a reported hypersensitivity reaction to CP-675,206. . .

Section 5.2; Arm B: Dacarbazine

Change From

Patients randomized to Arm B will receive either dacarbazine ~~ot~~ **or** temozolomide at the discretion of the investigator. Dacarbazine will be administered at a dose of 1000 mg/m^2 administered intravenously ~~over 60 minutes~~ on Day 1 of each 21-day cycle. Patients in Arm B who are treated with dacarbazine will receive treatment until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent.

Change To

Patients randomized to Arm B will receive either dacarbazine or temozolomide at the discretion of the investigator. Dacarbazine will be administered at a dose of 1000 mg/m^2 administered intravenously on Day 1 of each 21-day cycle. Patients in Arm B who are treated with dacarbazine will receive treatment until completion of 12 cycles of therapy, disease progression, unacceptable toxicity or withdrawal of consent.

Section 5.2.1; Dose Reduction of Dacarbazine

Change From

2nd paragraph

The height measured at baseline and the weight measured ~~at~~ **up to 10 days before** the beginning of each cycle should be used to calculate body surface area.

Change To

The height measured at baseline and the weight measured up to 10 days before the beginning of each cycle should be used to calculate body surface area.

Section 5.2.6; Administration of Dacarbazine

Change From

Dacarbazine (1000 mg/m^2) is to be administered intravenously ~~over 60 minutes~~ according to instructions in the package insert, on Day 1 of every cycle.

Change To

Dacarbazine (1000 mg/m^2) is to be administered intravenously according to instructions in the package insert, on Day 1 of every cycle.

Section 5.3.1; Dose Modification of Temozolomide

Change From

2nd paragraph

The height measured at baseline and the weight measured ~~at~~ **up to 10 days before** the beginning of each cycle should be used to calculate body surface area.

Change To

The height measured at baseline and the weight measured up to 10 days before the beginning of each cycle should be used to calculate body surface area.

Section 6.1.2; Pre-Study Assessments (Screening)

Change From

3. Counseling on contraception: All patients (male and female) must agree to practice a form of effective contraception prior to entry into the study and for 6 months **(males) or**

12 months (females) following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.

4. Tumor Assessments (Imaging/Clinical): Documentation of baseline target and non-target lesions by imaging techniques or by measurement of clinical lesion(s) must be performed at the institution participating in the study. Assessment must include CT scans with contrast or MRI of chest, abdomen and pelvis. Outside radiographic studies ~~must~~ **should** be repeated to establish baseline on the equipment that will be used throughout the study. Documentation of skin lesions that can be clearly visualized must be established by color photography, including a ruler to document size.

11. Collect urine for Urinalysis (~~specific gravity, pH, glucose, ketones,~~ blood, protein, **other** ~~bilirubin~~)

Change To

3. **Counseling on contraception:** All patients (male and female) must agree to practice a form of effective contraception prior to entry into the study and for 6 months (males) or 12 months (females) following the last dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.

4. **Tumor Assessments** (Imaging/Clinical): Documentation of baseline target and non-target lesions by imaging techniques or by measurement of clinical lesion(s) must be performed at the institution participating in the study. Assessment must include CT scans with contrast or MRI of chest, abdomen and pelvis. Outside radiographic studies should be repeated to establish baseline on the equipment that will be used throughout the study. Documentation of skin lesions that can be clearly visualized must be established by color photography, including a ruler to document size.

11. Collect urine for **Urinalysis** (blood, protein, other)

Section 6.2.1.1; Cycle 1: Within 72 Hours Prior to First Dose (CP-675,206)

Change From

Heading

Cycle 1: Within ~~48~~ **72** Hours Prior to First Dose (CP-675,206)

Paragraph

The following procedures may be performed on Day 1 prior to dosing or up to ~~48~~ **72** hours prior to dosing:

Item #2 and 5

2. Physical Examination and Vital Signs

~~4.~~ **5** Collect urine for Urinalysis (~~specific gravity, pH, glucose, ketones,~~ blood, protein, ~~bilirubin~~ **other**)

Change To

Heading

Cycle 1: Within 72 Hours Prior to First Dose (CP-675,206)

Paragraph

The following procedures may be performed on Day 1 prior to dosing or up to 72 hours prior to dosing:

Item #2 and #5

2. **Physical Examination** and **Vital Signs**

5. Collect urine for **Urinalysis** (blood, protein, other)

Section 6.2.1.2; Cycle 1, Day 1: Arm A (CP-675,206)

Change From

Item #1 and #4

1. Complete any assessments in the previous section that were not completed within ~~48~~ **72** hours prior to dosing.

~~4. Physical Exam~~

Change To

1. Complete any assessments in the previous section that were not completed within 72 hours prior to dosing.

Item #4 deleted

Section 6.2.1.5; Cycle 1, Day 60: Arm A (CP-675,206)

Change From

~~8. Collect urine for Urinalysis (specific gravity, pH, glucose, ketones, blood, protein, bilirubin)~~

Change To

Item #8 deleted; following number renumbered accordingly

Section 6.2.1.6; Within 10 Days Prior to Scheduled Dose 2: Arm A (CP-675,206)

Change From

3. **Collect urine for** Urinalysis **(blood, protein, other)**

Change To

3. Collect urine for **Urinalysis** (blood, protein, other)

Section 6.2.2.1; Day 1 of Cycle 2 and Subsequent Cycles: Arm A (CP-675,206)

Change From

9. Check results of **pregnancy test,** hematology labs, chemistry labs, thyroid function tests, and urinalysis.

Change To

9. Check results of pregnancy test, hematology labs, chemistry labs, thyroid function tests, and urinalysis.

Section 6.2.2.4; Within 10 Days Prior to Next Dose: Arm A (CP-675,206)

Change From

Item #3 and #4 added

Change To

3. Collect urine for **Urinalysis** (blood, protein, other)
4. Draw blood for:
   - Safety Labs, including Hematology (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), Blood Chemistry (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), Serum C-Reactive Protein (CRP)
   - **Thyroid Function** (thyroid stimulating hormone/TSH, T3, T4)
   - Serum Storage for Autoantibodies

Section 6.2.3; End of Treatment (EOT) Visit: Arm A (CP-675,206)

Change From

2nd and 3rd paragraphs added

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications. Draw blood for pharmacokinetics and human anti human antibodies only.

If the patient has not begun new therapy for melanoma, do the following assessments:

Items #2, #3 and #9

2. Review **Adverse Events** since previous visit. ~~(Do not record adverse events that begin after the patient begins new therapy for melanoma.)~~

3. Review **Concomitant Medications**.

~~If the patient has begun new therapy for melanoma (other than surgery or radiation therapy), draw blood for pharmacokinetics and human anti human antibodies only. If the patient has not begun new therapy for melanoma, do the following assessments:~~

9. Collect urine for Urinalysis (~~specific gravity, pH, glucose, ketones,~~ blood, protein, ~~bilirubin~~ **other**)

Change To

2nd and 3rd paragraphs added

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications. Draw blood for pharmacokinetics and human anti human antibodies only.

If the patient has not begun new therapy for melanoma, do the following assessments:

Items #2, #3 and #9

2. Review **Adverse Events** since previous visit.

3. Review **Concomitant Medications**

9. Collect urine for **Urinalysis** (blood, protein, other)

Section 6.3.1.1; Within 72 Hours Prior to First Dose: Arm B (Dacarbazine)

Change From

Heading

Within ~~48~~ **72** Hours Prior to First Dose: Arm B (Dacarbazine)

Paragraph

The following procedures may be performed on Day 1 prior to dosing or up to ~~48~~ **72** hours prior to dosing:

Item #2 and #3 added, following items renumbered accordingly

Change To

Heading

Within 72 Hours Prior to First Dose: Arm B (Dacarbazine)

Paragraph

The following procedures may be performed on Day 1 prior to dosing or up to 72 hours prior to dosing:

Item #2 and #3

2. **Vital Signs** (temperature, blood pressure while sitting, heart rate)

3. Physical Exam

Repeat **Pregnancy Test** for women of childbearing potential unless a previous pregnancy test was negative ≤7 days prior to dosing. Note: Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations

Section 6.3.1.2; Day 1 Cycle 1: Arm B (Dacarbazine)

Change From

From 1st Paragraph

The following should be done up to ~~48~~ **72** hours prior to the first dose of dacarbazine:

1. Baseline Signs and Symptoms

2. ~~**Vital Signs** (temperature, blood pressure while sitting, heart rate)~~

~~3. **Physical Exam**~~

~~**4.** Repeat **Pregnancy Test** for women of childbearing potential unless a previous pregnancy test was negative ≤7 days prior to dosing. Note: Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations~~

~~5.~~ **2.** Draw blood for the following:

- Safety Labs, including Hematology (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), Blood Chemistry (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), Serum C Reactive Protein (CRP)
- HLA class 1 typing
- Pharmacogenetics

After the assessments listed above are performed, **if a pregnancy test within 7 days is negative or not required,** the study drug may be administered.

Change To

Items #2 thru #4 deleted, following items renumbered accordingly

The following should be done up to 72 hours prior to the first dose of dacarbazine:

1. Baseline Signs and Symptoms

2. Draw blood for the following:

- **Safety Labs,** including **Hematology** (WBC with differential count and absolute neutrophil count/ANC, RBC count, hemoglobin, hematocrit, platelet count), **Blood Chemistry** (calcium, chloride, total protein, potassium, random glucose, sodium, blood urea nitrogen/BUN, creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase/ALP, gamma-glutamine transferase/GGT, lactic acid dehydrogenase/LDH, amylase, lipase, albumin, total bilirubin), **Serum C Reactive Protein (CRP)**
- **HLA class 1 typing**
- **Pharmacogenetics**

After the assessments listed above are performed, if a pregnancy test within 7 days is negative or not required, the study drug may be administered.

Section 6.3.2.2; Day 15 of Cycle 2 and Subsequent Cycles: Arm B (Dacarbazine)

Change From

Item # 2, and 3 added; following number renumbered accordingly

1. Review Adverse Events **and Concomitant Medications** since previous visit **if the patient is seen in clinic**.
2. **Vital Signs (temperature, blood pressure while sitting, heart rate) (optional)**
3. **Physical Examination (optional)**

Change To

1. Review **Adverse Events** and **Concomitant Medications** since previous visit if the patient is seen in clinic.
2. **Vital Signs** (temperature, blood pressure while sitting, heart rate) (optional)
3. **Physical Examination** (optional)

Section 6.3.3; End of Treatment (EOT) Visit: Arm B (Dacarbazine)

Change From

From 2nd paragraph

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer EORTC QLQ-C30 and HCRUQ questionnaires
2. Review Adverse Events since previous visit. ~~(Do not record adverse events that begin after the patient begins new therapy for melanoma.)~~

Change To

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires

2. Review **Adverse Events** since previous visit.

Section 6.4.1.1; Day 1 Cycle 1: Arm B (Temozolomide)

Change From

The following should be done up to ~~48~~ **72** hours prior to the first dose of temozolomide:

Change To

The following should be done up to 72 hours prior to the first dose of temozolomide:

Section 6.4.2.2; Day 22 of Cycle 2 and Subsequent Cycles: Arm B (Temozolomide)

Change From

1. Review Adverse Events since previous visit **if the patient is seen in clinic**.
2. Review Concomitant Medications **if the patient is seen in clinic**.
3. ~~**Weight**~~
4. ~~.~~ **3** Vital Signs (temperature, blood pressure while sitting, heart rate) **(optional)**
5. ~~.~~ **4** Physical Exam **(optional)**

Change To

1. Review **Adverse Events** since previous visit if the patient is seen in clinic.
2. Review **Concomitant Medications** if the patient is seen in clinic.
3. **Vital Signs** (temperature, blood pressure while sitting, heart rate) (optional)
4. **Physical Exam** (optional)

Section 6.4.3; End of Treatment (EOT) Visit: Arm B (Temozolomide)

Change From

From 2nd paragraph

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer EORTC QLQ-C30 and HCRUQ questionnaires
2. Review Adverse Events since previous visit. ~~(Do not record adverse events that begin after the patient begins new therapy for melanoma.)~~
3. Review Concomitant Medications.
4. ECOG Performance Status
5. Vital Signs (temperature, blood pressure while sitting, heart rate)
6. **Weight**
7. Physical Exam

Change To

Item #6 added, following items renumbered accordingly

If the patient has already begun new therapy for melanoma (other than surgery or radiation therapy) at the time of the EOT visit, review adverse events, but record only those adverse events that fall within the reporting period (See Section 8.2). Review concomitant medications.

If the patient has not begun new therapy for melanoma, do the following assessments:

1. Administer **EORTC QLQ-C30** and **HCRUQ** questionnaires
2. Review **Adverse Events** since previous visit.
3. Review **Concomitant Medications**.
4. **ECOG** Performance Status
5. **Vital Signs** (temperature, blood pressure while sitting, heart rate)
6. **Weight**
7. Physical Exam

Section 6.4.4; Follow-up Assessments: Arm B (Temozolomide)

Change From

From item #3

3. **All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or**

until the start of a new systemic treatment, so that the duration of response can be determined

~~All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the **duration of response** can be determined.~~

Change To

Item #3 added

3. All patients who have stable disease or an ongoing objective tumor response (CR, PR) should continue to be followed every 3 months until disease progression or until the start of a new systemic treatment, so that the **duration of response** can be determined

Section 7.1; Safety Assessments

Change From

1st paragraph

Laboratory safety assessments are detailed in the Schedules of Activities and include the following: hematology and chemistry labs; ECG; urinalysis; and function of endocrine organs including T3, T4, TSH, lipase, and amylase. Human antihuman antibody (HAHA) response to CP-675,206 will be monitored in patients on Arm A. **Serum samples are stored at baseline for patients in Arm A for potential testing for autoantibodies. If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of the those autoantibodies.** ~~Autoantibodies will be assessed in patients experiencing adverse events that are potentially immune mediated.~~

Change To

Laboratory safety assessments are detailed in the Schedules of Activities and include the following: hematology and chemistry labs; ECG; urinalysis; and function of endocrine organs including T3, T4, TSH, lipase, and amylase. Human antihuman antibody (HAHA) response to CP-675,206 will be monitored in patients on Arm A. Serum samples are stored at baseline for patients in Arm A for potential testing for autoantibodies. If a patient has an adverse event that is thought to be possibly related to autoimmune antibodies (eg, thyroiditis, hepatitis, thrombocytopenia), the investigator should send a blood sample for autoimmune antibody testing. If specific autoantibodies are present, the serum sample taken for storage at baseline can be tested for the presence of the those autoantibodies.

Section 7.2.1; Schedule of Tumor Assessments

Change From

Last paragraph

All patients **in Arm A** who have objective tumor response should have additional scans scheduled 4 to 6 weeks after the criteria for response are first met in order to confirm response. Additional scans should be done whenever clinically indicated.

Change To

All patients in Arm A who have objective tumor response should have additional scans scheduled 4 to 6 weeks after the criteria for response are first met in order to confirm response. Additional scans should be done whenever clinically indicated.

Section 7.2.3; Measurability of Tumor Lesions

Change From

Item 'a', 3rd bullet

- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules). Skin lesions ~~selected as target lesions~~ **documented by photography** must be at least 1.0 cm in longest diameter **in order to be considered measurable**. Documentation by color photography, including a ruler to document the size of the ~~target~~ lesions, is required.

Change To

- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules). Skin lesions documented by photography must be at least 1.0 cm in longest diameter in order to be considered measurable. Documentation by color photography, including a ruler to document the size of the lesions, is required.

Section 7.2.4; "Target" and "Non-Target" Lesions

Change From

Item 'b', 1st bullet

- All other lesions (or sites of disease) should be identified as non-target lesions and recorded as non-target lesions at baseline. Non-target lesions are not required to be measured, and should be recorded as "present" at baseline. Each non-target lesion should be documented as either present, absent or new in each subsequent evaluation.

Note that all in-transit skin lesions should be photographed at baseline, with a ruler to document size, regardless of size.

Change To

- All other lesions (or sites of disease) should be identified as non-target lesions and recorded as non-target lesions at baseline. Non-target lesions are not required to be measured, and should be recorded as "present" at baseline. Each non-target lesion should be documented as either present, absent or new in each subsequent evaluation. Note that all in-transit skin lesions should be photographed at baseline, with a ruler to document size, regardless of size.

Section 7.2.5; Techniques for Assessing Measurable Disease

Change From

1st bullet

- Clinical Examination: Documentation by color photography, including a ruler to document the size of the ~~target~~ lesion(s), is required.

Change To

- Clinical Examination: Documentation by color photography, including a ruler to document the size of the lesion(s), is required.

Section 7.3; Patient Reported Outcomes

Change From

3rd paragraph, 1st sentence

The HQoL questionnaire should be administered at baseline and at Day 1 of the each treatment cycle **starting with Cycle 2** (prior to dosing) in each treatment arm. . .

Change To

The HQoL questionnaire should be administered at baseline and at Day 1 of the each treatment cycle starting with Cycle 2 (prior to dosing) in each treatment arm. . .

Section 8.2; Reporting Period

Change From

Serious adverse events require immediate notification to Pfizer or its designated representative beginning from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the clinical trial, ie, prior to undergoing any trial-related procedure

and/or receiving investigational product, through and including **the End of Treatment visit or** 28 calendar days after the last administration of the investigational product**, whichever is later**. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of trial treatment through ~~last patient visit~~ **the End of Treatment Visit**.

If a patient begins a new anticancer therapy, the adverse event reporting period for non-~~serious~~ **fatal** adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

Change To

Serious adverse events require immediate notification to Pfizer or its designated representative beginning from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including the End of Treatment visit or 28 calendar days after the last administration of the investigational product, whichever is later. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of trial treatment through the End of Treatment Visit.

If a patient begins a new anticancer therapy, the adverse event reporting period for non-fatal adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

Section 8.5; Serious Adverse Events

Change From

3rd paragraph, last sentence

. . . However, if it is determined that the event may jeopardize the patient and/**or** may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Change To

. . . However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Section 8.9; Exposure In Utero

Change From

For investigational products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if**:**

1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product **(maternal exposure);**

2) a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial patient **or trial patient's partner** becomes or is found to be pregnant ~~while receiving~~ **during** the **trial patient's treatment with the** investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

Change To

For investigational products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if:

1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);

2) a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial patient or trial patient's partner becomes or is found to be pregnant during the trial patient's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

Section 16; References

Change From

Reference #2 and #3 added, following references renumbered accordingly

Change To

2. Eggermont A, Kirkwood J. Re-Evaluating the role of dacarbazine in metastatic melanoma: What have we learned in 30 years? European Journal of Cancer 40 (2004);1825-36.

3. Middleton MR, Grob JJ, Aaronson N, et al. Ranomized Phase III Study of Temozolomide Versus Dacarbazine in the Treatment of Patients With Advanced Metastatic Malignant Melanoma. J Clin Oncol 2000;18:158-66.

Appendix A; CP-675,206 Treatment-Emergent Diarrhea Management Guidelines

Change From

From Management

For mild diarrhea (Grade 1, ≤14 days):

- **Consider use of probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements). Probiotics have been shown to be effective with other types of diarrhea, including ulcerative colitis.**
- Drink 1.5-2 liters of water, electrolyte-containing liquid (eg Gatorade) or both a day.
- Eat potatoes, bananas, rice, applesauce, toast, jello, plain pasta. Avoid all lactose-containing products and supplements, fruits and vegetables.
- If *C. difficile* negative: Loperamide (Imodium) 4 mg initial dose, followed by 2 mg q2h until 12 hours without diarrhea (at night, take 4 mg q4h). Titrate up.
- **Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day. Mesalamine is an anti-inflammatory drug, and it is not immediately effective.**

If Grade 2 or if Grade 1 and persists > 14 days:

- **Consider use of probiotics**
- In addition to above measures, patient should be evaluated by clinician familiar with CP-675,206-related diarrhea
- **Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day**

If persistent despite loperamide and/or Grade 3 or 4 or severe per investigator's judgment:

- **Consider use of probiotics**
- Admit to hospital if required.
- Intravenous fluid, monitoring and replacement of electrolytes. (The required duration of intravenous fluids should be recorded on the Case Report Form to align with CTC severity grade)
- Evaluation of infection
- Consider octreotide (Sandostatin) 125 mcg subcutaneously, three times a day, only if secretory.
- Consider use of steroids, eg oral or intravenous dexamethasone up to 4 mg every 4 hours or budesonide (Entocort EC) 9mg once a day in the morning up to 8 weeks
- **For patients for whom steroids do not control the diarrhea, consider use of infliximab (Remicade), a monoclonal antibody indicated for Crohn's disease. Infliximab has been reported to be effective in patients with steroid-resistant diarrhea due to another anti-CTLA4 monoclonal antibody.[b]**

- Consider olsalazine (Dipentum): 500 mg oral twice a day
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day

Note: Any patient with Grade 3 diarrhea requiring systemic steroids for more than 10 days in any one cycle or with Grade 4 diarrhea must be withdrawn from treatment.

Drugs and probiotics used for treatment or prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

GUIDANCE: Prevention of CP-675,206 Treatment-Emergent Diarrhea

There is no data/evidence indicating effectiveness of prophylactic therapy for prevention of treatment emergent diarrhea secondary to ticilimumab. However, prophylaxis may be considered. If prophylaxis is used, one of the following drugs would be recommended:

- **Probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements) have been shown to be effective with other types of diarrhea, including ulcerative colitis, in clinical trials. Probiotics might prevent diarrhea by replacing gut bacteria with more benign strains, thereby decreasing the overactive T cell response to gut flora. This approach is not expected to present a risk to the patient.**
- **Mesalamine (Asacol) 1.6 g PO in divided doses. Mesalamine is an anti-inflammatory drug, and it is not immediately effective. It may be considered for prophylactic use, but to date there is no data to support its use.**

Loperimide treats only the symptoms of diarrhea and not the underlying cause. It should <u>not</u> be used prophylactically.

Steroids can be used to treat severe or prolonged diarrhea due to CP-675,206, but should <u>not</u> be used prophylactically.

Drugs and probiotics used for prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

- ~~Only to be considered in case that patient had an episode of diarrhea related to a prior dose of CP-675,206~~
- ~~There is no data/evidence indicating effectiveness of prophylactic therapy for prevention of treatment emergent diarrhea secondary to CP-675,206.~~
- ~~Premedication with loperamide is not recommended.~~

~~**Olsalazine 500 mg PO BID (Dipentum)**~~
~~**Or**~~
~~**Mesalamine 1.6 g PO in divided doses (Asacol) up to 30 days**~~
~~**----------**~~
~~**Octeotride acetate LAR depot 20 mg Injection (Sandostatin: long -acting)**~~

Change To

For mild diarrhea (Grade 1, ≤14 days):

- Consider use of probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements). Probiotics have been shown to be effective with other types of diarrhea, including ulcerative colitis.
- Drink 1.5-2 liters of water, electrolyte-containing liquid (eg Gatorade) or both a day.
- Eat potatoes, bananas, rice, applesauce, toast, jello, plain pasta. Avoid all lactose-containing products and supplements, fruits and vegetables.
- If *C. difficile* negative: Loperamide (Imodium) 4 mg initial dose, followed by 2 mg q2h until 12 hours without diarrhea (at night, take 4 mg q4h). Titrate up.
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day. Mesalamine is an anti-inflammatory drug, and it is not immediately effective.

If Grade 2 or if Grade 1 and persists > 14 days:

- Consider use of probiotics
- In addition to above measures, patient should be evaluated by clinician familiar with CP-675,206-related diarrhea
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day

If persistent despite loperamide and/or Grade 3 or 4 or severe per investigator's judgment:

- Consider use of probiotics
- Admit to hospital if required.

- Intravenous fluid, monitoring and replacement of electrolytes. (The required duration of intravenous fluids should be recorded on the Case Report Form to align with CTC severity grade)
- Evaluation of infection
- Consider octreotide (Sandostatin) 125 mcg subcutaneously, three times a day, only if secretory.
- Consider use of steroids, eg oral or intravenous dexamethasone up to 4 mg every 4 hours or budesonide (Entocort EC) 9mg once a day in the morning up to 8 weeks
- For patients for whom steroids do not control the diarrhea, consider use of infliximab (Remicade), a monoclonal antibody indicated for Crohn's disease. Infliximab has been reported to be effective in patients with steroid-resistant diarrhea due to another anti-CTLA4 monoclonal antibody.[b]
- Consider olsalazine (Dipentum): 500 mg oral twice a day
- Consider mesalamine (Asacol): 2 tablets of 400 mg orally three times a day

Note: Any patient with Grade 3 diarrhea requiring systemic steroids for more than 10 days in any one cycle or with Grade 4 diarrhea must be withdrawn from treatment.

Drugs and probiotics used for treatment or prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

GUIDANCE: Prevention of CP-675,206 Treatment-Emergent Diarrhea

There is no data/evidence indicating effectiveness of prophylactic therapy for prevention of treatment emergent diarrhea secondary to ticilimumab. However, prophylaxis may be considered. If prophylaxis is used, one of the following drugs would be recommended:

- Probiotics (active cultures of beneficial bacteria which can be found in some brands of yogurt or in supplements) have been shown to be effective with other types of diarrhea, including ulcerative colitis, in clinical trials. Probiotics might prevent diarrhea by replacing gut bacteria with more benign strains, thereby decreasing the overactive T cell response to gut flora. This approach is not expected to present a risk to the patient.
- Mesalamine (Asacol) 1.6 g PO in divided doses. Mesalamine is an anti-inflammatory drug, and it is not immediately effective. It may be considered for prophylactic use, but to date there is no data to support its use.

Loperimide treats only the symptoms of diarrhea and not the underlying cause. It should not be used prophylactically.

Steroids can be used to treat severe or prolonged diarrhea due to CP-675,206, but should not be used prophylactically.

Drugs and probiotics used for prophylaxis of diarrhea should be entered in the "Concomitant Diarrhea Medications" CRF.

Appendix A; CP-675,206 Treatment-Emergent Diarrhea Management Guidelines

Change From

Footnote 'b' added

Change To

b. Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner D, Quezado M, Lowy I, Yellin M, Rosenberg SA, Yang JC. Enterocolitis in Patients with Cancer After Antibody Blockade of Cytotoxic T-Lymphocyte- Associated Antigen 4. J Clin Oncol 24:2283-2289 2006.

Appendix E; List of Abbreviations

Change From

~~PAP~~ ~~Preparation and Administration Protocol~~

Change To

Abbreviation deleted

Appendix F; List of Investigational Vaccines for Melanoma

Change To

Entire Appendix F added