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GENERIC DRUG NAME/COMPOUND NUMBER: Tremelimumab/CP-675,206

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Oncology (this drug is not marketed in the United States)

NATIONAL CLINICAL TRIAL NO. NCT00257205

PROTOCOL NO.: A3671009

PROTOCOL TITLE: A Phase 3, Open Label, Randomized, Comparative Study of CP-675,206 and Either Dacarbazine or Temozolomide in Patients with Advanced Melanoma

Study Centers: Total of 115 study centers: 1 in Argentina, 5 in Australia, 1 in Austria, 6 in Belgium, 11 in Canada, 10 in France, 5 in Germany, 1 in Greece, 3 in Israel, 6 in Italy, 2 in Mexico, 4 in Netherlands, 5 in Poland, 3 in Russian Federation, 1 in Slovakia, 2 in South Africa, 8 in Spain, 2 in Sweden, 1 in Switzerland, 5 in United Kingdom, and 33 in the United States.

Study Initiation and Completion Dates: 10 March 2006 to 27 May 2010

Phase of Development: Phase 3

Study Objectives: The primary objective of this study was to compare overall survival (OS) for subjects with advanced melanoma who were randomized to receive tremelimumab with that of subjects who were randomized to receive either dacarbazine or temozolomide.

Secondary objectives included the following:

- To compare durable response (DR) rate (responses present at or after 6 months post randomization) for subjects in the 2 treatment arms.
- To compare 6-month progression-free survival (PFS; proportion of subjects who are alive and who have not progressed at 6 months or more post randomization) for subjects in the 2 treatment arms.
- To assess objective response (OR) rate for subjects in each treatment arm.
- To assess duration of response for subjects in each treatment arm.
- To assess time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status (PS) for subjects in each treatment arm.

- To further characterize the safety profile and toleration of tremelimumab.
- To characterize any human antihuman antibody (HAHA) response to tremelimumab.
- To compare health-related quality of life (HRQoL) outcomes in the 2 treatment arms.
- To compare subject reported healthcare resource utilization and loss of productivity in the 2 treatment arms.
- To explore any relationship between tremelimumab exposure, measured as maximum plasma concentration (C_{max}) and concentration at 4 weeks (C_{4wk}), and clinical response in this population.
- To explore whether the cytotoxic T lymphocyte-associated antigen 4 (CTLA4), FcgammaRIIa, and immunoglobulin (Ig)G2a genotypes influenced the safety, and/or efficacy of subjects treated with tremelimumab.
- To explore relationships between clinical response (efficacy or toxicity) and tumor or blood genomics.

METHODS

Study Design: This was a Phase 3, multi-national, open-label, 2-arm randomized study in subjects with unresectable metastatic melanoma who had received no prior chemotherapy, immunotherapy, or biological therapy for the treatment of metastatic disease. Approximately 630 subjects were to be enrolled. Randomization was to be 1:1 and stratified by disease stage (IIIC versus IV M1a, M1b versus IV M1c) and presence of measurable lesions (measurable disease versus no measurable disease). Subjects randomized to Arm A were to receive intravenous administration of tremelimumab at a dose of 15 mg/kg on Day 1 of every 90-day cycle, for up to 4 cycles. Subjects randomized to Arm B were to 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. OS was the primary endpoint. Subjects in Arm A had tumor assessments performed every cycle (approximately every 3 months). Subjects in Arm B had tumor assessments performed every 2 cycles (approximately every 6 weeks for dacarbazine, approximately every 2 months for temozolomide). For subjects in either arm, additional scans were to be performed when clinically indicated. Subjects in the control arm who progressed were not allowed to cross over to receive treatment with tremelimumab.

Number of Subjects (Planned and Analyzed): A total of 630 subjects were to be enrolled in order to achieve the expected number of events by the end of the minimum follow-up period. A total of 840 subjects were screened and 655 were assigned to study treatment (325 in Arm A and 319 to Arm B (Arm B-dacarbazine = 211, Arm B-temozolomide = 108).

Diagnosis and Main Criteria for Inclusion: To enter the study, subjects were required to have histologically confirmed melanoma (Stage IV or Stage III with N3 status for regional lymph nodes), measurable disease (or non-measureable disease that could be evaluated for

OR) and an ECOG PS of 0 or 1. Subjects must have recovered from all prior surgeries or adjuvant treatment-related toxicities.

Study Treatment: Subjects randomized to Arm A were to receive intravenous administration of tremelimumab 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 was defined as a 90 (± 4) day period. Subjects randomized to Arm B who were to be treated with dacarbazine or temozolomide would receive treatment until completion of 12 cycles of therapy, disease progression, unacceptable toxicity, or withdrawal of consent. Dacarbazine was administered intravenously at a dose of 1000 mg/m^2 on Day 1 of each 21-day cycle. Temozolomide was administered orally at a dose of 200 mg/m^2 on Days 1-5 of every 28-day cycle. Preparation and dispensing of dacarbazine were to be performed according to instructions in the package insert.

Efficacy Evaluations: The primary endpoint was OS. Secondary endpoints included DR, defined as an objective tumor response that is present at 6 or more months after randomization; PFS at 6 months post randomization; objective tumor response; and duration of tumor response.

Subject Reported Outcomes: Subject reported outcome endpoints included HRQoL, and healthcare resource utilization and loss of productivity assessment using the Healthcare Resource Utilization Questionnaire (HRUQ).

Safety Evaluations: Safety was assessed through the collection of observed adverse events (AEs), clinical laboratory test results, ECOG performance status scores, body weight and vital sign measurements, and physical examination findings (including visual symptoms). Serious adverse events (SAEs) were to be reported immediately to the sponsor.

Statistical Methods: Sample Size Determination: It was assumed that the median survival for subjects in the control arm treated with either dacarbazine or temozolomide would be approximately 7 months. The true hazard ratio (HR, control arm over tremelimumab arm) was assumed to be 1.33. This represents a 33% improvement in true median OS from 7 months to 9.33 months. A total of 537 events (deaths) was 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 was based on 2 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 subjects were to be enrolled in order to achieve the expected number of events by the end of the minimum follow-up period. It was expected that the maximum study duration would be 35 months. Analysis Populations: As Randomized Population was all randomized subjects with study drug assignment designated according to initial randomization, regardless of whether subjects received any study drug or received a different drug from that to which they were randomized. This was the primary population for evaluating all efficacy endpoints as well as subject characteristics. The primary analysis of the primary endpoint (OS) was performed in this population. As Treated Population was all subjects randomized in the study who received at least 1 dose of study medication with treatment assignments designated according

to actual study treatment received. This population was the primary population for evaluating safety. Per Protocol Population was all eligible subjects who had baseline assessments and received study treatment with the treatment assignments designated according to actual treatment received. This population was a secondary population for efficacy analysis. Evaluable for PK Population consisted of all subjects who had baseline and sufficient on-study blood samples to provide interpretable PK results. Evaluable for Patient Reported Outcomes (PRO) Population consisted of subjects who received at least 1 dose of study drug and had a baseline assessment on the PRO and at least 1 post-treatment assessment on the PRO. Subjects were analyzed according to the treatment group to which they were randomized. Primary endpoint: The primary comparison of the 2 arms of the trial was by an unstratified log-rank test using Kaplan-Meier methods. A secondary comparison of the arms was performed by a stratified log-rank test accounting for the specified stratification factors. A secondary analysis of OS was also performed for the As-Treated Population. A stratified Cox-regression model was used to assess the impact of prognostic factors on OS. The prognostic factors included age, gender, geographical region, site of the disease, baseline lactate dehydrogenase (LDH), and human leukocyte antigen (HLA) class 1 type. Other Parameters: Descriptive statistics were used to summarize all subject characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, clinical benefit endpoints, and PRO.

RESULTS

Subject Disposition and Demography: Subject disposition is shown in Table 1 below.

Table 1. Subject Disposition, All Randomized As-Randomized Population

		Arm B, by Treatment		
	Arm A	Dacarbazine	Temozolomide	Total
Number (%) of subjects:				
Screened: N=840				
Number of subjects randomized	328			327
Assigned to study treatment: N=655				
Treated	325	211	108	319
Completed	40	22	11	33
Discontinued	285	189	97	286
Reason for discontinuation:				
Adverse event	42 (12.9)	6 (2.8)	4 (3.7)	10 (3.1)
Subject died	16 (4.9)	6 (2.8)	4 (3.7)	10 (3.1)
Other	3 (0.9)	12 (5.7)	1 (0.9)	13 (4.1)
Progressive disease	216 (66.5)	161 (76.3)	85 (78.7)	246 (77.1)
Subject no longer willing to participate	8 (2.5)	4 (1.9)	2 (1.9)	6 (1.9)
Protocol violation	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Analyzed for efficacy:				
Tumor response per Investigator	300	200	97	297
Analyzed for safety:				
Adverse events	325	211	108	319
Laboratory data	321	209	108	317

Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

Overall, subjects ranged in age from 22 to 90 years with a mean age of 57 years in Arm A and 56 years in Arm B. The majority of subjects were under 65 years of age (67% in Arm A and 73% in Arm B) and white (93% in each arm). The mean duration since first diagnosis of disease was 3.6 years (range=0.02-33.05 years) in Arm A and 3.9 years (range=0.02-30.63 years) in Arm B. The most common stage was IV M1c (57% vs 59% in Arm A vs Arm B, respectively). Most subjects in each arm had an ECOG PS of 0 (68% vs 69% in Arm A vs Arm B, respectively).

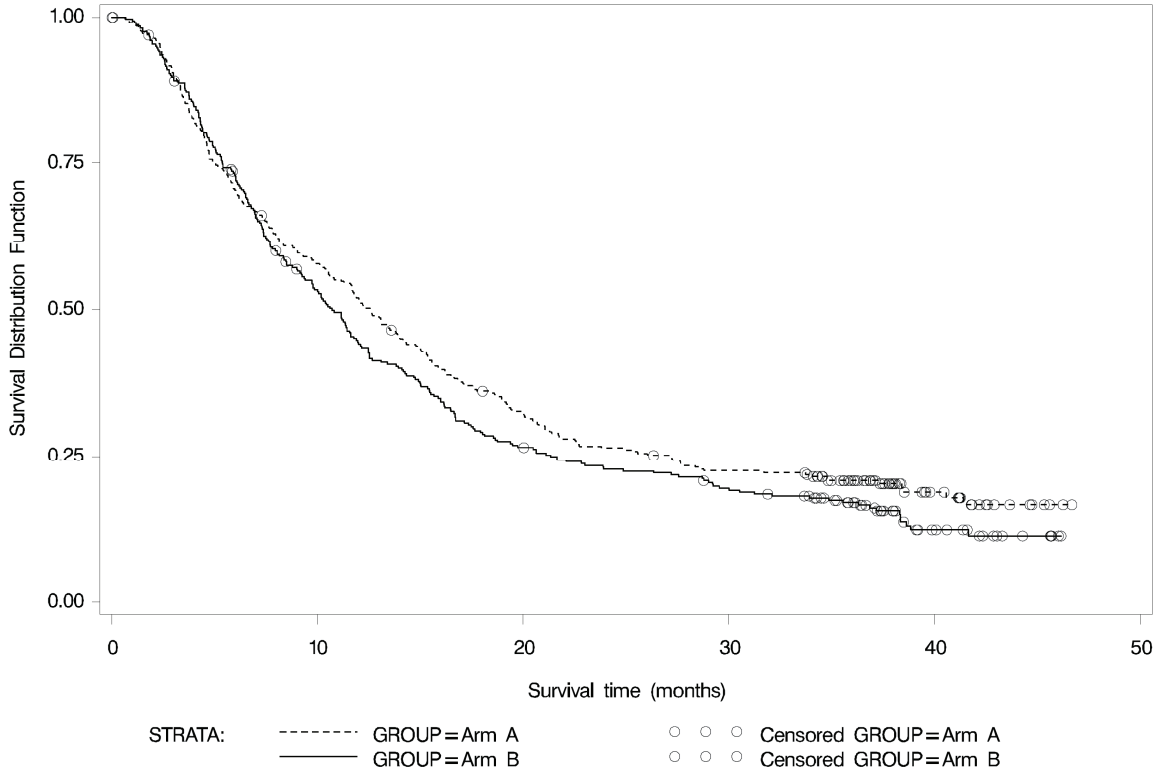
Measurable disease was present in 305 out of 328 randomized subjects (93%) in Arm A and 299 out of 327 randomized subjects (91%) in Arm B based on the Investigator's assessment. Target lesions were noted in 93% of subjects in Arm A and 91% of subjects in Arm B.

The number of involved sites was generally comparable between both treatment arms based on the Investigator's assessment. Lung, distant lymph node, and liver were the 3 most common involved disease sites.

Efficacy Results: At a protocol-specified second interim analysis with 340 deaths (03 March 2008) median OS was 11.7 months (95% CI: [10.3, 13.9]) in the tremelimumab arm and 10.7 months (95% CI: [9.3, 11.9]) in the chemotherapy arm (hazard ratio [HR]=1.04, P=0.73). At that time, the Data Safety Monitoring Board (DSMB) met and stated that the test statistic crossed the pre-specified futility boundary. Although the test statistic crossed the futility boundary, survival follow up continued.

At the time of database lock, the results of the primary analysis showed that the median OS was 12.58 months (95% CI: [10.81, 14.29]) in Arm A with tremelimumab and 10.71 months (95% CI: [9.36, 11.96]) in Arm B with dacarbazine or temozolomide (HR=1.1416 [Arm B:Arm A], 95% CI: [0.9633, 1.3530], P-value of an unstratified log-rank test was 0.1272). The probability estimate of OS at 12 months was 0.521 (95% CI: [0.467, 0.575]) in Arm A and 0.441 (95% CI: [0.387, 0.496]) in Arm B, P=0.0434. Figure 1 graphically displays the Kaplan-Meier plot for OS at the time of database lock.

Figure 1 Kaplan-Meier Plot of Overall Survival, All Randomized As-Randomized Population



Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

A stepwise stratified Cox-regression model was used to assess the impact of several baseline factors (ie, affect of disease stage, ECOG PS, age, gender, geographical region, HLA class 1 type, measurable disease, site of the disease, baseline LDH, prior radiation usage, and prior cancer treatment) on OS. The model showed that after adjusting for the treatment effect subjects who entered the study with elevated LDH levels died sooner than subjects who entered the study with normal LDH levels (P<0.0001). The model also indicated that those subjects having fewer involved disease sites lived longer than those subjects who had more than 1 involved disease site (P=0.0324). Furthermore, subjects entering the study with lower ECOG PS lived longer than those subjects entering the study with higher ECOG PS (P=0.0030).

Subset analyses were performed to investigate whether any baseline characteristic variables (ie, disease stage, baseline LDH, number of disease sites, subject characteristics, gender, baseline ECOG PS, prior adjuvant therapy, geographical region, laboratory assays [HLA class 1 type], C-reactive protein [CRP], and absolute lymphocyte counts) were associated with the treatment effect on OS of subjects taking tremelimumab. There was no statistically significant association between subject characteristics such as age (<65 vs ≥65 years), HLA (A2 vs non-A2), and ECOG PS (0 vs 1) or tumor factors such as baseline serum LDH

(<upper limit of reference range [ULN], ≥ULN-2 × ULN), stage (III, IV M1a/b, IV M1c), and number of disease sites (1 vs >1) with treatment effect of tremelimumab compared to chemotherapy. Low baseline serum CRP (CRP <1.5 × ULN) was identified as a potential predictive biomarker by selecting a subset of subjects with highly statistically significant survival benefit from tremelimumab compared to chemotherapy (P=0.0012). In addition, high baseline lymphocyte counts (≥0.9 × lower limit of reference range [LLN]) were also associated with survival benefit from tremelimumab compared to chemotherapy.

The study was not designed to compare PFS between the 2 treatment arms as there were different tumor assessment schedules for subjects on each drug treatment. The median PFS was 2.83 months (95% CI: [2.79, 2.89]) in Arm A and 2.14 months (95% CI: [1.91, 2.63] in Arm B. There was a prespecified comparison of PFS at 6 months because subjects in both arms were scheduled to have an assessment at about that time. The probability estimate of PFS at 6 months, as assessed by the sponsor, was 0.205 in Arm A (95% CI: [0.161, 0.249]) and 0.182 in Arm B (95% CI: [0.139, 0.224], P=0.4657).

As determined by the Investigators, for the As-Randomized Population, 35 subjects (10.7%) in Arm A and 32 subjects (9.8%) in Arm B achieved a best overall response (BOR) of OR (ie, complete response [CR] or partial response [PR]) (P>0.05). Similarly, there were 92 subjects (28.0%) in Arm A and 92 subjects (28.1%) in Arm B who achieved a BOR of clinical benefit response (CR or PR or stable disease [SD], where a BOR of SD was defined as an assessment of showing SD at least 70 days after randomization). According to the Investigator, 11 subjects in Arm A (3.4%) and 8 subjects in Arm B (2.4%) achieved a BOR of CR. Overall, treatment arms were not significantly different with respect to the number of subjects in each response category (P>0.05). Similarly, the Sponsor's assessment indicated that 36 subjects (11.0%) in Arm A and 32 subjects (9.8%) in Arm B achieved a BOR of OR (P>0.05). The Sponsor confirmed that 11 subjects (3.4%) in Arm A and 8 subjects (2.4%) in Arm B achieved a BOR of CR. Overall, treatment arms were not significantly different with respect to the number of subjects in each response category (P>0.05).

According to the Investigators, the treatment arms were not significantly different with respect to DR. Eleven subjects (3.4%) in Arm A and 8 subjects (2.4%) in Arm B had a durable CR; 23 subjects (7.0%) in Arm A and 16 subjects (4.9%) in Arm B had a durable PR; and 294 subjects (89.6%) in Arm A and 303 subjects (92.7%) in Arm B had no DR (P>0.05). Similarly, the Sponsor's assessment indicated that 11 subjects (3.4%) in Arm A and 7 subjects (2.1%) in Arm B had a durable CR; 21 subjects (6.4%) in Arm A and 16 subjects (4.9%) in Arm B had a durable PR.

The duration of OR per investigator was longer in Arm A than Arm B using both Method A (from the date of randomization to the date of progression or death due to disease progression) and Method B (from the date of first documentation of CR or PR to the date of progression or death due to progressive disease [PD]). Using Method A, the duration of OR was 32.24 months in Arm A and 13.03 months in Arm B (P=0.0195). Using Method B, the duration of OR was 26.79 months in Arm A and 11.21 months in Arm B (P=0.0612). Durations of response as confirmed by the Sponsor were similar.

"Mixed response" was not a pre-defined endpoint in the protocol, but was assessed during sponsor review of response for exploratory analysis. A mixed responder was defined as a subject whose BOR per Response Evaluation Criteria in Solid Tumors (RECIST) was PD, however, achieved response in target lesions (a 30% or greater reduction in the sum of the longest diameter of target lesion) in spite of PD due to either PD in non-target lesions or occurrence of a new lesion. A total of 8 subjects (2.4%) in Arm A and 7 subjects (2.1%) in Arm B met the criteria of mixed responder (P>0.05).

Both treatment arms were similar with respect to the number of subjects who had PD as BOR (291 subjects [88.7%] in Arm A and 290 subjects [88.7%] in Arm B). The primary reason for PD in each arm was new lesion(s) (60.4% vs 48.6% for Arm A vs Arm B, respectively).

Other Results (HAHA and Subject-Reported Outcome): Human anti human antibodies (HAHA) was found in 19 samples from 15 of 322 (4.7%) subjects treated with tremelimumab. Twelve of the 19 samples with positive HAHA results were also positive for neutralizing antibody with low titers. Most of the positive samples occurred at baseline and/or were subsequently followed by negative samples.

Statistically significant worsening in physical functioning, role functioning, and fatigue was observed for individuals in both Arm A and Arm B (Arm B-dacarbazine and Arm B-temozolomide data combined). The degree of worsening over the course of the study in physical functioning, role functioning, and fatigue was greater for Arm A than for Arm B. Moreover, Arm A had a lower percentage of subjects on the physical and role functioning scales who improved and a higher percentage of subjects who worsened. There was no statistically significant difference in response distribution between Arm A and Arm B for fatigue symptoms.

Overall, subject-reported hospitalization rates were consistently statistically significantly higher in Arm A at all time points compared to Arm B. Rates of emergency room visits were statistically higher in Arm A than Arm B but only at 3 time points (Weeks 12, 24 and at end of treatment [EOT] assessment).

Safety Results: Table 2 presents the most frequently reported (≥5%) treatment-emergent AEs (TEAE) of all causalities by all cycles and common toxicity criteria (CTC) grade. Table 3 presents the TEAEs that led to discontinuation in the study.

Table 2. Treatment-Emergent Adverse Events of All Causalities that Occurred in ≥5% of Subjects in All Cycles, by CTC Grade, As-Treated Population

MedDRA SOC / Preferred Term	Arm A N=325 G1/2 n (%)	Arm A N=325 G3/4 n (%)	Arm A N=325 G5 n (%)	Arm A N=325 All Grades n (%)	Arm B N=319 G1/2 n (%)	Arm B N=319 G3/4 n (%)	Arm B N=319 G5 n (%)	Arm B N=319 All Grades n (%)
Blood/lymphatic								
Anemia	13 (4.0)	11 (3.4)	0 (0)	24 (7.4)	22 (6.9)	5 (1.6)	0 (0)	27 (8.5)
Thrombocytopenia	4 (1.2)	1 (0.3)	0 (0)	5 (1.5)	38 (12.0)	25 (7.8)	0 (0)	63 (19.7)
Neutropenia	1 (0.3)	1 (0.3)	0 (0)	2 (0.6)	16 (5.0)	34 (10.7)	0 (0)	50 (15.7)
Leukopenia	2 (0.6)	0 (0)	0 (0)	2 (0.6)	13 (4.0)	7 (2.2)	0 (0)	20 (6.3)
Gastrointestinal								
Colitis	6 (1.8)	15 (4.6)	0 (0)	21 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	46 (14.2)	2 (0.6)	0 (0)	48 (14.8)	100 (31.3)	2 (0.6)	0 (0)	102 (32.0)
Diarrhea	108 (33.2)	51(15.7)	0 (0)	159 (48.9)	50 (15.7)	6 (1.9)	0 (0)	56 (17.6)
Abdominal pain	39 (12.0)	12 (3.7)	0 (0)	51 (15.7)	21 (6.6)	3 (0.9)	0 (0)	24 (7.5)
Abdominal pain upper	17 (5.2)	0 (0)	0 (0)	17 (5.2)	9 (2.9)	1 (0.3)	0 (0)	10 (3.1)
Nausea	95 (29.2)	14 (4.3)	0 (0)	109 (33.5)	148 (46.4)	10 (3.1)	0 (0)	158 (49.5)
Vomiting	60 (18.5	14 (4.3)	0 (0)	74 (22.8)	83 (26.1)	9 (2.8)	0 (0)	92 (28.8)
General/administrative site								
Pyrexia	49(15.1)	4 (1.2)	0 (0)	53 (16.4)	27 (8.5)	0 (0)	0 (0)	27 (8.5)
Asthenia	19 (5.9)	10 (3.1)	0 (0)	29 (8.9)	29 (9.1)	5 (1.6)	0 (0)	34 (10.7)
Chest pain	16 (4.9)	2 (0.6)	0 (0)	18 (5.5)	9 (2.8)	2 (0.6)	0 (0)	11 (3.4)
Fatigue	87 (26.8)	19 (5.8)	0 (0)	106 (32.6)	113 (35.4)	5 (1.6)	0 (0)	118 (37.0)
Edema, peripheral	27 (8.3)	5 (1.5)	0 (0)	32 (9.8)	17 (5.3)	1 (0.3)	0 (0)	18 (5.6)
Infections/infestations								
Urinary tract infection	16 (4.9)	1 (0.3)	0 (0)	17 (5.2)	5 (1.6)	1 (0.3)	0 (0)	6 (1.9)
Investigations								
Weight decreased	35 (10.8)	1 (0.3)	0 (0)	36 (11.1)	9 (2.8)	1 (0.3)	0 (0)	10 (3.1)
Metabolism/nutrition								
Decreased appetite	53(16.3)	14 (4.3)	0 (0)	67 (20.6)	39 (12.2)	1 (0.3)	0 (0)	40 (12.5)
Dehydration	7 (2.2)	10 (3.1)	0 (0)	17 (5.2)	2 (0.6)	1 (0.3)	0 (0)	3 (0.9)
Musculoskeletal/connective tissue								
Arthralgia	23 (7.1)	3 (0.9)	0 (0)	26 (8.0)	17 (5.3)	2 (0.6)	0 (0)	19 (6.0)
Myalgia	22 (6.8)	1 (0.3)	0 (0)	23 (7.1)	12 (3.8)	1 (0.3)	0 (0)	13 (4.1)
Back pain	23 (7.1)	5 (1.5)	0 (0)	28 (8.6)	20 (6.3)	6 (1.9)	0 (0)	26 (8.2)
Pain in extremity	19 (5.8)	2 (0.6)	0 (0)	21 (6.5)	19 (6.0)	0 (0)	0 (0)	19 (6.0)
Nervous								
Headache	35 (10.8)	2 (0.6)	0 (0)	37 (11.4)	41 (12.8)	1 (0.3)	0 (0)	42 (13.2)
Dizziness	24 (7.4)	1 (0.3)	0 (0)	25 (7.7)	18 (5.6)	0 (0)	0 (0)	18 (5.6)
Psychiatric								
Insomnia	25 (7.7)	0 (0)	0 (0)	25 (7.7)	16 (5.0)	0 (0)	0 (0)	16 (5.0)
Respiratory								
Cough	45 (13.8)	1 (0.3)	0 (0)	46 (14.2)	27 (8.4)	0 (0)	0 (0)	27 (8.5)
Dyspnea	32 (9.8)	7 (2.2)	0 (0)	39 (12.0)	20 (6.3)	2 (0.6)	0 (0)	22 (6.9)
Skin, subcutaneous								
Erythema	19 (5.8)	0 (0)	0 (0)	19 (5.9)	5 (1.6)	0 (0)	0 (0)	5 (1.6)
Pruritus	90 (27.7)	3 (0.9)	0 (0)	93 (28.6)	16 (5.0)	0 (0)	0 (0)	16 (5.0)
Rash	80 (24.6)	4 (1.2)	0 (0)	84 (25.8)	12 (3.7)	1 (0.3)	0 (0)	13 (4.1)

Abbreviations: CTC=common toxicity criteria, G=grade, MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects treated, n=number of subjects meeting criteria, SOC=system organ class.
Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

Table 3. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Treatment and/or Study, As-Treated Population

Page 1 of 2 MedRA Preferred Term	Maximum CTC Grade	AE Start-Stop Cycle Days	Drug Related?	SAE?
Arm A				
Hypopituitarism	4	C3D51-C3D71	Yes	Yes
Colitis	1	C2D91-C2D94	Yes	No
Asthenia	3	C3D84-FUD362	Yes	Yes
Fatigue	4	C3D84-FUD362	Yes	Yes
Lethargy	4	C3D84-FUD362	Yes	Yes
Confusional state	2	C3D84-FUD362	Yes	Yes
Arthritis bacterial	4	C2D11-C2D27	No	Yes
Lung infiltration	3	C1D34-C1D63	Yes	Yes
Pulmonary edema	3	C1D34-C1D63	Yes	Yes
Respiratory failure	4	C1D34-C1D63	Yes	Yes
Adrenal insufficiency	3	C2D86-Ongoing	Yes	Yes
Hepatitis acute	3	C2D16-C2D20	Yes	Yes
Metabolic acidosis	4	C1D55-C1D58	Yes	Yes
Myalgia	3	C1D31-C1D57	Yes	No
Suicide attempt	4	C1D63-C1D69	No	Yes
Abdominal pain	3	C2D64-C2D93	Yes	No
Colitis	3	C2D64-FUD72	Yes	Yes
Diarrhea	3	C2D65-C2D91	Yes	No
Diarrhea	1	C2D92-C2D106	Yes	No
Fatigue	1	C2D97-C2D97	No	No
Diarrhea	3	C1D56-C1D61	Yes	Yes
Colitis	3	C1D18-FUD9	Yes	Yes
Diarrhea	3	C1D47-FUD19	Yes	Yes
Colitis	3	C1D37-FUD34	Yes	Yes
Large intestinal perforation	4	C1D21-C1D24	Yes	Yes
Diarrhea	2	C3D90-FUD1	Yes	No
Intestinal obstruction	3	C1D21-C1D33	Yes	Yes
Asthenia	3	C1D78-C1D93	Yes	Yes
Muscle weakness	3	C1D82-C1D93	Yes	Yes
Diarrhea	2	C4D19-C4D25	Yes	No
Nausea	2	C4D19-C4D23	Yes	No
Septic shock	4	C4D22-C4D27	Yes	No
Diarrhea	3	C1D30-FUD6	Yes	Yes
Hypophysitis	2	C2D36-C2D168	Yes	No
Colitis	3	C2D10-C2D58	Yes	Yes
Diarrhea	3	C1D4-C1D15	Yes	Yes
Alanine aminotransferase increased	3	C2D32-C2D91	Yes	No
Aspartate aminotransferase increased	3	C2D32-C2D62	Yes	No
Blood alkaline phosphatase increased	3	C2D32-C2D91	Yes	No
Gamma-glutamyltransferase increased	3	C2D63-FUD71	Yes	No
Colitis	2	C1D52-FUD95	Yes	No
Diarrhea	3	C1D37-C1D44	Yes	Yes
Tubulointerstitial nephritis	3	C1D15-FUD44	Yes	Yes
Colitis	3	C1D23-C1D53	Yes	Yes
Colitis	3	C1D24-C1D41	No	Yes

Table 3. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Treatment and/or Study, As-Treated Population

MedRA Preferred Term	Maximum CTC Grade	AE Start-Stop Cycle Days	Drug Related?	SAE?
Arm B				
Vomiting	1	C10D1-C10D1	Yes	No
Thrombocytopenia	4	C1D26-C1D27	Yes	Yes
Thrombocytopenia	2	C1D30-C1D34	Yes	Yes
Musculoskeletal chest pain	3	C1D38-C1D45	No	Yes
Thrombocytopenia	1	C10D43-C10D43	Yes	No
Rash	3	C1D5-C1D29	Yes	No
Asthenia	1	C2D20-FUD221	Yes	No
Headache	1	C2D20-FUD291	Yes	No
Intestinal obstruction	3	C1D30-C1D63	No	Yes
Hypersensitivity	2	C3D2-C3D15	Yes	No
Aphagia	4	C2D15-C2D15	No	Yes
Fatigue	2	C4D1-C8D19	Yes	No

Abbreviations: AE=adverse event, C=cycle, CTC=common toxicity criteria, D=day, F=female, FU = follow-up, ID=identification, M=male, MedDRA=Medical Dictionary for Regulatory Activities, SAE=serious adverse event.
Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

Table 4 summarizes the deaths in the study. According to the investigator, there were 8 subjects who died (7 recorded in the clinical study database) from treatment-related AEs: 7 in Arm A (ie, cardiac arrest, pneumonia, septic shock, electrolyte imbalance, pulmonary embolism, perforation of the large intestine, and hemorrhage) and 1 in Arm B (pneumonia).

Table 4. Summary of Deaths, As-Treated Population

	Arm A N=325 n (%)	Arm B N=319 n (%)
Deaths from All Causes	261 (80.3)	269 (84.3)
Within 28 days of last dose of study drug, n (%)	5 (1.5)	7 (2.2)
More than 28 days after last dose of study drug	256 (78.8)	262 (82.1)
Cause of Death		
Disease under study	234 (72.0)	251 (78.7)
Study drug	7 (2.2)[b]	1 (0.3)
Unknown[a]	15 (4.6)	14 (4.4)
Other	19 (5.8)	12 (3.8)
Early Deaths (within 60 days of randomization)	11 (3.4)	15 (4.7)

A subject could have more than 1 reason for cause of death.
Abbreviations: N=number of subjects treated, n=number of subjects meeting criteria.
[a] Unknown cause of death included "Not Reported."
[b] There was a discrepancy in causality of death for 1 subject between the centralized safety database and the clinical study database. Pulmonary embolism was considered to be related to the study treatment in the centralized database (presented in table) and not related to treatment in the clinical study database
Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

Table 5 presents the treatment-emergent SAEs of all causalities that occurred in ≥2% of the subjects in all cycles, by CTC grade.

Table 5. Treatment-Emergent Serious Adverse Events of All Causalities that Occurred in ≥2% of Subjects in All Cycles, by CTC Grade, As-Treated Population

	Arm A N=325				Arm B N=319			
MedDRA SOC / Preferred Term	G1/2 n (%)	G3/4 n (%)	G5 n (%)	All Grades n (%)	G1/2 n (%)	G3/4 n (%)	G5 n (%)	All Grades n (%)
Gastrointestinal								
Colitis	0 (0)	14 (4.3)	0 (0)	14 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	8 (2.5)	30 (9.2)	0 (0)	38 (11.7)	0 (0)	3 (0.9)	0 (0)	3 (0.9)
Nausea	7 (2.1)	6 (1.8)	0 (0)	13 (4.0)	2(0.6)	0 (0)	0 (0)	2 (0.6)
Vomiting	11 (3.4)	8 (2.5)	0 (0)	19 (5.8)	2(0.6)	3 (0.9)	0 (0)	5 (1.6)
General/administrative site								
Pyrexia	8 (2.4)	3 (0.9)	0 (0)	11 (3.4)	4(1.2)	0 (0)	0 (0)	4 (1.3)
Disease progression	0 (0)	0 (0)	13 (4.0)	13 (4.0)	0 (0)	0 (0)	9 (2.8)	9 (2.8)
Metabolism/nutrition								
Dehydration	3 (0.9)	7 (2.2)	0 (0)	10 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: CTC=common toxicity criteria, G=grade, MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects treated, n=number of subjects meeting criteria, SOC=system organ class.
Arm A=Tremelimumab
Arm B=Dacarbazine or temozolomide

Conclusions:

- At a protocol-specified second interim analysis with 340 deaths (03 March 2008) median OS was 11.7 months (95% CI: [10.3, 13.9]) in the tremelimumab arm and 10.7 months (95% CI: [9.3, 11.9]) in the chemotherapy arm (HR=1.04, P=0.73). At that time, the DSMB met and stated that the test statistic crossed the pre-specified futility boundary. At the time of the database lock, the median OS was 12.58 months in Arm A and 10.71 months in Arm B (HR=1.1416, P=0.1272).

- The 2 treatment arms were not significantly different with respect to OR rate and DR rate (P>0.05).

- The probability estimate of PFS at 6 months, as assessed by the sponsor, was 0.205 in Arm A (95% CI: [0.161, 0.249]) and 0.182 in Arm B (95% CI: [0.139, 0.224], P=0.4657).

- Duration of OR was longer in Arm A than that in Arm B (35.76 months vs 13.74 months; P=0.0011).

- HAHA was found in 19 samples from 15 of 322 (4.7%) patients treated with tremelimumab. Twelve of the 19 samples with positive HAHA results were also positive for neutralizing antibody with low titers. Most of the positive samples occurred at baseline and/or were subsequently followed by negative samples.

- Statistically significant worsening in physical functioning, role functioning, and fatigue was observed for individuals in both Arm A and Arm B (Arm B-dacarbazine and Arm B-temozolomide data combined). Compared to Arm B, the degree of worsening over the course of the study in physical functioning, role functioning, and fatigue was greater for Arm A. Moreover, Arm A had a lower percentage of patients on the physical and role functioning scales who improved and a higher percentage of patients who worsened. There was no statistically significant difference in response distribution between Arm A and Arm B for fatigue symptoms.

- Overall, patient-reported hospitalization rates were consistently statistically significantly higher in Arm A at all time points compared to Arm B. Rates of emergency room visits were statistically significantly higher in Arm A than Arm B but only at 3 time points (Weeks 12, 24 and at EOT assessment).

- Toxicity of tremelimumab administered once every 90 days was considered manageable and acceptable in this patient population. The most common treatment-related toxicity was diarrhea, occurring in 44.0% of patients. Treatment-related diarrhea was Grade 3 or higher in 14.2% of patients and met criteria for reporting as an SAE in 11.1% of patients. The overall median duration of cumulative episodes of diarrhea in any cycle was 22.0 days. The overall median onset of the first event of diarrhea relative to Day 1 of the cycle was 23.0 days.

- In Arm A, a total of 78 patients (24%) had at least 1 treatment-emergent rash related to tremelimumab during the study compared to 9 patients (2.8%) in Arm B. Of these patients, 3 (0.9%) in Arm A and 1 (0.3%) in Arm B had Grade 3 or higher rash. The overall median duration of cumulative episodes of rash in any cycle was 29.0 days. The overall median onset of the first event of rash relative to the Day 1 of the cycle was 15.0 days.

- A total of 13 patients in Arm A reported 17 infusion-related TEAEs compared to 39 patients in Arm B who reported 62 infusion-related AEs. In Arm A, the majority of the infusion-related AEs were headaches, pruritus, dizziness, and flushing (2 patients each) and all infusion-related AEs were Grade 1 or 2 in severity.

- Seven patients died in Arm A and 1 patient died in Arm B from treatment-related AEs. The causes of death in Arm A were cardiac arrest, pneumonia, septic shock, electrolyte imbalance, pulmonary embolism, perforation of the large intestine, and hemorrhage. The cause of death in Arm B was pneumonia.

- Forty-three patients (13.2%) in Arm A and 10 patients (3.1%) in Arm B discontinued the study due to 1 or more TEAEs.

- One hundred eighty-nine patients (58.2%) in Arm A and 147 patients (46.1%) in Arm B had at least 1 worsening of at least 1 point in ECOG PS score. There was no statistically significant difference between the 2 arms with respect to time to first worsening of ECOG PS.