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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States.

NATIONAL CLINICAL TRIAL NO: 00254579

PROTOCOL NO.: A3671008

PROTOCOL TITLE: A Phase 2, Open Label, Single Arm Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of CP-675,206 in Patients with Advanced Refractory and/or Relapsed Melanoma

Study Centers: 54 centers (27, United States; 5, Australia; 5, United Kingdom; 4, Germany; 4, Spain; 4, Italy; 3, France; 1, Canada; 1, Argentina).

Study Initiation and Completion Dates: 13 December 2005 – 14 May 2009 (This synopsis is based on an interim data cutoff point).

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To assess the anti-tumor efficacy, as determined by objective response rate, of intravenous tremelimumab administered at a dose of 15 mg/kg every 90 days to patients with relapsed or refractory advanced melanoma.

Secondary Objectives: (1) to assess additional evidence of anti-tumor activity as measured by best on-study response rate, durable response rate, duration of response, progression-free survival, and overall survival; (2) to further characterize the safety profile and tolerability of tremelimumab in this setting; (3) to further characterize the pharmacokinetics (PK) of tremelimumab; (4) to identify any human antihuman antibody (HAHA) response to tremelimumab; (5) to explore whether the cytotoxic T lymphocyte-associated antigen 4 (CTLA4), FcgammaRIIa, and gamma-2a immunoglobulin (IgG2a) genotypes influence the safety, immune response and or efficacy of patients treated with tremelimumab; (6) to explore the relationships between clinical response (efficacy or toxicity) and tumor or blood genomics; and (7) to explore health-related quality-of-life outcomes (HQoL) and satisfaction of treatment.

METHODS

Study Design: This was a Phase 2, multicenter, open-label, nonrandomized, multinational study of tremelimumab administered intravenously at a dose of 15 mg/kg every 90 days in patients with previously treated advanced melanoma. This study included (1) a screening period that was to begin within 2 weeks of the first dose of study drug, (2) a treatment and assessment period of up to 24 months, with visits occurring at least once monthly, (3) an end-of-study (EOS) visit (after study completion or early discontinuation), and (4) a post-study visit at least 30 days after the EOS visit. After patients ended treatment, they were to be followed for survival information every 6 months.

Number of Patients (planned and analyzed): To provide 80% power to reject the null hypothesis (that the objective response rate in patients treated with tremelimumab does not exceed 10%) it was anticipated that a total of 215 patients would be required to be enrolled in the study. Therefore, a total of 315 patients were screened for the study. Of these patients, 251 were assigned to treatment and 246 patients were treated.

Diagnosis and Main Criteria for Inclusion: To enter the study, patients were required to have histologically documented Stage III unresectable melanoma or Stage IV melanoma and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients must have been previously treated for metastatic disease and must have progressed following the last dose of their prior therapy.

Study Treatment: Patients were permitted to receive up to 4 doses (4 cycles) of tremelimumab 15 mg/kg, administered every 90 days, in a 12-month period until they experienced progression of disease or intolerable toxicity. By mutual agreement between the investigator and the sponsor, patients who exhibited clinical benefit after 12 months of tremelimumab therapy and who met specific safety-related criteria could have been eligible to continue to receive additional doses of tremelimumab. Patients with a complete response (CR) were permitted to receive up to 2 additional doses, and patients with a partial response (PR) or stable disease (SD) were permitted to receive up to 4 additional doses, up to a maximum of 24 months after enrollment.

Efficacy Evaluations: Tumor assessments were performed by the investigator within no more than 14 days before initiation of tremelimumab therapy (baseline), and, following the initiation of treatment, approximately at the end of 3 months (Day 90) and every cycle subsequently, with the exception of Cycle 2, when an additional assessment on Day 60 occurred. A tumor assessment was also performed at discontinuation, unless an assessment had been performed within the last 4 weeks prior to discontinuation. The standardized Response Evaluation Criteria in Solid Tumors (RECIST) method of unidimensional tumor assessment was employed to evaluate tumor lesion size and response status. Disease status as determined by the investigator was recorded on the case report form (CRF) at each visit. Each patient's best overall response based on the investigator's disease status assessments at each time point using RECIST criteria was derived programmatically by the sponsor.

An independent endpoint review committee (IERC) was retained to provide disease status assessments for each patient at each time point as well as a best overall response assessment

for each patient. The IERC was responsible for reviewing (1) those images or clinical (non-radiographic) evidence of progression provided by the investigator that had been acquired during the on-study period up to the time when the investigator determined that the patient should be removed from the study due to any reason and (2) the data included in clinical dossiers provided to them by PAREXEL (Sheffield, South Yorkshire, United Kingdom. The IERC consisted of at least 3 radiologists and 1 oncologist. Two radiologists independently read each case, with a third radiologist serving as adjudicator, when necessary. The radiologists assessed all on-study scans in order to provide an overall response for each time point for a patient. Upon completion of the radiology review, the oncologist independently interpreted on-study digital photographs of skin lesions, if available, as well as all relevant clinical data and central radiology results, in order to provide an overall response at each time point. Upon completion of the review, the oncologist provided a best overall response for the case according to RECIST.

The IERC response assessments were used as the primary assessment in the objective response analysis. The investigator's response assessments were used in secondary analyses of objective response.

Pharmacokinetic and HAHA Evaluations: Blood specimens sufficient to provide 2.0 mL of plasma in heparinized tubes for PK analysis were obtained just prior to administration of tremelimumab and 1 hour after the end of infusion of tremelimumab at every treatment cycle. In Cycle 1, blood specimens were also obtained on Days 8, 30, and 60. In addition, blood specimens were collected at the EOS visit, at the first follow-up visit (30 days), and, when possible, at the final post-study assessment (12 month). Human plasma samples were analyzed for the detection of neutralizing anti-tremelimumab antibodies in sodium heparin by electrochemiluminescent (ECL) and for the detection of total anti-tremelimumab in sodium heparin human plasma samples by ECL immunoassay at PPD Development (Richmond, VA) using a validated analytical assay in compliance with Pfizer standard operating procedures.

A blood specimen for the HAHA assay was obtained just before administration of tremelimumab during every treatment cycle. Blood specimens were also collected at the EOS visit and at the Follow-up visit (30 day) for patients with on-going treatment-related adverse events (AEs). When possible, a sample was obtained at the final post-study assessment visit (12 month).

Pharmacogenetic and Pharmacogenomic Evaluations: Pharmacogenetic assessments included the collection of blood samples for analysis of polymorphisms in CLTA4, FcgammaRIIa, and IgG2a genes. Pharmacogenomic assessments included the collection of blood samples for analysis of expression of ribonucleic acid (RNA) as it related to tumor regression and toxicity. Optional anonymized analysis of accessible blood and/or tumor samples was also performed, subject to institutional review board/independent ethics committee (IRB/IEC) approval of favorable opinion.

Outcomes Research Evaluations: Health-related quality of life and patient satisfaction with treatment were assessed through the patient-completed European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), which

consists of 30 questions that measure functional status, symptoms, and global health, and 2 items/questions from the Cancer Treatment Satisfaction Questionnaire.

Safety Evaluations: Safety was assessed through the collection of observed 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 reported immediately to the sponsor. Serious adverse event information reported in this expedited manner was entered into a centralized AE monitoring database, which is distinct from the database that contains all AE information recorded on the CRF. Consequently, occasional differences may exist between the data in the centralized AE monitoring database and the clinical study database.

Statistical Methods: Primary efficacy endpoint and analysis. The primary endpoint was patients' best overall response as assessed by the IERC using standard RECIST criteria. This was used to determine the objective response rate, defined as the proportion of response-evaluable patients with a best overall response of CR or PR. The null hypothesis was that the objective response rate in patients treated with tremelimumab does not exceed 10%; this was tested at 2.5% level of significance (one-sided test) using a binomial distribution. Secondary efficacy endpoints and analyses. No formal, pre-specified secondary hypothesis testing was planned. The p-values for the hypothesis tests for the secondary endpoints were reported without any adjustments and were considered exploratory. Secondary endpoints included best overall response per the investigator's assessment, overall survival, and the following endpoints per both the IERC's and the investigator's assessments: clinical benefit response, defined as a best overall response of objective response, or stable disease for at least 10 weeks; best response on study, defined as best response recorded from the start of treatment until the patient was taken off-study, taking into account patients who experienced progression at the initial tumor assessment but subsequently achieved an objective response or stable disease for at least 10 weeks since the initial progression; best durable response, defined as an objective response that was present at 6 or more months (ie, ≥170 days) after enrollment; duration of objective response, calculated from enrollment and also from the first documentation of response to the date of first evidence of disease progression; progression-free survival, defined as the time from the date of enrollment to the date of first evidence disease progression; the relationship between tumor response and involved disease sites and AEs consistent with autoimmunity; reason for progression. Mixed response was defined post hoc as patients whose best overall response per 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 with PD in non-target lesions or occurrence of a new lesion within the first cycle. The Brookmeyer Crowley method was used to calculate the 95% confidence interval (CI) for the median duration of response, progression-free survival, and overall survival. Pharmacokinetics. Non-compartmental PK analyses were performed on individual plasma-time data from the first dose (Days 1 to 90) using WinNonlin Enterprise, Version 4.1.a (Pharsight Corporation, CA). Nominal collection times were used for these analyses. Peak and trough concentrations from the first to 8th dose were calculated and summarized. Safety. Data were summarized descriptively.

RESULTS

Subject Disposition and Demography: Patient disposition and data sets analyzed are summarized in Table S1.

Table S1. Patient Disposition and Data Sets Analyzed

	Tremelimumab 15 mg/kg Q3M
Screened 315	
Assigned to treatment (N)	**251**
Treated	246
Completed[a]	19
Discontinued	232
Evaluable for response (n)	
Investigator's assessment	241
IERC's assessment	241
Evaluable for PK (n)	**150**
Evaluable for safety (n)	
Adverse events	246
Laboratory data	240

Q3M = every 90 days ("quarterly"); IERC = independent endpoint review committee; PK = pharmacokinetics.

[a]A completer was defined as a patient who received at least 4 doses of tremelimumab and who discontinued for a reason other than progressive disease or intolerable toxicity, lack of compliance, protocol violation, or unwillingness to participate

Overall, patients ranged in age from 18 to 89 years with a mean age of 53.5 years. The majority of the patients were under 65 years of age (76%), white (93%), and male (60%). Demographics were consistent with the epidemiology of metastatic melanoma. All enrolled patients (100%) had a primary diagnosis of malignant melanoma. The mean number of years since melanoma was diagnosed was 5.0, and the range of years since diagnosis was 0.1 to 28.9. Nearly all (96.8%) patients had Stage IV disease.

At baseline, measurable disease was present in 245 (97.6%) patients, based on the investigators' tumor assessments. In most (>85%) patients, multiple target lesions were present at baseline. The median (range) baseline measurement of the longest diameter of patients' target lesions was 4.20 cm (1.00-24.00 cm). Eighty-one percent of patients had more than 1 involved disease site, based on the investigator's assessment. Lung, distant lymph node, liver, other, regional lymph node, soft tissue, subcutaneous, adrenal, bone, and mediastinum were the most common and known involved disease sites (64.5%, 33.9%, 33.9%, 24.3%, 21.9%, 18.7%, 18.3%, 12.4%, 11.2%, and 10.8%, respectively).

All enrolled patients (100%) had previously received 1 or more systemic cancer therapy. Prior cancer surgery and prior radiation therapy were reported for 249 (99.2%) and 83 patients (33.1%), respectively. Per protocol, nearly all (data not collected for 1 patient) patients 250 [99.6%]) had progressed after receiving the most recent prior therapy.

Efficacy Results: The results of the primary analysis showed that the objective response rate, based on the IERC's assessment of patients' best overall response using standard RECIST criteria, was 16/241 (6.6%) (95% CI: [3.84, 10.56]; p=0.9545 for H_0: ORR≤10%). Therefore, the study did not achieve the hurdle required to reject the null hypothesis that the true response rate does not exceed 10%.

Responding patients remained in stable disease per RECIST for up to several months before achieving a first objective response. The median time to first response among the 16 objective responders was 7.01 months, and the time to first response ranged from 2.73 to 12.22 months. The duration of objective response calculated from enrollment ranged from 8.94 to 29.77 months and, from the time a response was first noted, from 3.98 to 21.26 months. The responses were durable (present at least 170 days after enrollment) in all 16 (100%) objective responders, for a durable objective response rate of 16/241 (6.6%) (95% CI: [3.84, 10.56]). Three patients have progressed at the last time of tumor assessment; 1 within the first year and 2 within the second year (Appendix B4.4.7.2).

Eight additional patients were determined to be "mixed responders," based on the sponsor's evaluation of on-study tumor measurements and disease status assessments provided by the IERC. Mixed responders was defined as those patients whose best overall response per RECIST was progressive disease (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. Five of the 8 patients were still alive as of the data cutoff for this report.

Based on data assessed by the IERC, the clinical benefit response rate was 21.2% (51/241 patients), where clinical benefit response was defined as a complete or partial response or remaining in stable disease per RECIST for at least 10 weeks since the initiation of therapy. Using the as-enrolled population and response data as assessed by the IERC, median PFS was 2.79 months (95% CI: [2.73, 2.83]). The estimated probability of PFS at 6 months was 15.0% (95% CI: [10.6%, 19.5%]). All responders except one were still alive at the data cutoff (overall survival ranged from 24.8 to 37.5 months [censored].

Tumor response as assessed by the investigator was generally consistent with that as assessed by the IERC. The objective response rate based on the investigators' assessments was 9.1% (22/241 patients; 95% CI: [5.81, 13.49]; p=0.6247 for H_0: ORR≤10%). Fifteen patients were determined to be objective responders by both the IERC and the investigator. The 7 additional patients considered to be responders by the investigator included 5 patients with stable disease, 1 patient who was indeterminate, and 1 patient with progressive disease according to the IERC. There was 1 patient who was determined to be to be an objective responder by the IERC only.

Involved disease sites in objective responders (per the investigator) included lung (59.1%); distant and regional lymph nodes and liver (31.8%); other (27.3%), subcutaneous (18.2%); soft tissue and bone (13.6%); mediastinum and peritoneum (9.1%); and adrenal, visceral tissue, skin, pelvis, chest wall, breast, intestine and brain (nontarget disease site per the investigator) (4.5%). The distribution of visceral lesion sites in responding patients (per the

investigator) was similar to that in the enrolled population as a whole, suggesting that tremelimumab does not target specific sites.

Median overall survival was 9.99 months (95% CI: [7.92, 11.67]). Survival times ranged from 0.26 to 37.50 months. The estimated probability of overall survival was 40.3% (95% CI: [34.2%, 46.5%]) at 12 months and 21.6% (95% CI: [16.4%, 26.7%]) at 24 months.

Pharmacokinetic and HAHA Results: The systemic clearance rate (CL) of tremelimumab was low with a mean value of 0.152 mL/h/kg. The volume of distribution at steady state (V_{ss}) was small with a mean value of 85 mL/kg and the terminal disposition phase half-life ($T_{1/2}$) was long with a mean value of 19.2 days. These PK parameters are consistent with those of endogenous IgG2 and similar to PK parameters from previous studies of tremelimumab.

There was no evidence that either peak or trough concentrations changed significantly after multiple doses of tremelimumab at 15 mg/kg quarterly suggesting that tremelimumab did not accumulate significantly after multiple doses.

Very few patients had measurable HAHA. HAHA was found in 9 samples from 8 of 231 patients (3.5%). Seven of the 9 samples with positive HAHA results were also positive for neutralizing antibody with low titers. These scattered HAHA-positive samples with low titers did not appear to decrease drug levels of tremelimumab.

Health-Related Quality of Life: There were high completion rates during the study and lower rates at the EOS. However, there was considerable drop-off at each time point, eg, 212 patients completed forms for C1D1; 103 patients for C2D1; 61 patients for C3D1, and 40 patients for C4D1.

Safety Results:

An overview of the treatment-related safety results is provided in Table S2.

Table S2. Overview of Treatment-Related Safety Results, As-Treated Patients

Page 1 of 2	Tremelimumab 15 mg/kg Q3M N=246	
Drug-related TEAEs	**All CTC grades**	**CTC Grade ≥3[a]**
Patients with ≥1 event, n (%)	193 (78.5)	56 (22.8)
Most common (≥10% incidence all grades or ≥2% Grade ≥3) (all cycles)		
Diarrhea	101 (41.1)	28 (11.4)
Pruritus	58 (23.6)	0 (0)
Rash	56 (22.8)	3 (1.2)
Nausea	56 (22.8)	3 (1.2)
Fatigue	45 (18.3)	6 (2.4)
Vomiting	36 (14.6)	3 (1.2)
Anorexia	28 (11.4)	2 (0.8)
Colitis	10 (4.1)	7 (2.8)
Drug-related TEAEs leading to permanent DC from treatment and/or study	**All CTC grades**	**CTC Grade ≥3**
Patients with ≥1 event, n (%)	13 (5.3)	10 (4.1)
Most common (≥2% patients all grades or ≥1 patient Grade ≥3)		
Diarrhea	8 (3.3)	5 (2.0)
Colitis	2 (0.8)	2 (0.8)
Enterocolitis	1 (0.4)	1 (0.4)
Intestinal obstruction	1 (0.4)	1 (0.4)
Optic ischemic neuropathy	1 (0.4)	1 (0.4)
Tremelimumab-infusion–related TEAEs	**All CTC grades**	**CTC Grade ≥3**
Patients with ≥1 event, n (%)	12 (4.9)	1 (0.4)
Most common (>1 patient all grades or >1 patient Grade ≥3)		
Nausea	2 (0.8)	0 (0)
Tremelimumab-infusion–related TEAEs leading to interruption in infusion	**All CTC grades**	**CTC Grade ≥3**
Patients with event, n (%)	2 (0.8)	1 (0.4)
Chest pain	1 (0.4)	1 (0.4)
Dyspnea	1 (0.4)	1 (0.4)
Injection site extravasation	1 (0.4)	0 (0)
Deaths (fatal SAEs) due to drug-related causes[b]		
Patients who died due to drug-related causes, n (%)	2 (0.8)	
Diverticular perforation, diverticulitis	1 (0.4)	
Sudden death	1 (0.4)	

AE=adverse event; CTC=Common Terminology Criteria; DC=premature discontinuation; Grade ≥3=CTC severity grade of 3 or higher; N=number of patients treated; n=number of patients meeting criteria; Q3M=every 90 days (quarterly); TEAE=treatment-emergent adverse event; SAE=serious adverse event.
[a]Includes 2 patients with drug-related, Grade 5 TEAEs
[b]Death information is based on data entered into the sponsor's centralized AE monitoring database. The data were reconciled with death information included in the clinical study database.
Note: AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Table S2. Overview of Treatment-Related Safety Results, As-Treated Patients

Page 2 of 2	Tremelimumab 15 mg/kg Q3M N=246
Non-fatal drug-related SAEs[a]	
Patients with ≥1 event, n (%)	48 (19.5)
Most common (≥2% patients, all cycles)	
Diarrhea	18 (7.3)
Colitis/proctocolitis/enterocolitis	12 (4.9)
Vomiting	6 (2.4)
Nausea	6 (2.4)
Drug-related SAEs leading to permanent discontinuation	
Patients with ≥1 event, n (%)	9 (3.7)
Most common (>1% of patients)	
Diarrhea	5 (2.0)
Colitis/enterocolitis	3 (1.2)
Lab parameters that worsened to Grade ≥3 during treatment	
Most common (≥5% incidence), n / N* (%)	
Lipase	14/174 (8.0)
Gamma-glutamyltransferase	15/216 (6.9)

AE=adverse event; CTC=Common Terminology Criteria; Grade ≥3=CTC severity grade of 3 or higher; N=number of patients treated; N*=number of patients with result for particular laboratory test; n=number of patients meeting criteria; Q3M=every 90 days (quarterly); SAE=serious adverse event.
[a]Death information is based on data entered into the sponsor's centralized AE monitoring database. The data were reconciled with death information included in the clinical study database.
Note: AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Conclusions:

- The primary efficacy results, based on patients' BOR as determined by an IERC using RECIST criteria, showed that in this population of patients with relapsed or refractory advanced melanoma who had progressed following the most recent prior cancer therapy, single-agent tremelimumab induced objective responses in 16 of 241 (6.6%) response-evaluable patients (95% CI: [3.84, 10.56]). According to pre-specified criteria, these results indicate that the study failed to reject the null hypothesis that the true response rate exceeded 10%. The objective response rate based on the investigator's BOR assessment was 9.1% (22/241 patients; 95% CI: [5.81, 13.49]).

- Additional evidence of anti-tumor efficacy (per the IERC unless stated otherwise) was provided by the following results:

    - Responses were durable (present at ≥6 months [ie, ≥ 170 days] from enrollment) in all 16 responders (100%), for a durable response rate of 6.6% (95% CI: 3.84, 10.56).

    - Among the 16 objective responders, the time to first response ranged from 2.73 to 12.22 months (median = 7.01 months), and the duration of response when calculated from enrollment ranged from 8.94 to 29.77 months (median = 21.88 months). Three patients have progressed at the last time of tumor assessment; 1 within the first year and 2 within the 2nd year.

- The distribution of visceral lesion sites in responding patients (per the investigator) was similar to the distribution of involved disease sites in the as-enrolled population, suggesting that tremelimumab does not target specific sites.

- Eight patients were determined to be mixed responders, defined as those patients whose BOR per 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 according to the IERC. All 8 patients survived at least 21 months; 5 of the 8 patients were still alive as of the data cutoff for this report.

- Median PFS was 2.79 months (95% CI: [2.73, 2.83]), and PFS times ranged from 0.03 to 29.77 months. The estimated probability of PFS at 6 months was 15.0% (95% CI: [10.6%, 19.5%]).

- Median overall survival was 9.99 months (95% CI: [7.92, 11.67]), and survival times ranged 0.26 to 37.50 months. The estimated probability of overall survival was 40.3% (95% CI: [34.2%, 46.5%]) at 12 months and 21.6% (95% CI: [16.4%, 26.7%]) at 24 months.

- Toxicity of tremelimumab administered once every 90 days was considered manageable and acceptable in this patient population. Two deaths were considered related to tremelimumab; the causes of death were diverticulitis and diverticular perforation in 1 patient and sudden death in a second patient. The most common treatment-related toxicity was diarrhea, occurring in 41.1% of patients. Treatment-related diarrhea was Grade 3 or higher in 11.4% of patients and met criteria for reporting as an SAE in 7.3% of patients.

- The clearance of tremelimumab was low with a mean value of 0.152 mL/h/kg. The V_{ss} was small with a mean value of 85 mL/kg and $T_{1/2}$ was long with a mean value of 19.2 days. These PK parameters are consistent with those of endogenous IgG2 and similar to PK parameters from previous studies of tremelimumab.

- There was no evidence that either peak or trough concentrations changed significantly after multiple doses of tremelimumab at 15 mg/kg quarterly suggesting that tremelimumab did not accumulate significantly after multiple doses.

- Very few patients had measurable HAHA. HAHA was found in 9 samples from 8 of 231 patients (3.5%). Seven of the 9 samples with positive HAHA results were also positive for neutralizing antibody with low titers. These scattered HAHA-positive samples with low titers did not appear to decrease drug levels of tremelimumab.

- PRO analyses showed the following results. There were high completion rates during the study and lower rates at the EOS. However, there was considerable drop-off at each time point, eg, 212 patients completed forms for Cycle 1, Day 1; 103 patients for Cycle 2, Day 1; 61 patients for Cycle 3, Day 1, and 40 patients for Cycle 4, Day 1.

- During the study, pretreatment HQoL and symptom scores remained relatively unchanged.

- Increased treatment-related fatigue, appetite loss, and symptoms of diarrhea largely occurred in patients that progressed during Days 30 and 60 of Cycle 1 and occasionally during Cycle 2. These symptom increases were observed in the mean change from baseline, mean change from baseline by tumor response, and scale item analyses.