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PROPRIETARY DRUG NAME/INN: CP-675,206

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT #: NCT00313794

PROTOCOL NO.: PROTOCOL A3671014

PROTOCOL TITLE: Phase 2, Single Arm Study of CP-675,206 in Patients With Refractory Metastatic Adenocarcinoma of the Colon or Rectum

Study Center(s): Five centers; 3 centers in the United States and 2 centers in Canada

Study Initiation and Completion Dates: 08 May 2006 to 28 June 2008

Phase of Development: Phase 2

Study Objectives:

Primary Objective

- To assess the best response rate (BRR) per response evaluation criteria in solid tumors (RECIST) in patients with metastatic adenocarcinoma of the colon or rectum treated with CP-675,206.

Secondary Objectives

- To assess additional evidence of anti-tumor activity as measured by duration of response, progression free survival (PFS) and overall survival (OS).
- To evaluate the safety and tolerability of CP-675,206 in this population.
- To obtain pharmacokinetic data to be evaluated in a future meta-analysis of CP-675,206 pharmacokinetics.
- To identify any human anti-human antibody (HAHA) response to CP-675,206.
- To identify potential relationships between polymorphisms in the cytotoxic T lymphocyte-associated antigen 4 (CTLA4), Fcgamma receptor IIa (FcgRIIa), IgG2a genes with safety and/or immune response of patients treated with CP-675,206.

METHODS

Study Design: This was an open-label, single arm, multicenter, Phase 2 study evaluating the efficacy and safety of CP-675,206 in subjects with metastatic adenocarcinoma arising from the colon or rectum and who had received treatment for metastatic disease with subsequent disease progression or were intolerant to treatment.

Pre-study assessments were performed within 14 to 28 days prior to receiving CP-675,206. All subjects received CP-675,206 via intravenous injection at a dose of 15 mg/kg on Day 1 of every 90-day cycle. Subjects were allowed to receive up to 4 doses over an approximate 12-month period. Subjects exhibiting clinical benefit (complete response [CR], partial response [PR], stable disease [SD]) after 12 months were eligible to continue therapy with CP-675,206 for up to 4 additional doses or up to a maximum of 24 months after enrollment. The end of treatment (EOT) visit occurred at the end of Month 3 (Days 84-96) of the final dosing cycle. A follow-up visit, approximately 1 month (30 days) after the end of study evaluation, was required for subjects experiencing any on-going study drug-related adverse event (AE). Subjects were contacted at least every 3 months for up to 2 years after the date of randomization to collect information regarding first evidence of disease progression, start of new therapy, date and cause of death. If there was evidence of continuing study drug-related toxicity, the subject was followed at intervals deemed medically appropriate by the treating investigator.

Number of Subjects (planned and analyzed): It was anticipated that 40 subjects were required to be enrolled in the study to account for up to a 10% rate of non-evaluability for response. A total of 45 subjects were analyzed for efficacy (ie, tumor response). Forty-seven subjects were analyzed for AEs and 46 were analyzed for laboratory data.

Diagnosis and Main Criteria for Inclusion: Subjects were males or females aged ≥18 years with histologically or cytologically confirmed adenocarcinoma arising in the colon or rectum. To enter the study, subjects were to have radiographic evidence of metastatic, progressive disease following standard therapies, evidence of measurable disease as per RECIST, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and adequate bone marrow, hepatic and renal function determined within 14 days prior to initial dose of CP-675,206.

Study Treatment: Intravenous CP-675,206 was administered open-label at a dose of 15 mg/kg repeated every 90 days up to a maximum of 4 doses. In most cases the duration of the infusion was between 2 and 5 hours. Subjects exhibiting clinical benefit after 12 months were eligible to continue therapy with CP-675,206 for up to 4 additional doses or up to a maximum of 24 months after enrollment. No dose modifications were allowed except for those based on fluctuations in body weight over time. Dose delay of up to 12 weeks was permitted to allow recovery from treatment-related toxicities. To be treated with subsequent doses of CP-675,206, all subjects had to meet the pre-specified re-dosing criteria for laboratory parameters and treatment-related AEs by the day of dosing. The sponsor supplied CP-675,206 as a 5 mg/mL sterile solution in 10 mL vials, therefore containing 50 mg per vial. CP-675,206 was diluted with sterile normal saline (supplied by the investigator) prior to administration.

Efficacy Evaluations: Radiological and clinical evaluations were performed within 28 days prior to starting CP-675,206. On-study tumor assessments during Cycle 1 were performed within 10 days prior to Day 90 (or the second dose of CP-675,206) and approximately every 6 weeks thereafter (mid cycle and within 10 days prior to every dose). End of treatment assessments were required only if the last assessment was performed >28 days prior to EOT. Tumor responses were confirmed with repeat assessments no less than 4 weeks after the initial observation of response. Subjects were followed for disease progression and survival for 2 years from the date of enrollment.

All lesions were classified as measurable or non-measurable lesions. Target lesions were selected on the basis of their size and their suitability for accurate repetitive measurements. All other lesions (or sites of disease) were identified as non-target lesions. Accepted methods of tumor assessment included clinical examination, chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Imaging-based evaluation was preferred. RECIST was utilized for the assessment and reporting of tumor response data.

Pharmacokinetic and Other Evaluations: *Pharmacokinetic Evaluation:* Blood specimens, to provide 2 mL of plasma, were obtained prior to CP-675,206 administration and 1 hour after the end of CP-675,206 infusion in every treatment cycle. Blood specimens were also obtained on Days 30 and 60 (Cycle 1), at the end of study and, if possible, at the first follow-up visit.

Other Evaluations: A blood sample for carcinoembryonic antigen (CEA) was required at intervals to coincide with all tumor assessments (imaging/clinical). Blood samples for HAHA, to provide 2.0 mL of plasma, were obtained prior to CP-675,206 treatment, at the end of study, and, if possible, at the first follow-up visit.

Pharmacogenomic Evaluations: A blood sample (6 mL whole blood in ethylene diamine tetra acetate tube) for genotyping to evaluate polymorphisms in CTLA4, FcgRIIa and IgG2a was obtained from all enrolled subjects prior to CP-675,206 dosing (Cycle 1 Day 1). Under a separate informed consent, subjects could also donate a single optional blood specimen (9 mL) prior to CP-675,206 dosing (Cycle 1 Day 1) for pharmacogenomics.

Safety Evaluations: Adverse events were monitored throughout the study. Hematology, blood chemistry and thyroid function tests were performed ≤14 days of Cycle 1 Day 1, on Days 15, 30 and 60 (Cycles 1 and 2) and between Days 84 to 96 of last cycle (EOT). In order to meet requirements for re-dosing on subsequent cycles, laboratory tests were also performed within 10 days prior to Day 1 of the next cycle. These tests were only required on Days 30 and 60 after Cycle 2. Urinalysis was performed ≤14 days of Cycle 1, Day 1 and subsequently, within 10 days prior to every cycle (next dose). Physical examination findings and vital signs (temperature, sitting blood pressure, and heart rate) were recorded ≤14 days of Cycle 1 Day 1, on Days 15, 30 and 60 (Cycles 1, 2 and subsequent cycles), on Day 1 (Cycle 2 and subsequent cycles) and between Days 84 to 96 of last cycle (EOT). Vital signs were measured prior to treatment and monitored, as needed during drug infusion and for approximately 1-hour post-infusion. Subjects experiencing symptoms of uveitis were evaluated by an ophthalmologist ≤14 days of Cycle 1 Day 1 and between Days 84 to 96 of last cycle (EOT). A 12-lead resting electrocardiogram (ECG) was required prior to enrollment and at EOT. Additional ECGs were obtained if clinically indicated.

Statistical Methods: To achieve the study objectives, at least 40 subjects were required to be enrolled in the study to account for up to a 10% rate of non-evaluability for response. The 3 main study populations were as-enrolled, per-protocol and as-treated populations.

Primary Analysis: Best overall response rate per RECIST, defined as the proportion of subjects with a confirmed CR or PR relative to the total number of evaluable subjects, was the primary endpoint. The primary efficacy analysis was based on the per-protocol population. The null hypothesis that the objective response rate in subjects treated with CP-675,206 does not exceed 3% (H_0: BRR ≤3%) was tested with 1-sided binomial test at 5% level of significance. The study was 80% powered for the alternative hypothesis H_1: BRR ≥15%. Two-sided 90% confidence intervals (CIs) for proportions of subjects with CR and ORs were provided. The primary analysis was conducted when all enrolled subjects were either taken off study or completed at least 12 months of treatment.

Secondary Analysis: Duration of the 1 objective response and 95% CI were evaluated. Progression free survival was characterized in terms of the median, and the probability of remaining-progression free at 6 months (based on Kaplan-Meier estimates); range and 95% CI on the estimates (using Brookmeyer Crowley methodology for the median and Greenwood formula for the progression free survival rate at 6 months) were also computed. Overall survival was characterized in terms of the medians, and the probability of being alive at 12 months (based on Kaplan-Meier estimates); range and 95% CI (using Brookmeyer Crowley methodology for the median and Greenwood formula for the survival rate at 12 months) on the estimates were also computed. Kaplan-Meier plots for PFS and OS were also provided.

Pharmacokinetic Analysis: CP-675,206 concentration-time data from this study was to be analyzed at some future date in combination with pharmacokinetic data from other clinical studies using a population pharmacokinetic approach.

Analysis of Other Parameters: Descriptive statistics were used to summarize all subject characteristics and treatment administration/compliance.

Pharmacogenomic Analysis: Statistical analyses were performed to investigate the association between response and polymorphisms of CTLA4, FcgRIIa and IgG2a, and the association between AEs and polymorphisms of these genes.

Safety Analysis: Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 whenever possible. Adverse events were summarized by cycle and relatedness to study treatment.

Hematological and chemistry laboratory data were summarized by treatment and by cycle. The laboratory results were graded according to the NCI CTCAE severity grade. Descriptive statistics were generated for vital signs. Physical examination findings were summarized as past or present. The number of subjects with normal or abnormal 12-lead ECG findings was summarized.

RESULTS

Subject Disposition and Demography: A total of 50 subjects were screened to determine their eligibility for study entry. Of the 50 screened subjects, 49 subjects met the study entry criteria and were enrolled and assigned to CP-675,206 15 mg/kg (as-enrolled population). A total of 47 subjects received at least 1 dose of CP-675,206 15 mg/kg (as-treated population). Two subjects did not receive CP-675,206; 1 subject had increased bilirubin while another subject had a 'rough week' prior to the start of treatment. Forty-seven subjects were analyzed for AEs and 46 were analyzed for laboratory data. All 49 subjects discontinued from the study. One subject received 5 cycles of treatment and completed the protocol defined treatment period of 4 cycles; this subject received an additional cycle permitted for subjects receiving benefit. The most common reason for discontinuation was progressive disease (39 [79.6%] subjects), followed by AEs (5 [10.2%] subjects). A total of 45 subjects were evaluable for tumor response (per-protocol population).

Males comprised 59.2% of the as-enrolled population. The mean age was 60.2 years, and subjects ranged in age from 39 to 79 years. Approximately 41% subjects were 65 years or older. Most subjects (79.6%) were white. The mean number of years since colorectal cancer was diagnosed was 3.6, and the range in years since diagnosis was 0.0 to 12.6. All (100%) subjects had Stage IV disease at baseline. Per protocol, all subjects were required to have an ECOG performance status score of 0 or 1 (61.2% and 38.8% of subjects, respectively) at the time of enrollment. At baseline, measurable disease was present in 47 (95.9%) subjects based on the investigator's assessment (the 2 enrolled subjects with missing measurable disease who were not treated were counted under 'not reported'). In most (>75%) subjects, multiple target lesions were present at baseline. The median baseline sum of the longest diameters of subjects' target lesions was 4.40 cm, and the range of baseline sums was 1.00-18.00 cm. Approximately 55% of subjects had more than 1 involved disease site, based on the investigator's assessment. Liver and lung were the 2 most common and known involved disease sites (71.4% and 53.1%, respectively) according to the investigator.

Efficacy Results: The results of the primary analysis showed that only 1 out of 45 response-evaluable subjects achieved a confirmed objective response per RECIST. Therefore, the objective response rate was 2.2% (90% CI: [0.11%, 10.11%]). Therefore, the study did not meet the hurdle required to reject the null hypothesis that the true response rate does not exceed 3%.

In the treating investigators' assessment of best overall response, no subject was a complete responder or had a stable disease, 1 (2.2%) subject was a partial responder, 43 (95.6%) subjects were determined to have progressed and 1 (2.2%) subject was indeterminate due to early discontinuation.

The clinical benefit response rate was 1/45 (2.2%) based on the treating investigator's assessment. Table S1 summarizes the tumor response per the investigator.

Table S1. Tumor Response per the Investigator, Response-Evaluable Subjects

	CP-675,206 15 mg/kg	
Response	**n (%)**	**90% CI[a]**
Best overall response per RECIST		
Evaluable subjects	45	
Complete response	0	
Partial response	1 (2.2)	
Stable disease [b]	0	
Progressive disease [c]	43 (95.6)	
Indeterminate [d]	1 (2.2)	
Objective response (complete + partial response)	1 (2.2)	(0.11, 10.11)
Clinical benefit response [e]	1 (2.2)	

[a] Exact 90% confidence interval.
[b] To have a best overall response of stable disease, a subject must have been stable for ≥70 days after the start of therapy.
[c] Progressive disease included early death and progression.
[d] Indeterminate included early discontinuations.
[e] To have CBR, a subject must have had an OR, or been stable for ≥70 days after start of therapy.
CI = confidence interval; n = number of subjects meeting criteria; OR = objective response; CR = complete response; CBR = clinical benefit response; PD = progressive disease.

Among the 49 enrolled subjects, 44 (89.8%) subjects developed progressive disease. The most frequent reasons for progression included a greater than or equal to 20% increase in the size of target/evaluable lesions (29 [59.2%] subjects) and progression of non-target lesions (24 [49.0%] subjects).

The median progression-free survival time was 2.33 months (95% CI: [2.07, 2.60]), and the probability estimate of progression-free survival at 6 months was 2.1% (95% CI: [0.0%, 6.3%]). Two (4.1%) subjects were censored for progression-free survival as they were lost to follow-up; one subject moved out of the United States and the other was in a hospice.

All 49 enrolled subjects were included for survival analysis: 46 (93.9%) of those subjects died and 3 (6.1%) were censored for survival. The median overall survival time was 4.83 months (95% CI: [4.14, 7.72]), and survival times ranged from 0.72 to 23.72 months. The probability estimate of overall survival at 12 months was 10.7% (95% CI: [1.8%, 19.5%]).

Among all subjects who received at least 1 dose of CP-675,206, 44 (93.6%) subjects were reported to have died due to any cause. Disease under study was the most common cause of death (43 [91.5%] subjects). None of the subjects died due to causes considered related to CP-675,206 by the investigator. Information collected on follow-up disease status and survival indicated that 1 (2.1%) subject was alive, 44 (93.6%) subjects were dead, and 2 (4.3%) subjects were lost to follow-up. Subjects were followed up at various timepoints after discontinuing from the study.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: There were no pharmacokinetic, pharmacodynamic or other analyses done in this study and is pending pooled analysis at a program level. CEA tumor marker assessments were performed in this study at baseline and to coincide with all tumor assessments.

Safety Results: Forty-seven (100.0%) subjects who received at least 1 dose of CP-675,206 experienced a total of 360 TEAEs (all causalities). A total of 28 subjects experienced TEAEs that were CTC Grade 3 or 4 in severity, and 1 subject had disease progression that was considered Grade 5 in severity.

A total of 88 AEs were considered to be treatment-related. Nine subjects experienced treatment-related TEAEs that were CTC Grade 3 or 4 in severity, and no subject experienced treatment-related Grade 5 TEAEs. The most commonly reported treatment-related TEAEs were diarrhea (36.2%), fatigue (14.9%), nausea and pyrexia (12.8%) and vomiting (10.6%). Diarrhea was the most commonly reported Grade 3 or higher treatment-related TEAE, occurring in 5 (10.6%) subjects.

Among the less commonly reported treatment-related TEAEs were the events that occurred with a CTC severity grade of 4: autoimmune thrombocytopenia in 1 subject and with a CTC severity grade of 3: ulcerative colitis (1 subject), hypokalemia (1 subject) and hepatorenal syndrome (1 subject). Hepatorenal syndrome in 1 subject was due to disease under study and was not due to the study drug. The site did not provide the causality for this event (missing) and the event was mistakenly imputed to treatment-related as per sponsor's safety standards.

The treatment-related TEAEs that occurred during Cycle 1 with a CTC severity grade of 3 or higher were diarrhea (occurring in 5 [10.6%] subjects), autoimmune thrombocytopenia, ulcerative colitis, fatigue, hepatorenal syndrome and hypokalemia (each occurring in 1 [2.1%] subject). Hepatorenal syndrome in 1 subject was due to disease under study and was not due to the study drug. The site did not provide the causality for this event (missing) and the event was mistakenly imputed to treatment-related as per sponsor's safety standards. One [100.0%] subject with colitis was the only one with treatment-related TEAE occurring with a CTC severity grade of 3 or higher after Cycle 1 (> Cycle 1) and this was the only subject who received >1 treatment cycle.

There were 6 permanent discontinuations due to TEAEs (all causalities) in the study. Treatment-related TEAEs that led subjects to discontinue treatment prematurely were autoimmune thrombocytopenia (n=1) and ulcerative colitis (n=1).

Based on the clinical study database of treated subjects, 44 deaths (93.6%) were reported; 1 (2.1%) was within 30 days of last study drug dose while 43 (91.5%) were more that 30 days after the last study drug dose. The majority of deaths (43 [91.5%]) had the cause recorded as 'disease under study' while 1 death (2.1%) had the cause recorded as 'not reported'.

A total of 16 subjects were reported to have SAEs during the study; 8 of which were considered related to CP-675,206. Among the 16 subjects with SAEs, the most common treatment-emergent SAE was diarrhea (5 [10.6%] subjects), followed by pyrexia (4 [8.5%] subjects), colitis (3 [6.4%] subjects), vomiting (2 [4.3%] subjects), dehydration (2 [4.3%] subjects), confusional state (2 [4.3%] subjects) and dyspnea (2 [4.3%] subjects). The treatment-related treatment-emergent SAEs that occurred during Cycle 1 with a CTC severity grade of 3 or higher were diarrhea (occurring in 5 [10.6%]); autoimmune thrombocytopenia, ulcerative colitis and hepatorenal syndrome (each occurring in 1 [2.1%] subject). Hepatorenal syndrome in 1 subject was due to disease under study and was not due to the study drug. The site did not provide the causality for this event (missing) and the event was mistakenly imputed to treatment-related as per sponsor's safety standards. One [100.0%] subject with colitis was the only treatment-related treatment-emergent SAE occurring with a CTC severity grade of 3 or higher after Cycle 1 (> Cycle 1).

Greater than one-third of subjects with normal baseline lymphocyte values experienced on-study elevations in lymphocytes, and one-fifth of subjects with normal eosinophils experienced on-study elevations in eosinophils.

Of the 47 subjects with an ECOG performance status score of 0 or 1 prior to entering the study, 26 (55.3%) subjects had a worst on-study score that was 0 or 1. Twenty-one (44.7%) subjects had a worst on-study score that worsened to a score of 2 or higher. None of the subjects had a worst on-study score that was not evaluable. At the last visit that occurred, most treated subjects (61.7%) had an ECOG performance status score of 0 or 1, and 18 (38.3%) subjects had a score of 2 or higher.

CONCLUSIONS: The results of the primary analysis showed that there was 1 subject who achieved a PR per RECIST out of 45 response-evaluable subjects and the objective response rate was 2.2% (95% CI: [0.11%, 10.11%]). Therefore, the study did not meet the hurdle required to reject the null hypothesis that the true response rate does not exceed 3%.

In the treating investigators' assessment of best overall response, no subject was a complete responder or had a stable disease, 1 (2.2%) subject was a partial responder, 43 (95.6%) subjects were determined to have progressed and 1 (2.2%) subject was indeterminate due to early discontinuation. One subject was determined to be an objective responder by the investigator.

The clinical benefit response rate was 1/45 (2.2%) based on the treating investigator's assessment.

Forty-seven (100.0%) subjects who received at least 1 dose of CP-675,206 experienced a total of 360 TEAEs (all causalities). A total of 28 subjects experienced TEAEs that were

CTC Grade 3 or 4 in severity, and 1 subject experienced Grade 5 TEAEs attributed to the progression of disease under study.

A total of 88 AEs were considered to be treatment-related. Nine subjects experienced treatment-related TEAEs that were CTC Grade 3 or 4 in severity, and no subject experienced treatment-related Grade 5 TEAEs. The most commonly reported treatment-related TEAEs were diarrhea (36.2%), fatigue (14.9%), nausea and pyrexia (12.8%) and vomiting (10.6%). Diarrhea was the most commonly reported Grade 3 or higher treatment-related TEAE, occurring in 5 (10.6%) subjects.

There were 6 permanent discontinuations due to TEAEs in the study. Treatment-related TEAEs that led subjects to discontinue treatment prematurely were autoimmune thrombocytopenia (n=1) and ulcerative colitis (n=1).

Based on the clinical study database of treated subjects, 44 deaths (93.6%) were reported; 1 (2.1%) was within 30 days of last study drug dose while 43 (91.5%) were more that 30 days after the last study drug dose. The majority of deaths (43 [91.5%]) had the cause recorded as 'disease under study' while 1 death (2.1%) had the cause recorded as 'not reported'.

A total of 16 subjects were reported to have SAEs during the study; 8 of which were considered related to CP-675,206. Among the 8 subjects with treatment-related treatment-emergent SAEs, the most common was diarrhea (5 [10.6%] subjects), followed by colitis (3 [6.4%] subjects), vomiting, abdominal pain, ulcerative colitis, pyrexia, autoimmune thrombocytopenia, hepatorenal syndrome, dehydration and hypotension (1 [2.1%] subject each). Hepatorenal syndrome in 1 subject was due to disease under study and was not due to the study drug. The site did not provide the causality for this event (missing) and the event was mistakenly imputed to treatment-related as per sponsor's safety standards. Greater than one-third of subjects with normal baseline lymphocyte values experienced on-study elevations in lymphocytes, and one-fifth of subjects with normal eosinophils experienced on-study elevations in eosinophils.