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A phase I dose-escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer

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ABSTRACT

Background: Tremelimumab (CP-675,206) is a fully human monoclonal antibody binding to cytotoxic T lymphocyte–associated antigen 4 (CTLA4) on T cells that stimulates the immune system by blocking the CTLA4-negative regulatory signal. Combination with standard chemotherapy may strengthen antitumor therapy. This is a phase Ib, multi-site, open-label, nonrandomized dose escalation trial evaluating the safety, tolerability, and maximum tolerated dose (MTD) of tremelimumab combined with gemcitabine in patients with metastatic pancreatic cancer.

Patients and Methods: Gemcitabine (1000 mg/m^2 on days 1, 8, and 15 of each 28-day cycles) was administrated with escalating doses of intravenous tremelimumab (6, 10, or 15 mg/kg) on day 1 of each 84-day cycle for a maximum of 4 cycles. The first 18 patients had an initial 4-week gemcitabine-only lead-in period. Dose-limiting toxicities (DLTs) related to tremelimumab were evaluated during the first 6 weeks after the first dose of tremelimumab.

Results: From June 2008 to August 2011, 34 patients were enrolled and received at least one dose of tremelimumab. No DLTs related to tremelimumab were observed at any dose, even when the maximum dose established for tremelimumab (15 mg/kg) was used. Most frequent grade 3/4 toxicities were asthenia (11.8%) and nausea (8.8%). Only one patient had a serious drug-related event (diarrhea with dehydration). The median overall survival was 7.4 months (95% confidence interval 5.8–9.4 months). At the end of treatment, two patients achieved partial response, both in the tremelimumab 15-mg/kg group (*n* = 2/19, 10.5%).

Conclusion: Tremelimumab plus gemcitabine demonstrated a safety and tolerability profile, warranting further study in patients with metastatic pancreatic cancer.

Key words:, metastatic pancreatic cancer, gemcitabine chemotherapy, immunotherapy, tremelimumab

Clinical trials registration and ID: ClinicalTrials.gov, NCT00556023

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death. Diagnoses are generally made late in the disease with a 5-year survival rate <5% [1]. At present, treatment for metastatic disease is focused on improving survival and quality of life.

Since the 1990s, gemcitabine has been the standard treatment for advanced pancreatic cancer [2]. Many phase II studies demonstrated the efficacy of gemcitabine combination treatments, but only one randomized phase III trial has recently demonstrated improvement in overall survival (OS): gemcitabine and nab-Paclitaxel combination compared with gemcitabine alone [3]. A recent phase II/III randomized study of combination 5-fluorourcil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) versus gemcitabine defined an alternative strategy to gemcitabine monotherapy [4]. However, results with current standard therapies clearly underscore the need for new treatments.

Several different immunotherapeutic strategies (vaccination, adoptive cell transfers and targeting checkpoints) are being evaluated in pancreatic cancer [5]. In preclinical models, CTLA-4 blockade has demonstrated antitumor activity enhancing the endogenous immune response[6,7].

Tremelimumab (CP-675,206) is a fully humanized monoclonal antibody that binds the cytotoxic T-lymphocyte–associated antigen 4 molecule (CTLA-4) expressed on the surface of activated T lymphocytes and T-regulatory cells. Tremelimumab antagonizes binding of CTLA4 to its target ligands (B7-1 and B7-2) by inhibiting its negative regulatory signal to T-cell activation [6]. Blockade of inhibitory effects of CTLA4 may allow and potentiate effective immune responses against tumor cells . In several clinical studies, anti-CTLA4 agents have been shown to induce durable tumor responses through modulation of the immune system in patients with metastatic melanoma [8, 9].

Safety of single-agent tremelimumab has been analyzed in several studies in patients with cancer, particularly with melanoma. The first-in-human phase I dose-escalation study indicated that tremelimumab can safely be administered up to 15 mg/kg, with durable antitumor responses [10]. DLTs and autoimmune phenomena included diarrhea, dermatitis, vitiligo, panhypopituitarism, and hyperthyroidism. In a subsequent phase I/II study, patients with metastatic melanoma were

randomized to receive tremelimumab 10 mg/kg every 28 days or 15 mg/kg every 90 days [11]. The 15-mg/kg regimen was selected over the 10 mg/kg for further development based on similar response rate and OS between the two regimens, but a lower incidence of grade 3/4 adverse events (AEs) and serious AEs (SAEs).

A recent phase II study of single agent ipilimumab reported one delayed response out of 27 advanced pancreatic cancer. [12]. The present study is the first study of tremelimumab in patients with pancreatic cancer. The choice of gemcitabine as combination therapy has been sustained by the evidence of its role in increasing immune response [13, 14]. To provide synergistic antitumor activity without increasing toxicity was the rationale for exploring combination tremelimumab plus gemcitabine regimen.

PATIENTS AND METHODS

Patients

Eligible patients had histologically/cytologically confirmed metastatic pancreatic cancer and had not received prior systemic treatment with chemotherapy. Patients were aged 18 years or older with an ECOG PS 0 or 1 and adequate hematology, blood chemistry, and renal and liver function. Patients were excluded if they had received previous treatment with an anti-CTLA4 agent or radiotherapy for locally advanced disease within 4 weeks prior to randomization. Patients with inflammatory bowel disease or diarrhea at baseline; history of diverticulitis; or current (or active in the last 3 years) chronic inflammatory or autoimmune (except vitiligo) were excluded. All patients signed informed consent and the protocol was approved by local ethics committees. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Study Design and Treatment

Study A3671016 (ClinicalTrials.gov: NCT00556023) was a phase Ib, multi-site, open-label, nonrandomized dose escalation clinical trial evaluating the safety and tolerability of tremelimumab

plus gemcitabine in patients with metastatic pancreatic cancer. Secondary objectives included monitoring for preliminary evidence of efficacy for the combination and evaluation of drug pharmacokinetics.

There were four scheduled cycles. The study protocol was amended to allow a patient to receive up to 7 cycles. A cycle consisted of one dose of tremelimumab and up to 12 doses of gemcitabine. Gemcitabine 1000 mg/m^2 was administered for 3 weeks followed by 1 week of rest. Tremelimumab was administered by intravenous infusion on day 1 of each 84-day cycle.

The trial consisted of two treatment portions (Supplementary 1S). Portion A was a 1-month gemcitabine-only lead-in period (cycle 0) followed by combination tremelimumab/gemcitabine therapy. This lead-in period permitted exclusion of patients with early progression of disease as well as patients with gemcitabine-related diarrhea. Patients successfully completing the lead-in period were assigned to escalating doses of tremelimumab (6, 10, or 15 mg/kg) in addition to gemcitabine, using the standard 3+3 method. Dose escalation proceeded until the maximum tolerated dose (MTD) was identified (up to 15 mg/kg). The MTD was defined as the maximum dose level of tremelimumab in combination with gemcitabine at which ≤1 of 6 evaluable patients experienced dose-limiting toxicities (DLT) during the first 6 weeks following the first administration of tremelimumab (DLT observation window). Portion B commenced once the MTD expansion group had completed Portion A.

Patients enrolled in Portion B initiated therapy with combination tremelimumab/gemcitabine, i.e. without a lead-in period. The starting dose of tremelimumab was one dose-level lower than the MTD defined in Portion A. Dose escalation proceeded until the MTD was identified (up to 15 mg/kg). Once the MTD has been identified, a minimum of 12 patients had to be studied at the MTD to determine its suitability as recommended dose for further studies.

DLTs were graded according to the National Cancer Institute Common Terminology Criteria for Common Toxicity 3.0 [15]. A DLT was defined as any grade 4 treatment-related toxicity (except for lymphopenia without clinical consequences), or grade 3/4 toxicities not recovering to grade 1 or baseline within 7 days of maximal management and/or after delaying the gemcitabine infusion by a

maximum of 2 weeks (except lymphopenia, alopecia, and skin rash not requiring systemic steroid therapy or other immunosuppressive therapy), or grade 2–4 autoimmune toxicity of critical organs (except anterior uveitis), or failure to recover to grade 1 or baseline severity for drug-related toxicity after delaying the initiation of gemcitabine infusion by a maximum of 2 weeks.

Three or six patients were enrolled per dose level, based on the number of DLTs observed at that dose level. Treatment continued until disease progression, as defined by the 1st radiologic assessment without further confirmation, unacceptable toxicity, or consent withdrawal.

Assessments

Patients were assessed at baseline and throughout the trial with a complete physical examination, collection of signs and symptoms, and hematology/biochemistry. Tumors were assessed by computed tomography at baseline and every 8$\pm$2 weeks. Best overall response was determined according to the Response Evaluation Criteria in Solid Tumors 1.0 guidelines [16].

Pharmacokinetic (PK) Evaluations.

Blood samples for gemcitabine PK analyses were obtained prior to administration, at the end of the infusion, and 0.5, 1, 2, 3, 4, and 6 hours post-infusion in Cycle 0 on Day 1 and in Cycle 1 on Day 1. Blood specimens for assay of tremelimumab PK were obtained just prior to administration and 1 hour after the end of the infusion in Cycle 1 on Day 1. Blood specimens of tremelimumab were also obtained in Cycle 1 on Days 8, 29, and 57.

Tremelimumab PK data following tremelimumab given alone in the A3671008 study [9], ere compared with these following tremelimumab given with gemcitabine in this study.

The concentration-time data were analyzed by non-compartmental analysis. Parameters of drug exposure included area under the concentration curve from time zero to the last quantifiable concentration (AUC_{last}) and to infinity (AUC_{inf}).

AUC_{inf} was calcuated as:

(AUC_{inf}) = AUC_{0-last} + The last concentration/K_e,

Where K_e was the elimination rate constant calculated from the slope of the line plotted as at least 3 points of concentration versus time and having a regression coefficient (R^2) of at least 0.90. These criteria were used for the calculation of AUC_{inf}

Statistical Analysis

Summary statistics with 95% confidence intervals (CIs) were calculated for continuous variables and discreet variables. Kaplan-Meier estimators and curves were created to estimate time-to-event end points, OS, and progression-free survival. Pearson chi-square test or Fisher's exact test was used to compare proportions as appropriate.

RESULTS

Patient Characteristics

Thirty-eight patients were enrolled in five centers from June 2008 to August 2011. Two patients withdrew consent after 3 weeks of the gemcitabine lead-in period and two patients were excluded from analysis because they did not meet inclusion/exclusion criteria. Baseline demographic characteristics are summarized in Table 1.

Study Treatment

Thirty-four patients received at least one dose of tremelimumab in combination with gemcitabine. Eighteen patients were enrolled into portion A and 16 patients into Portion B. Four patients received tremelimumab 6 mg/kg (cohort-6), 8 received tremelimumab 10 mg/kg (cohort-10), and 22 received tremelimumab 15 mg/kg (cohort-15).

Patients received a median of two tremelimumab infusions (range 1–7). Median number of cycles was 1.5 (range 1–2), 1.5 (range 1–7), and 2.0 (range 1–4) in cohorts-6, 10, and 15, respectively. During the lead-in period, four patients had one dose of gemcitabine withheld due to hematologic

toxicities (neutropenia or thrombocytopenia). Gemcitabine dose was reduced in four patients due to hematologic toxicities (neutropenia or thrombocytopenia). Tremelimumab dose was never delayed. The main reasons for withdrawal were disease progression and non–treatment-related SAEs.

Toxicity

Treatment-related toxicities are summarized in Table 2. No DLTs occurred during the study. There was no clear trend in AEs across the different dose cohorts. Also, there was no significant difference in the event rate for diarrhea between patients in Portions A (33.3% - 6/18 patients) and B (31.2% - 5/16 patients); however, grade 3/4 diarrhea were reported in two patients in Portion B and none in Portion A.

Only two patients experienced autoimmune toxicities (hyperthyroidism and vitiligo).

Eleven patients experienced at least one SAE; one patient (cohort-10/Portion B) had an SAE (diarrhea and dehydration) related to tremelimumab/gemcitabine treatment and died 2 weeks after the onset despite hospitalization and maximal supportive care. Other non–treatment-related SAEs included one of each of the following: acute coronary ischemic event, pulmonary embolism, hyperbilirubinemia, and hematemesis in cohort-10 and acute renal failure, and gastrointestinal hemorrhage, and two hyperbilirubinemia in cohort-15. Treatment was withdrawn in these patients.

Treatment was temporarily discontinued in four patients who experienced hyperbilirubinemia for biliary stent occlusion (cohort-6/Portion A), vertigo for labyrinthitis (cohort-6/Portion A), and acute coronary ischemic event (cohort-10/Portion B).

Clinical Outcome

Tumor response was evaluable in 28 patients. Six patients were not evaluated because of premature withdrawal without disease re-evaluation. In the response-evaluable group, two patients (cohort-15/Portion A) who received two and four cycles of treatment, respectively, achieved a best overall response of partial response at 8 weeks. Duration of objective response for these two

responders was not calculated because no progression date was recorded for either patient; consequently, both were censored dead with no progression documented.

Seven patients had stable disease for >10 weeks. Two patients with stable disease completed the study (≥4 cycles of tremelimumab) and one continued treatment with stable disease for seven cycles. However, this patient later died for reasons not related to ongoing treatment.

Most patients in each cohort died due to progressive disease. However, six (17.6%) patients in cohort-15 were alive at the time of analysis. With a median follow-up time of 7.1 (95% CI 5.4-8.7) months, median OS (95% CI) was 5.3 (1.2–14.6), 8.0 (2.3–16.9), and 7.5 (6.0–9.5) months in cohort-6, cohort-10, and cohort-15, respectively. For all patients, median survival was 7.4 (95% CI 5.8–9.4) months (Supplementary 2S). Due to the limited number of patients in each cohort, all CIs were wide and overlapped with each other.

Pharmacokinetics

Pharmacokinetic data are reported only for patients in cohort-15 because the sample size was too small in cohort-6 and cohort-10. Plasma profiles and pharmacokinetic parameters of gemcitabine were similar in the presence and absence of tremelimumab (Supplementary 3S). The mean area under the curve (AUC_{last}) was 6114 ± 4104 hr*ng/mL (*n* = 10) and 7441 ± 5479 hr*ng/mL (*n* = 7) in the presence and absence of tremelimumab, respectively, with ratio of 0.82 in the two groups. Two plasma curves of tremelimumab in the presence and absence of gemcitabine overlapped. Mean AUC of tremelimumab/gemcitabine in this study were compared with results for tremelimumab given alone in the A3671008 study in patients with advanced refractory or relapsed melanoma (Supplementary 4S) [9].Since there were differences in PK sampling times between the 2 studies, the PK parameter of the AUC_{inf} in 5 patients (the concentration-time data from other 5 patients did not meet the criteria for the calculation of AUC_{inf}) instead of using AUC_{last} in 10 patients in this study was chosen to compare with that from A3671008 study. Mean AUC_{inf} was 112,900 ± 39,275 hr·µg/mL (*n* = 5) and 112,719 ± 40,933 hr·µg/mL (*n* = 150) in the presence and absence of gemcitabine, respectively, with a ratio of 1.0 in the two groups.

Overall, our analysis indicates that the combination regimen can be administered without PKinteractions.

DISCUSSION

This study demonstrated that tremelimumab can be safely administered at the dose of 15 mg/kg in a 84-day cycle in combination with gemcitabine. The tremelimumab regimen used is similar to that of other phase I-II studies of tremelimumab monotherapy [17, 18]. It can be inferred from these results that addition of gemcitabine did not appear to increase toxicity relative to administration of tremelimumab alone and there was no apparent modification in gemcitabine PK.

The majority (94.1%) of patients experienced at least one treatment-related AE; most frequently thrombocytopenia, diarrhea, nausea, hypertransaminasemia, asthenia, anemia, neutropenia, and fever. However, grade 3 toxicities occurred much less frequently, and included neutropenia, asthenia, and nausea. One patient had grade 5 nonhematologic treatment-related toxicity (diarrhea/dehydration). Two additional grade 4 nonhematologic toxicities (pulmonary embolism and gastrointestinal bleeding) were not attributed to treatment.

Previous studies with tremelimumab [10, 11, 17, 18] reported autoimmune or autoinflammatory side effects thought to be caused by activated T cells. The most frequently observed (>20%–30%) treatment-emergent AEs among these trials were rash, nausea, diarrhea, fatigue, and pruritus. Further, AEs appeared to increase with dose. Immune-mediated AEs in previous studies were, in general, hyperthyroidism, vitiligo, psoriasis, and hypophysitis and grade 3/4 diarrhea reported in <10% of cases [10, 11, 17, 18]. In the present study, toxicity associated with tremelimumab/gemcitabine did not appear to be greater than that of tremelimumab monotherapy. In addition, in this study, there was a lower incidence of grade 3/4 diarrhea compared with previous studies [10, 11, 17, 18]. In this regard, patients in the current study were divided into two groups (Portions A and B) to determine whether the timing of adding tremelimumab to gemcitabine treatment would significantly affect the frequency of treatment-emergent diarrhea. Grade 3/4 diarrhea occurred only in two Portion B patients (one each in cohorts-10 and 15). There was no

statistically significant difference in the proportion of patients with ≥1 treatment-emergent cases of diarrhea over all cycles between Portions A and B (33% versus 40%, respectively, *P* = 0.714) with tremelimumab 10-mg/kg or between Portions A and B (45% versus 27%, respectively, *P* = 0.505) in the 15-mg/kg group. Therefore, addition of tremelimumab did not appear to affect the frequency of treatment-emergent diarrhea. However, patients receiving tremelimumab 15 mg/kg in both Portions A and B experienced significantly earlier onset of diarrhea and shorter median duration of cumulative diarrhea-event days versus tremelimumab 10-mg/kg–treated patients (data not shown). Although these cohorts may not be large enough to give statistically meaningful conclusion, across the 10-mg/kg and 15-mg/kg tremelimumab dose groups, patients in Portion B tended to experience earlier onset of diarrhea compared with Portion A.

Grade 3 toxicities increased with increasing dose level, in particular, for thrombocytopenia, nausea, diarrhea, anemia, neutropenia, and asthenia. In the response-evaluable group, two patients achieved a best overall response of partial response and seven patients achieved stable disease for >10 weeks. Duration of objective responses was not calculated because no progression date was recorded for either patient.

Experience with other anti-CTLA4 agents, suggested a different pattern of response following immunotherapy [11, 18]. Initial increase in tumor burden during immunotherapy can be the effect of a heavy infiltrate of tumor site by immune and inflammatory cells. Evaluation for new response criteria are ongoing [19]. It is possible that, in patients without tumor response, continuation of treatment and observation would later provide benefits. The recent phase II study of ipilimumab in pancreatic cancer seems to confirm this hypothesis.[12].

The present study showed that tremelimumab in combination with gemcitabine demonstrated a safety and tolerability profile warranting further study and, in those patients who received 10 or 15 mg/kg tremelimumab, OS was longer than expected, based on historical data [3, 4], versus gemcitabine monotherapy. Phase II studies of tremelimumab in metastatic pancreatic cancer could address this point.

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DISCLOSURES

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LEGEND TO FIGURES

Supplementary 1S. Study schema.

Supplementary 2S. Kaplan-Meier plot of overall survival. GEM, gemcitabine.

Supplementary 3S. Median AUC for gemcitabine in cohort-15 during the lead-in period (cycle 0 week 1) and in association with tremelimumab 15 mg/kg (cycle 1 week 1). AUC, area under the plasma concentration–time curve.

Supplementary 4S. Median AUC for tremelimumab in combination with gemcitabine versus gemcitabine alone in the A3671008 study in melanoma [12]. AUC, area under the plasma concentration–time curve; GEM, gemcitabine.