SYNOPSIS

Final Clinical Study Report for CA183002

TITLE OF STUDY: A multicenter, randomized double-blind Phase 2/3 study in the first-line treatment of advanced transitional cell carcinoma (TCC) of the urothelium comparing vinflunine/gemcitabine to placebo/gemcitabine in patients who are ineligible to receive cisplatin-based therapy.

PURPOSE: This was a multi-center, double-blind, prospectively controlled, randomized study comparing vinflunine/gemcitabine (Vin/Gem) to placebo/gemcitabine (Pla/Gem) in the treatment of 1st line locally advanced or metastatic TCC of the urothelium in patients who were ineligible to receive cisplatin-based therapy. The primary endpoint in this study was progression free survival (PFS). In addition, overall survival (OS), tumor response rate and disease control rate were to be evaluated for all randomized subjects. Also, duration of response and time to response were to be evaluated for all responding subjects. Subjects randomized to Vin/Gem group were to be administered vinflunine 280 mg/m^2 on Day 1 and every 21 days as a 20 minute (± 5 minutes) intravenous (IV) infusion during the first cycle. If no hematologic toxicity causing a treatment delay or dose reduction occurred in Cycle 1, the dose was to be escalated to 320 mg/m^2 during the subsequent cycles. Subjects were to be administered gemcitabine 1000 mg/m^2 on Day 1 and Day 8 of every 21 day cycle as a 30 minute intravenous (IV) infusion if their calculated creatinine clearance was >60 mL/min. Subjects with a calculated creatinine clearance ≤60 mL/min were to initially receive gemcitabine 750 mg/m^2 on Day 1 and Day 8 during the first cycle. If no toxicity of Grade > 2 occurred in Cycle 1, the dose was to be escalated to 1000 mg/m^2 during the subsequent cycles. A placebo infusion of normal saline was to be administered (same volume as vinflunine infusion), to subjects randomized to Pla/Gem.

NUMBER OF SUBJECTS: 450 subjects were planned to be randomized onto Vin/Gem or Pla/Gem in a 1:1 ratio; 34 were randomized (17 in each group), 33 were treated (one subject randomized to Pla/Gem subject no longer met the study criteria). Further enrollment was stopped when the study was closed in view of the Sponsor's decision to discontinue development of vinflunine in this indication.

STUDY PERIOD: Study Initiation Date: 27-Jan-2007 **CLINICAL PHASE:** 2/3

Study Completion Date: 18-Jan-2008 (5 subjects were still receiving treatment)

DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS: The randomized study population consisted of 14 males / 3 females in the Vin/Gem group and 9 males / 8 females in the Pla/Gem group. The majority of subjects were white (14 of 17) in each treatment arm. Overall, the subjects ranged in age from 57 to 88 years (median age = 76 years). Six subjects were less than 65 years of age (4 in Vin/Gem group and 2 in Pla/Gem group) and the other 28 subjects were ≥65 years of age (13 in Vin/Gem group and 15 in Pla/Gem group). The subjects had an ECOG performance status of 0 (n=2 and n=6 in Vin/Gem and Pla/Gem group, respectively), 1 (n=10 and n=6 in Vin/Gem and Pla/Gem group, respectively) or 2 (n=5 and n=5 in Vin/Gem and Pla/Gem group, respectively). Serum creatinine at baseline was Grade 0 (n=7), Grade 1 (n=7) or Grade 2 (n=3) for subjects treated in Vin/Gem group, and Grade 0 (n=5), Grade 1 (n=9) or Grade 2 (n=2) for subjects treated in Pla/Gem group. Four subjects (2 in each treatment group) had received prior chemotherapy in adjuvant or neo-adjuvant setting.

SUMMARY OF EFFICACY RESULTS: Antitumor activity (as defined by RECIST and as assessed by the investigator) was observed in both treatment groups: confirmed PR in 2 subjects and SD in 5 subjects in Vin/Gem group; confirmed PR in 7 subjects and SD in 1 subject in Pla/Gem group.

SUMMARY OF SAFETY RESULTS: Overall, 6 of the 33 treated subjects died (4 in Vin/Gem group and 2 in Pla/Gem group); 3 of these deaths occurred within 30 days of administering the last dose of study drug (2 in Vin/Gem group and 1 in Pla/Gem group). The primary cause of death within 30 days of administering the last dose of study drug was: (i) deterioration of general physical health in 1 subject and

(ii) respiratory failure and sepsis in another subject in Vin/Gem group; and (iii) ventricular arrythmia in 1 subject in Pla/Gem group. Three other subjects died beyond 30 days of administering the last dose of study drug: 2 due to disease progression (both in Vin/Gem group) and 1 due to cause unknown (in Pla/Gem group).

Safety was evaluated for all treated subjects using the NCI CTCAE version 3.0. Serious adverse events (SAEs) were reported in 11 of 17 subjects in Vin/Gem group and 6 of 16 subjects in Pla/Gem group. Ten subjects in Vin/Gem group and 3 subjects in Pla/Gem group experienced at least one SAE that was considered related to study drug. SAEs led to discontinuation of study treatment in 4 of 17 subjects in Vin/Gem group and 3 of 16 subjects in Pla/Gem group. In addition, non-serious AEs led to discontinuation of study treatment in 2 other subjects in Vin/Gem group, and no other subject in the Pla/Gem group. Overall, AEs led to discontinuation of study treatment in 6 of 17 subjects in Vin/Gem group and 3 of 16 subjects in Pla/Gem group, and the events that led to discontinuation of treatment were considered related to study medication in 5 subjects in Vin/Gem group and 1 subject in Pla/Gem group. All 33 treated subjects experienced at least 1 AE regardless of relationship to study medication. Fifteen of 17 subjects (88.2%) in Vin/Gem group and 10 of 16 subjects (62.5%) in Pla/Gem group experienced at least 1 AE that was Grade 3-5 in severity. The predominant Grade 3-5 AEs (i.e., reported in >10% of subjects in Vin/Gem group were fatigue (29.4%), constipation, diarrhea, and urinary tract infection (11.8% each). The predominant Grade 3-5 AEs (i.e., reported in >10% of subjects) in Pla/Gem group were asthenia (18.8%), fatigue, anorexia, dehydration, and pain in extremity (12.5% each).

Grade 3-4 hematology abnormalities in Vin/Gem and Pla/Gem groups were: neutropenia (58.8% and 31.3%, respectively), leucopenia (41.2% and 25.0%, respectively), anemia (41.2% and 12.5%, respectively), and thrombocytopenia (0% and 12.5%, respectively). Grade 3-4 serum chemistry abnormalities in Vin/Gem and Pla/Gem groups were: hypokalemia (14.3%and 6.7%, respectively), decrease in albumin (14.3% and 6.3%, respectively), elevated serum creatinine (6.7% and 6.3%, respectively), hyperbilirubinemia (6.7% and 0%, respectively), hyponatremia (0% and 6.3%, respectively), and elevated alkaline phosphatase (0% and 6.3%, respectively).

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