Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: vinflunine		

SYNOPSIS

Final Clinical Study Report for Study CA183001

TITLE OF STUDY: A Phase II Study of Intravenous (IV) Vinflunine in Patients with Locally Advanced or Metastatic Transitional Cell Carcinoma (TCC) of the Urothelium

INVESTIGATORS/STUDY CENTERS: Investigators at 60 centers in 12 countries enrolled patients in this study (32 sites in the United States, 16 in Europe, 7 in Asia, 4 in Australia, and 1 in Canada)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 27-Jan-2005 **CLINICAL PHASE:** 2

Study Completion Date: 10-Apr-2007

OBJECTIVES: Primary: to estimate the response rate (complete response [CR] + partial response [PR]; as defined by modified WHO criteria) in patients with TCC of the urothelium (TCCU) receiving vinflunine, who had documented progression within 12 months after the last dose of a platinum-containing regimen and were not candidates for cystectomy.

Secondary: to estimate duration of response, time to response, disease control rate (CR + PR + stable disease [SD]), progression free survival (PFS), and overall survival (OS), and to evaluate the safety profile of vinflunine.

Additional secondary objectives of a population pharmacokinetic evaluation, potential future pharmacogenetic studies, and an electrocardiogram (ECG) analysis were added as amendments. The population pharmacokinetic evaluation and full ECG analysis will be presented in separate reports.

METHODOLOGY: Open-label, non-comparative, single-arm, multi-center Phase 2 study.

NUMBER OF PATIENTS: 150 planned; 175 enrolled, 151 treated, 146 off treatment, 5 still on treatment at the time of the database lock.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women ≥ age 18 years who had histologically proven locally advanced or metastatic TCCU, had documented progression up to 12 months after the last dose of a platinum-containing regimen, and KPS of 100, 90, or 80.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Vinflunine was administered every 21 days (each 21 days = 1 cycle) as a 15 to 20 minute infusion. Prior to Amendment 5, patients received vinflunine at a dose of 320 mg/m^2 every 3 weeks if they had a Karnofsky Performance Status [KPS] of 100 without prior pelvic radiation. Upon implementation of Amendment 5, patients also needed to be < 75 years of age and have a calculated creatinine clearance (CrCl) > 60 mL/min to receive vinflunine at a starting dose of 320 mg/m^2. Patients received vinflunine at an initial dose of 280 mg/m^2 if they had a KPS of 90 or 80, KPS of 100 with prior radiation, or after Amendment 5, if they had CrCl ≤ 60 mL/min or were ≥ 75 years old; these patients

could have their dose escalated to 320 mg/m^2 in Cycle 2 if no hematological toxicity causing a treatment delay occurred. Batch Numbers: 4K85173, 4K85174, 5B08095, 5D09764, and 5J08434.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: This was a single arm study.

CRITERIA FOR EVALUATION: Efficacy: The primary endpoint was response rate, defined as the proportion of patients achieving a response, either a CR or PR, as determined by an Independent Response Review Committee (IRRC). Response was determined according to modified WHO criteria. The IRRC reviewed data for All Treated patients. Tumor assessment was performed every 2 cycles until implementation of Amendment 5 which required tumor assessments every 6 weeks.

Primary analysis of response rate was performed on the All Treated population and secondary analysis of response rate was performed on the All Evaluable population. The response rate was also analyzed using the investigator assessment. PFS was computed based on IRRC assessment and also investigator assessment. Duration of response for patients who achieved an objective response, and PFS and OS were assessed by the Kaplan-Meier method.

Safety was assessed based on the frequency of adverse events (AEs) and their severity for patients who received at least 1 cycle of vinflunine. For safety analyses, all non-serious and serious AEs were considered on-study AEs except all AEs recorded with a resolution date prior to the first day of dosing and all AEs with an onset date later than 30 days after the last dosing date. Worst toxicity grades per patient were tabulated for AEs and laboratory measurements by using the NCI CTC Version 2.0. AEs were coded using MedDRA 9.1. Physical examination and vital signs (including serial ECG evaluations), complete blood cell counts, and serum biochemistry were also performed.

SUMMARY OF RESULTS:

Disposition, Demographics and Other Pertinent Baseline Characteristics: Among the 175 patients enrolled, 151 were treated with study medication. The majority of the untreated patients did not meet the eligibility criteria between screening and start of treatment, and 4 of the untreated patients died. Of the 151 treated patients, 5 (3.3%) were still on treatment at the time of database lock (3 had an imputed, investigator assessed response of stable disease and 2 had partial response). The median time of follow-up was 11.9 months (95% CI: 9.6, 13.0). These patients were from 12 countries and 60 sites: 32 sites in the US, 16 sites in Europe, 7 sites in Asia, 4 in Australia, and 1 in Canada. The majority of the patients were from the US (61%).

The majority of patients (80%) were male and white (86%). The median age was 66.0 years (range: 31 to 83 years), 69% had a history of cardiovascular disease, and 65% had a history of smoking. Key baseline characteristics were

- Karnofsky performance status (KPS): 100: 31%, 90: 37%, 80: 32%
- Calculated creatinine clearance (CrCl) < 60 mL/min: 40%
- Prior chemotherapy: cisplatin: 63%, carboplatin: 46%, gemcitabine: 91%;
- Prior chemotherapy setting: peri-operative 36%, advanced/metastatic 61%, both 3%
- Refractory status as per time from prior platinum to progression: < 3 months: 54%, < 6 months: 78%

Exposure: Dose selection criteria are detailed above under Test Product. Initial dose level: 320 mg/m^2: 40 patients (13 reduced to 280 mg/m^2 in Cycle 2); 280 mg/m^2: 105 patients (41 escalated to 320 mg/m^2 in Cycle 2; 24 reduced to ≤ 250 mg/m^2); and ≤ 250 mg/m^2: 6 patients. The median duration of treatment was 9 weeks, ranging up to approximately 16 months. The median number of cycles administered was 3; the maximum number was 21 cycles.

Efficacy Results: In the All-Treated population the primary endpoint of independently assessed response rate was 14.6% with a 95% CI of 9.4% to 21.2%. Many tumor responses were of long duration with a median of 6.0 months. The response rates in various patient subgroups, including those with visceral disease and renal impairment were similar to those in the overall population.

Overall Summary of Efficacy

IRRC Best Response: All Treated Patients, N = 151	
Partial response, n (%)	22 (14.6)
Stable disease, n (%)	64 (42.4)
Progressive disease, n (%)	49 (32.5)
Not evaluable, n (%)	16 (10.6)
Response Rate % (95% CI) [a,b]	14.6% (9.4%, 21.2%)
Investigator Best Response: All Treated Patients, N = 151	
Complete respnse, n (%)	2 (1.3)
Partial response, n (%)	13 (8.6)
Stable disease, n (%)	68 (45.0)
Progressive disease, n (%)	49 (32.5)
Not evaluable, n (%)	19 (12.6)
Response Rate % (95% CI) [a,]	9.9% (5.7%, 15.9%)
Duration of Response (IRRC), N = 22	
Median (95% CI), months [c]	5.95 (5.42, 9.46)
Progression Free Survival (IRRC), N = 151; 28 patients censored	
Median (95% CI), months [c]	2.76 (2.56, 3.84)
Overall Survival (IRRC), N = 151; 65 patients censored	
Median (95% CI), months [c]	7.89 (6.67, 9.69)

[a] Number of responders (CR or PR) / Number of treated patients
[b] Two sided confidence interval (CI) calculated using the Clopper-Pearson method
[c] Two sided CI computed using the Brookmeyer Crowley method

Safety Results:

The safety profile was manageable and similar for the two initial dose groups. Further, the most frequent adverse events noted were those expected with vinflunine (myelosuppression, constipation, fatigue).

Overview of Number (%) of Patients with Adverse Events: All Treated Patients

Categories of AEs	**All VFL (N=151)**	**Initial Dose VFL (280 mg/m^2) (N=111)**	**Initial Dose VFL (320 mg/m^2) (N=40)**
All Grade 3-4 AEs	121 (80.1)	91 (82.0)	30 (75.0)
Grade 3-4 treatment-related AEs	104 (68.9)	79 (71.2)	25 (62.5)
All deaths within 30 days of last vinflunine dose	10 (6.6)	9 (8.1)	1 (2.5)
All SAEs	77 (51.0)	58 (52.3)	19 (47.5)
Treatment-related SAEs	55 (36.4)	42 (37.5)	13 (32.5)
All AEs leading to discontinuation	33 (21.9)	26 (23.4)	7 (17.5)
Treatment-related AEs leading to discontinuation	22 (14.6)	17 (15.3)	5 (12.5)

AE = adverse event; SAE= serious adverse event; VFL = vinflunine

Eighty-six (57%) patients died after study start, and 10 of these 86 (7%) died within 30 days of their last vinflunine dose. Of the patients who died within 30 days of their last vinflunine dose, 5 (3%) died due to progressive disease and 2 (1%) due to events judged to be study drug toxicity (neutropenic sepsis, myocardial infarction). The other deaths were due to other or unknown reasons.

Myelosuppression was common and expected with vinflunine. Based on laboratory results, severe (Grade 3-4) events of neutropenia and leukopenia were reported by more than half of the patients, but only led to discontinuation of 3% of patients. Febrile neutropenia was uncommon (6.6%) and did not lead to discontinuation. The most common non-hematologic AEs were constipation, followed by fatigue, nausea, weight decrease, anorexia, diarrhea, vomiting, and abdominal pain, alopecia, and back pain. The most common (> 10%) non-hematologic severe (Grade 3-4) AEs were constipation and fatigue. The frequency of discontinuation due to treatment related AEs was 15%. Despite the recommendation to use constipation prophylaxis with the administration of vinflunine, constipation was reported frequently. Constipation is a known class effect of vinca alkaloids. The incidence of peripheral neuropathy was low in this platinum-pretreated population, and only 1 Grade 3 severe event was reported. Other AEs of special interest (ileus, intestinal obstruction, abdominal pain, injection/infusion site reactions, immediate hypersensitivity, extravasation, cardiac arrhythmias, nausea, vomiting, stomatitis/mucositis, infection with severe neutropenia, and diarrhea) were manageable, and few of these AEs led to discontinuation.

CONCLUSIONS:

- Data support the efficacy of single-agent vinflunine in patients with locally advanced or metastatic TCCU who have been treated with a platinum-containing chemotherapy regimen.
- The IRRC reviewed response rate was 14.6% (95% CI: 9.4%, 21.2%). Tumor responses were of long duration and even observed in patients with unfavorable characteristics (poor performance status, renal impairment, refractory disease, and visceral involvement).
- Adverse events were generally manageable and vinflunine-related events of constipation were non-cumulative.
- In patients with a good performance status and no other risk factors, the recommended dose of vinflunine is 320 mg/m^2 with a 15- to 20-minute IV infusion. For other patients, vinflunine should be initiated with the lower dose (280 mg/m^2).

DATE OF REPORT: 12-Dec-2007