SYNOPSIS

Final Clinical Study Report for Study CA196004

TITLE OF STUDY: A Randomized, Double-Blind, Phase II Trial of CT-322 (BMS-844203) plus Irinotecan, 5-FU and Leucovorin (FOLFIRI) versus Bevacizumab plus FOLFIRI as Second-Line Treatment for Metastatic Colorectal Cancer

PURPOSE: The purpose of this randomized, multicenter, double-blind, Phase 2 study was to determine if CT-322 (BMS-844203) plus irinotecan, infusional 5-flurouracil (5-FU) and leucovorin (FOLFIRI) increased progression-free survival (PFS) compared with bevacizumab plus FOLFIRI in subjects with histologically or cytologically confirmed unresectable metastatic colorectal cancer (CRC) after disease progression following treatment with at least one standard cytotoxic regimen in combination with bevacizumab (as adjuvant, neoadjuvant, first or second line therapy).

On 24-Sep-2010, enrollment in this study was terminated early due to slow accrual, and the resulting inability to enroll an adequate number of subjects within the established study timelines. Subjects who were receiving treatment at the time of termination of enrollment were given the option to either discontinue treatment or to continue receiving blinded study drug.

OBJECTIVES: The protocol-specified objectives analyzed in this synoptic report include the following:

Primary

- To compare the PFS of subjects with metastatic CRC when treated with CT-322 (BMS 844203) in combination with FOLFIRI chemotherapy versus bevacizumab in combination with FOLFIRI.

Secondary

- To compare overall survival (OS) between the 2 treatment arms.
- To compare the objective tumor response rate (ORR) between the 2 treatment arms.
- To evaluate the safety of CT-322 (BMS-844203) plus FOLFIRI.

NUMBER OF SUBJECTS: Approximately 116 subjects were expected to be enrolled in this study. A total of 17 subjects were randomized and treated, 9 subjects in Arm A (CT-322 [2 mg/kg weekly] plus FOLFIRI) and 8 subjects in Arm B (bevacizumab [5 mg/kg every 2 weeks] plus FOLFIRI).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition and pretreatment demographic characteristics for all randomized subjects are presented in the tables that follow.

The study was closed to enrollment on 24-Sep-2010, and 6 of the 17 randomized subjects were receiving study treatment. All 6 subjects (2 in the CT-322 arm and 4 in the

bevacizumab arm) chose to continue receiving blind treatment. Study treatment remained blinded until the database was locked on 28-Mar-2011.

As of the database lock, 3 subjects were still on treatment, 1 subject in the CT-322 arm, and 2 subjects in the bevacizumab arm. Subsequent to the database lock, the 3 subjects discontinued treatment due to disease progression (CT-322 arm), an unrelated AE (bevacizumab arm), and an administrative reason (bevacizumab arm).

SUMMARY OF EXPOSURE: The median duration of therapy was 11.9 weeks for the CT-322 arm, and 14.1 weeks for bevacizumab arm.

Discontinuation of Study Therapy (All Randomized Subjects)

	CT-322(BMS-844203) 2mg/kg N= 9	Bevacizumab 5mg/kg N= 8	TOTAL N= 17
ALL RANDOMIZED	9	8	17
ON STUDY THERAPY	1 (11.1)	2 (25.0)	3 (17.6)
OFF STUDY THERAPY (1)	8 (88.9)	6 (75.0)	14 (82.4)
REASON OFF STUDY THERAPY			
DISEASE PROGRESSION	4 (44.4)	5 (62.5)	9 (52.9)
SUBJ REQUEST TO DISCONTINUE STUDY TRT	2 (22.2)	0	2 (11.8)
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (11.1)	0	1 (5.9)
DEATH	1 (11.1)	0	1 (5.9)
STUDY DRUG TOXICITY	0	1 (12.5)	1 (5.9)

(1) Off all study therapies

Demographic Characteristics (All Randomized Subjects)

	CT-322(BMS-844203) 2mg/kg N= 9	Bevacizumab 5mg/kg N= 8	TOTAL N= 17
AGE (YEARS)			
N	9	8	17
MEAN	67.6	58.0	63.1
MEDIAN	69.0	57.5	62.0
MIN , MAX	52 , 78	46 , 75	46 , 78
Q1 , Q3	62.0 , 75.0	49.0 , 65.0	56.0 , 73.0
STANDARD DEVIATION	8.99	10.06	10.43
AGE CATEGORIZATION (%)			
< 65	4 (44.4)	6 (75.0)	10 (58.8)
>=65	5 (55.6)	2 (25.0)	7 (41.2)
GENDER (%)			
Male	7 (77.8)	5 (62.5)	12 (70.6)
Female	2 (22.2)	3 (37.5)	5 (29.4)
RACE (%)			
WHITE	8 (88.9)	8 (100.0)	16 (94.1)
BLACK/AFRICAN AMERICAN	0	0	0
AMERICAN INDIAN/ALASKA NATIVE	1 (11.1)	0	1 (5.9)
ASIAN	0	0	0
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	0	0	0
OTHER	0	0	0
ETHNICITY (%)			
HISPANIC/LATINO	1 (11.1)	1 (12.5)	2 (11.8)
NOT HISPANIC/LATINO	6 (66.7)	6 (75.0)	12 (70.6)
NOT REPORTED	2 (22.2)	1 (12.5)	3 (17.6)

Information on ethnicity primarily collected for subjects from United States only.

SUMMARY OF SAFETY RESULTS:

Although a limited number of subjects were treated, the safety profile of CT-322 given in combination with FOLFIRI chemotherapy in this population of subjects with previously treated metastatic CRC was consistent with that seen in other larger clinical studies of CT-322. The adverse events (AEs) seen were consistent with the known safety profiles of antiangiogenic agents and FOLFIRI chemotherapy.

Summary of Safety Results (Treated Subjects)

	CT-322 2 mg/kg (N = 9)	**Bevacizumab 5 mg/kg (N = 8)**
All Deaths, n (%)	4 (44.4)	0
Serious Adverse Events, n (%)		
All SAEs	5 (55.6)	1 (12.5)
Drug-related SAEs	2 (22.2)	0
AEs leading to discontinuation, n (%)	1 (11.1)	1 (12.5)
AEs, n (%)		
Overall AEs	9 (100.0)	8 (100.0)
Grade 3/4 AEs	5 (55.6)	4 (50.0)
Grade 5 AEs	2 (22.2)	0
Drug-Related AEs	7 (77.8)	6 (75.0)

AEs = adverse events; SAEs - serious adverse events

Deaths

Of the 4 deaths reported in the CT-322 arm, 3 subjects died due to disease progression. The remaining subject died suddenly at home.

Serious Adverse Events (SAEs)

Serious adverse events of any relationship and any grade were reported more often in the CT-322 arm than in the bevacizumab arm. Two subjects reported SAEs considered related to treatment with CT-322 plus FOLFIRI, including one subject's sudden death at home. The other subject had SAEs of Grade 3 febrile neutropenia, Grade 4 thrombocytopenia, and Grade 3 epistaxis that were considered related to treatment with CT-322 plus FOLFIRI.

Adverse Events Leading to Discontinuation

In the CT-322 arm, 1 subject discontinued due to a Grade 4 cerebrovascular accident (CVA) that was considered unrelated to study treatment, and in the bevacizumab arm, 1 subject discontinued due to Grade 2 fatigue that was considered related to study treatment.

Adverse Events

The most frequently reported AEs in both treatment arms were gastrointestinal events (GI) including diarrhea, nausea and vomiting.

Adverse events commonly associated with antiangiogenic therapy include thrombosis, proteinuria, bleeding events, and hypertension. One subject in the CT-322 arm had a Grade 4 CVA that was considered unrelated to treatment and led to treatment discontinuation; no other reports of thrombosis were noted. There were no reports of proteinuria in either treatment arm.

Bleeding events were reported in both treatment arms, in 3 subjects in the CT-322 arm and in 4 subjects in the bevacizumab arm. In the CT-322 arm, epistaxis was reported in 2 subjects, and rectal hemorrhage was reported in 1 subject. The epistaxis reports were considered related and the rectal hemorrhage was considered unrelated to study drug. In the bevacizumab arm, 1 subject reported 4 bleeding events: hematuria; epistaxis; vaginal hemorrhage; and post-procedural bleeding. Only the epistaxis and the vaginal hemorrhage were considered related to bevacizumab treatment. Other bleeding events in the bevacizumab arm included epistaxis, hematuria, and rectal hemorrhage, each reported in 1 subject; these events were considered unrelated to study drug. All bleeding events were Grade 1 or 2 in intensity.

Hypertension, another AE commonly associated with antiangiogenic therapy, was reported in 3 subjects treated with CT-322. Hypertension was Grade 1 or 2 in intensity and was considered drug-related in 1 subject and unrelated to study drug in 2 subjects.

SUMMARY OF EFFICACY RESULTS:

Median PFS was 2.56 months in the CT-322 arm and 3.26 months in the bevacizumab arm. Median OS could not be estimated in either the CT-322 or bevacizumab arms due to limited data. Since no subject had a complete or partial response, the ORR was 0% in both the CT-322 and bevacizumab arms.

CONCLUSIONS:

- Although a limited number of subjects were treated, the safety profile of CT-322 given in combination with FOLFIRI chemotherapy in this population of subjects with previously treated metastatic CRC was consistent with that seen in other larger clinical studies of CT 322.
  - Among 9 subjects treated on the CT-322 arm, there was one drug-related death, and one additional subject had drug-related SAEs.
  - The most frequently reported AEs were GI events including diarrhea, nausea and vomiting.
  - AEs commonly associated with antiangiogenic therapy were observed, including bleeding events, reported in 3 subjects on the CT-322 arm and 4 subjects on the bevacizumab arm, and hypertension, reported in 3 subjects on the CT-322 arm.
- Median PFS was 2.56 months in the CT-322 arm and 3.26 months in the bevacizumab arm. Analysis of OS was not feasible due to limited data. No objective

responses were observed in either treatment arm. As the study was terminated early for poor accrual, conclusions regarding the comparative safety and efficacy according to treatment arm are not warranted.

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