SYNOPSIS

Final Clinical Study Report for Study CA182025

TITLE OF STUDY: A Blinded, Randomized, Phase 1/2 Study of Brivanib Alaninate vs. Placebo in Combination with Erbitux and Irinotecan in K-Ras Wildtype Subjects with Metastatic Colorectal Cancer

PURPOSE: Part I of this study was designed to determine whether brivanib alaninate could be safely administered with Erbitux® (cetuximab) and irinotecan in K-Ras wild type subjects with progressive or relapsed metastatic colorectal carcinoma (MCRC). Part I initially evaluated escalating oral doses of brivanib alaninate 200 mg (Cohort 1, Treatment A), 400 mg (Cohort 2, Treatment B), 600 mg (Cohort 3, Treatment C), and 800 mg (Cohort 4, Treatment D), versus matching placebo, which was included to assess the background rate of events associated with the chemotherapy backbone. Subjects in Cohorts 1 to 4 received brivanib alaninate or matching placebo as a single dose on cycle 1 day 1 (C1D1) and as continuous daily doses beginning on C1D15, with coadministration of Erbitux (400 mg/m^2 loading dose, 250 mg/m^2 weekly [qw] thereafter) and irinotecan (350 mg/m^2 every 21 days [q3w]) beginning on C1D8. The toxicities observed in these initial cohorts (primarily neutropenia and diarrhoea) occurred with similar frequency in placebo-treated subjects and brivanib alaninate-treated subjects, and were consistent with the well-recognized side effects of irinotecan. To attempt to improve the tolerability of the regimen, a fifth dose cohort was added in Part I to evaluate a lower starting dose of irinotecan (300 mg/m^2) in combination with brivanib alaninate 800 mg and the same Erbitux regimen given in Cohorts 1 to 4 (Cohort 5, Treatment E); an optional dose increase to irinotecan 350 mg/m^2 was permitted on C3D1 in the absence of ≥Grade 3 toxicity during the first 2 cycles. Part I of the study completed as planned. Following the Sponsor's decision to discontinue development of brivanib alaninate as a combination therapy in MCRC, Part II of the study (dose expansion at the maximum tolerated dose [MTD] from Part I) was not conducted. Therefore, a synoptic clinical study report has been prepared for CA182025. As such, this report only provides safety analyses that address the primary objective.

NUMBER OF SUBJECTS: The planned enrollment was approximately 124 subjects (up to 42 subjects in Part I and 82 subjects in Part II). A total of 36 subjects were treated and analyzed in Part I of this study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Table 1 and Table 2 summarize disposition and demographic characteristics, respectively, for the 36 subjects treated in study CA182025.

Median duration of study treatment for subjects receiving brivanib alaninate in combination with Erbitux/irinotecan was 11.21 weeks (range: 0.1 to 159.7 weeks), and was slightly longer in the 200 mg (17.50 weeks) and 400 mg (16.21 weeks) cohorts compared with the 600 mg (10.00 weeks) and 800 mg (6.79 and 6.86 weeks) cohorts. Median duration of treatment for subjects receiving placebo in combination with Erbitux/irinotecan was 15.57 weeks (range: 1.1 to 33.1 weeks).

Table 1: Summary of Subject Disposition in Study CA182025

	Brivanib alaninate (dose in mg)[a] + Erbitux / Irinotecan[b]						Placebo[a] + Erbitux / Irinotecan[b]
	Trt A (200 mg)	Trt B (400 mg)	Trt C (600 mg)	Trt D (800 mg)	Trt E (800 mg)	Trt A to E (All Doses)	
No. of Subjects Treated	4	6	8	4	6	28	8
No. of Subjects Not Continuing in the Treatment Period, n (%)	4 (100)	6 (100)	8 (100)	4 (100)	6 (100)	28 (100)	8 (100)
Reasons for Not Continuing in the Treatment Period, n (%)							
Disease progression	4 (100)	4 (66.7)	6 (75.0)	0	4 (66.7)	18 (64.3)	5 (62.5)
AE unrelated to study drug	0	1 (16.7)	0	1 (25.0)	0	2 (7.1)	1 (12.5)
Study drug toxicity	0	0	2 (25.0)	1 (25.0)	0	3 (10.7)	0
Subject withdrew consent	0	0	0	1 (25.0)	0	1 (3.6)	2 (25.0)
Subject request to discontinue study treatment	0	1 (16.7)	0	0	0	1 (3.6)	0
Poor / non-compliance	0	0	0	0	1 (16.7)	1 (3.6)	0
Other	0	0	0	1 (25.0)	1 (16.7)	2 (7.1)	0
No. of Subjects Continuing in the Study (Follow-up Period)	4 (100)	6 (100)	6 (75.0)	3 (75.0)	4 (66.7)	23 (82.1)	6 (75.0)
No. of Subjects Not Continuing in the Study (Follow-up Period)	0	0	2 (25.0)	1 (25.0)	2 (33.3)	5 (17.9)	2 (25.0)

Trt = treatment; No. = number

[a] Brivanib alaninate (or matching placebo) was administered as a single oral dose on C1D1 and as continuous daily oral doses beginning on C1D15.

[b] Beginning on C1D8, IV Erbitux was administered qw at a loading dose of 400 mg/m^2 and thereafter at 250 mg/m^2, and IV irinotecan was administered q3w at 350 mg/m^2 (Cohorts 1 to 4 [Trt A, B, C, and D and placebo]) or at a starting dose of 300 mg/m^2 with an option to increase the dose to 350 mg/m^2 beginning at C3D1 in the absence of ≥Grade 3 toxicity in the first 2 cycles (Cohort 5 [Trt E]).

Table 2: Summary of Demographics Characteristics of Subjects Treated in Study CA182025

	Brivanib alaninate (dose in mg) [a] + Erbitux / Irinotecan [b]						Placebo [a] + Erbitux / Irinotecan [b]
	Trt A (200 mg) N=4	Trt B (400 mg) N=6	Trt C (600 mg) N=8	Trt D (800 mg) N=4	Trt E (800 mg) N=6	Trt A to E (All Doses) N=28	N=8
Age in years							
Mean (SD)	56.5 (5.2)	55.0 (11.6)	56.1 (11.8)	62.3 (8.9)	60.3 (9.2)	57.7 (9.8)	49.6 (8.5)
Min, Max	50, 62	42, 71	36, 70	54, 74	50, 75	36, 75	36, 58
Sex, n (%)							
Male	2 (50.0)	3 (50.0)	6 (75.0)	2 (50.0)	3 (50.0)	16 (57.1)	4 (50.0)
Female	2 (50.0)	3 (50.0)	2 (25.0)	2 (50.0)	3 (50.0)	12 (42.9)	4 (50.0)
Race, n (%)							
White	3 (75.0)	2 (33.3)	6 (75.0)	2 (50.0)	3 (50.0)	16 (57.1)	3 (37.5)
Black / African American	0	0	0	0	1 (16.7)	1 (3.6)	0
Asian	0	2 (33.3)	1 (12.5)	2 (50.0)	2 (33.3)	7 (25.0)	4 (50.0)
Other	1 (25.0)	2 (33.3)	1 (12.5)	0	0	4 (14.3)	1 (12.5)
Ethnicity, n (%)							
Hispanic/Latino	1 (25.0)	0	3 (37.5)	0	0	4 (14.3)	0
Not Hispanic/Latino	1 (25.0)	3 (50.0)	1 (12.5)	1 (25.0)	2 (33.3)	8 (28.6)	4 (50.0)
Not Reported	2 (50.0)	3 (50.0)	4 (50.0)	3 (75.0)	4 (66.7)	16 (57.1)	4 (50.0)

Max = maximum; Min = minimum; SD = standard deviation; Trt = treatment

[a] Brivanib alaninate (or matching placebo) was administered as a single oral dose on C1D1 and as continuous daily oral doses beginning on C1D15.

[b] Beginning on C1D8, IV Erbitux was administered qw at a loading dose of 400 mg/m^2 and thereafter at 250 mg/m^2, and IV irinotecan was administered q3w at 350 mg/m^2 (Cohorts 1 to 4 [Trt A to D and placebo]) or at a starting dose of 300 mg/m^2 with an option to increase the dose to 350 mg/m^2 beginning at C3D1 in the absence of ≥Grade 3 toxicity in the first 2 cycles (Cohort 5 [Trt E]).

SUMMARY OF SAFETY RESULTS:

The MTD of brivanib alaninate, when administered in combination with Erbitux/irinotecan, was 600 mg.

An overview of adverse events (AEs) reported in study CA182025 is provided in Table 3. The most frequently reported AEs (>50% of subjects on brivanib alaninate [any dose]), which were also the most frequent treatment-related AEs, were diarrhoea, nausea, rash, abdominal pain, alopecia, decreased appetite, and vomiting. While there were no clear dose-related trends in the frequency of AEs across doses of brivanib alaninate, the severity of some laboratory-related AEs (i.e., neutropenia, increased alanine aminotransferase [ALT], and increased aspartate aminotransferase [AST]) appeared to worsen with increasing dose of brivanib alaninate and this contributed to the greater frequency of dose limiting toxicities (DLTs) in the highest (800 mg) dose cohorts (see below).

Of the adverse events of special interest (AEOSIs) previously defined for the brivanib alaninate clinical program, events reported in this study for subjects receiving brivanib alaninate included increased ALT (9 [32.1%] subjects), increased AST (8 [28.6%] subjects), hypertension (4 [14.3%] subjects), proteinuria (4 [14.3%] subjects), hyponatremia, increased blood bilirubin, hyperbilirubinemia, increased gamma glutamyltransferase [GGT], or increased blood alkaline phosphatase (2 [7.1%] subjects each), and haemorrhagic diarrhoea, portal vein thrombosis, inferior vena cava thrombosis, and venous thrombosis (1 [3.6%] subject each). All AEOSIs were ≤ Grade 3 in severity, and all but 3 AEOSIs were non-serious. The 3 serious AEOSIs, all of which were unrelated to study treatment, were Grade 2 increased ALT, Grade 3 increased AST, and Grade 4 hyperbilirubinemia. No cases of Hy's law were identified based on medical review of data for subjects with elevations in ALT, AST, and bilirubin.

A majority of AEs were non-serious and Grade 1 or 2 in severity. Of the Grade 4 AEs, neutropenia was the only event assessed as related to treatment. Treatment-related Grade 4 neutropenia was reported for 4 brivanib alaninate-treated subjects at doses of 400 mg, 800 mg (Cohort 4), and 800 mg (Cohort 5, n=2), as well as for 2 placebo subjects.

Treatment-related SAEs were reported for 4 subjects receiving brivanib alaninate, and included Grade 3 diarrhoea (brivanib alaninate 400 mg), Grade 3 febrile neutropenia (1 subject each at brivanib alaninate 600 mg and brivanib alaninate 800 mg [Cohort 5]), and Grade 3 febrile neutropenia/Grade 4 neutropenia (brivanib alaninate 800 mg [Cohort 5]).

No treatment-related Grade 5 (fatal) AEs were reported for any subject receiving brivanib alaninate. One placebo subject died of cardiac arrest that was assessed (in a blinded manner) as related to study treatment. Deaths due to disease progression (and unrelated to treatment) were reported for 3 other brivanib alaninate-treated subjects and 1 placebo subject.

A total of 5 brivanib alaninate-treated subjects discontinued study treatment due to AEs, including 3 subjects who discontinued due to treatment-related AEs: alopecia, conjuctivitis, and abdominal pain (brivanib alaninate 600 mg), increased ALT and AST (brivanib alaninate 600 mg), and nausea and vomiting (brivanib alaninate 800 mg [Cohort 4]). In the latter case, the AEs of nausea and vomiting occurred concurrently with diarrhoea and were reported as DLTs. Overall, 7 subjects experienced DLTs during combination therapy with brivanib alaninate and Erbitux/irinotecan:

- Cohort 3 (600 mg, n=8): 1 subject, Grade 3 diarrhoea
- Cohort 4 (800 mg, n=4): 2 subjects, Grade 3 diarrhoea/nausea/vomiting and Grade 4 neutropenia
- Cohort 5 (800 mg, n=6): 4 subjects, Grade 3 febrile neutropenia; Grade 4 neutropenia; Grade 3 increased ALT/increased AST; and Grade 3 febrile neutropenia/haemorrhagic diarrhoea

Study treatment was interrupted in all 7 subjects due to these DLTs, and one subject ultimately discontinued treatment due to recurrent episodes of nausea, vomiting, and diarrhoea; the other 6 subjects were reported as discontinuing due to causes unrelated to study treatment (disease progression or other AEs). The occurrence of DLTs in 4 subjects in Cohort 5 met the pre-defined stopping criterion for the study.

Table 3: Summary of Subjects Reporting Adverse Events in Study CA182025

System Organ Class Preferred Term	Brivanib alaninate (dose in mg)[a] + Erbitux / Irinotecan[b]						Placebo[a] + Erbitux / Irinotecan[b]
	Trt A (200 mg) N=4	Trt B (400 mg) N=6	Trt C (600 mg) N=8	Trt D (800 mg) N=4	Trt E (800 mg) N=6	Trt A to E (All Doses) N=28	N=8
Subjects with Any AE, n (%)	4 (100)	6 (100)	8 (100)	4 (100)	6 (100)	28 (100)	8 (100)
Most Common AEs							
Diarrhoea	4 (100)	6 (100)	6 (75.0)	3 (75.0)	3 (50.0)	22 (78.6)	8 (100)
Nausea	3 (75.0)	3 (50.0)	5 (62.5)	3 (75.0)	5 (83.3)	19 (67.9)	7 (87.5)
Abdominal pain	2 (50.0)	3 (50.0)	5 (62.5)	3 (75.0)	3 (50.0)	16 (57.1)	3 (37.5)
Vomiting	3 (75.0)	3 (50.0)	3 (37.5)	3 (75.0)	3 (50.0)	15 (53.6)	6 (75.0)
Rash	4 (100)	4 (66.7)	3 (37.5)	2 (50.0)	4 (66.7)	17 (60.7)	3 (37.5)
Alopecia	3 (75.0)	4 (66.7)	5 (62.5)	1 (25.0)	3 (50.0)	16 (57.1)	3 (37.5)
Decreased appetite	2 (50.0)	4 (66.7)	3 (37.5)	3 (75.0)	4 (66.7)	16 (57.1)	5 (62.5)
Subjects with CTC Grade 4 AE[c], n (%)	0	1 (16.7)	1 (12.5)	1 (25.0)	3 (50.0)	6 (21.4)	4 (50.0)
Neutropenia	0	1 (16.7)	1 (12.5)	1 (25.0)	2 (33.3)	5 (17.9)	4 (50.0)
Decreased neutrophil count	0	0	0	0	1 (16.7)	1 (3.6)	0
Neutropenic infection	0	0	0	1 (25.0)	0	1 (3.6)	0
Hyperbilirubinemia	0	0	0	1 (25.0)	0	1 (3.6)	0
Subjects with Any SAE, n (%)	1 (25.0)	2 (33.3)	2 (25.0)	2 (50.0)	3 (50.0)	10 (35.7)	5 (62.5)
Deaths, n (%)	0	1 (16.7)	1 (12.5)	1 (25.0)	0	3 (10.7)	2 (25.0)
Subjects with AE Leading to Discontinuation, n (%)	0	1 (16.7)	2 (25.0)	2 (50.0)	0	5 (17.9)	1 (12.5)

AE = adverse event; CTC = Common Terminology Criteria; SAE = serious adverse event; Trt = treatment

[a] Brivanib alaninate (or matching placebo) was administered as a single oral dose on C1D1 and as continuous daily oral doses beginning on C1D15.

[b] Erbitux was administered IV at 400 mg/m^2 on C1D8 and qw thereafter at 250 mg/m^2. With the exception of Trt E, irinotecan was administered IV at 350 mg/m^2 on C1D8 and q3w thereafter at the same dose. In Trt E, irinotecan was administered IV at 300 mg/m^2 on C1D8 and q3w thereafter at the same dose or, in the absence of ≥ Grade 3 toxicity in the first 2 cycles and at the Investigator's discretion, at an increased dose of 350 mg/m^2 beginning on C3D1

[c] Includes all subjects for whom the AE of greatest severity during the treatment period was Grade 4. (This includes all subjects with a Grade 4 AE during the treatment period, as the one subject with a Grade 5 AE during the treatment period had no Grade 4 AEs.)

CONCLUSIONS:

Part I of study CA182025 accomplished its primary objective of defining a dose of brivanib alaninate that may be safely administered in combination with Erbitux/irinotecan in K-Ras wild type subjects with advanced MCRC.

- The MTD of brivanib alaninate, when administered in combination with Erbitux (400 mg/m^2 loading dose + 250 mg/m^2 qw) and irinotecan (350 mg/m^2 q3w), was 600 mg once daily.
- Reducing the dose of irinotecan from 350 mg/m^2 to 300 mg/m^2 did not appear to improve the tolerability profile of the regimen when administered in combination with brivanib alaninate and Erbitux.
- No new toxicities were reported with combination therapy that had not been previously observed with either brivanib alaninate monotherapy or the approved Erbitux and irinotecan regimens given in this study.

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