Supplementary Information

A phase 1b study evaluating the safety and pharmacokinetics of regorafenib in combination with cetuximab in patients with advanced solid tumors

Colin Weekes[1], A. Craig Lockhart[2], James J. Lee[3], Isrid Sturm[4], Adriaan Cleton[4], Funan Huang[5], Heinz-Josef Lenz[6]

[1]Massachusetts General Hospital, Boston, MA; [2]University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]Bayer AG, Berlin, Germany; [5]Bayer HealthCare Pharmaceuticals, Whippany, NJ; [6]University of Southern California/Norris Comprehensive Center, Los Angeles, CA.

Supporting Information

Table S1. Most frequent TEAEs irrespective of causality during the combination treatment phase (≥9 patients; safety analysis set, *N* = 42)

MedDRA preferred term, n (%)	Continuous regorafenib 60 mg plus cetuximab *n* = 5		Continuous regorafenib 100 mg plus cetuximab *n* = 6		Intermittent regorafenib 120 mg plus cetuximab *n* = 8		Intermittent regorafenib 160 mg plus cetuximab *n* = 23		Total *N* = 42	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Fatigue	4 (80)	0	5 (83)	3 (50)	4 (50)	1 (13)	9 (39)	3 (13)	22 (52)	7 (17)
Hypophosphatemia	3 (60)	3 (60)	3 (50)	0	6 (75)	6 (75)	8 (35)	4 (17)	20 (48)	13 (31)
Diarrhea	4 (80)	2 (40)	3 (50)	0	3 (38)	0	7 (30)	1 (4)	17 (40)	3 (7)
Hypertension	4 (80)	1 (20)	2 (33)	0	0	0	8 (35)	2 (9)	15 (36)	3 (7)
Decreased appetite	2 (40)	0	3 (50)	0	2 (25)	1 (13)	8 (35)	1 (4)	15 (36)	2 (5)
Nausea	2 (40)	1 (20)	0	0	3 (38)	0	9 (39)	2 (9)	14 (33)	3 (7)
AST increased	2 (40)	0	3 (50)	0	1 (13)	0	7 (30)	2 (9)	13 (31)	2 (5)
Dermatitis acneiform	3 (60)	1 (20)	3 (50)	0	1 (13)	0	6 (26)	0	13 (31)	1 (2)
Constipation	2 (40)	0	1 (17)	0	1 (13)	0	8 (35)	0	12 (29)	0
Hyponatremia	3 (60)	1 (20)	4 (67)	0	0	0	5 (22)	1 (4)	12 (29)	2 (5)
ALT increased	1 (20)	0	3 (50)	0	0	0	7 (30)	2 (9)	11 (26)	2 (5)
Hypoalbuminemia	2 (40)	1 (20)	3 (50)	0	0	0	6 (26)	1 (4)	11 (26)	2 (5)
Vomiting	1 (20)	0	0	0	3 (38)	0	6 (26)	2 (9)	10 (24)	2 (5)
Hypokalemia	3 (60)	0	1 (17)	0	1 (13)	0	6 (26)	1 (4)	11 (26)	1 (2)
Hypomagnesemia	1 (20)	0	2 (33)	0	1 (13)	0	7 (30)	1 (4)	11 (26)	1 (2)

Dysphonia	1 (20)	0	2 (33)	1 (17)	2 (25)	0	6 (26)	0	11 (26)	1 (2)
Hypocalcemia	4 (80)	0	3 (50)	0	1 (13)	0	3 (13)	0	11 (26)	0
Chills	0	0	0	0	2 (25)	0	7 (30)	0	9 (21)	0
Weight decreased	1 (20)	0	1 (17)	0	1 (13)	0	7 (30)	0	10 (24)	0
Dyspnea	2 (40)	0	2 (33)	0	1 (13)	0	5 (22)	0	10 (24)	0
Gamma-glutamyltransferase increased	1 (20)	1 (20)	3 (50)	2 (33)	1 (13)	1 (13)	3 (13)	0	8 (19)	4 (10)
Dehydration	2 (40)	1 (20)	3 (50)	0	0	0	3 (13)	0	8 (19)	1 (2)
Rash	0	0	0	0	6 (75)	0	3 (13)	0	9 (21)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

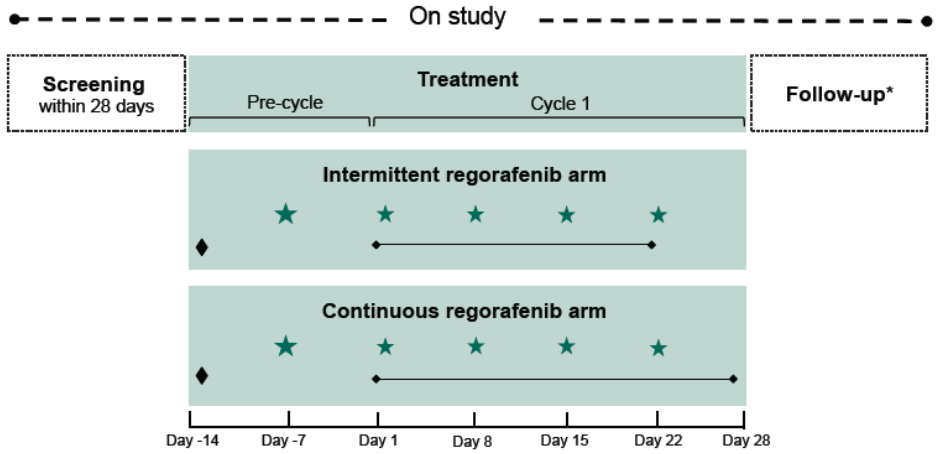
Table S2. Hematologic and biochemical toxicities of worst CTCAE grades 3 or 4 (safety analysis set)

NCI-CTCAE categories and terms	Worst CTCAE grade	Continuous regorafenib 60 mg plus cetuximab *n* = 5	Continuous regorafenib 100 mg plus cetuximab *n* = 6	Intermittent regorafenib 120 mg plus cetuximab *n* = 8	Intermittent regorafenib 160 mg plus cetuximab *n* = 23	Total *N* = 42
Blood and lymphatic system disorders, n/N (%)						
Anemia	Grade 3	1/4 (25)	0/6	0/8	0/21	1/39 (3)
Investigations, n/N (%)						
aPTT prolonged	Grade 3	0/2	0/2	0/5	2/8 (25)	2/17 (12)
ALT increased	Grade 3	0/4	1/6 (17)	0/8	2/21 (10)	3/39 (8)
Alkaline phosphatase increased	Grade 3	1/4 (25)	0/6	0/8	2/21 (10)	3/39 (8)
AST increased	Grade 3	0/4	1/6 (17)	0/8	1/21 (5)	2/39 (5)
	Grade 4	0/4	0/6	0/8	1/21 (5)	1/39 (3)
Blood bilirubin increased	Grade 3	0/4	2/6 (33)	0/8	1/21 (5)	3/39 (8)
Creatinine increased	Grade 3	0/4	0/6	0/8	1/21 (5)	1/39 (3)
Gamma-glutamyltransferase increased	Grade 3	2/4 (50)	2/6 (33)	1/8 (13)	6/21 (29)	11/39 (28)
INR increased	Grade 3	0/0	0/1	0/2	1/5 (20)	1/8 (13)
Lipase increased	Grade 3	1/4 (25)	1/6 (17)	0/8	2/21 (10)	4/39 (10)
	Grade 4	1/4 (25)	0/6	0/8	0/21	1/39 (3)
Lymphocyte count decreased	Grade 3	2/4 (50)	4/6 (67)	0/8	4/21 (19)	10/39 (26)
	Grade 4	1/4 (25)	0/6	0/8	1/21 (5)	2/39 (5)

Platelet count decreased	Grade 4	0/4	1/6 (17)	0/8	0/21	1/39 (3)
Serum amylase increased	Grade 3	1/4 (25)	0/6	0/8	0/21	1/39 (3)
Metabolism and nutrition disorders n/N (%)						
Hyperglycemia	Grade 3	0/4	1/6 (17)	0/8	5/21 (24)	6/39 (15)
Hyperkalemia	Grade 3	0/4	0/6	0/8	1/21 (5)	1/39 (3)
Hypoalbuminemia	Grade 3	1/4 (25)	0/6	0/8	1/21 (5)	2/39 (5)
Hypokalemia	Grade 3	0/4	0/6	0/8	1/21 (5)	1/39 (3)
Hypomagnesemia	Grade 3	0/4	0/6	1/8 (13)	1/21 (5)	2/39 (5)
Hyponatremia	Grade 3	1/4 (25)	1/6 (17)	0/8	2/21 (10)	4/39 (10)
Hypophosphatemia	Grade 3	3/4 (75)	0/6	7/8 (88)	4/21 (19)	14/39 (36)

Abbreviations: aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Figure S1. Study design



★ Cetuximab IV infusion every 7 days, including a loading dose on Day -7

♦ Oral regorafenib single-dose administration

◆—◆ Oral regorafenib once daily multiple-dose administration

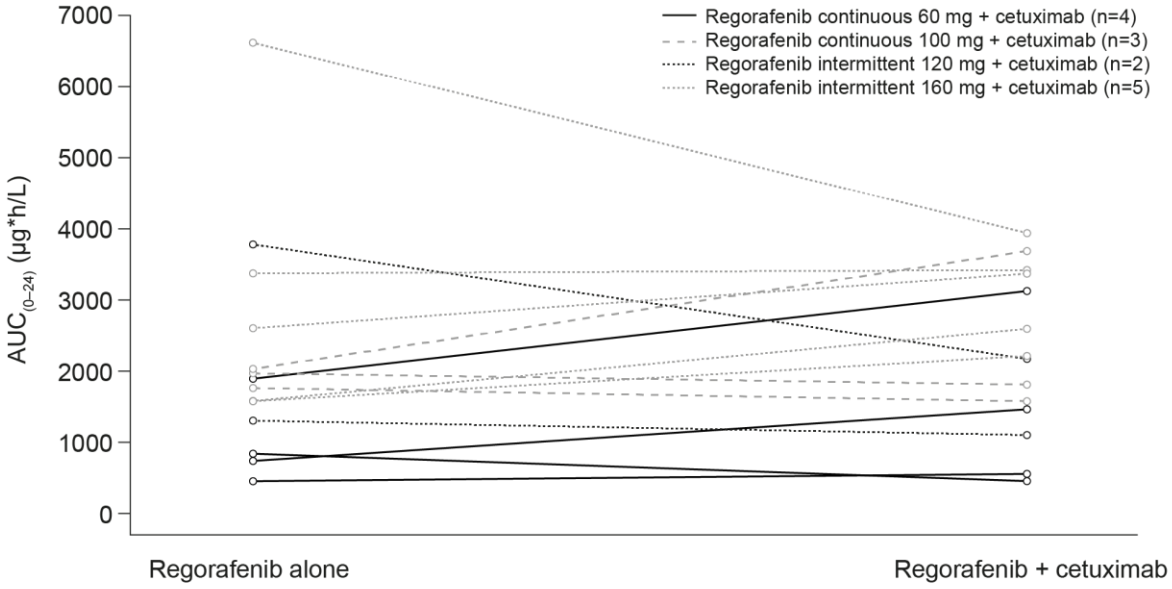
***Follow-up:**

- End-of-treatment visit within 7–14 days of last treatment
- Follow-up visit/contact at 30 days after last treatment

Patients could continue therapy until tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study.

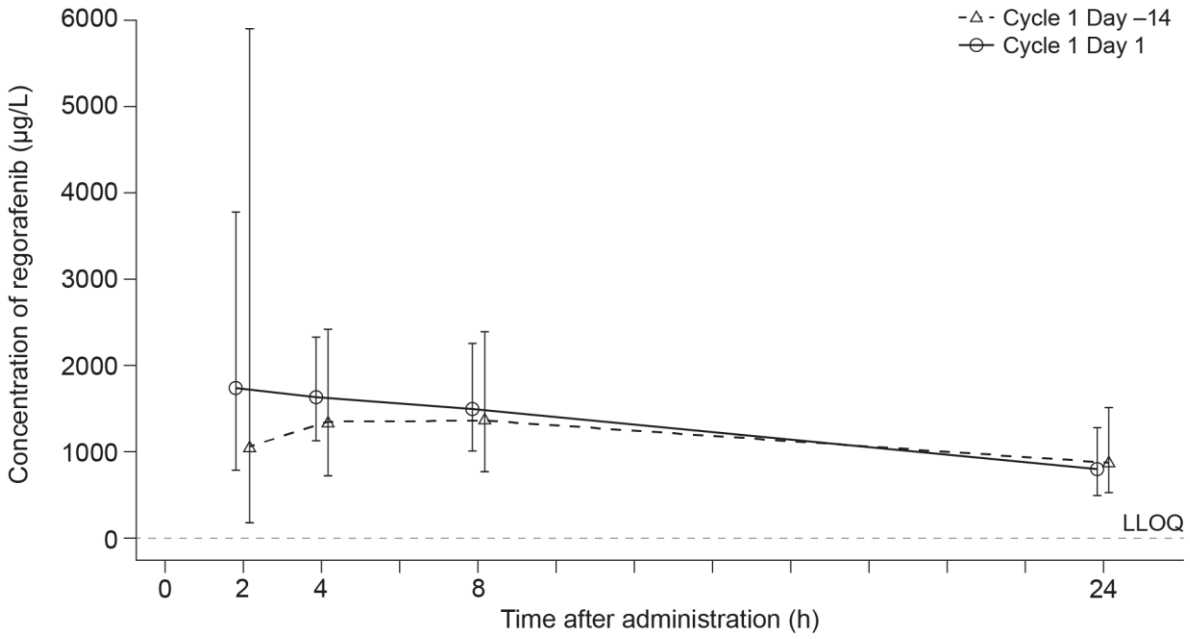
IV, intravenous.

Figure S2. Individual $AUC_{(0–24)}$ of regorafenib in the absence (Day –14) and presence of cetuximab (Day 1) at all dose levels



Abbreviations: AUC, area under the concentration–time curve.

Figure S3. Geometric mean plasma concentration–time profiles with standard deviation of regorafenib 160 mg QD administered alone (Day −14) or with a single dose of cetuximab (Day 1)



Abbreviations: LLOQ, lower limit of quantification; QD, once daily.