Phase I Study of Everolimus, Cetuximab and Irinotecan as Second-line Therapy in Metastatic Colorectal Cancer

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Abstract. *Aim: To evaluate feasible doses of weekly everolimus and irinotecan given with cetuximab for previously treated metastatic colorectal cancer (mCRC). Patients and Methods: Adults with mCRC that progressed after 5-fluorouracil or capecitabine-plus-oxaliplatin were treated using a sequential dose escalation scheme. Dosing decisions were based on the probability of experiencing a dose-limiting toxicity (DLT) during the first two 21-day treatment cycles. Results: Patients received everolimus 30 mg/week plus irinotecan 350 mg/m^2 q3w (n=5; dose A1) or everolimus 30 mg/week plus irinotecan 250 mg/m^2 q3w (n=14; dose B1). Among patients evaluable for the maximum tolerated dose, two out of four in A1 and one out of eight in B1 experienced four DLTs. The trial was terminated early based on changes in clinical practice and emerging data on everolimus dosing. Conclusion: The feasible doses of everolimus and irinotecan administered with cetuximab as second-line therapy in mCRC were 30 mg/week and 250 mg/m^2, respectively.*

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Modern chemotherapy agents such as fluoropyrimidines, oxaliplatin, and irinotecan have significantly improved the survival of patients with metastatic colorectal cancer (mCRC) (1, 2). Adding antibodies to vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) to standard cytotoxic chemotherapy extends survival in patients with mCRC (3, 4). The EGFR antibodies cetuximab and panitumumab, given as monotherapy or in combination with irinotecan, have become a standard of care for the treatment of mCRC (3, 5-9). Although some patients benefit from treatment with EGFR antibodies, many do not, and eventually, all patients experience disease progression.

Mutations in the Kirsten rat sarcoma viral oncogene homolog gene (*KRAS*) occur in approximately 40% of CRC and are a cause of primary and acquired resistance to EGFR-targeted therapy (10, 11). However, even *KRAS* wild-type tumors may not respond to EGFR-targeted therapy. Alterations in the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway, a central regulator of cell proliferation, growth, metabolism, and angiogenesis, have been proposed as one mechanism of resistance to EGFR-targeted therapy (12). In patients with CRC, 12%-20% harbor PIK3CA mutations, 61% demonstrate overexpression of mTOR and phosphorylated mTOR, and 50% show loss of PTEN, a negative pathway regulator (13, 14). The Cancer Genome Atlas Network reported that among a series of 276 CRC tumors that underwent whole-exome sequencing, more than 50% had alterations in PI3K signaling

(15). In patients, mTOR overexpression is significantly associated with tumor stage, metastatic potential, and degree of differentiation of CRC (16).

Everolimus is an orally-administered mTOR inhibitor approved for use for advanced renal cell carcinoma following failure of VEGF-targeted therapy; for advanced, progressive, low- to intermediate-grade pancreatic neuroendocrine tumors; and, in combination with exemestane, for advanced hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer following failure of anastrozole or letrozole (17-19). In pre-clinical CRC models, oral everolimus inhibited CRC cell proliferation and tumor growth (20-22). Of note, everolimus provided dose-dependent inhibition of cell growth in CRC cell lines regardless of their sensitivity to EGFR inhibitors and inhibited the growth of EGFR-sensitive and -resistant CRC xenografts (22). This same study demonstrated that everolimus and gefitinib provided a synergistic antitumor activity in both EGFR-sensitive and -resistant CRC xenograft models. Clinically, everolimus demonstrated anticancer activity in patients with mCRC enrolled in phase I studies of everolimus in advanced solid tumors (23, 24). In one study, 2 out of 18 patients with mCRC were progression-free for 4 to 6 months, and another patient experienced partial response (PR) and was progression-free for ≥6 months (23). In the second study, which included 16 patients with mCRC, one patient with heavily pretreated mCRC achieved a PR that lasted 5.3 months (24).

A phase I clinical study was conducted to determine the maximum tolerated dose (MTD) of everolimus given in combination with irinotecan and cetuximab in patients with mCRC who progressed on previous chemotherapy (ClinicalTrials.gov identifier NCT00478634).

Patients and Methods

Patients. Inclusion criteria were age 18 to 65 years, histopathologically or cytologically-confirmed mCRC, progressive disease despite previous therapy with FOLFOX (5-fluorouracil and oxaliplatin) or XELOX (capecitabine and oxaliplatin) plus bevacizumab (if given as part of local standard practice), one or more measurable lesions per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (25), World Health Organization performance status 0 or 1, and adequate organ function. Exclusion criteria included Gilbert's syndrome or other conditions associated with deficient bilirubin glucuronidation, homozygosity for the UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) *28 allele, previous irinotecan or mTOR inhibitor treatment, long-term immunosuppressive therapy, any severe or uncontrolled medical conditions, and untreated or unstable central nervous system metastases.

This study was conducted according to ethical principles of the Declaration of Helsinki and the study protocol, which was reviewed by the independent Ethics Committee or Institutional Review Board for each center. Before enrollment, all patients provided written informed consent.

Study design and treatment. This was a multicenter, open-label, sequential dose-escalation, phase I study. Up to three dose levels of oral everolimus (30 mg, 50 mg, and 70 mg once weekly) were to be investigated with a fixed dose of intravenous cetuximab (400-mg/m^2 loading dose followed by 250 mg/m^2 once weekly thereafter) and two possible dose levels of intravenous irinotecan (350 mg/m^2 or 250 mg/m^2 once every 3 weeks). The starting dose level (A1) was everolimus 30 mg/week plus irinotecan 350 mg/m^2. If the higher irinotecan dose was not tolerated, the lower dose was to be used for dose escalation from dose level B1 to B3. Dose-escalation decisions were driven by the probability of experiencing a dose-limiting toxicity (DLT) in the first two cycles, as evaluated using a Bayesian four parameter logistic model. Predefined DLTs were grade 3/4 noninfectious pneumonitis; febrile neutropenia or grade 4 thrombocytopenia of any duration; grade 3/4 neutropenia or grade 3 thrombocytopenia lasting 7 days or more or recurring in the same cycle; any grade 4 nonhematological adverse event (AE) despite appropriate prophylactic treatment occurring at any time; any grade 3 non-hematological AE despite appropriate prophylactic treatment lasting 7 days or recurring in the same cycle; or any AE resulting in more than 2 week interruption or delay in any study treatment. Hyperlipidemia, hyperglycemia, and alopecia of any grade were not considered DLTs. The next dose level chosen for evaluation was that which maximized the probability that the end-of-cycle-two DLT rate would be within the targeted toxicity interval (20% to <35%) and minimized the risk of overdose (<5% risk of unacceptable toxicity and <25% risk of excessive/unacceptable toxicity).

At each decision-making time point during dose level A1, the decision was to continue recruitment at dose level A1, declare 350 mg/m^2 the feasible irinotecan dose and recruit at dose level A2 (irinotecan 350 mg/m^2 plus everolimus 50 mg/week), or declare irinotecan 350 mg/m^2 unfeasible and recruit at dose level B1 (irinotecan 250 mg/m^2 plus everolimus 20 mg/week). If patients were recruited at dose level B1 and 250 mg/m^2 was considered unfeasible, the trial was stopped. Once the feasible irinotecan dose was determined, the everolimus dosing decision at each time point was to continue recruitment at the same dose level, commence recruitment at a higher or lower dose level, or stop and declare the feasible dose level if there was an acceptable level of confidence in the safety profile of the everolimus, irinotecan, and cetuximab doses.

Assessments. All patients were followed up for safety throughout the study and for 28 days following the last everolimus dose. Safety was assessed according to the frequency of AEs and abnormal laboratory values. AE severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (26).

Two-milliliter venous blood samples for pharmacokinetic assessment of everolimus were collected predose and 0.5, 1, 2, 4, 24, and 168 h post-dose on day 8 of cycle 1, on day 1 of cycle 2, and predose on day 1 of cycle 3 and every cycle thereafter. Everolimus concentrations in whole blood were determined by liquid chromatography/mass spectrometry following liquid extraction (lower limit of quantification, 0.368 ng/ml). For pharmacokinetic assessment of irinotecan, 5.5-ml venous blood samples were collected predose, at the end of infusion, and 4, 6, 8, 24, and 48 h after the start of infusion on day 1 of cycles 1 and 2. Irinotecan concentrations in plasma were determined by reverse-phase high-performance liquid chromatography with fluorescence detection (lower limit of quantification, 5 ng/ml).

Tumor assessments were performed by computed tomography or magnetic resonance imaging at baseline and every 9 weeks until documented disease progression. End-points included objective response rate (ORR) [*i.e.* proportion of patients with complete or partial response per RECIST (local review)]; progression-free survival (PFS) (*i.e.* time from start of study treatment to date of first documented disease progression per RECIST or death due to any cause); and overall survival (OS) (*i.e.* time from start of treatment to date of death from any cause).

Statistical analyses. The full analysis set included all patients who received one or more doses of study treatment and was used for all efficacy analyses. The safety set included all patients who received one or more doses of study treatment and had one or more post-baseline safety assessments. The MTD population included all patients from the safety population who had a relative dose intensity of ≥75% or experienced a DLT during the first two treatment cycles; patients who permanently discontinued any study drug during the first two treatment cycles for a reason other than a DLT were excluded. The pharmacokinetic population included all patients from the full analysis set with a sufficient number of evaluable blood samples.

Sample size was dependent on the number of dose levels assessed before the MTD was reached. Experience with similar four-parameter Bayesian logistic models suggested six patients per dose level would be sufficient. Once the selected dose combination was chosen, it was planned to expand that cohort to 24 patients to ensure sufficient data for pharmacokinetic analysis. With a total sample size of 70 patients and allowing for assessment of all six dose levels, at least eight patients could have been included in each of the non-MTD dose levels, assuming <10% of patients were excluded from the MTD population.

Results

Patients' characteristics. Patients were enrolled between May 15, 2007, and November 4, 2008. After enrollment of 19 patients (n=5 at dose level A1; n=14 at dose level B1), the study was terminated because of the low recruitment rate and changes in clinical practice related to irinotecan and everolimus dosing. All patients received more than one dose of any component of study drug. One patient at dose A1 was found to be ineligible during cetuximab infusion and was discontinued before receiving irinotecan or everolimus. Two patients at dose B1 did not receive everolimus; one patient withdrew consent after cetuximab and irinotecan infusion, and one patient died from advanced disease on day 3.

At the time of final analysis, all patients had discontinued treatment, most commonly because of disease progression (31.6% of patients across dose levels). The median patient age was 58.0 years, and most enrolled patients were Caucasian (84.2%) and male (63.2%) (Table I). Previous antineoplastic medications included oxaliplatin in 100% of patients, fluorouracil in 89.5%, folinic acid in 84.2%, and bevacizumab in 68.4% (Table I).

MTD determination. Four out of five patients enrolled at dose level A1 were included in the MTD population. Two of these patients reported three DLTs [grade 3 rash and stomatitis starting in cycle 2 and lasting more than 7 days (n=1); grade 3 stomatitis starting in cycle 1 and lasting more than 7 days (n=1)]. Based on the 50% DLT rate, enrollment was initiated at dose level B1. Eight of 14 patients enrolled at level B1 were included in the MTD population, and one of these patients experienced a DLT (grade 3 neutropenia starting during cycle 1 and lasting more than 7 days). Although the MTD was not reached before study termination, everolimus 30 mg/week plus irinotecan 250 mg/m^2 every 3 weeks and weekly cetuximab was concluded to be a feasible dose regimen in patients with previously treated mCRC.

Safety. At dose levels A1 and B1, the median (range) duration of exposure to any component of the study regimen was 4.0 weeks (1 to 31 weeks) and 6.0 weeks (1 to 55 weeks), respectively. The median (range) number of treatment cycles for everolimus, irinotecan, and cetuximab was 4 (1 to 9), 4 (1 to 9), and 1 (1 to 10), respectively, at level A1, and 3.5 (1 to 18), 2.5 (1 to 18), and 2.5 (1 to 18), respectively, at level B1.

All 18 patients in the safety population experienced ≥1 AE, most commonly abdominal pain, fatigue, nausea, and diarrhea (Table II). Most AEs were of grade 1 or 2 severity and resolved with appropriate treatment. Thirteen patients (72.2%) experienced grade 3/4 AEs, including all four patients treated at dose level A1 and nine patients (64.3%) treated at dose level B1. Grade 3/4 AEs reported in more than one patient were neutropenia (n=2 at A1; n=1 at B1), stomatitis (n=2, both at A1), and hypokalemia (n=2, both at B1). Grade 4 AEs, all of which were reported by one patient in dose level B1, were neutropenia, cardiac arrest, hypokalemia, musculoskeletal pain, and mental status changes. AEs of clinical interest for everolimus were observed in 15 patients (83.3%), most frequently myelosuppression (55.6%), stomatitis/oral mucositis/ulcers (50.0%), rash and similar events (44.4%), and infections and infestations (38.9%). Six patients at dose level B1 (42.9%) experienced serious AEs. AEs leading to treatment discontinuation were reported for one patient at dose level A1 (25.0%, grade 3 stomatitis) and five patients (35.7%) at dose level B1 (one event each of grade 2 diarrhea, fever, and abnormal liver chemistry; grade 3 abnormal liver chemistry; and grade 4 cardiac arrest). One patient died within 28 days of treatment discontinuation; this death was not considered to be related to study treatment.

Efficacy. In the full analysis set, the best overall response at dose level A1 was stable disease (n=2; 40.0%). At dose level B1, the best overall response was PR [n=2; ORR, 14.3%; 95% confidence interval (CI)=1.8% to 42.8%]; an additional four patients (28.6%) experienced stable disease. Median PFS and OS were 2.9 months (95% CI=1.2 months to not reached) and 5.8 months (95% CI=1.2 to 13.1 months), respectively, at dose A1, and 5.9 months (95% CI=0.1 to

Table I. *Disease history and baseline characteristics (full analysis set).*

Characteristic	Dose level A1 (n=5)	Dose level B1 (n=14)	All patients (N=19)
Median (range) age, years,	59.0 (52-63)	56.0 (18-67)	58.0 (18-67)
Male, n (%)	3 (60.0)	9 (64.3)	12 (63.2)
Race, n (%)			
Caucasian	3 (60.0)	13 (92.9)	16 (84.2)
Other	2 (40.0)	1 (7.1)	3 (15.8)
WHO performance status 0/1, n (%)	3 (60.0)/2 (40.0)	6 (42.9)/8 (57.1)	9 (47.4)/10 (52.6)
Primary site of cancer, n (%)			
Colon	3 (60.0)	8 (57.1)	11 (57.9)
Rectum	2 (40.0)	6 (42.9)	8 (42.1)
Histological grade, n (%)			
Well-differentiated	0	4 (28.6)	4 (21.1)
Moderately-differentiated	5 (100.0)	6 (42.9)	11 (57.9)
Poorly-differentiated	0	2 (14.3)	2 (10.5)
Unknown	0	2 (14.3)	2 (10.5)
Visceral involvement, n (%)	5 (100.0)	9 (64.3)	14 (73.7)
Prior antineoplastic therapy, n (%)			
Radiotherapy	1 (20.0)	6 (42.9)	7 (36.8)
Surgery	5 (100.0)	13 (92.9)	18 (94.7)
Medications			
Oxaliplatin	5 (100.0)	14 (100.0)	19 (100.0)
Fluorouracil	4 (80.0)	13 (92.9)	17 (89.5)
Folinic acid	3 (60.0)	13 (92.9)	16 (84.2)
Bevacizumab	5 (100.0)	8 (57.1)	13 (68.4)
Capecitabine	3 (60.0)	2 (14.3)	5 (26.3)
Calcium folinate	1 (20.0)	0	1 (5.3)
FOLFOX-4	0	1 (7.1)	1 (5.3)
Panitumumab	0	1 (7.1)	1 (5.3)

FOLFOX, Oxaliplatin + leucovorin + 5-fluorouracil; WHO, World Health Organization

10.3 months) and 17.5 months (95% CI=4.4 to 20.2 months), respectively, at dose B1.

The planned pharmacokinetic analyses could not be performed because of the low number of patients with valid pharmacokinetic samples.

Discussion

This phase I study assessed the MTD of weekly everolimus given with irinotecan and cetuximab in patients with mCRC who progressed on previous chemotherapy. While this study was in progress, emerging data indicated that cetuximab has limited to no efficacy in patients whose tumors harbor *KRAS* mutations (27) and that daily everolimus dosing would provide better efficacy than weekly dosing (24, 28). Furthermore, although administering irinotecan once every 3 weeks is at least as effective as and is less toxic than once-weekly dosing (29), irinotecan is now usually dosed once every other week when given with anti-EGFR antibodies (30). These changes in clinical practice, coupled with the low recruitment rate, led to the decision to terminate the study

Table II. *Adverse events of any grade occurring in ≥20% of all patients (safety set).*

Adverse event, n (%)	Dose level A1 (n=4)	Dose level B1 (n=14)	All patients (N=18)
Abdominal pain	3 (75.0)	7 (50.0)	10 (55.6)
Fatigue	4 (100.0)	6 (42.9)	10 (55.6)
Nausea	3 (75.0)	7 (50.0)	10 (55.6)
Diarrhea	2 (50.0)	7 (50.0)	9 (50.0)
Rash	1 (25.0)	7 (50.0)	8 (44.4)
Stomatitis	3 (75.0)	5 (35.7)	8 (44.4)
Anemia	2 (50.0)	5 (35.7)	7 (38.9)
Constipation	3 (75.0)	4 (28.6)	7 (38.9)
Anorexia	3 (75.0)	4 (28.6)	7 (38.9)
Hypokalemia	1 (25.0)	6 (42.9)	7 (38.9)
Vomiting	1 (25.0)	5 (35.7)	6 (33.3)
Alopecia	2 (50.0)	3 (21.4)	5 (27.8)
Hypomagnesemia	1 (25.0)	4 (28.6)	5 (27.8)
Neutropenia	2 (50.0)	3 (21.4)	5 (27.8)
Dehydration	3 (75.0)	1 (7.1)	4 (22.2)
Dry skin	1 (25.0)	3 (21.4)	4 (22.2)
Dyspnea	2 (50.0)	2 (14.3)	4 (22.2)

early. Based on data collected before termination, everolimus 30 mg/week given with irinotecan 250 mg/m^2 every 3 weeks plus weekly cetuximab (dose level B1) appears to be a feasible treatment regimen for CRC patients.

The overall tolerability of the combination is supported by the low DLT rate and the fact that most AEs were of grade 1 or 2 severity and were manageable without study discontinuation. Although 72.2% of patients experienced ≥1 grade 3/4 AEs, the only individual grade 3/4 AEs experienced by more than one patient were neutropenia (n=3), stomatitis (n=2), and hypokalemia (n=2). Overall, the safety profile observed was generally consistent with the known safety profile of study treatment. Toxicities associated commonly with everolimus and other mTOR inhibitors include stomatitis and pulmonary toxicity (17-19, 23, 24). In the present study, the stomatitis rate was 44.4%, similar to that reported with daily everolimus monotherapy (17, 18). Along with everolimus, cetuximab can cause pneumonitis in rare cases (31); however, no clinically notable pulmonary events were reported with the three-drug combination used in this trial. Diarrhea and neutropenia, irinotecan-associated AEs that can be therapy-limiting, were observed in 50.0% (5.6% grade 3/4) and 27.8% (16.7% grade 3/4) of patients, respectively. These rates are similar to those seen with cetuximab and irinotecan combination therapy (30).

Adding everolimus 30 mg/week to irinotecan 250 mg/m^2 every 3 weeks plus cetuximab showed some evidence of clinical activity, with an ORR of 14.3%, a stable disease rate of 28.6%, and median PFS and OS of 5.9 months and 17.5 months, respectively. In comparison, in a phase III trial of cetuximab plus irinotecan in patients not selected for *KRAS* mutation status, the ORR was 15.0% and median PFS and OS were 4.0 months and 10.7 months, respectively (30). Of note, interpretation of these results requires caution, as this was a small, nonrandomized, phase I study.

Since the completion of the present study, results of a second dose-finding study of everolimus plus irinotecan and cetuximab as second-line therapy in mCRC have been presented (32). In comparison with the present study, Shahda *et al*. evaluated daily everolimus and irinotecan 125 mg/m^2 given every 2 of 3 weeks; patients (N=30) were not enrolled on the basis of their *KRAS* mutational status. This study found the everolimus MTD to be 5 mg once daily. Clinical outcomes were similar to those in the present study, with ORR of 20.8%, median PFS of 4.0 months, and median OS of 16.3 months (32). Of note, efficacy was better in patients with *KRAS* wild-type tumors. Based on the acceptable safety profile and promising clinical benefit observed, a phase II trial of everolimus 5 mg/day plus irinotecan and cetuximab in *KRAS* wild-type and mutated CRC is ongoing (ClinicalTrials.gov identifier NCT00522665).

Overall, the present phase I dose-finding study identified everolimus 30 mg/week as a feasible dose when given in combination with irinotecan 250 mg/m^2 once every 3 weeks and cetuximab once weekly as second-line therapy in mCRC. Because of the early termination, conclusions related to the pharmacokinetics and efficacy of this regimen are limited. Nevertheless, the concept of dual EGFR and PI3K/mTOR pathway blockade should be further explored as a means of overcoming resistance to anti-EGFR antibodies.

Conflicts of Interest

J.R. Hecht's institution (David Geffen School of Medicine at University of California, Los Angeles, Santa Monica, CA, U.S.A.) has received research funding from Novartis Pharmaceuticals. T.R. Reid has nothing to disclose. C.R. Garrett received research funding from Novartis Pharmaceuticals to conduct this study. J.T. Beck has nothing to disclose. S.J. Davidson has nothing to disclose. M.J. MacKenzie has received honoraria for serving as a speaker for Novartis Pharmaceuticals. U. Brandt is an employee of Novartis Pharma AG. S. Rizvi is a former employee of and owns stock in Novartis Pharmaceuticals Corporation. S. Sharma has received research funding from and has served as a consultant to Novartis Pharmaceuticals.

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