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CLINICAL TRIAL REPORT

A phase I study of bevacizumab (B) in combination with everolimus (E) and erlotinib (E) in advanced cancer (BEE)

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Abstract
Purpose VEGF, mTOR, and EGFR inhibitors have demonstrated anti-tumor and anti-angiogenic effects alone and in combination with each other. This study evaluated the safety, tolerability, and pharmacokinetics of bevacizumab, everolimus, and erlotinib combination.
Methods Doublet therapy consisted of bevacizumab at 10 mg/kg every 14 days and everolimus 5 mg daily which escalated to 10 mg daily. Erlotinib 75 mg daily was added to the phase II dose recommended phase II dose (RPTD) of bevacizumab and everolimus. Dose-limiting toxicity (DLT) was assessed in cycle 1.
Results Forty-eight patients with advanced solid malignancies were evaluable for DLT and efficacy. No DLTs were observed in the doublet dose escalation. Two DLTs (grade 3 mucositis and grade 3 rash) were observed with the addition of erlotinib 75 mg daily. Consequently, triplet doses were adjusted and were better tolerated. Four patients had a partial response. Median progression-free survival (PFS) for the doublet therapy was 6.0 months (0.5 to 32+ months) and 5.5 months (0.8 to 27+ months) for the triplet therapy. Systemic exposure of everolimus was significantly higher in combination with erlotinib (476 ± 161 ng h/mL) compared to when given alone (393 ± 156 ng h/mL; $P = 0.020$).
Conclusions The RPTD for the doublet therapy is bevacizumab 10 mg/kg every 14 days and everolimus 10 mg daily, and the RPTD for the triplet therapy is bevacizumab 5 mg/kg every 14 days, everolimus 5 mg and erlotinib 75 mg daily. Prolonged disease stability was demonstrated in tumors known to respond to mTOR inhibition and potentially resistant to VEGF blockade.

Keywords Bevacizumab · Everolimus · Erlotinib · Phase I · Advanced cancer

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Introduction

Tumor growth and angiogenesis are regulated by multiple networked cellular pathways. Complementary pathway targeting may be more effective but may also be more toxic. The VEGF, mTOR, and EGFr pathways have each been clinically validated, and multiple agents have been approved by the Food and Drug Administration (FDA). The biology of EGFr, mTOR, and VEGF and the

Table 1 Determination of maximum tolerated dose

Dose level	Dose			No. of patients	No. of DLTs
	Bevacizumab (q2w) (mg/kg)	Everolimus (daily) (mg)	Erlotinib (daily) (mg)		
1	10	5	—	5*	0
2	10	10	—	15	0
3	10	10	75	6	Grade 3 mucositis Grade 3 rash
4	5	5	75	24	0

* Two patients did not finish cycle 1 due to early progressive disease

development of agents targeting these pathways have been extensively reviewed [1–5]. Preclinical studies have linked these pathways and suggest that combination targeting may improve anti-tumor effects as mTOR is an important effector and regulator of VEGF and of EGFr signaling. In addition, mTOR is a key regulator of HIF-1α (hypoxia inducible factor-1alpha) and upregulation of HIF is a potential mechanism of resistance to anti-VEGF therapy [6–8].

At the time this study was designed, there were safety and early efficacy data for the combination of anti-VEGF plus anti-EGFr therapy, including recent data on the combination of bevacizumab plus erlotinib, which was well tolerated among different tumor types [9–14]. However, there were no clinical data on the combination of anti-mTOR therapy with either anti-VEGF therapy or anti-EGFr therapy, while preclinical studies suggested the addition of everolimus in combination with a VEGF or EGFr inhibitor enhanced anti-tumor effects [15–19]. In addition, bevacizumab, erlotinib, and everolimus were expected to have mostly non-overlapping toxicities. The primary objectives of this tandem phase I study was to determine the maximum tolerated dose/recommended phase II dosing (MTD/RPTD) and safety profile of the mTOR inhibitor everolimus plus the VEGF inhibitor bevacizumab as a doublet anti-angiogenic therapy (BevEv regimen) and the triple targeted therapy of bevacizumab, everolimus, and erlotinib (BEE regimen). Detailed pharmacokinetic (PK) studies were conducted to fully evaluate potential PK interactions between everolimus and erlotinib. Biomarker data, which included serial plasma sampling for angiogenic markers and skin biopsies, will be presented separately.

Patients and methods

Patient selection

Eligible patients were required to have a histologically confirmed solid malignancy refractory to standard therapy or where standard therapies did not exist. Additional eligibility requirements included: age ≥18 years; an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; life expectancy ≥12 weeks; previous radiation therapy, hormonal therapy, biologic therapy or chemotherapy for cancer ≥3 weeks prior to study drug; surgery ≥4 weeks prior to study drug; leukocytes ≥3,000/μl with absolute neutrophil count (ANC) ≥1,500/μl; platelets ≥100,000/μl; total bilirubin ≤1.5 times the upper limit of normal (ULN); aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤2.5 times ULN or ≤5 times ULN if known hepatic metastases; urine protein to creatinine ratio (UPCR) ≤1.0; creatinine clearance ≥50 mL/min/1.73 m^2; absence of pregnancy; absence of central nervous system metastases, no clinically significant cardiovascular disease with intervention within 12 months, no thrombosis or bleeding diathesis within 6 months, uncontrolled hypertriglyceridemia (fasting serum triglyceride >350 mg/dL), uncontrolled hypercholesterolemia (fasting serum cholesterol >300 mg/dL). Serious medical conditions that could have significantly affected patient safety or toxicity assessment were prohibited. This study was approved by the Duke Institutional Review Board (IRB) and followed the Helsinki guidelines. All patients gave written informed consent according to institutional guidelines prior to any study-related procedure. Subjects were accrued at Duke University Medical Center.

Study design

This was a two-stage open-label, dose-escalation phase I pharmacokinetic and biomarker study to assess the doublet regimen of bevacizumab (Genentech, South San Francisco, CA, USA) and everolimus (Novartis, East Hanover, NJ, USA) and the triplet regimen of bevacizumab, everolimus, and erlotinib (Genentech, South San Francisco, CA, USA) administered to patients with advanced solid tumors. A standard phase I "3 + 3" design was used to establish the MTD/RPTD of the combinations.[20] The MTD was defined around toxicities in the first 28-day cycle, while the RPTD was selected based upon toxicities occurring in all cycles. At the MTD of the BevEv doublet, an additional six patients were to be treated to ensure the tolerability of the doublet regimen. Dose levels and drug doses are listed in Table 1.

At completion of dose escalation for the triplet BEE regimen, an expanded cohort of 20 patients at the RPTD was also enrolled to better define the tolerability of this combination. To better assess PK and biomarkers, patients in this expanded cohort were assigned in an alternating fashion into two groups containing 10 patients each. Group A received daily everolimus alone for the first 14 days, with biweekly bevacizumab and daily erlotinib being added on day 15. Group B received daily erlotinib alone for the first 14 days, with biweekly bevacizumab and daily everolimus being added on day 15.

A cycle was defined as 28 days. Treatment was continued until: disease progression; intercurrent illness that prevented further treatment; unacceptable adverse event(s); patient withdrawal from the study; and general or specific changes in the patient's condition that rendered the patient unacceptable for further treatment per judgment of the investigator.

Safety

The National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 3.0 was used to grade adverse events. The following adverse events were considered DLT in cycle 1: hematologic toxicity ≥grade 4 neutropenia or thrombocytopenia; nausea/vomiting or diarrhea ≥grade 3 and lasting ≥4 days despite adequate supportive measures; hypertension ≥grade 4; grade 3 hypertension that is poorly controlled (>160/100 on one measurement or >150/100 on three measurements over 1 week) despite two or more adjustments in anti-hypertensive medications; other non-hematologic toxicity ≥grade 3, excluding alopecia and rash; any treatment-related death or hospitalization. Patients were considered evaluable for toxicity if they received any treatment; patients were evaluable for DLT and MTD determinations if they completed cycle 1 or experienced a DLT in cycle 1; patients not evaluable for DLT and MTD were replaced. All toxicities were analyzed in cycle 1; in cycles 2 and beyond, only grade 3-5 and targeted grade 2 toxicities were analyzed. Targeted grade 2 toxicities included mucositis, rash, hypertension, and hyperlipidemia.

Clinical and radiographic assessment

Baseline evaluations, including a complete history, physical examination, routine laboratories, and EKG were conducted within 14 days prior to start of protocol therapy. Laboratories included complete blood count, serum chemistry with blood urea nitrogen, creatinine, albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, chloride, glucose, phosphorus, potassium, sodium, total protein, lactate dehydrogenase, AST, ALT, prothrombin time and partial thromboplastin time, fasting lipid panel, urine protein to creatinine ratio, and serum beta-human chorionic gonadotropin (if indicated). Radiologic scans were completed within 4 weeks prior to the start of therapy and every two cycles. Guidelines for supportive care and toxicity management, including dose modifications, were included in the protocol.

Radiographic response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [21].

Pharmacokinetics

Drug plasma pharmacokinetics were evaluated on days 8 and 22 for both groups in the BEE expanded cohort. The effect of erlotinib on everolimus disposition was assessed in Group A patients while the effect of everolimus on erlotinib disposition was studied in Group B. Blood samples were collected for everolimus measurement prior to drug administration and 1, 2, 3, 4, 6, 9, and 24 h post-dosing. Whole blood everolimus concentrations were determined following liquid/liquid extraction by an LC/MS/MS technique whose lower limit of quantitation was 0.368 ng/mL [22]. Erlotinib and its metabolite (OSI-420) were determined from samples collected prior to drug administration and at 1, 2, 3, 4, 6, 7, 8, 10, and 24 h postdosing. Plasma was prepared using a liquid/liquid extraction followed by LC/MS/MS in the positive ion mode, as previously described [23]. The lower limit of quantitation was 1 ng/mL for each analyte. Pharmacokinetic parameters were estimated from concentration time data sets for each drug on each day using a standard two-stage approach with WinNonlin software.

Statistical measurement

The primary objective of this study was to characterize the safety, tolerability, maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of the BevEv doublet and the triplet regimen BEE in subjects with advanced malignancy. Descriptive statistics were used to summarize demographic and baseline disease characteristics by dose group. Secondary objectives of this study were to preliminarily characterize any clinical activity. The sample sizes of the expanded cohorts in this pilot study were selected for convenience to better understand the safety and toxicity profile of each regimen; this information was intended to assist the design of future more definitive studies. Toxicities were recorded at each scheduled visit and tabulated by type and grade. AUC measures of day 8 and day 22 were compared using the Signed Rank Test.

Results

Patient characteristics

A total of 50 patients were treated and fully evaluable for toxicity; 48 patients were evaluable for efficacy. Patient demographics are described in Table 2.

DLT and MTD

Patient accrual and DLTs by dose level are summarized in Table 1. There were no DLTs in the BevEv doublet dose escalation, and the expanded cohort confirmed the doublet MTD was bevacizumab 10 mg/kg IV every 2 weeks and everolimus 10 mg orally daily. In dose level 3, when erlotinib 75 mg was added to this doublet combination, two of six patients had a DLT: grade 3 mucositis (1) and grade 3 rash (1). Consequently, bevacizumab and everolimus were dose reduced to bevacizumab 5 mg/kg IV every 2 weeks, everolimus 5 mg orally daily, and erlotinib 75 mg orally daily. For the initial 6 patients and for the 20 patients in the expanded cohort, dose level 4 was tolerable and was determined to be the MTD and RPTD for the triplet BEE regimen.

Toxicity

Treatment-related toxicities are listed in Table 3.

Nonhematologic

Across all cohorts, the most common adverse events were mild to moderate mucositis, rash, fatigue, musculoskeletal pain, diarrhea, hypertension, and hyperlipidemia. In all cycles, mucositis, primarily grade 1, occurred in approximately 75% of patients on the BevEv doublet and in approximately 87% of patients on the BEE triplet. Grade 3 mucositis was seen in six of 50 (12%) patients. Rash, usually grade 1, occurred in 60% of patients in the BevEv doublet and 80% of patients in the BEE triplet; grade 3 rash was seen in four of 50 (8%) patients.

Grade 3 hypertension was not seen in any BevEv-treated patient, but was seen in 7 patients (23%) of BEE triplet patients. There were no cases of grade 4 or 5 hypertension.

Hypertriglyceridemia and hypercholesterolemia (reported together as hyperlipidemia) occurred in 67% patients overall, typically after more than one cycle of treatment. Most cases were grade 1 or 2, except in two patients, one with asymptomatic grade 4 low-density lipoprotein elevation in the BevEv group and one with asymptomatic grade 4 hypertriglyceridemia in the BEE group.

Hematologic

There were no grade 4 events, and only one grade 3 hematologic adverse event. Neutropenia was uncommon and occurred only in the BEE group. One heavily pretreated patient in the BEE group developed recurrent grade 3 thrombocytopenia in cycle eight and above requiring dose reduction and subsequent discontinuation of everolimus.

Severe toxicity

Overall, grade ≥3 treatment-related toxicity occurred in 23 patients (45%) across dose levels 1–4. Grade ≥3 events such as hypertension, rash and mucositis usually occurred in the first three cycles. For BevEv, there were no ≥3 adverse events in cycle 1; for BEE, grade ≥3 adverse event occurring in cycle 1 included the following: mucositis, rash, musculoskeletal pain, hypertension, and infection. Hyperlipidemia and proteinuria typically occurred after prolonged therapy (>15 cycles); however, one subject developed grade ≥3 proteinuria during cycle 2. There were five grade 4 treatment-related events: two patients with asymptomatic hyperlipidemia and one patient each with left ventricular thrombus, nephrotic syndrome, and symptomatic hyperglycemia requiring hospital admission. Two additional patients had grade 3 cardiac ischemia. Three patients died while on trial or within 30 days of study drug discontinuation; however, all three death events were judged related to progressive disease not study treatment.

Efficacy

In this population of patients with heavily pretreated solid tumors, approximately half of all patients remained on

Table 2 Patient characteristics

Characteristic	Patients ($n = 50$)
Median age, years (range)	58 (29–73)
Female:male, no.	25:25
Caucasian: Black: Other	41:5:4
Median no. of prior regimens (range)	3 (0–10)
Tumor Type	
Colorectal	13
Sarcoma	7
Renal	6
Ovarian	4
Neuroendocrine	3
NSCLC	2
Pancreas	2
Breast	2
Endometrial	2
GIST	2
Other	7

Table 3 Targeted and grade ≥3 treatment-related adverse events

Toxicity	BevEv $n = 20$		BEE $n = 30$		All $n = 50$
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	Targeted grades 1–5 (%)
Non-Hematological					
Hypertension	0	0	7 (23)	0	9 (18)
Mucositis (proctitis, enterocolitis)	1 (5)	0	4 (13)	0	41 (82)
Rash (all)	1 (5)	0	3 (10)	0	36 (72)
Proteinuria	3 (15)	1 (5)	0	0	–
Thromboembolism	1 (5)	1 (5)	2 (7)	0	–
Fatigue	1 (5)	0	3 (10)	0	–
Infection (peri-rectal abscess, line infection)	0	0	3 (10)	0	–
Cardiac ischemia	1 (5)	0	1 (3)	0	–
Bowel perforation/fistula	0	0	2 (7)	0	–
Dyspnea	0	0	2 (7)	0	–
Hyperlipidemia	1 (5)	1 (5)	1 (3)	1 (3)	34 (67%)
GI bleeding	0	0	1 (3)	0	–
Wound healing	0	0	1 (3)	0	0
Interstitial nephritis	0	0	1 (3)	0	–
Nasal septal perforation	0	0	1 (3)	0	–
Diarrhea	0	0	1 (3)	0	16 (32%)
Constipation	1 (5)	0	0	0	–
Decreased strength	1 (5)	0	0	0	–
Nausea/vomiting	0	0	1 (3)	0	–
Pain (musculoskeletal)	0	0	2 (7)	0	–
Headache	0	0	1 (3)	0	–
Sinusitis	0	0	1 (3)	0	–
Hyperglycemia	0	0	0	1 (3)	–
Hematological					
Anemia	0	0	0	0	–
Thrombocytopenia*	0	0	3*	0	0
Neutropenia	0	0	0	0	1 (2%)

* One patient with the three separate events

study for at least 6 months. The median PFS for evaluable patients in the BevEv doublet therapy was 6.0 months (range, 0.5 to 32+ months). The median PFS for evaluable patients in the triplet BEE therapy was 5.5 months (range, 0.8 to 27+ months). Table 4 summarizes those patients with stable disease durable for at least 1 year. Ten patients were on treatment for over 1 year (renal cell carcinoma, $n = 2$; sarcoma, $n = 4$; pancreatic neuroendocrine tumor, pancreatic adenocarcinoma, medullary thyroid cancer, and parotid cancer, $n = 1$ each). Four patients were on treatment for over 2 years. Of the 10 patients with stable disease >1 year, two had minor responses (0–30% decrease per RECIST criteria on CT scan) and two had progressed on a prior anti-VEGF therapy.

There were three partial responses (PR) in the BevEv doublet: a 51-year-old woman with renal cell carcinoma and no prior therapy, a 58-year-old man with renal cell carcinoma and prior IL-2 therapy, and a 30-year-old man with a heavily pretreated osteosarcoma. In the triplet BEE therapy, there was one PR in a 54-year-old man with a pancreatic neuroendocrine tumor that had progressed on three prior treatments. Clinical activity (stable disease >6 months, partial response, or minor response) was seen in 19 patients (38%), eight (42%) of whom had progressed on a prior anti-VEGF therapy.

The largest tumor group represented in this study was colorectal cancer, all of whom previously progressed on a bevacizumab containing regimen. In this sub-population,

Table 4 Characteristics of patients with partial responses and prolonged stable disease

Patient	Age/sex	Tumor type	Dose level Bev/Ev/E (mg)	Prior therapies	Response	Duration (months)
1	73/F	Parotid	10/5	Cap	MR	29.5
2	58/M	Renal cell	10/10	IL-2	PR	32
3	51/F	Renal cell	10/10	None	PR	6.8
4	30/M	Osteosarcoma	10/10	MTX/Cis/Dox Ifos/Etop HD Ifos	PR	20.8
5	54/M	Neuroendocrine (pancreas)	5/5/75	Imatinib/Cap VEG 10003 Sunesis	PR	26.8+
6	54/M	Medullary thyroid	5/5/75	None	MR	27+
7	31/F	Alveolar soft part sarcoma	5/5/75	MTX/Cis/Dox Topotecan Bevacizumab	SD	15.8
8	63/M	Pancreatic	5/5/75	Cap Gemcitabine Gem+ Erlotinib	SD	13
9	59/F	Leiomyosarcoma	10/10/75	None	SD	24
10	64/M	Osteosarcoma	10/10/75	MTX/Cis/Dox HD Ifos	SD	25.8

Cap capecitabine, *MTX* methotrexate, *Cis* ciplatin, *Dox* doxorubicin, *Ifos* ifosfamide, *Etop* etoposide, *HD* high dose, *MR* minor response, *PR* partial response

there were two minor responses and the median PFS was 5.9 months (range, 1.3–10.5 months).

Pharmacokinetics

Systemic exposure (i.e. AUC_{0-24}) of erlotinib when administered alone was not statistically significantly different than systemic exposure of erlotinib after 2 weeks of concurrent everolimus (19,430 vs. 21,758 ng/mL h; *P* 0.359; Fig. 1). Erlotinib clearance was also not significantly affected by 2 weeks of everolimus treatment (Fig. 2). Two patients who were active tobacco smokers had the highest erlotinib clearances (>2 fold above the median value).

Inspection of the concentration/time profiles suggested that the disposition pattern of everolimus appeared shifted toward higher concentrations on day 22 compared to day 8 (Fig. 1). Pharmacokinetic determination of systemic everolimus exposure revealed an approximately 17 percent higher value when given after concurrent erlotinib for 2 weeks compared to alone (476.4 vs. 392.8 ng/mL h; *P* 0.02; Fig. 2). Apparent oral clearance values were correspondingly lower during concurrent administration (Fig. 2).

Discussion

This study established the RPTD for the anti-angiogenic doublet of bevacizumab plus everolimus and for the targeted triplet therapy of bevacizumab, everolimus, plus erlotinib. Full doses of bevacizumab and everolimus were tolerable together. However, full doses of bevacizumab, everolimus, and erlotinib were not tolerable and resulted in dose-limiting mucositis and rash, which are overlapping toxicities of the agents. In addition, pharmacokinetic analyses showed that the co-administration of erlotinib with everolimus reduced the clearance of the latter agent, perhaps at least partially explaining its dose tolerability. An increase in mucositis has been reported by others with the combination of anti-mTOR and anti-EGFR tyrosine kinase inhibitors [24–26]. A similar finding has also been reported recently for the combination of everolimus with the anti-EGFR monoclonal antibody panitumumab [27].

The increased frequency and severity of mucositis seen in this study is consistent with increased on-target effects within the EGFr axis and its concurrent signaling through mTOR. These results are also consistent with a pharmacokinetic as well as pharmacodynamic interaction between erlotinib and everolimus. When mucositis occurred, it responded well to dose holding and/or dose reduction, as well as traditional supportive measures. The pattern of mucositis seen in this study suggests these modifications should be early and aggressive.

Consistent with previous reports using mTOR inhibitors, hyperlipidemia was seen in approximately two-thirds of patients in this study, most requiring and readily responding to statin therapy.

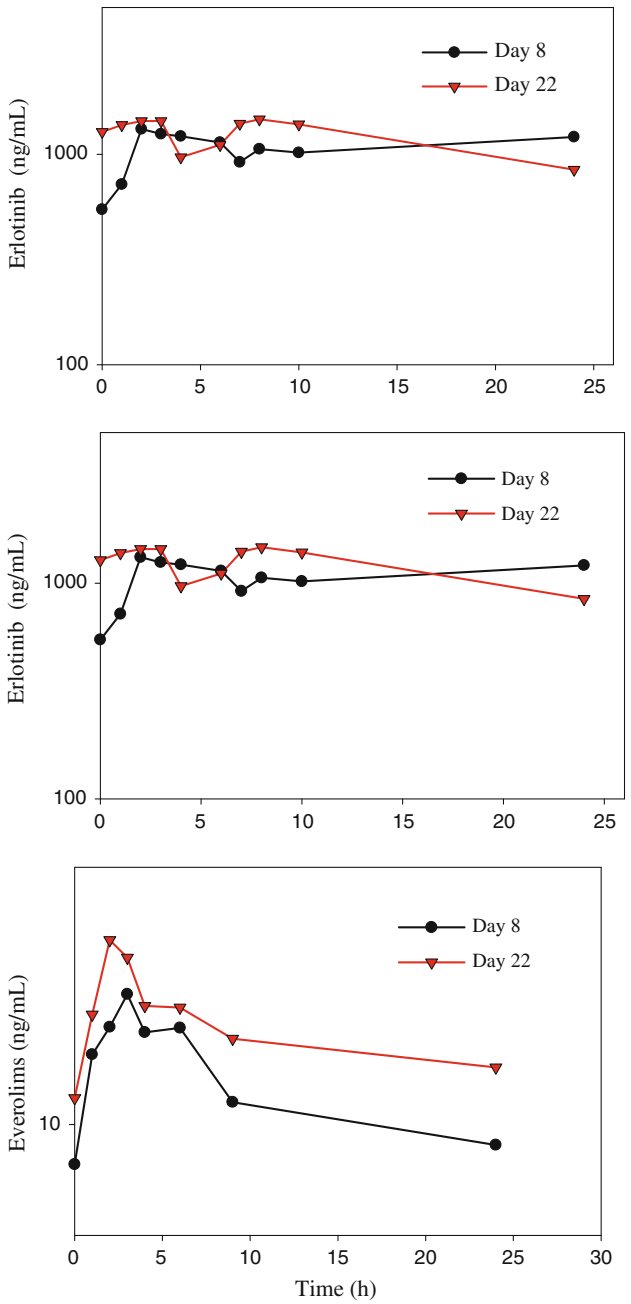


Fig. 1 Erlotinib, OSI-420 (erlotinib metabolite), and everolimus plasma pharmacokinetic disposition in a patient with the median systemic exposure

The BevEv and BEE regimens were associated with infrequent but severe side effects previously associated with both VEGF and mTOR inhibitors, including cardiac ischemia, hypertension bowel perforation, wound healing complications, and nephritic syndrome [4, 5, 28]. With the small patient population in this study, it is difficult to determine whether the frequency or severity of these events is increased or whether there is any contribution from the anti-EGFr therapy.

Although efficacy is often difficult to evaluate and interpret in patients with refractory solid tumors, the BevEv and BEE combinations showed preliminary signs of activity. Renal cell and pancreatic neuroendocrine cancers are known to exhibit sensitivity to single agent treatment with VEGF inhibitors and/or mTOR inhibitors [29–39]. Preliminary activity has also been reported in sarcoma for anti-mTOR therapy [40]. Clinical activity was seen in many patients with tumor types traditionally non-responsive to these agents and/or who had progressed on a VEGF inhibitor. The minor responses and prolonged stable disease in colorectal cancer may be noteworthy, since this tumor type is known to have a median progression-free survival of <2 months when treated with bevacizumab [41, 42], everolimus [43] or erlotinib monotherapy [44]. In addition, all of these patients had previously progressed on a bevacizumab containing regimen. Prolonged stable disease and minor responses have also been noted in a separate study of BevEv in refractory colorectal cancer [45]. These findings also suggest that clinical benefit for this combination may manifest primarily as disease stability, not response.

Everolimus is a substrate for p-glycoprotein and cytochrome p450 (CYP) 3A4. In vitro isoenzyme studies have shown it to be a potent inhibitor of CYP3A4; however, the limited clinical trials conducted to date suggest the effect is not relevant in vivo [46]. This is in agreement with our data which did not reveal significant changes in erlotinib pharmacokinetics (a CYP3A4 substrate) during concomitant administration of everolimus. In addition to CYP3A4, erlotinib is also thought to be metabolized by CYP1A2, an enzyme induced by tobacco smoke [47, 48]. We observed high oral clearance of erlotinib in smoking patients consistent with studies in lung cancer patients and volunteers.[23] In vitro and in vivo data suggest that co-administration of erlotinib with the CYP3A4 substrate midazolam accelerates the metabolism of the latter drug [49, 50]. In vitro studies conducted by the manufacturer have shown that erlotinib and its major metabolite are inhibitors of CYP3A4. Consistent with these data, we observed a 17 percent higher everolimus systemic exposure when it was given concurrently with erlotinib.

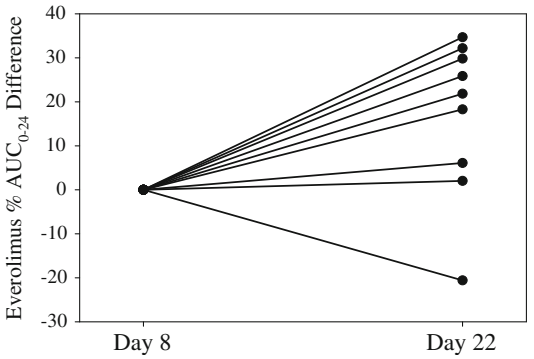
In conclusion, the BevEv regimen is well tolerated and can be delivered at full doses of each agent. The BEE regimen, however, must be given at reduced doses of everolimus and/or erlotinib due to dose-limiting mucositis and rash and other known overlapping toxicities of anti-EGFR and anti-mTOR therapies. Clinical activity in tumors types associated with primary or acquired resistance to anti-VEGF therapy suggests the anti-VEGF plus anti-mTOR therapies may overcome some of these resistance mechanisms. These data support the further testing of dual inhibition of the VEGF and mTOR axes, which are

Fig. 2 **a** Steady-state pharmacokinetic parameters when everolimus and erlotinib were given alone (day 8) compared to after 2 weeks of concomitant therapy (day 22). **b** Inter-patient assessment of everolimus systemic exposure depicted as the percent change from values obtained on day 8 (given alone) to those measured after 14 days of concomitant erlotinib (day 22; *P* 0.017)

A

	Everolimus (n = 9)			Erlotinib (n = 9)		
	Day 8	Day 22	P	Day 8	Day 22	P
AUC (ng h/mL)	392.8 ± 155.6	476.4 ± 161.4	0.020	19430 ± 7723	21758 ± 3567	0.359
Cl/F (L/h)	14.3 ± 4.8	11.7 ± 4.1	0.039	4.6 ± 2.3	4.4 ± 2.8	0.650
C_{max} (ng/mL)	44.4 ± 25.7	50.2 ± 18.6	0.844	1150 ± 326.1	1336 ± 438.0	0.129

B



ongoing in phase III for neuroendocrine and renal cell carcinoma.

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