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A Phase I Study of EKB-569 in Combination with Capecitabine in Patients with Advanced Colorectal Cancer

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Abstract

Purpose—To determine the maximum tolerated dose (MTD), characterize the principal toxicities, and assess the pharmacokinetics of EKB-569, an oral selective irreversible inhibitor of the epidermal growth factor receptor tyrosine kinase, in combination with capecitabine in patients with advanced colorectal cancer.

Experimental Design—Patients were treated with EKB-569 daily for 21days and capecitabine twice daily for14 days of a 21-day cycle. The dose levels of EKB-569 (mg/day) and capecitabine (mg/m^2 twice daily) assessed were 25/750, 50/750, 50/1,000 and 75/1,000. An expanded cohort was enrolled at the MTD to better study toxicity and efficacy. Samples of plasma were collected to characterize the pharmacokinetics of the agents. Treatment efficacy was assessed every other cycle.

Results—A total of 37 patients, the majority of whom had prior chemotherapy, received a total of 163 cycles of treatment. Twenty patients were treated at the MTD, 50 mg EKB-569, daily and 1,000 mg/m^2 capecitabine twice daily. Dose-limiting toxicities were diarrhea and rash. No patients had complete or partial responses but 48% had stable disease. The conversion of capecitabine to 5-fluorouracil was higher for the combination of EKB-569 and capecitabine (321 ± 151 ng*h/mL) than for capecitabine alone (176 ± 62 ng*hours/mL; $P = 0.0037$).

Conclusion—In advanced colorectal cancer, 50 mg EKB-569 daily can be safely combined with 1,000 mg/m^2 capecitabine twice a day. A statistically significant increase in plasma levels of 5-fluorouracil for the combination of EKB-569 and capecitabine may be due to the single-dose versus multiple-dose exposure difference, variability in exposure or a potential drug interaction.

Treatment options for patients with advanced-stage colorectal cancer (CRC) are expanding. Historically, 5-fluorouracil (5-FU) chemotherapy regimens have been used with objective response rates of ~20% and a median survival of 12 to 15 months (1–4). More recently, new

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Disclosure of Potential Conflicts of Interest

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agents including irinotecan, oxaliplatin, cetuximab, and bevacizumab have been introduced and have expanded median survival to 20 to 21 months (5–8). The fluoropyrimidines, however, remain an obligatory component in most first- and second-line regimens and remain the agent of choice in chemoradiation regimens. Capecitabine (Xeloda; Hoffmann-La Roche) is an oral fluoropyrimidine carbamate derivative that generates fluorouracil preferentially in tumor tissue (1, 2). After oral absorption, capecitabine is first converted to 5′-deoxy-5-fluorocytidine by liver carboxylesterase. Subsequently, 5′-deoxy-5-fluorocytidine is converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase. The final conversion to 5-FU seems to occur preferentially in the tumor site and is mediated by thymidine-phosphorylase (TP). The higher concentration of TP in tumor tissue enhances intratumoral delivery of 5-FU. Catabolism of 5-FU is mediated by thymidylate synthetase and dihydropyrimidine dehydrogenase. Head-to-head comparisons of capecitabine to 5-FU in advanced CRC show equal efficacy and better tolerability (3, 4). Capecitabine is now being studied in randomized clinical trials as a replacement for infusional 5-FU in combination regimens.

The epidermal growth factor receptor (EGFR) is one of a family of growth factor tyrosine kinase receptors in which ligand binding initiates a signaling cascade that influences tumor cell growth and survival. EGFR is deregulated in a number of human malignancies, including ~75% of colorectal adenocarcinomas. Overexpression of EGFR has been associated with poor survival and chemoresistance in other tumor types, and deregulation of the EGFR signaling network has been associated with tumor growth, metastasis, and angiogenesis (9–12) EGFR has become an important strategic target for anticancer drug development. Both small-molecule inhibitors of the receptor tyrosine kinase domain and monoclonal antibodies directed against the receptor extracellular domain have been developed and approved for cancer treatment. EGFR is a validated target in CRC, as evidenced by the approval of cetuximab (Erbitux; Imclone Systems, Inc.), a monoclonal antibody against EGFR, in refractory advanced CRC patients either as a single agent or in combination with irinotecan. In a preclinical study, inhibition of the EGFR tyrosine kinase increased the activity of TP and decreased the activity of thy-midylate synthetase, which resulted in higher levels of intracellular 5-FU. Supporting the preclinical observation, when the EGFR inhibitor erlotinib was combined with capecitabine and oxaliplatin, there was noted to be a trend for reduced capecitabine concentrations suggesting a pharmacokinetic interaction (13).

EKB-569 is a potent low molecular weight, selective, and irreversible inhibitor of the EGFR tyrosine kinase. At higher concentrations, it also inhibits the ErbB2 receptor. In a phase I study, p.o. administration of single-agent EKB-569 to patients with advanced solid tumors was well-tolerated at doses up to 75 mg per day on a continuous schedule with principal toxicities consisting of diarrhea and skin rash. At 50 mg EKB-569 per day, sustained plasma concentrations above the enzyme inhibitory target concentration were achieved (6). EKB-569 in combination with Irinotecan and infusional 5-FU has been recently shown to be safe, and at the 25 mg, EKB-569/full-dose Irinotecan and infusional 5-FU resulted in complete inhibition of phosphorylated EGFR as well as downstream signaling pathways in skin and tumor samples (14).

Based on these data, we investigated the use of the combination of capecitabine and EKB-569 for the treatment of patients with advanced CRC. The specific objectives were as follows: (*a*) to determine the maximum tolerated dose (MTD) of EKB-569 combined with capecitabine; (*b*) to characterize the toxicities of the combination; (*c*) to explore the pharmacokinetic behavior of the agents in this combination; and (*d*) to seek preliminary evidence of antitumor activity.

Patients and Methods

Patient selection

Eligible patients were required to have histologic/cytologic diagnosis of metastatic, relapsed, or advanced-stage CRC not amenable to curative treatment. Eligibility criteria also included (*a*) life expectancy of at least 3 mo; (*b*) age of ≥18 y; (*c*) measurable or evaluable disease; (*d*) Eastern Cooperative Oncology Group performance status of 0 to 2 (not declining within past 2 wk); and (*d*) adequate hepatic, renal, and bone marrow function including aspartate aminotransferase/alanine aminotransferase of ≤3 × institutional upper limit of normal or ≤5 × upper limit of normal if liver metastases, total bilirubin of ≤1.5 × upper limit of normal, creatinine of ≤1.25 × upper limit of normal, or ≤1.5 × upper limit of normal and calculated creatinine clearance of ≥60 mL/min, hemoglobin of ≥8.5 mg/dL, absolute neutrophil count of ≥1,500/mm^3, and platelets ≥100,000/mm^3. Patients were excluded if they had chemotherapy; radiotherapy; or investigative agents within 4 wk before study entry; prior treatment with EGFR inhibitors; prior treatment with capecitabine; more than four prior chemotherapy treatment regimens for relapsed/metastatic disease, hypersensitivity, or severe toxicity with prior 5-FU; surgery within 2 wk before study entry; or active central nervous system metastases (as indicated by clinical symptoms, cerebral edema, required use of corticosteroids, and/or progressive growth). Pregnant or nursing women were excluded. The prophylactic use of hematopoietic growth factors was not permitted in the first cycle but was allowed thereafter and for the treatment of febrile neutropenia. The study was approved by the institutional review boards of the three participating institutions.

Study design

This study was a three-center, dose-escalation, phase I and pharmacologic clinical trial. The dose levels tested are depicted in Table 2. EKB-569 was supplied by Wyeth Research as 25-mg capsules and was administered p.o. once daily with food. The starting dose of EKB-569 was 25 mg per day. Capecitabine was administered by p.o. administration twice daily for 2 wk followed by a 1-wk rest period (one 21-d cycle). EKB-569 was administered 30 min before capecitabine on days both agents were given. Patients were to receive up to eight treatment cycles of capecitabine if the combination with EKB-569 was well-tolerated and there was no evidence of progressive disease. After eight cycles, continuation of EKB-569 and capecitabine treatment in patients obtaining clinical benefit was at the discretion of the treating physician.

Three to six patients were enrolled in successive cohorts. To be evaluable for the dose escalation decision-making process, a patient must have received at least 18 and 11 d of treatment with EKB-569 and capecitabine, respectively, and not have missed >2 consecutive d of treatment.

Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Dose-limiting toxicity (DLT) was defined as any grade 4 neutropenia or thrombocytopenia lasting ≥7 d; febrile neutropenia; any grade 3 to 4 nonhematologic toxicity except grade 3 nausea, vomiting, or constipation refractory to medical treatment; and grade 3 diarrhea associated with fever or lasting >2 d despite medical treatment. At a given dose level, if no episode of DLT was observed by day 21 of the first treatment cycle, patients were treated at the next dose level. If one patient developed a DLT, three additional patients were enrolled at that dose level. If none of the additional patients had a DLT, dose escalation continued. If at least two patients had a DLT, dose escalation stopped and the prior dose level was considered to be the MTD. No intrapatient dose escalation was permitted. Up to 20 patients were to be treated at the MTD to better explore the pharmacokinetics, toxicity, and efficacy of the regimen.

If a patient developed an EKB-569–related DLT, EKB-569 was held and the patient retreated at the prior dose level upon recovery to at least grade 1 toxicity within 2 wk, if there was no evidence of disease progression. A maximum of three dose adjustments were allowed per patient. The dose of capecitabine was held for any patient who developed at least grade 1 toxicity and was reinitiated at a 25% or 50% dose reduction based on toxicity level and duration.

Pretreatment and follow-up studies

Physical examination, assessment of Eastern Cooperative Oncology Group performance status, review of concomitant medications, toxicity assessment, and routine laboratories were done before each cycle. Because of potential for ocular toxicity, an ophthalmologic exam including best-corrected visual acuity, visual field examination (Amsler grid), intraocular pressure, external eye exam, and dilated funduscopy was done at baseline and before cycles 2 to 9. Weekly routine laboratory and toxicity assessments were done on day 8 and 15 of each cycle.

Formalin-fixed paraffin-embedded tumor tissues from diagnostic specimens were collected if available to determine the expression of EGFR, ErbB2, and transforming growth factor-α by immunohistochemistry. Data were summarized using a sum histoscore obtained by multiplying the intensity of staining (from 0 to 3) by the proportion of cells staining (ranged from 0 to 300).

Radiological studies for disease assessment were repeated after every other course or as needed to confirm response. A complete response was scored if there was disappearance of all active disease on two measurements separated by a minimum of 4 wk. A partial response was scored if there was at least a 50% reduction in total tumor size (the sum of the product of the bidimensional measurements of all lesions) documented by two measurements separated by at least 4 wk. Stable disease was scored if there was less than a 50% reduction in total tumor or less than a 25% increase in the size of one or more measurable lesions. An increase in the size of any lesion by at least 25% or the appearance of any new lesion was considered disease progression. Patients were able to continue treatment if they had no evidence of progressive disease. Time to tumor progression was measured from day 1 of treatment.

Pharmacokinetic analysis

Pharmacokinetic studies were done in a total of 11 patients treated at the MTD. Venous blood samples were collected in tubes containing EDTA, and plasma was obtained by refrigerated centrifugation. Plasma was stored at −70°C until analysis. Samples for capecitabine analysis were collected before treatment and at 0.5, 1, 2, 3, 4, 6, 8, and 12 h posttreatment on days 1 and 8. EKB-569 treatment was started on day 2 to allow assessment of capecitabine kinetics alone. Samples for EKB-569 pharmacokinetics were obtained before treatment on day 0, and pretreatment at 1, 2, 3, 4, 6, 8, 12, and 24 h posttreatment on day 8.

Plasma concentrations of EKB-569, its N-desmethyl metabolite, capecitabine, 5′-DFUR, and 5-FU were measured using validated analytic methods (15, 16). The plasma concentration-versus-time curve for each analyte in each of the patients during each pharmacokinetic period was studied using standard noncompartmental methods as implemented in WinNonlin version 5.0 (Pharsight Corporation; ref. 17). Maximal plasma concentration (C_{max}) values were the observed values. Area under the concentration-versus-time curve to the last quantifiable time point ($AUC_{[0\text{-}t]}$) and that extrapolated to infinity ($AUC_{[0\text{-}\infty]}$) were calculated using the linear trapezoidal method. The terminal rate constant, λ_z, was

determined from the slope of the terminal phase of the plasma concentration-versus-time curve. The λ_z value was accepted if the r^2 value was >0.90. The terminal half-life ($T_{1/2}$) was calculated as 0.693 divided by λ_z. For EKB-569, the apparent oral clearance was calculated by dividing the dose administered by AUC. The apparent volume of distribution for EKB-569 was calculated by standard noncompartmental methods.

Statistical analysis

The sample size for this study was determined by clinical rather than statistical considerations. However, the probabilities of detecting at least one adverse event of grade ≥3 for 6 patients receiving EKB-569 are 0.469, 0.738, and 0.882 when the true rates are 10%, 20%, and 30%. All patients who received at least one dose of treatment were included in the safety analysis. Patients who received at least two cycles of treatment or discontinued treatment sooner because of progressive disease were evaluated for treatment efficacy. Pharmacokinetic variables were summarized using descriptive statistics for all assessable pharmacokinetic periods. The paired two-tailed Student's *t* test was used to compare mean pharmacokinetic variables of T_{max} and $T_{1/2}$ and the log-transformed mean of C_{max}, $AUC_{[0\text{-}t]}$, and $AUC_{[0\text{-}\infty]}$ for capecitabine and metabolites administered alone or in combination with EKB-569 within the same group of patients. Statistical analysis was done using JMP Statistical Discovery Software version 4.0.4 (SAS Institute). The *a priori* level of significance was a *P* value of <0.05.

Results

General

A total of 37 patients whose pertinent characteristics are listed in Table 1 received a total of 163 cycles of treatment (median 2, range 1–22). Seven patients, four of whom were treated at the first dose level, had not received prior chemotherapy treatment for advanced CRC.

The results of the dose escalation are summarized in Table 2. The first cohort of patients was treated with 25 mg EKB-569 and 750 mg/m^2 capecitabine. The second patient treated at this dose level developed a DLT of grade 3 diarrhea that lasted for 4 days. This patient withdrew from the study and four additional patients were enrolled at this dose level with no further episodes of DLT. At the second dose level of 50 mg EKB-569 and 750 mg/m^2 capecitabine, a patient experienced grade 3 diarrhea, hypotension, and dehydration. This patient recovered after 4 days of hospitalization and resumed treatment at a reduced dose of 25 mg EKB-569. Additional patients were recruited to this dose level for a total of six evaluable patients and none had DLTs. At the third dose level of 50 mg EKB-569 and 1,000 mg/m^2 capecitabine, the first patient treated developed a DLT of grade 3 diarrhea that lasted 6 days. This patient resumed treatment at a reduced dose of 25 mg EKB-569. Six additional patients were treated at this dose level without further episodes of DLT. Dose escalation proceeded to a dose level of 75 mg EKB-569 and 1,000 mg/m^2 capecitabine, and 4 patients were accrued. One patient developed a DLT of grade 3 diarrhea that resolved in 2 days but led the patient to withdraw from the study. A second patient developed grade 2 diarrhea and rash that lasted 2 and 11 days, respectively, and were considered DLTs by the investigator. This patient resumed treatment at a reduced dose of 50 mg EKB-569. Based on these events, the MTD was determined to be 50 mg EKB-569 daily and 1,000 mg/m^2 capecitabine twice a day. Thirteen additional patients were treated at this dose level for a total of 20 patients with no further episodes of DLT. Thus, this dose level was confirmed as the MTD.

Toxicity

The most frequently occurring treatment-emergent adverse events, regardless of causality, were diarrhea (86%), nausea (73%), asthenia (68%), anorexia (59%), and abdominal pain

(57%; Table 3). Most toxicities were only grade 1 to 2. Grade 3 to 4 treatment-emergent adverse events that occurred in 3 or more patients were diarrhea (8 patients), abdominal pain, gastrointestinal carcinoma, intestinal obstruction, and vomiting (3 each). Hematologic toxicity was rare; 5 patients had grade 1 to 2 anemia and 4 had grade 1 to 2 thrombocytopenia. No ocular toxicity was identified.

The rate of selected drug-related toxicities that occurred in >10% of the subjects is summarized in Fig. 1. The principal drug-related toxicities by patient were diarrhea (86%), asthenia (54%), nausea (65%), skin rash (46%), vomiting (32%), and abdominal pain (24%). Most toxicities were grade 1 to 2 with only 11 (30%) patients suffering a grade 3 event. There were no episodes of grade 4 toxicities in this study. At dose levels 1 and 2, there were only 2 episodes of grade 3 diarrhea. At dose level 3, there were 5 episodes of grade 3 diarrhea and 1 each of grade 3 abdominal pain, asthenia, and vomiting. Hematologic toxicity was rare with only 8 episodes of grade 1 to 2 thrombocytopenia observed.

A total of 7 patients across the different dose levels required a dose reduction of EKB-569 (19%), which was secondary to diarrhea in 5 (71%). Ten patients across the different dose levels required a dose reduction of capecitabine (27%), also mostly due to diarrhea (60%). At the MTD, four and six patients required a dose reduction of EKB-569 and capecitabine, respectively.

Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were collected from 11 patients treated at the MTD of 50 mg EKB-569 and 1,000 mg/m^2 capecitabine and were analyzed for EKB-569 and its N-desmethyl metabolite (N-desmethyl EKB-569). Relevant pharmacokinetic variables are summarized in Tables 4 and 5. On day 8, plasma concentrations of both EKB-569 and N-desmethyl EKB-569 reached peak levels at ~4 hours after p.o. administration of EKB-569 (Fig. 2). The mean elimination half-life of EKB-569 was 16.6 hours. The intersubject variability was moderate, and the coefficient of variation values for C_{max} and AUC were <40%.

Evaluable pharmacokinetic data of capecitabine and its metabolites were obtained from 13 patients involving 23 pharmacokinetic study periods. For capecitabine, 5′-DFUR, and 5-FU, the terminal half-life and $AUC_{[0-\infty]}$ were not reportable in 4, 1, and 1 pharmacokinetic study periods, respectively, due to the r^2 value associated with λ_z being <0.90. Capecitabine and metabolite plasma pharmacokinetic variables for monotherapy (cycle 1, day 1) and combination therapy with EKB-569 (cycle 1, day 8) are listed in Table 5. The C_{max} of capecitabine was observed at 1 hour after p.o. administration with a mean terminal half-life of half an hour. High interpatient variability was observed for capecitabine and metabolite pharmacokinetic variables when administered alone, and this variability tended to increase in combination with EKB-569. There was no statistically significant difference between capecitabine pharmacokinetic variables when administered as monotherapy or combination therapy. However, when capecitabine was given in combination with EKB-569, there was a statistically significant increase in 5′-DFUR $AUC_{[0-t]}$ (28%) and $AUC_{[0-\infty]}$ (31%), and 5-FU $AUC_{[0-t]}$ (88%) and $AUC_{[0-\infty]}$ (81%).

Efficacy

Thirty-three patients were evaluable for efficacy. Four patients were not evaluable for efficacy; two discontinued treatment during the first cycle due to adverse events, one withdrew consent and another was treated with capecitabine alone. No complete or partial responses were observed. Sixteen patients (48%) had stable disease as the best response: 6 (18%) had stable disease lasting between 5 and 11 weeks, 7 (21%) had stable disease lasting

between 11 and 35 weeks, and 3 had stable disease lasting between 41 and 71 weeks. The median time to tumor progression was 1.7 months (95% confidence interval, 1.4–4) for all evaluable patients.

Discussion

A major aim of this phase I study was to determine the tolerability of the combination of EKB-569, a novel, low molecular weight, irreversible inhibitor of the EGFR tyrosine kinase, and capecitabine in patients with advanced CRC. The rationale for this combination is provided by a preclinical study that indicated inhibition of EGFR kinase favorably modulated the activity of TP and thymidylate synthetase, the enzymes involved in the conversion of 5′-DFUR to 5-FU and the catabolism of 5-FU, respectively (5). This study shows that 50 mg EKB-569 daily can be safely combined with conventional doses of capecitabine in this patient population with tolerable side effects. As expected based on the toxicity profile of single-agent EKB-569, the most common toxicities of the combination were gastrointestinal and cutaneous (6). Because this treatment regimen is well-tolerated, in addition to potential use in CRC, there is the prospect of using it in patients with other gastrointestinal cancers and breast cancer, particularly in combination with radiation therapy.

After administration of EKB-569 in combination with capecitabine on day 8, AUC of 5′-DFUR and 5-FU were significantly higher than on day 1 when capecitabine was administered alone. Increases in the AUC of 5′-DFUR and 5-FU have been reported to be greater than proportional to the increase in dose with time. After continued daily dosing of capecitabine, AUC of 5-FU on day 14 is 34% higher than after a single dose with 85% interpatient variability (18). Studies exploring the pharmacokinetics of capecitabine with continual administration either alone or in combination with other anticancer agents have indicated a range of alterations from no increase to an 83% increase in 5-FU expo sure (19–21). Accumulation of 5′-DFUR with repeat administration has not been previously documented, but the effect noted in the current study is minimal. An additional explanation for the accumulation of active moieties of capecitabine in the presence of EKB-569 may be that the inhibition of the EGFR kinase by EKB-569 increased the activity of TP and decreased the activity of thymidylate synthetase as noted in a preclinical study (5).

Although no complete or partial responses were observed in this mostly pretreated patient population, 48% of the patients had stable disease that lasted from 5 to 71 weeks. There are several factors that need to be considered when analyzing the clinical activity of this regimen. First, the majority of patients were previously pretreated and it is well-known that neither capecitabine nor 5-FU has activity in this group of patients as measured by response rate (7, 8). The addition of EKB-569 does not seem to have a major effect on the baseline activity of capecitabine in this setting. This observation needs to be put into the perspective of the overall role of small-molecule EGFR kinase inhibitors in CRC. Although monoclonal antibodies against EGFR have efficacy in CRC, single-agent small-molecule inhibitors of EGFR kinase have not been particularly active (6, 9, 10). On the other hand, the combination of small-molecule EGFR kinase inhibitors with chemotherapy in CRC seems to be effective. Gefitinib in combination with FOLFOX resulted in a 33% response rate in a group of 27 patients who had progressed after first-line treatment that did not include oxaliplatin (11). The importance of this study is further supported by preclinical studies that show mechanism-dependent synergy between gefitinib and oxaliplatin in CRC cell lines as well as in a clinical trial showing a possible pharmacokinetic interaction between Capecitabine and erolininb (12, 13). EKB-569 has also been tested in combination with Irinotecan and infusional 5-FU and has been shown to be safe and active. At the 25 mg EKB-569/full-dose Irinotecan and infusional 5-FU, complete inhibition of phosphorylated

EGFR as well as downstream signaling pathways in skin and tumor samples was identified (14).

Capecitabine also is commonly used as the standard chemotherapeutic regimen in combined modality regimens both for rectal and upper gastrointestinal tumors (i.e., stomach, pancreas, and biliary tract). More recently, studies have attempted to combine this regimen with inhibitors of the EGFR kinase. The experimental basis for such combinations is 2-fold. First, there is well-known preclinical synergy between inhibition of the EGFR kinase and radiation therapy. Second, there is the modulation of TP and thymidylate synthetase activity with inhibition of the EGFR kinase, which should increase the effectiveness of capecitabine (5). Initial attempts to develop this strategy in gastrointestinal malignancies have been unsuccessful. The increased concentration of 5-FU observed with the use of the combination of EKB-569 and capecitabine in the current study may explain this increased toxicity. Single-agent, specific, small-molecule inhibitors of the EGFR kinase are inactive in breast cancer (22, 23). However, drugs such as lapatinib, which also target ErbB2, are very promising (24). EKB-569, in addition to targeting the EGFR kinase, also inhibits ErbB2 at clinically achievable concentrations and, therefore, may be active in this disease. Breast cancer is often managed with capecitabine alone, but the combination of capecitabine and EKB-569 may provide more effective management. Thus, the safety and dose recommendations from this trial may be useful for studies in breast cancer (25).

In summary, 50 mg EKB-569 administered daily can be safely combined with 1,000 mg/m^2 capecitabine administered twice a day. Of major interest, treatment with EKB-569 and capecitabine resulted in statistically significant higher plasma levels of 5-FU than treatment with capecitabine alone. The possible interaction between EKB-569 and capecitabine should be further evaluated. Although this regimen is not likely to be used in patients with CRC because, currently, capecitabine is rarely used to treat CRC, it may be useful for the treatment of other malignancies, such as breast cancer, or in multimodality strategies.

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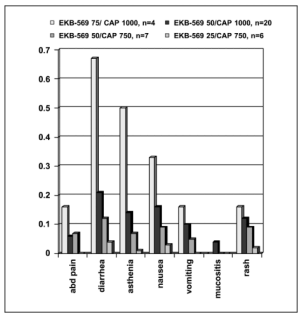

Fig. 1.
Principal drug-related toxicities of EKB-569/capecitabine expressed as adverse event divided by number of cycles.

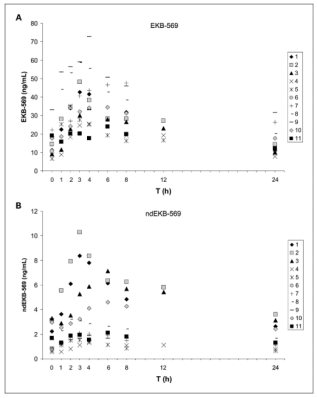

Fig. 2.

Pharmacokinetic profile of EKB-569 (*A*) and N-desmethyl-EKB-569 (*B*) on day 8 from 11 patients treated at the MTD of 50 mg EKB-569 and 1,000 mg/m^2 capecitabine.

Table 1

Patient characteristics

Characteristic	No. of patients
No. of patients	37
Sex, men/women	20/17
Age, y	
Median	56
Range	27–75
ECOG performance status	
0	16
1	21
Prior therapy	
Chemotherapy	
0	7
1	17
2	9
≥3	4
Radiotherapy	10
Surgery	37

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2

Dose-escalation and DLT experience

Dose level	EKB-569 Dose (mg/d)	Capecitabine dose (mg/m^2/twice daily)	No. of patients	No. of cycles	No. of patients with DLT
1	25	750	6	131	1 with grade 3 diarrhea
2	50	750	7*	42	1 with grade 3 diarrhea, hypotension, and dehydration
3	50	1,000	20	86	1 with grade 3 diarrhea
4	75	1,000	4	6	1 with grade 3 diarrhea
					1 with grade 2 diarrhea and rash
Total			37		

*One patient was removed from the study on cycle 1, day 4 to receive palliative radiation and was not considered evaluable for dose escalation.

Table 3

Patients (%) with treatment-emergent adverse events, regardless of causality, that occurred in ≥30% of patients

TEAE	All patients	EKB25, CAPE750	EKB50, CAPE750	EKB50, CAPE1000	EKB75, CAPE1000
	N = 37	*n* = 6	*n* = 7	*n* = 20	*n* = 4
Diarrhea					
Grade 1–4	32 (86)	5	5	18 (90)	4
Grade 3–4	8 (22)	1	5	1 (5)	1
Nausea					
Grade 1–4	27 (73)	6	4	15 (75)	2
Grade 3–4	2 (5)	2	0	0	0
Asthenia					
Grade 1–4	25 (68)	5	3	14 (70)	3
Grade 3–4	1 (3)	0	1	0	0
Anorexia					
Grade 1–4	22 (59)	4	2	13 (65)	3
Grade 3–4	1 (3)	1	0	0	0
Abdominal pain					
Grade 1–4	21 (57)	5	4	10 (50)	2
Grade 3–4	3 (8)	2	1	0	0
Rash					
Grade 1–2	18 (49)	3	4	10 (50)	1
Vomiting					
Grade 1–4	17 (46)	2	2	12 (60)	1
Grade 3–4	3 (8)	2	1	0	0
Skin disorder					
Grade 1–4	16 (43)	2	3	10 (50)	1
Grade 3–4	1	1	0	0	0
Stomatitis					
Grade 1–2	13 (35)	2	1	10 (50)	0
Fever					
Grade 1–4	11 (30)	2	0	8 (40)	1
Grade 3–4	1 (3)	0	1	0	0

TEAE	All patients	EKB25, CAPE750	EKB50, CAPE750	EKB50, CAPE1000	EKB75, CAPE1000
	N **= 37**	***n*** **= 6**	***n*** **= 7**	***n*** **= 20**	***n*** **= 4**
Pain					
Grade 1–4	11 (30)	2	3	5 (25)	1

Abbreviations: EKB25, CAPE750, EKB-569 25 mg and capecitabine 750 mg/m^2; EKB50, CAPE750, EKB-569 50 mg and capecitabine 750 mg/m^2; EKB50, CAPE1000, EKB-569 50 mg and capecitabine 1,000 mg/m^2; EKB75, CAPE1000, EKB-569 75 mg and capecitabine 1,000 mg/m^2; TEAE, treatment-emergent adverse event.

Table 4

Pharmacokinetic variables of EKB-569 and N-desmethyl EKB-569 on day 8

Compound	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng·h/mL)	Cl/F (L/h)	Vss/F (L)
EKB569	42.3 ± 15.1	4 (2–8)	16.6 ± 3.7	633 ± 234	57 ± 24	1,295 ± 445
N-Demethy EKB-569	4.2 ± 3.2	3.5 (2–6)	24.1 ± 9.2	64.4 ± 43.3		

NOTE: Values are mean ± SD except for T_{max}, which are mean and range.

Abbreviations: T_{max}, time to C_{max}; Cl/F, oral clearance; Vss/F, volume of distribution at steady-state after p.o. administration.

Table 5

Pharmacokinetic variables of capecitabine and its metabolites on day 1 and day 8

Compound	Concurrent EKB-569 administration	T_{max} (h)	C_{max} (ng/mL)	$AUC_{[0-t]}$ (h·ng/mL)	$AUC_{[0-\infty]}$ (h·ng/mL)	$T_{1/2}$ (h)
Capecitabine	Alone	1.00 (0.50–3.00)	3,808 ± 1,896	5,247 ± 971	5,296 ± 1,015	0.52 ± 0.17
	Combination	1.00 (0.50–3.00)	5,771 ± 6,838	6,868 ± 3,559	8,119 ± 3,595	0.53 ± 0.22
	P	0.89	0.81	0.15	0.072	0.51
5′-DFUR	Alone	2.00 (0.50–4.00)	5,787 ± 3,996	10,027 ± 4,052	10,228 ± 4,263 (12)	0.72 ± 0.14
	Combination	2.50 (0.50–4.00)	6,618 ± 5,043	12,846 ± 5,077	13,356 ± 5,336	0.87 ± 0.63
	P	0.12	0.92	0.036	0.028	0.33
5-FU	Alone	2.00 (0.50–4.00)	102 ± 96	165 ± 63	176 ± 62	0.73 ± 0.17
	Combination	2.50 (0.50–4.00)	191 ± 204	311 ± 155	321 ± 151	1.00 ± 0.75
	P	0.17	0.10	0.0012	0.0037	0.24

NOTE: Values are means ± SD (*n*) except T_{max} values are median (range; *n*). *P* values are for a paired two-tailed Student's *t* test.

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