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ORIGINAL ARTICLE

**David Z. Chang · Thomas Olencki · G. Thomas Budd
David Peereboom · R. Ganapathi · Bruno Osterwalder
Ronald Bukowski**

Phase I trial of capecitabine in combination with interferon alpha in patients with metastatic renal cancer: toxicity and pharmacokinetics

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Abstract *Purpose*: The present study was designed to determine the toxicity and maximum tolerated doses of oral intermittent oral capecitabine and subcutaneous (s.c.) rHuIFNα2a in patients with metastatic renal cell carcinoma (RCC). The pharmacokinetics of capecitabine and its metabolites were also investigated. *Methods*: A total of 27 patients were treated at four dose levels of capecitabine (825 or 1000 mg/m^2 twice daily orally, days 1–14, 22–36) and rHuIFNα2a (1.5 or 3.0 MU/m^2 s.c. three times weekly). Unchanged capecitabine and its metabolites were analyzed in plasma using liquid chromatography/mass spectrometry in ten patients. *Results*: The toxicity of combined capecitabine and rHuIFNα2a was moderate. Patients experienced mild nausea/vomiting (70%) and diarrhea (63%). The hand-foot syndrome was seen in 67% of patients and was generally mild, as was hematologic toxicity. Dose-limiting toxicity included diarrhea, mucositis, neutropenia and the hand-foot syndrome. The dose level recommended for further trials included capecitabine 1000 mg/m^2 twice daily and rHuIFNα2a 3.0 MU/m^2 three times weekly. One patient had a partial response of a liver lesion (duration >200 days). Pharmacokinetic parameters of capecitabine and its metabolites (5′-deoxy-5-fluorouridine, 5-fluorouracil and α-fluoro-β-alanine) were similar to those reported by other authors. There was rapid conversion to 5′-deoxyuridine. The peak plasma concentrations of capecitabine occurred between 0.5 and 3.0 h. *Conclusions*: The combination of capecitabine and rHuIFNα2a was well tolerated. The recommended dose levels for phase II trials are: rHuIFNα2a 3.0 MU/m^2 s.c. three times weekly and oral capecitabine 1000 mg/m^2 twice daily for 2 weeks. No evidence of an effect of rHuIFNα2a on the pharmacokinetics of capecitabine or its metabolites was apparent. A phase II trial in untreated patients with metastatic RCC is planned.

Keywords Capecitabine · Interferon · Renal cancer · Pharmacokinetics

D.Z. Chang · T. Olencki · G.T. Budd · D. Peereboom
R. Ganapathi · R. Bukowski (✉)
Experimental Therapeutics Program, 9500 Euclid Avenue,
Cleveland Clinic Taussig Cancer Center,
Cleveland, OH 44195, USA
E-mail: bukowsr@cc.ccf.org
Tel.: +1-216-4446825
Fax: +1-216-4440114

B. Osterwalder
F. Hoffman-La Roche Ltd., Basel, Switzerland

Introduction

Renal cell carcinoma (RCC) is the seventh leading cause of cancer death in the United States [7], and accounts for 2–3% of all cancers in adults [13]. In patients with metastatic disease, therapy remains inadequate. This neoplasm is unresponsive to conventional cytotoxic chemotherapy regimens [17]. Previous reports have suggested, however, that 5-fluorouracil (5-FU) or fluorodeoxyuridine (FUDR) when administered as a continuous intravenous infusion, do produce tumor regressions in 8–10% of patients with metastatic disease. Cytokines, such as interleukin-2 (IL-2) and/or interferon alpha (IFNα) produce responses in 10–15% of patients, with occasional complete remissions reported [3]. Despite significant advances in understanding the biology of RCC during the past decade, metastatic disease remains a therapeutic challenge, and patients have a median survival of approximately 12.0 months. Development of novel approaches and investigation of new agents is required.

Capecitabine (Xeloda), a carbamate derivative of 5′-deoxy-5-fluorouridine (5′-DFUR), is a rationally designed orally administered fluoropyrimidine. This prodrug is efficiently absorbed from the gastrointestinal tract, and is preferentially converted to 5-FU in tumor tissue by thymidine phosphorylase (dThdPase). It is one of a series of 5′-deoxy-5-fluorocytidine (5′-DFCR) derivatives which were synthesized with the objective of having orally active drugs formed under the action of

liver carboxylesterase, and then cytidine deaminase present in the liver or tumor tissue, preventing direct release of 5-FU by gastrointestinal dThdPase [1]. In murine xenograft models, capecitabine has proved to be more active than 5-FU and has demonstrated activity in a variety of solid human tumors, including those that are 5-FU-resistant [10, 11, 12].

Previous studies have demonstrated that either continuous or intermittent therapy with capecitabine is active and well tolerated. Budman et al. [2] have reported that capecitabine when administered in a continuous twice-daily schedule has a maximum tolerated dose (MTD) of 828 mg/m^2 twice daily. Dose-limiting toxicities are palmar/plantar erythrodysesthesia, nausea, vomiting, abdominal pain, diarrhea and thrombocytopenia. These are reversible upon drug discontinuation. In a second trial [14], capecitabine was administered in an intermittent schedule for 2 of 3 weeks. The MTD was 1500 mg/m^2 twice daily, with the dose-limiting toxicities being diarrhea, hypotension, abdominal pain and leukopenia. In view of the novel mechanisms of action of capecitabine and the activity of 5-FU and IFNα in metastatic RCC [3, 17], the toxicity of this combination was examined in a phase I trial. The intermittent schedule for capecitabine was utilized, with IFNα administered subcutaneously (s.c.) three times weekly.

The clinical and preclinical data available suggested that the combination of IFNα and capecitabine should be studied clinically. We hypothesized that concurrent administration of both agents was possible with acceptable toxicity. The objectives of the current trial were to determine the MTDs and safety profile of combined capecitabine and IFNα, and in a preliminary fashion investigate the antitumor activity in patients with metastatic RCC. Additionally, the pharmacokinetics of capecitabine during IFNα therapy were investigated in view of previous studies indicating pharmacologic interactions between IFNα and 5-FU [9] including a decrease in clearance, changes in catabolism, and increased area under the curve (AUC) for 5-FU.

Patients and methods

The current trial was an open-label, single-institution, phase I study conducted at The Cleveland Clinic Foundation, Cleveland, Ohio, USA. Patient entry was initiated in March 1997 and completed in January 1999.

Patient selection

Patients with advanced and/or metastatic RCC were eligible. All patients were ≥18 years of age, gave informed written consent, had measurable and/or evaluable histologically confirmed RCC, a Karnofsky performance status (KPS) of ≥70%, and a life expectancy of ≥3 months. Patients were required to have the following baseline hematologic values: hemoglobin > 9.0 g/dl, white blood cells > 3×10^9/l, granulocytes > 1.5×10^9/l, and platelets > 100×10^9/l. Additional biochemical requirements included: total bilirubin ≤ 1.5 mg/dl, ASAT no more than 2.5 times normal, serum creatinine ≤ 1.5 mg/dl (in patients with prior nephrectomy ≤ 2.0 mg/dl), and serum calcium ≤ 11.5 mg/dl. Exclusion criteria included any of the following: prior history of another malignancy within 3 years (except for basal cell carcinoma of the skin and carcinoma in situ of the cervix); major surgery within 4 weeks; clinical or CT evidence of CNS metastases; history of clinically significant psychiatric disabilities, seizures or central nervous system disorders; clinically significant cardiovascular abnormalities and/or New York Heart Association Functional classification III or IV; poor medical risk because of non-malignant organ or systemic disease; prior history of systemic liver disease; systemic bacterial or fungal infections; major organ grafts, seropositive for HIV, and/or HBV, and/or HCV; more than one previous chemotherapy regimen, or two previous immunotherapy regimens including biologic response modifiers, cytokines, monoclonal antibodies or antitumor vaccines.

Treatment

Capecitabine was administered orally twice daily within 30 min of the end of a meal. It was given intermittently for 2 weeks, followed by 1 week rest. rHuIFNα2a (Roferon-A) was administered s.c. three times weekly continuously. One cycle of therapy consisted of 6 weeks of capecitabine and rHuIFNα2a. Capecitabine was administered orally on days 1–14 and 22–36, and rHuIFNα2a on Monday-Wednesday-Friday of each week. Tumor response was assessed after 6 weeks of therapy utilizing World Health Organization (WHO) criteria. Individuals with a complete response, partial response or stable disease received additional cycles of therapy until evidence of progressive disease was seen, or unacceptable toxicity developed.

The dose escalation schema utilized is outlined in Table 1. The first cohort of patients received rHuIFNα2a 1.5 MU/m^2 s.c. three times weekly and capecitabine 825 mg/m^2 twice daily. Subsequent patient cohorts were treated with 1.5 to 3.0 MU/m^2 of rHuIFNα2a with capecitabine escalated from 825 to 1000 mg/m^2 twice daily. Patients were seen once weekly, and toxicity assessed using the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC). Hand-foot syndrome, a toxicity not listed in the NCIC-CTC system, was graded as mild (grade 1), moderate (grade 2), or severe (grade 3) as previously described [11].

The MTD was defined as the dose level of capecitabine and rHuIFNα2a that caused drug-related grade 3/4 toxicity in one-third or more of patients treated. Five additional patients were then treated at this dose level to further characterize the toxicity profile of the combination.

Dose modifications

In the presence of grade 1 toxicity, treatment was continued. If a patient experienced grade 2 drug-related toxicity that did not resolve despite symptomatic treatment drug administration was withheld until it resolved to grade 0 or 1. If the same NCIC-CTC grade 2 toxicity recurred, treatment was withheld until recovery, and restarted at the preceding dose level. For grade 3 toxicity, drug administration was withheld until the toxicity recovered to grade 1 or less. Subsequent therapy was continued at 75% of the original doses, and at 50% if this was the second appearance of the same

Table 1 Treatment scheme and dose levels of capecitabine and rHuIFNα2a: phase I trial

Dose level	Capecitabine (mg/m^2 twice daily, days 1–14, 22–36[a])	rHuIFNα2a (MU/m^2, s.c. three times weekly)	Number of patients
A	825	1.5	4
B	825	3.0	6
C	1000	1.5	6
D	1000	3.0	11

[a]Cycles repeated every 6 weeks

toxicity. Once a dose was reduced for grade 3 toxicity, it was not increased subsequently. For grade 4 toxicity, treatment was permanently discontinued unless the investigator considered it in the patient's best interest to continue therapy at a lower dose (e.g. in the case of a responding patient).

Pharmacokinetic studies

Blood samples were obtained on day 10 ± 2 of cycle 1 for estimation of plasma concentrations of capecitabine and its metabolites 5′-DFCR, 5′-DFUR, 5-FU, and α-fluoro-β-alanine (FBAL). To investigate the pharmacokinetics of capecitabine and its metabolites, patients had serial blood samples taken predose, and at 0.5, 1, 2, 3, 4, 5, 7 and 10 h after capecitabine administration. Blood was collected into glass Vacutainers containing EDTA. After centrifugation, plasma was removed, and 2-ml aliquots transferred to plastic tubes for storage at –20°C. Concentrations of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU, and FBAL) were measured using a validated liquid chromatography/mass spectrometry technique and a high-performance liquid chromatography-UV technique [15].

Pharmacokinetic parameters were determined according to standard non-compartmental methods [8], using the program SAS, version 6.12 for NT [16]. The maximum plasma concentration (C_{max}) and time (T_{max}) to reach this value were determined from the highest observed concentration and the time of its occurrence, respectively. The apparent elimination half-life ($t_{1/2}$) was estimated from the apparent rate constant of elimination $\square$ ($\ln 2/\square$), which in turn was estimated by linear regression on the logarithm of the plasma concentration versus time data. Area under the plasma concentration time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$) was estimated from the sum of AUC_{0-t} and C_{tlast}/k. AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which the concentration could be measured (C_{tlast}). AUC_{0-t} was estimated using the linear trapezoidal rule. The pharmacokinetic parameters of capecitabine and its metabolites were calculated for each patient from the concentration-time data.

Descriptive statistics were used to summarize all pharmacokinetic parameters. Mean, standard deviation, coefficient of variation (CV), and minimum, maximum and median values were calculated for all parameters. In addition, geometric mean and geometric CV were calculated for C_{max}, t_{last}, AUC_{0-t} and $AUC_{0-\infty}$. The geometric CV was calculated from the variance of the log-transformed variable using the relationship

$$CV = \sqrt{\exp(\sigma^2) - 1}$$

Because of the limited number of patients studied, confirmatory statistics were not performed.

Results

A total of 27 patients were entered into the study, and their characteristics are summarized in Table 2. Cohorts of 4 to 11 patients were treated at four different dose levels of capecitabine (825–1000 mg/m^2 twice daily) and rHuIFNα2a (1.5–3.0 MU/m^2 three times weekly). The majority of the patients were male and had had prior systemic therapy. The median KPS was excellent, and clear-cell carcinoma was the most common histologic type.

The combination of capecitabine and rHuIFNα2a was generally well tolerated, with the majority of toxicity reported as mild or moderate. Dose-limiting toxicity included diarrhea, neutropenia, mucositis, and the hand-foot syndrome. Patients received a median of two cycles of therapy (range less than one to six). At dose level D, 3 of 11 patients failed to complete one cycle of therapy. One patient treated at dose level C developed a partial response in a liver lesion. The duration was over 200 days. This individual had had a previous nephrectomy, had received radiation therapy, and had been previously treated with IL-2 and IFNα.

Table 2 Patient characteristics: phase I trial capecitabine and rHuIFNα2a (total number of patients 27)

Karnofsky performance status (%)	
Median	90
Range	70–100
Age (years)	
Median	56
Range	32–76
Sex	
Male	19
Female	8
Cancer subtype	
Clear cell	13
Papillary	4
Other	2[a]
Sarcomatoid	1
Unknown	8
Prior therapy	
Radiotherapy	12
Interleukin-2	10
Interferon alpha	4

[a]One patient with collecting duct carcinoma, and one with adult Wilm's tumor

The major (grade 3/4) toxicities experienced by the patients are summarized in Table 3. No treatment-related deaths occurred. The majority of patients experienced malaise, low-grade fever and chills related to rHuIFNα2a. Nausea and vomiting were frequent (70%), but were generally mild. Diarrhea during cycle 1 was reported by 63% of patients (17/27). One patient treated at dose level D (capecitabine 1000 mg/m^2 twice daily, rHuIFNα2a 3.0 MU/m^2 three times weekly) developed grade 4 diarrhea requiring hospitalization, which then cleared without sequelae. The hand-foot syndrome was seen in 60% of patients, and was generally mild (25%) or moderate (33%). Three patients developed severe hand-foot syndrome, two of whom were treated at dose level D. Hepatic toxicity in the form of grade 1 elevations of SGOT or LDH occurred infrequently. Hematologic toxicity was generally mild with thrombocytopenia or neutropenia seen in 33% and 37% of patients. One instance of grade 4 neutropenia was seen, and was not accompanied by fever. The patient recovered without sequelae. The MTD was determined to be dose level D (capecitabine 1000 mg/m^2 twice daily, rHuIFNα2a 3.0 MU/m^2 three times weekly).

Pharmacokinetics were assessed in ten patients on day 10 ± 2. Table 4 summarizes the data from this group. Five patients studied had received 825 mg/m^2 of capecitabine, and five 1000 mg/m^2 as a single dose. Peak plasma concentrations of capecitabine and its metabolites 5′-DFUR, FBAL, and 5-FU are shown in Figs. 1 and 2. The concentrations of 5′-DFCR were lower than

those found in other studies, and were frequently below the limit of the assay (not shown). These low concentrations of 5′-DFCR are felt to have resulted from the fact that assays were performed more than 1 year after specimen collection.

The data do demonstrate that capecitabine undergoes extensive and rapid conversion to 5′-DFUR after administration. The peak plasma concentration for the unchanged drug occurred between 0.5 and 3.0 h after capecitabine administration. Concentrations then declined exponentially with half-lives of 0.65 and 0.57 h for capecitabine and 0.70 and 0.68 h for 5′-DFUR. After administration of 825 mg/m^2 (dose level of 1650 mg/m^2 per day), a high $AUC_{0-\infty}$ was obtained for 5′-DFUR (mean 13.3 $\mu g \cdot ml^{-1} \cdot h$, CV 44%, $n = 5$). In plasma, the peak FBAL concentration occurred approximately 3.0 to 4.0 h after capecitabine administration. The half-life of FBAL was 3.55 ± 0.66 h in patients receiving 825 mg/m^2. Similar findings were seen in the patient group who received 1000 mg/m^2 of capecitabine. No clear differences were apparent among the patients receiving 1.5 or 3.0 MU/m^2 of rHuIFNα2a.

Table 3 Grade 3 and 4 toxicity in patients receiving capecitabine and rHuIFNα2a: phase I trial. Figures are the number of patients experiencing toxicity grade III or more/total number of patients, except as indicated (*dose levels:* rHuIFNα2a s.c. three times weekly, MU/m^2, plus capecitabine orally twice daily, days 1–14, mg/m^2: *A* 1.5 plus 825, *B* 3.0 plus 825, *C* 1.5 plus 1000, *D* 3.0 plus 1000)

Toxicity	Dose level			
	A	B	C	D
Nausea/ vomiting	0/4	0/6	0/6	0/11
Diarrhea	0/4	1/6	1/6[b]	1/11
Mucositis	0/4	0/6	0/6	1/11
Hand-foot syndrome[a]	0/4	1/6	0/6	2/11
Neutropenia	0/4	0/6	1/6[b,c]	1/11[d]

[a]Grade 3 only
[b]Same patient
[c]Grade 3
[d]Grade 4

Discussion

The efficacy of capecitabine in preclinical xenograft models correlates with the ratio of dThdPase to dihydropyrimidine dehydrogenase in tumors [10]. It has also been noted previously [5, 6] that cytokines such as the IFNs can increase intratumoral levels of dThdPase, and increase the efficacy of agents such as 5′-DFUR or capecitabine. The rationale for the current trial was therefore twofold. First, previous reports suggested that the fluoropyrimidines and IFNα have single-agent activity in patients with RCC [3, 17]. Second, preclinical data indicated that potential modulation of tumor cell dThdPase may occur during IFN therapy, and thereby increase the efficacy of an agent such as capecitabine. The toxicity, efficacy, and pharmacokinetics of the combination were therefore investigated in the current study.

The current trial provided the first clinical experience with intermittent capecitabine in combination with rHuIFNα. The toxicity experienced by patients receiving the combination was moderate. The dose-limiting toxicity seen resembled that found in phase I trials utilizing single-agent capecitabine [1, 2, 14]. In these studies, hand-foot syndrome, nausea/vomiting, diarrhea, neutropenia and abdominal pain were found to limit the capecitabine dose. The dose level recommended for phase II studies was 2510 mg/m^2 per day for 14 days divided into two equal daily oral doses. In the current study, the MTD for capecitabine was found to be 1000 mg/m^2 twice daily reflecting the possible effects of adding rHuIFNα2a. This latter agent was administered s.c. three times weekly on a continuous basis. The dose levels of rHuIFNα2a utilized were low, and therefore the systemic symptoms produced by cytokines such as this were not severe and/or dose limiting.

A total of 27 patients were treated in the current study with the majority having clear-cell or papillary carcinoma ($n = 18$). The performance status of the group was excellent, but the majority of individuals had had prior therapy with cytokines ($n = 14$), or radiation ($n = 12$). Efficacy was a secondary end-point of this trial, and one patient experienced a partial response of a liver lesion that was durable (duration > 200 days), and a

Table 4 Pharmacokinetic parameters of capecitabine and metabolites on day 10 ± 2 in ten patients receiving rHuIFN2α (C_{max} maximum plasma concentration, T_{max} time to maximum plasma concentration, AUC area under the curve, $T_{1/2}$ elimination half-life)

Parameter	Dose of capecitabine (mg/m^2)	No. of patients	Capecitabine	5′-DFUR	5-FU	FBAL
C_{max} (μg/ml)[a]	825	5	1.83 (51%)	7.07 (60%)	0.357 (74%)	5.69 (26%)
	1000	5	3.22 (87%)	8.93 (35%)	0.479 (36%)	6.40 (19%)
T_{max} (h)[b]	825	5	1.50 (0.50–3.00)	2.00 (1.08–3.00)	2.00 (1.08–3.00)	3.08 (2.00–4.00)
	1000	5	3.03 (1.00–3.17)	3.03 (1.00–3.17)	3.03 (1.00–3.17)	4.00 (2.50–5.17)
$AUC_{0-\infty}$[a]	825	5	2.52 (36%)	13.3 (44%)	0.600 (58%)	31.9 (32)
	1000	5	5.52 (61%)	17.5 (24%)	0.856 (24%)	35.0 (29%)
$T_{1/2}$ (h)[a]	825	5	0.65 (58%)	0.70 (19%)	0.69 (15%)	3.55 (19%)
	1000	5	0.57 (35%)	0.68 (16%)	0.67 (23%)	3.24 (28%)

[a]Arithmetic means (coefficients of variation)
[b]Medians (ranges)

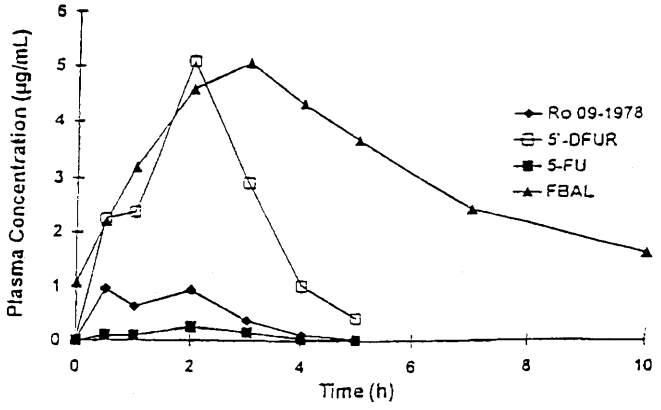

Fig. 1 Plasma concentrations (arithmetic mean values) versus time for capecitabine (Ro 09-1978) and its metabolites (5′-DFUR, 5-FU and FBAL) after administration of 825 mg/m^2 (dose level 1650 mg/m^2 per day) on day 10 ± 2 in patients ($n = 5$) receiving rHUIFNα2a

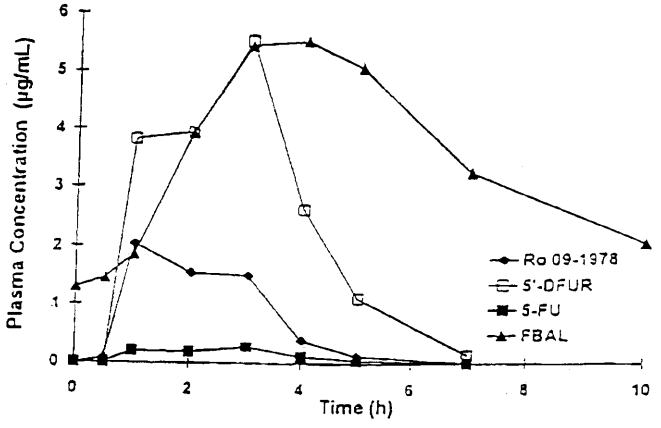

Fig. 2 Plasma concentrations (arithmetic mean values) versus time for capecitabine (Ro 09-1978) and its metabolites (5′-DFUR, 5-FU and FBAL) after administration of 1000 mg/m^2 (dose level of 2000 mg/m^2 per day) on day 10 in patients ($n = 5$) receiving rHuIFNα2a

second patient had minimal regression of a pulmonary lesion. Both these individuals had clear-cell carcinoma.

Pharmacokinetic studies were performed in ten patients on approximately day 10 of cycle 1, following four doses of rHuIFNα2a. Five individuals received 825 mg/m^2 and five 1000 mg/m^2 of capecitabine. The peak plasma concentration of the parent drug was seen at a median of 2–3 h, and the C_{max} was related to dose. The systemic exposure (AUC) to 5-FU was 20 times less to 5′-DFUR as has been previously reported [1, 2, 14]. All patients in the current trial received rHuIFNα2a, and the sample size studied was limited. Therefore alterations in the pharmacokinetic parameters of capecitabine and its metabolites are difficult to discern. When compared to prior reports [2, 4, 14, 18], the current values for C_{max}, T_{max}, $AUC_{0-\infty}$ and $T_{1/2}$ appeared similar, however. The effects on 5′-DFUR, 5-FU, FBAL, and the intact drug capecitabine did not appear different. In view of the small sample size, and very high interpatient variability, this conclusion is preliminary.

In conclusion, capecitabine and rHuIFNα were well tolerated, could be administered concurrently, and had an acceptable toxicity profile. Some evidence of antitumor activity in patients with metastatic RCC was found, but most patients included in this study were previously treated. The recommended phase II dose levels are: rHuIFNα2a 3.0 MU/m^2 s.c. three times weekly and capecitabine 1000 mg/m^2 twice daily for 14 days. This was repeated every 21 days. A phase II trial in untreated patients with metastatic RCC is currently in progress.

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