# A Phase I Dose-Escalation Study of Imatinib Mesylate (Gleevec/STI571) plus Capecitabine (Xeloda) in Advanced Solid Tumors

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**Abstract.** *The aim of this study was to determine the maximally tolerated dose, recommended phase II dose and toxicity profile of capecitabine plus imatinib mesylate combination. Patients and Methods: Twenty-four patients with advanced solid tumors were treated with capecitabine twice daily on days 1-14 and imatinib mesylate once daily on a 21-day cycle. Dose-limiting toxicity was assessed during the first cycle. Treatment continued until disease progression or undesirable toxicity. Results: Six patients were treated with capecitabine at 1000 mg/m$^2$ and imatinib mesylate 300 mg; unacceptable toxicity due to grade 2 intolerable hand-foot syndrome and/or grade ≥2 diarrhea was observed. Doses were subsequently reduced to capecitabine at 750 mg/m$^2$ and imatinib mesylate at 300 mg; toxicities were better tolerated at the lower dose. Dose-limiting toxicities consisted of grade 3 diarrhea, anorexia and fatigue lasting ≥4 days. Treatment-related adverse events greater than or equal to grade 3 included anemia, diarrhea, dysuria, hypophosphatemia and vertigo. Minor responses were observed in two patients: stable disease ≥6 months was observed in two out of twenty-one evaluable patients. Conclusion: Full doses of capecitabine and imatinib mesylate were not tolerable. The maximum tolerated dose and the recommended phase II dose for this drug combination is capecitabine at 750 mg/m$^2$ twice daily for 1-14 days and imatinib at 300 mg once daily on a 21-day cycle.*

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*Key Words:* Imatinib mesylate, capecitabine, phase I, advanced solid tumors.

Capecitabine (Xeloda™; Roche Laboratories, Nutley, NJ, USA) and imatinib mesylate (Gleevec™, Novartis Pharmaceuticals Corporation East Hanover, NJ, USA) are oral anti-neoplastic agents with unique mechanisms of action and predominantly non-overlapping toxicity profiles.

Capecitabine is a fluoropyrimidine prodrug that is converted to 5-fluorouracil (5-FU) in a series of enzymatic processes. In the first step, a carboxylesterase hydrolyzes capecitabine to 5'-deoxy-5-fluorocytidine in the liver. This is followed by the conversion of 5'DFCR to 5'-deoxy-5-fluorouridine which is subsequently hydrolyzed to the active drug, 5-FU, by thymidine phosphorylase. Thymidine phosphorylase is commonly overexpressed in tumors compared to normal surrounding tissue, thus allowing for more selective release of 5-FU in tumor cells (1, 2). Subsequent processing of 5-FU leads to 5-fluoro-2'-deoxyuridine monophosphates and 5-fluorouridine triphosphates that cause cellular injury by inhibiting DNA replication and inducing transcriptional errors which frequently lead to cellular death (3-5). Capecitabine is Food and Drug Administration (FDA)-approved as a monotherapy agent for adjuvant treatment of stage III colon cancer and as a first-line treatment for metastatic colorectal carcinoma. In metastatic breast cancer, capecitabine is used in combination with docetaxel after failure with anthracycline-containing compounds and as a monotherapy for patients resistant to paclitaxel and an anthracycline-containing regimen. The recommended dosage for capecitabine monotherapy is a twice daily dose of 1250 mg/m$^2$ taken for 14 consecutive days, followed by a 7-day rest period in a 21-day cycle (5-7). The most common and clinically significant toxicities are hand-foot syndrome, diarrhea, nausea, stomatitis, and vomiting; significant hematological toxicities such as neutropenia and thrombocytopenia are uncommon (8-11).

Imatinib mesylate is a selective small molecule inhibitor of several receptor tyrosine kinases including the chimeric breakpoint cluster region – Abelson kinase (BCR-ABL1) fusion protein, wild-type ABL and ABL2 (ARG), as well as

stem cell factor platelet-derived growth factor (PDGF), colony-stimulating factor (CSF), CSF-1 receptor, KIT, PDGF receptors (PDGFR)-α and -β, and discoidin domain receptor (DDR)-1 and -2 (12, 13). Imatinib inhibits tyrosine phosphorylation of substrate proteins by competitively binding to the catalytic domain of the kinase, which interrupts downstream signaling pathways involved in cell proliferation and angiogenesis. Imatinib mesylate monotherapy is FDA-approved for the treatment of chronic myelogenous leukemia which is typically characterized by the BCR-ABL fusion mutation, and gastrointestinal stromal tumors, which are characterized by the presence of activating *KIT* or *PDGFR* mutations (14-16). Imatinib also has antiangiogenic activity and has been shown to reduce interstitial pressure in tumors, which may allow better drug delivery (17). Imatinib is metabolized primarily *via* cytochrome p450 3A4 enzymatic activity (18). The most common toxicities associated with imatinib include musculoskeletal pain, muscle cramps, abdominal pain, diarrhea, vomiting, periorbital and peripheral edema and nausea (19).

Given the clinical activity and tolerability of each drug as monotherapy agents and in combination with other chemotherapeutics, it was hypothesized that their unique antitumor mechanisms combined may provide enhanced clinical activity if tolerable. Thus, the primary objectives of this study were to determine the maximally tolerated dose (MTD)/recommended phase II dosing (RPTD) and toxicity profile of capecitabine plus imatinib mesylate combination. Secondary objectives focused on assessing potential antiangiogenic properties of imatinib mesylate plus capecitabine using a dermal wound angiogenesis model and evaluating potential changes in plasma levels of PDGF-AA and PDGF-BB.

## Patients and Methods

*Patient selection*. Patients were required to have histologically proven solid tumor malignancies with no proven therapy or who had refused other therapies. Additional eligibility criteria included the following: age ≥18 years; Karnofsky performance status ≥70%; absolute neutrophil count (ANC) ≥2,000/mm$^3$, platelets ≥100,000/mm$^3$, hemoglobin ≥9.0 g/dl; alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× upper limit of normal (ULN) (or >5× ULN in the case of liver metastasis or >10× ULN in the case of bone disease); bilirubin ≤1.5× ULN; estimated creatinine clearance ≥50 ml/min; no prior chemotherapy, radiation therapy, hormonal or biological therapy within the previous 28 days; no prior nitrosoureas or mitomycin C within 42 days; no prior pelvic radiation to more than 30% of the bone marrow; no serious or poorly controlled medical or psychiatric conditions; not pregnant or lactating (negative pregnancy test within 7 days prior to registration for female patients of childbearing potential); no active central nervous system metastases. This study was approved by the Duke Institutional Review Board (IRB), and followed the Helsinki guidelines. All patients provided informed written consent prior to any study-related procedure. All patients were treated at Duke University Medical Center. Patient characteristics are summarized in Table I.

Table I. *Patient characteristics*.

| Characteristic | |
|---|---|
| Total patients, n | 24 |
| Gender, n | |
| Male | 12 |
| Female | 12 |
| Age, years | |
| Median | 57 |
| Range | 39-74 |
| Karnofsky performance status, (%) | |
| Median | 90 |
| Range | 70-100 |
| Prior treatments | |
| Surgery | 12 |
| Other (chemotherapy; radiation) | |
| 0 or unknown | 5 |
| 1-2 | 12 |
| 3-4 | 4 |
| 5-7 | 3 |
| Primary tumor type | |
| Colorectal | 4 |
| Prostate | 4 |
| Neuroendocrine (pancreas) | 4 |
| Renal | 2 |
| Lung | 2 |
| Thyroid | 2 |
| Other[a] | 5 |

[a]Includes one patient each with oral, thymus, breast, chondroma, carcinoid carcinoma.

*Patient evaluations*. All patients completed an extensive medical history and physical examination prior to receiving the study drugs. Toxicity and safety clinical assessments were performed weekly during the first cycle and on the first day of each subsequent cycle. Assessments included an interval history, performance status, complete blood count with differential, electrolytes, liver function tests, serum chemistry panel, prothrombin time and partial thromboplastin time, and urinalysis with microscopy. Appropriate serum tumor markers and radiographic imaging by computed tomography or magnetic resonance imaging were completed at baseline and every third cycle. Toxicities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 (20).

*Treatment schedule*. Capecitabine was given every 12 hours daily at a prescribed dose level determined by the dosing cohort and body surface area for the first 14 days of a 21-day cycle. Imatinib was given daily at the assigned dosing cohort level. Treatment was administered until disease progression, unacceptable toxicity or discontinued at physician and/or patient discretion.

Each new cycle could begin only if ANC ≥1,500 mm$^3$, platelets >75,000 mm$^3$ and non-hematologic toxicities resolved to grade ≤1. Dose modification was primarily for grade 3-4 toxicities or for

Table II. *Dose escalation scheme and cycle 1 dose-limiting events (DLTs).*

| Cohort level | Capecitabine (mg/m$^2$ *q*12h, days 1-14) | Imatinib (mg, daily) | No. of patients | No. of DLTs | DLT events |
|---|---|---|---|---|---|
| –1 | 750 | 300 | 18 | 1 | †Grade 3 anorexia and fatigue |
| 1 | 1000 | 300 | 6 | 1 | †Grade 3 diarrhea |
| 2 | 1000 | 400 | 0 | - | |
| 3 | 1000 | 600 | 0 | - | |
| 4 | 1000 | 800 | 0 | - | |
| 5 | 1250 | 800 | 0 | - | |

†Toxicity lasting ≥4 days despite adequate supportive care.

grade 2 toxicities deemed intolerable due to persistence, recurrence or effect on quality of life. Dose holding and modification of capecitabine for grade 2 hand-foot syndrome and diarrhea were consistent with its prescribing information (5). For toxicities potentially attributable to either drug, the dose of both drugs was reduced by 25% per toxicity occurrence; when toxicity could be attributed primarily to only one agent, only that drug was modified (*e.g.* hand-foot syndrome attributed to capecitabine). Modifications were based on the most severe toxicity.

*Dose escalation*. The dose escalation scheme is outlined in Table II. Dose escalation occurred when three patients had completed one treatment cycle without any dose-limiting toxicity (DLT). If one of the first three patients experienced a DLT, then three more patients were recruited to the same dose level for a total of six patients. Advancement to the next higher dose level could occur only if one out of six patients experienced a DLT. If two or more patients in a three to six patient cohort experienced a DLT, then the next three patients would be enrolled to the next lowest dose level. Dose escalation was scheduled to continue until the MTD was observed, or a total of six patients were treated at the highest dose level. When the MTD/RPTD dose was reached, twelve additional patients were scheduled to enroll to better describe the toxicities and activity of this regimen. The MTD was defined as the dose level immediately below that where 30% or more of patients experienced a DLT. Toxicities occurring beyond cycle 1 were not considered in DLT determinations but were considered in overall dose selection and for RPTD determination.

*DLT definitions*. DLTs were evaluated during cycle 1 and graded using the NCI CTCAE version 2.0 (20). The following toxicities were defined as dose limiting: any grade ≥4 neutropenia or thrombocytopenia; nausea/vomiting or diarrhea grade ≥3 lasting ≥4 days despite adequate support; non-hematological toxicity grade ≥3 lasting ≥4 days; treatment-related death or hospitalization; capecitabine or imatinib toxicities requiring modification that resulted in delivery of less than 90% of the planned dose for that cycle; delay of next cycle by >14 days due to toxicity.

*Response*. Radiographic responses were assessed *via* World Health Organization (WHO) response criteria measuring cross-sectional area as the product of the longest tumor diameter and its longest perpendicular diameter. Responses were defined as complete response (CR, 100% disappearance of tumor on CT scan with no sign of disease progression); partial response (PR, decrease in cross-sectional diameter >50%, but <100%, with no sign of disease progression; stable disease (SD, decrease in cross-sectional diameter <50%, or an increase <25%); progressive disease (PD, increase in cross-sectional diameter >25%, or the development of any of the following: new lesion with histological confirmation, a single new lesion that is >2 cm and that subsequently enlarges >50%, >2 new liver or pulmonary lesions or ≥2 lesions on bone scan, a malignant effusion. A minor response was defined as any decrease <50% of the sum of the target lesions.

*Plasma and urine biomarker analysis*. Peripheral blood and urine samples were obtained at baseline, the end of every third cycle and when the patient went offstudy. Blood was collected in EDTA-containing vacutainers, centrifuged at 2500×g 10 minutes, aliquoted, and stored at –80˚C until analysis. Plasma was analyzed for PDGF-AA and PDGF-BB using an enzyme-linked immunosorbant assay according to the manufacturer's instruction (R&D Systems, Inc. Minneapolis, MN, USA).

*Wound angiogenesis assay.* Skin biopsies were collected at baseline for a pre-treatment stimulation biopsy and an on-treatment granulation biopsy; a second set of stimulation and granulation biopsies was collected at the end of cycle 1 using methods previously reported (21). Briefly, after the patient's skin was anesthetized, a 4 mm punch biopsy was performed, which served to stimulate wound angiogenesis. Topical antibiotic ointment and a non-occlusive bandage were applied to the wound; patients were instructed in wound care. Dermal neovascularization was evaluated weekly using a digital camera with a special dermatologic adapter (Heine Dermaphot Optics, Medical Resources, Lewis Center, OH, USA). Vascularization was scored in a semi-automated fashion by two independent observers blinded to treatment status and image timing.

## Results

A total of twenty-four evaluable patients were enrolled and treated at two different dose levels. The median age was 57 (range 39-74) years. Eighteen patients had had at least one prior chemotherapy treatment and/or radiation, the median number of prior treatments was two (range 1-8); twelve patients had had prior surgery. A total of 114 cycles were completed; the median number of completed cycles/patient was three (range 1-18). All patients were evaluable for toxicity and 21 out of 24 were evaluable for tumor response. The dose escalation schema and number of patients in each cohort level with corresponding DLTs are listed in Table II.

Three patients were initially enrolled in cohort 1 (1,000 mg/m$^2$ twice daily of capecitabine and 300 mg daily of imatinib). One of the first three patients experienced a DLT of grade 3 diarrhea lasting ≥4 days despite adequate supportive care; therefore three additional patients were enrolled. Although there were no more DLTs in this cohort, five out of six patients in cohort 1 required dose reductions during cycles 1 and/or 2 related to grade 2 intolerable hand-foot syndrome and/or diarrhea. Two patients required multiple dose reductions. As a result, cohort level 1 was considered intolerable because of excessive toxicity, and doses were de-escalated to cohort level –1 (750 mg/m$^2$ twice daily of capecitabine and 300 mg once daily of imatinib). No DLTs were observed in the first three patients of this cohort, however, the fourth patient experienced grade 3 fatigue and anorexia lasting ≥4 days, so an additional three patients were enrolled to confirm tolerability. Cohort level –1 was expanded to a total of eighteen patients to better understand the toxicity profile for this dose as the MTD and RPTD.

Treatment-related toxicities are summarized in Table III. Dose reduction to cohort –1 significantly reduced the frequency and severity of both diarrhea and hand-foot syndrome; three out of eighteen patients experienced grade 2 intolerable hand-foot syndrome in cohort –1 compared to four out of six patients in cohort 1. Likewise, three out of six patients in cohort 1 had grade 2 intolerable or grade 3 diarrhea, whereas no diarrhea higher than grade 1 was observed in cohort –1. Other common grade 1-2 non-hematologic toxicities for both cohorts included fatigue, anorexia, insomnia, pain and gastrointestinal-related problems (nausea, vomiting and constipation). Hematologic-related toxicities included grade 1 neutropenia and thrombocytopenia; one patient experienced grade 4 anemia. Other grade 3 toxicities included one episode of dizziness (disequilibrium, lightheadedness and vertigo), dysuria, hypophosphatemia and allergic reaction. One patient in the expanded cohort experienced grade 3 fatigue, although this patient started protocol therapy with a baseline of grade 2 fatigue.

Table III. *Treatment-related adverse events (maximum toxicities per patient, n=24).*

| | Capecitabine 1000 mg/m$^2$ (*q*12h) Imatinib 300 mg (daily) (n=6) | | Capecitabine 750 mg/m$^2$ (*q*12h) Imatinib 300 mg (daily) (n=18) | |
|---|---|---|---|---|
| | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 |
| Toxicity | N (%) | N (%) | N (%) | N (%) |
| Hematological | | | | |
| Neutropenia | 2 (33) | 0 | 2 (11) | 0 |
| Thrombocytopenia | 0 | 0 | 5 (28) | 0 |
| Anemia | 2 (33) | 0 | 10 (56) | 1 (6) |
| Gastrointestinal | | | | |
| Diarrhea | 3 (50) | 2 (33) | 8 (44) | 0 |
| Constipation | 3 (50) | 0 | 4 (22) | 0 |
| Nausea | 4 (47) | 0 | 11 (61) | 0 |
| Vomiting | 1 (17) | 0 | 7 (39) | 0 |
| Other | | | | |
| Hand-foot syndrome | 5 (83) | 0 | 4 (22) | 0 |
| Mucositis | 0 | 0 | 2 (11) | 0 |
| Dyspnea | 2 (33) | 0 | 0 | 0 |
| Anorexia | 4 (67) | 0 | 5 (28) | 1 (6) |
| Dizziness | 0 | 1 (17) | 5 (28) | 0 |
| Edema | 3 (50) | 0 | 4 (22) | 0 |
| Fatigue | 4 (67) | 0 | 7 (39) | 2 (11) |
| Fever | 1 (17) | 0 | 2 (11) | 0 |
| Headache | 2 (33) | 0 | 2 (11) | 0 |
| Insomnia | 2 (33) | 0 | 4 (22) | 0 |
| Pain | 3 (50) | 0 | 4 (22) | 0 |
| Neuropathy | 2 (33) | 0 | 3 (17) | 0 |
| Hypophosphatemia | 0 | 1 (17) | 2 (11) | 0 |

Table IV summarizes the best radiographic response. Twenty-one treated patients were evaluable for efficacy. Stable disease was observed in nine patients, ranging in duration from three to nine months. While there were no partial responses, two patients showed minor responses with stable disease, including one patient with colorectal cancer whose minor response lasted four months and another patient with refractory non-small cell lung cancer whose minor response included the resolution of two lesions and lasted six months.

Wound angiogenesis assays were evaluable in thirteen patients. Plasma levels for PDGF-AA and PDGF-BB were measured at baseline and after 1-2 cycles of treatment in six patients. While the assays demonstrated good technical assay reproducibility, no treatment-related changes were detected in the small number of evaluable patients with either assay (data not shown).

Table IV. *Best radiographic response*.

| Cohort level | No of patients | Partial response | Stable disease | | Progressive disease | Not assessed |
|---|---|---|---|---|---|---|
| | | | <6 months* | ≥6 months | | |
| –1 | 18 | 0 | 4 | 1 | 10 | 3 |
| 1 | 6 | 0 | 3 | 1 | 1 | 0 |

*Range 3-5 months.

## Discussion

The present study explored the safety, tolerability and the MTD/RPTD for a capecitabine and imatinib treatment combination. Although initial doses of capecitabine at 1000 mg/m$^2$ and imatinib at 300 mg were acceptable in cycle 1, most patients in cohort 1 required multiple dose reductions in the first two cycles indicating unacceptable cumulative toxicity. Consequently, the dosing schedule was adjusted to reflect a dose reduction to capecitabine at 750 mg/m$^2$ twice daily for days 1-14 and imatinib at 300 mg once daily in a 21-day cycle. Overall, this lower dose was well tolerated as the RPTD evidenced by significantly fewer dose reductions in cohort –1 compared to cohort 1. Among the 18 patients treated in cohort –1, only one patient experienced a DLT (grade 3 fatigue and anorexia lasting ≥4 days). Other clinically significant toxicities for both cohorts included, diarrhea, fatigue and hand-foot syndrome. Most toxicities were grade 1-2 and readily manageable.

Interestingly, grade 2 intolerable hand-foot syndrome and/or diarrhea were the primary toxicities that prevented the full doses of capecitabine and imatinib from being clinically tolerated. In cohort 1, five out of six patients required early dose reductions due to these toxicities; however, in dose level –1, only three out of eighteen required dose modification specifically for hand-foot syndrome and/or diarrhea. These two toxicities have also been noted in other treatment regimens when capecitabine has been combined with other agents that inhibit PDGFR such as sorafenib and sunitinib (22-24). Many of these agents also inhibit vascular endothelial growth factor (VEGF) receptors, among other targets. Taken together, these data suggest the potential for augmented toxicity when combining capecitabine with a PDGFR inhibitor and/or with angiogenesis inhibitors.

Only modest signs of clinical activity were noted. Nine patients exhibited stable disease; one patient with neuroendocrine carcinoma in the pancreas had stable disease for nine months. Minor responses with stable disease were observed in two patients. Pilot correlative studies showed there were no treatment-related changes in wound angiogenesis or plasma PDGF-AA or PDGF-BB levels; however, the sample size for both assays was too small to make any definitive conclusions regarding drug effect.

In conclusion, the results of this study demonstrated that full doses of capecitabine and imatinib are not tolerable. The reduced doses of capecitabine at 750 mg/m$^2$ twice daily for days 1-14 of a 21-day cycle and imatinib at 300 mg daily are well tolerated and are the RPTD suggested for further evaluation.

## Acknowledgements

We gratefully acknowledge the invaluable contributions of the patients, their families and the Duke University Phase I Oncology clinical team and health care providers. In memorial, we honor Roxanne Truax, who was one of the founding members of the Duke University Phase I Oncology clinical team and provided outstanding clinical care and mentorship throughout her nursing career at Duke University.

## References

1 Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I and Ishitsuka H: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer *34*: 1274-1281, 1998.

2 Schuller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, Utoh M, Mori K, Weidekamm E and Reigner B: Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol *45*: 291-297, 2000.

3 Budman DR, Meropol NJ, Reigner B, Creaven PJ, Lichtman SM, Berghorn E, Behr J, Gordon RJ, Osterwalder B and Griffin T: Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. J Clin Oncol *16*: 1795-1802, 1998.

4 Takebayashi Y, Yamada K, Miyadera K, Sumizawa T, Furukawa T, Kinoshita F, Aoki D, Okumura H, Yamada Y, Akiyama S and Aikou T: The activity and expression of thymidine phosphorylase in human solid tumours. Eur J Cancer *32A*: 1227-1232, 1996.

5 F. Hoffman-La Roche, Ltd: Capecitabine Investigator's Brochure 2009.

6 Hoff P: Capecitabine as first-line treatment for colorectal cancer (CRC): Integrated results of 1207 patients (pts) from 2 randomized, phase III studies. On behalf of the Capecitabine CRC study group. Ann Oncol *11*: 60(abstract A263), 2000.

7 Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz J-F, Thompson P, Vieitez JM, Weitzel C and Harper P: Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol *19*: 4097-4106, 2001.

8 Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schoffski P, Sobrero A, Van Cutsem E and Diaz-Rubio E: XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol *22*: 2084-2091, 2004.

9 Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO and Wong R: Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. J Clin Oncol *19*: 2282-2292, 2001.

10 Twelves C, Wong A, Nowacki MP, Abt M, Burris H, 3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J and Scheithauer W: Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med *352*: 2696-2704, 2005.

11 Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C and Harper P: Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol *19*: 4097-4106, 2001.

12 Bin P, Lloyd P and Schran H: Clinical pharmacokinetics of imatinib. Clinical Pharmacokinetics *44*: 879-894, 2005.

13 Day E, Waters B, Spiegel K, Alnadaf T, Manley PW, Buchdunger E, Walker C and Jarai G: Inhibition of collagen-induced discoidin domain receptor 1 and 2 activation by imatinib, nilotinib and dasatinib. Eur J Pharmacol *599*: 44-53, 2008.

14 Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CDM and Joensuu H: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med *347*: 472-480, 2002.

15 Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Niederwieser D, Resta D, Capdeville R, Zoellner U, Talpaz M, Druker B for the International STI571 CML Study Group: Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med *346*: 645-652, 2002.

16 O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ and the IRIS Investigators: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med *348*: 994-1004, 2003.

17 Vlahovic G, Ponce AM, Rabbani Z, Salahuddin FK, Zgonjanin L, Spasojevic I, Vujaskovic Z and Dewhirst MW: Treatment with imatinib improves drug delivery and efficacy in NSCLC xenografts. Br J Cancer *97*: 735-740, 2007.

18 Peng B, Lloyd P and Schran H: Clinical pharmacokinetics of imatinib. Clin Pharmacokinet *44*: 879-894, 2005.

19 Novartis: Imatinib mesylate (gleevec) Investigator's Brochure, 2008.

20 Cancer Therapy Evaluation Program, National Cancer Institute, Washington, D.C. U.S.A., Common toxicity criteria for adverse events, version 2.0. 1999.

21 Lockhart AC, Braun RD, Yu D, Ross JR, Dewhirst MW, Klitzman B, Yuan F, Grichnik JM, Proia AD, Conway DA, Mann G and Hurwitz HI: A clinical model of dermal wound angiogenesis. Wound Repair Regen *11*: 306-313, 2003.

22 Chiorean EG, Sweeney CJ, Verschraegen CF, Lee FC, Jones SF, Rabinowitz I, Tye L, Bello A, Chao R and Burris III HA: Tolerability/safety of sunitinib (SU) on schedule 2/1 in combination with capecitabine (C) in patients (pts) with advanced solid tumors (STs): A phase I dose-finding study. J Clin Oncol *26*: abstract 3562, 2008.

23 McKay CE, Infante J, Jones S, Bendell J, Greco FA, Markus T, Spigel DR, Yardley DA, Woudenberg J, Lathia CD and Burris HA: A pharmacokinetic (PK) and safety study of sorafenib plus capecitabine in advanced solid tumors. J Clin Oncol *27*: abstract e14548, 2009.

24 Sweeney C, Verschraegen C, Chiorean G, Lee F, Jones S, Tye L, Bello A, Chao R and Burris H: A phase I dose escalation study of sunitinib plus capecitabine in patients with advanced solid tumors. J Clin Oncol *25*: abstract 3592, 2007.

*Received February 13, 2010*
*Revised March 19, 2010*
*Accepted March 22, 2010*