FootLocal Protocol #: OS12903

TITLE: Pilot Study Evaluating Pharmacokinetic Parameters of Capecitabine Dosing in Patients with Advanced Cancer and Elevated Body Mass Index.

Coordinating Center:
University of Wisconsin Carbone Cancer Center
600 Highland Ave
Madison, WI 53792

University of Wisconsin Participating Site:
University of Wisconsin Health Oncology at 1 South Park
1 South Park St.
Madison, WI 53715

***Principal Investigator:**
Name: Kari B. Wisinski, MD
Address: 1111 Highland Ave.
WIMR Room 6033
Madison, WI 53705-2275
Phone: 608- 262- 2876
Fax: 608-265-6905
E-mail: kbwisinski@medicine.wisc.edu

Co-Investigators:
Name: Jill Kolesar, PharmD, BCPS, FCCP, R.Ph
Address: 600 Highland Avenue
CSC Room K4/554
Madison, WI 53792
Phone: 608-262-5549
Fax: 608-265-5421
Email: jmkolesar@pharmacy.wisc.edu

Statistician:
Name: Jens Eickhoff
Address: 600 Highland Avenue
CSC, Room K6/434
Madison WI 53792
Telephone: (608) 265-5376
Fax: (608) 265-5579
E-Mail: eickhoff@biostat.wisc.edu

Study Coordinator:
Name: Jennifer Heideman
Address: 600 Highland Avenue
CSC, Room K5/601
Madison, WI 53792
Telephone: (608) 263-6222
Fax: (608) 263-9132
E-Mails: jlv@medicine.wisc.edu

Research Nurses:
Kim Binger, BSN, RN
Heidi Brandon, BSN, RN
Maria Kruse, BSN, RN
Chris Feierabend, BSN, RN
Kara Mattox, BSN, RN
Karen Schroeder, BSN, RN

Data Managers:
Amy Forsyth, BS
Jess Gunderson, MSc
Jeff Ockuly, BS
Sandra Black, BS – 1 S. Park

Commercial Agent: Capecitabine

Protocol Type / Version # / Version Date: Version 1 / 10.15.12
Version 2 / 2.25.13
Version 3 / 12.6.13
Version 4 / 10.1.14
Version 5 / 5.16.16

SCHEMA

Cycle 1						
	Day 1	Days 2-7	Day 8	Day 9	Days 10-15	Day 16-21
Capecitabine Dose	(1,250mg/ m^2 orally twice daily)	(1,250mg/ m^2 orally twice daily)	none	(1,250mg/ m^2 orally twice daily)	(1,250mg/ m^2 orally twice daily)	none
Weight Used for BSA	Ideal Body Weight	Ideal Body Weight	n/a	Actual Body Weight	Actual Body Weight	n/a
PK Collection	On CRU	Day 7	n/a	On CRU	Day 15	n/a

Cycle 2 and beyond will be dosed using Actual Body Weight at 1,250mg/ m^2 orally twice daily days 1-14 of 21 day cycles.

TABLE OF CONTENTS

1. OBJECTIVES

1.1. **Primary Objective**: To characterize the effect on pharmacokinetic parameters of capecitabine, when dosed using actual versus ideal body weight in obese patients with advanced solid tumors.

1.2. **Secondary Objectives:**

1.2.1 To characterize the response rate and progression free survival with capecitabine therapy in obese subjects with advanced solid tumors

1.2.2 To determine capecitabine pharmacokinetics in obese patients compared with normal weight historical controls.

2. BACKGROUND

2.1 Study Disease

Cancer is the second leading cause of death in the United States.[1] The prognosis associated with distant metastases from adult solid tumors is poor for most malignancies. The goal of treatment with systemic therapies is primarily palliative for these patients. Determining the optimal dosing of systemic therapies would improve anti-tumor efficacy and limit drug – related toxicities.

2.2 Rationale

In 2012, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines regarding appropriate chemotherapy dosing for obese adult patients with cancer.[1] Although these guidelines recommended that full weight-based chemotherapy doses be used to treat obese patients, the authors highlighted the limited data for these recommendations and emphasized that ***further research into the role of pharmacokinetics to guide appropriate dosing of chemotherapy in obese patients is critically needed***. This issue is particularly relevant given the increasing obesity epidemic in the United States and worldwide. Obesity is defined as a body mass index of 30kg/m^2 or greater. Currently, more than 1/3 (35.7%) of U.S. Adults are obese, which has doubled since 1980.[2] This is also pertinent for the University of Wisconsin patient population. In 2010, the Center for Disease Control estimated that 26.3% of Wisconsin adults were obese.[2]

Optimal doses of oncology treatments are established through clinical trials. However, the majority of chemotherapy agents and many targeted anti-cancer agents are dosed based on weight, with chemotherapy most often dosed based on estimated body surface area (BSA). The estimated BSA is calculated using standardized formulas.[3] BSA was initially used for chemotherapy dosing because of its ability to correlate with many of the physiologic parameters which impact drug pharmacokinetics, such as blood volume and renal clearance. [4] Pharmacokinetic parameters, such as AUC and Cmax, have been associated with clinical efficacy and toxicity of chemotherapy agents.[5] However, inter-individual pharmacokinetic variation remains a challenge, as this can impact drug efficacy and adverse events. Obesity may account for some of this pharmacokinetic variation. Based on concerns about increased

toxicity with higher doses of chemotherapy in obese patients, many oncologists elect to either cap chemotherapy dosing or use an adjusted BSA formula for obese patients.[6,7] However, empirically lowering the dose of chemotherapy may lead to compromised anti-tumor efficacy, as several studies have indicated that dose-intensity of chemotherapy correlates with outcomes.[8,9] Obesity has been associated with poorer cancer outcomes.[10] Although this correlation is likely multi-factorial, in part this may reflect sub-optimal chemotherapy dosing.

To date, there have been no prospective, randomized studies comparing cancer outcomes using a full weight based approach to a limited-weight dosing approach of chemotherapy in obese cancer patients.[1] The ASCO guidelines for dosing of chemotherapy in obese patients based their recommendations on several retrospective and observational studies which suggested that there is no increased toxicity in obese patients administered full weight based doses.[11,12] In order to better understand the impact of full weight based chemotherapy dosing, we propose a pilot study evaluating intra-patient changes in pharmacokinetic parameters using two dosing approaches of the commonly used chemotherapy agents, capecitabine.

2.3 **Study Drug: Capecitabine**

Capecitabine is an oral anti-metabolite chemotherapy. It is a prodrug of 5-FU[13] and is FDA approved and commonly used in the treatment of gastrointestinal and breast cancers. } It has a short half-life and is typically dosed twice daily for 14 consecutive days, followed by a 1 week break.[14] Capecitabine is converted by three enzymes in the liver and tumors to 5-FU. The final step in this being conversion of 5'deoxy-5-fluorouridine to 5FU by thymidine phosphorylase. 5FU inhibits thymidilate synthase causing inhibition of DNA synthesis.[13]

Clinical Experience with Capecitabine:

Colon and rectal cancers rank as the third most common cancer in the United States and CRC the second leading cause of U.S. cancer deaths.[15] Obesity has been linked with an increased risk for development of colorectal cancers.[16,17] Although survival rates for limited-stage disease remain high, metastatic disease has a five-year survival of less than 10%, although median survival now approaches two years with combination therapy.[18,19]

As a single agent in metastatic colorectal cancer, capecitabine has response rates ranging from 18.9-25.8% with equal efficacy compared to 5-FU/leucovorin but significantly fewer toxicities.[20,21] It also has been demonstrated to have activity in 3rd line metastatic colorectal cancer. [22] Capecitabine has also been studied in conjunction with oxaliplatin in advanced colorectal cancer with response rates of 35-55%.[23,24] Capectabine has become a standard chemotherapy agent used to treat metastatic colorectal cancers. Interesting, there is an emerging body of literature suggesting that pharmacokinetically- guided fluorouracil (5-FU) dose adjustment versus standard body-surface-area (BSA) dosing in metastatic colorectal cancer may be more effective. [25,26] This suggests that understanding the pharmacokinetic impact of a limited-weight based dosing approach would be important with this drug, with the evidence suggesting that lower steady state concentrations may negatively impact clinical outcomes.

Breast cancer is the most common cancer in women and the second leading cause of cancer death in women. Despite the availability of many targeted, endocrine and chemotherapy agents, over 40,000 women die each year from metastatic breast cancer.[19]Interestingly, obesity and weight gain have been demonstrated to increase a woman's risk of developing breast cancer, in particular, post-menopausal breast cancer.[27,28]

Capecitabine has been extensively studied in metastatic breast cancer. Single agent therapy yields response rates of 15-29% in patients pre-treated with anthracyclines and taxanes, [29-31] As a component of combination therapy with paclitaxel, docetaxel or ixabepilone, capecitabine improves response rates and progression-free survival, although the impact of doublet therapy on overall survival is less clear.[32-34] Capecitabine has also been studied and approve in combination with lapatinib, a human epidermal growth factor receptor tyrosine kinase inhibitor.[35] Based on these results, capecitabine is commonly used to treat patients with advanced breast cancer, either as a single agent or as a component of combination therapy.

Capecitabine Adverse Events/Toxcity

The main side effects of capecitabine seen across multiple studies include: hand-foot reaction, diarrhea, nausea, vomiting, anorexia, stomatitis, dermatitis, hyperbilirubinemia, leukopenia, thrombocytopenia, and anemia. (see Tables 1-2 below from package insert http://www.gene.com/gene/products/information/xeloda/pdf/pi.pdf).

Patients over 80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events. Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30mL/min or those with known dihydropyrimidine dehydrogenase (DPD) deficiency. Capecitabine may cause fetal harm when given to a pregnant woman. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving capecitabine therapy.

Table 1: Pooled Phase 3 First Line Colorectal Trials: Percent Incidence of Adverse Reactions in ≥5% of Patients.

Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Number of Patients With > One Adverse Event	96	52	9	94	45	9
Body System/Adverse Event						
GI						
Diarrhea	55	13	2	61	10	2
Nausea	43	4	–	51	3	<1
Vomiting	27	4	<1	30	4	<1
Stomatitis	25	2	<1	62	14	1
Abdominal Pain	35	9	<1	31	5	–
Gastrointestinal Motility Disorder	10	<1	–	7	<1	–
Constipation	14	1	<1	17	1	–
Oral Discomfort	10	–	–	10	–	–
Upper GI Inflammatory Disorders	8	<1	–	10	1	–
Gastrointestinal Hemorrhage	6	1	<1	3	1	–
Ileus	6	4	1	5	2	1
Skin and Subcutaneous						
Hand-and-Foot Syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Skin Discoloration	7	<1	–	5	–	–
Alopecia	6	–	–	21	<1	–
General						
Fatigue/Weakness	42	4	–	46	4	–
Pyrexia	18	1	–	21	2	–
Edema	15	1	–	9	1	–
Pain	12	1	–	10	1	–
Chest Pain	6	1	–	6	1	<1
Neurological						
Peripheral Sensory Neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Dizziness*	8	<1	–	8	<1	–
Insomnia	7	–	–	7	–	–
Taste Disturbance	6	1	–	11	<1	1
Metabolism						
Appetite Decreased	26	3	<1	31	2	<1
Dehydration	7	2	<1	8	3	1
Eye						
Eye Irritation	13	–	–	10	<1	–
Vision Abnormal	5	–	–	2	–	–

Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Respiratory						
Dyspnea	14	1	–	10	<1	1
Cough	7	<1	1	8	–	–
Pharyngeal Disorder	5	–	–	5	–	–
Epistaxis	3	<1	–	6	–	–
Sore Throat	2	–	–	6	–	–
Musculoskeletal						
Back Pain	10	2	–	9	<1	–
Arthralgia	8	1	–	6	1	–
Vascular						
Venous Thrombosis	8	3	<1	6	2	–
Psychiatric						
Mood Alteration	5	–	–	6	<1	–
Depression	5	–	–	4	<1	–
Infections						
Viral	5	<1	–	5	<1	–
Blood and Lymphatic						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13
Hepatobiliary						
Hyperbilirubinemia	48	18	5	17	3	3

– Not observed
* Excluding vertigo
NA = Not Applicable

Table 2: Percent Incidence of Adverse Reactions Considered Remotely, Possibly or Probably Related to Treatment in ≥5% of Patients Participating in the Single Arm Trial in Stage IV Breast Cancer

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
Body System/Adverse Event	Total %	Grade 3 %	Grade 4 %
GI			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
Body System/Adverse Event	Total %	Grade 3 %	Grade 4 %
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–
Nail Disorder	7	–	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
Neurological			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
Metabolism			
Anorexia	23	3	–
Dehydration	7	4	1
Eye			
Eye Irritation	15	–	–
Musculoskeletal			
Myalgia	9	–	–
Cardiac			
Edema	9	1	–
Blood			
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Anemia	72	3	1
Lymphopenia	94	44	15
Hepatobiliary			
Hyperbilirubinemia	22	9	2

– Not observed
NA = Not Applicable

Clinical Pharmacokinetics

Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo. Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.[36] Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0).

The pharmacokinetics of capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day.[14,37] Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about 3/4 of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Capecitabine reached peak blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and $AUC_{0\text{-infinity}}$ decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0\text{-infinity}}$ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours. Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, ß-ureido-propionase cleaves FUPA to alpha-fluoro-ß-alanine (FBAL) which is cleared in the urine.

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Drug-Drug Interactions:
(http://www.gene.com/gene/products/information/xeloda/pdf/pi.pdf)

Anticoagulants: In four patients with cancer, chronic administration of capecitabine (1250 mg/m^2 bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8 fold, and the maximum observed mean INR value was increased by 91%. Patients receiving concomitant capecitabine and oral coumarin-derived anticoagulant therapy should have their anticoagulant response (INR, PT) monitored closely with great frequency and the anticoagulant dose adjusted accordingly.

Drugs Metabolized by Cytochrome P450 Enzymes: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL) had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1.

Antacid/ Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (1250 mg/m^2, n=12 cancer patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of capecitabine.

Capecitabine has a low potential for pharmacokinetic interactions related to plasma protein binding.

Based on the standard reference resources from the FDA

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) capecitabine is a weak inhibitor of CYP2C9. Thus, based on the drug interaction table in Appendix C, no medications would be contraindicated.

2.4 **Hypothesis:** ***Our hypothesis is that use of full weight based chemotherapy dosing will be associated with a significantly higher AUC and Cmax.*** The results of this study will advance oncologists' understanding of the potential impact of using limited weight-based dosing for capecitabine and provide preliminary data to demonstrate the need evaluate the importance of weight-based dosing for other chemotherapy and targeted agents.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed advanced or metastatic cancer for which capecitabine treatment is considered a standard treatment option.

3.1.2 Patients with **measurable or evaluable** disease are eligible

3.1.3 Patient's Body Mass Index must be 30 kg/m^2 or higher.

3.1.4 Eastern Cooperative Oncology Group performance status 0-2.

3.1.5 Age ≥18 years.

3.1.6 Life expectancy of greater than 12 weeks.

3.1.7 Patients must have adequate organ and marrow function as defined below:

- Hematologic: ANC >1000/mcL, Hemoglobin > 8gm/dL (transfusions permitted) and platelets > 75,000/mcL

- Renal: serum creatinine ≤ upper limit of normal (ULN) or creatinine clearance (either estimated or calculated) ≥60 mL/min/1.73 m for patients with creatinine levels above institutional normal.

$$\text{Females: } Cr_{cl} = \frac{(140-\text{age})(\text{weight in kg})(0.85)}{72 \times \text{Serum creatinine}}$$

$$\text{Males: } Cr_{cl} = \frac{(140-\text{age})(\text{weight in kg})}{72 \times \text{Serum creatinine}}$$

- Hepatic: Serum Bilirubin ≤ 1.5x ULN and
  - No liver metastases: AST and ALT ≤ 2.5x ULN
  - Liver metastases: AST and ALT ≤ 5x ULN

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Capecitabine is contra-indicated in pregnant women because of known detrimental effects on the fetus. A negative pregnancy test is required in all premenopausal women within 14 days of study therapy initiation. Women of child-bearing potential and men with an active female sexual partner must agree to use adequate contraception (hormonal, surgical, barrier methods or abstinence allowed) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.2 Exclusion Criteria

3.2.1 Patients who have had systemic chemotherapies or targeted therapies within 3 weeks or radiotherapy within 2 weeks prior to entering the study or those patients whose adverse events from prior therapies have not recovered to $\leq$ grade 1 (other than grade 2 neuropathy, lymphopenia and alopecia which are permitted.)

3.2.2 Patients receiving any other investigational agents for cancer treatment.

3.2.3 Patients with treated, stable brain metastases are allowed to enroll. Patients must be at least 4 weeks from brain radiation and off any medications used to treat brain metastases including steroids. Patients are allowed to be on anti-epileptic medications that are not contraindicated as listed in Appendix C.

3.2.4 Patients with any condition of the gastrointestinal tract that is expected to result in an inability to swallow or absorb oral medications (ie. prior surgical procedures affecting absorption and requiring i.v. alimentation). This will be determined at the discretion of the PI.

3.2.5 Patients may not be taking any concomitant drugs that are contraindicated based on the drug-interaction table in Appendix C.

3.2.6 Concurrent treatment with warfarin (coumadin) is allowed, but close monitoring of the PT/INR is recommended.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active severe infection, symptomatic congestive heart failure, unstable angina pectoris, clinically significant or symptomatic cardiac arrhythmia, other malignancies requiring therapy or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women or women who are breastfeeding are excluded from this study because capecitabine is a pregnancy category D drug and is known to pass to the infant in breastmilk.

3.2.9 Patients with known deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme.

3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to capecitabine.

3.3 Inclusion of Women and Minorities

Members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study using the University of Wisconsin Carbone Cancer Center Oncore Database (uwccc.wisc.edu/oncore) in accordance with standard UWCCC guidelines.

In accordance with institutional policies approved by the U.S. Department of Health and Human Services, each subject must acknowledge consent for treatment as a human subject in this study. Informed consent must be obtained prior to the initiation of protocol therapy.

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

To register a patient, the following documents should be reviewed and compiled by the research nurse or data manager prior to registering subject into Oncore, where a study ID will be automatically assigned.

- Copy of all baseline tests/procedures verifying eligibility
- Signed patient consent form.
- Signed HIPAA authorization form.
- Eligibility Screening Worksheet filled out in Oncore.

5. TREATMENT PLAN

5.1 Administration

▪ Capecitabine treatment will be administered on an **outpatient** basis with the exception that cycle 1 days 1 and 9 will be administered on the Clinical Research Unit for pharmacokinetic blood draws. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

▪ The minimum number of hours between capecitabine doses should be 10 hours.

▪ Subjects should then be instructed to take the capecitabine dose 30 minutes after eating a normal meal.

▪ Subjects will be provided with a Medication Diary for capecitabine, instructed in its use, and asked to bring the diary with them to each appointment. Subjects will be instructed on what to do if missed, skipped, or vomited dose, and how to record this information. Please see Appendix B for the medication diary template.

Capecitabine Dosing

Cycle 1						
	Day 1	Days 2-7	Day 8	Day 9	Days 10-15	Day 16-21
Capecitabine Dose*	(1,250mg/ m^2 twice daily)	(1,250mg/ m^2 twice daily)	none	(1,250mg/ m^2 twice daily)	(1,250mg/ m^2 twice daily)	none
Weight Used for BSA	Ideal Body Weight	Ideal Body Weight	n/a	Actual Body Weight	Actual Body Weight	n/a

* The final dose will be rounded to nearest 150mg due to available pill sizes.

Cycle 2 and beyond: Capecitabine 1,250mg/m^2 orally twice daily days 1-14 of a 21 day cycle, using actual body weight.

The Mosteller calculation and the patient's ideal or actual body weight will be used to calculate the BSA[3] (calculations below).

Mosteller BSA formula: BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}

Ideal Body Weight (men) = 50 + 2.3 (Height in inches - 60)
Ideal Body Weight (women) = 45.5 + 2.3 (Height in inches - 60)

5.2 General Concomitant Medication and Supportive Care Guidelines

Capecitabine (Xeloda) and Coumadin

Capecitabine (XELODA) Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important XELODA-Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time XELODA was introduced. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within one month after stopping XELODA. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Bone Metastases: For patients with documented bony metastases, treatment with zolendronic acid, pamidronate or denosumab per standard UWCCC protocol is recommended.

Nausea/Emesis: Patients must be counseled on the use of antiemetics for treatment of nausea and vomiting with a standard antiemetic regimen (for example, prochlorperazine 10 mg orally every 6 hours as needed for nausea, or lorazepam 0.5 mg orally every 4 hours as needed for nausea). Any patient who is vomiting medications or pill fragments should be instructed NOT to repeat dosing. If nausea or emesis leads to the patient feeling lightheaded or dizzy or unable to stay hydrated at home should be instructed to seek medical attention.

Colony Stimulating Factors: CSFs should not be used during the first course of therapy and should not be used subsequently unless there are significant medical circumstances that require CSFs. Use of any CSFs must be discontinued at least 24 hours prior to initiation of the next cycle of chemotherapy and must be documented in the patient record.

Diarrhea: Patients should be instructed prior to cycle 1, day 1 in the proper use of antidiarrhea agents (such as loperamide [Imodium AD]). For example, with loperamide [Imodium AD], instruct patients to take 4 mg (2 capsules) after the first loose stool of the day, and 2 mg each loose stool thereafter. 4 mg may be taken every 4 hours overnight. Instruct the patient to stop taking the Imodium when they have not had a bowel movement for 12 hours. Total daily dose should not exceed 16 mg. Patients should be instructed to call for any diarrhea not improved by Imodium.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Patient decides to withdraw from the study or is unevaluable after cycle 1.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Treatment delay greater than 2 weeks

5.4 Duration of Follow Up

All patients enrolled in the study will be followed until both of the following criteria are met:
1. Study drug is discontinued (for any reason)
2 All study drug related adverse events have either resolved to grade 1 or stable per the discretion of the treating physician.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.6 Definition of Evaluable Patients

Patients will be evaluable for the primary endpoint if he or she takes 100% of their capecitabine dose days 1 through 9 and at least 90% of their capecitabine dose days 10 through 15 in cycle one. Unevaluable patients will go off study after cycle 1, but may continue to be treated with commercial capecitabine per the discretion of the treating physician.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 General Guidance for Dose Reductions and Modifications

Additional cycles of therapy may be administered provided that the patient meets the following criteria on Day 1 of each cycle:

- ANC $\geq$ 1,000/mcL
- Platelets $\geq$ 75,000/mcL
- Non-hematologic toxicity recovered to $\leq$ grade 1
- No evidence of progressive disease

Dose Modifications: Dose modification for toxicity will be based on the worst toxicity observed during the previous course. Dose modifications apply only when the event(s) are felt to be probably or definitely attributable to the study drugs. After recovery, dose adjustments for toxicity should be applied as below. Patients will be instructed to call with any new or worsening symptoms between clinical evaluations. Held doses will not be made up. All dose modifications will be permanent and continue through subsequent cycles.

Toxicities which are manageable with supportive therapy (ie. antiemetics or anti-diarrhea agents unless occurring despite maximal medical management.) do not require dose reductions. Toxicities which are determined to be clinically insignificant (ie. Lymphopenia) do not require dose reductions.

If an adverse event is not covered in section 6.2, doses may be reduced or held at the discretion of the investigator for the subject's safety.

Table 3. Capecitabine Dose Levels

	Initial Dose	**1st reduction**	**2nd reduction**
Capecitabine	1,250 mg/m^2 orally twice daily	1,000mg/m^2 orally twice daily	750mg/m^2 orally twice daily

Dose delays for more than 2 weeks or subjects requiring more than 2 dose reductions will be removed from the study.

6.2 Dose modifications

All adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events v4.0.

Hematologic toxicity (Neutropenia, Anemia, Thrombocytopenia): No dose modification for grade 1-2 toxicities. For Grade 3 hematologic toxicity, hold dose until $\leq$ grade 1 or baseline. The may resume capecitabine with dose reduced to the next lower dose level. For grade 4 hematologic toxicity, the patient should discontinue drug and be removed from study. Consider testing for DPD deficiency.

Stomatitis/pharyngitis and other GI toxicities (excluding diarrhea, nausea and vomiting) For grade 1-2 toxicities, initiate supportive care measures. For grade 3 or 4 toxicities, hold capecitabine until the toxicity returns to $\leq$ grade 1 and then restart capecitabine with a dose reduction to the next lower dose level.

Diarrhea: For grade 1 toxicities, initiate supportive care measures such as loperamide. For grade 2 toxicities, hold capecitabine and give loperamide or other anti-diarrhea medications until ≤ grade 1, then resume capecitabine at same dose level. If grade 2 diarrhea occurs a second time at a specific dose level, hold capecitabine and give anti-diarrhea medications until ≤ grade 1, then resume capecitabine at the next lower dose level.

For grade 3-4 diarrhea, hold capecitabine, start anti-diarrhea medications, and consider iv fluids/electrolyte replacement. Once resolved to ≤ grade 1, then may resume capecitabine at the next lower dose level.

Nausea and vomiting: For grade 1-2 toxicities, initiate supportive care measures such as lorazepam or prochlorperazine. For grade 3-4 toxicities (or intolerable grade 2), hold capecitabine and give antiemetics and consider iv fluids/electrolytes as needed. Once resolved to ≤ grade 1, then resume capecitabine at same dose level unless grade 3-4 (or intolerable grade 2) nausea/vomiting occurred despite maximal medical management (at least 2 anti-emetics), then reduce by 1 dose level.

Hepatic Toxicity: For grade 1-2 toxicities, no dose adjustment required. For Grade 3-4 elevation in AST (SGOT), ALT (SGPT), alkaline phosphatase or bilirubin, hold capecitabine dose until ≤ grade 1 or back to baseline (whichever is higher). Then may resume capecitabine with dose reduced to the next lower dose level.

Hand-foot reaction (HFR or Palmar-plantar erythrodysesthesia syndrome**):** Please see table below.

Other toxicity: For other grade 3 or greater toxicities that are considered clinically significant by the treating physician and thought to be at least probably related to study drug, hold treatment until toxicity resolves to grade 1 or less, then reduce the dose of capecitabine to the next lowest dose level.

Table 4: Dose Modifications for HFR or Palmar-plantar erythrodysesthesia syndrome

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patients normal activity	Any occurrence	Institute supportive measures immediately
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Institute supportive measures and hold capecitabine until toxicity resolves to Grade 1 or less. Institute at full dose when restarting therapy.
	2nd or 3rd occurrence	Continue supportive measures and hold capecitabine until toxicity resolves to Grade 1 or less. Upon resuming capecitabine treatment, decrease capecitabine to next lower dose level
	4th occurrence	Off study
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st occurrence	Institute supportive measures and hold capecitabine treatment for a minimum of 7 days and until toxicity has resolved to Grade 1 or less. When resuming treatment after dose interruption, resume capecitabine at next lower dose level
	2nd occurrence	Institute supportive measures and interrupt capecitabine treatment for a minimum of 7 days and until toxicity has resolved to Grade 1 or less. When resuming treatment after dose interruption, resume capecitabine at next lower dose level
	3rd occurrence	Off study

7. REGULATORY AND REPORTING REQUIREMENTS

7.1 Oversight And Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all UWCCC clinical studies. A summary of DSMC activities follows:

- Review of all clinical trials conducted at the UWCCC for data integrity and safety
- Review of all serious adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by the UWCCC data quality control review process
- Submit recommendations for corrective action to the CRC
- Notify the Study Chair of the DSMC's recommendation to the CRC
- Work in conjunction with the Health Sciences IRB in the review of protocol deviations, violations and unanticipated problems reported by the UWCCC DOWGs.
- The committee ensures that notification is provided to all external sites participating in multiple-institutional clinical trials coordinated by the UWCCC of serious adverse events requiring expedited reporting.

7.2 Monitoring And Reporting Guidelines

Investigators will conduct continuous review of data and subject safety at their weekly Phase I/Disease Group meetings where the results of each subject's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each dose level: the number of subjects, significant toxicities as described in the protocol, doses adjustments, and responses observed. Quarterly Protocol Summary Reports (PSR) are required for submission to the Data and Safety Monitoring Committee (DSMC) for review.

7.3 REVIEW AND OVERSIGHT REQUIREMENTS

a) Serious Adverse Event – Reported within 7 Days

Serious Adverse Events requiring reporting within 7 calendar days (as described in the protocol) will also be sent to the UWCCC DSMC Chair via email to saenotify@uwcarbone.wisc.edu. A 7 day "SAE Details" report, generated in the UWCCC database must be attached to the email along with pertinent information regarding the SAE and the UWCCC SAE Routing Form. The Committee Chair will review the information and determine if further action is required. This information is entered and tracked in the UWCCC database.

b) **Study Progress Review**

Study Progress Review- Protocol Summary Reports

Protocol Summary Reports (PSR) are required to be submitted to the DSMC commensurate with the Phase of the study. The PSR provides a cumulative report of serious adverse events, as well as any protocol violations, deviations or unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is also provided by Disease Oriented Working Group meeting minutes, internal audit and/or response review reports. In addition, the DSMC requires the DOWG or protocol Study Chair to submit external DSMB reports or any other significant study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings. The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies.

EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to the table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table.

SAE Requiring 7 Day Reporting Occurs at UWCCC:

1. **Report to the UWCCC:**

   Reference the **SAE SOP** and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for 7 day reports.

   For this protocol, the following entities are required to be notified:

   a) saenotify@uwcarbone.wisc.edu
   b) Any appropriate parties listed on SAE Routing Form

2. **Report to the IRB:**

Consult the UW-IRB website for reporting guidelines.

3. **Reporting to the FDA**

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Report the SAE using the FDA Med Watch form available at
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf .

Print the completed Med Watch form and fax it to the FDA.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only—Arms I, A, B, and C.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	**Expected**	**Unexpected**	**Expected**
Unrelated or Unlikely			7 calendar days	7 calendar days
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days

7 Calendar Days: Indicates a full MedWatch report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.
NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via MedWatch within 7 calendar days of learning of the event.

8. PHARMACEUTICAL INFORMATION: CAPECITABINE

Other Names: Xeloda

Chemical name: 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine.

Molecular Weight: 359.35

Description: Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.

How Supplied: Capecitabine (Xeloda) is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine.

Solution Preparation: Not applicable.

Route of Administration: Oral.

Availability: Commercial supplies of capecitabine will be used for this study.

Storage and Stability: Store tightly closed at 25 degrees C (77 degrees F); stable for brief periods at 15 to 30 degrees C (59 to 86 degrees F).

8.1 **Adverse events and potential risks of Capecitabine (see also tables 1 and 2)**

Hand-and-Foot Syndrome: Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity (median time to onset of 79 days, range from 11 to 360 days). This is much more commonly observed with capecitabine or infusional 5-FU rather than bolus 5-FU.

Cardiotoxicity: The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.

Hepatic Insufficiency: Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is not known.

Hyperbilirubinemia: In the overall clinical trial safety database of capecitabine monotherapy (N=875), grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of 875 patients with either metastatic breast or colorectal cancer who received at least one dose of capecitabine 1250 mg/m^2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also

had postbaseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases. In the 596 patients treated with capecitabine as first-line therapy for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of capecitabine monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and median total bilirubin increased from 8 μm/L at baseline to 13 μm/L during treatment with capecitabine. Of the 136 colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

Hematologic: In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m^2 administered twice daily as monotherapy for 2 weeks followed by a 1-week rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in hemoglobin, respectively. Carcinogenesis, Mutagenesis and Impairment of Fertility: Adequate studies investigating the carcinogenic potential of capecitabine have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test).

Reproductive: In studies of fertility and general reproductive performance in mice, oral capecitabine doses of 760 mg/kg/day disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In males, this dose caused degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

Coagulopathy: See Boxed WARNING regarding interaction with Coumadin in Section 5.2.

Diarrhea: Capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. This is expected to be common for this combination therapy. Necrotizing enterocolitis (typhlitis) has been reported with capecitabine. Toxic deaths have been reported for the combination of oxaliplatin with 5-FU and leucovorin in patients with diarrhea and concomitant neutropenia. Consideration of hospitalizing any such patients should be given.

Drug-Drug Interactions with Capecitabine

Capecitabine (Xeloda) and Coumadin: see boxed warning in Section 5.2

CYP2C9 substrates: Other than warfarin, no formal drug-drug interaction studies between XELODA and other CYP2C9 substrates have been conducted. Care should be exercised when XELODA is co-administered with CYP2C9 substrates.

Phenytoin: The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need to be reduced. Postmarketing reports indicate that some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites.

8.2 **Availability**

Capecitabine (Xeloda®) is an FDA approved medication and is available by prescription at pharmacies throughout the United States.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

Capecitabine pharmacokinetics: Plasma samples for the analysis of capecitabine and metabolites (5-FU, DFCR, and DFUR) will be obtained at baseline (prior to dosing) and 1, 2, 3, 4, 6, and 8 hours after administration on day 1 and day 9 of cycle 1 and at steady state on cycle 1 days 7 and 15. Plasma and tissue concentrations will be measured by HPLC as previously described.[38]. For 5FU, the standard curve is linear from 0.019 to 20 μg/ml, r2 = 0.999, with an intraday variability ranging from 4.49%-5.52% over the standard curve. Inter-day variability over 2 weeks ranges from 4.33-5.42% over the standard curve and the lower limit of quantitation (LLOQ) is 0.0195 μg/ml. For capecitabine, the standard curve is linear from 0.019 to 20 μg/ml, r2 = 0.999, with intraday variability ranging from 1.2-7.8% and inter-day variability from 7.6-13.9% over 3 months and a LLOQ of 0.019 μg/ml. The standard curves for DFCR and DFUR are both linear from 0.625 to 40 ug/ml, r2 = 0.999, with an intraday variability ranging from 4.21%-4.66% and 0.74%-2.08%, interday variability over 4 weeks ranging from 3.45%-6.36% and 4.24-6.45% and LLOQ of 0.312 μg/ml and 0.0195 μg/ml, respectively.

Pharmacokinetic variables will be determined by noncompartmental methods with WinNonlin Pro version 5.2 (Pharsight Corporation, Cary, N.C.). Area under the plasma concentration–time curve is estimated using the trapezoidal rule from time 0 to peak concentration and the log-trapezoidal rule from the peak concentration to the last measurable plasma concentration (AUClast). AUC(0− ∞) is then calculated from the time of dosing and extrapolated to infinity.

9.2 **PK Sample Collection**

Blood samples are collected in 6-mL EDTA (purple top) tubes at the timepoints described in Table 5, below on day 1, 7, 9 and 15 of cycle 1. Samples are then centrifuged at 3500RPM at 4ºC to obtain plasma, aliquotted into cryovials and stored at -70C until analysis.

Time	Time
C1D1	**C1D9**
0 (prior to first capecitabine dose)	0 (prior to AM capecitabine dose)
1 hr post capecitabine dose	1 hr post capecitabine
2 hr post	2 hr post
3 hr post	3 hr post
4 hr post	4 hr post
6 hr post	6 hr post
8 hr post	8 hr post
C1D7	**C1D15**
0 (prior to AM dose of capecitabine)	0 (prior to AM capecitabine dose)

10. STUDY CALENDAR

Pre-study evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans, x-rays and informed consent must be done ≤4 weeks prior to the start of therapy.

	Pre-Study	C1 Day 1	C1 Days 2-7	C1 Day 8	C1 Day 9	C1 Days 10-15	C2+ Day 1[i]	C2+ Days 2-14	Off Study
Capecitabine[a]		X	X		X	X	X	X	
Informed Consent	X								
Demographics	X								
Medical History	X								
Concurrent Meds	X						X		X
Physical Exam[b]	X	X					X		X
Vital Signs	X						X		X
Performance Status	X						X		X
CBC, ANC	X	X[g]			X		X[h]		X
Chemistries[c]	X	X[g]			X		X[h]		X
Pregnancy test[d]	X								
Adverse Event evaluation	X----------								----------X
Tumor Measurements including radiology assessments[e]	X						X (every 2-3 cycles)		X

Pharmacokinetics[f]		X	X (day 7)		X	X (day 15)			

a. See schema for capecitabine dosing
b. Including height and weight at pre-study evaluation and weight on day 1 of each cycle for first 2 cycles, then every other cycle allowed. If treatment delayed, physical exam may be done at the investigator's discretion.
c. Na, K, Cl, bicarbonate, BUN, Creatinine, ALT, AST, Alk Phos, Tbili, and albumin.
d. For premenopausal women only (Postmenopausal women are those who are age >60, or age < 60 who have had oophorectomy or have not had a menses for > 1 year without another etiology for amenorrhea).
e. Tumor measurements by exam and imaging every 2 -3 cycle per discretion of treating MD. Imaging should include chest (CXR or CT of chest) and abdomen (CT or MRI) with optional imaging for pelvis (CT or MRI) or bones (bone scan or PET) depending on known sites of disease. A PET/CT can be used to replace CT chest, abdomen and pelvis.
f. See Table 5 for timing of pharmacokinetic blood draws.
g. Do not need to repeat if done within 1 week prior to course 1 day 1. If done on c1d1 don't use as eligibility labs, use pre-study labs
h. may be done within 72 hours of each cycle
i. May be delayed for holidays and unforeseen circumstances

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response once at 6-9 weeks (+/- 1 week) after initiation of therapy, and then per discretion of treating physician.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with capecitabine.

Evaluable for Pharmacokinetic Comparison: Patients will be evaluable for the primary endpoint if he or she takes 100% of their capecitabine dose days 1 through 9 and at least 90% of their capecitabine dose days 10 through 15 in cycle one.

Evaluable for objective response. Only those patients who have measurable disease present at baseline who have received at least one cycle of therapy (21

days) will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.3 **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when

both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes and subcutaneous lesions. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 **Response Criteria**

11.1.4.1 **Evaluation of Target Lesions**

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

11.1.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the

treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria at least 4 weeks after initial response is documented.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.1.6 **Progression-free survival:**

Progression-free survival (PFS) will be defined as time from first dose of capecitabine to time to clinical or imaging evidence of progressive disease.

11.1.7 **Response Review**

The imaging for any subjects obtaining a CR or PR will be reviewed centrally at the University of Wisconsin by an independent investigator.

12. DATA REPORTING / REGULATORY CONSIDERATIONS

Guidelines and instructions for AE reporting can be found in Section 7.0 (Adverse Event Reporting Requirements).

Study sites are responsible for entering case report forms directly into the Oncore database in accordance with the UWCCC data management policy. Data must be submitted within 2 weeks of a subject visit and will be monitored monthly by the Phase I Cancer Research office at the UWCCC.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoints are the PK parameters (AUC and Cmax) of capecitabine when dosed using actual versus ideal body weight. Secondary endpoints are response and progression-free survival.

A single arm study design will be used to characterize the effect on pharmacokinetic parameters of capecitabine, when dosed using actual versus ideal body weight. Ideal body with based dosing of capecitabine when be used for cycle 1 from day 1 to day 7 followed by an actual body weight based dosing from Day 9 to Day 15. There will be a wash-out period on Day 8.

PK parameters will be summarized in terms of number of observations, means, standard deviations, medians, and ranges, stratified by assessment time point. The non-compartmental method will be used to estimate PK parameters. AUC will be estimated using the Lagrange approximation method. A paired t-test will be used to compare the PK parameters between the full weight and limited weight based dosing. If the PK parameters are not normally distributed, then an appropriate transformation will be identified before conducting the comparison. The comparison of AUC and Cmax between full weight and limited based dosing will be also performed using a population pharmacokinetics analysis, based on a nonlinear mixed effects modeling approach.

13.2 Sample Size/Accrual Rate

The primary objective is to characterize the effect on pharmacokinetic parameters when capecitabine is dosed on actual versus ideal body weight results in obese patients with advanced solid tumors. A mean difference in the AUC and Cmax of at least 30% between the ideal body weight dosing versus the actual body with based dosing will be considered as a minimal important difference. Based on the results of several previous PK studies involving capecitabine, it is anticipated that the overall standard deviation for the difference between the two dosing strategies is at most 25% of the mean difference. The following table shows the required sample sizes to detect various mean differences in PK parameters between the two dosing strategies at the two-sided 0.025 (=0.05/2 – a Bonferroni adjustment for comparing both AUC and Cmax) significance level with 80%

power, assuming a standard deviation ranging from 20-30%.

Table 13.1: *Required sample sizes to detect various mean differences in PK parameters with 80% power at the two-sided 0.025 significance level*

	Mean difference in PK parameters between the ideal versus actual weight based dosing strategy				
Standard Deviation	20%	25%	30%	35%	40%
20%	13	9	7	6	6
25%	18	13	10	8	7
30%	24	17	13	10	9

A sample size of n=10 patients is proposed for this study. With a sample size of 10 patients, a clinically important difference of 30% between the ideal and actual body weight based dosing will be detected with 82% power at the one-sided 0.025 (=0.05/2 – a Bonferroni adjustment for evaluating both AUC and Cmax) significance level, assuming an overall standard deviation of 25%. A mean difference of only 25% will be detected with 68% power. Patients will be evaluable for the primary endpoint if he or she completes cycle 1, capecitabine therapy without dose reduction or skipped doses. Any patient who does not meet these criteria will be replaced.

The anticipated accrual is 1-2 patients per month. Therefore, the study is expected to be completed within 6-12 months after first accrual.

13.3 Stratification Factors

n/a

13.4 Analysis of Secondary Endpoints

Responses will be determined using RECIST as described in Section12 and summarized in tabular format. The complete and partial response rates will be calculated and reported along with the corresponding 95% confidence intervals. All eligible subjects (intent-to-treat population) will be included in the calculation of the response rate. Progression-free survival will be analyzed using the Kaplan-Meier method.
PK parameters (based on ideal body weight and actual body weight) of the study participants will be summarized using standard descriptive statistics in terms means, standard deviations and ranges. A two-sample t-test will be used to compare the mean values in the PK parameters in obese patients with normal weight historical controls.

13.5 Reporting and Exclusions

13.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with capecitabine.

13.5.2 **Evaluation of response.** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable due to measurable disease only or insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES:

1. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol;30:1553-61.
2. . (Accessed June 21, 2012, at http://www.cdc.gov/obesity/data/adult.html.)
3. Mosteller RD. Simplified calculation of body-surface area. The New England journal of medicine 1987;317:1098.
4. Pinkel D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. Cancer Res 1958;18:853-6.
5. Canal P, Chatelut E, Guichard S. Practical treatment guide for dose individualisation in cancer chemotherapy. Drugs 1998;56:1019-38.
6. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003;21:4524-31.
7. Thompson LA, Lawson AP, Sutphin SD, Steinke D, Adams VR. Description of current practices of empiric chemotherapy dose adjustment in obese adult patients. J Oncol Pract 2010;6:141-5.
8. Budman DR, Berry DA, Cirrincione CT, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst 1998;90:1205-11.
9. Lepage E, Gisselbrecht C, Haioun C, et al. Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: application to LNH-87 protocol. The GELA. (Groupe d'Etude des Lymphomes de l'Adulte). Ann Oncol 1993;4:651-6.
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.
11. Rosner GL, Hargis JB, Hollis DR, et al. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: results from cancer and leukemia group B study 8541. J Clin Oncol 1996;14:3000-8.
12. Georgiadis MS, Steinberg SM, Hankins LA, Ihde DC, Johnson BE. Obesity and therapy-related toxicity in patients treated for small-cell lung cancer. J Natl Cancer Inst 1995;87:361-6.
13. Ishikawa T, Fukase Y, Yamamoto T, Sekiguchi F, Ishitsuka H. Antitumor activities of a novel fluoropyrimidine, N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (capecitabine). Biol Pharm Bull 1998;21:713-7.
14. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 2001;40:85-104.
15. Siegel R, Desantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220-41.
16. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. The American journal of clinical nutrition 2007;86:556-65.
17. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920-31.
18. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and

oxaliplatin in the course of treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004;22:1209-14.
19. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
20. Hoff PM, Ansari R, Batist G, et al. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2001;19:2282-92.
21. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2001;19:4097-106.
22. Gubanski M, Naucler G, Almerud A, Lidestahl A, Lind PA. Capecitabine as third line therapy in patients with advanced colorectal cancer. Acta Oncol 2005;44:236-9.
23. Boige V, Raoul JL, Pignon JP, et al. Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. Br J Cancer 2007;97:862-7.
24. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004;22:2084-91.
25. Capitain O, Asevoaia A, Boisdron-Celle M, Poirier AL, Morel A, Gamelin E. Individual Fluorouracil Dose Adjustment in FOLFOX Based on Pharmacokinetic Follow-Up Compared With Conventional Body-Area-Surface Dosing: A Phase II, Proof-of-Concept Study. Clin Colorectal Cancer 2012.
26. Gamelin E, Delva R, Jacob J, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2099-105.
27. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA : the journal of the American Medical Association 1997;278:1407-11.
28. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer causes & control : CCC 2002;13:741-51.
29. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1999;17:485-93.
30. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 2004;40:536-42.
31. Lee SH, Lee J, Park J, et al. Capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Med Oncol 2004;21:223-31.
32. Gradishar WJ, Meza LA, Amin B, et al. Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: a multicenter phase II study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004;22:2321-7.
33. O'Shaughnessy J. Capecitabine and docetaxel in advanced breast cancer: analyses of a phase III comparative trial. Oncology 2002;16:17-22.
34. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast

cancer progressing after anthracycline and taxane treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:5210-7.
35. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. The New England journal of medicine 2006;355:2733-43.
36. Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291-7.
37. Mackean M, Planting A, Twelves C, et al. Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998;16:2977-85.
38. Mulkerin D, LoConte NK, Holen KD, et al. A phase I study of an oral simulated FOLFOX with high dose capecitabine. Invest New Drugs 2009;27:461-8.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Pill Diary

PATIENT'S MEDICATION DIARY - TEMPLATE

Today's date _____ **Agent: Capecitabine**

Patient Name_____(*initials acceptable)* **Patient Study ID**

_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take _____ **Capecitabine** tablets twice daily. You should take the tablets in the morning 30 minutes after eating and in the evening 30 minutes after eating at approximately same time each day..
3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of Capecitabine tablets when you return for each appointment.

Day	Date	Time of AM dose	Time of PM dose	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Patient's signature

_____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study_____
3. Patient's planned total daily dose _____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX C: UWinRx: The University of Wisconsin Policy for Standardizing Assessment of CYP Mediated Drug Interaction in Clinical Trials

Effective Date: October 1, 2011
Version: New
Section: Phase I

I. Purpose

The purpose of this policy is to provide a framework for standardizing assessment of cytochrome p450 drug interactions with respect to clinical trial eligibility.

II. Definitions

A. Investigational drug(s) is/are the drug(s) being evaluated in the clinical trial as determined by the study chair, lead investigator and Drug Interaction Task Force (DITF). In some cases these agents are commercially approved, but for the purpose of this policy they will be considered investigational.

B. Concurrent medications are commercially available prescription and OTC being taken by the study subject but not mandated by the study protocol

C. Pharmacokinetic Definitions

a. Inhibitors

i. *Strong inhibitor* is one that causes a ≥ 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

ii. *Moderate inhibitor* is one that causes a ≥ 2-fold, but <5-fold increase in the plasma AUC values or 50-79% decrease in clearance.

iii. *Weak inhibitor* is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-49% decrease in clearance.

b. Inducers are drugs which cause ≥30% change in plasma AUC values. Drugs with < 30% change are defined as noninducers. Lexi-comp defined major or moderate inducers are defined as inducers.

c. Substrates are categorized as sensitive or not sensitive.

i. Sensitive refers to drugs whose plasma AUC values have been shown to increase 5-fold (CYP3A) or 2-fold (All other CYP) when co-administered with a known inhibitor.

ii. Lexi-comp defined major substrates are sensitive, minor substrates are not sensitive.

d. Narrow therapeutic index drugs are those where exposure-response indicates that increases in their exposure levels by the concomitant use of interacting medications may lead to serious toxicity

D. Cmax is the maximum plasma concentration of the investigational agent

E. Ki is the dissociation constant of enzyme inhibitor, which is needed to categorize an agents metabolic profile

F. IC50 is the inhibitory concentration 50% and is not interchangeable with the Ki.

G. Km, or the Michaelis–Menten concentration is when the rate of enzyme binding equals the rate of enzyme unbinding (steady state). If the IC50 determination was conducted at Km, the Ki=IC50/2

H. In vitro Definitions

a. Inhibitors

Strong inhibitors: Cmax/Ki ≥ 1
Moderate inhibitors: Cmax/Ki = 0.1-0.91
Weak inhibitors: Cmax/Ki < 0.1

b. Inducers: > 100% increase in enzyme activity

c. Substrates

Sensitive: ≥ 30% of metabolism occurs via a given CYP
Not sensitive: < 30% of metabolism occurs via a given CYP

III. Policy

a. UWCCC clinical trials must include a section in the protocol or a "cheat sheet" in Oncore that defines the metabolic pathway (CYP enzyme and whether it is a substrate, (sensitive or not sensitive), inducer or inhibitor (strong, moderate or weak) of the investigational agent as well as the contraindicated concurrent medications.

b. If there is no metabolic pathway section in the protocol, the study chair and/or lead investigator will prepare this section of the protocol or cheat sheet.

c. The DITF, or subcommittee of the DITF, including one medical oncologist and one pharmacist, has responsibility for reviewing and approving the metabolic pathway section within 1 week.

d. Patient concurrent medications,

    i. Medications including route and schedule, for study candidates will be collected by Phase I nurses by patient interview

    ii. List will be reviewed and categorized (CYP enzyme and whether it is a substrate, inducer and inhibitor) by PRC.

e. Pharmacokinetic definitions from previous in vivo trials are the preferred method for categorizing interaction potential. In vitro data (Ki values) will be utilized if clinical definitions are not available.

f. If only IC50 values are available, they should be converted to Ki values, as recommended by Cer et al, using the relationship Ki=IC50/2 with the assumption that the IC50 was conducted at the Km.

g. The most recent version of the Drug Information Handbook (Lexi-Comp) will be used as the primary reference for assessment of interaction potential of concurrent medications. This reference is updated annually. The secondary references will be Micromedix and drug information leaflets (package inserts).

h. The most recent version of the investigational drug brochure (IDB) will be used for assessment of interaction potential of the investigational agent.

i. Transdermal products designed for systemic delivery must be assessed for interaction potential. Topical products not designed to provide systemic delivery, (including inhaled products, ophthalmologic products and transvaginal preparations) do not need to be considered since they do not have appreciable systemic absorption.

j. All protocol mandated anti-cancer medications will be considered to be “narrow therapeutic index” drugs

k. Concurrent medication that are “narrow therapeutic index” are defined as agents where a small change in plasma concentrations may result in substantial clinical impact, such as warfarin and drugs that affect the QT interval (Class I and III antiarrhythmics, antipsychotics, azoles, bepridil, dolasetron, fluoroquinolones,

fluoxetine, loratadine, macrolide antibiotics, methadone, ondansetron, phenothiazines, sulfamethoxazole, tolterodine, trazodone, tricyclic antidepressants, trimethoprim). Definition of narrow therapeutic index will be left to physician discretion

IV. Procedure for Eligibility Determination

a. Phase I office will review medication regimens, including OTCs ; and email this medication profile to the PRC.

b. PRC will evaluate investigational agents and concurrent medications for interactions using table 1 or as stipulated in the protocol and categorize medications as Contraindicated, Use with Caution or Allowed.

    i. PRC will determine the metabolic pathway of the investigational agent from the cheat sheet or protocol and locate on grey panel of table 1.

    ii. PRC will determine the metabolic pathway of each concurrent medication from the most recent version of Lexi-Comp and locate on pink panel of table 1.

    iii. PRC will determine the intersecting box.

c. Contraindicated medications must be discontinued for a patient to be eligible for the clinical trial. Since time frame for discontinuation will vary with type of interaction and drug half-life, this will be determined on a case by case basis by the study chair, PCR and/or DITF.

d. If patient is on one or more "Use with Caution" medications, the study chair and treating physician must be contacted for an eligibility determination.

e. Allowed medications are allowed without consultation with the study chair or treating physician

Table 1: Matrix for Assessment of Interactions

Investigational Agent	**Concurrent Medication**					
	No CYP Interaction	Nonsensitive Substrate but narrow therapeutic index	Sensitive Substrate	Weak Inhibitor	Strong and Moderate Inhibitor	Inducer
No CYP Interaction	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
Nonsensitive Substrate	Allowed	Allowed	Allowed	Allowed	Use with caution	Use with caution
Sensitive Substrate	Allowed	Allowed	Use with caution	Use with caution	**Contraindicated**	**Contraindicated**
Weak Inhibitor	Allowed	Allowed	Use with caution	Allowed	Use with caution	Use with caution
Strong and Moderate# Inhibitor	Allowed	Use with** caution	**Contraindicated***	Use with caution	**Use with caution**	**Contraindicated**
Inducer	Allowed	Use with** caution	**Contraindicated***	Use with caution	**Contraindicated**	**Contraindicated**

*Contraindicated unless close monitoring with labs or drug levels and dose adjustment feasible

**Use with caution and consider monitoring with labs or drug levels and dose adjustment if feasible

If an investigational agents is categorized as a moderate inhibitor based on in vitro data only, follow recommendations for weak inhibitors

V. References

www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Cer RZ, Mudunuri U, Stephens R, and Lebeda FJ. IC50-to-Ki: a web-based tool for converting IC50 to Ki values for inhibitors of enzyme activity and ligand binding. Nucleic Acids Res. 2009 July 1; 37

VI. Coordination

Phase 1 research office