To: CTEP Protocol and Information Office

From: Timothy Kinsella, M.D.

Date: June 2, 2022

Re: Change of PI for Protocol #**10410**: "A Phase 1 Study of IPdR in Combination with Capecitabine and Radiotherapy in Rectal Cancer"

I. Summary of Changes:

#	Section	Comments
1.	Title page	PI information has been updated. PI transfer information is below: Current PI: Dr. Timothy Kinsella, Lifespan (via North American Star Consortium) New PI: Dr. Charles Kunos, University of Kentucky (via Ohio State University Consortium)
2.	Title page	Updated revision numbers and dates in the Protocol Type / Version # / Version Date section to match CTEP release dates: Amended: Revision 7 / January 24, 2022 Inserted: Revision 8 / April 25, 2022 Revision 9 / June 2, 2022
3.	Title page	Updated study coordinator and responsible research nurse from Patrick Marban to Jeri Reynolds, and responsible data manager staff from Patrick Marban to Charles Kunos.
4.	Title page	Updated Coordinating Center information from LAO-11030 / University Health Network Princess Margaret Cancer Centre LAO to LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO

NCI Protocol #: 10410

Local Protocol #: TBD

ClinicalTrials.gov Identifier: NCT04406857

TITLE: A Phase 1 Study of IPdR in Combination with Capecitabine and Radiotherapy in Rectal Cancer

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NCI-Supplied Agent: 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR) (NSC726188)
Commercial Agent: Capecitabine (Xeloda) (NSC712807)

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SCHEMA

This is a phase 1 dose escalation study of 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR) in combination with capecitabine and radiation therapy (RT) that consists of two parts, Part IA and Part IB.

Part IA:
Part IA uses an accelerated titration design with a single patient cohort, and a 100% dose escalation between patient cohorts until a treatment-related Grade 2 non-hematologic toxicity or grade 3 neutropenia or thrombocytopenia is observed. The accelerated titration design may reduce the number of patients potentially undertreated by receiving oral (PO) IPdR doses that are not expected to result in clinically relevant radiosensitization.

Part IA dose escalation schema			
Dose Level	**Total radiation Gy (45 Gy primary field, 5.4 Gy boost @1.8 Gy/fraction/day)**	**Capecitabine (mg/m^2 BID) Monday am – Friday pm throughout RT**	**IPdR (mg BID) Administered throughout radiation**
1A	50.4	825 mg/m^2 BID	75 mg BID
2A	50.4	825 mg/m^2 BID	150 mg BID
3A	50.4	825 mg/m^2 BID	300 mg BID
4A	50.4	825 mg/m^2 BID	600 mg BID
5A	50.4	825 mg/m^2 BID	1,200 mg BID
BID – Twice Daily, RT – Radiation therapy			

Part IA is closed to further accrual.

Part IB:
Part IB will commence when toxicity is encountered in Part IA. Cohorts of 3-6 patients will be entered per dose level until dose-limiting toxicity (DLT) is reached, and the maximum tolerated dose (MTD) is defined. An IPdR dose of 2,400 mg QD is the maximum allowed dose. Dose escalation between dose levels will be adjusted to accommodate the availability of 75mg and 600mg IPdR capsules.

Part IB dose escalation schema			
Dose Level	**Total radiation Gy (45 Gy primary field, 5.4 Gy boost @1.8 Gy/fraction/day)**	**Capecitabine (mg/m^2 BID) Monday am – Friday pm throughout RT**	**IPdR (mg QD) Administered throughout radiation[1,2]**
1B	50.4	825 mg/m^2 BID	75mg QD
2B	50.4	825 mg/m^2 BID	150mg QD
3B	50.4	825 mg/m^2 BID	300mg QD

Part IB dose escalation schema			
Dose Level	**Total radiation Gy (45 Gy primary field, 5.4 Gy boost @1.8 Gy/fraction/day)**	**Capecitabine (mg/m^2 BID) Monday am – Friday pm throughout RT**	**IPdR (mg QD) Administered throughout radiation[1,2]**
4B	50.4	825 mg/m^2 BID	600mg QD
5B	50.4	825 mg/m^2 BID	1200mg QD
6B	50.4	825 mg/m^2 BID	1800mg QD
7B	50.4	825 mg/m^2 BID	2400mg QD
QD – Once Daily, BID – Twice Daily, RT – Radiation therapy [1] The maximum allowed dose of IPdR is 2,400mg QD [2] Actual doses will be rounded to account for availability of only 75 mg and 600 mg IPdR capsules			

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Study Length**
IPdR	Take on an empty stomach, either 1 hour before or 2 hours after meals.	Dose as appropriate for the assigned dose level.	PO	QD[A]	38 days (6 weeks)
Capecitabine	Take within 30 minutes after a meal (breakfast and dinner).	825 mg/m^{2}[C]	PO	BID Monday morning through Friday evening on RT days [B,C]	
RT		1.8 Gy/fraction/day × 28 doses (50.4 Gy total dose)		5 doses per week until week 5 and 3 doses during Week 6[D]	
[A]On the days of radiation therapy, the daily dose of IPdR will be administered within 30 min - 2 hours prior to radiation.Patients may take dose at home if the timing allows. [B]Capecitabine will be taken Monday morning through Friday evening each week of RT. [C]Dosing will be with 150 mg and 500 mg tablets [D]RT will be given only Monday through Friday QD – Once Daily, BID – Twice Daily, PO – Oral, RT – Radiation therapy					

Patients will be assessed 4 weeks following completion of study treatment (Week 10 unless there were delays in therapy). This will be the final assessment for study-related toxicity. Patients will undergo surgical resection 8-12 weeks following completion of chemoRT (IPdR), and study-related response will be assessed at that time.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the maximum tolerated dose (MTD) of oral (PO) IPdR when administered with capecitabine (825 mg/m^2 BID) and radiation therapy (RT) (50.4 Gy in 28 fractions)

1.1.2 To determine the toxicities Common Terminology Criteria for Adverse Events (CTCAE) v5) of the combined modality therapy, IPdR + capecitabine + RT

1.2 Secondary Objectives

1.2.1 To establish the pharmacokinetics (PK) of QD IPdR when combined with capecitabine.

1.2.2 To evaluate IUdR incorporation in circulating granulocytes and correlate these levels with IPdR plasma PK and clinical/laboratory toxicities.

1.2.3 To assess IUdR incorporation in tumor cells obtained from the surgical resection specimen and correlate IUdR incorporation in tumor cells with IPdR PK.

1.2.4 To assess IUdR incorporation in tumor cells obtained from the surgical resection specimen and correlate IUdR incorporation in tumor cells with tumor response as measured by pCR rate and Neoadjuvant Rectal (NAR) score.

1.2.5 To determine the pCR rate of IPdR + capecitabine + RT at the IPdR MTD as a measure of anti-tumor activity. Although the clinical benefit of IPdR has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.6 To determine the NAR score of IPdR + capecitabine + RT at the IPdR MTD.

1.3 Exploratory Objectives

1.3.1 To explore the relationship between extent of exposure to RT and the development and severity of adverse events.

1.3.2 To explore the drug/drug/metabolite interactions between capecitabine, IPdR, and their metabolites.

2. BACKGROUND

2.1 Rectal Adenocarcinoma

There are approximately 43,000 new cases of rectal cancer diagnosed each year in the United States (Seigel *et al.,* 2020). Stage-for-stage, recurrence rates are higher in rectal cancer in

comparison to colon cancer (Heald *et al.,* 1982).

2.1.1 Standard-of-care treatment for Locally Advanced Rectal Cancer (LARC):

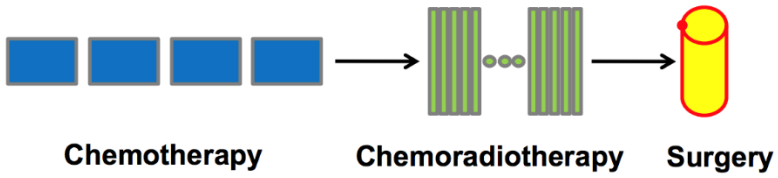
2.1.1.1 Neoadjuvant chemoradiotherapy (chemoRT):

The use of neoadjuvant chemoRT is the established standard-of-care for LARC. Studies performed in the early 2000's demonstrated improved local control with less toxicity for neoadjuvant chemoRT compared with postoperative chemoRT (Sauer *et al.,* 2004, Roh *et al.,* 2009). The goals of neoadjuvant chemoRT are to improve local control, increase the likelihood of sphincter preservation, and increase the rate of relapse-free survival by acting on gross tumor volume and micrometastatic disease. Efforts to improve local control, disease-free survival (DFS) and overall survival (OS) are currently focused on enhancing the benefits of the chemotherapy (systemic) and chemoradiotherapy components of therapy for patients with LARC.

2.1.1.2 Systemic chemotherapy:

The rationale for the addition of systemic chemotherapy to the treatment regimen for patients with LARC was based on the demonstrated benefit of systemic chemotherapy for patients with colon cancer. For patients with LARC, the paradigm of neoadjuvant chemoRT followed by surgical resection relegated the use of systemic chemotherapy to the adjuvant setting. In studies where patients with rectal cancer were randomly assigned to postoperative observation or adjuvant therapy, the benefit of systemic therapy was as apparent as it is for the treatment of patients with colon cancer. Unfortunately, in the setting of neoadjuvant chemoRT, the administration of adjuvant chemotherapy is challenging with large, multicenter clinical trials consistently reporting delay, dose reduction, or discontinuation in 25% - 50% of patients (Breugom *et al.,* 2015). To optimize delivery of trimodality therapy, a new sequence of administration was developed incorporating all neoadjuvant therapy prior to surgery, so-called total neoadjuvant therapy (TNT) (Figure 1).

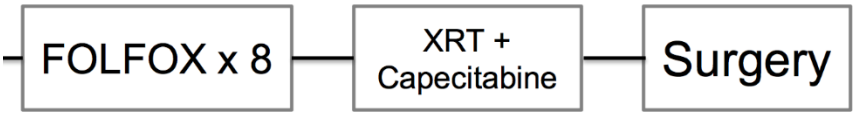
Figure 1: LARC Total Neoadjuvant Therapy (TNT) paradigm



By ensuring delivery of systemic treatment prior to surgery, it is hoped that TNT will address early micrometastases, improve tolerability of therapy, and improve tumor response. Recent trials have demonstrated that a TNT approach can improve compliance with systemic therapy without compromising a patient's ability to undergo surgery or increase the risk of surgery, and accumulated data from international studies suggest the TNT approach is a safe and feasible treatment option. TNT is now endorsed by the National Comprehensive Cancer Network guidelines, and is the framework upon which newer therapies are tested. Current standard-of

care TNT for patients with LARC uses a FOLFOX-based regimen (See Appendix E) for the neoadjuvant chemotherapy phase and capecitabine + RT for the chemoRT phase, followed by surgery (Figure 2).

Figure 2: Current Total Neoadjuvant Therapy (TNT) schema



2.1.1.3 Chemoradiotherapy:

Preoperative fluoropyrimidine (FP) chemotherapy, fluorouracil (5-FU) or capecitabine (cape), with concurrent radiation therapy (RT) improves survival in patients with rectal cancer (Douglass *et al.,* 1986; Krook *et al.,* 1991; and Kollmorgen *et al.,* 1994) and is a standard-of-care for LARC (Sauer *et al.,* 2004). Preoperative chemoRT improves local control and enhances tumor shrinkage facilitating improved options for surgical resection (Sauer *et al.,* 2004). In an effort to improve the chemoradiotherapy component of LARC treatment, several large randomized phase 3 trials have addressed the potential benefit of adding oxaliplatin (ox) to FP + RT regimens based on the rationale that oxaliplatin's cytotoxic and radiosensitizing effects may decrease rates of distant recurrence and local progression (Table 1) (Aschele *et al.,* 2011; Gerard *et al.,* 2010; Gerard *et al.,* 2012; Allegra *et al.,* 2015; O'Connell *et al.,* 2014; Rodel *et al.,* 2012; Rodel *et al.,* 2015; Haustermans *et al.,* 2014; Schmoll *et al.,* 2018; Jiao *et al.,* 2015, Deng *et al.,* 2016; Deng *et al.,* 2019). The clinical results of the addition of ox to FP + RT have been disappointing, in part due to the toxicities encountered with this combination.

Table 1: Randomized clinical trials of fluoropyrimidine + RT ± oxaliplatin

Trial	Endpoints	Year	N	Control Arm		Experimental Arm		p
				Treatment	pCR	Treatment	pCR	
STAR-1 (Aschele *et al.,* 2011)	Primary endpoint: OS Planned early endpoint that would be analyzed: pCR	2011	747	5FU + RT	16%	5FU + RT + ox	16%	NS
ACCORD 12/0405 PRODIGE 2 (Gerard *et al.,* 2010, Gerard *et al.,* 2012)	Primary endpoint: pCR (reported JCO 2010) Secondary endpoints: local recurrence rate, OS, DFS (reported JCO 2012)	2012	598	Cape + RT	13.9 %	Cape + RT + ox	19.2 %	.09
NSABP R-04 4 arm study cape vs 5FU ± ox (O'Connell *et al.,* 2014, Allegra *et al.,* 2015)	Primary endpoints were all "surgical endpoints": pCR, sphincter-sparing surgery, and surgical downstaging (conversion to sphincter-sparing surgery)	2014	1608	5FU or cape + RT	17.8 %	5FU or cape + RT + ox	19.5 %	.42
German CAO/ARO/AIO-04 (Rodel *et al.,*	Primary endpoint: DFS (reported 2015)	2015	1236	5FU + RT	13%	5FU + RT + ox	17%	.03

Trial	Endpoints	Year	N	Control Arm		Experimental Arm		p
				Treatment	pCR	Treatment	pCR	
2012, Rodel *et al.*, 2015)	Secondary endpoints: pCR, toxicity, compliance (reported 2012)							
PETACC-6 (Haustermans *et al.*, 2014, Schmoll *et al.*, 2018)	Primary endpoint: DFS (reported 2018 JCO abstract only) Secondary endpoints: pCR, sphincter-sparing surgery, and surgical downstaging (conversion to sphincter-sparing surgery)	2014	1069	Cape + RT	11%	Cape + RT + ox	13%	.31
Jiao *et al.*, 2015)	Primary endpoints: DFS, OS Secondary endpoints: pCR, toxicity, compliance	2015	206	Cape + RT	19%	Cape + RT + ox	23%	.49
FOWARC (Deng *et al.*, 2016, Deng *et al.*, 2019)	Primary endpoint: 3-year DFS Secondary endpoints: pCR, toxicity	2015	495	5FU + RT	14%	mFOLFOX6 + RT	27.5 %	.005

2.1.2 Pathologic complete response (pCR) as outcome measure in rectal cancer:

In rectal cancer, the absence of viable tumor cells in the resection specimen (primary tumor mass, surrounding tissue and lymph nodes) at the time of surgery, termed pathologic complete response (pCR), has been shown to correlate with improved outcome (Ryan *et al.,* 2005, Martin *et al.,* 2012). pCR is considered a standard endpoint for LARC clinical trials, although correlations of pCR with surgical results (*e.g.* extent of resection, sphincter preservation, downstaging) and OS are needed for definitive documentation of benefit. pCR rates for FP + RT *vs.* FP + RT + ox from recent phase 3 trials are presented in Table 1. In these 7 international, multi-institutional, randomized phase 3 trials, pCR was a primary or secondary endpoint in every trial.

2.1.3 Neoadjuvant Rectal Score (NAR score) as an outcome measure in rectal cancer:

The NAR score was developed by Yothers *et al.* as a short-term clinical trial surrogate endpoint that is particularly sensitive to changes in factors that are affected by neoadjuvant therapy (George *et al.,* 2015). The NAR score was built upon the Valentini nomogram to go beyond pCR to predict local recurrence, distant metastases and OS for patients with LARC (Valentini *et al.*, 2011). NAR is calculated based on the clinical T stage (cT), pathological T (pT) and pN stages as:

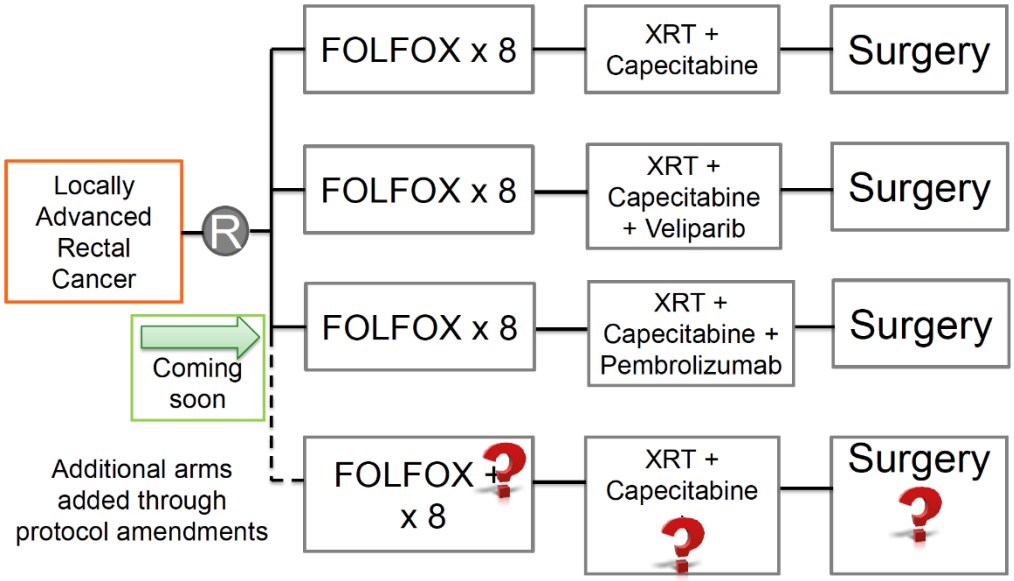
$$NAR = [5pN- 3 (cT- pT) + 12]^2 / 9.61$$

The NAR score has been validated in the randomized NSABP R04 study that evaluated four different FP-based radioensitizing regimens in 1479 patients with resectable rectal cancer. NAR score in this dataset was significantly associated with overall survival (George *et al.,* 2015).

2.1.4 NRG Oncology TNT trial (NRG-GI002; NCT02921256):

The current NRG Oncology TNT trial (NRG-GI002; NCT02921256) is a randomized, phase 2, signal-finding platform study, designed with parallel, noncomparative investigational arms and a single comparative TNT control group (George *et al.,* 2019b) (Figure 3). This NCTN multi-arm randomized phase 2 modular clinical trial platform utilizes TNT (mFOLFOX6 × 8 cycles, See Appendix E) with parallel experimental arms (EA) in LARC. The EAs are not intended for direct comparison, but rather to test a variety of sensitizers or hypotheses in a consistent and homogenous high-risk patient population with correlative biomarkers. Success of any EA will be determined by achievement of pathologic endpoints compared to a control arm. Target accrual is 79 evaluable patients/arm with additional EAs added through protocol amendments. NAR score is the primary endpoint used in the NRG-GI002 trial. The current study will provide data to be used to determine the appropriateness of evaluating IPdR as an EA in the NRG-GI002 trial. Because patients on the current study will receive identical treatment to those on NRG-GI002 (minus IPdR), results of this study will facilitate expeditious incorporation of IPdR into NRG-GI002 as an EA (George *et al.,* 2019b; George *et al.,* 2019).

Figure 3: NRG-G1002 (NCT02921256) TNT Schema (Non-comparative Phase 2 experimental arms)



The study schema for randomized phase 2 arms of NRG-GI002 (clinicaltrials.gov identifier NCT02921256) is illustrated. Additional arms are added through protocol amendments and are compared with the ongoing control arm. The FOLFOX regimen consists of oxaliplatin 85 mg/m^2 intravenously (IV) on Day 1 + leucovorin 400 mg/m^2 IV on Day 1 + 5-fluorouracil (5-FU) 400 mg/m^2 as an IV bolus, followed by 5-FU 2400 mg/m^2 as a continuous infusion over 46 hours every 2 weeks for 8 cycles. Radiotherapy (XRT) starts 3 to 4 weeks after the last dose of FOLFOX, with 4500 centigrays (cGy) delivered in 25 fractions over 5 weeks and a 540-cGy boost in 3 fractions; intensity-modulated radiotherapy is allowed. Surgery is performed 8 to 12 weeks after the last dose of RT.

2.2 CTEP IND Agent

2.2.1 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR)

2.2.1.1 Iododeoxyuridine (IUdR)-mediated radiosensitization

5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR) is a prodrug of iododeoxyuridine (IUdR), a pyrimidine analog that has been recognized as a radiosensitizing agent since the early 1960's (Kinsella 1996; McGinn *et al.,* 1996b). The mechanism of IUdR-mediated radiosensitization involves the cellular uptake and metabolism of IUdR through the thymidine salvage pathway. IUdR undergoes initial intracellular phosphorylation to the monophosphate derivative by the rate-limiting enzyme, thymidine kinase, followed by sequential phosphorylation to the triphosphate. Kinsella and others have demonstrated that this modified analog is then utilized (*i.e.* incorporated) by DNA polymerase during scheduled (S-phase) and unscheduled DNA synthesis, in competition with thymidine triphosphate (Kinsella *et al.,* 1987; Rieber and Rieber, 2008). DNA incorporation is needed for radiosensitization by ionizing radiation (IR), in human tumors as well as normal cells, and the extent of radiosensitization correlates directly with the %IUdR DNA replacement (Kinsella *et al.*, 1987; Lawrence *et al.,* 1990; Rieber and Rieber, 2008). IR-mediated radiosensitization by IUdR results in the generation of highly reactive uracil free radicals by IR, which may also damage unsubstituted complementary-strand DNA, resulting in increased DNA single strand breaks (SSBs) and increased double strand breaks (DSBs) (Kinsella *et al.,* 1987; Fornace *et al.,* 1990; Lawrence *et al.,* 1990; Rieber and Rieber, 2008). The repair of IR damage may also be reduced by pre-IR exposure to IUdR. IUdR is rapidly metabolized in both rodents and humans when given as a bolus infusion with a plasma half-life of <5 min (Kinsella 1996). Consequently, prolonged continuous drug infusion over several weeks before and during RT is necessary to maximize the proportion of tumor cells that incorporate IUdR during the S phase of the cell cycle (Rodriguez *et al.,* 1994; Fowler and Kinsella, 1996).

In the 1980-1990s, clinical trials of IUdR as a radiosensitizer were performed, focusing on patients presenting with high-grade gliomas (Kinsella *et al.,* 1988; Sullivan *et al.,* 1994; Urtasun *et al.,* 1996; Schulz *et al.,* 2004) and sarcomas (Goffman *et al.,* 1991; Robertson *et al.,* 1995). These studies demonstrated that the magnitude of radiosensitization correlates directly with plasma IUdR levels and the %IUdR-DNA tumor cellular replacement and can serve as radiosensitization biomarkers (Kinsella *et al.,* 1984; Speth *et al.,* 1988b). Additionally, in small series of patients with head and neck cancers or liver metastases from colorectal cancer, the %IUdR-DNA cellular incorporation in tumors ranged to 5%, but was less than 1% in adjacent normal liver tissue, further supporting a therapeutic window for IUdR-mediated radiosensitization (Kinsella *et al.,* 1984; Speth *et al.,* 1988b). Although IUdR has clear activity as a radiosensitizer, its development has been limited by the need for prolonged continuous infusion before and during RT that results in myelosuppression and gastrointestinal toxicities, limiting the tolerated dose and the potential for clinical radiosensitization (Kinsella *et al.,* 1988; Sullivan *et al.,* 1994; Urtasun *et al.,* 1996; Schulz *et al.,* 2004).

2.2.1.2 IPdR

IPdR offers several key advantages compared to IUdR, including a more favorable therapeutic index. IPdR produces minimal cytotoxic effect, and can be considered a classic radiosensitizer. IPdR is a prodrug of IUdR that is administered PO and then efficiently converted to IUdR by a hepatic aldehyde oxidase (Chang *et al.,* 1992). Preclinical studies of IPdR as a potential radiosensitizer included pharmacology and toxicology studies performed in athymic mice, rats, ferrets, and Rhesus monkeys (Kinsella *et al.,* 1994; Kinsella *et al.,* 1998; Kinsella *et al.,* 2000;

Kinsella *et al.,* 2000b; Kinsella *et al.,* 2008); and *in vivo* radiosensitization studies using human tumor xenograft models in athymic mice (two colorectal cancer cell lines, HT29 and HCT-116, and two glioblastoma [GBM] cell lines, U251 and U87) (Kinsella *et al.,* 1994; Kinsella *et al.,* 2000; Kinsella *et al.,* 2000b; Seo *et al.,* 2005). These preclinical studies demonstrated that: 1.) IPdR could be administered and tolerated PO using multiple daily dosing; 2.) IPdR is efficiently and predictably metabolized into the active metabolite, IUdR; 3.) relatively prolonged plasma levels of IUdR can be achieved; 4.) %IUdR-DNA incorporation was demonstrated to be 2-3 times more in proliferating tumor and 2-3 fold less in proliferating normal tissues (bone marrow and GI epithelium) compared to continuous infusion IUdR at the MTD; 5.) radiation sensitizer enhancement ratios of 1.3-6 were achieved using human cancer xenograft models, and compared favorably with those of continuous infusion IUdR at the MTD ($\leq$1.1); and, 6.) systemic toxicity was minimal at effective doses. These data were used to support an Investigational New Drug Application and to conduct an initial phase 0 trial of single-dose IPdR at the NCI in patients with advanced malignancies that demonstrated that radiosensitizing plasma levels of IUdR could be achieved following PO administration of IPdR (Kummar *et al.,* 2013).

Table 2: IPdR pre-clinical and early clinical studies

Study	Description	Summary of Findings
IPdR Metabolism by hepatic aldehyde oxidase		
Chang *et al.*, 1992	Metabolism of IPdR *vs.* IUdR	Elucidated IPdR metabolism by aldehyde oxidase Characterized properties of aldehyde oxidase
Kinsella *et al.*, 2000b; Kinsella *et al.*, 2008	IPdR Metabolism in rats and ferrets	Characterized kinetics of IPdR metabolism
Pharmacokinetic and toxicology studies		
Kinsella *et al.*, 1994; Kinsella *et al.*, 1998; Kinsella *et al.*, 2000b	Pharmacokinetics of PO IPdR in mice	Established absorption, distribution, metabolism, and elimination kinetics of PO IPdR in mice
Kinsella *et al.*, 2000	Pharmacokinetics (PK) and toxicity/toxicology of IPdR in ferrets (PO) and rhesus monkeys (IV)	Established distribution, metabolism, and elimination kinetics of IPdR in non-rodent species. Noted mild weight loss at highest dose; but no significant hematologic, biochemical, or histopathologic changes

Study	Description	Summary of Findings
Kinsella *et al.*, 2008	Pharmacokinetics and toxicity/ toxicology of PO IPdR in Fischer rats	Established IPdR and IUdR concentration-time profiles Reported HPLC/tandem mass spectroscopy methods for plasma IPdR and IUdR levels.
Pre-clinical efficacy studies of IPdR-mediated radiosensitization		
Kinsella *et al.*, 1998; Kinsella *et al.*, 2000b **Seo *et al.*, 2004; Seo *et al.*, 2005**	Efficacy/toxicity studies of PO IPdR *vs.* continuous intravenous (ci) IUdR using human colorectal and glioblastoma tumor xenografts.	Increased IUdR-DNA incorporation in tumors; decreased in normal tissues, PO IPdR *vs.* ci IUdR. 1.3-1.5 fold enhancement of response to RT with PO IPdR
Kinsella *et al.*, 1994	Efficacy, PK, toxicity, and DNA incorporation of PO IPdR *vs.* PO IUdR in human colon cancer xenografts.	Demonstrated improved therapeutic index of PO IPdR *vs.* PO IUdR for IUdR-mediated radiosensitization
Early clinical studies of IPdR		
Kummar *et al.*, 2013	Pharmacokinetics of single-dose PO IPdR in humans	Phase 0 study of PO IPdR, 150mg-2400mg in humans: No toxicities.
Kinsella *et al.*, 2019	Phase I and Pharmacology study of Ropidoxuridine (IPdR) as prodrug for iododeoxyuridine-mediated tumor radiosensitization in advanced GI cancer undergoing radiation	PO IPdR daily × 28 days with RT is feasible and tolerable at doses that produce plasma IUdR levels of ≥ 1µM/L

2.2.1.3 Phase 1 Study of IPdR + RT For GI Malignancies:

The Brown University Oncology Research Group has recently reported results of a phase 1 study of IPdR + RT in patients with advanced GI malignancies (NCI #9882; NCT02381561) (Kinsella *et al.,* 2019). Adult patients with locally advanced or metastatic GI cancers referred for palliative RT to the chest, abdomen or pelvis were eligible for study. Patients received IPdR PO once daily (QD) × 28 days beginning seven days prior to the initiation of RT and continuing through the final day of RT (37.5 Gy in 2.5Gy × 15 fractions). A two-part dose escalation scheme was used, PK studies were performed at multiple time points, and all patients were assessed for toxicity and response to Day 56 (Figures 4, Table 3, and Table 4)

Table 3: Schema – Phase 1 and pharmacology trial of oral IPdR as a prodrug for IUdR-mediated radiosensitization in patients receiving palliative RT for metastatic GI

cancers (NCT02381561) (Kinsella *et al.*, 2019)

	Week 1 Days 1-7	Week 2 Days 8-14	Week 3 Days 15-21	Week 4 Days 22-28	Week 5 Days 29-35	Week 6	Week 8
IPdR	PO QD dose × 28 days, Days 1-28						
RT		2.5 Gy/day × 15 doses (37.5 Gy total dose) Days 8-12, 15-19, 22-26					
PK studies plasma levels of IPdR, IUdR, IP and IU	Day 1[a]		Day 15[b]	Day 22[b]			
Radiologic assessment of tumor (CT or MRI)	Within I week of study entry						4 weeks following end of therapy

[a] Day 1, a pre-study sample was obtained and then sampling was done at 30, 60, 120, 240 minutes and 24 hours (just prior to Day 2 IPdR dose) following the initial PO dose of IPdR

[b] Days 15 and 22 of the 28-day dosing schedule, samples were obtained just prior to PO IPdR and then at 30, 60, 120, and 240 minutes following PO IPdR dose

Nineteen patients were enrolled on study and received dosages from 150mg/day to 1800mg/day (Kinsella *et al.,* 2019). The first and second patients received 150 mg and 300 mg PO QD, respectively, without toxicity using single-patient-per-cohort dose escalation. The third study patient (600 mg PO QD) developed grade 3 transaminase elevation on Day 22 of study. This event triggered the Stop/Switch rule, and Part II of the dose escalation scheme was initiated. Cohorts of three evaluable patients each for dose levels 600 mg, 900 mg, and 1200 mg received therapy with IPdR without additional grade 2 or higher treatment related toxicity. At 1800 mg PO QD, two of three patients experienced Grade 3 toxicity deemed probably or definitely related to IPdR. One patient developed grade 3 dehydration and a second patient had grade 3 diarrhea. No Grade 4 toxicities were encountered. The MTD and recommended phase 2 dose (RP2D) of IPdR based on this study is 1200 mg PO QD.

Table 4: Phase 1 trial (NCI #9882): Study treatment, toxicity and response (Kinsella *et al.*, 2019)

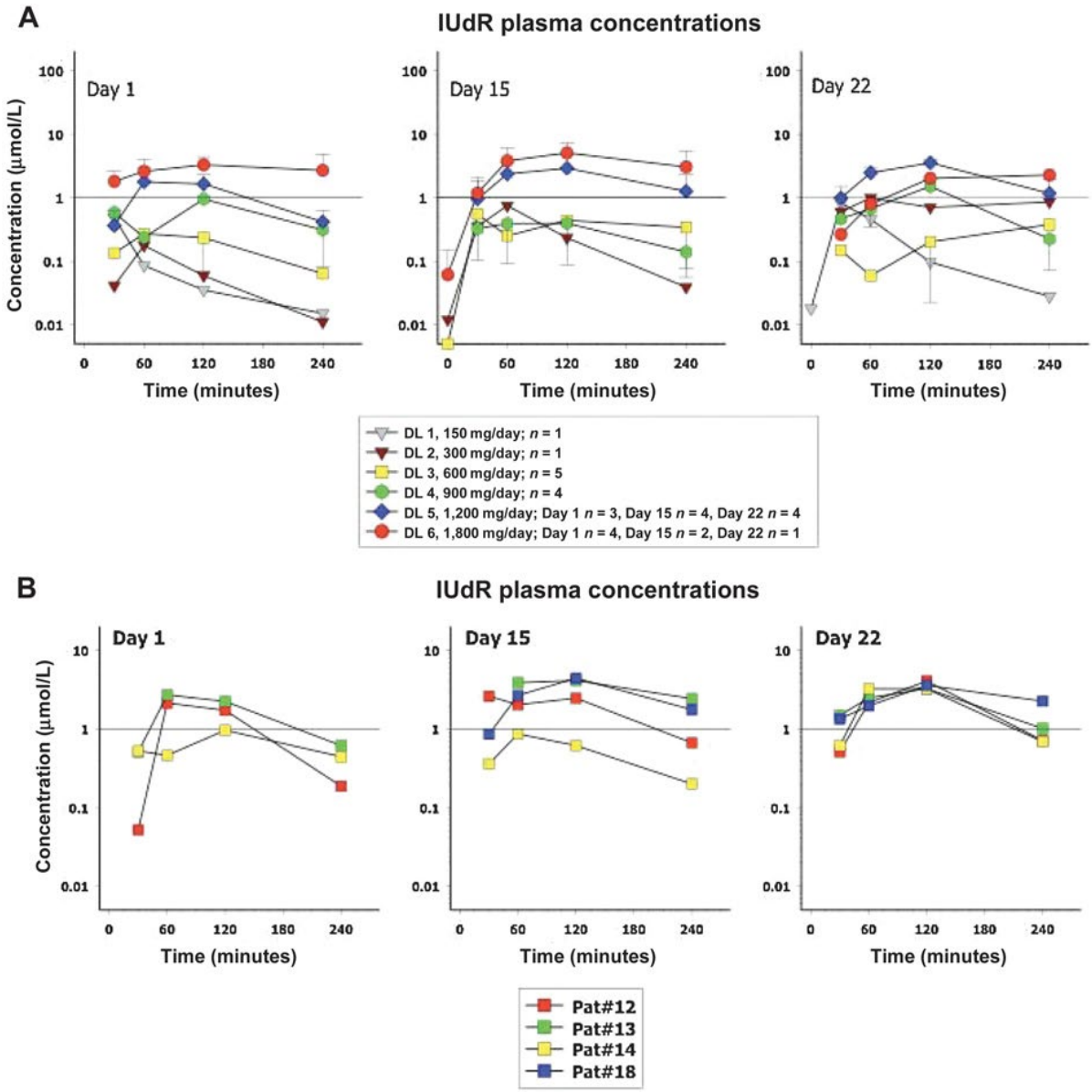
Primary tumor histology	Primary tumor site	IPdR dose (mg every day)	Target site (RT field)	Toxicity (≥grade 2 and attribution ≥ 3[a])	Grade	Attribution to IPdR[a]	Target tumor response[b]	Nontarget tumor response[b]
AC	Colon	150	Liver Met				SD	SD
AC	Colon	300	Liver Met				SD	SD
AC	Pancreas	600[c]	Pancreas tail	ALT	3	3	PD at D 23[c]	PD at D 23[c]
				AST	2	4		
				rash	2	3		
AC	Colorectal	600[c]	Rectum				NE[c]	NE[c]
AC	Rectum	600	L2 spine, adj soft tissue				Pathologic PR	PD
AC	Rectum	600	Posterior pelvis/sacrum				SD	SD
CholangioCA HCC	Bile duct liver	600	Porta hepatis LN				SD	PD
AC	Colon	900[c]	RLQ abdomen				NE[c]	NE[c]
AC	Ampulla	900	Liver Met				CR	SD
AC	Rectum	900	Liver Met;				CR	SD
			R lung Met				PR	
AC	Colon	900	Liver Met; R lung Met				SD	SD
AC	Pancreas	1,200	L adrenal Met; para-aortic LN				SD	SD
SCC	Esophagus	1,200	R supraclav LN				SD	NE
HCC	Liver	1,200	R pulmonary artery Met; R lung hilum LN				PR	PD
AC	Colon	1,800[c]	Para-aortic, upper abd LN	Dehydration	3	5	NE[c]	NE[c]
				Pneumonia	3	3		
AC	Bile duct	1,800	L upper tracheal supraclav LN	Esophagitis/mucositis/ anorexia/mouth pain	2	5	SD	PD
				Dysphagia	2	3		
				Perianal irritation	2	3		
AC	Colon	1,800[c]	L acetabulum bone Met	Anorexia	2	3	NE[c]	PD
				Diarrhea	3	4		
AC	Colon	1,200	Retroperit LN				SD	SD
SCC	Esophagus	1,200[c]	Gastrohep LN				NE[c]	NE[c]

Abbreviations: L, left; LN, lymph nodes; Met, metastasis; R, right.
[a]Attribution: 1 = unrelated, 2 = unlikely, 3 = possible, 4 = probable, 5 = definite.
[b]RECIST criteria: NE, not evaluable.
[c]Did not complete study therapy.

Pharmacokinetics analyses:

In the phase 1 trial, PK analyses demonstrated achievable and sustainable levels of plasma IUdR ≥1μM/L (levels previously shown to mediate radiosensitization) at dose levels ≥600mg/day (Figure 4).

Figure 4: PK analyses – Phase 1 trial and pharmacology trial of oral IPdR as a prodrug for IUdR-mediated radiosensitization in patients receiving palliative RT for metastatic GI cancers (NCI #9882) (Kinsella *et al.*, 2019).
(A) Mean plasma concentrations of IUdR by IPdR dose level. (B) Plasma concentrations of IUdR in individual patients on Days 1, 15, and 22 at 1200 mg dose level (MTD, recommended phase 2 dose [RP2D])



Although not the primary objective of the study, all patients had measurable disease at study entry. Evaluation of target lesions within the radiation field 4 weeks following completion of therapy (at Week 8), using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, revealed two Complete Response (CR), three Partial Response (PR), nine Stable Disease (SD), and no progressive disease (PD) in these patients.

In conclusion, this first-in-human tolerance study of IPdR confirmed that IPdR is predictably and readily absorbed following PO administration, is metabolized to IUdR principally by hepatic aldehyde oxidase, and demonstrates PK that compare favorably to those of IUdR. The administration of IPdR PO QD × 28 days with RT is feasible and tolerable at doses that produce plasma IUdR levels $\geq$1μM/L, achieving plasma IUdR levels that have previously been associated with clinically significant radiosensitization. This phase 1 study supports further testing of IPdR as a potential radiosensitizing agent. In this subsequent trial, we propose evaluating the addition of PO IPdR to preoperative capecitabine + RT for patients with rectal cancer.

2.3 Other Agents

2.3.1 Capecitabine

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate (TTP), which is essential for the synthesis of DNA, so a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

2.3.1.1 Capecitabine + RT: ChemoRT phase of LARC therapy:

Fluoropyrimidine therapy concurrent with RT for rectal cancer currently represents the standard of care for this disease (Sauer *et al.,* 2004). The Gastrointestinal Tumor Study Group showed that adjuvant combined modality therapy with RT and 5-fluorouracil (5-FU)-based chemotherapy improved outcomes in patients with rectal cancer both in terms of local control OS compared to postoperative RT alone (Krook *et al.*, 1991). The incorporation of protracted infusional 5-FU with RT further improved clinical outcomes (O'Connell *et al.,* 1994). NSABP R-04 demonstrated similar clinical outcomes between capecitabine and continuous infusion 5-FU when added to RT for rectal cancer (O'Connell *et al.,* 2014). Pathologic complete responses were similar between the two arms (22.2 *vs.* 18.8%; p=0.12) while toxicity clinically favored capecitabine.

2.4 Rationale

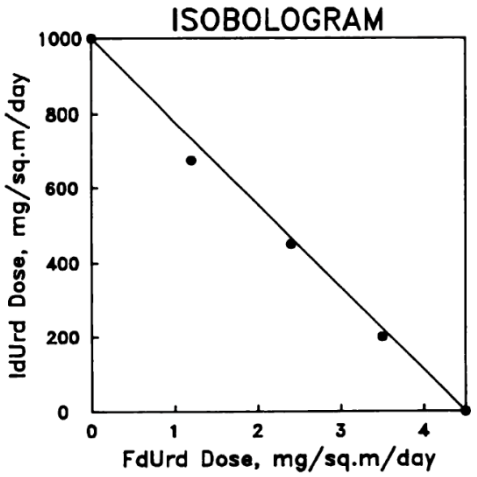
2.4.1 Mechanism of fluoropyrimidine (FP)-based radiosensitization (RS) and interactions of IPdR on FP-based binding (inhibition) of thymidylate synthetase (TS) to enhance FP-RS:

While the precise mechanisms of FP-mediated RS of rectal tumors are not clearly understood, we and others have shown experimentally that RS is principally mediated by FP effects on the production and balance of intracellular DNA nucleotide pool via binding of the principal FP metabolite, FdUMP, to TS causing TS inhibition and depletion of dTTP pools (Bruso *et al.,* 1990; Miller and Kinsella, 1992). The level of TS expression in colorectal cancer (CRC) cell lines and in patient tumor specimens is of prognostic significance where high TS expression correlates with reduced RS (Miller and Kinsella, 1992). In experimental studies, the addition of IPdR further inhibits TS with a greater than additive effect as a result of the generation of the intracellular IPdR monophosphate metabolite, IdUMP that further inhibits (by binding) TS leading to increased FP-mediated RS (Lawrence *et al.*, 1992; Miller *et al.*, 1995).

2.4.2 FP + IPdR/IUdR:

The phase 1 and clinical pharmacology study combining a fluoropyrimidine (fluorodeoxyuridine, FUdR) and a halogenated pyrimidine (HP) analog (IUdR) provides data that may be applied to the combination of capecitabine + IPdR proposed in this study (Speth *et al.,* 1988). FUdR and IUdR were administered concomitantly, as 14-day continuous intravenous (IV) infusions with standard fractionated RT. The majority of patients in this study had glioblastoma multiforme (GBM), and the trial tested the hypothesis that FP would modulate the extent of cellular %IUdR-DNA incorporation (Speth *et al.,* 1988). In retrospect, GBM was a poor choice for testing this hypothesis in light of the limited FP cytotoxicity in this tumor. However, using %IUdR-DNA incorporation in circulating granulocytes as a biochemical endpoint and both fixed and escalating doses of either FUdR or IUdR, no modulation of %IUdR-DNA incorporation was found in the granulocytes. Indeed, the different MTDs of IUdR and FUdR plotted in an isobologram suggested only additive effects (Figure 5). Additionally, no changes in the expected plasma levels of either drug were found. This clinical study provides data regarding the concomitant use of a FP and IUdR as radiosensitizers.

Figure 5: Isobologram of the relationship between the MTDs of FdUrd and IdUrd administered as single agents or co-administered in different dosage combinations (Speth *et al.*, 1988)



In contrast, RT + FP (using either continuous infusion 5-FU for up to 96 hours or twice daily PO capecitabine) is an internationally established treatment for LARC with acceptable acute and late normal tissue toxicities (Table 1). Three *in vivo* preclinical studies in two representative CRC (HT29 and HCT-116) xenograft models supporting the superiority of PO IPdR given daily or up to three times a day *vs.* continuous infusion IUdR (at the MTD) as a radiosensitizer demonstrating an improved therapeutic index have been published (Kinsella *et al.,* 1994; Kinsella *et al.,* 1998; Seo *et al.,* 2004)

2.4.3 Twice-a-Day Dosing of IPdR:

Based on laboratory studies by Seo *et al.,* 2005 and discussions with Dr. Jerry Collins (Developmental Therapeutics Program [DTP], NCI), this protocol will utilize a twice a day (BID) dosing schema of IPdR with capecitabine and RT. Seo *et al.,* evaluated and compared four different IPdR treatment schedules: once a day, three-times a day, every-other-day, and every third day. Plasma PK, IUdR-DNA incorporation in tumor and normal proliferating tissues, tumor growth delay following irradiation, and body weight loss were used as end points. The three-times-daily schedule with the same total daily doses as the daily schedule improved the efficiency of IPdR conversion to IUdR. This study will initially utilize a twice daily schedule to correspond to capecitabine administration.
.

Based on IPdR's interactions with FPs and RT in preclinical studies, IPdR is expected to improve the efficacy of the chemoRT phase of treatment for patients with LARC. This phase 1 study will determine the MTD of the concomitant administration of IPdR with capecitabine + RT. The favorable toxicity profile of IPdR given with concurrent RT in NCI #9882 provides support for the expected tolerability of this chemoRT combination (IPdR + capecitabine + RT). NRG Oncology TNT trial (NRG-GI002; NCT02921256) is a multi-arm randomized phase 2 modular clinical trial platform utilizing TNT with parallel experimental arms. Because patients on this trial will receive identical treatment to those on NRG-GI002 (minus IPdR), results of this

trial will facilitate expeditious incorporation of IPdR into NRG-GI002 as an experimental arm.

2.5 Correlative Studies Background

2.5.1 IPdR PK

On Day 8, plasma PK analyses will be performed. A 10 cc blood sample will be obtained just prior to the PO IPdR dose and then at 30, 60, 120, and 240 minutes following the PO dose of IPdR. On Days 21 and 35, 10 cc of blood will be drawn 1-2 hours following the PO dose of IPdR for plasma IPdR and IUdR levels.

Methodologies for the PK analyses are those detailed and reported previously (Kummar *et al.,* 2013) and the same as used in the prior phase 1 trial (Kinsella *et al.,* 2019). Employing a similar schedule for PK sampling in this trial as that used in the prior phase 1 study will allow comparison of the results, and the potential impact of concomitant capecitabine dosing.

2.5.2 Capecitabine PK

Levels of capecitabine and its metabolites will be performed on Days 8, 21, and 35 in conjunction with the IPdR PK studies, using a portion of the 10-mL blood samples described above (Section 2.5.1).

Methodologies for the capecitabine PK analyses are those detailed and reported previously (Reigner *et al.*, 2001).

2.5.3 %IUdR-DNA cellular incorporation into tumor biopsy specimen

As the %IUdR-DNA cellular incorporation in human tumor xenografts in athymic mice was linearly related to the IPdR dose when given PO QD × 6-14 days (Kinsella *et al.,* 1994; Kinsella *et al.,* 2000b; Seo *et al.,* 2004), we will evaluate for correlation between %IUdR-DNA cellular incorporation in tumor cells obtained from the surgical resection specimen and the dose of IPdR received as a biomarker of tumor radiosensitization. Evaluation for correlation of tumor response using pCR rate and NAR score and the %IUdR-DNA cellular incorporation in tumor cells obtained from the surgical resection specimen will also be performed.

2.5.4 %IUdR-DNA cellular incorporation in peripheral (circulating) granulocytes:

%IUdR-DNA cellular incorporation in peripheral (circulating) granulocytes will be performed as a biomarker of bone marrow acute normal tissue toxicity. These analyses will be performed at three time points on study, Days 8, 21, and 35. %IUdR-DNA cellular incorporation in peripheral (circulating) granulocytes will be correlated with peripheral blood counts, other systemic toxicities (CTCAE v5.0) and plasma PK obtained at the same time points. This assay was originally developed in Dr. J. Collins' laboratory at NCI (Belanger et al., 1986; Belanger *et al.*, 1987).

Based on our pre-clinical data regarding %IUdR-DNA cellular incorporation in bone marrow

cells harvested directly from the femurs of athymic mice and ferrets following a 14 day exposure to PO QD IPdR (Kinsella *et al.,* 1994; Kinsella et al., 2000; Seo et al., 2004; Seo *et al.,* 2005) we would not expect a significant correlation between the %IUdR-DNA cellular incorporation in circulating granulocytes and PK measurements, peripheral blood counts, or systemic toxicities.

We have used circulating granulocytes as surrogate cells for bone marrow toxicity using the %IUdR-DNA cellular incorporation in several clinical trials of continuous intravenous (ci) IUdR (Belanger *et al.,*1986; McGinn *et al.,* 1996; Schulz *et al.,* 2004; Seo *et al.,* 2004). For example, using a 28-day schedule of ci IUdR, we found an increase in the %IUdR-DNA incorporation in circulating granulocytes that: peaked by Day 21 of the 28-day ci treatment; reached nearly 5% at the highest dose level (781 mg/m^2/day); correlated with steady-state plasma IUdR of 1.5 ± 0.3 μM; and was associated with Grade 4 neutropenia in 2 of 6 patients and Grade 3 thrombocytopenia in 1 of 6 patients (Schulz *et al.,* 2004). In contrast, PO QD dosing of IPdR at 1 gm/kg/day × 28 days in rats showed no significant myelosuppression and %IUdR-DNA incorporation <2% with steady-state plasma IUdR levels of 2-3 ± 0.5 μM.(Schulz *et al.,* 2004)

3. PATIENT SELECTION

This study involves the chemoradiotherapy phase of treatment for LARC. The intent is for patients to receive treatment as per NRG-GI002 with the addition of IPdR during the chemoradiotherapy phase. As such, patients must have been diagnosed with LARC and received 8 cycles of mFOLFOX6 (Appendix E) prior to study entry, with the intent to undergo surgical resection following chemoradiotherapy.

3.1 Eligibility Criteria

3.1.1 At diagnosis, patients must have had histologically proven adenocarcinoma of the rectum with no evidence of distant metastases.

3.1.2 At diagnosis, the major portion of the tumor must have been intact, and the following must be documented:

- distance of the lowest tumor margin from the anal verge; *and*
- intent for sphincter sparing or non-sphincter sparing surgical resection according to the primary surgeon; *and*
- the majority of the untreated tumor must be <12 cm from the anal verge or below the peritoneal reflection as determined by the treating surgeon.

3.1.3 At diagnosis, the tumor must have been locally advanced Stage II (T3-4 N0) or Stage III (N+) rectal cancer with at least one of the following:

- *Distal location (as defined by measurement on MRI, ERUS/pelvic CT [with IV contrast] scan or palpable on digital rectal exam [DRE])*: cT3-4 ≤5 cm from the anal verge, any N
- *Bulky:* any cT4 or evidence that the tumor is adjacent to (defined as within 3 mm of) the mesorectal fascia on MRI or ERUS/pelvic CT (with IV contrast) scan
- *High risk for metastatic disease* with 4 or more regional lymph nodes (cN2). **Clinical**

Nodal or "**cN**" status for eligibility includes the total number of nodes (N2 = 4 or more) in the mesorectal and superior rectal stations measuring ≥1.0 cm in any axis on cross sectional or endoscopic imaging. Nodes must measure 1.0 cm or greater to be considered positive for this eligibility requirement.

- *Not a candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy* (as planned by the primary surgeon)

3.1.4 Patients must have received 8 cycles of neoadjuvant mFOLFOX and must have completed this therapy at least 3 weeks (and no more than 6 weeks) prior to enrollment on this study (see Appendix E).

3.1.5 Patients must intend to undergo surgical resection of the rectal primary tumor following chemoradiotherapy.

3.1.6 Age ≥18 years.

Because no dosing or adverse event (AE) data are currently available on the use of IPdR in combination with Capecitabine and RT in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,200/mcL
– platelets	≥100,000/mcL
– hemoglobin	>10 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN)
– AST(SGOT)	≤2.5 × institutional ULN
– ALT(SGPT)	≤2.5 × institutional ULN
– creatinine	≤1.5 × institutional ULN OR
– glomerular filtration rate (GFR)	≥60 mL/min/1.73 m^2 (see Appendix B)
– alkaline phosphatase	≤3 × institutional ULN
– sodium, potassium, chloride, bicarbonate and magnesium	Within institutional normal limits

3.1.9 Patients with acquired immunodeficiency syndrome (AIDS-related illnesses) or known human immunodeficiency virus (HIV) disease **must**:

- Have a CD4 count ≥200 cells/μL within 30 days before enrollment,
- Be off all antiretroviral therapy (prophylaxis/treatment) more than 60 days before

enrollment, *and*

- Have no evidence of opportunistic infections.

3.1.10 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured and be receiving no therapy.

3.1.11 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.12 Patients must have the ability to swallow and retain oral medication.

3.1.13 The effects of IPdR on the developing human fetus are unknown. For this reason and because radiosensitizing agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (WOCBP)* and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP must have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test will be required. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of IPdR administration.

*Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 Patients who have not recovered from adverse events due to prior mFOLFOX6 chemotherapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with impaired GI function or GI disease that may significantly alter the absorption of oral IPdR and capecitabine (*e.g.* ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with

active inflammatory bowel disease (*i.e.,* patients requiring current medical interventions or who are symptomatic) or have a history of abdominal surgery or other medical condition that may, in the opinion of the treating physician, interfere with GI motility or absorption. Patients with colostomies are allowed unless colostomy is for one of the precluded reasons above.

3.2.4 Treatment with warfarin is not allowed. However, therapy with heparin, low molecular weight heparin (LMWH), and DOACs (Direct oral anticoagulating agent) such as dabigatran (Pradaxa), rivaroxaban, and apixaban [Eliquis] is allowed.

3.2.5 Patients with an active concurrent invasive malignancy.

3.2.6 History of prior invasive rectal malignancy, regardless of disease-free interval.

3.2.7 Patients who have received pelvic RT for rectal cancer, or prior pelvic RT for any other malignancy that would prevent the patient from receiving the required RT for this study.

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

3.2.9 Patients with uncontrolled intercurrent illness.

3.2.10 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Pregnant women are excluded from this study because IPdR may have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with IPdR, breastfeeding should be discontinued if the mother is treated with IPdR. These potential risks may also apply to other agents used in this study.

3.2.12 Patients that received live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.

3.2.13 Known homozygous DPD (dihydro pyrimidine dehydrogenase) deficiency

3.2.14 History of, or any evidence of, active non-infectious pneumonitis.

3.2.15 Active autoimmune disease that has required systemic treatment within the past 2 years (*i.e.,* with use of modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (*e.g.,* thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, *etc.*) is not considered a form of systemic treatment.

3.2.16 History of active TB (*Bacillus Tuberculosis*).

3.2.17 Active or chronic infection requiring systemic therapy.

3.2.18 Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study therapy. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI.

3.2.19 Active seizure disorder uncontrolled by medication.

3.2.20 Synchronous colon cancer.

3.2.21 Other invasive malignancy within 5 years. Exceptions are colonic polyps, non-melanoma skin cancer, or carcinoma-*in-situ* of the cervix.

3.2.22 Antineoplastic therapy (*e.g.,* chemotherapy or targeted therapy) for other invasive malignancy within 5 years (For the purposes of this study hormonal therapy is not considered chemotherapy).

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status,
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster,
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s)record,
- Includes the IRB number of the IRB providing approval in the FDA Form 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the FDA Form 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal-wide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization,
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-11030, and protocol number 10410,
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU)

4.2.2 Protocol Specific Requirements For 10410 Site Registration

- Site Initiation Teleconference
- Sites must be credentialed for NRG-GI002 in order to administer pelvic radiation therapy to patients enrolled in this trial.
- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review

and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.
.

- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their FDA Form 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.3.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

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.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

All specimen collections on this study are mandatory.

Time Point	Specimen	Send Specimens To:
Day 8		
• Prior to IPdR dose; and then after IPdR dose at • 30 min • 60 min • 120 min • 240 min	• 10 mL blood in sodium heparin tube, processed for plasma	ETCTN Biorepository
	• 5 mL blood in EDTA tube (only prior to IPdR dose)	Collins Laboratory
Day 21		
1-2 hours after IPdR dose	• 10 mL blood in sodium heparin tube, processed for plasma	ETCTN Biorepository
	• 5 mL blood in EDTA tube	Collins Laboratory
Day 35		
1-2 hours of after IPdR dose	• 10 mL blood in sodium heparin tube, processed for plasma	ETCTN Biorepository
	• 5 mL blood in EDTA tube	Collins Laboratory
8-12 weeks following completion of study treatment (Surgical Resection)		
	• Snap-frozen surgical resection specimen[1]	ETCTN Biorepository
[1]A copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave.		

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Procurement Kits

Kits for the collection and shipment of frozen specimens to the ETCTN Biorepository can be

ordered online via the Kit Management system:
(https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Specimens submitted frozen [Surgical resection specimen, plasma] can be collected on any day but must be stored frozen and shipped to the ETCTN Biorepository on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -90°C or colder freezer.

- Fresh blood specimens [blood in EDTA] may be collected and shipped to Dr. Collins' laboratory Monday through Thursday.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include

the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s), and the diagnostic pathology report must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and collection time (to be added by hand)

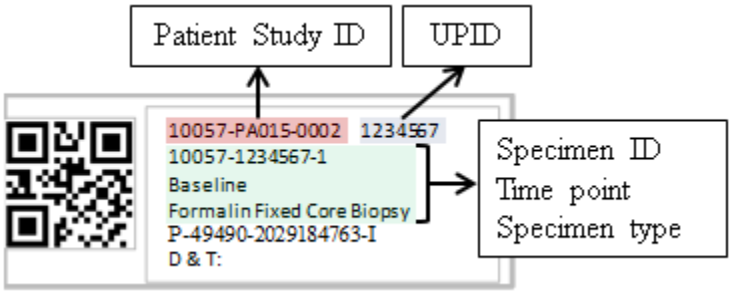
5.3.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, Frozen tissue *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (if applicable)
- Collection date (to be added by hand)

5.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date and collection time on each label. After collection, store labeled specimens as described in Section 5.3.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates (such as collection date), and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 Collection of Snap-Frozen Resection Tissue

1. Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from resection.
2. Label a 2-mL cryovial(s) according to instructions in Section 5.3.2.
3. Using clean forceps place the tissue in a pre-chilled cryovial and freeze the vial(s) in either vapor phase liquid nitrogen, on dry ice, or by immediate placement in a -70 to -90°C or colder freezer. Keep frozen until shipment to the ETCTN Biorepository.

5.4.2 Blood Collection

5.4.2.1 Collection of Blood in Sodium Heparin Tubes for Plasma Processing

1. Label sodium heparin tube(s) according to the instructions in Section 5.3.2.
2. Collect 10 mL of whole blood in sodium heparin tube(s).
3. Process plasma by centrifuging for 10 minutes at 1,200 × g at room temperature.
4. Using a clean transfer pipette, transfer 1 mL of plasma into each of the labeled cryovials (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.3.2). Avoid picking up the blood cells when aliquoting by keeping the pipet above the cell layers and leaving a small amount of plasma in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of plasma specimens should be completed within 1 hour of centrifugation.
5. Store plasma cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.

5.4.2.2 Collection of Whole Blood in EDTA Tubes

1. Label EDTA tubes according to the instructions in Section 5.3.2.
2. Collect 5 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
4. If blood cannot be shipped on the day of collection (*e.g.,* a late scheduled collection), then refrigerate until shipment.

5.5 Shipping Specimens from Clinical Site to the ETCTN Biorepository

5.5.1 Specimen Shipping Instructions

Frozen specimens may be shipped on Monday through Thursday.

5.5.1.1 Shipping Frozen Specimens in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type

and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2 Shipping Address

Ship to the address below. Frozen specimens may be shipped on Monday through Thursday. Do not ship specimens the day before a holiday.

ETCTN Biorepository
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for all costs for shipments to the ETCTN Biorepository.

5.5.3 Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository

Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

5.6 Shipping Specimens from Clinical Sites to Other Laboratories

5.6.1 Shipping Blood for IUdR Incorporation to the Collins Laboratory

Fresh blood specimens should be collected and shipped Monday through Thursday.

5.6.1.1 Shipping Ambient Blood in Your Own Container

Fresh blood for 10410 must be shipped using institutional supplies. Packaging guidelines for sending blood are provided below.

1. Before packaging specimens, verify that the collection tube is labeled according to instructions in section 5.3.2.
2. Place the blood collection tube into a zip-lock bag.
3. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months, please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.1.2 Shipping Address

Kimberly Hill/Larry Anderson
FNLCR
OAD/DTP
150 Boyles Street; Building 1036/1047
Frederick, MD 21702

5.6.1.3 Contact Information for Assistance

Larry Anderson: Larry.anderson@nih.gov

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	IUdR Incorporation	IUdR-DNA cellular incorporation CLIA: N	Integrated To correlate %IUdR incorporation in tumor cells with IPdR PK and clinical tumor response	Surgical resection (snap frozen)	At 8-12 weeks following completion of therapy	M	Clinical Pharmacology Branch at Developmental Therapeutics Program (DTP), DCTD, National Cancer Institute (NCI) Jerry Collins, Ph.D. collinsje@mail.nih.gov
Blood-based Biomarkers							
1	IPdR pharmacokinetics Plasma levels of IPdR, IUdR, IP and IU	PK CLIA: N	Integrated Plasma levels of IPdR, IUdR, IP and IU	Plasma (Blood collected in sodium heparin tubes)	Day 8 – Prior to the PO IPdR dose and then at 30, 60, 120, and 240 minutes following PO IPdR dose Days 21 and 35 – 1-2 hrs. following PO IPdR dose (at the time of sampling for %IUdR incorporation in circulating granulocytes)	M	Clinical Pharmacology Branch at Developmental Therapeutics Program (DTP), DCTD, National Cancer Institute (NCI) Jerry Collins, Ph.D. collinsje@mail.nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	IUdR incorporation (granulocytes)	IUdR-DNA cellular incorporation CLIA: N	Integrated To correlate IUdR incorporation in granulocytes with peripheral blood counts, other systemic toxicities (CTCAE v5.0), and plasma PK obtained at the same time points.	Blood (EDTA)	Day 8 – Prior to the PO IPdR dose Days 21 and 35 – 1-2 hrs. following PO IPdR dose	M	Clinical Pharmacology Branch at Developmental Therapeutics Program (DTP), DCTD, National Cancer Institute (NCI) Jerry Collins, Ph.D. collinsje@mail.nih.gov
3	Capecitabine pharmacokinetics Plasma levels of capecitabine, 5'-DFUR, FBAL, and 5-FU	PK CLIA: N	Exploratory Plasma levels of capecitabine, 5'-DFUR, FBAL, and 5-FU	Plasma (collected as part of the IPdR PK biomarker)	Day 8 – Prior to the PO IPdR dose and then at 30, 60, 120, and 240 minutes following PO IPdR dose Days 21 and 35 – 1-2 hrs. following PO IPdR dose (at the time of sampling for %IUdR incorporation in circulating granulocytes)	M	Clinical Pharmacology Branch at Developmental Therapeutics Program (DTP), DCTD, National Cancer Institute (NCI) Jerry Collins, Ph.D. collinsje@mail.nih.gov

5.8 Integrated Correlative Studies

5.8.1 IUdR Incorporation in Surgical Resection Specimen

5.8.1.1 Specimen(s) Receipt and Processing at the ETCTN Biorepository

At the time of resection, the surgical specimen will be snap-frozen by individual sites according to instruction in Section 5.4.1 and sent to the ETCTN Biorepository as soon as possible after surgical resection is performed. The ETCTN Biorepository will accession, barcode, and weigh tissue upon receipt. Frozen tissue will be stored in a liquid nitrogen vapor phase freezer until the end of the study, when they are shipped to Dr. Collins' laboratory in dry ice via overnight shipping. Do not allow specimens to thaw after freezing.

Prior to distribution to Dr. Collins' laboratory at the end of the study, the Biorepository will embed a piece of tissue in OCT media to section and stain for pathology QA review, including % tumor *vs.* stroma, % tumor *vs.* necrosis, and confirming concordance with the institutional diagnosis.

5.8.1.2 Site Performing Correlative Study

This study will be performed under the supervision of Dr. Jerry Collins in the Clinical Pharmacology Branch at Developmental Therapeutics Program (DTP), DCTD.

Actual shipment of specimens from the ETCTN Biorepository should be coordinated with the laboratory. Please contact Larry.anderson@nih.gov for any questions regarding the shipment of samples.

Shipping Information:

Kimberly Hill/Larry Anderson
FNLCR
OAD/DTP
150 Boyles Street; Building 1036/1047
Frederick, MD 21702

5.8.2 IPdR and Capecitabine PK

5.8.2.1 Specimen(s) Receipt and Processing at the ETCTN Biorepository

Upon receipt, the ETCTN Biorepository will accession, barcode, and bank frozen plasma aliquots in a -80°C freezer until distribution. Plasma samples for each patient should be batched and sent to Dr. Collins' laboratory as soon as the Day 35 sample is received at the Biorepository.

5.8.2.2 Site Performing Correlative Study

This study will be performed under the supervision of Dr. Jerry Collins in the Clinical Pharmacology Branch at DTP, DCTD.

Actual shipment of specimens from the ETCTN Biorepository should be coordinated with the laboratory. Please contact Larry.anderson@nih.gov for any questions regarding the shipment of samples.

Shipping Information:

Kimberly Hill/Larry Anderson
FNLCR
OAD/DTP
150 Boyles Street; Building 1036/1047
Frederick, MD 21702

5.8.3 IUdR incorporation in granulocytes

5.8.3.1 Specimen(s) Receipt and Processing at the Collins Laboratory

Upon receipt of fresh blood specimens in EDTA, Dr. Collins' laboratory will accession and barcode the samples prior to processing. Processing will be according to the methodology described in Section 2.5.4, including granulocyte isolation using a histopaque (Sigma Chemical Co., St. Louis, MO) 1077/1119 gradient.

5.8.3.2 Site Performing Correlative Study

This study will be performed under the supervision of Dr. Jerry Collins in the Clinical Pharmacology Branch at DTP, DCTD.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1.1 IPdR dose escalation schema

This is a phase 1 dose escalation study that consists of two parts, Part IA and Part IB. Part IA uses an accelerated titration design with a single patient cohort, and a 100% dose escalation between patient cohorts until a treatment related Grade 2 non-hematologic toxicity or grade 3 neutropenia or thrombocytopenia is observed. The accelerated titration design may reduce the number of patients potentially undertreated by receiving PO IPdR doses that are not expected to result in clinically relevant radiosensitization. After the completion of part 1A, the protocol will

be amended to incorporate the dose levels for part 1B. Part IB will commence when toxicity is encountered in Part IA. Cohorts of 3-6 patients will be entered per dose level until dose-limiting (DLT) is reached, and the MTD is defined. An IPdR dose of 2400 mg QD is the maximum allowed dose. Dose escalation between dose levels will be adjusted to accommodate the availability of 75mg and 600mg IPdR capsules.

Part IA:

An initial single patient dose escalation of twice daily PO IPdR × 38 days with concomitant capecitabine (825 mg/m^2/BID Monday morning through Friday evening on RT days) will be conducted in Part IA. Dosing will be based on the patient's assigned dose level. The starting dose is 75 mg BID (Dose 1) × 38 days (≅ 1/10th MTD in ferrets, as previously determined [Kinsella *et al.,* 2000]). A 100% dose escalation will be used until a treatment related Grade 2 non-hematologic toxicity or grade 3 neutropenia or thrombocytopenia is observed. Two additional patients will then be entered at this dose level. If a second patient of these 3 patients experiences a treatment related Grade 2 systemic toxicity (or if a single patient develops treatment related ≥ grade 3 toxicity), then a stop/switch rule is invoked for Part IA and Part IB of the dose escalation scheme commences. If not, the dose is incremented to the next level in Part IA (after each patient is evaluated for 4 weeks of follow up to assess acute toxicity).

Definitions of "Dose-limiting" and "Moderate" toxicities for Part IA (for exceptions see Section 6.2)

Grade 2 non-hematologic	Moderate
Grade 3 non-hematologic	DLT
Grade 4 non-hematologic	DLT
Grade 2 ANC and/or Plt	Moderate
Grade 3 ANC and/or Plt	Moderate
Grade 4 ANC and/or Plt	DLT

In part IA, if a patient develops:

- a DLT, the stop/switch rule is invoked, and part IB commences
- a "moderate" toxicity, two additional patients will be entered at this dose level, and if
  - one of these patients develops a DLT, the stop/switch rule is invoked, and part IB commences
  - one of these patients develops a "moderate" toxicity, the stop/switch rule is invoked, and part IB commences
  - neither of the two additional patients develops a DLT or "moderate" toxicity, part IA recommences at the next dose level

A patient will be considered unevaluable if they receive <67% of their total intended dose of any study treatment (IPdR, capecitabine, or RT) for non-protocol required reasons. Patient medication diaries and RT documentation will be reviewed as each patient comes off-study to determine the actual total doses of each study treatment they received. If a patient is deemed unevaluable by this definition, they will be replaced by a new patient to be treated at the same intended dose level.

Part IA dose escalation schema			
Dose Level	**Total radiation Gy (45 Gy primary field, 5.4 Gy boost @ 1.8 Gy/fraction/day)**	**Capecitabine (mg/m^2 BID) Monday am – Friday pm throughout RT**	**IPdR (mg BID) Administered throughout radiation**
1A	50.4	825 mg/m^2 BID	75 mg BID
2A	50.4	825 mg/m^2 BID	150 mg BID
3A	50.4	825 mg/m^2 BID	300 mg BID
4A	50.4	825 mg/m^2 BID	600 mg BID
5A	50.4	825 mg/m^2 BID	1,200 mg BID
BID – Twice Daily, RT – Radiation therapy			

Part IA is closed to further accrual.

Part IB:

Under Part IB of this protocol, cohorts of 3-6 patients will be entered per dose level. In Part IB, 3 patients will initially be accrued to a dose level. If 0 of 3 patients do not experience grade 3 non-hematopoietic or grade 4 hematopoietic/GI DLT, then dose escalation will proceed. If a DLT is observed in one of the first 3 patients in a dose level cohort, the cohort will be expanded to a maximum of 6 patients.

Part IB dose escalation schema			
Dose Level	**Total radiation Gy (45 Gy primary field, 5.4 Gy boost @1.8 Gy/fraction/day)**	**Capecitabine (mg/m^2 BID) Monday am – Friday pm throughout RT**	**IPdR (mg QD) Administered throughout radiation[1,2]**
1B	50.4	825 mg/m^2 BID	75mg QD
2B	50.4	825 mg/m^2 BID	150mg QD
3B	50.4	825 mg/m^2 BID	300mg QD
4B	50.4	825 mg/m^2 BID	600mg QD
5B	50.4	825 mg/m^2 BID	1200mg QD
6B	50.4	825 mg/m^2 BID	1800mg QD
7B	50.4	825 mg/m^2 BID	2400mg QD
QD – Once Daily, BID – Twice Daily, RT – Radiation therapy [1] The maximum allowed dose of IPdR is 2,400mg QD [2] Actual doses will be rounded to account for availability of only 75 mg and 600 mg IPdR capsules			

Patients will be assessed 4 weeks following completion of study treatment (Week 10 unless there were delays in therapy). This will be the final assessment for study-related toxicity. Patients will undergo surgical resection 8-12 weeks following completion of chemoRT (IPdR), and study-related response will be assessed at that time.

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Study Length**
IPdR	Take on an empty stomach, either 1 hour before or 2 hours after meals.	Dose as appropriate for the assigned dose level.	PO	QD[A]	38 days (6 weeks)
Capecitabine	Take within 30 minutes after a meal (breakfast and dinner).	825 mg/m^{2}[C]	PO	BID Monday morning through Friday evening on RT days [B,C]	
RT		1.8 Gy/fraction/day × 28 doses (50.4 Gy total dose)		5 doses per week until week 5 and 3 doses during Week 6[D]	
[A]On the days of radiation therapy, the daily dose of IPdR will be administered within 30 min - 2 hours prior to radiation.Patients may take dose at home if the timing allows. [B]Capecitabine will be taken Monday morning through Friday evening each week of RT. [C]Dosing will be with 150 mg and 500 mg tablets [D]RT will be given only Monday through Friday QD – Once Daily, BID – Twice Daily, PO – Oral, RT – Radiation therapy					

6.1.2 IPdR administration

- Method of delivery is by oral administration in capsule form BID × 38 days for Part IA and once daily for Part IB (Week 6).
- Dosing will be based on the patient's assigned dose level.
- The initial drug dose is 75 mg BID.
- The capsules will be taken on an empty stomach (*i.e.* either 1 hour before or 2 hours after meals).
- On the days of radiation therapy, the daily dose will be administered within 30 min - 2 hours prior to radiation and can be taken at home if timing allows.
- Assessment of compliance with treatment: Patients will be instructed to keep a medication log, recording the date, time and numbers of capsules of each dose (See Appendix D)

6.1.3 Capecitabine

6.1.3.1 Dose and Schedule

Capecitabine should be dosed at 825 mg/m^2 PO BID on days of radiation only. The usual radiation schedule will be Monday through Friday, and in that case, the first capecitabine dose of the week will be taken on Monday morning, and the last dose of the week will be taken on

Friday evening. Dosing will be with 150 mg and 500 mg tablets to achieve a dose as close as possible to 825 mg/m^2. Additional dose adjustments will be made as needed. At the discretion of the treating physician, the body surface area (BSA) may be capped at 2.20 – 2.25 for calculating capecitabine dosage (optional). Please refer to package insert for exact dose calculation details.

6.1.3.2 Guidance for Administration:

Capecitabine is to be taken roughly 12 hours apart at approximately the same times each day with about 200 ml of water within 30 minutes after a meal. Capecitabine tablets should be swallowed as whole and should not be crushed or cut. Capecitabine tablets should be stored at room temperature (15° to 30° C) in the container in which they are provided.

6.1.4 Radiation therapy

Radiation Therapy Schema:

The treatment is delivered in 2 phases, an initial phase to treating the entire PTV_4500 including the PTV_5040 volume to 45 Gy, followed by a boost phase, treating the PTV_5040 with an additional 5.4 Gy to a total of 50.4 Gy. The fraction size is 1.8 Gy for all phases.

<table>
<tr><th>Phase</th><th>Target</th><th>Dose (Gy)</th><th>Number of Fractions</th><th>Fraction Size</th><th>Rx Length</th><th>Rx Days</th></tr>
<tr><td>Initial</td><td>PTV_4500</td><td>45</td><td>25</td><td rowspan="3">1.8 Gy</td><td>5 weeks</td><td rowspan="3">Monday through Friday</td></tr>
<tr><td>Boost</td><td>PTV_5040</td><td>5.4</td><td>3</td><td rowspan="2">3 days</td></tr>
<tr><td>Total</td><td></td><td>50.4</td><td>28</td></tr>
</table>

6.1.4.1 Treatment technology

This protocol allows, but does not require, the use of Intensity Modulated Radiation Therapy (IMRT). This protocol requires treatment with photons with minimum nominal energy specification of 6 MV. IMRT is allowed and can be used either with static gantry or arcs (VMAT). Tomotherapy delivery is allowed.

6.1.4.2 Immobilization and simulation

<u>Immobilization</u>

Proper immobilization is important for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. A custom immobilization device (such as Alpha Cradle or Vac-Loc for supine patients and an Alpha Cradle with bowel displacement device for prone patients) is suggested to minimize set-up variability. Simulation may be done with the patient in the supine "arms up" position for patients with very thin body habitus or the prone

"arms up" position for patients of moderate or large body habitus.

Simulation imaging

CT Simulation is required, and the images must be acquired using a CT-simulator with a slice thickness ≤3 mm. Care should be taken to use the smallest possible FOV that contains the entire surface of the patient with a 512×512 image matrix. Oral CT contrast is strongly suggested. An anal marker at the verge is required. The CT simulation must be performed with the patient in the treatment position.

Typical CT scan limits are mid-femur inferiorly to include the L2 vertebral body superiorly. The CT scan needs to include the following structures in their entirety: Treatment volumes (PTVs), bladder, and femoral heads.

6.1.4.3 Definition of target volumes and margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

The volumes are to be defined by planning CT/MRI techniques as well as PET scans when clinically appropriate. While PET scans are not mandated as part of the protocol, for those patients who have PET scans available, the information may be used to aid in treatment planning. The inferior extent of palpable tumors should be determined by physical examination.

Examples of contoured patients (anorectal atlas) are available for review on the NRG Oncology website (https://www.nrgoncology.org/Resources/Contouring-Atlases). These examples are excellent resources for the contouring of normal structures as well as GTV, CTV, and PTV design, and their use is strongly encouraged.

Standard Name	**Description**	**Validation**
GTV_5040	GTV to receive 50.4 Gy	Required
PTV_5040	PTV to receive 50.4 Gy	Required
CTV_4500	CTV to receive 45 Gy	Required
PTV_4500	CTV to receive 45 Gy	Required

Detailed specification:

Gross tumor volume (GTV): This includes the primary tumor and any pelvic nodes felt involved grossly with metastatic disease. Assessment of the primary tumor and nodal disease may be made on the basis of endoscopy, CT, PET-CT, MRI, or transrectal ultrasonography. The entire rectal circumference at the level of the tumor should be included as GTV_5040.

Clinical target volume (CTV_4500): This includes the GTV and the following nodal groups: perirectal nodes; presacral nodes; internal iliac; and common iliac nodes below the L5-sacral junction.

Planning target volume 4500 (PTV_4500): This will provide a margin around the CTV_4500 to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV_4500 will consist of a symmetrical 7 mm expansion around the CTV_4500. In the event that a PTV_4500 extends outside of the skin surface, the clinician should manually trim the PTV_4500 contours to be 3 mm inside the outer skin (unless there is direct skin involvement).

The following are guidelines for generating the CTV_4500 and PTV_4500 and PTV_5040. The CTV_4500 can be formed from the following CTV sub-volumes:

- CTV_rectal (CTV_4500) = Rectal GTV +1.5 cm radially, +2.5 cm craniocaudally along the mucosal surface. The radial expansion can be shrunk to within the mesorectal fascia and off organs/sidewall if no clinical/radiographic evidence of an involved mesorectal fascia OR T4 disease.
- CTV_nodal (CTV_4500) = Nodal GTV + 1.5cm symmetrical expansion. The symmetric expansion can be shrunk to within the mesorectal fascia and off organs/sidewall if no clinical/radiographic evidence of an involved mesorectal fascia.
    - External iliac LNs are to be included in CTV_4500.
    - Inguinal LN basins will not be included in the CTV_4500 or CTV_5040 volume in low-lying rectal cancer except in patients with high likelihood of pathologic involvement by MRI or PET/CT imaging. A LN biopsy of inguinal LNs is not recommended.
- CTV_vessels = Uninvolved iliac vessels + 1.0 cm. This expansion can be trimmed off pelvic sidewall/bowel.
- CTV_presacral = the entire sacral hollow from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone.
- CTV_perirectal (CTV_4500) = The mesorectum and perirectal lymphatic CTV should be identified on cross-sectional imaging and is best seen on an MRI. If the fascia cannot be confidently visualized, it can be generated by utilizing anatomic landmarks:
    - Posterior Border: anterior border of the sacrum and gluteus maximus
    - Lateral Border: ileum, piriformis and obturator muscles
    - Anterior Border: should include the interface with the bladder, vagina, uterus or prostate
    - Inferior Border: the levators. The caudal extent of CTV_4500 is the pelvic floor/levators. If there is radiographic evidence of extension into the ischiorectal fossa, the CTV_4500 will extend to 2-3 mm beyond the levator muscles. For very

advanced cT4 tumors extending through the levators, a 2-cm margin up to bone is recommended.

- The PTV_4500 is generated by expanding all of the above structures by 0.7 cm symmetrically and unifying them into one 3-dimensional volume for planning purposes.
- The PTV_5040 is an expansion of the GTV_5040 by 3 cm and the presacrum, this volume should not extend beyond PTV_4500.

6.1.4.4 Definition of critical structures

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing, and use of underscores must be applied exactly as indicated.

Standard Name	**Description**	**Validation Required/Required when applicable/Optional**
Bladder	Bladder	Required
Femur_R	Right femur	Required
Femur_L	Left femur	Required
Bowel_Small	Small Bowel	Required

Notes from RTOG Anorectal Atlas for contouring of normal structures:

Small Bowel:
The small and large bowel are important structures to consider when planning treatment. To avoid unnecessary time spent contouring the entire abdominal contents, they only need to be contoured up to ~ 1 cm above the PTV. This, in turn, implies that absolute volume of bowel (in cc) is more important than relative volume (in %). Otherwise cases with good exclusion of small bowel from the pelvis (*e.g.,* with a belly board) will be unfairly penalized.

Femoral Heads:
The femoral head and neck should be avoidance structures. Only the femoral heads, not the neck should be drawn.

Large bowel constraint:
There is no large bowel constraint. However, "uninvolved colon" defined as part of the large bowel that lies outside of the CTVs (rectum and part of the rectosigmoid) should be contoured separately from the rectum.

6.1.4.5 Dose Prescription

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of fractions	Dose specification technique
PTV_4500	45	1.8	25	Covering 95% of PTV
PTV_5040	50.4	1.8	3	Covering 95% of PTV

6.1.4.6 Planning technique

A 3D conformal radiotherapy planning technique must be used. If not using IMRT, field edges, and MLC blocking must be conformal to the PTVs. The dose distributions must include corrections for tissue density heterogeneities. Regardless of planning technique, the dose prescription criteria specified in Section 6.1.4.7 on compliance criteria must be used.

3-D treatment planning guidelines for rectal cancer for this protocol are detailed in: http://econtour.org/training/rectal_cancer_module.pdf

6.1.4.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

VxGy (cc), VxGy (%), Vx%(cc), Vx%(%): Volume (cc or %) receiving Dose (Gy, or %)

Dvcc(Gy), Dvcc(%), Dv%(Gy), Dv%(%): Dose (Gy or %) to Volume (cc or % of total volume)

Dmin(Gy) or Dmin(%): Minimum dose is defined to a volume that is the total volume minus 0.03 cc

Dmax(Gy) or Dmax(%): Maximum dose is defined to a volume of 0.03 cc

Dmean(Gy) or Dmean(%): Mean dose in Gy or %

For Normalization purposes two treatment plans are generated, one for each phase of treatment (initial 45 Gy, and subsequent boost volume to 50.4 Gy), each plan normalized to a PTV covering isodose volume of 95% as described in the prescription section (Section 6.1.4.5), V95%= 100%. A combination (plan sum) is required to evaluate the dosimetric compliance criteria for critical structures.

Heterogeneities will be taken into account in the radiation dose calculation, in accordance with the guidelines provided on the IROC website: http://rpc.mdanderson.org/RPC/home.htm.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not

met.

6.1.4.8 Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_4500	D95% (%)	≥95	≥90
PTV_5040	D95% (%) D10(%) (%)	≥95 ≤110	≥90 ≤120
*Note: Percentiles are normalized to prescription doses of 45 Gy and 50.4 Gy respectively.			

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
Bowel_Small	D150cc(Gy)	≤15	≤16.5
	D120cc(Gy)	≤35	≤38.5
	D70cc(Gy)	≤40	≤44
	D35cc(Gy)	≤45	≤49.5
	Dmax(Gy)	≤50	≤55
Femur_L&Femur_R	D50%(Gy)	≤30	≤33
	D40%(Gy)	≤40	≤44
	D5%(Gy)	≤45	≤49.5
	Dmax(Gy)	≤50	≤55
Bladder	Dmean(Gy)	≤40	≤44
E-PTVs	D1cc(Gy)	≤49.5	≤54.5

E-PTVs include any non-PTV tissues.

Note: Constraints related to bowel and bladder are recommendations. Constraints will be scored but any Unacceptable Deviations will not affect the overall plan score. However, all femoral head constraints and the D0.03cc (Gy) for the Bowel_Small will be scored an Unacceptable Deviation if parameters are not met and will be counted in overall plan score.

6.1.4.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines. Only sites credentialed for NRG-GI002 can administer pelvic radiation therapy to patients enrolled in this trial. For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Typically, measured dose distributions will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

6.1.4.10 Daily Treatment Localization/IGRT

Daily IGRT localization is required for patients treated with IMRT. Either a daily orthogonal kV pair, or CBCT (or MVCT) is acceptable. The boost plan should be imaged with daily CBCT. Institutional guidelines should be followed for daily treatment localization and IGRT. For patients not treated with IMRT, patients should be imaged with an Orthogonal kV (2D) image pair or CBCT (or equivalent) prior to the first fraction, and weekly henceforth. IGRT credentialing is not required for this protocol.

Management of Radiation Dose to the Patient from IGRT

Due to concern about the estimated doses given from IGRT, efforts will be made to limit the imaging dose when IGRT is used. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (*e.g.* requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

6.2 Definition of Dose-Limiting Toxicity

Management and dose modifications associated with the above AEs are outlined in Section 7.

DLTs will be captured until 4 weeks after completion of IPdR therapy and will be graded according to the CTCAE v5.0. DLTs will be defined as clinically significant grade 3 or 4 toxicities possibly or probably related to study treatment.

- Grade 4 neutropenia (ANC < 500/mm^3)
- Grade 4 electrolyte toxicities
- ANC <1000/mm^3 with fever (temp >101 F) or infection
- Grade 4 thrombocytopenia: Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia.
- Patients who receive <67% of intended IPdR secondary to treatment related toxicities will also be considered as having a DLT

In addition, during chemoradiation, DLTs will also include AEs requiring interruptions of radiation for >5 consecutive scheduled fractions (and / or ≥9 total scheduled fractions) or for >10 consecutive scheduled doses of capecitabine (and / or ≥19 total scheduled doses of capecitabine). The following AEs will not be considered DLTs:

- Any grade of alopecia,
- Grade 3 arthralgia or myalgia,
- Brief (<1 week) grade 3 fatigue,
- Grade 3 fever,

- Grade 3 diarrhea or vomiting responding to supportive care
  - Grade 3 nausea, vomiting or diarrhea will be considered a DLT if it occurs for greater than 48 hours despite maximal medical support.
- Grade 3 radiation dermatitis,
- Grade 3 or 4 electrolyte abnormalities will not be considered DLTs if the electrolyte disorder can be corrected to grade 2 or less within 72 hours.

All patients who have received at least one dose of IPdR are evaluable for toxicities.

For dose escalation decisions, patients should have completed ≥80% of the planned chemoradiation doses unless the reason for discontinuation is an AE that qualifies for DLT.

Dose escalation will proceed within each cohort in Part IB according to the following scheme. DLT is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped.
1 out of 3	Enter 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT (*i.e.* 2 of 6 patients), then dose escalation is stopped, and this dose is declared the maximally administered dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

During the MTD dose finding portion, patients who are removed from study for reasons other than a DLT will be replaced.

6.3 Dose Expansion Cohorts:

For the expansion cohort, patients will continue to be monitored for occurrence of DLT. Three additional patients will be treated at the dose level below the dose associated with DLT to establish the MTD. The MTD is defined as the dose below which 2 or more of 3 to 6 patients experience DLT. The MTD will be deemed to be RP2D if ≥80% of the patients are able to receive ≥80% of the planned treatment doses. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.4 General Concomitant Medication and Supportive Care Guidelines

6.4.1 Hematopoietic growth factors

Hematopoietic growth factors are not permitted on this study.

6.4.2 Management of anemia

Transfusion is acceptable for improving the hemoglobin value to ≥10 gm/dL to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. Use of erythropoiesis-stimulating agents is prohibited.

6.4.3 Management of diarrhea

Diarrhea is a commonly occurring toxicity with therapy for rectal cancer. With combination chemoradiation, it is anticipated that diarrhea is likely to occur. Without appropriate treatment, diarrhea can be prolonged, severe, and lead to dehydration and other complications (See Appendix F for clinical management of diarrhea and Appendix G for patient instructions for diarrhea management).

Patients who have multiple loose bowel movements and any worsening of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, or eosinophilia should be promptly evaluated for changes in liver function (See Appendix G for sample patient instructions for diarrhea management).

Refer to the ASCO Recommended Guidelines for Treatment of Cancer Treatment-Induced Diarrhea for additional recommendations regarding diarrhea (Benson *et al.,* 2004).

Antidiarrheal medications:

All patients must be instructed to begin taking loperamide at the earliest sign of poorly formed or loose stools (≥ grade 1). Early intervention is important for patient safety.

Aggressive supportive care should be provided for patients with grade 4 ANC and ≥ grade 3 diarrhea until neutropenia and diarrhea resolve. See Appendix F for clinical management of diarrhea. Hospitalization for evaluation and management of grade 3 or grade 4 complicated diarrhea, as defined in Appendix F, is strongly recommended.

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

6.4.4 Management of nausea or vomiting

Grade 3 nausea and vomiting has been seen in early phase studies with capecitabine. Therefore, to optimize dose intensity and maintain quality of life, early initiation or prophylactic management with scheduled anti-emetic therapy (5HT-3 antagonists, metoclopramide, prochlorperazine) and/or lorazepam should be considered when patients begin treatment with

veliparib and capecitabine. In addition, management should include counseling regarding these toxicities and may include brief interruption of dosing or dose modification.

Investigators should also rely on standard clinical practice and guidelines for nausea management.

Antiemetic Therapy:

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) clinical practice guidelines.

6.4.5 Mucocutaneous and Dermatologic Toxicity

Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with capecitabine. Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction possibly attributable to capecitabine treatment.

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving capecitabine monotherapy in the metastatic setting. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. See Section 7.3 for details on capecitabine dose modification.

6.4.6 Prohibited Therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited:

- **Chemotherapy**
  Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited **prior to** resection of the primary rectal cancer.

- **Targeted therapy**
  Administration of targeted therapy for malignancy is prohibited **prior to** resection of the primary rectal cancer.

- **Radiation therapy**
  Administration of radiation therapy other than the radiation therapy specified in this

protocol is prohibited.

- **Live vaccines**
  Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.

- **Systemic glucocorticoids**
  Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment; however, patients should continue to be followed per protocol.

6.4.7 Drug/drug interactions

- **Phenytoin:** Increased phenytoin levels have also been reported in patients taking capecitabine concurrently with phenytoin and, therefore, need to be monitored.

Because there is a potential for interaction of IPdR with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Clinical Trial Wallet Card) should be provided to patients if available.

Interaction of IPdR with other drugs was not encountered in a previous trial of IPdR in patients with GI malignancies (Kinsella *et al.*, 2019). However, as stated above, the potential for such interactions and overlapping toxicities exists and will be closely monitored.

6.5 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue until study completion or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Patient decides to withdraw from the study

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.6 Surgery

Surgery must be performed within 8 to 12 weeks following the completion of study treatment.

6.7 Adjuvant Therapy

Per protocol, adjuvant therapy is not recommended but allowed at the investigator's discretion.

6.8 Duration of Follow-Up

Patients will be followed for 4 weeks after completion of study treatment, removal from study, or until death, whichever occurs first. Patients will be assessed at 4 weeks (approximately 30 days) following completion of IPdR (Week 10 unless there were delays in therapy). This will be the final assessment for study-related toxicity. Patients will undergo surgical resection 8-12 weeks following completion of study treatment, and study-related response will be assessed at that time. Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 IPdR Treatment Management

IPdR dose modifications are as follows:

Table 5: Part IA IPdR dose levels

Dose Level	IPdR Dose
1A (starting dose, Part IA)	75 mg PO BID
2A	150 mg PO BID
3A	300 mg PO BID
4A	600 mg PO BID
5A	1200 mg PO BID

Table 6: Part IB IPdR dose levels

Dose Level	IPdR Dose[1,2]
1B (starting dose, Part IB)	75mg QD
2B	150mg QD
3B	225mg QD
4B	300mg QD
5B	See Part IB dose escalation schema, Section 6.1.1
[1] The maximum allowed IPdR dose is 2400 mg QD. [2] Actual doses will be rounded to account for availability of only 75 mg and 600 mg IPdR capsules.	

7.2 RT Treatment management

Delays in radiation therapy occur for a variety of reasons (*e.g.* holidays, equipment issues, weather, *etc.*). Treatment interruptions of radiation therapy are discouraged but may be necessitated by acute complications. The reason for and duration of any such interruption must be documented. **A minimum of 4 daily radiation therapy treatments are required in any given week.** Any missed radiation treatments will be made up at the end of the treatment schedule such that the total number of delivered 1.8 Gy fractions remains 28.

During this study, if chemotherapy is held, radiation therapy will continue. If radiation is held, capecitabine will also be held; however, treatment with IPdR will continue unless otherwise contraindicated. Radiation may be held for grade 3 dermatitis radiation, grade 4 neutropenia, or other radiation-associated toxicity > grade 3 by CTCAE v5.0 at the discretion of the treating radiation oncologist. Radiation should be restarted subsequent to recovery at the discretion of the radiation oncologist consistent with standard practice.

7.2.1 Management of capecitabine for delay in radiation therapy

Capecitabine is administered BID on each day that the patient receives radiation treatment. If radiation therapy is held, no capecitabine is administered on that day. If the patient has taken the

AM capecitabine dose prior to arrival for radiation therapy, that is allowed, and the PM dose would be held. The patient should resume the AM capecitabine dose on the morning of the next scheduled radiation therapy appointment.

The duration of radiation therapy will be extended so that the total number of delivered fractions is 28 (Section 6.1). The patient should receive a minimum of 56 doses of capecitabine (BID on each day of radiation therapy and additional doses if an AM dose was taken prior to cancellation of radiation therapy for a given day).

7.2.2 Management of IPdR for delay in radiation therapy

IPdR is administered either once daily or twice daily, 7 days a week, beginning with the first dose of capecitabine on Day 1. IPdR must be taken 7 days/week for the duration of radiation therapy (*i.e.* to be discontinued only following the final dose of radiation therapy). If radiation therapy is held, IPdR continues unless criteria for dose adjustment is met per Section 6.2. IPdR either once daily or twice daily, 7 days a week, will continue through the last dose of radiation therapy. Patients may receive up to 5 additional days (10 doses) of IPdR to accommodate delays in radiation therapy.

7.3 IPdR and Capecitabine treatment management

Capecitabine and IPdR dose modifications are detailed in Table 7 and Table 8.

Additionally, the following dose modification instructions must be followed:

- All dose modifications should be based on the AE requiring the greatest dose modification.
- If RT is not administered (holiday, weekend, RT related toxicity, *etc.*), capecitabine is held; however, IPdR and RT continue per protocol unless otherwise contraindicated.
- If capecitabine and/or IPdR are held or discontinued, RT continues per protocol unless otherwise contraindicated.
- Capecitabine doses that have been reduced may not be escalated.
- IPdR doses that have been reduced may not be escalated.

Table 7: Capecitabine and IPdR dose levels

	Dose Level 0 ***Starting Dose*** **(mg/m2)**	**Dose Level -1 (mg/m2)**	**Dose Level -2 (mg/m2)**	**Dose Level -3**
Capecitabine	825 (BID) *on days when RT is given*	620 (BID) *on days when RT is given*	465 (BID) *on days when RT is given*	Discontinue
	Dose Level 0 ***Starting Dose***	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**

	Dose Level 0 ***Starting Dose*** **(mg/m2)**	**Dose Level -1 (mg/m2)**	**Dose Level -2 (mg/m2)**	**Dose Level -3**
IPdR	Part IA: Assigned dose level Part IB: see Table 6	Decrease one dose level (minimum dose is 75 mg QD; subjects requiring further dose reduction must have IPdR discontinued) See Tables 5 and 6 for Parts IA and IB dose levels	Decrease one dose level (minimum dose is 75 mg QD; subjects requiring further dose reduction must have IPdR discontinued) See Tables 5 and 6 for Parts IA and IB dose levels	Decrease one dose level (minimum dose is 75 mg QD; subjects requiring further dose reduction must have IPdR discontinued) See Tables 5 and 6 for Parts IA and IB dose levels

Table 8: Treatment management for capecitabine and IPdR

Important table instructions:

- **Hold capecitabine and IPdR doses until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, study therapy must be discontinued.
- All modifications in dose levels **apply to both capecitabine and IPdR unless otherwise noted.**

CTCAE v5.0 Adverse Event/Grade	**Modifications for AEs that REQUIRED DELAY IN TREATMENT**
Neutrophil count decreased: Grade 2 (1000-1199/mm^3), 3, and 4	Hold capecitabine until ≥1200/mm^3. If recovery takes: 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Hold until ≥75,000/mm^3. If recovery takes: 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	Hold until ≥75,000/mm^3. ↓ one dose level

Important table instructions: • **Hold capecitabine and IPdR doses until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, study therapy must be discontinued. • All modifications in dose levels **apply to both capecitabine and IPdR unless otherwise noted.**	
CTCAE v5.0 **Adverse Event/Grade**	**Modifications for AEs that REQUIRED DELAY IN TREATMENT**
GI : **Diarrhea** (despite optimal antidiarrheal management) Grades 2, 3	**Treatment must be held for grades 2 and 3 diarrhea to avoid severe complications.** 1st occurrence – ↓ one dose level 2nd occurrence –↓ one dose level 3rd occurrence – Discontinue
Grade 4	Discontinue
Mucositis - oral Grade 2	Maintain dose or ↓ capecitabine one dose level
Grade 3	↓ capecitabine one dose level
Grade 4	Discontinue capecitabine
Vomiting (despite antiemetics) Grades 2, 3	Hold and delay until ≤ grade 1, then ↓ one dose level
Grade 4	↓ one dose level
Investigations (hepatic): **Bilirubin, AST, alk phos** Grades 2, 3	Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤ grade 1; then ↓ **one dose level**
Grade 4	Discontinue chemotherapy
Febrile neutropenia: Grade 3	Hold until clinical resolution, then ↓ one dose level
Grade 4	Discontinue chemotherapy
Infection: Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	↓ one dose level or discontinue
Nervous system disorders: **Seizure** Grades 1, 2, 3, 4	Any event of seizure, regardless of grade or attribution, requires discontinuation of IPdR and discussion with the PI regarding the decision to resume treatment.

Important table instructions: • **Hold capecitabine and IPdR doses until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, study therapy must be discontinued. • All modifications in dose levels **apply to both capecitabine and IPdR unless otherwise noted.**	
CTCAE v5.0 Adverse Event/Grade	**Modifications for AEs that REQUIRED DELAY IN TREATMENT**
Skin and subcutaneous tissue disorders: **Palmer-planter erythrodysesthesia syndrome** Grades 2, 3	1st occurrence – ↓ capecitabine one dose level 2nd occurrence – ↓ capecitabine one additional dose level 3rd occurrence – discontinue capecitabine
Other clinically significant AEs:* Grade 2	Maintain dose or ↓ attributable agent one dose level
Grade 3	↓ attributable agent one dose level
Grade 4	Discontinue attributable agent
* Determination of "clinically significant" AEs is at the discretion of the PI	

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent

8.1.1 IPdR (NSC 726188)

Chemical Name: 5-iodo-2-pyrimidinone-2′-deoxyribose

Classification: Pyrimidinone nucleoside analog

Molecular Formula: $C_9H_{11}IN_2O_4$ **M.W.:** 338

Mode of Action:

Oral pro-drug hepatically converted by aldehyde oxidase to IUdR, for IUdR-mediated radio-sensitization.

Description:

IPdR drug substance is a light-yellow powder.

How Supplied:

IPdR is supplied by the DCTD, NCI and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI as 75 mg and 600 mg capsules.

- The 600 mg capsules are dark green, opaque, hard gelatin capsules, size 0 and contain the inactive ingredients: microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Capsules are packaged in 60 cc white, high-density polyethylene (HDPE) bottles with induction seals and white child-resistant polypropylene plastic caps. Each bottle contains 30 capsules with a polystyrene coil and a silica gel desiccant.
- The 75 mg capsules are white, opaque, hard gelatin capsules, size 1 and contain the inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. Capsules are packaged in 60 cc white, high-density polyethylene (HDPE) bottles with induction seals and white child-resistant polypropylene plastic caps. Each bottle contains 30 capsules with a polystyrene coil and a silica gel desiccant.

Storage:

Store bottles refrigerated at 2°-8°C in the original manufacturer's container. Do not re-package capsules or remove the desiccant.

If a storage temperature excursion is identified, promptly return IPdR capsules to 2°-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability:

Shelf life stability testing of the intact bottles is on-going.

Route and Method of Administration:

Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after meals.

Availability

IPdR is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol

number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Subjects must be enrolled prior to submission of a Clinical Drug Request via the PMB Online Agent Order Processing (OAOP) application. No starter supplies of IPdR are available.

Submit agent requests through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Capecitabine

Product description: Capecitabine is commercially available as 150 mg or 500 mg tablets. Capecitabine tablets should be stored at room temperature (15° to 30°C) in the container in which they are provided. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC. Capecitabine 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: Capecitabine is an oral medication

Route of administration: Capecitabine should be taken by mouth twice daily on days of radiation approximately 12 hours apart, within 30 minutes of a meal with about 200 ml of water

Agent Ordering: Capecitabine is commercially available

Please refer to Capecitabine FDA package insert for complete product information

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a phase 1 study using an accelerated titration design according to Simon et al. (Simon *et al.,* 1997). A 100% dose increment will be used in Part IA (single-patient cohorts), and a more conservative dose increment (dose increment adjusted to accommodate availability of 75mg and 600mg IPdR capsules) will be used in Part IB (3+3 cohort). The doses of RT and capecitabine will be identical in Part IA and Part IB. Part IA and Part IB are designed with a stopping rule rather than a pre-specified statistical model (Le Tourneau *et al.,* 2009). As a phase 1 study, the primary objective is to determine the MTD and document the toxicities of once daily PO IPdR when administered with capecitabine (825 mg/m^2 BID) and RT (50.4 Gy in 28 fractions).

DLT in Part IB will be reached when each of at least two of six patients enrolled at a dose level experience:

- any two grade 3 treatment-related non-hematologic toxicities, OR
- any one grade 4 treatment-related hematologic and/or GI toxicity.

Three additional patients will be treated at the dose level below the dose associated with DLT to establish the MTD. The MTD is defined as the dose below which 2 or more of 6 patients experience DLT attributable to IPdR.

The total of six patients treated at the MTD will suffice to recognize common toxicities; common toxicities at MTD (those occurring in 30% of patients to be treated at the MTD) will rarely be

unobserved ($p=0.117=0.7^6$) and very common toxicities (those occurring in 50% of patients) will almost never be missed ($p=0.016=.5^6$).

9.2 Sample Size/Accrual Rate

Planned sample size: 10-30 patients

As this is a phase 1 study, the sample size will be determined by the number of patients required to establish the MTD of IPdR given with capecitabine and RT. The statistical power of the correlative analyses with samples sizes of up to 30 patients is presented in Section 9.4.1.

Estimated patient accrual rate:

- Part IA: The accelerated titration design with single-patient cohorts will allow for an estimated patient accrual rate of 1 patient every 3 months.
- Part IB: Up to 3 patients at a time may be treated at a given dose level, allowing for an estimated patient accrual rate of 2-3 patients every 3 months.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	3	3	0	0	**6**
White	5	5	3	3	**16**
More Than One Race	2	2	1	1	**6**
Total	**11**	**11**	**4**	**4**	**30**

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9.3 Stratification Factors

N/A

9.4 Analysis of Secondary Endpoints

9.4.1 Correlative and exploratory biomarker analyses

Pre- to post-treatment changes in tissue biomarker levels measured on continuous and binary scales will be assessed using Wilcoxon signed rank or McNemar's tests, respectively (two-sided; α=0.05). Associations between therapeutic response and baseline biomarker values or temporal changes in biomarkers will be explored using Fisher's exact tests or Wilcoxon rank sum tests. For the correlations between %IUdR-DNA incorporation and plasma PK, a two-sided Fisher's z-test with significance level of 0.05 and power of 80% will be used and the study will reject the null hypothesis (lack of correlation or r_0=0) if we observe a correlation with r ranging from 0.79 for N=10 subjects to 0.49 for N=30 subjects. For the correlation of %IUdR DNA incorporation in circulating granulocytes and peripheral blood counts and toxicities, assuming the target prevalence of grade 3/4 toxicity of 30%, the study will have a power of 80% with significance level of 0.05 on a two-sample means test to rule out the null hypothesis (equal means in groups with/ without grade 3/4 toxicity, m_0=m_1) if the observed mean %IUdR-DNA incorporation for patients with grade 3/4 toxicity is m_1=3.3 times the mean m_0 in the other group for N=10 enrolled subjects, and m_1=2.1 times the mean m_0 for N=30.

9.4.2 Determination of the pCR rate of IPdR + capecitabine + RT at the MTD

In rectal cancer, the absence of viable tumor cells in the resection specimen (primary tumor mass, surrounding tissue and lymph nodes, T0 N0 M0) at the time of surgery, termed pathologic complete response (pCR) (Ryan *et al.,* 2005; Martin *et al.,* 2012). pCR determination will be made by the pathologist at the treating institution.

9.4.3 Determination of the Neoadjuvant Rectal Score

NAR is calculated based on the clinical T stage (cT), pathological T (pT) and pN stages as (Valentini *et al.,* 2011; George *et al.,* 2015):

$$NAR = [5pN- 3 (cT- pT) + 12]^2 / 9.61$$

9.5 Analysis of Exploratory Endpoints

9.5.1 To explore the relationship between extent of exposure to RT and the incidence and severity of adverse events

9.5.2 To explore the interactions of capecitabine, IPdR and their metabolites

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

10.1.1 CAEPR for IPdR (NSC 726188)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For IPdR (NSC 726188)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 1.2, April 12, 2019[1]

Adverse Events with Possible Relationship to IPdR (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
A Phase 1 safety study of single dose IPdR in 10 subjects resulted in no treatment-related adverse events.[2, 3]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]We expect the safety profile for oral IPdR to vary somewhat from the safety profile of iododeoxyuridine (IUdR), administered via continuous intravenous infusion in conjunction with localized radiation. Since oral IPdR is converted in the body to IUdR, the side effects of oral IPdR therefore may be similar to those adverse events observed in clinical trials of intravenous IUdR. The adverse events observed in IUdR clinical trials include: acute bowel obstruction, acute gastrointestinal hemorrhage, alanine aminotransferase increased, alkaline phosphatase

increased, anemia, aspartate aminotransferase, blood bilirubin increased, diarrhea, nausea, neutrophil count decreased, platelet count decreased, and weight loss.

[3]One early phase 1 single-dose safety clinical trial of IPdR (5-iodo-2-pyrimidinone-2'-deoxyribose) was conducted that treated 10 subjects resulting in no toxicities associated with IPdR. The safety profile may be revised during and after clinical trials are conducted using repeated dosing.

There is minimal (i.e., 10 subjects in a single-dose study) human data for IPdR to date, however no adverse events were noted in the study. The following toxicities have been observed during pre-clinical animal studies with IPdR:

Ferrets Only
Gastrointestinal disorders - Diarrhea; Nausea; Vomiting
HEPATOBILIARY DISORDERS - Increased liver weights
INVESTIGATIONS - Alkaline phosphatase increased
Metabolism and nutrition disorders - Anorexia
Nervous system disorders - Decreased motor activity
RENAL AND URINARY DISORDERS - Decreased kidney weights
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Decreased uterus weights
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bradypnea

Monkeys Only
Nervous system disorders - Lethargy

Rats Only
Blood and lymphatic system disorders - Anemia; Bone marrow (hyperplasia)
Investigations - Decrease alkaline phosphatase; Decreased hematocrit (Hct); Decrease in serum globulin; Decrease in total protein; Decreased RBC; Increased percentage of reticulocytes; Lobular atrophy in mandibular salivary glands; Lymphocyte count decreased

Ferrets, Rats, and Mice (events seen in all three species)
GASTROINTESTINAL DISORDERS - Acute bowel obstruction; Acute GI bleed
HEPATOBILIARY DISORDERS - Increased hepatic cytoplasmic vacuolization
Investigations - Alanine aminotransferase increased; Aspartate aminotransferase increased; Weight loss

Note: IPdR in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 Adverse Event List for Capecitabine

- Gastrointestinal Disorders: Diarrhea, nausea, stomatitis, vomiting, abdominal pain, constipation, dyspepsia, elevated liver function tests

- Skin and Subcutaneous Tissue Disorders: Hand-foot syndrome, alopecia, rash, erythema, skin discoloration

- General Disorders: Fatigue, Pyrexia, asthenia, lethargy, anorexia

- Nervous System Disorders: Dizziness, headache, dysgeusia

- Blood and Lymphatic Disorders: Anemia, thrombocytopenia and neutropenia

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Include the following (highlighted) paragraphs about pre-treatment AEs only if the study requires reporting of pre-treatment AEs. Pre-existing medical conditions are not considered adverse events and therefore should not be reported on an Adverse Event form.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS

using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred less than 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in

future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and X-rays must be done $\leq$4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to

initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 10 (4 wks following chemoRT) End of study for toxicity assessment	Wk 14-18 (8-12 wks following chemoRT) End of study for response assessment
IPdR		A	A	A	A	A	A		
Capecitabine		B	B	B	B	B	B		
Radiation therapy		C	C	C	C	C	C		
Surgical resection									X
mFOLFOX6 × 8 cycles	X								
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Performance status[a]	X	X				X		X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Carcinoembryonic Antigen (CEA)	X							X	X
Comprehensive Chemistry Panel[b]	X	X	X	X	X	X	X	X	X
EKG (as indicated)	X								
Blood draws for PK and IUdR incorporation in granulocyte assays (mandatory)			X[c,d]	X[c,d]		X[c,d]			
Adverse event evaluation		X	X	X	X	X	X	X	
Radiologic evaluation	X								X[e]
Digital rectal exam and proctoscopic or sigmoidoscopic exam									X[e]
Pregnancy test[f]	X								

A: IPdR: Dose as assigned; PO QD administered throughout radiation (38 days, 6 weeks)
B: Capecitabine: 825 mg/m^2 PO BID on days of radiation therapy (taken Monday morning through Friday evening each week of RT)
C: Radiation therapy: 1.8 Gy/day × 28 doses (50.4 Gy total dose), M-F Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-38
a: Performance status evaluations are to be conducted every 4 weeks.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c: 10 mL Blood for PK studies in sodium heparin tubes will be drawn on Day 8, prior to IPdR dose; and then after IPdR dose at 30 min, 60 min, 120 min and 240 min. On Day 21 and Day 35, blood will be drawn at 1-2 hours after the IPdR dose.
d: 5 mL blood for measuring IUdR incorporation in granulocytes will be drawn in EDTA tubes prior to IPdR dose on Day 8, and at 1-2 hours after the IPdR dose on Day 21 and Day 35.
e: Scans, digital rectal exam, and proctoscopic or sigmoidoscopic exam will be obtained at 6-10 weeks following completion of therapy (pre-operatively within 2 weeks of surgery)
f: Pregnancy test for women of childbearing potential.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of this drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

12.1 Antitumor Effect – Solid Tumors

Disease response in this study will be measured by achievement of pathologic complete response at the time of surgical resection and determination of the NAR score. The NAR score requires determination of clinical complete response by digital rectal examination and either proctoscopic or sigmoidoscopic examination. Radiologic assessment of response is not used in this study, except to confirm that no metastatic disease has developed after chemoradiotherapy (assessment performed within 2 weeks of surgical resection).

12.1.1 Clinical Complete Response (CCR)

12.1.1.1 Timing of assessments

For the purposes of this study, patients must have a formal perioperative assessment documenting clinical response of the primary rectal tumor via digital rectal exam (DRE) ***and*** proctoscopic or sigmoidoscopic exam. DRE and proctoscopic or sigmoidoscopic exam may be done immediately before surgery.

12.1.1.2 Definition of CCR

No visible or palpable rectal tumor on direct examination. Nodes are not included in this definition.

12.1.2 Pathologic complete response (pCR)

In rectal cancer, the absence of viable tumor cells in the resection specimen (primary tumor mass, surrounding tissue and lymph nodes, T0 N0 M0) at the time of surgery, termed pathologic complete response (pCR) (Ryan *et al.,* 2005; Martin *et al.,* 2012). pCR determination will be made by the pathologist at the treating institution.

12.1.3 Neoadjuvant Rectal Score (NAR)

NAR is calculated based on the clinical T stage (cT), pathological T (pT) and pN stages as (Valentini *et al.,* 2011, George *et al.,* 2015):

$$NAR = [5pN- 3 (cT- pT) + 12]^2 / 9.61$$

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
- Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
- Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once

every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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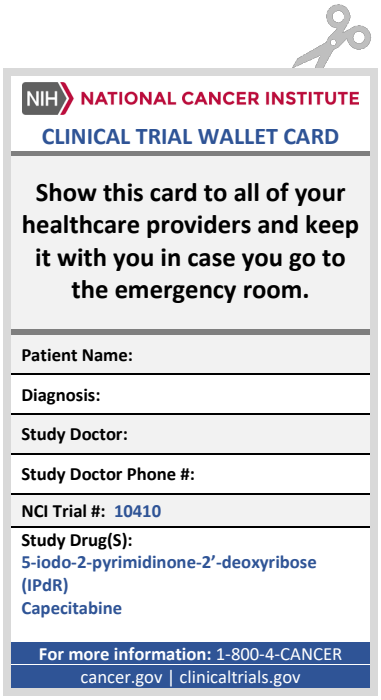
APPENDIX C PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10410

Study Drug(S):
5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR)
Capecitabine

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D PATIENT MEDICATION DIARY

CTEP-assigned Protocol # 10410
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – IPdR

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

Patient Name: _____(*initials acceptable*) **Patient Study ID:** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for the study.
2. You will take your dose of IPdR at the same time, once a day each day, 7 days a week, until your radiation therapy is complete.

   ☐ ___75 mg capsule(s); (and) ☐ ___600 mg capsule(s)
   You should take IPdR on an empty stomach, either 1 hour before or 2 hours after meals.
   On Days 8, 21, and 35, you will receive instructions about the time you should take your IPdR, depending on the schedule of your radiation.
3. On the days of radiation therapy, the dose of IPdR should be taken within 30 min - 2 hours prior to radiation. You can take this at home as time allows.
4. Store IPdR capsules in the original bottle in the refrigerator. Record the date, the number of capsules you took, and when you took them.
5. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 4 hours of the scheduled time. If not within 4 hours, take your next dose at the regularly scheduled time.
6. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please remember to bring this diary (all pages) and your IPdR containers (even if they are empty) to each visit with your study team.

Day	Date	What time was dose taken?	# of Capsules taken		Comments
			75mg	600mg	
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
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11.					
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28.					

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for the study.
2. You will take your dose of IPdR at the same time, once a day each day, 7 days a week, until your radiation therapy is complete.

   ☐ ___75 mg capsule(s); (and) ☐ ___600 mg capsule(s)
   You should take IPdR on an empty stomach, either 1 hour before or 2 hours after meals.
   On Days 8, 21, and 35, you will receive instructions about the time you should take your IPdR, depending on the schedule of your radiation.
3. On the days of radiation therapy, the dose of IPdR should be taken within 30 min - 2 hours prior to radiation. You can take this at home as time allows.
4. Store IPdR capsules in the original bottle in the refrigerator. Record the date, the number of capsules you took, and when you took them.
5. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 4 hours of the scheduled time. If not within 4 hours, take your next dose at the regularly scheduled time.
6. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please remember to bring this diary (all pages) and your IPdR containers (even if they are empty) to each visit with your study team.

Day	Date	What time was dose taken?	# of Capsules taken		Comments
			75mg	600mg	
29.					
30.					
31.					
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35.					
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37.					
38.					

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 capsules taken during the study (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:

CTEP-assigned Protocol # 10410
Local Protocol # TBD

PATIENT'S MEDICATION DIARY – Capecitabine

Today's date: _____ **Agent: Capecitabine** **Dose:**_____
Patient Name: _____(*initials acceptable)* **Patient Study ID:** _____

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for the study.
2. You will take your dose of capecitabine at the same time twice a day, about 12 hours apart, on Monday morning through Friday evening each week during the time you receive radiation therapy.
   ☐ ___150 mg tablets and ☐ ___500 mg tablets
   You should take capecitabine within 30 minutes after eating breakfast and dinner.
3. Store capecitabine tablets in the original bottle at room temperature. Record the date, the number of tablets you took, and when you took them.
4. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 4 hours of the scheduled time. You should not take the missed dose if it is within 8 hours of your next scheduled dose. Take your next dose at the regularly scheduled time.
5. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
6. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please remember to bring this diary (all pages) and your capecitabine containers (even if they are empty) to each visit with your study team.

Day	Date	What time was dose taken?		# of tablets taken (morning)		# of tablets taken (evening)		Comments
		AM	PM	150 mg	500 mg	150 mg	500 mg	
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INSTRUCTIONS TO THE PATIENT:

1. Complete one form for the study.
2. You will take your dose of capecitabine at the same time twice a day, about 12 hours apart, on Monday morning through Friday evening each week during the time you receive radiation therapy.
   ☐ ___150 mg tablets and ☐ ___500 mg tablets
   You should take capecitabine within 30 minutes after eating breakfast and dinner.
3. Store capecitabine tablets in the original bottle at room temperature. Record the date, the number of tablets you took, and when you took them.
4. If you forget to take a dose at the scheduled time, you can still take that dose as long as it is within 4 hours of the scheduled time. You should not take the missed dose if it is within 8 hours of your next scheduled dose. Take your next dose at the regularly scheduled time.
5. If you vomit after taking a dose, do not retake the dose. Take the next dose at the regularly scheduled time.
6. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please remember to bring this diary (all pages) and your capecitabine containers (even if they are empty) to each visit with your study team.

Day	**Date**	**What time was dose taken?**		**# of tablets taken (morning)**		**# of tablets taken (evening)**		**Comments**
		AM	**PM**	**150 mg**	**500 mg**	**150 mg**	**500 mg**	
34.								
35.								
36.								
37.								
38.								

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 capsules taken during the study (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:

APPENDIX E MODIFIED FOLFOX6

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV diluted in separate infusion bags of 250 mL D5W, given concurrently through separate lines connected by Y-line tubing, over approximately 2 hours. Flush infusion line.	Day 1 every 2 weeks	8 cycles
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended over 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		

APPENDIX F CLINICAL MANAGEMENT OF DIARRHEA

Pharmacologic diarrhea management

- For patients with persistent grade 1 diarrhea on loperamide, diphenoxylate hydrochloride and atropine sulfate (Lomotil®) 1 tablet every 6 to 8 hours may be added.
- For ≥ grade 2 diarrhea despite intensive antidiarrheal therapy, consider adding octreotide (short acting) 150 micrograms subcutaneous injection as needed up to three times per day; or after the initial dose of short acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg IM.
- For grade 3 or grade 4 diarrhea with complicating features (dehydration, fever, and/or grade 3-4 neutropenia)
  - Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).
  - Administer octreotide (100-150 µg SC BID or [25–50 µg/hr IV if dehydration is severe, with dose escalation up to 500 µg SC TID).
  - Use IV therapy as appropriate.
  - Stool cultures should be done to exclude infectious causes of grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3 or 4 neutropenia) per the Investigator's discretion. Positive results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella, and Shigella* testing, if performed, must be reported using the appropriate eCRF.
  - Consider prophylactic antibiotics as needed (*e.g.,* fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia.
- Patients should be monitored for constipation and prophylaxis adjusted accordingly. Do not discontinue antidiarrheals completely; doses may be adjusted.
- For the second and subsequent cycles, the dose of loperamide should be titrated to keep diarrhea controlled to <4 stools a day.

Dietary management

Instruct patients to:

- Stop all lactose-containing products (milk, yogurt, cheese, *etc.*).
- Drink 8-10 large glasses (64-80 ounces) of clear liquids per day.

- Eat frequent small meals.
- Maintain a low fat diet enriched with rice, bananas, and applesauce, and/or toast.

APPENDIX G PATIENT-FRIENDLY DIARRHEA MANAGEMENT GUIDE

You will likely experience diarrhea while getting the therapy in this study, and possibly for several weeks after the study therapy has stopped. Below are guidelines for how to best manage diarrhea, both with medications and by adjusting your diet.

1. Be sure to have ready access to antidiarrheal medication (for example, loperamide) starting on Day 1 of the study treatment.
2. Start antidiarrheal medication at the very first sign of loose or more frequent stools, and continue taking it as directed.
3. Promptly report diarrhea symptoms to your doctors.
4. Record your usual number of daily bowel movements before starting the study treatment, as well as each occurrence of loose stools and all use of antidiarrheal medication while you receive the study treatment. Bring all pages of this record with you to each treatment visit so you and your doctors can review it together.
5. Stop eating and drinking all lactose-containing foods (milk, yogurt, cheese, *etc.*).
6. Drink 8-10 large glasses (64-80 ounces) of clear liquids every day.
7. Eat frequent small meals.
8. Maintain a low-fat diet enriched with rice, bananas, applesauce, and toast.
9. If you experience constipation, report this to your doctors *before* taking any laxatives or stopping any antidiarrheal medication.