Date: September 4, 2020

To: CTEP Protocol and Information Office

From: Pranshu Mohindra, MD, MBBS, DABR

Re: Amendment #9 in response to the Dr. Gore's request for amendment dated 8/24/2020

SUMMARY OF CHANGES - Protocol

I. Response to request for amendment:

#	Section	Comments
1.	**Title Page**	Add CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations as a Participating Organization.

II. Changes requested by the PI:

#	Section	Comments
2.	**General**	General formatting throughout the document.

SUMMARY OF CHANGES – Consent Forms

III. Consent Form Part 1

#	Section	Comments
3.	**Header**	Updated protocol version date.

IV. Consent Form Part 2

#	Section	Comments
4.	**Header**	Updated protocol version date.

Phase 1 and Pharmacology Study of Oral 5-iodo-2-pyrimidinone-2-deoxyribose (IPdR) as a Prodrug for IUdR-Mediated Tumor Radiosensitization in Brain Metastases

Corresponding Organization: **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO

Principal Investigator: Pranshu Mohindra, M.D., M.B.B.S., D.A.B.R. ®
University of Maryland School of Medicine
Department of Radiation Oncology
22 South Greene Street, Room GGJ-35
Baltimore, MD 21201
Telephone: (410) 328-9155
Telefax: (410) 328-5279
Email: pmohindra@som.umaryland.edu

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

Co-Investigators:

Medical Oncology
Aaron Mansfield, M.D.
Mayo Clinic
Email: mansfield.aaron@mayo.edu

Radiology
Rao Gullapalli, M.D.
University of Maryland
Email: rpg@umm.edu

Prashant Raghavan, M.D.
University of Maryland
Email: praghavan@umm.edu

Timothy Kaufmann, M.D.
Mayo Clinic
Email: kaufmann.timothy@mayo.edu

Statistician
Jacob Allred, M.S.
Mayo Clinic
Rochester, MN 55905
Telephone: (507) 266-2874
Email: allred.jacob@mayo.edu

Protocol Manager:
Judy Murray
JHU Sidney Kimmel Comprehensive Cancer Center
Telephone: 410-955-4044
Email: jmurra33@jhmi.edu

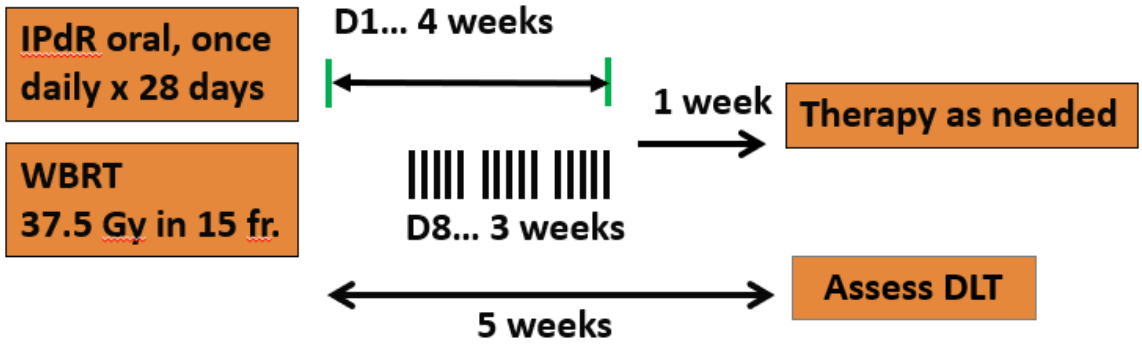
NCI-Supplied Agent: 5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR; NSC # 726188)

IND Sponsor: DCTD, NCI.

Protocol Type / Version # / Version Date:
Original / Version 1 / December 15, 2015
Resubmission / Version 2 / February 11, 2016
Resubmission / Version 3 / March 22, 2016
Resubmission / Version 4 / April 1, 2016
Resubmission / Version 5 / April 19, 2016
Resubmission / Version 6 / June 27, 2016
Resubmission / Version 7 / September 21, 2016
Resubmission / Version 8 / October 26, 2016
Resubmission / Version 9 / November 3, 2016
CTSU Activation on December 7, 2016
Amendment 1 / FDA Response / Version 10 / January 6, 2017
Amendment 2 / Version 11 / January 19, 2017
Amendment 3 / Version 12 / July 26, 2017
Amendment 4 / Version 13 / October 2, 2017
Amendment 5/ Version 14/ October 23, 2017
Amendment 6/ Version 15/ December 12, 2017
Amendment 6 / Version 15 / April 3, 2018
Amendment 6 / Version 16 / May 3, 2018
Amendment 7 / Version 17 / February 5, 2020
Amendment 8 / Version 18 / July 7, 2020
Amendment 9 / Version 19 / September 4, 2020

SCHEMA

	Pre-study	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
IPdR		po qd dose x 28 days, days 1-28 →				
RT			2.5 Gy/fraction x 15 fractions days 8-12, 15-19, 22-26 →			



PROTOCOL SYNOPSIS

Title	**Phase 1 and Pharmacology Study of Oral 5-iodo-2-pyrimidinone-2-deoxyribose (IPdR) as a Prodrug for IUdR-Mediated Tumor Radiosensitization in Brain Metastases**
Study Objectives	**Primary Objective** • To conduct a phase 1 dose escalation trial in patients with brain metastases to determine the recommended Phase II dose (RP2D) of daily oral IPdR administered alone for 7 days then concurrently with conventionally fractionated whole brain radiation therapy (WBRT) for 3 weeks. **Secondary Objectives** • To evaluate radiographic overall response rates (ORR) using RECIST 1.1. Only patients in Part 2 of the study will be included in this evaluation. • To estimate 6-month intracranial progression-free survival (PFS). • To establish the pharmacokinetics of daily oral dosing of IPdR times 8 days. • To evaluate safety and tolerability of oral IPdR x 28 days and WBRT. • To estimate the incidence of delayed neurological toxicity at 2, 4, 6-months (± 1 week) post-completion of WBRT (for patients without intracranial progression) including: a. Delayed-recall through HVLT-R b. Quality of life as measured by the FACT-BR. **Correlative Objectives (in 6 additional patients accrued at** RP2D**)** • To evaluate %IUDR-DNA incorporation into normal tissues. • To evaluate %IUDR-DNA incorporation in tumor only in patients with easily accessible tumor outside of the brain
Study Design	This is a phase 1 study to determine the RP2D of IPdR when delivered with WBRT using a 2-part accelerated titration design.

Treatment Interventions

IPdR:
Eligible patients with brain metastases (BM) will receive daily oral IPdR for 28 consecutive days.

An initial single patient dose escalation of IPdR will be conducted in Part 1. The starting dose is 150 mg (dose level 1A). A 100% dose escalation was used until dose level 1B of 300 mg.

Part 1 IPdR Dose Increment Schedule

Dose Level	Dose (mg)	Multiple of starting dose	% increase above previous dose level
1A	150	1x	
1B	300	2x	100

In Part 2 of this Phase 1 protocol, a modified cohort 3+3 design (see table below) was planned where up to three patients were planned to be accrued to a given dose level (starting with 1200 mg IPdR dose).

Part 2 IPdR Dose Increment Schedule

Dose level	**Dose (mg)**
2A	1200
2B	1800
2C	2400

Design Amendment #2:

The study accrued per plan with three patients accrued to the dose-level 2A (1200 mg) showing no DLTs. Dose-level 2B (1200 mg) was opened with 1st pt demonstrating a serious DLT. In the meantime, a previously ongoing study with IPdR and palliative radiation for gastrointestinal cancers completed accrual establishing 1200 mg as RP2D. As described in section 2.5.2, after accruing one patient at the dose-level 2B of table 5, the study is being amended to close the dose-level 2B and re-open 2A (1200 mg) to enroll 3 additional patients. The results of 6 total patients at dose-level 2A (1200 mg) will be evaluated per the table below

Table: Part 2 Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3 (0 out of 6 patients)	This dose-level is declared the recommended phase 2 dose (RP2D). The study will proceed to the expansion phase.

<table>
<tr><td></td><td>
<table>
<tr><td>1 or 2 out of 3
(total 1 or 2 out of 6 patients)</td><td>This dose level is declared the RP2D. The study will proceed to the expansion phase.</td></tr>
<tr><td>3 out of 3
(total 3 out of 6 patients)</td><td>MTD is exceeded and the dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level such that a total of 6 patients are treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the RP2D and the study will proceed to the expansion cohort).</td></tr>
</table>

Whole brain radiation therapy (WBRT):
WBRT will be delivered concurrently once daily Monday through Friday for 3 consecutive weeks starting during the second week of IPdR (Day 8). The prescribed dose will be 37.5 Gy in 15 fractions of 2.5 Gy each. IPdR will be administered 0.5-2 hours prior to WBRT.
</td></tr>
<tr><td>Sample Size</td><td>A sample size estimate is quite cumbersome in this situation, as the study team does not know at what level Part 1 will end or how many dose levels will be required in Part 2. In the proposed amendment #6 (Dec. 2017), to accelerate accrual, the dose-escalation design was changed such that part -1 was truncated at dose level IB, with one patient accrued at each dose-level (total 2). The study opened part-2 as a modified 3+3 design with three dose-levels accruing up to 6 patients each depending on the occurrence of DLT. Thereby, the number of patients accrued in part 1 and 2 were expected to range from 8 (2+6) to 20 (2+6+6+6). Till date (December 2019), 2 patients have been accrued in part 1 (1+1), 3 patients at dose-level 2A and 1 patient at dose-level 2B. In the current proposed design amendment #2, since dose-level 2B is being stopped with one patient and dose level 2A will be reopend for additional 3 patients, the expected accrual in the two parts will range from 9 (2+7) to 15 (2+7+6) patients. Ten patients will be accrued at the RP2D in the expansion cohort to help narrow the confidence interval on the estimate of incidence of toxicity at the MTD which makes the range of accrual between 19 and25. The maximum accrual will be 25 patients. Up to a total of six patients in the expansion cohort will be analyzed for the %IUdR-DNA cellular incorporation in circulating granulocytes and tumor once RP2D has been determined.</td></tr>
<tr><td>Sponsor</td><td>DCTD, NCI.</td></tr>
</table>

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To conduct a Phase 1 dose escalation trial in patients with brain metastases to determine the recommended phase -2 dose of IPdR when administered alone orally once daily for 7 consecutive days and then concurrently with conventionally fractionated whole brain radiation therapy (WBRT) for additional 21 days.

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity to IPdR-mediated radiosensitization. Although the clinical benefit of this drug used before and during radiation therapy 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 at 6 months using RECIST criteria in addition to safety and tolerability. Only patients in Part 2 of the study will be included in this evaluation.

1.2.2 To estimate 6 month intracranial progression-free survival (PFS) in brain metastasis cancer patients who receive daily oral IPdR x 28 days and WBRT.

1.2.3 To establish the pharmacokinetics of daily oral dosing of IPdR times 8 days.

1.2.4 To evaluate safety and tolerability of oral IPdR x 28 days and WBRT.

1.2.5 To estimate the incidence of delayed neurological toxicity at 2, 4 and 6 months (± 1 week) post-completion of WBRT (for patients without intracranial progression) including:

a. Delayed-recall through HVLT-R
b. Quality of life as measured by the FACT-BR.

1.3 Correlative Objectives (in 6 additional patients accrued at RP2D)

1.3.1 To assess for biochemical evidence of IPdR effect in normal tissues (circulating granulocytes) by measuring %IUdR-DNA cellular incorporation by flow cytometry and high-pressure liquid chromatography (HPLC) analyses as an exploratory biomarker for the following effects:

a. The %IUdR-DNA tumor cell incorporation from Day 8 extracranial tumor biopsies in brain metastasis cancer patients receiving RP2D doses of IPdR as an exploratory biomarker of tumor radiosensitization using RECIST criteria.

b. The %IUdR-DNA cellular incorporation in patients' circulating granulocytes taken weekly during the 28-day IPdR RP2D dose, on Day 29, and Week 8 as an exploratory biomarker of IPdR systemic toxicities to bone marrow as measured by serial CBC/differential values

2. BACKGROUND

2.1 Brain Metastases

Brain metastases (BMs) are the most common type of intracranial malignancy, occurring in 10-30% of adults with cancer; in fact, BMs are 10 times more common than primary brain tumors.[1, 2] The prognosis for patients with BMs is very poor with median survivals typically measured in months rather than years. Even BM patients with the best prognostic score according to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) have estimated median survival of only 7.1 months; that number drops dramatically to 2.3 months for those with the worse RPA score.[3] The RTOG index notably is not disease-specific and while any extracranial malignancy cancer can spread to the brain, certain cancers have a higher predilection for brain involvement including those starting in the lung and breast.[4] A newer prognostic index, the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) score, accounts for primary tumor type with median survival being shorter for certain tumors (e.g. melanoma: 3.38-13.23 months) compared to others (e.g. breast: 3.35-25.30 months).[5]

The treatment options for patients with BMs is influenced by various factors including the primary tumor type, extent and control of extracranial disease, performance status, symptoms from BMs, and also important the number, size, and location of the intracranial lesion(s). The most commonly used treatments are surgery and/or radiation therapy (RT).

Whole brain radiation therapy (WBRT) has played an integral role in the treatment of BMs for decades. The most commonly used WBRT dose fractionation schedules are 30-40 Gy in 10-20 daily fractions. There is no clear evidence that treatment efficacy differs based on the particular dose fractionation schedule used, but higher dose per fraction (especially >3 Gy per fraction) may be associated with a higher rate of neurotoxicity.[6-8] The benefits of WBRT include improved neurologic symptoms from BMs, [9] improved local control of macroscopic intracranial disease,[10-13] and lower incidence of intracranial relapse.[11, 14, 15] Overall survival may also be extended with WBRT, particularly in patients with control of limited extracranial disease.[16, 17] Although WBRT can provide significant clinical benefit, there is a need to improve outcomes after WBRT. In a European randomized trial of patients with 1-3 BMs, 28% of patients who received adjuvant WBRT after either surgery or stereotactic radiosurgery (SRS) for BM died due to intracranial progression (compared to 44% who did not received adjuvant WBRT).[13] In a recently reported U.S. cooperative group trial, 12-month intracranial tumor control was 85% with the addition of WBRT (compared to 51% without, $p<0.001$); no difference in overall survival was reported.[18]

Attempts to improve survival and intracranial response rates by adding radiosensitizing drugs including lonidamine, metronidazole, misonidazole, motexafin gadolinium, bromodeoxyuridine, and efproxiral to WBRT have been unsuccessful.[19-24] Subgroup analyses suggested that efproxiral improved response and survival in breast cancer patients [21] while motexafin gadolinium improved neurocognitive function in lung

cancer patients [24] although these trials were not powered for these subgroup analyses. Because intracranial disease progression is a significant cause of morbidity and mortality despite WBRT, there is a significant clinical need to identify an effective radiosensitizer that is well tolerated and enhances the effect of WBRT.

2.2 Radiosensitization

It is estimated that 1,658,370 men and women will be diagnosed with cancer in 2015 (http://seer.cancer.gov/statfacts/html/all.html) and approximately two-thirds of patients will receive radiation at some time during the course of their cancer treatment (http://www.rtanswers.org/statistics/aboutradiationtherapy/). Therefore, any intervention to improve the efficacy and/or toxicity profile of radiation therapy (RT) will have a profound impact on the field of oncology.

A strategy to improve the efficacy/toxicity profile of RT is to use a drug(s) that specifically target(s) mechanisms of tumor cell resistance to RT, thereby making the tumor more susceptible to the damaging effects of RT relative to the normal tissues. While it is an appealing strategy, *there are currently no drugs with a specific FDA approved indication of radiosensitization.* However, it is well recognized that the primary cellular target of RT is DNA. RT kills cells by causing irreversible DNA strand breaks, making them unable to divide and proliferate. Well over 50 years ago it was recognized that certain drugs called nucleoside analogs are falsely incorporated into DNA and when these cells with defective DNA are exposed to RT tumor cell killing is increased by up to two-three fold compared to cells without the defective DNA.[25]

2.3 5-iododeoxyuridine (IUdR)

To date, the nucleoside analog that has been found to be the most effective as a specific radiosensitizing drug is 5-iododeoxyuridine (IUdR).[26, 27] IUdR, a halogenated thymidine (TdR) analog, has been recognized as a potential radiosensitizing agent since the early 1960s and clinical trials during the 1980's-1990's showed that IUdR enhanced the effectiveness of RT in the treatment of RT-resistant brain and soft tissue/bone cancers (Tables 1 and 2).[28-30] However, IUdR is rapidly dehalogenated by both hepatic and extrahepatic metabolism with plasma half-life of < 5 minutes after bolus infusion. Therefore, the clinical use of IUdR is impractical because it needs to be administered as a continuous intravenous (CIV) infusion, 24 hours/day for 5-6 weeks during RT to maintain steady-state plasma concentration.[31] A consequence of this is that IUdR accumulates in rapidly proliferating normal tissues and has dose limiting systemic toxicity to bone marrow and bowel, limiting the tolerated doses and the potential for further clinical radiosensitization.[32, 33] Consequently, NCI did not pursue further development of IUdR.

Table 1. NCI sponsored clinical efficacy studies of IUdR (compared to historical RT-alone controls) for treatment of high grade primary brain tumors (RTOG*, NCI trials) [28-30]**

Tumor	Treatment	Median survival (Months)
Anaplastic astrocytomas (Grade 3 of 4)*, **	RT alone	24
	RT + IUdR	39
Glioblastoma Multiforme (Grade 4 of 4)**	RT alone	9
	RT + IUdR	14

Table 2. Clinical efficacy studies of IUdR (compared to historical RT-alone controls) for treatment of high grade retroperitoneal (RP) sarcomas (NCI; University of Michigan*** trials) [34-36]**

Tumor	Treatment	Local Control at 2 years
High grade RP sarcomas (resectable)***	RT + Surgery	25%
	RT + IUdR + Surgery	45%
High grade RP sarcomas (un-resectable)**	RT alone	<10%
	RT + IUdR	60%

*RTOG: Radiation Therapy Oncology Group, **NCI, *** University of Michigan

2.4 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR)

2.4.1 Mechanism of Action

More recently a newer nucleoside analog, 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR), has been developed.[37] IPdR is taken by mouth (PO) and is a prodrug of IUdR. That is, when IPdR is ingested, the body converts it into IUdR via an aldehyde oxidase principally in liver. IPdR is essentially a way to conveniently administer IUdR that is known to enhance the effectiveness of RT.[38] IUdR is then phosphorylated by thymidine kinase (TK), and subsequently sequentially phosphorylated into a triphosphate, which is incorporated into replicating DNA in competition with deoxythymidine triphosphate (dTTP). The incorporation of the thymidine analog leads to the generation of highly reactive uracil-based free radicals by ionizing radiation (IR), which could also damage unsubstituted complementary-strand DNA by creating double-strand breaks (DSB).

2.4.2 Non-Clinical Studies

IPdR has been specifically developed as a radiosensitizing drug, this development having

been sponsored by the NCI through a series of extramural and intramural grants over the last two decades. As summarized in Table 3, the extensive preclinical studies of IPdR passed the rigid guidelines from the FDA, leading to an investigator initiated IND (T. Kinsella, PI, # 70,333). The IND was subsequently transferred to CTEP. Importantly, IPdR was found to be more effective as a tumor radiosensitizing drug with minimal normal tissue toxicity when directly compared to continuous infusions of IUdR.

2.4.2.1 *In Vitro* Antitumor Studies

There are no *in vitro* data published to date.

2.4.2.2 *In Vivo* Antitumor Studies

In preclinical studies, PO IPdR was found to be a more effective radiosensitizer versus CIV IUdR infusions, due in part to the 2-3 times greater percentage of IUdR-DNA incorporation in tumors treated with PO IPdR compared to IUdR. Therefore, PO IPdR in combination with radiation therapy (RT) may be an effective regimen for drug-resistant tumors. Studies in athymic mice using two different human colorectal cancer cell lines (HT-29 and HCT116) and one human glioblastoma cell line (U251) grown as subcutaneous xenografts found > 2-fold *increases* in %IUdR-DNA tumor cell incorporation and > 2-fold *decreases* in %IUdR-DNA incorporation in proliferating dose-limiting normal tissues (bone marrow and intestine) with IPdR (up to 1.5 gm/kg/day x 6 or 14 days) compared to IUdR (MTD: 100 mg/kg/day x 6 days).[39-41] Additionally, a 1.3-1.5 fold enhancement in radiosensitization was reported, as measured by a standard xenograft tumor regrowth delay assay, with IPdR (given daily for 6-14 days) plus fractionated RT (2 Gy/d for 4 days) in the same human tumor xenografts compared to fractionated RT alone.[40-42] Based on prior studies, the calculated radiosensitizer enhancement for IPdR of 1.3-1.5 would be predicted to result in clinically relevant radiosensitization in human cancers.

2.4.2.3 Pharmacokinetics and Product Metabolism in Animals

Extensive pharmacokinetic studies were performed in mice, rats, ferrets and rhesus monkeys, showing rapid and efficient clearance of IPdR from the plasma following single and multiple once daily oral dosing (gastric gavage) with plasma IUdR levels peaking within 30 minutes of IPdR dosing and persisting for up to 4 hours at >1 μmol/L (plasma level associated with radiosensitization)[43-45]. The absorption and elimination kinetics of IPdR were found to be linear over the dose range studied although repeated PO IPdR administration enhanced its elimination. Finally, in all models there was little incorporation of IUdR-DNA into bone marrow or intestinal tissue.

2.4.2.4 Toxicology

A series of IPdR-related toxicology studies were performed under a NCI RAID grant (#197), using escalating daily doses of IPdR for 14 or 28 days in mice, rats, and ferrets,

showing a 10-15% reversible weight loss at 1500-2000 mg/kg/d for 14 or 28 days in ferrets and rats, respectively, but no clinical toxicities (CBC, LFTs, BUN, Cr) or histopathologic changes at full necropsy.[44, 45] In ferrets, the most sensitive species, the MTD for PO IPdR administration was found to be ≤1.5 g/kg/day for 14 days. There were no systemic toxicities. Dose-limiting toxicities (DLTs) included hepatic toxicities (increase in liver weight and cytoplasmic vacuolation of hepatocytes) and gastrointestinal toxicities (vomiting, diarrhea, decreased food intake). Based on these data, the recommended phase I dose was 85 mg/m^2 once-daily for 14 days, which is $1/10^{th}$ of the MTD in ferrets. The results of these preclinical studies documented the feasibility of repeated daily dosing, reproducible pharmacokinetics, modest (tolerable) systemic toxicities, and efficacy of IPdR as a radiosensitizer.

2.4.3 Clinical Studies

2.4.3.1 First In-Human Phase 0 Study

Protocol 8866, "An Early Phase 0 Study of IPdR Absorption, Metabolism, and Safety in Patients with Advanced Solid Tumors and Lymphomas" was conducted at the Developmental Therapeutics Clinic (DTC), NCI and completed February 19, 2013; Dr. Shivaani Kummar was the principal investigator. This was a first-in-human study and the initial dose was selected based on $1/10^{th}$ of the MTD in ferrets, the most sensitive preclinical species tested. As an additional safety factor, only a single dose of the agent was administered, rather than repeated dosing.

The primary objectives were to determine the safety of administering a single PO dose of IPdR, and to measure the plasma concentrations of IPdR, the active metabolite IUdR, and IUdR metabolites. The study was to be closed for futility if IUdR could not be detected in patient plasma samples.

The patients received a single PO dose of IPdR on Day 1. Blood and urine samples for PK analyses were collected over a 24-hour period after IPdR dosing to measure concentrations of IPdR, IUdR, and IUdR metabolites. The total duration of study participation was 14 days for each patient. All patients were carefully monitored for side effects while on study. The trial was conducted using five dose levels (DL) of IPdR: 150 mg (DL 1), 300 mg (DL 2), 600 mg (DL 3), 1200 mg (DL 4), 2400 mg (DL 5). One evaluable patient was enrolled successively in each cohort starting at DL 1. Patients were followed for a total of 14 days on study. Once each patient completed the 14-day course and there were no significant AEs, the next patient was enrolled at the next dose level, until the highest level (DL 5) was reached. A total of six patients were to be enrolled at DL 5. In May 2011, the protocol was amended to allow multiple patients to be concurrently enrolled at DL 5 (patients were still followed for 14 days, but additional patients could be enrolled during this period).

As of May 2011, one patient had been treated at each DL, up to and including DL 5 (2400 mg), with no AEs reported as at least possibly drug-related (Protocol Amendment, May 2011). The protocol was amended in order to accelerate the accrual rate at DL 5 (see above). Dose escalation was halted at DL 5, as the objectives of this trial were solely to determine the PK and safety of single-dose IPdR, not to establish the MTD. A total of 10 patients were enrolled on the trial, including 6 patients at DL

5.[46] All patients tolerated the drug well, with no treatment-related AEs. The trial was closed to accrual and treatment in May 2012 and completed in February 2013.

The final published results (Kummar et al., Clin Cancer Res. 2013 Apr 1;19(7):1852-7. doi: 10.1158/1078-0432), confirmed no drug related AE. The authors noted that the plasma concentrations remained above 1 μM for 3–4 hours and declined with a half-life of 1.5 hours. Per trial eligibility, prior anti-neoplastic therapy must have been completed at least 2 weeks prior to enrollment.

Table 3: IPdR pre-clinical studies leading to IND application and initial clinical Phase 0 trial

Study	Description	Summary of Findings
A. IPdR Metabolism by hepatic aldehyde oxidase		
Chang, 1992 [38]	Metabolism of IPdR vs IUdR	Elucidated IPdR metabolism by aldehyde oxidase Characterized properties of aldehyde oxidase
Kinsella, 2000, 2008 [41, 44]	IPdR Metabolism in rats and ferrets	Characterized kinetics of IPdR metabolism
B. Pharmacokinetic and toxicology studies		
Kinsella, 1994,1998, 2000 [39-41]	Pharmacokinetics of PO IPdR in mice	Established absorption, distribution, metabolism, and elimination kinetics of PO IPdR in mice
Kinsella, 2000 [45]	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
Kinsella, 2008 [44]	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.
Kummar, 2013 [46]	Pharmacokinetics of single-dose PO IPdR in humans	Phase 1 study of PO IPdR, 150mg-2400mg in humans: No toxicities.
C. Pre-clinical efficacy studies of IPdR-mediated radiosensitization		
Kinsella, 1998, 2000 [40, 41] Seo, 2004, 2005 [43, 47]	Efficacy/toxicity studies of PO IPdR vs 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, 1994 [39]	Efficacy, PK, toxicity, and DNA incorporation of PO	Demonstrated improved therapeutic index of PO IPdR vs PO IUdR for IUdR-

	IPdR vs PO IUdR in human colon cancer xenografts.	mediated radiosensitization

2.4.3.2 Completed Phase-1 study:

In the current ongoing study, NCI 9882/ NCT02381561: Phase I and Pharmacology Study of Oral 5-Iodo-2-Pyrimidinone-2'- Deoxyribose (IPdR) as a Prodrug for IUdR-Mediated Tumor Radiosensitization in Gastrointestinal Cancers, is a phase I dose escalation trial to determine the safety and the maximum tolerated dose (MTD), of oral (po) IPdR (ropidoxuridine) given daily for 28 consecutive days starting 7 days prior to the initiation of RT with concurrent intensity-modulated radiation therapy (IMRT) to a dose of 37.5 Gy in 15 fractions in patients with advanced gastrointestinal cancers treated with palliative radiation. Beginning on day 8, patients undergo IMRT 5 days a week for 3 weeks in the absence of disease progression or unacceptable toxicity. IPdR starts on Day 1 and is taken 30 minutes to 2 hours prior to radiation therapy. After completion of study treatment, patients are followed up for 4 weeks. The study has completed accrual with final results published (https://www.ncbi.nlm.nih.gov/m/pubmed/31337643/). Nineteen patients were entered on study. Dose limiting toxicity was encountered at 1,800 mg every day, and the recommended phase II dose is 1,200 mg every day. Patients each for dose levels 600, 900, and 1,200 mg received therapy without evidence of IPdR-related grade 2 or higher clinical or laboratory toxicity. At 1,800 mg orally every day, 2 of 3 patients experienced grade 3 toxicity deemed probably or definitely related to IPdR. These were related to development of a community acquired pneumonia and peri-anal abscess respectively. Neither patient demonstrated leukopenia or neutropenia at any time. Both patients had resolution of their toxicity without sequelae. The plasma PK data shows good intra- and interpatient levels of IPdR and IUdR on days 1,1 and 22-above 1uM at 900 and 1200 mg dosing.

2.5 Rationale

Preclinical and early Phase 0 data demonstrated that IPdR was well tolerated and effective as a radiosensitizer. These data provide justification for further clinical evaluation since there are no clinical data of IPdR and WBRT.

BMs are the most common intracranial malignancy, and a cause of significant neurologic morbidity and mortality. While there is a higher likelihood for development of BMs based on tumor type, any malignancy may metastasize to the brain. Therefore, all tumor types will be evaluated with the exception of traditionally radiosensitive tumors (germ cell, lymphoma, leukemia).

The starting dose for po IPdR for Phase 1 testing is based on the most sensitive (lower MTD) of the two animal species tested, *i.e.* ferrets and rats.[44, 45] The MTD for po IPdR in ferrets, the most sensitive species, was determined to be ≤ 150 mg/kg/d x 14 days [45], which is equivalent to 850mg/M^2/day x 14 days. The human equivalent dose (HED) is also 850 mg/M^2/day, the same as the ferret dose, based on body surface area (BSA).[48] Based on these calculations and pre-clinical animal data, 1/10^{th} of the MTD is 85mg/M^2/day (≈150mg), the proposed starting dose for our proposed Phase 1 trial.

This Phase 1 study will determine the maximum tolerated dose of single agent IPdR when given in conjunction with WBRT for palliation in patients with brain metastases. Once the MTD of single agent IPdR and WBRT is determined, future studies will evaluate the efficacy of IPdR and WBRT in controlling intracranial metastatic disease.

2.5.1 Rationale for study modification (Amendment #06 including revised submissions)

Multiple amendments were requested in the study protocol to boost accrual. These are detailed below:

a. Change in two part dose-escalation design: Based on the published results from the study 8866 (phase-0) and updated results from the NCI 9882/ NCT02381561 noted in sections above along with recommendations from the CTEP medical officer, it was elected to stop accrual to part 1 at dose-level 1B (300 mg) and directly activate part 2 of the study at 1200 mg dosing.

   At the time of submission of amendment #6 (Dt 12/12/2017), #6 rev (02/26/2018) and the current version, one patient each was accrued at dose levels of 150 and 300 mg with no DLT.

   Based on the recommendations noted in the amendment #6rev disapproval letter, the study accrual will be suspended at dose level 1B with the plan to open the study directly at 1200 mg dose level of part 2, once the amendment has been approved.

b. Change in dose-escalation schedule: The dose-escalation schedule was also amended. The original modified accelerated design was found to restrict speed of accrual, since once a patient was registered, for the duration of pre-study work-up, study treatment and post-study DLT assessment, no other patient could be accrued on the study. This lead to non-availability of slots for any other eligible patient and was felt to be a barrier in accrual. Hence, per the communication received from the CTEP medical officer, a change to a 3+3 design was recommended.

   A conservative 3+3 phase-1 study design poses unique challenges for the brain metastases population to be treated with WBRT + study drug related to high baseline incidence of adverse events in this population and due to inherent limitations of a conservative 3+3 design. The most recent large-scale multi-institutional randomized trial of post-operative SRS to the surgical cavity versus WBRT (NCCTG N107C/CEC.3, Brown et al., Lancet Oncol 2017), showed grade 3 or worse adverse events (irrespective of attribution) in 36 (39%) patients in the SRS group and 37 (40%) patients in the WBRT group. Corresponding grade 3 or more events that were possibly related to treatment were 11 (12%) patients in the SRS group compared with 17 (18%) patients in the WBRT group. Despite, 77% of patients having only one lesion which was surgical resected and an ECOG PS of 1 or less in 90% patients, only about 50% patients survived one year in both the arms. In patients with 1-3 brain metastases (SRS alone candidates), another multi-institutional randomized trial of SRS alone or SRS + WBRT (NCCTG N0574 study, Brown et al, JAMA 2016), at least one grade 3 or more AE was seen in 41.4-43.1% of patients. Median overall survival

was only 10.4 months in SRS alone and 7.4 months in SRS + WBRT patients. The rates of adverse events are expected to be higher and survival outcomes lower in non-surgical patients with multiple brain metastases, which form the patient population in this study. Indeed, in the phase 3 randomized trial of WBRT plus motexafin gadolinium for patients with brain metastases from non-small cell lung cancer (Mehta et al, Int J Radiat Oncol Biol Phys 2009) or with WBRT + efaproxiral for breast cancer (Suh t al., J Clin Oncol 2006), the incidence of ≥ Grade 3 toxicity with WBRT alone was approximately 10%, while with WBRT + drug combination was approximately 25-30%.

As such, in the setting of poor overall prognosis, high baseline incidence of adverse events (related to the presence of brain metastases or WBRT) and since the study design is changed to a more conservative 3+3 design which may be at risk of falsely under-predicting MTD due to random occurrence of an AE at a lower dose level, it is justified to explore treatments with higher incidence of adverse events if it can help improve the dismal survival outcomes.

In the current proposed revision, a modified 3+3 design was proposed that includes a 10 patient expansion cohort in addition to 3-6 patients accrued at each dose-level. Based on the design proposed, the highest acceptable probability of DLT is 31.25% (5 or less events in 16 patients), with the target expected probability of DLT of 20-30% (of which 18-20% is expected from WBRT alone). The operating characteristics are described in section 5.1.

Finally, per the first-in-human phase 0 trial eligibility, prior anti-neoplastic therapy must have been completed at least 2 weeks prior to enrollment. Hence, to boost further accrual and increase clinical applicability, the time-period of prior chemotherapy or immunotherapy was reduced to 2 weeks from the start of study therapy, keeping 3 weeks for investigational agents, or radiotherapy to a non-brain site for 2 weeks before initiation of IPdR therapy. With regards to any standard of care, oral targeted agent, based on the comments from amendment #6rev disapproval letter and recognizing the variation in half-lives of different drugs, the study investigators have standardized pre-study treatment time to 2 weeks irrespective of whether oral administration or not. For oral investigational agents, however, a time of 4 half-life and for other investigational agents a time interval of 3 weeks is retained.

2.5.2 To date, the current study has completed accrual to dose-level 1A, 1B and 2A. No DLTs were noted at these dose-levels. Hence, per the study design, decision was taken to continue dose-escalation opening dose-level 2B (1800 mg). However, the 1st patient enrolled to dose level 1800mg had multiple concerning adverse events: acute kidney injury grade 3, acute oral mucositis grade 3 and acute vomiting grade 3. Per local study team, these were attributed to study drug as ‘Probable’ to ‘Definite’.

In discussion with the CTEP Medical Officer, Dr Charles Kunos, based on the review of results of the completed phase 1 study detailed in 2.4.2 and recognizing the challenges with study accrual, a recommendation was received from CTEP to close dose-level 2B (1800 mg). Instead, dose-level 2A (1200 mg) is being re-opened to enroll 3 additional patients at the 1200mg dose level. Enrollment of 6 total patients at 1200 mg dose would

allow more robust assessment of safety of the 1200 mg level and could allow to complete the trial labeling 1200 mg daily IPdR x 28 days as the RP2D.

2.6 Correlative Studies Background

As the %IUdR-DNA cellular incorporation in human tumor xenografts in athymic mice was linearly related to the IPdR dose when given po qd x 6-14 days [39, 41, 47], we will correlate %IUdR-DNA cellular incorporation in human tumor biopsies as an exploratory biomarker of tumor radiosensitization in a cohort of 6 brain metastases cancer patients receiving the RP2D by linear regression. Dr. Jerry Collins, Associate Director for Developmental Therapeutics, DCTP, NCI will actively participate in the PK and %IUdR-DNA cellular incorporation analyses.

2.6.1 Pharmacokinetics of IPdR

The clinical pharmacology of PO IPdR was characterized in the initial, DCTD-sponsored phase 1 trial 8866. Patients received a single PO dose of IPdR.[46] Plasma concentrations of the active metabolite IUdR generally increased with increasing dose. At dose level (DL) 5 (2400 mg IPdR), plasma IUdR levels reached a peak of 4.0 ± 1.02 mcM after 1.67 ± 1.21 hours, remained above 1 mcM for 3 to 4 hours, and declined with a half-life of 1.5 hours. Plasma exposure values of the major secondary metabolite IU increased more than proportionally as doses were doubled, and remained at a sustained high level (near 100 mcM) for 10 hours in four of the 6 patients treated at DL 5, indicating disproportionate accumulation due to saturation of metabolic elimination. IPdR and its metabolites, IUdR, IP, and IU, were detectable in urine samples from patients receiving 2400 mg of IPdR. Twelve percent (± 8%) of the dose was recovered over 24 hours; of the metabolites measured in urine, 90 ± 13% consisted of IU. Previous clinical trials had defined 1 mcM as the minimum IUdR plasma concentration for efficacy[31, 49]; since DL 5 of this trial had achieved a mean peak IUdR plasma concentration of around 4 mcM, investigators concluded that PO IPdR may prove to show clinical antitumor activity, and future trials may focus on determining the optimal dosing schedule in sequence with RT.

2.6.2 %IUdR-DNA Incorporation into Tumor

Athymic nude mice bearing HCT-116 human colon cancer xenografts, either as liver metastases, subcutaneous (SC) flank tumors, or both, were administered IPdR PO for 6 days at its RP2D (1 g/kg/day).[39] This treatment resulted in a 2-to 3-fold greater incorporation of IUdR into tumor DNA than IUdR administered at its RP2D (250 mg/kg/day), indicating a greater potential for radiosensitization.
In a second study, athymic mice with HT29 human colon cancer xenografts were treated up to 2 g/kg PO IPdR for 6 days and the investigators found < 1.5 times increase in the percentage of IUdR-DNA in the tumor xenografts.[40] A subset of the mice with SC xenografts measuring 0.25-0.3 cm^2 were treated with RT (2 Gray [Gy]/day for 4 days) with or without PO doses of IPdR at the RP2D of 1000 mg/kg/day for 6 days. A tumor

regrowth assay demonstrated a 1.5-fold improvement in outcome (time to regrowth of tumor to 300% of pre- treatment volume) of the IPdR + RT group versus RT alone. Mice with U251 human glioblastoma xenografts were treated with 750 or 1500 mg/kg/day IPdR over 14 days.[41] A significant sensitizer enhancement ratio (SER), calculated as the ratio of growth delay [time to 300% original tumor volume] after agent + RT to the delay after RT alone) was found for PO IPdR + RT (SER=1.31, P=0.05) but not for 14-day CIV IUdR + RT (SER=1.07, P=0.57), indicating that IPdR could be a useful clinical radiosensitizing agent.

Deficiencies in the mismatch repair (MMR) system have been implicated in the genesis of hereditary nonpolyposis colon cancer and an increasing number of sporadic cancers (Peltomaki, 2003). Athymic nude mice with an isogenic pair of human colon cancer xenografts HCT116 (MMR^-, $hMLH1^-$) and HCT116/3-6 (MMR^+, $hMLH1^+$), were treated with PO IPdR (1g/kg/d) every day for 14 days.[47] On Days 11 to 14, RT was delivered to the tumor xenografts with 2 Gy or 4 Gy per fraction for 4 days. The tumor size and the body weight were monitored daily until the tumors grew to ≤ 300% of their pre-irradiation volume. The tumor volumes were estimated by the formula: $R1$x $R2$ x $R2/2$, where $R1$ is the maximum diameter and $R2$ is the rectangular diameter. Tumor regrowth delay was calculated as the area between the 300% volume line and the growth curves for the various control and treatment groups. Substantial increases in regrowth delay were found in both HCT116 and HCT116/3-6 tumor xenografts and there was substantial radiosensitization in both HCT116 and HCT116/3-6 tumor xenografts.

Athymic nude mice with human glioblastoma (U251) SC xenografts were treated with IPdR: 1) 500 mg/kg of every other day (QOD); 2) 500 mg/kg QD; 3) 166 mg/kg three times a day (TID); or 4) vehicle alone (control).[43] On the IPdR treatment Days 11 to 14 (for the QD, TID, and control groups) and Days 25 to 29 (for the QOD group), RT was delivered using 2 Gy/fraction for 4 days to the tumor xenografts. The tumor regrowth assay showed in all three IPdR treatment groups enhanced tumor growth delay compared to control (QOD, 29.4 days; QD, 29.7 days; TID, 34.7 days; radiotherapy alone 15.7 days). The SER of each schedule was calculated: QOD 2.17; QD, 2.20; and TID, 2.56. The QOD schedule also resulted in reduced systemic toxicity.

In the most recent study in mice, athymic male nude mice (6–8 weeks old) were implanted with SC U87 xenograft tumors (4×10^6 cells) and then randomized to 10 treatment groups receiving increasing doses of PO IPdR (0, 100, 250, 500, and 1000 mg/kg/d) administered QD for 14 days with or without RT (0 or 2 Gy/d for 4 d) on Days 11–14 of IPdR treatment.[42] At Day 31, the mean tumor volume reduced from 1609 ± 285 mm^3 to 821 ± 113 mm^3 with RT alone. IPdR treatment with or without RT caused a dose-dependent reduction in tumor volume: 250 mg/kg/d for 14 days (IPdR alone, 1040 ± 105 mm^3; IPdR + RT, 551 ± 86 mm^3); 500 mg/kg/d for 14 days (IPdR alone, 960 ± 131 mm^3; IPdR + RT, 268 ± 69 mm^3); 1000 mg/kg/d for 14 days (IPdR alone, 718 ± 99 mm^3; IPdR + RT, 309 ± 60 mm^3). The SER was approximately 2–3 for the two lower IPdR dose groups and 5–6 for the two higher IPdR dose groups. These results indicated that the efficacy of PO IPdR plateaus around ≥ 500 mg/kg/day.

Correlation of tumor response using RECIST Criteria with the %IUdR-DNA cellular incorporation in tumor from biopsies of tumors in patients with brain metastases at the RP2D will be analyzed to determine the tumor response relationship to the %IUdR-DNA cellular incorporation in tumor on Day 8 of the 28-day IPdR treatment based on HPLC and flow cytometry measurements. A tumor biopsy on Day 8 of IPdR treatment was selected to provide for measurable IUdR-DNA incorporation in tumor and to eliminate the effect of RT on tumor tissue as the tumor biopsy will be performed prior to the initiation of RT. Tumor biopsy is not required for participation in this study. Tumor biopsy should only be considered for tumors that are easily accessible and would not subject that patient to a high risk of morbidity as a result of a tumor biopsy. Otherwise, if tumor is easily accessible and biopsy would pose minimal risk to the patient, then tumor biopsy should be performed. A biopsy may be taken of the primary tumor or any extracranial metastasis. A biopsy of the brain metastasis is not permitted. In this analysis, tumor response is the dependent variable and can be binomial (i.e. response vs. no response) or multinomial (i.e. complete response, partial response, stable disease or progressive disease) and the %IUdR-DNA cellular incorporation is the independent variable.

The survival times will also be obtained from the brain metastases cancer patients and, if data allow, will be analyzed using a Cox proportional hazards model with %IUdR-DNA cellular incorporation in tumor as the covariate. However, given the variable tumor types and extent of disease, according to the eligibility criteria, a valid survival analysis is unlikely.

2.6.3 %IUdR-DNA Incorporation into Normal tissues

In the pre-clinical *in vivo* testing of po IPdR as a prodrug for IUdR-mediated radiosensitization, ≥ 2-fold decreases in %IUdR-DNA incorporation in proliferating dose-limiting normal tissues (bone marrow and intestine) following PO IPdR were consistently found compared to PO or CIV infusions of IUdR (using RP2D schedules) in 4 different human tumor xenografts in athymic mice.[39-42] In prior clinical Phase 1 trials of CIV infusions of IUdR (± biochemical modulators), the %IUdR-DNA incorporation in circulating granulocytes during and following the IUdR infusion as a surrogate for a proliferating normal human tissue (bone marrow) has been measured.[32, 50-54] In general, the %IUdR-DNA incorporation in circulating granulocytes increased linearly with a linear increase in steady-state plasma levels of IUdR. Additionally, high (≥ 6%) %IUdR-DNA levels in peripheral granulocytes predicted for systemic bone marrow toxicity to CIV IUdR. In the pre-clinical studies of po IPdR daily for 14 days in athymic mice and ferrets,[39, 41, 47] the %IUdR-DNA incorporation was ≤ 2% in circulating granulocytes following treatment and no changes in blood counts were found in ferrets and rats,[44, 45] suggesting that bone marrow toxicity may not be dose-limiting for PO IPdR in humans. Additionally, no myelosuppression or bone marrow abnormalities were seen in the IPdR toxicology studies, where IPdR was given once daily for 14 days in ferrets and for 28 days in rats.[44, 45]

Correlation will be performed of the %IUdR-DNA cellular incorporation in peripheral (circulating) granulocytes as an exploratory biomarker of bone marrow acute normal tissue toxicity with the po IPdR RP2D and RP2D pharmacokinetics. This exploratory assay was originally developed in Dr. Jerry Collins' laboratory at NCI.[55] Additionally, we do not expect a linear relationship between the %IUdR-DNA cellular incorporation in circulating granulocytes and peripheral blood counts measured weekly during RP2D drug exposures and at Day 29 and Week 8 follow-up. Nevertheless, we will test the hypothesis that IPdR drug dose and drug plasma pharmacokinetics will be linearly related to the %IUdR-DNA cellular incorporation in circulating granulocytes.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed malignancy with brain metastases and are recommended palliative WBRT.

3.1.2 Life expectancy of greater than 2 months to allow completion of study treatment and assessment of dose-limiting toxicity.

3.1.3 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of IPdR in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

3.1.5 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥ 3,000/mcL
- absolute neutrophil count ≥ 1,000/mcL
- platelets ≥ 100,000/mcL
- calculated creatinine clearance ≥ 45 mL/min/1.73 m^2

- Total bilirubin, AST (SGOT) and ALT (SGPT):
  If no known liver metastases:
  Total bilirubin < 1.5 x institutional upper limit of normal (ULN), AST/SGOT and ALT/SGPT both < 2 x ULN.

  If known liver metastases, then:
  Total bilirubin < 2.5 x ULN, AST/SGOT and ALT/SGPT both < 5 x ULN.

3.1.6 HIV+ patients with CD4 counts ≥ 250 cells/mm^3 on anti-viral therapy are eligible for the study.

3.1.7 Negative urine or serum pregnancy test result for females of child bearing potential only. Note: The effects of IPdR on the developing human fetus are unknown. For this reason and because radiation therapy is known to be teratogenic, women of child-bearing potential 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. 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 and women 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.

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

3.2 Exclusion Criteria

3.2.1 Presence of diffuse lepto or pachy meningeal carcinomatosis (focal/localized involvement from limited meningeal based metastases are acceptable), greater than 1 cm mid-line shift, uncal herniation, or severe hemorrhage/hydrocephalous (small intra-lesional or anticipated surgical cavity hemorrhage is acceptable). Patients with seizure at presentation who have been started on Levetiracetam and have been stable for 48 hours prior to study registration are eligible at the discretion of treating physician.

3.2.2 Patients who have received systemic cytotoxic chemotherapy or approved oral targeted therapy or immunotherapy for 2 weeks, or other investigational agents for 3 weeks (4 half-lives for any oral targeted agents), or radiotherapy to a non-brain site for 2 weeks before initiation of IPdR therapy. Patients who have recovered from serious (CTCAE grade 3 or more higher) to grade 1 or less adverse events from the previous therapies are eligible. Prior/current/future hormonal therapy and/or bisphosphonates are permitted with no minimum interval to initiation of study therapy. If indicated, patients can receive palliative radiation therapy to a non-brain site concurrent or immediately post-study treatment with no minimum interval to initiation of study therapy.

3.2.3 Patients must not have received prior whole brain radiation therapy. Previous SRS/SRT done at least 3 weeks from the planned start of IPdR therapy is acceptable. SRS/SRT/fractionated boosts or neurosurgery can be performed once the DLT assessment has been completed, if felt clinically necessary.

3.2.4 Patients with primary tumors including germ cell tumor, or lymphoma/leukemia.

3.2.5 Patients who are receiving any other investigational agent.

3.2.6 Patients needing more than 8 mg dexamethasone per day at the time of start of WBRT will not be eligible to participate in the study. However, patients will be allowed entry into the study if it is medically safe to reduce the daily dose of dexamethasone to 8 mg or less from the day of the start of WBRT. The dexamethasone dose for such patients may be increased beyond 8 mg per day during the course of treatment if medically necessary. This increased need for dose should be communicated to the study's Principal Investigator, Dr Mohindra at the University of Maryland.

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

3.2.8 Uncontrolled intercurrent illness if itwould increase the risk of toxicity or limit compliance with study requirements. This includes, but is not limited to, ongoing uncontrolled serious infection requiring i.v. antibiotics, progressive congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because IPdR is an agent with 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.

3.3 Inclusion of Women and Minorities

Patients are eligible for this trial regardless of sex/gender, race, or ethnicity. Subject selection is equitable if they meet the inclusion and exclusion criteria. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 (amended in October, 2001) with regard to inclusion of women and minorities in clinical research, possible interaction between race/ethnicity and treatment have been considered.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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 (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

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

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization

A valid IRB approval

- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB are not required to submit separate IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9979 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree or Click on the By Lead Organization folder to expand, then select LAO-MN026 and protocol # 9979.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB

initiative, IRB data will load to RSS as described above.)

4.2.2 Submitting Regulatory Documents

Requirements For 9979 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Credentialing for performing neurocognitive testing through existing mechanisms within cooperative groups including but not limited to participation in a prior NRG or Alliance or any other cooperative group study or other PI approved measures including but not limited to credentialing through training arranged by the stud PI (or representative) or participating site's internal training. Each participating site should review the credentialing process with the study PI (or representative) prior to site activation.
- Completion of a Site Initiation Visit teleconference (SIV TC) with the lead site

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.
Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU Web site.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. 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

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab 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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which

is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment as rapidly as possible. 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. TREATMENT PLAN

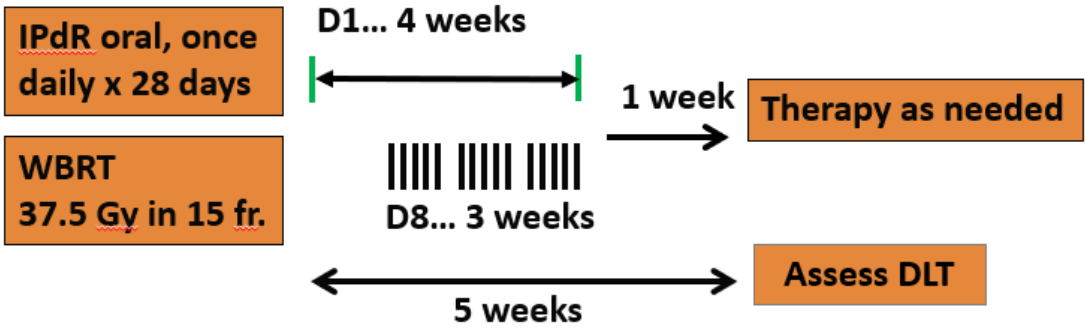
5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. 5-iodo-2-pyrimidinone-2'-deoxyribose (IPdR) (NSC 726188) will be delivered by oral (po) administration in capsule form once daily x 28 days. The capsules will be taken on an empty stomach (either 1 hour before or 2 hours after meals).

IPdR will be administered alone without WBRT during Week 1 (7 calendar days) and with WBRT during Weeks 2-4. On days when IPdR and WBRT are given concurrently, IPdR should be administered within 30 minutes to 2 hours prior to WBRT.

Because IPdR is an orally administered agent patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

Since the IPdR half-life is <1 day, 5 half-lives will be less than 1 week. Hence, an observation period up to D35 (D1 being 1st day of IPdR) is required to assess toxicity before enrolling a patient at the next IPdR dose level. Patients will be allowed to initiate systemic therapy per clinician preference after the D35 assessment.



The starting dose for IPdR for Phase 1 testing is based on the most sensitive (lower MTD) of the two animal species tested, *i.e.* ferrets and rats [44, 45]. The MTD for IPdR in ferrets, the most sensitive species, was determined to be ≤ 150 mg/kg/d for 14 days[45], which is equivalent to 850 mg/M^2/day for 14 days. The human equivalent dose (HED) is also 850 mg/M^2/day, the same as the ferret dose, based on body surface area (BSA).[48] Based on these calculations and pre-clinical animal data, 1/10th of the MTD is 85 mg/M^2/day (150 mg), the starting dose for this trial.

5.1.1 Part 1 IPdR Dose Escalation Schedule

Original Design (no longer active, reference only): An initial single patient dose escalation of IPdR will be conducted in Part 1. The starting dose is 150 mg (dose level 1A). A 100% dose escalation will be used until a treatment-related Grade 2+ toxicity or otherwise a DLT (as defined in Section 5.2) is observed. If a grade 2+ toxicity or DLT is observed in a patient, two additional patients will then be entered at this dose level. Subsequent steps would be guided by the occurrence of any grade 2+ toxicity or DLT in the cohort of 3 patients (including the initial single patient) with rules as states below:

a. If only 1 of the 3 patients experiences Grade 2+ toxicity and this is not a DLT, then the design will stay with Part 1.

b. If any of the 3 patients experience a DLT or 2+ patients experience Grade 2+ toxicity, then the design will switch to Part 2.

   i. If only 1 of 3 patients has experienced a DLT or 2+ patients experience Grade 2+ toxicity, the dose level in Part 2 will be the same and that dose level will be expanded to 6 patients (3 more patients)
   ii. If 2+ patients have experienced a DLT, then the dose will be de-escalated on Part 2 to half of the current dose (same as one level lower dose of part 1).

If dose level 1A results in 2 DLTs, then the trial will be closed as no maximum tolerated dose will have been identified. Dose Increment Schedule will be as shown in table 4 after 4 weeks of follow up of the prior cohort to assess acute, but delayed, toxicity).

Design Amendment:

The above text in section 5.1.1 is how the study was originally designed. However, to speed up accrual at the recommendation of CTEP medical officer and based on updated results of study 8866 and 9882 demonstrating safety of the drug IPdR at higher doses both alone and in combination with radiation (section 2.4) it was recommended to stop accrual to part 1 of the study at dose level IB and open Part 2 at dose level 2A (1200mg), following the modified 3+3 design outlined in the Part 2 below.

Table 4: Part 1 IPdR Dose Increment Schedule

Dose Level	Dose (mg)	Multiple of starting dose	% increase above previous dose level
1A	150	1x	N/A
1B	300	2x	100

5.1.2 Part 2 IPdR Dose Escalation Schedule

Original Design (no longer active, reference only): In Part 2 of this Phase 1 protocol, a standard cohort 3+3 design (see table 5) will be used where up to three patients will be accrued to a given dose level (starting with no increase of the final Part 1 dose and escalating per table 6). After each cohort has been accrued the study will temporarily close to assess DLT status of each patient. The decisions to re-open, and at what level to re-open, are on the following:

- If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the MTD has been exceeded and the next 3 patients will be treated at the next lower dose level (unless there have already been 6 accrued to that lower level).
- If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional patients (at least 2 of 6), the MTD will have been exceeded. If DLT is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.
- After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose level unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.
- If a patient fails to complete the initial course of therapy (cycle 1) for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the MTD goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

The MTD is defined as the dose below which 2 or more of 6 patients experience dose-limiting toxicity.

Design Amendment #1 (to be superceded by Design amendment #2 below):
In Part 2 of this Phase 1 protocol, a modified cohort 3+3 design (see table 5) will be used where up to three patients will be accrued to a given dose level (starting with 1200 mg IPdR dose and escalating per table 6). After each cohort has been accrued the study will temporarily close to assess DLT status of each patient. The decisions to re-open, and at what level to re-open, are on the following:

- If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level.
- If DLT is seen in 3 of 3 patients treated at a given dose level, then the maximally tolerated dose (MTD) has been exceeded and the next 3 patients will be treated at the next lower dose level such that a total of 6 patients are

treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the MTD and the study will proceed to the expansion cohort).

- If DLT is seen in 1 or 2 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. Including the three additional patients, following rule will be applied:
    - DLT is seen in 1 of the total 6 patients, proceed to the next higher dose level.
    - DLT is seen in 2 of the total 6 patients, then dose escalation is stopped, and this dose level is declared the MTD. The study will proceed to the expansion phase.
    - DLT is seen in 3 or more of the 6 patients have DLT, the MTD will have been exceeded and the next 3 patients will be treated at the next lower dose level such that a total of 6 patients are treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the MTD and the study will proceed to the expansion cohort).
- If a patient fails to complete the initial course of therapy (cycle 1) for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the MTD goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.
- In the event MTD is exceeded in part 2 at the first dose level (1200mg), the next lower dose of IPdR will be 900 mg. If MTD is exceeded even at 900 mg, then a dose level of 600 mg will be tested. At both these levels, a minimum of 6 patients will be evaluated.

The MTD is defined as the highest dose that has fewer than 3 (out of 6) patients experiencing dose-limiting toxicity.

Table 5: Part 2 IPdR Dose Increment Schedule

Dose level	Dose (mg)
2A*	1200
2B	1800
2C	2400

* See text in 5.1.2 for the scenario MTD is exceeded at 1200 mg dose.

Table 6: Part 2 Dose Escalation Decision Rules

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. If this is the highest dose-level, then accrue additional 3 patients at the dose-level.
3 out of 3	MTD is exceeded and the dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level such that a total of 6 patients are treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the MTD and the study will proceed to the expansion cohort).
1 or 2 out of 3	Enter 3 more patients at this dose level. • DLT is seen in 1 of the total 6 patients, proceed to the next higher dose level. • DLT is seen in 2 of the total 6 patients, then dose escalation is stopped, and this dose level is declared the maximally tolerated dose (MTD). The study will proceed to the expansion phase. • DLT is seen in 3 or more of the total 6 patients, then MTD is exceeded and the dose escalation is stopped. This dose level is declared maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level such that a total of 6 patients are treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the MTD and the study will proceed to the expansion cohort).
≤ 2 out of 6 at highest dose level below the maximally administered dose	This is the maximally tolerated dose, MTD.

Design Amendment #2:

As described in section 2.5.2, after accruing one patient at the dose-level 2B of table 5, the study is being amended to close the dose-level 2B and re-open 2A (1200 mg) to enroll 3 additional patients. The results of 6 total patients at dose-level 2A (1200 mg) will be evaluated per the table 7 below

Table 7: Part 2 Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3 (0 out of 6 patients)	This dose-level is declared the recommended phase 2 dose (RP2D). The study will proceed to the expansion phase.
1 or 2 out of 3 (total 1 or 2 out of 6 patients)	This dose level is declared the RP2D. The study will proceed to the expansion phase.
3 out of 3 (total 3 out of 6 patients)	MTD is exceeded and the dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level such that a total of 6 patients are treated to more fully assess the toxicities (unless there have already been 6 accrued to that lower level which will then be labeled as the RP2D and the study will proceed to the expansion cohort).

5.1.3 Expansion Cohort

An expansion cohort of 10 additional patients will be treated at the RP2D to confirm safety and further test the exploratory biomarkers. If after 16 patients have been treated at the RP2D (6 in part 2 and 10 in the expansion cohort), there are at most 5 patients with a DLT (31.25%) then this dose will remain as the RP2D. If there are more than 5, then the next lower dose will be RP2D.
Based on the design proposed, the highest acceptable probability of DLT is 31.25% (5 or less events in 16 patients), with the target expected probability of DLT of 20-30% (of which 18-20% is expected from WBRT alone).

The following table shows some of the operating characteristics for the current design under a number of possible DLT rates. For each given dose, the table displays the likelihood of increasing to the next dose and the probability of having at most 5 patients with DLTs (out of 16). For example, if the true DLT rate is 0.4 for a given dose level, there is only a 31% chance of accruing above that dose level. If on the other hand, the true DLT rate for a given dose is 0.3 (close to target acceptable rate) and if this dose level is determined to be the MTD during the dose finding stage, then there is a 66.6% chance of having 5 or fewer patients with DLT (out of 16).

DLT Rate	Probability of dose escalation	Probability of having at most 5 Patients with DLT (out of 16)
0.1	0.906	0.997
0.2	0.709	0.918

0.3	0.494	0.660
0.4	0.309	0.329
0.5	0.172	0.105
0.6	0.082	0.019

When a patient at any site is undergoing the study treatment or is pending DLT assessment, the PI of the study (or representative) will regularly meet (in person, by teleconference or by email) with the study statistician and the participating site's study team to review any updates regarding potential adverse events being experiences by the study subject from the WBRT (or any other extracranial RT, if applicable). If necessary, clinical inputs from the treating physician and the participating site PI will be obtained to assist in the decision regarding the adverse event being labeled as a DLT.

Unexpected severe late neurologic radiation toxicity or extra-cranial radiation toxicity will be recorded as a secondary end-point. These events will be reviewed by the independent DSMB who will be charged with considering cessation of the trial if the long term/delayed (6 months) ≥ grade 3 symptomatic neurotoxicity or other extra-cranial radiation toxicity is > 20%.

Use of other therapies post-DLT assessments which might impact neurological functioning (including but not limited to immunotherapy, for which safety data of immune-related neurological adverse events after WBRT is relatively limited) will be considered for this decision.

5.1.4 Whole Brain Radiation Therapy

5.1.4.1 Dose Specifications

Protocol whole brain radiation therapy (WBRT) will begin on Day 8 (7 days after the start of PO IPdR administration). One treatment (fraction) of 2.5 Gy will be given daily for not more than 5 days per week (15 fractions), once daily fractionation, Monday through Friday, without any planned interruptions for a total of 37.5 Gy over 3 weeks. Therefore, WBRT will be delivered from days 8 onward (Week 2 through 4). All portals shall be treated during each treatment session. Doses are specified as the target dose, which will be the dose on the central ray at mid-separation for two opposed coaxial equally weighted beams. "Compensating beams" that minimize hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve optimal dose homogeneity.

5.1.4.2 Technical Factors

Treatment will be delivered with megavoltage (MV) machines of energy ranging from 4 MV to 6 MV photons. Patients will be planned and treated using three-dimensional conformal radiation technique (3D-CRT). Field-in-field approaches to

3DCRT to optimize homogeneity are permitted. Intensity Modulated Radiotherapy (IMRT) with or without hippocampal avoidance (Fixed-gantry IMRT, helical tomotherapy or VMAT) will be allowed per institutional protocols. Partial brain cone down, stereotactic radiosurgery boost, electron therapy, particle therapy, or brachytherapy boost are not permissible during the course of the study treatment and until the DLT assessments are complete. However, patients will be eligible to undergo SRS/SRT/fractionated boosts or neurosurgery, once the DLT assessment has been completed, if felt clinically necessary.

5.1.4.3 Localization, Simulation,Immobilization and Dose prescription.

The patient will be treated in the supine position to allow planning and delivery of WBRT. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure daily treatment reproducibility. A non-contrast treatment-planning CT scan of the entire head region extending into neck should be obtained. When using hippocampal avoidance WBRT, it is recommended he axial slice thickness should match the MRI axial slice thickness as much as possible (preferred 1.5 mm). The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment.

For 3D-CRT, the target volume will include the entire cranial contents, with flashing beyond skin and adequate margin on the skull base as visualized on the simulator or portal films to account for beam penumbra and day-to-day set-up variation. Attempts will be made to exclude the lenses and the anterior globe from the beam either by field arrangement or shielding. 'Helmet' portals with customized immobilization and shielding are permitted. The dose is specified as the target dose, which shall be the dose on the central x-ray at mid-separation for two opposed coaxial equally weighted beams. "Compensating beams" that block hot spots (these hot spots are typically present along midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity. All portals shall be treated during each treatment session.

5.1.4.4 Hippocampal avoidance WBRT should be planned in accordance with the ongoing (or most recently completed, if no ongoing study) cooperative group protocol. The target volume will include the entire cranial contents to the foramen magnum (labeled as CTV). Care should be taken to delineate cribriform plate in the CTV. The PTV is equal to CTV without the hippocampal avoidance region. IMRT plan should be normalized such that 95% of the PTV volume receives prescription dose of 37.5 Gy (V37.5 Gy $\geq$ 95%), D2% (Dose to hottest 2% of PTV) is $\leq$ 40 Gy, D98% (Dose to 2% of PTV) is $\geq$ 32.5 Gy. Variation Acceptable include, V37.5 Gy $\geq$ 90%, D2% is $\leq$ 43 Gy and D98% is $\geq$ 30 Gy. QA for the physician-approved plan should be performed per institutional policies.Critical Structures

For both 3DCRT and hippocampal avoidance WBRT, the left (Lens_L) and right (Lens_R) lens should be contoured using the CT dataset only. For patients post-cataract surgery, a surrogate lens structure should be created.

For hippocampal avoidance WBRT, bilateral hippocampal contours (Hippocampi) will be manually generated on the fused planning MRI/CT image set by the treating physician according to contouring instructions specified on http://www.rtog.org//corelab/contouringatlases/hippocampalsparing.aspx . Hippocampal avoidance region (Hippocampi_05) will be generated by three-dimensionally expanding the hippocampal contours by 5 mm. Bilateral hippocampal contours will be subdivided into Left (Hippo_L) and Right (Hippo_R) hippocampi. Due to variance in eye position between the CT and MRI, if possible, the left (OpticNerve_L) and right (OpticNerve_R) optic nerve should be contoured using the CT dataset only. Located above the pituitary fossa, the optic chiasm (OpticChiasm) includes both anterior and posterior limbs. It is best visualized on SPGR/MPR/TFE T1 MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

OAR constraints for hippocampal avoidance WBRT are shown below:

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**	**Notes**
	D100%(Gy)	≤ 11	11 to 13	Dose to 100% of Hippocampus
	D_{max}(Gy)	≤ 16	16 to 20	Dose to hottest 0.03 cc volume of Hippocampus
OpticNerve_L	D_{max}(Gy)	≤ 37.5	37.5 to 40 Gy	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 37.5	37.5 to 40 Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 37.5	37.5 to 40 Gy	Dose to hottest 0.03 cc volume of OpticChiasm

In optimizing planning, the following treatment-planning priorities should be followed:
1. OpticChiasm
2. OpticNerve_L or OpticNerve_R
3. Hippocampus
4. PTV_3000
5. Lens_L or Lens_R

In the event that an OAR with higher priority than PTV cannot be constrained within Unacceptable Deviation limits, then D98% and/or V30Gy for PTV should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits. Please contact the study PI (or representative) if there are challenges meeting above.

5.1.4.5 Documentation Requirements

The following documents should be submitted to the PI at the University of Maryland

- Radiation Total Dose
- Radiation Dose per Fraction
- Radiation Number of fractions
- Radiation Technique: 3D-CRT or IMRT/VMAT/Tomotherapy
- Use of Hippocampal avoidance: Yes or No
- Radiation Start Date
- Radiation Completion Date
- Treatment Interruptions/Delays
- Acute on-treatment toxicity with grades
- RT plan report with dose to organs at risk, if applicable.
- Dexamethasone pill diary during WBRT and for three weeks post-WBRT (DLT assessment period)

Copies of simulation and port films and the complete WBRT daily treatment record and calculations will be submitted to the University of Maryland, Baltimore, Department of Radiation Oncology ONLY if specifically requested.

5.1.4.6 Compliance Criteria

The planned protocol treatment should be completed without any unplanned breaks/ interruptions. Dose delay/modification table has been noted in section 7.

5.1.4.7 Radiation Adverse Events

A focused history and physical examination should be performed at least once weekly during Weeks 1 through 4 (study treatment) and then towards the end of week 6 and 8 (observation period) to assess for acute treatment-related toxicity.

Acute (≤ 90 days from treatment start): Expected adverse events include hair loss, erythema of the scalp, headache, nausea and vomiting, eye/ear irritation, mucositis, taste/salivary changes, loss of appetite, fatigue, lethargy, and transient worsening of neurological deficits.

Late (> 90 days from treatment start): Possible adverse events include radiation necrosis, cognitive dysfunction, visual difficulties, accelerated atherosclerosis, and radiation-induced neoplasms.

5.1.4.8 Radiation Adverse Event Reporting

See Section 8 for Adverse Event Reporting

5.2 Definition of Dose-Limiting Toxicity

Patients who are removed from protocol treatment due to non-treatment related toxicities requiring treatment delay of > 14 days are not assessable for determination of the MTD and will be replaced.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 5.

Dose-limiting toxicity (DLT) in Parts 1 and 2 includes toxicity that is attributable to the IPdR and/or whole brain radiotherapy per the following:

- Any Grade 4+ neurologic adverse event, of any duration.
- Any Grade 3 neurologic adverse event that does not improve to baseline or Grade 1 within 7 days of onset.
- Any Grade 3 symptomatic CNS hemorrhage or ischemia
- Any Grade 4+ non-neurologic toxicity
    - An exception is Grade 4 cytopenia or metabolic abnormality without associated serious clinical symptoms (grade 4+) that improves to < Grade 4 within ≤ 7 days of onset

Patients with brain metastases are likely to have other sites of symptomatic extra-cranial disease in need of palliative radiation. Hence, per standard clinical practice, patients in this study protocol will be allowed to receive palliative extra-cranial irradiation, concurrently or sequentially, as indicated. This reflects best clinical practice.

However, such a procedure, may pose a possible risk of exaggerated radiation toxicity at the extra-cranial site, due to ongoing IPdR therapy. Since the use of palliative extra-cranial irradiation may be for a variety of extra-cranial indications, it is not feasible to account for all possible scenarios in the DLT definition. Further, for a more focused assessment of safe dose of IPdR in combination with WBRT, it is important to keep the DLT focused on neurological toxicity. Nevertheless, it will important to monitor patients for toxicity from extra-cranial palliative radiotherapy. Hence, to note that "Any grade 3+ adverse event that might occur from palliative radiation therapy to a non-brain site concurrent or immediately post-study treatment will not be considered as DLT for the study. But such events will be recorded by the local study team and communicated to the study PI. A final decision regarding RP2D will take these events into account. Further, the local site should update the study PI (or representative) of the plan for palliative radiation, including location, dose and fractionation. No such treatment should be

started without the study PI's approval."

Any grade 3+ adverse event that might occur from SRS/SRT/fractionated boosts or neurosurgery, once the DLT assessment has been completed will be accounted for as unexpected severe late radiation toxicity and noted as secondary end-point (See 5.1 above). Use of other therapies post-DLT assessments which might impact neurological functioning (including but not limited to immunotherapy, for which safety data of immune-related neurological adverse events after WBRT is relatively limited) will be considered for this decision.

5.3 General Concomitant Medication and Supportive Care Guidelines

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.

Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) and documented on each site's source documents as concomitant medication. Hematologic growth factor support is acceptable. Prior/current/future hormonal therapy and/or bisphosphonates are permitted with no minimum interval to initiation of study therapy. If indicated, patients can receive palliative radiation therapy to a non-brain site concurrent or immediately post-study treatment with no minimum interval to initiation of study therapy. Any grade 3+ adverse event that might occur from this treatment will not be considered as DLT for the study.

Patients with symptoms, neurologic signs or imaging evidence of edema or mass effect should be placed on dexamethasone at the time of brain metastasis diagnosis. Steroids will be continued without taper until WBRT is completed. For this patient population, variations in the amount and frequency of steroid usage are anticipated. Per standard of care, the least amount of steroid necessary is used. Hence, it is not appropriate to define a uniform stable dose of steroid for all patients accrued to the clinical study. Patients will be used to record the use of steroid medications using the steroid medication diary in Appendix E from time of consent through the DLT assessment period.

Nevertheless, to reduce/limit any potential PK impact of the concurrent use of dexamethasone, the maximum dose of dexamethasone for the patients at the time of the start of IPdR will be restricted to 8 mg per day or lower (2 mg qid, 4 mg bid or 8 mg once a day). Patients needing more than 8 mg dexamethasone on the day of the start of IPdR will not be eligible to participate in the study. Patients already accrued in the study at a dose of 8 mg or less who subsequently need more than 8 mg of dexamethasone per day while undergoing study treatment should be reported to the study PI. This will be recorded as an AE. Steroids will be continued without taper until the whole brain radiation therapy is completed.

At the completion of WBRT, a steroid taper should be initiated provided that the patient

does not have persistent symptoms related to edema or mass effect from brain metastases. Every four days, the dose should be lowered as follows:

Table 8: Dexamethasone Taper Schedule after Completion of WBRT

8 mg Starting Dose*		Duration
2 mg four times a day	**4 mg two times a day**	
2 mg four times a day	4 mg two times a day	Throughout course of WBRT
2 mg two times a day	3 mg two times a day	4 days
1 mg two times a day	1 mg two times a day	4 days
1 mg once daily	1 mg once daily	4 days
1 mg every other day	1 mg every other day	4 days
Discontinue	Discontinue	

* If the daily dose is < 8 mg per day, then maintain the same dose during WBRT and thereafter reduce dose by half every 4 days until 1 mg every other day times 4 days and then stop.

In patients who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice. Patients on steroids are recommended to receive gastritis prophylaxis and monitoring/treatment for oropharyngeal candidiasis.

Anticonvulsant usage and dosage should be noted at the time of study entry, at each follow-up evaluation and at any changes in medication use. Please refer to Section 6.4 for choice of anticonvulsant therapy.

Since, memantine use is increasingly becoming part of routine clinical practice and was considered part of the standard of care arm in the recently concluded NRG CC001 study, both twice daily memantine and extended release memantine (Namenda XR), including generic forms, will be strongly recommended. It is recommended to start memantine with the start of WBRT or the earliest feasible thereafter. The target daily dose for memantine is 20 mg (10mg divided twice daily). Dose is escalated by 5 mg per week to target of 10 mg twice daily (i.e., 5 mg a day for week 1, then 5 mg BID for week 2, then 10 mg in AM and 5 mg in PM for week 3, then 10 mg in AM and 10 mg in PM by week 4). The target dose for extended release memantine is 28 mg. Dose is escalated by 7 mg per week to target of 28 mg daily (i.e., 7 mg a day for week 1, then 14 mg a day for week 2, then 21 mg a day for week 3, then 28 mg a day for by week 4). Patients continue on memantine for 24 weeks.

At the same time, variations in practice patterns and insurance coverage for memantine exist. Variation in memantine use between patients in this phase-1 study may result in potential challenges in interpreting neurocognitive evaluations. Any future phase-II study will either require either standard use of memantine (like NRG CC001 study) or stratification by its use. However, given that the primary end-point of this phase-1 study is serious DLT as defined in section 5.2, to prevent any slow down in accrual, memantine use will not be mandatory.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will be planned for 4 weeks followed by 1 week for observation of acute toxicity and 6-months from the completion of WBRT for delayed toxicity or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be evaluated for up to two years from the study registration or until death, whichever occurs first. From the date of completion of WBRT, follow-ups would be done through clinic visits every 2 months (± 1 week) for the first 6 months, every 3-4 months (± 2 weeks) for the next 6 months and every 6 months (± 3 weeks) for the next one year. After the first DLT assessment visit (primary endpoint), these visits in the first 6 months can be performed at an outside institution if appropriate research staff (credentialed and registered as a study team member) is available to complete adverse event and neurocognitive evaluation. After the first 6 months of follow up, clinic visits may be replaced by phone calls or visits at an outside institution, if not felt feasible for logistic reasons. Follow up notes or documentation of phone calls must be included in the study chart. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Follow-up MRI at 6 months (± 2 weeks) from the completion of WBRT is required to assess intracranial treatment response and disease control. As guided by institutional practices, MRIs are also recommended to be performed during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT.

5.6 Criteria for Removal from Study

Patients will go off study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Since treatment for this Phase 1 study includes only 1 cycle of treatment consisting of 4 weeks of IPdR with 15 fractions of concurrent radiation, treatment with IPdR and WBRT will continue as long as there is no DLT as defined above. There will be no dose modifications if a DLT occurs. Patients experiencing a DLT will be removed from IPdR protocol treatment and may complete WBRT when toxicities recover to < Grade 3 as per institutional standard of care.

Patients experiencing non-treatment related toxicities may have IPdR and WBRT held until toxicities resolve to < Grade 3 for up to 14 days and then they may resume IPdR (at the assigned dose level) and WBRT to complete protocol treatment. Patients who are removed from protocol treatment due to non-treatment related toxicities requiring treatment delay of > 14 days are not assessable for determination of the MTD and will be replaced.

7. 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 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

7.1.1 CAEPR for IPdR

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.

7.2 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 web site 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 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when 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 phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 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.

7.3.3 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. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade
Injury, Poisoning and Procedural Complications	Radiation Dermatitis	1 or 2
Skin and Subcutaneous Connective Tissue Disorder	Scalp Alopecia	1 or 2
Respiratory, Thoracic and Mediastinal Disorders	Pharyngeal mucositis	1 or 2
Ear and Labyrinth Disorder	Otitis	1 or 2
	Hearing Loss	1
	Tinnitus	1
Eye Disorder	Conjunctivitis	1 or 2
	Blurred vision	1
Nervous System Disorder	Dysgeusia	1 or 2
Gastrointestinal Disorders	Dry mouth	1 or 2

7.4 Routine Adverse Event Reporting

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

7.5 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.

7.6 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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 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 and distributed by the Pharmaceutical Management Branch, NCI as 300 mg and 600 mg capsules.

- The 300 mg capsules are Swedish orange, opaque, hard gelatin capsules, size 2 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 silica gel desiccant.
- 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.

Storage: Store bottles refrigerated at 2-8^{o}C in the original manufacturer's container. Do not re-package capsules or remove the desiccant.

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.

8.1.1 Agent Ordering and Agent Accountability

8.1.1.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (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 and a "current" password. 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.

8.1.1.2 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.

8.1.1.3 Useful Links and Contact

- 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 Associate Registration and IAM account help: ctepreghelp@ctep.nci.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)

8.1.1.4 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.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacokinetics of IPdR

The plasma pharmacokinetics sampling strategy for the human subjects in this Phase 1 study is based on drug clearance measurements of IPdR in athymic mice,[39-41] Fischer-344 rats [44] and Rhesus monkeys [45] and the studies of hepatic IPdR-aldehyde oxidase activity following IPdR treatment in athymic mice [40], Fischer-344 rats [44] and ferrets [45]. In athymic mice, rats and Rhesus monkeys, peak plasma levels of IPdR were noted within 15-30 minutes of IPdR administration.[38, 41, 44] In Rhesus monkeys, the measured initial plasma distributive half-life ($T_{1/2\,\alpha}$) was 6.5 min and the elimination half-life ($T_{1/2\beta}$) in plasma was 63 min following an iv dose of 50 mg/kg.[45] In athymic mice, the plasma pharmacokinetics at higher po IPdR doses (≥ 1000 mg/kg) showed longer elimination phases suggestive of partial hepatic enzyme saturation.[39] In a follow-up study in athymic mice,[40] we found that a single IPdR dose of 1000 mg/kg resulted in a 50% reduction in hepatic IPdR-aldehyde oxidase activity at 24 hours following drug administration that returned to normal levels at 48-96 hours. Additionally, measurement of hepatic IPdR-aldehyde oxidase activity in ferrets receiving 150 or 1500 mg/kg/d x 14 d showed a decrease in enzyme activity to 50% and 30% of controls, respectively, when measured at the end of the 14-day treatment period.[45] In the recently published Phase 0 clinical trial of single dose oral IPdR, peak plasma levels after 2400 mg reached 4.0 μmol/L at ~90 minutes with a half-life of elimination of 90 minutes.[46]

Based on these pre-clinical data, we have designed an initial plasma pharmacokinetic strategy that will be limited to 16 blood samples per study patient.

- On Day 1, a pre-study blood will be obtained and then sampling will be done at 30, 60, 120, 240 minutes and 24 hours (just prior to Day 2 po dose) following the initial po drug administration.

- On Days 15 and 22 of the 28-day dosing schedule, blood will be obtained just prior to the po drug administration and then at 30, 60, 120 and 240 minutes following po dosing.

- A five minute positive or negative margin on each of the above times on Day 1 (30 through 240 minutes) and 10 min for the 24 hours timepoint is acceptable.

Five cc of blood in a heparinized tube will be taken on Days 1, 15 and 22 at each time point and the plasma separated and frozen in liquid nitrogen or an -80º C freezer and stored in a -80º C freezer. The samples will be shipped under dry ice in individual patient batches (Day 1, Day 15 and Day 22 all sent in one shipment) for later processing using the LC/MS/MS method in the research laboratory of Dr. Jerry Collins at NCI. The plasma samples from the initial Part I patient group will then be analyzed to determine plasma levels of IPdR, IUdR, IP and IU and the data plotted for pharmacokinetics observations (modeling). Adjustments in sampling will then be decided to provide appropriate data points in humans for Part 2 of the Phase 1 study. For measurement of

levels of IPdR and its metabolites in plasma, the methods, equipment and personnel are the same as utilized in the CTEP protocol for the Phase 0 study of IPdR as published.[46]

If the mouse, ferret, and Rhesus monkey data are not predictive of po IPdR metabolism in humans, then the initial sampling strategy should point to the best approach. All pharmacokinetic data will be monitored in collaboration with Jerry Collins, Ph.D. at DCTP. The previously described LC/MS/MS technique will be used, as previously published,[44] to measure the extracted nucleoside analogs and metabolites. The final pharmacokinetic sampling protocol will monitor IPdR decay in plasma for at least 2 to 3 half-lives on Days 1 (including just prior to dosing on Day 2), 15, and 22.

9.2 Measurement of %IUdR-DNA Incorporation in Peripheral Granulocytes and Tumor Tissues as an Exploratory Biomarker for IPdR Effects at the MTD.

9.2.1 Background

%IUdR-DNA incorporation in a cell (*in vitro*) or tissue (*in vivo*) has been shown to correlate directly with the extent of radiosensitization.[25, 26] In the pre-clinical *in vivo* testing of po IPdR as a prodrug for IUdR-mediated radiosensitization, ≥ 2-fold increases in %IUdR-DNA tumor cell incorporation and ≥ 2-fold decreases in %IUdR-DNA incorporation in proliferating dose-limiting normal tissues (bone marrow and intestine) following po IPdR compared to oral or continuous intravenous infusions of IUdR (using MTD schedules) have been found in 4 different human tumor xenografts in athymic mice.[39-42] In prior clinical Phase 1 trials of continuous intravenous infusions of IUdR (± biochemical modulators), the %IUdR-DNA incorporation in circulating granulocytes during and following the IUdR infusion has been measured as a surrogate for proliferating normal human tissue (bone marrow).[32, 50-54] In general, the %IUdR-DNA incorporation in circulating granulocytes increased linearly with a linear increase in steady-state plasma levels of IUdR. Additionally, high (≥ 6%) %IUdR-DNA levels in peripheral granulocytes predicted for systemic bone marrow toxicity to continuous infusion IUdR. In the pre-clinical studies of oral IPdR daily for 14 days in athymic mice and ferrets,[39, 41, 47] the %IUdR-DNA incorporation was ≤ 2% in circulating granulocytes during and following treatment and no changes in blood counts were found in ferrets and rats,[44, 45] suggesting that bone marrow toxicity may not be dose-limiting for oral IPdR in humans. Additionally, no myelosuppression or bone marrow abnormalities were seen in the IPdR toxicology studies, where IPdR was given once daily x 14 days in ferrets and x 28 days in rats.[44, 45]

In some human Phase 1 studies of ci IUdR, tumor biopsies have been obtained at defined intervals to correlate %IUdR-DNA incorporation in tumor cells to the duration and/or plasma steady state drug levels of CIV IUdR.[59-64] Again, a linear relationship of the %IUdR-DNA incorporation in tumor tissue and the steady-state plasma IUdR level was found.

9.2.2 Plan for Measurement of %IUdR-DNA Incorporation in Peripheral Granulocytes and Tumor Tissues as an Exploratory Biomarker for IPdR Effects at the MTD

When the MTD of oral IPdR given once daily for 28 days is established, we will measure the %IUdR-DNA incorporation in circulating granulocytes as a surrogate of bone marrow using MTD dosing in 1st 6 patients accrued in the expansion cohort at the MTD. For these patients, the measurements will be done prior to study (Day 1) and at Days 8, 15, 22 and 29 of the 28-day treatment and at the first two-month follow-up. Granulocyte isolation will be accomplished using a histopaque (Sigma Chemical Co., St. Louis, MO) 1077/1119 gradient, based on a previously used technique.[32] Following digestion of DNA to nucleosides, the %IUdR-DNA incorporation will be determined by HPLC using a previously published technique by our group.[32] The % thymidine replacement will be calculated using authentic nucleoside standards as:

$$\frac{[mMoles\ IUdR] \times 100}{[mMoles\ IUdR + mMoles\ TdR]}$$

We also propose to measure the %IUdR-DNA incorporation in tumor tissue in patients with brain metastases receiving the MTD of po IPdR whose tumor(s) can be biopsied by direct visualization (*i.e.* subcutaneous mass or endoscopy) or by CT guidance. Tumor biopsy is not required for participation in this study. Tumor biopsy is not recommended if tumor is not easily accessible for biopsy (i.e. tumor biopsy should not be attempted if it is associated with a greater than minimal risk of complications as determined by the treating physician). However, if tumor is easily accessible and biopsy would have a minimal risk of complications, then tumor biopsy should be performed. Tumor biopsies may be obtained from the primary tumor or extracranial metastasis, whichever is most easily accessible. Biopsy of the brain metastasis is not permitted. Tumor biopsies will be obtained at Day 8 of the 28-day IPdR treatment. For cutaneous tumors, a 6 mm punch biopsy will be performed. For subcutaneous tumors or deep-seated tumors, a 14-gauge Tru-cut needle biopsy will be performed. For endoscopy, snare biopsy (ies) of the luminal mass will be performed. CT-guidance will be used for needle biopsies or deep-seated tumors. The sample will be collected on aluminum foil and flash frozen in liquid nitrogen. Both flow cytometry and HPLC analysis will be performed on tumor tissue to determine the %IUdR-DNA incorporation in tumor cells. Sections of the tumor biopsy will also be evaluated to confirm the presence of tumor using hematoxylin and eosin staining.

For flow cytometry and HPLC analysis, the remainder of the tumor specimen will be fixed in 70% ethanol (2 ml Hanks balanced salt solution + 5 ml 95% ethanol) within 1 hour of tissue acquisition and stored at 4°C. Flow cytometry and HPLC samples will be processed in Dr. Collins' lab at NCI as previously published by Drs. Collins, Kinsella and collaborators.[32, 55, 59-64] Briefly for flow cytometry, nuclei from tumor tissue will be isolated with pepsin, partially denatured with 2N HCl, incubated with a mouse anti-BUdR/IUdR monoclonal antibody (Becton Dickinson, Mountain View, CA) followed by incubation with a fluorescein isothiocyanate-labeled goat anti-mouse secondary antibody. Finally, the nuclei will be incubated with propidium iodide to label DNA. Up to 1×10^4

nuclei will be analyzed using an EPICS V cell sorter (Coulter, Corp. Inc., Hialeah, FL). For HPLC, DNA from isolated nuclei will be enzymatically digested into free nucleosides. A Waters 600 E solvent delivery system on a 3.9 x 300 mm μ Bondapak reverse-phase column (Waters Corp., Milford, MA) will be used, according to the method of Belanger et al.[32, 55] The mobile phase consists of 100 mm of sodium acetate buffer (pH 5.45) plus 7% (v/v) acetonitrile. Peak identification and quantitation of IUdR and thymidine (TdR) will again be performed against authentic nucleoside standards and the %IUdR-DNA incorporation will be calculated as above.

9.2.3 Specimen submission

Please email Dr. Larry Anderson (larry.anderson@nih.gov) and Ms. Kimberly Hill (hillk2@mail.nih.gov) when the shipment is sent and avoid a Friday delivery. The shipping address of Dr. Collins' laboratory for the plasma PK samples and the granulocyte and tumor tissue samples for %IUdR-DNA cellular incorporation is:

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

10. STUDY CALENDAR

Pre-treatment laboratory tests and exams must be completed, eligibility confirmed and the patient registered within 6 weeks; baseline brain imaging evaluations to be done within 4-6 weeks before start of the study treatment. Study treatment should begin within 2 weeks after registration. Vital signs and performance status should be obtained within 1 week before the start of study treatment.

	Pre-Study treatment	Wk 1	Wk 2	Wk 3	Wk 4	DLT Assessment On D35 (or ≤ 3 days after D35)	Follow-Up [i]	Off Study [k]
Informed consent	X							
WBRT planning	X[a]	X[a]						
IPdR [R]		X	X	X	X			
WBRT			X	X	X			
Urine or serum pregnancy test (if indicated)	X							
History and physical exam [b]	X	X	X	X	X	X	X	X
Adverse Events [b]		X	X	X	X	X	X	X
Blood work [c]	X	X	X	X	X	X		
PK studies [R]		X[d]		X[e]	X[e]			
Up to 6 RP2D/MTD patients only (expansion cohort): Blood for granulocytes [R]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	
Up to 6 RP2D/MTD patients only (expansion cohort): Extracranial tumor biopsy mandatory [l, R]			X[f]					
MRI brain w/ IV contrast [h]	X						X[g]	X
Neurocognitive and Quality of life evaluation [R]	X					X[j]	X[j]	X

a. May be performed prior to study registration per standard of care
b. Baseline physical examinations are to be conducted within 1 week prior to start of protocol therapy. In the event that the patient's condition is

deteriorating, these evaluations should be repeated within 48 hours prior to the initiation of therapy. Physical examination includes vital signs (pulse, blood pressure, temperature), concomitant medications, performance status, weight and at pre-study only, height. The evaluations are recommended to be done towards the end of the respective week.

c. Blood work to include CBC with differential count, comprehensive metabolic profile including serum albumin, alkaline phosphatase, total bilirubin, BUN, creatinine, total protein, SGOT [AST], SGPT [ALT]. The evaluations are recommended to be done towards the end of the respective week.

d. On Day 1, a pre-study blood will be obtained and then sampling will be done at 30, 60, 120 and 240 minutes and 24 hours (just prior to Day 2 dosing) following the initial po drug administration. A five minute positive or negative margin on each of the above times on Day 1 (30 through 240 minutes) and 10 min for the 24 hours timepoint is acceptable.

e. On Days 15 and 22 of the 28-day dosing schedule, blood will be obtained just prior to the po drug administration and then at 30, 60, 120 and 240 minutes following po dosing. A five minute positive or negative margin on each of the above times on Day 1 (30 through 240 minutes) is acceptable.

f: %IUdR-DNA cellular incorporation. Sample collection will be prior to study (Day 1) and at Days 8, 15, 22 and 29 of the 28-day treatment followed by first two-month follow up.

g: Follow-up MRI at 6 months (± 2 week) from the completion of WBRT is required. As guided by institutional practices, MRIs are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT. If progressive disease is seen on MRI, subsequent evaluations are not required for study.

h. For patients accrued to part 2 of the study, please send anonymized pre- and post-treatment (up to 6 months from the date of completion of WBRT) scans via FTP or hard copy CD to the study PI for central review of response.

i From the date of completion of WBRT, follow-up visits to be done every 2 months (± 1 week) for the first 6 months, then and are recommended every 3-4 months (± 2 weeks) for the next 6 months then every 6 months (± 3 weeks) for the next one year. These visits can be performed at an outside institution if appropriate research staff (credentialed and registered as a study team member prior to the evaluations) is available to complete adverse event, neurocognitive testing and QOL evaluation. After the first 6 months of follow up, clinic visits may be replaced by phone calls or visits at an outside institution. Follow up notes or documentation of phone calls must be included in the study chart.

j. Neurocognitive and quality of life evaluation to be performed at the D35 assessment time-point and then during follow-up visits every 2 months (± 1 week) for the first 6 months from the date of completion of WBRT (for patients without intracranial progression). A total of 5 neurocognitive and quality of life evaluations will be performed: Baseline, D35, 2-, 4- and 6- months from the date of completion of WBRT.

k. To be performed only if feasible if the patient is removed from the study.

l. Perform biopsy only if patient has an easily accessible tumor.

R. Research.

10.1 Neurocognitive Evaluation

10.1.1 Hopkins Verbal Learning Test (HVLT-R)

The HVLT-R incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) for memorization with 4 words drawn from 3 semantic categories, which differ across the 6 forms. Patients will be asked to recall from the list of 12 targets for 3 consecutive trials (immediate recall), identify the 12 targets from a list of semantically related or unrelated items (immediate recognition), and recall the 12 targets after a 20-minute delay (delayed recall). Raw scores will be derived for total recall, delayed recall, retention (percentage retained), and a recognition discrimination index. Each patient will serve as his/her own control, as the difference in scores obtained at baseline and at pre-specified post-treatment intervals will be calculated. The HVLT-R is owned and copyright protected by Psychological Assessment Resources, Inc. (PAR). Electronic distribution of the HVLT form is not currently permitted by PAR; please send an email to the study PI, Dr Mohindra, University of Maryland, to request a paper copy of the HVLT prior to enrolling any patients (or to get information regarding procuring institutional copies for the study). Future updates regarding electronic handling of these forms if allowed will be provided directly to the study teams, as and when available. Based on the copyright agreement with PAR, completed HVLT-R forms can be uploaded to NCI's secure, password protected online portal, iMedidata RAVE ("web portal"). The uploaded forms should contain the original copyright notice on the form. Access to the web portal shall be limited to authorized study personnel at the study site. Completed HVLT-R forms shall not be printed or downloaded from the web portal. Once uploaded to iMedidata RAVE, a hard copy of the completed HVLT-R forms should be mailed to the study PI.

Study personnel administering the HVLT must be previously credentialed in performing neurocognitive testing through existing mechanisms within cooperative groups including but not limited to participation in a prior NRG or Alliance or any other cooperative group study. Email a copy of this certification to the study PI, Dr Mohindra. The PI may also approve other measures as applicable including but not limited to credentialing through training arranged by the stud PI (or representative) or participating site's internal training. Each participating site should review the credentialing process with the study PI (or representative) prior to site activation. This requirement is necessary before any patients can be enrolled into the study at the site; see Site Registration, section 4.2.2. These assessments can be performed at an outside institution if appropriate research staff (credentialed and registered as a study team member prior to the evaluations) is available to complete adverse event and neurocognitive evaluation.

Scoring of HVLT-R

1. HVLT-R Delayed Recall
   Patient scores on the HVLT-R delayed recall section have an integer range from 0 to 12 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words. The change in score

from baseline to 2-, 4- and 6- months ranges from - 12 to 12. Change scores from 1 to 12 indicate declining cognitive function. A change score of 0 indicates preserved cognitive function. Change scores from -1 to -12 indicate improved cognitive function and are not expected.

2. HVLT-R Free Recall
   Patient scores on the HVLT-R free recall section have an integer range from 0 to 36 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words in three trials.

3. HVLT-R Delayed Recognition
   10.1.2 Patient scores on the HVLT-R delayed recognition section have an integer range from -12 to 12 with lower scores indicating declining cognitive function. The score is the number of correctly identified words from the list of 12 words minus the number of incorrectly identified words from the list of 12 words.

10.2 Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) for Quality of Life (QOL)

The FACT-BR is a multidimensional, self-report QOL instrument specifically designed and validated for use with brain malignancy patients. It is written at the 4th grade reading level and can be completed in 5 to 10 minutes with little or no assistance in patients who are not neurologically incapacitated. It measures quality of life related to symptoms or problems across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Items are rated on a five-point scale: 0-“not at all”, 1- “a little bit”, 2-“somewhat”, 3-“quite a bit” and 4-“very much”. The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. Patient scores on the FACT-Br range from 0 to 92 with lower scores indicating declining quality of life. FACT-BR is self-administered and does not require precertification. It has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at: **http://www.facit.org/facitorg/questionnaires**.

The assessments will be scored centrally by a blinded reviewer to avoid potential bias. The self-report of quality of life can be completed by the patient or the examiner and does not require pre-certification.

Scoring of FACT-BR Assessments:
The change scores from pretreatment from baseline to 2, 4 and 6 months will be estimated. A mean difference of 5 points represents a clinically meaningful change (CMC). A difference of less than 5 will not be considered meaningful, even if it has statistical significance.

11. MEASUREMENT OF EFFECT

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 patients in part 2 of the study (to exclude patients treated at lower doses in part 1 thereby minimizing heterogeneity in response) will be carefully monitored for tumor response in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria noted below. Each eligible patient must have at least one measurable lesion that will be included in the radiation treatment volume. If the measurable disease is restricted to a solitary lesion, the presence of malignancy must be confirmed by cytology/histology. Tumor lesion(s) included within the high dose radiation treatment volume (≥ 95% isodose line) will be considered as the target lesions for response evaluation. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be evaluated at baseline at 6 months (± 2 weeks) from the completion of WBRT. As guided by institutional practices, MRIs are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT.

11.1 Antitumor Effect – Intracranial Metastases

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

Evaluable for objective response. All patients will be evaluable for objective response from the time of their first treatment with IPdR.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 7 daily doses of IPdR and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions including small lesions (longest diameter <10 mm [< 1 cm]) are considered non-measurable disease.

Target lesions. All measurable lesions up to a maximum of 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the longest diameters for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional MRI. MRI-scan based response evaluation is based on the assumption that MRI slice thickness is 5 mm (0.5 cm) or less. If MRI scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. It is recommended that MRI sequences be followed per the consensus recommendations as detailed in the article: "Consensus recommendations for standardized brain tumor imaging protocol in clinical trials. Benjamin M. Ellingson *et al.* Neuro Oncol. 2015 Sep; 17(9):1188-98. doi: 10.1093/neuonc/nov095. Epub 2015 Aug 5."

Please contact the PI and the Radiology Co-Investigators, Dr. Prashant Raghavan, Dr Timothy Kaufmann or Dr Rao Gullapalli, with any questions.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ Not evaluated	No	PR
SD	Non-CR/ Non-PD/ Not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment

until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Intracranial Progression-Free Survival

The date at which intracranial progression is radiographically identified will be used to calculate the intracranial PFS. Intracranial PFS will be measured from the date of start of treatment to time of progression or death, whichever occurs first. Intracranial PFS will be assessed 2, 4, 6 and 8 months after the initiation of study therapy. If intracranial progressive disease is seen on MRI, any subsequent MRI scans will be performed as clinically indicated standard of care.

11.1.7 Response Review

All responses will be reviewed by the radiology investigator of the study at the study's completion to allow simultaneous review of the patients' files and radiological images. Raw data from baseline and follow up MRI will be obtained from the participating institutions for volumetric, perfusion and diffusion-based response assessments. Sites should send anonymized pre- and post-treatment scans via FTP or as a hard copy CD to the study PI, Dr Mohindra at the University of Maryland, as listed on the title page. The scans and data will be stored in HIPAA compliant secure servers within the Department of Radiology. Each patient will be identified only with the patient number assigned by the study.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 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.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. 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 RSS, all persons with Rave roles

assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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 link in the upper right pane of the iMedidata screen.

Users 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, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 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) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 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.

An End of Study CRF is to be completed by the PI and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). 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).

12.3 CTEP Multicenter Guidelines

Not Applicable

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the

clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance

with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints – Determination of the Maximum Tolerated Dose

The primary endpoint of this study is to determine the RP2D dose of daily oral IPdR administered alone for 7 days and then concurrently with conventionally fractionated whole brain radiation therapy (WBRT) for 3 weeks in patients with brain metastases. In order to determine the RP2D, an expansion cohort will be utilized, which is outlined in detail in sections 5.1.3. Dose limiting toxicity (DLT) is fully defined in section 5.2.

13.2 Sample Size/Accrual Rate

Any estimate of accrual in a dose escalation study is difficult because the study team does not know when the MTD will be found. In the original design, assuming both Parts 1 and 2 require 3 dose escalations to determine the MTD, the sample size was estimated between 17 (1 patient at 2 levels and 3 at the third level in Part 1 and 3 patients at the first level, 6 at the second level, and 3 at the third in Part 2) and 27 (3 patients at each of the 3 levels in Part 1 and 6 at each level in Part 2). Six patients were planned to be accrued at the MTD in the expansion cohort to permit the analyses of the %IUdR-DNA cellular incorporation in circulating granulocytes and tumor once MTD has been determined. This would also help narrow the confidence interval on the estimate of incidence of toxicity at the MTD which makes the expected accrual between 23 and 33. The low number of the expansion cohort was chosen considering the logistics of arranging for a study screening, consent, registration, biomarker testing and limiting total patient numbers/budget**.** The maximum accrual will be 47. This includes 7 in Part 1 (1 patient at the first 4 levels followed by 3 at level IE), 30 in Part 2 (6 patients at each of the 5 dose levels), 6 additional patients at the MTD, and an additional 4 to account for replacements.

In the proposed amendment #6 (Dec. 2017), to accelerate accrual, the dose-escalation design was changed such that part -1 was truncated at dose level IB, with one patient accrued at each dose-level (total 2). The study wasopened to part-2 as a modified 3+3 design with three dose-levels accruing up to 6 patients each depending on the occurrence of DLT. Thereby, the number of patients accrued in part 1 and 2 will range from 8 (2+6) to 20 (2+6+6+6).
Till date (December 2019), 2 patients have been accrued in part 1 (1+1), 3 patients at dose-level 2A and 1 patient at dose-level 2B. In the current proposed design amendment #7, since dose-level 2B is being stopped with one patient and dose level 2A will be re-opened for additional 3 patients, the expected accrual in the two parts will range from 9 (2+7) to 15 (2+7+6) patients. Ten patients will be accrued at the RP2D in the expansion cohort to help narrow the confidence interval on the estimate of incidence of toxicity at the RP2D which makes the range of accrual between 19 and 25. The maximum accrual will be 25 patients. Up to a total of six patients in the expansion cohort will be analyzed for the %IUdR-DNA cellular incorporation in circulating granulocytes and tumor once RP2D has been determined.

Assuming an accrual rate of 1-2 patients per month, for a minimal accrual of 18 patients

will require approximately18-24 months. Additionally the study will close for evaluation of DLT leading to atotal estimated study time of 30 months

Both men and women of all races and ethnic groups, when appropriate, will be eligible for these studies. Subject selection is equitable if they meet the inclusion and exclusion criteria. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 (amended in October, 2001) with regard to inclusion of women and minorities in clinical research, possible interaction between race/ethnicity and treatment have been considered. Based on the historical number of brain metastases patients who receive WBRT per month at the University of Maryland and Mayo Clinic, there are expected to be approximately 15% of participants classified as minorities by race and 50% of participants to be female.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	**1**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	2	1	0	**4**
White	19	19	1	1	**40**
More Than One Race	0	0	0	0	**0**
Total	**21**	**23**	**2**	**1**	**47**

13.3 Stratification Factors

None.

13.4 Analysis of Secondary Endpoints

13.4.1 Tumor Response

Best Response is defined to be the best objective status recorded from the start of the treatment until disease progression/recurrence. The patient's best response assignment will depend on the achievement of measurement criteria as described in section 11.0. Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population (overall and by tumor group). The number of responses may indicate further evaluation for specific tumor types in a Phase 2 setting. Only patients in Part 2 of the study will be included in this evaluation.

13.4.2 Pharmacokinetics

The pharmacokinetics of daily oral dosing of IPdR for 28 days will be explored.

13.4.3 Biomarkers

Biomarker data will be explored in a simple descriptive manner as data are limited in this small phase 1 study.

13.4.4 Intracranial progression free survival (icPFS) and Overall Survival (OS)

These will be explored using the Kaplan-Meier method. For estimation of icPFS, patients alive without intracranial progression at last follow-up will be censored at the date of the last radiologic assessment whereas intracranial progression or death will be scored as events. The icPFS estimates at 6 months with their standard error of the estimate will be reported. For calculation of OS, patients alive at last follow-up will be censored.

13.4.5 Incidence of delayed neurological toxicity at 2, 4 and 6-months (± 1 week) post-completion of WBRT (for patients without intracranial progression) including:

a. Delayed-recall through HVLT-R
b. Quality of life as measured by the FACT-BR

REFERENCES

1. Posner, J.B. and N.L. Chernik, Intracranial metastases from systemic cancer. Adv Neurol, 1978. 19: p. 579-92.

2. Stewart, B.W., P. Kleihues, and I.A.f.R.o. Cancer, World cancer report. Vol. 57. 2003: IARC press Lyon.

3. Gaspar, L.E., et al., Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys, 2000. 47(4): p. 1001-6.

4. Nussbaum, E.S., et al., Brain metastases. Histology, multiplicity, surgery, and survival. Cancer, 1996. 78(8): p. 1781-8.

5. Sperduto, P.W., et al., Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol, 2012. 30(4): p. 419-25.

6. Tsao, M.N., et al., Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev, 2012. 4: p. CD003869.

7. Young, D.F., et al., Rapid-course radiation therapy of cerebral metastases: results and complications. Cancer, 1974. 34(4): p. 1069-76.

8. Rades, D., et al., Dose escalation beyond 30 grays in 10 fractions for patients with multiple brain metastases. Cancer, 2007. 110(6): p. 1345-50.

9. Chao, J.H., R. Phillips, and J.J. Nickson, Roentgen-ray therapy of cerebral metastases. Cancer, 1954. 7(4): p. 682-9.

10. Gaspar, L.E., et al., The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol, 2010. 96(1): p. 17-32.

11. Chang, E.L., et al., Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol, 2009. 10(11): p. 1037-44.

12. Patchell, R.A., et al., Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA, 1998. 280(17): p. 1485-9.

13. Kocher, M., et al., Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol, 2011. 29(2): p. 134-41.

14. Mehta, M., The dandelion effect: treat the whole lawn or weed selectively? J Clin Oncol,

2011. 29(2): p. 121-4.

15. Aoyama, H., et al., Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA, 2006. 295(21): p. 2483-91.

16. Pirzkall, A., et al., Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol, 1998. 16(11): p. 3563-9.

17. Wang, T.J., et al., Outcomes of gamma knife radiosurgery, bi-modality & tri-modality treatment regimens for patients with one or multiple brain metastases: the Columbia University Medical Center experience. J Neurooncol, 2015. 122(2): p. 399-408.

18. Brown, P.D., et al. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. in ASCO Annual Meeting. 2015. Chicago.

19. DeAngelis, L.M., et al., The combined use of radiation therapy and lonidamine in the treatment of brain metastases. Journal of neuro-oncology, 1989. 7(3): p. 241-247.

20. Phillips, T.L., et al., Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. Int J Radiat Oncol Biol Phys, 1995. 33(2): p. 339-48.

21. Suh, J.H., et al., Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. Journal of clinical oncology, 2006. 24(1): p. 106-114.

22. Eyre, H.J., et al., Randomized trial of radiotherapy versus radiotherapy plus metronidazole for the treatment metastatic cancer to brain. A Southwest Oncology Group study. J Neurooncol, 1984. 2(4): p. 325-30.

23. Komarnicky, L.T., et al., A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). Int J Radiat Oncol Biol Phys, 1991. 20(1): p. 53-8.

24. Mehta, M.P., et al., Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. J Clin Oncol, 2003. 21(13): p. 2529-36.

25. Kinsella, T.J., et al., The use of halogenated thymidine analogs as clinical radiosensitizers: rationale, current status, and future prospects: non-hypoxic cell sensitizers. International journal of radiation oncology, biology, physics, 1984. 10(8): p. 1399-406.

26. Kinsella, T.J., An approach to the radiosensitization of human tumors. Cancer J Sci Am, 1996. 2(4): p. 184-93.

27. Shewach, D.S. and T.S. Lawrence, Antimetabolite radiosensitizers. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2007. 25(26): p. 4043-50.

28. Sullivan, F.J., et al., National Cancer Institute (phase II) study of high-grade glioma treated with accelerated hyperfractionated radiation and iododeoxyuridine: results in anaplastic astrocytoma. International journal of radiation oncology, biology, physics, 1994. 30(3): p. 583-90.

29. Urtasun, R.C., et al., Survival improvement in anaplastic astrocytoma, combining external radiation with halogenated pyrimidines: final report of RTOG 86-12, Phase I-II study. International journal of radiation oncology, biology, physics, 1996. 36(5): p. 1163-7.

30. Jackson, D., et al., Halogenated pyrimidines as radiosensitizers in the treatment of glioblastoma multiforme. American journal of clinical oncology, 1987. 10(5): p. 437-43.

31. Klecker, R.W., et al., Clinical pharmacology of 5-iodo-2′-deoxyuridine and 5-iodouracil and endogenous pyrimidine modulation. Clinical Pharmacology & Therapeutics, 1985. 38(1): p. 45-51.

32. Belanger, K., et al., Incorporation of iododeoxyuridine into DNA of granulocytes in patients. Cancer research, 1986. 46(12 Pt 1): p. 6509-12.

33. Kinsella, T.J., et al., Pharmacology and phase I/II study of continuous intravenous infusions of iododeoxyuridine and hyperfractionated radiotherapy in patients with glioblastoma multiforme. J Clin Oncol, 1988. 6(5): p. 871-9.

34. Sindelar, W.F., et al., Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Archives of surgery, 1993. 128(4): p. 402-10.

35. Robertson, J.M., et al., Preoperative radiation therapy and iododeoxyuridine for large retroperitoneal sarcomas. International journal of radiation oncology, biology, physics, 1995. 31(1): p. 87-92.

36. Goffman, T., Z. Tochner, and E. Glatstein, Primary treatment of large and massive adult sarcomas with iododeoxyuridine and aggressive hyperfractionated irradiation. Cancer, 1991. 67(3): p. 572-6.

37. Saif, M.W., et al., IPdR: a novel oral radiosensitizer. Expert opinion on investigational drugs, 2007. 16(9): p. 1415-24.

38. Chang, C.N., S.L. Doong, and Y.C. Cheng, Conversion of 5-iodo-2-pyrimidinone-2'-deoxyribose to 5-iodo-deoxyuridine by aldehyde oxidase. Implication in hepatotropic drug design. Biochemical pharmacology, 1992. 43(10): p. 2269-73.

39. Kinsella, T.J., et al., An in vivo comparison of oral 5-iodo-2'-deoxyuridine and 5-iodo-2-

pyrimidinone-2'-deoxyribose toxicity, pharmacokinetics, and DNA incorporation in athymic mouse tissues and the human colon cancer xenograft, HCT-116. Cancer research, 1994. 54(10): p. 2695-700.

40. Kinsella, T.J., et al., Preclinical evaluation of 5-iodo-2-pyrimidinone-2'-deoxyribose as a prodrug for 5-iodo-2'-deoxyuridine-mediated radiosensitization in mouse and human tissues. Clinical cancer research: an official journal of the American Association for Cancer Research, 1998. 4(1): p. 99-109.

41. Kinsella, T.J., et al., Preclinical toxicity and efficacy study of a 14-day schedule of oral 5-iodo-2-pyrimidinone-2'-deoxyribose as a prodrug for 5-iodo-2'-deoxyuridine radiosensitization in U251 human glioblastoma xenografts. Clinical cancer research : an official journal of the American Association for Cancer Research, 2000. 6(4): p. 1468-75.

42. Kinsella, T.J., et al., 5-iodo-2-pyrimidinone-2'-deoxyribose-mediated cytotoxicity and radiosensitization in U87 human glioblastoma xenografts. International journal of radiation oncology, biology, physics, 2007. 69(4): p. 1254-61.

43. Seo, Y., et al., Schedule-dependent drug effects of oral 5-iodo-2-pyrimidinone-2'-deoxyribose as an in vivo radiosensitizer in U251 human glioblastoma xenografts. Clinical cancer research: an official journal of the American Association for Cancer Research, 2005. 11(20): p. 7499-507.

44. Kinsella, T.J., et al., Toxicology and pharmacokinetic study of orally administered 5-iodo-2-pyrimidinone-2'deoxyribose (IPdR) x 28 days in Fischer-344 rats: impact on the initial clinical phase I trial design of IPdR-mediated radiosensitization. Cancer chemotherapy and pharmacology, 2008. 61(2): p. 323-34.

45. Kinsella, T.J., et al., Preclinical study of the systemic toxicity and pharmacokinetics of 5-iodo-2-deoxypyrimidinone-2'-deoxyribose as a radiosensitizing prodrug in two, non-rodent animal species: implications for phase I study design. Clinical cancer research: an official journal of the American Association for Cancer Research, 2000. 6(9): p. 3670-9.

46. Kummar, S., et al., First-in-human phase 0 trial of oral 5-iodo-2-pyrimidinone-2'-deoxyribose in patients with advanced malignancies. Clinical cancer research: an official journal of the American Association for Cancer Research, 2013. 19(7): p. 1852-7.

47. Seo, Y., et al., Differential radiosensitization in DNA mismatch repair-proficient and -deficient human colon cancer xenografts with 5-iodo-2-pyrimidinone-2'-deoxyribose. Clinical cancer research: an official journal of the American Association for Cancer Research, 2004. 10(22): p. 7520-8.

48. Reagan-Shaw, S., M. Nihal, and N. Ahmad, Dose translation from animal to human studies revisited. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 2008. 22(3): p. 659-61.

49. Kinsella, T., et al., Pharmacology and phase I/II study of continuous intravenous infusions of iododeoxyuridine and hyperfractionated radiotherapy in patients with glioblastoma multiforme. Journal of Clinical Oncology, 1988. 6(5): p. 871-879.

50. Simon, R., et al., Accelerated titration designs for phase I clinical trials in oncology. Journal of the National Cancer Institute, 1997. 89(15): p. 1138-47.

51. Krenitsky, T.A., et al., A comparison of the distribution and electron acceptor specificities of xanthine oxidase and aldehyde oxidase. Comparative biochemistry and physiology. B, Comparative biochemistry, 1974. 49(4): p. 687-703.

52. Schulz, C.A., et al., Continuous 28-day iododeoxyuridine infusion and hyperfractionated accelerated radiotherapy for malignant glioma: a phase I clinical study. International journal of radiation oncology, biology, physics, 2004. 59(4): p. 1107-15.

53. Speth, P.A., et al., Fluorodeoxyuridine modulation of the incorporation of iododeoxyuridine into DNA of granulocytes: a phase I and clinical pharmacological study. Cancer research, 1988. 48(10): p. 2933-7.

54. McGinn, C.J., et al., Leucovorin modulation of 5-iododeoxyuridine radiosensitization: a phase I study. Clinical cancer research: an official journal of the American Association for Cancer Research, 1996. 2(8): p. 1299-305.

55. Belanger, K., J.M. Collins, and R.W. Klecker, Jr., Technique for detection of DNA nucleobases by reversed-phase high-performance liquid chromatography optimized for quantitative determination of thymidine substitution by iododeoxyuridine. Journal of chromatography, 1987. 417(1): p. 57-63.

56. Chuong, M., et al., Induction gemcitabine-based chemotherapy and neoadjuvant stereotactic body radiation therapy achieve high margin-negative resection rates for borderline resectable pancreatic cancer. Journal of Radiation Oncology, 2012. 1(3): p. 273-281.

57. Kunzmann, V., et al., Intensified Neoadjuvant Chemotherapy with Nab-Paclitaxel plus Gemcitabine Followed by FOLFIRINOX in a Patient with Locally Advanced Unresectable Pancreatic Cancer. Case Rep Oncol, 2014. 7(3): p. 648-55.

58. Cunningham, D., et al., Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol, 2009. 27(33): p. 5513-8.

59. Cook, J.A., et al., Measurement of thymidine replacement in patients with high grade gliomas, head and neck tumors, and high grade sarcomas after continuous intravenous infusions of 5-iododeoxyuridine. Cancer research, 1992. 52(3): p. 719-25.

60. Epstein, A.H., et al., Treatment of locally advanced cancer of the head and neck with 5'-iododeoxyuridine and hyperfractionated radiation therapy: measurement of cell labeling and

thymidine replacement. Journal of the National Cancer Institute, 1994. 86(23): p. 1775-80.

61. Speth, P.A., et al., Selective incorporation of iododeoxyuridine into DNA of hepatic metastases versus normal human liver. Clinical pharmacology and therapeutics, 1988. 44(4): p. 369-75.

62. Speth, P.A., et al., Iododeoxyuridine (IdUrd) incorporation into DNA of human hematopoietic cells, normal liver and hepatic metastases in man: as a radiosensitizer and as a marker for cell kinetic studies. International journal of radiation oncology, biology, physics, 1989. 16(5): p. 1247-50.

63. Chang, A.E., et al., A phase I study of intra-arterial iododeoxyuridine in patients with colorectal liver metastases. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 1989. 7(5): p. 662-8.

64. Kinsella, T.J., et al., Pharmacology and phase I/II study of continuous intravenous infusions of iododeoxyuridine and hyperfractionated radiotherapy in patients with glioblastoma multiforme. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 1988. 6(5): p. 871-9.

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: IPdR MEDICATION DIARY

Patient's Name _____

Patient's Study ID _____

Capsule strength _____ mg

Assigned Dosage _____mg (_____) capsules

Instructions

1. Take IPdR capsules by mouth once daily for 28 days at approximately the same time each day and on an empty stomach, either 1 hour before or 2 hours after meals. The capsules should be swallowed whole and must not be crushed or broken.

2. IPdR capsules should be stored in the refrigerator.

3. Record the date and time when you take each IPdR dose.

4. On days you receive radiation therapy, IPdR capsules will be taken within 30 minutes and 2 hours prior to your radiation.

5. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose.
    a. If the next dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled.
    b. Make a note in the Comments column if you miss a dose.

6. If vomiting occurs after taking IPdR, do not take a replacement dose on that day. Resume at the next scheduled dose. Make a note in the Comments column.

7. If you have any comments or notice any side effects, record them in the Comments column.

Please bring this diary with you to all study visits!

Day	***Date/Time***	***Number of IPdR capsules taken***	***Comments***
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			

23			
24			
25			
26			
27			
28			

Participants Signature_____ Date _____

Area Below Only To Be Completed only by Coordinator

Number of capsules returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____

APPENDIX C: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug **IPdR (Oral 5-iodo-2-pyrimidinone-2-deoxyribose, NSC 726188)**. This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

There are no potential drug interactions with **IPdR** that are known at present**.** Because of the absence of potential for interaction with agents that induce or inhibit cytochrome P450 enzymes, there are no prohibitions of specific medications on the basis of anticipated drug-drug interactions.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

There are no potential drug interactions drug interactions with **IPdR** that are known at present**.**

It is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **IPdR (Oral 5-iodo-2-pyrimidinone-2-deoxyribose, NSC 726188).** This clinical trial is sponsored by the NCI. **There are no potential drug interactions with IPdR that are known at present**. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.