SUMMARY OF CHANGES

For Protocol Amendment #12:

NCI Protocol #: 9892
Local Protocol #: 15-157

NCI Version Date: 01/12/2023
Protocol Date: 01/12/2023

#	Section	Change
2.	**Administrative Throughout**	Updated section numbering. Corrected number formatting as well as updated the Table of Contents to reflect the updates.
3.	**Study Team**	Removed statistician ~~Dan Normolle~~, and updated to: Hong Wang, PhD UPMC Cancer Pavilion POB2, Suite 4C 5150 Centre Ave Telephone: 412-383-1588 Email: how8@pitt.edu
4.	**5.4.1**	Clarified Dose Escalation criteria: Enrollment will not be time-limited but will be limited to patients with a histologically confirmed diagnosis of locally advanced cervical or vaginal carcinoma not amenable to curative surgical resection alone to facilitate achievement of secondary objectives.
5.	**10**	Update made to STUDY CALENDAR to ensure all screening evaluations and drug can be ready within window: Baseline evaluations are to be conducted within ~~10~~ 14 days prior to start of protocol therapy.
6.	**10**	Update made to STUDY CALENDAR for secondary objective 1.2.2 analysis: Follow up for progression and survival status will occur via medical record review or phone call and should occur every 6 months (+/- 2 weeks) for a total of 5 years from the off treatment date.

NCI Protocol #: 9892

Local Protocol #: HCC# 15-157

ClinicalTrials.gov Identifier: NCT02595879

TITLE: Phase I Dose-Escalation Bioavailability Study of Oral Triapine in Combination with Concurrent Chemoradiation for Locally Advanced Cervical Cancer (LACC) and Vaginal Cancer

Corresponding Organization: **LAO-PA015** / UPMC Hillman Cancer Center LAO

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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-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

For the ex-US participating institutions, Triapine exportation by the Pharmaceutical Management Branch/CTEP is contingent on approval by the pharmaceutical collaborator.

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NCI-Supplied Agent(s): 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, triapine, NSC #663249)

Commercial Agent(s): cisplatin (platinol®, NSC #119875)

IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original / Version #1/ 06/09/15
Original / Version #2/ 07/27/15 (Response to consensus review dated, July 6, 2015)
Original / Version #3/ 09/04/15 (Response to consensus review follow-up, dated August 18, 2015)
Original/Version #4 / 12/07/15 (Response to CIRB reviewer comments, dated 11/23/15)
Original/Version #5 / 01/21/16 (Response to CTEP reviewer comments, dated 12/22/15)
Original/Version #6 / 03/21/16 (Response to CIRB reviewer comments/Outcome Letter, CIRB meeting held on 03/15/16)
Amendment 1/Version #7/03/15/2018 (CTCAE version change, study coordinator change)
Amendment 2/Version #8/ 09/10/2018 [Response to RRA from Dr. Charles Kunos (charles.kunos@nih.gov)]
Amendment 3/Version #9/ 11/09/2018 (Response to Comments dated 10/11/18 from Dr. Charles Kunos following Amendment 2 Disapproval on 10/10/2018)
Amendment 4/Version #10/ 01/16/2019 [Response to Comments dated 01/04/2019 from Dr. Charles Kunos (charles.kunos@nih.gov)]
Amendment 5/Version #11/ 02/21/2019 (Response

to CIRB Stipulations dated 02/07/2019)
Amendment 6/Version #12/ 05/17/2019 [Response to an RA from Dr. Charles Kunos (charles.kunos@nih.gov)]
Amendment 7/Version #13/08/27/2020 (Changes made to align with a Corrective Action Plan for study enrollment requested from CTEP and in response to an RA from CTEP)
Amendment 8/Version #14/11/03/2020 (Response to comments dated 09/03/2020 from Dr. Charles following Amendment 7 Disapproval on 09/04/2020 and response to CIRB stipulations dated 10/21/2020)
Amendment 9/Version #15/03/17/2021 (Response to CTEP Review Comments and a CTEP Amendment Request, and changes elicited by the University of Pittsburgh)
Amendment 10/Version #16/ 06/13/2022 (MTD addition, response to CTEP comments, & other minor changes)
Amendment 11/Version #17/ 06/29/2022 (TRIAD removal and responses to CTEP comments)
Amendment 12/Version #18 01/12/2023 (Administrative formatting updates, clarified eligibility for expansion cohort, follow up period, baseline evaluation window and study team update.)

SCHEMA

Dose Escalation Schema

Radiation Therapy	Dose Level	IV Cisplatin Weekly	PO Triapine*
Pelvic RT + Brachytherapy (+/- Extended	-2	40 mg/m^2	50 mg D1, 3, 5
	-1	40 mg/m^2	50 mg QD x 5
	1	40 mg/m^2	100 mg QD x 5
	2	40 mg/m^2	150 mg QD x 5
	3	40 mg/m^2	200 mg QD x 5

*1 of the planned 25 doses of triapine will be delivered IV (day 1) at a fixed dose of 50 mg to allow PK and PD studies.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the Maximum Tolerable Dose (MTD) and Recommended Phase II Dose (RP2D) of oral triapine when used in combination with cisplatin plus radiation therapy.

1.1.2 To determine the oral bioavailability of triapine.

1.1.3 To describe the pharmacokinetics (PK) of oral and intravenous triapine.

1.2 Secondary Objectives

1.2.1 To determine whether the metabolic complete response (mCR) rate of oral triapine in combination with cisplatin chemoradiation using 18F-FDG-PET/CT at posttherapy (3-month) is at least 70%.

1.2.2 To determine clinical overall response rate, progression-free survival, and overall survival.

1.2.3 To determine the correlation of methemoglobin proportion (%) and triapine pharmacokinetic exposure.

1.3 Exploratory Endpoints

1.3.1 To determine whether active human immunodeficiency virus (HIV) antiretroviral therapy impacts the antitumor activity of triapine.

2. BACKGROUND

2.1 Locally Advanced Cervical Cancer (LACC)

In the United States, cervical cancer is the third most common gynecologic cancer with approximately 12,000 new cases and 4,000 succumbing to disease per year.[1] There is no curative surgical option for this patient cohort, and since 1999, concurrent chemoradiation with cisplatin 40 mg/m^2 weekly has been widely adopted as standard of care for this cohort of patients.[2] While the majority of women are diagnosed with early-stage disease, women with locally advanced cervical cancer (LACC, stage IB2 to IVA) have a 5-year survival rate ranging from 80% (stage IB) to 30% (stage III), and it is this subgroup that accounts for the large majority of deaths associated with cervical cancer.[3] As a result, there remains an urgent need to identify novel agents and/or combination regimens to improve overall survival in patients with locally advanced cervical cancer.

2.2 CTEP Agent: Triapine

2.2.1 IV Triapine

NCI-CTEP has supported a phase I trial (NCI 7336, clinicaltrials.gov NCT00335998) and a phase II trial (NCI 8327, clinicaltrials.gov NCT00941070) evaluating the safety and clinical efficacy of intravenous triapine combined with cisplatin chemoradiation for the management of IB2-IVA cancer of the uterine cervix[6, 7]. Triapine is a 500-to-1000-fold more potent inhibitor of ribonucleotide reductase (RNR) M2 and M2b than hydroxyurea, which has previously shown clinical activity in cervical cancer[9]. The half-life of triapine is approximately 2 hours, suggesting that repeat dosing is needed within one treatment week to optimize clinical efficacy. Cervical cancer cells treated at human pharmacokinetic (PK) concentrations and exposure times survive at a rate of 80% after triapine alone, 40% after triapine plus cisplatin, and 10% after 3-AP plus cisplatin plus radiation[10, 11]. In phase I and II trials, intravenous triapine (25 mg/m^2) was given three times weekly co-administered with weekly cisplatin (40 mg/m^2) and daily radiation (50.4 Gy in 28 fractions) plus brachytherapy (35-40 Gy) in 35 patients with advanced stage cervical and vaginal cancer[6, 7]. This regimen was well-tolerated as a total of 500 (95%) of 525 2-hour 3-AP infusions were administered with the most common side effects being grade 2 diarrhea, grade 2 electrolyte imbalance, grade 2 fatigue, and infrequent grade 3 pancytopenia. In the IV trial (NSC 3663249), 90% of toxicity for this combined regimen occurred within the first 5 weeks of treatment, there is no currently known cumulative risk of toxicity associated with triapine (C. Kunos, MD, personal communication). With respect to the secondary objectives of this trial, 3-month metabolic complete responses (mCRs), as determined by PET-CT, were observed in 23 (96%) of 24 patients in whom images were obtained in the phase II study[6]. To date, 29 of 35 (86%) locally advanced cervical cancer patients are alive and disease-free at a median follow-up of 24 months. Four of 35 (11%) patients have died from extra-pelvic disease progression. Based on these findings, a randomized phase II trial of IV triapine in combination with concurrent cisplatin and radiation therapy was initiated (clinicaltrials.gov NCT01835171; Target accrual 188; opened 01/15/2016).

2.2.2 Oral Triapine

While the clinical activity of IV triapine in combination with standard chemoradiation therapy appears to be promising, it is quite time-intensive to perform a 2-hour infusion 3 times a week. Additionally, the PK data from IV triapine indicated that peak serum concentrations occur 1-2 hours after a 2-hour infusion, suggesting only a potential transient therapeutic benefit. It is conceivable, therefore, that daily dosing of triapine may yield greater clinical benefit. Recently, a phase I trial evaluated single-agent oral triapine in patients with a wide range of advanced solid tumors, enrolling 20 patients, including 1 woman with cervical cancer. Treatment consisted of oral triapine administered every 12 hours for 5 consecutive doses on days 1-3, 8-10, and 15-17 of an every 28-day cycle. Triapine was initially dosed at 50 mg every 12 hours and then increased to dose levels of 100, 150, and 200 mg every 12 hours. On this trial, grade 3/4 adverse events were uncommon at the 50 mg (1 hypertensive episode) and at the 100 mg (1 anemia) dose levels. Three patients experienced (38%) grade 3 or 4 neutropenia at the 150 mg dose level. At the 200 mg dose level, two grade 3-4 hypoxia events and grade 3-4 anemia, neutropenia,

thrombocytopenia, infection, fatigue, hepatic enzyme elevation, and anorexia adverse events were observed rarely. The recommended phase II dose was 150 mg every 12 hours for five consecutive doses on days 1–3, 8–10, and 15–17 of each 28-day cycle. Ultimately, 8 patients were treated at the 150 mg dose level with 1 DLT observed. Pharmacokinetic (PK) analysis suggested that the 150 mg dose achieved a minimum inhibitory concentration of RNR for six hours, which is similar to what is observed with IV dosing[12]. In addition, the PK data suggested that the population average bioavailability of triapine was approximately 55-70%.

2.3 Rationale for the combination of triapine with concurrent chemoradiation

Ribonucleotide reductase (RNR) is the rate-limiting enzyme in the synthesis and repair of DNA, and it is directly involved in the cellular response to radiation, making RNR-targeted therapy to enhance radiation treatment a rational therapeutic strategy. Inhibition of this pathway may be both radiosensitizing and chemosensitizing, thereby making investigation of combination therapy with chemoradiation a promising therapeutic strategy. There is an unmet therapeutic need to improve complete metabolic response during definitive chemoradiation in patients with locally advanced disease who are at high risk for recurrence.

RNR is the only enzyme responsible for conversion of ribonucleoside diphosphate to deoxyribonucleotide diphosphate (dNDP), the key building blocks for DNA synthesis. RNR is composed of a heterodimeric tetramer comprised of two dimers M1·M2 or M1·M2b. When RNR is inhibited, the supply of dNDPs and dNTPs is reduced. Inhibition of key nucleotide precursors for DNA biosynthesis results in a protracted repair of damaged DNA, which in turn, enhances the potential cytotoxic effects of chemotherapy and radiation therapy. Cervical cancer preferentially overexpresses the RNR M2b and M2 subunits, and this overexpression is associated with resistance to cisplatin-based chemoradiotherapy[5]. As such, RNR inhibitors have been developed as potential radiation sensitizers over the past 30 years. While the initial data was promising, the older inhibitor compounds had displayed mixed clinical effectiveness, and they were associated with significant toxicity. However, there was sufficient proof of concept to suggest that a RNR inhibitor may be efficacious when used in combined modality therapy. Newer RNR inhibitors have increased potency and improved binding characteristics, which has significantly renewed interest in their clinical development. The RNR inhibitor 3-aminopyridine-2- carboxaldehyde-thiosemicarbazone (3-AP, triapine, NSC#663249) was developed by the Sartorelli laboratory at the Yale Cancer Center, and extensive pre-clinical studies have shown it this agent to be an equipotent inhibitor of M2b and M2[6-8].

2.4 Correlative Studies Background

2.4.1 Pharmacokinetics

Previous studies of a different oral formulation have shown that triapine may have an oral bioavailability of 67% (range 35-128%). As the oral dose of triapine is escalated in this trial, it will be possible to determine oral bioavailability, within and between subject variability in bioavailability and clearance, and linearity of absorption. Assay methodology has been developed and validated by Dr. Jan Beumer at the University of Pittsburgh Cancer Pharmacokinetics and Pharmacodynamics Facility (CPPF): LC-MS/MS assay for the quantitation of the ribonucleotide reductase inhibitor triapine in human plasma. Matsumoto J, et al. J Pharm

Biomed Anal. 2017; 146: 154-160. PMID: 28881312.

2.4.2 FDG-PET/CT Imaging as Biomarker of Response

Prior studies have demonstrated that metabolic response can be determined by positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) obtained within 10-16 weeks after the completion of therapy to predict clinical response of cervical cancer[13-15]. The current recommendations by the National Comprehensive Cancer Network (NCCN) is imaging based on symptoms or suspicious examination findings or a one-time PET-CT at 3-6 months following treatment in LACC can be used to suggest early or asymptomatic persistence/recurrence. This study provides the opportunity to further assess ^{18}F-FDG-PET/CT metabolic response rate as an early surrogate endpoint in cancer clinical trials.

Complete metabolic response, defined as ^{18}F-FDG-PET/CT with no evidence of local or distant disease, is approximately 70% after completion of cisplatin-based chemoradiation[13,14]. Early determination of durable chemoradiation therapy response is an important objective in oncologic care.

2.4.3 Methemoglobinemia

Previous studies of triapine have shown methemoglobinemia as a potential side-effect. Therefore, we will perform studies to monitor the % of methemoglobinemia on specific PK and PD days, which will allow us to correlate this effect with e.g. exposure.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patient has a new, untreated histologic diagnosis of stage IB2 (> 5 cm), II, IIIB, IIIC or IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix or stage II-IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the vagina not amenable to curative surgical resection alone. The presence or absence of lymph node metastasis will be based on pre-therapy 18F-FDG PET/CT. The patient must be able to tolerate imaging requirements of an 18F-FDG PET/CT scan.

3.1.2 Age ≥18 years old.

3.1.3 ECOG performance status score of 0, 1, or 2. See Appendix A

3.1.4 Life expectancy greater than 6 months.

3.1.5 Normal organ and marrow function as defined below:

-Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
-Platelets ≥ 100 x 10^9/L
-Hemoglobin (Hgb) ≥ 10.0 g/dL (blood transfusions to reach this amount are allowed)
-Serum creatinine ≤ 1.5 mg/dL to receive weekly cisplatin

If serum creatinine is between 1.5 and 1.9 mg/dL, patients are eligible for cisplatin if the estimated creatinine clearance (CCr) is > 30 ml/min (for the purpose of estimating the CCr, the formula of Cockcroft and Gault for females should be used)
-Total serum bilirubin ≤ 1.5 x ULN (in patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN)
-AST and ALT ≤ 2.5 x ULN

3.1.6 Able to take oral medication.

3.1.7 Not pregnant and not breastfeeding. The effects of triapine on the developing human fetus are unknown. For this reason, as well as because heterocyclic carboxaldehydethiosemicarbazones and radiation are known to be teratogenic, women of child-bearing potential and men must agree to use two forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Patient must have documented negative urine pregnancy test must be resulted within 7 days before initiating protocol therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with triapine, breastfeeding should be discontinued if the mother is treated with triapine. These potential risks may also apply to other agents used in this study.

3.1.8 For HIV and HEPB/C:

- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for the dose escalation portion of this trial. For those patients who are enrolled in the HIV+ expansion cohort, they must be HIV infected and be on retroviral therapy with an undetectable viral load within 6 months of enrollment.
- For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
- Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.9 Able to understand and willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patient has had a prior invasive malignancy diagnosed within the last three years (except [1] non-melanoma skin cancer or [2] prior in situ carcinoma of the cervix);

3.2.2 Patients are excluded if they have received prior pelvic radiotherapy for any reason that would contribute radiation dose that would exceed tolerance of normal tissues at the discretion of the treating physician.

3.2.3 Patients receiving any other investigational agents

3.2.4 Patients with known glucose-6-phosphate dehydrogenase deficiency (G6PD) are excluded due to an inability to administer the antidote for methemoglobinemia, methylene blue. Pre-registration testing for G6PD is at the investigator's discretion and is not required for study enrollment.

3.2.5 Patients who are taking any medication associated with methemoglobinemia, see "5.6 General Concomitant Medication and Supportive Care Guidelines" for examples. Medication must be discontinued and must have a washout period of 4 halflives or 4 weeks, whichever is shorter.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to triapine or cisplatin.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection; symptomatic congestive heart failure; unstable angina pectoris; cardiac arrhythmia; known inadequately controlled hypertension; significant pulmonary disease including dyspnea at rest, patients requiring supplemental oxygen, or poor pulmonary reserve; or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Patients with uncontrolled diabetes mellitus (fasting blood glucose controlled by medication, ≤ 200 mg/dL allowed)

3.2.9 Patients who have had a hysterectomy or are planning to have an adjuvant hysterectomy following radiation as part of their cervical cancer treatment are ineligible

3.2.10 Patients scheduled to be treated with adjuvant consolidation chemotherapy at the conclusion of their standard chemoradiation

3.3 Inclusion of Women and Minorities

This clinical trial will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol to address the study objectives in a population representative of the entire cervical cancer population treated by any of the participating institutions. (See Planned Enrollment Table in Section 13.2)

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

4.2 Site Registration

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

IRB Approval

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

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

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

Additional Requirements

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

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

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU

members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-PA015, and protocol number 9892,

Click on *Documents*, *Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Submitting Regulatory Documents

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

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

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

4.2.3 Checking Site Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

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

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

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

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

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

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

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 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 at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

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

5. TREATMENT PLAN

ENROLLMENT

Primary Locally Advanced Cervical or Vaginal Carcinoma

↓

Baseline 18F-FDG-PET/CT

Treatment Schedule

Week	*Day 1**	*Day 2**	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*
1	**EBRT Triapine (IV)**	**EBRT Triapine (PO) CISPLATIN**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**OFF DAY**	**OFF DAY**
2	*Day 8**	*Day 9**	*Day 10*	*Day 11*	*Day 12*	*Day 13*	*Day 14*
	EBRT Triapine (PO)	**EBRT Triapine (PO) CISPLATIN**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**OFF DAY**	**OFF DAY**
3	*Day 15*	*Day 16*	*Day 17*	*Day 18*	*Day 19*	*Day 20*	*Day 21*
	EBRT Triapine (PO)	**EBRT Triapine (PO) CISPLATIN**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**OFF DAY**	**OFF DAY**
4	*Day 22*	*Day 23*	*Day 24*	*Day 25*	*Day 26*	*Day 27*	*Day 28*
	EBRT Triapine (PO)	**EBRT Triapine (PO) CISPLATIN**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**OFF DAY**	**OFF DAY**
5**	*Day 29*	*Day 30*	*Day 31*	*Day 32*	*Day 33*	*Day 34*	*Day 35*
	EBRT Triapine (PO)	**EBRT Triapine (PO) CISPLATIN**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**EBRT Triapine (PO)**	**OFF DAY**	**OFF DAY**

Brachytherapy (see Section 5.2)

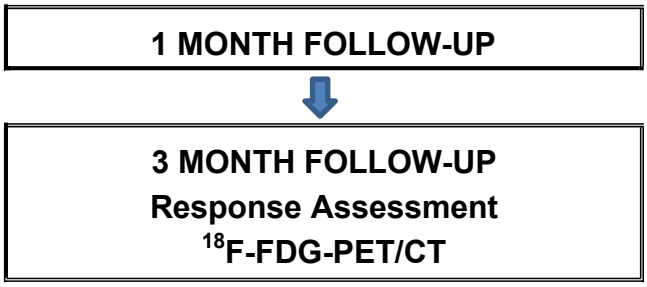
***Correlative blood sample collections on these days (see protocol Appendix B and C)**

****EBRT make-up is permissible. See Section 5.2**

↓

END OF THERAPY

↓


1 MONTH FOLLOW-UP
3 MONTH FOLLOW-UP
Response Assessment
18F-FDG-PET/CT

5.1 Agent Administration

Chemotherapy and Radiation Regimen				
Agent[a]	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**
Pelvic external beam radiation	Skin, antiemetic, or anti-diarrheal medications may be administered as needed.	1.8 Gy/ day	**N/A**	Days 1 to 5 (Mon-Fri), Weekly x 5 weeks (25 treatments)
Pelvic brachytherapy *(See Section* **5.2***)*	Antiemetic and anti-diarrheal medication may be administered as needed.	30 to 40 Gy in one or multiple fractions using LDR or HDR techniques	**N/A**	
IV Triapine (See Section 5.3.3 for required clinical monitoring)	All patients will receive dexamethasone IV prior to each IV triapine (3-AP) infusion. Pre-medicate with antiemetic as needed for patients developing nausea or vomiting with a previous dose of triapine.	Fixed dose – 50 mg diluted in 500 ml NS or 500 ml 5% dextrose in water	IV infusion over 120 +/- 10 minutes within 90 minutes **after** pelvic irradiation using **DEHP-free low sorbing infusion set**.	Day 1
Oral Triapine (See Section 5.3.3 for required clinical monitoring)	No premedications needed. Antiemetic as needed for nausea or vomiting.	As per assigned Dose Level (see "Dose-Escalation Schedule", section 5.1.1)	PO taken within 90 minutes of completion of pelvic external beam radiation treatment	Days 2-5, 8-12, 15-19, 22-26, 29-33

Cisplatin	IV hydration before cisplatin and antiemetic and steroid prophylaxis pre-medication **as per institution protocol**.	40 mg/m^2 (70 mg maximum), diluted with 25g mannitol in 1L normal saline or per institutional practice.	IV infusion over 60-120 minutes or as per institution protocol using **non-aluminum administration sets**. Following cisplatin, post-hydration therapy should be administered **as per institution protocol**.	Once weekly x 5 weeks (Days 2, 9, 16, 23, 30)

[a]Radiation therapy (RT) and chemotherapy must be administered in the order provided in the above table (Chemotherapy and Radiation Regimen)

Treatment will be administered on an outpatient basis. 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.

Radiation therapy will be standard of care with no dose variation (see Section 5.2). The cisplatin chemotherapy dose will remain stable at 40 mg/m2 to maximize standard of care effects. The dose of oral triapine will be escalated as per the Dose Escalation Schedule below. The dose escalation component will enroll any patients with stage IB2-IVA cervical cancer or stage II-IVA vaginal cancer for which cisplatin chemoradiation would be standard of care treatment. If de- escalation to DL-2 is necessary, the protocol will be amended to escalate triapine doses on the D1,3,5 schedule (previously explored with the intravenous (IV) route).

Reported adverse events and potential risks are described in Section 7.

5.1.1 Dose Escalation

For the first dose level, 3 patients were enrolled without issues. Given the scarcity of patients and the thus far favorable toxicity profile, dose level 2 will be enrolled per an accelerated titration approach using a single patient cohort. Dose escalation will revert to the standard 3+3 design if the patient on dose level 2 experiences a DLT or a ≥ grade 2 toxicity or when dose level 3 is reached. The standard 3+3 design is as follows: Escalation at 0/3 DLTs, dose-reduction if >1/3 DLT, and expansion to 6 if 1/3 DLTs. The highest dose level at which <2/6 DLTs are observed will be declared the MTD.

Dose Escalation Schedule

Radiation Therapy	**Dose Level**	**IV cisplatin weekly**	**PO Triapine* Dose / Days / Weekly x5**
Pelvic RT + Brachytherapy (+/- Extended Field)	-2	40 mg/m^2	50 mg D1,3,5
	-1	40 mg/m^2	50 mg QD x5
	1	40 mg/m^2	100 mg QD x5
	2	40 mg/m^2	150 mg QD x5
	3	40 mg/m^2	200 mg QD x5

*1 of the planned 25 doses of triapine will be delivered IV (day 1) at a fixed dose of 50 mg to allow PK and PD studies (assuming 60% bioavailability and a BSA of 1.73 m^2). If DL-2 needs to be explored, the PK-PD days will be rearranged to the first day of the first 2 weeks of treatment.

5.1.2 RP2D

Once 6 evaluable patients have been enrolled at a dose-level that is determined to be the MTD (according to the criteria outlined in Section 13.1) the observation period will be extended by 30 days in those 6 patients. If no more than 1 of 6 subjects experiences a DLT at this dose level, including in the extended observation window, the RP2D is equal to the MTD, and the expansion cohort will be treated at this dose level. If more than 1 of 6 subjects experiences a DLT at this dose level, including in the extended observation window, the expansion cohort will be enrolled in the next lower dose level to further confirm tolerability, which may then be declared the

RP2D.

5.1.3 Dose to be used for expansion

Dose escalation has been completed as of Amendment 10. The dose to be used for expansion is 100 mg triapine PO daily in combination with cisplatin based chemoradiation as described in this protocol. Data supporting this dose decision are detailed below and have been discussed with the CTEP Medical Monitor.

5.1.3.1 Safety
The addition of oral triapine to standard of care cisplatin based chemoradiation was safe. There were no treatment related deaths.

5.1.3.2 Tolerability

Evaluability/DLT Overview:

Dose Level	Triapine (mg QD)	Subject ID	Evaluable	DLT
1	100	PA015-001	Y1	N
1	100	PA015-002	Y2	N
1	100	PA015-003	Y3	N
2	150	PA015-0004	Y1	Y1
2	150	KY010-005	Y2	N
2	150	NJ066-006	N	Y*
2	150	KY010-007	Y3	Y2
1	100	PA015-008	Y4	N
1	100	PA015-009	N	N
1	100	KY010-010	Y5	Y1
1	100	KY010-011	Y6	N

Y: Yes, N: No, *see below for details

There were no reported dose limiting toxicities noted in the first three individuals enrolled at dose level 1 (PO triapine 100 mg). The first person on dose level 2 (PO triapine 150 mg) experienced a DLT with grade 4 neutrophil count decrease and grade 4 WBC decrease on her week 3 labs. Repeat labs the following day showed normalization of both. The third person on dose level 2 experienced grade 3 methemoglobinemia. She started therapy and completed dosing with oral and IV triapine as scheduled without any signs or symptoms concerning for methemoglobinemia for the first three weeks of her therapy. At the end of treatment week 3 the patient noted dysuria. She was initially started on pyridium and then Bactrim was added. After 5 days of pyridium and 3 days of Bactrim, the patient presented for start of week 4 therapy. After completion of treatment for week 4, day 2, the patient noted chest tightness and feeling lightheaded while ambulating. She had a pulse ox ranging between 85-88% on room air. She was placed on 4L oxygen via nasal cannula and her oxygen saturation came up to 90%. EKG showed sinus tachycardia, BP and temperature within normal limits. Patient denied shortness of breath, nausea, vomiting, diarrhea, loss of consciousness. Due to hypoxia and the requirement of supplemental oxygen, the patient

was sent to the ER. ABG revealed arterial P02 of 48 and methemoglobin of 17.2%. The patient was put on a non-rebreather mask and given methylene blue (100mg IV) for the reversal of methemoglobinemia. Repeat methemoglobin was drawn 30 minutes after dosing and improved to 5.3%. ABG was repeated 1 hour after dosing, arterial P02 was 271. The following morning, the patient was put on room air and pulse ox was 92-94%. She was discharged home in stable condition without any further symptoms and no need for supplemental oxygen. It is clear from the clinical course that a grade 3 non-hematologic toxicity occurred. However, triapine, pyridium and Bactrim can all cause methemoglobinemia and there is data to support that combination of more than one causative agent can increase risk of methemoglobinemia. The patient received three full weeks of treatment with triapine without complications. Only after starting on the pyridium and Bactrim for treatment of a urinary tract infection, combined with week 4 triapine initiation, did toxicity result. It is therefore most likely that this toxicity was a consequence of the combined methemoglobinemic actions of all three agents. As a result, an amendment was made to the protocol to add a list of concomitant medications that should be avoided to decrease the risk of methemoglobinemia. Because of this, and after reviewing the clinical scenario with the drug monitor, the patient was considered inevaluable and replaced with another individual. This fourth person on dose level 2 also experienced a DLT with grade 4 lymphocyte count at the end of week 5 when labs were drawn in the setting for new onset fever. The patient was treated for a UTI (Urinary Tract Infection) and her final dose of triapine was held the following week. Given two individuals with DLTs at this dose level, the decision was made to cease enrollment at this level and drop back down to dose level 1 for expansion to 6 total evaluable patients. An additional four individuals were enrolled at dose level 1. One had no DLTs, one withdrew prior to treatment start so was not evaluable, and one experienced two DLTs, grade 4 neutrophil count decrease and grade 4 WBC decrease. The final individual presented with cystitis symptoms without systemic signs of infection (ie fever, chills) to the ED at the end of week 3. She had labs drawn that showed a grade 4 decreased lymphocyte count and grade 3 hypokalemia. She was given 40mEq of potassium in the ED and sent home with a prescription to treat a UTI. On her standard of care labs at the beginning of week 4, her lymphocyte count had improved to grade 3 and her potassium level was at a grade 1 toxicity level. She was evaluated by her physician and found to be medically suitable for continued therapy. After reviewing the clinical scenario with the drug monitor, it was felt that the patient could safely continue to with therapy, including PO triapine as the labs would not have otherwise been drawn for a simple UTI and did not meet criteria for DLT at the time the decision needed to be made for therapy the following week. She was able to complete the remainder of her therapy without any noted DLTs. Based on the summation of these findings, dose level 1, triapine at 100 mg PO given concurrently with external beam radiation 5 days a week for 5 weeks with weekly cisplatin at 40 mg/m^2 is the maximum tolerated dose.

Beyond the DLTs described above, the regimen was well tolerated with expected hematologic events in the context of known baseline toxicity data for standard of care cisplatin base chemoradiation. Among the nine evaluable patients, seven experienced at least one grade 3 toxicity, including lymphocyte decrease (n=7), anemia (n=4), neutrophil count decrease (n=4), white blood cell count decrease (n=4), platelet count decreased (n=1), hypertension (n=1), hyponatremia (n=1). A comprehensive list of adverse events is outlined in Table below.

Adverse Events by Frequency during the dose escalation of NCI 9892.

AEFamily	AETerm	Grade1	Grade2	Grade3	Grade4	Total
GENERAL/ADM. SITE CONDITIONS	Fatigue	7 (70%)	3 (30%)			10 (100.0%
GI DISORDERS	Nausea	10 (100%)				10 (100.0%
BLOOD/LYMPH DISORDERS	Anemia		4 (40%)	5 (50%)		9 (90.0%)
GI DISORDERS	Diarrhea	7 (70%)	2 (20%)			9 (90.0%)
INVESTIGATIONS	Lymphocyte count decreased		1 (10%)	5 (50%)	3 (30%)	9 (90.0%)
METABOLISM & NUTRITION	Hypomagnesemia	6 (60%)	1 (10%)			7 (70.0%)
METABOLISM & NUTRITION	Hyponatremia	6 (60%)		1 (10%)		7 (70.0%)
INVESTIGATIONS	Neutrophil count decreased	2 (20%)		3 (30%)	2 (20%)	7 (70.0%)
INVESTIGATIONS	White blood cell decreased		2 (20%)	3 (30%)	2 (20%)	7 (70.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Methemoglobinemia	1 (10%)	4 (40%)	1 (10%)		6 (60.0%)
INVESTIGATIONS	Platelet count decreased	3 (30%)	2 (20%)	1 (10%)		6 (60.0%)
RENAL & URINARY DISORDERS	Urinary frequency	5 (50%)	1 (10%)			6 (60.0%)
GI DISORDERS	Gastroesophageal reflux disease	2 (20%)	3 (30%)			5 (50.0%)
METABOLISM & NUTRITION	Hypocalcemia	5 (50%)				5 (50.0%)
EAR & LABYRINTH	Tinnitus	5 (50%)				5 (50.0%)
GI DISORDERS	Vomiting	5 (50%)				5 (50.0%)
GI DISORDERS	Constipation	4 (40%)				4 (40.0%)
RENAL & URINARY DISORDERS	Hematuria	3 (30%)	1 (10%)			4 (40.0%)
METABOLISM & NUTRITION	Hyperglycemia	4 (40%)				4 (40.0%)
METABOLISM & NUTRITION	Hypokalemia	3 (30%)		1 (10%)		4 (40.0%)
METABOLISM & NUTRITION	Anorexia	3 (30%)				3 (30.0%)
GI DISORDERS	Bloating	3 (30%)				3 (30.0%)
NERVOUS SYSTEM	Dizziness	3 (30%)				3 (30.0%)
RESPIRATORY/THORACIC/MEDIASTINAL	Dyspnea	2 (20%)	1 (10%)			3 (30.0%)
GENERAL/ADM. SITE CONDITIONS	Fever	2 (20%)	1 (10%)			3 (30.0%)
NERVOUS SYSTEM	Headache	3 (30%)				3 (30.0%)
VASCULAR DISORDERS	Hypertension	1 (10%)	1 (10%)	1 (10%)		3 (30.0%)
PSYCHIATRIC DISORDERS	Insomnia	3 (30%)				3 (30.0%)
RENAL & URINARY DISORDERS	Renal & urinary disorders - Other - Dysuria	3 (30%)				3 (30.0%)
GI DISORDERS	Abdominal pain	1 (10%)	1 (10%)			2 (20.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Thrombocytopenia	2 (20%)				2 (20.0%)
METABOLISM & NUTRITION	Dehydration		2 (20%)			2 (20.0%)
GENERAL/ADM. SITE CONDITIONS	Edema limbs	2 (20%)				2 (20.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Generalized muscle weakness	2 (20%)				2 (20.0%)
METABOLISM & NUTRITION	Hypoalbuminemia	2 (20%)				2 (20.0%)

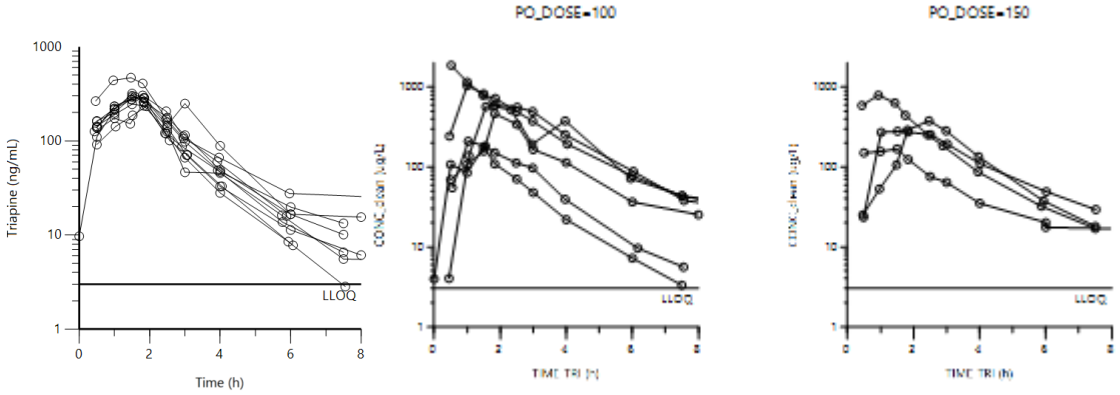
INVESTIGATIONS	Investigations - Other, specify - Fogginess	2 (20%)				2 (20.0%)
CARDIAC DISORDERS	Sinus tachycardia	1 (10%)	1 (10%)			2 (20.0%)
INFECTIONS & INFESTATIONS	Urinary tract infection		1 (10%)	1 (10%)		2 (20.0%)
RENAL & URINARY DISORDERS	Urinary urgency	2 (20%)				2 (20.0%)
REPRODUCTIVE & BREAST DISORDERS	Vaginal hemorrhage	2 (20%)				2 (20.0%)
REPRODUCTIVE & BREAST DISORDERS	Vaginal pain	2 (20%)				2 (20.0%)
INVESTIGATIONS	Weight loss	2 (20%)				2 (20.0%)
INVESTIGATIONS	ALT increased	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Arthralgia	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Back pain	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Bladder spasm	1 (10%)				1 (10.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Increased Medthemoglobin Level		1 (10%)			1 (10.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Increased Methemoglobin		1 (10%)			1 (10.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Methameoglobinemia		1 (10%)			1 (10.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Methemoglobin Increase		1 (10%)			1 (10.0%)
BLOOD/LYMPH DISORDERS	Blood/Lymph - Other - Methemoglobinemina		1 (10%)			1 (10.0%)
EYE DISORDERS	Blurred vision	1 (10%)				1 (10.0%)
CARDIAC DISORDERS	Cardiac disorders - Other - Chest Tightness	1 (10%)				1 (10.0%)
CARDIAC DISORDERS	Chest pain - cardiac	1 (10%)				1 (10.0%)
GENERAL/ADM. SITE CONDITIONS	Chills	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Cystitis noninfective	1 (10%)				1 (10.0%)
GI DISORDERS	Dysphagia		1 (10%)			1 (10.0%)
GENERAL/ADM. SITE CONDITIONS	Edema face	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Flank pain	1 (10%)				1 (10.0%)
VASCULAR DISORDERS	Flushing	1 (10%)				1 (10.0%)
GENERAL/ADM. SITE CONDITIONS	General and admin site - Other - Light Headedness	1 (10%)				1 (10.0%)
EAR & LABYRINTH	Hearing impaired	1 (10%)				1 (10.0%)
GI DISORDERS	Hemorrhoids	1 (10%)				1 (10.0%)
VASCULAR DISORDERS	Hot flashes	1 (10%)				1 (10.0%)
SKIN & SUBCUTANEOUS DISORDERS	Hyperhidrosis	1 (10%)				1 (10.0%)
VASCULAR DISORDERS	Hypotension	1 (10%)				1 (10.0%)
RESPIRATORY/THORACIC/MEDIASTINAL	Hypoxia			1 (10%)		1 (10.0%)
INVESTIGATIONS	Investigations - Other, specify - Increase Ldh	1 (10%)				1 (10.0%)
INVESTIGATIONS	Investigations - Other, specify - Methemoglobinemia		1 (10%)			1 (10.0%)
PSYCHIATRIC DISORDERS	Irritability	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Musculoskel/connect tissue -Other - Muscle Cramping	1 (10%)				1 (10.0%)

MUSCULOSKELETAL/CONNECTIVE TISSUE	Musculoskel/connect tissue -Other - Pelvic Muscle Spasm	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Myalgia	1 (10%)				1 (10.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE	Pain in extremity	1 (10%)				1 (10.0%)
REPRODUCTIVE & BREAST DISORDERS	Pelvic pain	1 (10%)				1 (10.0%)
NERVOUS SYSTEM	Peripheral sensory neuropathy	1 (10%)				1 (10.0%)
RESPIRATORY/THORACIC/MEDIASTINAL	Productive cough	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Proteinuria	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Renal & urinary disorders - Other - Bladder Pain	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Renal & urinary disorders - Other - Pyelonephritis			1 (10%)		1 (10.0%)
RENAL & URINARY DISORDERS	Renal & urinary disorders - Other - Urinary Pressure	1 (10%)				1 (10.0%)
REPRODUCTIVE & BREAST DISORDERS	Reproductive and breast - Other - Dysuria	1 (10%)				1 (10.0%)
REPRODUCTIVE & BREAST DISORDERS	Reproductive and breast - Other - Vaginal Bleeding	1 (10%)				1 (10.0%)
PSYCHIATRIC DISORDERS	Restlessness	1 (10%)				1 (10.0%)
SKIN & SUBCUTANEOUS DISORDERS	Skin & subcutaneous tissue -Other - Dermatitis	1 (10%)				1 (10.0%)
SKIN & SUBCUTANEOUS DISORDERS	Skin & subcutaneous tissue -Other - Parasthesia		1 (10%)			1 (10.0%)
SKIN & SUBCUTANEOUS DISORDERS	Skin & subcutaneous tissue -Other - Skin Patches	1 (10%)				1 (10.0%)
RESPIRATORY/THORACIC/MEDIASTINAL	Sore throat	1 (10%)				1 (10.0%)
GI DISORDERS	Toothache	1 (10%)				1 (10.0%)
RENAL & URINARY DISORDERS	Urinary incontinence	1 (10%)				1 (10.0%)
INJURY, POISONING & PROCEDURAL	Vascular access complication			1 (10%)		1 (10.0%)

Looking only at the highest grade for each Adverse Event experienced by a Patient, this report displays the number of patients that experienced each Adverse Event, by Grade, for each Organ Class and for each Preferred Term within an Organ Class. It also displays the percentage of treated patients in the study that experienced the Adverse Event with that Grade as their highest grade for that event.

5.1.3.3 Pharmacokinetics

Summary PK of triapine in the dose escalation is reported below. PK is comparable to earlier reports of triapine for both routes. PO bioavailability observed in this trial was 66%, which is also comparable to previous reports of 67% (Chao 2012). There was no discernable difference between triapine exposure at 100 vs 150 mg PO, and between patient variability at each dose level was substantial.



Pharmacokinetics of triapine at 50 mg IV (left), 100 mg PO (middle) or 150 mg PO (right).

Pharmacokinetic parameters of triapine at 50 mg IV.

PT (#')	Cmax (ug/L)	Tmax (h)	HL (h)	AUClast (h*ug/L)	AUCINFobs (h*ug/L)	Extrap (%)	Cl_obs (L/h)	Vss_obs (L)	Vz_obs (L)	Tlast (h)
Geo Mean	294	1.6	1.3	718	734	2.0	68	119	124	10
Geo SD	1.2	1.1	1.3	1.4	1.4	1.7	1.4	1.4	1.3	1.8
N	10	10	10	10	10	10	10	10	10	10

Pharmacokinetic parameters of PO triapine.

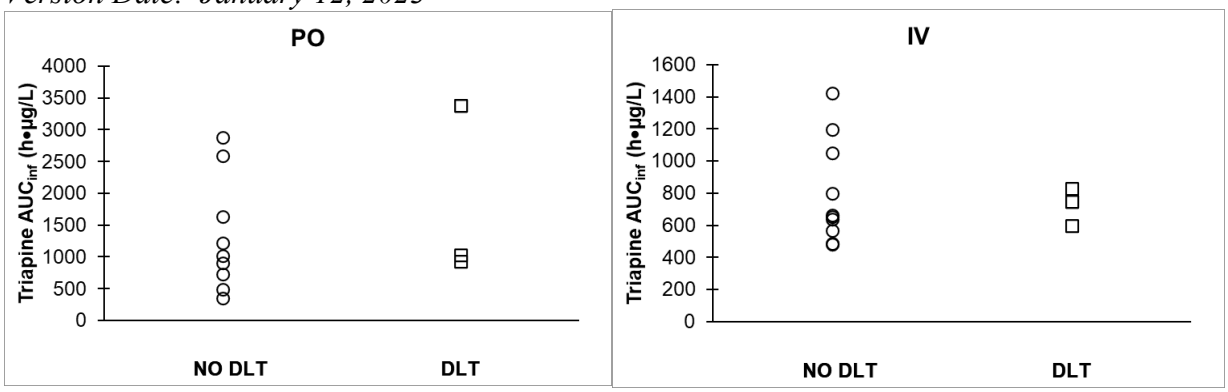
PO_DOSE (mg)	PT (#')	Cmax (ug/L)	Tmax (h)	HL (h)	AUClast (h*ug/L)	AUCINFobs (h*ug/L)	%Extrap (%)	Cl_F_obs (L/h)	Vz_F_obs (L)	Tlast (h)
100	**GeoMean**	**520**	**1.2**	**1.3**	**1187**	**1209**	**0.8**	**83**	**156**	**14**
	GeoSD	**2.5**	**1.6**	**1.2**	**2.6**	**2.5**	**4.2**	**2.5**	**2.6**	**1.9**
	N	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
150	**GeoMean**	**344**	**1.5**	**1.5**	**990**	**1034**	**3.9**	**145**	**322**	**10**
	GeoSD	**1.9**	**1.5**	**1.3**	**1.4**	**1.4**	**1.7**	**1.4**	**1.5**	**1.7**
	N	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**

Bioavailability of triapine.

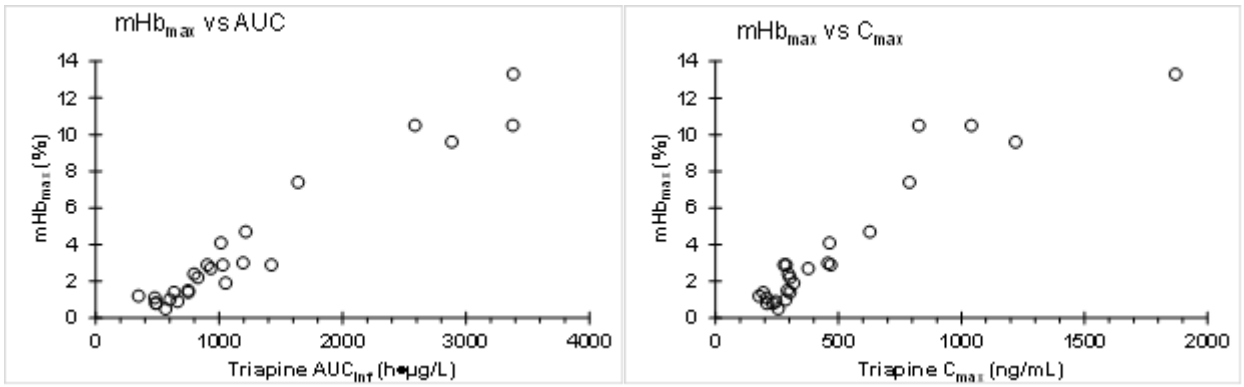
PO_DOSE		F
100	**Geometric Mean**	**0.75**
	Geometric SD	**2.2**
	N	**6**
150	**Geometric Mean**	**0.54**
	Geometric SD	**1.5**
	N	**4**
Overall	**Geometric Mean**	**0.66**
	Geometric SD	**1.9**
	N	**10**

5.1.3.4 Pharmacodynamics

There was no obvious relationship between occurrence of DLT and triapine AUC. Methemoglobin levels were sampled at approximately 4 h after dosing on PK days, and the observed levels had a clear correlation with triapine exposure both when expressed as AUC and Cmax.



Relationship of triapine AUC and DLT.



Relationship of triapine AUC and Cmax vs methemoglobin levels.

5.1.3.5 Activity

Eleven patients were enrolled into the dose escalation. One patient withdrew prior to treatment, so was not evaluable. Patient number 6, who experienced grade 3 methemoglobinemia during week 4 of treatment, was withdrawn from the study and was replaced by patient 7. Of the remaining nine patients, 6 had a documented complete metabolic response on 3-month post therapy PET-CT. One had documented stable disease on PET-CT but had complete resolution of her remaining disease on follow-up MRI imaging and remains disease-free 18 months after treatment. One patient had disease progression in her lung, but complete metabolic response within the treatment field. The individual most recently enrolled has not undergone PET-CT imaging yet. Patient 6 did complete therapy with standard of care cisplatin based chemoradiation without triapine and had a document partial response on her PET-CT; however, repeat imaging obtained 6 months later demonstrated no evidence of disease.

5.1.3.6 Conclusion

Based on the 3+3 design, 100 mg PO daily was determined to be the MTD with 1 out of 6 evaluable patients experiencing a DLT, while 150 mg PO daily resulted in 2 out of 3 evaluable patients with a DLT. The side effect profile at 100 mg PO daily was considered acceptable and consistent with the expected side effect profile of the cisplatin chemoradiation therapy backbone. Exposures were comparable to previous reports (Chao 2012), patients treated at 150 mg did not achieve higher plasma exposures than at 100 mg PO, and patients with DLT did not appear to have markedly different exposures than patients that without DLT.

In summary, 100 mg triapine PO daily in combination with cisplatin based chemoradiation is the appropriate dose to take forward into the expansion phase of this phase 1 trial.

5.2 Radiation therapy:

5.2.1 Radiation Therapy for Cervical Cancer or Vaginal Cancer

Patients will receive 5 consecutive days of external beam radiation (EBRT) preferably given Monday-Friday, and repeated for 5 consecutive weeks. A three consecutive day parametrial may be given in the sixth week or in the week after completion of chemoradiation if treatment missed in days 1-35 has to be made up. Radiation therapy must be completed within 56 ± 3 days of its initiation (two (2) make-up weeks are permitted).

External beam radiation will be delivered using a linear accelerator with a photon energy of 6 MV or greater. Source-to-axis distance (SAD) of 100 cm is required. Intracavitary therapy could be delivered by low dose-rate (LDR) brachytherapy using ^{137}cesium or high dose-rate (HDR) brachytherapy using ^{192}iridium. ***Intensity modulated radiation therapy (IMRT) is permitted on this study (see Section 5.2.1.1).***

Localization and Simulation: Patients to be simulated in the supine position with feet tied together for immobilization (may use vacuum-evacuated device if desired). CT simulation is required, if feasible with full and empty bladder (for generation of an internal target volume for the cervical contour when feasible) and an empty rectum. CT scan should extend at least 4 cm above and below the target volumes with inter slice thickness of ≤ 3mm. Intravenous contrast may be used during simulation to help better define the vessels.

Contouring: The lymph node Clinical target volume (CTV1) includes entire bilateral common iliac, external/internal iliac, upper pre-sacral (from S1-S3) and obturator regions. For patients with pelvic node positive and para-aortic node not surgically staged include the entire para-aortic nodal region up to renal vessels. For patients with para-aortic node positive include the entire para-aortic nodal region up to renal vessels or at least 2 cm above highest para-aortic node. The involved nodes are contoured as GTV and expanded by 5 to 7 mm with editing for the small bowel and duodenal region to create PTV2 for the concomitant boost or sequential boost. Involved nodes are defined as all lymph nodes ≥ 1cm in the short axis, those with a necrotic center and/or PET avidity

The primary CTV2 included the entire gross tumor plus the entire cervix, uterus, parametria, and proximal ½ of the vagina (unless vaginal involvement where the entire vagina is included). CTV1 is expanded 5-7 mm to create nodal PTV. CTV2 is expanded by 1.5-2 cm to account for target motion and set up uncertainty to create primary PTV. If ITV created, then 7-10 mm to ITV should be sufficient for primary PTV. Nodal PTV and Primary PTV is combined to create a final PTV1. Involved node with 5 to 7 mm expansion as described would be PTV2. Normal tissue structures will be contoured on the CT scan obtained with a full bladder since treatment will be delivered with a full bladder with the goal of reducing the volume of irradiated bowel. A description for the technique on how to contour these structures can be found at http://www.rtog.org/CoreLab/ContouringAtlases/FemaleRTOGNormalPelvisAtlas.aspx.
Bladder will be outlined on every slice, including the portion inferior to the planning target volume. Rectum will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid. Bowel space will be outlined on every slice which has visible bowel, extending

2 cm above the planning target volume. Bowel space will include the volume surrounding loops of bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment. Bowel space will include the ENTIRE bowel, including small bowel, colon and sigmoid, in one bowel bag contour. This contour will be named 'bowel space'. The pelvic bone will be contoured as a surrogate for the bone marrow. The pelvic bone from the superior to the inferior aspect of the PTV can be auto-contoured. This can be accomplished with use of a CT-density–based auto-contouring algorithm. The femoral heads but not femoral necks should be included in the bone marrow contour.

5.2.1.1 Intensity Modulated Radiation Therapy (IMRT) Dose Specifications

Prescription dose shall be according to the following specifications:
Planning target volume (PTV1) will receive 45Gy in 25 fractions. Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8Gy. All targets will be treated simultaneously. The dose is prescribed to cover 97% of the PTV1. A volume of at least 0.03 cc within any PTV 1 should not receive > 110% of the maximum prescribed dose. No volume within the PTV that is 0.03 cc or larger can receive a dose that is < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the PTVs must not receive > 110% of the maximum prescribed dose to the PTV. If PTV2 is created, then it can receive concomitant boost of 55 to 57.5 Gy in 25 fractions or sequential boost to a total dose of 58-60Gy.

IMRT Technical Factors: Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. VMAT is allowed. Six or more fields should be utilized with a minimum source-axis distance of 100 cm. The exception is the use of the tomotherapy unit that uses 80 cm. 6-10 MV energy photon beams should be used.

3D EBRT technique: Four field technique with field borders 7 mm from PTV1 in all directions. Target dose is 45Gy in 25 fractions. The minimum dose to the dose specification point (isocenter or calculation point) is greater than or equal to 43.2Gy Maximum dose to a volume of ≥0.03 cc of tissue within the convergence of the treatment fields should not exceed 107% of the prescription dose. The PTV2 if created would receive sequential boost to a total dose of 58-60Gy.

Parametrial Boost Fields: The parametrial boost field is an anterior-posterior and posterior-anterior field arrangement. The superior border should be reduced to include only the true pelvis. The upper border of the true pelvis field is defined at the inferior aspect of the sacroiliac joint. The inferior border remains the same as in the pelvis fields or mid obturator foramen. A parametrial central field block is a minimum of 6 cm wide. The dose for parametrial boost is 5.4Gy in 3 fractions.

Dose constraints for IMRT (recommended but not mandated, as below). Priority should be given to PTV1 coverage IMRT arm:
Bowel up to 30-40% receives 40Gy,
Bladder up to 50-60% receives 40Gy
Rectum up to 50-60% receives 40Gy
Bone marrow up to 75-80% receives

20Gy
Kidneys for extended field up to < 10% receives 16Gy

In patients with nodal boost V55 Gy for small bowel < 5-15cc and Duodenum V55 < 1cc

Verification Requirements: Image should be performed at least weekly for patients treated on the IMRT and standard therapy arms, respectively. For patients treated with IMRT dose delivery, orthogonal films or CBCT to localize the isocenter placement shall be obtained. For patients treated with standard therapy, weekly port films should be obtained. The length of the treatment field shall be indicated on these films. These films will not be collected but should be held by the institution and available for review if requested.

5.2.1.2 Intracavitary Brachytherapy:

At the time of registration, institutions will select the one brachytherapy dose rate to be used for all accrued patients at that institution, either low-dose-rate (LDR) or high-dose-rate (HDR).

Low Dose Rate (LDR) Brachytherapy: Following the completion of external beam RT, the patient will receive 4000cGy to Point A or 3D image based brachytherapy following GEC ESTRO guidelines by intracavitary tandem and ovoid implant with ^{137}cesium. The patient may receive this in one or two applications at the discretion of the radiation oncologist. The first insertion should be performed promptly upon completion of external beam irradiation. If two implants are contemplated, the second implant should be completed within three weeks of the completion of external beam irradiation.

High Dose Rate (HDR) Brachytherapy: 3D image based brachytherapy using MRI or CT based planning using GEC ESTRO guidelines. Dose of each brachytherapy fractions is 550- 600cGy for a total 5 or 700 cGy per fraction to total of 4 fractions. HDR brachytherapy should start at week 4 or 5. When HDR brachytherapy begins, at least one insertion will be performed per week with no external beam therapy given on the day of the insertion. If the majority of the external beam radiation has been given, then two or three insertions per week could be done separated by at least 48 to 72 hours in order to complete all treatment within 56 ± 3 days.

HDR Instruments: It is recommended that tandem and ovoids or tandem or ring or hybrid applicator be used for HDR brachytherapy for patients with cervical cancer. Interstitial brachytherapy with a Vienna, a Venezia applicator or Syed template should be used for patients with vaginal cancer who are not candidates for intracavitary brachytherapy.

HDR Dosimetry: The planned total dose to high risk clinical target volume (HRCTV) after summating for EBRT and brachytherapy should be EQ2 of 80-90Gy. Similarly total dose to bladder, rectum and sigmoid should be ≤ 80Gy, 65Gy and 70Gy respectively. If intracavitary brachytherapy cannot be performed, then interstitial or hybrid applicator brachytherapy can be performed as per standard institutional guidelines and practice. Reasons for not performing intracavitary brachytherapy should be documented for those patients with cervical cancer.

5.2.1.3 Interstitial Brachytherapy

Interstitial brachytherapy such as with a Vienna, Venezia applicator or Syed template is allowed for those patients with vaginal cancer who are not candidates for intracavitary therapy or if it is felt to be clinically imperative to change the plan after treatment start because of poor response of the tumor to external beam therapy.

5.3 Chemotherapy

5.3.1 Cisplatin

Cisplatin will be given by IV infusion at a dose of 40 mg/m^2 on days 2, 9, 16, 23, and 30 (Tues) for a total of 5 weekly cycles. It will also be permitted to include a 6th cycle of cisplatin during the parametrial boost or any make-up radiation treatment in a sixth week of external beam radiotherapy. Patients will be strongly encouraged to increase oral hydration 24 hours prior and after chemotherapy administration. Normal saline will be infused IV as pre- and post-hydration to cisplatin infusion as per institutional standard protocol and investigator discretion. Standard premedication with antiemetic, steroid, and H2 blocker will be administered as per institution protocol. Cisplatin 40 mg/m^2 (maximum dose, 70 mg) may be mixed with mannitol 25 g in 1L normal saline, but sites may also follow institutional practice. It will be infused over 60-120 minutes or per institutional protocol. All patients receive weekly cisplatin on this protocol.

5.3.2 Intravenous Triapine

Triapine 50 mg intravenous infusion over 120 +/- 10 minutes is administered once during the study within 90 minutes after pelvic irradiation, on day 1 to obtain PK data. Triapine 50 mg is diluted in 500 mL normal saline or 500 mL 5% dextrose in water and administered using DEHP-free low sorbing infusion set. All patients will receive dexamethasone IV prior to each IV triapine infusion. Premedicate with antiemetic as needed for patients developing nausea or vomiting with a previous dose of triapine.

5.3.3 Oral triapine

Oral triapine will be given at the assigned phase I dose level (see 5.1.1 Dose Escalation Schedule). Patients will be asked to fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose (triapine complexes strongly with iron ions). Patients will ingest one dose of triapine in the clinic within 90 minutes after each daily radiation treatment, starting with the first radiation treatment through the last day of radiation treatment (completion of EBRT). Each oral triapine dose will be administered in the clinical area within 90 minutes of each daily RT dose. Triapine will not be administered on days that radiation is not given (Sat- Sun, holidays) or on the days that radiation is missed or held. Study staff will observe and document triapine administration and will document dosing time in the patient's record. The patient will be requested to maintain a medication diary of each dose of medication (see APPENDIX D PATIENT MEDICATION DIARY – TRIAPINE). The medication diary will be reviewed by clinic staff each week.

5.3.3.1 Clinical Monitoring for Methemoglobin

Patients should be observed clinically during the first week of treatment.

Test	Frequency	
	IV Triapine, Days 1	PO Triapine, Days 2-5
Blood pressure Pulse Respiratory rate O_2 saturation (pulse oximeter)	Pre-dose, then every 60 minutes x 3	Pre-dose, then every 60 minutes x 3
EKG	Only if patient is hypotensive or dyspneic	

If patient is symptomatic or has hypoxia (≤92%) requiring oxygen, obtain "spot" methemoglobin level and serial sampling as clinically indicated (based on symptoms such as but not limited to skin discoloration, cyanosis, coma, dysrhythmia, levels can be repeated every 6-8 hours until levels <20%). A repeat spot methemoglobin should be obtained prior to the next triapine dose to determine whether dose modification or further treatment is indicated. Supportive care should be provided as clinically indicated.

Starting week 2, if no changes in O_2 saturation are seen during the treatment and observation periods noted in the table above, the patient may be discharged immediately post subsequent triapine dosing.

See Section 6 for dose modification instructions for methemoglobinemia

5.4 Duration of Study

Patients are considered on study from the date of enrollment until the completion of the secondary endpoint, the 3-month post-treatment ^{18}F-FDG-PET/CT scan (90 days +/- 7 days from completion of therapy).

5.4.1 Expansion cohorts

An expansion cohort will be treated at the MTD or the dose below that as stipulated above. Subjects will be enrolled into a non-HIV+ cohort (n=12) to further expand pharmacokinetic investigations and provide additional safety information or a 28-patient cohort of regionally advanced stage HIV+ uterine cervix cancer patients on active retroviral therapy. (Subject enrolled into this cohort may include such patients enrolled as part of the MTD determination.) Enrollment will not be time-limited but will be limited to patients with a

histologically confirmed diagnosis of locally advanced cervical or vaginal carcinoma not amenable to curative surgical resection alone to facilitate achievement of secondary objectives.

5.5 Definition of Dose-Limiting Toxicity

DLTs are defined as the following adverse events if considered at least "possibly related" to a component of the study therapy and which occur from the start of treatment until completion of EBRT, prior to initiation of brachytherapy (i.e. the first 5 weeks if no treatments are missed):

- Any nausea, vomiting, diarrhea and elevation of serum creatinine level Grade 3 toxicity **not resolved with maximal intervention to Grade 0-2 over 7 days** (*except alopecia and fatigue*);
- Any nausea, vomiting, diarrhea and elevation of serum creatinine level Grade 4 toxicity
- Any other non-hematologic toxicity ≥Grade 3;
- Any hematologic toxicity of ≥ Grade 4;
- Grade ≥3 dyspnea;
- Inability to deliver at least 20 of the scheduled 25 administrations of triapine at the planned dose, **allowing for 2 weeks to make up missed radiation days**.
- Inability to deliver at least 4 of the scheduled 5 administrations of IV cisplatin at the planned dose.

Dose escalation will proceed within each cohort according to the following schema, unless stated otherwise.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be enrolled at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be enrolled at the next lowest dose level if only 3 patients were treated previously at that dose.

≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the Recommended Phase 2 Dose (RP2D). At least 6 patients must be enrolled at the RP2D (section 5.1.2).

5.6 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of intravenous and oral triapine with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

The following medications or drug classes listed should be avoided while taking triapine in order to minimize the risk for signs and symptoms of methemoglobinemia. This is not an all-inclusive list and should be utilized along with clinical judgement and other patient risk factors, if applicable:

- Amino salicylic acid (also called p-aminosalicylic acid or 4-aminosalicylic acid)
- Chloroquine
- Dapsone
- Local anesthetics, topical sprays and creams including benzocaine, lidocaine, and prilocaine
- Methylene Blue (used for treatment but it is also a risk in certain high risk populations like G6PD deficiency)
- Metoclopramide
- Nitroglycerin
- Phenazopyridine
- Primaquine
- Rasburicase
- Quinones
- Sulfonamide

5.6.1 Supportive care

IV Triapine: pre-treatment glucocorticoids (IV dexamethasone); antiemetic therapy*
Oral Triapine: antiemetic therapy*
Cisplatin: steroid prophylaxis and antiemetic therapy*
Pelvic External Beam Radiation (EBRT): skincare; antiemetic therapy; and anti-diarrheal medication*
Pelvic Brachytherapy: antiemetic therapy and anti-diarrheal medication*
* *Per institutional policy.*

5.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue until the completion of brachytherapy. Two-weeks to make up missed EBRT doses are allowable. Therapy may continue until one of the following criteria applies:

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

5.8 Duration of Follow Up

All patients will be followed until completion of 3-month post-treatment PET-CT scan (90 days +/- 7 days from completion of therapy). Patients removed from study for unacceptable adverse event(s) should also be followed until resolution or stabilization of the adverse event. Long term follow up will begin after post-treatment PET-CT-scan and will occur every six months (+/- 2 weeks) for a total of 5 years.

5.9 Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in Section 5.7 apply, or once they have completed follow-up as described in Section 5.8. The reasons for treatment discontinuation and study removal and the associated dates must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose Level	PO Triapine Dose
-2	50 mg D1,3,5 Weekly x5
-1	50 mg QD D1-5 Weekly x5
1	100 mg QD D1-5 Weekly x5
2	150 mg QD D1-5 Weekly x5
3	200 mg QD D1-5 Weekly x5

6.1 Nausea/vomiting

Nausea/vomiting	**Management/Next Dose for *Triapine***	**Management/Next Dose for *Cisplatin***
≤ Grade 2	No change in dose Treat with antiemetics.	No change in dose Treat with antiemetics.
Grade 3	Hold[a] until ≤ Grade 2. Resume at one dose level lower, if indicated[b] Treat with antiemetics.	Hold[a] week-to-week until ≤ Grade 2. Treat with antiemetics.
Grade 4	Off protocol therapy[c]	Off protocol therapy[c]
[a]Patients should hold triapine if N/V refractory to anti-emetic therapy. [b]If appropriate antiemetic treatment does not resolve toxicity down to grade 2 or less within 72 hours. [c]Off protocol therapy and continue standard of care treatment per treating physician.		
Recommended management: antiemetics.		
• External-beam pelvic radiation should be held until Grade 3 toxicity is ≤Grade 2.		

6.2 Diarrhea

Diarrhea	**Management/Next Dose for *Triapine***	**Management/Next Dose for *Cisplatin***
≤ Grade 2	No change in dose Treat with antidiarrheal therapy.	No change in dose Treat with antidiarrheal therapy.
Grade 3	Treat with antidiarrheal therapy. Hold[a] until ≤Grade 2. Resume at one dose level lower, if indicated[b]	Hold[a] week-to-week until ≤ Grade 2. Treat with antidiarrheal therapy
Grade 4	Off protocol therapy[c]	Off protocol therapy[c]
[a]Patients should hold triapine if diarrhea refractory to anti-diarrheal [b]If appropriate antidiarrheal treatment does not resolve toxicity to ≤Grade 2 within 72 hrs.		
[c]Off protocol therapy and continue standard of care treatment per treating physician.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		
• External-beam pelvic radiation should be held until Grade 3 toxicity is ≤ Grade 2.		

6.3 Neutropenia

Neutropenia	**Management/Next Dose for *Triapine***	**Management/Next Dose for *Cisplatin***
≤ Grade 2	No change in dose	No change in dose
Grade 3	No change in dose	Hold[a] week-to-week until ≤ Grade 2. Resume at same dose level
Grade 4	Off protocol therapy[b]	Off protocol therapy[b]
[a]Patients requiring a delay of >2 weeks should go off protocol therapy. [b]Off protocol therapy and continue standard of care treatment per treating physician.		
• *G*-CSF is not allowed during this therapy • External-beam pelvic radiation and Triapine dosing should continue while any or all courses of cisplatin are withheld.		

6.4 Thrombocytopenia

Thrombocytopenia	**Management/Next Dose for *Triapine***	**Management/Next Dose for *Cisplatin***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	Hold[a] week-to-week until ≤ Grade 1. Resume at same dose level.
Grade 3	No change in dose	Hold[a] week-to-week until < Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy[b]	Off protocol therapy[b]
[a]Patients requiring a delay of >2 weeks should go off protocol therapy. [b]Off protocol therapy and continue standard of care treatment per treating physician.		
• External-beam pelvic radiation and Triapine dosing should continue while any or all courses of cisplatin are withheld.		

6.5 Non-hematologic toxicity

Non-hematologic toxicity	**Management/Next Dose for *Triapine***	**Management/Next Dose for *Cisplatin***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold[a] until ≤ Grade 1 (SEE NOTE)	Hold[a] until ≤ Grade 1. (SEE NOTE)
Grade 3	Hold[a] until < Grade 1 (SEE NOTE)	Hold[a] until < Grade 2. (SEE NOTE)
Grade 4	Off protocol therapy[b]	Off protocol therapy[b]
[a]Patients requiring a delay of >2 weeks should go off protocol therapy. [b]Off protocol therapy and continue standard of care treatment per treating physician. [c]NOTE: Decision to maintain dose or resume at dose reduction must be reviewed with study PI		
• External-beam pelvic radiation should be held until Grade 3 toxicity is ≤Grade 2.		

6.6 Methemoglobinemia

If patients had prolonged methemoglobinemia or hypoxia requiring dose adjustment during any of the observation periods noted in the table above (5.3.3.1 Clinical Monitoring for Methemoglobin), follow the schema until stable.

Please note, it is the *trend* in the O_2 saturation that is of importance. Since pulse oximetry is known to be unreliable in the presence of significant methemoglobinemia, weight should not be given to a single value alone. In any case where there is significant doubt, serial spot methemoblobins should be obtained (as clinically indicated based on symptoms such as but not limited to skin discoloration, cyanosis, coma, or dysrhythmia and levels can be repeated every 6-8 hours until levels <20%) and consultation as needed.

It is expected that all patients will show a transient rise in methemoglobin (up to 10-15%) while on study but unless accompanied by hypoxia, or symptoms (e.g., dyspnea), no changes to treatment or dose may be required. However, for patients not fitting this pattern, the following guidelines should be followed:

- If methemoglobin is asymptomatic, <20%, and NOT accompanied by hypoxia (oxygen saturation <92%) : treat without change in dose.

- **IF** methemoglobin >15% lasts more than 3 hours OR if methemoglobin >20% OR if oxygen saturation <92%, **THEN**: obtain arterial blood gases (a pO2 <80 should result in hospitalization and will be counted as DLT). If pO2 normalizes within 24 hours, retreatment at a lower dose level may be considered by the Principal Investigator at UPCI.

Treatment options for methemoglobinemia could include methylene blue, 1-2 mg/kg IV over five minutes[32]. However, methylene blue is contraindicated in patients with glucose-6-phosphate deficiency, since its pharmacologic action as an electron carrier in the reduction of methemoglobin is itself dependent on the generation of NADPH by G6PD through the hexose monophosphate shunt[33]. Thus, methylene blue may be at best ineffective in such patients and may have the potential to complicate the clinical situation by provoking hemolysis, although this association is less clear[33]. In situations where the use of methylene blue may be contraindicated (e.g., in those individuals who are in the high-risk group (patients of African, Asian or Mediterranean origin/ancestry), who may have had a false negative G6PD deficiency test), the successful use of ascorbic acid (1000 mg IV q6h) has been described[33].

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. For this trial, routine and expedited reporting will begin at the start of study therapy (i.e., with the first dose of triapine, cisplatin and/or radiation therapy). 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(s) (CAEPRs)

The Comprehensive Adverse Event 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 of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. 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.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for for Triapine® (NSC 663249)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Triapine® (NSC 663249)

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. *Frequency is provided based on 182 patients.* Below is the CAEPR for Triapine®.

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 2.6, March 19, 2019[1]

Adverse Events with Possible Relationship to Triapine® (CTCAE 5.0 Term) [n= 182]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
		Hemolysis	***Hemolysis (Gr 3)***
	Methemoglobinemia		***Methemoglobinemia (Gr 2)***
CARDIAC DISORDERS			
	Cyanosis		***Cyanosis (Gr 2)***
		Left ventricular systolic dysfunction	
GASTROINTESTINAL DISORDERS			
	Colitis		***Colitis (Gr 2)***
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bicarbonate decreased		***Blood bicarbonate decreased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Investigations - Other (Elevated ST and T wave changes)		***Investigations - Other (Elevated ST and T wave changes) (Gr 2)***
	Lipase increased		***Lipase increased (Gr 2)***
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypercalcemia		***Hypercalcemia (Gr 2)***

Adverse Events with Possible Relationship to Triapine® (CTCAE 5.0 Term) [n= 182]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Hypoxia		***Hypoxia (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***
	Hypertension		***Hypertension (Gr 2)***
	Hypotension		***Hypotension (Gr 2)***

[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]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Triapine® trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Triapine® caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (spleen disorder); Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Hemolytic uremic syndrome; Leukocytosis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (premature ventricular contraction); Myocardial infarction; Palpitations; Pericardial effusion; Restrictive cardiomyopathy; Sinus tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ear congestion); Ear and labyrinth disorders - Other (hyperacusis); Ear pain; Hearing impaired; Middle ear inflammation; Tinnitus; Vertigo
EYE DISORDERS - Dry eye; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (leukoplakia of the mouth); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (salivary hypersecretion); Gastrointestinal disorders - Other (steatorrhea); Gastrointestinal disorders - Other (stool discoloration); Gastrointestinal disorders - Other (tongue discoloration); Hemorrhoids; Ileus; Oral hemorrhage; Pancreatitis; Rectal hemorrhage; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema

limbs; Flu like symptoms; General disorders and administration site conditions - Other (extravasation); Malaise; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice); Hepatobiliary disorders - Other (liver tenderness)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood lactate dehydrogenase increased; CPK increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (BUN increased); Investigations - Other (C-reactive protein increased); Investigations - Other (NPN increased); Investigations - Other (PT decreased); Investigations - Other (sedimentation rate increased); Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Iron overload; Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (hypertonia); Musculoskeletal and connective tissue disorder - Other (leg cramps); Musculoskeletal and connective tissue disorder - Other (myoglobin); Musculoskeletal and connective tissue disorder - Other (twitching); Pain in extremity
NERVOUS SYSTEM DISORDERS - Amnesia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Nervous system disorders - Other (cerebellar toxicity); Nervous system disorders - Other (reflexes decreased); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delayed orgasm; Delirium; Depression; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Urinary frequency; Urinary tract pain; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Genital edema; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Epistaxis; Hiccups; Laryngospasm; Pleural effusion; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hirsutism; Hyperhidrosis; Photosensitivity; Pruritus; Skin and subcutaneous tissue disorders - Other (Skin nodule); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hematoma; Phlebitis; Thromboembolic event; Vascular disorders - Other (pallor); Vascular disorders - Other (vasodilation)

Note: Triapine® 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.

7.1.2 Adverse Event List for Cisplatin

Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia and acute myeloid leukemia. NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible. Severe renal toxicity can be largely avoided by induction of a diuresis before, during and after treatment. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if creatinine> 1.5 x institutional upper limit normal (ULN) develop. Mild or severe electrolyte abnormalities may occur (5%) as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and

electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin. Local necrosis and thrombophlebitis can be avoided by careful administration. Neurotoxicity may be related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described. Ototoxicity may occur. NOTE: Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms is a well-documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each course of cisplatin. Refer to package insert for additional information.

Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment. Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area.

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 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (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 website (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 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

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**	**≥24h Hospitalization[a]**
Skin and subcutaneous tissue disorders	Alopecia	2	No
Gastrointestinal disorders	Diarrhea	2	No

Gastrointestinal disorders	Nausea Vomiting	2	No

a Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

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 or commercial agents administered in this study can be found in Section 7.1.

8.1 Triapine NSC 663249

Chemical Name: 3-aminopyridine-2-carboxaldehyde thiosemicarbazone

Other Names: 3-AP

Classification: Triapine®, an α-heterocyclic carboxaldehyde thiosemicarbazone (HCT), is a ribonucleotide reductase (RNR) inhibitor that acts on the M2 (R2) subunit. The HCTs are the most potent RNR inhibitors, being 65 -5,000 times more potent than hydroxyurea.

Mechanism of Action: Ribonucleotide reductase (RNR) inhibitor

CAS Registry Number: 143621-35-6

Molecular Formula: $C_7H_9N_5S$ **M.W.:** 195

Approximate Solubility: Water = 0.1 mg/mL
Ethanol = 1.25 mg/mL
PEG-300 = 15 mg/mL

Potential Drug Interactions: In in vitro cellular and subcellular liver studies, triapine was not metabolized by glucuronyltransferases, FMO, AO/XO, MAO-A/B, or NAT-1/2, but was metabolized by CYP450s. CYP1A2 accounted for most of the depletion of triapine. Triapine reduced CYP1A2 activity and increased CYP2C19 activity. (Joshi et al. Cancer Chemotherapy and Pharmacology (2020) 86:633–640)

8.1.1 Triapine Injection

How Supplied: Triapine® Injection is supplied by DCTD, NCI and distributed by the CTEP, DCTD, NCI. Triapine® Injection is supplied in 10 mL amber vials containing 10 mL of a clear yellowish slightly viscous, sterile, non-aqueous solution for IV administration. Each 10 mL vial contains 50 mg of Triapine® (5 mg/mL), 60 mg of citric acid, anhydrous, 10 mg of L-ascorbic acid, 3 mL of ethyl alcohol, and 7 mL of polyethylene glycol 300.

Preparation: Withdraw the Triapine dose volume from the vial and add to 0.9% sodium chloride or 5% dextrose in water to a final concentration of 0.01 to 2 mg/mL. Triapine infusion should be a clear, yellow solution with no discernible haziness. If haziness appears or persists after dilution, do not use the product.

Dilutions of Triapine® must be performed in glass bottles, or in plastic IV bags that do not contain di (ethylhexyl) phthalate (DEHP), since the nonaqueous solvents in Triapine® injection have been shown to extract DEHP.

Storage: Store Triapine® injection between 2-8°C (36-46°F). Do not freeze.

If a storage temperature excursion is identified, promptly return Triapine® injection to refrigerated temperature and quarantine the supply. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: When diluted with 0.9% sodium chloride or 5% dextrose in water, to a final concentration of 0.01 to 2 mg/mL, Triapine® infusions have been found to be stable for 8 hours at room temperature or at 2 - 8ºC. Do not freeze. Do not expose diluted solutions of Triapine® injection to direct sunlight or temperatures above 25°C (77°F).

Shelf life stability studies of Triapine® injection vials are on-going.

Route of Administration: Intravenous

Method of Administration: Infuse intravenously over 120 +/- 10 minutesusing a DEHP-free (e.g., polyethylene) low sorbing infusion set on day 1.

8.1.2 Triapine Capsules

How Supplied: Triapine® Capsules are supplied by Nanopharmaceutics, LLC and distributed by the CTEP, DCTD, NCI. Each Triapine® Capsule contains 50 mg of Triapine® in combination with Starch 1500 and Magnesium Stearate in a size 1, hard gelatin, white, opaque capsule. Each bottle contains 30 capsules.

Storage: Store Triapine® Capsules at room temperature 25ºC, excursions permitted to 15ºC to 30ºC.

If a storage temperature excursion is identified, promptly return Triapine® Capsules to between 15 and 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life stability studies of Triapine® Capsules are on-going.

Route of Administration: Oral administration per the protocol treatment schedule. No oral administration on day 1 when triapine is delivered intravenously.

Method of Administration: Patients will be asked to fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose (triapine complexes strongly with iron ions).

Patients will ingest one dose of triapine in the clinic within 90 minutes after each daily radiation treatment, starting with the first radiation treatment through the last day of radiation treatment (completion of EBRT). Each oral triapine dose will be administered in the clinical area within 90 minutes of each daily RT dose. Triapine will not be administered on days that radiation is not given (Sat- Sun, holidays) or on the days that radiation is missed or held. Study staff will observe and document triapine administration and will document dosing time in the patient's record.

8.1.3 Agent Ordering and Agent Accountability

Availability: Triapine is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. 3-AP is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3). In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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

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, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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.

8.1.4 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.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Cisplatin (NSC #119875)

Formulation:	PLATINOL®-AQ (cisplatin injection) infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively.
Supplier:	Commercially available. Refer to individual FDA-approved package insert.
Preparation:	PLATINOL®-AQ (cisplatin injection) infusion concentrate (1 mg/mL) must be further diluted prior to administration. Cisplatin (40 mg/m^2) will be diluted in 250 mL of normal saline. NOTE: Aluminum reacts with cisplatin causing precipitation formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.
Storage:	Store at 15° to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light.
Stability:	The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.
Administration:	Once weekly intravenous cisplatin (40 mg/m^2) is administered. 1000 mL of normal saline should be infused intravenously one hour before cisplatin. Increased oral intake should be encouraged starting the day before. Additional fluid may be given as needed for symptomatic support. The solution should be infused at a rate of 1 mg/min, usually over a total of 60 to 120 minutes. The cisplatin dose will not exceed 70 mg maximum. Immediately after completion of the cisplatin infusion, an additional 1000

mL of normal saline should be given.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Integrated Laboratory Studies - Secondary objective

9.1.1 Pharmacokinetics

General

Blood samples to be obtained through a peripheral or central line blood draw. Samples should be drawn from the opposite arm if infusion is a peripheral infusion. Samples should NOT be drawn from the infusion line.

Drawing and Processing

Document exact start and stop times of each infusion and drug dose and exact times of blood draws per Appendix B-C.

1. Collect in a ~4 mL (3-5) mL purple top tube (*e.g.* BD vacutainer 367861 plastic 13 x 75 4 mL tube).
2. Invert the vacutainer tubes several times to mix blood with EDTA anticoagulant and immediately place on ice.
3. Processing should begin within 30 minutes of collection.
4. Samples should be centrifuged for 10 min at approximately 1000 x g in a refrigerated tabletop centrifuge so as to produce plasma.
5. The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes, and stored at -70 °C until shipment.

Pharmacokinetics of IV triapine

To assess oral bioavailability, IV triapine at a fixed dose of 50 mg for all dose levels will be given on day 1. On the day when IV triapine is administered, oral triapine will not be given.

Day 1:

EDTA anti-coagulated blood samples will be obtained at the following timepoints:

prior to IV triapine infusion
30 (±5) min after start of infusion
60 (±5) min after start of infusion
90 (±5) min after start of infusion
110 (±5) min after start of infusion
2 h 30 min (±10 min) after start of infusion
3 h (±10 min) after start of infusion
4 h (±10 min) after start of infusion
6 h (±15 min) after start of infusion
8 h (±30 min) after start of infusion
24 h (±2 h) after start of infusion

Pharmacokinetics of PO triapine

To assess oral bioavailability, blood samples will be obtained on 1 day of PO triapine.

Day 8:

EDTA anti-coagulated blood samples will be obtained at the following timepoints:

prior to PO triapine dose 30
(±5) min after dose
60 (±5) min after dose
90 (±10) min after dose
110 (±10) min after dose
2 h 30 min (±10 min) after dose
3 h (±10 min) after dose
4 h (±10 min) after dose
6 h (±15 min) after dose
8 h (±30 min) after dose
24 h (±2 h) after dose

9.1.1.1 Shipping of Specimen(s)

Preparing the shipment

- Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", L x W x H).
- Please organize the samples by Patient and Time point in the box.
- Do not store in plastic bags (they break on dry-ice and labels will detach).
- A copy of each of the pharmacokinetic sample collection forms (Appendix B-C) for the respective patients should be included with each shipment. If applicable, to prevent problems with illegible writing on tubes, consider numbering them and numbering samples on the sample sheet.
- *Note the study number, PI, and the drugs used/to be measured.
- *A name, phone number, and email address should be included with the samples so that receipt can be acknowledged.
- Please notify the lab by email (PITT-PK@UPMC.EDU), telephone (412-623-3248) or fax (412-623-1212) at least 24 hours prior to shipment.

Shipping

*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state (if samples are to be shipped frozen). All specimens are to be shipped on either Monday, Tuesday or Wednesday to:

Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G27 Hillman Research Laboratories 5117 Centre Avenue
Pittsburgh, PA 15213.

Regulations

Shipment of samples must comply with appropriate regulations as specified by the carrier. At a

minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture-resistant (e.g. cardboard mailing tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

Contact Information for Assistance
Lab phone: 412-623-3248
Lab fax: 412-623-1212
PK Lab email: PITT-PK@upmc.edu
PK director email: beumerjh@upmc.edu

9.2 Special Studies

9.2.1 ^{18}F-FDG-PET/CT

9.2.1.1 Subject Preparation

Prior to Arrival

-Subjects must fast (except for water) for at least 4 hours before administration of 18F-FDG for the PET/CT exam.
-Subjects should avoid strenuous exercise for 24 hours before the FDG injection to minimize uptake of the radiotracer in muscles.

Upon Arrival

-Upon arrival at the PET facility, confirm subject compliance with pre-procedure instructions, particularly that the fasting requirement was met.
-The subject's weight and height shall be measured and recorded (not verbally relayed by the subject).
-The pre-injection blood glucose level must be < 200 mg/dL (measured ideally within one hour of FDG injection). If the serum glucose is > 200 mg/dL, the study should be rescheduled. The referring physician or primary physician of the subject should be contacted to optimize blood glucose control.
-A large-bore intravenous line (typically, a 20 or 22 gauge angiocatheter) or a butterfly needle in a vein of the participant's arm.
-Prior to positioning the subject on the PET scanner the subjects should be asked to urinate.
-Use of a Foley catheter and a single furosemide administration per institutional policy is permitted.

Injection of 18F-FDG

-The dose of FDG to be administered is 10-20 mCi.
-The exact time of calibration of the dose should be recorded and the exact time of injection noted to permit correction of the administered dose for radioactive decay. In addition, the dose remaining in the tubing or syringe, or that was spilled during injection should be recorded. The injection should be performed through an intravenous catheter.

FDG-PET/CT Imaging Procedure

-The time between the injection of FDG and PET emission scan start (tracer uptake time) should begin between 50-70 minutes after injection.
-The injection to start of imaging time for the 3-month post therapy PET/CT scans should be within 10 minutes of that for the baseline study.
-The CT component of the PET/CT study will be performed for attenuation correct and anatomical localization (AC, AL).
-All participants must void prior to imaging to ensure clearance of bladder activity.
-A Foley catheter and a single furosemide administration per institutional policy is permitted.
-Participants will be positioned with their arms above their head or on their chest if unable to keep their arms above the head.

9.2.1.2 Typical acquisition parameters for the low-dose CT scan for attenuation correction should be: kVp = 120; effective mAs = 30–80 (participant dependent); gantry rotation time ≤ 0.5 sec; maximum reconstructed width = 3–5 mm without overlap. The parameters should use the standard reconstruction algorithm, without any iodinated intravenous contrast agent. Dilute oral contrast is acceptable, if part of typical institutional practice.

9.2.1.3 ^{18}F-FDG PET/CT Reporting: Images will be evaluated on baseline and 3-month scans qualitatively for focal areas of abnormally increased ^{18}F-FDG uptake in the primary tumor. This will be performed by visually identifying ^{18}F-FDG uptake. Assessment of uptake in regional lymph nodes also will be performed by visual inspection. New sites of confirmed^{18}F-FDG PET/CT activity at 3-months post therapy will be classified as progressive metabolic disease. Local institution nuclear medicine reports should be submitted (section 12.1). Local institution investigators will resolve discrepancies by teleconference.

9.2.1.4 Semi-quantitative18F-FDG PET/CT Reporting of Standardized Uptake Value (SUV): Images will be evaluated quantitatively for abnormally increased 18F-FDG uptake in the primary tumor by measurement of the maximum standardized uptake value normalized for body mass (SUVmax). As a second metric, SUV normalized by lean body mass (SUL) will be calculated. On the baseline, 3-month scans, the SUVmax and SUL within the primary cancer will be recorded. The PET/CT Form recording this data must accompany pre-therapy and 3-month data submissions. As a secondary analysis, an 18F-FDG PET/CT post therapy: pre-therapy SUVmax ratio will be calculated. Ratios greater than 1.25 will be classified as progressive metabolic disease. Ratios of 0.76 to 1.25 will be classified as stable metabolic disease. Ratios of 0.34 to 0.75 will be considered partial metabolic response. Ratios lower than 0.33 will be marked as complete metabolic response. Ratios indistinguishable from cardiac or liver blood pool activity because of complete resolution of tumor 18F-FDG uptake (i.e., a cervix indistinguishable from surrounding normal tissue on post therapy imaging) will be labeled also as quantitative metabolic complete response.

9.2.1.5 Evaluation of ^{18}F-FDG PET CT Target:

Complete Response (CR): A metabolic complete response on PET/CT will be defined as greater than -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Partial Response (PR): A metabolic partial response on PET/CT will be defined as -25% to -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Progressive Disease (PD): Progressive metabolic disease on PET/CT is classified as an increase in tumor FDG uptake greater than +25% within the tumor region defined on baseline scan (considering normal cardiac or liver blood pool), or appearance of new FDG uptake in new metastatic lesions.

Stable Disease (SD): Stable metabolic response will be defined as a change in tumor FDG uptake by less than +25% (increase) or by less than -25% (decrease) at sites of abnormal tumor FDG uptake (considering normal cardiac or liver blood pool) when compared to pre-treatment FDG-PET study.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

9.2.1.5.1 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.

9.2.1.6 Outcome Measure

^{18}F-FDG-PET/CT to assess treatment response

9.2.1.7 Assessment

9.2.1.7.1 Method of Assessment

standard of care total body scan (skull base to mid-thigh)

9.2.1.7.2 Timing of Assessment

2 scans: pre-treatment and 3-month post-treatment (90 days +/- 7 days from completion of therapy) for acquiring the scans

9.2.2 Methemoglobin

9.2.2.1 Outcome Measure

% methemoglobin

9.2.2.2 Assessment of methemoglobin

9.2.2.2.1 Method of Assessment

Per institutional clinical chemistry procedures

9.2.2.2.2 Timing of Assessment

-On PK days (1, 8) before triapine, 4 h after triapine and the next day before any treatment

-Spot methemoglobin if clinically indicated.

9.2.2.3 Handling of Specimens(s)

Per institutional clinical chemistry procedures. Suggestion: 1-2 mL in heparinized blood gas syringe, analyzed within 30 minutes of being drawn.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy.

Procedure/Test	Pre-Study	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	EOT	1mo F/U	3mo F/U	L/T F/U
Informed consent	X										
Demographics	X										
Concurrent meds	X	X	X	X	X	X	X	X	X	X	
Medical history	X										
Current nicotine use status [P]		X									
Physical exam [A,B]	X	X	X	X	X	X	X	X	X	X	
Vital signs [A,B,Q]	X	X	X	X	X	X	X	X	X	X	
Height and Weight [A,B]	X	X	X	X	X	X	X	X	X	X	
Performance status [A,B]	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts [A,B]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry [A,B,C]	X	X	X	X	X	X	X	X	X	X	
PTT/PT/INR [D]	X										
EKG [D]	X										
FDG-PET/CT, Whole body	X									X	
MRI, Pelvis [E]	X									X	
Tumor Measurements	X									X	
Baseline signs & symptoms	X										
Methemoglobin monitoring[F]		X	X	X	X	X					
Adverse event evaluation		X	X	X	X	X	X	X	X	X	
Triapine IV [G]		X									
Triapine PO [H, I]		X	X	X	X	X					
Cisplatin IV [J]		X	X	X	X	X					
Radiation Therapy [H,K]		X	X	X	X	X					
Brachytherapy [L]							X				
Urine or serum B-HCG (WOCBP)	X	X[M]									
Pharmacokinetic Sampling [N]		X	X								
Patient Diary Review[O]		X	X	X	X	X					
Review of disease status and Survival [R]											X

A. These procedures do not need to be repeated in Week 1 if done pre-study within 7 days prior to start of protocol therapy.
B. The procedures must be repeated within 1 day prior to cisplatin each week in Weeks 2-5.
C. Albumin, alkaline phosphatase, total bilirubin, direct bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, phosphorus
D. Required pre-study, then as clinically indicated
E. This is optional.
F. Clinical monitoring required Week 1; as clinically indicated Weeks 2-5 (See Section 5.3.3.1). Monitor the % of methemoglobinemia on specific PK and PD days to correlate effect with exposure (see Section 9.2.2)
G. Day 1
H. M-F (except holidays); Oral triapine dosing for Dose Level -2 is M/W/F.
I. Not on the IV triapine day
J. Tuesdays (Days 2, 9, 16, 23, 30). Weeks 3-5, cisplatin may be given on Monday or Tuesday.
K. EBRT make-up is permissible (see Section 5.2).
L. See Section 5.2.1.2
M. Pregnancy test for women of childbearing potential (WOCBP) must be repeated within 24 hours prior to Cycle 1 Day 1.
N. See Appendix B and C for detailed schedule.
O. Study staff should review the patient medication diary each week.
P. Current nicotine use status will be collected on C1D1.
Q. Vital signs will have the following windows: +/- 5m for 60m post-dose and +/-10m for 120 and 180m post.
R. Long term survival follow up: Follow up for progression and survival status will occur via medical record review or phone call and should occur every 6 months (+/- 2 weeks) for a total of 5 years from the off treatment date.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of oral triapine in combination with chemoradiation 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 and symptom relief in addition to safety and tolerability. Patients will be assessed by standard criteria. For the purposes of this study, patients will undergo a clinical assessment every week while receiving chemotherapy and radiation therapy and at 1 month and 3 months post-treatment. Tumor response will be re-evaluated at the 3-month post-treatment ^{18}F-FDG PET/CT scan (approximately 150 days +/- 7 days following completion of all treatment).

11.1 Antitumor Effect – Solid Tumors

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 triapine and cisplatin.

Evaluable for objective response. Only those patients, have received at least 3 cycles of therapy (cisplatin + triapine), and have had their disease re-evaluated (with a 3 month post treatment PET-CT) will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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 one cycle of therapy, 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 ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be

considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non- cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition 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 diameters (longest for non- nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. 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 (or sites of disease) 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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the

study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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 18F-FDG PET CT Target:

Complete Response (CR): A metabolic complete response on PET/CT will be defined as greater than -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Partial Response (PR): A metabolic partial response on PET/CT will be defined as -25% to -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Progressive Disease (PD): Progressive metabolic disease on PET/CT is classified as an increase in tumor FDG uptake greater than +25% within the tumor region defined on baseline scan (considering normal cardiac or liver blood pool), or appearance of new FDG uptake in new metastatic lesions.

Stable Disease (SD): Stable metabolic response will be defined as a change in tumor FDG uptake by less than +25% (increase) or by less than -25% (decrease) at sites of abnormal tumor FDG uptake (considering normal cardiac or liver blood pool) when compared to pre-treatment FDG-PET study.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.4.3.1 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.

11.1.4.4 Evaluation of Overall Response

The overall response is the response recorded from the start of the treatment until the 3-month post-treatment PET-CT.

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

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

12. 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

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

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
- Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and

- Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.

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

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

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

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) 619-7862 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.

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

N/A

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

The **primary safety endpoint** of this study is DLT, and the first primary objective is the determination of the MTD and recommended phase II dose for oral triapine when used concomitantly with cisplatin chemoradiation.

The **primary PK endpoint** of this study is oral bioavailability of triapine, which will be determined with sufficient precision that the 95% CI of the mean population bioavailability falls within 80-125% of that mean. Based on reported preliminary data and assuming a normal distribution at log base 10 level, a true bioavailability rate of 0.67, and a standard deviation of 0.175 at log base 10 level, with 28 patients on RP2D, we will be able to establish the bioavailability with the 95% confidence interval of the population mean falling within 0.53-0.83.

Other PK parameter, including AUC, C_{max}, T_{max} and $T_{1/2}$ will be evaluated in the expansion cohort. Descriptive statistics will be used.

The **secondary efficacy endpoints** include metabolic complete response (mCR) by FDG-PET/CT, clinical overall response (OR), overall survival (OS) and progression free survival (PFS).

For the first dose level, 3 patients were enrolled without issues. Given the scarcity of patients and the thus far favorable toxicity profile, dose level 2 will be enrolled per an accelerated titration approach using a single patient cohort. Dose escalation will revert to the standard 3+3 design if the

patient on dose level 2 experiences a DLT or a ≥ grade 2 toxicity or when dose level 3 is reached. The standard 3+3 design is as follows: Escalation at 0/3 DLTs, dose-reduction if >1/3 DLT, and expansion to 6 if 1/3 DLTs. DLT is defined as the severe toxicity event that leads to the termination of the treatment as defined in section 5.5. The highest dose level where <2/6 DLTs are observed will be declared MTD.

13.1.1 The RP2D will be determined as described in section 5.1.2. Once the RP2D is determined, two expansion cohorts will be enrolled. Subjects will be enrolled into a non-HIV+ cohort (n=12) to further expand pharmacokinetic investigations and provide additional safety information. Additionally, up to 28 HIV+ cervical cancer patients (including the patients who were treated at the RP2D during the dose escalation stage) will be treated on RP2D to determine whether active HIV antiretroviral therapy impacts the antitumor activity of triapine. A Bayesian continuous monitoring will be used to ensure that the true DLT rate is controlled at 20%. To establish the stopping rule, a week prior distribution of DLT rate is set to be beta (α=1, β=5). If the posterior probability that the true underlying DLT rate exceeds 20% at RP2D is 70% or higher then the study accrual will be suspended and the toxicity data will be examined by the PI and the research team, who will subsequently decide on whether the trial should be terminated or not.

The enrollment suspension rule using the Bayesian analysis mentioned above can be represented as a table of possible outcomes for DLTs, as shown below.

Bayesian rule for suspending enrollment	
Suspend accrual if n patients experience a DLT	in N patients treated
2	3-4
3	5-8
4	9-13
5	14-17
6	18-22
7	23-26
8	27

The operating characteristics of this study design can be expressed in terms of probability of early suspending the enrollment at RD2P under the assumptions of various the true rates of DLT. The following table calculated these probabilities for a single dose level based on the simulation of 10,000 hypothetical trials.

Frequentist properties of Bayesian rule for suspending enrollment		
Probability of DLT	Probability of suspending	Median sample size for

	the enrollment	each dose level
0.1	0.10	28
0.17	0.32	28
0.2	0.45	28
0.25	0.66	13
0.3	0.83	8

13.2 Sample Size/Accrual Rate

13.2.1 The number patients accrued to the study will depend on the MTD; an additional 12 cervical cancer patients may be treated at the RP2D to further define the spectrum of toxicities associated with the regimen and up to an additional 28 HIV+ patients will be enrolled to explore whether active (HIV) antiretroviral therapy impacts the antitumor activity of triapine . Although unlikely to happen, for the worst-case scenario, we could have needed 6x6 =36 patients for the phase dose escalation portion of the protocol, 12 for the non-HIV+ expansion cohort and none of the 6 patients on the MTD (or RP2D) is HIV+ cervical cancer patient. Thus, the maximum number of patients for this trial is 36+12+28=76. Patients who do not complete at least 80% the first cycle of therapy and do not suffer a DLT which leads to the termination of the treatment during the observation period (5 weeks excluding treatment delay period) will not be evaluable and will be replaced. Review of patient toxicity and DLT monitoring will be conducted on a weekly basis by the PI and Phase I clinical team.

We expect that the accrual rate will be approximately 1 per 5 weeks. The follow-up period of the primary endpoint, DLT, is approximately 5 weeks after the starting of the treatment (excluding the treatment delay time as described in section 5.5). During the 3+3 dose escalation stage, we will allow the first 2 patients to be enrolled without stopping. During the expansion cohort, the patients will be accrued continuously. On the other hand, the treatment may be delayed during the DLT follow up period as described in section 5.5. Therefore, for a portion of the patients, the overall follow up time may be longer than 5 weeks. Thus, the accrual rate of 1 per 5 weeks is an estimate considering the facts stated above.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**		**Total**
	Not Hispanic or Latino	**Hispanic or Latino**	
	Female	**Female**	
American Indian/ Alaska Native	0	0	**0**
	Ethnic Categories		

Asian	1	0	**1**
Native Hawaiian or Other Pacific Islander	0	0	**0**
Black or African American	3	0	**3**
White	72	0	**72**
More Than One Race	0	0	**0**
Total	**76**	**0**	**76**

13.3 Data Analysis

13.3.1 Analysis Sets

Evaluable patients: patients who meet all of the protocol inclusion/exclusion criteria and begin treatment with the protocol regimen.

Evaluable patients for DLT: evaluable patients who received at least 80% of the treatment intended during the DLT follow up period as defined in section 5.5 and patients who received any amount of treatment and experienced a protocol defined DLT which leads to the termination of the treatment are evaluable for DLT.

Safety set: data from all evaluable patients who receive initial treatment of the study treatment will be used in the analysis of safety.

Efficacy set: data from all evaluable patients who receive initial treatment of the study treatment will be used in the analysis of efficacy endpoints.

PK and correlative biomarker set: the data from all study-eligible patients (i.e. those meeting all of the protocol inclusion/exclusion criteria) who begin the study treatment and have adequate blood and tissue samples taken will be used in the analyses to address the PK and correlative biomarker aims.

13.3.2 Analysis of baseline demographic variables

Baseline descriptive statistics on all evaluable patients will be provided for demographic variables

(age, BMI, race/ethnicity), ECOG performance status, disease stage and status at the time of enrollment (stable disease, progressive disease), and treatment regimens previously used.

13.3.3 Analysis of Safety Endpoints

The NCI common terminology criteria for adverse events (CTCAE 5.0) will be used to evaluate toxicity; we will consider a toxicity to be an adverse event that is possibly, probably or definitely related to treatment. The rate of DLT at RP2D will be calculated and the exact 95% CI will be provided. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all DLTs and other serious (≥ Grade 3) adverse events on a patient-by-patient basis; descriptions will include dose level and any relevant baseline data. Statistics on the number of cycles received by patients and any dose reductions will also be tabulated.

13.3.4 Analysis of Efficacy Endpoints

We will determine the post-therapy, 3-month ^{18}F-FDG-PET/CT metabolic complete response rate of oral triapine in combination with cisplatin chemoradiation. The mCR rate and the ORR at RP2D will be calculated with corresponding 95% exact confidence interval (CI). The IV triapine version of this regimen has demonstrated a high response rate of >90% in patients with stage IB2, II, IIIA, IIIB, and IVA cervical carcinoma [6, 7]. Thus, we could consider the oral treatment not worthy of further study if the response rate is <70%. Assuming an inferior margin of 5%, we will conclude that the mCR rate for the study regimen is non-inferior to 70% in this population if we observe at least 23 mCR events in the 28 patients. This is based on a non-inferiority test with type I error of 5%. OS and PFS will be analyzed using the Kaplan-Meier's method. Median survival time will be reported with corresponding 95% CIs.

The proportion of patients experiencing mCR and experiencing objective response will be estimated in both the HIV+ and non-HIV+ cohorts, along with exact 95% binomial confidence intervals. This is an exploratory objective and the trial is not powered for formal statistical tests comparing the cohorts.

13.3.5 Analysis of PK Data

The oral bioavailability of triapine will be determined with sufficient precision that the 95% CI of the mean population bioavailability falls within 80-125% of that mean. Based on reported preliminary data and assuming a normal distribution at log base 10 level, a true bioavailability rate of 0.67, and a standard deviation of 0.175 at log base 10 level, with 28 patients on RP2D, we will be able to establish the bioavailability with the 95% confidence interval of the population mean falling within 0.53-0.83.

Standard PK parameters will be determined and will include Cmax, Tmax, Cl, Vss, and half-life. These parameters will be descriptively reported.
The association of methemoglobin proportion (%) and PK parameters will be evaluated by Spearman correlation coefficients.

REFERENCES

Please provide the citations for all publications referenced in the text.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B PHARMACOKINETIC SHEET DAY 1-2

NCI 9892 (Triapine (TRI) in Plasma): Phase I of Oral Triapine with Concurrent Chemoradiation for Locally Advanced Cervical Cancer (LACC) and Vaginal Cancer

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~4 mL** of peripheral blood will be collected in a **purple-topped (EDTA)**, mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 9 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Triapine (TRI)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Day 1 Triapine (TRI) infusion (nominal 2 h) TRI Dose (mg): ___50 _____			
pre sample			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
TRI infusion **start**			
30 min post TRI start			
60 min post TRI start			
90 min post TRI start			
110 min post TRI start (~10 min prior to EOI)			
TRI infusion **end**			
30 min post end TRI			
1 h post end TRI			
2 h post end TRI			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
4 h post end TRI			
6 h post end TRI			
Day 2 Triapine (TRI) oral (PO) dose	TRI Dose (mg) _____		
~24 h post start TRI infusion =pre PO dose (D2 AM)			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
TRI PO dose time (D2 AM)			

APPENDIX C PHARMACOKINETIC SHEET DAY 8-9

NCI 9892 (Triapine (TRI) in Plasma): Phase I of Oral Triapine with Concurrent Chemoradiation for Locally Advanced Cervical Cancer (LACC) and Vaginal Cancer

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~4 mL** of peripheral blood will be collected in a **purple-topped (EDTA)**, mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 9 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through this completed form).*

Note the start and stop times of infusions in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Triapine (TRI)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Day 8 Triapine (TRI) oral (PO) dose TRI Dose (mg): _____			
pre sample			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
TRI PO dose time (D8 AM)			
30 min post TRI			
60 min post TRI			
90 min post TRI			
110 min post TRI			
2 h 30 min post TRI			
3 h post TRI			
4 h post TRI			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
6 h post TRI			
8 h post TRI			
Day 9 Triapine (TRI) oral (PO) dose TRI Dose (mg) _____			
~24 h post D8 dose =pre PO dose (D9 AM)			Also obtain Methemoglobin sample, (See 9.3.2) (2cc)
TRI PO dose time (D9 AM)			

APPENDIX D PATIENT MEDICATION DIARY – TRIAPINE

CTEP-assigned Protocol# 9892

Local Protocol # _____

Today's Date: _____ Agent: __Triapine_____

Patient's name:_____ Patient Study ID:_____

Instructions to the patient:

1.) **You will take ___ capsules on each of the indicated days.**
2.) **You should take within 90 minutes after completion of pelvic radiation therapy.**
3.) **Take on an empty stomach (except water). No food for 2hours prior to dosing, and for 1 hour after ingesting the oral dose.**
4.) **Triapine will not be administered on days that radiation is not given, or on the days that radiation is missed or held.**
5.) **Record the date, the number of capsules you took, and when you took them.**
6.) **If you have any comments or notice any side effects, please record them in the comments column.**
7.) **Please return the form to the study team at the Week 6 visit.**

Day		Date	Time	# of capsules taken	Comments
Week 1	1	IV Triapine in clinic			
	2				
	3				
	4				
	5				
	6				
	7				
Week 2	8				
	9				
	10				
	11				
	12				
	13				
	14				
Week 3	15				
	16				
	17				
	18				
	19				
	20				
	21				

Day		Date	Time	# of capsules taken	Comments
Week 4	22				
	23				
	24				
	25				
	26				
	27				
	28				
Week 5	29				
	30				
	31				
	32				
	33				
	34				
	35				

Physician's office will complete this section:

1.) **Date patient started protocol treatment:**_____
2.) **Date patient was removed from study:**_____
3.) **Patient's planned total daily dose:** _____
4.) **Total number of pills taken:** _____

Physician/Nurse/Data Manager's signature:_____

Patient's signature:

_____