NCI Protocol #: 10388
Version Date: 17.May.2023

To: CTEP Protocol and Information Office
From: Susanne Arnold, M.D.
Date: 17.May.2023
Re: Amendment 12 of Protocol #10388: "A Phase I Trial of Triapine and Lutetium Lu 177 Dotatate in Combination for Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)."

SUMMARY OF CHANGES
PVD 17MAY2023

I. Edits made to protocol – Investigator-initiated amendment:		
#	***Section***	***Comments***
1.	6.6	6.6: Clarified the duration of follow-up. Deleted "from treatment completion"; inserted "from the time of enrollment". Thus, patients will be followed every 3 months beginning with study enrollment through either 2 years or death.
2.	11 Study Calendar	Updated Footnote B on study calendar to align with revised Section 6.6 as follows: - Deleted this original language: ~~"until disease progression or until patient is off study (24 months from time of study enrollment or death, whichever comes first". Survival checks will be conducted via telephone every 6 months until patient is off study."~~ - Inserted clarification to Footnote b re: follow-up that aligns with Section 6.6.
3.		Protocol version number and version date was updated throughout this document.

II. Edits requested by CTEP:		
#	**Section**	**Comments**
4.	13.6	*CTEP: Please delete the following language from the Protocol:* "13.6 Genomic Data Sharing Plan The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals. " **PI Response**: Deleted the former Section 13.6 per CTEP request.
5.	13.7	*CTEP: Please delete the following language from the Protocol:* "13.7 Incidental/Secondary Findings Disclosure Procedure Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016): The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review. For each participant with a pathogenic or likely pathogenic germline and/or somatic variant

II. Edits requested by CTEP:		
#	**Section**	**Comments**
		detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding. If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling. **PI Response**: Deleted the former Section 13.7 per CTEP request.

NCI Protocol #: 10388

Local Protocol #: NCI-CIRB-10388-PMC

ClinicalTrials.gov Identifier: NCT04234568

TITLE: A Phase I Trial of Triapine and Lutetium Lu 177 Dotatate in Combination for Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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Participating Organizations: Participating sites should have a track record of administering Lutetium Lu 177 dotatate and have required nuclear medicine logistical support.

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
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NCI-Supplied Agent: Triapine (NSC # 663249)
Commercial Agent: Lutetium Lu 177 Dotatate (NSC # 815530)

IND #: [redacted]
IND Sponsor: DCTD, NCI

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Revision 5 [aka Amendment 2] / October 14, 2020
Revision 6 [aka Amendment 3]/ January 6, 2021
Revision 7 [aka Amendment 4] / April 8, 2021
Revision 8 [aka Amendment 5] / June 16, 2021
Revision 9 [aka Amendment 6] / July 6, 2021
Revision 10 [aka Amendment 7] / December 7, 2021
Revision 11 [aka Amendment 8] / July 19, 2022
Revision 12 [aka Amendment 9] / Sept 29, 2022
Revision 13 [aka Amendment 10] / Dec 14, 2022
Revision 14 [aka Amendment 11] / May 3, 2023 *****
*CTEP disapproved the A 11 submission pvd 03MAY2023
Revision 15 [aka Amendment 12] / May 17, 2023

SCHEMA

This study is a multicenter phase 1 trial of triapine and Lutetium Lu 177 Dotatate in combination for well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) after the failure of at least one line of prior systemic cancer treatment. An expansion cohort with 14 additional patients will be enrolled at the recommended phase II dose to further assess safety, obtain initial estimates of clinical response outcomes, and perform exploratory comparisons of biomarkers.

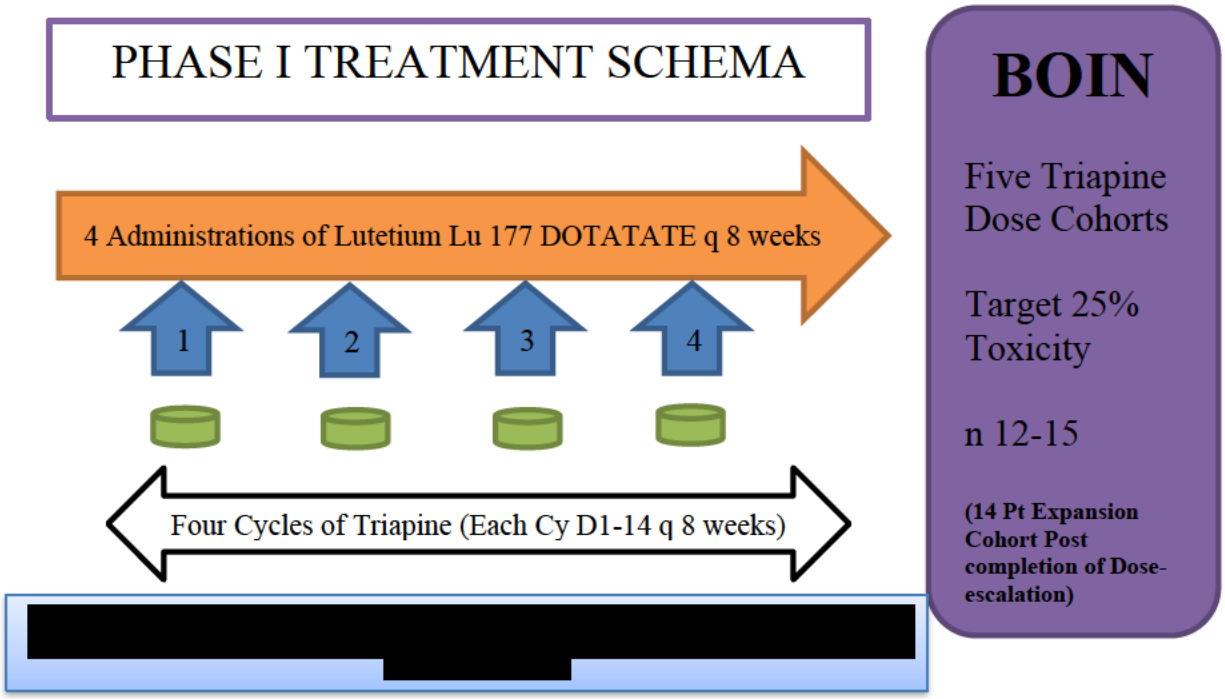

Figure 1: Phase 1 Treatment Schema

Dose Escalation Schedule		
Dose Level	**Dose***	
	Triapine	**Lutetium Lu 177 Dotatate**
Level -2	50 mg PO QOD, Days 1-14	200 mCi IV, Day 1
Level -1	50 mg PO QD, Days 1-14	
Level 1#	100 mg PO QD, Days 1-14	
Level 2	150 mg PO QD, Days 1-14	
Level 3	200 mg PO QD, Days 1-14	
PO = orally; QOD = every other day; QD = every day; IV = intravenously **Doses are stated as exact dose in units (*e.g., mg/m^2, mcg/kg,* etc.*) rather than as a percentage.* #*Starting dose.*		

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To evaluate the safety and to determine the recommended phase 2 dose (RP2D) of Lutetium Lu 177 Dotatate in combination with triapine.

1.2 Secondary Objectives

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

1.2.2 To determine the overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 at 2, 4, 6, and 8 months post therapy in dose escalation cohort.

1.2.3 To determine the Best overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 in dose expansion cohort.

1.2.4 To measure duration of response (DOR) associated with the combination.

1.2.5 To evaluate progression-free survival (PFS), 24-month PFS, and overall survival (OS).

1.3 Correlative Objectives

1.3.1 Measure baseline ^{68}gallium-dotatate (or Copper 64 dotatate) biodistribution.

1.3.2 Evaluate oral triapine plasma pharmacokinetics and corresponding methemoglobin level by venous blood gas proportion.

1.3.3 Collect blood at baseline and at disease progression to correlate result with clinical outcome. [*NOTE*: originally this blood was collected to analyze hPG80 but will now the frozen blood samples will be biobanked for future correlative analysis]

1.3.4 Describe the tumor molecular profile using whole exome sequencing (WES), as well as RNAseq by the National Clinical Laboratory Network (NCLN), and correlate it with treatment outcome.

1.3.5 Collect plasma for circulating DNA (ctDNA) assessment.

1.3.6 Assess the effect of triapine on single deoxyribonucleoside concentrations by an LC/MSMS assay in baseline (pre-treatment) and disease progression blood samples (processed to plasma).

2. BACKGROUND

2.1 Study Disease

Neuroendocrine tumors (NETs) are rare neoplasms which can arise anywhere in the body (Dasari *et al.*, 2017). However, a recent review of the Surveillance, Epidemiology, and End Results (SEER) database confirms a six-fold overall increase in the incidence of NETs (Figure 2). Due to the indolent nature of NETs, the prevalence is disproportionate to the incidence. Per the North American Neuroendocrine Society (NANETS.org) it is estimated that there are over 150,000 gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients in the US. In 2018, we published incidence rates of GEP-NETs in Kentucky and found that the incidence is higher than national average at 10 per 100,000 patients (Chauhan *et al.*, 2018). Despite the development of several effective targeted therapies, including everolimus and sunitinib, resistant disease is common and treatment options remain limited. Peptide receptor radionuclide therapy using Lutetium Lu 177 Dotatate has recently been approved by the Food and Drug Administration (FDA) for metastatic, progressive GEP-NETs. Despite an impressive PFS advantage over the control group, about 20% of patients do not respond to peptide receptor radionuclide therapy (Strosberg *et al.*, 2017). Moreover, 29-39% of patients who initially show objective radiological responses will eventually progress after peptide receptor radionuclide therapy treatment (Bodei *et al.*, 2011; Brabander *et al.*, 2017; van der Zwan *et al.*, 2019). Thus, there is an unmet medical need for the management of NET patients who have progressed on peptide receptor radionuclide therapy.

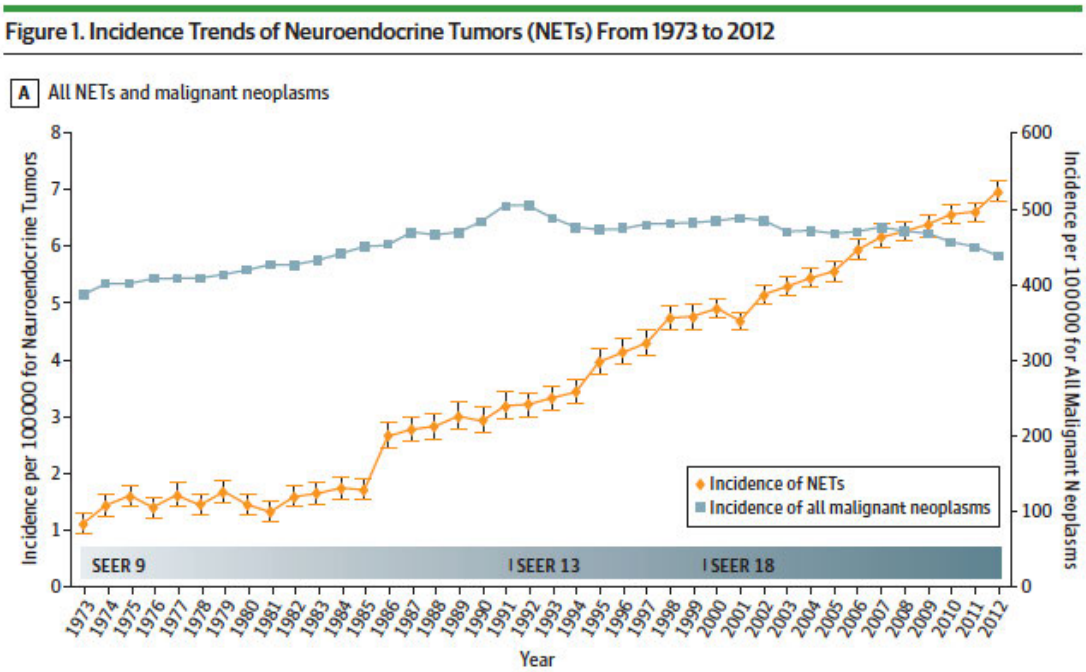


Figure 2: Increasing incidence of NETs in the US (Dasari *et al*., 2017).

2.2 Triapine, CTEP IND Agent

Triapine is a ribonucleotide reductase (RNR) inhibitor (Investigator's Brochure, 2018). RNR is an enzyme that is responsible for the reduction of ribonucleotides to deoxyribonucleotides in the biosynthesis of DNA. This reduction process is a rate-limiting step due to the extremely low levels of deoxyribonucleotides in mammalian cells. A direct relationship between tumor growth rate and specific RNR activity has been established. RNR potentiates antitumor activity of DNA-damaging agents by inhibiting DNA repair by cheating the active site iron and thus inhibiting tyrosine free radical generation at the RNR active site. Accordingly, an inhibitor of RNR is expected to be effective in treating cancer.

Mammalian RNR is at least a heterodimer (α_2, β_2) consisting of two subunits, but higher order forms exist in humans (α_2, β_6 or α_6, β_6) (Investigator's Brochure, 2018). The M1 subunit contains the nucleotide binding site and the M2 subunit contains the metal binding site. The M1-affecting RNR inhibitors are nucleoside analogs, several of which are currently under clinical development. One analog has recently been approved for the treatment of pancreatic cancer (*i.e.*, gemcitabine). The M2 subunit contains non-heme iron and a tyrosine free radical, which are required for the enzymatic reduction of ribonucleotides. Inhibitors of the M2 subunit act by destroying the free radical. In the case of hydroxyurea (HU), which is the only clinically approved RNR inhibitor acting at the iron/free radical site (M2), the inhibition is reversible due to the ease in regenerating the tyrosine free radical by mammalian cells.

Triapine is available in both intravenous (IV) and capsule formulations. 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 1 trial evaluated single-agent oral (PO) triapine in patients with a wide range of advanced solid tumors, enrolling 20 patients (Chao *et al*., 2012). Treatment consisted of 100 mg IV triapine on Day -7 with blood samples drawn over 8 hours to determine PK. PO triapine was then 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 were reported; grade 3-4 anemia, neutropenia, thrombocytopenia, infection, fatigue, hepatic enzyme elevation, and anorexia adverse events were observed in one patient each. The RP2D 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 dose limiting toxicity (DLT) observed. 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. In addition, the PK data suggested that the population average bioavailability of triapine was approximately 55-70%.

2.3 Lutetium Lu 177 Dotatate

Lutetium Lu 177 Dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2) (Package Insert, 2018). Upon binding to SSTR expressing cells, including malignant SSTR-positive tumors, the compound is internalized. The beta emission from Lu 177 induces cellular damage by formation of free radicals in SSTR-positive cells and in neighboring cells.

The PK of Lutetium Lu 177 Dotatate have been characterized in patients with progressive, SSTR-positive NETs (Package Insert, 2018). The mean blood exposure (area under the concentration-time curve [AUC]) of Lutetium Lu 177 Dotatate at the recommended dose is 41 ng.h/mL (coefficient of variation [CV] 36 %). The mean maximum blood concentration (C_{max}) for Lutetium Lu 177 Dotatate is 10 ng/mL (CV 50%), which generally occurred at the end of the Lutetium Lu 177 Dotatate infusion. The mean volume of distribution for Lutetium Lu 177 Dotatate is 460 L (CV 54%).

Within 4 hours after administration, Lutetium Lu 177 Dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid (Package Insert, 2018). The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of Lutetium Lu 177 Dotatate by 36%. The non-radioactive form of lutetium dotatate is 43% bound to human plasma proteins. The mean clearance (CL) is 4.5 L/h (CV 31%) for Lutetium Lu 177 Dotatate. The mean (± standard deviation) effective blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (±28) hours. Lutetium Lu 177 Dotatate does not undergo hepatic metabolism.

Lutetium Lu 177 Dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following Lutetium Lu 177 Dotatate administration (Package Insert, 2018). Prolonged elimination of Lutetium Lu 177 Dotatate in the urine is expected; however, based on the half-life of Lutetium Lu 177 D and terminal half-life of Lutetium Lu 177 Dotatate, greater than 99% will be eliminated within 14 days after administration of Lutetium Lu 177 Dotatate.

The efficacy of Lutetium Lu 177 Dotatate in patients with foregut, midgut, and hindgut GEP-NETs was assessed in 360 patients in the ERASMUS study (Package Insert, 2018). In ERASMUS, Lutetium Lu 177 Dotatate was initially provided as expanded access under a general peptide receptor radionuclide therapy protocol at a single site in the Netherlands. A subsequent Lutetium Lu 177 Dotatate-specific protocol written eight years after study initiation did not describe a specific sample size or hypothesis testing plan but allowed for retrospective data collection. A total of 1214 patients received Lutetium Lu 177 Dotatate in ERASMUS, of which 601 (50%) were assessed per RECIST criteria. Of the 601 patients evaluated by investigators using RECIST criteria, 360 (60%) had GEP-NETs. Lutetium Lu 177 Dotatate 200 mCi was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. The major efficacy outcome was investigator-assessed ORR. The median age in the efficacy subset was 61 years (25 to 88 years), 52% were male, 61% had a baseline Karnofsky performance status ≥90 (60 to 100), 60% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. Fifty five percent of patients received a concomitant somatostatin analog. The median dose of Lutetium Lu 177 Dotatate was 800 mCi. Baseline tumor assessments were

obtained in 39% of patients. The investigator assessed ORR was 16% (95% CI 13, 20) in the 360 patients with GEP-NETs. Three complete responses (CRs) were observed (<1%). Median DOR in the 58 responding patients was 35 months (95% CI: 17, 38).

2.4 Rationale

NETs are a very heterogeneous group of tumors that develop predominantly in the gastrointestinal and pulmonary systems (Dasari *et al.*, 2017). Clinical detection and diagnosis occur more frequently at late stages when metastatic spread has occurred. Patients with advanced disease may suffer from complications of uncontrolled hormone secretion and usually succumb due to tumor progression. Patients with advanced NETs have a median survival of 33 months (Kwekkeboom *et al.*, 2008). Conventional therapies such as radiation and chemotherapy are not effective in NET and first-line systemic therapy usually consists of a somatostatin analogue for the control of both hormonal secretion and tumor growth (Kvols *et al.*, 1986; Rinke *et al.*, 2009; Caplin *et al.*, 2014). With the exception of everolimus and Lutetium Lu 177 Dotatate for the treatment of nonfunctional NETs (Yao *et al.*, 2016), no standard second-line systemic treatment options are currently FDA approved. Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to NETs that express SSTRs. This targeted form of systemic radiotherapy allows for the delivery of radionuclides directly to tumor cells. Radiolabeled somatostatin analogue Lutetium Lu 177 Dotatate is a beta- and gamma-emitting radionuclide (van der Zwan *et al.*, 2015). In a single-group trial of Lutetium Lu 177 Dotatate involving 310 patients who had GEP-NETs, CR occurred in 2% of the patients and partial response (PR) in 28% (Kwekkeboom *et al.,* 2008). Despite these initial responses, high relapse rates following Lutetium Lu 177 Dotatate radionuclide indicate the urgent requirement for novel radio sensitizing strategies (van der Zwan *et al.*, 2015).

Radiation is a potent inducer of DNA double-strand breaks (DSBs) (Begg *et al.*, 2011); targeting signaling networks involved in DSB repair is a promising approach for enhancing cellular radio sensitivity. 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. There is an unmet therapeutic need to improve radiological responses during peptide receptor radionuclide therapy-based treatments. 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 deoxyribonucleotide triphosphates (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. 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 an 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 this agent to be an equipotent inhibitor of M2b and M2 (Kunos *et al.*, 2010;

Kunos *et al.*, 2013). Kunos *et al*. have studied triapine in both *TP53*-mutated and wild type human cancer cell lines and have found that inhibition of RNR by triapine enhances radiation-mediated cytotoxicity independent of p53 regulation by impairing DNA repair processes that rely on deoxyribonucleotide production, thereby substantially increasing the radiation sensitivity of human cancers (Kunos *et al.*, 2009).

This study will test the hypothesis that triapine is an effective radiation sensitizer which can be safely combined with peptide receptor radionuclide therapy and can improve antitumor activity of Lutetium Lu 177 Dotatate. Ninety-nine percent of radiation is excreted by Day 14 after Lutetium Lu 177 Dotatate administration. Since most of the DNA damage from Lutetium Lu 177 Dotatate happens in the first 7-14 days, 14 days of triapine administration should be adequate treatment as a radiation sensitizer.

2.5 Correlative Studies Background

2.5.1 Integrated Correlative Studies

2.5.1.1 Whole Exome Sequencing (WES)

Biological rationale: Molecular and genomic characterization of NETs is still in its infancy. Recently some studies have looked into WES of NETs however limited sample size often restricts interpretation of these results. Moreover, validation of mutation pattern needs to come from a different geographical pool of patient population. Our study will add to the limited data on NET WES and will explore potential targetable mutations.

Hypothesis: To explore potential targetable mutations and hypothesis generating mutational biomarkers of response.

Preclinical and clinical data: Some of the prevalent genomic alterations in seen in pancreatic NETs (PNETs) include *MEN1* (43%), *DAXX* (28%), *ATRX* (11%), *TSC2* (6%), and *PTEN* (5%) (Yao *et al*., 2019). Data on genomic alteration of small bowel NETs is less robust as compared to PNETs. However, it seems that a marked intra-tumoral genetic heterogeneity exists in small bowel NETs, but mutational pattern seems to be concordant between primary site and metastatic site (Walter *et al*., 2018).

2.5.1.2 Triapine Pharmacokinetics

Biological rationale: Triapine, an α-heterocyclic carboxaldehyde thiosemicarbazone (HCT), is a RNR inhibitor that acts on the M2 (R2) subunit. Triapine has never been combined with Lutetium Lu 177 Dotatate radionuclide. Based on the metabolism and mechanism of elimination of both study drugs, we do not anticipate that the combination would result in alterations in individual drug pharmacokinetics nor heightened toxicities. Triapine has a direct toxicity of generating higher circulating blood levels of methemoglobin, and so, methemoglobin levels by venous blood gas proportion are obtained to monitor this adverse event after oral triapine administration.

Hypothesis: The PK of PO triapine can be appropriately documented and concentrations comparable with previous reports can be achieved with this new formulation when administered concurrently with Lutetium Lu 177 Dotatate.

Preclinical and clinical data: Currently no preclinical or clinical data exist pertaining to the

combination of triapine and Lutetium Lu 177 Dotatate.

2.5.1.3 Methemoglobin Determination

Previous studies of triapine have shown methemoglobinemia as a potential side-effect. Therefore, we will perform studies to monitor the percentage of methemoglobin at the same time points for triapine PK, which will allow us to correlate this effect with exposure.

2.5.2 Exploratory Correlative Studies

2.5.2.1 Frozen blood samples for biobanking

NOTE: Originally, blood was collected and frozen on all enrolled patients for 1.3.3 correlative endpoint (i.e., hPG80 assay). After the study closed to accrual, it was determined that frozen blood is inadequate for hPG80 analysis. Thus, it was decided that these collected samples of frozen blood will be biobanked with NCI for future analysis. The text below is retained for clarity and transparency of collection of these blood samples underlying original exploratory endpoint 1.3.3. Note that in addition to 1.3.3 and this section, the Study Calendar and Section 5 also retain text/language regarding hPG80, in order to maintain transparency on collection, handling and processing of these now-frozen biobanked blood samples. The retention of this language should support utilization of these frozen samples in a future analysis).

~~hPG80 Assay:~~
~~Rationale: Current blood-based biomarkers for neuroendocrine neoplasms (NENs) lack both sensitivity and specificity. Human circulating progastrin (hPG$_{80}$) is a novel biomarker that can be easily measured in plasma by ELISA. Recent examination of hPG$_{80}$ in NENs was presented at ENETS 2021 and the findings published in Cancers *[Chauhan 2022]*. Plasma hPG$_{80}$ was quantified from 95 stage IV NEN patients, using DxPG80 technology (ECS Progastrin, Switzerland) and compared with hPG$_{80}$ concentrations in two cohorts of healthy donor controls aged 50-80 (n=252) and 18-25 (n=137). Median hPG$_{80}$ in NENs patients was 5.54 pM compared to 1.5 pM for the 50-80 controls and 0.29 pM the 18-25 cohort (p<0.0001). Subgroup analysis revealed median hPG$_{80}$ levels significantly higher than for either control cohort in neuroendocrine carcinoma (NEC; n=25) and neuroendocrine tumors (NET; n=70) including the small cell lung cancer (SCLC) sub-cohort (n=13). Diagnostic accuracy, estimated by AUCs, was high for NENs, as well as both sub-groups (NEC/NET) when compared to the younger and older control groups. Plasma hPG$_{80}$ in NENs may be a diagnostic blood biomarker for both low and high-grade NENs. Hypothesis: To prospectively validate the efficacy of plasma hPG80 as a diagnostic biomarker in NETs.~~ **NOTE**: This planned analysis was not conducted, per rationale above.

2.5.2.2 RNAseq

Biological rationale: RNA can be a potential biomarker for tumor characterization. In this exploratory analysis, we would like to evaluate differences in RNA expression between various grades of NETs and between PNET and small bowel NETs.

Hypothesis: To explore differences in RNA expression of NETs based on the grade and site of origin.

Preclinical and clinical data: There are data which suggest that RNA sequencing can help classify NETs and add as a valuable adjunct to morphological classification of NETs (Panarelli, *et al*., 2019). More studies are needed to validate the role of RNA sequencing in characterizing NETs.

2.5.2.3 ctDNA Sequencing

Biological rationale: The role of ctDNA has grown exponentially in the field of oncology. ctDNA provides an easy avenue to explore not only potential targetable mutations but to also monitor disease status. Studies looking at ctDNA in NETs are extremely limited. We would like to evaluate tumor specific genetic alterations in ctDNA. Our data can help future studies to evaluate most prevalent genomic alterations found in ctDNA as biomarker of treatment response.

Hypothesis: To explore tumor specific genetic alterations in ctDNA

Preclinical and clinical data: Boons *et al.* (2018) were first one to detect tumor specific genetic alteration in cell free DNA in pancreatic neuroendocrine tumor patients. More recently Starr and colleagues looked into circulating tumor DNA in neuroendocrine tumor patients. Of 27 patients evaluated for ctDNA, 19 (70%) were reported to have genomic alterations (Starr *et al*., 2019). Both these studies suggest that ctDNA can be evaluated in metastatic neuroendocrine tumor patients. We would like to prospectively validate these smaller studies and generate pilot data to support that tumor specific mutation can be detected on ctDNA.

2.5.3 Imaging Correlative Studies

2.5.3.1 Gallium-68 dotatate Scan and Copper-64 dotatate (64Cu) scan

Theranostics is a new term that describes the utility of targeting the same biological marker for both diagnosis and therapy by radiolabeling it once with a diagnostic radioisotope (gamma or positron emitter) and the other time using a therapeutic radioisotope (beta emitter). The main purpose of that is the ability to assess binding and efficiency of the targeted agent prior to administration of therapy. Gallium-68 Dotatate, Copper-64 Dotatate and Lutetium Lu 177 Dotatate are prominent examples of theranostics. They share the same biological targeting part, Dotatate, which is a SSTR analogue. A study by Boy *et al.*, investigated correlation between maximum standardized uptake value (SUV_{max}) of lesion on Gallium-68 Dotatoc and SSTR expression on normal human tissues. The study found correlation between SUV_{max} and SSTR2 expression in normal human tissues (Boy *et al.*, 2011). The NETTER clinical trial (Strosberg *et al.*, 2017) proved significant survival benefit of Lutetium Lu 177 Dotatate in patients with midgut NET, which facilitated its FDA approval. One of the inclusion criteria for the Lutetium Lu 177 Dotatate treatment arm was confirmation of SSTR expression on target lesions by ^{111}In-Octreoscan. Gallium-68 Dotatate is a PET/CT radiopharmaceutical that binds to SSTRs and has widely replaced ^{111}In-Octreoscan in assessment of well differentiated low grade NETs.

The Krenning score was used to evaluate SSTR binding in NETTER trial. It is based on comparing the uptake level of target and nontarget lesions to liver, spleen, and kidneys.

Krenning score	Criteria
Grade 1	Lesion uptake < normal liver uptake
Grade 2	Lesion uptake = normal liver uptake
Grade 3	Lesion uptake > normal liver uptake
Grade 4	Lesion uptake > spleen or kidney uptake

Baseline Gallium-68 Dotatate PET/CT prior to therapy is standard-of-care and covered by insurance, as is Copper-64 Dotatate scan. Gallium-68 dotatate scan (or Copper-64 Dotatate scan) will be performed per standard operating procedure of participating institutions. Prior to administration of the novel treatment combination, Gallium-68 Dotatate PET/CT (or Copper-64 Dotatate) will be performed for all patients to confirm adequate SSTR binding. To confirm receptor expression, Krenning's score will be applied to Gallium-68 Dotatate PET/CT images (or Copper-64 Dotatate). Advanced quantitative analysis will be performed as well and parameters such as SUV_{max}, SUV_{peak}, Molecular Tumor Volume (MTV), and Tumor Binding Index (TBI= $MTV*SUV_{mean}$) will be obtained per organ and for the patient. Advanced analysis to determine the optimum quantitative parameter that correlates with objective response measures, PFS, as well as overall survival (OS).

2.5.4 Measure single deoxyribonucleoside concentrations

Prior *in vitro* work demonstrates that DNA damage stimulates ribonucleotide reductase activity and DNA repair, which reduces radiation efficacy (Kunos et al, 2011a) and that triapine can inhibit ribonucleotide reductase, reduce DNA repair and restore sensitivity to radiation (Kunos et al, 2010). The clinical effectiveness of this approach has been established in clinical trials combining radiation therapy and triapine for the treatment of advanced uterine and vaginal cancers (Kunos et al, 2018, 2019). In addition, *in vitro* results indicated that the deoxyribonucleoside salvage pathway facilitates DNA repair when ribonucleotide reductase is inhibited by triapine (Kunos et al, 2011b). The *in vivo* effect of triapine on the deoxynucleoside pathway will be evaluated.

Hypothesis: To measure the increase in plasma deoxynucleosides after triapine administration

Our hypothesis is triapine inhibits ribonucleotide reductase and the *de novo* DNA repair pathway with a resulting increase of deoxyribonucleosides via the salvage pathway as measured by blood levels of dexoynucleosides.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Metastatic, histologically confirmed well-differentiated neuroendocrine tumor with positive Dotatate scan (Gallium-68 or Copper-64) within 6 months. Lesions on Dotatate scan (Gallium 86 or Copper-64 Dotatate scan) will be considered positive if the SUV_{max} is >2 times SUV mean of normal liver parenchyma.

3.1.2 Failure of at least one prior systemic cancer treatment, including somatostatin analogs.

3.1.3 Patients must have progressive disease based on RECIST Criteria, Version 1.1 evidenced with CT scans/MRI obtained within 24 months from enrollment.

3.1.4 Patients must have measurable disease per RECIST 1.1.

3.1.5 No prior exposure to peptide receptor radionuclide therapy.

3.1.6 Recovered from adverse events of previously administered therapeutic agents to Grade 1 or less toxicity according to CTCAE version 5.0.

3.1.7 Archival tissue no longer than 6 months old should be present, otherwise baseline research biopsy is needed for WES.

3.1.8 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of triapine in combination with Lutetium Lu 177 Dotatate in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.9 ECOG performance status 0,1, or 2 (Karnofsky ≥60%, see *Appendix A*).

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

– leukocytes	≥2,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥75,000/mcL
– total bilirubin	≤3 × institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– glomerular filtration rate (GFR)	≥50 mL/min using Cockcroft-Gault method (see *Appendix B*)
– hemoglobin	≥8.0 g/dL

3.1.11 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.12 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.13 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.

3.1.14 Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.

3.1.15 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen, in the opinion of the enrolling physician, are eligible for this

trial.

3.1.16 Pregnancy Precaution: Men and women should avoid pregnancy for seven months after the date of their last treatment with Lutetium Lu 177 Dotatate. It is noteworthy that β-HCG may be secreted by a small percentage of NETs, such that, in addition to being a pregnancy marker, it also is a tumor marker. Consequently, NET female patients with positive β-HCG (>5 mIU/mL) at baseline can be eligible to enter the study and receive treatment if pregnancy can be excluded by lack of expected doubling of β-HCG and negative pelvic ultrasound. Normally, in pregnant subjects β-HCG doubles every 2 days during the first 4 weeks of pregnancy and every 3.5 days by Weeks 6 to 7. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral ovariectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months, and for women on hormone replacement therapy, only with a documented plasma follicle-stimulating hormone (FSH) level >35 mIU/mL). Even women who are using oral, implanted, or injected contraceptive hormones, an intrauterine device (IUD), or barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, are practicing abstinence or where the partner is sterile (*e.g.*, vasectomy) should be considered to be of childbearing potential. Postmenopausal women who have fertilized eggs implanted are also considered to be of childbearing potential. Acceptable methods of contraception may include total abstinence at the discretion of the Investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Periodic abstinence (*e.g.*, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception (hormonal or barrier method of birth control; abstinence) should be maintained throughout the study and for 7 months after study treatment discontinuation. All women of childbearing potential and male partners must use a double-barrier method of birth control or practice continuous abstinence from heterosexual contact throughout the study and for seven months after the end of the last treatment.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had major surgical procedures in the prior 6 weeks.

3.2.2 Patients with an inability to swallow oral medications or gastrointestinal disease limiting absorption of oral agents.

3.2.3 Patients who have received prior external beam radiotherapy to more than 50% of bone marrow, as determined by a radiation medicine physicist who will calculate the volume of bone marrow exposure in prior radiotherapy portals divided by the volume of total bone marrow harboring tissues. This ratio must be less than 50 percent.

3.2.4 Uncontrolled congestive heart failure (NYHA III, IV).

3.2.5 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study.

3.2.6 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia.

3.2.7 Patients who are receiving any other investigational agents.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to triapine or Lutetium Lu 177 Dotatate.

3.2.9 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection; symptomatic decompensated congestive heart failure; unstable angina pectoris; cardiac arrhythmia; and known inadequately controlled hypertension.

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

3.2.11 Pregnant women are excluded from this study because triapine is an RNR inhibitor and Lutetium Lu 177 Dotatate is a peptide receptor radionuclide therapy with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with triapine and Lutetium Lu 177 Dotatate, breastfeeding should be discontinued if the mother is treated with triapine and Lutetium Lu 177 Dotatate and for 2.5 months following the last treatment.

3.2.12 Discontinue long-acting somatostatin analogs (*e.g.*, long-acting octreotide) for at least 4 weeks prior to initiating Lutetium Lu 177 dotatate. Long-acting somatostatin analog will be allowed to continue if patient has history of carcinoid syndrome and requires long-acting somatostatin analog for control of his/her functional syndrome.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

4.2 Site Registration

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) 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).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

1. An active Federal-wide Assurance (FWA) number,
2. An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO), and
3. Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. One way to search for a protocol is listed below.

- 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-OH007, and protocol number 10388,
- Click on *Documents*, select *Site Registration*, and 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 Protocol Specific Requirements For 10388 Site Registration

Upon University of Kentucky (UK) approving the RTI provider for the study modality, UK will send the approval to the Regulatory Support System (RSS) to comply with the protocol specific requirement. Participating sites will send de-identified Gallium-68 (or Copper-64) dotatate scan images/discs to Dr. Aman Chauhan at amanchauhan@uky.edu or 800 Rose Street, CC 447, Ben Roach Building, Markey Cancer Center, 40536, Lexington Kentucky. This imaging (Gallium-68 or Copper-64 dotatate scan) is collected for correlative analysis on all enrolled participants.

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

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU 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 1-866-651-2878 in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.
The DTL for this study has training requirements as follows:

- At least one authorized user physician investigator of lutetium Lu177 for medical use must be registered with CTEP at the Investigator level and be listed on the site DTL with the appropriate task(s).

Authorized user physician investigators should be identified as such by the site Radiation Material License or site Radiation Safety Officer authorized list indicating their authority as an authorized user of lutetium Lu177 for medical use.

Study investigators and staff must review initial site initiation slides and/or attend site initiation webinar, as well as reviewing all amendments.

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of individuals is assigned to the task and have met the training requirements.

4.2.4 Checking Site Registration Status

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

- Click on *Regulatory* at the top of 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 the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the 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. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and 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 or the IWRS 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 Special Instructions for Patient Enrollment

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

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

Detailed instructions can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

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

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 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 30 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Timepoint	Specimen	Send Specimens To:
Archival		
	• Archival[1] FFPE tumor block OR 1 H&E stained slide (3-5 µm) and 30-40 uncharged, unstained, air-dried 10-micron slides (mandatory)	EET Biobank
Baseline		
Pre-treatment	**If Archival tissue is unavailable:** 2 tissue cores in formalin[2] (mandatory if archival tissue is unavailable or older than 6 months)	EET Biobank
Cycle 1, Day 1		
Pre-treatment	• 2 mL peripheral venous blood for methemoglobin per institutional standards (mandatory – only for the dose escalation cohort)[3]	Standard of Care at Participating site
Pre-treatment	• 20 mL blood in Streck cfDNA tube (1 tube mandatory and 1 tube optional)	EET Biobank
Pre-treatment	• 5 mL blood in purple top EDTA tube frozen whole[4] (mandatory) – for Objective 1.3.3	EET Biobank
Pre-treatment	• Two 8mL K2 EDTA white top (mandatory)	Kolesar Lab
Cycle 1, Day 9		
Pre-treatment 0.5 h 1 h 1.5 h 2 h 3 h 4 h 6 h 8 h	• 2 mL peripheral venous blood for methemoglobin per institutional standards at each PK draw (mandatory – only for the dose escalation cohort) [3]	Standard of Care at Participating site
Pre-treatment 0.5 h 1 h 1.5 h 2 h 3 h 4 h 6 h 8 h	• 3-4 mL blood in Purple-top EDTA tube, processed for plasma and frozen (mandatory – only for the dose escalation cohort) [5]	Beumer Laboratory
Cycle 2, Day 1		
Pre-treatment	Two 8mL K2 EDTA white top (mandatory)	Kolesar Lab

Disease Progression		
	• 20 mL blood in Streck cfDNA tube (optional) •	EET Biobank
	• 1 × 5 mL blood in purple top EDTA tube frozen whole[4] (mandatory) – for Objective 1.3.3	
	• Two 8mL K2 EDTA white top (mandatory)	Kolesar Lab

FOOTNOTES:

[1]Archival tissue can be no older than 6 months. Biopsies are to only be performed if archival tissue is unavailable or older than 6 months. For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (*e.g.*, H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – n).

[2] For new biopsies, a completed copy of the Tissue Biopsy Verification Form (Appendix H*)* and a copy of the radiology and/or operative reports from the tissue removal procedure *and* the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.

[3] Venous blood on ice sample for methemoglobin determination on Cycle 1, Day 1 and Cycle 1, Day 9. (+/- 1 day)

[4] Collect in a plastic EDTA tube

[5] PK and Methemoglobin windows:
Pre dose: within 30 minutes
30 minutes: +/- 5 minutes
60 minutes: +/- 5 minutes
1 hour 30 minutes: +/- 5 minutes
2 hours: +/- 5 minutes
3 hours: +/- 10 minutes
4 hours: +/- 10 minutes
6 hours: +/- 10 minutes
8 hours: +/- 10 minutes

5.2 Summary Table for Interventional Radiologist for Research Biopsies

Biopsy #: 1				
Trial Time Point: Pretreatment				
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.)				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	WES	25-50%	Formalin
2	Integrated	WES	5-25%	Formalin

Note: Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system (see Appendix E).

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: https://kits.bpc-apps.nchri.org/.

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

Note: Kits or supplies are only provided for specimens shipped to the Biorepository. Institutional supplies must be used for all other specimen collection and processing.

5.3.2 Scheduling of Specimen Collections to the EET Biobank

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

- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection.
- Tissue in formalin can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
- Specimens submitted frozen, such as frozen whole blood and frozen plasma, can be collected on any day but must be stored frozen and shipped to the EET Biobank on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -80°C freezer.
- Fresh blood specimens may be collected and shipped Monday through Friday.

5.3.3 Scheduling of Specimen Collections to the Beumer Laboratory

Beumer Laboratory: Blood samples will be collected at the timepoints specified in Section 5.1. Frozen plasma/serum will be shipped overnight on either Monday, Tuesday, or Wednesday (and not before a federal or university holiday) to the Beumer Laboratory at the University of Pittsburgh.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

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

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

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

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

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

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

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

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

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

5.4.2.2 Tissue Specimen Labels

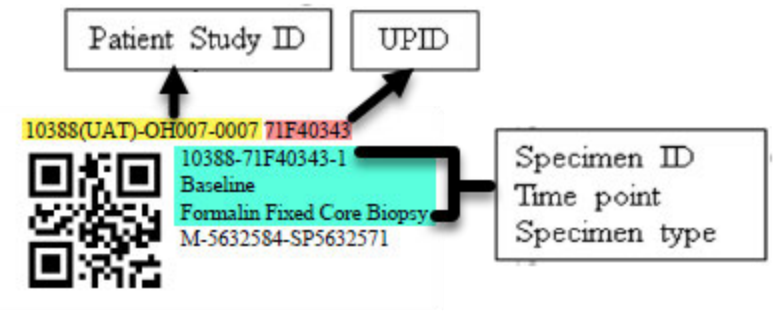
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, etc.)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

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

Space is provided at the bottom of the label for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

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

Registration without eligibility specimen analysis:

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

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

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

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

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

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date (and time for PK samples) on each label.
- After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand writing).

Step 3: Complete specimen data entry.

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

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

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

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

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

Step 6: Send email notification.

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

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

5.5.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- FFPE tumor tissue block must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide (3-5 μm),
- Thirty to fifty (30 – 40) 10 μm unstained air-dried, uncharged slides.

Process and number slides sequentially (*e.g.,* H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n).

See Section 5.4.2 for labeling instructions.

5.5.2 Formalin-Fixed Tumor Biopsies

1. Label formalin-filled containers according to instructions in Section 5.4.2.
2. Obtain 2 16-gauge or 18-gauge core needle biopsy specimens, and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.6.2.3. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.

5.5.3 Blood Collection

5.5.3.1 Collection of Blood in Streck cfDNA tube for ctDNA and germline sequencing

1. Label two 10 mL Streck cfDNA tube according to the instructions in Section 5.4.2.
2. Collect 10 mL of blood into the pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. If patients may have an

indwelling catheter: heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.

3. **After collection, blood in Streck cfDNA tubes should never be refrigerated,** as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature until shipment to the EET Biobank.

5.5.3.2 Collection of Blood in EDTA Tubes for Plasma Processing for PK Studies

General

Blood samples to be obtained through a peripheral or central line blood draw. EDTA Vacutainer tubes shall be prepared for this purpose.

Processing
Document exact administration time and exact times of blood draws per Appendix F.

1. Collect in a 3 or 4 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 preferably within 30 minutes of collection (note that within 2-hours is allowable).
4. Samples should be centrifuged for 10 min at approximately 1000-2000 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.

5.5.3.3 Collection of Peripheral Venous Blood

1. 1 × 2mL collections (peripheral venous blood) per institutional standards.
2. Immediately place the sample on ice and route to institutional lab.
3. Sample should be analyzed within 30 minutes (up to 2 hours) of being drawn per institutional SOPs.

5.5.3.4 Collection of Blood in Purple-top EDTA Tubes for future Studies (1.3.3)

NOTE: Originally collected to analyze hPG80, but instead will be biobanked (as of 12/13/2022) for use in future correlative analysis. We retained the instructions on collection and processing/handling of these now-frozen biobanked blood samples for transparency in future analysis.

1. Collect 5 mL of **peripheral blood** in an EDTA tube (**purple top**)
2. After collection thoroughly mixed by inverting (8 -10 times)
3. Immediately freeze at **-80°C** and store frozen until shipment to the EET Biobank.
4. If blood cannot be frozen immediately then it can be stored on ice up to 2 hours before freezing.

5.5.3.5 Collection of Blood in EDTA Tubes for Deoxyribonucleoside Studies

1. Collect 16 mL of **peripheral blood** in two K2 EDTA tubes (8mL each, **white top**)
2. Invert the vacutainer tubes several times to mix blood with EDTA anticoagulant and immediately place on ice. Processing should begin preferably within 30 minutes of collection (note that within 2-hours is allowable).
3. Samples should be centrifuged for 12 min at approximately 1700 x g in a refrigerated tabletop centrifuge so as to produce plasma.
4. The resulting plasma should be aspirated from the tubes, placed into four appropriately-labeled microcentrifuge tubes, and stored at -70 °C until shipment.

5.6 Shipping Specimens from Clinical Site to the EET Biobank

5.6.1 General Shipping Information

Core biopsies that are fixed in formalin should be shipped in the single chambered kit that is provided, whenever possible. The shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For new biopsies, the Tissue Biopsy Verification Form (Appendix H) and a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.
For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

5.6.1.1 Required Forms for Specimen Submissions:

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	Required Forms
Archival	1. Shipping List 2. Corresponding Pathology Report
Tumor biopsies in formalin	1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Pathology Report 4. Surgical and/or Radiology Report
Blood in Streck cDNA tubes or purple top EDTA tubes	1. Shipping List

5.6.2 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Frozen specimens and archival (FFPE) tissue may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.6.2.1 Shipping of FFPE Blocks and Glass Slides

1. Before packaging slides, verify that slides are labeled according to Section 5.4.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.2 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.

2. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.3 Shipping Ambient Formalin-Fixed Tissue in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed. The lids of formalin jars should be wrapped in parafilm. Absorbent material must be placed around each primary container that holds liquid.
2. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
3. Place specimens into the secondary pressure vessel surrounded by bubble wrap. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
4. Place a copy of the shipping manifest and corresponding reports such as pathology, surgical, or radiology reports into the insulated shipping container.
5. Set the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Attach an Exempt Human Specimen sticker to the side of the container.
8. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.4 Shipping Frozen Specimens in Your Own Container

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.

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

5.6.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

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

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

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

5.7 Shipping of Specimens from Clinical Site to Other Laboratories

5.7.1 Shipping of Specimens to Beumer Laboratory

5.7.1.1 Specimen Shipping Instructions

Preparing the shipment:
1. Samples should be stored in cardboard boxes (5 1/8" × 5 1/8" × 2", L × W × H).
2. Organize the samples by Patient and Time point in the box.
3. Do not store in plastic bags (they break on dry-ice and labels will detach).
4. A copy of each of the pharmacokinetic sample collection forms for the respective patients should be included with each shipment (see Appendix F). 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.

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.

Shipping Restrictions: All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. All specimens are to be shipped on either Monday, Tuesday, or Wednesday, and not before federal or university holidays.

5.7.1.2 Shipping Address

Jan Beumer, University of Pittsburgh
Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G27E, Hillman Research Pavilion
5117 Centre Avenue
Pittsburgh, PA 15213

5.7.1.3 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

5.7.2 Shipping of Specimens to Kolesar Laboratory

5.7.2.1 Schedule of Shipment

Frozen specimens (plasma) may be shipped on Monday through Thursday. Frozen specimens are batch shipped every 6 months.

5.7.2.2 Packing Instructions for Frozen Plasma

Frozen plasma samples should be batch shipped using the instructions below:

1. Place the plasma specimens in zip-lock bags. Use a separate zip-lock bag for each time point and collection.
2. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal the envelope.
3. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal the envelope.
4. Place the Tyvek envelope in a Styrofoam container filled with dry ice. Layer the bottom with dry ice until it is approximately one-third full. Place the Tyvek envelope containing frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
5. Insert a copy of the specimen manifest from the Specimen Tracking System into a plastic bag and place in the container.
6. Place the Styrofoam lid on top to secure specimens during shipment.
7. Close the lid with filament or other durable sealing tape. Do not completely seal the container.
8. Complete a FedEx air bill and attach to top of shipping container.
9. Complete a dry ice label.
10. Attach the dry ice UN1845 label and an Exempt Human Specimen sticker or UN3373 sticker to the side of the shipping container.
11. Arrange for courier pickup. Note: FedEx Priority Overnight is strongly recommended for next day delivery to prevent delays in package receipt.

5.7.2.3 Shipping Address

Ship plasma for PK analysis overnight courier on dry ice to the University of Kentucky for processing and storage.

Attn: Rob McCorkle, Ph.D. Kolesar Lab
B0551-02 HKRB
760 Press Avenue
Lexington, KY 40536

5.7.2.4 Contact Information for Assistance

Phone: 859 323-4978
Fax: 859 323-3561
Email: jill.kolesar@uky.edu

5.8 Biomarker Plan

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	Whole Exome Sequencing	NGS CLIA: N	Integrated Molecular characterization of the tumor	DNA from Tumor Tissue	Pre-treatment (or archival tissue within 6 months)	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. Mickey.williams@nih.gov
2	RNAseq	NGS CLIA: N	Exploratory Molecular characterization of the tumor	RNA from Tumor Tissue	Pre-treatment (or archival tissue within 6 months)	O	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. Mickey.williams@nih.gov
Blood-based Biomarkers							
1	Triapine PK studies	LC-MS/MS CLIA: N	Integrated PK exposure of Triapine in plasma.	Plasma from peripheral blood	C1D9: Pre-treatment, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hr (Dose escalation cohort only)	M	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center Jan Beumer, Ph.D. beumerjh@upmc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
	Methemoglobin Determination	Commercial Assay CLIA: N	Integrated To measure the amount of methemoglobin	Peripheral venous blood	C1D1: Pre-treatment C1D9: Pre-treatment, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hr (Dose escalation cohort only)	M	Local Labs as per standard of care
2	Banking (1.3.3)	ELISA CLIA: Y	Exploratory Banking of frozen blood for future research	Frozen blood in EDTA (purple-top)	Cycle 1, Day 1 pre-treatment and at progression	M	TBD. Originally collected to analyze hPG80 but instead all samples will be biobanked (as of 12/13/22) for future use.
3	Whole Exome Sequencing	NGS CLIA: N	Integrated Germline control	Germline DNA from Blood (Streck)	Germline DNA from blood in Streck cfDNA tubes	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. Mickey.williams@nih.gov
4	ctDNA Sequencing	NGS CLIA: N	Exploratory Developing insight into tumor and genomic landscape of disease	Plasma from Blood (Streck)	Cycle 1, Day 1 pre-treatment and at progression	O	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. Mickey.williams@nih.gov
5	Deoxyribo-nucleosides	LC/MSMS CLIA: N	Exploratory Explore mechanisms of triapine resistance	Plasma from Blood (EDTA)	Cycle 1, Day 1 pre-treatment Cycle 2, Day 1 pre-treatment At progression	M	Kolesar Laboratory Jill Kolesar, PharmD jill.kolesar@uky.edu

5.9 Integrated Correlative Studies

5.9.1 Whole Exome Sequencing

5.9.1.1 Specimens Receipt and Processing at the EET Biobank

Archival formalin-fixed paraffin-embedded (FFPE) or pre-treatment formalin-fixed tumor will be processed for this assay. Tumor tissue received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial H&E-stained slide for pathology QA review. As needed, tumor tissues may be annotated for macrodissection to enrich tumor content
DNA and RNA will be co-extracted from tumor tissue. Germline DNA will be extracted from blood collected in the Streck cfDNA tube at C1D1, following plasma processing. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of tumor and germline DNA will be shipped to the central sequencing laboratory for analysis.

5.9.1.2 Site Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Mickey Williams, Ph.D. (mickey.williams@nih.gov).

5.9.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.1.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.9.2 Triapine PK Studies

5.9.2.1 Specimen(s) Receipt and Processing at the Beumer lab

Frozen Plasma aliquots will be received at the Beumer laboratory for storage and analysis.

An LC-MS/MS assay to quantitate triapine was developed and validated in the UPMC Hillman Cancer Center, Cancer Pharmacokinetics and Pharmacodynamics Facility (Matsumoto et al., 2017).

5.9.2.2 Site(s) Performing Correlative Study

This study will be performed in the Beumer laboratory under the supervision of Jan Beumer, Ph.D. (beumerjh@upmc.edu).

5.9.2.3 Contact information for notification of specimen shipment

Refer to section 5.7.1.2 and 5.7.1.3.

5.9.3 Methemoglobin Determination

5.9.3.1 Specimen(s) Receipt and Processing at Local Labs

Local labs should process these samples per institutional SOPs as part of standard of care.

5.9.3.2 Site(s) Performing Correlative Study

This study will be conducted at local labs.

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 Blood-Based Predictive Assay (1.3.3)

5.10.1.1 Specimen Receipt and Processing at the EET Biobank

Frozen blood (5mL purple-top EDTA tube) received at the EET Biobank will be accessioned, barcoded, and stored frozen in a -80°C freezer. **Note**: originally this blood was collected and frozen to conduct hPG80 assay, however it was determined that frozen blood is not suitable for this assay so these samples will be biobanked for future analysis. See also notes in Sections 2.5.2.1, 5.5.3.4 and 11 Study Calenar for details on blood sample collection.

5.10.1.2 Site Performing Correlative Study
N/A (as frozen samples are being biobanked).

5.10.1.3 Contact Information for Notification of Specimen Shipment
N/A (as frozen samples are being biobanked).

5.10.2 RNAseq

5.10.2.1 Specimens Receipt and Processing at the EET Biobank

Archival formalin-fixed paraffin-embedded (FFPE) or pre-treatment formalin-fixed tumor will be processed for this assay. Tumor tissue received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial H&E-stained slide for pathology QA review. As needed, tumor tissues may be annotated for macrodissection to enrich tumor content.

DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to

determine concentration and quality. Aliquots of RNA will be shipped to the central sequencing laboratory for analysis.

5.10.2.2 Site Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Mickey Williams, Ph.D. (mickey.williams@nih.gov).

5.10.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.10.2.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10.3 ctDNA sequencing

5.10.3.1 Specimen(s) Receipt and Processing at the EET Biobank

Upon receipt, blood in Streck cfDNA tubes will be processed for plasma and either DNA (at C1D1 only) or buffy coat (at Disease Progression) and stored frozen in a -80°C freezer. Plasma will be stored in 1-mL aliquots, and buffy coat will be stored as 1-2 aliquots.

5.10.3.2 Site(s) Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Mickey Williams, Ph.D. (mickey.williams@nih.gov).

5.10.3.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.10.3.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10.4 Single Deoxyribonucleoside Concentrations

5.10.4.1 Specimen Receipt and Processing at the University of Kentucky

Frozen plasma aliquots will be received at the University of Kentucky. Upon receipt, plasma will be accessioned, barcoded, and stored in a -80°C freezer until distribution for testing.

5.10.4.2 Site Performing Correlative Study

The Kolesar Lab at the University of Kentucky, under the direction of Dr. Jill Kolesar, will conduct the proposed studies. The Kolesar lab has more than 20 years of experience in analytical chemistry and PK analysis.

5.10.4.3 Contact information for notification of specimen shipment

Refer to section 5.7.2.3 and 5.7.2.4.

5.11 Special Studies

5.11.1 Gallium-68 Dotatate (*OR* Copper-64 Dotatate)

5.11.1.1 Outcome Measure

Baseline Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT prior to therapy is standard of care and covered by insurance. Prior to administration of the novel treatment combination, Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT will be performed for all patients to confirm adequate somatostatin receptor binding. Participating sites will send de-identified Dotatate (Gallium-68 or Copper-64) scan images/discs of all enrolled study participants to Dr Aman Chauhan at amanchauhan@uky.edu, 800 Rose Street, CC 447, Ben Roach Building, Markey Cancer Center, 40536, Lexington Kentucky.

To confirm receptor expression, Krenning's score will be applied to Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT images. Advanced quantitative analysis will be performed as well and parameters such as SUV_{max}, SUV_{peak}, MTV, and TBI will be obtained per organ and for the patient. Advanced analysis will be performed to determine the optimum quantitative parameter that correlates with Objective response measures, PFS, as well as OS.

5.11.1.2 Assessment

5.11.1.2.1 Method of Assessment

- Radiopharmaceutical: Standard dose of Gallium-68 Dotatate will be administered IV (0.054 mCi/kg) **OR** the standard dose for Copper-64 Dotatate.
- Uptake time: 55-75 minutes
- CT images of the torso from vertex to mid-thigh will be acquired.
- PET images will be acquired with the following parameters: 5 minutes/table position.

See Appendix G for additional details for Dotatate scans (Gallium-68 dotatate, Copper-64 dotatate).

5.11.1.2.2 Timing of Assessment

Assessment will be performed at baseline unless patients have already had a Gallium-68 Dotatate or Copper-64 Dotatate scan within 6 months of enrollment.

5.11.1.3 Data Recording

5.11.1.3.1 Method of Recording

- Images will be post-processed using iterative reconstruction method (2 iterations and 8 subsets), Matrix
- Image analysis will be performed using MIRADA XD and Syngo Via software.

5.11.1.3.2 Timing of Recording

Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT scans will be assessed for inclusion determination during the pre-screening period within 2 weeks of patient's enrollment. This will include review of either newly performed Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT scans or reassessment of previously performed Gallium-68 Dotatate (or Copper-64 Dotatate) PET/CT scans within the predetermined acceptable period (within 6 months of enrollment). Participating sites with access to Copper-64 Dotatate scans can consider either scan per institutional standards.

6. TREATMENT PLAN

6.1 Agent Administration in Dose Escalation Phase

Treatment will be administered on an outpatient or inpatient basis per institutional standard operating procedures (SOPs). Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Oral triapine will be given at the assigned phase 1 dose level. 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 within 90 minutes after Lutetium Lu 177 Dotatate treatment and once daily after that for 14 days. Ninety-nine percent of Lutetium Lu 177 Dotatate radiation is undetectable by Day 14. Lutetium Lu 177 Dotatate will be administered as IV infusion per FDA label every 2 months at dose of 200 mCi for total of 4 doses. All dose cohorts will be treated with same dose of Lutetium Lu 177 Dotatate.

Dose Escalation Schedule		
Dose Level	**Dose ***	
	Triapine	**Lutetium Lu 177 Dotatate**
Level -2	50 mg PO QOD, Days 1-14	200 mCi IV, Day 1
Level -1	50 mg PO QD, Days 1-14	
Level 1 #	100 mg PO QD, Days 1-14	
Level 2	150 mg PO QD, Days 1-14	
Level 3	200 mg PO QD, Days 1-14	
* Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, *etc.*) rather than as a percentage. # Starting dose.		

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Triapine	Fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose	As per assigned dose level (See dose escalation schedule above)	Oral;	Days 1-14 of each cycle; on Day 1, within 90 minutes after Lutetium Lu 177 Dotatate treatment.	8 weeks (56 days)
Lutetium Lu 177 Dotatate	Administer antiemetics 30 minutes before the recommended amino acid solution. Administer amino acid solution IV 30 minutes before Lutetium Lu 177 Dotatate.	200 mCi	IV; Please refer to section 8.2.1 for details regarding Lutetium Lu 177 Dotatate route of administration.	Day 1 of each cycle	

The patient will be requested to maintain a medication diary of each dose of triapine (Appendix D). The medication diary will be returned to clinic staff at the end of each course.

6.1.1 Triapine

Patients will be instructed to take triapine PO at the assigned dose level. Triapine will be administered on Days 1-14 of every 8 week cycle to overlap with the four administrations of Lutetium Lu 177 Dotatate. On Day 1 of each cycle, patients will ingest one dose of triapine within 90 minutes after Lutetium Lu 177 Dotatate treatment. Triapine will be discontinued after the last cycle of Lutetium Lu 177 Dotatate administration since triapine does not have anti-tumor activity by itself.

Patients will be asked to fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose. Capsules should not be opened.

Missed doses for any reason, including vomiting, can be taken up to 6 hours after the scheduled dose. If it has been more than 6 hours since the missed dose, this dose should be skipped.

6.1.2 Lutetium Lu 177 Dotatate:

Lutetium Lu 177 dotatate and related supportive care drugs will be administered per participating institution standard operating procedure per FDA approved label indication, dose and route of administration. Please refer to section 8.2.1 for details regarding Lutetium Lu 177 Dotatate route of administration.

Somatostatin Analogs: If patients were on somatostatin analog long acting release (SSA-LAR) depot injections prior to enrollment in the trial, they will continue to be on SSA LAR during the trial. Patient will need to discontinue long-acting somatostatin analogs for at least 4 weeks prior to initiating Lutetium Lu 177 dotatate unless long-acting somatostatin analog is required for control of patients carcinoid syndrome. Patient can receive either long acting octreotide 30 mg every 4 weeks as deep intramuscular depot injection or lanreotide 120 mg every 4 weeks as deep subcutaneous injection, per FDA guidelines. Injections are administered in the superior external quadrant of the buttock.

Patients who need rescue short-acting octreotide to control their functional neuroendocrine symptoms per recommendations of their treating physician.

Antiemetic: Administer antiemetics 30 minutes before the recommended amino acid solution.

Amino Acid Solution: Initiate an IV amino acid solution containing L-lysine and L-arginine (Table 1) 30 minutes before administering Lutetium Lu 177 Dotatate. Use a three-way valve to administer amino acids using the same venous access as Lutetium Lu 177 Dotatate or administer amino acids through a separate venous access in the patient's other arm. Continue the infusion during, and for at least 3 hours after Lutetium Lu 177 Dotatate infusion. Do not decrease the dose of the amino acid solution if the dose of Lutetium Lu 177 Dotatate is reduced.

Table 1. Amino Acid Solution	
Item	*Specification*
Lysine HCl content	Between 18 g and 24 g

Arginine HCl content	Between 18 g and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1050 mOsmol

6.2 Definition of Dose-Limiting Toxicity

DLT will be defined by Grade 3 or greater hematological or non-hematological toxicity per CTCAE version 5.0 that is **possibly, probably or likely** related to study treatment. The following will not be considered DLTs unless determined to be clinically significant and related to study treatments by the treating physician:

- Grade 1-4 lymphopenia
- Grade 3 nausea, vomiting or diarrhea lasting <72 hours and controlled by optimal antiemetic/anti diarrheal therapy;

DLT will be assessed at the end of Cycle 1. Patients need to have at least one dose of Lutetium Lu 177 Dotatate and at least 80% of the dose cohort-specific triapine during Cycle 1 to be evaluable for adverse effects and DLT criteria for dose escalation/de-escalation decisions.

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

Dose escalation will proceed within each cohort according to the BOIN design described in Section 9.1. Dose-limiting toxicity (DLT) is defined above.

6.3 Triapine Administration: Dose Expansion Cohort

This study's dose escalation cohort enrolled 15 patients in order to identify the recommended Phase 2 Dose (RP2D) of Triapine. The Recommended Phase II Dose (RP2D) is based on data available from 15 patients who were treated with varying doses of Triapine (100mg, 150mg and 200mg) using BOIN dose escalation design.

6.3.1 Triapine RP2D

After completion of dose escalation on 15 patients, **Dose Level 2 was selected as the RP2D** for the dose expansion cohort. Thus, all patients enrolled in the dose expansion cohort will be administered **Triapine 150mg** orally once a day on Days 1-14 of each Lu-177 dotatate cycle.

An additional 14 patients will be treated at the RP2D dose (i.e., enrolled in the dose expansion cohort). For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2DMonitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.3.2 Dose Expansion Treatment Regimen

Regimen Description: Dose Expansion Cohort					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Triapine	Fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose	RP2D is **150mg once daily** (dose expansion cohort)	Oral;	Days 1-14 of each cycle; on Day 1, within 90 minutes after Lutetium Lu 177 Dotatate treatment.	8 weeks (56 days)
Lutetium Lu 177 Dotatate	Administer antiemetics 30 minutes before the recommended amino acid solution. Administer amino acid solution IV 30 minutes before Lutetium Lu 177 Dotatate.	200 mCi	IV; See 8.2.1	Day 1 of each cycle	

The patient will be requested to maintain a medication diary of each dose of triapine (Appendix D). The medication diary will be returned to clinic staff at the end of each course.

6.4 General Concomitant Medication and Supportive Care Guidelines

There are no known drug interactions with triapine. The non-radioactive form of lutetium is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 *in vitro*. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 *in vitro*. Because there is a potential for interaction of 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 Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Clinical Trial Wallet Card) should be provided to patients if available.

Risk from Radiation Exposure: Minimize radiation exposure during and after treatment with Lutetium Lu 177 Dotatate consistent with institutional good radiation safety practices and patient management procedures.

Myelosuppression: Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity. Please refer to section 7 for specific guidance regarding dose modification.

Renal Toxicity: Advise patients to urinate frequently during and after administration of Lutetium Lu 177 Dotatate. Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue based on severity. Please refer to section 7 for specific guidance regarding dose modification.

Hepatotoxicity: Monitor transaminases, bilirubin, and albumin. Withhold, reduce dose, or permanently discontinue based on severity.

Neuroendocrine Hormonal Crisis: Monitor for flushing, diarrhea, hypotension, broncho-constriction, or other signs and symptoms.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 4 cycles or until one of the following criteria applies:

- Disease progression (patient will however be monitored for OS)
- Intercurrent illness which would, in the judgment of the investigator, a) affect assessments of clinical status to a significant degree, b) require discontinuation of drug, or c) both a and b
- Unacceptable adverse event(s)
- Delay in treatment of more than 6 weeks.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor

- The drug manufacturer can no longer provide the study agent

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

In April-May 2022 there was a global shortage of Lutetium 177 dotatate. Study enrollment and treatment was held per NCI CTEP's recommendation. The study was not affected as all patients had received cycle 1 of treatment had cleared DLT window. Delay in treatment due to global shortage will not trigger protocol deviation and treatment will resume when drug supply is restored. Patient will then get back on treatment schedule per protocol.

6.6 Duration of Follow-Up

Patients will be followed for 24 months from the time of enrollment *or* until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Recommended Dose Modifications of Lutetium Lu 177 Dotatate for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction	Dose Modification
Thrombocytopenia	Grade 2, 3, or 4	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume Lutetium Lu 177 Dotatate at 100 mCi in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer Lutetium Lu 177 Dotatate at 200 mCi for next dose. Permanently discontinue Lutetium Lu 177 Dotatate for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 2, 3, or 4	Permanently discontinue Lutetium Lu 177 Dotatate.
Anemia and Neutropenia	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume Lutetium Lu 177 Dotatate at 100 mCi in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer Lutetium Lu 177 Dotatate at 200 mCi for next dose. Permanently discontinue Lutetium Lu 177 Dotatate for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue Lutetium Lu 177 Dotatate.
Renal Toxicity	Defined as: • Creatinine clearance less than 40 mL/min; calculate using Cockcroft Gault with actual body weight, or • 40% increase in baseline serum creatinine, or • 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Withhold dose until complete resolution. Resume Lutetium Lu 177 Dotatate at 100 mCi in patients with complete resolution. If reduced dose does not result in renal toxicity, administer Lutetium Lu 177 Dotatate at 200 mCi for next dose. Permanently discontinue Lutetium Lu 177 Dotatate for renal toxicity requiring a treatment delay of 16 weeks or longer.

Adverse Reaction	Severity of Adverse Reaction	Dose Modification
	Recurrent renal toxicity	Permanently discontinue Lutetium Lu 177 Dotatate.
Hepatotoxicity	Defined as: • Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%. • Grade 4 AST or ALT elevation	Withhold dose until complete resolution. Resume Lutetium Lu 177 Dotatate at 100 mCi in patients with complete resolution. If reduced Lutetium Lu 177 Dotatate dose does not result in hepatotoxicity, administer Lutetium Lu 177 Dotatate at 200 mCi for next dose. Permanently discontinue Lutetium Lu 177 Dotatate for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue Lutetium Lu 177 Dotatate.
Other Non-Hematologic Toxicity	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume Lutetium Lu 177 Dotatate at 100 mCi in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer Lutetium Lu 177 Dotatate at 200 mCi for next dose. Permanently discontinue Lutetium Lu 177 Dotatate for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue Lutetium Lu 177 Dotatate.

7.2 Recommended Dose Modifications of Triapine

Dose modification should follow the triapine dose levels in the dose escalation table in Section 6.1.

Nausea/vomiting	Management/Next Dose for *Triapine*
≤ Grade 2	No change in dose. Treat with antiemetics.
Grade 3	Hold[a] until ≤ Grade 2. Resume at one dose level lower, if indicated. Treat with antiemetics.
Grade 4	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.	

Diarrhea	**Management/Next Dose for *Triapine***
≤ Grade 2	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.
Grade 4	Off protocol therapy[b]
[a]Patients should hold triapine if diarrhea refractory to anti-diarrheal (Loperamide is recommended). Adjunct anti-diarrheal therapy is permitted and should be recorded when used. [b]Off protocol therapy and continue standard of care treatment per treating physician.	

Neutropenia	**Management/Next Dose for *Triapine***
≤ Grade 2	No change in dose
Grade 3	No change in dose
Grade 4	Off protocol therapy[a]
[a]Off protocol therapy and continue standard of care treatment per treating physician.	

Thrombocytopenia	**Management/Next Dose for *Triapine***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	No change in dose
Grade 4	Off protocol therapy[a]
[a]Off protocol therapy and continue standard of care treatment per treating physician.	

Non-hematologic toxicity	**Management/Next Dose for *Triapine***
≤ Grade 1	No change in dose
Grade 2	Hold[a, b] until ≤ Grade 1 (See NOTE below)
Grade 3	Hold[c] until < Grade 1 (See NOTE below)
Grade 4	Off protocol therapy[b]
[a]Patients requiring a delay of >2 weeks should go off protocol therapy. [b] Grade 2 hypertension unrelated to study drugs in a patient with history of chronic hypertension does not warrant holding treatment. [c]Off protocol therapy and continue standard of care treatment per treating physician. NOTE: Decision to maintain dose or resume at dose reduction must be reviewed with study PI.	

7.2.1 Methemoglobinemia

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.

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 methemoglobins 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. However, methylene blue is contraindicated in patients with glucose-6-phosphate (G6PD) 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. 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. 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.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent - Triapine

8.1.1 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

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. Patients will be asked to fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose. Capsules should not be opened.

Availability

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

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

Triapine is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

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

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

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.

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

8.1.3 Investigator Brochure Availability

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

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines:

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

8.2 Commercial Agent - Lutetium Lu 177 Dotatate (NSC 815530)

Product description:

Lutetium Lu 177 Dotatate injection containing 10 mCi/ml of Lutetium Lu 177 Dotatate is a sterile, preservative-free and clear, colorless to slightly yellow solution for IV use supplied in a colorless Type I glass 30 mL single-dose vial containing 200 mCi ±10% of Lutetium Lu 177 Dotatate at the time of injection. The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 200 mCi of radioactivity. Each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65 mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5 to 6.

Solution preparation:

Lutetium Lu 177 Dotatate is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure. Use waterproof gloves and effective radiation shielding when handling Lutetium Lu 177 Dotatate. Radiopharmaceuticals, including Lutetium Lu 177 Dotatate, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

- Use aseptic technique and radiation shielding when administering the Lutetium Lu 177 Dotatate solution. Use tongs when handling vial to minimize radiation exposure.

- Do not inject Lutetium Lu 177 Dotatate directly into any other IV solution.

- Confirm the amount of radioactivity of Lutetium Lu 177 Dotatate in the radiopharmaceutical vial with an appropriate dose calibrator prior to and after Lutetium Lu 177 Dotatate administration.

- Inspect the product visually for particulate matter and discoloration prior to administration under a shielded screen. Discard vial if particulates or discoloration are present.

- Insert a 2.5 cm, 20 gauge needle (short needle) into the Lutetium Lu 177 Dotatate vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport Lutetium Lu 177 Dotatate during the infusion). Ensure that the short needle does not touch the Lutetium Lu 177 Dotatate solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the Lutetium Lu 177 Dotatate vial prior to the initiation of the Lutetium Lu 177 Dotatate infusion and do not inject Lutetium Lu 177 Dotatate directly into the sodium chloride solution.

- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Lutetium Lu 177 Dotatate vial ensuring that this long needle touches and is secured to the bottom of the Lutetium Lu 177 Dotatate vial during the entire infusion. Connect the long needle to the patient by an IV catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the Lutetium Lu 177 Dotatate infusion into the patient.

Route of administration: Lutetium Lu 177 Dotatate is administered IV.

- Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the Lutetium Lu 177 Dotatate vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the Lutetium Lu 177 Dotatate from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).
- Do not administer Lutetium Lu 177 Dotatate as an IV bolus.
- During the infusion, ensure that the level of solution in the Lutetium Lu 177 Dotatate vial remains constant.
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an IV flush of 25 mL of 0.9% sterile sodium chloride.
- Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Storage: The product vial is in a lead shielded container placed in a plastic sealed container. The product is shipped in a Type A package. Store below 25 °C (77 °F). The shelf life is 72 hours. Discard appropriately at 72 hours.

Agent Ordering: Lutetium Lu 177 Dotatate is commercially available. For ordering information, please visit: https://hcp.lutathera.com/ordering-lutathera/

Lutetium Lu 177 Dotatate, accompanying amino acid infusion as well as supportive care medication can be administered per treating hospital standard operating procedure per standard of care, as approved by FDA.

For additional information, please refer to the package insert.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This study is a multicenter phase 1 trial of triapine and Lutetium Lu 177 Dotatate in combination for well-differentiated somatostatin receptor-positive GEP-NETs after the failure of at least one line of prior systemic cancer treatment. An expansion cohort with 14 additional patients will be enrolled at the RP2D to further assess safety, obtain initial estimates of clinical response outcomes, and perform exploratory comparisons of biomarkers.

The primary objective of the **phase 1 trial** is to determine the MTD and identify the RP2D of triapine in combination with Lutetium Lu 177 Dotatate. The Bayesian optimal interval design (BOIN) (Yuan *et al*., 2016) will be employed to guide dose escalation. DLT is defined in Section 6.2 and will be assessed after the first cycle (8 weeks post treatment). Patients will be enrolled in cohorts of 3 beginning at dose level 1. A target DLT rate of 25% will be assumed with dose escalation, λ_e, and de-escalation boundaries, λ_d, set at 0.197 and 0.298, respectively. Based on the BOIN design, dose escalation will proceed as shown in the table below until a total of 15 patients have been enrolled in the dose escalation part of this phase 1 trial. MTD and RP2D will be estimated using isotonic regression based on toxicity data from all patients.

Dose escalation and de-escalation boundaries Table

Number of patients treated at the current dose:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if DLTs ≤	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2
De-escalate if DLTs ≥	1	1	1	2	2	2	3	3	3	3	4	4	4	5	5

An expansion cohort with 14 additional patients will be enrolled at the RP2D to further assess safety, obtain initial estimates of clinical response outcomes, and perform exploratory comparisons of biomarkers. Assuming that the minimum number of patients enrolled at the RP2D is equal to 17, the proposed sample size from the phase 1 portion and expansion cohort will produce a two-sided 95% exact confidence interval with a width equal to 0.44, when the DLT rate is 0.25.

<u>Interim Analysis for Phase 1 (Dose escalation)</u>

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 bi-monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, adverse events, and unanticipated problems. DLT will be assessed as defined in Section 6.2 using CTCAE version 5.0 which will be assessed after the first cycle for each patient enrolled in the trial. The dose escalation and cohort sizes are specified in the table above. Automated triggers developed by the Biostatistics and Bioinformatics Shared Resource at Markey Cancer Center (MCC) will be run after each patient is enrolled in order to perform real-time evaluation of DLT to make recommendations to the study team to implement the dose

escalation rule defined in the Table above. The Protocol Principal Investigator will make dose escalation decisions based on evaluation of all patient data, including type of DLT and non-DLT events. The appropriate dose level available for patient enrollment is made available in the OPEN and IWRS system described in Section 4.3.

Expansion Cohort Safety Assessment

For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the PI will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D; isotonic regression will also be utilized to estimate the DLT rate. Monitoring of all safety and toxicity data is done by the PI and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the PI when a DLT has occurred.

Analysis of Safety Data

The MTD will be estimated using isotonic regression based on observed DLT from all patients enrolled in the phase 1 portion and expansion cohort. All patients who received study drugs will be included in the safety analysis. DLTs based on Section 6.2 will be summarized descriptively at each dose level. Adverse events will be summarized based on CTCAE version 5.0. The maximum grade of toxicity for each adverse event category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all serious (≥ grade 3) toxicity events on a patient-by-patient basis. Frequency and incidence tables of toxicity and adverse events will be generated in the overall patient group and by dose level depending on patient enrollment.

9.2 Sample Size/Accrual Rate

A total of 29 patients will be enrolled in the dose escalation and dose expansion cohorts. The study will be open through the entire ETCTN for any Lutetium Lu 177 Dotatate compatible site. However, University of Kentucky and Ohio State University are willing to establish the RP2D, using a limited LAO network if requested, before the expansion phase being offered to the entire ETCTN. Both Ohio State University and University of Kentucky offer PPRT therapies. We are currently treating 2-3 patients per week with Lutetium Lu 177 Dotatate at University of Kentucky alone and do not foresee difficulties with accrual to the RP2D. The study is expected to complete accrual in approximately 3 years.

PLANNED ENROLLMENT REPORT

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

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	5	5	0	0	**10**
White	8	8	0	0	**16**
More Than One Race	1	0	0	0	**1**
Totals	**15**	**14**	**0**	**0**	**29**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

9.3 Stratification Factors

N/A

9.4 Results of Phase 1: RP2D for the Dose Expansion Cohort

As noted in 9.1, this study includes an expansion cohort upon completion of phase 1 (i.e., dose escalation which determines the RP2D). An expansion cohort with 14 additional patients will be enrolled and treated with the RP2D in order to further assess safety, obtain initial estimates of clinical response outcomes, and perform exploratory comparisons of biomarkers.

9.4.1 Results of the dose escalation phase (interim analysis of Phase 1)

The Phase 1 dose escalation enrolled 15 patients using the BOIN design. Isotonic regression provided posterior estimates of the DLT rate at each dose level. The DLT estimate for DL2 = 0.18, 95% credible interval: (0.03, 0.045) and at DL2 the Prob (DLT rate > 0.25) = 0.25. All evaluable patients completed the DLT window.

9.4.2 Recommended Dose for Dose Expansion Cohort

The RP2D is DL2, **Triapine 150mg once a day during Days 1-14 of each Lu-177 dotatate cycle**.

9.4.3 Plan for Dose Expansion Phase

The dose expansion cohort opened to accrual on 10/08/2021. As noted above in 9.1, patients enrolled in the dose expansion cohort phase will continue to be monitored for occurrence of DLT.

If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the PI will discuss with all study

investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D; isotonic regression will also be utilized to estimate the DLT rate. Monitoring of all safety and toxicity data is done by the PI and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the PI when a DLT has occurred.

9.5 Analysis of Secondary and Correlative Endpoints

ORR will be estimated along with 95% exact binomial confidence interval. PFS and OS will be estimated using the Kaplan-Meier curve and median estimates and confidence intervals will be calculated. Correlative endpoints such as radiographic expression of somatostatin receptors and changes from pre to post-treatment will be summarized using descriptive statistics and changes from baseline *vs.* follow-up time points will be assessed using paired test methodologies. WES data will be processed using the data processing and data analysis pipelines from the Biostatistics and Bioinformatics shared resource of MCC to identify candidate mutated genes with adjustment for false discovery rate. PK analysis will be performed and PK parameters will be estimated from patients enrolled in the dose escalation portion of the phase 1 trial. PK parameters will be compared with historical controls, and exploratorily, we may correlate exposure to toxicity, and incorporate data into a population PK model. Krenning score from the Gallium-68 Dotatate (or Copper-64 Dotatate) will be summarized by calculating the proportion of patients in each Krenning score category and exploratory assessments for association with clinical response (ORR) will be performed using Fisher's exact test. Median, interquartile range will be calculated for quantitative image measurements from Gallium-68 Dotatate (or Copper-64 Dotatate) and exploratory comparison of levels with clinical response (ORR) will be performed using two sample t-test or nonparametric analogs. Mean change in deoxynucleosides between baseline and post treatment samples will be assessed by paired t-test or other methods. Deoxynucleoside plasma concentration as a predictor of clinical outcomes will explored by linear (progression free survival) and logistic regression (response).

Correlative endpoint analyses will be based on patients who received the RP2D from the dose escalation portion and expansion cohort. See details in Sections **6.3** and **9.4** for RP2D.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPR)

10.1.1 CAEPR for Triapine, CTEP IND Agent (Version 2.6, 19MARCH2019)

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)***

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%)**	
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)***
	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			

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%)**	
	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.

10.1.2 CAEPR for Lutetium Lu 177 dotatate – Version 2.0, October 22, 2020

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Lutetium Lu 177 dotatate (NSC 815530)

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 1326 patients.* Below is the CAEPR for Lutetium Lu 177 dotatate.

> **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 2.0, October 22, 2020[1]

Adverse Events with Possible Relationship to Lutetium Lu 177 dotatate (CTCAE 5.0 Term) [n= 1326]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Blood and lymphatic system disorders - Other (pancytopenia)		
		Bone marrow hypocellular	
GASTROINTESTINAL DISORDERS			
		Nausea	
		Vomiting	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Injury, poisoning and procedural complications - Other (acute radiation toxicity)		
INVESTIGATIONS			
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	

[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.

Adverse events reported on Lutetium Lu 177 dotatate trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Lutetium Lu 177 dotatate caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Febrile neutropenia; Hemolysis; Leukocytosis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Aortic valve disease; Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cardiac valve disease); Chest pain - cardiac; Conduction disorder; Heart failure; Mitral valve disease; Myocardial infarction; Palpitations; Pulmonary valve disease; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Tricuspid valve disease; Ventricular fibrillation
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (arterial septal defect)
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Diarrhea; Ileal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fatigue; Fever; Generalized edema; Malaise
HEPATOBILIARY DISORDERS - Hepatic hemorrhage; Hepatobiliary disorders - Other (cholestases)
INFECTIONS AND INFESTATIONS - Lung infection
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hypokalemia; Tumor lysis

syndrome
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Ischemia cerebrovascular; Stroke; Transient ischemic attacks
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Nephrotic syndrome; Renal and urinary disorders - Other (urethral stenosis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (aortic valve replacement); Surgical and medical procedures - Other (atherectomy); Surgical and medical procedures - Other (atrial septal defect repair); Surgical and medical procedures - Other (bladder catheterization); Surgical and medical procedures - Other (cardiac ablation); Surgical and medical procedures - Other (cardiac pacemaker insertion); Surgical and medical procedures - Other (cardioversion); Surgical and medical procedures - Other (coronary angioplasty); Surgical and medical procedures - Other (coronary arterial stent insertion); Surgical and medical procedures - Other (coronary artery bypass); Surgical and medical procedures - Other (dialysis); Surgical and medical procedures - Other (heart valve operation); Surgical and medical procedures - Other (hemodialysis); Surgical and medical procedures - Other (pulmonary valve replacement); Surgical and medical procedures - Other (tricuspid valve repair); Surgical and medical procedures - Other (tricuspid valve replacement)
VASCULAR DISORDERS - Hypertension; Hypotension; Vascular disorders - Other (atherosclerosis)

Note: Lutetium Lu 177 dotatate in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

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

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

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

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

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

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

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

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

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

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides & Help Topics.

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

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

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

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

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

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

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- 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:
1 All Grade 3, 4, and Grade 5 AEs
Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

10.3.4 Adverse Events of Special Interest

Adverse events of special interest (AESIs): **Grade 3 or higher gastrointestinal adverse events** will be reported via Medidata Rave.

10.4 Routine Adverse Event Reporting

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

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. Adverse events 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 adverse event reporting in Rave.

10.5 Pregnancy

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

10.6 Secondary Malignancy

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

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

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

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

10.7 Second Malignancy

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

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 30 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Screening	Pre-treatment [a]	Cycle 1 (8 weeks)							Cycle 2 (8 weeks)				Cycle 3 (8 weeks)				Cycle 4 (8 weeks)				Disease Progression	Follow-Up and Off-Treatment Visits [b,c]
			Day 1 [c]	Day 9	Day 14 [c]	Day 15 [c]	Day 29 [c]	Day 43 [c]	Days 44-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56		
Triapine			A----------A							A--------A				A--------A				A--------A					
Lutetium Lu 177 Dotatate			B							B				B				B					
Informed consent	X																						
Demographics	X																						
Medical history	X																						
Concurrent meds	X		X----------X																				
Physical exam	X		X				X			X		X		X		X		X		X			X
Vital signs	X		X				X			X		X		X		X		X		X			X
Height	X																						
Weight	X		X				X			X		X		X		X		X		X			X
Performance status [d]	X		X				X			X		X		X		X		X		X			X
CBC w/diff, plts	X		X			X	X	X		X		X		X		X		X		X			X
Comprehensive Chemistry Panel [e]	X		X			X	X	X		X		X		X		X		X		X			X
EKG (as indicated)	X																						

	Screening	Pre-treatment [a]	Cycle 1 (8 weeks)							Cycle 2 (8 weeks)				Cycle 3 (8 weeks)				Cycle 4 (8 weeks)				Disease Progression	Follow-Up and Off-Treatment Visits [b,c]
			Day 1[c]	Day 9	Day 14[c]	Day 15[c]	Day 29[c]	Day 43[c]	Days 44-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56		
Ga-DOTATATE PET/CT Scan [f] (or 64-Cu DOTATATE PET/CT scan)	X																						
Adverse event evaluation			X----------																				X
Radiologic evaluation (CT/MRI Scan) [g]	X[h]		Radiologic measurements should be performed every 8 weeks in the dose escalation cohort. Radiologic measurements should be performed every 12 weeks in the dose expansion cohort.																				X
Pregnancy test [i]	X																						
24-Hour Urine 5HIAA [j]			X																	X[j]		X[j]	
blood collection (EDTA) for 1.3.3 – frozen blood will be biobanked for future analysis in lieu of hPG80 assay			X																			X	
ctDNA blood collection (Streck)			X																			X[k]	
Deoxyribonucleosides blood collection (EDTA) [l]			X							X												X	
Tumor tissue collection [m]		X																					
PK blood collection [n]				X																			

	Screening	Pre-treatment [a]	Cycle 1 (8 weeks)							Cycle 2 (8 weeks)				Cycle 3 (8 weeks)				Cycle 4 (8 weeks)				Disease Progression	Follow-Up and Off-Treatment Visits [b,c]
			Day 1 [c]	Day 9	Day 14 [c]	Day 15 [c]	Day 29 [c]	Day 43 [c]	Days 44-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56	Day 1 [c]	Day 14 [c]	Day 29 [c]	Days 30-56		
Methemoglobin Level by peripheral venous blood [o]			X	X																			

STUDY CALENDAR NOTES:

A: Triapine: Dose as assigned on Days 1-14 of each cycle. Cycle length = 8 weeks
The recommended Phase 2 Dose of Triapine was determined to be: 150mg once a day on Days 1-14 of each cycle. Cycle length = 8 weeks

B: Lutetium Lu 177 Dotatate: 200 mCi IV, Day 1 of each cycle for a total of 4 doses. Cycle length = 8 weeks.

a: Pre-treatment collections should be preferably collected on a separate day from screening, but may be collected on the same day at the discretion of the site.

b: Follow-up checks and surveillance CT/MRI scans to be conducted every 3-months for 24 months from the time of enrollment *or* until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Additional scan not needed at the end-of-study visit.

c: Cycles 1-4 visit windows: Days 9,14 +/- 2 days. All other visits +/- 3 days.
Visit windows for Follow-up (Q3-mos visits): ± 3 weeks visit windows.
The following exception applies to visit windows: Dosing of Lu-177 dotatate cannot be given prior to scheduled date. It can be delayed per visit windows in appropriate situations.

d: Performance status evaluations should be evaluated every 4 weeks.

e: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

f: To be performed if NETSPOT, DETECTNET (64Cu dotatate scan) or Octreoscan has not been performed within 6 months.

g: 7 days +/- window is allowed for scans to accommodate logistical issues in obtaining timely scans for unforeseeable circumstances.

h: To confirm progression within the last 3 years.

i: Pregnancy test for women of childbearing potential.

j: 24-Hour Urine 5HIAA should be collected prior to dosing Lutetium Lu-177 dotatate. 24 Hr Urine 5HIAA should be collected unless in exceptional circumstances that patient cannot collect or deliver a 24-Hr sample, alternative 5HIAA assessment per institutional standard can be allowed.
5HIAA will also be collected at the end of PRRT treatment (clinic visit for Cycle 4 Day 29) or at disease progression, whichever happens first. If patient does not receive all 4 doses of PRRT then 24 Hr Urine 5HIAA can be collected at the end-of-treatment visit for that particular patient.

k: Optional collection.

l: Two 8mL K2 EDTA white top tubes will be collected at three timepoints for all participants on C1D1 (pre-treatment), on C2D1 (pre-treatment), and at disease progression.

m: If archival tissue within the last 6 months is not available, a fresh biopsy will be mandatory.

	Screening	Pre-treatment [a]	Cycle 1 (8 weeks)							Cycle 2 (8 weeks)				Cycle 3 (8 weeks)				Cycle 4 (8 weeks)				Disease Progression	Follow-Up and Off-Treatment Visits [b,c]
			Day 1[c]	Day 9	Day 14[c]	Day 15[c]	Day 29[c]	Day 43[c]	Days 44-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56	Day 1[c]	Day 14[c]	Day 29[c]	Days 30-56		

n: PKs: To be collected in the dose-escalation cohort only.
PK time points on Cycle 1, Day 9 (+/- 1 day) include: Pre, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours.

PK WINDOWS:
Pre dose: within 30 minutes
30 minutes: +/- 5 minutes
60 minutes: +/- 5 minutes
1 hour 30 minutes: +/- 5 minutes
2 hours: +/- 5 minutes
3 hours: +/- 10 minutes
4 hours: +/- 10 minutes
6 hours: +/- 10 minutes
8 hours: +/- 10 minutes

o: Methemoglobin: to be collected in dose-escalation cohort only, on Cycle 1 Day 1 and Cycle 1 Day 9.
Methemoglobin timepoint on Cycle 1 Day 1 is pre-treatment.
Methemoglobin timepoints on Cycle 1 Day 9 (+/- 1 day) include: Pre, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours, i.e., blood is to be drawn at each of the PK blood draws.

Methemoglobin Windows for C1D9 are:
Pre dose: within 30 minutes
30 minutes: +/- 5 minutes
60 minutes: +/- 5 minutes
1 hour 30 minutes: +/- 5 minutes
2 hours: +/- 5 minutes
3 hours: +/- 10 minutes
4 hours: +/- 10 minutes
6 hours: +/- 10 minutes
8 hours: +/- 10 minutes

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs 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 with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans (CT or MRI) will also be obtained 8 weeks (+/- 7 days), following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

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.

12.1.1 Definitions

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least three cycle of therapy, and have had their disease re-evaluated post-baseline will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. 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.

24-Month Progression-Free Survival: 24-month PFS is defined as the percentage of patients alive with no evidence of radiological progression per RECIST 1.1 at 24 months from the time of enrollment.

Overall survival: OS is defined as the time from date of enrollment to the date of death due to any cause.

12.1.2 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 not be considered measurable.

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.

12.1.3 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.

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.

12.1.4 Response Criteria

12.1.4.1 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.

12.1.4.2 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).

12.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

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

12.1.5 Duration of Response

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

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

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

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from registration to time of progressive disease as defined by RECIST 1.1 criteria or death from any cause, whichever occurs first.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

13.1 Study Oversight

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

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

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

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

13.2 Data Reporting

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

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.

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. 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 link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; 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 display 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.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if

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

13.2.2 Responsibility for Data Submission

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

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

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

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

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

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

13.3 Data Quality Portal

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

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 CTEP Multicenter Guidelines

N/A

13.5 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.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

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

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

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

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

References

1. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10388

Study Drug(S): triapine and lutetium Lu 177 Dotatate

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

APPENDIX D PATIENT'S MEDICATION DIARY – ONCE DAILY (QD)

CTEP-assigned Protocol # 10388

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent** _____Triapine_____

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle. Each cycle is 8 weeks.
2. You will take your dose of triapine every day for the first 14 days of the cycle. You will take ____ 50 mg capsules every day for the first 14 days of the cycle. You need to fast (except for water) for 2 hours prior to dosing and for 1 hour after ingesting the oral dose. You should swallow the capsule whole. **Do not open the capsules or take capsules until the bottle is empty.**
3. Record the date, the number of capsules you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
Do not take triapine after Day 14 of each cycle				

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 this month (each size)_____
5. Physician/Nurse/Data Manager's Signature and Date_____

Patient's signature:_____

APPENDIX E PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

    1. Biopsy should not be done
        A. Due to safety concerns
        B. Due to lack of suitable lesion for biopsy

    2. Uncertainty about success
        A. Due to access path to lesion
        B. Due to lesion characteristics

    3. Likely successful

- Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX F PHARMACOKINETICS (PK) SHEET CYCLE 1, DAY 9

NCI 10388 (triapine (TRI) in Plasma): A Phase I Trial of Triapine and Lutetium Lu 177 Dotatate in Combination for Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**		**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~4-5 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 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this sheet must be transferred also.*

Note the start and stop times of infusions in this form. Whenever the timing of drawing samples is dependent on the administration of drug, 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**
Cycle 1 Day 9 Triapine (TRI) administration. TRI Dose (mg):_____			
ASK SUBJECT time of prior dose			Ask for cycle 1 day 8 time of dose
pre sample			
TRI administration			
30 min post TRI			
60 min post TRI			
1h 30min post TRI			
2 h post TRI			
3 h post TRI			
4 h post TRI			
6 h post TRI			
8 h post TRI			

APPENDIX G IMAGE ACQUISITION AND ANALYSIS

Image Acquisition:

Contrast Computed Tomography: All pretreatment and post treatment imaging will include CT scans with the following parameters:

Liver protocol triple phase spiral CT studies including arterial, portal venous and 3 minutes delayed phases with image of the abdomen and pelvis acquired from base of lungs, above diaphragm, and includes the entire liver to iliac crest ± a single phase from above diaphragm to symphysis pubis (shown in figure 1). Scan parameters detailed in Table 1. Images will be reconstructed with thick (3-5 mm) and thin (1-1.5 mm) slice thickness.

Table 1: CT acquisition parameters		
	Contrast CT	Non-contrast CT*
Contrast	Omnipaque 350	None
Ref kV*	120	120
Ref. mAs	150-200	88
Care kV	On	On
Pitch	0.6-1	1.5
FOV	400	500
*** Part of the PET/CT acquisition; kV= KiloVolt; mAs=Milli-Ampere second; FOV=Field of View**		

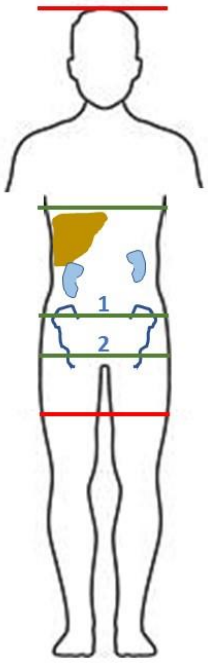

Figure 3: Illustration of CT scan coverage. Green lines represent CT coverages and red lines represent PET/CT coverage.

Positron Emission Tomography PET/CT: All patients will undergo at least one ^{68}Ga-DOTATATE PET/CT scan (**or** one 64-Cu Dotatate scan).

No specific patient preparations were required. Our study protocol was developed according to the SNMMI guidelines. Sixty minutes after the intravenous administration of a weight-based ^{68}Ga-DOTATATE activity (0.054 mCi/kg; or after administration of a 64-Cu Dotatate per FDA approved dosing), both PET and CT images of the torso from vertex to mid-thigh (Figure 1) will be acquired with the patient in supine position and arms placed above head. Patients will be asked to evacuate the bladder prior to scan acquisition.

CT images will be acquired without iodinated contrast administration with parameters illustrated in Table 1. Images with 5 mm slice thickness will be reconstructed using a standard soft tissue reconstruction kernel (standard filtered back projection B30s).

Following CT image acquisition, List-mode 3-dimensional PET images will be acquired with the following parameters; acquisition time of 4 minutes per table position, 168 x168 matrix and 50 x 50 cm FOV. CT-based attenuation correction was performed. After decay and scatter correction, PET data were reconstructed using ordered-subsets expectation maximization (OSEM) with 2 iterations and 8 subsets using the algorithm.

PET/CT Quality Control:

The Radiology Department at the University of Kentucky is an American College of Radiology Designated Diagnostic Imaging Center of Excellence (ACR DICOE). All required quality control (QC) procedures are performed regularly in both CT and PET/CT scanners.

Image Analysis:

DOTATATE Scan (Gallium-68 Dotatate or 64Cu Dotatate): Theranostics is a new term that describes the utility of targeting the same biological marker for both diagnosis and therapy by radiolabeling it once with a diagnostic radioisotope (gamma or positron emitter) and the other time using a therapeutic radioisotope (beta emitter). The main purpose of that is the ability to assess binding and efficiency of the targeted agent prior to administration of therapy. ^{68}Ga-DOTATATE, 64-Cu Dotatate and Lutetium Lu 177-DOTATATE are prominent examples of theranostics. They share the same biological targeting part, DOTATATE, which is a SSTR analogue. A study by Boy *et al.*, investigated correlation between maximum standardized uptake value (SUV_{max}) of lesion on ^{68}Ga-DOTATOC and SSTR expression on normal human tissues. The study found correlation between SUV_{max} and SSTR2 expression in normal human tissues (Boy *et al.*, 2011). The NETTER clinical trial (Strosberg *et al.*, 2017) proved significant survival benefit of ^{177}Lu-DOTATATE in patients with midgut NET, which facilitated its FDA approval. One of the inclusion criteria for the ^{177}Lu-DOTATATE treatment arm was confirmation of SSTR expression on target lesions by ^{111}In-Octreoscan. ^{68}Ga-DOTATATE is a PET/CT radiopharmaceutical that binds to SSTRs and has widely replaced ^{111}In-Octreoscan in assessment of well differentiated low grade NETs.

The Krenning score was used to evaluate SSTR binding in NETTER trial. It is based on comparing the uptake level of target and nontarget lesions to liver, spleen, and kidneys.

Krenning score	Criteria
Grade 1	Lesion uptake < normal liver uptake
Grade 2	Lesion uptake = normal liver uptake
Grade 3	Lesion uptake > normal liver uptake
Grade 4	Lesion uptake > spleen or kidney uptake

Baseline ^{68}Ga-DOTATATE (or 64-Cu Dotatate) PET/CT prior to therapy is standard-of-care and should be covered by insurance. Prior to administration of the novel treatment combination, ^{68}Ga-DOTATATE (or 64-Cu Dotatate) PET/CT will be performed for all patients to confirm adequate SSTR binding. To confirm receptor expression, Krenning's score will be applied to ^{68}Ga-DOTATATE (or 64-Cu Dotatate) PET/CT images. Advanced quantitative analysis will be performed as well and parameters such as SUV_{max}, SUV_{peak}, Molecular Tumor Volume (MTV), and Tumor Binding Index ($TBI = MTV * SUV_{mean}$) will be obtained per organ and for the patient. Advanced analysis to determine the optimum quantitative parameter that correlates with objective response measures, PFS, as well as overall survival (OS).

RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009)

The complete criteria are included in the published RECIST document (Eisenhauer EA et al., 2009), also available at http://www.eortc.be). A summary is provided below.

Measurability of Tumor at Baseline

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- Measurable tumor lesions: Must be accurately measured in at least one dimension (longest
- diameter in the plane of measurement is to be recorded) on CT scan (CT scan slice thickness no greater than 5 mm) with a minimum size of
    - Lesions: 10 mm longest diameter.
    - Lymph nodes: 15 mm in short axis.
- Non-measurable lesions: Non-measurable are all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions.
        - Leptomeningeal disease
        - Ascites
        - Pleural or pericardial effusion
        - Inflammatory breast disease
        - Lymphangitic involvement of skin or lung
        - Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by Methods of Measurements

Measurement of Lesions: All measurements should be recorded in metric notation, using calipers if clinically assessed.

Method of Assessment: 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.

Tumor Response Evaluation

- **Assessment of Overall Tumor Burden and Measurable Disease:** To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response can be assessed. Measurable disease is defined by the presence of at least one measurable lesion.
- **Baseline Documentation of 'Target' and 'Non-Target' Lesions:** When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on 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.

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, 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. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions will be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

Percent change in tumor burden is measured from baseline/Nadir using the following equation:

$$Percent\ change = \frac{\text{Sum at TPx} - \text{Sum in baseline/Nadir}}{\text{Sum in caseline/nadir}} * 100$$

Where TPx= Time point (1, 2, etc…); Nadir= the smallest sum (tumor burden).

Response Criteria:

Response criteria	Percent change
Complete response (CR)	Complete disappearance of all target lesions*
Partial Response (PR)	$\leq$ 30% reduction in tumor burden^
Progressive Disease (PD)	$\geq$ 20% increase in tumor burden+
Stable Disease (SD)	Neither suffuicient change in size to qualify for PR, nor for PD

***Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.**
^ Tumor Burden= Sum of target lesions
+ From Nadir (the smallest sum of target lesions, whether from baseline or subsequent scans)

Starting April 2022 there was a global shortage of IV contrast for CT scan. We recommended that sites shall try their best to obtain an equivalent imaging modality to get best possible data for tumor measurement. Due to unprecedented nature of the shortage, we are allowing alternative imaging (non-contrasted CT scans or MRI scans) in the interim till shortage has resolved. This will not trigger protocol deviation.

APPENDIX H TISSUE BIOPSY VERIFICATION

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Baseline

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____
Clinician Signature Date

_____
Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

Version: 1
Effective Date: 9/2019