**NCI Protocol #:** 10732

**Local Protocol #:** TBD

**ClinicalTrials.gov Identifier:** TBD

**TITLE:** Phase I Trial of ATR Inhibitor Camonsertib Combined with Stereotactic Body Radiation Therapy for Recurrent Head and Neck Squamous Cell Carcinoma

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**NCI-Supplied Agent:** Camonsertib (RP-3500) (NSC 851929)

**IND #:**  TBD

**IND Sponsor:** NCI DCTD/CTEP

**Protocol Type / Version # / Version Date:** Original / April 25, 2025

**SCHEMA**

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|  |  |  |
| --- | --- | --- |
| **Dose Escalation Schedule** | | |
| **Dose Level** | **Dose\*** | |
| **Camonsertib**  **(mg)** | **Stereotactic Body Radiation Therapy** |
| Level -1\*\* | 100 | 7 Gy in 4 fractions |
| Level 1 (Starting Dose) | 100 | 8 Gy in 4 fractions |
| Level 2 | 100 | 8 Gy in 5 fractions |
| Level 3 | 120 | 8 Gy in 5 fractions |
| Level 4 | 160 | 8 Gy in 5 fractions |
| Level 1B\*\* | 120 | 7 Gy in 4 fractions |
| Level 2B\*\* | 160 | 7 Gy in 4 fractions |
| \* Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.  \*\* Deescalated dose levels | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Regimen Description** | | | | | |
| **Agent** | **Premedications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Camonsertib | N/A | \* | PO in the morning | Once per day on the day of and day following radiation | N/A |
| Stereotactic Body Radiation Therapy | N/A | \* | N/A | Twice weekly  2-3 days apart |
| \*Doses as appropriate for assigned dose level. | | | | | |

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# OBJECTIVES

## Primary Objectives

* + 1. To evaluate the safety and tolerability of camonsertib with concurrent head and neck stereotactic body radiotherapy (SBRT) reirradiation for patients with recurrent head and neck squamous cell carcinoma (HNSCC).
    2. To determine the recommended phase 2 dose (RP2D) of camonsertib in combination with concurrent SBRT in these patients.

## Secondary Objectives

* + 1. To assess overall response rate within the radiation therapy field for patients treated with camonsertib and SBRT. Although the clinical benefit of camonsertib has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit. The patient will therefore be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.
    2. To assess progression-free survival (PFS) with camonsertib and SBRT in patients with recurrent or new primary HNSCC within a previously irradiated field*.*

## Exploratory Objectives

* + 1. To identify predictive biomarkers of response to camonsertib and SBRT, including, but not limited to genetic alterations of *ATM* and *TP53*, HPV status, tumor mutational load, and circulating tumor DNA.
    2. To characterize the pharmacokinetics (PK) of camonsertib.
    3. To evaluate the quality of life of patients receiving camonsertib and SBRT for recurrent or new primary HNSCC within a previously irradiated field.

# BACKGROUND

## Study Disease

Head and neck squamous cell carcinoma (HNSCC) includes a group of malignancies involving the oral cavity, pharynx, hypopharynx, larynx, nasal cavity, and paranasal sinuses that account for the eighth most common cancer diagnosis. With 771,037 new cases and 384,631 deaths in 2022 per GLOBOCAN estimates, HNSCC accounts for roughly 3.8% of cancer diagnoses and deaths worldwide (Bray et al., 2024). In the United States, oral cavity, larynx and pharynx cancers account for approximately 3.4% of new cancer diagnoses, with 66,920 new cases and 15,400 deaths in 2023 (Seigel et al., 2023). Tobacco and alcohol use are major contributing factors to development of HNSCC. Human papillomavirus (HPV), primarily type 16, represents another etiologic factor for a rising number of HNSCC cases, particularly oropharyngeal cancers, in North America and Western Europe (Chaturvedi et al., 2011; O’Sullivan et al., 2016). While clinical outcomes are generally favorable for HPV-related oropharyngeal cancer, prognosis remains poor for HPV-negative locally advanced HNSCC, with recurrence rates approaching 40% (Ang et al., 2010; Ang et al., 2014; Huang et al., 2015). Surgery or radiotherapy (RT) alone is typically used to treat early-stage head and neck cancer, while locally advanced disease generally requires cisplatin-based chemoradiation with or without surgical resection. Unfortunately, outcomes have been relatively stagnant for patients with locally advanced HPV-negative HNSCC over the past 20 years (Wen and Grandis, 2015), and locoregional recurrence is a major cause of mortality from HNSCC. Although immunotherapy with programmed cell death protein-1 (PD-1) inhibitors (pembrolizumab and nivolumab) are FDA-approved for use in recurrent or metastatic head and neck cancer, treatment options for recurrent disease after standard therapies remain limited. There is therefore an unmet need for new therapeutic approaches for patients with recurrent HNSCC.

## CTEP IND Agent (Camonsertib [RP-3500])

Camonsertib (RP-3500) is a potent and selective small molecule ataxia telangiectasia and Rad3-related protein (ATR) inhibitor (Investigator’s Brochure, 2024). ATR inhibitors elicit cell death in rapidly growing tumor cells by exacerbating endogenous replication stress and replication fork collapse and by disabling cell cycle checkpoints.

* + 1. Nonclinical Summary

Camonsertib shows pM activity in biochemical assays and low nM cytotoxic activity in a panel of cancer cell lines including colon adenocarcinoma, non-small cell lung adenocarcinoma, pancreatic adenocarcinoma, and triple negative breast cancer (Investigator’s Brochure, 2024). Camonsertib demonstrated selectivity over >300 kinases in biochemical and cell-based assays, even within the closely related phosphatidylinositol 3' kinase-related kinase (PIKK) family. Single agent efficacy was demonstrated in several models in vivo, and exploration of intermittent dose schedules determined that both once daily (QD) × 5 and QD × 3 doses were most efficacious with minimal hematological toxicity (anemia). Inhibition of phosphorylation of the ATR substrate checkpoint kinase 1 (CHK1) and increased phosphorylation of the DNA damage response (DDR) marker pKAP1 were demonstrated in tumor tissue from camonsertib treated mice.

* + 1. Clinical Summary

Camonsertib was well-tolerated as a monotherapy in a recent Phase 1/2a trial in patients with advanced solid tumors with loss-of-function mutations in DNA damage response genes, including ataxia telangiectasia-mutated (*ATM*) (Fontana et al., 2024; Yap et al., 2023). The most common adverse events were anemia, fatigue, neutropenia, thrombocytopenia, and nausea. Among patients who received >100 mg/day of camonsertib (biologically effective dose), 13% (13 of 99) demonstrated tumor response. The response rate among patients with ATM loss of function was 12% (4 of 34). The preliminary recommended phase 2 dose based on this study was 160 mg once daily 3 days on, 4 days off (160 3/4), and the dose-optimization phase included two additional step-down regimens: 120 mg daily 3 days on, 4 days off (120 3/4) and 160 mg daily 3 days on, 4 days off for 2 weeks on and 1 week off (160 3/4, 2/1w). Due to significantly lower risk of grade 3 anemia in the 160 3/4, 2/1w group compared to the 160 3/4 group without any reduction in antitumor activity, this intermittent weekly schedule was recommended for future camonsertib monotherapy studies.

## Stereotactic Body Radiotherapy (SBRT)

Stereotactic body radiation therapy (SBRT) is a technique which uses image guidance to deliver high doses of radiation capable of ablating tumors. Because there is greater precision in dose delivery and a smaller volume of normal tissue irradiated, the normal tissue toxicities of SBRT are usually less than those of conventional 3-dimensional (3D) and intensity-modulated radiation therapy (IMRT) approaches.

* + 1. Clinical Summary

The safety of head and neck reirradiation with SBRT at a dose of 40 Gy in 5 fractions, has been previously shown in a prospective phase II trial (Vargo et al., 2017). Patients received 40-44 Gy in 5 fractions with concurrent cetuximab, and no grade 4+ toxicities were observed. In a multi-institutional analysis that included 197 patients with recurrent HNSCC previously irradiated to >40 Gy who were treated with SBRT reirradiation to a median dose of 40 Gy in 5 fractions, grade 4+ acute toxicity was 0.5% (Vargo et al., 2018). Additionally, a cohort study that included 137 patients treated with head and neck SBRT reirradiation to a median dose of 45 Gy in 5 fractions (range 36 – 47.5 Gy) reported one grade 5 toxicity secondary to bone and soft tissue necrosis with death at 23.3 months after SBRT (Diao et al., 2021). The proposed dosing for the current study aligns with NCCN Guidelines (version 1.2025) indicating that current SBRT reirradiation schedules range from 35 to 44 Gy in 5 fractions.

## Rationale

Tumor recurrence within the radiation treatment field is the most common pattern of failure for HNSCC, suggesting persistence of radioresistant clones. Up to 50% of HNSCCs exhibit distal 11q loss, which has been associated with poor prognosis and reduced radiosensitivity (**Figure 1**) (Ambatipudi et al., 2011; Parikh et al., 2007; Sankunny et al., 2014). Notably, the distal 11q locus contains several DNA damage response genes including ATM kinase. DNA double-strand breaks trigger activation of the ATM kinase, leading to phosphorylation of checkpoint kinase 2 (CHK2) and activation of downstream signaling to cause cell cycle arrest, DNA repair, and/or apoptosis (**Figure 2**). Thus, ATM plays an active role in cellular response to DNA-damaging agents, such as radiation therapy and cisplatin. ATM copy number loss may increase dependence on the ATR pathway for response to DNA damage. Single-strand DNA breaks and stalled replication forks trigger activation of the ATR kinase, which signals through CHK1 to regulate progression through the S-phase and G2/M checkpoints. Similar to CHK2, activated CHK1 signaling can lead to cell cycle arrest, DNA repair and/or apoptosis (**Figure 2**). Due to rapid proliferation rates, HNSCC cells often demonstrate replication stress and dependence on ATR/CHK1 signaling to process through S phase. Interestingly, a study utilizing human oral squamous cell carcinoma cell lines demonstrated that in vitro inhibition of ATR/CHK1 signaling enhanced radiosensitivity in cells with distal 11q loss (Sankunny et al., 2014). This suggests that targeting ATR may improve radiation response in HNSCC, particularly in tumors with distal 11q loss.

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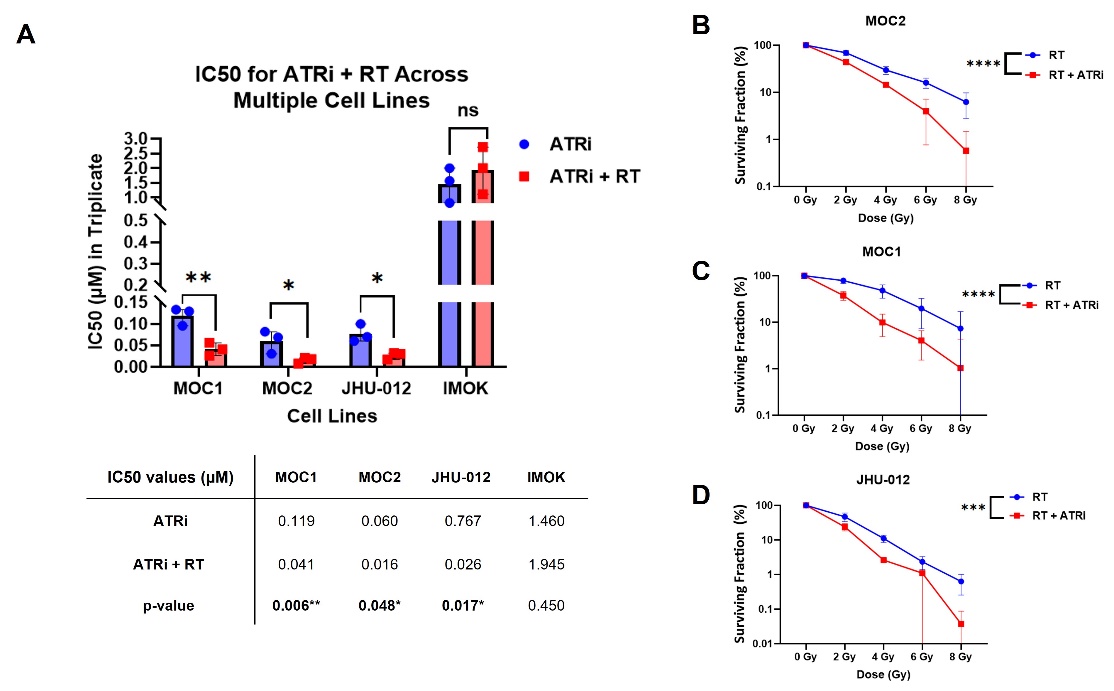
**Figure 1**. Clonogenic assay demonstrating relative radioresistance of human oral cavity squamous cell carcinoma cell lines with distal 11q loss relative to cell lines without distal 11q loss.

A diagram of a dna strand

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**Figure 2**. Schematic of ATM and ATR-mediated DNA damage response pathways.

Numerous studies have demonstrated that ATR inhibitors can radiosensitize cancer cells, including HNSCC (Bright et al., 2024; Karukonda et al., 2022; Odhiambo et al., 2024; Schnoell et al., 2023; Tu et al., 2018). Odhiambo et al. recently demonstrated that the ATR inhibitor BAY 1895344 has single-agent cytotoxic activity against several HPV-negative HNSCC cell lines, in addition to causing significant radiosensitization (**Figure 3**) (Odhiambo et al., 2024). Notably, the half maximal inhibitory concentration (IC50) for BAY 1895344 with or without RT was ~10-fold lower for HNSCC cell lines compared to an immortalized oral keratinocyte cell line (IMOK), suggesting a favorable therapeutic window. The combination of BAY 1895344 with fractionated radiation therapy also significantly improved tumor growth delay (data not shown) and overall survival in the relatively radioresistant HPV-negative MOC2 syngeneic mouse model of HNSCC (**Figure 4)** and JHU-012 xenograft model of HNSCC (data not shown).



**Figure 3**. **(A)** HNSCC cell lines (MOC1, MOC2, JHU-012) or immortalized oral keratinocytes (IMOK; normal tissue control) were treated with vehicle or serial dilutions of BAY 1895344 (ATRi) for 30 min before sham RT (blue circle) or RT (4 Gy, red square). After 72h, metabolic activity was evaluated by MTT assay. IC50s between ATRi and ATRi + RT were compared by unpaired T test (ns, not significant, \*p<0.05, \*\*p<0.01). Clonogenic assays were performed on MOC2 **(B)**, MOC1 **(C)**, and JHU-012 **(D)** cells pre-incubated with vehicle (RT, blue circle) or 100nM BAY 1895344 (ATRi + RT, red square). Vehicle/drug-containing media was replaced with fresh media after 4h. After 7-10 days, fixed cells were stained with Coomassie blue and colonies counted. Percent surviving fraction is shown, with RT compared to ATRi + RT by 2-way ANOVA.

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**Figure 4**. C57BL/6 mice were induced with the MOC2 syngeneic HNSCC cell line in the hind limb. When hind limb IM tumors reached >45mm3 (Day 0), mice were randomized to Control (blue dotted-dashed line), ATRi (red solid line), RT (green dashed line for survival), and ATRi + RT (purple upside-down triangle for growth delay; purples dotted line for survival). Mice received vehicle or 40mg/kg BAY 1895344 (ATRi; 3 doses surrounding each fraction) with sham RT or 8 Gy for 3 fractions with 4d between RT fractions. Kaplan-Meier survival curves are shown with pairwise group comparisons by Log-Rank test (ns=not significant, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001).

In addition to its radiosensitizing effects, ATR inhibition has also been shown to increase antigen presentation, immune cell infiltrate, and anti-tumor T cell activity when combined with RT (Dillon et al., 2019; Patin et al., 2024; Sheng et al., 2020; Vendetti et al., 2023; Vendetti et al., 2018). The combination of ATR inhibitor AZD6738 and RT caused significant tumor growth delay in a syngeneic transplant mouse model of colorectal cancer (CT26) and autochthonous model of lung adenocarcinoma (*KrasG12D/Twist1*). A subset of mice with CT26 tumors exhibited a complete response to AZD6738 and RT and were resistant to tumor rechallenge, indicative of immunologic memory. The combination of RT and ATR inhibition with AZD6738 also led to increased CD8+/Treg ratio within tumors (Vendetti et al., 2018). Vendetti et al., recently demonstrated that the duration of ATR inhibitor therapy combined with radiation therapy impacts the anti-tumor immune response (Vendetti et al., 2023). Short course AZD6738 (3 days) with concurrent radiation therapy (2 Gy x 2) promoted expansion of tumor antigen-specific CD8+ T cells and increased CD8+ T cell activation in the draining lymph nodes in a CT26 model, whereas prolonged AZD6738 (9 days) abolished the adaptive CD8+ T cell response. Importantly, proliferation of CD8+ T cells rebounded within 4 days of discontinuing the ATR inhibitor. The combination of radiation therapy (2 Gy x 2), short course AZD6738 (3 days), and anti-PD-L1 therapy significantly improved overall survival compared to radiation therapy alone, with a subset of mice being cured and immune to tumor-rechallenge. However, long course AZD6738 (9 days) combined with radiation therapy and anti-PD-L1 therapy did not improve survival compared to radiation therapy alone.

Given the limited activity of ATR inhibitor monotherapy in patients with solid tumors, combination with DNA-damaging agents such as radiation therapy warrants further investigation. Building on the preclinical data summarized above, the study team previously conducted a phase I clinical trial (NCT04576091; ETCTN 10405) to evaluate the safety and efficacy of ATR inhibitor BAY 1895344 combined with stereotactic body radiation therapy (SBRT) and pembrolizumab for patients with recurrent or new primary HSNCC within a previously irradiated field. Patients received one cycle of pembrolizumab with 30 mg BAY 1895344 administered twice daily 3 days on/4 days off for 2 weeks. Based on preclinical data, pembrolizumab was administered prior to BAY 1895344. During the second cycle of pembrolizumab, patients received three fractions of radiation therapy (8 Gy/fraction, 2-3 days between fractions) with 10 mg BAY 1895344 administered twice daily surrounding each dose of radiation therapy. A total of 6 patients were treated prior to early study closure due to discontinuation of the drug BAY 1895344. No dose-limiting toxicities were observed. The overall response rate was 83.3%, with 4 complete responses (CR) and 1 partial response (PR). Two patients (one with initial complete response and one with partial response) have subsequently had disease progression within the radiation treatment field. One patient with a complete response had experienced disease progression on pembrolizumab prior to enrollment and has no evidence of disease at two years post-treatment. The 83.3% overall response rate (66.7% CR and 16.7% PR) compares favorably to the 51% overall response rate (21% CR, 30% PR) reported in a Phase II clinical trial of SBRT reirradiation (40 Gy/5 fractions) with concurrent cetuximab for recurrent HNSCC (Vargo et al., 2015), despite the radiotherapy dose being 40% lower in the BAY 1895344 clinical trial. The current study is a similar Phase I clinical trial with camonsertib and SBRT reirradiation.

Since current clinical data regarding whether immune checkpoint inhibition augments the outcomes of radiation therapy are indeterminate and the best sequence of adding anti-PD-1 therapy to radiation therapy remains unclear, pembrolizumab will not be included in this study. Given the two in-field progressions in the prior trial, we plan to increase the total radiation therapy dose by changing the SBRT regimen from three fractions to four fractions for the initial dose cohort, with a further increase to a standard dose of 40 Gy in 5 fractions if the four-fraction regimen is tolerated. The safety of head and neck reirradiation with SBRT at a dose of 40 Gy in 5 fractions has been previously shown in a prospective phase II trial (Vargo et al., 2015), multi-institutional analysis (Vargo et al., 2018), and cohort study (Diao et al., 2018) discussed in section 2.3.1.

No ongoing clinical trials are evaluating camonsertib in combination with radiation therapy, nor are any camonsertib trials specifically enrolling patients with HNSCC. Given the limited treatment options and median survival <15 months for patients with recurrent unresectable HNSCC, the current proposal will focus on this patient population. Furthermore, HNSCC commonly demonstrates ATM deficiency due to distal 11q loss, and ATM loss has been associated with response to camonsertib (Ng et al., 2024; Yap et al., 2023). Additionally, preclinical studies demonstrate that ATR inhibition radiosensitizes HNSCC. Finally, our small phase I trial of the ATR inhibitor BAY 1859344 in combination with pembrolizumab and stereotactic body radiation therapy (SBRT) reirradiation (ETCTN 10405) demonstrated promising responses in patients with recurrent or new primary HNSCC without any dose-limiting toxicities. Thus, the current trial evaluating camonsertib with concurrent SBRT reirradiation has strong rationale and addresses an unmet clinical need. Potential safety concerns with this combination include increased risk of acute and late RT-related toxicities, including mucositis, xerostomia, fatigue, dysphagia/feeding tube requirement to meet nutritional needs, osteoradionecrosis of the mandible, fistula formation, and carotid blowout, although these concerns have been ameliorated with the data generated during our preceding trial with BAY 1895344.

## Correlative Studies Background

* + 1. Whole Exome Sequencing (WES)

*Biologic rationale*: WES of tumor tissue (with blood-based WES of germline cells to facilitate mutation calling) provides comprehensive insights into the genetic landscape of each patient’s tumor, enabling the identification of mutations that may influence treatment response. This approach can help understand how genetic alterations affect therapeutic outcomes and identify novel biomarkers of response. Prior studies have shown that patients with mutations in DNA damage response genes, e.g., *ATM*, are more likely to respond to ATR inhibition. Identifying mutations that correlate with response will inform patient selection/personalized treatment strategies for a subsequent phase II trial if results of this trial are promising.

*Hypothesis*: We hypothesize that WES of tumor tissue will reveal actionable mutations that correlate with clinical response to camonsertib + RT.

*Relevant preclinical and clinical data*: Preclinical studies have shown that WES can identify genetic alterations predictive of response to targeted therapies. Clinical trials, such as the EXaCT-1 study, have demonstrated the utility of WES in guiding therapeutic decisions for patients with advanced cancer by identifying actionable mutations and novel biomarkers of response (Beltran et al., 2015). A recent preclinical study demonstrated synergy between ATR inhibition with camonsertib and radiation therapy in Atm-null cell lines. A phase I trial showed response to single-agent camonsertib in DNA damage response-deficient tumors, with the best results in patients with bilallelic loss of function alterations in *ATM* (Yap et al., 2023).

* + 1. WES (blood-based)

*Biologic rationale:* Blood-based WES serves as a critical control for distinguishing between germline and somatic mutations identified through tissue-based WES of tumors. By analyzing blood samples, we can identify and exclude germline mutations, thereby allowing us to focus on somatic mutations that are specific to the tumor. This approach is essential for accurately interpreting the genetic landscape of the tumor and understanding how somatic mutations may influence treatment response.

*Hypothesis:* We hypothesize that blood-based WES will effectively differentiate germline from somatic mutations, enabling us to precisely identify tumor-specific genetic alterations that correlate with treatment response and disease progression.

*Relevant preclinical and clinical data:* Studies have demonstrated the utility of blood-based sequencing in distinguishing somatic from germline mutations, which is crucial for personalized medicine approaches. By comparing blood and tumor WES data, researchers can identify actionable somatic mutations that may inform therapeutic decisions and predict treatment outcomes (Feng et al., 2022).

* + 1. Camonsertib PK

*Biologic rationale*: Understanding the PK of camonsertib is crucial for optimizing dosing regimens and ensuring that patients receive biologically effective doses. PK studies help in determining how camonsertib is absorbed, distributed, metabolized, and eliminated. Camonsertib is a relatively novel agent, and the proposed PK studies will further define the properties in a homogeneous population.

*Hypothesis*: We hypothesize that camonsertib exposure will be associated with toxicity and efficacy.

*Relevant preclinical and clinical data*: Clinical data from ongoing phase 1 trials of camonsertib have shown a linear PK profile with low intra-patient and inter-patient variability, supporting the hypothesis that camonsertib can achieve biologically effective concentrations at doses above 100 mg/day with oral administration (Yap et al., 2023).

* + 1. Circulating Tumor DNA (ctDNA)

*Biologic rationale*: ctDNA is a promising biomarker for monitoring tumor burden and response to therapy. Changes in ctDNA levels can reflect treatment-induced tumor cell death and may predict clinical outcomes. This approach offers a non-invasive means of monitoring genetic changes over time.

*Hypothesis*: We hypothesize that longitudinal analysis of ctDNA will provide early indicators of treatment response and disease progression.

*Relevant preclinical and clinical data*: Clinical studies have demonstrated that early changes in ctDNA levels can predict treatment response and outcomes. For example, rapid clearance of ctDNA has been associated with favorable clinical responses in various cancers (Hilke et al., 2020; Ng et al., 2018). In the context of camonsertib, preliminary data suggest that molecular responses, defined by changes in ctDNA, occur early in treatment and correlate with clinical benefit (Yap et al., 2023).

# PATIENT SELECTION

## Eligibility Criteria

* + 1. Patients must have histologically confirmed recurrent or metachronous (second primary) unresectable head and neck squamous cell carcinoma involving the oral cavity, oropharynx, larynx, hypopharynx, and/or paranasal sinus, or cervical lymphadenopathy with unknown primary. **Core needle biopsy (preferably at least three 18-gauge cores) or incisional biopsy is preferred over FNA for diagnosis of recurrent disease or new primary head and neck squamous cell carcinoma to provide sufficient tumor tissue for correlative studies.** Unresectable refers both to patients who have declined surgery and patients deemed unresectable by otolaryngology. This includes patients for whom curative resection is medically contraindicated and/or would be associated with excessive surgical risk (as deemed by the consulting otolaryngologist) or undue surgical morbidity (*e.g.*, total glossectomy, laryngectomy, and/or major resection requiring free flap reconstruction).
    2. Patients must have recurrent disease within a previously irradiated area (radiotherapy to dose ≥30 Gy; in-field recurrence).
    3. Patients must have completed prior radiotherapy at least 6 months prior to enrollment. Due to safety concerns, reirradiation within less than 6 months to the head and neck is very rarely recommended per standard of care.
    4. Patients must have measurable disease (at least one measurable lesion) as per RECIST version 1.1. **Baseline imaging must include neck CT (preferably contrast-enhanced) and chest CT or skullbase to midthigh PET/CT** (preferably with contrast-enhanced neck CT if diagnostic contrast-enhanced neck CT not available).Patients who have undergone surgery aside from biopsy may be included if gross disease is present within the surgical resection bed or at another site.
    5. Age ≥18 years. Because no dosing or adverse event data are currently available on the use of camonsertib in combination with radiotherapyin patients <18 years of age, children are excluded from this study.
    6. ECOG performance status ≤2 (Karnofsky ≥60%, see [Appendix A](#appendix_A)) with life expectancy >3 months.
    7. Patients must have adequate organ and marrow function as defined below:
* leukocyte count ≥3,000/mcL
* absolute neutrophil count ≥1,500/mcL
* platelets ≥100,000/mcL
* hemoglobin ≥9 g/dL or ≥5.6 mmol/L without transfusion or erythropoietin dependency (within 7 days of assessment)
* serum bilirubin ≤1.5 × institutional upper limit of normal (ULN) (If total serum bilirubin >1.5 × institutional ULN, then direct bilirubin must be <ULN)
* AST(SGOT)/ALT(SGPT) ≤3 × institutional ULN
* albumin >2.5 mg/dL
* glomerular filtration rate (GFR) ≥60 mL/min/1.73 m2 (see [Appendix B](#appendix_B))

1. *GFR can be measured directly or estimated using the site’s institutional standards.*
   * 1. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
     2. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
     3. 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.
     4. 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 (e.g., basal cell carcinoma, early-stage differentiated thyroid carcinoma, low-risk prostate cancer, ductal carcinoma in situ of the breast, squamous cell carcinoma of the skin that has undergone potentially curative therapy, *in situ* cervical cancer) are eligible for this trial.
     5. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class II or better.
     6. Ability to take pills by mouth.
     7. The effects of camonsertib on the developing human fetus are unknown. For this reason and because ATR inhibitors and radiation are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after completion of camonsertib administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
     8. Ability to understand and the willingness to sign a written informed consent document. Legally authorized representatives may sign and give informed consent on behalf of study participants.

## Exclusion Criteria

* + 1. 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.
    2. Patients who are receiving any other investigational agents for a current cancer diagnosis.
    3. Patients with distant metastatic disease.
    4. Patients who have received more than one prior course of head and neck radiotherapy.
    5. Patients who have disease surrounding >180 degrees of the carotid artery.
    6. Patients with tumors invading the mandible or tumors with gross skin involvement (i.e., tumor ulceration through the skin).
    7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to camonsertib or radiation.
    8. Patients with uncontrolled intercurrent illness or any other significant condition(s) that would make participation in this protocol unreasonably hazardous.
    9. Pregnant women are excluded from this study because camonsertibisan ATR inhibitor 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 camonsertib*,* breastfeeding should be discontinued if the mother is treated withcamonsertib. These potential risks may also apply to other agents used in this study.
    10. Patients diagnosed with scleroderma.

## 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>.

# REGISTRATION PROCEDURES

## Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at <https://ctepcore.nci.nih.gov/rcr/>. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this trial.

* Investigator (IVR): MD, DO, or international equivalent,
* Non Physician Investigator (NPIVR): advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),
* Associate Plus (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, and
* Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

* Addition to a site roster,
* Selection as the treating, credit, or consenting person in OPEN,
* Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
* Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

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

Refer to the [NCI RCR](https://ctep.cancer.gov/investigatorResources/default.htm) page on the [CTEP website](https://ctep.cancer.gov) for additional information. For questions, please contact the **RCRHelp Desk** by email at [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov).

## Site Registration

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

**IRB Approval**

Sites participating through the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB’s approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [CTSURegPref@ctsu.coccg.org](mailto: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 email ([CTSURegPref@ctsu.coccg.org](mailto:CTSURegPref@ctsu.coccg.org)) or by calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

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

**Additional Requirements**

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

* An active Federal Wide Assurance (FWA) number,
* An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
* An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
* Compliance with all applicable protocol-specific requirements (PSRs).
  + 1. Downloading Site Registration Documents

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

* Log in to the CTSU members’ website ([https://www.ctsu.org](https://www.ctsu.org/)),
* Click on *Protocols* in the upper left of the screen
  + Enter the protocol number in the search field at the top of the protocol tree, or
  + Click on the By Lead Organization folder to expand, then select LAO-PA015 - UPMC Hillman Cancer Center LAO, and protocol number 10732,
* Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)
  + 1. Protocol Specific Requirements For 10732 Site Registration
* A Study Initiation Visit (SIV) or Site Initiation Teleconference (SIT) is required for each participating site prior to activation. The local site PI must participate on the call with the site research team. To schedule a SIV or SIT, please email the study team email listed on the front page of the protocol. SIV checklist and sign-in sheet must be completed and signed by the site study PI and sent back to the Protocol Liaison of the lead LAO.
  + - 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. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time
    - This training will need to be completed before the first patient enrollment at a given site.
* Only institutions that have a credential from IROC for this study may activate this study. The IROC credential for this study will be derived from prior IROC evaluation of sites' ability to deliver radiation therapy in National Clinical Trial Network (NCTN) studies employing similar radiation techniques. Before study activation, IROC will develop the list of institutions eligible to open this study and will make the list publicly available. To activate the study, an eligible site must request a credential letter from IROC and must submit the letter to the CTSU at the time of site activation.
* RT-Specific Pre-Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

|  |  |  |  |
| --- | --- | --- | --- |
| **Credentialing Requirements** | **Web Link for Procedures and Instructions: www.irochouston.meanderson.org** | | |
| **Treatment Modality** | | **Key Information** |
| **Photons** |  | |
| Facility Questionnaire |  | The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link. | |
| Credentialing Status Inquiry Form |  | To determine if your institution has completed the requirements above, please complete a “Credentialing Status Inquiry Form” found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org** ). | |
| Phantom Irradiation |  | An IMRT Head and Neck phantom irradiation provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org)**. Note that an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as TomoTherapy and CyberKnife | |
| IGRT Verification Study |  | Institutions must be credentialed for boney anatomy IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing. | |
| **Credentialing Issued to:** | | | |
| Institution |  | IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated. | |

* + 1. Submitting Regulatory Documents

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

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

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

**Delegation of Tasks Log (DTL)**

Each site must complete a protocol-specific DTL using the DTL application which is accessible via the Delegation Log link on the CTSU members’ website or directly at <https://dtl.ctsu.org>. 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 describes DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

The DTL for this study has training requirements as follows:

1. All staff assigned the Rave CRA task on the DTL for this study must complete the *Theradex Specimen Tracking System (STS) Training* course. The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study with the same course requirement, the training does not need to be completed again. However, new versions of the Specimen Tracking System may require new training.

A task-related training requirement is satisfied by completing the course in the Compliance, Learning, and SOP Solutions (CLASS) application at <https://classlms.org>; until that takes place, the task assignment will remain in a Pending status.

* When a Rave CRA is assigned the task on an ETCTN DTL, the system will check to see if they have completed the appropriate course, and if not, they will be automatically enrolled in the course. They will receive an enrollment email from [CLASSHelpDesk@westat.com](mailto:CLASSHelpDesk@westat.com) that will include instructions on how to access the course.

When an assignee completes the necessary course, their completion will be automatically communicated from CLASS to the DTL application and the task status will go to Active or Awaiting CI Approval, depending on the situation (please allow up to four hours for this to happen). The DTL cannot be submitted for CI sign-off until the minimum number of persons are assigned to the task(s) and have met all task requirements including any training requirements.

* + 1. Checking Site Registration Status

Site’s registration status may be verified on the CTSU members’ 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.

## Patient Registration

* + 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:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
* 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.
* 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, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Boards (IRB) number used on the site’s IRB approval on their Form Food and Drug Administration (FDA) 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

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

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

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

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment 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.

* Availability of a pre-treatment tissue specimen for correlative studies must be confirmed by site staff before enrollment.
  + 1. Special Instructions for Patient Enrollment

Not applicable

* + 1. 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](mailto:ctsucontact@westat.com).

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; [CTMSSupport@theradex.com](mailto:CTMSSupport@theradex.com).

## General Guidelines

Following registration, patients should begin protocol treatment within 14 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.

# BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

## Summary Table for Specimen Collection

| **Time Point** | **Specimen** | **Send Specimens To:** |
| --- | --- | --- |
| **Archival (mandatory)** | | |
| Dose Escalation & Dose Expansion | * Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)1   If a block is not available, then submit:   * 1 H&E stained slide (3-5 µm) * 30-50 unstained, uncharged, air-dried slides (10 µm). If not feasible, then a minimum of 20 unstained air-dried uncharged slides (10 µm) should be submitted with a minimum tumor content of 30-40%2. | EET Biobank |
| **Baseline** | | |
| Dose Escalation Only | * 10 mL blood in Streck cfDNA tube (mandatory) | EET Biobank |
| Dose Expansion Only | * 20 mL blood in Streck cfDNA tubes (mandatory) | EET Biobank |
| **Day 1** | | |
| Dose Escalation and Dose Expansion:   * Pre-dose, * 0.5 hr post-dose, * 1 hr post-dose, * 1.5 hr post-dose, * 2 hr post-dose, * 4 hr post-dose, * 6 hr post-dose, * 8 hr post-dose | * 3-5 mL blood in an EDTA tube, processed to plasma, and frozen (mandatory) | Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins |
| **Day 2** | | |
| Dose Escalation and Dose Expansion:   * 24 hr after D1 dose, pre-D2 dose | * 3-5 mL blood in an EDTA tube, processed to plasma, and frozen (mandatory) | Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins |
| **Week 7** | | |
| Dose Expansion Only | * 20 mL blood in Streck cfDNA tubes (optional) | EET Biobank |
| **Disease Progression** | | |
| Dose Expansion Only | * 20 mL blood in Streck cfDNA tubes (optional) | EET Biobank |
| 1 For archival tissue, **a copy of the anatomic pathology report corresponding to the tissue collection procedure 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 2–51).  2**Submission of specimens with <30% tumor content may not provide sufficient material for analysis.** | | |

## Summary Table(s) for Interventional Radiologist for Research Biopsies

Not applicable.

## Specimen Procurement Kits and Scheduling

* + 1. Specimen Procurement Kits

Kits for the collection and shipment of select specimens to the EET Biobank can be ordered online via the Kit Management system: (<https://kits.bpc-apps.nchri.org>). Institutional supplies will be used for the collection and shipment of all other specimens.

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 EET Biobank. Institutional supplies must be used for all other specimen collection and processing.

* + 1. Scheduling of Specimen Collections

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

* Tissue submitted as FFPE (blocks or slides) can be collected on any day but must be shipped to the EET Biobank on Monday through Thursday.
* Fresh blood specimens may be collected and shipped Monday through Friday.

## Specimen Tracking System Instructions

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

* All biospecimens collected for this trial must be submitted using the ETCTN STS unless otherwise noted.
* The system is accessed through Rave user roles: “Rave CRA” and “Rave CRA (Labadmin)” for data entry at the treating institutions. The “Biorepository” role is assigned to users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).

**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 on use of the STS can be found below.

* + 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 without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when available. **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](mailto:STS.Support@theradex.com).

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

* + 1. Specimen Labeling
       1. Blood Specimen Labels

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

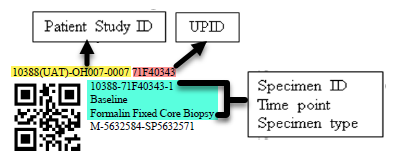
* Patient Study ID
* Universal Patient ID (UPID)
* Specimen ID (automatically generated by Rave)
* Time point
* Specimen type (e.g., blood, plasma)
* Collection date (all specimens) and time (only blood for PK)(to be added by hand)
  + - 1. Tissue Specimen Labels

Include the following on all tissue specimens (e.g., FFPE block or slides):

* 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)
* 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 (FFPE tissue, when applicable)
* Collection date (to be added by hand)
* Slide section number (only if archival tissue is submitted as slides) (to be added by hand)
  + - 1. 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.** The last line on the example label is for the handwritten date and optional time.

* + 1. Overview of Process at Treating Site
       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.

* + - 1. 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 (all specimens) and time (only blood for PK)on each label. After collection, store labeled specimensas described in Section 5.5.
* 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), and 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 the 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** CRFto 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.

## Specimen Collection

* + 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:

* Please submit the most recent archival tissue that is available.
* FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size recommendation is as follows:
  + Surface area: 25 mm2 is optimal. Minimum is 5 mm2.
  + Volume: 1 mm3 optimal. Minimum volume is 0.2 mm3, 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 – 50) 10 µm unstained air-dried uncharged slides (preferred). If not feasible, then a minimum of twenty (20) 10 µm unstained air-dried uncharged slides should be submitted with a minimum tumor content of at least 30%. **Submission of specimens with <30% tumor content may not provide sufficient material for analysis.**

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 2–51)*.*

See Section 5.4.2 for labeling instructions.

* + 1. Blood Collection
       1. Collection of Blood in Streck cfDNA Tubes

1. Label one or two 10 mL Streck cfDNA tube(s) according to the instructions in Section 5.4.2.
2. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. 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.
   * + 1. Collection of Blood in EDTA Tubes for Plasma Processing

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

Document exact dose times (start and stop times in case of infusions) and exact times of blood draws per [Appendix E](#appendix_E). Listed sample time points should be used as an approximate target. Small deviations are allowed, as long as the actual time drawn is accurately documented.

1. Collect in a ~3-5 mL purple top tube (*e.g.* BD vacutainer 367861 plastic 13 x 75 mm 4 mL tube).
2. Invert the vacutainer tubes several times to mix blood with EDTA anticoagulant and immediately place on wet ice.
3. Processing should begin within 30 minutes of collection.
4. Samples should be centrifuged for 10 min at approximately 1000 x *g* in a refrigerated tabletop centrifuge to produce plasma.
5. The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes (see Section 5.4.2.1; label should include at a minimum the Study ID, Patient ID, sample type, sample collection date, exact sample collection time), and stored at -70 °C until shipment.

## Shipping Specimens from Clinical Site to the EET Biobank

* + 1. General Shipping Information
       1. **Required Forms for Specimen Submissions**

| **Specimen** | **Required Forms** |
| --- | --- |
| Archival Tissue | 1. Shipping List 2. Anatomic Pathology Report corresponding to the tissue collection procedure |
| Other (blood) | 1. Shipping List |

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

Minimum required personally identifiable information:

* Remove patient identifiers such as name, date of birth, medical record number, social security number, and insurance information from the pathology or other clinical reports.
* Do not remove the date of procedure, surgical pathology ID (SPID) number, block number, and diagnosis.
  + 1. Specimen Shipping Instructions

When kits are provided, 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 with ambient specimens.

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.

* + - 1. Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is 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 relevant required forms listed above and the Shipping List 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.
   * + 1. Shipping Blood in an Ambient Shipper
7. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
8. 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.**
9. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
10. Place the blood collection tubes in zip-lock bags.
11. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
12. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
13. Place packaged blood collection tube(s) and a copy of the Shipping List from the Specimen Tracking System on top of SAF-T-TEMP Pak.
14. Place the lid on the insulated chest.
15. Close the outer flaps of the shipping box and tape shut.
16. Attach a shipping label to the top of the shipping container.
17. Attach an Exempt Human Specimen sticker to the side of the box.
18. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * 1. 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

2200 International Street

Columbus, Ohio 43228

PH: (614) 722-2865

FAX: (614) 722-2897

E-mail: [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org)

**FedEx Priority Overnight** service is very strongly preferred.

**NOTE:** The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

* + 1. Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank

PH: (614) 722-2865

E-mail: [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org)

## Shipping of Specimens from Clinical Site to Other Laboratories

* + 1. Shipping of Specimens to Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
       1. Specimen Shipping Instructions

Preparing the Specimen Shipment:

1. Samples should be stored in cardboard boxes (5 1/8” x 5 1/8” x 2”, LxWxH) with dividers (e.g., VWR Box item number is 82021-114; divider item number is 82007-154.).

2. Please organize the samples by Patient and Time point in the box.

3. Do not store only 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 or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet. Place the paperwork along with boxes in a plastic bag.

5. Note the study number, PI, and the drugs used/to be measured (i.e., “Camonsertib PK”).

6. A name, phone number and email address should be included with samples so that receipt can be acknowledged.

Specimen Shipping Instructions:

1. All samples should be shipped via overnight express courier in insulated containers with enough dry ice (~4 inches above and below the box) to maintain the samples in a frozen state.

2. Overnight shipments should occur on Monday through Wednesday (and not before federal or university holidays) by overnight courier for delivery by 10:00 a.m. on the following day.

Please notify the JHU APSR lab by email (onc-pharmacology@lists.johnshopkins.edu) within 24 hours prior to shipment. Attach a scanned copy of the Pharmacokinetic Time Record ([Appendix E](#appendix_E)) for all samples included in the shipment to the email.

* + - 1. Shipping Address

Analytical Pharmacology Core Laboratory

Attn: NCI 10732 Study Samples

1650 Orleans St., CRB1 Rm 184

Baltimore, MD 21231-1000\*\*

Phone: 410-502-7192 or 410-955-1129

Email: [onc-pharmacology@lists.johnshopkins.edu](mailto:onc-pharmacology@lists.johnshopkins.edu)

\*\*This zip code is for FedEx shipments. Please change to 21287 if utilizing UPS to ship.

* + - 1. Contact Information for Assistance

Analytical Pharmacology Core Laboratory SKCCC at Johns Hopkins

Jan Beumer PharmD, PhD, and Linping Xu

Phone: 410-502-7192 or 410-955-1129

Email: [onc-pharmacology@lists.johnshopkins.edu](mailto:onc-pharmacology@lists.johnshopkins.edu)

## Biomarker Plan

**List of Biomarker Assays in Order of Priority**

***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.***

| **Priority** | **Biomarker Name** | **Assay and**  **CLIA: Y/N** | **Use in the Trial and Purpose** | **Specimens Tested** | **Collection Time Points** | **Mandatory or Optional** | **Assay Laboratory, Lab PI, and Lab PI Email** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Tissue-based** | | | | | | | |
| 1 | Whole Exome Sequencing (WES) | NGS  CLIA: N | Exploratory  To determine whether certain molecular alterations in ATM and/or other gene mutation signatures (impaired DNA damage response) predict sensitivity to the treatment | DNA from FFPE tumor tissue | Dose Escalation and Expansion:  Archival | M | MoCha, Frederick National Laboratory for Cancer Research (FNLCR)  Chris Karlovich  chris.karlovich@nih.gov |
| **Blood-based** | | | | | | | |
| 1 | Camonsertib PK | LC-MS/MS  CLIA: N | Integrated  Document PK; correlate with outcome | Plasma from blood in EDTA tube | Dose Escalation and Expansion:  Day 1: Pre, and 0.5, 1, 1.5, 2, 4, 6, and 8 hr post  Day 2: 24 h after D1 dose, pre-D2 dose | M  M | Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins  Jan Beumer  Jan.beumer@jhu.edu; onc-pharmacology@lists.johnshopkins.edu |
| 2 | Whole Exome Sequencing (WES) | NGS  CLIA: N | Exploratory  Germline control | Germline DNA from blood in Streck cfDNA tubes | Dose Escalation and Expansion:  Baseline | M | MoCha, Frederick National Laboratory for Cancer Research (FNLCR)  Chris Karlovich  chris.karlovich@nih.gov |
| 3 | Circulating Tumor DNA (ctDNA) | TSO500  CLIA: N | Exploratory  Analysis of DNA damage response-related genes | Plasma from blood in Streck cfDNA tubes | Dose Expansion Only:  Baseline  Week 7  Disease progression | M  O  O | MoCha, Frederick National Laboratory for Cancer Research (FNLCR)  Chris Karlovich  chris.karlovich@nih.gov |

## Integrated Correlative Studies

* + 1. Camonsertib PK
       1. Specimen(s) Receipt and Processing at the Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Plasma will be processed for LC-MS/MS to analyze camonsertib PK.

* + - 1. Site(s) Performing Correlative Study

Analytical Pharmacology Core Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

* + - 1. Contact Information for Notification of Specimen Shipment

See Section 5.7.1.3

## Exploratory/Ancillary Correlative Studies

* + 1. Whole Exome Sequencing (WES)
       1. Specimen(s) Receipt and Processing at the EET Biobank

The EET Biobank will receive formalin-fixed paraffin-embedded (FFPE) tumor tissue and blood from participating sites.

FFPE tissue will be received as an FFPE tissue block or as H&E-stained and unstained slides. FFPE tissue blocks and stained slides will be stored at room temperature, and unstained slides will be vacuum sealed and banked in refrigerated storage until processing.

H&E stained slides will undergo a pathology QA review to assess tumor content and annotate for macrodissection, when needed. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality prior to storage in a -80°C freezer. The remaining FFPE block and H&E stained slides will be stored at room temperature. Aliquots of DNA will be shipped to the central sequencing laboratory for analysis.

Germline DNA will be extracted from blood collected in Streck cfDNA tubes at baseline, following plasma processing. DNA will be quantitated and then stored in a -80°C freezer. An aliquot of germline DNA will be shipped to the central sequencing laboratory for analysis.

* + - 1. Site(s) Performing Correlative Study

The assay will be performed at MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, PhD.

* + - 1. 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

* + - 1. Contact Information for Notification of Specimen Shipment

Thomas Forbes, [mochasamplereceiving@nih.gov](mailto:mochasamplereceiving@nih.gov)

* + 1. Circulating Tumor DNA (ctDNA)
       1. Specimen(s) Receipt and Processing at the EET Biobank

Whole blood collected in Streck cfDNA tubes will be centrifuged to separate plasma. Following plasma processing, DNA will be processed from blood at baseline. At week 7 and disease progression, plasma and buffy coat will be processed. Plasma and buffy coat aliquots will be stored in a -80°C freezer until distribution for analysis. Either aliquots of plasma or extracted cfDNA from select time points will be distributed for this assay.

* + - 1. Site(s) Performing Correlative Study

The assay will be performed at MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, PhD.

* + - 1. 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

* + - 1. Contact Information for Notification of Specimen Shipment

Thomas Forbes, [mochasamplereceiving@nih.gov](mailto:mochasamplereceiving@nih.gov)

# TREATMENT PLAN

## Agent Administration

Treatment will be administered on an outpatient basis. 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.

|  |  |  |
| --- | --- | --- |
| **Dose Escalation Schedule** | | |
| **Dose Level** | **Dose\*** | |
| **Camonsertib**  **(mg)** | **Stereotactic Body Radiation Therapy** |
| Level -1\*\* | 100 | 7 Gy in 4 fractions |
| Level 1 (Starting Dose) | 100 | 8 Gy in 4 fractions |
| Level 2 | 100 | 8 Gy in 5 fractions |
| Level 3 | 120 | 8 Gy in 5 fractions |
| Level 4 | 160 | 8 Gy in 5 fractions |
| Level 1B\*\* | 120 | 7 Gy in 4 fractions |
| Level 2B\*\* | 160 | 7 Gy in 4 fractions |
| \* Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.  \*\* Deescalated dose levels | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Regimen Description** | | | | | |
| **Agent** | **Premedications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Camonsertib | N/A | \* | PO in the morning | Once per day on the day of and day following radiation | N/A |
| Stereotactic Body Radiation Therapy | N/A | \* | N/A | Twice weekly  2-3 days apart |
| \*Doses as appropriate for assigned dose level. | | | | | |

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

* + 1. Camonsertib

Adequate hematologic function and coagulation parameters are required per protocol prior to initiating camonsertib treatment. Weekly monitoring of blood counts is required per protocol (with additional testing per clinical judgement) during the first cycle of treatment. In case of any hematologic toxicity, weekly monitoring of blood count is required until the adverse event resolves.

For GI toxicities, routine prophylactic antiemetics or premedications are not recommended at the initiation of treatment. However, prophylactic medication can be given as per investigator’s discretion as needed by the patient.

Patients should be monitored for events of fatigue and supportive care should be implemented in addition to evaluation for reversible contributing clinical factors as per investigator’s discretion following institutional guidelines.

* + 1. Stereotactic Body Radiation Therapy (SBRT)

For the purposes of this protocol, the term ‘stereotactic body radiation therapy’ (SBRT) implies the targeting, planning, and aiming of radiation beams along any trajectory in three-dimensional (3-D) space toward a target of known 3-D coordinates. The coordinate system is defined by reliable ‘fiducials.’ A fiducial may be external or internal to the patient’s body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers or reliably identifiable anatomy that is clearly visible on orthogonal kilovolt (KV) imaging inclusive of the tumor itself. In all cases, the relationship between the fiducial and the actual tumor position in real time should be reliably understood for both SBRT treatment planning and treatment delivery.

* + - 1. Stereotactic Body Radiation Therapy Prescription

SBRT will be administered in 4 or 5 fractions as assigned twice weekly, 2-3 days apart. The prescription dose per fraction is 7 or 8 Gy. The total prescription dose is 28, 32, or 40 Gy. SBRT is scheduled on trial between Days 1 and 21 of the study.

* + - 1. Technical Factors
         1. Physical Factors

Only photon (x-ray) beams with photon energies greater than or equal to 6MV are allowed. Cobalt-60 or charged particle beams (including electrons, proton, and heavier ions) are not allowed on this protocol.

Most commercially available photon-producing treatment platforms are allowed. Conventional linear accelerators or specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TrueBeam) are allowed. These units can be used with conformal dose delivery or intensity-modulated radiation therapy (IMRT). Specialized dose-painting accelerators (Cyberknife, or Tomotherapy) are allowed provided that the units meet the technical specifications of the protocol and are used in a fashion that passes any credentialing required by the protocol. Conventional linear accelerators without add-on image-guided radiation therapy (IGRT) must have some other IGRT capability such as orthogonal 2-dimensional KV or computed tomography (CT)-on-rails in the treatment room.

3-D conventional radiation therapy (3-DCRT) or IMRT (including volumetric-modulated arc therapy [VMAT]) are all acceptable planning techniques. SBRT is regarded here as a 3-D conformal treatment. IMRT (including VMAT) can result in dosimetric inaccuracies especially in circumstances where tumor motion is either unknown or not properly accounted. When required for successful compliance, IMRT should only be utilized if tumor motion is less than five millimeters (5 mm), or if motion management inherently diminishes motion effects (e.g., gating, breath hold, or tracking). Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique.

* + - * 1. Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of three centimeters (3 cm) is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the planning tumor volume is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions (<2.0 cm axial, <1.0 cm craniocaudal gross tumor volume dimension). In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume. For sites using dose painting including IMRT techniques, where by design the entire planning tumor volume is not encompassed for each beam, smaller beam apertures are allowed.

* + - * 1. Patient Positioning

Patients will be positioned in a stable position for accurate reproducibility of the target position during treatment and between treatments. Positions uncomfortable for the patient should be avoided so as to minimize uncontrolled movement during treatment. Immobilization with a thermoplastic mask must be reliable to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV). Positioning patients on flat couches without a rigid pillow or frame and relying solely on image-guidance for reproducible set-up is strongly discouraged. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides.

* + - 1. Simulation and Planning

The patient will undergo a treatment planning simulation. In preparation for the radiotherapy planning CT scan, patients should fast for two hours to minimize the volume of stomach contents. In order to visualize the lymph nodes, the patient should be given intravenous contrast per institutional practice guidelines if there are no contraindications. All patients will be immobilized using customized thermoplastic masks with reference to the stereotactic coordinate system per institutional routine in order to prevent any inadvertent patient motion during SBRT treatment.

All patients must undergo CT-based treatment planning in custom-made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used) and be adequate to ensure contouring of all targeted cancers, as well as necessary organs at risk (OAR), as defined below. High-resolution CT scans should be obtained with uniform slice thickness of less than or equal to one millimeter (≤1 mm). Intravenous contrast may be used at the discretion of the treating physician. Vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for treatment planning. Datasets without intravenous contrast may be used for dose calculation. Triphasic CT scan is recommended to aid in identification of the irradiation lesion(s).

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT abdominal or liver windows (aided by additional diagnostic imaging studies as needed [PET/CT or MRI]). Soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged (i.e., the GTV and the clinical target volume [CTV] are identical [GTV=CTV]). An additional up to three millimeters (3 mm) in the axial plane and up to 3 millimeters (3 mm) in the longitudinal plane (craniocaudal) are added to the GTV to constitute a planning target volume (PTV).

* + - 1. SBRT Treatment Planning Technique
         1. Planning Parameters

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, nine (9) or more beams of radiation will be used with roughly equal weighting. In general, large lesion size requires more treatment beams. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam’s eye view (i.e., no additional “margin” for dose buildup at the edges of the blocks or multi-leaf collimator jaws beyond the PTV). The only exception will be when observing the minimum field dimension of three centimeters (3cm) when treating small lesions. Prescription lines covering the PTV will typically range between 60-90% line (rather than 95-100% as is common with conventional radiotherapy); however, higher isodose line hotspots must be manipulated to occur within the target and not in adjacent normal tissue.

* + - * 1. Heterogeneity Correction

All institutions must use heterogeneity correction algorithms.

* + - * 1. SBRT Planning Definitions

**Normalization:** The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.

**Prescription Isodose Surface Coverage**: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted above.

**Target Dose Heterogeneity**: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.

**Critical Organ Doses**: Respect all critical organ dose-volume limits listed below.

**High-Dose Spillage:**

* 1. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.
  2. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.
  3. The ratio of the prescription isodose volume to the PTV volume should be <1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V\_prescription (i.e., V\_5000, V\_4800, V\_5400) with the prescription changing to reflect the prescription dose in cGy. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in the table below. The 50% isodose volume may be elongated deliberately in order to avoid AOR making it difficult to meet the guidelines below. This is acceptable as long as normal tissue constraints are met.
  4. Elliptically shaped metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.
  5. These criteria will not be required in treating very small tumors (<2.5 cm axial GTV dimension or <1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm (see Section 6.1.2.2) results in the inability to meet a conformity ratio of 1.5.

**Planning Priorities:** Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria without deviation. In some circumstances, it may not be possible to meet all the ideal criteria leading to plans with an acceptable deviation. Thus, suggested priority of planning goals in order of importance is (1) respect spinal cord and brachial plexus dose constraints; (2) meet dose “compactness” constraints including the prescription isodose surface coverage, high dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the “essence” of SBRT (dose compactness should be assessed for plans based on treatment dose for a single lesion at a time); (3) meet critical structure constraints other than those listed in item #1 as the OAR constraints are last in priority (except for nervous system tolerance) and as an example, in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation; (4) unacceptable deviations should be avoided in all cases; and (5) in cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OAR, coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose only in this clinical situation.

**Organs at Risk (OAR):** Protocol-specific OARs contoured depend on the location of cancers to be treated. In general, an OAR within three (3 cm) of the PTV should be contoured and might include:

* Lungs, left/right/combined
* Heart
* Great vessels
* Esophagus
* Spinal cord/Brain
* Pharynx
* Carotid arteries
* Parotid glands
* Submandibular glands
* Larynx
* Oral cavity
* Mandible
* Carotid arteries
* Skin

**Contouring of Normal Tissue Structures:** In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

Brain

The brain will be contoured as one complete structure within the cranial vault.

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal ending at L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations

Great Vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Non-adjacent Wall of a Structure

For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV. These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

Oral Cavity

The oral cavity will be defined as a composite structure consisting of the anterior 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands

Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. The retromandibular vein is included in the contour. Left and right parotid glands should be contoured as separate structures.

Submandibular glands

Submandibular glands will be defined in their entirety based on the treatment planning CT scan. Left and right submandibular glands should be contoured as separate structures.

Pharynx

This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles (approximately 3 mm). This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Larynx

This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis. For patients who have had a total laryngectomy, this structure is not applicable.

Brachial Plexus

This will be contoured as the ventral rami from C5 (exiting at C4-C5) through T1 (exiting at T1-T2) as they exit through the neural foramina joining to form the trunks extending through the space between the anterior and middle scalene muscles. At the level where the scalene muscles insert into the first rib, the major trunks of the brachial plexus should follow the subclavian artery into the axilla. For more detailed step-by-step instructions, refer to Truong *et al*., *Radiographics* 2010 (<https://pubs.rsna.org/doi/full/10.1148/rg.304095105>). The left and right brachial plexuses should be contoured as separate structures.

Mandible

This includes the entire boney structure of the mandible from TMJ through the symphysis. Teeth are not included. Contouring should be carried out using bone windows.

Carotid artery

The carotid artery will be defined as the common carotid artery and the internal carotid artery, including the vascular wall and lumen. The right carotid artery contour starts at its origin from the brachiocephalic trunk. The left carotid artery contour starts at its origin from the aortic arch. The upper border will be defined at the level of the sella turcica. The left and right carotid arteries should be contoured as separate structures. Each contour will be uniformly expanded by 2 mm to generate an additional avoidance structure (carotid artery + 2 mm).

PTV + 2 cm

As part of the QA requirements for “low dose spillage” listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible, this structure should be constructed as a single contour that is 2 cm larger than the PTV.

* + - 1. Radiation Dose Constraints

**Dose Constraints for SBRT Plan**

| Structures | Goal | Variation  Acceptable | Deviation Unacceptable | Avoidance Endpoint |
| --- | --- | --- | --- | --- |
| Spinal Cord\* | V12Gy <0.035 cc | Dmax 12.5 Gy | Dmax <12.5 Gy required | Myelitis |
| Brainstem\* | Dmax <10 Gy | Dmax <12 Gy | Dmax <12 Gy required | Brainstem necrosis |
| Brachial plexus\* | V25Gy <0.035 cc | V22Gy <3cc | V22Gy ≥3 cc | Brachial plexopathy |
| Oral Cavity | Dmean <25 Gy | Dmean <30 Gy | Dmean ≥30 Gy | Soft tissue necrosis |
| Pharynx | Dmean <20 Gy | Dmean <25 Gy | Dmean ≥25 Gy | Feeding tube dependence |
| Esophagus | Dmax ≤25 Gy | Dmax >25 and <30 Gy | Dmax > 30 Gy  V15Gy ≥5 cc | Perforation; feeding tube dependence |
| Larynx | Dmean ≤20 Gy  V22Gy <2 cc | Dmean >20 Gy and ≤25  V24Gy <2 cc | Dmean >25 Gy  V24Gy >2 cc | Laryngeal edema; chondronecrosis |
| Mandible | Dmax ≤ 41 Gy | Dmax > 41 Gy and < 42 Gy | Dmax > 42 Gy | Osteoradionecrosis |
| Left carotid artery+2 mm | V42Gy <0.035 cc  D50% ≤32 Gy | V44Gy <0.035 cc  D50% >32 Gy and ≤34 Gy | V44Gy ≥0.035 cc  D50% >34 Gy | Carotid blowout |
| Right carotid artery+2 mm | V42Gy <0.035 cc | V44Gy <0.035 cc | V44Gy≥0.035 cc | Carotid blowout |
| Lung | V14Gy <750 cc | V14Gy <1,000 cc | V14Gy ≥1,000 cc | Pneumonitis |
| Skin | V30Gy <0.035 cc | Dmax ≤35 Gy | Dmax > 35 Gy | Ulceration |
| Left cochlea | Dmax ≤12 Gy | Dmax ≤15 Gy | Dmax >15 Gy | Hearing loss |
| Right cochlea | Dmax ≤12 Gy | Dmax <15 Gy | Dmax >15 Gy | Hearing loss |
| Temporal lobe | V20Gy <0.035 cc | V20Gy <2 cc | V20Gy ≥2 cc | Temporal lobe necrosis |
| Target Volume | Goal | Variation Acceptable | Deviation Unacceptable |  |
| PTV | D1cc ≤110%  D100% ≥90% | D1cc ≤120%  D95% ≥90% | D1cc >120%  D95% <90% |  |
| GTV | Dmin >95% | Dmin >90% | Dmin <90% |  |

Given that patients with paranasal sinus or nasopharynx cancers are excluded from enrollment, dose constraints have not been listed for retinas, optic nerves, and optic chiasm. However, these structures will be reviewed during the radiation therapy plan QA process.

\*When possible, a plan sum should be generated utilizing the original head and neck radiation treatment plan and the new reirradiation SBRT plan. If the spinal cord, brainstem, and/or brachial plexus maximum doses are available from radiation therapy treatment records but a plan summary cannot be generated, then the prior maximum doses should be utilized to calculate personalized dose constraints that may be stricter than the above table based on equivalent dose in 2-Gy fractions with an alpha/beta of 2 (EQD22) for each of these normal structures per below:

* **Spinal cord**: EQD22 Dmax on plan sum = 50 Gy
  + Calculate EQD22 Dmax from initial plan and multiply by dose recovery factor based on time passed since prior radiation therapy (0.75 if 6 to 12 months; 0.67 if >12 but <24 months; 0.5 if >24 months)
  + Utilize the above adjusted EQD22 Dmax from initial plan to account for dose recovery in calculating the EQD22 Dmax for plan sum of prior plan and SBRT plan
* **Brainstem**: EQD22 Dmax on plan sum = 55 Gy
* **Brachial Plexus**: EQD22 Dmax on plan sum = 95 Gy if feasible without sacrificing GTV coverage

 For tumors immediately adjacent or involving these structures, the PTV may be subtracted from the organ at risk contour.

* + - 1. Online Treatment Image-Guided Localization and Treatment

SBRT image-guided radiation therapy is the delivery of SBRT with online imaging capabilities and verification. This is accomplished with standard treatment planning with position verification using 2-dimensional kilovoltage (KV) images to evaluate the position of the fiducial markers as well as 3-D cone beam imaging. 3D KV cone beam CT (CBCT) scan is a CT scan taken of the patient and target structure of interest while the patient is immobilized on the treatment table. During the treatment, the patient is immobilized exactly as was done for the simulation. The patient is then set-up in the treatment position according to laser-guiding body tattoos in the treatment room. Live images of the patient are obtained with diagnostic X-ray tubes and amorphous silicon detectors for patient positioning. A therapist may either initially obtain a KV image (gated KV for the respiratory gating patients) to align the fiducial markers or a CBCT for image registration based on the location of the fiducial markers and visible tumor abnormality (if possible) noted in the CT. The patient position is then adjusted to move the patient into the exact position corresponding to the designed treatment plan.

If the patient requires additional repositioning, another set of KV orthogonal images will be obtained to confirm tumor localization. Once the latter is confirmed, treatment may be delivered. Treatment may be delivered with the abdominal compression belt or using respiratory gating using the gating interval as determined from the simulation. The patient may be monitored during treatment with intra-fraction imaging (IMR) to prevent non-respiratory body motions greater than three millimeters (3 mm).

All planned SBRT treatment segments will be delivered whenever possible. If SBRT treatment must be terminated prematurely on any fractions of one to five, compensate as follows: If 2/3 or more of all non-zero segments were delivered, then the untreated segments plus the full next fraction should be treated on the next treatment day (this should introduce an error of < 5% in biologic effective dose delivered). If fewer than 2/3 of the non-zero segments were treated, then the untreated portion of this fraction (only) will be made up for on the following interval day. If treatment must be terminated prematurely on the lastfraction, and 90% of the non-zero segments were treated, then no further treatment shall be given (this should introduce an error of < 5% for total biologic effective dose delivered). If fewer than 90% of the non-zero segments were treated, then the deficit shall be delivered on the following day. All such variations shall be recorded.

## Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as any Grade 4 or greater adverse event per the NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) that is at least possibly related to study treatment and observed within 90 days of the last dose of radiation therapy. The target toxicity rate for the MTD is ≤ 0.33. Given that head and neck reirradiation without concurrent systemic therapy results in high rates of acute Grade 3 toxicities, and clinical outcomes for this patient population are poor with current therapy, this is considered an acceptable toxicity rate.

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 following scheme (see section 9.1.2.1 for additional information). Dose-limiting toxicity (DLT) is defined above. The target DLT rate is 0.33 and the overdose control parameter is 0.8. The maximum number of patients in any dose level is limited to 9, and the maximum number of patients for the dose escalation phase is 30. No decision will be made regarding dosing until all eligible participants are assessed for DLT.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of patients treated at current dose level** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Escalate if # of DLT ≤ | 0 | 1 | 1 | 1 | 1 | 2 | 2 |
| Stay if # of DLT = | 1 | NA | NA | 2 | 2 | 3 | 3 |
| De-escalate if # of DLT ≥ | 2 | 2 | 2 | 3 | 3 | 4 | 4 |
| Eliminate if # of DLT ≥ | 2 | 3 | 3 | 3 | 4 | 4 | 5 |

## Dose Expansion Cohorts

The study PI will consult with CTEP at the end of the dose escalation phase to review all available safety, pharmacokinetic and pharmacodynamic data prior to opening the dose expansion phase. The recommended phase 2 dose (RP2D) to be used in the expansion cohort(s) will be determined based on the totality of safety, tolerability, clinical activity, and pharmacokinetic (PK) data as appropriate. The tolerability of doses administered in cycles after the dose limiting toxicity (DLT) observation window should be taken into account in determination of the RP2D. For example, if 2 dose levels have equivalent PKs and the lower dose has a better safety profile, this dose may be chosen as the RP2D. The RP2D may be determined to be the highest dose level, the maximum tolerated dose (MTD), or it may be a lower dose based on the consensus of the investigators, CTEP and pharmaceutical company collaborators.

The PI will write a summary of the RP2D discussion with CTEP and submit the summary to the CTEP lead reviewer for confirmation. The PI will submit an amendment to the study summarizing the experience of the dose escalation phase and specifying the RP2D.

Once the RP2D is reached, an additional 12 patients will be treated at this dose. 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 RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

## General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of camonsertib 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 D](#appendix_D) (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

FDA-approved biosimilar growth factors will be acceptable according to institutional policies.

## Duration of Therapy

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

* Disease progression
* Intercurrent illness that prevents further administration of treatment
* Unacceptable adverse event(s)
* Patient decides to withdraw from the study
* 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).

## Duration of Follow-Up

Patients will be followed for 2 years after removal from study 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.

# DOSING DELAYS/DOSE MODIFICATIONS

|  |  |  |
| --- | --- | --- |
| **Dose Escalation Schedule** | | |
| **Dose Level** | **Dose\*** | |
| **Camonsertib**  **(mg)** | **Stereotactic Body Radiation Therapy** |
| Level -1\*\* | 100 | 7 Gy in 4 fractions |
| Level 1 (Starting Dose) | 100 | 8 Gy in 4 fractions |
| Level 2 | 100 | 8 Gy in 5 fractions |
| Level 3 | 120 | 8 Gy in 5 fractions |
| Level 4 | 160 | 8 Gy in 5 fractions |
| Level 1B\*\* | 120 | 7 Gy in 4 fractions |
| Level 2B\*\* | 160 | 7 Gy in 4 fractions |
| \* Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.  \*\* Deescalated dose levels | | |

## Recommended Dose Modifications for Camonsertib

If camonsertib is held due to toxicity, SBRT will continue as scheduled without concurrent camonsertib. Camonsertib will be resumed when/if the adverse event improves as indicated in the tables below.

| **Nausea** | **Management/Next Dose for Camonsertib** |
| --- | --- |
| ≤ Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | |
| Recommended management: antiemetics. | |

| **Vomiting** | **Management/Next Dose for Camonsertib** |
| --- | --- |
| ≤ Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | |
| Recommended management: antiemetics. | |

| **Diarrhea** | **Management/Next Dose for Camonsertib** |
| --- | --- |
| ≤ Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | |
| Recommended management: Loperamide antidiarrheal therapy  Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours)  Adjunct anti-diarrheal therapy is permitted and should be recorded when used. | |

| **Neutropenia** | **Management/Next Dose for Camonsertib** |
| --- | --- |
| ≤ Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | |

| **Thrombocytopenia** | **Management/Next Dose for Camonsertib** |
| --- | --- |
| ≤ Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | |

# PHARMACEUTICAL AGENT INFORMATION

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

## CTEP IND Agent

* + 1. Camonsertib (RP-3500) (NSC 851929)

**Chemical Name or Amino Acid Sequence:** (3-*Endo*)-3-[6-[(3*R*)-3-methyl-4-morpholinyl]-1-(1*H*-pyrazol-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]-8-oxabicyclo[3.2.1]octan-3-ol hydrogen sulfate

**Other Names**: RP-3500 hydrogen sulfate

**Classification:** ataxia telangiectasia-mutated and rad3-related kinase (ATR) inhibitor

**CAS Registry Number**: 2417489-10-0 (free base)

**Molecular Formula:** C21H26N6O3•H2SO4 **M.W.:** 508.55

**Approximate Solubility:** Camonsertib hydrogen sulfate disproportionate rapidly in water to the hydrated free-base form. The equilibrium solubility of this same free base form is 0.050 mg/mL in water.

**Mode of Action:** Camonsertib is an ATR inhibitor, which is involved in DNA damage repair. ATR inhibitors elicit cell death in rapidly growing tumor cells by exacerbating endogenous replication stress and replication fork collapse, as well as by disabling cell cycle checkpoints.

**Description**: The drug substance is an off-white powder.

**How Supplied:** Camonsertib (RP-3500) issupplied by Repare Therapeutics and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI as hard-shell capsules, 5mg and 40 mg strengths expressed as free base equivalent of camonsertib hydrogen sulfate. Excipients include silicified microcrystalline cellulose (SMCC), dicalcium phosphate, anhydrous, croscarmellose sodium, and magnesium stearate. The capsule shell is either hydroxypropyl methylcellulose (HPMC) or gelatin. The bottle is high-density polyethylene (HDPE) with child-resistant caps. Each 5 mg bottle contains 10 capsules and each 40 mg bottle contains 24 capsules.

**Storage:** Store in original bottles in dry place at 15-25°C (59-77°F). They should not be frozen.

If a storage temperature excursion is identified, promptly return camonsertib to 15-25°C (59-77°F) 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](mailto:PMBAfterHours@mail.nih.gov) for determination of suitability.

**Stability:** Stability studies are ongoing. Repackaging is allowed up to shelf life of original container.

**Route and Method of Administration:** Take by mouth with or without food. Swallow whole. Do not open or chew. If a dose is missed, take as soon as possible that day but there must be at least an 8 hour interval before the next dosing time. If it is within the 8 hours of the next usual dosing time, skip the missed dose and take the next dose at the usual time. If a dose is vomited, skip the dose and take the next dose at the usual time.

**Potential Drug Interactions:**

Camonsertib (RP-3500) is mainly metabolized by CYP3A4/5 and also CYP2C8 and 2C19 to lesser extent. *In vitro*, camonsertib is not a strong direct inhibitor of CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4/5; but is a weak inhibitor of CYP2C8. There’s no induction potential for CYP1A2 and weak induction potential for CYP2B6 and 3A4. Concomitant use of strong CYP3A4/5 inhibitors and inducers should be avoided.

Camonsertib (RP-3500) is a substrate of MDR1 (P-gp) and BCRP transporters. *In vitro*, it is a weak inhibitor of P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, and OAT1. Concomitant use of strong P-gp and BCRP inhibitors should be avoided.

Based on a physiological-based PK model, there is low risk of interaction with acid-reducing agents.

Based on in vitro and in vivo data, camonsertib has potential to induce mild phototoxicity. Use caution to limit sun exposure while taking camonsertib (e.g. wear sunscreen or clothing to cover extremities and avoid direct sun exposure.)

**Patient Care Implications:** Do not administer to pregnant or nursing women. Highly effective contraception should be used for both female and male patients during treatment and up to 6 months after last dose. Egg and sperm donation is prohibited during camonsertib treatment and for up to 6 months after last dose.

**Availability**

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

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

* + 1. Agent Ordering and Agent Accountability
       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.

*[The CTEP Pharmaceutical Management Branch (PMB) will provide direction as to when sites can order PMB-supplied agents.]*

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, 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 or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB’s website for specific policies and guidelines related to agent management.

* + - 1. Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a complete accountability 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.

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) or by using the dialog function in AURORA to communicate with PMB staff.

* + 1. Material Safety Data Sheets
* The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) or by using the dialog function in AURORA to communicate with PMB staff.
  + 1. Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, 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.

* + 1. Useful Links and Contacts
  + CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
  + NCI CTEP Investigator Registration: [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov)
  + PMB policies and guidelines: <http://ctep.cancer.gov/branches/pmb/agent_management.htm>
  + PMB AURORA application: <https://ctepcore.nci.nih.gov/aurora/login>
  + CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
  + CTEP IAM account help: [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov)
  + IB Coordinator: [IBCoordinator@mail.nih.gov](mailto:IBCoordinator@mail.nih.gov)
  + PMB email: [PMBAfterHours@mail.nih.gov](mailto: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)

# STATISTICAL CONSIDERATIONS

## Study Design/Endpoints

This is a multi-center, single-arm, open-label phase I (dose escalation and dose expansion) study to determine the maximally tolerated dose levels (MTD) for camonsertib and concurrent SBRT head and neck reirradiation. Patients will be treated with SBRT, delivered in four or five fractions (7 Gy or 8 Gy/fraction depending on assigned dose level), with two treatments per week and fractions separated by at least two days and no more than three days.

* + 1. Study Endpoints

The primary endpoint of the dose escalation phase is the safety and tolerability of camonsertib. The MTD for camonsertib and concurrent SBRT reirradiation will be determined. The information about MTD will be used for determining the recommended phase 2 dose. After completion of the initial dose-finding phase, there will be an expansion cohort at the MTD to provide better characterization of the late toxicity profile.

The primary endpoint for the dose expansion phase will be late toxicities within 1 year of treatment initiation.

The secondary endpoints are overall response rate within the radiation therapy field and progression-free survival.

The exploratory endpoints are biomarkers of response, pharmacokinetic data, and patient-reported quality of life.

* + 1. Study Design
       1. Dose-Escalation Phase

The primary endpoint of the dose escalation phase is to determine the MTD of camonsertib and concurrent SBRT reirradiation. DLT will be defined as any Grade 4 or greater adverse event per the CTCAE v5.0 that is at least possibly related to study treatment and observed within 90 days of the last dose of radiation therapy. The target toxicity rate for the MTD is ≤0.33 and the maximum number of patients for dose escalation is 30. Given that head and neck reirradiation without concurrent systemic therapy results in high rates of acute Grade 3 toxicities and clinical outcomes for this patient population are poor with current therapy, this is considered an acceptable toxicity rate.

The dose-escalation phase will utilize a Bayesian Optimal Interval Design (BOIN) to determine the MTD for combined camonsertib and SBRT. This Bayesian dose-finding method aims to minimize the chance of exposing patients to subtherapeutic and overly toxic doses. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs. This trial was designed and will be conducted using shiny app BOIN for combination trials (<http://www.trialdesign.org>). Five dose levels will be studied (**Table 1**), starting with a radiation dose of 8 Gy x 4 fractions with 100 mg camonsertib (Dose Level 1).

**Table 1.** Dose levels of camonsertib + SBRT combination treatment.

|  |  |  |
| --- | --- | --- |
| **Dose Level** | **Dose** | |
| **Camonsertib**  **(mg)** | **Stereotactic Body Radiation Therapy** |
| Level -1 | 100 | 7 Gy in 4 fractions |
| Level 1 (Starting Dose) | 100 | 8 Gy in 4 fractions |
| Level 2 | 100 | 8 Gy in 5 fractions |
| Level 3 | 120 | 8 Gy in 5 fractions |
| Level 4 | 160 | 8 Gy in 5 fractions |

**Table 2.** Dose escalation/de-escalation rule under the BOIN design for the starting dose level (Dose Level 1 in Table 1).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of patients treated at current dose level** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Escalate if # of DLT ≤ | 0 | 1 | 1 | 1 | 1 | 2 | 2 |
| Stay if # of DLT = | 1 | NA | NA | 2 | 2 | 3 | 3 |
| De-escalate if # of DLT ≥ | 2 | 2 | 2 | 3 | 3 | 4 | 4 |
| Eliminate if # of DLT ≥ | 2 | 3 | 3 | 3 | 4 | 4 | 5 |

**Table 2** describes the dose escalation/de-escalation rule under the BOIN design for the starting dose level. Three patients will be treated at this starting dose level, and subsequent patients will be treated in cohorts of 3. The target DLT rate is 0.33 and the overdose control parameter is 0.8. The maximum number of patients for the dose escalation phase is 30, and the maximum in any dose level is limited to 9. No decision will be made regarding dosing until all eligible participants are assessed for DLT.

If the number of DLTs required for dose de-escalation (2) and elimination (2) are reached after three patients have been studied, we will suspend the study and discuss other options with NCI CTEP, e.g., 1) the 8 Gy x 4 SBRT dose will be eliminated; 2) a BOIN design will be implemented starting with 7 Gy x 4 SBRT with 100 mg camonsertib (Dose Level -1) with two other possible dose levels as outlined in **Table 3**.

**Table 3.** De-escalated dose levels of camonsertib + SBRT combination.

|  |  |  |
| --- | --- | --- |
| **Dose Level** | **Dose** | |
| **Camonsertib**  **(mg)** | **Stereotactic Body Radiation Therapy** |
| Level -1 | 100 | 7 Gy in 4 fractions |
| Level 1B | 120 | 7 Gy in 4 fractions |
| Level 2B | 160 | 7 Gy in 4 fractions |

**Figure 5** shows the decision rule for the BOIN design.

A diagram of a patient's flow

Description automatically generated

**Figure 5**. Flowchart of single agent BOIN design with assumptions described above.

To guide dose-escalation/de-escalation decisions under each scenario shown in **Figure 5**, if the observed DLT rate at the current dose level combination is <0.26, the next cohort of patients will be treated at the next higher dose level. However, if it is >0.395, the next cohort will be treated at the next lower dose level. The trial design is described as follows:

1. Patients in the first cohort are treated at the starting dose combination.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in **Figure 5**. When using **Figure 5**, please note the following:
   1. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
   2. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
   3. If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, we treat the new patients at the current dose.
   4. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
   5. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size for dose escalation phase of 30 is reached, or the number of evaluable patients treated at the current dose reaches 9, and the decision according to step 2 is to stay at the current dose.

After the trial is completed, the MTD is selected based on isotonic regression (Liu and Yuan, 2017). This computation is implemented by the shiny app “BOIN” available at <http://www.trialdesign.org>. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, the higher dose level is selected when the isotonic estimate is lower than the target toxicity rate; the lower dose level is selected when the isotonic estimate is greater than or equal to the target toxicity rate.

Monitoring for Late Toxicity

At each dose level, the proportions of total patients experiencing DLTs will be estimated at 6 months, 1 year, and 2 years post SBRT. Analyses will be conducted when all patients in each dose level cohort (minimum 3; maximum 9) have reached the specified follow-up time points. The RP2D will be reassessed once late toxicity data are available for the expansion cohort at 1 year post-treatment before proceeding to a phase 2 clinical trial. If at any time the late toxicity rate at 1 year is ≥0.33 (1 of 1; ≥1 of 2; ≥1 of 3; ≥2 of 4, 5, 6; ≥3 of 7, 8, 9; ≥4 of 10, 11, 12), then the study team will determine if the study should be suspended to investigate and consider dose reduction.

* + - 1. Dose-Expansion Phase

After completion of the initial dose-finding phase, there will be an expansion cohort at the RP2D in order to provide better characterization of the late toxicity profile. The primary endpoint of the dose expansion phase will be late toxicities within 1 year of treatment initiation. Up to 12 patients will be studied for safety at the MTD, including those entered on the dose-finding portion of this study (minimum 3; maximum 9 patients). In addition to monitoring for late toxicities, patients in the expansion cohort will also be monitored for DLTs occurring within the DLT window. If at least 6 patients have been enrolled to the expansion cohort and the observed DLT rate is >0.33, then accrual will be suspended and the Principal Investigator will discuss next steps with CTEP. The proportions of total patients experiencing late toxicities will be estimated at 6 months, 1 year, and 2 years post SBRT. The RP2D will be reassessed once late toxicity data are available for the expansion cohort at 1 year post-treatment before proceeding to a phase 2 clinical trial. If at any time the late toxicity rate at 1 year is ≥0.33 (1 of 1; ≥1 of 2; ≥1 of 3; ≥2 of 4, 5, 6; ≥3 of 7, 8, 9; ≥4 of 10, 11, 12), then the study team will determine if the study should be suspended to investigate and consider dose reduction.

Approximately a third of patients (n=4) are anticipated to die of disease within the first year post-treatment. A competing risk analysis for survival and time to DLT will be conducted, and the cumulative incidence and 95% confidence interval of DLT will be estimated. If the observed cumulative incidence of DLT is greater than 0.33, the Principal Investigator will discuss with CTEP and all study investigators to determine whether additional patients are needed to re-assess the MTD.

## Sample Size/Accrual Rate

The expected number of patients studied in the dose-finding portion of the trial is approximately 12. Up to 12 patients will be treated at MTD with the addition of the dose-expansion cohort. The accrual ceiling is set at 39 patients. The expected average accrual rate is 1-2 patients per month.

**PLANNED ENROLLMENT REPORT**

| **DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| **Not Hispanic or Latino** | | **Hispanic or Latino** | |
| **Female** | **Male** | **Female** | **Male** |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 0 | 1 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 | 0 | 1 |
| Black or African American | 2 | 6 | 0 | 1 | 9 |
| White | 6 | 19 | 0 | 2 | 27 |
| More Than One Race | 0 | 1 | 0 | 0 | 1 |
| **Total** | 8 | 28 | 0 | 3 | 39 |

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## Stratification Factors

Not applicable

## Analysis of Secondary Endpoints

Overall response will be defined as a CR or PR based on the RECIST 1.1 criteria. The proportion of patients responding to the treatment regimen and corresponding 95% confidence interval estimates will be calculated. Progression-free survival (PFS) will be measured from the start of treatment regimen until documented local or distal failure or death from any cause. PFS will be estimated using the method of Kaplan-Meier. The frequency and percentage of responses to the quality of life (QoL) questionnaire will be summarized at 3, 6, and 12 months post-treatment and interpreted descriptively. The frequency and percentage of adverse events (AEs) will be provided overall and by dose level for any grade and attribution as well as for Grade 3 or greater AEs, at least possibly related to treatment.

# ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

## Comprehensive Adverse Events and Potential Risks List (CAEPR)

* + 1. CAEPRs for CTEP IND Agent
       1. CAEPR for Camonsertib (RP-3500)

*Pending*

## Adverse Event Characteristics

* **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>.
* **For expedited reporting purposes only:**
* AEs for the agent that are ***bold and italicized*** in the CAEPR (i.e., those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
* **Attribution** of the AE:
  + Definite – The AE *is clearly related* to the study treatment.
  + Probable – The AE *is likely related* to the study treatment.
  + Possible – The AE *may be related* to the study treatment.
  + Unlikely – The AE *is doubtfully related* to the study treatment.
  + Unrelated – The AE *is clearly NOT related* to the study treatment.

## Expedited Adverse Event Reporting

* + 1. Rave-CTEP-AERS Integration

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

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational agent/intervention are collected using the Late Adverse Event form.

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

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

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

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

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

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

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

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

* NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at <https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf>.
  + 1. 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.

* + 1. 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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).  An AE is considered serious if it results in **ANY** of the following outcomes:   1. Death 2. A life-threatening AE 3. An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). | |
| **ALL SAEs** that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below. | |
| **Grade 1-2 Timeframes** | **Grade 3-5 Timeframes** |
| 24-Hour notification, 10 Calendar Days | 24-Hour notification, 5 Calendar Days |
| **NOTE:** Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.  **Expedited AE reporting timeframes are defined as:**   * “24-Hour notification, 5 Calendar Days” - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. * “24-Hour notification, 10 Calendar Days” - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report. | |
| 1SAEs 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 notifications are required for all SAEs followed by a complete report**   * Within 5 calendar days for Grade 3-5 SAEs * Within 10 calendar days for Grade 1-2 SAEs   2For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024 | |

* + 1. Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not applicable

## Routine Adverse Event Reporting

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

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

## 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.

## 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.

## Second Malignancy

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

# STUDY CALENDAR

***Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.***

With the exception of imaging, baseline evaluations are to be conducted within 21 days prior to start of protocol therapy. Baseline imaging must be done ≤6 weeks prior to the start of therapy (preferably ≤4 weeks). Baseline imaging must include neck CT (preferably contrast-enhanced) and either non-contrast chest CT or skullbase to mid-thigh PET/CT (preferably with contrast-enhanced neck CT if another diagnostic contrast-enhanced neck CT is not available). In the event that the patient’s condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

|  | Pre-Study | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 7 (± 1 wk) | Wk 16 (± 2 wk) | Wk 29 (± 3 wk) | Wk 42 (± 3 wk) | Wk 55 (± 5 wk) | Disease Progressiona | Off Studyb |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Camonsertib |  | A | A | A |  |  |  |  |  |  |  |  |  |  |
| Radiotherapy |  | 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 |  | X |
| Vital signs | X | X | X | X | X |  |  | X | X | X | X | X |  | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X | X | X | X |  |  | X | X | X | X | X |  | X |
| Performance status | 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 |  | X |
| Serum chemistryc | X | X | X | X | X | X | X | X | X | X | X | X |  | X |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event evaluation |  | X-------------------------------------------------------------------------------------------------------------------------------------------------------------------X | | | | | | | | | | | | X |
| Tumor measurements | X | Tumor measurements are repeated every 13 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | X |
| Radiologic evaluationd | X | Radiologic measurements should be performed every 13 weeks after completion of study therapy. | | | | | | | | | | | | X |
| Pregnancy teste | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| FFPE tumor tissue blockf | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood in Streck Tubes | X |  |  |  |  |  |  | Xf |  |  |  |  | Xf |  |
| Blood in EDTA Tubes |  | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Quality of Life Assessment | X |  |  |  |  |  |  |  | X | X |  | X |  |  |
| A: Camonsertib: Dose as assigned; administered orally on the morning of each radiotherapy dosing and on the morning after each radiotherapy dosing.  B: Radiotherapy: Dose as assigned*;* radiotherapy fractions will be separated by at least two days and no more than three days without radiotherapy.  a: Patients will be considered to be “off-study due to progression” if they develop progressive or recurrent disease. Any patient who received radiation therapy should continue to be followed for quarterly (every 13 weeks) for radiation toxicity/safety assessments for at least one year after completing SBRT, and if feasible until death, withdrawal of consent, or loss to follow-up. While in-person follow-up is preferred, this assessment can be performed via telephone and/or medical record review.  b: Off study evaluation. In the second year after completing radiation therapy, patients without evidence of disease progression will ideally continue to be evaluated in person every 13 weeks (+/- 6 weeks), ideally with imaging. If any of these follow-up evaluations are performed by a provider not at the clinical trial site, clinic notes should be securely sent to the clinical trial team for data extraction.  c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.  d: Radiologic evaluation will preferably be skullbase to mid-thigh PET/CT (with contrast-enhanced neck CT if another diagnostic contrast-enhanced neck CT is not available). Alternatively, neck CT (preferably contrast-enhanced) and either non-contrast chest CT or contrast-enhanced chest CT may be performed.  e: Pregnancy test for women of childbearing potential.  f: If a block is not available, then 1 H&E stained slide (3-5 µm) and 15-20 unstained, uncharged, air-dried slides (10 µm).  g: Blood collection in Streck tubes at week 7 and in patients with disease progression will only be performed for patients in the dose expansion cohort. | | | | | | | | | | | | | | |

# MEASUREMENT OF EFFECT

Although the clinical benefit of this treatment 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.

## Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 13 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 8-12 (not less than 4) weeks following initial documentation of an 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.

* + 1. Definitions

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

Evaluable for Objective Response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

* + 1. Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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.

* + 1. Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

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

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. 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.
3. 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.

* + 1. Response Criteria
       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.

* + - 1. 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).

* + - 1. 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. |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. |
| 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.   \*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.  Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.”* Every effort should be made to document the objective progression even after discontinuation of treatment. | | | | |

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

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

* + 1. Duration of Response

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

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

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

* + 1. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

# STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

## 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, the Protocol Principal Investigator will have at least monthly conference calls with the Study Investigators [and, if needed, 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.

## Data Reporting

Medidata Rave is the 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:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.
  + Refer to <https://ctep.cancer.gov/investigatorResources/default.htm> for registration types and documentation required.
* DTL Rave CRA task assignment requirements (for write access):
* Corresponding role (Rave CRA or Rave CRA (Lab Admin)) on the site roster; and
* Completion of the Theradex Specimen Tracking System (STS) Training course in CLASS (see Section 4.2.3 – Delegation of Tasks Log (DTL)).

Protocol Specific Requirements For Rave Access

* + - Specimen Tracking System Training Requirement for full read/write Rave access:
    - All site staff assigned the Rave CRA task on the DTL must complete the online specimen tracking training, which is administered via the Compliance, Learning, and SOP Solutions (CLASS) system.
    - Completion of the training will be automatically communicated to the CTSU Regulatory application and to Medidata Rave, and the individual will receive an invitation to 10732 in Rave. *There is no need to submit a training completion certificate 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 (either within CLASS, or via the procedure in place prior to CLASS), the training does not need to be completed again. However, new versions of the Specimen Tracking System training course may require new training.
    - For questions about the training content or the tracking system itself, please contact STS Support at Theradex ([STS.Support@theradex.com](mailto:STS.Support@theradex.com)).
    - For questions or concerns about **accessing the training in CLASS**, please contact the CLASS Help Desk [CLASSHelpDesk@westat.com](mailto:CLASSHelpDesk@westat.com).

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata.  No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed.  Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > [Medidata Account Activation and Study Invitation](https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-DQP#RaveResources) (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members’ website in the Data Management [Rave Resources](https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-DQP#RaveResources) section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

Transfer of Images and Data (TRIAD) is the American College of Radiology’s (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
* Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the [CTEP](file:///C:/Users/dmanfredi/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Content.Outlook/IRDNJLHZ/NRG-BN001%203%2011%2014.docx#_5.0__REGISTRATION) Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
* TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at <https://triadinstall.acr.org/triadclient/>.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [TRIAD-Support@acr.org](mailto:TRIAD-Support@acr.org) or 1-703-390-9858.

* + 1. Method

*For studies assigned for* ***CTMS Comprehensive*** *Monitoring:*

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](mailto:CTMSSupport@theradex.com) for additional support with Rave and completion of CRFs.

*For studies assigned for* ***CTMS Routine*** *Monitoring:*

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 on an 18-36 month basis. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. 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](mailto:CTMSSupport@theradex.com) for additional support with Rave and completion of CRFs.

* + 1. 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 (<https://datascience.cancer.gov/resources/metadata>). 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>).

## Data Quality Portal

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

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

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website.  Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members’ website.

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

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

## CTEP Multicenter Guidelines

Not applicable.

## 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](mailto: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.

# REFERENCES

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# APPENDIX A PERFORMANCE STATUS CRITERIA

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

# APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

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

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| 1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).   Formulae:   |  |  |  | | --- | --- | --- | | **Race and Sex** | **Serum Creatinine (SCr), *µmol/L (mg/dL)*** | **Equation** | | **Black** |  |  | | Female | ≤62 (≤0.7) | GFR = 166 × (SCr/0.7)−0.329 × (0.993)Age | |  | >62 (>0.7) | GFR = 166 × (SCr/0.7)−1.209 × (0.993)Age | | Male | ≤80 (≤0.9) | GFR = 163 × (SCr/0.9)−0.411 × (0.993)Age | |  | >80 (>0.9) | GFR = 163 × (SCr/0.9)−1.209 × (0.993)Age | |  |  |  | | **White or other** |  |  | | Female | ≤62 (≤0.7) | GFR = 144 × (SCr/0.7)−0.329 × (0.993)Age | |  | >62 (>0.7) | GFR = 144 × (SCr/0.7)−1.209 × (0.993)Age | | Male | ≤80 (≤0.9) | GFR = 141 × (SCr/0.9)−0.411 × (0.993)Age | |  | >80 (>0.9) | GFR = 141 × (SCr/0.9)−1.209 × (0.993)Age |   SCr in mg/dL; Output is in mL/min/1.73 m2 and needs no further conversions. |
| 1. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).   175 x SCr–1.154 × age–0.203 × 0.742 (if female) × 1.212 (if black)  Output is in mL/min/1.73 m2 and needs no further conversions. |
| 1. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).     Followed by conversion to a value normalized to 1.73 m2 with the patient’s body surface area (BSA). |

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# APPENDIX C PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient Name:** |  | **Diagnosis:** |  | **Trial #:** |  |
| **Study Doctor:** |  | **Study Doctor Phone #:** |  | **Study Drug(s):** |  |

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

**These are the things that your healthcare providers need to know:**

Camonsertib (RP-3500) interacts with CYP3A4/5, 2C8, 2C19, and 2B6, P-gp and BCRP, and MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, and OAT1.

|  |  |
| --- | --- |
|  | **Explanation** |
| **CYP isoenzymes** | The enzymes in question are CYP3A4/5, 2C8, 2C19, and 2B6. Camonsertib (RP-3500) is broken down by CYP3A4/5 and to a lesser extent 2C8 and 2C19 and may be affected by other drugs that inhibit or induce this enzyme. It is also a weak inhibitor of CYP2C8 and weak inducer of 2B6 and 3A4. |
| **Protein transporters** | The proteins in question are P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, and OAT1. Camonsertib (RP-3500) is moved in and out of cells/organs by P-gp and BCRP and may be affected by other drugs that inhibit these transporters. Camonsertib (RP-3500) is a weak inhibitor of P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, and OAT1. |

**These are the things that you need to know:**

The study drug camonsertib (RP-3500),may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John’s Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors or inducers of CYP3A4/5 and strong inhibitors of P-gp and BCRP.

* Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
  + Avoid grapefruit, grapefruit juice and Seville oranges while taking camonsertib.
  + Avoid or limit sun exposure while taking camonsertib (e.g. use sunscreen, wear clothing to cover extremities, avoid direct sun exposure).
* Make sure your doctor knows to avoid certain prescription medications.
* Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version MAR2025

**PATIENT DRUG INTERACTION WALLET CARD**

**A white and grey scissors

AI-generated content may be incorrect.**

|  |  |  |  |
| --- | --- | --- | --- |
| **A red text on a white background  AI-generated content may be incorrect.** | **A red text on a white background  AI-generated content may be incorrect.** | **A red text on a white background  AI-generated content may be incorrect.** | **A red text on a white background  AI-generated content may be incorrect.** |
| **EMERGENCY INFORMATION** |  | **dRUG INTERACTIONS** | |
| **Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.** | Tell your doctors **before** you **start** or **stop** any medicines.  **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!** | **Carry this card with you at all times**  Camonsertib (RP-3500) interacts with mainly CYP3A4/5, P-gp, and BCRP and must be used very carefully with other medicines. | |
| **Patient Name:** | **Use caution and avoid the following if possible:**  Avoid grapefruit, grapefruit juice and Seville oranges while taking camonsertib (RP-3500). Avoid or limit sun exposure while taking camonsertib (RP-3500). | Your healthcare providers should be aware of any medicines that are strong inhibitors and inducers of CYP3A4/5 and strong inhibitors of P-gp and BCRP.  Camonsertib (RP-3500) is also a weak inhibitor of CYP2C8 and weak inducer of 2B6 and 3A4. Camonsertib (RP-3500) is also a weak inhibitor of P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, and OAT1. | |
| **Diagnosis:** |
| **Study Doctor:** |
| **Study Doctor Phone #:** |
| **NCI Trial #:** | **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. | |
| **Study Drug(S):** camonsertib (RP-3500) |
|  | VersionMAR2025 |
| **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER |
| cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov |

# APPENDIX D MEDICATION DIARY

The medication diary is located on the next page.

**PATIENT’S MEDICATION DIARY – Camonsertib**

**Today’s Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** **Cycle \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ CTEP-assigned Protocol # 10732**

**Patient Study ID \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Patient Initials \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Local Protocol #**

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of camonsertib each day **in the morning**. You will take four 5 mg capsules and two 40 mg capsules (100 mg dose), three 40 mg capsules (120 mg dose), or four 40 mg capsules (160 mg dose) every day. You should swallow the capsules whole.
3. You should take the capsules with 8 oz. water, with or without any moderate fat or low-fat food.
4. **Keep the capsulesintact, they must not be broken, chewed, or crushed**.
5. If you forget to take a dose, take it as soon as possible that day. There must be at least an 8 hour interval before the next dosing time. If it is within 8 hours of the next usual dosing time, skip the missed dose and take the next dose at the usual time.
6. If vomiting occurs, do not take an additional dose. Take the next dose at your usual time.
7. Record the date, the number of capsules you took, and when you took them.
8. If you have any comments or notice any side effects, please record them in the Comments column for that day.
9. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
10. Please return this form and your bottle(s) of capsules to your physician when you go for your next appointment.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Day** | **Date** | **What time was dose taken?** | **# of capsules taken** | | **Comments** |
| **5 mg** | **40 mg** |
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| **Physician’s Office will complete this section:**  1. Date patient started protocol treatment \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  2. Date patient was removed from study \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  3. Patient’s planned total daily dose \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  4. Total number of capsules taken this month \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  5. Physician/Nurse/Data Manager’s Signature/Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

**Patient’s Initials / Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

# APPENDIX E PHARMACOKINETICS (PK) SHEET C1D1, C1D2

