NATIONAL CANCER INSTITUTE
Center for Cancer Research

Date: December 15, 2022

From: Vassiliki Saloura, MD, TGMB, NCI

To: CTEP, NCI

Subject: Response to Amendment to CTEP for protocol 19C0041_10184 entitled, Birinapant and Intensity Modulated Re-Irradiation Therapy (IMRRT) for Locoregionally Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC)

We respectfully submit an amendment to protocol #10184 (**version date 12/15/2022**) to CTEP for **urgent** review. The main purpose of this amendment is to allow 3 participants at a time to be enrolled in each dose cohort. The protocol currently allows just one participant to be enrolled at a time. There are currently 2 eligible participants awaiting enrollment at 2 participating sites. This study has been very slow to accrue and this change will allow both participants to enroll soon for treatment and concurrently. The risk profile of the study so far has been very safe, with no DLTs that mandated enrollment of 3 more participants in each of the first two dose cohorts. Furthermore, the safety of birinapant as monotherapy at much higher doses (47mg/m^2) has already been established in other phase I studies (https://pubmed.ncbi.nlm.nih.gov/26333381).

This amendment has been discussed with Dr. Steven Gore who agrees this may be submitted as an urgent amendment for expedited review.

Thank you for your consideration of this amendment. The changes are detailed below.

SUMMARY OF CHANGES – Protocol

#	Section	Change
1.	Header	The version date was updated in the header throughout.
2.	**Title** Page	• Carter VanWaes has been removed as a co-investigator. He has left the NIH. • Study coordinator and contact info has been updated. • The protocol version number and date were updated.
3.	Section **6.1.1,** Dose Escalation Cohort	Language has been added in order to allow up to 3 patients to be enrolled in each remaining cohort for the remainder of the trial. The protocol currently allows just one participant to be enrolled at a time. There are currently 2 eligible participants awaiting enrollment at 2 participating sites. This study has been very slow to accrue and this change will allow both participants to enroll soon for treatment and concurrently. The risk profile of the study so far has been

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NCI Protocol #: 10184
Local Protocol Number: 19-C-0041
ClinicalTrials.gov Identifier: NCT03803774

Title: Birinapant and Intensity Modulated Re-Irradiation Therapy (IMRRT) for Locoregionally Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC)

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NCI-Supplied Agent:

Drug Name:	Birinapant (NSC 756502)
IND #:	
Sponsor	DCTD, NCI
Manufacturer	IGM Biosciences

Protocol Type / Version # / Version Date: *Amendment / Version 20 / December 15, 2022*

SCHEMA

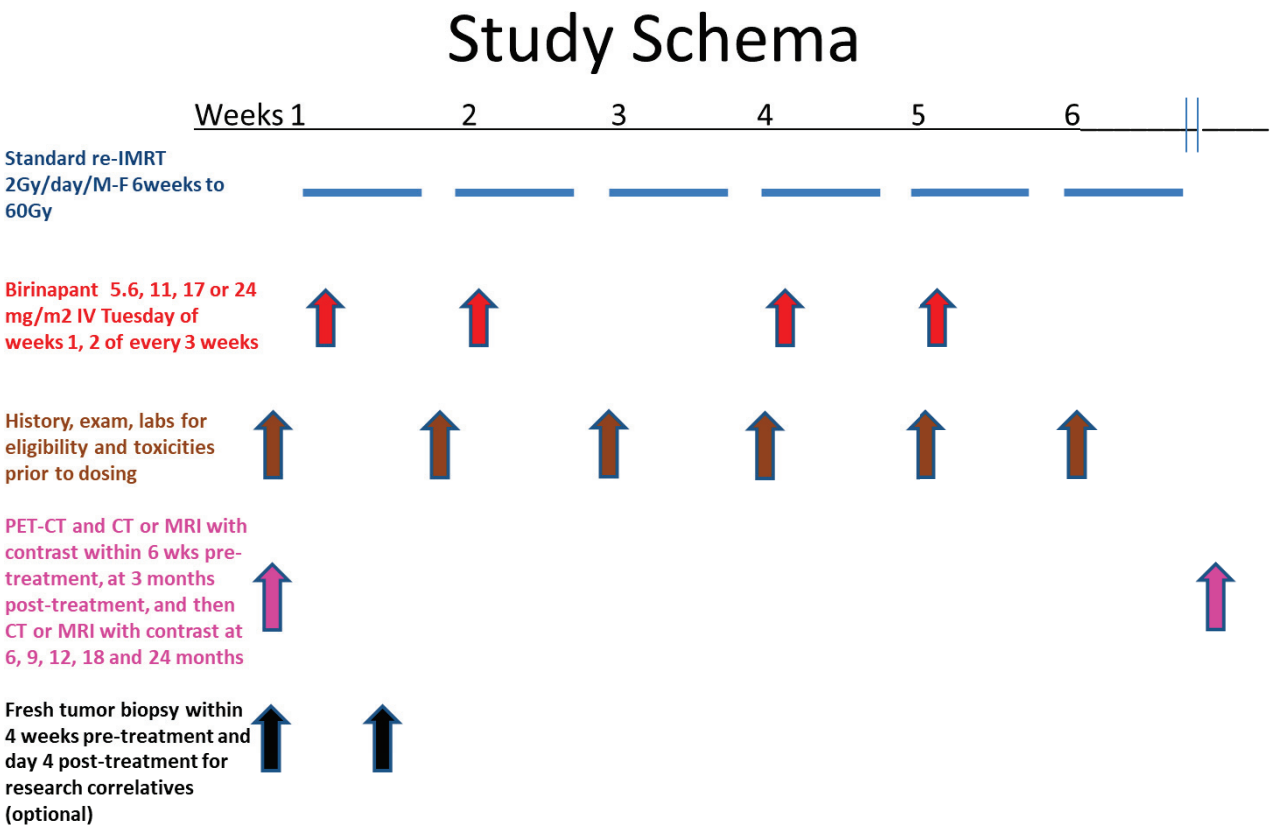

Study Schema
Weeks 1
2
3
4
5
6
Standard re-IMRT 2Gy/day/M-F 6weeks to 60Gy
Birinapant 5.6, 11, 17 or 24 mg/m2 IV Tuesday of weeks 1, 2 of every 3 weeks
History, exam, labs for eligibility and toxicities prior to dosing
PET-CT and CT or MRI with contrast within 6 wks pre-treatment, at 3 months post-treatment, and then CT or MRI with contrast at 6, 9, 12, 18 and 24 months
Fresh tumor biopsy within 4 weeks pre-treatment and day 4 post-treatment for research correlatives (optional)

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objectives

- Determine the toxicities and maximum tolerated dose (MTD) of birinapant concurrent with intensity modulated re-irradiation therapy (IMRRT).

1.2 Secondary Objectives

- Determine the objective response rate of patients with locoregionally recurrent head and neck squamous cell carcinoma (HNSCC) treated with re-irradiation and birinapant.
- Determine the local-regional control, progression free survival (PFS), and overall survival.
- Determine if FADD and/or BIRC2/3 copy gain in tumor tissue are associated with improved response, locoregional control (LCR), progression-free survival and overall survival.
- Determine the feasibility of detecting effects of birinapant and re-irradiation on pilot pharmacodynamic biomarkers in tumor tissue, by using microwestern to assess decrease in drug targets IAP1/2 and increase in apoptosis/necroptosis markers Caspase 3 and MLKL.

1.3 Exploratory Objectives

- Explore if mutational load detected with whole exome sequencing of tumor tissue influences objective response rate.
- Explore if PD-L1, CD8 T-cell tumor infiltration, and other immune related biomarkers in tumor tissue are associated with objective response rate.
- Explore the pharmacokinetics of birinapant in combination with radiotherapy in blood samples.
- Explore whether specific germline single-nucleotide polymorphisms (SNPs) are associated with response to birinapant and reirradiation.

2 BACKGROUND

2.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinomas (HNSCC) affect ~52,000 new patients and cause ~11,000 deaths in the U.S. annually(1). HNSCC include a subset linked to human papillomavirus (HPV+) with better prognosis, and an HPV- subtype linked to tobacco use and worse prognosis in patients receiving standard treatment. The Cancer Genome Atlas recently uncovered amplifications of chromosome 11q13/22 in ~30% of HNSCC associated with an HPV- subtype and worse 5-year survival of<50% (2). The 11q13/22 loci harbor genes Fas Associated Death Domain (FADD) and Baculovirus Inhibitor of apoptosis Repeat Containing (BIRC2/cIAP1). A mutually exclusive subset harboring mutations of caspase 8 (CASP8) affects an additional 10% of HPV- cases (2, 3). Further, deletions in Tumor Necrosis Factor Associated Factor 3 and overexpression of BIRC3 (cIAP2) are detected in ~20% of HPV+ HNSCC(2). Together, these genes encode proteins that form critical components of the Tumor Necrosis Factor

Receptor/Death Domain Receptor signaling complex, which is deregulated and implicated in cell survival and therapeutic resistance in cancer (3, 4). Significantly, our pan-cancer comparison of TCGA data reveals that HNSCC are among the cancers with the highest frequency of genomic alterations in these cell death pathway genes, making them a potentially important target for therapy(5). Of clinical importance, since FADD/BIRC2 are associated with worse prognosis in patients with HPV- HNSCC receiving standard treatment(2), patients with recurrent HNSCC should be enriched for FADD/BIRC2 amplification or CASP8 mutations.

Binding of TNFα, or other death agonists to their receptors typically leads to cell death via FADD through the activation of caspase-8 and induction of apoptosis, or alternatively, by activation of RIP kinase 1 (RIPK1), MLKL, and induction of necroptosis(6, 7); **Figure 1**. However, the cellular Inhibitor of Apoptosis proteins cIAP1 and 2 encoded by BIRC2/3, are key antagonists of cell death signaling by TNF/FADD/CASP8 and cytotoxic therapies. Of therapeutic significance, IAP degradation and cell death signaling may be enhanced by Second Mitochondrial Activator of Caspases (SMAC) released during cell death, or SMAC peptidomimetics(4, 8).

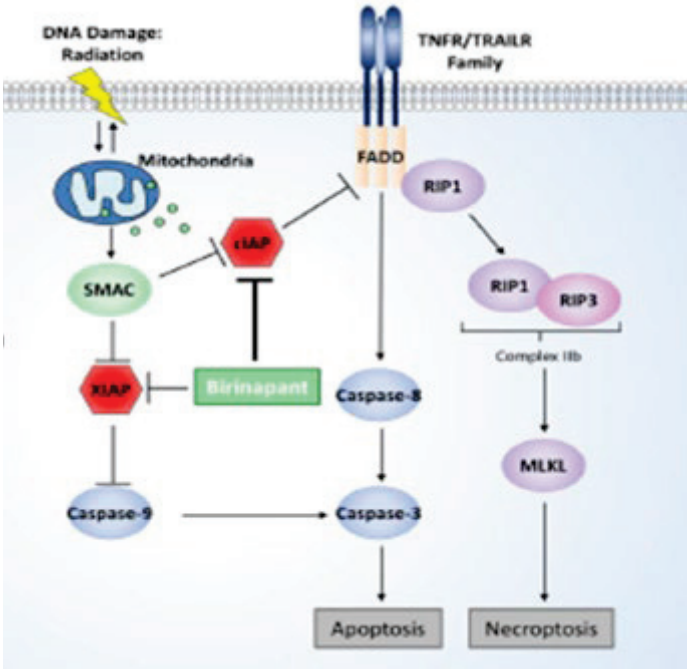


Figure 1: The intrinsic cell death pathway, induced by mitochondria in response to cell injury, and the extrinsic pathway, triggered by ligands of the death receptor ligand family are two pathways that converge on caspase-3 to induce apoptosis. Death ligand binding via the extrinsic pathway results in cytoplasmic complex that includes RIPK1 and FADD.

2.2 CTEP Agent

Birinapant is a novel bivalent small molecule peptidomimetic of SMAC, shown to preferentially target cIAP1, relative to cIAP2 and XIAP(9, 10). Birinapant demonstrated anti-tumor activity in preclinical models of hematological cancers and solid tumors including melanoma, colorectal, ovarian, and breast cancer (11, 12). In early phase clinical trials, birinapant has demonstrated tolerability and safety at effective doses, with a prolonged plasma half-life of 31 hours and tumor

half-life of 52 hours(12). In a 5-arm phase I/II dose escalation study of birinapant administered intravenously in combination with different chemotherapies (docetaxel, irinotecan, gemcitabine, carboplatin/paclitaxel, liposomal doxorubicin) in patients with solid tumors, safety and tolerability was confirmed and a phase II dose was established (13). Interestingly, birinapant demonstrated prolonged progression free survival in previously relapsed or refractory patients when combined with chemotherapies that induce TNFα, such as irinotecan(13). Importantly, induction of TNFα is also a critical effector of the cytotoxic effects of radiation therapy, which is a major modality in treatment of patients with HNSCC(14, 15).

In pre-clinical studies, we identified several HNSCC cell lines harboring FADD/BIRC2 amplifications by exome sequencing (5) (**Figure 2**). Birinapant, a novel SMAC mimetic that promotes cIAP degradation, sensitized multiple HNSCC lines to cell death by agonists TNFα or TRAIL, including lines harboring FADD-/+BIRC2 amplification (**Figure 2**).

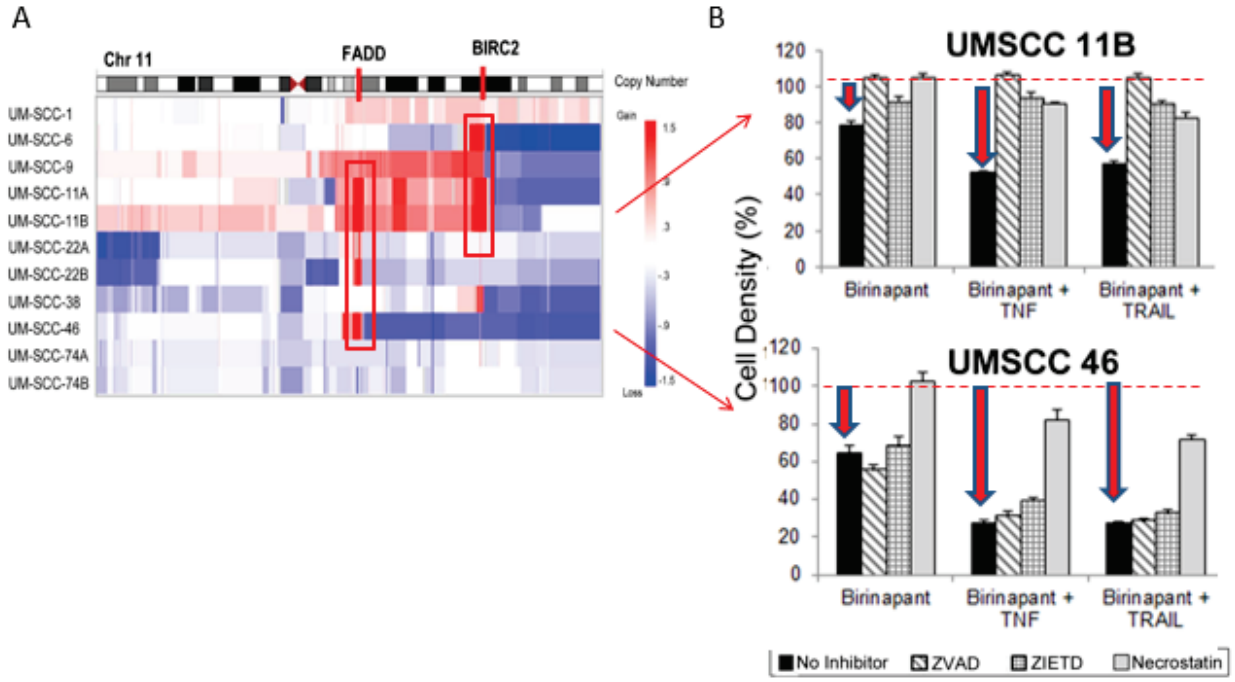


Figure 2: A, UM-SCC cell lines with focal amplifications of Chromosome 11q13/22 harboring FADD and BIRC2/3. B, Birinapant (1mM) plus death ligands TNFa (20ng/ml) or TRAIL (100ng/ml) inhibit UM-SCC11B and 46. Inhibition was reversed by inhibitors of pan-caspase (ZVAD), caspase 8 (ZIEDT) and/or necrosis (necrostatin).

The HNSCC varied in mechanisms of cell death mediated by caspase-dependent apoptosis inhibited by ZVAD or ZIEDT and/or RIPK1/MLKL-mediated necroptosis inhibited by necrostatin, corresponding with genomic amplification and overexpression of FADD-/+ BIRC2 (**Figure 2**). We confirmed that FADD or BIRC2 siRNA knockdown inhibited these HNSCC displaying gene amplification and increased expression, while transfection of a plasmid overexpressing FADD in the UM-SCC38 line lacking FADD amplification (**Figure 2**) sensitized it to the combination of birinapant and TNFα, supporting their functional importance(5) (data not

shown).

Western blot confirmed that birinapant plus TNF-α induces cIAP1 degradation and is accompanied by predominantly sustained caspase 8 and 3 cleavage in UM-SCC11B, and predominant induction of necroptosis marker MLKL in UM-SCC46 **Figure 3**.

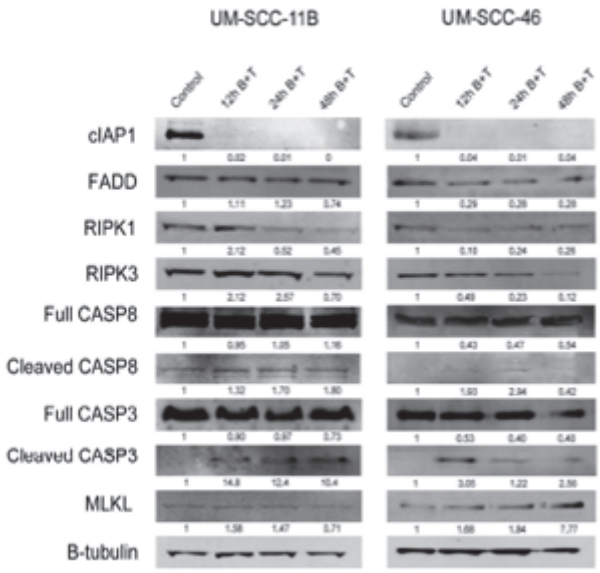


Figure 3. Birinapant (1mM) plus TNFa (20ng/ml) promotes degradation of cIAP1 and enhances caspase 8 and 3 activation in UM-SCC11B, and caspase 3 and MLKL activation in UM-SCC46. Fold change normalized to untreated control and beta-tubulin loading control is indicated

In vivo, birinapant monotherapy (15 or 30 mg/kg) every 3 days for 21 days significantly inhibited tumor growth and prolonged host survival in xenograft models of the UM-SCC 46 and 11B lines overexpressing FADD+/-BIRC2 (**Figure 4**).

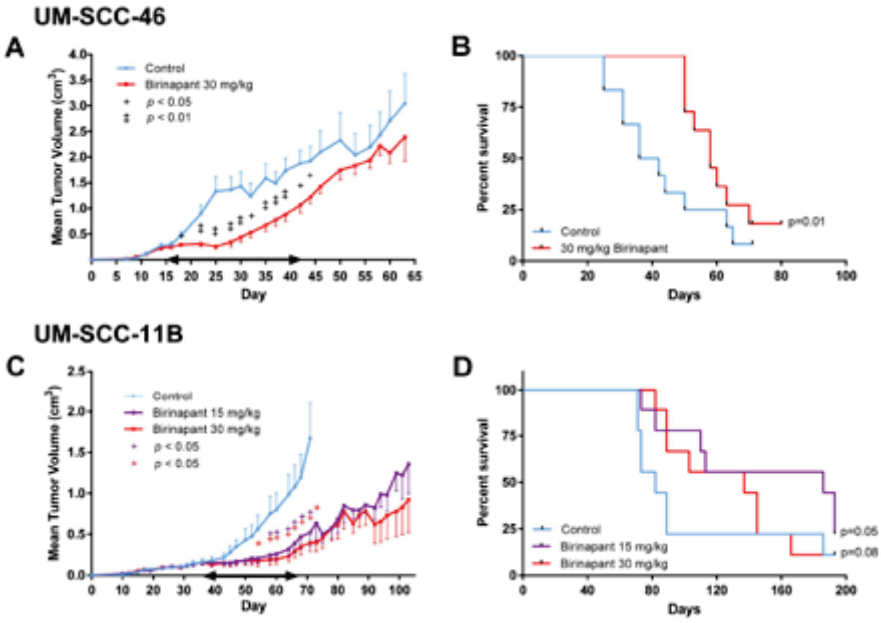


Figure 4: Birinapant slows tumor growth and improves survival in two mouse models of HNSCC with FADD-/+BIRC2 co-amplification. 5x106 UM-SCC-46 (FADD) or -11B (FADD+BIRC2) amplified cells were injected subcutaneously into the right hind flanks of SCID/NCr-Balb mice. Mice were randomized into treatment groups (UM-SCC-46 n=15 mice/group; UM-SCC-11B n=9 mice/group), and treatment was initiated 15 (UM-SCC-46) or 35 (UM-SCC-11B) days after tumor inoculation, when tumors reached 200 mm3. Mice received control vehicle, 15 or 30 mg/kg birinapant i.p. every 3 days as indicated for a total of 10 doses. A, B, In the UM-SCC46 model, birinapant-treated mice showed significant inhibition of tumor volume versus control vehicle (+, $p<0.05$; ++, $p<0.01$), and improved median survival of 58 days compared with 39 days for control (median survival advantage of 19 days). C, D, In the UM-SCC-11B model, birinapant-treated mice showed significant inhibition of tumor volume versus control vehicle (+, $p<0.05$; ++, $p<0.01$), and increased survival was seen with medians of 82 days (control), 186 days (15 mg/kg group), and 137 days (30 mg/kg group). For survival analysis, the Gehan-Breslow-Wilcoxon test was used and significance set to 0.05 using the Bonferroni method.

2.3 Prior Phase I/II Studies

Up to October 2016, approximately 400 patients with solid tumors or hematological malignancies had been treated with birinapant at doses up to 63 mg/m2/dose, either as a single agent or in combination with chemotherapies.

The MTD of birinapant administered IV weekly for 3 consecutive weeks followed by 1 week off has been determined to be 47 mg/m^2 when administered as a single agent in subjects with solid tumors. Birinapant-related Grade 3 or 4 adverse events (AEs) have included nausea, vomiting, rash, hypophosphatemia, headache, fatigue, amylase increase, lipase increase, lymphopenia, and thrombocytopenia, and have been reversible without sequelae. Other subjects have experienced a constellation of AEs that appeared to be dose-related and included rash, fever, chills, hypotension, nausea, headache, and hypophosphatemia; however, other etiologies of these events may have been possible. These AEs occurred with first drug exposure and resolved without sequelae.

Cranial nerve palsies (most commonly Bell's palsy) have occurred in subjects who have received birinapant. The cranial nerve palsies are typically mild to moderate in severity and in those cases

treated with corticosteroids, symptoms have either resolved or were resolving at the last follow-up visit. Some subjects who reported cranial nerve palsy elected to continue birinapant treatment, and of those that continued on treatment, none had a recurrent event. The onset of cranial nerve palsy may be preceded by a prodromal syndrome of headache, ear, facial pain and/or diplopia.

Other safety considerations observed with birinapant treatment are events of Grade 3 or greater increases in serum amylase and serum lipase. Most of these events were reversible and all subjects remained asymptomatic.

2.4 Rationale

Radiation therapy is a major modality in treatment of patients with HNSCC. Radiation therapy induces reactive oxygen species that mediate DNA damage, intrinsic death pathway activation, as well as TNFα that induces extrinsic death pathway activation (**Figure 1**). Remarkably, concurrent birinapant 15mg/kg every 3 days plus radiation 2 Gy/day M-F for 2 weeks followed by an additional 2 weeks of birinapant induced durable cures >100 days and potentiated expression of TNFα (**Figure 5**).

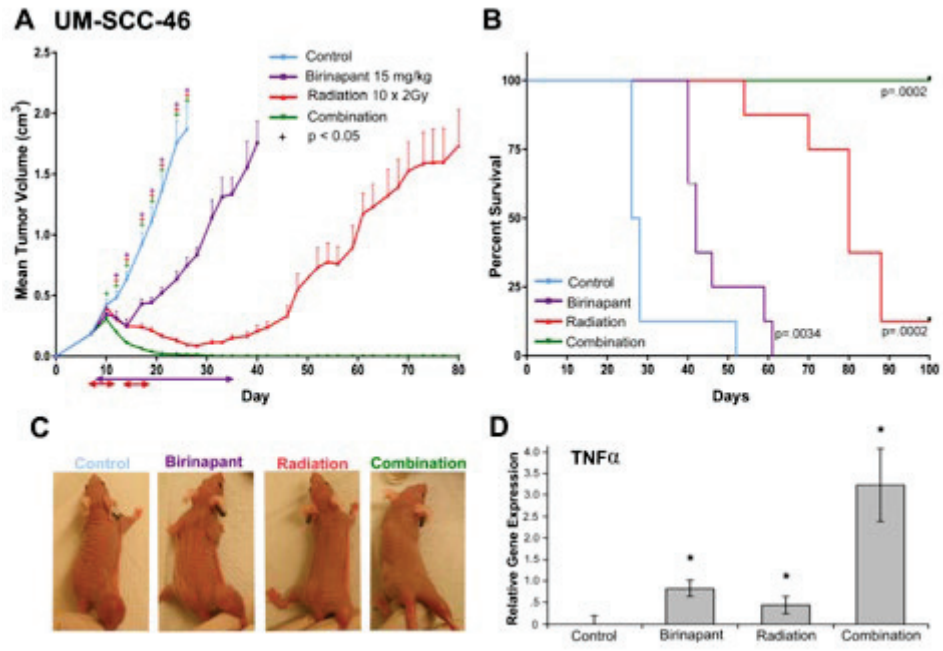


Figure 5: Combination of birinapant plus radiation induces tumor regression and durable cure in the UM-SCC-46 xenograft model. A, Effects of birinapant, radiation, and combination therapy on growth of UM-SCC-46 xenografts. 2.5 × 106 UM-SCC-46 cells were implanted into the upper portion of the right leg in athymic nu/nu mice. Mice were randomized into four treatment groups (vehicle control n=12, 15 mg/kg birinapant n=12, 10 × 2 Gy radiation n=12, or combination n=12) seven days after tumor inoculation (day 7) when average tumor volume reached ~200 mm3. Radiation treatment began on day 7: 2 Gy of radiation given M-F for two weeks—a total of 20 Gy (double headed arrows). Birinapant treatment began on day 8: 15 mg/kg birinapant i.p. every three days for a total of ten doses (purple double headed arrow). Treated mice in all groups showed significantly decreased tumor volume compared to the control. Combination treated animals showed durable regression compared to all other groups. Statistical difference vs control by student t-test (+; $p < 0.05$). Error bars, SEM. B, treated mice showed significantly enhanced survival. Survival analysis was performed using the Gehan-Breslow-Wilcoxon test to determine p-value. Median survival times were 27 days (control), 42 days (birinapant, p=0.003), 80 days (radiation, p=0.0002), and combination treatment group is currently without death, at 130 days. C, Photos of tumors on right hind leg of

representative mice from each treatment group on day 21 (after five doses of birinapant and 20 Gy radiation). D, Relative TNFa gene expression in tumors from each treatment group on day 21. Endogenous mTNFa was compared by qRT-PCR as described in methods. Statistical difference by Student t-test (+; $p < 0.05$).

Birinapant and radiation treated mice trended toward lower weight but showed no evidence of worse acute radiation dermatitis or decrease in mobility or contracture involving the irradiated limb (**Figure 5**, right panel). Together, these findings unveil a novel therapeutic approach for HNSCC harboring FADD/BIRC2 genomic alterations associated with worse prognosis.

Current standard treatment for advanced stage III/IV HNSCC typically includes surgery with post-operative radiotherapy, or definitive concurrent chemo-radiotherapy alone(16). About 50% recur within 5 years. The majority of these are patients with HPV- cancers. Survival analysis of 243 TCGA patients with HPV- cancers harboring 11q13 amplification of FADD indicate they are enriched among those recurring in the first two years(2). Based on these observations, patients with local-regionally recurrent HNSCC who are otherwise unselected would thus be expected to be enriched for FADD-/+BIRC2 amplification.

The treatment of such patients with recurrent HNSCC after prior surgery and irradiation or chemo-radiation presents a unique challenge, as many patients present with unresectable disease. Median survival with palliative chemotherapy is ~5-9 months, with 1-yr survival of ~20-30% (16, 17). Reirradiation remains the only potentially curative treatment option. Salvage reirradiation with concurrent radiosensitizing chemotherapy is the current standard of care (17). The data supporting this approach are mainly derived from Phase I/II trials, and investigation of a number of different radiation and chemotherapy regimens have been considered acceptable in this setting. With targeting of re-irradiation to recurrent tumor, dosing to 60Gy or higher is associated with greater local control, and is usually feasible, with sparing of the spinal cord and acceptable toxicities (18). In a phase I study of bortezomib and re-irradiation at NIH, 15/17 patients completed re-RT to 60-70Gy(19). At Ohio State University, 60-70Gy re-RT is given as standard of care with acceptable toxicity. Local control rates for reirradiation with chemotherapy are nearly 50% at 1 year (18), and demonstrate improved overall survivals (OS) of 8-28 months, with 2-year OS rates of 15-38%(20, 21), but greater toxicity when combined with cisplatin(18), highlighting the potential benefit for more efficacious and tolerable regimens.

Based on our pre-clinical studies, birinapant plus radiation demonstrates anti-tumor activity and improved survival, but the dose, schedule and tolerability in human studies needs to be determined. We propose a phase I trial for patients with local-regionally recurrent HNSCC who are candidates for irradiation, to determine the feasibility, toxicities and maximally tolerated dose (MTD) and schedule of concurrent therapy with birinapant. The dose steps proposed include 5.6, 11, 17 and 24 mg/m^2 IV, which in prior studies has been administered week 1 and 2 every three weeks, and tolerated in single agent and combination regimens with several cytotoxic chemotherapy agents (12, 13). The starting dose of 5.6 mg/M2 is the lowest dose along the previously used dose escalation schedule predicted to be potentially therapeutically active, and the first dose below 1/6 the MTD of 47mg/M2 for single agent birinapant, considered a margin of safety for starting combination with radiation, for which toxicities are unknown. Doses above 24mg/M2 in chemotherapy combinations were associated with dose limiting toxicities (12, 13). Weekly dosing is consistent with the prolonged half-life demonstrated in tumors. Dose limiting toxicities have included facial nerve and other cranial neuropathies, reversible with cessation or delayed dosing of birinapant. Because of the potential for the combination to exacerbate cranial

neuropathy or mucosal toxicity, the schedule incorporating the 1 week break every 3 weeks and weekday visits to radiation oncology provides an added level of safety for observation and drug dose modification or cessation, if detected.

2.5 Correlative Studies Background

Included as secondary objectives are several hypotheses generating candidate biomarkers, based on prior preclinical and clinical findings. We have demonstrated the feasibility of detecting FADD, BIRC2 and other genomic alterations in human HNSCC by exome sequencing(2) (5). At the conclusion of the study, whole exome sequencing and microwesterns will be performed on tumor biopsy specimens as an integrated biomarker for the proposed biomarkers to be investigated as secondary endpoints. More specifically, we will assess pretreatment specimens for copy number alteration compared to DNA from patient-matched blood, to explore if patients with recurrent HNSCC are enriched for FADD and BIRC2, and if these correlate with response. We further demonstrated the feasibility of detecting birinapant-mediated IAP1 degradation, and activation of caspase-dependent apoptosis or MLKL-dependent necroptosis by western blot in HNSCC lines and xenografts(5), and piloted capillary western assays for cIAP1 and caspase 3 in a recent Phase II study of birinapant in ovarian cancer (20). In preclinical studies, we observed inhibition of IAP1 expression and increased cell death markers in human HNSCC xenografts on day 4 at the end of a week of RT given daily M-F (days 0-4), and birinapant given on day 1 (Tuesday). Thus, at the conclusion of the study, we will compare matched day 4 on-treatment and pretreatment biopsies for degradation of target cIAP1, cleaved caspase 3, and/or increased MLKL, as candidate pharmacodynamic markers. These genomic alterations and cell death proteins may help determine the feasibility of incorporating their study as biomarkers for selection and pharmacodynamic effects in future phase II studies and will not be used for patient selection in the present study.

With regard to the exploratory objectives, recent trials for immune checkpoint expression and inhibitors in recurrent HNSCC have demonstrated increased expression of PDL1 and activity. As birinapant and radiation could enhance immunogenic cell death and PDL1 expression, pilot studies comparing pre- and on treatment effects of birinapant and radiation on the immune checkpoint molecule PD-L1, and CD8 effector T cells will be explored, provided sufficient tumor specimens remain.

Pharmacokinetic assessment of birinapant will be pursued, because we want to know how radiotherapy may alter the pharmacokinetic properties of birinapant.

Pharmacogenomic studies (SNP analysis) will also be conducted. OATP1B3 and P-glycoprotein are each expressed both the liver and in head and neck cancers. Since birinapant is a substrate of the OATP1B3 transporter and inhibits P-glycoprotein, variation in genes encoding these transporters may be associated with pharmacokinetic or pharmacodynamic variability, potentially affecting birinapant clinical outcome.

3 PATIENT SELECTION

In order to determine eligibility, subjects will be screened per the **STUDY CALENDAR** once the subject has signed the appropriate consent. In addition, the following minimal risk activities may be performed prior to obtaining subject consent:

a. Email, written, in person or telephone communications with prospective subjects
b. Review of existing medical records to include H&P, laboratory studies, etc.
c. Review of existing MRI, x-ray, or CT images
d. Review of existing photographs or videos
e. Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed locally recurrent HNSCC, including nasopharyngeal or sinonasal cancer for whom re-irradiation for local control is considered standard of care.

3.1.2 Patients with HPV-negative or HPV-positive head and neck cancer are eligible.

3.1.3 Patients who have had prior treatment with immune therapies are eligible.

3.1.4 Patients must have received curative-intent platinum- and/or cetuximab-based chemoradiotherapy or radiotherapy alone.

3.1.5 Patients must have completed their last treatment dose with chemotherapy or immunotherapy at least 4 weeks (6 weeks for nitrosoureas or mitomycin C) before enrolling on study.

3.1.6 Patients must have completed their last treatment dose with radiotherapy at least 6 months before enrolling on study.

3.1.7 Patients who have had major surgery must be fully recovered and require a recovery period of at least 4 weeks prior to enrolling on study.

3.1.8 Age ≥18 years.

3.1.9 ECOG performance status ≤2 (see **Appendix A**).

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

– Hemoglobin	≥ 9 g/dL (transfusion permitted)
– Absolute neutrophil count	≥1,500/mcL
– Platelets	≥100,000/mcL
– Total bilirubin institutional limits	within 1.5 x the upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– Serum creatinine	≤1.5x upper limit of normal (ULN), **OR**:
Creatinine clearance	≥50 mL/min according to Cockcroft Gault formula or other institutional methods.
– Cardiac function	Patients must have a QTcF ≤ 480 msec.
– INR	INR ≤ 1.5 and no clinically significant bleeding event

within the past six months

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

3.1.12 Patients must have measurable disease, per RECIST 1.1. See Section **12** for the evaluation of measurable disease.

3.1.13 The effects of birinapant on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) beginning at study entry and for the duration of study participation. Male study participants should use an additional barrier method of contraception for 30 days following the last dose of birinapant. 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.

3.2 Exclusion Criteria

3.2.1 Eligibility for curative-intent surgery, unless the patient is considered a poor surgical candidate related to resectability, functional outcome, or prefers non-surgical therapy.

3.2.2 More than 2 lines of palliative systemic therapy (platinum-, taxane- or cetuximab-based chemotherapy or immunotherapy)

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnancy or lactation period. Pregnant women are excluded from this study because birinapant may have 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 birinapant, breastfeeding should be discontinued prior to enrollment. A negative pregnancy test is required for women of childbearing potential. Women who are postmenopausal (age-related amenorrhea $\geq$ 12 consecutive months, or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary, to confirm postmenopausal status, a FSH level may be included at screening.

3.2.8 HIV positive patients on combination antiretroviral therapy are

ineligible because of the potential for pharmacokinetic interactions with birinapant.

3.2.9 Patients requiring the use of anti-tumor necrosis factor (anti TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug (48 days for infliximab, 55 days for golimumab, 70 days for certolizumab and adalimumab, and16 days for etanercept).

3.2.10 Patients with previous exposure to birinapant.

3.3 Inclusion of Women and Minorities

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

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

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

Documentation requirements per registration type are outlined in the table below.

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

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

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

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

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

4.2 Site Registration

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

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

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

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

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

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI protocol # 10184 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # 10184 in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-NCI, and protocol #10184.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements for NCI Protocol # 10184 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.)
- For applicable ETCTN studies with a radiation and/or imaging (RTI) component,

the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place)

- Theradex-led ETCTN Specimen Tracking Training by one individual per participating site is required prior to site registration. Certificates of completion will be submitted to the CTSU through the Regulatory Submission Portal.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with

the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

As this trial has a slot reservation requirement, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment. Slots can be reserved for a maximum of 14 calendar days.

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

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

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

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

4.3.3 Special Instructions for Patient Enrollment

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 3.1.
- 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 ETCTN Biobanking and Molecular Characterization portion of this protocol. 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) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.3.4 OPEN/IWRS Questions?

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

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

4.4 General Guidelines

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

5 BIOMARKERS, CORRELATIVES AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Research specimens should be collected only after subject has signed consent and all eligibility criteria have been met.

Of the requested samples in the table below, the following are mandatory (see Section **5.7**):

- Archival FFPE tumor block or a minimum of 20 unstained + 2 H&E slides at baseline, if fresh biopsies cannot be obtained
- One 10ml blood sample in ETDA (for control DNA) at baseline
- Blood samples for PK assessments (C1D2, C1D9, C2D2, C2D9)

M=mandatory O=optional

Time Point	Specimen and Quantity (see Section 5.3.1.1 for specimen allocation details)	Send Specimens to:
Baseline		
	Tissue: 1 archival FFPE tumor block or 22-32 slides[5]: 1 leading H&E 3-5 micron stained slide, 20-30 unstained uncharged 10-micron slides, 1 lagging H&E 3-5 micron stained slide. NOTE: slides must be serially sectioned and numbered [1] (See Section **5.3.2.2**) [M] **OR** • 1-2 tissue cores in formalin[1] [O] and • 1-2 cores snap-frozen[1,3] [O]	EET Biobank[3]
	Blood: • 10 mL blood in EDTA - PBMCs for control DNA [M]	EET Biobank
	• 10 mL blood in EDTA (for pharmacogenomic studies)[6] [O]	NCI Blood Processing Core (BPC, Figg lab)
Cycle 1 Day 2 (C1D2)		
	• 6 mL blood in EDTA[4] for PK [M] o Pre-infusion (within 60 minutes prior to infusion) o Post-infusion (within 60 minutes post-infusion)	NCI Blood Processing Core (BPC, Figg lab)
Cycle 1 Day 4 (C1D4)		
	• 1-2 cores snap-frozen[1,3] [O] • 1-2 cores in formalin[1] [O]	EET Biobank[3] (for cores)
	• 6 mL blood in EDTA[4] (+/- 4 hr from scheduled tumor biopsy, for PK) [O][7]	NCI Blood Processing Core (for PK)
Cycle 1 Day 9 (C1D9)		
	• 6 mL blood in EDTA[4] for PK [M] o Pre-infusion (within 60 minutes prior to infusion) o Post-infusion (within 60 minutes post-infusion)	NCI Blood Processing Core

Cycle 2 Day 2 (C2D2)		
	• 6 mL blood in EDTA[4] for PK [M] o Pre-infusion (within 60 minutes prior to infusion) o Post-infusion (within 60 minutes post-infusion)	NCI Blood Processing Core
Cycle 2 Day 9 (C2D9)		
	• 6 mL blood in EDTA[4] for PK [M] o Pre-infusion (within 60 minutes prior to infusion) o Post-infusion (within 60 minutes post-infusion)	NCI Blood Processing Core

[1] A copy of the radiology and operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology reports to Rave and send a copy to the EET biobank. Formalin cores collected from all sites will be shipped to the EET Biobank.
[2] For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. Archival tissues will also be shipped to the EET Biobank.
[3] Snap frozen specimens will be shipped to the EET Biobank.
[4] Blood in EDTA for PK specimens will be processed and plasma will be aliquoted and stored frozen at sites for shipment to the NCI Blood Processing Core.
[5] 20 unstained plus 2 H&E slides are required. 10 additional unstained slides, for a total of 30 unstained plus 2 H&E would be preferred to pursue exploratory biomarkers.
[6] 10ml blood in EDTA for pharmacogenomic studies may be collected at baseline, C1D1 or C1D2.
[7] C1D4 6ml EDTA blood is required only if fresh biopsy is performed on C1D4. It is not required if archival tissue is submitted.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits

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

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types 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.

5.2.2 Scheduling of Specimen Collections

Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection. Formalin fixed tissue can be collected Monday through Thursday and shipped overnight for arrival on Tuesday through Friday at the EET Biobank at Nationwide Children's Hospital. The EET Biobank must be notified on Wednesday or Thursday by e-mail at BPCBank@nationwidechildrens.org prior to shipping formalin fixed tissue for receipt on Friday. For centers that can accommodate the transition from formalin to 100% ethanol, 24 hours after collection, the C1D4 biopsy can be scheduled on a Friday (if C1D1 falls on a Tuesday, or for other treatment delays), and tissue shipped the next business day. Frozen specimens, such as frozen tissue, may be collected, processed and shipped to the EET Biobank on Monday through Thursday, since the Biorepository does not need to perform additional processing. In the event that frozen specimens cannot be shipped immediately, they must be

maintained at -80°C.

Fresh blood specimens for DNA may be collected and shipped to EET Biobank Monday through Friday. Saturday delivery is only available for shipments of fresh blood for this protocol.

Fresh blood specimens for PK studies will be processed and plasma aliquoted and stored frozen at non-NCI sites for shipment to NCI Blood Processing Core. Those from NCI will be sent directly to the NCI Blood Processing Core for processing.

5.3 Specimen Collection Procedures

5.3.1 Biopsy Collection Procedure

Core biopsies will be obtained under local or general anesthesia (depending on the accessibility of the tumor). Ideally, 4 core biopsies should be obtained. The site of locoregional recurrence will be biopsied. US or CT-guidance may be used depending on the accessibility of the biopsy site (per head and neck surgeon's assessment)

For the collection of biopsy specimens, core needle biopsy is the preferred technique. It is preferred that 4 core biopsies 16-18 gauge in diameter and at least 1 cm in length, are obtained at baseline and 4 core biopsies on C1D4. Allocation of the core biopsies is dependent on the total number of cores procured and is detailed as follows:

5.3.1.1 Allocation of Core Biopsies at Baseline

Number of cores procured	FFPE (to ETCTN/MoCha)	Snap-frozen (to ETCTN/Annunziata lab)	FFPE (to ETCTN/van Waes/ Saloura labs)
1	1	0	0
2	1	1	0
3	1	1	1
4	1	2	1

5.3.1.2 Allocation of Core Biopsies on C1D4

Number of cores procured	Snap-frozen (to ETCTN/Annunziata lab)	FFPE (to ETCTN/van Waes lab)
1	1	0
2	2	0
3	2	1
4	2	2

Each specimen must be properly labeled. See Section **5.4.3** for label instructions.

5.3.2 Biopsy Processing Procedures

5.3.2.1 Formalin-Fixed Core Biopsy

1. Label formalin-filled containers according to instructions in section 5.4.2.
2. Following the allocation charts in 5.3.1, place tissue in cassettes, using a separate cassette for each tissue biopsy.

3. Snap the cassette lids closed and place cassettes in the pre-labeled formalin-filled container as soon as possible after collection to prevent air-drying. Up to 2 cassettes can be placed in one formalin container.
4. Record the time of fixation.
5. Secure container lids and package containers into the shipping kit according to instruction in section 5.5. Keep tissue in formalin jars at room temperature (20-25°C) until shipment to the EET Biobank.
6. Enter time of fixation into the Sample Tracking System (Rave) for all submitted specimens.

5.3.2.2 Archival Formalin Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously collected FFPE tissue will be submitted due to inaccessible or insufficient formalin fixed core tissue, then the following criteria must be met:

- Tissue from the most recent biopsy is preferred; however, older samples, including from the primary tumor are acceptable
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

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

Sequentially processed and numbered slides:

- One (1) H&E slide (3-5 µm) (slide #1)
- Twenty to thirty* (20-30) 10 µm unstained air-dried *uncharged* slides* (slides #2-21 or 31)
- One (1) H&E stained slide (3-5 µm) (slide #22 or #32 if 10 more slides can be provided as per the footnote below)

*20 slides are mandatory and an additional 10 unstained slides are requested, if available, for exploratory biomarkers (slides #2-31).

FFPE tissues must be shipped on the days of collection, on Monday and Thursday, for arrival to the EET Biobank no later than Friday. The EET Biobank must be notified on Wednesday or Thursday at the following email address: BPCBank@nationwidechildrens.org prior to shipping formalin fixed tissue, for receipt on Friday.

For centers that can accommodate the transition of formalin to ethanol 24h after collection, the C1D4 biopsy can be scheduled on a Friday (if C1D1 falls on a Tuesday). Then the sample can be shipped to the EET Biobank the next business day.

All remaining tissue from FFPE blocks should be returned from EET Biobank to the NCI for optional immune-related biomarker studies, once request to distribute samples for MoCha has been fulfilled. Tissue should be shipped to:

ATTN: Dr. Paul Clavijo

5.3.2.3 Snap-Frozen Core Biopsy

1. Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from resection.
2. Label cryovial(s) according to instructions in section **5.4.3**.
3. Using clean forceps place the tissue in a pre-chilled cryovial and freeze the tube in either vapor phase liquid nitrogen, on dry ice or by immediate placement in a -70 to -80°C freezer. Keep frozen until shipment to the EET Biobank.

5.3.3 Blood Collection

5.3.3.1 Collection of Blood in EDTA Tubes for DNA studies

1. Collect 10 mL blood in a pre-labeled EDTA tube(s) and gently invert tube to mix. Refer to Section **5.4.2** for labeling instructions.
2. Ship on day of collection (whenever possible) to EET Biobank according to instructions below.
3. If blood cannot be shipped on the day of collection (e.g. a late scheduled collection), then refrigerate until shipment.

5.3.3.2 Collection of Blood in EDTA Tubes for Pharmacokinetics (PK)

1. Label EDTA tubes with the Rave generated specimen ID (which includes the protocol number and Universal Patient ID), a patient study ID, specimen type (blood), and collection date.
2. At *each* PK time point, collect 6 mL blood from the arm opposite the site of infusion or distal to the site of infusion in pre-labeled EDTA tube(s) and gently invert tube to mix.
3. Immediately place on wet ice and within 1 hour after collection, centrifuge blood at 1,500 x g for 10 minutes at 4°C. Aliquot plasma into 1.8 – 2 mL cryovials and store in a -70 to -80°C freezer until shipment. Ship to NCI Blood Processing Core (BPC) according to instructions below (see Section **5.6.1**). Note: NCI site will send to the NCI Blood Processing Core (BPC) on wet ice for processing – see Section **5.6.1**.

5.3.3.3 Collection of Blood in EDTA Tubes for Pharmacogenomic studies

1. Collect 10 mL blood in a pre-labeled EDTA tube and gently invert tube to mix. Refer to Section **5.4.2** for labeling instructions.
2. Ship on day of collection (whenever possible) to NCI Blood Processing Core (BPC) according to instructions below (see Section **5.6.1**).
3. If blood cannot be shipped on the day of collection (e.g. a late scheduled collection), then refrigerate at 4ºC until time of shipment. Samples will be accepted no later than noon on Friday.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

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

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

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

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

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

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

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

5.4.2 Blood Specimen Labels

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

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (e.g. blood, serum)

- Collection date (to be added by hand)
- Note: PK labels must also include *exact* time of collection

5.4.3 Tissue Specimen Labels

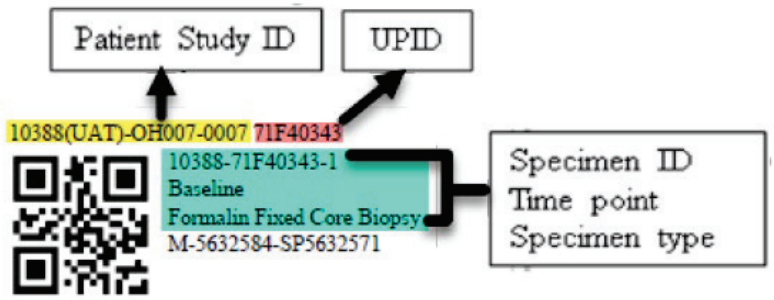
Include the following on all tissue specimens or containers (e.g., formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, etc.)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

5.4.4 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.

5.4.5 Overview of Process at Treating Site

5.4.5.1 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 with eligibility specimen analysis:

1. Site enters first step data into OPEN.
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 first step registration data, including the IDs and a TAC of "NOT REG" directly to Rave.
4. The specimen tracking system in Rave is utilized for the specimen that contributes to eligibility determination.
5. Site enters second and any subsequent step data into OPEN including results of specimen analysis.
6. IWRS receives all data from OPEN, then sends it onto Rave with either the treatment TAC or a TAC of "SCRN FAIL".
7. In addition to the specimen tracking forms completed to determine eligibility, data entry for screen failure patients should include Histology and Disease, all forms in the Baseline folder, any lab forms connected to eligibility determination, and Off Treatment/Off Study.

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

5.4.5.2 Rave Specimen Tracking Process Steps

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

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

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, 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 on each label.
- After collection, store labeled specimens as described in Section **5.3**.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or the Tissue Biopsy Verification form, when applicable (see **Appendix C**). 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 1st specimen in a shipment.
- **Copy Shipping** CRF**:** In the specimens folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status**.

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

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

Step 6: Send email notification.

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

Step 7: Ship the specimen(s).

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

5.5 Shipping Specimens from Clinical Site to the EET Biobank

5.5.1 General Shipping Information

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.

Core biopsies that are fixed in formalin and whole blood in EDTA should be shipped as one shipment at ambient temperature, whenever possible.

5.5.2 Required Forms for Tissue Submissions:

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

Tissue	**Required Forms**
Archival	1. Shipping List 2. Corresponding Pathology Report 3. The pathology report must also be uploaded in the ETCTN specimen tracking system*.
New Biopsy	1. Shipping List 2. Corresponding Pathology Report* OR all three of the following: • Surgical and/or Radiology Report • Tissue Biopsy Verification Form (see **Appendix C**) • Diagnostic Pathology Report
Research Blood	1. Shipping List

* If the pathology report is not available at the time of shipment, then it must be uploaded to the ETCTN specimen tracking system as soon as it's available, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

5.5.3 Specimen Shipping Instructions

Archival (FFPE) tissue may be shipped on Monday through Thursday.

Frozen specimens may be shipped on Monday through Thursday. Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment.

Formalin-fixed tissue must be shipped on the day of collection, on Monday through Friday.

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

5.5.3.1 Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to

Section **5.4.3**.

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

5.5.3.2 Shipping Ambient Blood Using Supplies Provided by the Institution

1. Before packaging specimens, verify that the collection tube is labeled according to instructions in section **5.4.2**.
2. Place the blood collection tube into a zip-lock bag.
3. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

Archival tissue and research blood for EET Biobank may be shipped together.

If new biopsies are performed, please follow instructions in the following section,

5.5.3.3 Shipping Ambient and Frozen Specimens in a Dual-Chamber Kit

The Dual Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit but should not be put in both.** The dual chambered kit is only used for shipments that contain both frozen and ambient specimens. If formalin-fixed or archival tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in **5.4.3** and that lids of all primary receptacles containing liquid are tightly sealed.

2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Prepare the frozen specimens for shipment:
   a. Place the specimens into zip-lock bags.
   b. Place the zip-lock bags into a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the biohazard envelope.
   c. Put each biohazard envelope into a Tyvek envelope. Expel as much air as possible and then seal the Tyvek envelope.
4. Quickly place the Tyvek envelope containing frozen specimens in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
5. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
6. Prepare the ambient specimens for shipment:
   a. Seal the lids of the formalin jars with parafilm. Place absorbent material around the primary container of each liquid specimen. Place the specimens into zip-lock bags.
   b. Place specimens inside the secondary pressure vessel with bubble wrap.
   c. Secure the lid on the secondary pressure vessel and set it inside the kit chamber.
7. Insert a copy of the required forms in the kit chamber with the ambient specimens.
8. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
9. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
10. Complete a FedEx air bill and attach to top of shipping container.
11. Complete a dry ice label.
12. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
13. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.4 Shipping Address

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

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

FedEx Priority Overnight service is very strongly preferred.

Note: The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for all costs for overnight

shipment per specimen shipment to the EET Biobank.

5.5.5 Contact Information for Assistance

For all queries, please use the contact information below:

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

5.6 Shipping of Specimens to Other Laboratories

5.6.1 Blood in EDTA for Birinapant Pharmacokinetics and Pharmacogenomic Studies – NCI Blood Processing Core (BPC/Figg Lab)

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting or shipping samples (the Friday before is preferred).

For NCI sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing or shipment, contact NCIBloodcore@mail.nih.gov.

For non-NCI sites, please ship PK samples to the NCI Blood Processing Core at the following address:

National Cancer Institute
NCI Blood Processing Core/Figg Lab
10 Center Drive, Room 5A08
Bethesda, MD 20892
Ph: 240-760-6180

5.6.2 Snap-frozen tissue for Microwestern for IAP1/2, CASP3 and MLKL in tumor tissue – Dr. Annunziata Laboratory

Snap-frozen cores collected at baseline and C1D4 will be placed in dry ice and sent to the EET Biobank. In the event that frozen samples cannot be shipped immediately, maintain frozen specimens in a -80°C freezer. Once accrual is completed and all samples are collected, they will then be sent from the EET Biobank to Dr. Annunziata's lab.

The EET Biobank will contact Dr. Annunziata prior to shipping of specimens:

Bldg 10 Room 3B43C
10 Center Dr.
Bethesda, MD 20814
E-mail: ca180n@nih.gov
Phone: 240-760-6125

5.6.3 FFPE for Immunohistochemistry for PD-L1 and CD8 T-cell infiltration, and other immune-related biomarkers in tumor tissue – Dr. Van Waes Laboratory

FFPE specimens or slides will be collected by each site and sent to the EET Biobank. Once accrual is completed and all samples are collected, they will then be sent from the EET Biobank to Dr. Van Waes' lab.

Please page/contact Dr. Paul Clavijo in advance of shipping FFPE specimens or slides:

Dr. Paul Clavijo
Building 10 Room 7S250
10 Center Dr
Bethesda, MD 20814
E-mail: paul.clavijo@nih.gov
Phone: 301-594-6091 or alternate 240-449-6727

The FFPE specimens or slides will be used commonly by Drs. Van Waes and Saloura's labs for optional immune-related biomarker studies.

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

NOTE: For baseline and C1D4 biopsies, all remaining tissue from FFPE blocks should be returned to the NCI for optional immune-related biomarker studies, once request to distribute samples for MoCha has been fulfilled.

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	Biomarker Assay	Biomarker Type and Purpose	M/O[1]	Specimen and Timepoint(s)	Laboratory
1	FADD / BIRC2 copy number gain	Whole exome sequencing (normal DNA will be used as control for the FADD/BIRC2 copy number gain assay)	Integrated To determine if FADD/BIRC2 copy number gain is associated with response rate, LCR rate, OS and PFS	**M**	Baseline: 1 archival FFPE block or 20 unstained archival slides from the most recent biopsy available OR 1-2 formalin-fixed fresh tumor biopsies	Mickey Williams / Molecular Characterization laboratory (MoCha) at NCI Frederick
2	FADD / BIRC2 copy number gain	Whole exome sequencing (germline) DNA will be used as control for the FADD/BIRC2 copy number gain assay)	Integrated To determine if FADD/BIRC2 copy number gain is associated with response rate, LCR rate, OS and PFS	**M**	Baseline: DNA from blood in EDTA	Mickey Williams / Molecular Characterization laboratory (MoCha) at NCI Frederick
	Whole exome copy number and mutations	Whole exome sequencing	Exploratory To determine if other copy alterations or mutations detected with whole exome sequencing influences objective response rate			
3	IAP1/2, CASP3, MLKL	Microwestern for IAP1/2, CASP3 and MLKL Performed with Simple Western™ system/capillary	Integrated To determine the effect of birinapant and re-irradiation on the candidate pharmacodynamic	**O**	Baseline and C1D4: 1-2 cores snap-frozen tumor biopsies	Annunziata, NCI

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O[1]	Specimen and Timepoint(s)	Laboratory
		Western	biomarkers IAP1/2, CASP3 and MLKL			
4	PD-L1, CD8 T-cell infiltration and other immune-related biomarkers	Immunohistochemistry for PD-L1 and CD8 T-cell infiltration, and other immune-related biomarkers	Exploratory Pilot immune markers to explore correlation with objective response rate	**O**	Baseline: 1 FFPE core or 10 unstained archival FFPE slides CID4: 1 FFPE core	Van Waes, Allen, NIDCD, Saloura, NCI
5	Birinapant Pharmacokinetics	Birinapant Pharmacokinetics	Exploratory	**M[2]**	6 mL whole blood in EDTA (see section 5.1 for timepoints)	NCI Blood Processing Core
6	Birinapant Pharmacogenomics (single-nucleotide polymorphisms-SNPs)	Birinapant Pharmacogenomics	Exploratory	**O**	Baseline: 10 mL whole blood in EDTA	NCI Blood Processing Core

[1] Mandatory or optional
[2] C1D4 6ml blood in EDTA is required only if a fresh biopsy is performed on C1D4.

5.8 Integral Laboratory Studies

5.8.1 FADD / BIRC2 *copy* number gain in tumor tissue

5.8.1.1 Specimens and Processing

- Tissue

Formalin-fixed tissue at baseline (or archival FFPE if baseline biopsy tissue not available) will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA extraction. DNA will be banked in a stock vial; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

- Blood

DNA will be extracted from blood collected in EDTA tubes at the baseline time point and will be stored in a -80°C freezer until distribution for testing. For DNA sequencing, 250 ng of genomic DNA from tumor and blood is required.

5.8.1.2 Site Performing Correlative Study

Molecular Characterization laboratory (MoCha) at NCI Frederick directed by Dr. Mickey Williams.

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

Specimens will be shipped from the EET Biobank to:

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

5.8.1.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.8.2 Microwestern for IAP1/2, CASP3 and MLKL in tumor tissue

5.8.2.1 Specimens and Processing

Snap-frozen tumor at baseline and C1D4 time points will be used for this assay. Upon receipt at the EET Biobank, the snap-frozen tissue will be accessioned, barcoded, weighed, and banked in a liquid nitrogen vapor phase freezer until distribution for testing.

If specimens collected on C1D4 (Thursdays) cannot be shipped to ETCTN the same day or on next day (Friday), they should be stored at -80°C and sent to ETCTN on the upcoming Monday or Tuesday.

Once all specimens are collected, they will be sent to Dr. Christina Annunziata's Laboratory.

Core tumor samples will be lysed in T-per buffer (Thermo Scientific) for protein quantification by an automated capillary electrophoresis immunoassay system (Simple Western™).

5.8.2.2 Site Performing Correlative Study

Dr. Christina Annunziata's laboratory

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

Specimens will be shipped from the EET Biobank to:

Refer to Section **5.6.2**.

5.8.2.4 Contact Information for Notification of Specimen Shipment

Refer to Section **5.6.2**.

5.8.3 Whole exome copy number, mutations and expression

The specimens used for the FADD/BIRC2 will be used for this assay; refer to Section **5.8.1.1** for specimen handling and processing.

5.8.4 Immunohistochemistry for PD-L1 and CD8 T-cell infiltration, and other immune-related biomarkers in tumor tissue

5.8.4.1 Specimens and Processing

Formalin-fixed tissue at baseline will be used for this assay. Tissue cores in formalin will be processed and embedded or archival specimens or slides will be provided to the EET Biobank, where 10 5µM slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content. The tissue cores will then be barcoded and banked at the ETCTN.

Core biopsies collected on C1D4 will be placed in formalin and sent to ETCTN for delivery on Friday. If the sample is shipped on Friday for delivery on Saturday at ETCTN, the cores will then be placed in PBS or ethanol (to prevent overfixation) and stored until Monday, when they will be paraffin embedded.

Once all cores are collected, they will be distributed to Dr. Van Waes' Laboratory. If a biopsy cannot be obtained, 10 unstained slides will be instead distributed to Dr. Van Waes' laboratory for use by Dr. Van Waes and Saloura's labs.

5.8.4.2 Handling of Specimens

Tissues used for immunofluorescence analysis of PD-L1 expression and CD8 tumor infiltrating lymphocyte (TIL) will be fixed in 4% formalin for 24 hours, then transferred to 70% ethanol and stored at room temperature. Fixed tissue will be paraffin embedded and sectioned. CD8 TIL infiltration and PD-L1 expression will be assessed in appropriate sections by multiplex immunofluorescence (IF), performed by NIDCD Laboratory personnel in collaboration with LTIB Tissue Core personnel using standard IF staining techniques using Perkin-Elmer Opal staining kits, a Perkin-Elmer Vectra Polaris Image Analysis Platform and Perkin-Elmer inForm software. This platform has been validated for use in fixed human tissue analysis of CD8+ cell tissue infiltration and PD-L1 expression. (21, 22)

5.8.4.3 Site Performing Correlative Study

Dr. Van Waes laboratory

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

Specimens will be shipped from the EET Biobank to:

Refer to Section **5.6.3**.

5.8.4.5 Contact Information for Notification of Specimen Shipment

Refer to Section **5.6.3**.

5.8.5 Birinapant Pharmacokinetics

5.8.5.1 Specimens and Processing

Upon receipt, frozen, processed plasma aliquots will be barcoded and banked in -80°C freezers until distribution for testing to the NCI Center for Cancer Research Clinical Pharmacology Program (see Section **5.6.1**).

5.8.5.2 Handling of Specimens

Upon arrival in the NCI Blood Processing Core (BPC), samples will be kept on wet ice until centrifugation at 1500 g for approximately 10 min at 4°C. Samples will be processed within one hour of sample collection. Plasma will be transferred into 1.8 mL Nunc cryovials and stored at -70°C until the time of analysis. If sufficient plasma volume, each sample will be split into equal volume aliquots.

All samples sent to the NCI Blood Processing Core (Figg Lab) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined BPC personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information are required to complete the Human Subjects Research course.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or

destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the CTEP.

5.8.5.3 Site Performing Correlative Study

NCI Center for Cancer Research Clinical Pharmacology Program (CPP)

5.8.5.4 Contact information for notification of specimen shipment

Refer to Section **5.6.1.**

5.8.6 Birinapant Pharmacogenomics (Single-nucleotide polymorphisms – SNPs)

5.8.6.1 Specimens and Processing

Upon receipt, EDTA blood samples will be barcoded and the buffy coat will be extracted. PBMCs of the buffy coat will be placed in media containing 10% DMSO and 90% FBS and then frozen in a -80degree freezer using a Mr. Frosty isopropanol container.

PBMCs will be processed using a QiaAmp DNA blood kit. DNA will be extracted and SNP analysis will be run using the Pharmacoscan assay kit: (https://www.thermofisher.com/order/catalog/product/903010TS#/903010TS). Approximately 4500 SNPs in absorption, distribution, metabolism and excretion (ADME) genes will be evaluated.

5.8.6.2 Handling of Specimens

Upon arrival in the NCI Blood Processing Core, samples will be kept on wet ice until centrifugation at 1500g for approximately 10 minutes at 4°C. Samples will be processed within one hour of sample collection as described above.

All samples sent to the NCI Blood Processing Core will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. The handling procedure will be the same as described in Section **5.8.5.2**.

5.8.6.3 Site Performing Correlative Study

NCI Center for Cancer Research Clinical Pharmacology Program (CPP)

5.8.6.4 Contact information for notification of specimen shipment

Refer to Section **5.6.1**.

6 TREATMENT PLAN

This is an open-label Phase I study enrolling patients in 2 cohorts: dose escalation cohort and expansion cohort.

Treatment will be delivered in 2 cycles, lasting 3 weeks each.

Birinapant will be administered IV on Days 2 and 9 of each cycle in combination with IMRRT starting on Day 1 of cycle 1 and continuing for 5 days a week (Monday-Friday) for 6 weeks.

If a dose of birinapant is missed due to a scheduled holiday, inclement weather, personal emergency, or other reasons, then it should be given the following day.

If daily radiation treatment is missed due to a scheduled holiday, inclement weather, personal emergency, or other reasons, then the day(s) and fraction(s) missed should be added at the end of the course to complete the total planned treatment dose (e.g. 60Gy).

Patients in the dose escalation cohort will be treated with escalating doses of birinapant with IMRRT until MTD of birinapant in combination with IMRRT is established.

Patients in expansion cohort will be treated with the estimated MTD of birinapant in combination with IMRRT.

6.1 Agent Administration

Treatment will be administered primarily on an outpatient basis unless inpatient admission is indicated. 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.

6.1.1 Dose Escalation Cohort

Birinapant will be administered IV over 30 minutes on Days 2 and 9 of each 3-week cycle with starting dose 5.6 mg/m^2 per dose in combination with IMRRT starting on Day 1 of cycle 1 at 2Gy/day x 5 days/week/M-F for two cycles (6 weeks) to a total of 60-66Gy.

IMRRT will start within 1-4 hours after the infusion of birinapant.

Vital signs will be collected prior to and after every birinapant infusion.

An ECG will be performed within 2 hours prior to the start of infusion and 2 hours after infusion completion to evaluate for pre- and post-treatment abnormalities, including QT/QTc prolongation. Further continuous monitoring will be performed for ECG abnormalities following infusion until resolved.

After the first and second infusion of birinapant, patients will be observed for 30-60 minutes for adverse events.

Dose escalation (**Table 1**) will proceed in dose levels of 3–6 patients. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during 42 days after the start of therapy, and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of the drug.

Patients who have not received at least 80% of the total planned dose of birinapant and radiation therapy within the planned 42 days of treatment will not be evaluable for DLT assessment, even if they have not experienced any DLTs while receiving the treatment.

The first subject in each dose level group will be observed for at least 14 (+/-3) days after Cycle 2 radiation is completed before the second subject can be treated. If no DLT is observed within that period, the second patient can enroll. An interval of 14 (+/-3) days without a DLT must pass before treatment of the next patient, i.e. before treating patients within each dose cohort.

<u>As of Amendment version date 12/15/2022</u>, up to 3 patients may be enrolled in each remaining dose cohort (3 and 4). DLT observation periods noted in above paragraph are no longer required prior to enrolling subsequent patients.

A safety assessment for each dose cohort will be conducted 14 days (+/- 3 days) after the last

patient of each dose cohort has completed treatment. If no DLTs are observed for the specific dose cohort, enrollment in the next dose cohort can proceed, following approval by the Medical Monitor.

The study team will meet weekly to review the ongoing results of the trial during the dose escalation portion of the study.

Dose levels are defined in the table below. Starting dose will be 5.6 mg/m2. If >1/6 patients develop a DLT at level 1 dose and a maximum 1/6 patients develop a DLT at the level -1 dose, the latter will be determined as the MTD.

Table 1: **Dose Escalation Schedule**

Dose Level	Birinapant (mg/m2)
Level -1	2.8
Level 1	5.6
Level 2	11
Level 3	17
Level 4	24

6.1.2 Radiation Therapy

- Start Date: All patients with remaining teeth will have a pre-radiotherapy dental evaluation. Feeding tube will be placed in patient at the discretion of the radiation oncologist and medical oncologist. Radiation therapy will begin on Day 1.
- Immobilization: Immobilization should include neck and shoulders utilizing the standard practice of Aquaplast mask.
- Treatment Planning CT: will be obtained with standard 0.3 cm slices through the regions that include the target volumes. PET/CT and/or MR scans may be used to assist in the definition of the target volumes, especially when the targets extend near the base of skull.

6.1.2.1 Target Volumes:

The treatment volume will include the gross tumor volume with an organ at risk (OAR) adapted margin of 0.1-1.5 cm to the planning target volume. Elective nodal coverage will not be included.

The definition of volumes will be in accordance with The International Commission on Radiation Units and Measurements (ICRU) Report # 50 and 62.

- Gross Tumor Volume (GTV) is the gross palpable or visible/demonstrable extent and location of the malignant growth. The GTV will be determining utilizing a combination of clinical examination (including endoscopy) and radiographic exams (utilizing CT, PET/CT or MRI).
- Clinical Target Volume (CTV) is a tissue volume that contains a demonstrable GTV and/or is considered to contain microscopic, subclinical extensions at a certain probability level. This volume thus has to be treated adequately in order to achieve the aim of

therapy. In the re-irradiation setting we will at most treat 1-2 nodal levels in addition to the gross tumor volume and the margin will be 3-5mm.

- Planning Target Volume (PTV) is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV. A minimum of 3-5 mm around the CTV will be utilized, excluding extension into the spinal cord and non-involved normal tissue.
- Spinal Cord: The spinal cord will be defined based upon CT scan. A spinal cord "planning" volume (PRV) also will be defined by adding a symmetrical margin of at least 0.5 cm in all dimensions around the cord.
- Mandible: The mandible includes the entire bony structure from TMJ through the symphysis.
- Brainstem: The brainstem will be defined based upon the CT scan. A brainstem "planning" volume (PRV) also will be defined by adding a symmetrical margin of at least 0.3 cm in all directions around the brainstem.
- Larynx: The larynx will be defined as the portion of the larynx from the top of the thyroid cartilage to the bottom of the cricoid cartilage that does not include any portion of the PTV. No additional margin will be added around the larynx.
- Brachial Plexus: defined per RTOG atlas (https://www.rtog.org/CoreLab/ContouringAtlases.aspx)
- Cervical Esophagus: This is defined as a tubular structure that starts at the bottom of pharynx and extends to the thoracic inlet.

6.1.2.2 Lymph Node Regions and Normal Tissues:

The lymph node groups at risk will be determined and their volumes (CTVs) will be outlined on the treatment planning CT according to image-based nodal classifications (RTOG online nodal atlas can be used as a reference; www.rtog.org). In the re-irradiation setting the patients will not receive elective nodal irradiation, however 1-2 lymph nodal levels may be added at the discretion of the radiation oncologist based on imaging and other clinical factors.

The normal tissue volumes to be contoured will include the brainstem, brain stem + 0.3 cm margin, spinal cord, spinal cord + 0.5 cm margin, mandible, larynx, parotid glands, cochlea, oral cavity, optic nerves, optic chiasm, globes, brachial plexus.

6.1.2.3 Dosimetric Planning:

Intensity Modulated Radiation Therapy (IMRT) and/or Volumetric Modulate Arc Therapy (VMAT) planning and delivery will be performed in all cases. The treatment plan used for each patient will be based on an analysis of the volumetric dose, including DVH analyses of the PTV and critical normal structures. The treatment aim will be the delivery of radiation to the PTVs and exclusion of noninvolved tissue as much as feasible.

6.1.2.4 Dose Specification:

The dose prescription is to be based on a dose distribution corrected for heterogeneities.

A list of the approved Treatment Planning Systems (TPS) and algorithm for dose calculation can be found on the IROC Houston web site.

The prescription dose will be normalized to the isodose which encompasses at least 95% of the planning target volume (PTV).

No more than 20% of the PTV will receive > 110% of its prescribed dose.

No more than 1% of any planning target volume will receive < 93% of its prescribed dose.

No more than 1% or 1 cc of tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

The dose prescription will be based on dose distribution corrected for tissue inhomogeneity.

PTV 60 Gy will include the primary tumor and involved nodal regions if adjacent nodal regions have disease or are at high risk. 1-2 levels of lymph nodal levels can be treated at the discretion of the radiation oncologist and based on imaging data (CT, PET/CT and/or MRI). The dose in this region can go as high as 66 Gy as long as the normal structure tolerances are met.

6.1.2.5 Suggested Dose restraints for critical normal structures

For CNS structures, Brainstem, Optic nerve and Optic chiasm: No more than 0.03 cc can exceed 60 Gy (from current AND previous radiation therapy treatments combined). Mandible: There are no specific requirements for brachial plexus dose, but if it is not grossly involved with or immediately adjacent to tumor, the dose should be kept as low as reasonably possible. Minimize hot spots.

Brachial plexus: There are no specific requirements for brachial plexus dose, but if it is not grossly involved with or immediately adjacent to tumor, the dose should be kept as low as reasonably possible. Minimize hot spots.

Larynx: There are no specific requirements for larynx dose, but if it is not grossly involved with or immediately adjacent to tumor, the dose should be kept as low as reasonably possible. Minimize hot spots.

6.1.2.6 Treatment Delivery/ Equipment:

Megavoltage equipment capable of delivering static-gantry intensity modulation beams with a multi-leaf collimator or dynamic intensity modulation (using a multi-leaf collimator or tomotherapy) is required. Other techniques are acceptable as long as dose specifications and constraints are satisfied. This includes tomotherapy and Volumetric Modulated Arc Therapy (VMAT) techniques. It is expected that the entire treatment of definitive irradiation will be completed in approximately seven weeks. Radiation course should be continuous (Monday-Friday) for 5 days. However, if an interruption is required for radiation reaction, it should be kept to a minimum, recorded, and justified.

6.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as any one of the following adverse events, possibly attributable to the combination of birinapant and radiotherapy, that occur within 42 days of the start of therapy:

- Any grade 5 toxicities.

- Any grade ≥ 4 hematologic toxicity except for lymphopenia.
- Any grade ≥ 3 non-hematologic toxicity, **except for any of the following**:
  - nausea and vomiting that can be managed with standard supportive care over 2 weeks
  - alopecia,
  - drug-related fever,
  - radiation-induced in-field related side effects, including but not limited to dermatitis, oral mucositis and related pain, dysphagia, dysgeusia, esophagitis, xerostomia, weight loss, thickened oral secretions that can be managed with standard supportive care over 2 weeks
  - isolated laboratory abnormalities without clinical sequelae
- ≥ grade 3 prolonged (> 7 days) serum amylase or lipase elevation*
- ≥ grade 3 prolonged (> 7 days) aspartate aminotransferase (AST) elevation*
- ≥ grade 3 prolonged (> 7 days) alanine aminotransferase (ALT) elevation*
- Concurrent elevation of AST/ALT >3 times the upper limit of normal and bilirubin > 2 times the upper limit of normal (i.e., Hy's law)
- Any grade toxicity that mandates discontinuation of birinapant treatment for more than 2 weeks

* all of which will be considered to be dose limiting.

Grade 5 AEs are unacceptable, though the chances of their occurrence are considered to be quite low. The probability of DLTs with birinapant in combination with radiotherapy at the specified dose levels are expected not to exceed 30% of patients. All AEs ≤ grade 4 are considered acceptable in terms of risk, given that the median overall survival of patients with locoregionally recurrent head and neck cancer who have received 1 or 2 lines of standard of care treatment is very short (approximately 3-6 months).

Criteria are based on the NCI Common Terminology Criteria for Adverse Events, Version 5.0.

Dose escalation will proceed within each dose level according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

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

	the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the MTD. At least 6 patients must be entered at the MTD.

This dose escalation plan, on average, will select a maximum tolerated dose with the specified acceptable probabilities of DLT.

6.3 Dose Expansion Cohort

Birinapant will be administered IV over 30 minutes on days 2 and 9 of every cycle at the MTD estimated during dose escalation part of the study.

IMRRT will be administered starting on Day 1 at 2Gy/day x 5 days/week/M-F for 2 cycles (6 weeks) to a total of 60-66Gy.

IMRRT will start within 1-4h after the infusion of birinapant.

The study team will meet weekly to review the ongoing results of the trial and will continue to monitor and record AEs during the dose expansion portion of the study.

An expansion cohort of 10 additional patients will be treated at the MTD and the results combined with those of patients at the MTD to obtain improved estimates of safety and toxicity as well as to perform analyses to address secondary objectives.

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of birinapant 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. A Patient Drug Information Handout/Wallet Card is provided (**Appendix B**).

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) as described in Sections **6.2** and **7**.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator

- Clinical progression
- Patient experiences a grade 4 non-hematologic toxicity or any grade 3 toxicity not returning to ≤ grade 1 after 2 weeks of supportive care. The patient may continue with IMRRT but will be taken off birinapant.
- Patient non-compliance with <80% of birinapant doses (less than 3 out of the 4 total doses) or with scheduled appointments for investigational treatment that may affect treatment outcome, per PI discretion.
- Pregnancy
    - All women of child bearing potential will be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.6 Duration of Follow Up

Patients will be evaluated for safety with follow up visits approximately 14 (+ 7) days and 28 (+/- 7) days after completion of, or removal from treatment. Patients removed from treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients will be evaluated at 3 (+/- 2 weeks), 6 (+/- 4 weeks), 9 (+/- 4 weeks), 12 (+/- 4 weeks), 18 (+/- 4 weeks) and 24 (+/- 4 weeks) months after completion of treatment for tumor evaluations. These visits will be stopped after confirmation of disease progression.

If patients are unable or unwilling to come to these visits, they will be contacted by phone or e-mail.

7 DOSING DELAYS/DOSE MODIFICATIONS

General guidelines for treatment modifications at the time of re-treatment:

Adverse Events: All adverse events in this trial will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A complete listing is available at the CTEP website: http://ctep.cancer.gov/forms/CTCAEv5.pdf.

7.1 Birinapant

7.1.1 Safety Consideration When Administering Birinapant

7.1.2 Dose Adjustments

Dose adjustments are allowed during both the dose escalation and the expansion phase of the study. Patients that have a DLT as defined in Section **6.2** may have their treatment held or will

incur up to 2 dose level reductions, as indicated in Section **7.1.3**. If an AE that fulfills DLT criteria recurs, treatment will be held as noted below and resumed at 1 dose level lower. If a third AE fulfilling DLT criteria occurs, treatment with birinapant will be permanently discontinued, but IMRRT may be continued, provided in-field radiation toxicity is not limiting. Patients that are retreated at a lower dose level than initially assigned will not be included in the assessment of DLTs for that lower dose level (with the exception of level -1 dose) but will be included in the analysis of secondary endpoints.

In case of grade 4 non-hematologic toxicity or any grade 3 toxicity not returning to ≤ grade 1 after 2 weeks of supportive care, patients will be taken off birinapant treatment and may continue with IMRRT only. Patients who experience a DLT related to the combination at a specific dose level will have both their treatments held (both birinapant and IMRRT) for up to 2 weeks and supportive measures will be implemented to ameliorate the AE. Once the AE is ≤ grade 1, treatment with birinapant will be resumed at 1 dose level lower. In case of concurrent elevation of AST/ALT > 3 times the upper limit of normal and bilirubin > 2 times the upper limit of normal (i.e., Hy's law), study treatment will be permanently discontinued.

Dose adjustments are allowed during the expansion part of the study according to the guidelines below, with dose levels defined as follows:

Dose Level	**Birinapant (mg/m^2)**
-1	2.8
1	5.6
2	11
3	17
4	24

7.1.3 Dose Modifications for Hematologic Toxicity

7.1.3.1 Dose Modification Guidelines for Birinapant-related Neutropenia

Event Name	**Neutropenia**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	**First occurrence:** Hold* birinapant until return to ≥ 1500/mm^3; restart therapy at 1 dose level lower. Use of cytokine growth factor (G-CSF or GM-CSF) supportive care may be implemented. **Second occurrence:** Hold* birinapant until return to ≥ 1500/mm^3; restart therapy at 1 dose level lower **. Use of cytokine growth factor (G-CSF or GM-CSF)

	supportive care may be implemented based on the judgment of the investigator for continued treatment. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up.
Grade 4	**First occurrence:** Hold* birinapant until return to ≥ 1500/mm^3; restart therapy at 1 dose level lower. Use of cytokine growth factor (G-CSF or GM-CSF) supportive care may be implemented based on the judgment of the investigator for continued treatment. **Second occurrence:** Hold* until return to ≥ 1500/mm^3; restart therapy at 1 dose level lower **. Use of cytokine growth factor (G-CSF or GM-CSF) supportive care may be implemented. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up as described in Section **6**
*Participants requiring a delay of ≥16 consecutive days must stop birinapant **Participants requiring > two dose reductions must stop birinapant.	

7.1.3.2 Dose Modification Guidelines for Birinapant-related Thrombocytopenia

Event Name	**Thrombocytopenia**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold* birinapant until ≤ Grade 1. Resume at same dose level.
Grade 3	**First occurrence:** Hold* birinapant until return to ≥ 75,000/mm^3; restart therapy at 1 dose level lower. **Second occurrence:** Hold* birinapant until return to ≥ 75,000/mm^3; restart therapy at 1 dose level lower**. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up as described in Section **6**

Grade 4	**First occurrence:** Hold* birinapant until return to ≥ 75,000/mm^3; restart birinapant at 1 dose level lower**. **Second occurrence:** Hold* birinapant until return to ≥ 75,000/mm^3; restart therapy at 1 dose level lower**. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up as described in Section **6**
*Participants requiring a delay of ≥16 consecutive days must stop birinapant **Participants requiring > two dose reductions must stop birinapant.	

7.1.3.3 Dose Modification Guidelines for Birinapant - related Anemia

Event Name	**Anemia**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold* birinapant until return to Hgb ≥ 10 g/dL**; transfusion is allowed to achieve Hgb >10 g/dL***. No change in dose
Grade 3	**First occurrence:** Hold birinapant until return to Hgb ≥ 10 g/dL*; transfusion is allowed to achieve Hgb >10 g/dL***. Restart birinapant at 1 dose level lower. **Second occurrence:** Hold birinapant until return to Hgb ≥ 10 g/dL*; transfusion is allowed to achieve Hgb >10 g/dL. Restart birinapant at 1 dose level lower****. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up as described in Section **6**
Grade 4	Transfuse and initiate appropriate supportive therapy. Continuation of birinapant is at the discretion of the Investigator depending on the attribution assigned to the anemia.
*Participants requiring a delay of ≥16 consecutive days must stop birinapant. **Transfusion is allowed to achieve Hgb >10 g/dL. *** Erythropoiesis stimulating agents are not allowed due to possible increased risk of inhibition of apoptosis pathway and disruption of NFκB-mediated tumor cell killing. ****Participants requiring > two dose reductions must stop birinapant.	

7.1.4 Dose Modification Guidelines for Birinapant-related Non-hematologic Toxicities

	Non-hematologic Toxicities
Grade of Event	**Dose Modification**
Grade 1	Continue at same dose level.
Grade 2	Hold* dose until recovery to baseline or Grade ≤ 1 with standard supportive therapy. Resume at current dose. For second hold for Grade 2, hold until recovery to grade 1 and restart at one dose level lower. If no recovery to grade 1 within 16 days, the study participant will not receive additional birinapant and will stop further birinapant administration but continue on study for follow up as described in Section **6**
Grade 3	**First occurrence:** Discontinue further birinapant or withhold birinapant until recovery to baseline or Grade ≤ 1 with standard supportive therapy. Birinapant will be restarted at 1 dose level lower. As an exception, grade 3 non-hematologic laboratory abnormalities without clinical symptoms that resolve to Grade 1 or baseline (if the study participant entered the study with existing toxicity) within 7 days will not lead to dose modification. **Second occurrence:** Discontinue further birinapant or withhold birinapant until recovery to baseline or Grade ≤ 1 with standard supportive therapy. Therapy will be restarted at 1 dose level lower. **Third occurrence:** The study participant will not receive additional birinapant and will stop further birinapant but continue on study for follow up as described in Section **6**.
Grade 4	The study participant will stop further birinapant but continue on study for follow up as described in Section **6**. If a study participant experiences a grade 4 toxicity lasting less than 24 hours, re-initiation of birinapant at 1 dose level lower may be considered after recovery to baseline or Grade ≤ 1 with standard supportive therapy.
*Participants requiring a delay of ≥16 consecutive days must stop birinapant **Participants requiring > two dose reductions must stop birinapant.	

7.1.5 Management of Expected Toxicities

7.1.5.1 Management of Nausea

Event Name	**Nausea**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold birinapant until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.**
*Participants requiring a delay of ≥16 consecutive days must stop birinapant **Participants requiring > two dose reductions must stop birinapant.	
Recommended management: antiemetics (see Section **6**).	

7.1.5.2 Management of Vomiting

Event Name	**Vomiting**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 1. Resume at same dose level.**
Grade 4	The study participant will stop further birinapant but continue on study for follow up as described in Section **6**. If a study participant experiences grade 4 vomiting lasting less than 24 hours, reinitiation of birinapant at 1 dose level lower may be considered after recovery to baseline or Grade ≤ 1 with standard supportive therapy.
*Participants requiring a delay of ≥16 consecutive days should go off birinapant **Participants requiring > two dose reductions should go off birinapant.	
Recommended management: antiemetics.	

7.1.5.3 Management of Diarrhea

Event Name	**Diarrhea**
Grade of Event	**Management/Next Dose for Birinapant**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower.**

Grade 4	The study participant will stop further birinapant but continue on study for follow up as described in Section **6**. If a study participant experiences grade 4 diarrhea lasting less than 24 hours, re-initiation of birinapant at 1 dose level lower may be considered after recovery to baseline or Grade ≤ 1 with standard supportive therapy.
*Participants requiring a delay of ≥16 consecutive days must stop birinapant **Participants requiring > two dose reductions must stop birinapant.	
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.	

7.1.5.4 Management of Cranial Nerve Palsies

Cranial nerve palsies (most frequently Bell's palsy) have occurred in subjects who have received birinapant. The cranial nerve palsies are typically mild to moderate in severity and in those cases treated with corticosteroids, symptoms have either resolved or were resolving at the last follow-up visit. Some subjects who reported cranial nerve palsy elected to continue birinapant treatment, and of those that continued on treatment, none had a recurrent event.

The onset of cranial nerve palsy may be preceded by a prodromal syndrome of headache, ear, facial pain and/or diplopia. Therefore, it is recommended that subjects should be given non-steroidal anti-inflammatory agents (NSAIDs) at an appropriate anti-inflammatory dose. If within 24 hours symptoms do not resolve a course of steroids should be started. In addition, sites are advised to delay the next dose of birinapant by 1 week.

7.1.5.5 Management of Inflammatory Reactions

Subjects have experienced birinapant-related inflammatory reactions of rash, fever, chills, hypotension, nausea, headache, and hypophosphatemia. These occurred with first drug exposure and resolved without sequelae. This clinical diagnosis of "cytokine release syndrome" may have been related to mechanism-based induction of cytokines, but there was no detectable increase in serum levels of a panel of cytokines, no significant cardiovascular or pulmonary compromise, and no recurrent risk with repeated exposures. Most of these events were reversible and all were asymptomatic. Although no information is available as to the amount of drug retained in the skin or mechanism of action of the reported skin reactions in pre-clinical studies, until more is known, patients should be advised to avoid prolonged periods of unprotected sun exposure. Skin reactions can be medically managed as clinically indicated by the type and severity of the skin reactions. Other events should be managed with standard medical care, such as anti-inflammatory agents, diphenhydramine, acetaminophen, IV fluids, analgesics, and anti-emetic agents.

7.2 Radiation treatment

In the event of febrile neutropenia or severe radiation related toxicity (grade 4), that in the judgement of the PI or local PI would contraindicate continuing radiation, radiation treatment

may be held temporarily. Similarly, medical events that require hospitalization or would interfere with patient setup, alignment, or delivery of radiation may also result in a temporary treatment break. If a patient requires a cumulative treatment break for 10 business days (2 weeks) they will be removed from protocol therapy.

If IMRRT is held temporarily, birinapant will be held too and restarted with IMRRT.

If IMRT is discontinued, birinapant will be stopped and patient will be taken off study treatment.

8 PHARMACEUTICAL INFORMATION

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

8.1 CTEP AGENT BIRINAPANT (NSC 756502)

Chemical Name: Propanamide, N,N'-[(6,6'-difluoro[2,2'-bi-1H-indole]-3,3'-diyl)bis[methylene[(2R,4S)-4- hydroxy-2,1-pyrrolidinediyl][(1S)-1- ethyl-2-oxo-2,1-ethanediyl]]]bis[2-(methylamino)-, (2S,2'S)-

Classification: SMAC mimetic selective IAP antagonist

Other names: TL32711

Molecular Formula: C42H56F2N8O6 **Molecular Weight:** 806.9 g/mol as free base

Approximate Solubility: Solubility in 50mM citrate buffer pH 5 is ≥ 5 mg/mL

Mode of Action: Birinapant is a potent and selective small molecule peptidomimetic of SMAC that binds to multiple members of the IAP family. SMAC (secondary mitochondrial activator of caspase) is a natural IAP antagonist that rapidly antagonizes IAPs resulting in caspase activation and apoptosis. Members of the Inhibitors of Apoptotic Proteins (IAPs) family can block cell death by directly binding to and suppressing caspase activity. The activity of the IAPs is regulated by SMAC.

How Supplied: IGM Biosciences supplies and CTEP, DCTD, NCI distributes birinapant in single-use 10 mL amber-glass vials containing sterile-filtered liquid in 50 mM citrate buffer solution pH 5. Each vial contains 10 mg (1 mg/mL, 10 mL) of birinapant as a clear, colorless to pale yellow drug solution. Excipients include citric acid monohydrate, sodium citrate dihydrate, sodium chloride, citric acid and sodium citrate.

Each vial is packaged in a secondary carton to further protect the product from potential photodegradation on exposure to UV/visible light.

Preparation: Thaw birinapant at ambient temperature for approximately 2.5 hours (or at 2-8 °C for 16-64 hours) while protected from light. Invert the vials several times to mix.

Aseptically remove desired dose from the vial and inject into an intravenous bag containing sterile 250 mL 0.9% sodium chloride injection USP. Invert several times to mix. Inspect bag for particulates. If particulates are present, do not use and repeat the preparation process using new vials. If particulates are present for a second time, report the finding to PMB. Do not use a filter.

If preparing a large dose, remove a sufficient amount of normal saline from the IV bag beforehand to accommodate the birinapant volume. There is no specific final concentration range

required by the manufacturer.

The manufacturer conducted compatibility studies with latex-free materials only. Only latex-free infusion bags, administration sets and syringes may be used to prepare birinapant doses.

Vials are for single use only and must be discarded after preparation.

Storage: Store birinapant in the freezer (-10 to -30° C) in the carton that is provided by the manufacturer. The agent is potentially light sensitive.

If a storage temperature excursion is identified, promptly return birinapant to between -10 to -30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life studies of intact vials are ongoing. The prepared solution is stable for up to 4 hours at -room temperature in ambient light. The dose must be administered within 4 hours after preparation. Only store prepared solution at room temperature.

Route and Method of Administration: Intravenous over 30 minutes. Solution must be diluted prior to administration and should not be filtered at any point.

Potential Drug Interactions: The drug-drug interaction potential of birinapant has not been fully assessed. In vitro studies indicate that birinapant is not a substrate for CYP450-mediated metabolism. Birinapant is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A11, but some moderate, partially-reversible, time-dependent inhibition of CYP3A4/5 is observed. Overall results indicate that birinapant has a low potential for CYP-mediated drug interactions.

Birinapant is not a P-gp substrate; however, P-gp inhibition was observed at 3μM in vitro. For reference, the average Cmax observed was approximately 5μM following a dose of 47 mg/m2. Birinapant is likely a substrate of the OATP1B3 transporter, which may be involved in the biliary excretion of birinapant. Birinapant moderately binds to plasma proteins. The excretion of the drug is mainly biliary per PK studies in animals. In humans, a phase I trial (12), has shown that the renal excretion of the drug is low.

Population PK analysis showed that the central volume of distribution increased with body surface area (BSA) and a reduction in the central volume of distribution of approximately 60% was observed when birinapant was administered in combination with carboplatin/paclitaxel relative to birinapant alone and other combination therapies studied. Also, a reduction in clearance of birinapant of 65% was observed with the combination of birinapant and carboplatin/paclitaxel.

At present, based on the available clinical data, it is judged that no change of birinapant dosing is indicated for the combination with carboplatin/paclitaxel, however awareness of the above PK observations in patient studies using this combination is important.

Patient Care Implications: The pharmaceutical collaborator reports that birinapant synergizes with TNFα in vitro. Patients with a serious active infection (within 2 weeks of dosing) or who have ongoing autoimmune disease or a recent history (within last 5 years) of autoimmune disease should not receive birinapant. Patients receiving anti-TNF therapies should not receive birinapant.

Birinapant should not be administered to women study participants who are pregnant or nursing. Women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. The effect of birinapant on male fertility is unknown; however, a 14 week animal study indicated that it caused testicular atrophy/degeneration with effects on spermatogenesis noted microscopically and reduced sperm count. Due to a long half-life in tissue, male study participants should use an additional barrier method of contraception for 30 days following the last dose of birinapant.

8.1.1 Availability

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

Birinapant is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section **13.3**).

8.1.2 Agent Ordering and Agent Accountability

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

8.1.2.2 Birinapant clinical supplies may be ordered when a patient is in screening.

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

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

8.1.3 Investigator Brochure Availability

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

8.1.4 Useful Links and Contacts

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

9 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The primary objective is to determine the toxicities and MTD of birinapant administered concurrently with IMRRT.

The secondary objectives are to determine the response rate, local-regional control, PFS and OS; to determine if FADD and/or BIRC2/3 copy gain in tumor tissue are associated with improved response, locoregional control, progression-free survival and overall survival; and to determine the feasibility of detecting effects of birinapant and re-irradiation on pilot pharmacodynamic markers in tumor tissue, including microwestern for decrease in drug targets IAP1/2; increase in apoptosis/necroptosis markers Caspase 3 and MLKL.

9.2 Sample Size/ Accrual Rate

This trial will initially consist of a 4 dose levels 3+3 escalation phase; with up to 6 patients per dose level, up to 24 patients may be required to determine the MTD. Then, at the MTD, an additional 10 patients will be treated in order to determine more precise estimates of safety and toxicity of patients as well as to address secondary objectives. If there are 16 patients at the MTD including the expansion cohort, then there would be approximately 80% power to detect an effect size of 2.0 for a given test comparing two groups or comparing pre-treatment values to on-treatment values with a 1.0 effect size, with a 0.01 two-tailed significance test. This would be sufficient to allow for up to 6 tests to be performed while holding the overall significance level to 0.05, taking into consideration enough patients to allow for a Bonferroni correction. In practice, given the exploratory nature of the marker and related analyses, the results may be presented without any such formal correction, but in the context of the number of such tests performed. As an illustration, if IAP1, CASP3, and MLKL were each obtained pre-treatment and at day 4 on treatment, with 16 total patients at the MTD, there would be adequate patients so that the

differences could each be tested with at least 80% power with an effect size equal to 1.0 times the standard deviation of the difference, with a 0.01 two-tailed significance test. In addition, although with less power depending on the fraction of patients who respond, comparisons could be made of the changes in these parameters between patients who respond or do not respond.

If all dose levels are evaluated and 10 additional patients are included at the MTD, we anticipate enrolling a minimum of 16 patients and a maximum of 34 patients. It is anticipated that 1-2 patients/month may be enrolled onto this trial.

Primary endpoints will be the DLTs and other toxicities, and the MTD for the regimen.

For DLT and MTD determination, escalation will proceed with the 3+3 dose escalation design until either the stopping rule below or the MTD is reached.

No. of patients with DLT's at this dose level	No. of patients treated at this dose level	Action
Dose escalation rules		
0	3	Treat 3 patients at the next higher dose level (or add 3 patients if at the highest level).
1	3	Treat 3 additional patients at this dose level.
1	6	Treat 3 patients at the next higher dose level (or if at the highest level, declare the dose at this level to be the MTD).
>1	3 or 6	Stop dose escalation; begin dose de-escalation. De-escalate one dose level.

The DLT evaluation period between dose levels will be 42 days during drug/radiation treatment plus 14 (+/- 3) days of follow-up thereafter. Patients are considered evaluable for toxicity if they have received at least 1 dose of birinapant. Patients that are not evaluable will be replaced. A standard “3+3” design, described in the table below, will be followed.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	2	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	3	0	2	**6**
White	5	19	0	1	**25**
More Than One Race	0	1	0	0	**1**
Total	**6**	**25**	**0**	**3**	**34**

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9.3 Stratification Factors

There will be no stratification in this study.

Analysis of primary endpoints

The toxicity and MTD will be evaluated by reporting the DLTs obtained at each dose level, and reporting toxicities noted in tabular form.

9.4 Analysis of Secondary Endpoints

1. Overall Response is the best response by RECIST 1.1 criteria recorded from the start of the treatment until response assessment by PET-CT at 3 months post treatment as below. Estimates of response rates, local control, PFS and OS will be determined at the MTD level, including the expansion cohort. Each of these will be presented along with a 95% two-sided confidence interval appropriate to the outcome measure. For example, the PFS and OS will have confidence intervals presented for the median times.

2. FADD/ BIRC2 Copy Number Variation will be evaluated as a secondary endpoint to estimate if recurrent HNSCC are enriched for these alterations associated with worse prognosis and associated with response to birinapant and IMRRT. A bioinformatics analysis algorithm has been established for determination of copy number variation and somatic mutation calling, by comparison and validation with DNA from matched blood (13). Archived tumor samples will be subjected to exome sequencing to estimate copy number variations, from all evaluable patients.

Results will be classified according to whether they have a FADD and/or BIRC2 copy gain (more than 2 copies) or not (13), and this classification will be compared between patients who respond or do not respond, in a descriptive fashion. A Fisher's exact test will be used to provide a p-value to help interpret the potential importance of any association, but in the context of a limited size evaluation. The association between results according to whether or not they have a copy gain will be presented for OS and PFS, by comparing Kaplan-Meier curves with a two-tailed log-rank test. In addition, as exploratory analyses, the association between FADD copy gain and BIRC2 copy gain will individually be evaluated for any association with response.

The feasibility of detecting effects of birinapant and re-irradiation on pilot pharmacodynamic markers in fresh frozen tumor biopsies, including micro-western for decrease in drug targets IAP1/2; increase in apoptosis/necroptosis markers Caspase 3 and MLKLI will be evaluated. If IAP1/2, CASP3, and MLKL were each obtained pre-treatment and at day 4 on treatment, with 16 total patients at the MTD, there would be adequate patients so that the differences could each be tested using a paired t-test (or a Wilcoxon signed rank test if the differences are not normally distributed) with at least 80% power with an effect size equal to 1.0 times the standard deviation of the difference, with a 0.01 two-tailed significance test. In addition, although with less power depending on the fraction of patients who respond, comparisons could be made of the changes in these parameters between patients who respond or do not respond.

9.5 Analysis of exploratory objectives:

To determine if mutational load detected with whole exome- sequencing influences response, differences in patterns noted can be compared descriptively between responders and non-responders.

To determine if PD-L1, CD8 T-cell tumor infiltration, TNFα, and other immune related biomarkers are associated with response, changes in these parameters from baseline can be compared between responders and non-responders using a Wilcoxon rank sum test. Any tests performed will be done without adjustment for multiple comparisons but in the context of the number of tests performed.

To determine pharmacokinetic of birinapant, bioanalytical measurements will be conducted on an ultra HPLC-MSMS system using a validated assay by the Clinical Pharmacology Program (CPP) at the NCI. These data will be used to monitor birinapant plasma concentrations in order to assess any PK changes with radiation, as well as to correlate with pharmacodynamic endpoints, clinical response, and toxicity.

10 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPR) for Birinapant (TL32711, NSC 756502)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform

presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Birinapant.

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

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Adverse Events with Possible Relationship to Birinapant (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	
Febrile neutropenia	
GASTROINTESTINAL DISORDERS	
Diarrhea	
Nausea	
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	***Fatigue (Gr 2)***
Fever	
IMMUNE SYSTEM DISORDERS	
Cytokine release syndrome	
INVESTIGATIONS	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS	
Anorexia	
NERVOUS SYSTEM DISORDERS	
Facial nerve disorder(24)	
Headache	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	

Adverse Events with Possible Relationship to Birinapant (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Rash maculo-papular	
VASCULAR DISORDERS	
Hypotension	

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

[2]Facial nerve disorder may manifest itself as Bell's palsy possibly secondary to cytokine release syndrome.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - Restrictive cardiomyopathy

EYE DISORDERS - Eye disorders - Other (diplopia)

GASTROINTESTINAL DISORDERS - Abdominal pain; Constipation; Dyspepsia; Typhlitis

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (V. zoster infection); Lung infection; Sepsis; Skin infection

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Lipase increased; Platelet count decreased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Myalgia

RENAL AND URINARY DISORDERS - Acute kidney injury

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

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section (**10.1** CAEPR for Birinapant) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section **10.3.3**.

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

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

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

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

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

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

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

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

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

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

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

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

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

Note: : A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. A death on study more than 30 days after last treatment requires both routine and expedited reporting, only if attribution to study intervention is possible, probably or definite. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be

considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

No exclusions.

10.4 Routine Adverse Event Reporting

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

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

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

10.5 Pregnancy

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

10.6 Secondary Malignancy

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

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

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

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

10.7 Second Malignancy

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

11 STUDY CALENDAR

A time window of -2 days on treatment days and +/- 2 days on non-treatment days will be permitted for weekly physical exam, performance status, routine vital signs, weight and routine labs. Cycle days will be numbered relative to treatment.

Procedure/ Assessment	Screening ≤ 4 weeks of first treatment	Baseline	C1D1 Wk1	C1D2 Wk1	C1D4 Wk1	C1D8 Wk2	C1D9 Wk2	C1D15 Wk3	C2D1 Wk4	C2D2 Wk4	C2D8 Wk5	C2D9 Wk5	C2D15 Wk6	14 Day Post tx Safety Visit [j, l]	28 Day Post tx Safety Visit [j, l]	Long term Follow Up [k, l]
Informed consent	X	X														
Birinapant[a]				X[c]			X			X		X				
Re-IMRT[b]			X	X	X	X	X	X	X	X	X	X	X			
Demographics	X															
Medical history	X															
Concurrent meds	X		X			X		X	X		X		X	X	X	X[p]
Physical exam[q]	X		X			X		X	X		X		X	X	X	
Vital signs	X		X	X[d]		X	X[d]	X	X	X[d]	X	X[d]	X	X	X	
Height		X														
Weight		X	X						X					X	X	
Performance status	X		X						X					X	X	
CBC/diff, platelets	X		X			X		X	X		X		X	X	X	
Serum chemistry[e]	X		X			X		X	X		X		X	X	X	
PT/PTT/INR	X															
HIV test	X															
ECG[n]	X			X			X			X		X				
Adverse events			X			X		X	X		X		X	X	X	X[o]
Tumor biopsy [f, r]		X			X											

Procedure/ Assessment	Screening ≤ 4 weeks of first treatment	Baseline	C1D1 Wk1	C1D2 Wk1	C1D4 Wk1	C1D8 Wk2	C1D9 Wk2	C1D15 Wk3	C2D1 Wk4	C2D2 Wk4	C2D8 Wk5	C2D9 Wk5	C2D15 Wk6	14 Day Post tx Safety Visit [j, l]	28 Day Post tx Safety Visit [j, l]	Long term Follow Up [k,l]
Blood (for control DNA) [r]		X														
Urine HCG [g]	X		X								X					
Tumor measurements [h]	X															X
Blood for Pharmacokinetics				X[i]	X[m]		X[i]			X[i]		X[i]				
Blood for Pharmacogenomics		X														
Phone call or e-mail																X
Dental Evaluation	X															

a: Birinapant on days 2 and 9 of every cycle. If a patient misses a dose on each of those days, the infusion can be given up to 2 days later, but the C1D4 biopsy will not be performed.

b: Standard re-IMRT 2GY/day/5 days a week/ M-F for 6 weeks to 60-66Gy.

c: Patients will be observed for 30-60 minutes post the first and second infusion of birinapant for adverse events.

d: Vital signs will be collected prior to and after every birinapant infusion.

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

f: All attempts will be made to obtained optional tumor biopsies within 28 days before treatment and on C1D4 for biomarkers studies. A blood sample for control DNA will be drawn and sent together with the pre-treatment tumor biopsy.

g: Women of childbearing potential only.

h: Tumor measurements within 6 weeks pre-treatment (PET/CT and CT or MRI neck/chest/upper abdomen with contrast), at 3 (+/- 2 weeks, PET/CT and CT or MRI with contrast), 6 (+/- 4 weeks, CT or MRI with contrast), 9 (+/- 4 weeks, CT or MRI with contrast), 12 (+/- 4 weeks, CT or MRI with contrast), 18 (+/- 4 weeks, CT or MRI with contrast), 24 (+/- 4 weeks, CT or MRI with contrast) months post-radiation treatment. Evaluations will be stopped after confirmation of disease progression. MRI neck with gadolinium and PET/CT can substitute CT with contrast if patient has contrast allergy.

i: Pharmacokinetics samples will be drawn within 60 minutes prior to start of infusion and within 60 minutes after end of infusion of the birinapant. Dates and exact times of start and stop of the infusions and sample collection dates and times will be noted in the PK sheet

j: Patients will be invited for safety follow up visits approximately 14 (+/- 3) days and 28 (+/-7) days after completion of treatment. Patients removed from treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

k: Patients will be clinically evaluated at 3 (+/- 2 weeks), 6 (+/- 4 weeks), 9 (+/- 4 weeks), 12 (+/- 4 weeks), 18 (+/- 4 weeks) and 24 (+/- 4 weeks) months after completion of treatment. These visits will be stopped after confirmation of disease progression. After completion of visits, participants will be followed by phone or email every 6 months for survival for up to 2 years.

l: If patients are unable or unwilling to come to these visits, they will be contacted by phone or e-mail for survival. After progression, participants will be followed every six months for survival.

m: On C1D4 a PK sample will be collected within +/- 4h of the biopsy. Dates and exact times of start and stop of the infusions and sample collection dates and times will be noted in the PK sheet.

n: An ECG will be performed within 2 hours of the start of infusion and within 2 hours after infusion completion and QTcF will be evaluated by the PI or clinician AI.

o: New AEs will be captured through the first 3-month follow-up visit, with the exception of SAEs considered possibly, probably or definitely related to study agents, which will continue to be reported per section **10.3.3**.

p: Concurrent medications will be captured up through the first 3-month follow up visit.

q: Physical exam and clinic evaluation should occur 1-5 working days prior to birinapant infusion.

r: Research specimens should be collected only after subject has signed consent and all eligibility criteria have been met.

12 MEASUREMENT OF EFFECT

Although the clinical benefit of birinapant has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated at 3, 6, 9, 12 and 24 months after completion of the protocol treatment.

12.1 Antitumor Effect – Solid Tumors

Patients will be evaluated at baseline and at 3, 6, 9, 12 and 24 months after completion of the protocol treatment. The details of timing and imaging types are specified in Study Calendar in Section **11**.

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)(25). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

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

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.

12.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.1.3 Methods for Evaluation of Measurable Disease

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

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

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

Conventional CT: 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.

Conventional MRI: MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm), as long as the scans are performed with slice thickness of 5mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

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. 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.

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

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake

greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.5 Evaluation of Target Lesions

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

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

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

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

12.1.6 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

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

12.1.6.1.1 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. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

12.1.7 Duration of Response

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

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

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

12.1.8 Progression-Free Survival

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

12.1.9 Response Review

Radiographic response evaluation will be conducted by the Department of Radiology at the NIH.

13 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

13.1 Study Oversight

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

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol

Principal Investigator through the CTMS/IWRS. In addition, for the dose escalation part of the study the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

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

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

This protocol is monitored at several levels, as described elsewhere 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.

13.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed

by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. 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) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

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

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

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

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository

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

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

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

13.3 Collaborative Agreements Language

The agent birinapant supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

13.4 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.4.1 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure

procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (26), (27):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling

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15 APPENDICES

15.1 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.

15.2 Appendix B: Patient Drug Information Handout and Wallet Card

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, birinapant. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.

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

Birinapant interacts with certain specific enzymes in your liver.

- The enzymes in question are CYP3A4 and 3A5. Birinapant may moderately inhibit these enzymes and affect other drugs that are broken down by them.
- The transport proteins in question are P-glycoprotein (P-gp) and OATP1B3. Birinapant can inhibit P-glycoprotein which may affect how other drugs are transported in and out of cells. Birinapant is a substrate of OATP1B3 and its clearance from the body may be affected by other drugs that inhibit OATP1B3.

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

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

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

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

Birinapant must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. 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 of OATP1B3 or sensitive substrates of CYP3A4/5 or P-gp.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **birinapant.** This clinical trial is sponsored by the NCI. **Birinapant** may interact with drugs that are processed by your liver or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Birinapant interacts with a specific liver enzyme called CYP3A4/**5** and transport proteins called P-gp and OATP1B3, and must be used very carefully with other medicines that interact with CYP3A4/5, P-gp and OATP1B3.

- 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 of OATP1B3 or sensitive substrates of CYP3A4/5 or P-gp."
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

15.3 Appendix C: Tissue Biopsy Verification

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

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

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

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

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

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

Tissue Type (circle one): **Locoregionally recurrent site** **Distant Metastatic Site**

Time point (circle one): **Baseline** **C1D4**

Site Tissue Taken From: _____

Diagnosis: _____

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

_____ _____

Clinician Signature Date

_____

Clinician Printed Name

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

Version: 1
Effective Date: 9/2019