Phase 2 study using Tazemetostat in patients with recurrent/refractory and/or metastatic malignant peripheral nerve sheath tumors (MPNST)

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase (also SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (also SGOT)
AUC	area under curve
BID	twice daily
BAP1	Breast cancer gene 1 (BRCA1)-associated protein 1
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CBR	Clinical Benefit Rate
CL	clearance
CNS	Central nervous system
CR	complete remission
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trials management system
CRO	Clinical Research Office
CTO	Clinical Trials Office
DCR	Disease Control Rate
DISC	Data Integrity and Safety Committee
DLBCL	diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusion
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	Duration of Response
DTR	decreased tendon reflex
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	embryonic ectoderm development
EFS	Event Free Survival

EMT	epithelial-mesenchymal transition
EOT	End of Treatment
EZH2	Enhancer of zeste homolog 2
EPSGG	European Pediatric Soft Tissue Sarcoma Group
FDG	fluorodeoxyglucose positron emission
FSH	follicle stimulating hormone
GAP	GTPase-activating protein
GCB	germinal center B-cell
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	Graft vs. Host Disease
HMT	histone methyltransferase
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonization
INI1	integrase interactor 1
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram(s)
KPMB1	Karyopherin β1
LDH	lactic dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MPNST	Malignant Peripheral Nerve Sheath Tumors
Mg	milligrams
MDS	myelodysplastic syndromes
miRNA	micro RNA
MPN	myeloproliferative neoplasms
MRI	magnetic resonance imaging
MRT	malignant rhabdoid tumors
MT	Mutant type
MTD	maximum tolerated dose
NCI	National Cancer Institute

NF1	Neurofibromatosis type 1
NHL	Non-Hodgkin's Lymphoma
NK	Natural killer
NSAE	non-serious adverse event
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PMO	Project Management Office
PI	principal investigator
PK	pharmacokinetics
PR	partial remission
PRC2	polycomb repressive complex 2
PRO	Subject Reported Outcome
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase II Dose
R/R	Relapsed or Refractory
SAE	serious adverse event
SC	subcutaneous
SCCOHT	small cell carcinoma of the ovary of the hypercalcemic type
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (also AST)
SGPT	serum glutamic pyruvate transaminase (also ALT)
SMARCA4	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 4
STS	Soft tissue sarcoma
SUZ12	suppressor of zeste 12
SWI/SNF	SWItch/Sucrose Non-Fermentable

T-ALL	T-cell acute lymphoblastic leukemia
TBI	Traumatic brain injury
T-LBL	T-cell lymphoblastic lymphoma
Tmax	time to maximum plasma concentration
TTP	Time to Progression
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WT	Wild type
XRT	Radiation therapy
ZH2	zeste homolog 2

Protocol Signature Page

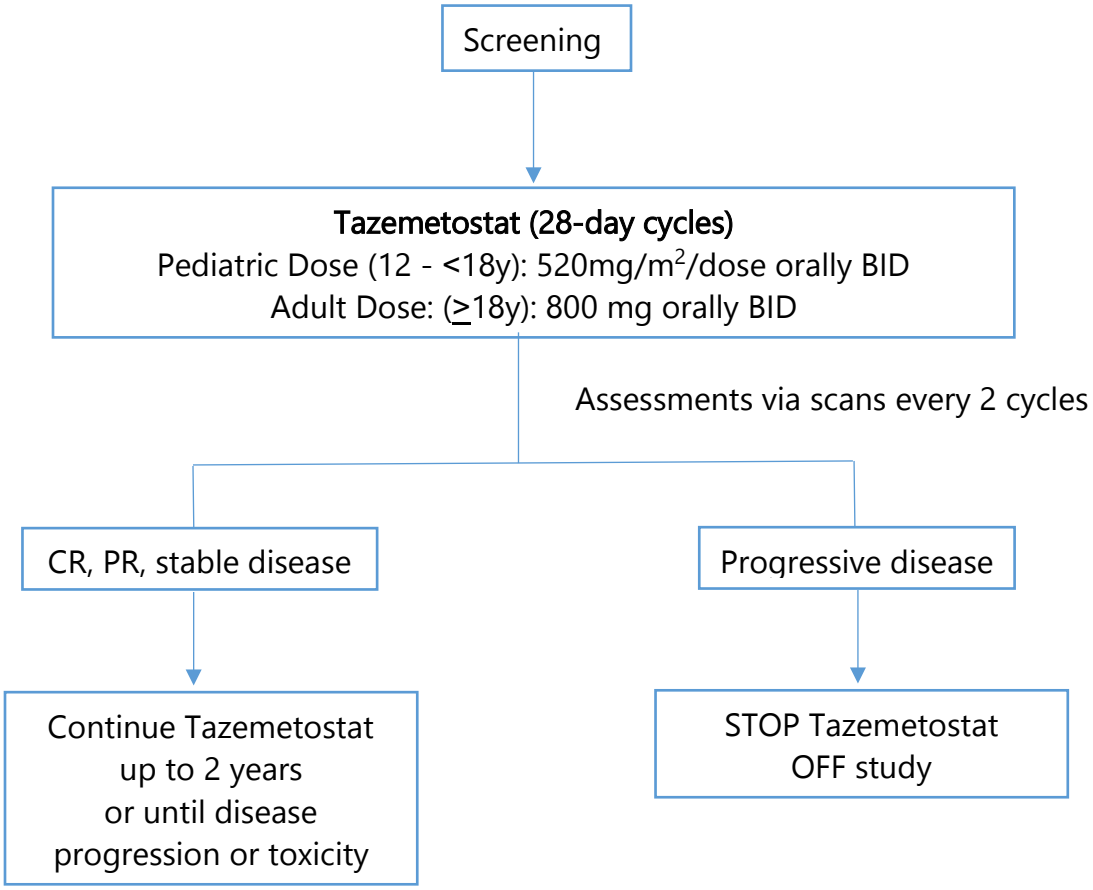
Phase 2 study using Tazemetostat in patients with recurrent/refractory and/or metastatic malignant peripheral nerve sheath tumors (MPNST)

Study Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	
Name of Facility	
Location of Facility (City/State)	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY SCHEMA – SINGLE ARM



Cycle = 28 days

Accrual Goal: 29 evaluable subjects (Up to 50 total accrued)

PROTOCOL SYNOPSIS

Title:	Phase 2 study using Tazemetostat in patients with recurrent/refractory and/or metastatic malignant peripheral nerve sheath tumors (MPNST)
Funding Source(s):	Epizyme, University of Florida
Investigational Agent Source:	Epizyme
Rationale:	Enhancer of zeste homolog 2 (EZH2) is a critical component of polycomb repressive complex 2 (PRC2), a multimeric protein complex which plays an essential role in the epigenetic maintenance. EZH2 has been shown to be a critical regulator of epithelial-mesenchymal transition, which is a critical step for initiation of cancer invasion and metastasis. Recent research showed that EZH2 expression is significantly higher in MPNST than in neurofibromas and normal nerve tissues. EZH2 knockdown by RNA interference in MPNST cell lines induces MPNST cell apoptosis in vitro and inhibits MPNST tumor growth in vivo. Pharmacological inhibition of EZH2 has been shown to inhibit MPNST cell growth and induce apoptosis in vivo, in vitro and in mouse xenograft models. In addition, inhibition of EZH2 has been shown to ameliorate MPNST invasion and metastasis. These preclinical data suggest that EZH2 is a potential therapeutic target in MPNST.
Objectives:	Primary: To assess the objective response rate of Tazemetostat in subjects with recurrent/refractory and/or metastatic MPNST. Secondary: • To determine the progression free survival (PFS) in subjects with recurrent/refractory and/or metastatic MPNST. • To determine the time to progression (TTP) in subjects with recurrent/refractory and/or metastatic MPNST. • To determine the clinical benefit using subject reported outcome (PRO) • To assess the clinical benefit rate (CBR).

	Exploratory aims: • Assess circulating tumor DNA (ctDNA) as a potential treatment response tool • Correlate clinical data, outcomes and toxicity with biomarkers of EZH2 inhibition and resistance, potentially including but not limited to circulating or tumor molecular profiling, epigenetics, and immune system activity.
Study Design:	This is a single institution, single-arm, open label phase 2 study.
Accrual Goal:	Up to 50 people will be enrolled in this study to achieve 29 evaluable subjects.
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria at enrollment: A. A histologic confirmation of recurrent/refractory and/or metastatic MPNST with RECIST measurable disease. B. Subjects ≥ 12 years of age at the time of enrollment. C. Performance status: • 12-15 years old- Lansky > 50 • 16-17 years old- Karnofsky > 50 • ≥18 years old- ECOG score 0-2 D. Subjects must have adequately recovered from the acute toxic effects of all prior anti-cancer therapy per enrolling physician and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. • Anti-cancer agents known to be Myelosuppressive: ≥ 28 days after the last dose of agent. • Anti-cancer agents not known to be myelosuppressive: ≥ 7 days after the last dose of agent. • Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1. • Systemic Corticosteroids: if related to prior therapy ≥ 14 days must have elapsed, or on stable dose for treatment of CNS disease.

	• Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor. • Interleukins, Interferons, and Cytokines (other than hematopoietic growth factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic growth factors). • XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation. • Radiopharmaceutical therapy: ≥ 42 days after systemically administered radiopharmaceutical therapy. • Major Surgery: ≥ 14 days prior, with evidence of wound healing and no active surgical complications. E. Subjects must not have had prior exposure to Tazemetostat or other inhibitor(s) of EZH2. F. Adequate laboratory values of organ function, defined as: • Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3. • Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment). • Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions). • Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m^2, or serum creatinine based on age/gender as followed in Appendix H. • Total bilirubin ≤ 1.5 ULN or direct bilirubin ≤ 1 x ULN. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; if liver metastases present, then AST and ALT must be ≤ 5 x ULN. Serum albumin ≥ 2 g/dL. • Coagulation INR ≤ 1.5, if on anti-coagulation INR ≤ 2.5. G. Nervous system disorders (CTCAE v5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible. H. Subjects must not have more than one active malignancy at the time of enrollment (Subjects with a prior or concurrent

	malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treating physician and approved by the PI] may be included). I. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures. All subjects and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional standard practice. J. Use of contraception: • Women of childbearing potential (WOCBP) who are heterosexually active must be using two highly effective methods of contraception to avoid pregnancy throughout the study and for at least 6 months after the last dose of study drug to minimize the risk of pregnancy as Tazemetostat might counteract the effects of hormonal contraceptives. Birth control methods that can be used while in this study include: established use of oral, injected or implanted hormonal birth control or placement of an intrauterine device [IUD] or intrauterine system [IUS]. They or their partner must also use a second method, (e.g., condom with spermicidal foam/gel/film/cream/suppository or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository. If their male partner is vasectomized, they do not need to use any of the birth control methods listed above. The type of birth control they use must be discussed with the study doctor before beginning the study. The study doctor must approve the method you use before they can enter the study. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. • Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (e.g., abstinence, condoms, vasectomy) throughout the study and

	should avoid donating sperm, for 90 days following the last dose of study drug.
Exclusion Criteria:	Subjects with any of the following present at time of enrollment will not be eligible for study participation: A. Subjects who are currently taking the following concomitant medications: • Anti-cancer Agents: Subjects who are currently receiving other anti-cancer agents are not eligible. • CYP3A4 Agents: Subjects who are currently receiving drugs that are strong inducers or strong inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 are prohibited from 14 days prior to the first dose of Tazemetostat to the end of the study. Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is allowed. • Grapefruit, grapefruit juice, Seville oranges and food/drinks containing them should be avoided one week before the first dose of the study intervention B. Subjects who are acutely ill with an uncontrolled active infection on systemic anti-infective agents are not eligible. C. Subjects with a prior history of T-LBL/T-ALL, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL) or other myeloproliferative neoplasm (MPN). D. Subjects who have any of the following underlying major cardiac issues or conditions: • Known QTc prolongation or documentation • Documented New York Heart Association (NYHA) Class III or IV congestive heart failure. • Myocardial infarction within 6 months prior to registration. • Unstable angina within 6 months prior to registration. • Symptomatic arrhythmia.

	E. Subjects who in the opinion of the investigator may be high risk for treatment complications or unable to comply with the safety monitoring requirements of the study are not eligible. F. Heterosexually active males or females of reproductive potential may not participate unless they have agreed to use two highly effective contraceptive methods for the duration of study treatment as Tazemetostat might counteract the effects of hormonal contraceptives. Female subjects of childbearing potential should agree to remain abstinent or use adequate contraceptive methods for 6 months after the last dose of Tazemetostat. Male subjects should agree to remain abstinent or use adequate contraceptive methods, and agree to refrain from donating sperm, and for 90 days after the last dose of Tazemetostat. G. Females who are pregnant or breastfeeding will not be entered on this study because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. H. Administration of a vaccine containing live virus within 30 days prior to the first dose of trial treatment. For examples, see Section 7.3.3: Prohibited Concomitant Therapy. **Note**: Most flu vaccines are killed viruses, with the exception of the intra-nasal vainer (Flu-Mist) which is an attenuated live virus and therefore prohibited for 30 days prior to first dose. Non-live versions of the COVID-19 vaccine are allowed. I. Prisoners or subjects who are involuntarily incarcerated, or subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. J. Known hypersensitivity to tazmetostat or any component of the formulation of tazmetostat K. Inability to take oral medication OR have malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, vomiting) that might impair the bioavailability of tazmetostat
Efficacy Assessments:	RECIST (Version 1.1)

Sample Size Justification	Simon's two-stage Optimum design will be used for the study to evaluate the primary endpoint of objective response rate (ORR, defined as CR+PR) of Tazemetostat. Assuming that with current treatment (chemotherapy with doxorubicin and ifosfamide), the null hypothesis that the true ORR is 21% (Kroep JR et al, 2011) will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 2 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 20 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 10 or more responses are observed in 29 patients. This design yields a type I error rate of 5% and power of 80% when the ORR is 45%.
Estimated Enrollment Period:	24 months
Estimated Study Duration:	36 months

1. BACKGROUND

1.1 MPNST in neurofibromatosis type 1 (NF1)

NF1 is an autosomal-dominant cancer predisposition syndrome afflicting 1 in 3500 individuals worldwide, making it one of the most common genetic disorders, and a de novo incidence rate of 1 in 3000. NF1 subjects have up to 60% lifetime predisposition to cancer. NF1 gene is a tumor suppressor gene in chromosome 17q11.2 which codes for *neurofibromin,* a GTPase-activating protein (GAP) which negatively regulates Ras signaling keeping cell proliferation in check. All NF1 tumors show biallelic inactivation of NF1 gene and activated Ras pathway driving cancer formation. [1,2]

Malignant peripheral nerve sheath tumors (MPNST) are highly aggressive sarcomas that frequently develop in the context of NF1 and represent the leading cause of death in individuals with this disease. The lifetime risk of development of MPNST in individuals with NF1 is 8-13%[3], with a 1000-fold higher risk than the general population. [4,5] MPNST constitute 10% of all malignant sarcomas overall, with highly aggressive clinical behavior characterized by high local recurrence rates and early metastases. The cornerstone of MPNST treatment is surgical resection, but is often not possible due to large lesions at presentation, and at sites adjacent to neurovascular bundles and vital organs. Thus, unresectable and metastatic tumors are considered incurable. MPNSTs rapidly develop resistance to chemotherapy.

Even with aggressive surgery and chemotherapy, MPNST subjects have a 5-year survival rate of just 35%– 50%. [3, 4]

1.2 Malignant peripheral nerve sheath tumor systemic therapy

The role of adjuvant therapies in unresectable MPNST has recently been investigated in both pediatric and adult trials. A large adult soft tissue sarcoma (STS) study evaluated the chemosensitivity of advanced MPNST and compared these results with other advanced soft tissue sarcoma histologic subtypes. Out of 2675 chemo naïve eligible STS, the outcome of 175 MPNST patients after a median follow up of 4.1 years showed response rate, median PFS and overall survival of 21% (versus 22%), 17 weeks (versus 16 weeks) and 48 weeks (versus 51 weeks), respectively. Chemotherapy regimen was an independent prognostic factor for response ($p < 0.0001$) and PFS ($p = 0.009$). Compared with standard first-line doxorubicin, the doxorubicin–ifosfamide regimen had the best response, whereas ifosfamide had the worst prognosis.[6] A prospective European Pediatric Soft Tissue Sarcoma Group (EpSGG) study of MPNST patients under 21 years old showed 5-year event-free survival (EFS) and overall survival (OS) to be 52.9% (95% confidence interval, 38.1-65.8) and 62.1% (46.7-74.3), respectively. Similar to the adult series, standard ifosfamide-doxorubicin chemotherapy for unresectable MPNST rendered the best reported outcome, with a response rate to chemotherapy (partial response + complete response) in patients with measurable disease of 46%, higher than adults.[7]

Preclinical studies have identified several novel candidate molecular targets for therapeutic intervention. Several early phase trials using these novel drugs have been conducted but to date, no targeted therapies have yet been proven effective (Table 1).8 Due to the limited number of therapeutic options in advanced MPNST, identification of novel drug targets and development of new treatment strategies are urgently needed.

Therapy	Molecular targets	No. of MPNST	Study design and population	Response	References
Erlotinib	EGFR	20	Phase II study in MPNST	No objective responses, 1 stable disease	72
Sorafenib	VEGFR, RAF, PDGFR	12	Phase II study in soft tissue sarcomas	No objective responses	73
Imatinib	c-KIT, PDGFR, VEGFR	7	Phase II study in 10 subtypes of sarcoma	No objective responses, 1 stable disease	74
Dasatinib	c-KIT, c-SRC	14	Phase II study in bone and soft tissue sarcomas	No objective responses	75
Alisertib	Aurora Kinase A	10	Phase II study in advanced sarcomas	No objective responses	76
Bevacizumab/RAD001	VEGF/mTOR	25	Phase II study in MPNST	2 stable disease, 1 partial response after 2 cycles that progressed after cycle 4	77, 78
Ganetespib/Sirolimus	HSP90/mTOR	20	Phase I/II study in MPNST	Not fully reported	79
Pexidartinib/Sirolimus	c-KIT, PDGFR, CSF1R/mTOR	6	Phase I study in MPNST, PVNS, and other sarcomas	5 stable disease	80
Selumetinib/Sirolimus	MEK/mTOR	21	Phase II study in MPNST	Enrolling	N/A

c-KIT, stem cell factor receptor; CSF1R, colony stimulating factor 1 receptor; c-SRC, cellular SRC kinase; EGFR, epidermal growth factor receptor; HSP90, heat shock protein 90; mTOR, mammalian target of rapamycin; PDGFR, platelet derived growth factor receptor; PVNS, pigmented villonodular synovitis; RAF, rapidly accelerated fibrosarcoma; VEGF, vascular endothelial growth factor (ligand); VEGFR, vascular endothelial growth factor receptor.

Table 1. Clinical trials of targeted therapied for MPNST8

1.3 Overview of Pre-clinical Studies

The role of epigenetics in cancers has been well elucidated. Post translational modifications of core histone proteins of chromatin are important in controlling the fidelity of gene transcription pattern in cells. Paramount among these transcription-controlling modifications are methylation events at lysine and arginine residues, catalyzed by histone methyltransferase (HMTs).[9] Genetic alterations in a number of HMTs have been identified in human cancers where they are purported to play a causal role in malignancies.[10]

Enhancer of zeste homolog 2 (EZH2), is the catalytic subunit of the multi-protein histone-lysine N-methyltransferase complex polycomb repressive complex 2 (PRC2), involved in chromatin remodeling and transcriptional silencing[11] (Figure 1). PRC2 plays an essential role in the epigenetic maintenance of the repressive H3K27me3 chromatin mark [12]. Trimethylation form H3K27Me3 is associated with repression of genes important for differentiation. WI/SNF is another multi-protein complex involved in chromatin remodeling. It antagonizes PRC2 activity in regulating self-renewal and differentiation of cells. In stem or progenitor cells, EZH2 activity is high, and the expression of PRC2 target genes is therefore repressed. When EZH2 activity is down-regulated, PRC2 target gene expression is increased through augmented SWI/SNF activity, and cells can differentiate and become quiescent[13] (Figure 2).

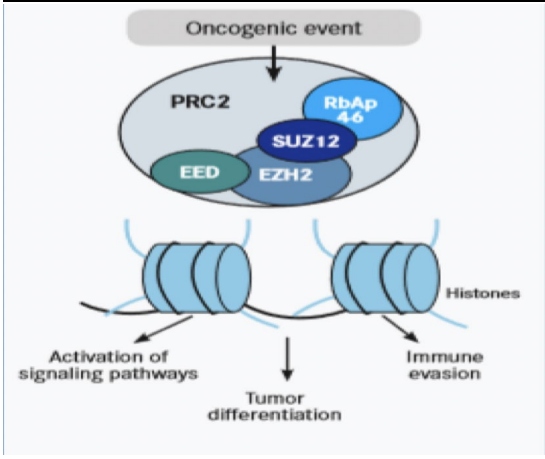


Figure 1. EZH2, a core subunit of PRC2 regulates transcriptional activity and chromatin remodeling transcriptional activity. The other subunits are embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12) and retinoblastoma-associated protein 46v (RbAp46) (*Adapted from Burns EM Targeted Oncology 6 (11), 2017)* [47].

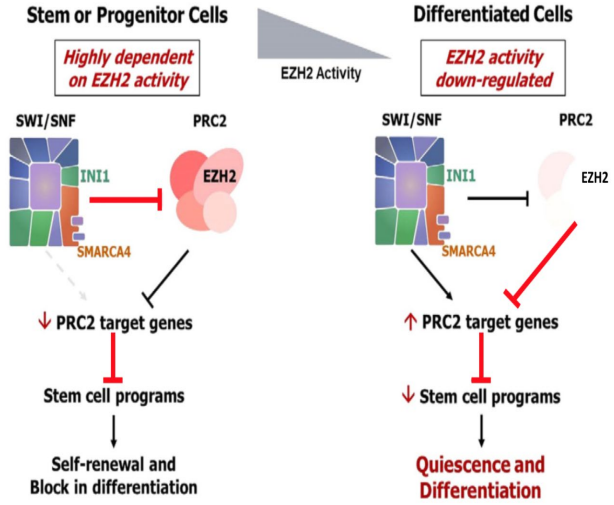


Figure 2. The SWI/SNF and the PRC2 complexes antagonistically regulate gene expression. If the components of the SWI/SNF complex such as INI1 or SMARCA4 are mutated or deleted in certain cancers, PRC2-SWI/SNF1 antagonism is perturbed leading to hyperexpression of PRC2 targets, potentiation of stem cell programs and oncogenic transformation. In normal stem cells, EZH2 is highly expressed in cancer stem cell populations and suppresses differentiation via repression of lineage-specific factors to maintain these populations. It has been hypothesized that EZH2 blocks differentiation, which facilitates cell transformation (*Adapted from Italiano A J Pharm Therap 165(2016) 26-31).*

Abnormal EZH2 expression has been associated with various human malignancies such as prostate, bladder, breast, endometrium, colorectal and melanoma [13]. In glioblastoma multiforme, EZH2 has been shown to be a functional oncogene, a prognostic factor, and a potential therapeutic target [14]. EZH2 overexpression is associated with adverse outcome, enhanced progression and advanced disease in cancers of the prostate, bladder, breast, and endometrium, as well as melanoma. High expression of EZH2, defined as greater than 10% in immunohistochemical analysis and up to 4-fold increased expression via real-time polymerase chain reaction testing, has been associated with increased disease aggressiveness. [12, 15, 16]

Several mechanisms have been implicated in overexpression of EZH2 in tumors. EZH2 overexpression as a result of gene amplification was identified in prostate cancer. Increased EZH2 expression can be also the result of various signals and pathways depending on the tumor type. For instance, Fujii et al (2011) [17] has demonstrated that MEK–ERK–Elk-1 pathway, which is one of the signal

transduction pathways that are upregulated in cancer cells, is linked to overexpression of EZH2 in triple-negative and ERBB2 overexpressing subtypes of breast cancer. EZH2 depletion has been shown to accelerate KRas (G12D)-driven neoplasia in a pancreatic cancer model, suggesting that its role is tumor context dependent. [18]

Several studies have shown that EZH2 expression can be negatively regulated by different miRNA, which are a class of small, non-coding RNA important in post-transcriptional gene silencing. For instance, the upregulation of EZH2 has been linked to loss of expressions of miR-101, miR-26a, and miR-124 in different tumor types. [19-21] Conversely, EZH2 also epigenetically represses tumor suppressive miRNAs to facilitate tumor growth. EZH2 overexpression is mainly found in solid tumors, whereas missense mutations of EZH2 are identified in hematologic malignancies. In fact, gain-of-function missense mutations Y641 and A677 residues within the catalytic SET domain of EZH2 have been discovered in up to 25% of follicular lymphoma and diffuse large B-cell lymphoma. [22] These mutations result in an increased EZH2 stability and an increase in H3K27 trimethylation. [23] In mouse models of the germinal center B-cell-like (GCB) subtype of diffuse large B-cell lymphoma (DLBCL), EZH2 mutations induce differentiation arrest, resulting in germinal center hyperplasia, and accelerated lymphomagenesis in the presence of BCL2 overexpression. Interestingly, the small molecule inhibitor of EZH2 methyltransferase activity are able to decreases global H3K27me3 levels, to reactivate silenced PRC2 target genes and to inhibit the proliferation of EZH2 mutant DLBCL cells in vitro and in vivo.

1.3.1 EZH2 in sarcomas

INI1 is a potent tumor suppressor gene, a member of the SWI/SNF complex whose integrated functions control diverse cellular processes such as differentiation and proliferation. Loss of INI1 function leads to elevated expression and recruitment of EZH2 to target genes that become trimethylated on H3K27 and repressed, which results in the upregulation of several oncogenic signaling pathways, including Sonic Hedgehog, Wnt/β-Catenin, and MYC. [24] INI1 loss was first identified in malignant rhabdoid tumors (MRTs) which are rare and aggressive cancers that principally occur in childhood and can arise in various locations, mainly the kidney, brain, and soft tissues. MRTs harbor recurrent and specific biallelic-inactivating mutations or deletions of INI1 located in the 22q11.2 region. [25] Interestingly, apart from this specific alteration, MRTs have a remarkably low rate of mutations and no genomic instability, suggesting a potential oncogenic driver role of INI1 loss in MRT tumorigenesis. INI1 loss has also been found

with high frequency (50 to 80%) in epithelioid sarcomas or other sarcomas with epithelioid features such as malignant peripheral sheath tumors (MPNSTs). [26, 27]

EZH2 overexpression has been noted in MPNST, compared to normal nerves, and neurofibroma, and levels appear to be 8-fold higher compared to atypical plexiform neurofibromas. [28] It has shown that EZH2 directly inhibits miR-200b expression in MPNST, which may ultimately also contribute to epithelial-mesenchymal transition (EMT) progression, MPNST invasion and metastasis. [29] EZH2 has been shown to be a critical regulator of epithelial-mesenchymal transition (EMT), which is a critical step for initiation of cancer invasion and metastasis. [30]. EZH2 promotes EMT directly by inhibiting the expression of E-cadherin and indirectly through the NF-κB/Twist pathway. [31, 32] Additionally, miR-200b is known to act as an inhibitor of EMT by targeting the transcription faction ZEB1/2 and then by activating E-cadherin. [33, 34] MPNSTs typically have known mutations in SUZ12 (56%) and EED (32%).

EZH2 knockdown by RNA interference in MPNST cell lines induced MPNST cell apoptosis in vitro and inhibits MPNST tumor growth in vivo, suggesting that EZH2 is a potential therapeutic target in MPNST. [35] Zhang et al [29, 35] found that pharmacological inhibition of EZH2 by DZNep depleted EZH2 expression, induced expression of miR-30a and miR-30d, and inhibited Karyopherin β1 (KPNB1) expression in MPNST cells. By impairing the EZH2/miR-30a,d/KPNB1 pathway, DNZep induced MPNST cell apoptosis and cell cycle arrest, which together decreased MPNST cell viability and suppressed cell survival in vitro. They also demonstrated that DZNep treatment inhibited MPNST tumor initiation and growth rates in a mouse xenograft model.

1.4 Overview of Clinical Studies

Tazemetostat (EPZ-6438) is a potent and highly selective, first-in-class oral small molecule EZH2 inhibitor. Tazemetostat has been shown to have anti-tumour activity in *in vitro* and xenograph models of EZH2- mutant B-cell non-Hodgkin lymphoma, INI1-negative malignant rhabdoid tumor, and SMARCA4-negative malignant rhabdoid tumor of the ovary. [36-38]

1.4.1 Hematologic malignancies

A Phase 1 study for relapsed/refractory solid tumors and B cell lymphoma (NCT01897571) was conducted with the primary endpoint being the maximum tolerated dose of Tazemetostat. Tazemetostat was administered

orally from 100 mg twice daily to 1600 mg twice daily in 28-day cycles between June 13, 2013, and Sept 21, 2016. 64 patients (21 with B-cell non-Hodgkin lymphoma, and 43 with advanced solid tumors) received Tazemetostat, the most common treatment-related adverse events were asthenia (21 [33%] of 64 treatment-related events), anemia (nine [14%]), anorexia (four [6%]), muscle spasms (nine [14%]), nausea (13 [20%]), and vomiting (six [9%]), usually grade 1 or 2 in severity. The recommended phase 2 dose was determined to be 800 mg twice daily. Durable objective responses, including complete responses, were observed in eight (38%) of 21 patients with B-cell non-Hodgkin lymphoma and two (5%) of 43 patients with solid tumors. Tazemetostat showed a favorable safety profile and antitumor activity in patients with refractory B-cell non-Hodgkin lymphoma and advanced solid tumors, including epithelioid sarcoma. [39]

An interim update from a Phase 2 multicenter study using Tazemetostat in patients with relapsed or refractory follicular lymphoma showed that Tazemetostat was generally well tolerated, with 5% patients discontinued treatment due to a treatment-related AE, 9% patients needing a dose reduction due to a treatment-related AE, low rate of grade ≥3 treatment related AEs and no treatment related deaths. This study demonstrated durable, single agent, antitumor activity in difficult-to-treat patients with relapsed / refractory follicular lymphoma with an ORR of 77% and 34% in MT (mutant type) and WT (wild type) EZH2, respectively. All patients in the MT cohort and a majority of patients in WT cohort demonstrating a reduction in tumor volume. There was durable clinical activity across both MT and WT cohorts, with patients on therapy up to 23 months, and responses continuing to deepen over time, with a PFS of 11.1 and 5.7 months in MT and WT EZH2, respectively. [40]

An open-label, single-arm, phase 2 trial done at 38 clinics or hospitals in France, the UK, Australia, Canada, Poland, Italy, Ukraine, Germany, and the USA using Tazemetostat 800 mg twice daily in patients with relapsed/refractory follicular lymphoma (NCT01897571). [41] This study showed meaningful clinical activity and durability of response in patients with recurrent/refractory follicular lymphoma, with ORR pronounced in patients with EZH2 activating mutations. Late onset responses have been reported on Tazemetostat. Tazemetostat was generally well tolerated in heavily pretreated patients with relapsed or refractory follicular lymphoma. Between July 9, 2015, and May 24, 2019, 99 patients (45 in the EZH2mut cohort and 54 in the EZH2WT cohort) were enrolled in the study with median follow-up of

22 months for the EZH2MT cohort and 35.9 months for the EZH2WT cohort. The objective response rate was 69% (95% CI 53–82; 31 of 45 patients) in the EZH2mut cohort and 35% (23–49; 19 of 54 patients) in the EZH2WT cohort. Median duration of response was 10.9 months (95% CI 7.22–not estimable [NE]) in the EZH2mut cohort and 13 months (5.6–NE) in the EZH2WT cohort; median progression-free survival was 13.8 months (10.7–22.0) and 11.1 months (3.7–14.6). Among all 99 patients, treatment-related grade 3 or worse adverse events included thrombocytopenia (3%), neutropenia (3%), and anemia (2%). Serious treatment-related adverse events were reported in four (4%) of 99 patients. There were no treatment-related deaths.

In 2016, the Food and Drug Administration (FDA) granted Tazemetostat Fast Track status in 2016 for patients with relapsed/refractory DLBCL with EZH2-activating mutations. On June 18, 2020, the Food and Drug Administration (FDA) granted accelerated approval to Tazemetostat for adult patients with relapsed or refractory (R/R) follicular lymphoma whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies, and for adult patients with R/R follicular lymphoma who have no satisfactory alternative treatment options.

Tazemetostat is still being evaluated as a combination therapy in ongoing clinical trials. One study is evaluating Tazemetostat in combination with R-CHOP (NCT02889523), a chemotherapy regimen, as a first-line treatment for newly diagnosed elderly, high-risk patients with diffuse large B-cell lymphoma (DLBCL), the most common type of NHL. Another clinical trial (phase 1) is evaluating Tazemetostat in combination with Tecentriq™ (atezolizumab), in patients with relapsed or refractory DLBCL. Tecentriq is an anti-PD-L1 cancer immunotherapy approved by FDA, and in a phase 1b study as a combination therapy with prednisolone, in patients with relapsed or refractory DLBCL (NCT02220842, NCT01897571).

1.4.2 Solid tumors

There are preclinical data on impact of inhibition of EZH2 overexpression in various solid tumors, including MPNST, but degree of downstream effects is tumor dependent and overall clinical impact in terms of response rates in MPNST is unknown. Tazemetostat has been shown to have antitumor activity in preclinical malignant rhabdoid tumor (MRT) models that were negative for the INI1 protein and in phase I trials of MRT and epithelioid sarcoma.[43] In an open-label, phase 2 basket study, patients were enrolled from 32 hospitals and clinics in Australia, Belgium, Canada, France, Germany,

Italy, Taiwan, the USA, and the UK into seven cohorts of patients with different INI1-negative solid tumors or synovial sarcoma (NCT02601950). Patients eligible for the epithelioid sarcoma cohort (cohort 5) were aged 16 years or older with histologically confirmed, locally advanced or metastatic epithelioid sarcoma; documented loss of INI1 expression by immunohistochemical analysis or biallelic SMARCB1 (the gene that encodes INI1) alterations, or both. Patients received Tazemetostat 800 mg orally twice per day in continuous 28-day cycles and primary endpoint was objective response rate per RECIST 1.1. Between Dec 22, 2015, and July 7, 2017, 62 patients with epithelioid sarcoma were enrolled in the study. Tazemetostat was well tolerated and showed clinical activity in this cohort of patients with advanced epithelioid sarcoma. Nine (15%) of 62 patients had an objective response at data cutoff (Sept 17, 2018). At a median follow-up of 13.8 months, median duration of response was not reached (95% CI 9.2 -not estimable). 16 (26%) patients had disease control at 32 weeks. Median time to response was 3·9 months. Median progression-free survival was 5·5 months (95% CI 3.4-5.9), and median overall survival was 19 months (11-not estimable). Grade 3 or worse treatment-related adverse events included anemia (6%) and weight loss (3%), without treatment-related deaths. [43] A phase 1b/3 trial of Tazemetostat plus doxorubicin in the front-line setting is currently underway (NCT04204941).

Breast cancer gene 1 (BRCA1)-associated protein 1 (BAP1), a nuclear deubiquitinase, is commonly inactivated in malignant mesothelioma and preclinical data showed that BAP1 inactivation sensitizes mesothelial cells to inhibition of EZH2. A 2-part, open label phase 2 study evaluated the safety and efficacy of Tazemetostat in relapsed/refractory (R/R) malignant mesothelioma with BAP1-inactivation (NCT02860286). Primary endpoints were PK profiling of Tazemetostat in all patients (part 1), and disease control rate (DCR) at week 12 in patients with BAP1-deficient R/R malignant mesothelioma (part 2). Secondary endpoints included safety, overall response rate (ORR), progression-free survival, overall survival, and duration of response (DOR). The study enrolled 74 patients with R/R malignant mesothelioma, of which 70 (95%) were centrally confirmed to be BAP1-deficient. Median prior lines of therapy were two. The 12-week DCR was 47% (n = 35). The ORR per RECIST version 1.1 was 3% [complete response: 0%; partial response (PR): 3% (n = 2)]. Of the 2 patients with PR, 1 had a duration of response (DOR) of 21 weeks and the other is ongoing (15.3 weeks at data cut off). 47 subjects (64%) and 21 subjects (28%) had stable disease (SD) and progressive disease, respectively. Overall, 91% of subjects discontinued,

either due to disease progression (n = 65), death (n = 5), or treatment discontinuation (n = 1). Grade ≥3 treatment-emergent adverse events occurred in ≤5% of patients, most commonly anemia (5%) and dyspnea (4%). No subjects discontinued due to treatment-emergent adverse events and there were no treatment-related deaths. Based on disease control rate and stable disease, Tazemetostat showed antitumor activity in patients with BAP1-deficient R/R malignant mesothelioma. [44]

Recent literature has described genomic features of small cell carcinoma of the ovary of the hypercalcemic type (SCCOHT), a rare highly aggressive tumor that affects young women. This cancer was found to have loss-of-function mutations in SMARCA4 (Brahma-related gene 1, BRG1) as a highly recurrent event in SCCOHT. [45, 46.] SMARCA4 encodes one of the two possible catalytic subunits of the Switch/Sucrose Non-Fermentable chromatin-remodeling complex. Others have since confirmed this finding, with SMARCA4 mutations being found in over 90% of cases.

1.4.3 Pediatrics

Tazemetostat is among the first investigational therapies to be tested in the multicenter, phase II Pediatric MATCH trial, which is being sponsored by the National Cancer Institute. The trial is examining targeted agents in children with advanced metastatic/recurrent tumors that are refractory and have EZH2, SMARCA4, or SMARCB1 gene mutations. The primary endpoint is ORR, with a secondary endpoint of PFS and additional evaluations of biomarker predictors of treatment response and change in tumor dynamics (NCT03213665, NCT03155620).

1.5 Rationale for Regimen/Doses/Schedule

EPZ-6438 (Tazemetostat) is a selective small molecule inhibitor of the histone methyltransferase EZH2. Tazemetostat is an inhibitor of both wild type and mutated EZH2 containing residues Y646, A682G and A692 with half maximal inhibitory concentrations (IC50) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits H3K27 methylation in a concentration and time dependent manner leading to selective killing of cell lines, specifically, human lymphoma cell lines with mutant or wildtype EZH2, *SMARCB1*-deficient malignant rhabdoid tumor (MRT) cell lines, and SMARCA2/A4 negative SCCOHT cell lines with IC50 in the nanomolar range. Tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 wild type and mutant human lymphoma xenograft murine models. [36]

SMARCB1 mutant MRT xenografts treated for 21-28 days demonstrated near elimination of the tumors with no regrowth observed. The MRT tumors demonstrated strong inhibition of H3K27Me3 which correlated with anti-tumor activity. [37]

1.5.1 Rationale for Doses Indicated in Current Study

The first pediatric phase 1 study of Tazemetostat (EZH-102, NCT02601937) for children with relapsed/refractory MRT including CNS ATRT and other INI-deficient tumors and synovial sarcoma enrolled its first patient in January 2016 and completed the dose escalation phase of the trial (dose expansion is ongoing). As of July 2017, the RP2D was determined to be 1200 mg/m2 twice daily (for CNS primary tumors). The dose that will be utilized in the current protocol for children is lower (520mg/m2 twice daily, up to a maximum of 800 mg per dose), due to the non-CNS MPSNT subjects under study.

For adults, the current study proposes 800mg twice daily, which is the dose studied in the previous described hematologic and solid tumor trials. 39, 41, 43

Additional information, including animal toxicology data, is provided in the Investigator's Brochure (IB) for Tazemetostat.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary

2.1.1 Primary Objective:

To assess the objective response rate of Tazemetostat in subjects with recurrent/refractory and/or metastatic MPNST

2.1.2 Primary Endpoint:

Objective response rate (ORR, defined as proportion of subjects who achieve complete response CR or partial response PR) based on radiographic evaluation of treatment response via RECIST1.1.

2.2 Secondary

2.2.1 Secondary Objectives:

- To determine the progression free survival (PFS) in subjects with recurrent/refractory and/or metastatic MPNST.
- To determine the time to progression (TTP) in subjects with recurrent/refractory and/or metastatic MPNST.

- To determine the clinical benefit using subject reported outcome (PRO)
- To assess the clinical benefit rate (CBR).

2.2.2 Secondary Endpoints:

- PFS, defined as the duration of time from start of treatment to time of progression (RECIST 1.1 criteria) or death, whichever occurs first.
- TTP, defined as the length of time from the start of treatment until the evidence of disease progression, as defined by RECIST 1.1 criteria.
- Patient Reported Outcome (PRO) Numbered Pain Rating Scale 11 pain score mean (Appendix I).
- Clinical Benefit Rate (CBR), defined as the proportion of subjects with objective response (CR or PR) or stable disease (SD) lasting ≥ 4 months.

2.3 Exploratory

- Assess circulating tumor DNA (ctDNA) as a potential treatment response tool.
- Correlate clinical data, outcomes and toxicity with biomarkers of EZH2 inhibition and resistance - potentially including but not limited to circulating or tumor molecular profiling, epigenetics, and immune system activity.

3. STUDY DESIGN

3.1 Study Overview

This is a single institution, open label, single-arm phase 2 trial. We plan to accrue up to 50 subjects in order to meet our goal of 29 evaluable subjects. Each subject will be administered Tazemetostat orally twice daily for subjects with recurrent and/or metastatic MPNST. Subjects will be dosed in continuous 28 day cycles, and as follows:

- Pediatric (12y- <18y): 520 mg/m^2/dose orally BID, not to exceed 800 mg orally twice daily
- Adult: (≥18y): 800 mg orally BID (flat dose for adults)

Surveillance imaging of primary and metastatic sites will be performed every 2 cycles, +/- 7 days after Cycle 1 Day 1, until disease progression or death. ctDNA testing results will be collected whenever performed per standard of care. Response to treatment will be evaluated via RECIST 1.1. Treatment with Tazemetostat will continue until disease progression, unacceptable toxicity or withdrawal of consent or termination of study. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Total duration of subject participation will be 24 months. Total duration of the study is expected to be 36 months.

4. SELECTION OF SUBJECTS

Subjects with a clinical diagnosis of recurrent and/or metastatic MPNST who meet the following inclusion and exclusion criteria at study enrollment will be eligible for participation in this study. **Per UFHCC guidelines, exceptions to inclusion and exclusion criteria are not permitted.** For questions concerning eligibility, please contact the PMO (pmo@cancer.ufl.edu).

4.1 Number of Subjects

Up to 50 people will be enrolled in this study to achieve 29 evaluable subjects.

4.2 Inclusion Criteria

Individuals eligible for study participation must meet the following criteria at enrollment:

A. A histologic confirmation of recurrent/refractory and/or metastatic MPNST with RECIST measurable disease.
B. Subjects ≥ 12 years of age at the time of enrollment
C. Performance status:
   - 12-15 years old- Lansky > 50
   - 16-17 years old- Karnofsky > 50
   - ≥18 years old- ECOG score 0-2
D. Subjects must have adequately recovered from the acute toxic effects of all prior anti-cancer therapy per enrolling physician and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. Subjects who have not received any anti-cancer treatment prior to study treatment are also eligible to enroll.
   - Anti-cancer agents known to be Myelosuppressive: ≥ 28 days after the last dose of agent.
   - Anti-cancer agents not known to be myelosuppressive: ≥ 7 days after the last dose of agent.
   - Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.
   - Systemic Corticosteroids: if related to prior therapy ≥ 14 days must have elapsed, or on stable dose for treatment of CNS disease.
   - Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor.

- Interleukins, Interferons, and Cytokines (other than hematopoietic growth factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic growth factors).
- XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.
- Radiopharmaceutical therapy: ≥ 42 days after systemically administered radiopharmaceutical therapy.
- Major surgery ≥ 14 days prior, with evidence of wound healing and no active surgical complications

E. Subjects must not have had prior exposure to Tazemetostat or other inhibitor(s) of EZH2.

F. Adequate laboratory values of organ function, defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3.
- Platelet count ≥ 100,000/mm^2 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment).
- Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions).
- Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m^2, or serum creatinine based on age/gender as followed in Appendix H.
- Total bilirubin ≤ 1.5 ULN or direct bilirubin ≤ 1 x ULN.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; if liver metastases present, then AST and ALT must be ≤ 5 x ULN.
- Serum albumin ≥ 2 g/dL.
- Coagulation INR ≤ 1.5, while on anti-coagulation INR ≤ 2.5.

G. Nervous system disorders (CTCAE v5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

H. Subjects must not have more than one active malignancy at the time of enrollment (Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treating physician and approved by the PI] may be included).

I. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures. All subjects and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional standard practice.

J. Use of contraception:

- Women of childbearing potential (WOCBP) who are heterosexually active must be using two highly effective methods of contraception to avoid pregnancy throughout the study and for at least 6 months after the last dose of study drug to minimize the risk of pregnancy as Tazemetostat might counteract the effects of hormonal contraceptives. Birth control methods that can be used while in this study include: established use of oral, injected or implanted hormonal birth control or placement of an intrauterine device [IUD] or intrauterine system [IUS]. They or their partner must also use a second method, (e.g., condom with spermicidal foam/gel/film/cream/suppository or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository. If their male partner is vasectomized, they do not need to use any of the birth control methods listed above. The type of birth control they use must be discussed with the study doctor before beginning the study. The study doctor must approve the method you use before they can enter the study. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.
- Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (e.g., abstinence, condoms, vasectomy) throughout the study and should avoid donating sperm, for 90 days following the last dose of study drug.

4.3 Exclusion Criteria

Subjects with any of the following present at time of enrollment will not be eligible for study participation:

A. Subjects who are currently taking the following concomitant medications:
   - Anti-cancer Agents: Subjects who are currently receiving other anti-cancer agents are not eligible.
   - CYP3A4 Agents: Subjects who are currently receiving drugs that are strong inducers or strong inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 are prohibited from 14 days prior to the first dose of Tazemetostat to the end of the study. Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is allowed.
   - Grapefruit, grapefruit juice, Seville oranges and food/drinks containing them should be avoided one week before the first dose of the study intervention

B. Subjects who are acutely ill with an uncontrolled active infection on systemic anti-infective agents are not eligible.

C. Subjects with a prior history of T-LBL/T-ALL, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL), or other myeloproliferative neoplasm (MPN).

D. Subjects who have any of the following underlying major cardiac issues or conditions:

- Known QTc prolongation or documentation
- Documented New York Heart Association (NYHA) Class III or IV congestive heart failure.
- Myocardial infarction within 6 months prior to registration.
- Unstable angina within 6 months prior to registration.
- Symptomatic arrhythmia.

E. Subjects who in the opinion of the investigator may be high risk for treatment complications or unable to comply with the safety monitoring requirements of the study are not eligible.

F. Heterosexually active males or females of reproductive potential may not participate unless they have agreed to use two highly effective contraceptive methods for the duration of study treatment as Tazemetostat might counteract the effects of hormonal contraceptives. Female subjects of childbearing potential should agree to remain abstinent or use adequate contraceptive methods for 6 months after the last dose of Tazemetostat. Male subjects should agree to remain abstinent or use adequate contraceptive methods, and agree to refrain from donating sperm, and for 90 days after the last dose of Tazemetostat.

G. Females who are pregnant or breastfeeding will not be entered on this study because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal.

H. Administration of a vaccine containing live virus within 30 days prior to the first dose of trial treatment. For examples, See Section 7.3.3: Prohibited Concomitant Therapy. **Note**: Most flu vaccines are killed viruses, with the exception of the intra-nasal vainer (Flu-Mist) which is an attenuated live virus and therefore prohibited for 30 days prior to first dose. Patients may receive non-live versions of the COVID-19 vaccine.

I. Prisoners or subjects who are involuntarily incarcerated, or subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

J. Known hypersensitivity to tazmetostat or any component of the formulation of tazmetostat
K. Inability to take oral medication OR have malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, vomiting) that might impair the bioavailability of tazmetostat

4.4 Inclusion of Women and Minorities

Any subjects who meet eligibility criteria may enroll in this trial.

5. REGISTRATION PROCEDURES

All consented subjects must be entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number. The study team must submit the completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu) or their assigned Project Manager. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. No subject may be enrolled until his/her eligibility packet is complete and eligibility is verified by PMO. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial.

All eligible and enrolled subjects will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

6. STUDY PROCEDURES

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in Section 6.2. Laboratory tests need **not** be repeated at the baseline visit (C1D1) if therapy starts **within 72 hours** of obtaining screening labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If

the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within 30 days prior to start of protocol therapy.

6.1 Schedule of Events

Procedure: / Visit:	SCREENING (Windows outlined in Section 6.2)	CYCLE 1	CYCLES 2 AND BEYOND (WITHIN 72 HRS PRIOR)	END OF TREATMENT (WITHIN 14 DAYS OF LAST STUDY DRUG ADMINISTRATION)	FOLLOW UP (28 +/- 7 DAYS AFTER LAST DOSE OF TREATMENT)	SURVIVAL FOLLOW UP EVERY 90 +/- 14 DAYS AFTER LAST DOSE
Informed Consent	X					
Medical History, Demographic Information	X					
Clinical Exam	X	X	X	X		
Performance status (PS)[1]	X	X	X	X		
Vital Signs (VS) including height[8], weight, and BSA[8]	X	X	X	X		
Numbered Pain Rating Scale [2]		X	X	X		
Labs (CBC diff, CMP) [3,9]	X	WEEKLY [3]	X			X[12]
Pregnancy Test (Urine or Serum) [4]	X	X	X			
INR	X					
Tibial x-ray[10]	X		X[11]			
Provide Study Drug for home administration		X	X			
Tumor disease evaluation[5]	X		EVERY 2 CYCLES[5]	X		
Tumor NGS[6]	X					
Circulating tumor DNA (ctDNA) [7]			X	X		
Provide and/or Review Subject Diary		X	X	X		
Concomitant Medication Review[9]	X	X	X	X		
Adverse Event Review[9]		X	X	X	X	
Survival Assessment						X

Abbreviations: VS=vital signs (blood pressure, temperature, pulse and respiratory rates, weight and height); CBC/diff=complete blood count and white blood cell differential; CMP = complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, protein), NGS Next Generation Sequencing

1 Performance status: Pediatric Karnofsky for subjects ≥ 16 years of age and Lansky for subjects 12-15 years of age; Adult ECOG score (18+)

2	Numbered Pain Rating Scale , refer to Appendix G.
3	Laboratory tests at baseline need not be repeated if therapy starts within 72 hours of obtaining labs to assess eligibility. Labs are to be collected weekly for Cycle 1 (Days 1, 8, 15, and 22) +/- 72 hours. If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. Automated differentials acceptable unless concern for blasts; then please obtain manual differential.
4	Female subjects of childbearing potential only.
5	Patients must have either CT or MRI of primary and metastatic tumors, as well as whole body 18F-FDG PET/CT. Radiographic Tumor Assessment using RECIST 1.1 criteria. Imaging to be obtained every 2 cycles +/- 7 days from Cycle 1 Day 1 until disease progression or death. Screening imaging studies must be obtained within 30 days prior to start of protocol therapy.
6	Tumor NGS will be sent as part of standard of care, if not already done. If already done, results will be recorded as part of medical history review.
7	Circulating tumor DNA (ctDNA) results will be collected whenever obtained per standard of care.
8	Height and BSA only collected for pediatric subjects.
9	Adverse events, conmed collection, and all sample collections, should be performed pre-dose at every cycle. The study drug will be provided at study visits, but self-administered at home throughout the trial. Cycles may be repeated for up to a total duration of therapy of 2 years (maximum 26 cycles), provided the patient meets the criteria for starting subsequent cycles and does not meet any of the criteria for removal from protocol therapy criteria.
10	Only to be completed for subjects <18 years of age. Screening tibial x-ray may have been performed within the past 6 months (180 days) before treatment (C1D1).
11	Tibial x-rays to be completed every 180 +/- 30 days only for those with open growth plates at screening.
12	CBC only – at each survival follow-up visit for five years, then yearly (at least once per calendar year) up to 10 years. Once a subject begins new anti-cancer therapy, they will be followed for survival only.

6.2 Allowable Visit Windows

Visit Name	Window
Screening	
Informed Consent	≤ 28 days prior to Cycle1 Day 1 (C1D1)
Medical History, Physical examination, Performance Status, Concomitant Medications, and Labs (CBC Diff, CMP, INR, pregnancy test)	≤ 28 days prior to Cycle1 Day 1 (C1D1)
Tibial X-Ray	≤ 180 days prior to Cycle1 Day 1 (C1D1)
Imaging (CT and PET)	≤ 30 days prior to Cycle1 Day 1 (C1D1)
All other screening procedures	≤ 7 days prior to C1D1
Cycle 1 Day 1	
Labs	Laboratory tests at screening need not be repeated if therapy starts within 72 hours of obtaining labs to assess eligibility. All others to be done ≤ 72 hours of C1D1 dosing. Labs are to be collected weekly for Cycle 1 (Days 1, 8, 15, and 22) +/- 72 hours
All other baseline procedures (which include complete physical exam, performance status, vital signs, and concomitant medication review)	Baseline procedures completed at screening need not be repeated if therapy starts within 72 hours of performing procedures to assess eligibility. All others to be done ≤ 72 hours of C1D1 dosing.
Day 1 of subsequent cycles (after Cycle 1)	
Assessments	Within 72 hours prior to dosing
Study treatment administration (dosing)	Every 28 days
Tibial X-Ray	Every 180 +/- 30 days
Tumor Assessments	Imaging every 2 cycles +/- 7 days from Cycle 1 Day 1 until disease progression or death.
End of Treatment (EOT) Procedures	Within 14 days of last dose of therapy
28-Day Safety Follow-up	28 +/- 7 days after last dose of treatment

Survival Follow-Up	Every 90 +/- 14 days

6.3 End of Treatment Evaluations

The end of treatment visit as well as evaluations will occur within 14 days following the last dose of therapy. End of treatment evaluations will also be performed within 14 days if the subject is discontinued as per section 8.2.

6.4 Follow up/ Evaluations

Subjects will have a follow-up visit for the evaluation of adverse events 28 days (± 7 days) after the last dose of study medication. Any adverse events ongoing at the follow up visit will be followed until resolution or start of a new therapy. If the subject is unavailable to travel to the institution, the visit may be made via telephone interview to review for adverse event resolution or the occurrence of any new adverse events. Additionally, external or internal medical records may be consulted with permission of the subject to complete remote visit reporting.

Subjects will continue to be contacted via telephone for survival approximately every 90 +/- 14 days until death. Safety labs (CBC) will be performed as part of these visits for 5 years, then annually until 10 years (at least once per calendar year) after last dose of therapy. Labs may be collected at an outside laboratory as standard of care. If study therapy is discontinued for reasons other than progression, continue imaging/disease assessments per standard of care until progression or until start of another therapy or death. Following discontinuation of study therapy for any reason, report the date the first non-protocol anti-cancer therapy is administered. Once a subject begins new anti-cancer therapy, the subject will be followed for survival only.

If a subject becomes unreachable during the course of the study, the investigator or study team will make a reasonable effort to contact the subject and document each attempt (in accordance with Section 4.3.4 of the ICH E-6 GCP). If these attempts are not successful, the subject may be declared "lost to follow up." For subjects lost to follow-up, the termination date will be the date of last contact with the subject.

7. STUDY TREATMENT

7.1 Treatment Schedule/Administration

Tazemetostat will be administered orally twice daily with the dose beginning at the baseline visit (Cycle 1/Day 1) according to the Table 2 below.

Table 2: Tazemetostat Dosing

Baseline Criteria (age at enrollment)	Dose (continuous 28-day cycles)
Pediatric (12y - < 18y)	520 mg/m^2/dose orally twice daily, not to exceed 800 mg orally twice daily, rounded up if between doses
Adult (≥ 18y)	800 mg orally twice daily (flat dose for adults)

7.2 Overview of treatment plan

Tazemetostat will be administered at a dose of 520 mg/m^2/dose for pediatric patients 12- <18 years of age (rounding up if between doses), and for adults ≥ 18 years of age, 800 mg, orally twice daily. The powder for suspension must be reconstituted prior to administration. Patients can take Tazemetostat without regard to meals, with no less than 8 hours between each dose. The oral suspension should be given by mouth immediately after the dose is prepared in the oral syringe. Patients should drink additional water after administration (about 4 ounces). For feeding tube dosing, administer directly into the feeding tube with the syringe. Rinsing with 10 mL of water for NG tubes and 40 mL of water for G-tubes is recommended. If vomiting occurs after taking oral suspension formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time.

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (Section 7.6). A cycle of therapy is considered to be 28 days. Cycles may be repeated for up to a total duration of therapy of 2 years (maximum 26 cycles), provided the patient meets the criteria for starting subsequent cycles and does not meet any of the criteria for removal from protocol therapy criteria.

Pediatric drug dosages should be adjusted based on the BSA calculated from height and weight, measured within 7 days prior to the beginning of each cycle. Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose.

7.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section (Section 4) and remains eligible to continue agent administration per the

requirements in the Investigator Brochure, package insert, and Sections 4 and 7 of this document.

7.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All appropriate treatment areas should have access to a copy of version 5.0 of the CTCAE. A copy of the CTCAE v5 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Project Management Office (PMO@cancer.ufl.edu) and the PI.

7.5 Supportive Care and other concomitant therapy

7.5.1 Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Bisphosphonates or denosumab are allowed for subjects with bone metastases.

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection when approved by the Principal Investigator.

7.5.2 Concomitant Therapy

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within 4 weeks prior to screening, regardless of indication, should be recorded.

Any therapy or medication (except study drugs), administered from screening until thirty days after the last dose of either study drug, is considered a concomitant therapy or medication. However, if another course of anti-cancer therapy is initiated prior to the thirty-day follow-up period visit, a record of concomitant medications will no longer be performed. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, expected duration, and frequency of treatment.

Assessment and documentation of concomitant medications will be done at each visit.

7.5.3 Prohibited Concomitant Therapy

Supportive care measures consistent with optimal subject care will be permitted throughout the study, as long as the therapy is not included in this section as prohibited.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.
- Investigational agents other than the study drug in this trial.
- Radiation therapy (allowed if ≥ 14 days prior to study registration).
- Cancer-Related Surgery (allowed if ≥ 14 days prior to study registration).
- Strong inhibitors and inducers of CYP2C8, CYP2D6, and P-glycoprotein (P-gp) should be used with caution.
- Medications that are sensitive or narrow therapeutic range substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, CYP2D6 should be avoided if possible. Other substrates of CYP2C8, 2C9, 2C19, 2D6, 3A, P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K should be used with caution.
- CYP3A4/5 inhibitors or inducers: Strong CYP3A4/5 inhibitors or inducers are prohibited from 14 days prior to the first dose of Tazemetostat to the end of the study (Appendix F). Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is allowed.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed. Patients may receive non-live versions of the COVID-19 vaccine.

7.6 Dose Modifications

The National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE Version 5.0) for Adverse Events (CTCAE) will be used to grade toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). See Table 3 for Dose Modification Tables for children and adults.

7.6.1 Non- Hematologic Toxicity

Non- Hematological dose limiting toxicity is defined as any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting of less < 3 days duration.
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- **Note:** Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

7.6.2 Dose Modifications for Non-Hematological Toxicity

If a patient experiences non-hematological dose-limiting toxicity as defined in Section 7.6.1, treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as below.

Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose. For subjects taking 800 mg twice daily (dispensed as 4, 200-mg tablets twice daily), dosage should be reduced to 600 mg, dispensed as 3, 200mg tablets twice daily.

Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. If dose-limiting toxicity recurs in a patient who has resumed treatment, the patient must be removed from protocol therapy.

7.6.3 Hematologic Toxicity

Hematological dose limiting toxicity is defined as:

- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration.
- Grade 3 thrombocytopenia that persists for ≥ 7 days.
- Grade 3 thrombocytopenia requiring a platelet transfusion on two separate days, within a 7-day period.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Neutropenia or thrombocytopenia that causes a delay of > 14 days between treatment cycles (e.g. platelets < 100K or ANC < 1000).
- NOTE: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

7.6.4 Dose Modifications for Hematological Toxicity

If a patient experiences hematological dose-limiting toxicity as defined in Section 7.6.3, treatment will be held.

Counts should be checked every 3-4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose. The dose will be reduced by 25% so that patients receive 75% of the original administered dose. For subjects taking 800 mg twice daily (dispensed as 4, 200-mg tablets twice daily), dosage should be reduced to 600 mg, dispensed as 3, 200-mg tablets twice daily.

Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If toxicity does not resolve to meet eligibility parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. If hematological dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

7.6.5 Dose Modification Tables

The table in this section (Table 3) should be used for dose modifications as a result of toxicities outlined in section 7.6.

Table 3: Tazemetostat Dose Modifications for Adverse Reactions

Adults

Dose level	Initial Dose: 8 capsules per day
Starting Dose	Four 200-mg capsules twice daily (1600 mg/day)
Dose Reduction (by 25%)	Three 200-mg capsules twice daily (1200 mg/day)

Children

Dose level	Initial Dose: 8 capsules per day
Starting Dose	520 mg/m^2/dose orally twice daily (up to 1600 mg/day)
Dose Reduction (by 25%)	390 mg/m^2/dose orally twice daily (up to 1200 mg/day)

8. TREATMENT DISCONTINUATION

8.1 Screen Failures

Subjects who sign informed consent, but do not meet eligibility criteria, or withdraw prior to eligibility being verified, and undergo at least some of the screening procedures will be considered screening failures. Subjects who sign informed consent and are verified as eligible, but do not proceed to formal registration will be considered "unregistered." A record of screen failures and unregistered subjects will be maintained by the study site.

8.2 Criteria For Study Treatment Discontinuation

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals.

A subject will be discontinued from protocol therapy under the following circumstances:

- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the principal investigator (in collaboration with any co-sponsors or collaborators) continued treatment with study drug is appropriate.
- The subject becomes pregnant. Pregnancy will be reported along the same timelines as a serious adverse event.
- The subject uses illicit drugs or other substances, or takes part in activities that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to follow-up.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.
- If subject desires to discontinue.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all EOT evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study, even for a brief period of time. Subjects who discontinue following entry will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should experience a serious adverse event during the trial or within **30** days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee.

8.3 Replacement of Subjects

Subjects may be replaced if they are not screen failures, have not completed at least 75% of intended doses in the first cycle, or are not discontinued for disease progression, toxicity, or any of the reasons listed in section 8.2.

Subjects who receive at least 75% of the intended doses in their first cycle will be evaluable for clinical response. Additionally, subjects who receive any dose will be evaluable for toxicity.

9. BIOLOGICAL SPECIMENS AND CORRELATIVES

9.1 Preparation, Shipment and Storage of Specimens

See Study Procedure Manual for collection, processing and shipping instructions for all tissue and blood specimens.

10. STUDY DRUG INFORMATION

10.1 Study Drug Name

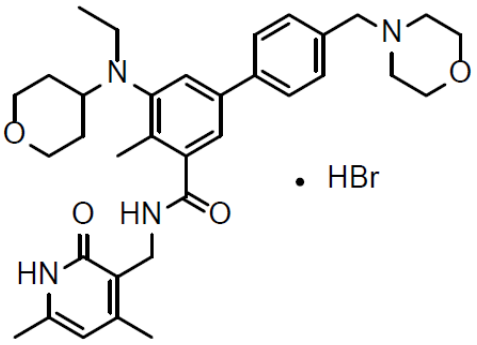
Tazemetostat (Tazverik, Epizyme)

10.1.1 Identification

Tazverik is a methyltransferase inhibitor indicated for the treatment of adults and pediatric subjects aged 16 years and older with metastatic or locally advanced epithelioid sarcoma, a rare slow-growing type of soft tissue cancer, who are not eligible for complete resection. Tazemetostat is taken orally, with or without food. Swallow the tablet whole and do not crush, chew or break it.

Chemical Name: [1,1'-Biphenyl]-3-carboxamide, N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-,hydrobromide(1:1).

Chemical Structure:



Molecular Formula: $C_{34}H_{44}N_4O_4 \cdot HBr$
Molecular Weight: 653.66 g/mol

Physical Description: Tazemetostat hydrobromide is a white to off-white solid that is slightly soluble in water. Tazemetostat tablets contains 200 mg Tazemetostat, equivalent to 228 mg Tazemetostat hydrobromide. Each Tazemetostat tablet is film-coated, red, round, biconvex shape, and debossed with "EZM 200" on one side and plain on the other.

10.1.2 Packaging and Labeling

Study drug is provided in bottles of 240 tablets with a desiccant; NDC 72607-100-00.

All study treatment supplies must be stored in accordance with the storage and handling manual instructions and package labeling. Until dispensed to subjects, the study treatment will be stored in a securely locked area, accessible to authorized staff only.

10.1.3 Drug Supply

The Sponsor Epizyme (or designee) will ship Study Drug to the investigational site, University of Florida. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

10.1.4 Storage, Handling and Dispensing

Tablets

Do not store Tazverik tablets above 86°F (30°C). Drug is administered orally, with or without food. Swallow tablets whole; do not cut, crush, or chew. Store at room temperature away from moisture and heat. Keep the tablets in their original container, along with the packet or canister of moisture-absorbing preservative.

Powder suspension

Do not store above 25°C (77°F). Protect from light. Once oral suspension is prepared, store refrigerated between 2-8 °C (36-46 °F) and protect from light. Brief excursion (less than 4 hours) up to 30°C is allowable for transfer from the clinic to home, but bottles must be immediately refrigerated upon arrival. A cold pack may be provided to the patient as required.

If a storage temperature excursion is identified, promptly return tazemetostat un-reconstituted powder for oral suspension to below 25°C (77°F) and prepared oral suspension to 2-8°C (36-46 °F) and quarantine the supplies.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. Shake the bottle for one minute before you take tazemetostat; do not shake too much (if there are bubbles wait for them to dissipate before measuring the dose). Note: If multiple bottles are dispensed, daily shaking of all bottles is required to ensure the suspension stays properly suspended. Store your oral suspension in the refrigerator.

Table 4. Suspension preparation guidance table

Total tazemetostat required	2 gm bottles	7 gm bottles	Ora-Sweet® volume* (mL)	Allowable medication bottle size** (mL)
< 2 grams	1	0	65	100-150
2 to < 4 grams	2	0	130	200-300
4 to < 6 grams	3	0	195	250-500
6 to < 7 grams	0	1	228	250-500
7 to < 9 grams	1	1	293	400-700
9 to < 11 grams	2	1	358	400-800
11 to < 12 grams	3	1	423	600-1000
12 to < 14 grams	0	2	455	600-1100
14 to < 16 grams	1	2	520	600-1200
18 to < 20 grams	3	2	650	750-1500
20 to < 21 grams	0	3	683	850-1600
21 to < 23 grams	1	3	748	1000-1800
23 to < 25 grams	2	3	813	1000-2000
25 to < 27 grams	3	3	878	1100-2100
27 to < 28 grams	0	4	910	1200-2400

28 to < 30 grams	1	4	975	1300-2500
30 to < 32 grams	2	4	1040	1400-2600
32 to < 34 grams	3	4	1105	1500-2800
This table is for guidance purposes only, larger volumes should be calculated using the Tazemetostat Oral Suspension Preparation Worksheet.				

*The volume of Ora-Sweet® to obtain a concentration of 30 mg tazemetostat/mL of suspension accounts for the volume of tazemetostat in the solution.
** Total volume listed may require more than one medication bottle to accommodate. Each medication bottle must be prepared separately but multiple whole bottles of tazemetostat powder for oral suspension can be combined into one medication bottle.

10.1.5 Contraindications

None

10.1.6 Special Warnings and Precautions for Use

Secondary Malignancies: TAZVERIK increases the risk of developing secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise subjects of potential risk to a fetus and to use effective non-hormonal contraception.

10.1.7 Adverse Event Profile

The most common (≥20%) adverse reactions are pain, fatigue, nausea, decreased appetite, vomiting, and constipation.

10.1.8 Drug Interactions

Strong and Moderate Cytochrome P450 (CYP)3A Inhibitors: Avoid coadministration of strong and moderate CYP3A inhibitors with TAZVERIK. Reduce the dose of TAZVERIK if coadministration of moderate CYP3A inhibitors cannot be avoided.
Strong and Moderate CYP3A Inducers: Avoid coadministration with TAZVERIK.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

The term "adverse event" (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). An abnormal lab value or test results constitute an adverse event if they are considered clinically significant or require therapy. An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

The Investigator or his/her designee will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. AEs will be recorded in the subject CRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is

not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories "serious" and "non-serious."

11.1.2 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death;
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s).

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event).
- elective surgery planned before signing consent.
- admissions as per protocol for a planned medical/surgical procedure.
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).

- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Clarification of the difference in meaning between "severe" and "serious"
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse event per CTCAE is generally considered severe AE. This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

11.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for **30 days** after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until 30 days following the last dose of study treatment (i.e., the Follow-up Visit). However, if another course of anti-cancer therapy is initiated prior to the 30-day follow-up

period visit, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

11.3 Documenting and Reporting of Adverse Events by Investigator

All adverse events must be fully recorded in the subject's case record form. Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

11.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, unlikely related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

Unlikely Related: There is little or no chance that the study drug

administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.

Probably Related: When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

Related: When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re-administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

11.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the most up-to-date CTCAE version. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

11.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study drug as a result of the adverse event.

Interrupted – Study drug was stopped due to the adverse event, but was later resumed at the same dose.
Dose decreased – The dose of study drug was decreased as a result of the adverse event.

Permanently discontinued – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry: permanently discontinued > dose decreased > interrupted.

11.3.4 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.

Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.

Not resolved – The adverse event was present at the time of last observation.

Death – The subject died as a result of the adverse event.

11.4 Immediately Reportable Events

11.4.1 Serious Adverse Events

Serious adverse events (SAE's) must be reported to the UFHCC CRO Project

Management Office (PMO; pmo@cancer.ufl.edu), and entered into OnCore, within **24 hours** of discovery of the event. The FDA MEDWATCH 3500 form must be completed and sent to Epizyme within **7 business days**. If only limited details are known, these should be reported within that time frame and follow up reports can be submitted for elaboration, clarifications, or corrections. Any email correspondence must be kept in the trial file at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be submitted to the UFHCC CRO PMO (pmo@cancer.ufl.edu), stating that this is a follow-up to a previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. PMO will confirm that the event and any necessary follow-ups are reported to the UFHCC Data and Safety Integrity Committee (DISC), the sponsor, and any other regulatory authorities as required (FDA, etc.)

11.4.2 Other Events Requiring Immediate Reporting

All pregnancies, regardless of outcome, must be reported to the UFHCC CRO Project Management Office (PMO; pmo@cancer.ufl.edu), including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome. Pregnancies and follow-ups will be submitted by PMO to DISC, the sponsor if required, and any other regulatory authorities required.

Although overdose and cancer are not always serious by regulatory definition, these events should also be reported to the UFHCC CRO Project Management Office (PMO; pmo@cancer.ufl.edu) in an expedited manner. In case the overdose did not result in any adverse event, the Investigator should report this as "overdose, no adverse event" and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician. Overdose events and follow-ups will be submitted by PMO to DISC, the study sponsor if required, and any other regulatory

authorities required.

Pregnancies and overdoses should be documented and reported per the reporting guidelines below.

Institution Immediate Reporting Information
SAEs and pregnancies must be reported to the UFHCC CRO Project Management Office (PMO), or assigned designee at: Email: pmo@cancer.ufl.edu As well as entered in OnCore, the study CTMS.

11.4.3 Reporting to Epizyme

The UFHCC CRO Project Management Office (PMO) will forward any SAE, AESI, or pregnancy to Epizyme as agreed upon in the contract. PMO will forward both initial and follow-up versions of each report.

Epizyme AE and Pregnancy Reporting Information
Email: *drugsafety.USA@ipsen.com* ***AND*** ***pharmacovigilance@ipsen.com***

12. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

12.1 Data collection and management plan

Data will be collected via paper source documents and the medical record, and will subsequently be entered into a validated Electronic Data Capture (EDC), REDCap, which will be monitored and audited on a regular basis to ensure accuracy. Data will be accessible only to certified members of the research team, under the supervision of the PI, and will be fully de-identified prior to analysis. All paper records will be archived for a pre-specified length of time as per applicable regulations and federal laws.

12.2 Sample Size Justification

Simon's two-stage Optimum design will be used for the study to evaluate the primary endpoint of objective response rate (ORR, defined as CR+PR) of Tazemetostat. Assuming that with current treatment (traditional chemotherapy with doxorubicin and ifosfamide), ORR is 21% for the target study subjects (*Kroep*

JR et al Annals Oncol 22:207-214, 2011), the null hypothesis that the true ORR is 21% and this will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 2 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 20 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 10 or more responses are observed in 29 subjects. This design yields a type I error rate of 5% and power of 80% when the true ORR is 45%.

Assuming an enrollment rate of 6-12 subjects per year per institutional experience, this protocol is expected to accrue within 2-4 years.

12.3 Analysis of Primary Endpoint

The analysis for the primary endpoint, ORR, is based on the intent-to-treat approach. ORR will be calculated as the proportion of the patients with objective response divided by the total number of the study patients. The 95% confidence interval for ORR will be calculated based on the exact binomial distribution.

12.4 Analysis of Secondary Endpoints

Secondary endpoints include PFS, TTP, PRO and CBR. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions. All subjects surviving at the time of analyses without events will be censored at their last follow-up date. PFS along with the confidence intervals will be estimated using the Kaplan-Meier method. TTP will be reported as the length of time from the start of treatment until the evidence of disease progression. Clinical benefit will be described using subject reported outcomes using PRO Numerical Rating Scale 11 as well as reporting the clinical benefit rate (CBR), defined as the proportion of subjects experiencing of objective response (CR+PR) or stable disease ≥ 4months.

12.5 Analysis of Exploratory Endpoints

Exploratory studies will be performed post hoc, in a pre-planned manner, and will include measurement of immune correlate T cell receptor beta chain V gene family (TCRVB) for patients who underwent radiation therapy to primary or metastatic sites. All data will be summarized using descriptive statistics along with graphical illustrations. Exploratory studies will also examine circulating tumor DNA (ctDNA) when performed as standard of care.

12.6 Analysis of Safety Data

The incidence, severity and reversibility of toxicities will be performed on all subjects who receive any dose of study medication. Non-serious adverse events that occur more than 30 days after the administration of the last dose of treatment will not be included. The safety and tolerability of treatment is determined by reported AEs, physical examinations, and laboratory tests.. AEs will be summarized with the incidence and percentage of subjects with at least one occurrence of a preferred term (NCI - CTCAE Version 5 grade) will be included. The number of AEs reported will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE, Version 5.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI- CTCAE Version 5.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated.

12.7 Interim Analysis for Efficacy

According to the two-stage design, an interim analysis will be performed after the first 9 subjects are enrolled in the trial and have response data available for analysis of the primary endpoint. If there are 2 or fewer responses in these 9 subjects, the study will be stopped. Otherwise, 20 additional subjects will be accrued for a total of 29. The study will stay open to enrollment during the interim analysis due to the rareness of the disease and lack of available treatment options, barring any unexpected safety concerns.

12.8 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center Data Integrity and Safety Committee (UFHCC DISC) in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise, the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety.
- Review of all adverse events requiring expedited reporting as defined in the protocol.

- Review of reports generated by data quality control review process.
- Notification of the sponsor-investigator of recommended action.
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.

In compliance with the UFHCC data and safety monitoring plan, the PI will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC (Scientific Review and Monitoring Committee) review, which occurs prior to initial IRB approval.

UFHCC investigator-initiated protocols will be classified into one of the following categories of risk by the SRMC (see SRMC manual for further details):

Level 1 – **Low risk** Investigator Initiated interventional trials.
Level 2 – **Moderate risk** Investigator Initiated or externally sponsored interventional (such as drug, biologic or device) trials using FDA approved or commercially available compounds or interventions.
Level 3 – **High risk** Investigator Initiated or externally sponsored interventional trials (such as investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
Level 4 – Complex trials involving **very high risk** to subjects and a high level of complexity such as first in human or gene transfer studies.

The risk level assigned by SRMC will determine the appropriate level of DISC monitoring required, with increased monitoring required for higher-risk trials.

12.9 Data Monitoring

UFHCC (University of Florida Health Cancer Center) Quality Assurance team and/or project management officers will perform remote monitoring and may make monitoring visits to the trial sites periodically during the trial to confirm that all sites are complying with the protocol. Source documents will be reviewed for completion and validated against data submitted electronically via Electronic Data Capture. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies. As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

12.10 Principal Investigator Responsibilities

Per UF IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB.
Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements, as outlined in the UFHCC Guidance: *Principal Investigator Responsibilities and Oversight.*

The PI will be primarily responsible for continuous monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

13. EMERGENCY PROCEDURES

13.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

13.2 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

14. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

14.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities. All potential serious breaches must be reported immediately to the UFHCC Project Management Office (PMO, pmo@cancer.ufl.edu, who will then report the breach to UFHCC DISC) and the IRB of record, if applicable. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

14.3 Compliance with Laws and Regulations

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the following references.

International Conference on Harmonization and GCP:
https://www.fda.gov/media/93884/download

Declaration of Helsinki:
https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

Code of Federal Regulations, Title 21:
https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=2fa30a11d9a46ebee8122c33aefd684c&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Project Management Officer (PMO) or assigned designee. All studies must be registered prior to enrollment of the first participant. The Project Management Officer or assigned designee will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study. The PMO will determine if registration and updates to the NCI CTRP are required.

14.4 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom s/he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

14.5 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language

understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions and a copy of the consent form (preferably signed) must be given to the subject for their records.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

14.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health DISC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

14.7 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will sent out to the applicable study teams, prior to implementing the amendment.

On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and UFHCC CRO PMO (pmo@cancer.ufl.edu) are notified within **5** business days with a full justification and description of the event.

14.8 Case Report Forms

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document protocol-required outcomes for safety monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.

All protocol data is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

14.9 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).
Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

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16. APPENDICES

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Appendix A: PROTOCOL VERSION HISTORY / SUMMARY OF CHANGES

Protocol Version Number	Protocol Version Date	Affected Section(s)	Summary of Revisions Made
1.0	June 15, 2021	N/A- Initial protocol	
1.1	August 6, 2021	Added Epizyme reporting information and email; Removed repeated exclusion criteria (inclusion I)	
1.2	September 22, 2021	Clarified amount of time between screening and baseline procedures needing to be repeated; Added language regarding abnormal lab values as AEs; Added clarifying language to appendix E so study team can use a comparable drug accountability log.	
1.3	January 10, 2022	Removed Phos, Mag, and Uric Acid from labs to be done at each cycle and weekly for cycle 1. Removed ECG and urinalysis from screening and eligibility criteria (exclusion D). Modified inclusion criteria D to include washout period for prior myelosuppressive chemotherapy. Clarified section 3.1 ctDNA testing to be collected whenever obtained per SOC.	
1.4	May 3, 2022	Added tibial x-rays for pediatric subjects. Added surveillance CBCs with every surveillance visit until 5 years, then yearly until 10 years. Expanded screening visit windows to accommodate subject schedules and standard of care. Changed wording of "physical" exam to "clinical" exam. Removed research blood section 9.1 as it was not being collected per protocol before but there was one sentence not removed.	
1.5	October 27, 2023	Sample Size Justification Interim Analysis for Efficacy Exclusion Criteria Section 11.4.3	Changed statistical design from Simon's two-stage Minimax to Simon's two-stage Optimum. Clarified Exclusion Criteria A and D Added Exclusion Criteria J and K. Updated safety reporting email address.
1.6	December 8, 2023	Section 6.1 Section 6.4 Section 6.2	Clarified that subjects who begin new anti-cancer therapy while in follow up will be followed for survival only. Added 72 hour window for weekly labs.
1.7	August 12, 2024	Section 6.2	Corrected typo in the Allowable Visit Window Table, which was previously IRB approved with Protocol v1.6.

		Exclusion Criteria	Added B-cell acute lymphoblastic leukemia (B-ALL) to exclusionary medical history in Exclusion Criteria C, per sponsor request.

Appendix B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale		Lansky Performance Scale
Grade	**Descriptions**	**Percent**	**Description**	**Description**
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity.
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	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or to do active work	Both greater restriction of and less time spent in play activity.
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	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
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	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated Death not imminent	In bed; needs assistance even for quiet play.
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	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly	No play; does not get out of bed.
5	Dead	0	Dead	

Appendix C: RECIST GUIDELINES (VERSION 1.1)

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or non-measurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm).
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable).
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If non-cystic lesions are presented in the same subjects, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters).

Non-target Lesions

All other lesions (or sites of disease) are identified as non-target lesions (chosen based on the representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion). Lymph nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject. If prior to enrollment it is known a subject is not able to undergo CT scans with intravenous contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast.

CT or MRI (with or without intravenous contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

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

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response (CR).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

PET Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

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. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter 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 (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression. For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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.

Not Evaluable (NE): When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Non-target Lesions

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

Non-CR/ non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. The best overall response will

be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point.) Table 17.2.1 provides a summary of the overall response status calculation at each time point for subjects who have *measurable disease* at baseline.

Table 17.2.1- Time Point Response: Subjects with Target or Measurable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 17.2.2 is to be used when subjects have *non-measurable* disease only.

Table 17.2.2- Time Point Response: Subjects with Non-Target or Non-Measurable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluable	No	NE
Unequivocal	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease. [a] non-CR/non-PD is preferred over SD for non-target disease due to SD being increasingly used as an endpoint for assessment in trials; to assign this category when no lesions can be measured is not advised.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before a subject begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Appendix D: SUBJECT TREATMENT DIARY

TABLET MEDICATION DIARY FOR TAZEMETOSTAT

Subject ID:	_____		
Protocol ID#:	UF-SC-001	Study Site:	University of Florida
Study MD:	_____	Study Coordinator:	_____
Prescribed Dose:	_____ mg, twice daily	# Tablets to be taken at each dose:	_____

Swallow tablets whole, with or without food. Do not store Tazemetostat above 86°F (30°C).

NOTE: Avoid eating grapefruit or drinking grapefruit juice during treatment with Tazemetostat. Avoid taking St. John's Wort during treatment with Tazemetostat. Do not take an additional dose if a dose is missed or vomiting occurs after Tazemetostat, but continue with the next scheduled dose.

WHEN TO CONTACT THE STUDY TEAM AND/OR YOUR PROVIDER:
Contact your health care provider *immediately* or seek emergency medical treatment if you experience any of the following symptoms (also alert the Study Team within 24 hours):

- Fever of 100.4º F (38º C) or higher, chills (possible signs of infection)
- Shortness of breath
- Have persistent pain or pressure in your chest
- Develop new confusion
- Are unable to wake up or stay awake
- Have bluish lips or face

Contact the Study Team and/or your health care provider within 24 hours of noticing any of the following:

- Nausea (interferes with ability to eat and unrelieved with prescribed medication)
- Feel feverish
- Develop a cough
- Develop mild symptoms like sore throat, muscle aches, tiredness, or diarrhea
- Vomiting (vomiting more than 4-5 times in a 24-hour period)
- Diarrhea (4-6 episodes in a 24-hour period)
- Unusual bleeding or bruising
- Black or tarry stools, or blood in your stools
- Blood in the urine
- Pain or burning with urination
- Extreme fatigue (unable to carry on self-care activities)
- Mouth sores (painful redness, swelling or ulcers)

TABLET DIARY INSTRUCTIONS: Please complete each day with the time and dose given for Tazemetostat. If a dose is not due or is missed, leave that day blank. Please bring this diary, along with any remaining medication and medication bottles to your next clinical visit.

EXAMPLE:					
	Date	Time		Number of tablets taken	Comments
Day 1	01/01/2020	8:30	AM	1	*Felt nauseated an hour after taking, did not vomit, took a Zofran*
			PM		

CYCLE # _____ **Cycle Start Date:** _____ **Dose:** _____

Cycle End Date: _____

Week 1	Date	Time		Number of tablets Prescribed AM#: PM# / Number of tablets taken	Comments (Describe any missed or extra doses, vomiting and/or bothersome side effects)
Day 1			AM		
			PM		
Day 2			AM		
			PM		
Day 3			AM		
			PM		
Day 4			AM		
			PM		
Day 5			AM		
			PM		
Day 6			AM		
			PM		
Day 7			AM		
			PM		
Day 8			AM		
			PM		
Day 9			AM		
			PM		
Day 10			AM		
			PM		
Day 11			AM		

			PM		
Day 12			AM		
			PM		
Day 13			AM		
			PM		
Day 14			AM		
			PM		
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
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Day 18			AM		
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Day 19			AM		
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Day 20			AM		
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Day 21			AM		
			PM		
Day 22			AM		
			PM		
Day 23			AM		
			PM		
Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

[STUDY STAFF VERIFYING SIGNATURE & DATE]

LIQUID MEDICATION DIARY FOR TAZEMETOSTAT

Subject ID:			
Protocol ID#:	UF-SC-001	Study Site:	University of Florida
Study MD:		Study Coordinator:	
Prescribed Dose:	mg/mL, twice daily	# mL to be taken at each dose:	

Shake the bottle for one minute before you take Tazemetostat; do not shake too much (if there are bubbles, wait for them to settle before measuring the dose). Daily shaking of all bottles is required to ensure the liquid stays properly mixed. Store your medication in the refrigerator.

NOTE: Avoid eating grapefruit or drinking grapefruit juice during treatment with Tazemetostat. Avoid taking St. John's Wort during treatment with Tazemetostat. Do not take an additional dose if a dose is missed or vomiting occurs after Tazemetostat, but continue with the next scheduled dose.

WHEN TO CONTACT THE STUDY TEAM AND/OR YOUR PROVIDER:
Contact your health care provider *immediately* or seek emergency medical treatment if you experience any of the following symptoms (also alert the Study Team within 24 hours):

- Fever of 100.4° F (38° C) or higher, chills (possible signs of infection)
- Shortness of breath
- Have persistent pain or pressure in your chest
- Develop new confusion
- Are unable to wake up or stay awake
- Have bluish lips or face

Contact the Study Team and/or your health care provider within 24 hours of noticing any of the following:

- Nausea (interferes with ability to eat and unrelieved with prescribed medication)
- Feel feverish
- Develop a cough
- Develop mild symptoms like sore throat, muscle aches, tiredness, or diarrhea
- Vomiting (vomiting more than 4-5 times in a 24-hour period)
- Diarrhea (4-6 episodes in a 24-hour period)
- Unusual bleeding or bruising
- Black or tarry stools, or blood in your stools
- Blood in the urine
- Pain or burning with urination
- Extreme fatigue (unable to carry on self-care activities)
- Mouth sores (painful redness, swelling or ulcers)

LIQUID DOSING DIARY INSTRUCTIONS: Please complete each day with the time and dose given for Tazemetostat. If a dose is not due or is missed, leave that day blank. Please bring this diary, along with any remaining medication and medication bottles to your next clinical visit.

EXAMPLE:					
	Date	Time		Dose taken (in mL)	Comments
Day 1	01/01/2020	8:30	AM	*XX mL*	*Felt nauseated an hour after taking, did not vomit, took a Zofran*
			PM		

CYCLE # _____ **Cycle Start Date:** _____ **Dose (mg/mL):** _____

Cycle End Date: _____

Week 1	Date	Time		Prescribed Dose (in mL) _____ Dose taken (in mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome side effects)
Day 1			AM		
			PM		
Day 2			AM		
			PM		
Day 3			AM		
			PM		
Day 4			AM		
			PM		
Day 5			AM		
			PM		
Day 6			AM		
			PM		
Day 7			AM		
			PM		
Day 8			AM		
			PM		
Day 9			AM		
			PM		
Day 10			AM		
			PM		
Day 11			AM		
			PM		
Day 12			AM		
			PM		
Day 13			AM		

			PM		
Day 14			AM		
			PM		
Day 15			AM		
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Day 16			AM		
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Day 17			AM		
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Day 22			AM		
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Day 23			AM		
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Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

[STUDY STAFF VERIFYING SIGNATURE & DATE]

Appendix E: ORAL MEDICATION ACCOUNTABILITY LOG

Subject Name:	MRN:	Subject ID#:
Protocol #: UF-SC-001	IRB #:	PI Name:
Product Name: TAZEMETOSTAT		

Oral Medication Accountability Log (Tablets)

Date MMDDYYYY	Dispensed or Received	# of tablets	Compliance (Express as %)	Lot #	Exp. Date	Comments	Staff initials
	Dispensed						
	Received						
	Dispensed						
	Received						
	Dispensed						
	Received						
	Dispensed						
	Received						

**The study team may use a comparable internal form in place of this form regarding drug accountability, provided all the same data is captured and recorded in EDC.

Subject Name:	MRN:	Subject ID#:
Protocol #: UF-SC-001	IRB #:	PI Name:
Product Name: TAZEMETOSTAT		

Oral Medication Accountability Log (Liquid)

Date MMDDYYYY	Dispensed or Received	# mL	Compliance (Express as %)	Lot #	Exp. Date	Comments	Staff initials
	Dispensed		[redacted]				
	Received						
	Dispensed		[redacted]				
	Received						
	Dispensed		[redacted]				
	Received						
	Dispensed		[redacted]				
	Received						

Appendix F: CYP3A4 SUSBTRATES, INDUCERS AND INHIBITORS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

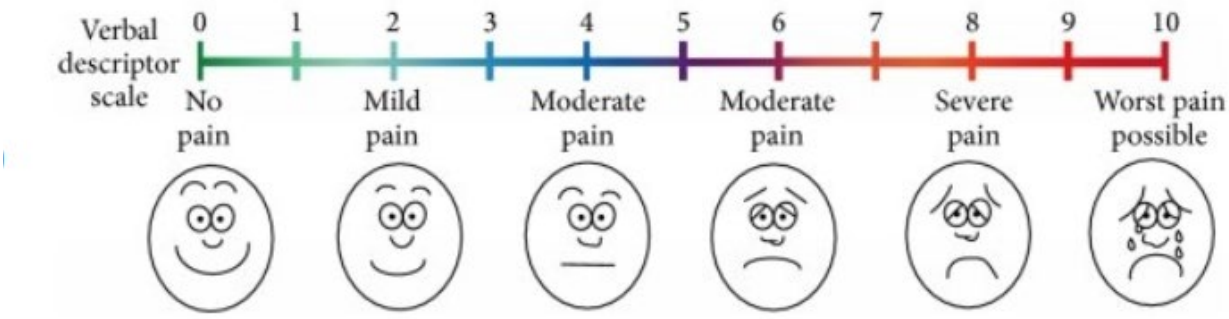
CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5] alfentanil[4,5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5]	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib				

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

1 Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
2Refer to Section 4.3 regarding use of corticosteroids.
3The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
4Narrow therapeutic range substrates.
5Sensitive substrates (drugs that demonstrate an increase in AUC of ⩾ 5-fold with strong inhibitors).

Appendix G: NUMBERED PAIN RATING SCALE 11



11-point Pain Numbered Rating Scale (NRS-11).

Appendix H: ADEQUATE RENAL FUNCTION

Adequate Renal Function Defined as: Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m^2 or serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.