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A National Cancer Institute-supported member group of the National Clinical Trials Network

April 15, 2022

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Please find attached Amendment #1 to **PEPN2112**, *A Phase 1/ 2 Study of BAY 1895344 (elimusertib, IND#[redacted], NSC#810486) in Pediatric Patients with Relapsed or Refractory Solid Tumors.*

The primary purpose of this amendment is to provide clarifications to the eligibility criteria. This amendment also provides updates to sample processing and shipping instructions.

Administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please contact us if you have any further questions.

Sincerely,

Samuel Baird, MPH, Protocol Coordinator (for)

Michael Ortiz, M.D., **PEPN2112** Study Chair, and
Brenda Weigel, M.D., PEP-CTN Chair
Elizabeth Fox, M.D., PEP-CTN Vice Chair.

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in strikethrough font.

#	Section	Comments
1.	Throughout	Updated version date.
2.	Title Page	Updated amendment number
3.	Table of Contents	Updated on repagination.
4.	Cover Page	Updated CTSU protocol template language.
5.	Study Committee	• Included study pathologist, study pharmacist, updated Study RN and included COG PEP-CTN research coordinator. • Included "**PEP-CTN**" next to the COG PEP-CTN pharmacist for consistency with all other COG PEP-CTN staff.
6.	Abstract	Deleted the word "~~double~~" and replaced with the word "**single**" in the sentence… "Ataxia telangiectasia and Rad3 related (ATR) protein kinase is a key regulator involved in repairing **single** stranded DNA breaks, particularly secondary to oncogenic replication fork stress," as ~~double~~ had been included in error.
7.	3.0	• Ensured Section 3 is updated per the most recently approved PEP-CTN template. • Updated CTSU protocol template language for patient enrollment. • Removed screening procedures language that was originally included in error.
8.	4.1.5.1; 4.1.5.2	• Revised sentence for Part A and B3 eligibility, to be more precise and less ambiguous "Any (non-CNS primary) solid tumor including lymphoma with **inactivating alterations** (~~monoallelic or biallelic) mutation~~ of any of the DNA Damage Repair (DDR) genes:" • Included note: "**Please note that a FISH showing FOXO1 breakapart is NOT sufficient for eligibility onto this cohort since it cannot distinguish between FOXO1 partners"** for both parts A and B eligibility.
9.	4.1.6.1	• Replaced the word "~~considered~~" with "**categorized**", as this is more precise language.
10.	5.2.1	• Ensured that the eligibility criteria referenced for ANC and platelets are consistent with section 4.1.11.1. Removed ANC ≥ 1000/µL and Platelets ≥ 100,000/µL and replaced with ANC ≥ 1000/µL and Platelets ≥ 100,000/µL.
11.	5.6; 5.7	• Removed the word "~~received~~" for those patients on Part B who are greater than or equal to 18, as it was erroneously placed there in the previous protocol version. • In the Cycle 1 TDM, ensured that observations **g, f and h** are also included in Day 1, Cycle 1, as this is consistent with the observation table in section 8.1.
12.	5.7	• Removed ~~weekly vital signs and medication diary~~ as a requirement for subsequent cycles, as they are only needed weekly in Cycle 1. • Clarified footnote for CBCs in subsequent cycles to be obtained within 72 hours before the start of each cycle and ensured that CBC footnote is consistent with footnote for CBCs in section 8.1. This includes that **patient who experience a dose reduction as a result of a DLT attributable to BAY 1895344 (elimusertib) will be required to have CBCs performed weekly. Additionally, CBC will only be required before the start of cycles 2+ and on day 15 of cycles 2+.** • Ensured observations are consistent with the observation table in section 8.1 and included additional observations for the end of therapy in Cycles 2 +, **where history, physical exam, height, weight and BSA and vital signs and optional correlative studies** were included and included **end of therapy knee x-ray** that is required if not already taken within the last month of therapy.
13.	8.1	• Removed weekly observations for medications diary, CBCs and vitals in Cycles 2+, to be consistent with changes made in the TDMs. • Revised schedules for tumor samples to be consistent with sections 8.3.1-8.3.3.

#	Section	Comments
		• Moved footnote 7 to be in the pre-study column for CBC and serum chemistry observations, as this is more appropriate. • Added clarifying information to the **knee x-ray observation that it is also required at the end of study treatment, if not already obtained within the last month of therapy**.
14.	8.3.1.4	Removed the word "~~archival~~" from the Tumor Tissue for WGS transmittal form, as the form found in RAVE will be revised to also remove the word "archival".
15.	8.3.2	In the description of the R-loop and PGDB5 study, removed reference to obtaining samples that are ~~post-treatment~~, as this is inconsistent with the sample schedule that only require one, pre-therapy sample to be submitted.
16.	8.3.1; 8.3.2; 8.3.3	Including clarifications to the handling and processing information for optional tumor samples.
17.	8.3.6	Updated archival tumor tissue for biobanking labelling and shipping instructions.
18.	8.3.3.4	Updated shipping information for Tumor Tissue for Immunohistochemistry pH2AX, pKAP1 and pATR.
19.	8.3.4.1	Clarified that ctDNA samples are to be collected "**after enrollment, but before treatment**" as opposed to "~~at time of enrollment~~".
20.	8.3.4.2	• Edited language to specify tube type preferences for collection of ctDNA samples. • Included sample labelling instructions, as they were not previously added.
21.	8.3.4.3	Clarified centrifuging temperature, excursion temperature and processing of ctDNA samples.
22.	8.3.4.4	Clarified shipping information for ctDNA samples, that were not previously included.
23.	8.5.4	• Clarified that PK samples should be centrifuged for **15 minutes** and not ~~10 minutes~~. • Clarified that plasma samples should be transferred "…**into two separate cryovials or small (2-4) mL polypropylene screw-capped tubes,**" as this was not previously included.
24.	8.5.6	Included clarifying language that a copy of the PK worksheets for A or B will be submitted with PK samples to the receiving lab and that they will also be uploaded into RAVE.
25.	8.7	Included that a knee x-ray is also required at the end of study treatment if it has not already been conducted within the last month of therapy. This is consistent with the observation table in section 8.1 and was erroneously left out of the previous version of the protocol.
26.	Appendix I	• Updated CTSU protocol template language for IRB approval. • Updated CTSU protocol template language for Submitting Regulatory Documents • Updated CTSU protocol template language for Data Submission/ Data Reporting • Updated CTSU protocol template language for Data Quality Portal
27.	Appendix VII	Included optional tumor tissue to the youth information sheets, because it was not previously included due to oversight.
28.	Appendix X	For PK sample 13, corrected day the sample is taken from ~~day 1~~ to **day 10** and the window for obtaining the sample from ~~15~~ to **30** minutes.
29.	Appendix XI	Included **Dose given** line for Cycle 1, Day 1, as it was erroneously left out of the previous version of the protocol.
30.	Appendix VIII;	• Revised quantity of blood for ctDNA samples being obtained from ~~5-10mL~~ to just **~10mL,** upon request by receiving lab PI. • Included archival tumor tissue samples for biobanking, as it was not previously included.
31.	Appendix IX	• Included pH2AX, pKAP1 and pATR Tumor Tissue, archival tumor tissue for biobanking, and pharmacokinetic studies into the appendix, as it was not previously included. • Revised quantity of blood being obtained.

Activated: 12/03/2021
Closed:
Version Date: 04/15/2022
Amendment: 1

PEPN2112

A Phase 1/ 2 Study of BAY 1895344 (elimusertib, IND#[redacted] NSC#810486) in Pediatric Patients with Relapsed or Refractory Solid Tumors

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

NCI Supplied Agent: BAY 1895344 (elimusertib) (NSC# 810486, IND#[redacted]

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CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at http://www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (ie, patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	**NSC#**	**Supplier**
BAY 1895344 (elimusertib)	810486	Bayer

IND Number (or IND Exempt): [redacted]
IND Sponsor: CTEP

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
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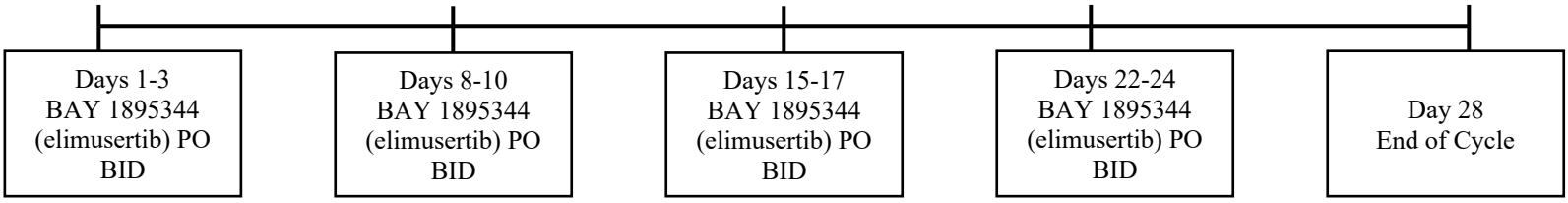
ABSTRACT
Dysregulation of the DNA damage response (DDR) is both a hallmark of cancer and a potential targetable vulnerability. Ataxia telangiectasia and Rad3 related (ATR) protein kinase is a key regulator involved in repairing single stranded DNA breaks, particularly secondary to oncogenic replication fork stress. BAY 1895344 (elimusertib) is a highly potent and selective ATR inhibitor which has been shown to be well tolerated in adult cancer patients, most commonly causing myelosuppression, particularly anemia, as well as nausea and fatigue. Tumors with complementary DNA repair pathway defects, particularly the loss of ataxia-telangiectasia mutated (ATM), exhibited durable objective responses during the phase I monotherapy study in adult cancer patients. Future clinical trials, including combination studies, are now underway in several medical oncology settings.

Many childhood solid tumors are driven by genomic alterations which may render them vulnerable to ATR inhibitors. BAY 1895344 (elimusertib) has specifically demonstrated promising preclinical activity in both Ewing Sarcoma (EWS) and PAX3-FOXO1 fusion positive Alveolar Rhabdomyosarcoma (ARMS) tumors for which there are few effective treatments in the relapsed setting. PEPN2112 is a phase 1/2 trial of BAY 1895344 (elimusertib) in children and young adults with relapsed or refractory non-CNS solid tumors and lymphomas which exhibit an EWS-fusion, PAX3-FOXO1 fusion, as well as loss of function mutations in ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, or XRCC2. The study will require confirmation of qualifying genomic alterations but will allow for such genomic testing to have been performed in any CLIA certified setting. The phase 1 dose-determining portion will evaluate children less than 18 years of age with qualifying genomic findings with either evaluable or measurable tumors using a Rolling 6 design with up to 2 dose levels, starting at the adult maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) and then de-escalating if not well tolerated in children. The phase 2 portion will evaluate children and young adults with measurable tumors at the pediatric RP2D determined in the phase 1 portion of the study and patients at least 18 years of age will receive the recommended phase 2 dose determined in previous studies in adults. A Simon 2 stage design in separate cohorts of EWS-fusion positive tumors, PAX3-FOXO1 fusion positive ARMS, and non-CNS solid tumors and lymphomas with a qualifying DDR panel defects will be utilized. Eligible patients at least 18 years old may enroll on the Phase 2 portion of the trial while the Phase 1 component of the study is being conducted in patients younger than 18 years old. The aims of the trial will be to establish the RP2D and MTD of BAY 1895344 (elimusertib) in children less than 18 years old, to investigate the toxicities, pharmacokinetics, and pharmacodynamics of BAY 1895344 (elimusertib) in children with these tumors, to explore the anti-tumor efficacy in children and young adults with EWS-fusion positive tumors, PAX3-FOXO1 fusion positive ARMS and tumors with qualifying DDR panel defects, and to evaluate whether response is influenced by ATM, PGBD5, R-loops, alternative lengthening of telomeres (ALT), as well as other tumor mutations as evaluated using whole genome sequencing.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

Phase 1 Dose Escalation Primary Aim

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BAY 1895344 (elimusertib) administered as an oral tablet, twice per day for 3 days on and 4 days off to patients < 18 years of age with recurrent or refractory Ewing Sarcoma, PAX3-FOXO1 Alveolar Rhabdomyosarcoma, and non-CNS solid tumors or lymphoma with specific DDR pathway alterations.

Phase 2 Primary Aim

1.1.2 To define the antitumor activity of BAY 1895344 (elimusertib) in pediatric patients and young adults with recurrent or refractory Ewing Sarcoma.

1.1.3 To define the antitumor activity of BAY 1895344 (elimusertib) in pediatric patients and young adults with recurrent or refractory PAX3-FOXO1 fusion positive Alveolar Rhabdomyosarcoma.

Additional Primary Aims (Phase 1)

1.1.4 To define and describe the toxicities of BAY 1895344 (elimusertib) administered on this schedule.

1.2 Secondary Aims

1.2.1 To characterize the pharmacokinetics of BAY 1895344 (elimusertib) in children and adolescents with recurrent or refractory cancer.

1.2.2 To assess the biologic activity of BAY 1895344 (elimusertib) by immunohistochemical assessments of pATR, pH2AX, and pKAP1 in paired tissue samples before and after treatment with BAY 1895344 (elimusertib).

1.2.3 To assess whether the activity of BAY 1895344 (elimusertib) is influenced by ALT, as well as tumor tissue expression of ATM, PGBD5, and/or R-loops.

1.2.4 To assess whether the activity of BAY 1895344 (elimusertib) is associated with tumor mutational processes, as measured by whole genome tumor tissue sequencing.

1.2.5 To preliminary determine the anti-tumor activity of BAY 1895344 (elimusertib) in children < 18 years of age within the confines of a phase 1 study (Part A).

Phase 2 Secondary Aims

1.2.6 To assess the antitumor activity of BAY 1895344 (elimusertib) in pediatric patients with non-CNS solid tumors or lymphomas with specific deleterious alterations in DDR pathway genes.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development in Pediatric Population

DNA damage occurs frequently in all cells because of exposure to endogenous or environmental toxins. The DNA damage response (DDR) is a coordinated network of proteins which recognizes DNA damage, signals to cell cycle checkpoints to stall cell cycle progression, initiates DNA repair, and if unable to repair DNA damage, directs the cell to undergo apoptosis. Dysregulation of genes involved in DDR leading to genomic instability is a hallmark of cancer, allowing for more rapid acquisition of mutations critical to cancer evolution.[1] When cancers develop a defect in one DDR pathway, they may compensate by overexpressing alternative pathways or developing dependency on another.[2] This overexpression or addiction can be leveraged as a synthetic lethality, as described in BRCA mutant cancers which are sensitive to PARP inhibition due to inability of cells to undergo homologous recombination (HR).

When double stranded DNA undergoes breaks or replication forks are stalled, single stranded DNA is exposed and to prevent further degradation, they are coated by the replication protein A (RPA). [2-5] RPA coated single stranded DNA is recognized by the ataxia telangiectasia and Rad3 related (ATR) protein kinase and a related complex of proteins leading to CHEK1 phosphorylation, replication fork stabilization, deceleration of cell cycle progression, and ultimately DNA repair.[2-5] Since ATR is a ubiquitous regulator of DNA damage repair, we hypothesize that DDR pathway aberrations recurrent in pediatric cancers, particularly those leading to increased replication fork stress, will create a dependency on the ATR-CHEK1 pathway which can be rationally inhibited.

BAY 1895344 (elimusertib) is a highly potent and selective ATR inhibitor which is available as an oral tablet and demonstrates potent preclinical activity in a variety of malignancies with DDR pathway aberrations. A Phase 1 study of BAY 1895344 (elimusertib) has been completed in adults with solid tumors demonstrating promising activity in selected patients with pathogenic DDR mutations, particularly in those with ATM loss. We propose a pediatric Phase 1/2 study with 1 planned and 1 potential lower dose level in the Phase 1 portion followed by signal finding cohorts to determine the objective response rate to BAY 1895344 (elimusertib) in pediatric patients with tumors for which there is pre-clinical rationale. Given the significant evidence to support ATR inhibition in Ewing Sarcoma and PAX3-FOXO1 fusion positive Alveolar Rhabdomyosarcoma, separate cohorts for patients with relapsed or refractory disease in either of these diagnoses are planned as well as a histology-agnostic cohort for patients with tumors with pre-defined deleterious genomic alterations in related DDR pathways. We will evaluate the pharmacokinetics of BAY 1895344 (elimusertib) in children and young adults and confirm pharmacodynamic targeting by evaluating pKAP1, pATR, and pH2AX. Finally, in addition to whole genomic sequencing, this study will explore alternative lengthening of telomeres (ALT) as measured by C-circle analysis as well as immunohistochemical expression of ATM, PGBD5, and R-loops as potential predictive biomarkers of response.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

2.2.1.1 **DDR pathway defects predicted to sensitize to BAY 1895344 (elimusertib):**

The DDR pathway alterations included in this study which are anticipated to sensitize pediatric tumors to inhibition with BAY 1895344 (elimusertib) include loss of function of ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, and XRCC2. This panel was chosen because it had been previously clinically validated through its use on the adult phase 1 study of BAY 1895344 (elimusertib). Figure 1A demonstrates the prevalence of these genomic alterations in a series of pediatric pan-cancer studies using cBioPortal (Figure 1A) as well as the NCI-COG Pediatric MATCH (Figure 1B).[6-10] Using cBioPortal, putative driver mutations were detected in 3.7% of all pediatric tumors in this pan-

pediatric cohort and another 12.6% of tumors also exhibited mutations of unknown significance in one or more genes on this panel. On the NCI-COG Pediatric MATCH, 3.8% of screened relapsed/refractory pediatric solid tumor patients tested exhibited inactivating mutations in one of the panel of genes tested. Excluding Ewing Sarcoma, ARMS, and CNS tumors this would account for 2.2% of screened patients, although notably the MATCH did not include all the genes on the proposed panel. Of note, in addition to the genomic alterations included in this DDR panel, several additional genomic alterations have potential to influence response to BAY 1895344 (elimusertib) therapy, such as loss of function in TP53, ARID1A, XRCC1, and ERCC4 as well as increased activity of MYC, CHEK1, APOBEC, MLL, CCNE1, and CDC24A.[11] In order to evaluate the contribution of these known vulnerabilities and discover novel dependencies, whole genome sequencing will be performed on all available tumors with frozen samples available for testing.

Patients who have biallelic inactivating mutations in sensitizing DDR genes are most likely to respond to ATR inhibition. However, an important and currently unknown question is whether clonal monoallelic inactivating mutations would sensitize to BAY 1895344 (elimusertib). The conditional haploinsufficiency model proposes that germline carriers of DDR pathway defects are more prone to malignancy, because oncogenic activity in pre-malignant lesions leads to increased replication fork stress which would normally be resolved in normal tissues but exceed a stress threshold in haploinsufficient cells.[12] Analogously, in tumors which have resulted from such haploinsufficiency and thereby exhibit monoallelic inactivation of a DDR pathway gene, they too will have significantly increased replication fork stress such as is caused by oncogenic activation, ALT, PGBD5, R-loops, or other factors. As replication fork stress is chiefly repaired by ATR, we hypothesize that such tumors may similarly be sensitive to BAY 1895344 (elimusertib).[4]

This hypothesis that monoallelic inactivating mutations may respond to BAY 1895344 (elimusertib) is predicated upon clinical data with related therapies. A pan-cancer study evaluating the effectiveness of DNA damaging radiation therapy amongst 357 patients harboring ATM alterations in their tumors revealed that, as compared with ATM variants of uncertain significance, biallelic loss of function mutations were most susceptible to radiation with a hazard ratio of 0.19, however the hazard ratio was still 0.57 for monoallelic inactivating mutations suggesting a clinical benefit.[13] This is further corroborated by clinical data in adult oncology with DDR pathway inhibitors. For example, in the landmark TOPARP study which administered the PARP inhibitor Olaparib to adults with metastatic colorectal cancer, 16/49 (33%) evaluable patients exhibited an objective response, and 3/16 (19%) of these responders had monoallelic inactivation of DDR genes.[14] Berzosertib (M6620) is the first-in-class ATR inhibitor, and during the adult phase 1 study a durable complete response was evident in a patient with metastatic colorectal cancer with monoallelic deleterious mutations in CHK1, FANCM, RAD50, POLD1, and FANCP as well as compound heterozygous truncating mutations in ARID1A, although notably this tumor did exhibit complete loss of ATM by IHC.[15] As shown in Figure 11, of the 4 adult patients with a partial response to BAY 1895344 (elimusertib) during the dose escalation, a durable partial response was seen in an appendiceal tumor that exhibited a frameshift mutation in ATM (mutant allele frequency 45%) and 60% ATM protein expression by immunohistochemistry.[16,17]

Figure 1A. Prevalence of select DDR pathway aberrations predicted to sensitize to BAY 1895344 (elimusertib) in pediatric tumors

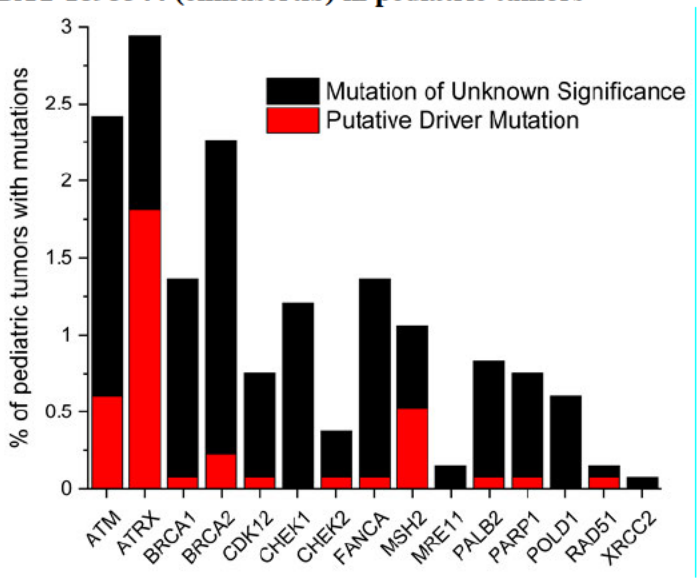
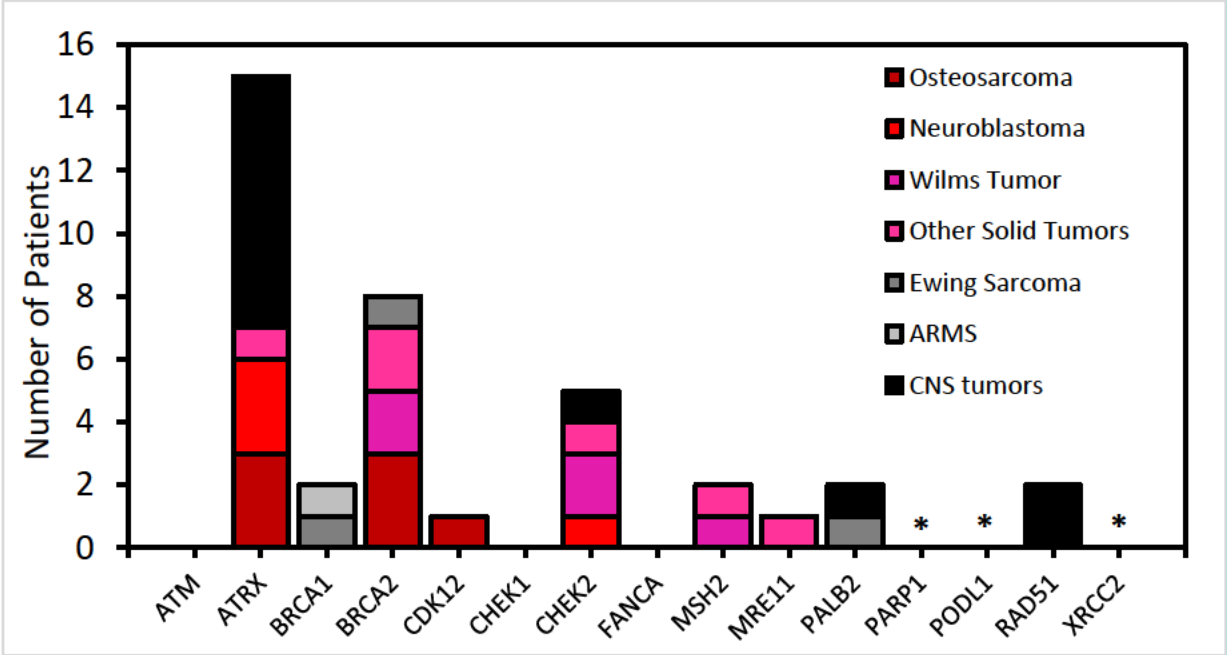


Figure 1B. Inactivating mutations in select DDR pathway genes detected on the first 1000 patients enrolled onto the NCI-COG Pediatric MATCH
(Source: Parsons W, Janeway K, et al. J Clin Oncol (2021) [abstract])
** Denotes that these genes are not included on the MATCH panel*

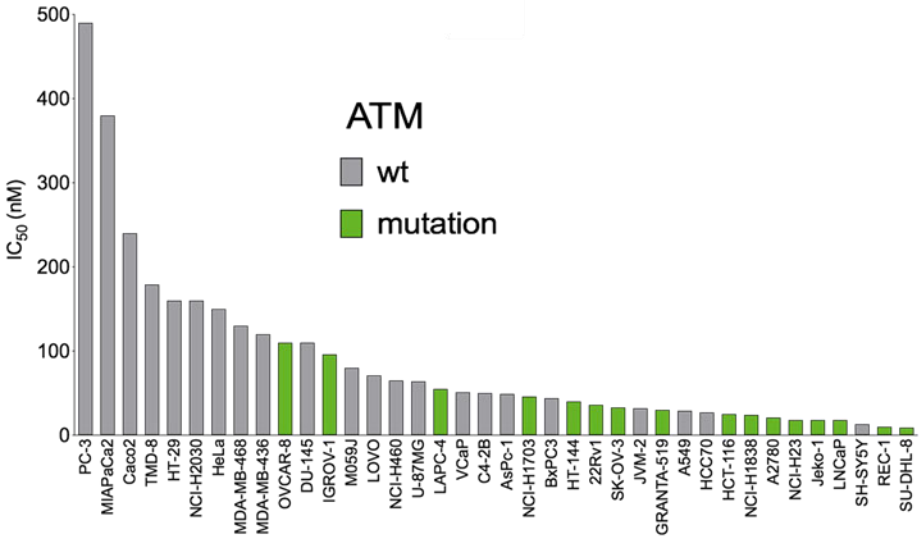


2.2.1.2 **Candidate Predictive Biomarkers of Response to BAY 1895344 (elimusertib)**

a. ATM:
The most well-established interdependency for ATR is with ataxia-telangiectasia mutated (ATM), a key DDR regulator involved in repair of double stranded DNA breaks which primarily interfaces with CHEK2, and secondarily TP53, to mediate the DNA repair program.[3,18] End resection converts double stranded breaks into

single stranded DNA structures that activate ATR, whereas nucleases cleave single stranded DNA to yield double stranded breaks that activate ATM. Cancers with a deficiency in ATM are thus expected to be dependent upon ATR, which can be leveraged to create synthetic lethality using an ATR inhibitor. This paradigm has been validated preclinically for BAY 1895344 (elimusertib) in several adult malignancies including ATM-deficient chronic lymphocytic leukemia, mantle cell lymphoma, non-small cell lung cancer, gastric cancer, and pancreatic cancer. *In vitro* studies of BAY 1895344 (elimusertib) treated for 72-96 hours (Figure 2) demonstrate particular sensitivity of ATM deficient, as compared with ATM wild type, cancer cell lines to BAY 1895344 (elimusertib).[19] ATM loss of expression via IHC may be evident even in tumors without biallelic ATM mutations so we plan to evaluate ATM via IHC as a predictive biomarker of response in this trial.

Figure 2. *In vitro* sensitivity of cancer cell lines to BAY 1895344 (elimusertib) stratified by ATM status

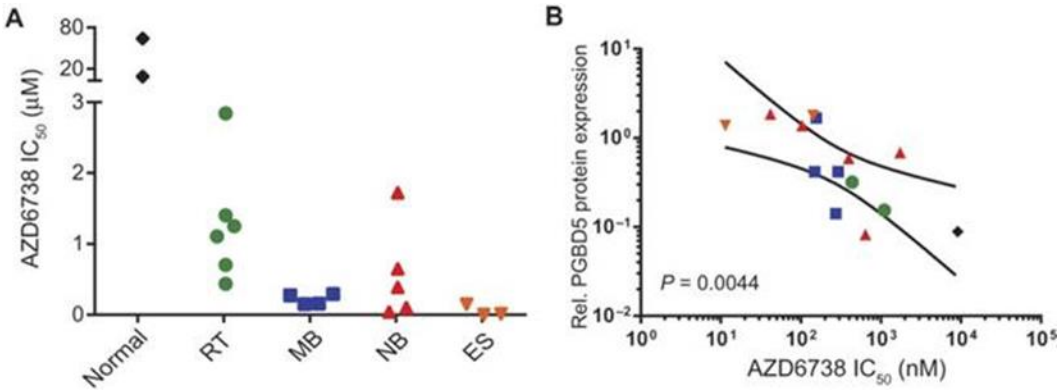


b. PGBD5:

Recent studies from the laboratory of Dr. Alex Kentsis (Memorial Sloan Kettering Cancer Center, New York, NY) suggest that a previously uncharacterized human gene, *PGBD5*, with homology to the PiggyBac DNA transposase from the looper moth capable of catalyzing bona fide 'cut-and-paste' DNA transposition in human cells may also confer susceptibility to ATR inhibition. PGBD5 is highly expressed in most childhood solid tumors and ectopic expression of PGBD5 in primary human cells is sufficient to promote penetrant cell transformation *in vitro* and in immunodeficient mice *in vivo*. This activity requires specific catalytic residues in the PGBD5 transposase domain, as well as efficient non-homologous end-joining (NHEJ) DNA repair, and induces distinct structural rearrangements characterized by deletions and inversions involving PGBD5-specific signal sequence (PSS) motifs.[20] Clinical grade DDR inhibitors were screened against PGBD5-expressing tumor cells and isogenic controls lacking PGBD5 and demonstrated that the ATR inhibitor AZD6738 had exceptional selective activity against the majority of PGBD5-expressing childhood solid tumor cells *in vitro*.[21] For example, Figure 3A reveals the exquisite sensitivity of rhabdoid tumor (RT), medulloblastoma (MB), neuroblastoma (NB), and Ewing sarcoma (ES) cells to ATR inhibition and in Figure 3B, it is evident that the relative PGBD5 expression levels correlate with sensitivity. These findings demonstrate, in multiple preclinical models, that

PGBD5 is both necessary and sufficient to confer the dependency on ATR kinase signaling and susceptibility to ATR kinase inhibition which we will further investigate on this trial.

Figure 3. PGBD5 expression is a candidate biomarker of susceptibility to ATR inhibition



c. <u>R-Loops:</u>

During transcription, the nascent RNA generated by RNA polymerases can hybridize with the DNA template, giving rise to a three-stranded structure called an R-loop.[22] Although physiologic in some contexts, R-loops can accumulate and cause genomic instability, chiefly via collisions with DNA replication forks causing double stranded breaks. Recently it was shown that in response to aberrant R-loop accumulation, ATR is recruited to facilitate DNA repair or cell death.[22] Moreover, R-loop associated chromosomal instability is an emerging hallmark of certain pediatric tumors, notably including Ewing sarcoma as well as Embryonal Tumor with Multilayered Rosettes (ETMR).[23, 24] Current studies are ongoing to investigate the degree to which R-loops are prognostically relevant. In the context of this study, the presence of R-loops and any relationship to response to BAY 1895344 (elimusertib) will be investigated.

d. <u>Alternative Lengthening of Telomeres (ALT):</u>

Telomeres are repetitive sequences at the ends of chromosomes that are progressively lost during successive rounds of cell division and eventually lead to p53 and RB dependent permanent growth arrest which is termed senescence.[25, 26] Inactivation of p53 and Rb allows for continued cell division and further shortening until telomeres eventually erode to a length at which they are unable to protect chromosome ends resulting in crisis of end to end chromosome fusions and apoptotic cell death.[25, 26] However, in cancers, rare cells may emerge that are able to maintain their telomere length, thereby allowing the cancer cell to continue to divide.[25, 26] These cells can do so by either increasing the activity of telomerase, which happens in most situations, or rarely alternative repair DNA mechanisms, termed ALT, are invoked to lengthen telomeres, and this is well described in pediatric tumors with ATRX mutations.[27] During ALT, ATR is recruited to RPA coated single stranded DNA to enact repair processes. In fact, ATRIP the ATR associated DNA repair protein, has been found associated with telomeres in cancer cells that utilize ALT, but not in those with increased telomerase activity.[25] Hence, we anticipate that tumors which utilize ALT to maintain telomere length will be more sensitive to BAY 1895344 (elimusertib). This study will utilize DNA C-circles, a specific and quantifiable marker of ALT, to evaluate the degree of ALT

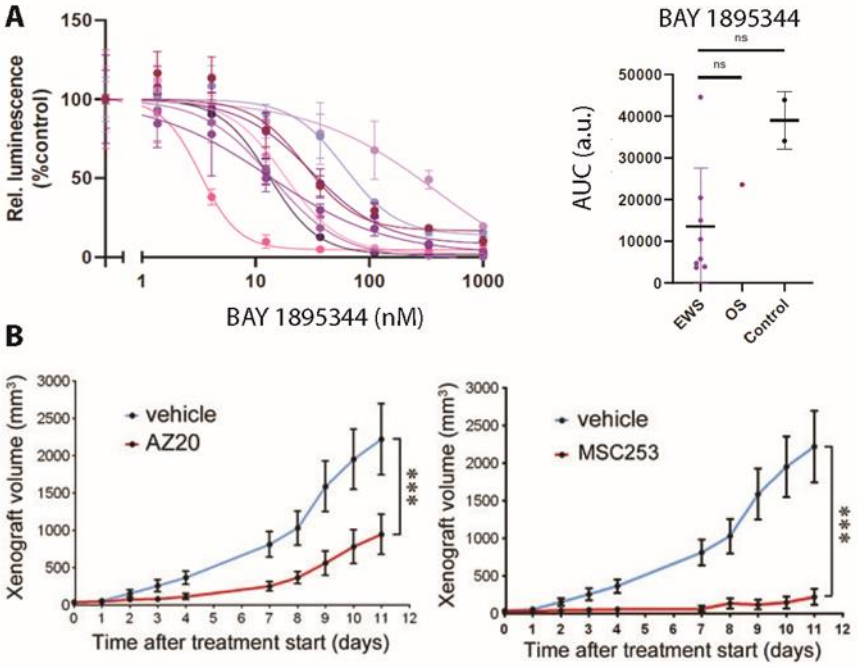
in both tumors and peripheral blood.[28] Concurrent with this, telomerase activity will be measured by TERT RT-PCR.

2.2.1.3 Currently Planned Dose Expansion Cohorts, Based on Preclinical Studies

a. Ewing Sarcoma:

Ewing Sarcomas demonstrate elevated levels of endogenous replication stress and have a unique dependency on the ATR-CHK1 pathway.[24,29] As a result, there are several studies which have shown that this tumor histology is sensitive to ATR inhibition. [20,21,24,29,30] Although likely multifactorial, posited mechanisms of this dependency include elevated expression of PGBD5 [20,21,31], increased presence of the DNA/RNA hybrid R-loops [24,32], and decreased expression of compensatory DNA pathway genes such as BRCA1 and ATM [29,32,33] A query of the "Genomics of Drug Sensitivity in Cancer" (https://www.cancerrxgene.org/) revealed that there was a statistically significant decreased IC_{50} (suggesting increased sensitivity) for both EWS-FLI1 mutant and STAG2 mutant cells compared with cancer cell lines wild type for these molecular aberrations, tested with two different ATR inhibitors.[34] Notably, both the EWS-FLI1 and EWS-ERG translocations have been shown to sensitize cells to ATR inhibitors so dependency is not unique to the fusion partner nor junction.[11,30] Although much of the initial data was developed with other ATR inhibitors, exquisite sensitivity to several Ewing Sarcoma cell lines has been shown with the BAY 1895344 (elimusertib), as shown in Figure 4.

Figure 4. Ewing Sarcomas are sensitive to BAY 1895344 (elimusertib)

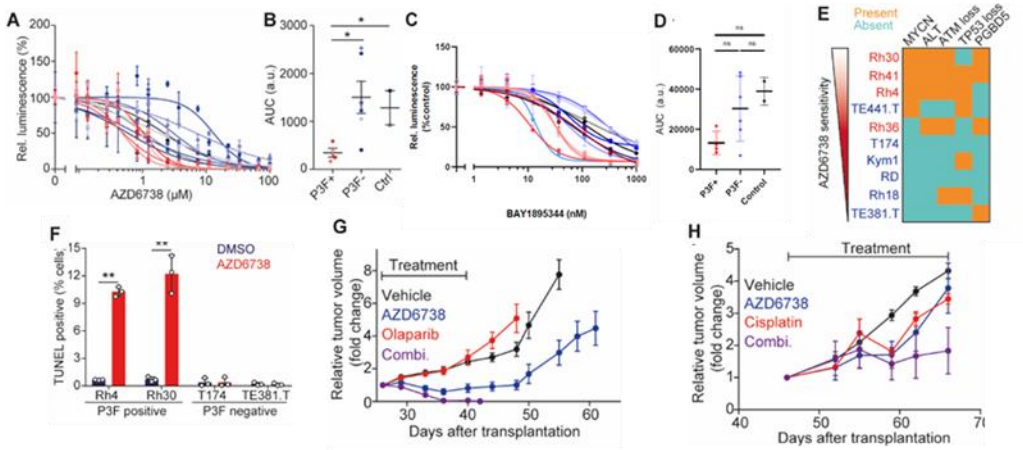


Panel A: All cell lines are EWS except 1 OS (Saos-2) and 2 control cell lines (BJ fibroblasts and RPE epithelial cells) the latter two only shown on right panel; AUC is denoted in arbitrary units (a.u.). (Source: Anton Henssen, MD; Charite, Berlin, Germany) Panel B is derived from Figure 4 of Nieto-Soler, et al. Oncotarget, 2016 and compares the single agent activity of two different ATR inhibitors, AZ20 and MSC253.

b. PAX3-FOXO1 Fusion Positive Alveolar Rhabdomyosarcoma (ARMS):

The laboratory of Dr. Anton Henssen (Charité, Berlin, Germany) has been investigating the role of ATR inhibitors, both AZD6738 and BAY 1895344 (elimusertib), in rhabdomyosarcomas (Figure 5A-D). They determined that the presence of the PAX3-FOXO1 fusion is predictive of sensitivity to both ATR inhibitors (Figure 5) and often, but not always, are associated with increased MYCN, ALT, loss of ATM, loss of TP53, as well as PGBD5 expression (Figure 5E). Ultimately, these replication stress-inducing molecular factors confer a synthetic lethal dependency on ATR-mediated DNA damage repair and signaling in alveolar, PAX3-FOXO1-expressing rhabdomyosarcomas. Consistent with previous reports of oncogenic fusion gene-induced replication stress in Ewing sarcoma, expression of PAX3-FOXO1 itself induced replication stress, as measured by Tunel positive cells in ATR treated rhabdomyosarcoma cells with or without the fusion (Figure 5F). These effects, observed specifically in PAX3-FOXO1 expressing rhabdomyosarcoma cells, resulted from decreased phosphorylation of homologous recombination pathway members, and were accompanied by induction of genomic instability, increased G2/M arrest and apoptosis (not shown). In turn, single agent treatment with the ATR signaling inhibitor AZD6738 exhibited potent antitumor activity against high-risk patient-derived rhabdomyosarcoma models expressing PAX3-FOXO1 (Figure 5G/H). Moreover, decreased homologous recombination activity through pharmacological ATR inhibition sensitized cells to PARP inhibition and platinum chemotherapy (Figure 5G/H). Further studies are still needed to establish whether PAX7-FOXO1 or other variant fusion positive rhabdomyosarcomas will exhibit analogous sensitivity to ATR inhibition.

Figure 5. Alveolar Rhabdomyosarcomas are sensitive to ATR pathway inhibition[35]



(Source: Anton Henssen, MD; Charite, Berlin, Germany)

c. DNA Damage Repair Pathway Aberrations:

As described previously, loss of function mutations in complementary DNA pathways are predicted to increase the dependency on ATR repair within tumor cells only, leading to synthetic lethality for patients with deleterious alterations in ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11A, PALB2, PARP1, POLD1, RAD51, and XRCC2. Hence, pediatric patients with either biallelic or monoallelic loss of function in these specific DDR pathway genes within their tumors will be eligible for this expansion cohort.

2.2.2 Preclinical *In Vitro* Studies:

In vitro, BAY 1895344 (elimusertib) potently inhibits proliferation of a broad spectrum of human tumor cell lines (median IC_{50} 7.8×10^{-8} mol/L; mean IC_{50} 1.5×10^{-7} mol/L).[19] As shown previously in Figure 2, 72-96 hour treatment and viability assessment using crystal violet staining or Cell Titer Glo in a panel of 38 pan-cancer cell lines demonstrates increased sensitivity of ATM deficient cancer cell lines to BAY 1895344 (elimusertib).[19] Furthermore, as shown in Table 1, the combination of BAY 1895344 (elimusertib) with a variety of DNA-damaging agents or DDR pathway inhibitors results in exquisite synergy in several cell lines, particularly with the platinum chemotherapy agent cisplatin and the irinotecan metabolite SN-38.[19] Note that a combination index (CI) ≤ 0.8 is synergism; 0.8 < CI < 1.2 is additivity; CI ≥ 1.2 is antagonism.

Table 1: Combination index of BAY 1895344 (elimusertib) at the EC_{50} plus the following drugs at their EC_{50}

		HT-29	LOVO	PC-3	HT-144
Cisplatin	DNA platination	0.14	0.17	0.15	0.27
Bleomycin	dsDNA breaks	0.59	0.80 – 1.0	0.21	0.32
SN-38	Topo 1 inhibitor	0.43	0.55	0.27	0.21
AZD0156	ATM inhibitor	0.45	0.52	0.48	1.0 – 1.2
M9831	DNA-PK inhibitor	< 0.61	0.85 – 1.16	< 0.69	< 0.72
AZD7762	CHEK1/2 inhibitor	0.49	0.19		
PF00477736	CHEK1 inhibitor	0.69	< 0.43		
MK8776	CHEK1 inhibitor	0.72	0.63		
AZD1775	WEE1 inhibitor	0.64	< 0.29		

2.2.3 Preclinical *In Vivo* Studies:

BAY 1895344 (elimusertib) was compared with other DNA damage repair inhibitors, including Berzosertib (M6620; in red) and Ceralasertib (AZD6738; in blue) and found to be superior in both the GRANTA-519 (Figure 6A) and Rec-1 (Figure 6B) human mantle cell lymphoma models in vivo.[36] BAY 1895344 (elimusertib) was shown to synergize with carboplatin in the IGROV-1 human ovarian adenocarcinoma model (Figure 7A).[36] BAY 1895344 (elimusertib) was shown to synergize with the PARP inhibitor Olaparib in the 22Rv1 human prostate carcinoma model (Figure 7B).).[36] In addition to synergizing with DNA damaging chemotherapy, BAY 1895344 (elimusertib) synergized with DNA damaging radiation both in an in vitro colony forming assay as well as in a LoVo human colorectal cancer model in vivo, shown below in Figure 8.[36]

Figure 6: BAY 1895344 (elimusertib) compared with other ATR inhibitors[19]

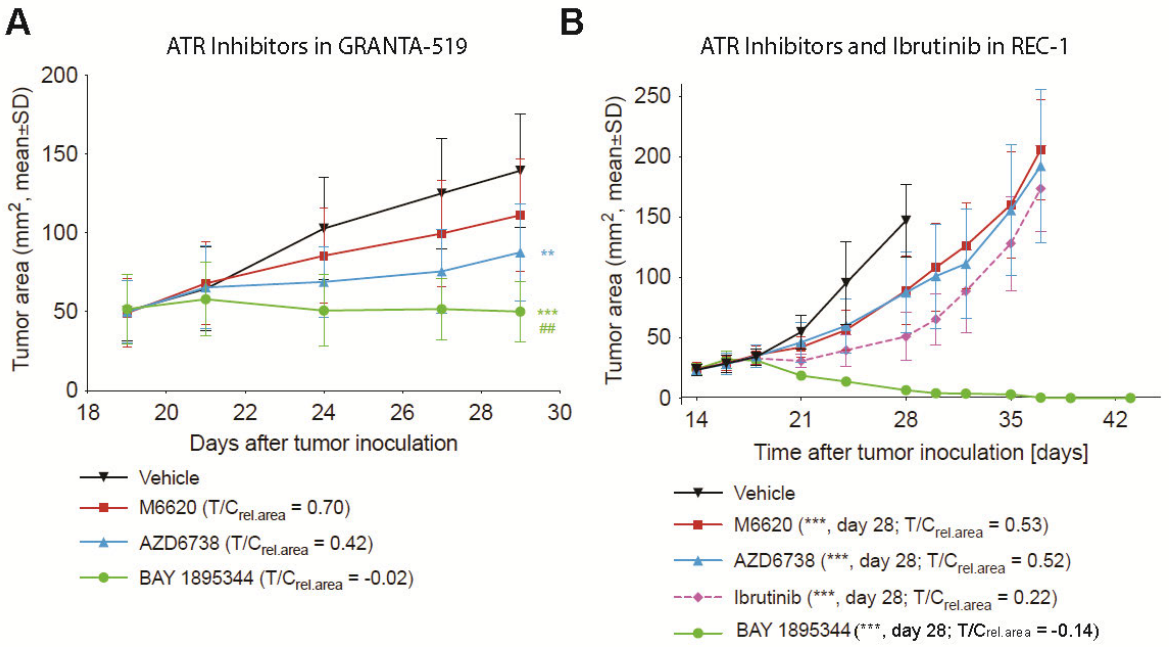


Figure 7: Combination of BAY 1895344 (elimusertib) in vivo with DNA damaging agents and DDR pathway inhibitors[19]

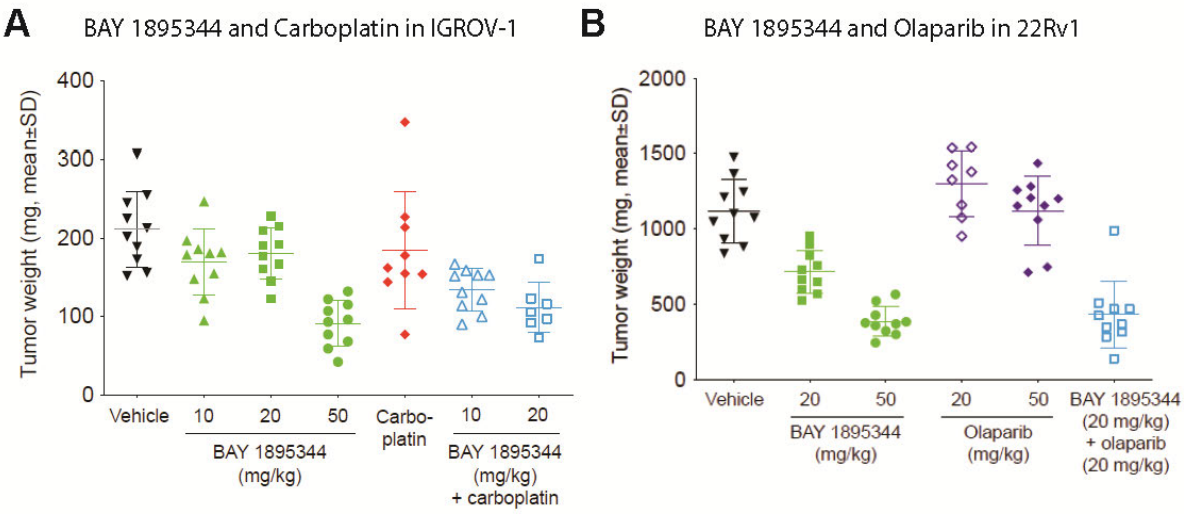
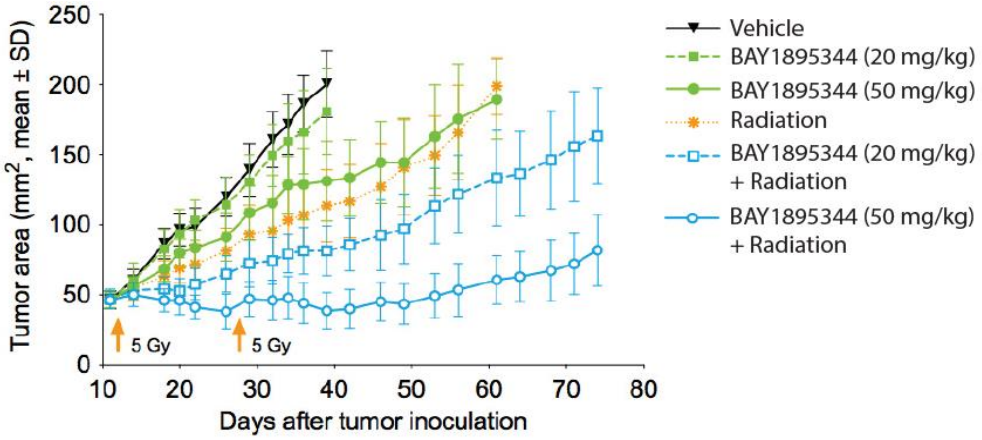


Figure 8. In vivo synergy of BAY 1895344 (elimusertib) and radiation at non-curative doses[19]



2.2.2 Dosing Strategy:

Evaluation of BAY 1895344 (elimusertib) efficacy and tolerability in preclinical xenograft models in mice indicated optimal dosing using 40 mg/kg twice daily (BID) using a 3 day on and 4 day off schedule, as shown below in Table 2. As described below, to date the 3 day on and 4 day off schedule has been tested clinically, although an alternative 3 day on and 11 day off schedule is still in the early phases of clinical investigation.

Table 2. Preclinical Efficacy of Optimized Dosing Schedule of BAY 1895344 (elimusertib)

Tumor Name (Type)[mutations]	Treatment	Dose	Schedule	Tumor/Control Ratio	Day of Assessment
HCC1806 (TNBC)[1]	Vehicle	---	---	1.0	16
	BAY 1895344 (elimusertib)	40 mg/kg BID	3 on / 4 off PO	0.32	
MKN-45 (Gastric Cancer)[2]	Vehicle	---	---	1.0	18
	BAY 1895344 (elimusertib)	40 mg/kg BID	3 on / 4 off PO	0.57	
Hs746T (Gastric Cancer)[3]	Vehicle	---	---	1.0	21
	BAY 1895344 (elimusertib)	40 mg/kg BID	3 on / 4 off PO	0.03	
Rec1 (MCL)[4]	Vehicle	---	---	1.0	27
	BAY 1895344 (elimusertib)	40 mg/kg BID	3 on / 4 off PO	0.00	
22RV1 (Prostate Cancer)[5]	Vehicle	---	---	1.0	29
	BAY 1895344 (elimusertib)	40 mg/kg BID	3 on / 4 off PO	0.04	

1 - CCNE1$^{amp\ [CN\ 8]}$, TP53^{T256fs}
2 - FANCA$^{A636V;T508A}$, POLD1^{R1086W}, TP53^{R110C} , BRCA1^{S1598P}, EGFR^{A1048V}, LIG4^{I840V}, PPP6R3^{T845A}, RPA4^{R254W}
3 - APC$^{D1688H;S2625I}$, ARID1A^{G444S}, PPP4R4^{Q241H}, TP53^{K319*} , BRCA1^{S186F}, FANCG^{K317N}, HFM1^{A1003E}
4 - ATM^{S707P}, p53$^{Q317*,\ G245D}$
5 - BRAF^{L597R}, PIK3CA^{Q546R} , BRCA2^{V1810I}, TP53^{Q331R}, TP53BP1^{P1059X}, ARID1A$^{1847\text{-}1848X;Y1324X;P1325X}$, ATM^{K1101E}

2.2.3 Pharmacodynamic Biomarkers of Response to BAY 1895344 (elimusertib):

ATM kinase phosphorylates histone H2AX (pH2AX) at the site of DNA damage where it acts as a scaffolding for the assembly of repair machinery.[37] KAP1, another phosphorylated substrate of ATM, is a co-repressor for Kruppel-associated box zinc finger proteins that bind to and repress DNA through their zinc fingers.[37] Replication stress and more broadly DNA damage, are commonly measured by the presence of pH2AX and pKAP1.[11,37] In this study, pH2AX and pKAP1 as well as the activated pATR will be evaluated in matched pre- and post- treated tumor samples, where available, in order to evaluate the impact of BAY 1895344 (elimusertib) on DNA damage repair.

2.3 Adult Studies

2.3.1 Clinical Trials of ATR inhibitors:

In addition to BAY 1895344 (elimusertib), as of September 2020, there are 5 additional ATR inhibitors undergoing clinical development. The first-in-class ATR inhibitor was Berzosertib (M6620, VX-970) and the first oral ATR inhibitor was Ceralasertib (AZD6738), both of which have been studied in numerous clinical trials in the adult oncology setting.[2] M4344 (VX-803) (NCT04149145; NCT02278250), M1774 (NCT04170153) and RP-3500 (NCT04497116) are the other ATR inhibitors with clinical trials although have been less well studied than BAY 1895344 (elimusertib).

BAY 1895344 (elimusertib) has a strong rationale for its use in pediatric tumors, as previously described, and promising preclinical evidence to suggest it may be more effective than other ATR inhibitors (Figure 6). The "First-in-human Study of ATR Inhibitor BAY 1895344 (elimusertib) in Patients with Advanced Solid Tumors and Lymphomas" (NCT03188965) was recently published and has provided much of the essential clinical data to support the proposed design of this pediatric trial.[16] As of January 2021, there are now 7 additional ongoing human clinical studies involving this drug, including combination studies with the anti-PD1 checkpoint inhibitor Pembrolizumab (NCT04095273), Pembrolizumab and radiation (NCT04576091), the PARP inhibitor Niraparib (NCT04267939), the topoisomerase 1 inhibitors topotecan and liposomal irinotecan (NCT04514497), as well as DNA damaging chemotherapeutics cisplatin and gemcitabine (NCT04491942), gemcitabine alone (NCT04616534) and the FOLFIRI (irinotecan, fluorouracil, and leucovorin) chemotherapy regimen (NCT04535401).

2.3.2 Dose Escalation and MTD Determination:

The first-in-human study of BAY 1895344 (elimusertib) began with a dose escalation which included 22 patients. Six cohorts of patients were treated using a 3 day on and 4 day off schedule weekly whereas 1 cohort of patients was treated with a 3 day on and 4 day off schedule for 2 weeks followed by 1 week off drug. The adult maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 40 mg BID 3 days on and 4 days off weekly on the basis of dose limiting toxicities observed at the higher dose levels which were predominately myelosuppression, as shown in Table 3 below.

MTD Determination of BAY 1895344 (elimusertib)[16]

Cohort	Dose level (mg)	All patients	Evaluable patients	DLTs	DLT description
1	5	1	1	0	---
2	10	2	1	0	---
3	20	2	1	0	---
4 (MTD)	40	2	2	0	---
5	80	3	2	2	G4 neutropenia; G4 leukopenia & G4 thrombocytopenia
6	60	8	7	2	G4 neutropenia & G3 leukopenia; G2 fatigue
7	60*	4	3	2	G3 thrombocytopenia; G3 neutropenia

** Patients in this cohort were given a 3 day on and 4 day off schedule for 2 weeks followed by 1 week off drug*

2.3.3 Pharmacokinetics:

In humans, BAY 1895344 (elimusertib) is 96-97.5% protein bound, primarily binding to albumin. Relative bioavailability comparison of the oral suspension and 40 mg tablets in adults has been completed. At the 40 mg dose level in adults the 40 mg tablet geomean (%CV) T_{max} was 1 (1-1) h, C_{max} 1468 µg/L (37%), and $AUC_{0\text{-}24h}$ 10437 µg•h/L (61%).

Preliminary PK from the first-in-human study (Figure 9) show that after oral administration BAY 1895344 (elimusertib) is rapidly absorbed with a median T_{max} of 1 hour and a geometric mean

terminal half-life of 11.5 hours.[16] In the dose expansion portion of the trial, 64 patients had first dose pharmacokinetics and 52 patients had repeat sampling on day 10 at the 40 mg BID dose level on the 3 day on 4 day off schedule. On day 1, the C_{max} was 1226 µg/L (3 µM), AUC_{0-12h} was 7118 µg•h/L (17 µM•h); on day 10, the C_{max} was 1661 µg/L (4 µM) and AUC_{0-12h} was 11539 µg•h/L (28 µM•h). Unit conversion was based on BAY 1895344 (elimusertib) MWT 412 g/mol). Exposure was observed to be broadly dose-proportional across the dose range investigated (5-80 mg), and accumulation was consistent with observed half-life.[16]

2.3.4 Pharmacodynamics:

Pre-therapy and on-therapy biopsies were obtained during the dose escalation and studied for increased expression of pH2AX and pKAP1. For example, a patient with BRCA1 mutant ovarian cancer who had stable disease demonstrated increased pH2AX and pKAP1; this increase in DNA damage markers was evident in many of the matched tumor pairs, as shown in Figure 10.[16]

2.3.5 Efficacy:

In the dose escalation of the first-in-human study of BAY 1895344 (elimusertib), 4 of 20 patients treated in the dose escalation exhibited a partial response (PR) (Figure 11). Notably, all 4 of these responders had ATM loss of expression on immunohistochemistry and/or ATM loss of function mutations.[16]

Figure 9. BAY 189544 PK Profile for Single Dose (Cycle 1, Day 1) and Multiple Dose Administration (Cycle 1, Day 10)[38]

	Dose escalation: 3 days on / 4 days off							Japan-Arm		Dose expansion
	5 mg BID	10 mg BID	20 mg BID	40 mg BID (MTD)	60 mg BID	80 mg BID	60 mg* BID	20 mg BID	40 mg BID	40 mg BID
Cycle 1, Day 1	**n=1**	**n=1**	**n=3**	**n=2**	**n=8**	**n=3**	**n=4**	**n=4**	**n=4**	**n=64**
C_{max} (µg/L)	178	258	569 (42%)	1817-1863	2442 (37%)	3255 (26%)	1590 (49%)	667 (38%)	1783 (44%)	1226 (36%)
AUC(0-12) (µg·h/L)	937	1613	4060 (26%)	7269-9590	13395 (32%)	19716 (28%)	11647 (45%)	3882 (29%)	9160 (30%)	7118 (31%)
AUC(0-24) (µg·h/L)	1347	2081	6431 (24%)	9461-14497	18458 (39%)	30894 (26%)	16664 (38%)	5506 (30%)	12651 (34%)	9890 (36%)
$t_{1/2}$ (h)	11.6	8.61	17.2 (27%)	9.08-10.9	9.10 (42%)	17.8 (41%)	10.3 (33%)	11.7 (34%)	10.9 (26%)	9.81 (54%)
t_{max} (h)[a]	1.0	4.0	0.5 (0.5-1.0)	1.0-1.0	1.0 (0.5-1.0)	1.0 (0.5-2.0)	1.5 (0.5-2.0)	1.0 (0.5-2.0)	1.0 (0.5-1.0)	1.0 (0.5-4.0)
Cycle 1, Day 10	**n=1**	**n=1**	**n=1**	**n=2**	**n=7**	**n=3**	**n=3**	**n=4**	**n=4**	**n=52**
C_{max} (µg/L)	263	420	1075	2201-2363	3285 (55%)	4383 (56%)	2884 (33%)	1018 (52%)	2577 (39%)	1661 (45%)
AUC(0-12) (µg·h/L)	1609	2502	8159	11432-15642	18430 (50%)	29138 (73%)	22375 (36%)	7345 (35%)	16674 (28%)	11539 (46%)
t_{max} (h)[a]	0.5	2.0	0.5	1.0-1.0	0.5 (0.5-4.0)	1.0 (1.0-2.0)	2.0 (2.0-2.0)	1.5 (1.0-2.0)	1.5 (0.5-4.0)	1.5 (0.5-8.0)
R_ACmax	1.5	1.6	2.8	1.2-1.3	1.3; n=6	1.4	1.7	2.0	1.2	1.3
R_AAUC[b]	1.7	1.6	2.4	1.6-1.6	1.4; n=6	1.5	1.7	2.2	1.6	1.6

[a]for n ≥ 3: median (range);
[b]R_AAUC is Day 10 AUC(0-12)/Day 1 AUC(0-12)
*3 days on /4 days off for 2 weeks + 1 week drug holiday
AUC: area under the plasma concentration vs. time curve; AUC(0-12): AUC from 0 to 12 hours; R_AAUC: accumulation ratio calculated from AUC(0-τ) after multiple dosing and AUCτ after single dosing; AUC(0-24): AUC from 0 to 24 hours; C_{max}: maximum observed drug concentration in plasma; t_{max}: time to reach maximum drug concentration in plasma; R_ACmax: accumulation ratio calculated from C_{max} after multiple dosing and C_{max} after single dosing; $t_{1/2}$: half-life; n: number; BID: twice daily; MTD: maximum tolerated dose; CV: coefficient of variation

Figure 10: Pharmacodynamic markers of DNA damage in patients treated with BAY 1895344 (elimusertib) [16]

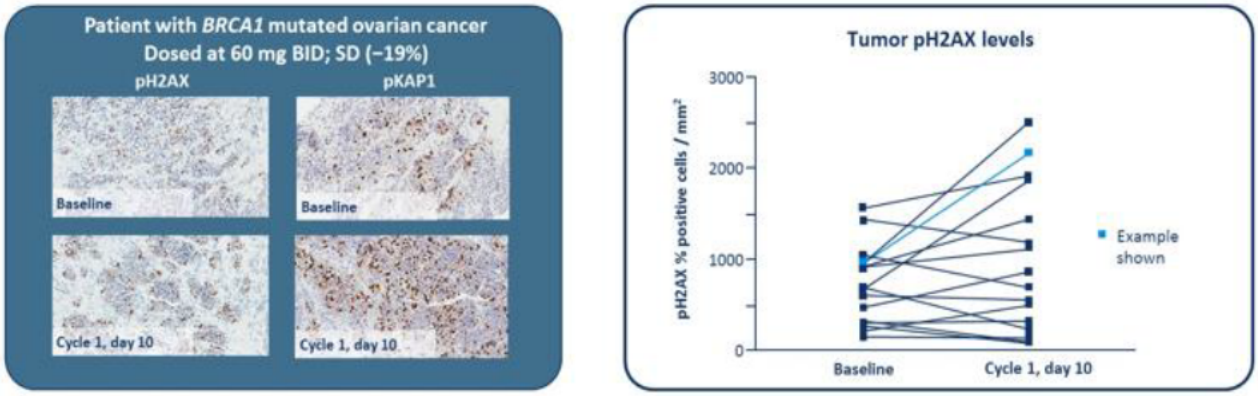
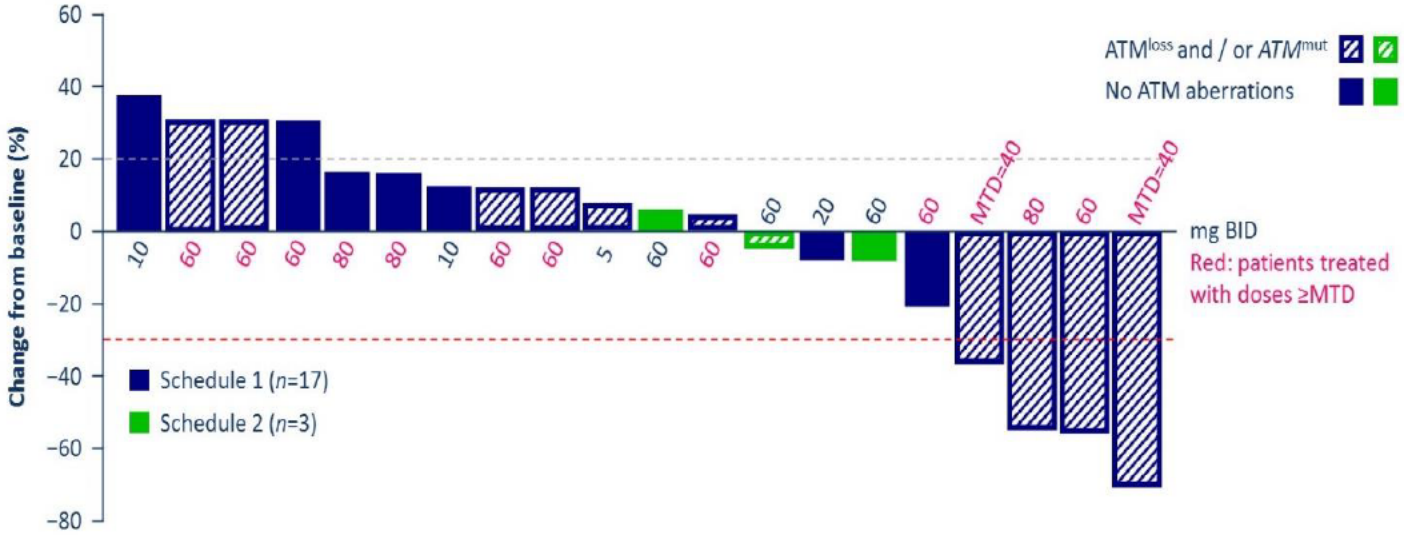


Figure 11: RECIST Response by Patients in Dose Escalation (based on dose and ATM status)[16]



2.4 Pediatric Studies

There are currently no other pediatric studies published or in development of BAY 1895344 (elimusertib). There is an open study of the ATR inhibitor Ceralasertib (AZD6738) given in combination with the PARP inhibitor Olaparib to adolescents and young adults with osteosarcoma (NCT04417062).

2.5 Overview of Proposed Pediatric Study

2.5.1 Rationale for starting dose and dose finding:

We propose a Phase 1/2 study of BAY 1895344 (elimusertib) monotherapy in pediatric patients with advanced non-central nervous system (CNS) solid tumors or lymphomas that harbor specific genetic alterations in DNA damage repair pathways as well as pre-selected histologies with anticipated susceptibility to ATR inhibition including Ewing Sarcomas (EWS) and PAX3-FOXO1 ARMS.

BAY 1895344 (elimusertib) tablets will be given orally twice daily for 3 days followed by 4 days without drug administration. This trial will use 10 mg and 20 mg tablets. Dosing will be administered according to a BSA based dosing nomogram. The pediatric dose was extrapolated from the adult RP2D and MTD of 40 mg BID 3 days on/4 days off weekly adjusted for BSA. Using

average adult BSA of 1.7 m^2, the corresponding pediatric dose of BAY 1895344 (elimusertib) is 24 mg/m^2/dose BID 3 days on and 4 days off, repeated 4 times per cycle (28-day cycle). Patients who do not have progression of disease or meet other criteria for discontinuation of protocol therapy may continue BAY 1895344 (elimusertib) for up to 26 cycles (since each cycle is 28 days, 26 cycles is equal to 2 years of treatment).

2.5.2 Rationale for Phase 2 Cohorts and Biomarker Selected Cohorts:

The initial Phase 1 portion will utilize the Rolling 6 design and will initially treat pediatric patients at dose level 1 (24 mg/m^2/dose), approximately the adult RP2D. If this dose level is not well tolerated, we will next evaluate dose level -1 (18 mg/m^2/dose), a 25% dose reduction. The RP2D will be the highest dose level for which < 33% of evaluable patients experience a dose limiting toxicity during Cycle 1. Once the RP2D is defined, a PK expansion cohort will be opened and will enroll up to 6 additional patients for PK analysis. Three phase 2 expansion cohorts will also open for enrollment:

(1) EWS cohort
(2) PAX3-FOXO1 ARMS cohort
(3) DDR cohort

The Phase 2 cohorts will initially open concurrently with the Phase 1 portion but will only enroll patients at least 18 years of age. Patients <18 years of age will be included in the Phase 2 cohorts only after the RP2D/MTD has been estimated in the Phase 1 portion.

Eligibility criteria for the phase 1 and 2 portions of the study will be identical except for the following:

(1) The phase 1 portion will allow tumors which are either evaluable or measurable whereas the phase 2 will only allow measurable tumors.
(2) In phase 2 expansion cohorts for EWS and PAX3-FOXO1 ARMS, the upper age of eligibility will be increased to 30 years to enhance access of this drug to young adults with biologically analogous tumors.

Both the EWS and PAX3-FOXO1 ARMS cohorts will utilize the 10+10 Simon optimal two-stage design. Given that qualifying deleterious mutations are expected to occur quite rarely, as summarized in Figure 1, the DDR cohort will utilize a smaller 7+6 Simon two-stage design.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient Enrollment:

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

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.
Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).
  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

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

Please see **Appendix I** for detailed CTEP and CTSU Registration Procedures including: Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual.

3.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients.

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see **Appendix I**.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.4 Reservation and Contact Requirements

Prior to enrolling a patient, a reservation must be made following the steps below and the Study Chair or Vice Chair notified. (The patient will need a COG patient ID number in order to obtain a reservation). Reservations may be obtained 24 hours a day through the OPEN system. Patients must be enrolled within 7 calendar days of making a reservation.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE**' a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
   https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child. All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines

3.6 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.7 Institutional Pathology and Genomics Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. All pathology testing will be completed at a CLIA certified lab. For Part A patients with confirmation of an eligible mutation, and all Part B expansion cohorts, documentation of eligible mutation and/or pathology report are required (See section 4.1.4.3). The reports must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from all institutional reports prior to submission.

3.8 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered

enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria.

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

Prior to accessing OPEN, site staff should verify the following:
- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

3.9 Dose Assignment

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

Laboratory Studies:
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility.

If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), albumin 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.

Clinical Studies:
All clinical studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Imaging studies must be obtained within 14 days prior to enrollment (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

4.1 Inclusion Criteria

4.1.1 **Part A:**

4.1.1.1 **Age:**
Patients between ≥ 12 months and < 18 years of age.

4.1.2 **Part B:**

4.1.2.1 **Age:**
Patients between ≥ 12 months and ≤ 30 years of age for the phase 2 expansion cohorts for both EWS and PAX3-FOXO1 ARMS.

Patients between ≥ 12 months and ≤ 21 years of age for the phase 2 DDR expansion cohort.

The Phase 2 cohorts will initially open concurrently with the Phase 1 portion but will only enroll patients at least 18 years of age. Patients <18 years of age will be included in the Phase 2 cohorts only after the RP2D/MTD has been estimated in the Phase 1 portion.

4.1.3 **BSA:**
All patients for both Parts A and B must have a minimum BSA ≥ 0.74 m^2

4.1.4 All patients for both Parts A and B must have the ability to swallow BAY 1895344 (elimusertib) tablets intact.

4.1.5 **Diagnosis:**
Patients with recurrent or refractory solid tumors. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.5.1 **Part A Diagnosis Criteria:**
Any (non-CNS primary) solid tumor diagnosis including lymphoma which meets one of the following criteria:

a. Any Ewing Sarcoma (**histological confirmation alone is adequate**) or any EWS-fusion positive solid tumor (i.e. including related Ewing's family of tumors with EWS fusions such as EWS-WT1, EWS-ATF1, etc.).

   Alveolar rhabdomyosarcoma (ARMS) with the PAX3-FOXO1 fusion. This does not include PAX7-FOXO1 or other variant fusion ARMS. Please note that a FISH showing FOXO1 breakapart is NOT sufficient for eligibility onto this cohort since it cannot distinguish between FOXO1 partners.

b. Any (non-CNS primary) solid tumor including lymphoma with inactivating alterations of any of the DNA Damage Repair (DDR) genes: ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, or XRCC2.

4.1.5.2 **Part B Diagnosis Criteria:**
Any (non-CNS primary) solid tumor diagnosis including lymphoma which meets one of the following criteria:

a. B1, EWS Cohort:
Any Ewing Sarcoma (**histological confirmation alone is adequate**) or any EWS-fusion positive solid tumor (i.e. including related Ewing's family of tumors with EWS fusions such as EWS-WT1, EWS-ATF1, etc.).

b. B2, PAX3-FOXO1 ARMS Cohort:
Alveolar rhabdomyosarcoma (ARMS) with the PAX3-FOXO1 fusion. This does not include PAX7-FOXO1 or other variant fusion ARMS. Please note that a FISH showing FOXO1 breakapart is NOT sufficient for eligibility onto this cohort since it cannot distinguish between FOXO1 partners.

c. B3, DDR Non-statistical Cohort:
Any (non-CNS primary) solid tumor including lymphoma with inactivating alterations of any of the DNA Damage Repair (DDR) genes: ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, or XRCC2.

4.1.6 **Genomic Testing: (all parts) with the exception of histologically verified Ewing Sarcoma**

4.1.6.1 Determination of whether a mutation is oncogenic:
All the genes on the DDR panel are annotated with OncoKB, a precision oncology knowledge base which is publicly available here: https://www.oncokb.org/. Alterations which are categorized either 'Oncogenic' or 'Likely Oncogenic' would be considered sufficient for eligibility on either the phase 1 or phase 2 portions of this study. Alterations which are not annotated in OncoKB will need to be reviewed with locally qualified experts in molecular pathology, such as via an established molecular tumor board, in order to determine the likely oncogenicity AND will require approval by the study chair, Dr. Michael Ortiz. If such experts are not available at any institution, the study chair will review.

4.1.6.2 How to address multiple tumor samples or mutations:
In cases where multiple mutations are present or multiple samples are available, either at different locations or different points in time, the presence of a single qualifying genomic alteration in any of those samples will is considered sufficient for eligibility on the phase 2 portions of this study.

4.1.6.3 Determination of adequacy of genomic testing:
Qualifying aberrations must be detected in either DNA or RNA in any tumor tissue sample (i.e. detection of a variant on circulating tumor DNA/RNA is not sufficient to qualify) using a somatic (and/or germline) mutational testing approach with either a targeted panel or whole exome/genome sequencing in the context of a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory setting. Any CLIA certified laboratory is acceptable to use. A list of qualifying CLIA-certified laboratories is here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

4.1.7 Disease Status:

4.1.7.1 **Part A:** Patients must have either measurable or evaluable disease.

4.1.7.2 **Part B (1, 2, 3):** Patients must have measurable disease.

4.1.7.3 **CNS Metastases**: Patients with a prior history of CNS metastases may enroll on study, provided there is no current evidence of active disease at the time of enrollment.

4.1.8 Therapeutic Options:
Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.9 Performance Level:
Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50% for patients ≤ 16 years of age. Note that neurologic deficits in patients with tumors previously metastatic to the CNS (or other non-oncologic reasons) must have been stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

See https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials under Standard Sections for Protocols.

4.1.10 Prior Therapy:

4.1.10.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g., blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive: ≥ 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea). See DVL homepage on the COG Members site for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment. Refer here for details: https://www.cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf

b. Anti-cancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See the DVL homepage on the COG Members site for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. 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.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

f. Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusions (DLI) or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 30 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g., modified T cells, NK cells, dendritic cells, etc.).

i. 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.

j. Radiopharmaceutical therapy (eg, radiolabeled antibody, ^{131}I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

k. Study specific prior therapy: Patients must not have received prior exposure to BAY 1895344 (elimusertib) or any other specific ATR inhibitors including Berzosertib (M6620, VX-970), Ceralasertib (AZD6738), M4344 (VX-803), M1774, and RP-3500. Treatment with other DNA damage repair inhibitors which do not specifically inhibit ATR (e.g., PARP inhibitors, WEE1 inhibitors, CHEK1 inhibitors, etc.) does not exclude them from eligibility on this study.

4.1.11 Organ Function Requirements

4.1.11.1 Adequate Bone Marrow Function Defined As:

a. For patients with solid tumors without known bone marrow involvement
- Peripheral absolute neutrophil count (ANC) ≥ 1000/uL
- Platelet count ≥ 100,000/uL (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)

b. Patients with known or possible bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.11.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.11.2 Adequate Renal Function Defined As:
- Serum creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A 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[39] utilizing child length and stature data published by the CDC.

4.1.11.3 Adequate Liver Function Defined As:

- Bilirubin (sum of conjugated + unconjugated or total) ≤ 1.5 x upper limit of normal (ULN) for age.
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

4.1.11.4 Adequate Neurologic Function Defined As:

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled as evidenced by no increase in seizure frequency in the prior 7 days. For patients a history of seizure but not on anticonvulsants, no seizure in the past 3 months. If needed, evaluate use of enzyme-inducing anticonvulsants as stated in Section 4.2.2.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, OR because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control, including a medically accepted barrier or contraceptive method (e.g., male or female condom) for the duration of the study and for 3 months + 2 days for males and 6 months + 2 days for females after receiving the last dose of BAY 1895344 (elimusertib) on the study. Abstinence is an acceptable method of birth control. Female patients must not breastfeed during treatment and until 4 months after last study drug administration.

4.2.2 Concomitant Medications:

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (see Section 4.1.7.1.d).

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.2.4 Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.2.5 CYP3A4 Agents: Patients who are currently receiving drugs that are strong inducers or inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. Drugs that are considered sensitive or narrow therapeutic range CYP3A4 substrates should be avoided for the duration of protocol therapy. See Appendix III for a list of agents.

4.2.3 Study Specific:
Dedicated CNS imaging is not required but patients with current active CNS metastasis whether symptomatic or discovered incidentally without clinical symptoms, will be excluded from study participation.

4.2.4 Infection:
Patients who have an uncontrolled infection are not eligible.

4.2.5 Solid Organ Transplant:
Patients who have received a prior solid organ transplantation are not eligible.

4.2.6 Compliance:
Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PLAN

5.1 Overview of Treatment Plan

Week	Day	Agent
1	1-3	BAY 1895344 (elimusertib) PO BID
	4-7	
2	8-10	BAY 1895344 (elimusertib) PO BID
	11-14	
3	15-17	BAY 1895344 (elimusertib) PO BID
	18-21	
4	22-24	BAY 1895344 (elimusertib) PO BID
	25-28	End of Cycle on day 28

A cycle of therapy is considered to be 28 days. A cycle may be repeated for a total of 26 cycles, up to a total duration of therapy of approximately 24 months.

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. The starting dose for patients ≥ 18 years of age is 40 mg BID 3 days on and 4 days off per week.

If a patient vomits within 30 minutes after the dose of BAY 1895344 (elimusertib) is administered, that dose should NOT be repeated.

On days that BAY 1895344 (elimusertib) is due to be given, it should be administered twice daily, preferably at the same time of day each day. Take BAY 1895344 (elimusertib) on an empty stomach one (1) hour before or two (2) hours after a meal with plenty of water. If a dose of BAY 1895344 (elimusertib) is missed and it is less than 4 hours since the scheduled dosing time, the dose should be taken immediately, otherwise the dose should be skipped.

Patient or caretaker must complete the medication diary with the date, time and number of agent tablets taken each day (see Appendix VI). The medication diary should be reviewed after completion of each treatment cycle and loaded into Rave.

See Section 5.6 for Therapy Delivery Maps for each cycle.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient 1) has at least stable disease 2) all pre-cycle studies required per Section 8.1 meet eligibility criteria as defined in Section 4.0 and 3) is otherwise eligible to continue agent administration per the requirements in Section 6.0.

5.2.1 Recommendations for Starting Each Weekly 3-day Course:

BAY 1895344 (elimusertib) is administered on a 3-day on and 4-day off schedule, repeated 4 times each cycle. Hematologic toxicities are the most common toxicities with BAY 1895344 (elimusertib). Eligibility criteria require an ANC ≥ 1000/µL and Platelets ≥ 100,000/µL, hence these parameters also need to be met to start any cycle (See section 4.1.11.1). Once a cycle has started, patients are required to have an ANC > 500/µL and Platelets > 50,000/µL within 48 hours prior to initiation of each 3 day interval of BAY 1895344 (elimusertib) administration (i.e. ANC and platelet parameters must be met (without transfusion) within 48 hours of initiation of days 8, 15, and 21). If parameters are not met, this 3-day interval of BAY 1895344 (elimusertib) will be omitted and attempted to restart the following week (e.g. day 15 or 21). If more than one 3-day block of BAY 1895344 (elimusertib) is missed within a cycle (i.e. < 75% of planned therapy is given for a particular cycle), that would be considered a hematologic DLT.

5.3 Dose Schema

5.3.1 Part A Interpatient dosing:

Part A is restricted to patients < 18 years of age. The starting dose will be 24 mg/m^2/dose BID (Dose Level 1) with dose levels for subsequent groups of patients as follows.

Dose Level	Dose (mg/m^2)
-1	18 mg/m^2/dose BID (maximum 30 mg/dose BID)
1*	**24 mg/m^2/dose BID** (maximum 40 mg/dose BID)

** Starting Dose Level*

There will be no planned escalations beyond Dose Level 1 (24 mg/m^2), the adult RP2D. Please see dosing nomogram in Appendix V.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 18 mg/m^2/dose BID (Dose Level -1). If Dose Level -1 is not well tolerated, further de-escalation will not occur and Part A will close to accrual and Part B will continue and be limited to those age 18 years and older.

Note: Part A, PK expansion cohort will be opened when the RP2D/MTD has been defined and treated at that RP2D/MTD. If required number of responses per the Simon two-stage design for expansion is not met for either the ARMS or EWS phase 2 cohorts whilst the PK expansion is still enrolling, the PK expansion will be closed to those patients. Patients who have qualifying DDR alterations will always be allowed on the PK expansion cohort.

5.3.2 Part B Dose Level:

Patients <18 years of age in the B1, B2 and B3 phase 2 expansion cohorts defined in section 4.1.2 will be treated at the RP2D/MTD defined in Part A. Patients ≥ 18 years of age will be treated at the adult RP2D (40 mg BID 3 days on and 4 days off of each week of a 28 day cycle).

If the patient experiences a toxicity, please refer to Section 6.0 for dose modifications.

5.3.3 Intra-Patient Escalation:

Intra-patient dose escalation is not allowed.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair. For laboratory values in CTCAE with grading definitions including both baseline and ULN definitions, utilize the ULN for CTCAE grading.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of study dose-escalation (Part A) will be the first cycle of therapy. Please refer to Section 13.5.4 for AE resolution definitions

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 **Non-Hematological Dose-Limiting Toxicity:**

5.5.1.1 Any Grade 3 or greater non-hematological toxicity attributable to protocol therapy with the specific exclusion of:

- Grade 3 nausea and vomiting of < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to Grade ≤ 1 within 7 days. See Appendix IV for Adverse Event grading for liver function grading parameters in children and adolescents.

Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.

- 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.

5.5.2 **Hematological dose limiting toxicity:**

- Grade 4 neutropenia (ANC < 500/μL) that persists for ≥ 7 days despite holding BAY 1895344 (elimusertib) for 3 days
- Grade 4 thrombocytopenia (Platelet count < 25,000/μL)
- Grade 3 thrombocytopenia (Platelet count < 50,000/μL) that persists for ≥ 7 days despite holding BAY 1895344 (elimusertib) for 3 days *OR* is associated with clinically significant bleeding
- Failure to meet hematological criteria to initiate weekly dosing (Section 5.2.1) or subsequent cycles of therapy (Section 5.2) by cycle day 42 (within 14 days of planned start of the subsequent cycle) will be considered dose limiting toxicity.
- Failure to receive at least 75% of the planned number of BAY 1895344 (elimusertib) doses during any cycle (i.e., 9 of 12 planned doses) due to delays attributable to myelosuppression would be considered a hematologic DLT.

5.5.2.1 **Note**: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

5.6: THERAPY DELIVERY MAPS (TDMS) FOR CYCLE 1

Therapy Delivery Map – Cycle 1
This Therapy Delivery Map (TDM) relates to Cycle 1. Cycle 1 lasts 28 days. Please record the dose level in the chart below. Treatment may continue in the absence of unacceptable toxicity. Use a copy of this page once for Cycle 1.

This form is to be completed and uploaded into RAVE at the end of every cycle.

_____ Accession #

_____ Patient COG ID number

_____ Institution

Criteria to start this cycle are listed in Section 5.2. Extensive details are in Section 5.0 and Section 9.0.
This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
BAY 1895344 (elimusertib) IND# [redacted]	Oral (Tablet)	_____ mg/m^2/dose BID Dose level 1 max dose = 40 mg BID Dose level -1 max dose = 30 mg BID Part B patients ≥ 18 years old: 40 mg BID	1-3 8-10 15-17 22-24	On days that BAY 1895344 (elimusertib) is due to be given, it should be administered twice daily preferably at the same time of day each day. Take BAY 1895344 (elimusertib) one (1) hour before or two (2) hours after a meal with plenty of water.

Assigned Dose Level ___Ht _____cmWt _____kgBSA _____m^2 Age ≥ 18 years ___yes. ____no

Date Due	Date Given	Day	BAY 1895344 (elimusertib) Nomogram Dose _____ _____mg qAM. ____mg qPM	Studies
			Enter actual dose administered below	
		PRE		a-e, f*, g-i, j^, k, m#, n%, q$, r@
		1	_____ mg _____mg	a, b, d, e, f*, g, h, l, o&, p!
		2	_____ mg _____mg	
		3	_____ mg _____mg	o&
		4		
		5		
		6		
		7		
		8	_____ mg _____mg	e, f*l
		9	_____ mg _____mg	
		10	_____ mg _____mg	o&,p!
		11		
		12		
		13		
		14		
		15	_____ mg _____mg	e, f*, l
		16	_____ mg _____mg	
		17	_____ mg _____mg	
		18		
		19		
		20		
		21		
		22	_____ mg _____mg	e, f*, j^, l
		23	_____ mg _____mg	
		24	_____ mg _____mg	
		25		
		26		
		27		
		28		

*** Please refer to Section 8.1 for the specific timing of these observations.**

Cycle 1

Observations in Cycle 1

a. History
b. Physical Exam
c. Performance Status
d. Height, Weight, BSA
e. Vital Signs
f. CBC, differential, platelets: *__Once weekly. If patients develop Grade 4 neutropenia or Grade 3 or 4 thrombocytopenia, CBC/differential/platelets should be checked at least twice per week (every 3-4 days) until recovery to Grade 3 neutropenia or Grade 2 thrombocytopenia, or until the criteria for dose limiting toxicity are met. For patients who experience hematological dose limiting toxicity, CBCs should be checked at least weekly until recovery of ANC and platelet count to eligibility criteria__
g. SGPT (ALT), Albumin, Bilirubin
h. Electrolytes including serum creatinine, calcium (Ca^{++}), phosphorus (PO_4), magnesium (Mg++)
i. Creatinine Clearance or GFR
j. Tumor disease evaluation: ^__can occur any time during the last week of cycle 1. Should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.__
k. Pregnancy test: __Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control. All women of childbearing potential must have a pregnancy test done every cycle prior to initiation of a new cycle.__
l. Medication Diary
m. Pathology & Genomics Report: #__Indicate a qualifying molecular aberration to enroll on study. Must be submitted via upload to MediData/RAVE. Details of genomic studies noted in Section 4.1.4.3.__
n. Knee X-Ray: %__ Knee X-Ray should only be obtained in patients without epiphyseal closure at the time of enrollment, prior to start of therapy. If the baseline tibial radiographs demonstrate open growth plates (epiphysis) then knee X-rays for tibial growth plate assessment will be obtained after cycle 1, every 3 cycles thereafter and at the end of study treatment. The end of study treatment observation is not required, if already obtained within the final month of therapy. .Reference Section 8.7 for further instruction on monitoring for growth plate toxicity.__
o. Pharmacokinetics (required): &__See Section 8.5.2 for timing of PK studies__
p. Pharmacokinetics (optional): !__See Section 8.3.5 for timing of optional PK studies__
q. Correlative Studies (required): $__See Section 8.6 for details__
r. Correlative Studies (optional): @__See Section 8.3 for details__

Cycle 1

5.7: THERAPY DELIVERY MAPS (TDMS) FOR CYCLES 2 +

Therapy Delivery Map – Cycle 2 +

This Therapy Delivery Map (TDM) relates to Cycle 2+. This TDM can be used for any dose level of BAY 1895344 (elimusertib). Please record the dose level in the chart below. Treatment may continue in the absence of unacceptable toxicity. Use a copy of this page once for Cycle 2 +.

This form is to be completed and uploaded into RAVE at the end of every cycle.

_____ Accession #

_____ Patient COG ID number

_____ Institution

Criteria to start this cycle are listed in Section 5.2. Extensive details are in Section 5.0 and Section 9.0.
This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
BAY 1895344 (elimusertib) IND#[redacted]	Oral (Tablet)	_____ mg/m^2/dose BID Dose level 1 max dose = 40 mg BID Dose level -1 max dose = 30 mg BID Part B patients ≥ 18 years old: 40 mg BID	1-3 8-10 15-17 22-24	On days that BAY 1895344 (elimusertib) is due to be given, it should be administered twice daily, preferably at the same time of day each day. Take BAY 1895344 (elimusertib) one (1) hour before or two (2) hours after a meal with plenty of water.

Assigned Dose Level ____ Ht _____cm Wt _____kg BSA _____m^2 Age ≥ 18 years ____yes ___no

Date Due	Date Given	Day	BAY 1895344 (elimusertib) Nomogram Dose ___ mg qAM. ____mg qPM	Studies
			Enter actual dose administered below	
		1	_____ mg _____ mg	a-d, e*, f, g, i, j&
		2	_____ mg _____ mg	
		3	_____ mg _____ mg	
		4		
		5		
		6		
		7		
		8	_____ mg _____ mg	
		9	_____ mg _____ mg	
		10	_____ mg _____ mg	
		11		
		12		
		13		
		14		
		15	_____ mg _____ mg	e*
		16	_____ mg _____ mg	
		17	_____ mg _____ mg	
		18		
		19		
		20		
		21		
		22	_____ mg _____ mg	
		23	_____ mg _____ mg	
		24	_____ mg _____ mg	a-d, h^, j&, k!, l#
		25		
		26		
		27		
		28		

*** Please refer to Section 8.1 for the specific timing of these observations.**

Cycle 2 +

Required Observations in Cycle 2 +

a. History
b. Physical Exam
c. Height, Weight, BSA
d. Vital Signs
e. CBC, differential, platelets: * **Must be obtained within 72 hours of the start of each cycle and on day 15 of all subsequent cycles. If patients develops Grade 4 neutropenia or Grade 3 or 4 thrombocytopenia, CBC/differential/platelets should be checked at least twice weekly (every 3-4 days) until recovery to Grade 3 neutropenia, Grade 2 thrombocytopenia or until the criteria for dose limiting toxicity are met. For patients who experience hematological dose limiting toxicity, CBCs should be checked at least weekly until recovery of ANC and platelet count to eligibility criteria. Patients who have dose adjustment due to hematologic toxicity attributable to BAY 1895344 (elimusertib), are required to have CBCs once weekly to confirm the safety of this adjusted dose during the cycle. Please see Section 6.1 for details.**
f. SGPT (ALT), Albumin, Bilirubin
g. Electrolytes including serum creatinine, calcium (Ca^{++}), phosphorus (PO_4), magnesium (Mg^{++})
h. Tumor disease evaluation: ^ **Can occur any time during the last week of cycles 2, 4 and 6 and then every 3 cycles thereafter. Should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.**
i. Medication Diary
j. Knee X-Ray: & **Knee X-Ray should only be obtained in patients without epiphyseal closure at the time of enrollment, prior to start of therapy. If the baseline tibial radiographs demonstrate open growth plates (epiphysis) then knee X-rays for tibial growth plate assessment will be obtained after cycle 1, every 3 cycles thereafter and at the end of study treatment. The end of study treatment observation is not required, if already obtained within the final month of therapy.**
k. Tumor Tissue for Immunohistochemistry pH2AX, pKAP1 and pATR (Optional): [!] **See Section 8.3.3 for details.**
l. Tumor Tissue for Whole Genome Sequencing (Optional): # **See Section 8.3.1 for details.**

Cycle 2 +

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have dose-limiting thrombocytopenia or neutropenia (defined in section 5.2, section 5.2.1 and section 5.5.2) should receive subsequent cycles with at least a 25% dose reduction (75% of the original dose). Please see dosing nomograms in Appendix V. For patients ≥18 years of age with starting dose of 40 mg BID, dose should be reduced to 30 mg BID 3 days on, 4 days off per week (25% dose reduction).

6.1.2 Patients who experience dose-limiting thrombocytopenia and/or neutropenia (as defined in Section 5.5.2) after one dose reductions must be removed from protocol therapy.

6.1.3 Patients who have a dose-limiting hematological toxicity that does not resolve to eligibility parameters within 14 days after the planned start of the next treatment cycle (42 days from start of previous cycle) must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or Grade ≤ 1 but should receive subsequent doses with at least a 25% dose reduction (75% of the original dose). . Please see dosing nomograms in Appendix V. For patients ≥18 years of age with starting dose of 40 mg BID, dose should be reduced to 30 mg BID 3 days on, 4 days off per week (25% dose reduction).

6.2.2 If a non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to Grade ≤ 1 or eligibility within 14 days after the planned start of the next treatment cycle (42 days from start of previous cycle) must be removed from protocol therapy

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

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.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Please see COG Supportive Care guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. Based on the UV absorption properties of BAY 1895344 (elimusertib), patients should be instructed to use topical sun block and UV-blocking sunglasses during treatment with BAY 1895344 (elimusertib). Direct exposure of patients to sun light after administration should be avoided. Please see Patient Instructions for Sun Protection in Appendix XIV.

BAY 1895344 (elimusertib) has low emetogenic potential. Please see COG Guidelines on Chemotherapy Induced Nausea and Vomiting for recommendations on prevention options https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document.pdf.

7.4 Growth Factors

Growth factors are not approved for use on this study.

7.5 Concomitant Medications

In vitro, BAY 1895344 (elimusertib) is metabolized mainly by CYP3A4 and to a much lesser extent CYP1A1.
Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. BAY 1895344 (elimusertib) is predicted to be a moderate inducer toward sensitive CYP3A4 substrates. Drugs that are considered sensitive or narrow therapeutic range CYP3A4 substrates should be avoided for the duration of protocol therapy. See Appendix III for a list of agents. Substrates of CYP2C8, 2C9, and 2C19 should be used with caution.

BAY 1895344 (elimusertib) was identified as an *in vitro* inhibitor of BCRP, P-gp, BSEP, OATP1B1, and OATP1B3. The risk for clinically relevant drug-drug interactions due to inhibition of BSEP is considered to be negligible, but substrates of BCRP, P-gp, OATP1B1, and OATP1B3 should be used with caution. BAY 1895344 (elimusertib) is not a P-gp or BCRP substrate.

Because of pH dependent solubility, antacid drugs, H2-blockers, and proton pump inhibitors may affect absorption and exposure of BAY 1895344 (elimusertib).

Because there is a potential for interaction of BAY 1895344 (elimusertib) with other concomitantly administered drugs, the case report form will capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies only in Cycle 1. Appendix XV– Patient Drug Interactions Handout and Wallet Card should be provided to patients and includes recommendations on medications to avoid due to potential interactions.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol)

8.1 Required Clinical, Laboratory and Disease Evaluation (See Section 4.0 for eligibility criteria to start therapy)

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to and During Cycles 2 +^	End of Study Treatment
History	X	X[6]	X	X
Physical Exam	X	X[6]	X	X
Performance Status	X			
Height, weight, BSA	X	X[6]	X	X
Vital Signs	X	Weekly	X	X
CBC, differential, platelets[1]	X[7]	Weekly	X[6]	As clinically indicated
SGPT (ALT), Albumin, Bilirubin	X[7]	X	X [6]	As clinically indicated
Electrolytes including serum creatinine, Ca^{++}, PO_4, Mg^{++}	X[7]	X	X [6]	As clinically indicated
Creatinine Clearance or GFR	X			
Pregnancy Test[2]	X			
Tumor Disease Evaluation[3]	X	Last week of Cycle 1	Last week of cycles 2, 4, and 6 then q 3 cycles [3]	X
Tibial Radiographs (Knee X-Ray)[4]	X		X	X
Medication Diary see Appendix VI		Weekly	X	
Pathology & Genomics Report[5]	X			
Pharmacokinetics (Required) See Section 8.5		X		
Pharmacokinetics (Optional) See Section 8.3.5		X		
Archival Tumor Tissue for immunohistochemistry: ATM. (Required) See Section 8.6.	X			
Tumor Tissue for Whole Genome Sequencing (Optional) Section 8.3.1	X			X
Archival Tumor Tissue for Immunohistochemistry: PGBD5 and R-Loops (Optional) Section 8.3.2	X			
Tumor Tissue for Immunohistochemistry pH2AX, pKAP1 and pATR (Optional) Section 8.3.3	X			X
Blood for ctDNA for ALT (Optional) Section 8.3.4	X			
Archival Tumor Tissue for Biobanking (Optional) Section 8.3.5	X			

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

[1] If patients develop Grade 4 neutropenia or Grade 3 or 4 thrombocytopenia, CBC/differential/platelets should be checked twice per week (every 3 to 4 days) until recovery to Grade 3 neutropenia, Grade 2 thrombocytopenia, or until the criteria for dose limiting toxicity are met. For patients with hematological dose limiting toxicity, CBCs should be checked at least weekly until recovery to eligibility criteria. Please see Section 5.2.1 for details.

[2] Women of childbearing potential require a negative pregnancy test prior to starting treatment; See Section 4.2.1
[3] Tumor Disease Evaluation ^**should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.**
[4] Tibial Radiographs should only be obtained in patients without epiphyseal closure at the time of enrollment, prior to start of therapy and if baseline tibial radiographs are open then another will be obtained after cycle 1, every 3 cycles thereafter and at the end of study treatment. The end of study treatment observation is not required, if already obtained within the final month of therapy. Reference Section 8.7 for further instruction on monitoring for growth plate toxicity.
[5] Tumor pathology and genomics report indicating a qualifying molecular aberration to enroll on study must be submitted via upload to MediData/RAVE. Details of genomic studies noted in Section 4.1.3.
[6] Must be obtained within 72 hours of the start of each cycle and on day 15 of all subsequent cycles. If patients develop Grade 4 neutropenia or Grade 3 or 4 thrombocytopenia, CBC/differential/platelets should be checked at least twice weekly (every 3-4 days) until recovery to Grade 3 neutropenia, Grade 2 thrombocytopenia or until the criteria for dose limiting toxicity are met. For patients who experience hematological dose limiting toxicity, CBCs should be checked at least weekly until recovery of ANC and platelet count to eligibility criteria. Patients who have a dose adjustment due to hematologic toxicity attributable to BAY 1895344 (elimusertib), are required to have CBCs checked once weekly to confirm the safety of this adjusted dose during the cycle. Please see Section 6.1 for details.
[7] If greater than 7 days from pre study labs, please collect CBC, differential, platelets, bilirubin, albumin and serum creatinine within 48 hours prior to cycle 1, dose 1. These labs must still meet eligibility to receive dose 1 (as per Section 4.0).

8.2 Required Observations Following Completion of Protocol Therapy

The following studies are required until the patient is off study as defined in Section 10.2. These observations are not applicable to patients enrolled on Part A who are not treated at the MTD/ RP2D.

See COG Late Effects Guidelines for recommended post treatment follow-up:
http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

STUDIES TO BE OBTAINED	Every 3 Months up to 12 Months[1] (Months 3, 6, 9, 12)	Every 6 Months up to 24 Months[1] (Months 18, 24)	Annually up to 60 Months[1] (Months 36, 48, 60)
History	X	X	X
Physical Exam	X	X	X
Vital Signs	X	X	X
CBC with differential[3]	X	X	X
SGPT (ALT), Albumin, Bilirubin[3]	X	X	X
Electrolytes, Ca++, PO4, Mg++, Creatinine[3]	X	X	X
Disease evaluation[2]	X	X	X

[1] Only for phase 2 cohort patients that come off protocol therapy and have long-term responses.
[2] Imaging studies should be obtained only if required as per standard of care or if disease progression is suggested by symptoms, physical findings, or abnormal laboratory values.
[3] As clinically indicated.

8.3 Research Studies for which Patient Participation is Optional

Every effort should be made to include these optional studies. Sites which cannot collect samples for any reason other than lack of availability should contact the study chair. If insufficient amount for all tests, the priority from highest to lowest is as follows:

1. PGBD5
2. R-Loops
3. pKAP1
4. pH2AX
5. pATR

8.3.1 Tumor Tissue for Whole Genome Sequencing (Optional):

Whole genome sequencing (WGS) can be performed on up to 3 tumors samples per patient. We will request additional blood for control in patients who submit for WGS. The goal of this study is to evaluate whether other genomic findings sensitize patients to BAY 1895344 (elimusertib).

DNA C-circles will also be utilized from surplus DNA collected for WGS to evaluate the degree of ALT in tumor tissue and to investigate the sensitivity of tumors exhibiting ALT to BAY 1895344 (elimusertib). Concurrent with this, telomerase activity will be measured by TERT RT-PCR.

8.3.1.1 Sampling Schedule

- At diagnosis
- At relapse
- Post-treatment

Note: Peripheral blood can be collected at any time.

8.3.1.2 Sample Collection and Handling Instructions:

a. Frozen Tumor Tissue
No minimum size if frozen tumor is available; Up to 3 samples may be sent, preferably one at diagnosis one at relapse and one at post-study. Tissues should be processed per standard institutional pathology guidelines. Tumor tissue should be kept frozen at -80 ℃ and should not be thawed prior to or during shipping. The tumor tissue collection date and time as well as the ID label should be included.

b. Peripheral Blood
This is only required if a patient is submitting a frozen tumor sample. Blood samples (3mL +/- 1mL) will be collected in EDTA tubes from a peripheral vein and should be kept frozen at -80 ℃ and should not be thawed prior to or during shipping. Note that even if multiple tumor samples are available, this sample is for control blood so is only required once per patient.

8.3.1.3 Frozen tumor sample processing as per standard institutional pathology guidelines.

8.3.1.4 Sample Shipping Instructions

Frozen tumors and peripheral blood should not be thawed prior to or during shipping. Tumor samples and peripheral blood will be held until all samples have been obtained and then sent as a single batch frozen on dry ice using overnight delivery to the address listed below:

Dr. Alex Kentsis
Kentsis Research Group
408 East 69 Street, ZRC-1845
New York, NY 10065, USA

Phone: 1-646-888-3557
E-mail: kentsisresearchgroup@gmail.com

Friday collections are not permitted. Deliveries will be accepted Tuesday through Friday. Saturday and holiday shipments are not accepted. Please contact lab, prior to shipping.

Please include qualifying genomic testing report. Additionally, complete the PEPN2112 Tumor Tissue for Whole Genome Sequencing transmittal form in RAVE. Include the transmittal form with the shipment.

NOTE: DNA for WGS will be extracted at the Kentsis lab. If sufficient DNA is able to be extracted for WGS and there is at least 200 ng surplus, this will be then sent to the Reynolds lab from the Kentsis lab for ALT evaluation.

8.3.2 **Archival Tumor Tissue for Immunohistochemistry: PGBD5 and R-Loops (Optional):**

The archival tumor tissue will be used to identify biomarkers of response. Tumor tissue will be analyzed by Dr. Alex Kentsis' lab. Immunohistochemistry for R-loops and PGBD5 will be performed on pre-treatment tumor samples. This study will primarily investigate whether R-Loop presence and/or PGBD5 expression predicts response to BAY 1895344 (elimusertib). Secondarily, we will evaluate the prevalence of R-loops and PGBD5 loss in certain pediatric tumors.

8.3.2.1 Sample Schedule

- Archival tumor tissue sample(s) must be submitted for all consenting patients at time of enrollment, prior to the start of therapy.

8.3.2.2 Sample Collection and Handling

A minimum of 1 and a preference of 2, unstained slides of FFPE tumor tissue samples will be obtained at the above time point for PGBD5 and R-Loops, respectively.

8.3.2.3 Sample Processing

Samples can be processed at any institution and either slides or blocks may be sent. Both slides and blocks can be stored prior to shipment, refrigerated at 4 °C.

If sending slides, cut tumor into 5 µm sections and place, unstained, on a positive charged glass slide for conventional IHC (Superfrost plus slides are recommended). Place unstained slides in a plastic slide holder with sample ID label affixed. Place the slide holder in a Zipper lock bad and eliminate as much air (and therefore moisture) as possible prior to sealing the bag.

FFPE tumor blocks may alternatively be sent to the Kentsis lab if preferable. If sending a block, aim to submit a piece approximately 0.5-1 cm^3. After cutting an appropriately sized FFPE tumor block, place appropriate sample ID label onto the back of the cassette then place labeled cassette in a Zipper lock bag.

8.3.2.4 Sample Shipping Instruction

Samples will be held until all samples have been obtained and then sent as a single batch kept cold using ice packs with overnight delivery to the address below.

Dr. Alex Kentsis
Kentsis Research Group
408 East 69 Street, ZRC-1845
New York, NY 10065, USA

Phone: 1-646-888-3557
E-mail: kentsisresearchgroup@gmail.com

Friday collections are not permitted. Deliveries will be accepted Tuesday through Friday. Saturday and holiday shipments are not accepted. Please contact lab, prior to shipping.

Please include qualifying genomic testing report. Additionally, complete the PEPN2112 Archival Tumor Tissue for IHC transmittal form in RAVE. Include the transmittal form with the shipment.

8.3.3 **Tumor Tissue for Immunohistochemistry pH2AX, pKAP1 and pATR (Optional):**
Immunohistochemistry for pH2AX, pKAP1 and pATR will be performed on pre- and, where available, post- treatment tumor samples. These studies will primarily investigate whether treatment with BAY 1895344 (elimusertib) increases pH2AX and pKAP1 and decreases pATR and thus supports the proposed mechanism of DNA damage repair inhibition and ATR inhibition. Secondarily, we will evaluate whether pH2AX and pKAP1 and pATR are expressed at baseline in certain pediatric tumors.

8.3.3.1 Sampling Schedule
- Prior to the start of therapy
- With any biopsy occurring on-study or within 30 days of end-of treatment.

8.3.3.2 Sample Collection and Handling Instructions
A minimum of 1 and a preference of 2, unstained slides of FFPE tumor tissue samples will be obtained at the above time points for pH2AX, pKAP1 and pATR, respectively. An FFPE tumor block instead would also be sufficient.

8.3.3.3 Sample Processing
Samples can be processed at any institution and either slides or blocks may be sent. Both slides and blocks can be stored prior to shipment, refrigerated at 4 ℃.

If sending slides, cut tumor into 5 µm sections and place, unstained, on a positive glass slide for conventional IHC (Superfrost plus slides are recommended). Place the slide holder in a Zipper lock bag and eliminate as much air (and therefore moisture) as possible prior to sealing the bag.

FFPE tumor blocks may alternatively be sent to the Kentsis lab if preferable. If sending a block, aim to submit a piece approximately 0.5-1 cm^3. After cutting an appropriately sized FFPE tumor block, place appropriate sample ID label onto the back of the cassette then place labeled cassette in a Zipper lock bag.

8.3.3.4 Sample Shipping Instructions
Samples will be kept cold using ice packs with overnight delivery to the address below. Include the corresponding copy of the completed PEPN2112 Tumor Tissue for Immunohistochemistry pH2AX, pKAP1 and pATR Transmittal form (from RAVE) with each shipment.
Dr. Alex Kentsis

Kentsis Research Group
408 East 69 Street, ZRC-1845
New York, NY 10065, USA

Phone: 1-646-888-3557
E-mail: kentsisresearchgroup@gmail.com

Please include qualifying genomic testing report.

Friday collections are not permitted. Deliveries will be accepted Tuesday through Friday. Saturday and holiday shipments are not accepted. Please contact lab, prior to shipping.

NOTE: Prioritize pKAP1, pH2AX, and pATR if there are matched samples pre-/post-BAY 1895344 (elimusertib) therapy.

8.3.4 **Blood for ctDNA for ALT (Optional):**

ctDNA will be utilized to identify patients with alternate lengthening of telomeres (ALT) tumors, to investigate the sensitivity of tumors using ALT to BAY 1895344 (elimusertib).

8.3.4.1 Sampling Schedule

- Collected prior to the start of therapy, after enrollment but before the start of treatment.

8.3.4.2 Sample Collection and Handling Instructions

a. Peripheral Blood

Blood samples (~10mL) will be collected in EDTA anticoagulant tubes from a central line of from a peripheral vein, and then stored on ice or at 4 ℃. When clinically necessary, collecting 5mL of blood is acceptable.

label samples with the following information:

- COG patient ID
- Sample Collection Date
- Study Name (PEPN2112)

8.3.4.3 Sample Processing

1. The plasma samples are prepared within 2 hours of blood draw by centrifuging the blood tube at 1350g for 12 minutes at 4 ℃.
2. the faint yellow plasma samples are carefully transferred (free of any of the cell pellet) into a 15mL DNase tube. **Do not touch buffy coat with pipet when transferring plasma**.
3. The plasma is then centrifuged at 1350g for 12 minutes at 4 ℃.
4. the supernatant is transferred to 1.5-3mL DNase free tubes.
5. Ensure the plasma is cleared of cells. Freeze plasma and blood cell pellet samples separately at -80 ℃ immediately and store at -80 ℃ until both plasma and blood cell pellet samples are shipped in separate containers to the lab listed in section 8.3.4.4 **on dry ice**.

All the steps are processed at 4℃ (or on ice) until samples are stored.

8.3.4.4 Sample Shipping Instructions

Ensure samples are stored at -80 ℃, prior to shipment and ship on dry ice Monday through Wednesday. Batch shipment is accepted. Include the corresponding copy of the completed PEPN2112 Blood for ctDNA for ALT Transmittal form (from RAVE) with each shipment.

Dr. Charles Patrick Reynolds
Cancer Center, TTUHSC School of Medicine
3601 4th Street, STOP 94451
Lubbock, TX 79430-94451, USA

Phone: (806) 743-1558
E-mail: Dr. Reynolds: patrick.reynolds@ttuhsc.edu; Kristyn McCoy: Kristyn.Mccoy@ttuhsc.edu; Jonas Nance Jonas.Nance@ttuhsc.edu.

Please notify those listed above via email when samples have been shipped and provide the shipment tracking number.

8.3.5 **Part A Additional Pharmacokinetic Samples (Optional):**

8.3.5.1 Description of Studies

In addition to the required pharmacokinetic samples for Part A outlined in Section 8.5.2.1, we are requesting two optional samples.

8.3.5.2 Sample Schedule

- Day 1 of Cycle 1: 12 hours post dose.
- Day 10 of Cycle 1: 12 hours post dose.

Each sample will consist of 1-2 mL per sample.

NOTE: 12-hour sample collection is optional and should be a trough, obtained prior to the next dose.

8.3.5.3 Sample Collection and Handling

Please reference Section 8.5.3.

8.3.5.4 Sample Processing

Please reference Section 8.5.4.

8.3.5.5 Sample Labeling

Please reference Section 8.5.5.

8.3.5.6 Sample Shipping Instruction

Please reference Section 8.5.6.

8.3.6 **Archival Tumor Tissue for Biobanking (Optional):**

8.3.6.1 Description of Studies

The archival tumor tissue will be used for future research.

8.3.6.2 Sample Schedule

- Archival tumor tissue sample(s) must be submitted for all consenting after they are determined to be eligible and after enrollment is completed.

8.3.6.3 Sample Collection and Handling

A formalin-fixed paraffin-embedded (FFPE) tissue block that has not been acid decalcified, will be shipped to the Biopathology Center. If a block is not available then submit 1 H&E stained slide (3-5 µm) and 10 unstained, uncharged, air-dried slides (10 µm).

Labelling:

Blocks:

- COG patient ID
- Surgical Pathology ID (SPID) number and block number from the corresponding pathology report

Slides:

- COG patient ID
- Surgical Pathology ID (SPID) and block number from the corresponding pathology report
- Number slides sequentially

Labeling must be on the frosted end of slide.

Pathology Report:

- COG patient ID

Redact personally identifiable information such as the name, date of birth, medical record number and insurance information. The procedure/collection date, surgical pathology ID, block number, and diagnosis must be left on the report.

8.3.6.4 Sample Shipping Instruction

FFPE Blocks and slides must be shipped at room temperature. Ship on Monday – Thursday for receipt on Tuesday – Friday. Include the corresponding pathology report and a copy of the completed PEPN2112 Archival Tumor Tissue for Biobanking Transmittal form (from RAVE) with each shipment.

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

*The room number is required. Packages not listing the room number will be denied and returned to the sender.

8.4 Radiology Studies

8.4.1 **Central Radiology Review for Response:**

Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. Patients with osteosarcoma who are on therapy for 4 months or more, will have all imaging centrally reviewed. PEP-CTN ODSC will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the baseline and all on-study imaging for central review. The imaging evaluation results will be entered into RAVE for review by the PEP-CTN ODSC and for data analysis. The results will not be returned to the sites.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the LifeImage.

Institutions that are not connected via the LifeImage can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number PEPN2112 and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, Imaging Research Center
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054
E-mail: saamer@chla.usc.edu

8.5 Pharmacology (Required)

8.5.1 Description of Studies and Assay:

BAY 1895344 (elimusertib) pharmacokinetic (PK) studies will be determined by a validated LC/MS/MS method. Samples will be analyzed by the laboratory of Dr. Joel Reid (Mayo Clinic, Rochester, MN), PEP-CTN Pharmacology Vice Chair.

8.5.2 Sampling Schedule (See Appendix XI for Part A schedule and Appendix XII for Part B schedule):

8.5.2.1 **Part A:**

Blood samples will be obtained prior to drug administration and at the following time points:

- Day 1 of Cycle 1:
  - Pre-dose.
  - Within ± 15 minutes of 1 hour post-dose.
  - Within ±15 minutes of 2 hours post-dose.
  - Within ± 15 minutes of 4 hours post-dose.
  - Within ± 30 minutes of 8 hours post dose.

- Day 3 of Cycle 1:
  - Pre-dose (within 1-hour before AM dose).
  - Within ± 15 minutes of 1 hour post-dose.

- Day 10 of Cycle 1:
  - Pre-dose (within 1-hour before AM dose)

- Within ± 15 minutes of 1 hour post-dose.
- Within ± 15 minutes of 2 hour post dose.
- Within ± 15 minutes of 4 hours post-dose.
- Within ± 30 minutes of 8 hours post dose.

Each sample will consist of 1-2 mL per sample hence in the Part A (phase 1) we will request 12 samples for a total of 12-24 mL of peripheral blood.

8.5.2.2 **Part B:**

Plasma samples will be obtained at the following time points:

- Day 1 of Cycle 1:
  - Pre-dose
  - Within ± 15 minutes of 1 hour post-dose.
- Day 3 of Cycle 1:
  - Pre-dose (within 1-hour before AM dose).
  - Within ± 15 minutes of 1 hour post-dose.
- Day 10 of Cycle 1:
  - Pre-dose (within 1-hour before AM dose).
  - Within ± 15 minutes1 hour post-dose.

Each sample will consist of 1-2 mL per sample hence in the Part B (phase 2) we will request 6 samples for 6-12 mL of peripheral blood.

8.5.3 Sample Collection and Handling Instructions:

Blood samples (1-2 mL) will be collected in EDTA tubes from a peripheral vein. Collection from a central line is also acceptable. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.5.4 Sample Processing:

Blood collected into EDTA tubes should be gently mixed by immediately inverting the tubes. Blood samples will then be centrifuged immediately for 15 minutes in a refrigerated centrifuge set at 4 degrees C. After centrifugation (805 g for 15 min), remove the plasma using a transfer pipette and transfer the plasma into two separate cryovials or small (2-4) mL polypropylene screw-capped tubes. Next, immediately freeze the tubes at -80 degrees C and store until delivery to the Mayo Clinic (see section 8.5.6 for shipping instructions)

8.5.5 Sample Labeling:

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (Appendix X for Part A and Appendix XI for Part B), which must accompany the sample(s).

8.5.6 Sample Shipping Instructions:

Samples will be held until all samples have been obtained and then sent as a single batch. Batched samples should be sent frozen on dry ice by FedEx priority overnight to:

Dr. Joel Reid
Pharmacology Shared Resource
Guggenheim 17-37
Mayo Clinic
200 First street, SW

Rochester, MN 55905

Phone: 507-284-4303

A copy of the BAY 1895344 (elimusertib) Pharmacokinetics Study Form for Parts A and B (Appendix X for Part A and Appendix XI for Part B) should accompany the shipment and a second copy emailed to Dr. Reid (reid@mayo.edu). One copy of the Pharmacokinetics Study Forms used for either Parts A or B should be uploaded into RAVE.

Samples should only be shipped on a Monday-Wednesday to allow for weekday delivery. Avoid holiday shipments. Email the tracking number to Dr. Reid (reid@mayo.edu) at the time of sample shipment.

8.6 Tumor Tissue for Immunohistochemistry: ATM (Required)

8.6.1 Description of Studies:
Immunohistochemistry for ATM will be performed on pre-treatment tumor samples, using archival tumor tissue. This study will primarily investigate whether ATM loss predicts response to BAY 1895344 (elimusertib). Secondarily, we will evaluate the prevalence of ATM loss in certain pediatric tumors.

8.6.2 Sampling Schedule (See Appendix IX):

- Archival tumor tissue sample(s) must be submitted at time of enrollment, prior to the start of therapy.
- After the end of therapy, with any biopsy occurring within 30 days of end-of treatment.

NOTE: If no tissue is available prior to the start of therapy, the patient will still be eligible for therapy.

8.6.3 Sample Collection and Handling Instructions:
A minimum of 1 and a preference of 2, unstained slide of FFPE tumor tissue samples will be obtained at the above time points.

8.6.4 Sample Processing:
Samples can be processed at any institution. Cut tumor into 5µm sections and place, unstained, on a glass slide for conventional IHC. FFPE tumor blocks may alternatively be sent to the Kentsis lab if preferable. Samples can be stored prior to shipment, for up to 5 years, refrigerated at 4 ℃.

8.6.5 Sample Shipping Instructions:
Samples will be held until all samples have been obtained and then sent as a single batch kept cold using ice packs with overnight delivery to the address below. Include the corresponding copy of the completed PEPN2112 Tumor Tissue for Immunohistochemistry: ATM transmittal form (from RAVE) with each shipment.

Dr. Alex Kentsis
Kentsis Research Group
408 East 69 Street, ZRC-1845
New York, NY 10065, USA

Phone: 1-646-888-3557
E-mail: kentsisresearchgroup@gmail.com

Please include qualifying genomic testing report.

Friday collections are not permitted. Deliveries will be accepted Tuesday through Friday. Saturday and holiday shipments are not accepted. Please contact lab, prior to shipping.

8.7 Monitoring for Specific Toxicities

8.7.1 Growth Plate Toxicity:
Patients will have a plain AP radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.

b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained after cycle 1, every 3 cycles thereafter and at the end of study treatment.

NOTE: The end of study treatment observation is not required, if already obtained within the final month of therapy.

- Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and may undergo more frequent x-ray follow up as clinically indicated. MRI should be performed without contrast.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of BAY 1895344 (elimusertib) should be made after discussion with the Study Chair or Study Vice-Chair and DVL Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to BAY 1895344 (elimusertib). Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue BAY 1895344 (elimusertib) or not.

9.0 AGENT INFORMATION

9.1 BAY 1895344

(Elimusertib) NSC# (810486) IND# [redacted]

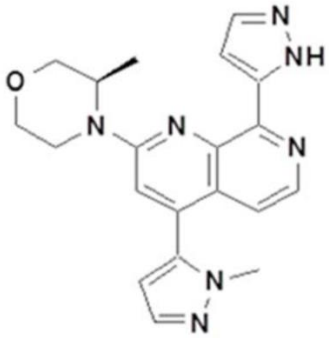
9.1.1 Structure and molecular weight:

BAY 1895344 (elimusertib) is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related (ATR) pathway. Activation of the ATR pathway may be critical for survival in tumors harboring defects in DNA repair or DNA damage signaling pathways.

Chemical Name: 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol5-yl)-1, 7-naphthyridine

Molecular Formula: C20H21N7O M.W.: 375 g/mol

Structure:



9.1.2 Supplied by:

BAY 1895344 (elimusertib) is supplied by Bayer and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

9.1.3 Formulation:

The agent is supplied as oral film-coated tablets.

Tablets will be packaged in bottles containing 18 tablets.

- 20 mg film-coated tablets are red and round with 6 mm diameter
- 10 mg film-coated tablets are red and round with 5 mm diameter

Tablet core components include active drug substance, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol, titanium dioxide, and ferric oxide red.

9.1.4 Storage:

Store at or below 25 °C. Do not freeze.

If a storage temperature excursion is identified, promptly return BAY 1895344 (elimusertib) to 25 °C or below and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Stability:
Shelf life stability studies are on-going. Dispense in original package.

9.1.6 Administration: See Treatment and Dose Modification sections of the protocol.

Swallow tablets immediately following removal from package. Take BAY 1895344 (elimusertib) one (1) hour before or two (2) hours after a meal with plenty of water.

9.1.7 Potential Drug Interactions:
No formal drug interactions studies have been conducted with BAY 1895344 (elimusertib) in humans.

In vitro, BAY 1895344 (elimusertib) is metabolized mainly by CYP3A4 and to a much lesser extent CYP1A1. BAY 1895344 (elimusertib) is not a P-gp or BCRP substrate. Strong inhibitors and inducers of CYP3A4 should be avoided.

BAY 1895344 (elimusertib) is a weak to moderate inhibitor of CYP3A4, 2C8, 2C9, and 2C19 *in vitro*. BAY 1895344 (elimusertib) had no significant inhibitory effect on CYP1A2, 2A6, 2B6, 2D6, and 2E1. *In vitro*, BAY 1895344 (elimusertib) was also shown to be an inducer of CYP3A4 and 2C19 but not 1A2. BAY 1895344 (elimusertib) is predicted to be a moderate inducer toward sensitive CYP3A4 substrates. CYP3A4 substrates with narrow therapeutic index should be avoided, and substrates of CYP2C8, 2C9, and 2C19 should be used with caution.

BAY 1895344 (elimusertib) was identified as an *in vitro* inhibitor of BCRP, P-gp, BSEP, OATP1B1, and OATP1B3. The risk for clinically relevant drug-drug interactions due to inhibition of BSEP is considered to be negligible but substrates of BCRP, P-gp, OATP1B1, and OATP1B3 should be used with caution.

Because of pH dependent solubility, antacid drugs, H2-blockers, and proton pump inhibitors may affect absorption and exposure of BAY 1895344 (elimusertib).

9.1.8 Patient Care Implications:
Based on the UV absorption properties of BAY 1895344 (elimusertib), patients should be instructed to use topical sun block and UV-blocking sunglasses on the days BAY 1895344 (elimusertib) is administered for 3 days after treatment with BAY 1895344 (elimusertib). Direct exposure of patients to sun light after administration should be avoided.

Both male and female patients of reproductive potential should use highly effective contraceptive measures throughout the duration of the study and for 3 months + 2 days for males and 6 months + 2 days for females after receiving the last dose of BAY 1895344 (elimusertib). Female patients must not breastfeed during treatment and until 4 months after last study drug administration.

9.1.9 Toxicities:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For
BAY 1895344 (NSC 810486)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 197 patients.* Below is the CAEPR for BAY 1895344.

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

Version 2.1, September 5, 2020

Adverse Events with Possible Relationship to BAY 1895344 (CTCAE 5.0 Term) [n= 197]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Diarrhea		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		

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

Adverse events reported on BAY 1895344 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BAY 1895344 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
GASTROINTESTINAL DISORDERS - Abdominal pain; Dysphagia
INFECTIONS AND INFESTATIONS - Shingles
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (medication error)
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hypophosphatemia
NERVOUS SYSTEM DISORDERS - Dysgeusia; Presyncope
PSYCHIATRIC DISORDERS - Irritability
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypotension

Note: BAY 1895344 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.10 Agent Ordering and Agent Accountability:
NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH BioSketch, Agent Shipment Form, If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Note: No starter supplies will be provided. Drug orders of BAY 1895344 should be placed with CTEP PBM after enrollment and treatment assignment to PEPN2112 with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

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

9.2 Clinical Drug Request

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account

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

9.3 Agent Inventory Records

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

9.3.1 Investigator Brochure Availability:

The current version(s) of the IB for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.3.2 Useful Links and Contacts:

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12)
b) Adverse Events requiring removal from protocol therapy (See Section 13).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 26 cycles of therapy.
f) Physician determines removal from protocol is in the patient's best interest.
g) Repeat eligibility studies are outside the parameters required for eligibility prior to the start of cycle 1 BAY 1895344 (elimusertib) (See Section 4.0).
h) Study is terminated by Sponsor.
i) Pregnancy
j) Development of secondary malignancy

Patients who are removed from protocol therapy during Cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.5 whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see Section 10.2). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) The fifth anniversary of the date the patient was enrolled on this study.
b) Withdrawal of consent for any required observations or data submission.
c) The patient does not receive protocol treatment after study enrollment.
d) Patient enrollment onto another COG study with therapeutic (anti-cancer) intent.
e) Lost to follow-up
f) Death.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Dose escalation (Part A) will require a minimum of 4 DLT-evaluable patients and a maximum of 12. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory solid tumors without restrictions on heme evaluability may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Therefore, a maximum of 23 patients is anticipated for Part A allowing for 2 dose levels, PK expansion, and 20% inevaluability. Review of the enrollment rate into previous COG early phase new agent studies indicates that 1-2 patients per month are available, which will permit completion of the study within 12-23 months.

In the unlikely event that both dose levels are expanded to 12 patients each (see section 11.2.2), the absolute maximum number of patients enrolled in Part A will be 38 which would require up to 38 months accounting for 2 dose levels, PK expansion, and 20% inevaluability.

The three disease-specific phase 2 cohort studies will require a minimum of 20 response-evaluable patients. The maximum number of patients will be 67 allowing for 20% inevaluability. This part of the study is expected to be completed within about 25 months assuming 1 patient per month per cohort is available. However, completion of enrollment to Part B3 (DDR) will not be required for termination of the study.

Overall, this study will plan to enroll up to 90 patients within 48 months.

11.2 Definitions

11.2.1 Evaluable for Adverse Events:

Any patient who receives at least one dose of BAY 1895344 (elimusertib) or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, during Cycle 1, patients not experiencing a DLT must receive at least 75% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and are not considered evaluable for dose limiting toxicity in Part A will be replaced.

11.2.2 Maximum Tolerated Dose:

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (eg, hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, PEP-CTN statistician, PEP-CTN committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will contribute towards the total number of DLTs observed at the RP2D/MTD during the dose escalation portion of the

study. If ≥ 1/3 of the cohort of patients at the RP2D/MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

- If required number of responses per the Simon two-stage design for expansion is not met for either the ARMS or EWS phase 2 cohorts whilst the PK expansion is still enrolling, the PK expansion will subsequently be closed to those patients.

11.3 Dose Escalation and Determination of MTD

Rolling Six Design

The rolling six phase 1 trial design will be used for the conduct of this study.[40] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*

6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.4 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of BAY 1895344 (elimusertib) will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of BAY 1895344 (elimusertib), patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

All these analyses will be descriptive and exploratory and hypothesis-generating in nature.

11.5 Study Design - Phase 2

Part B will include three separate, Phase 2 cohort studies. The three disease cohorts will include B1) Ewing sarcoma, B2) PAX3-FOXO1 ARMS, and B3) disease agnostic DDR. Data collected from patients from the dose escalation portion (Part A) and PK expansion portion, treated at the MTD/RP2D and who meet eligibility criteria for Part B of the study will be counted in the Phase 2 evaluation. The best response of disease to BAY 1895344 (elimusertib) will be examined separately for each cohort.

Parts B1 (Ewing sarcoma) and B2 (PAX3-FOXO1 Alveolar Rhabdomyosarcoma (ARMS)) will use the 10+10 Simon's optimal two stage design.

The two-stage design is illustrated below:

	Cumulative Number of Responses	**Decision**
Stage 1: Enter 10 evaluable patients	0	Terminate the trial: conclude the agent is ineffective.
	1 or more	Inconclusive result: Proceed to stage 2
Stage 2: Enter 10 additional evaluable patients	2 or less	Conclude the agent is ineffective.
	3 or more	Conclude the agent is effective.

We will consider BAY 1895344 (elimusertib) not of sufficient interest for further evaluation in a disease category if the true response rate is ≤5% and of sufficient activity if the true response rate is ≥25%. If BAY 1895344 (elimusertib) has a true response rate 5%, the rule described above will identify it of sufficient activity for further study with probability 7% (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If BAY 1895344 (elimusertib) has a true response rate

25%, the rule described above will identify it of sufficient activity for further study with probability 88% (power).

Part B3 (DNA Damage repair (DDR)) will use the 7+6 Simon's two stage design if sufficient enrollment is observed in the study.

The two stage design is illustrated below:

	Cumulative Number of Responses	Decision
Stage 1: Enter 7 evaluable patients	0	Terminate the trial: conclude agent is ineffective.
	1 or more	Inconclusive result: Proceed to stage 2
Stage 2: Enter 6 additional evaluable patients	1 or less	Conclude the trial because the agent is ineffective.
	2 or more	Conclude the trial because the agent is effective.

We will consider BAY 1895344 (elimusertib) not of sufficient interest for further evaluation in a disease category if the true response rate is ≤5% and of sufficient activity if the true response rate is ≥25%. If BAY 1895344 (elimusertib) has a true response rate 5%, the rule described above will identify it of sufficient activity for further study with probability 11% (type I error), and the trial will have an expected sample size of 8.8 patients with 70% probability of early termination. If BAY 1895344 (elimusertib) has a true response rate 25%, the rule described above will identify it of sufficient activity for further study with probability 81% (power to reject the null hypothesis P=0.05).

Response in all patients, regardless of age group, with solid tumors will be determined according to RECIST or appropriate disease-specific response criteria as defined in the protocol as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) or as described in Section 12.0 for other categories or response assessment, and reported as final results.

11.6 Method of Analysis - Phase 2

Response in Part B patients will be determined as defined in Section 12.0. A responder is defined as a patient who achieves a best confirmed response of PR or CR on the study. Response is defined relative to baseline disease. A report on the efficacy assessment will be posted on the completed cohorts as part of the semi-annual study committee meeting book report.

The response rate will be estimated by the uniform minimum variance unbiased estimate[41] with one-sided p-value and confidence interval.[42] Each disease cohort will be separately analyzed without adjusting for multiple hypothesis tests.

Toxicities for patients will be described separately. Every effort will be made to accrue the number of patients needed to evaluate efficacy according to the schema in Section 11.5. For strata not appropriately filled, descriptive statistics will be employed to describe outcomes.

11.7 Evaluability for Response

See Section 12.2.1.2 for information regarding evaluability for response.

11.8 Evaluability for Toxicity

All patients who experience DLT or receive at least at least 75% of the planned dose of BAY 1895344 (elimusertib) during cycle 1 according to protocol guidelines will be evaluable for toxicity.

11.9 Evaluability for Pharmacokinetic Analysis

All eligible patients who receive BAY 1895344 (elimusertib) and have at least one post treatment PK sample will be considered in the evaluation of pharmacokinetics

11.10 Gender and Minority Accrual Estimates

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG early phase studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

The gender and minority distribution of the study population is expected to be:

	PLANNED ENROLLMENT REPORT				
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian / Alaska Native	0	0	0	0	0
Asian	2	3	0	0	5
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	6	6	1	0	13
White	25	35	6	5	71
More Than One Race	0	0	0	0	0
Total	**34**	**44**	**7**	**5**	**90**

This distribution was derived from enrollment observed in prior COG studies.

11.11 Analysis of the Pharmacokinetic Parameters

A descriptive analysis of pharmacokinetic (PK) parameters of BAY 1895344 (elimusertib) will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit). All these analyses will be descriptive and exploratory and hypotheses generating in nature.

11.12 Analysis of Biological and Correlative Endpoints

A descriptive analysis of biomarkers will assess associations with disease response. The parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit). All these analyses will be descriptive and exploratory and hypotheses generating in nature.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v.5.0' is understood to represent the most current version of CTCAE v.5.0 as referenced on the CTEP website.

12.2 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 and Therapy Delivery Maps for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

See Appendix XIII – Response Criteria for Solid Tumors, for imaging guidelines on solid tumors (measurable versus evaluable disease) in addition to disease assessment and imaging guidelines for Ewing sarcoma, PAX3-FOXO1 ARMS, and DDR.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[43] Key points are that 5 target lesions are identified and that changes in the largest diameter (unidimensional measurement) of the tumor lesions but the shortest diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for toxicity:

All patients who experience a cycle 1 DLT or receive at least 75% of the planned dose will be evaluable for toxicity from the time of their first treatment with BAY 1895344 (elimusertib). Enrolled patients who have not received any treatment will not be considered evaluable for toxicity.

12.2.1.2 Evaluable for objective response:

All patients who receive at least one dose of BAY 1895344 (elimusertib) will be evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-

responders. The evaluation period for determination of the best response will be 6 treatment cycles. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally. Centers will be notified by the PEP-CTN about requests for scans of patients with CR, PR, or long-term stable disease. See Section 8.4 regarding shipping instructions.

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

12.3 Best Response

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

Table 4. Sequences of overall response assessments with corresponding best response per RECIST 1.1.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the adverse (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: Grade the adverse event using the NCI CTCAE v.5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

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

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

- The NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events (i.e., a hospital visit where a patient is admitted for observation or minor treatment such as hydration and released in less than 24 hours). Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Early Phase Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.10 of the protocol. Additional protocol-specific exceptions to expedited reporting of serious adverse events are the toxicities in bold font listed under the drug information section of the protocol (Section 9.1).

  As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A and B) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://ctepcore.nci.nih.gov/ctepaers/pages/task.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at https://ctepcore.nci.nih.gov/ctepaers/pages/task.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at https://ctepcore.nci.nih.gov/ctepaers/pages/task.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Email supporting documentation to the PEP-CTN Study Assigned Research Coordinator. ALWAYS include the ticket number on all faxed documents.

For COG held IND studies, only email the Research Coordinator; do not fax CTEP.

13.4 Specific Examples for Expedited Reporting

13.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug:

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

13.4.2 Persistent or Significant Disabilities/Incapacities:

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI or non-NCI IND/IDE since these are considered serious AEs.

13.4.3 Reportable Categories of Death:

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

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

Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring **greater than 30 days** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

13.4.3 Secondary Malignancy:

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

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms in the following section.

13.4.3.1 Reporting Secondary AML/MDS

All cases of AML and MDS that occur in patients following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

13.4.4 Second Malignancy:

A **second malignancy** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

13.4.5 Pregnancy, Pregnancy Loss, and Death Neonatal:

Note: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, should be completed and emailed to the PEP-CTN Study Assigned Research Coordinator along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.4.5.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal**

conditions - Other (pregnancy)" under the **"Pregnancy, puerperium and perinatal conditions"** SOC.

Pregnancy needs to be followed until the outcome is known if the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.4.5.2 Pregnancy Loss (Fetal Death)
Pregnancy loss is defined in CTCAE as "Death in utero" Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy, loss"** under the **"Pregnancy, puerperium and perinatal conditions"** SOC. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.4.5.3 Death Neonatal
Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth"* should be reported expeditiously, as **Grade 4 "Death neonatal" under the "General disorders and administration" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.4.6 Syndrome Reporting:
Unless otherwise specified in this protocol, syndromes should be reported as a single event using the CTCAE term for the composite syndrome, and not as the individual events that make up the syndrome. For example, Tumor Lysis Syndrome should be reported under the composite definition rather than reporting the component events (hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) separately.

13.5 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG PEP-CTN case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.5.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.5.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.5.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.5.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing".

13.5.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.6 Other Recipients of Adverse Event Reports

13.6.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 9.1.10) should be reported at the end of each cycle using the forms provided in the CRF packet.

13.6.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.6.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Therapy Delivery Maps (TDMs), Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the PEP-CTN Operations and Data/Statistics Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

Data Mapping Utility (DMU) Reporting Complete

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. More information on the DMU is available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm. **DMU reporting is not a responsibility of institutions participating in this trial.**

14.3 CRADA/CTA/CSA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property

rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

14.4 Monitoring

On-site, retrospective source data verification is completed by Theradex on an annual basis for 100% of COG PEP-CTN patients enrolled in early phase clinical trials.

This study will additionally include central monitoring as part of data review. Source documents will be uploaded via CTSU's Source Document Portal. (See Appendix II for details).

14.5 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the Data and Safety Monitoring Committee.

14.5.1 Data and Safety Monitoring Committee:

This study will be monitored in accordance with the Children's Oncology Group PEP-CTN policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG PEP-CTN Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG member's Web site.

14.5.2 Monitoring by the Study Chair and the Steering Committee:

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

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APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

IRB Approval

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

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

Additional Requirements

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

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

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

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

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

Checking Your Site's Registration Status

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

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

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

Requirements for PEPN2112 Site Registration:

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification, and/or Protocol Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

Delegation of Tasks Log

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study.

To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

Data Submission / Data Reporting

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

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

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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

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

Rave CTEP-AERS Integration

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

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

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

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

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

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

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

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

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

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

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

Data Quality Portal

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

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

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

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

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

Central Monitoring

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

APPENDIX II: PROTOCOL CENTRAL MONITORING PLAN

Central monitoring will be required for all patients enrolled at each site. All documents must be uploaded with 2 weeks of the corresponding time point or cycle.

Monitored Data	Protocol Section	CRF Question/ Data Element	Monitoring Conditionality	Source document	CTSU Document Type	Time point
Eligibility						
Confirmation of eligible diagnosis	4.1.5	*Does patient have histologic verification of the malignancy at the indicated time point?*	**Required**	E.g., clinical note, laboratory test report, pathology report, etc.	Clinical Note, Laboratory Report or Pathology report	Enrollment
Performance Level	4.1.9	*ECOG performance status*	**Required**	E.g., clinical note, eligibility checklist	Clinical Note, Eligibility Determination Checklist	
Adequate Bone Marrow function	4.1.11.1	*Does patient have adequate bone marrow function?*	**Required**	Laboratory test report	Laboratory Report	
Adequate Renal Function	4.1.11.2	*Does patient have adequate renal function?*	**Required**	Laboratory test report	Laboratory Report	
Adequate Neurologic Function	4.1.11.4	*Does patient have adequate neurologic function?*	**Required**	E.g. clinical note	Clinical Note	
Date of Informed Consent	3.5	*Date of Informed Consent*	**Required**	Informed consent (redacted signature pages with dates)	Informed Consent	
Drug Administration Elements						
Total **BAY 1895344 (elimusertib)** dose	5.1	*Total Dose:*	**Required**	Medication administration record	Treatment Administration Document	Cycle 1 Cycle 3
Disease Evaluation Elements						
Tumor Disease Evaluation	8.1	*Was the patient's disease status evaluated during this reporting period?*	**Required**	E.g. CT report, MRI report, FDG-PET report, PET-CT report	Scan Reports	Cycle 1 Cycle 3
Adverse Event Capture						

Labs/reports documenting protocol specific CTEP-AERS reportable events	13.0	*Has an Adverse Event Expedited Report been submitted?*	**Conditional:** If response is YES, CM is required	E.g., hospital admission report, laboratory reports, etc.	Relevant Document	Cycle 1 Cycle 3

Addressing Monitoring Findings

In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan to COGRegComp@childrensoncologygroup.org within two weeks.

In the event of significant repeated major deviations from the protocol, COGQA, in consultation with the study chair, may recommend that COG leadership suspend accrual at the site.

APPENDIX III: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is NOT an all-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
abemaciclib	atazanavir	aprepitant	apalutamide	bosentan
acalabrutinib[5]	boceprevir	conivaptan	barbiturates	cenobamate
alfentanil[4,5]	clarithromycin	crizotinib	carbamazepine	dabrafenib
alprazolam[5]	ceritinib	diltiazem	enzalutamide	efavirenz
amiodarone[4]	cobicistat	dronedarone	fosphenytoin	eslicarbazepine
amlodipine	danoprevir/ritonavir	duvelisib	lumacaftor/	etravirine
aprepitant/fosaprepitant	darunavir	erythromycin	ivacaftor	lorlatinib
atorvastatin	delavirdine	fedratinib	mitotane	modafinil
avanafil[5]	elvitegravir/ritonavir	fluconazole	phenobarbital	nafcillin
axitinib	grapefruit[3]	fosamprenavir	phenytoin	rifabutin
bortezomib	grapefruit juice[3]	fosnetupitant	primidone	rifapentin
bosutinib[5]	idelalisib	grapefruit[3]	rifampin	
brexpiprazole	indinavir/ritonavir	grapefruit juice[3]	St. John's wort	
brigatinib	itraconazole	imatinib		
budesonide[5]	ketoconazole	isavuconazole		
buspirone[5]	lopinavir/ritonavir	lefamulin		
cabozantinib	nefazodone	letermovir		
calcium channel blockers	nelfinavir	mifepristone		
cisapride	paritaprevir/ritonavir/	netupitant		
citalopram/escitalopram	ombitasvir +/- dasabuvir	nilotinib		
cobimetinib[5]	posaconazole	ribociclib		
colchicine[5]	ritonavir	verapamil		
conivaptan[5]	saquinavir			
copanlisib	telaprevir			
crizotinib	telithromycin			
cyclosporine[4]	tipranavir/ritonavir			
dabrafenib	tucatinib			
dapsone	voriconazole			
darifenacin[5]				
darunavir[5]				
dasatinib[5]				
dexamethasone[2]				
diazepam				
dihydroergotamine				
docetaxel				
doxorubicin				
dronedarone[5]				
ebastine[5]				
eletriptan[5]				
eliglustat[5]				
eplerenone[5]				
ergotamine[4]				
erlotinib				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
gefitinib				

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
haloperidol				
ibrutinib[5]				
idelalisib				
imatinib				
indinavir[5]				
irinotecan				
isavuconazole[5]				
itraconazole				
ivacaftor				
ketoconazole				
lansoprazole				
lapatinib				
lomitapide[5]				
lorlatinib				
losartan				
lovastatin[5]				
lurasidone[5]				
macrolide antibiotics				
maraviroc[5]				
medroxyprogesterone				
methadone				
midazolam[5]				
midostaurin[5]				
modafinil				
naloxegol[5]				
nefazodone				
nilotinib				
nisoldipine[5]				
olaparib				
ondansetron				
osimertinib				
paclitaxel				
palbociclib				
pazopanib				
pimozide[5]				
quetiapine[5]				
quinidine[4]				
regorafenib				
rilpivirine[5]				
rivaroxaban[5]				
romidepsin				
saquinavir[5]				
sildenafil[5]				
simvastatin[5]				
sirolimus[4,5]				
sonidegib				
sunitinib				
tacrolimus[4,5]				
tamoxifen				
tadalafil[5]				
telaprevir				
temsirolimus				
teniposide				
tetracycline				

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
ticagrelor[5] 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.
[2]Refer to Section 4.2.2.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX IV: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for SGOT is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX V: BAY 1895344 (elimusertib) DOSING NOMOGRAM

Patients < 18 years of Age Part A and B:

Dose Level 1: BAY 1895344 (elimusertib) Dose Assignment: 24 mg/m^2/dose PO BID			
BSA (m^2)	**Starting Dose Dose to be administered (PO) 3 days on 4 days off per week**	**Dose Reduction Dose to be administered (PO) 3 days on 4 days off per week**	**Percent Reduction**
0.74-0.94	20 mg BID	20 mg Q AM and 10 mg Q PM	25%
0.95-1.15	30 mg Q AM and 20 mg Q PM	20 mg Q AM and 10 mg Q PM	40%
1.16-1.35	30 mg BID	20 mg BID	35%
1.36-1.56	40 mg Q AM and 30 mg QPM	30 mg Q AM and 20 mg Q PM	30%
≥ 1.57	40 mg BID	30 mg BID	25%

Dose Level -1: BAY 1895344 (elimusertib) Dose Assignment: 18 mg/m^2/dose PO BID			
BSA (m^2)	**Starting Dose Dose to be administered (PO) 3 days on 4 days off per week**	**Dose Reduction Dose to be administered (PO) 3 days on 4 days off per week**	**Percent Reduction**
0.74-0.94	20 mg Q AM and 10 mg Q PM	10 mg BID	35%
0.95-1.35	20 mg BID	20 mg Q AM and 10 mg Q PM	25%
1.36-1.56	30 mg Q AM and 20 mg Q PM	20 mg Q AM and10 mg Q PM	40%
≥ 1.57	30 mg BID	20 mg BID	35%

Patients ≥18 years of age on Part B receiving the starting dose of 40 mg BID, the dose reduction for toxicity should be to 30 mg BID, 3 days on 4 days off per week (25% dose reduction).

APPENDIX VI: MEDICATION DIARY FOR BAY 1895344 (elimusertib)

COG Patient ID:_____ **Acc#**_____
Institution:_____
Please do not write patient names on this form.

Complete each day with the time and dose given for BAY 1895344 (elimusertib). If a dose is not due or is accidentally skipped leave that day blank. **Make note of other drugs and supplements taken under the Comments section below.** BAY 1895344 (elimusertib) tablets should not be crushed but should be swallowed whole. If you vomit after taking a dose, the dose should NOT be repeated. If you miss or forget a dose, it can be taken up to 8 hours before the next dose is due. Otherwise the dose should be skipped. If tablet is broken and the powder of the tablet gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. BAY 1895344 (elimusertib) should be taken on an empty stomach (1 hour before or 2 hours after a meal) with plenty of water. Add the dates to the calendar below and return the completed diary and the empty bottle or any leftover tablets the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE			***Number of BAY 1895344 (elimusertib) tablets***		***Comments***
	Date	***Time***	**10 mg**	**20 mg**	
Day 1	*1/15/19*	*8:30 AM*	1	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Start Date: |__/__|__/__|__/__|
End Date: | / | / | / | Dose Level: _____mg/m^2/dose Part of Study:

WEEK 1	**Date**	**Time**		**# of 10 and/or 20 mg tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				10 mg	**20 mg**	
				AM# **PM#**	**AM#** **PM#**	
				# of 10 and/or 20 mg tablets taken twice daily		
				10 mg	**20 mg**	
Day 1			**AM**			
			PM			
Day 2			**AM**			
			PM			
Day 3			**AM**			
			PM			
WEEK 2	**Date**	**Time**		**# of 10 and/or 20 mg tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				10 mg	**20 mg**	
				AM#___ **PM#**	**AM#___** **PM#**	
				# of 10 and/or 20 mg tablets taken twice daily		
				10 mg	**20 mg**	
Day 8			**AM**			
			PM			
Day 9			**AM**			

			PM			
Day 10			AM			
			PM			
WEEK 3	Date	Time		# of 10 and/or 20 mg tablets prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				10 mg	20 mg	
				AM#___ PM#	AM#___ PM#	
				# of 10 and/or 20 mg tablets taken twice daily		
				10 mg	20 mg	
Day 15			AM			
			PM			
Day 16			AM			
			PM			
Day 17			AM			
			PM			
WEEK 4	Date	Time		# of 10 and/or 20 mg tablets prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				10 mg	20 mg	
				AM#___ PM#	AM#___ PM#	
				# of 10 and/or 20 mg tablets taken twice daily		
				10 mg	20 mg	
Day 22			AM			
			PM			
Day 23			AM			
			PM			
Day 24			AM			
			PM			

If this form will be used as a source document, the site personnel who administered the study drug must sign and date this form below:

Signature: _____ Date: _____
(site personnel who reviewed the diary)

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A Phase 1/ 2 Study of BAY 1895344 (elimusertib) in Pediatric Patients with Relapsed or Refractory Solid Tumors

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.

3. Children who are part of this study will be treated with a cancer-fighting medicine called BAY 1895344 (elimusertib). You will have some tests and check-ups done more often than if you weren't part of the study. Some of these tests will require extra needle sticks for blood. The doctors want to see if BAY 1895344 (elimusertib) will make children with your type of cancer get better. We don't know if BAY 1895344 (elimusertib) will work well to get rid of your cancer. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that BAY 1895344 (elimusertib) may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from BAY 1895344 (elimusertib) than other treatments. Other things may happen to you that we don't yet know about.

6. You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. The blood samples would be taken when other standard blood tests are being performed and we are asking for extra tumor tissue already taken and stored during your diagnosis or removed with procedures that happen while you are on the study, so there would be no extra procedures. You and your family can still take part in this study even if you don't allow us to collect the extra blood or tumor tissue samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A Phase 1/ 2 Study of BAY 1895344 (elimusertib) in Pediatric Patients with Relapsed or Refractory Solid Tumors

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.

3. Children and teens who are part of this study will be treated with a cancer-fighting medicine called BAY 1895344 (elimusertib). You will also have some tests and exams done more often while you are in this study. Some of these tests will require extra needle sticks for blood tests. The doctors want to see if BAY 1895344 (elimusertib) will make children with your type of cancer get better. We don't know if BAY 1895344 (elimusertib) will work well to get rid of your cancer. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that BAY 1895344 (elimusertib) may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from BAY 1895344 (elimusertib) than other treatments. Other things may happen to you that we don't yet know about.

6. You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. The blood samples would be taken when other standard blood tests are being performed and we are asking for extra tumor tissue already taken and stored during your diagnosis or removed with procedures that happen while you are on the study, so there would be no extra procedures. You and your family can still be treated on this study even if you don't allow us to collect the extra blood or tumor tissue samples for research.

APPENDIX VIII: BIOMARKER STUDIES

Phase 1 (Part A):

Time Point	Specimen and Quantity	Send Specimens to:
Baseline		
	• *1 Archival FFPE tumor block or 1-2 unstained slides of archival tumor tissue samples for ATM IHC (Required)*[1] • *1 Archival FFPE tumor block (can be the same block as previous bullet) or 5-8 unstained slides for other IHC studies (Optional)* [1] • *1-2 snap-frozen tumor blocks of any size*[1] *(optional size for WGS and ALT (Optional)* [2] • *2-4 mL blood in purple top EDTA tube for control blood (Optional)*[3]	*Dr. Kentsis's Lab*
	• *~10 mL plasma in purple top EDTA tube for ALT ctDNA (Optional)*	*Dr. Reynold's Lab*
	• *Archival FFPE tumor block or 1 H&E stained slide (3-5 µm) and 10 unstained, uncharged, air-dried slides (10 µm) (Optional)*	*Biopathology Center Nationwide Children's Hospital*
Cycle 1, Day 1		
	• *5-10 mL blood in purple top EDTA tube for five required PK levels (Required)* • *1-2 mL blood in purple top EDTA for 12 hour trough PK levels(Optional)*	*Dr. Reid's Lab*
Cycle 1, Day 3		
	• *2-4 mL blood in purple top EDTA tube (Required)*	*Dr. Reid's Lab*
Cycle 1, Day 10		
	• *5-10 mL blood in purple top EDTA tube for five required PK levels (Required)* • *1-2 mL blood in purple top EDTA for 12 hour trough PK levels(Optional)*	*Dr. Reid's Lab*
Any biopsy occurring on-study or within 30 days of end-of treatment		
	• *Archival FFPE tumor block or 2up to 10 unstained slides, cut into 5 micron sections for each slide (optional)* • *1 snap-frozen tumor block of any size (optional)*	*Dr. Kentsis's Lab*

[1]FFPE tumor blocks can be used as an alternative for unstained slides
[2]Ideally 1 from diagnosis, 1 from relapse

[3]Control blood for WGS is collected once at any time, but preferably at the same time as the frozen tumor blocks

Phase 2 (Part B):

Time Point	Specimen and Quantity	Send Specimens to:
Baseline		
	• *1 Archival FFPE tumor block or 1-2 unstained slides of archival tumor tissue samples for ATM IHC (Required)[1]* • *1 Archival FFPE tumor block (can be the same block as previous bullet) or 5-8 unstained slides for other IHC studies (Optional) [1]* • *1-2 snap-frozen tumor blocks of any size for WGS and ALT (Optional) [2]* • *2-4 mL blood in purple top EDTA tube for control blood (Optional)[3]*	*Dr. Kentsis's Lab*
	• *~10 mL plasma in purple top EDTA tube for ALT ctDNA (Optional)*	*Dr. Reynold's Lab*
	• *Archival FFPE tumor block or 1 H&E stained slide (3-5 µm) and 10 unstained, uncharged, air-dried slides (10 µm) (Optional)*	*Biopathology Center Nationwide Children's Hospital*
Cycle 1, Day 1		
	• *2-4 mL blood in purple top EDTA tube for PK levels (Required)*	*Dr. Reid's Lab*
Cycle 1, Day 3		
	• *2-4 mL blood in purple top EDTA tube for PK levels (Required)*	*Dr. Reid's Lab*
Cycle 1, Day 10		
	• *2-4 mL blood in purple top EDTA tube for PK levels (Required)*	*Dr. Reid's Lab*
Any biopsy occurring on-study or within 30 days of end-of treatment		
	• *Archival FFPE tumor block or up to 10 unstained slides, cut into 5 micron sections for each slide (optional)* • *1 snap-frozen tumor block of any size (optional)*	*Dr. Kentsis's Lab*

[1]FFPE tumor blocks can be used as an alternative for unstained slides
[2]Ideally 1 from diagnosis, 1 from relapse
[3]Control blood for WGS is collected once at any time, but preferably at the same time as the frozen tumor blocks

APPENDIX IX: CORRELATIVE STUDIES GUIDE

Correlative Studies	Appx.	Volume per Sample (ml)	Total Volume (ml)
ATM Tumor Tissue	2	0	0
Tumor Whole Genome Sequencing Tumor Tissue	3	0	0
Tumor Whole Genome Sequencing Control Blood	1	2-4 mL	2-4 mL
R-Loops & PGBD5 Tumor Tissue	1	0	0
pH2AX, pKAP1 and pATR Tumor Tissue	1-2	0	0
Circulating tumor DNA to evaluate for ALT	1	~10 mL	~10 mL
Archival Tumor Tissue for Biobanking	1	0	0
Required Pharmacokinetics for Patients on Part A	12	~2	~24
Required Pharmacokinetics for Patients on Part B	6	~2	~12
Optional Pharmacokinetics for Patients on Part A	2	~2	~4
Total Blood Volume =			~52-54 mL

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]
	Tissue-based Biomarkers						
1	ATM	IHC CLIA: N	Exploratory Correlative See section 8.6.1 for purpose.	FFPE Tumor	Pre-dose, archival tumor tissue, post treatment study	M	Dr. Alex Kentsis (MSKCC, New York City, NY) kentsisa@ mskcc.org

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]
2	Tumor Whole Genome Sequencing	Whole Genome Sequencing CLIA: N	Exploratory Correlative See section 8.3.1 for purpose.	Frozen Tumor	Pre-dose, archival tumor tissue, at relapse, post treatment study	O	Dr. Alex Kentsis (MSKCC, New York City, NY) kentsisa@ mskcc.org
3*	pH2AX, pKAP1 and pATR	IHC CLIA: N	Exploratory Correlative See section 8.3.3 for purpose	FFPE Tumor	Pre-dose, archival tumor tissue	O	Dr. Alex Kentsis (MSKCC, New York City, NY) kentsisa@ mskcc.org
4*	R-loops PGBD5	IHC CLIA: N	Exploratory Correlative See section 8.3.2 for purpose	FFPE Tumor	Pre-dose, archival tumor tissue	O	Dr. Alex Kentsis (MSKCC, New York City, NY) kentsisa@ mskcc.org
5	ALT	RT-PCR for TERT and C-circle assay CLIA: N	Exploratory Correlative See section 8.3.1 for purpose	FFPE Tumor	Pre-dose archival tumor tissue, post-dose (Analyzed with WGS tumor tissue)	O	Dr. Charles Patrick Reynolds (COGCCXR, Lubbock, TX) patrick.reynolds@ttuhsc.edu
6.	Archival Tumor Tissue for Biobanking	Archival Tumor Tissue CLIA: Y	Exploratory Correlative See Section 8.3.6	FFPE Tumor or slides	Pre-dose archival tumor tissue	O	Biopathology Center Nationwide Children's Hospital BPCBank@nationwidechildrens.org
	Blood-based Biomarkers						
1	ALT	ctDNA CLIA: N	Exploratory Correlative See section 8.3.4 for purpose	Blood (pre-dose)	Pre-Dose	O	Dr. Charles Patrick Reynolds (COGCCXR, Lubbock, TX) patrick.reynolds@ttuhsc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]
2	ALT	RT-PCR for TERT and C-circle assay CLIA: N	Exploratory Correlative See section 8.3.1 for purpose	Blood (pre-dose)	Pre-Dose (Analyzed with WGS blood samples)	O	Dr. Charles Patrick Reynolds (COGCCXR, Lubbock, TX) patrick.reynolds@ttuhsc.edu
2	Tumor Whole Genome Sequencing	Whole Genome Sequencing CLIA: N	Exploratory Correlative See section 8.3.1 for purpose.	Blood (pre-dose)	Pre-Dose	O	Dr. Alex Kentsis (MSKCC, New York City, NY) kentsisa@ mskcc.org
3.	Pharmacokinetics	Pharmacokinetics CLIA: Y	Integrated Correlative See section 8.5.1 for purpose	Blood	Part A: Cycle 1, Day 1; Cycle 1, Day 3; Cycle 1, Day 10 Part B: Cycle 1, Day 1; Cycle 1, Day 3; Cycle 1, Day 10	M	Dr. Joel Reid Pharmacology Shared Resource reid@mayo.edu
4.	Pharmacokinetics	Pharmacokinetics CLIA: Y	Exploratory Correlative	Blood	Part A: Cycle 1, Day 1; Cycle, 1, Day 10	O	Dr. Joel Reid Pharmacology Shared Resource reid@mayo.edu

* Will prioritize pH2AX, pKAP1 and pATR over R-loops and PGBD5 if there are pre-/post- matched samples. If not, will prioritize R-Loops and PGBD5.

APPENDIX X: PART A PHARMACOKINETIC WORKSHEET (SAMPLE)

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient BSA: _____m2 Dose: _____ mg/m2 Dose given prior to PK sampling: _____ mg

Blood samples will be collected in consenting patients in EDTA tubes at the following time points:

Peripheral blood samples for PK analysis should be obtained as follows:

Record the exact date and time the sample is drawn.

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Cycle 1, Day 1	Pre-dose	___/___/___	|__|__| : |__|__|
2	Cycle 1, Day 1	1 hour post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|
3	Cycle 1, Day 1	2 hours post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 1	4 hours post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|
5	Cycle 1, Day 1	8 hours post-dose (± 30 minutes)	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 1*	12 hours post-dose (± 30 minutes)	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 1	**Date:**___/___/___	**Time Dose Given:** |__|__| : |__|__| **Dose Given:** _____**mg**

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	Cycle 1, Day 3	Pre-dose (within 1 hour before AM dose)	___/___/___	|__|__| : |__|__|
8	Cycle 1, Day 3	1 hour post-dose	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 3	**Date:**___/___/___	**Time Dose Given:** |__|__| : |__|__| **Dose Given:**_____ **mg**

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
9	Cycle 1, Day 10	Pre-dose (within 1 hour before AM dose)	___/___/___	|__|__| : |__|__|
10	Cycle 1, Day 10	1 hour post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|
11	Cycle 1, Day 10	2 hours post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|
12	Cycle 1, Day 10	4 hours post-dose (± 15 minutes)	___/___/___	|__|__| : |__|__|

13	Cycle 1, Day 10	8 hours post-dose (± 30 minutes)	___/___/___	|__|__| : |__|__|
14	Cycle 1, Day 10*	12 hours post-dose (± 30 minutes)	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 10	**Date:**___/___/___	**Time Dose Given:** **Dose Given: _____ mg** |__|__| : |__|__|

***12-hour PK collection on cycle 1, day 1 and cycle 10, day 1 is optional, and if obtained, should be drawn before the PM dose.**

One copy of this PK Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.5.2, in addition to detailed guidelines for packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX XI: PART B PHARMACOKINETIC WORKSHEET (SAMPLE)

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient BSA: _____m2 Dose: _____ mg/m2 Dose Given Prior to PK sampling: _____ mg

Blood samples will be collected in consenting patients in EDTA tubes at the following time points:

Peripheral blood samples for PK analysis should be obtained as follows:

Record the exact date and time the sample is drawn.

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Cycle 1, Day 1	Pre-dose	___/___/___	|__|__| : |__|__|
2	Cycle 1, Day 1	1 hour post-dose	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 1	**Date:**___/___/___	**Time Dose Given:** |__|__| : |__|__| **Dose Given:** _____ **mg**

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Cycle 1, Day 3	Pre-dose (within 1 hour before AM dose)	___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 3	1 hour post-dose	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 3	**Date:**___/___/___	**Time Dose Given:** |__|__| : |__|__| **Dose Given:** _____ **mg**

Sample ID	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 1, Day 10	Pre-dose (within 1 hour before AM dose)	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 10	1 hour post-dose	___/___/___	|__|__| : |__|__|

BAY 1895344 (elimusertib) BID Dose on Cycle 1, Day 10	**Date:**___/___/___	**Time Dose Given:** |__|__| : |__|__| **Dose Given:** _____ **mg**

One copy of this PK Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.5.2, in addition to detailed guidelines for packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:
Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX XII: RESPONSE CRITERIA FOR LYMPHOMA

Response Criteria for Non-Hodgkin Lymphoma

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric Non-Hodgkin Lymphoma Criteria[44], with modification from the Lugano classification.[45]

Disease Parameters

Measurable disease: A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measured disease: All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

Target lesions: For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks prior to the beginning of the treatment.

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

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

Conventional CT and MRI: The major response designations will be established by CT or MRI of involved sites in conjunction with morphologic evaluation of bone marrow (BM) if involved at diagnosis. With growing concerns about the risks of cumulative ionizing radiation exposure to children from CT, MRI could be considered as an alternative to CT for evaluating non-pulmonary disease sites. eg, assessment of abdominal/pelvic disease. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the response guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Pulse sequences should include at a minimum, axial and coronal fat-saturated FRFSE-T2, coronal T1 and axial and coronal post-gadolinium fat-saturated T1 weighted imaging. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

Tumor markers: There will be no use of tumor markers to assess response in the protocol. EBV qPCR of peripheral blood PBMCs will be performed centrally to measure the presence of active viral replication and disease activity but results will not be used to stratify assignment to treatment arms.

FDG-PET: For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric Non-Hodgkin Lymphoma Response Criteria.

Response Criteria

Evaluation of Measurable Disease

- **Complete Response (CR):** Disappearance of all disease. CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative.
- **CR unconfirmed (Cru):** Residual mass is negative by FDG-PET; no new lesions by imaging examination; no new and/or progressive disease elsewhere
- **Partial Response (PR):** 50% decrease in SPD (the sum of the products of the largest diameter and the perpendicular diameter for a tumor mass) on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells
- **Progressive Disease (PD):** For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM
- **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.

Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)

- **Complete Response (CR):** Absent non-measured lesions.
- **Partial response (PR):** Absent/normal, regressed, lesions, but no increase.
- **Stable Disease (SD):** No increase consistent with progression
- **Progressive Disease (PD):** New or clear progression of preexisting non-measured lesions.

Evaluation of organ enlargement

- **Complete Response (CR):** Regress to normal
- **Partial response (PR):** Spleen must have regressed by > 50% in length beyond normal
- **Stable Disease (SD):** No increase consistent with progression
- **Progressive Disease (PD):** In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline.

New or recurrent splenomegaly

Duration of Response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met.

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

Response Review
Response will be as per institutional evaluations.

Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.3 from a sequence of overall response assessments.

Response Criteria for Hodgkin Lymphoma

Baseline Imaging Lesion Evaluation at Diagnosis
Imaging guidelines and response criteria have been revised from previous COG protocols, including AHOD0031, AHOD0431, AHOD0831, CCG 5942, CCG 59704, POG 9425, and POG 9426 and incorporate International Lymphoma Working Group's revised recommendations and the Euro net consortium guidelines for malignant lymphoma.

Note: The determination of RRL or SRL and CR will be based on interim and end-of-therapy FDG-PET response, and will not be based on size change on CT, with the exception of macronodular splenic involvement. CT-based size criteria will still be used in the determination of PD and in cases of macronodular splenic involvement. As such, diagnostic quality contrast-enhanced CT imaging will still be required for staging and at the time of interim and end of therapy response assessment. This will also facilitate comparison with prior COG studies, and allow the importance of CT imaging to be prospectively assessed within the context of the proposed PET response criteria.

Staging Considerations
Measurable disease indicates the presence of at least one measurable lesion. Superficial lesions (eg, palpable lymphadenopathy) measurable only by clinical exam or ultrasound are operator dependent and are not admissible as target

lesions. A measurable lesion by CT is a lesion that can be accurately measured in 2 orthogonal dimensions. For extranodal sites, this typically involves lesions of at least 1 cm diameter. Lymph nodes are considered abnormal if the long axis is > 2.0 cm, regardless of the short axis. Lymph nodes with a long axis measuring between 1.0-2.0 cm are only considered abnormal if they are part of a conglomerate of nodes and are FDG-PET positive.

Evaluable disease
Non-measurable evaluable lesions include permeative bone lesions, malignant ascites, malignant pleural/pericardial effusions, pulmonary or cutaneous lymphangitic spread, and lesions too small to accurately measure in 2 dimensions by CT. All non-target and non-measurable assessable lesions will be recorded at baseline and noted on follow-up.

Lymph node involvement
Any lymph node is considered involved if and only if it is FDG-PET positive.

FDG-PET positive is defined as:

a. For moderately sized (≥ 2 cm in greatest transverse diameter by CT) regardless of their location, mild and diffusely increased FDG uptake with intensity higher than that of mediastinal blood pool structures should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.

b. For smaller masses or normal sized lymph nodes (< 2 cm in greatest transverse diameter by CT), any FDG uptake more than that of surrounding background activity should be considered positive.

Bulk Disease (See Appendix XII, subsection C)

Extra nodal involvement

- Extra-lymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Exception: liver and/or bone marrow involvement is considered Stage 4.

- Pleural and pericardial effusions alone are not considered E-lesions.

- Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion that is PET positive is considered an E-lesion.

Organ involvement

Lung
Lung involvement is assumed if there is at least one intrapulmonary focus that is >1 cm and is PET positive or 3 or more lesions between 0.5 and 1 cm regardless of FDG-PET activity. Solitary lung nodules that are < 1 cm in transverse diameter, but are FDG avid, are also considered disease.

FDG-PET positive is defined as:

a. For lung nodules that are ≥ 1 cm in greatest transverse diameter by CT, FDG uptake exceeding that of mediastinal blood pool structures should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.
b. For lung nodules < 1 cm in greatest transverse diameter by CT, due to partial volume averaging effects, any uptake is considered positive.

Visceral organs (liver, spleen, kidney)
Any focal mass lesion large enough to characterize is considered due to lymphomatous involvement unless the imaging characteristics indicate an alternative nature (eg, cyst, hemangioma, abscess, etc.). Ultrasound or MRI may be utilized if clarification is necessary. Focal splenic lesions seen on an appropriately timed IV contrast enhanced CT scan can be considered positive if they are PET positive; small lesions below limits of detection by PET/CT must be confirmed by ultrasound or MRI. Splenomegaly without focal lesions does not indicate splenic involvement with disease.

Hepatic and Splenic Lesions:

FDG-PET positive is defined as:

a. For hepatic or splenic lesions ≥ 1.5 cm on CT, FDG uptake greater than or equal to that of normal liver or spleen parenchyma, respectively, should be considered positive.
b. For hepatic or splenic lesions < 1.5 cm on CT, FDG uptake greater than that of normal liver or spleen parenchyma, respectively, should be considered positive.
c. In the absence of focal splenic involvement at diagnosis, diffusely increased splenic FDG uptake greater than normal liver parenchymal FDG uptake but in the absence of lesions seen on CT will not be considered evidence of involvement.

Bone and bone marrow involvement

Focal bone lesions that are permeative, sclerotic, or both and are PET positive are considered involved. A bone focus of PET positivity outside the regions included in pre-study diagnostic CT evaluation should be assessed on the attenuation correction CT. Alternatively this can be evaluated individually by dedicated regional CT or preferably MRI. If there are three or more PET positive bony foci with no CT or MRI correlate these likely represent bone marrow involvement and are sufficient to establish Stage IV disease. As part of the Imaging aim, these will be recorded and will be correlated with bone marrow biopsy results at a later time. For this reason bone marrow biopsy results (required in children < 18 years of age; optional in patients who are ≥ 18 years of age) should be recorded on all patients when they are performed.

Bone Marrow FDG Uptake:

FDG-PET positive is defined as:

a. Three or more FDG-PET positive lesions in bone marrow. Suggest MRI correlation for confirmation of these FDG-PET positive marrow foci if possible. Diffusely increased bone marrow FDG uptake, regardless of level of uptake – including more intense than liver, is not considered positive.
b. A negative bone marrow FDG-PET does not exclude bone marrow involvement or preclude a bone marrow biopsy/aspirate assessment.

CLINICAL AND STAGING CRITERIA FOR HODGKIN LYMPHOMA

A. Stage

(See the diagram below for definitions of regions).

Stage I: Involvement of single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II: Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of a single extralymphatic organ or site and its regional lymph node(s) with involvement of 1 or more lymph node regions on the same side of the diaphragm (IIE).

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized contiguous involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).

Stage IV: Disseminated (multifocal) involvement of 1 or more extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

B. Symptoms and Presentations

"A" Symptoms: Lack of "B" symptoms.

"B" Symptoms: At least one of the following:

- Unexplained weight loss > 10% in the preceding 6 months;

- Unexplained recurrent fever ≥ 38°C in the preceding month; or
- Recurrent drenching sweats in the preceding month.

C. Bulk disease

Each of the following presentations are considered "bulk" disease:

- **Large mediastinal Adenopathy (LMA):**
  Mediastinal Bulk (LMA) = transverse tumor diameter > 1/3 the thoracic diameter at the dome of the diaphragm on a 6 foot PA upright CXR. ***A portable exam is not acceptable*** for measuring LMA and if this is the only exam available at the treating institution, a repeat exam must be performed prior to establishing bulk as it is a criterion for targeting subsequent radiotherapy.

  The hilum is technically not part of the anterior mediastinum, but if the hilar adenopathy is confluent with the anterior mediastinal adenopathy, it may be included in the transverse measurement.

- **Large extra-mediastinal nodal aggregate:**
  Extra-mediastinal bulk is defined as a continuous aggregate of nodal tissue outside the mediastinum that measures > 6 cm in transverse dimension on axial CT or longest dimension on coronal or sagittal reformatted CT. This would not include a contiguous chain of small nodes.

D. Splenic lesions:

Splenomegaly without focal lesions does not indicate splenic involvement with disease. Focal splenic lesions seen on an appropriately timed IV contrast enhanced CT scan can be considered positive if they are PET positive; small lesions below limits of detection by PET/CT must be confirmed by ultrasound or MRI, and are also considered positive. Diffusely increased splenic FDG uptake greater than normal liver parenchymal FDG uptake but in the absence of lesions seen on CT will not be considered evidence of involvement at diagnosis.

E. E-Lesions Defined:

Extra-lymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion that is PET positive would be considered an E-lesion. Liver and/or bone marrow involvement is not considered an E lesion, but rather considered Stage IV. Pleural and pericardial effusions alone are not considered E-lesions.

F. Regions of Nodal Involvement

Peripheral Upper Regions (indicate laterality: right or left)

- Neck: cervical (upper, lower/supraclavicular), occipital, and pre-auricular
- Infraclavicular
- Axilla
- Pectoral
- Epitrochlear
- Brachial

Central Regions

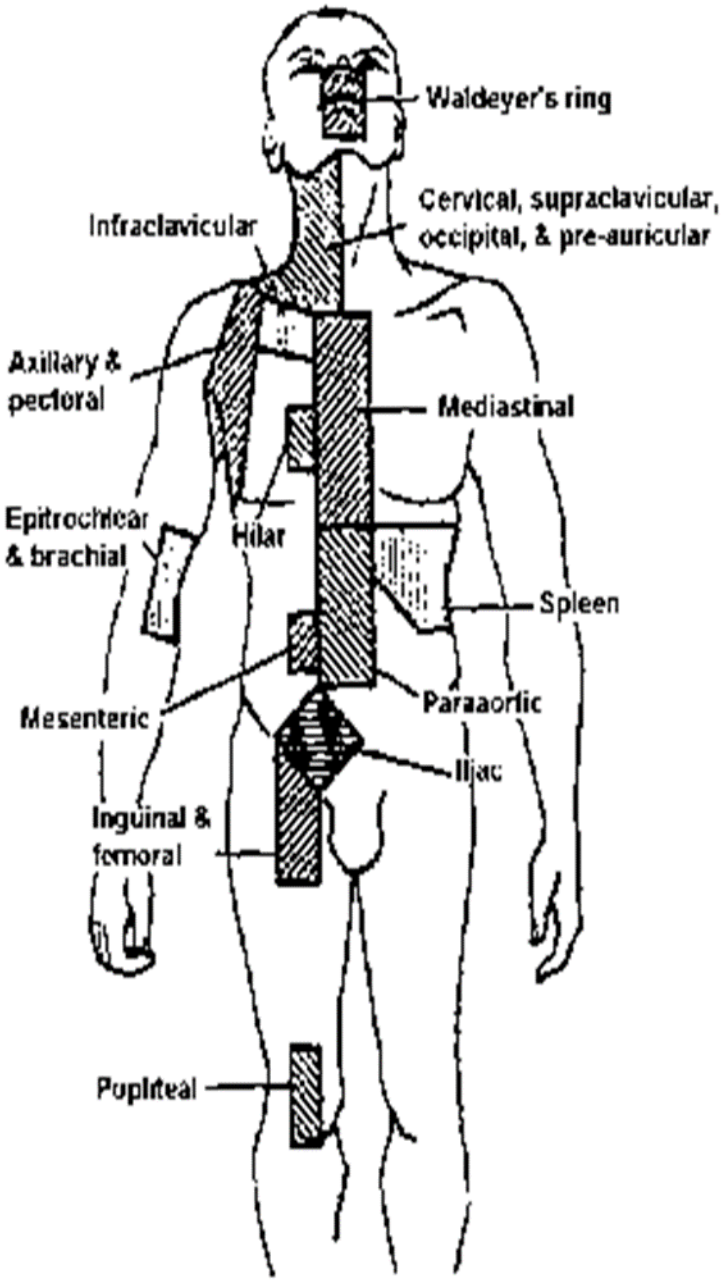
- Waldeyer's ring (including base of tongue)
- Mediastinum (anterior; hilar; cardiophrenic; subcarinal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Peripheral Lower Regions (indicate laterality: right or left)

- Iliac
- Inguinal
- Femoral
- Popliteal

Other Non-Nodal Sites

- Lung (right, left or bilateral)
- Bone
- Bone marrow



Anatomical Regions for the Staging of Hodgkin's Disease

APPENDIX XIII: RESPONSE CRITERIA FOR SOLID TUMORS

Disease Parameters

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

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

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

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

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

Methods for Evaluation for Patients with Solids Tumors and Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

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

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

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

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

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

- Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

  Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

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

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

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

Response Criteria for Patients with Solid Tumors and Evaluable Disease

Evaluation of Target Lesions:

- **Complete Response (CR):** Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

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

- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: In presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

- **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

Evaluation of Non-Target Lesions

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

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

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

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

Overall Response Assessment - Solid Tumors

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	
*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.				

Overall Best Response Assessment – Solid Tumors

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.3 from a sequence of overall response assessments.

- **Response Criteria for Patients with Solid Tumors and Evaluable Disease**

  Evaluable Disease

  The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

  Complete Response

  Disappearance of all evaluable disease.

  Partial response

  Partial responses cannot be determined in patients with evaluable disease

  Stable Disease (SD)

  That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

  Progressive Disease

  The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

APPENDIX XIV: PATIENT INSTRUCTIONS FOR SUN PROTECTION

Guidelines for Sun Protection

The following precautions should be taken for at least 3 days after each dose of BAY 1895344 (elimusertib):

- You should avoid sun exposure in the post-dose period after leaving the clinic
- You should not purposefully engage in skin tanning
- Avoid being outside during daylight hours for more than 15 minutes (even on cloudy days)
- Sun exposure should be particularly avoided during the hours of 10am and 4pm, or in areas where reflection of sunlight from snow, water, or sand might intensify exposure
- Special arrangements for children should be made at school to ensure that they are not exposed to sunlight from an open window, that they are not exposed to any unfiltered (bare) fluorescent light bulbs, and that they are not permitted outside for gym, recess, fire drills, or other activities unless they are under ultraviolet light-blocking shelters and away from reflective surfaces such as snow, sand or water
- You should wear protective clothing (e.g. long-sleeved shirt, full-length pants, wide-brimmed hat) to minimize sun exposure. Two layers of clothing protect more than one layer. Tightly woven fabrics generally give more sun protection than loose weaves.
    - Wear clothing that you can't see the light through. Some companies make light-weight clothing specifically designed to provide a high degree of sun protection.
- Long hair styles help protect the neck and ears. Any skin not covered by clothing or hair should be protected by sunscreen
- You should apply sunscreen to any potentially sun-exposed skin, even on cloudy days. Sunscreen should have a sun protection factor (SPF) of 50 or higher and should provide broad-spectrum protection from both ultraviolet A (UVA) and ultraviolet B (UVB) rays
    - Sunscreen should be applied at least 30 minutes before going out in the sun
    - Sunscreen may also be used indoors to protect against unrecognized sources of ultraviolet light
- You should apply a sun-protective lip balm. The lip balm should have an sun protection factor (SPF) of 30 or higher and should provide broad-spectrum protection from both ultraviolet A (UVA) and ultraviolet B (UVB) rays
- You should wear sunglasses or clip-ons when in ambient external light that provide full protect against UV light. Glasses with side-shields protect the eyelids and skin around the eyes. When selecting appropriate sunglasses or clip-ons, look for a label or sticker that indicates one or more of the following:
    - Lenses block 99% or 100% of UVB **and** UVA rays
    - Lenses meet American National Standards Institute (ANSI) Z80.3 blocking requirements or Australian/New Zealand Standard for Sunglasses and Fashion Spectacles, AS/NZS 1067
    - Lenses provide UV 400 protection (providing protection against light rays with wavelengths as high as 400 nanometers, which covers the entire UV spectrum)

APPENDIX XV: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD
Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**	PEPN2112
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	BAY 1895344 (elimusertib)

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

These are the things that your healthcare providers need to know:
BAY 1895344 (elimusertib) interacts with certain specific enzyme(s) in your liver or other tissues like the gut, and certain transport proteins that help move drugs in and out of cell.

	Explanation
CYP isoenzymes	The enzymes in question are **CYP3A4, 2C8, 2C9, and 2C19**. BAY 1895344 (elimusertib) is broken down by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Strong inhibitors and inducers of CYP3A4 should be avoided. BAY 1895344 (elimusertib) weakly to moderately inhibits CYP3A4, CYP2C8 2C9, and 2C19. BAY 1895344 (elimusertib) induces CYP3A4 and 2C19. Substrates of CYP3A4 with narrow therapeutic window should be avoided. Other drugs that are broken down by CYP2C8, 2C9, and 2C19 may be affected when used at the same time.
Transport proteins	The proteins in question are **P-gp, BCRP, OATP1B1, and OATP1B3**. BAY 1895344 (elimusertib) inhibits these transport proteins and may affect other drugs that require them to move in and out of the cells.

These are the things that you need to know:
The study drug BAY 1895344 (elimusertib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors and inducers of CYP3A4, substrates of CYP3A4 with narrow therapeutic window, substrates of CYP2C8, 2C9, 2C19, BCRP, P-gp, OATP1B1, and OATP1B3.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Make sure your doctor knows to avoid certain prescription medications.

- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on BAY 1895344 (elimusertib).
- Antacids, H2 receptor antagonists, and proton pump inhibitors should be used with caution.
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

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(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

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EMERGENCY INFORMATION

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

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

NIH NATIONAL CANCER INSTITUTE

Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following:

- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on BAY 1895344 (elimusertib).
- Antacids, H2 receptor antagonists, and proton pump inhibitors should be used with caution.
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when in the sun.

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

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DRUG INTERACTIONS

Carry this card with you at all times

BAY 1895344 (elimusertib) interacts with specific liver enzymes called CYP3A4, 2C8, 2C9, and 2C19 and transport proteins BCRP, P-gp, OATP1B1, and OATP1B3 and must be used very carefully with other medicines that interact with these enzymes or transporters.

Your healthcare providers should be aware of any medicines that are strong inhibitors or inducers of CYP3A4 and substrates of CYP3A4 with narrow therapeutic window, which should be avoided. Use caution with substrates of CYP2C8, 2C9, 2C19, BCRP, P-gp, OATP1B1, and OATP1B3.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version Nov/2019

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