To: CTEP Protocol and Information Office

From: Thatcher Heumann, M.D.

Date: July 31, 2024

Re: Revision #19 of Protocol #10402

- NCI requested changes to protocol with regards to the correlative specimen analysis. These changes are required in order for the NCI laboratories to analyze the samples.

Summary of Changes-Protocol

I. Protocol Changes

#	Section	Page	Comments
1.	Protocol	**Protocol**	Updated protocol version date throughout protocol and Revision # to 19.
2.	**5.8**	**52, 53, 59**	Updated laboratory name and PI contact information in Biomarker plan
3.	**5.9** **5.10**	**61** **62, 63**	Updated laboratory name and PI contact information.
4	**13.6** **13.7**	**115**	Deleted sections as these are no longer relevant.

NCI Protocol #: 10402

Local Protocol #: VICCNCIPH110402

ClinicalTrials.gov Identifier: NCT04514497

TITLE: BAY 1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Patients with Advanced Solid Tumors, Phase I Studies with Expansion Cohorts in Small Cell Lung Carcinoma (SCLC), Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) and Pancreatic Adenocarcinoma (PDA)

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Participating Organizations: Dose Escalation

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LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO

Participating Organizations: Dose Expansion

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
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NCI-Supplied Agent: BAY 1895344 (NSC 810486)
Other Agents: Topotecan (NSC 609699) (Commercial), Irinotecan (NSC 759878)

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

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Revision 8 / December 18, 2020
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SCHEMA

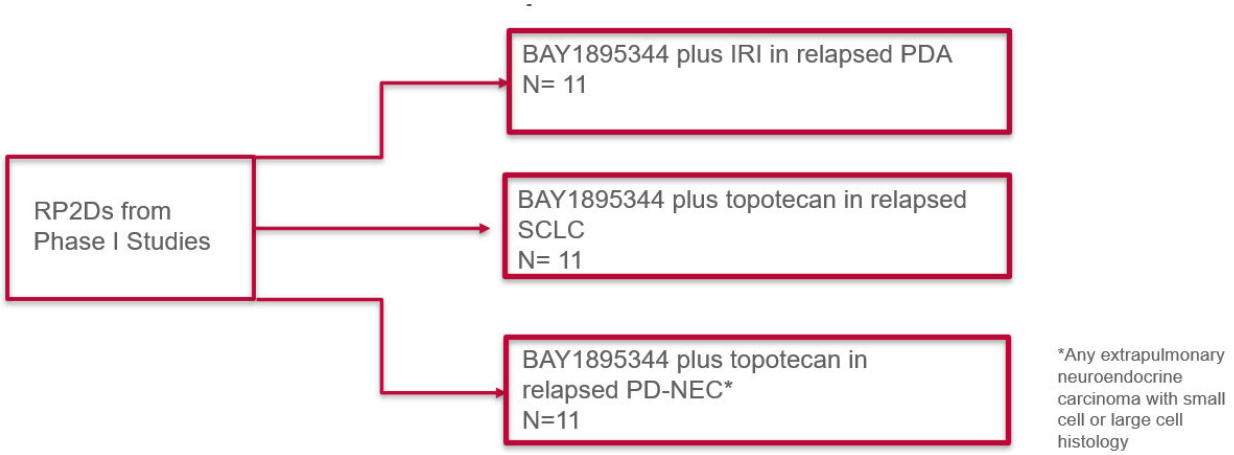

Figure 1: Dose Expansion Schema. Abbreviations: RP2D = recommended phase 2 dose, IRI = irinotecan, PDA = pancreatic adenocarcinoma, SCLC = small cell lung cancer, PD-NEC = poorly differentiated neuroendocrine carcinoma.

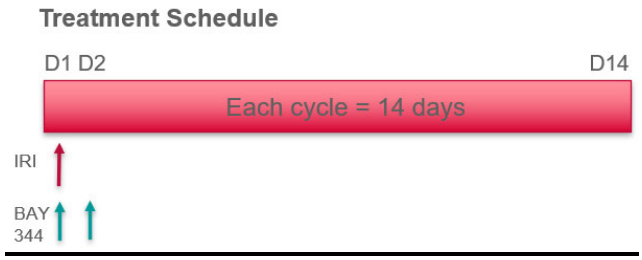

Figure 2: Treatment schedule for irinotecan plus BAY 1895344 (irinotecan cohort #1). Abbreviations: IRI = irinotecan; BAY344 = BAY 1895344.

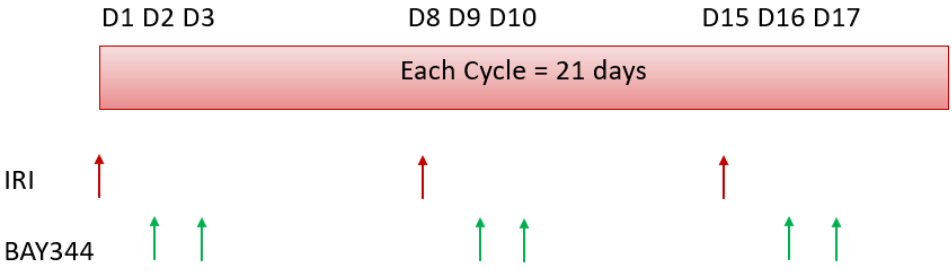

Figure 3: Treatment schedule for alternative irinotecan plus BAY 1895344 (irinotecan cohort #2). **Note:** After 2 cycles, treatment will be 2 weeks on and 1 week, therefore doses on Day 15-17 will be omitted in Cycle 3+. Abbreviations: IRI= irinotecan; BAY344 = BAY 1895344

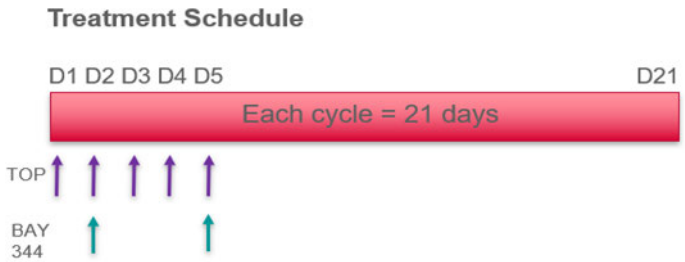

Figure 4: Treatment schedule for topotecan plus BAY 1895344. Abbreviations: TOP = topotecan; BAY344 = BAY 1895344.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess safety and tolerability of each of the BAY 1895344 plus topoisomerase 1 (top1) inhibitor (irinotecan or topotecan) combinations.

1.1.2 To estimate maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of each of the combinations.

1.2 Secondary Objectives

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

1.2.2 To estimate objective response rate (ORR), progression free survival (PFS), overall survival (OS) and duration of response (DOR) in patients treated with each combination

1.2.3 To estimate plasma pharmacokinetic (PK) characteristics of BAY 1895344 plus each top1 inhibitor (irinotecan or topotecan) when used in combination

1.2.4 To estimate changes in pharmacodynamic (PD) markers of DNA damage (γ-H2AX, pS343-NBS1) elicited by each combination from on-treatment tumor biopsies (in dose expansion cohorts only)

1.3 Exploratory Objectives

1.3.1 To estimate response outcomes (ORR, PFS, OS, DOR) in study patients by tumor ataxia telangiectasia mutated (ATM) expression loss (assessed by immunohistochemistry (IHC))

1.3.2 To estimate response outcomes (ORR, PFS, OS, DOR) in study patients with tumor DDR mutations (assessed by Whole Exome Sequencing (WES), RNA Sequencing (RNA Seq) and ctDNA analysis)

2. BACKGROUND

2.1 Study Diseases

Small cell lung cancer (SCLC), which accounts for 10–15% of new lung cancer cases, extrapulmonary poorly differentiated neuroendocrine carcinoma (PD-NEC), which accounts for 10-20% of new gastroenteropancreatic neuroendocrine tumor cases, and pancreatic adenocarcinoma (PDA), which is expected to become the second leading cause of cancer mortality in the United States within the next decade, are aggressive diseases characterized by

rapid growth and early widespread metastases (American Cancer Society (About Small Cell Lung Cancer), 2019; American Cancer Society Cancer Facts and Figures 2019; Sorbye *et al.*, 2014; Siegel *et al.*, 2019). Patients with any of these diseases carry dismal prognoses post-progression on first-line chemotherapy, typically platinum-based, with median overall survival (OS) times of < 12 months (Siegel *et al.*, 2019, O'Brien *et al.,* 2006, Sorbye *et al.*, 2013, Conroy *et al.*, 2011, Von Hoff *et al.*, 2013, Paz-Ares *et al*, 2019). Novel therapeutics with the potential to elicit durable cytoreduction are gravely needed in the post-first-line setting in these diseases. Drugs targeting DDR pathways represent one such promising option given the dependence of SCLC, PD-NEC and PDA on DDR pathways to maintain genomic integrity in the face of unbridled replication stress. Replication stress in these tumors arises from their genetic profile as nearly all SCLC, PD-NEC and PDA are characterized by *TP53* mutations (90-100% in SCLC, > 80% in PD-NEC, > 75% in PDA). The majority of SCLC and PD-NEC tumors also demonstrate Retinoblastoma-associated (RB1) protein loss (80-90% in SCLC and > 50% in PD-NEC). Both characteristics enable tumor cells to evade the G1/S checkpoint and enter S phase readily (George *et al.*, 2015, Sorbye *et al.*, 2018, Bailey *et al.*, 2016, Witiewicz *et al.*, 2015, Rickman *et al.*, 2017). *In vitro* testing has revealed SCLC and PD-NEC cell lines, along with other cancer cell lines with deleterious RB1 mutations, to be especially sensitive to ataxia telangiectasia and Rad3 related (ATR) inhibitors (Mancusi *et al.*, 2019). Though PDA does not exhibit RB1 loss, it is characterized by a milieu of other factors such as oncogenic activation (*KRAS, Myc)* promoting cell-cycle entry along with tumor suppressor loss (*CDKN2A*), which create an environment of perpetual replication stress. *In vitro* testing has revealed PDA cell lines to be particularly sensitive to ATR inhibition in combination with other DNA damage inducing cytotoxic therapies (Wallez *et al.*, 2018). The ATR kinase appears to be integral for DDR in SCLC, PD-NEC and PDA.

2.2 CTEP IND Agent

2.2.1 BAY 1895344

DDR is a multicomplex network of signaling pathways involved in detection and repair of DNA damage, transient cell cycle arrest to ensure genomic stability and cell viability (Fokas *et al.*, 2014; Zeman and Cimprich, 2014; Weber and Ryan, 2015). Deficiencies in DDR mechanisms have been shown to contribute to tumor development. Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) protein kinases are key regulators of DDR. They both contribute to maintaining genome integrity in response to various exogenous and endogenous genotoxic insults, *e.g.*, cytotoxic chemotherapy, ultraviolet light, ionizing radiation, or hypoxia (Fokas *et al.*, 2014; Pitts *et al.*, 2014; Yan *et al.*, 2014). Although ATR and ATM have broadly overlapping substrate specificities, they have non-redundant functions, which are well coordinated during DDR. ATR is a key replication-stress-response kinase (Cimprich and Cortez, 2008; Zeman and Cimprich, 2014; Fokas *et al.*, 2014; Wengner *et al.*, 2019). While ATM is primarily activated by DNA double-strand breaks (DSBs), ATR is recruited to regions of replication protein A (RPA)-coated ssDNA generated at stalled replication forks or during the of processing DSBs (Menezes *et al.,* 2014; Reaper *et al.*, 2011; Yan *et al.,* 2014). ATR phosphorylates/activates checkpoint kinase 1 (CHK1) at serine 345 ($CHK1pS^{345}$), which stabilizes stalled replication forks until replication stress is resolved and DNA damage is repaired (Fokas *et al.*, 2014; Pitts *et al.*, 2014). Unlike normal cells, cancer cells are often deficient in

ATM signaling, which renders them more reliant on the ATR-controlled S/G2-phase checkpoints for repairing DNA damage and survival (Fokas *et al.*, 2014, Menezes *et al.*, 2015; Reaper *et al.*, 2011). ATR inhibition in the ATM-signaling deficient tumors results in synthetic lethality. Preclinical data suggest therapeutic utility of ATR inhibitors for cancer treatment as they may mediate synthetic lethality in DDR-deficient tumors and in combination with DNA-damaging agents (*e.g.*, radiation, cytotoxic chemotherapy), targeted therapies compromising DNA-damage repair, such as poly(ADP-ribose)polymerase (PARP) inhibitors or anti-androgen therapies may enhance their activity (Wengner *et al.,* 2019)

2.2.1.1 Nonclinical studies

Nonclinical *In Vitro* Activity and Mechanism of Action

BAY 1895344 is a highly potent and selective inhibitor of ATR kinase activity, with a 50% inhibitory concentration (IC_{50}) of 7 nmol/L of this enzyme (Investigator's Brochure, 2019; Luecking *et al.,* 2017). The activity and selectivity of BAY 1895344 were evaluated in biochemical assays against a panel of 395 kinases (Investigator's Brochure, 2019). Mechanistic target of rapamycin (mTOR) was identified as the most sensitive off-target kinase (IC_{50}=35 nmol/L). BAY 1895344 inhibited proliferation of a broad spectrum of human tumor cell lines with a median IC_{50}=78 nmol/L (mean IC_{50}=150 nmol/L). A clear separation between highly sensitive (IC_{50} <100 nmol/L) and less sensitive cell lines was observed. The majority of sensitive cell lines were characterized by mutations affecting the ATM pathway. Lymphoma cell lines appeared to be most sensitive with IC_{50s} ranging from 8.6 to 32 nmol/L. BAY 1895344 effects against lymphoma cell lines were mostly cytotoxic, with induction of apoptosis observed in 61% of the tested cell lines (Gaudio *et al.*, 2019).

BAY 1895344 activity was evaluated in cellular mechanistic assays specific for inhibition of kinase activity of ATR, ATM, or DNA-dependent protein kinase (DNA-PK) catalytic subunits (DNA-PKcs) (Investigator's Brochure, 2019). The cellular level of phosphorylated H2AX (γH2AX) was used to monitor kinase activity of ATR, ATM and DNA-PKcs. By selection of appropriate cells and stimuli to induce either DSBs or replication stress, γH2AX served as a specific read-out for the activity of ATR, ATM or DNA-PKcs. In the ATR-specific mechanistic assay in HT-29 cells BAY 1895344 inhibited hydroxyurea-induced γH2AX with an IC_{50} of 36 nmol/L. BAY 1895344 did not inhibit ATM- or DNA-PKcs-mediated H2AX phosphorylation up to a concentration of 10 mcmol/L.

Nonclinical *In Vivo* Activity

In vivo, BAY 1895344 was evaluated in several human tumor xenograft models of different tumor indications (prostate cancer, mantle cell lymphoma [MCL], diffuse large B-cell lymphoma [DLBCL], cervical cancer, lung cancer, ovarian cancer, melanoma, colorectal cancer [CRC]) in mice (Investigator's Brochure, 2019). BAY 1895344 demonstrated strong antitumor activity with good tolerability as monotherapy at a dose of 50 mg/kg administered orally (PO) twice a day (BID) for 3 days followed by 4 days off treatment in biomarker-positive tumor models. BAY 1895344 had superior antitumor effects compared to other ATR inhibitors (AZD-6738, VX-970, or VX-803) as well as a PARP inhibitor, olaparib, in several tumor models. BAY 1895344 showed synergistic antitumor effects in combination with DNA damage inducing therapy, such as chemotherapy (cisplatin, carboplatin, oxaliplatin, 5-FU, Irinotecan)

(Investigator's Brochure, 2019), α-radiation by radium-223 dichloride (Wengner *et al.*, 2018; Bannik *et al.*, 2019) or thorium 227 (Wickstroem *et al.*, 2019a; Wickstroem *et al.*, 2019a), external beam radiation therapy [EBRT] (Wengner *et al.*, 2019), therapies compromising DNA damage repair such as a PARP inhibitor olaparib (Wengner *et al.*, 2019) or anti-androgen agent darolutamide (Wengner *et al.*, 2019), therapies targeting a programmed cell death protein 1 (PD1], PD ligand 1 (PD-L1), or other targeted therapies (PI3K inhibitor) (Investigator's Brochure, 2019).

Nonclinical Pharmacology

Following single intravenous administration of BAY 1895344, a high volume of distribution (V_d) was observed in all species (mice, rats, and dogs) (Investigator's Brochure, 2019). In mice and dogs, elimination of the drug was bi-phasic with a short initial (distribution phase) half-life ($t_{1/2}$) of 0.2 and 1 hour, respectively, followed by a long elimination $t_{1/2}$ of 12.2 and 8.3 hours, respectively. In rats only the distribution phase $t_{1/2}$ (1.3 hours) was observed.

Following single oral dosing of BAY 1895344, the elimination $t_{1/2}$ was intermediate to long in rats and could not be calculated in dogs (Investigator's Brochure, 2019). In single dosing studies in dogs, plasma exposure measured as an area under s concentration time curve (AUC) increased more than dose-proportionally over the dose range of 3-8 mg/kg, whereas a maximum concentration (C_{max}) increased dose-proportionally. After multiple oral dosing of BAY 1895344, AUC and C_{max} on day 17 were lower than on day 1 in rats. In dogs, exposure increased only slightly between days 1 and 23. Oral bioavailability was moderate to high (67%- 87%) in rats and moderate in dogs (51%). The binding of BAY 1895344 to plasma proteins was low to moderate in all investigated species. A slight concentration dependency was observed with a decrease in protein binding at the highest test concentrations (increase in the unbound fraction from 2.6% to 4.2% in humans).

Hepatic route appears to be the key clearance mechanism for this compound (Investigator's Brochure, 2019). Metabolic pathways were highly comparable across all investigated species. In human hepatocytes, BAY 1895344 was metabolized *via* oxidation and dealkylation at the methylmorpholine moiety and direct glucuronidation. Oxidative metabolism was mainly catalyzed by cytochrome P450 (CYP) isoform 3A4 (CYP3A4). BAY 1895344 appears to have a potential to inhibit as well as induce CYP3A4. BAY 1895344 showed the inhibitory potential towards protein transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), with IC_{50} of 7.4 mcM and 1.9 mcM, respectively. BAY 1895344 had the inhibitory potential toward organic anion transporting polypeptide (OATP)1B1 and OAT1B3.

Nonclinical Safety and Toxicology

Safety pharmacology studies revealed no effect on the human ether-a-go-go-related (hERG) potassium tail current was observed (Investigator's Brochure, 2019). No clinically relevant or major effects were observed on the central nervous system (CNS). Cardiovascular examinations revealed a moderate increase in diastolic blood pressure without clear effects on systolic blood pressure. ECG intervals were not substantially influenced.

Major target organs for BAY 1895344 in oral repeat-dose toxicity studies in rats and dogs with continuous and intermittent (3 days on/4 days off) dosing were the lymphatic organs and bone

marrow, epithelial tissues including skin and gastrointestinal (GI) tract, and male reproductive organs (Investigator's Brochure, 2019). Additional toxicity observed in adult animals was atrophy of bone spongiosa in both species. All findings were reversible.

BAY 1895344 showed genotoxicity *in vitro* (micronucleus test in Chinese hamster cells for aneugenicity and clastogenicity) and *in vivo* (bone marrow [BM] micronucleus test in rats after a 4-week repeat dosing) (Investigator's Brochure, 2019).

No specific studies on reproductive and developmental toxicity of BAY 1895344 were conducted at this stage of development. (Investigator's Brochure, 2019). Degenerative findings in male reproductive organs were seen in 4-week repeat-dose toxicity studies in rats and dogs. Thus, an influence on fertility can be expected. Homozygous ATR know-out mice are embryo-lethal, indicating that ATR is essential in embryogenesis. Based on its mode of action, BAY 1895344 is regarded as a potential teratogen.

There was an indication for phototoxicity in an *in vitro* assay (Investigator's Brochure, 2019).

Overall, BAY 1895344 displayed an acceptable nonclinical safety profile to initiate clinical development in patients with advanced disease (Investigator's Brochure, 2019). The toxicities observed are regarded as monitorable and/or manageable in humans.

2.2.1.2 Clinical studies

Preliminary clinical experience is derived from the ongoing company-sponsored First-in-Human (FiH) study of BAY 1895344 (data cut-off date June 16, 2019) (Investigator's Brochure, 2019).

Clinical Pharmacokinetics
Preliminary PK show that BAY 1895344 administered at the maximum tolerated dose (MTD) of 40 mg PO BID for 3 days every week (3 days on/4 days off) in patients with advanced solid tumors was absorbed rapidly with a median time to reach maximum drug concentration (t_{max}) of 1 hour and a geometric mean terminal $t_{1/2}$ of 9.8 hours in plasma (Investigator's Brochure, 2019). Exposure increase was observed to be broadly dose-proportional across the dose range investigated (5-80 mg), and accumulation was consistent with observed $t_{1/2}$. Clinical exposure was observed to be in the range associated with efficacy in nonclinical models.

Clinical Safety
A. Dose-escalation cohort
Dose-limiting toxicities were observed with BAY 1895344 administered at doses 60 mg BID and 80 mg BID, as well as on the intermittent schedule of 60 mg BID 3 days on/4 days weekly for 2 weeks of a 3-week cycle (Investigator's Brochure, 2019). BAY 1895344 administered at 40 mg PO BID on the 3-day-on/4-day-off schedule every week on a 3-week cycle has been declared the MTD.

All 39 patients who started BAY 1895344 treatment in the dose-escalation phase (as of June 16, 2019) experienced at least one treatment-emergent adverse event (TEAE) and 94.9% of patients experienced at least one BAY 1895344-related TEAE of any grade; 61.5% had grade 3, and

17.9% had grade 4 (Investigator's Brochure, 2019). The most common study drug-related TEAEs by (occurring in ≥10% of patients) were: anemia (74.4%), neutropenia (46.2%), fatigue, nausea (38.5% each), white blood cell (WBC) count decreased (28.2%), platelet count decreased (23.1%), thrombocytopenia, and neutrophil count decreased (20.5%), diarrhea, decreased appetite (15.4% each), and vomiting (12.8%). Overall, 35.9% of patients experienced at least one treatment-emergent serious adverse event (TESAE) in the dose-escalation phase and 7.7% of patients experienced at least one BAY 1895344-related TESAE: grade 4 neutropenia, grade 3 diarrhea, nausea, hypotension, and grade 2 pyrexia 2.6% each). One patient (80 mg BID cohort) died within 30 days of treatment discontinuation but the death was assessed as unrelated to the study drug.

B. Expansion cohort
At least one TEAE was observed in 97.4% of patients (75/77) treated at the MTD and at least one BAY 1895344-related TEAE of any grade was experienced by 88.3% of patients, grade 3 (in 62.3% of patients), and grade 4 (in 13.0% of patients) (Investigator's Brochure, 2019). The most common drug-related TEAEs (occurring in ≥10% patients) were: anemia (71.4%), neutropenia (41.6%); fatigue (28.6%), thrombocytopenia, nausea (18.2% each), WBC count decreased (15.6%), neutrophil count decreased (11.7%), and vomiting (10.4%). Four patients (5.2%) experienced at least on BAY 1895344-related TESAE. There were three deaths in the expansion cohort, occurring within 30 days of permanent treatment discontinuation and all three were considered unrelated to the study drug.

Guidance for Investigators Summary (Investigator's Brochure, 2019)

Based on BAY 1895344 preclinical findings and its mode of action, BAY 1895344 has a genotoxic potential (Investigator's Brochure, 2019). The compound was phototoxic in an *in vitro* assay, so that patients should avoid direct exposure to sunlight as a precaution. Effects on male reproductive organs were found, so that male fertility may be impaired. In addition, embryo-fetal toxicity including teratogenicity are expected for BAY 1895344 based on its mode of action. Therefore, women of child-bearing potential should use effective contraceptive measures during treatment, and pregnant women should be excluded from studies of BAY 1895344. Men should use barrier contraception when having sexual intercourse with women of child-bearing potential. In addition, breast-feeding should be discontinued during treatment.

<u>Drug-Drug Interactions</u>
BAY 1895344 bears a potential risk to have a weak to moderate inhibitory potential on sensitive CYP3A4 substrates (*e.g.*, midazolam), possibly resulting in clinically relevant drug-drug interactions. BAY 1895344 was also shown to be an inducer of CYP3A4 *in vitro* (Investigator's Brochure, 2019). However, this induction potential may be alleviated by administering BAY 1895344 on the intermittent dosing schedule (3 days on/4 days off). Medications that are a) predominantly metabolized by CYP3A4 and have a narrow therapeutic window and b) strong CYP3A4 inducers and inhibitors have been prohibited in the BAY 1895344 FiH study.

<u>*Prohibited strong inhibitors of CYP3A4*</u>: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or

dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, and voriconazole

Prohibited strong inducers of CYP3A4: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin and St. John's wort

Prohibited drugs that are CYP3A4 substrates and have narrow therapeutic index: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.

Undesirable effects with a causal relationship to BAY 1895344 in Humans (Investigator's Brochure, 2019)

- Anemia: 82.1% (any grade); 76.9% (grade 3)
- Neutropenia: 46.2% (any grade); 35.9% (grade 3)
- Thrombocytopenia (20.5%); 2.6% (grade 3)

The hematological disorders caused by BAY 1895344 are in line with the mode of action of the compound targeting rapidly dividing cells in the hematopoietic system and leading to bone marrow suppression.

BAY 1895344 Dose and Schedule in Humans
In the FiH study, BAY 1895344 40 mg PO BID administered with the 3-day-on/4-day-off weekly schedule on a 21-day cycle was declared the MTD (Investigator's Brochure, 2019).

2.3 Commercial Agents

2.3.1 Irinotecan

Topoisomerase I is intimately involved in DNA replication and RNA transcription as it relieves the torsional strain introduced ahead of the moving replication fork. The cytotoxicity of irinotecan results from single and double strand DNA breaks that are produced by the inhibited topoisomerase I during the course of DNA and RNA synthesis. Irinotecan is a prodrug is converted by a carboxylesterase to 7-ethyl-10-hydroxycamptothecin (SN-38), which is the active metabolite. SN-38 is metabolized by UGT1A1 in the liver to an inactive glucuronide. Irinotecan can also be metabolized by CYP3A4 into inactive metabolites. SN-38 binds and stabilizes the topoisomerase I cleavable complex, leading to double-stranded DNA breaks and irreversible DNA synthesis inhibition. Cells are arrested in the S-G2 phase, ultimately leading to cell death. Irinotecan has shown a broad range of antitumor activity in vitro and in vivo. Irinotecan has been approved by the FDA 1) for first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum, 2) as monotherapy for metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy (Camptosar® Package Insert, 2014)

2.3.2 Topotecan

Topotecan has been approved by the FDA for the treatment of 1) metastatic carcinoma of the

ovary after disease progression on or after initial or subsequent chemotherapy, 2) SCLC platinum-sensitive disease in patients who progressed after first-line chemotherapy, and 3) as a combination therapy with cisplatin for Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment (Hycamtin® Package Insert, 2015). Topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single-strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these DSBs. Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan at the approved doses (Hycamtin® Package Insert, 2015). The FDA approved dose of topotecan for treating SCLC is 1.5 mg/m^2. However, lower doses at 1.25 mg/m^2 appear to be as effective as the approved dose, but with reduced toxicity (Huber, *et al.*, 2006).

2.4 Rationale

Cell line and xenograft models of SCLC have demonstrated susceptibility to single agent ATR inhibitors such as M6620 and BAY 1895344 (Doer *et al.*, 2017, Investigators Brochure 2019, Josse *et al.*, 2014). In H82 SCLC xenograft mice (N=10), BAY 1895344 at 50 mg/kg twice daily PO for 3 days on and 4 days off produced a response rate (RR) of 50% and disease control rate (DCR) of 80% (Investigators Brochure 2019). In the KPC PDA xenograft models, the ATR inhibitor AZD6738 at 25 mg/kg for 4 days combined with gemcitabine at 100 mg/kg for 9 days (on a 12-day treatment schedule) elicited tumor cytoreduction in 30% of tumors and tumor growth stabilization in 40% of tumors (Wallez *et al.*, 2018). *ATR* has been identified as a leading synthetic lethal target for topoisomerase 1 (top1) inhibitors through siRNA screening, and combining ATR inhibitors with top1 inhibitors in SCLC, PD-NEC and PDA patients is therapeutically intuitive given the routine use of irinotecan or topotecan in later-line settings for these patients (von Pawel *et al.*, 1999, Kondo *et al.*, 2018, Apostolidis *et al.*, 2016, Apostolidis *et al.*, 2019). In a HT29 (*TP53* mutant, *myc* amplified) colorectal cancer xenograft model, mice treated with irinotecan 30 mg/kg IV weekly and BAY 1895344 50 mg/kg PO 2 days on and 5 days off weekly, demonstrated greater growth inhibition than mice treated with either compound alone (Investigators Brochure 2019) (**Figure 4)**.

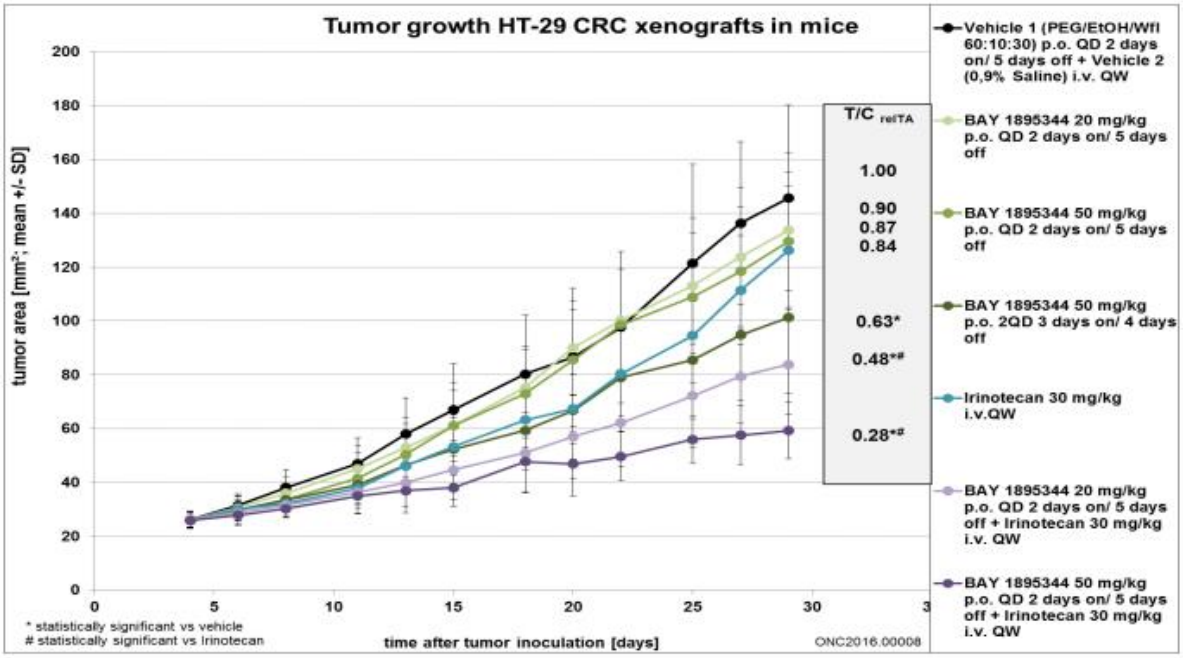


Figure 3: HT-29 CRC xenograft mice models treated with BAY 1895344 monotherapy or in combination with irinotecan at different dose schedules

M6620 was combined with topotecan in a phase I study in refractory solid tumor patients (Thomas *et al.*, 2018). The highest planned dose level was reached during MTD determination (topotecan 1.25 mg/m^2 IV D1-5, M6620 210 mg/m^2 IV D2,5). This trial included patients with platinum-refractory SCLC and durable responses (> 6 months of disease control), were seen in 3 of 5 patients. Based on this data, a single arm phase II study of M6620 plus topotecan has been in initiated in SCLC and extrapulmonary small cell carcinoma (EP-SCC) patients [NCT02487095]. Twenty-five patients have been enrolled to date and from unpublished interim data, median PFS is 4.8 months (**Figure 5**). No difference in median PFS between platinum-sensitive or platinum-refractory patients has been observed (p=.12). In our topotecan dose escalation and dose expansion cohorts, we are mimicking the ATR inhibitor administration schedule used in NCT02487095, thus utilizing historical precedent for administering BAY 1895344 on D2,5 of each treatment cycle.

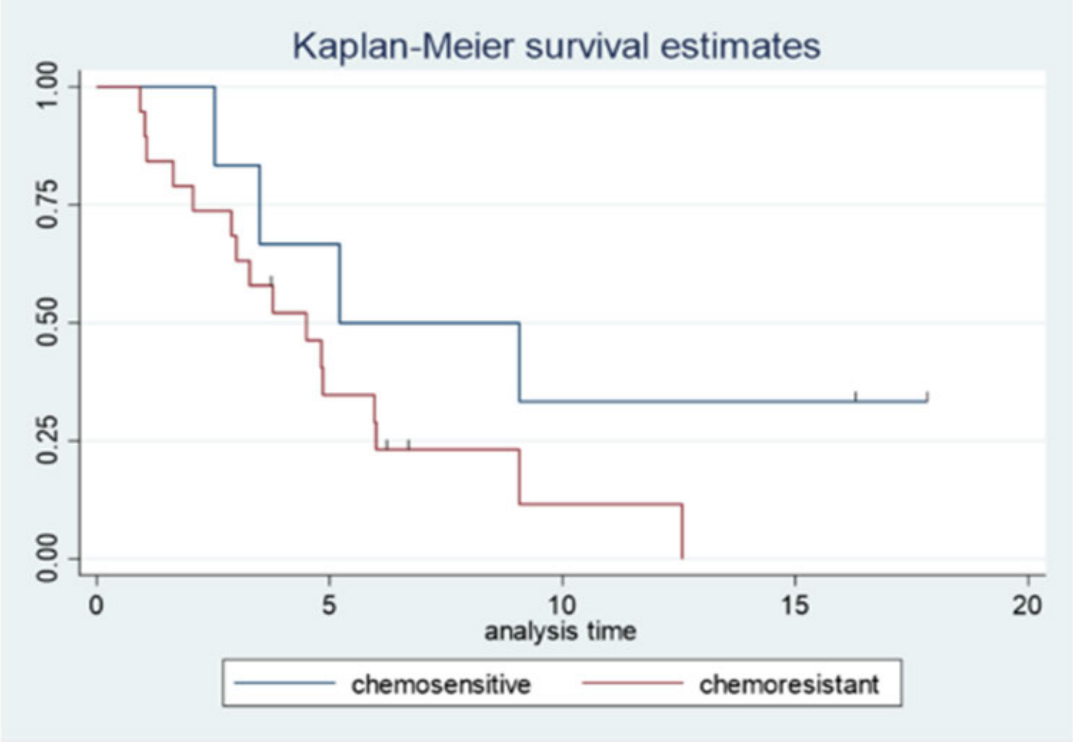


Figure 4: Kaplan-Meier curves of SCLC and EP-SCC treated with M6620 plus topotecan. Chemosensitive refers to platinum-sensitive while chemoresistant refers to platinum-refractory

BAY 1895344 is a unique ATR inhibitor given its cytoreductive potential, even as monotherapy, compared to other ATR inhibitors (**Figure 6**). In H82 SCLC xenograft models, the compound also appeared to be more tolerable than other ATR inhibitors with less observed toxicity in treated mice. The toxicity profile of the agent clinically, however, appears to be consistent with that of other ATR inhibitors. The most common (≥ 18%) treatment related adverse events (TRAEs) reported in the phase I study of BAY 1895344 monotherapy were anemia, neutropenia, thrombocytopenia, nausea and fatigue. The most common grade 3/4 TRAEs seen in the study were anemia (68.2%), neutropenia (36.4%), thrombocytopenia (13.6%) and fatigue (9.1%) (De Bono *et al.*, 2019). The myelosuppression from the agent is the only true overlapping toxicity with the TRAEs from topotecan and irinotecan, and because of this, we have started with a conservative dosing schedule. The study compound is being given for 2 days in each treatment cycle rather than at its MTD from the phase I study of 3 days on 4 days off weekly. In light of its impressive activity, and moderate toxicity profile, we hypothesize that the combination of BAY 1895344 with top1 inhibitors will represent a meaningful novel therapeutic option for patients with SCLC, PD-NEC and PDA.

Selected in vivo models of different indications with DDR deficiencies

Cancer type	Model / Mutation	Treatment/Control (T/C) based on tumor area Response rate (RR)			
		BAYER ATRi	ATRi competitors		
		BAY 1895344 50 mg/kg BID 3on/4off p.o.	AZD-6738 50 mg/kg QD p.o.	VX-970 100 mg/kg QD p.o.	VX-803 150 mg/kg QD 1on/6off p.o.
Lymphoma (MCL)	Rec-1 *ATM, TP53, KRAS*	**-0.13** 100% RR (n=10) 10 CR	**0.52** 0% RR (n=10) 10 PD	**0.53** 0% RR (n=8) 8 PD	-
Prostate cancer	PC-3 *TP53, MSH3, MYC*	**-0.02** 90% RR (n=10) 9 PR, 1 SD	-	-	-
CRC	LOVO *CHEK2, ARID1A, RAD50, KRAS*	**0.13** 0% RR (n=10) 3 SD, 7 PD	**0.44** 0% RR (n=10) 10 PD	**0.71** 0% RR (n=10) 10 PD	**0.23** 0% RR (n=10) 2 SD, 8 PD
SCLC	NCI-H82 *RB1-loss*	**-0.08** 50% RR (n=8) 5 PR, 3 SD, 2 PD	**0.42** 0% RR (n=10) 2/ SD, 8 PD	**1.30** 0% RR (n=10) 10 PD tox 4/10	**-0.09** 20% RR (n=10) 2 PR, 8 PD tox 4/10

Figure 5: Activity of various ATR inhibitors in DDR deficient xenograft models. The BAY 1895344 compound, across models, demonstrates more profound cytoreduction than other ATR inhibitors as evidenced by response rate (RR) and tumor volume (T/C ratios).

If positive, the study results could have profound implications on the treatment landscape for SCLC, PD-NEC and PDA patients. The topotecan combination in SCLC patients, if found to demonstrate an efficacy signal, could be compared against topotecan monotherapy, one of the only currently FDA approved therapies in progressive SCLC, in a subsequent study to establish a new standard of care in this patient population. The topotecan combination in PD-NEC patients would provide prospective evidence for a second-line treatment standard. Even though first-line treatment approaches in PD-NEC patients have been extrapolated from SCLC patients, this has not been the case in the later-line setting as most current treatment approaches have been based upon findings from small retrospective studies (Apostolidis *et al.*, 2016, Apostolidis *et al.*, 2019). Irinotecan has demonstrated first-line (FOLFIRINOX) and second-line activity (as monotherapy or FOLFIRI) in patients with progressive unresectable PDA (Conroy *et al*, 2011, Yi *et al*, 2009, Neuzillet *et al.*, 2011). In this palliative setting, given the toxicity profile of FOLFIRINOX, many patients initiate first-line treatment with gemcitabine-based therapy. The only existing FDA approved second-line treatment regimen in PDA patients is 5-FU plus irinotecan liposome, which demonstrated a modest OS and response rate benefit compared to 5-FU alone (Wang-Gillam *et al.*, 20). If found to demonstrate an efficacy signal, the chosen BAY 1895344 plus irinotecan combination could be compared against 5-FU plus irinotecan liposome to establish a second-line treatment standard in PDA patients who received initial gemcitabine-based therapy.

Given the early clinical experience from our trial, it has become evident that dosing changes to both escalation cohorts need to be considered. In the irinotecan arm (referred to as irinotecan cohort #1 throughout the protocol), at dose level 1 (irinotecan 150 mg/m2 D1 and BAY 1895344

20 mg BID D1,2), 2 of 3 DLTs were encountered in patients (febrile neutropenia and grade 3 thrombocytopenia with bleeding), making it the maximal administered dose. The -1 dose level is currently enrolling patients. After discussions with Bayer and CTEP on a Project Team call on 1/31/2022, the following new preclinical data was presented that we believe supports consideration of an alternative irinotecan plus BAY 1895344 escalation arm (referred to as irinotecan cohort#2 throughout the remainder of the protocol). *In vitro* data (**Figure 7**) suggests that the strongest synergy between irinotecan plus BAY 1895344 occurs when the ATR inhibitor is administered sequentially, 24 hours after the top1 inhibitor. Concomitant treatment of the two agents demonstrates 4-fold less synergy.

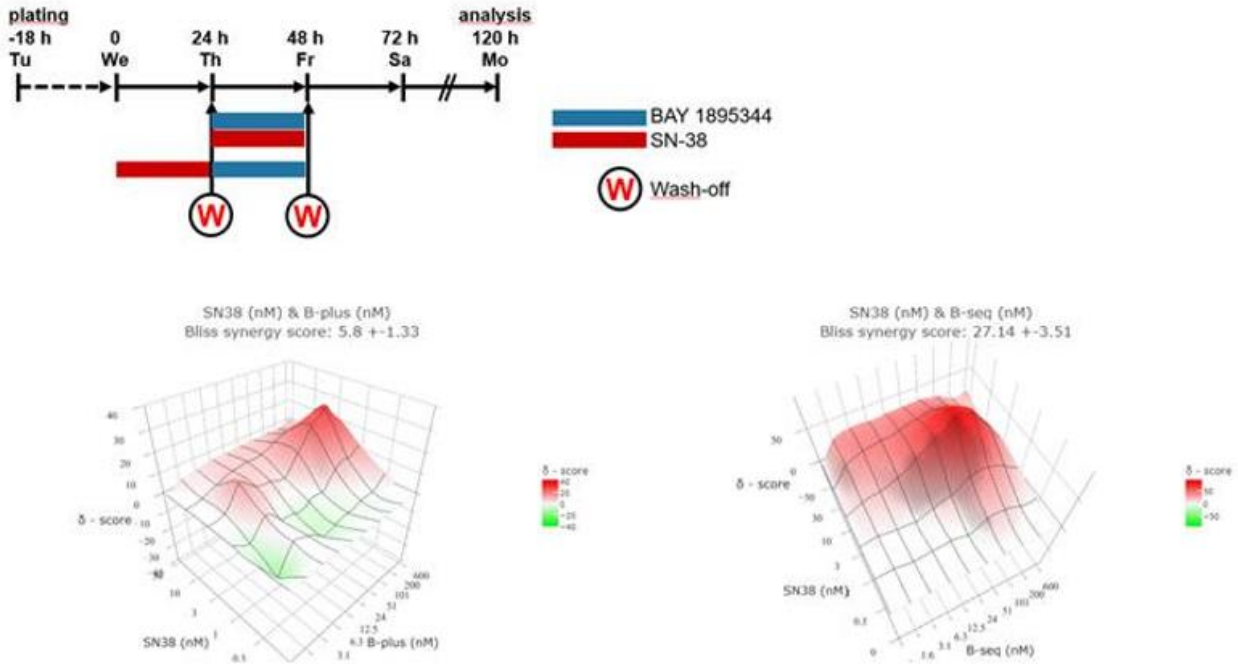


Figure 7: In vitro evaluation of the irinotecan metabolite SN-38 plus BAY 1895344 in HT29 CRC cell line looking at Bliss synergy score.

In vivo studies in the COLO205 xenograft model support sequential administration of low dose irinotecan with BAY 1895344 (**Figure 8).** In this model, weekly IV irinotecan 30 mg/kg followed by PO BAY 1895344 40 mg/kg two days on, 5 days off (on D2,3) induced the most profound tumor regression compared to monotherapy with each of the agents at the MTD. The tumor regression observed with this schedule was even more profound than weekly IV irinotecan 30 mg/kg followed by PO BAY 1895233 40 mg/kg 1 day on, 6 days off (D2).

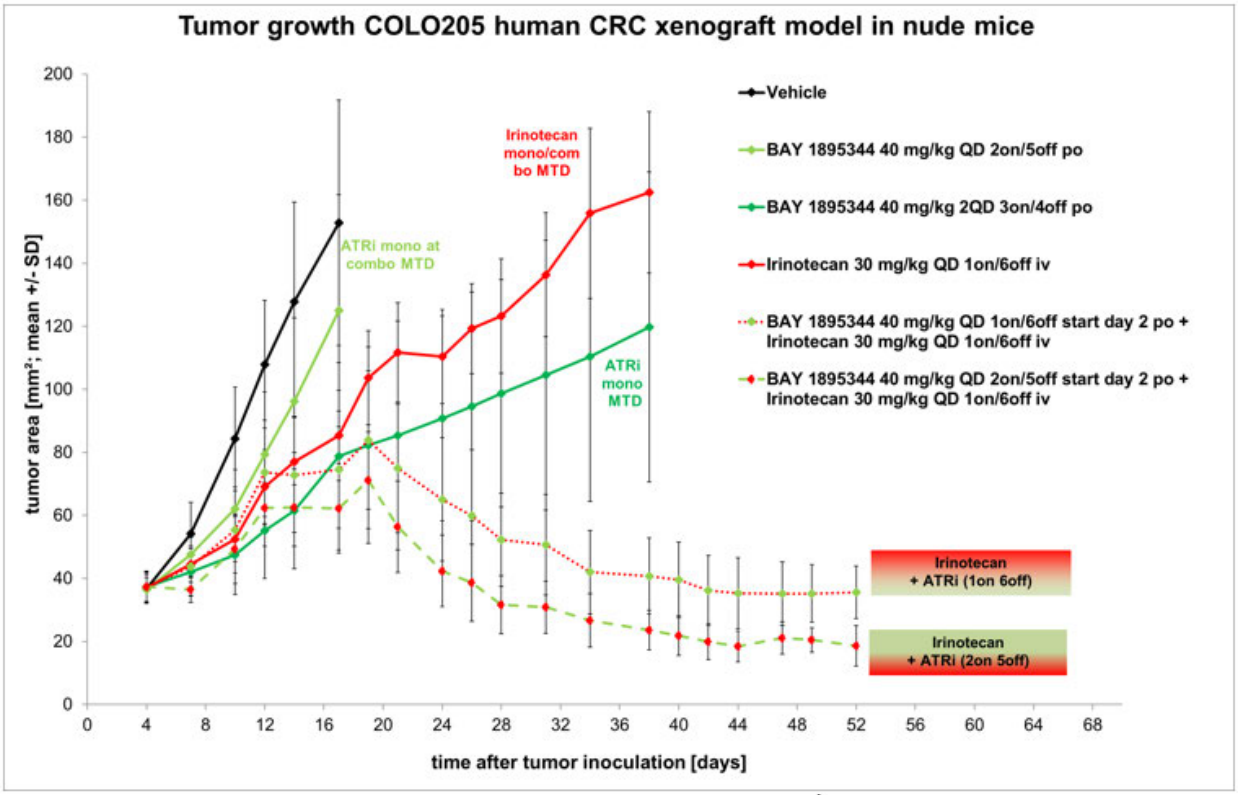


Figure 8: COLO205 xenograft models treated with BAY 1895344 monotherapy or in combination with irinotecan at various dosing schedules.

It is likely that the early toxicity experience observed in our trial is due to overdosing of the top1 inhibitors. This dosing schedule affords an ability to circumvent that and explore whether it is feasible to escalate BAY 1895344 so that meaningful anti-tumor activity can be observed in study patients. If allowed to open this separate dose escalation cohort, we will choose between this alternative escalation scheme and the original irinotecan escalation scheme to choose which schedule should be moved forward for the expansion cohort in PDA patients. Further, the Bayer team is highly interested in developing the dose schedule in irinotecan cohort #2 in other disease sites and will utilize the safety information gleaned from our study to do so.

In the topotecan arm, at dose level 1 (topotecan 1 mg/m2 D1-5, BAY 1895344 20 mg BID D2,5), despite growth factor support, the first patient experienced a DLT (G4 thrombocytopenia) and ultimately succumbed to sepsis from a pneumonia. A second patient also experienced a DLT (G4 thrombocytopenia), making dose level 1 the maximal administered dose. Given the fact that we have two expansion cohorts with topotecan plus BAY 1895344 (PD-NEC, SCLC), it is very important for the success of this trial to define a safe RP2D to move forward in these cohorts. After our discussions with Bayer and CTEP on the Project Team call, we are proposing the addition of three lower dose levels (-2, -3 and -4 levels) to the current dose escalation scheme along with a change in the -1 level dosing of BAY 1895344 to QD. With these additions, we believe we will at least be able to define a RP2D to move forward to the expansion cohorts.

2.5 Correlative Studies Background

2.5.1 ɣH2AX, pNBS1 IFA with βCATN segmentation.

γ-H2AX and pS343-NBS1 represent biomarkers of DNA damage. γ-H2AX is a well validated marker of DNA double-strand breaks while pS343-NBS1 more specifically represents a marker of DDR signaling through the homologous recombination pathway (Redon *et al.*, 2010, Kinders *et al.*, 2010, Lee *et al.*, 2007, Wu *et al.*, 2000, Deshpande *et al.*, 2016). βCATN segmentation refers to a tumor segmentation technique used to quantify y-H2AX and p-NBS1 through the multiplex immunofluorescence (an NCLN pharmacodynamic assay).

We will obtain pretreatment biopsies to measure baseline levels of γ-H2AX and pS343-NBS1 and on-treatment biopsies during Cycle 1 to measure stimulated levels of γ-H2AX and pS343-NBS1 after exposure to the experimental combinations. We anticipate a spike in levels of both markers post-treatment and believe the degree of rise may be correlated with extent of anti-tumor response in individual patients.

γ-H2AX and pS343-NBS1 have been measured in preclinical and clinical settings. Most recently, Wilsker *et al.* Measured their levels in human xenografts and from tumor tissue in patients being treated on an experimental study (Wilsker *et al.*, 2019). pS343-NBS1 rise was detected within 2 hours of treatment and the signal was sustained for 24 hours. γ-H2AX rose in in a delayed fashion after 24 hours. Baseline levels for these biomarkers was also established from this analysis at a nuclear area positive (NAP) of ≤ 4% (from analysis of an array of human tumor specimens); thus, activated levels are considered when post-treatment NAP > 4%. These biomarkers were measured from pre- and post-treatment biopsies in 3 colorectal cancer patients being treated with temozolomide plus the experimental DDR inhibitor TRC102. Individual patients differed in induction levels of γ-H2AX and pS343-NBS1, however activated levels were consistently > 4% NAP.

2.5.2 Whole Exome Sequencing (WES)

We are primarily interested in assessing whether certain gene mutations in tumor DDR genes are associated with improved responsiveness to the experimental combinations being tested in our study. Many of these genes (*ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FAM175A, FANCM, GEN1, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, RAD51B, RAD51C, RAD51D, RB1, SLX4, TP53 and XRCC2*) are involved directly or indirectly with homologous recombination, though also cross-talk with other pathways of DDR.

We anticipate that patients with tumors with some of these DDR gene mutations will be particularly responsive to the BAY 1895344 plus top1 inhibitor combinations due to an inability to repair the DNA damage elicited by the treatments.

The DDR genes we have identified have been validated across assays in breast, ovarian and most recently prostate cancer however are merely being used for exploratory purposes in this study (Walsh *et al.*, 2015, De Bono *et al.*, 2020). Furthermore, BAY 1895344 has potent antitumor activity in multiple DDR deficient xenograft models including CRC, prostate and lymphoma xenografts (Investigator's Brochure, 2019). The agent also demonstrated meaningful antitumor

effects in patients with tumors with DDR defects in its phase I monotherapy study (De Bono *et al.*, 2019).

2.5.3 RNA Sequencing (RNA Seq)

We are primarily interested in assessing whether certain gene mutations in tumor DDR genes are associated with improved responsiveness to the experimental combinations being tested in our study. Many of these genes (*ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FAM175A, FANCM, GEN1, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, RAD51B, RAD51C, RAD51D, RB1, SLX4, TP53 and XRCC2*) are involved directly or indirectly with homologous recombination, though also cross-talk with other pathways of DDR. Beyond exploring DDR gene mutations through exome sequencing, we are also interested in the mRNA expression of these genes and thus are utilizing RNA Seq.

We anticipate that patients with tumors with some of these DDR gene mutations will be particularly responsive to the BAY 1895344 plus top1 inhibitor combinations due to an inability to repair the DNA damage elicited by the treatments.

The DDR genes we have identified have been validated across assays in breast, ovarian and prostate cancer however are merely being used for exploratory purposes in this study (Walsh *et al.*, 2015, De Bono *et al.*, 2020). Furthermore, BAY 1895344 has potent antitumor activity in multiple DDR deficient xenograft models including CRC, prostate and lymphoma xenografts (Investigator's Brochure, 2019). The agent also demonstrated meaningful antitumor effects in patients with tumors with DDR defects in its phase I monotherapy study (De Bono *et al.*, 2019).

2.5.4 ATM Expression

Tumors with ATM deficiency are reliant on ATR for homologous recombination repair. This creates an opportunity for synthetic lethality in these tumors by inhibiting ATR. Study patients with ATM deficient tumors will be particularly susceptible to the combination of BAY 1895344 plus top1 inhibitors. ATM loss has been well validated as a predictive biomarker for ATR inhibitors. In preclinical and clinical experience with BAY 1895344 as a monotherapy, ATM loss has been the strongest predictive marker for anti-tumor effect (Investigator's Brochure, 2019, De Bono *et al.*, 2019). Other ATR inhibitors such as M6620 have also demonstrated profound anti-tumor effect in patients with tumors with ATM loss (Yap *et al.*, 2015).

2.5.5 PK BAY 1895344

BAY 1895344 is a novel agent, and the proposed PK studies will further define the properties in a homogeneous population. In addition, monotherapy BAY 1895344 has its own bone marrow suppressive toxicity, allowing us to explore correlations of exposure with toxicity and/or response. BAY 1895344 exposure correlates with toxicity. The pharmacokinetic profile of BAY 1895344 has been well described in its phase I monotherapy study (DeBono *et al.*, 2019).

2.5.6 PK Topotecan

The PK analysis of the topotecan and BAY 1895344 combination is of specific interest because topotecan is a substrate of breast cancer resistance protein (BCRP) while BAY 1895344 is an inhibitor of the protein (Molina *et al.*, 2008). Theoretically, the ATR inhibitor may increase intracellular concentrations of topotecan which makes this analysis particularly salient.

We anticipate that BAY 1895344, at its dosing schedule, will not significantly elevate intracellular concentrations of topotecan and lead to excess toxicity in study patients.

2.5.7 PK Irinotecan

The PK analysis of the irinotecan and BAY 1895344 combination is of specific interest because both irinotecan and BAY 1895344 are glucuronidated.

We anticipate that BAY 1895344, at its dosing schedule, will not significantly change the glucuronidation of irinotecan and lead to excess toxicity in study patients.

2.5.8 ctDNA Sequencing

Tumor DDR mutations are now also able to be detected from ctDNA in addition to from tumor tissue. At times, ctDNA may be a means of detecting tumor mutations when tumor tissue is insufficient. The rationale for testing ctDNA for these DDR mutations is identical to the rationale described above for the WES section. Furthermore, by obtaining post-progression ctDNA from dose-expansion cohort patients, we may be able to detect dynamic changes in certain tumor gene expression patterns which may suggest particular resistance mechanisms to the experimental therapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Dose Escalation Cohorts

3.1.1.1 Patients must have a biopsy-proven solid tumor that is metastatic or unresectable and has progressed on at least one line of standard therapy.

3.1.1.2 Patients must have a solid tumor for which irinotecan or topotecan is considered standard of care.

3.1.2 Dose Expansion Cohorts

3.1.2.1 Patients must have biopsy proven metastatic or unresectable SCLC, PD-NEC (any extrapulmonary neuroendocrine carcinoma with small cell or large cell histology) or PDA and have progressed on at least one line of standard therapy.

3.1.2.2 Patients must have at least one measurable lesion outside of the lesion to be biopsied.

3.1.3 Dose Escalation and Dose Expansion Cohorts

3.1.3.1 Patients must be able to swallow pills.

3.1.3.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of BAY 1895344 in combination with irinotecan or topotecan in patients <18 years of age, children are excluded from this study..

3.1.3.3 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).

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

- Hemoglobin > 9 g/dL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤ 2 × institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN (≤5 X institutional ULN if liver metastases present)
- glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2 (see Appendix B)

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

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

3.1.3.7 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.3.8 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression. Furthermore, these patients must be asymptomatic from previously treated brain metastases (*e.g.* not on steroids for neurologic symptoms within 30 days of study enrollment).

3.1.3.9 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.3.10 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.3.11 The effects of BAY 1895344 on the developing human fetus are unknown. For this reason and because DNA-damage response inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for 6 months after completion of BAY 1895344 administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of BAY 1895344 administration.

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

3.2 Exclusion Criteria

3.2.1 Patients who have previously been treated with irinotecan will not be eligible to participate in the irinotecan arm and patients who have previously been treated with topotecan will not be eligible to participate in the topotecan arm. However, patients who previously received irinotecan may be treated with topotecan (and vice versa) should the other agent be considered a possible standard of care for their disease. Patients who have previously been treated with BAY 1895344 will be excluded from the study.

3.2.2 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

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

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 The investigator(s) must state a medical or scientific reason if patients who have brain metastases will be excluded from the study.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BAY 1895344 or other agents used in study.

3.2.7 Patients receiving any medications or substances that are substrates of CYP3A4 with a narrow therapeutic window, or strong inhibitors/inducers of CYP3A4 are ineligible, if they cannot be transferred to alternative medication. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be

counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Appendix C should be presented to the patient.

3.2.8 Patients with uncontrolled intercurrent illness.

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

3.2.10 Pregnant women are excluded from this study because BAY 1895344 is agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with BAY 1895344, breastfeeding should be discontinued if the mother is treated with BAY 1895344. These potential risks may also apply to other agents used in this study.

3.2.11 Patients with an uncontrolled infection requiring IV antibiotics will not be eligible to participate in the study.

3.2.12 Patients on strong CYP3A4 inhibitors must discontinue them at least 1 week prior to starting irinotecan therapy.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- 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 Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the

RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

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

IRB Approval

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide 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).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the 10402 protocol page located on the CTSU website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,

- Click on Protocols tab in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-CT018 / Yale University Cancer Center LAO and protocol number 10402.
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For 10402 Site Registration

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

4.2.3 Submitting Regulatory Documents

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

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

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

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating

roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

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

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

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

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

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

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

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

4.3.2 Special Instructions for Patient Enrollment

Every other slot in dose escalation will be available to a non-Yale LAO (LAO-CT018) and must be approved by the principal investigator. All slot enrollments will proceed through IWRS as above.

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

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

Detailed instructions on the use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

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

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 21 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival (all cohorts)		
Dose escalation and expansion:	Formalin-fixed paraffin-embedded (FFPE) tumor rich tissue block (preferred)[1] If archival tissue is not available, then tissue obtained at D -7[2] will be utilized. (dose expansion only) If archival tumor tissue block is not available, then submit: • 1 H&E stained slide (3-5 µm) • 15-20 (10-micron) unstained uncharged slides from resection specimens or 30-50 (10-micron) unstained uncharged slides from biopsy specimens	EET Biobank
Baseline (all cohorts)		

	• 20 mL whole blood in Streck cfDNA tubes (mandatory)	EET Biobank
Day -7[2] (all cohorts)		
Dose expansion	• 2 tissue cores, flash frozen[3] (mandatory) • 1-2 tissue cores in formalin[3] (mandatory)	EET Biobank
C1D1 (Irinotecan cohort #1)		
Dose escalation and expansion: Pre-infusion, 30 min, 1 hr, 1 hr 20 min, 2 hr, 4 hr, 6 hr, (and 8 hr if possible)	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D1 (Alternative Irinotecan cohort)		
Dose escalation and expansion: Pre-infusion, 30 min, 1 hr, 1hr 20 min after start; 30 min, 2h 30min, 4h 30 min after end of infusion	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D1 (topotecan cohort)		
Dose escalation and expansion: Pre-infusion, 5 min, 15 min, and 25 minutes during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D2 (Irinotecan cohort #1)		
Dose escalation and expansion: Trough sample (pre 3rd BAY dose)	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory

C1D2 (Alternative Irinotecan cohort)		
Dose escalation and expansion: Pre-BAY 1895344, 30 min, 1 hour, 1 hour 20 min, 2 hour, 4 hour and 6 hour (and 8 hour if possible) post-dose (in expansion cohort patients undergoing biopsies on this day the 2 hour, 4 hour and 6 hour post-dose blood draws may be skipped)	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
Dose expansion: 2-5 hours post-BAY 1895344	• 2 tissue cores, flash frozen[3] (mandatory)	EET Biobank
C1D2 (topotecan cohort)		
Dose escalation and expansion: Pre-infusion, 5 min, 15 min, and 25 min during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D3 (topotecan cohort)		
Dose expansion: Pre D3 infusion	• 2 tissue cores, flash frozen[3] (mandatory)	EET Biobank
Dose escalation and expansion: Pre D3 infusion	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D3 (Irinotecan cohort #1)		

Dose expansion:	• 2 tissue cores, flash frozen[3] (mandatory)	EET Biobank
Dose escalation and expansion: Appr. 48 h post 1st BAY dose	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D3 (Alternative Irinotecan cohort)		
Dose escalation and expansion: Trough sample (Pre-2nd BAY 1895344 dose)	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
C1D4 (topotecan cohort)		
Dose escalation and expansion: Pre D4 infusion	• 1 x 3-5 mL blood in purple-top EDTA tube, processed for plasma and frozen, per time point (mandatory)	Beumer Laboratory
Disease Progression (all cohorts)		
	• 20 mL whole blood in Streck cfDNA tubes (optional)	EET Biobank

[1]For archival tissue, **a copy of the corresponding anatomic pathology report, labeled with the patient study ID and Universal ID, must be sent with the tissue and uploaded to Rave.** If submitting slides, then slides must be processed in order, and numbered sequentially.
[2] Day -7 (±3 days). Specimens are collected after patient registration.
[3]For new biopsies, a fine needle aspirate (FNA) should be obtained for diagnostic purposes and submitted to pathology. Cores should be obtained for research and not submitted to pathology for review. **The Tissue Biopsy Verification Form (Appendix F, a copy of the radiology and/or operative reports from the tissue removal procedure *and* the diagnostic anatomic pathology report** must be sent with the tissue to the EET Biobank. All reports must be labeled with the patient study ID and Universal ID

Of note: only one irinotecan cohort will move to dose expansion and only one set of instructions will be followed in dose expansion.

5.2 Summary Tables for Interventional Radiologist for Research Biopsies

Biopsy #: 1
Trial Time Point: Archival or D-7
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient)

Core Priority	Use in the Trial	Biomarker Name(s)	Tumor Content Required	Post-Biopsy Processing
1	Integrated	ɣH2AX, pNBS1 IFA with βCATN segmentation	25-50%	Frozen
2	Exploratory	Whole Exome Sequencing (WES)	>20%	FFPE
3	Exploratory	RNA Sequencing (RNA Seq)	>20%	FFPE
4	Exploratory	ATM	>50%	FFPE

Biopsy #: 2 (irinotecan cohort #1)
Trial Time Point: C1D3
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient)

Core Priority	Use in the Trial	Biomarker Name(s)	Tumor Content Required	Post-Biopsy Processing
1	Integrated	ɣH2AX, pNBS1 IFA with βCATN segmentation	25-50%	Frozen

Biopsy #: 2 (irinotecan cohort #2)
Trial Time Point: C1D2
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient)

Core Priority	Use in the Trial	Biomarker Name(s)	Tumor Content Required	Post-Biopsy Processing
1	Integrated	ɣH2AX, pNBS1 IFA with βCATN segmentation	25-50%	Frozen

Biopsy #: 2 (topotecan)
Trial Time Point: C1D3 (topotecan cohort)
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient)

Core Priority	Use in the Trial	Biomarker Name(s)	Tumor Content Required	Post-Biopsy Processing

1	Integrated	ɣH2AX, pNBS1 IFA with βCATN segmentation	25-50%	Frozen

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

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

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

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

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

5.3.2 Scheduling of Specimen Collections for the EET Biobank

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

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

5.3.3 Scheduling of Specimen Collections for the Beumer Laboratory

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

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

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

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 2.5.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

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

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

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

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

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

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood

products – like serum and plasma):

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

5.4.2.2 Tissue Specimen Labels

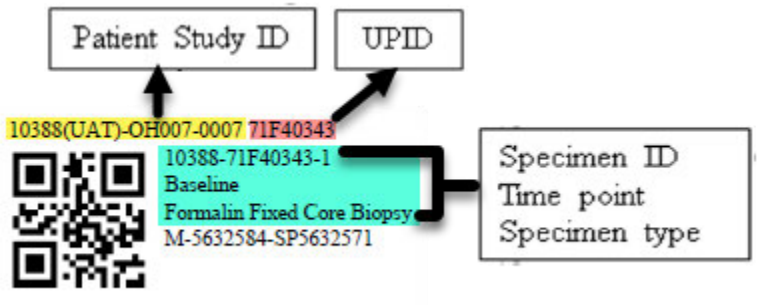
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

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

5.4.2.3 Example of Specimen Label Generated by STS

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

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



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

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

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

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

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

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

Registration without eligibility specimen analysis:

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

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

5.4.3.2 Rave Specimen Tracking Process Steps

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

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

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

Specimen ID.

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

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 5.4.2.

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

Step 3: Complete specimen data entry.

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

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

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

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

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

Step 6: Send email notification.

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

Step 7: Ship the specimen(s).

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

5.5 Specimen Collection

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

A copy of the corresponding anatomic pathology report must be sent with the Archival tissue and uploaded to Rave

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

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

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

- 1 H&E stained slide (3-5 μm)
- 15-20 (10-micron) unstained uncharged slides from resection tissue or 30-50 (10-micron) slides from biopsy tissue.
- Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n).

See Section 5.4.2 for labeling instructions.

5.5.2 Formalin-Fixed Tumor Biopsies

The Tissue Biopsy Verification Form (Appendix F), a copy of the radiology and/or operative reports from the tissue removal procedure *and* the diagnostic anatomic pathology report must be sent with the tissue and uploaded to Rave.

1. Label formalin-filled containers according to instructions in Section 5.4.2.
2. Obtain 1 to 2 16-gauge or 18-gauge core needle biopsy specimens, and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.6. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.

5.5.3 Collection of Snap-Frozen Biopsies

1. Follow step 5.3.1 to request specimen procurement kits for frozen sample collection before scheduled biopsy collection.
2. Biopsy specimens should be collected into pre-chilled 1.5mL Sarstedt, O-ring screw cap tubes (VWR, Cat#: 83009-010).
    a. Label Sarstedt tube(s) according to instructions in Section 5.4.2, prior to pre-chilling.
3. It is imperative that biopsies are flash frozen within 2 minutes of collection in order to preserve key pharmacodynamic biomarkers.
4. As described in Appendix G, place the tissue in a pre-chilled cryovial and freeze the tube in liquid nitrogen or dry ice/ethanol bath. Keep frozen at -80 ºC or lower until shipment to the EET Biobank.

Sites are strongly encouraged to contact the NCLN PD Laboratory at NCI_PD_Support@mail.nih.gov to initiate training and clarify biopsy collection procedure.

5.5.3 Blood Collection

5.5.3.1 Collection of Blood in EDTA Tubes for PK Plasma Processing

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

Document exact start and stop times of each infusion and drug dose, and exact times of blood draws per Appendices H–M.

Drawing and Processing

1. Invert the vacutainer tubes several times to mix blood with EDTA anticoagulant and immediately place on ice.
2. Processing should begin within 30 minutes of collection.
3. Samples should be centrifuged for 10 min at approximately 1000 x g in a refrigerated tabletop centrifuge so as to produce plasma.
4. The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes (See Section 5.4.2.1), and stored at -70 °C until shipment.

5.5.3.2 Collection of Blood in Streck cfDNA Tubes

1. Label two 10-mL Streck cfDNA tubes according to the instructions in Section 5.4.2.
2. Collect 10 mL blood in each Streck tube and gently invert tube to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. Heparin should be

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

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

5.6 Shipping Specimens from Clinical Site to the EET Biobank

5.6.1 General Shipping Information

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For formalin-fixed biopsies, the surgical and/or radiology reports from the tissue removal procedure, the Tissue Biopsy Verification Form (Appendix F) and the diagnostic anatomic pathology report must be included in the package, or the specimen will not be processed.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be sent to the EET Biobank as soon as possible and uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

5.6.1.1 Required Forms for Specimen Submissions

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

Tissue	**Required Forms**
Archival	1. Shipping List 2. Corresponding Pathology Report
New Biopsy	1. Shipping List 2. Corresponding Pathology Report OR all three of the following: • Surgical and/or Radiology Report • Tissue Biopsy Verification Form (Appendix F) • Diagnostic Pathology Report

Tissue	Required Forms
Blood in Streck cfDNA Tube	1. Shipping List

5.6.2 Specimen Shipping Instructions

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

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

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

5.6.2.1 Shipping of FFPE Blocks and Glass Slides

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

5.6.2.2 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.

7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.

    Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.3 Shipping Frozen Specimens in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

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

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

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.2 and that lids of all primary receptacles containing liquid are tightly sealed.
2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Prepare the frozen specimens for shipment:
    a. Place the specimens into zip-lock bags.
    b. Place the zip-lock bags into a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the biohazard envelope.
    c. Put each biohazard envelope into a Tyvek envelope. Expel as much air as possible and then seal the Tyvek envelope.
4. Quickly place the Tyvek envelope containing frozen specimens in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
5. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
6. Prepare the ambient specimens for shipment:
    a. Seal the lids of the formalin jars with parafilm. Place absorbent material around the primary container of each liquid specimen. Place the specimens into zip-lock bags.
    b. Place specimens inside the secondary pressure vessel with bubble wrap.
    c. Secure the lid on the secondary pressure vessel and set it inside the kit chamber.
7. Insert a copy of the required forms in the kit chamber with the ambient specimens.
8. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
9. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
10. Complete a FedEx air bill and attach to top of shipping container.
11. Complete a dry ice label.
12. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
13. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 Shipping Address

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

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

FedEx Priority Overnight service is very strongly preferred.

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

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

5.7 Shipping of Specimens from Clinical Site to Other Laboratories

5.7.1 Shipping of PK Specimens to Beumer Laboratory

5.7.1.1 Specimen Shipping Instructions

Preparing the Shipment

1. Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", L x W x H).
2. Please organize the samples by patient and time point in the box.
3. Do not store in plastic bags (they break on dry-ice and labels will detach).
4. A copy of each of the pharmacokinetic sample collection forms (Appendix H-M) for the respective patients should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them and numbering samples on the sample sheet.
*Note the study number, PI, and the drugs used/to be measured.
*A name, phone number, and email address should be included with the samples so that receipt can be acknowledged.
5. Please notify the lab by email (PITT-PK@UPMC.EDU), telephone (412-623-3248) or fax (412-623-1212) at least 24 hours prior to shipment.

Regulations:

Shipment of samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture-resistant (e.g. cardboard mailing tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

5.7.1.2 Shipping Address

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

Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC hillman cancer center
Room G27 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

5.7.1.3 Contact Information for Assistance
Lab phone: 412-623-3248
Lab fax: 412-623-1212
PK Lab email: PITT-PK@upmc.edu
PK director email: beumerjh@upmc.edu

5.8 Biomarker Plan

List of Biomarker Assays in Order of Priority

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

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	γH2AX, pNBS1 IFA with βCATN segmentation	Multiplex IFA CLIA: N	Integrated To measure biomarkers of DNA damage elicited by the treatment combination.	Fresh Frozen Tumor	Dose Expansion: D-7* and C1D3 (irinotecan cohort #1) D-7* and C1D2 (2-5 hours post-BAY 1895344) (irinotecan cohort #2) D-7* and C1D3 (Pre-infusion) (topotecan)	M	NCLN PD Assay Laboratory at MD Anderson Kate Ferry-Galow, Ph.D. ferrygalowkv@mail.nih.gov
2	Whole Exome Sequencing (WES)	NGS CLIA: N	Exploratory To determine whether certain gene mutations (in DDR genes) predict sensitivity to the treatment combinations. The genes of interest in our query include the specific listed genes.[1]	DNA from FFPE Tumor Tissue	Dose Escalation: Archival Dose Expansion: Archival or D-7*	O	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	RNAseq	NGS CLIA: N	Exploratory To determine whether certain RNA expression mutations in DDR genes predict sensitivity to the treatment combinations. The genes of interest in our query include the specific listed genes. [1]	RNA from FFPE Tumor Tissue	Dose Escalation: Archival Dose Expansion: Archival or D-7*	O	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov
4	ATM	ATM IHC (Clone Y170, Abcam) CLIA: N	Exploratory To identify patients in the trial with tumors which are particularly responsive to ATR inhibition.	FFPE Tumor Tissue Block	Dose Escalation: Archival Dose Expansion: Archival or D-7*	O	Ventana
Blood-based Biomarkers							

1	PK BAY 1895344	LC-MS CLIA: N	Integrated	Plasma from blood in EDTA	Dose Escalation and Dose Expansion: Irinotecan Cohort #1: C1D1 (Pre-infusion, 30 min, 1 hr, 1 hr 20 min, 2 hr, 4 hr, 6 hr, and possibly 8h) C1D2 (24 hr post-BAY dose 1) C1D3 (48 hr post-BAY dose 1) Irinotecan Cohort #2: C1D1 (Pre-infusion, 30 minutes, 1 hr, 1 hr 20 min after start; 30 min, 2 hr 30 min, 4h 30 min after end of infusion) C1D2 (Pre-BAY 1895344 dose, 30 min, 1 hour, 1 hour 20 min, 2 hour** 4** hour and 6** hour (and 8 hr if possible) post-dose) C1D3 (Trough sample) pre-2nd BAY 1895344 Topotecan Cohort: C1D1 (Pre-infusion, 5 min, 15 min, and 25 minutes during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion) C1D2 (Pre-infusion, 5 min, 15 min, and 25 min during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion)	M	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center Jan Beumer beumerjh@upmc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
					C1D3 (Pre-infusion) C1D4 (Pre-infusion) The PK time points are approximate. Please collect samples as close to times listed above as possible. Document actual collection times on the PK sheets.		

2	PK Topotecan	LC-MS CLIA: No	Integrated	Plasma from blood in EDTA	Dose Escalation and Dose Expansion: Irinotecan Cohort #1: C1D1 (Pre-infusion, 30 min, 1 hr, 1 hr 20 min, 2 hr, 4 hr, 6 hr, and possibly 8h) C1D2 (24 hr post-BAY) C1D3 (48 hr post-BAY) Irinotecan Cohort #2: C1D1 (Pre-infusion, 30 min, 1 hr, 1 hr 20 min after start; 30 min, 2h 30 min, 4h 30 min after end of infusion) C1D2 (Pre-BAY1895344 dose, 30 min, 1 hr, 1 hr 20 min, 2** hr, 4** hr and 6** hr, (and 8 hr if possible) post-dose C1D3 (Trough sample (Pre-2nd BAY 1895344 dose) Topotecan Cohort: C1D1 (Pre-infusion, 5 min, 15 min, and 25 minutes during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion) C1D2 (Pre-infusion, 5 min, 15 min, and 25 min during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion) C1D3 (Pre-infusion) C1D4 (Pre-infusion) The PK time points are approximate. Please	M	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center Jan Beumer beumerjh@upmc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
					collect samples as close to times listed above as possible. Document actual collection times on the PK sheets.		

3	PK Irinotecan	LC-MS/MS CLIA: No	Integrated	Plasma from blood EDTA	Dose Escalation and Dose Expansion: Irinotecan Cohort: C1D1 (Pre-infusion, 30 min, 1 hr, 1 hr 20 min, 2 hr, 4 hr, 6 hr, and possibly 8h) C1D2 (24 hr post-BAY) C1D3 (48 hr post-BAY) Irinotecan Cohort #2: C1D1 (Pre-infusion, 30 min, 1 hr, 1 hr 20 min after start; 30 min, 2h 30 min, 4h 30 min after end of infusion) C1D2 (Pre-BAY1895344 dose, 30 min, 1 hr, 1 hr 20 min, 2** hr, 4** hr and 6** hr, (and 8 hr if possible) post-dose C1D3 (Trough sample (Pre-2nd BAY 1895344 dose) Topotecan Cohort: C1D1 (Pre-infusion, 5 min, 15 min, and 25 minutes during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion) C1D2 (Pre-infusion, 5 min, 15 min, and 25 min during infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr post-infusion) C1D3 (Pre-infusion) C1D4 (Pre-infusion) The PK time points are approximate. Please collect samples as close	M	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center Jan Beumer beumerjh@upmc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
					to times listed above as possible. Document actual collection times on the PK sheets.		
4	ctDNA sequencing	NGS	Integrated Analysis of DNA damage response-related genes	Plasma from blood in cfDNA Streck Tube	Dose Escalation: Baseline Dose Expansion: Baseline and Disease Progression	M (baseline) O (disease progression)	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov
5	Whole Exome Sequencing (WES)	NGS	Exploratory Germline Control	DNA from buffy coat from blood in cfDNA Streck Tube	Dose Escalation: Baseline Dose Expansion: Baseline (Collected as part of ctDNA biomarker)	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov

**Day -7 (± 3 days)*
***For patients in irinotecan cohort #2 undergoing biopsies on C1D2, the 2 hour, 4 hour, and 6 hour post- BAY1895344 blood draws can be skipped*
[1] DDR genes of interest include the following: ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FAM175A, FANCM, GEN1, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, RAD51B, RAD51C, RAD51D, RB1, SLX4, TP53 and XRCC2.

5.9 Integrated Correlative Studies

5.9.1 ɣH2AX, pNBS1 IFA with βCATN segmentation

5.9.1.1 Specimen Receipt and Processing at the EET Biobank

Frozen cores will be sent to the Biobank and stored in a liquid nitrogen vapor phase freezer until shipment to the NCLN PD Laboratory for analysis.

5.9.1.2 Site Performing Correlative Study

This assay will be performed by NCLN PD Assay laboratory at MD Anderson, under the leadership of Dr. Kate Ferry-Galow, Ph.D.

5.9.1.3 Contact information for notification of specimen shipment

PathTQL@mdanderson.org

5.9.2 BAY 1895344 PK

5.9.2.1 Specimen Receipt and Processing at UPMC Hillman Cancer Center

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

5.9.2.2 Site Performing Correlative Study

This assay will be performed at Dr. Jan Beumer's laboratory at UPMC Hillman Cancer Center

5.9.2.3 Contact information for notification of specimen shipment

See Section 5.7.1.

5.9.3 Topotecan PK

5.9.3.1 Specimen Receipt and Processing at UPMC Hillman Cancer Center

Collection of blood Frozen Plasma aliquots will be received at the Beumer laboratory for processing and storage.

5.9.3.2 Site Performing Correlative Study

This assay will be performed at Dr. Jan Beumer's laboratory at UPMC Hillman Cancer Center

5.9.3.3 Contact information for notification of specimen shipment

See Section 5.7.1.

5.9.4 Irinotecan PK

5.9.4.1 Specimen Receipt and Processing at the UPMC Hillman Cancer Center

Collection of blood Frozen Plasma aliquots will be received at the Beumer laboratory for processing and storage.

5.9.4.2 Site Performing Correlative Study

This assay (irinotecan, SN38, SN-38-G) will be performed at Dr. Jan Beumer's laboratory at the University of Pittsburgh.

5.9.4.3 Contact information for notification of specimen shipment

See Section 5.7.1.

5.9.5 ctDNA Sequencing

5.9.5.1 Specimen Receipt and Processing at the EET Biobank

. Whole blood collected in Streck cfDNA tubes will be centrifuged to separate plasma. Following plasma processing, DNA will be processed from blood at baseline. At disease progression, plasma and buffy coat will be processed and stored. Plasma and buffy coat aliquots will be stored in a -80°C freezer.

5.9.5.2 Site Performing Correlative Study

ctDNA sequencing will be performed at MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Dr. Chris Karlovich (chris.karlovich@nih.gov).

5.9.5.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.5.4 Contact information for notification of specimen shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 Whole Exome Sequencing

5.10.1.1 Specimen Receipt and Processing at the EET Biobank

FFPE tissue blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection, when needed. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA will be shipped to the central sequencing laboratory for analysis.

DNA will be extracted from blood collected in Streck cfDNA tubes at baseline, following whole blood processing. DNA will be quantitated, and then stored in a -80°C freezer until shipping for analysis.

5.10.1.2 Site Performing Correlative Study

This assay will be performed by MoCha, Frederick National Laboratory for Cancer Research (FNLCR), under the leadership of Dr. Chris Karlovich (chris.karlovich@nih.gov).

5.10.1.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.10.1.4 Contact information for notification of specimen shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10.2 RNA Sequencing

5.10.2.1 Specimen Receipt and Processing at the EET Biobank

FFPE tissue blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection, when needed. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of RNA will be shipped to the central sequencing laboratory for analysis.

5.10.2.2 Site Performing Correlative Study

This assay will be performed by MoCha, Frederick National Laboratory for Cancer Research (FNLCR), under the leadership of Dr. Chris Karlovich (chris.karlovich@nih.gov).

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

Specimens will be shipped from the EET Biobank to:
MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.10.2.4 Contact information for notification of specimen shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10.3 ATM Expression

5.10.3.1 Specimen Receipt and Processing at the EET Biobank

Archival (preferably from within 6 months) or pretreatment tissue from study patients will be sent to EET Biobank for storage at room temperature. Tissue received in formalin will be processed and embedded in paraffin, and stored as an FFPE tissue block at room temperature. Uncut tissue blocks are required for this assay. The specific Bayer laboratory where samples will be shipped has not yet been delineated. Any FFPE tumor tissue remaining will be returned to the EET Biobank for long term storage.

5.10.3.2 Site Performing Correlative Study

This assay will be performed by an internal Bayer laboratory. The specific Bayer laboratory where the samples will be shipped has not been determined.

5.10.3.3 Contact information for notification of specimen shipment

Bayer CRO. Contact information will be provided once available.

6. TREATMENT PLAN

6.1 Agent Administration

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

The dose escalation schemes for each combination are listed in the following tables.

If dose level 3 is not tolerated due to DLTs encountered beyond the acceptable threshold, the following alternative de-escalation scheme will be employed with the subsequent dose level being level 2B.

Dose Escalation Schedule – Irinotecan Cohort #1				
Dose Level	**BAY 1895344 (PO)**	**Irinotecan (IV)**	**Cycle Length**	**Status**
Level -1	10 mg BID, Days 1, 2	150 mg/m^2, Day 1	14 Days	Dose escalation ongoing
Level 1*	20 mg BID, Days 1, 2	150 mg/m2, Day 1		Closed, 3 DLTs
Level 2	20 mg BID, Days 1, 2	180 mg/m2, Day 1		Will not be evaluated
Level 2A[#]	60 mg BID, Day 2	180 mg/m2, Day 1		Will not be evaluated
Level 2B[#]	80 mg BID, Day 2	180 mg/m2, Day 1		Will not be evaluated
Level 3	40 mg BID, Days 1, 2	180 mg/m2, Day 1		Will not be evaluated
Level 4	60 mg BID, Days 1, 2	180 mg/m2, Day 1		Will not be evaluated
*Indicates starting dose level [#]Levels 2A and 2B will only enroll if Level 3 is not tolerated due to DLTs PO = Per Oral, IV = Intravenous, BID = Twice a Day				

Table below represents a new dose escalation cohort for irinotecan

Dose Escalation Schedule – Irinotecan Cohort #2			
Dose Level	**BAY 1895344 (PO) (D2,3,9,10,16,17)**	**Irinotecan (IV)(D1,D8,D15)**	**Cycle Length**
Level -2	10 mg QD	25 mg/m2	
Level -1	20 mg QD	25 mg/m2	21 Days
Level 1*	20 mg QD	50 mg/m2	
Level 2	40 mg QD	50 mg/m2	
Level 3	60 mg QD	50 mg/m2	

Level 4	80 mg QD	50 mg/m2	
Level 5	80 mg QD	75 mg/m2	

*Indicates starting dose level
**After completion of 2 cycles, all patients will be given a 1-week break and then will be switched to a 2-weks-on/1-week-off schedule. Thus, dosing on D16,D17 of BAY 1895344 and D15 irinotecan will be dropped.

PO = Per Oral, IV = Intravenous, BID = Twice a Day

For irinotecan cohort #1 only: If dose level 2 is not tolerated due to DLTs encountered beyond the acceptable threshold, the following alternative de-escalation scheme will be employed with the subsequent dose level being level 1B.

Dose Escalation Schedule - Topotecan				**Status**
Dose Level	**BAY 1895344 (PO)**	**Topotecan (IV)**	**Cycle Length**	
Level -3	10 mg QD, Days 2,5	0.5 mg/m2 Days 1-5		
Level -2	10 mg QD, Days 2,5	0.75 mg/m2, Days 1-5		
Level -1	20 mg QD, Days 2,5	0.75 mg/m2, Days 1-5		
Level 1*	**20 mg QD, Days 2,5**	**1 mg/m^2, Days 1-5**	**21 Days**	Escalation will not proceed higher than this dose
Old Level 1	**20 mg BID, Days 2,5**	**1 mg/m2, Days 1-5**		Maximum administered dose

***Indicates new starting dose level after amendment**

PO = Per Oral, IV = Intravenous, BID = Twice a Day

Regimen Description – Irinotecan Cohort #1					
Agent	***Premedications; Precautions***	***Dose****	***Route***	***Schedule***	***Cycle Length***
BAY 1895344	None	**	Oral, twice daily D1* and D2	Days 1 and 2, week 1	14 days (2 weeks)
Irinotecan	Premedicate with a steroid	**	IV over 90 minutes	Day 1	14 days (2 weeks)

	and antiemetic (e.g. ondansetron 12 mg IV), dexamethasone 8 mg IV 30 minutes prior to agent as per institutional guidelines. Subcutaneous atropine may be used for early onset cholinergic diarrhea as per institutional policy.				
**On days of co-administration, BAY 1895344 to be given at start of infusion (± 5 minutes). Please note this only applies to the traditional dose escalation scheme. If, as described above, dose level 2B or level 2A need to be explored, BAY 1895344 will only be administered on D2.* ***Doses as appropriate for assigned dose level. Doses may be rounded per institutional policy.* *Currently we are suggesting that physicians treat their patients with pegfilgrastim or a biosimilar on D3 and add levofloxacin 500 mg daily D8-D15 to mitigate hematotoxicity.*					
IV = intravenously; PO = by mouth					

Regimen Description – Irinotecan Cohort #2					
Agent	***Premedications; Precautions***	***Dose*****	***Route***	***Schedule***	***Cycle Length***
BAY 1895344	None	**	Oral, once daily	Days 2-3, 9-10 and 16-17*	21 days (3 weeks)
Irinotecan	Premedicate with a steroid and antiemetic (e.g. ondansetron 12 mg IV), dexamethasone 8 mg IV 30 minutes prior to agent as per	**	IV over 90 minutes	Day 1,8,15*	21 days (3 weeks)

	institutional guidelines. Subcutaneous atropine may be used for early onset cholinergic diarrhea as per institutional policy.				
**After 2 cycles, the day 16,17 of BAY 1895344 and day 15 dosing of irinotecan will be dropped* ***Doses as appropriate for assigned dose level. Doses may be rounded per institutional policy.*					
IV = intravenously; PO = by mouth					

Regimen Description – Topotecan Cohort					
Agent	***Premedications; Precautions***	***Dose*****	***Route***	***Schedule***	***Cycle Length***
BAY 1895344	None	**	Oral, once daily D2* and D5	Days 2 and 5, week 1	21 days (3 weeks)
Topotecan	Premedicate with an antiemetic. (e.g.,ondansetron 16 mg PO or IV) 30 minutes prior to topotecanas per institutional guidelines. Additionally, take home antiemetics are recommended as needed (e.g., ondansetron 8 mg PO q6 prn).	**	IV over 30 minutes	Days 1-5	21 days (3 weeks)
**On days of co-administration, BAY 1895344 to be given at start of infusion (± 5 minutes). If, as described above, dose level 1B or level 1A need to be explored, BAY 1895344 will only be administered on D2.* ***Doses as appropriate for assigned dose level. Doses may be rounded per institutional policy. Currently we are suggesting that physicians treat their patients with pegfilgrastim or a biosimilar on D6 and add levofloxacin 500 mg daily D8-D15 to mitigate hematotoxicity.*					

IV = intravenously; PO = by mouth; q6 prn = every 6 hours as needed

The treatment schedules of each BAY 1895344 plus top1 inhibitor combination are listed in following figures.

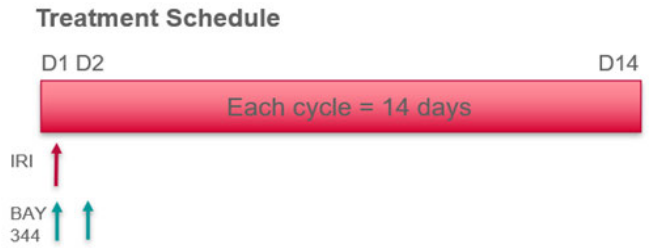


Figure 9: Treatment schedule for irinotecan plus BAY 1895344. Abbreviations: IRI = irinotecan; BAY344 = BAY 1895344.

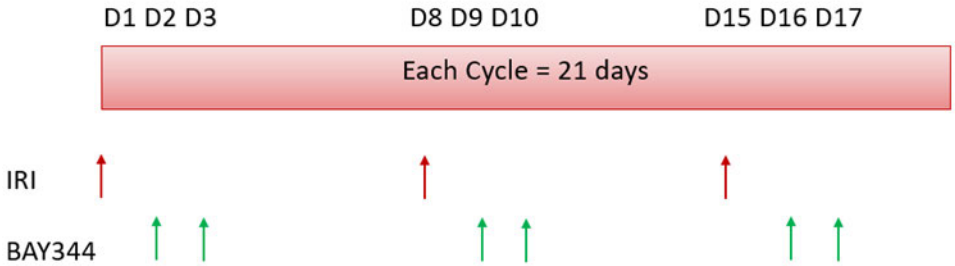


Figure 10: Treatment schedule for alternative irinotecan plus BAY 1895344. Abbreviations: IRI= irinotecan; BAY344 = BAY 1895344

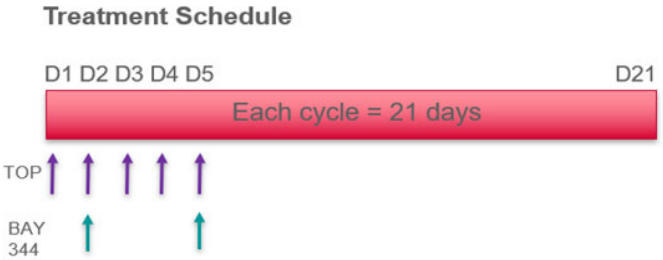


Figure 11: Treatment schedule for topotecan plus BAY 1895344. Abbreviations: TOP = topotecan; BAY344 = BAY 1895344.

Each top1 inhibitor is administered intravenously (IV) with irinotecan infused over 90 min and topotecan infused over 30 min. BAY 1895344 is an oral pill and is administered twice daily. On the days in each schedule when the drugs are both administered, BAY 1895344 will be given at the beginning of the infusion of each top1 inhibitor.

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

6.1.1 CTEP and/or CIP IND Agent(s)

BAY 1895344 tablets should be taken at least one (1) hour before or two (2) hours after a meal with approximately 240 mL of water. On days of co-administration, BAY 1895344 to be given at start of infusion (± 5 minutes)..

If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next dose as originally scheduled.

6.1.2 Irinotecan

Irinotecan is typically available in three single-dose sizes: 2, 5 and 15 mL-fill vials, respectively containing 40, 100 and 300 mg irinotecan hydrochloride.

Irinotecan vials should be stored consistent with the product label at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until time of until time of use.

Solution preparation: Irinotecan will be prepared consistent with established local procedures and the package insert:

- Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.
- Irinotecan injection is intended for single use only and any unused portion should be discarded.
- Irinotecan injection must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.
- The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing irinotecan and admixtures of irinotecan may result in precipitation of the drug and should be avoided.

Route of administration: Infuse diluted solution intravenously over 90 minutes.

6.1.3 Topotecan

Topotecan is a cytotoxic anticancer drug. Prepare topotecan under a vertical laminar flow hood while wearing gloves and protective clothing. If topotecan solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If topotecan contacts mucous membranes, flush thoroughly with water. Use procedures for proper handling and disposal of anticancer drugs.

Each 4-mg powder for injection vial of topotecan is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution or solution for injection is diluted in 5% Dextrose IV Infusion prior to administration. Topotecan will be administered as an intravenous infusion over 30 minutes

6.2 Definition of Dose-Limiting Toxicity

DLTs will be assessed only during cycle 1 and will be defined any of the following events that are possibly, probably or definitely related to treatment: grade 4 neutropenia lasting ≥ 7 days, grade 4 thrombocytopenia, grade 4 anemia, grade 3 neutropenia with fever, grade 3 thrombocytopenia with bleeding, any grade 3 hematologic toxicity lasting ≥ 7 days (counting from first day of toxicity grade recognition) or any non-hematologic grade ≥ 2 AEs lasting ≥ 7 days (with the exception of grade 2 fatigue, grade 2 nausea or grade 2 diarrhea) (counting from first day of toxicity grade recognition).

Patients will remain on study until they develop progression or can no longer tolerate the study treatment; the number of treatment cycles in the is study is not pre-determined.

Hematological:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <0.5 x 109/L) lasting >7 days
- Febrile neutropenia, defined as ANC <1000/mm3 with a single temperature of >38.3ºC (>101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour
- Neutropenic infection (ANC <1,000/mm3 or <1.0 x 109/L, and Grade >3 infection
- Grade ≥3 thrombocytopenia (platelet count <50.0 × 109/L) with bleeding
- Grade 4 thrombocytopenia (platelet count <25.0 x 109/L)
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated)

Non-hematological:

- Non-hematological toxicities:
    - Grade ≥4 toxicities
    - Grade ≥3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
    - Any non-hematologic grade ≥ 2 AEs lasting ≥ 7 days (with the exception of G2 fatigue, G2 nausea or G2 diarrhea) (counting from first day of toxicity grade recognition)) in any dose level
    - Grade 3 diarrhea lasting ≥ 72 hours despite maximal medical intervention
    - Grade 3 nausea/vomiting lasting ≥ 72 hours despite maximal medical intervention

- Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of dosing schedule of more than 14 days
- Any treatment-related event judged to be a DLT by the Safety Review Committee (Study PI and site PIs in concert with CTEP drug monitors)
- Any other toxicity in the first treatment cycle that in the opinion of the investigators and medical monitors is dose-limiting

The following toxicities will not be considered DLTs:

- Alopecia of any grade.
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

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

Dose escalation will proceed within each cohort according to the following scheme. DLTs are defined above.

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

< 2 out of 6 at highest dose level	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

The maximum tolerated dose (MTD) is defined as the highest dose level at which < 33% among 6 patients of the dose level (0 or 1 of 6) experience a DLT in the first cycle. For purposes of this study, the MTD will be the recommended phase II dose (RP2D). If 2 or more patients experience a DLT, we will adopt this dose level as the maximum administered dose (MAD) and the next lower dose will be evaluated as the MTD and the phase 2 dose.

6.3 Dose Expansion Cohorts:

Once the RP2D is reached, enrollment into the dose expansion cohorts will ensue. A single irinotecan RP2D (from the more tolerable escalation schedule) will be carried forward to the irinotecan dose expansion cohort in patients with PDA after discussions with CTEP. For the expansion cohorts, patients will continue to be monitored for occurrence of grade 4 hematologic toxicity, along with other adverse events. In each expansion cohort, if more than 1 of the first 3-6 patients or more than 2 of the first 7-10 patients experience grade 4 hematologic toxicity, study accrual will cease and the Principal Investigator will discuss with CTEP whether further addition of patients is needed to re-assess the RP2D in the dose escalation phase (see rule described in section 9.1.1). Additionally, the study will cease accrual to conduct a detailed toxicity review if 2 grade 4 hematologic toxicities are observed among the first 3 to 6 patients treated in each dose expansion cohort. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred. The secondary endpoints of changes in tumor expression patterns of γ-H2AX and pS343-NBS1 will be estimated for expansion cohort only study patients. We have accounted for up to 40% of the patients in the dose expansion phase to not undergo mandatory biopsies due to patient wishes or technical inability in our sample size calculation (Section 9.3). Patients who do not undergo mandatory biopsies in the dose expansion portions will be allowed to continue treatment and their data will be utilized.

6.4 General Concomitant Medication and Supportive Care Guidelines

6.4.1 BAY 1895344

Because BAY 1895344 is primarily metabolized by CYP3A4, drugs that are strong inhibitors or inducers of CYP3A4 should be avoided. BAY 1895344 has the potential to inhibit and induce CYP3A4 and 2C19, inhibit CYP2C8, 2C9, P-gp, BCRP, OAT1B1, and OAT1B3. CYP3A4 substrates with narrow therapeutic window should be avoided, and substrates of CYP2C8, 2C9, 2C19, 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.

Because there is a potential for interaction of BAY 1895344, Irinotecan, and topotecan with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix D (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

6.4.2 Irinotecan

Irinotecan is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

Patients should be advised to avoid any foods known to aggravate diarrhea. Avoid diuretics or laxatives in patients with diarrhea.

Monitor and replace fluid and electrolytes as clinically indicated. Consider antibiotic support for ileus, fever, or severe neutropenia.

Exposure to irinotecan or its active metabolite SN-38 is substantially reduced in patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort. The appropriate starting dose for patients taking these or other strong inducers such as rifampin and rifabutin has not been defined.

- Consider substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy.

- Do not administer strong CYP3A4 inducers with irinotecan unless there are no therapeutic alternatives.

Irinotecan and its active metabolite, SN-38, are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), respectively. Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan hydrochloride and its active metabolite SN-38.

Coadministration of irinotecan with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38.

- Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting irinotecan therapy.

- Do not administer strong CYP3A4 or UGT1A1 inhibitors with irinotecan unless there are no therapeutic alternatives.

The irinotecan infusion site should be monitored for signs of inflammation; care should be taken to avoid extravasation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

6.5 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.6 Duration of Follow-Up

If patients choose to participate in the study, they will be followed with clinic visits every 2 weeks or every 3 weeks depending on the drug combination they receive. After patients are removed from the study, they will be followed for six months or until death, whichever occurs

first. The follow-up will be through physician review of the charts and phone calls (every two months). For patients that are removed for reasons other than progression, they will be followed with office visits (every two months) and CT scans (every two months) until progression or starting a new therapy. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Irinotecan Cohort

No dose modifications of irinotecan may be made during cycle 1.

The dose of irinotecan may be reduced for drug-related toxicity (except during cycle 1) using the toxicity-dependent guidelines in the table below.

To initiate subsequent cycles of irinotecan, the day 1 ANC should be ≥ 1000/mm^3 and platelets ≥ 100,000/mm^3. Physicians may use growth factor support at their discretion to reduce the significance of future neutropenia. If patients were to experience symptomatic grade 3 anemia or grade 4 anemia with a treatment cycle, they may be transfused packed red blood cells (PRBCs) prior to next cycle initiation. Treatment interruptions may occur for a maximum of 14 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted. Dose reductions for BAY 1895344 will be based on the dose levels in Section 6.1.

Irinotecan Dose Modification Cohort #1

<table>
<tr><th>Toxicity
NCI CTCAE
v5.0</th><th>Occurrence</th><th>Irinotecan adjustment in patients receiving 180 mg/m2</th><th>Patients homozygous for UGT1A1*28 without previous increase to 180 mg/m2</th></tr>
<tr><td rowspan="4">Grade 3 or 4 adverse reactions</td><td colspan="3">Withhold irinotecan
Initiate loperamide for late onset diarrhea of any severity.
Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1 resume irinotecan at:
Upon recovery to ≤ Grade 1, resume irinotecan at:</td></tr>
<tr><td>First</td><td>150 mg/m2</td><td>120 mg/m2</td></tr>
<tr><td>Second</td><td>120 mg/m2</td><td>90 mg/m2</td></tr>
<tr><td>Third</td><td>Discontinue irinotecan</td><td>Discontinue irinotecan</td></tr>
<tr><td>Interstitial Lung Disease</td><td>First</td><td>Discontinue irinotecan</td><td>Discontinue irinotecan</td></tr>
</table>

Anaphylactic Reaction	First	Discontinue irinotecan	Discontinue irinotecan

Irinotecan Dose Modification Cohort #2

Toxicity NCI CTCAE v5.0	Occurrence	Irinotecan adjustment in patients receiving 50 mg/m2	Patients homozygous for UGT1A1*28 without previous increase to 50 mg/m2
Grade 3 or 4 adverse reactions	Withhold irinotecan Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1 resume irinotecan at: Upon recovery to ≤ Grade 1, resume irinotecan at:		
	First	40 mg/m2	25 mg/m2
	Second	25 mg/m2	20 mg/m2
	Third	Discontinue irinotecan	Discontinue irinotecan
Interstitial Lung Disease	First	Discontinue irinotecan	Discontinue irinotecan
Anaphylactic Reaction	First	Discontinue irinotecan	Discontinue irinotecan

Nausea	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold* until < Grade 1. Resume at 1 dose level lower, if indicated.**	Hold* until < Grade 1. Resume at 1 dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
≤ Grade 1	No change in dose	No change in dose

Vomiting	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at 1 dose level lower, if indicated.**	Hold* until < Grade 2. Resume at 1 dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2. Resume at 2 dose levels lower.***	Hold* until < Grade 2. Resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold* until resolved to baseline. Resume at same dose level.	Hold* until resolved to baseline. Resume at same dose level.
Grade 3	Hold* until resolved to baseline, then resume at one dose level lower, if indicated.**	Hold* until resolved to baseline, then resume at one dose level lower, if indicated.**
Grade 4	Hold* until resolved to baseline, then resume at 2 dose levels lower, if indicated.***	Hold* until resolved to baseline, then resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Neutropenia	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
≤ Grade 2	No change in dose	No change in dose
Grade 3	Hold* until ≤ Grade 2. Resume at 1 dose level lower.**	Hold* until ≤ Grade 2. Resume at 1 dose level lower.**
Grade 4	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***
Febrile Neutropenia****	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		

Neutropenia	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
****Febrile neutropenia defined as an absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour.		

Thrombocytopenia	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Irinotecan
≤ Grade 1	Hold* until platelets ≥ 100,000/mm^3, then resume with no change in dose.	Hold* until platelets ≥ 100,000/mm^3, then resume with no change in dose.
Grade 2	Hold* until platelets ≥ 100,000/mm3, then resume with no change in dose.	Hold* until platelets ≥ 100,000/mm^3, then resume with no change in dose.
Grade 3	Hold* until platelets ≥ 100,000/mm3, then resume at 1 dose level lower, if indicated.**	Hold* until platelets ≥ 100,000/mm^3, then resume at 1 dose level lower, if indicated.**
Grade 4	Hold* until platelets ≥ 100,000/mm3, then resume at 2 dose levels lower, if indicated.***	Hold* until platelets ≥ 100,000/mm^3, then resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		

7.2 Topotecan Cohort

No dose modifications of topotecan may be made during cycle 1.

The dose of topotecan may be reduced for drug-related toxicity (except during cycle 1) using the toxicity-dependent guidelines in the table below. Topotecan dose reductions will be accomplished by decreasing the dose of topotecan for each of the 5 days.

To initiate subsequent cycles of topotecan, the day 1 ANC should be ≥ 1000/mm^3 and platelets ≥ 100,000/mm^3. Physicians may use growth factor support at their discretion to reduce the significance of future neutropenia. If patients were to experience symptomatic grade 3 anemia or grade 4 anemia with a treatment cycle, they may be transfused PRBCs prior to next cycle initiation. Treatment interruptions may occur for a maximum of 14 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted. Dose reductions for BAY 1895344 will be based on the dose levels in Section 6.1.

A. Dose adjustments for renal functions (to be made regardless of whether the decrease in renal function is

drug related or not)	
Creatinine clearance (Cockcroft-Gault formula)	Topotecan 1st Dose Reduction (mg/m^2)
>60	no adjustment
40-59	1
20-39	0.75
<20	Discontinue

B. Dose adjustments for non-hematologic toxicities		
Non-hematologic toxicity	Topotecan 1st Dose Reduction (mg/m^2)	Topotecan 2nd Dose Reduction (mg/m^2)
Grades 1 and 2	no adjustment	
Grades 3 and 4 (except grade 3 nausea)	1	0.75

C. Dose adjustments for hematologic toxicities		
Hematologic toxicity	Topotecan 1st Dose Reduction (mg/m^2)	Topotecan 2nd Dose Reduction (mg/m^2)
Grades 1 and 2	no adjustment	
Grade 3 neutropenia persisting after day 21	1	0.75
Grade 4 thrombocytopenia or Grade 4 neutropenia with fever or infection or of duration ≥ 7 days	1	0.75

In addition, in case of Grade 3 or higher toxicity during any cycle beyond Cycle 1, treatment may be interrupted and may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator.

Nausea	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold* until < Grade 1. Resume at 1 dose level lower, if indicated.**	Hold* until < Grade 1. Resume at 1 dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at	Hold* until ≤ Grade 1. Resume at

Vomiting	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
	same dose level.	same dose level.
Grade 3	Hold* until < Grade 2. Resume at 1 dose level lower, if indicated.**	Hold* until < Grade 2. Resume at 1 dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2. Resume at 2 dose levels lower.***	Hold* until < Grade 2. Resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold* until resolved to baseline. Resume at same dose level.	Hold* until resolved to baseline. Resume at same dose level.
Grade 3	Hold* until resolved to baseline, then resume at one dose level lower, if indicated.**	Hold* until resolved to baseline, then resume at one dose level lower, if indicated.**
Grade 4	Hold* until resolved to baseline, then resume at 2 dose levels lower, if indicated.***	Hold* until resolved to baseline, then resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Neutropenia	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
≤ Grade 2	No change in dose	No change in dose
Grade 3	Hold* until ≤ Grade 2. Resume at 1 dose level lower.**	Hold* until ≤ Grade 2. Resume at 1 dose level lower.**
Grade 4	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***
Febrile Neutropenia****	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***	Hold* until ≤ Grade 2. Resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy. ****Febrile neutropenia defined as an absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour.		

Thrombocytopenia	**Management/Next Dose for** BAY 1895344	**Management/Next Dose for** Topotecan
≤ Grade 1	Hold* until platelets ≥ 100,000/mm^3, then resume with no change in dose.	Hold* until platelets ≥ 100,000/mm^3, then resume with no change in dose.
Grade 2	Hold* until platelets ≥ 100,000/mm3, then resume with no change in dose.	Hold* until platelets ≥ 100,000/mm3, then resume with no change in dose.
Grade 3	Hold* until platelets ≥ 100,000/mm3, then resume at 1 dose level lower, if indicated.**	Hold* until platelets ≥ 100,000/mm3, then resume at 1 dose level lower, if indicated.**
Grade 4	Hold* until platelets ≥ 100,000/mm3, then resume at 2 dose levels lower, if indicated.***	Hold* until platelets ≥ 100,000/mm3, then resume at 2 dose levels lower, if indicated.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent

8.1.1 BAY 1895344 **(NSC 810486)**

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

Classification*:* ATR inhibitor

CAS Registry Number: 1876467-74-1

Molecular Formula: $C_{20}H_{21}N_7O$ **M.W.:** 375 g/mol

Approximate Solubility: BAY 1895344 is practically insoluble in water at pH≥4.5, slightly soluble in ethanol, acetonitrile and acetone and sparingly soluble in 0.1 N HCl and polyethylene glycol (PEG)400.

Mode of Action*:* BAY 1895344 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.

Description: Yellow solid.

How Supplied: Bayer supplies and the Pharmaceutical Management Branch, CTEP, DCTD, NCI distributes BAY 1895344 as oral film-coated tablets. Tablets will be packaged in bottles containing 18 tablets.

Strength	Description	Availability
20 mg	film-coated tablets are red and round with 6 mm diameter	Not available after July 31, 2024
10 mg	film-coated tablets are red and round with 5 mm diameter	Not available after February 28, 2025

All patients who receive the 20 mg strength will need to switch to using the 10 mg strength after July 31, 2024.

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.

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

If a storage temperature excursion is identified, promptly return BAY 1895344 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.

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

Route of Administration: Oral

Method of Administration: Swallow tablets immediately following removal from package. Take BAY 1895344 one (1) hour before or two (2) hours after a meal with approximately 240 mL of water.

Potential Drug Interactions:
No formal DDI studies have been conducted with BAY 1895344 in humans.

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

BAY 1895344 is a weak to moderate inhibitor of CYP3A4, 2C8, 2C9, and 2C19 *in vitro*. BAY

1895344 had no significant inhibitory effect on CYP1A2, 2A6, 2B6, 2D6, and 2E1. *In vitro*, BAY 1895344 was also shown to be an inducer of CYP3A4 and 2C19 but not 1A2. BAY 1895344 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 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.

Patient Care Implications:

- Women of childbearing potential and their male partners should use appropriate contraceptive measures during and for 6 months after last study drug administration.
- Breast-feeding should be discontinued during treatment and for 4 months after last study drug administration.
- Based on the UV absorption properties of BAY 1895344, patients should be instructed to use topical sun block and UV-blocking sunglasses during treatment with BAY 1895344. Direct exposure of patients to sun light after administration should be avoided.

Availability

BAY 1895344 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

BAY 1895344 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

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

Sites can place orders for PMB-supplied agents only after enrollment onto the study. Please provide the patient ID# when placing an order.

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

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

8.1.3 Investigator Brochure Availability

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

8.1.4 Useful Links and Contacts

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

8.2 Commercial Agent(s)

8.2.1 Irinotecan

Irinotecan (CAMPTOSAR) is a topoisomerase inhibitor. Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which

relieves torsional strain during DNA replication by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks.

How Supplied

Irinotecan is typically available in three single-dose sizes: 2, 5 and 15 mL-fill vials, respectively containing 40, 100 and 300 mg irinotecan hydrochloride.

Storage and Handling

Irinotecan vials should be stored consistent with the product label at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until time of until time of use. This is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Agent Ordering
This agent is commercially available

Preparation and storage instructions
Please refer to section 6.1.2. For more information refer the package insert.

8.2.2 Topotecan

For additional information see the topotecan package insert. Chemical name: (s)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1hpyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14-(4h ,12h)-dione monohydrochloride
Classification: anti-tumor topoisomerase inhibitor Cas registry number: 123948-87-8
Molecular formula: c23h23n3o5 mw: 421.45 d
Mode of action: topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase i-inhibitory activity. Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Topotecan binds to the topoisomerase i-DNA complex and prevents re-ligation of these single-strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase i, and DNA. Mammalian cells cannot efficiently repair these double-strand breaks.

How supplied:

Powder for injection (4 mg)
Topotecan powder for injection is supplied as a sterile, lyophilized, buffered, light yellow to greenish powder for reconstitution available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion.

Solution for injection (4 mg/4 ml)

Topotecan injection is supplied as a clear yellow to yellow-green solution in single use vial for intravenous infusion only following dilution. Each ml contains topotecan hydrochloride equivalent to 1 mg of topotecan free base.

Preparation:
Topotecan injection is a cytotoxic anticancer drug. Prepare topotecan hydrochloride injection under a vertical laminar flow hood while wearing gloves and protective clothing. If topotecan injection solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If topotecan injection contacts mucous membranes, flush thoroughly with water. Handle and dispose of topotecan for injection consistent with recommendations for the handling and disposal of hazardous drugs.

Powder for injection (4 mg)
Reconstitute each 4-mg vial of topotecan with 4 ml sterile water for injection, usp.

Powder for injection (4 mg) and solution for injection (4 mg/ml)
Dilute the appropriate volume of the solution in a minimum of 50 ml of 5% dextrose in water injection, usp prior to administration.

Storage:

Powder for injection (4 mg)
Store at controlled room temperature between 20°c and 25°c (68°f and 77°f) [see usp]. Protect from light in original carton.

Solution for injection (4 mg/ml)
Unopened vials of topotecan injection are stable until the date indicated on the package when stored at 2°c to 8°c (36°f and 46°f) and protected from light in the original package.

Stability: unopened vials of topotecan powder for injection are stable until the date indicated on the package when stored between 20°c and 25°c (68°f and 77°f) [see usp] and protected from light in the original carton. Because the vials contain no preservative, contents should be used immediately after reconstitution. Topotecan diluted for infusion is stable at approximately 20°c to 25°c (68°f to 77°f) and ambient lighting conditions for 24 hours.

Route of administration: topotecan injection is administered by intravenous infusion over 30 Minutes.

Method of administration: verify dose using body surface area prior to dispensing. Recommended dosage should generally not exceed 4 mg intravenously.

Agent ordering: topotecan is commercially available.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Study Design

The study is a phase I a/b trial with three dose escalation cohorts and three dose expansion cohorts. Only one irinotecan escalation cohort will be carried forward to the expansion phase. Dose escalation will occur according to a standard 3 + 3 design with an accepted DLT rate of < 33%.

Patients will be enrolled in cohorts of 3. Toxicity for all patients in a cohort must be fully evaluated before the next cohort is enrolled. If no DLT's are experienced in the initial cohort of a dose level, the next cohort of 3 patients may be treated at the next higher dose level. If 1 DLT is experienced in the initial cohort of a dose level, an additional cohort of 3 patients will be treated at the same dose level. The MTD is defined as the highest dose in which < 2 DLT's were experienced by 6 patients treated at that dose. Six patients must be treated at a dose level to declare the MTD.

If patients are unable to tolerate dose level 3 in the irinotecan cohort or dose level 2 in the topotecan cohort, an alternative dose de-escalation scheme (described in section 6.1) utilizing single day dosing of the BAY1895344 compound will be employed. This was established per discussions with Bayer.

Analysis of Primary Endpoints

- The primary endpoint of the dose escalation phase is to estimate MTD which is defined by occurrence of ≥ 2 dose limiting toxicities (DLT defined as grade 4 neutropenia lasting ≥ 7 days, grade 4 thrombocytopenia, grade 4 anemia, grade 3 neutropenia with fever, grade 3 thrombocytopenia with bleeding, any grade 3 hematologic toxicity lasting ≥ 7 days (counting from first day of toxicity grade recognition) or any non-hematologic grade ≥ 2 AEs lasting ≥ 7 days (with the exception of G2 fatigue, G2 nausea or G2 diarrhea) (counting from first day of toxicity grade recognition)) in any dose level during C1 of treatment. DLTs will be graded by CTCAE v5.0.

- The primary endpoint of the dose expansion phase is to estimate hematologic safety and tolerability which is defined by the occurrence of grade 4 hematologic AEs in expansion cohort patients. Should a prespecified number of patients in specific cohorts exceed a tolerated rate of grade 4 hematologic toxicity (as per the rule below), accrual will cease and discussions will be initiated with CTEP about revisiting the RP2D of the study combinations.

With regard to safety and monitoring for toxicity, stopping rules apply to each expansion group. Toxicity monitoring will be performed for each expansion group separately using the following stopping rules:

Cease Accrual if Number of Grade 4		In Number of Patients

Hematologic AE's is **more** than		(inclusive)
1		3-6
2		7-10

Grade 4 hematologic toxicity will be monitored using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). A maximum of 25 patients will be enrolled and toxicity monitoring will begin when the 5th patient in a cohort is evaluable for toxicity. We assume the phase I portion of the study targets a 20% grade 4 hematologic toxicity rate. The probabilities of toxicity for the historical data the experimental regimen are modeled by vague beta distributions (*Beta*(0.4,1.6) and *Beta*(0.4, 1.6), respectively. The prior probabilities of toxicity for both historical data and the experimental regimen have the same *means* and an Effective Sample Size of 2. Denoting the historical probabilities of a grade 4 hematologic toxicity and cohort by {p(TOX,H) , p(TOX,E)}, the following decision criteria will be applied; stop if Prob{p(G4Tox,H) < p(G4Tox,E)| data}>0.70. The probability of 0.65 is titrated to produce acceptable operating characteristics for the design. Pursuant to this rule, patients will be monitored according to the following stopping boundaries in the table above. For example, the protocol will cease accrual to conduct a detailed toxicity review if 2 grade 4 hematologic toxicities are observed among the first 3 to 6 patients treated. Two grade 4 hematologic toxicities will be allowed in each of the expansion cohorts.

The operating characteristics are summarized in the following table. The probabilities of ceasing accrual are exact calculations. The probability of ceasing accrual for a true grade 4 hematologic toxicity rate of 20% is 42% with an average sample size of 8.59 and an average 1.72 grade 4 hematologic toxicities. For excessive toxicity (30% grade 4 hematologic toxicity or greater), the study will cease accrual early with a probability of 69% with average sample size and grade 4 hematologic toxicity number of 6.85 and 2.1, respectively.

True Rate of Grade 4 Hematologic Toxicity	Number of Patients	Probability (ceasing accrual)
15%	3	6.1%
	6	27.2%
	10	19%
20%	3	10.4%
	6	34.5%
	10	42.3%
25%	3	15.6%
	6	46.6%
	10	56.8%

30%	3	21.6%
	6	58.0%
	10	69.5%

Clinical safety data (e.g. AEs) will be tabulated and summarized using descriptive statistics as requested by the sponsor investigator, executive committee, medical monitor or DSMB using methods described in the Data Safety Monitoring Plan (DSMP).

9.2 Sample Size/Accrual Rate

Sample Size/Accrual Rate

6-9 patients (based upon current safety findings) will be enrolled in the irinotecan cohort #1 dose escalation phase, 9-30 patients will be enrolled in the irinotecan cohort #2 dose escalation phase and 15-24 patients will be enrolled in the topotecan dose escalation phase. In the dose expansion cohorts, 33 total patients are expected to be enrolled, 11 in each expansion cohort. The maximum number of patients in the study will be 96. We anticipate accruing 2 patients per month as the study will open across ETCTN centers.

Assuming a standard deviation (SD) of 10% in γ-H2AX and pS343-NBS1 levels between pretreatment and the subsequent C1 biopsies using a paired t-test, 15 paired samples provide >90% power to detect a δ of 10% (e.g. post-treatment value of 14% minus baseline value of 4%. Assuming 60% of patients undergo paired tumor biopsies and 80% of those samples yield results, 33 total expansion cohort patients will yield (33 x 0.6 *0.8) 15 paired samples sufficient for meeting the pharmacodynamic aims of this study.

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	3	3	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	6	0	0	11
White	29	30	8	9	76
More Than One Race	1	2	0	0	3
Total	38	41	8	9	96

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9.3 Stratification Factors

None

9.4 Analysis of Secondary Endpoints

9.4.1 Analysis of Secondary Endpoints

ORR: The secondary endpoint of ORR will be estimated by measuring the number of patients who achieve complete response or partial response by RECIST 1.1 criteria on 12-week restaging CT scans from the total number of patients who received the study treatment.

DOR: The secondary endpoint of DOR will be estimated by the Kaplan-Meier method. DOR for each individual patient will be defined as the length of time from when a patient achieves disease control (complete response, partial response, stable disease) on a restaging scan to the time of radiographic progression.

PFS: The secondary endpoint of PFS will be estimated by the Kaplan-Meier method. PFS in an individual patient will be defined as the time period between when a patient starts treatment to when he demonstrates radiographic progression or succumbs to the disease.

OS: The secondary endpoint of OS will be estimated by the Kaplan-Meier method. OS in an individual patient will be defined as the time period from when a patient starts treatment to the date he succumbs to the disease.

PK: The secondary endpoints of Cmax and AUC will be estimated for each study drug based upon plasma collections from cycle 1 in all study patients. Methods to determine Cmax and AUC have previously been described in existing literature. Individual PK parameters will be estimated, specifically maximum concentration (Cmax), area under the concentration-time curve (AUC), half-life (t1/2), apparent clearance (Cl/F), and apparent volume of distribution (V/F) using non-compartmental methods. The PK variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters will be reported descriptively for exploratory comparison with historical data.
Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Advanced population PK methods may be employed at a later stage to assess the link between drug exposure and biological effects and efficacy.

PD: The secondary endpoints of changes in tumor expression patterns of γ-H2AX and pS343-NBS1 will be estimated for expansion cohort only study patients. Based on published findings, background levels of γ-H2AX and pS343-NBS1 expression and stimulated (post-DNA-damaging chemotherapy) levels are 4% and 11-14%, respectively [30]. Let δ equal the average paired difference of the post-treatment percent expression of a biomarker minus the baseline percent expression of a biomarker. Assuming a standard deviation (SD) of 10% in γ-H2AX and pS343-NBS1 levels between pretreatment and the subsequent C1 biopsies using a paired t-test, 15 paired samples provide >90% power to detect a δ of 10% (e.g. post-treatment value of 14% minus baseline value of 4%; a standardized effect size of 1) with a two-sided type I error rate of 5%. Only 10 paired samples are necessary to achieve 80% power to detect ($p<0.05$) the same standardized effect size. More conservatively, assuming a higher standard deviation of 15%, 15 paired samples provide 80% power to detect a 11.7% difference between post-treatment and

baseline values. Assuming 60% of patients undergo paired tumor biopsies and 80% of those samples yield results, 33 patients will yield (33 x 0.6 *0.8) 15 paired samples sufficient for meeting the objectives of this aim. Despite the anticipated effect size between pretreatment and post-treatment levels of γ-H2AX and pS343-NBS1 we used to justify the number of patients in our expansion cohorts, any post-treatment biomarker level > 4% NAP will be considered a marker of treatment effect.

9.4.2 Analysis of Exploratory Endpoints

Assess the prevalence of tumor ATM expression loss in all patients. Estimate response outcomes (ORR, PFS, OS, DOR) in study patients by tumor ATM expression loss.

Assess the specific tumor DDR gene mutations present in study patients from tumor and ctDNA analyses. Estimate response outcomes (ORR, PFS, OS, DOR) in study patients with tumors with DDR gene mutations.

Categorical variables (e.g. ATM expression loss, adverse events) will be summarized as frequencies and percent of total patients. Continuous variables (e.g. percent cells positive) will be summarized using the minimum, 25^{th}, 50^{th} (median), 75^{th}, and maximum percentiles as well as with the mean and standard deviation as appropriate. Associations among predictor variables will be assessed using the Spearman correlation coefficient. The distribution of time to event endpoints will be estimated using the method of Kaplan and Meier with standard errors estimated using Greenwoods formula. Logistic regression will be used to estimate association between biomarkers and categorical outcomes. The odds ratio will be the estimator of effect size. Cox (proportional hazards) regression will be used to estimate the association between biomarker expression and time to event endpoints. The hazard ratio will be the estimator of effect size. Since secondary endpoints are not powered, estimation, not comparison is the primary objective of these analyses. Consequently, precision, the half-width the 95% confidence interval, will be constructed for all estimates.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

10.1.1 CAEPRs for CTEP IND Agent

10.1.1.1 CAEPR for BAY 1895344 (NSC 810486)

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[1]

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.

10.1.2 Adverse Event List(s) for Commercial Agent(s)

10.1.2.1 Irinotecan

The irinotecan package insert contains a black box warning for the following:

- **Early and late forms of diarrhea can occur.** Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt irinotecan and reduce subsequent doses if severe diarrhea occurs.

- **Severe myelosuppression may occur.**

The package insert also includes a listing of adverse reactions:

- Common adverse reactions (≥30%) observed in combination therapy clinical studies of irinotecan are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

- Common adverse reactions (≥30%) observed in single agent therapy clinical studies of irinotecan are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia.

Please refer to the irinotecan package insert for the comprehensive list of adverse events.

10.1.2.2 Topotecan

The most common hematological grade 3/4 adverse reactions (≥5%) experienced by SCLC patients were neutropenia, anemia, thrombocytopenia and febrile neutropenia. The most common non-hematological grade 3/4 adverse reactions (≥5%) experienced by SCLC patients were sepsis, dyspnea, pneumonia, abdominal pain, nausea, fatigue, asthenia, and pain. See the topotecan package insert for more information

10.2 Adverse Event Characteristics

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

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

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

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

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

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

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

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

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

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

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

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

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

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

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

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

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

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).

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

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

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

<u>Expedited AE reporting timelines are defined as:</u>

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

10.4 Routine Adverse Event Reporting

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

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

10.5 Pregnancy

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

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

10.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the investigational products should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities

or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented using the Pregnancy Reporting Form as described in the NCI Guidelines for Investigators (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform CTEP within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

- Women of childbearing potential and their male partners should use appropriate contraceptive measures during and for 6 months after last study drug administration.
- Breast-feeding should be discontinued during treatment and for 4 months after last study drug administration.

10.6 Secondary Malignancy

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

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

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

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

10.7 Second Malignancy

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

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans

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

11.1 Irinotecan Cohort #1 Combination

	Pre-Study	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6+		Off Study[a]
		Wk 1	Wk 2	Wk 1	Wk 2	Wk 1	Wk 2	Wk 1	Wk 2	Wk 1	Wk 2	Wk 1	Wk 2	
BAY 1895344		A		A		A		A		A		A		
Irinotecan		B		B		B		B		B		B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X	X		X		X		X		X		X		
Weight	X	X		X		X		X		X		X		X
Performance status[b]	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X		X		X		X		X		X		X
Comprehensive Chemistry Panel [c]	X	X		X		X		X		X		X		X
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every _6_ weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every _6_ weeks.												X
Pregnancy test[d]	X													
Archival Tumor Collection	X													
Tumor Biopsy[e]	X	X												
PK Analysis[f]		X												
Blood collection for ctDNA[g]	X													X

A: BAY 1895344: Dose as assigned; D1,D2 PO BID Q14 days (D2 PO BID only dosing may be utilized if dose de-escalation to level 2B or 2A is needed) Cycle length = 14 days.

B: Irinotecan: Dose as assigned; D1 IV. Cycle length= 14 days.

a: Off-study evaluation.

b: Note: Performance status evaluations are based on a 2 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.

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

d: Pregnancy test for women of childbearing potential.

e: Initial biopsy within 7 days (+- 3 days) of study initiation. Second biopsy on C1D3 in irinotecan arm.

f: The PK studies will only occur during cycle 1 of the study. PK collections will occur on D1-3.

g: Blood collections for ctDNA at baseline for dose escalation and dose expansion groups; optional collection at disease progression in dose expansion cohort.

11.2 Irinotecan Cohort #2 Combination

	Pre-Study	Cycle 1			Cycle 2			Cycle 3*			Cycle 4+			Off Study[a]
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
BAY 1895344		A	A	A	A	A	A	A	A		A	A		
Irinotecan		B	B	B	B	B	B	B	B		B	B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X	X			X			X			X			
Weight	X	X			X			X			X			X
Performance status[b]	X	X			X			X			X			X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X		X	X		
Comprehensive Chemistry Panel [c]	X	X	X	X	X	X	X	X	X		X	X		
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every _6_ weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every _6_ weeks.												X
Pregnancy test[d]	X													
Archival Tumor Collection	X													
Tumor Biopsy[e]	X	X												
PK Analysis[f]		X												
Blood collection for ctDNA[g]	X													X

*Please note after cycle 2, patients will be given a 1 week treatment break (7 days) before starting Cycle 3

A: BAY 1895344: Dose as assigned; D2,3, D9,10 and D16,17 PO. After cycle 2, D16,17 doses are dropped. Cycle Length = 21 days.

B: Irinotecan: Dose as assigned D1,8, 15 IV. After cycle 2, D15 dose is dropped. Cycle Length= 21 days.

a: Off-study evaluation.

b: Note: Performance status evaluations are based on a 3 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.

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

d: Pregnancy test for women of childbearing potential.

e: Initial biopsy within 7 days (+- 3 days) of study initiation. Second biopsy on C1D2.

f: The PK studies will only occur during cycle 1 of the study. PK collections will occur on D1,2 and D15,16.

g: Blood collections for ctDNA at baseline for dose escalation and dose expansion groups; optional collection at disease progression in dose expansion cohort.

11.3 Topotecan Combination

	Pre-Study	Cycle 1			Cycle 2			Cycle 3			Cycle 4+			Off Study[a]
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
BAY 1895344		A			A			A			A			
Topotecan		B			B			B			B			
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X	X			X			X			X			
Weight	X	X			X			X			X			X
Performance status[b]	X	X			X			X			X			X
CBC w/diff, plts	X	X			X			X			X			
Comprehensive Chemistry Panel [c]	X	X			X			X			X			
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every _6_ weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every _6_ weeks.												X
Pregnancy test[d]	X													
Archival Tumor Collection	X													
Tumor Biopsy[e]	X	X												
PK Analysis[f]		X												
Blood collection for ctDNA[g]	X													X

A: BAY 1895344: Dose as assigned; D2,D5 PO BID (D2 PO BID only dosing may be utilized if dose de-escalation to level 1B or 1A is needed). Cycle Length = 21 days.

B: Topotecan: Dose as assigned D1-D5 IV Cycle Length= 21 days.

a: Off-study evaluation.

b: Note: Performance status evaluations are based on a 3 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.

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

d: Pregnancy test for women of childbearing potential.

e: Initial biopsy within 7 days (+- 3 days) of study initiation. Second biopsy on C1D3 pre D3 infusion in topotecan arm.

f: The PK studies will only occur during cycle 1 of the study. PK collections will occur on D1-4.

g: Blood collections for ctDNA at baseline for dose escalation and dose expansion groups; optional collection at disease progression in dose expansion cohort.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of [this/these] drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 6 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 6 weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 6 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with BAY 1895344 +Irinotecan or BAY 1895344 + topotecan.

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

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

12.1.2 Disease Parameters

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

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

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

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

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

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

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

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

12.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

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

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

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

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

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

12.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥6 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥6 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥6 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR

until the first date that progressive disease is objectively documented.

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

12.1.6 Progression-Free Survival

The secondary endpoint of PFS will be estimated by the Kaplan-Meier method. PFS in an individual patient will be defined as the time period between when a patient starts treatment to when he demonstrates radiographic progression or succumbs to the disease.

12.1.7 Overall Survival

The secondary endpoint of OS will be estimated by the Kaplan-Meier method. OS in an individual patient will be defined as the time period from when a patient starts treatment to the date he succumbs to the disease.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

13.1 Study Oversight

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

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

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

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring

plan.

13.2 Data Reporting

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

Requirements to access Rave via iMedidata:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

13.2.1 Method

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

13.2.2 Responsibility for Data Submission

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

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

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

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

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

above.

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

13.3 Data Quality Portal

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

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

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

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

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

13.4 CTEP Multicenter Guidelines

N/A

13.5 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can

Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-

Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

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

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

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

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

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

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al.* (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
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3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**	10402
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	BAY 1895344

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 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 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 weakly to moderately inhibits CYP3A4, CYP2C8 2C9, and 2C19. BAY 1895344 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 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 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.
- 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.

Version Nov/2019

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE EMERGENCY INFORMATION	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE DRUG INTERACTIONS	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** BAY 1895344 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.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** 10402 **Study Drug(S):** BAY 1895344	**Use caution and avoid the following:** • No grapefruit juice, Seville oranges, or grapefruit can be consumed while on BAY 1895344. • 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.	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	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Fold at dotted lines:

APPENDIX D PRE-BIOPSY ASSESSMENT

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

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

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

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

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

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

    3. Likely successful

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

APPENDIX E MEDICAL DIARY

APPEDNIX E.1 Irinotecan Cohort #1 – Dose Levels -1, 1, 2, 3, and 4

CTEP-assigned Protocol #_____

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent** ____**BAY 1895344**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets of ___mg each day, ___ in the morning and ___ in the evening. You should take the tablets with 8 oz. water, one hour before or two hours after a meal..
3. You will only take BAY 1895344 on Days 1 and 2. You will not take BAY 1895344 on the shaded days.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
7. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Day	Date	Time of morning dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Time of evening dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Comments
1								
2								
3	Do not take BAY 1895344 on Days 3-14							
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								

Patient's

Signature_____

_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E.2 Irinotecan Cohort #1 – Dose Levels 2A and 2B

CTEP-assigned Protocol #_____

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent** ____**BAY 1895344**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets of ___mg each day, ___ in the morning and ___ in the evening. You should take the tablets with 8 oz. water, one hour before or two hours after a meal..
3. You will only take BAY 1895344 on Day 2. You will not take BAY 1895344 on the shaded days.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
7. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Day	Date	Time of morning dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Time of evening dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Comments
1	Do not take BAY 1895344 on Day 1							
2								
3	Do not take BAY 1895344 on Days 3-14							
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								

Patient's

Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month

   _____
5. Physician/Nurse/Data Manager's Signature

   _____

APPENDIX E.3 Irinotecan Cohort #2 – Dose Levels -2, -1, 1, 2, 3, 4, and 5

CTEP-assigned Protocol #_____
Local Protocol # _____

PATIENT'S MEDICATION DIARY
Cycle 1 and Cycle 2

Today's date _____ **Agent** ____**BAY 1895344**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets of ___mg each day in the morning. You should take the tablets with 8 oz. water, one hour before or two hours after a meal..
3. You will only take BAY 1895344 on Days 2, 3, 9, 10, 16 and 17. You will not take BAY 1895344 on the shaded days.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
7. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.
8. After 2 cycles, patients will transition to 2 weeks on and 1 week off, so doses on day 16 and 17 will be dropped.

Day	Date	Time of morning dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Comments
1	Do not take BAY 1895344 on Day 1				
2					
3					
4	Do not take BAY 1895344 on Days 4-8				
5					
6					
7					
8					
9					
10					
11	Do not take BAY 1895344 on Days 11-15				
12					
13					
14					
15					
16					
17					
18	Do not take BAY 1895344 on Days 18-21				
19					
20					
21					

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

PATIENT'S MEDICATION DIARY
Cycle 3+

Today's date _____ **Agent** ____**BAY 1895344**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets of ___mg each day in the morning. You should take the tablets with 8 oz. water, one hour before or two hours after a meal..
3. You will only take BAY 1895344 on Days 2, 3, 9, and 10. You will not take BAY 1895344 on the shaded days.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
7. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Day	Date	Time of morning dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Comments
1	Do not take BAY 1895344 on Day 1				
2					
3					
4	Do not take BAY 1895344 on Days 4-8				
5					
6					
7					
8					
9					
10					
11	Do not take BAY 1895344 on Days 11-21				
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E.4 Topotecan Cohort – Dose Levels 1, -1, -2, and -3

CTEP-assigned Protocol #_____
Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent** ____**BAY 1895344**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets of ___mg each day in the morning. You should take the tablets with 8 oz. water, one hour before or two hours after a meal.
3. You will only take BAY 1895344 on Days 2 and 5. You will not take BAY 1895344 on the shaded days.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
7. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Day	Date	Time of morning dose	# of tablets taken (10mg)	# of tablets taken (20mg)	Comments
1	Do not take BAY 1895344 on Day 1				
2					
3	Do not take BAY 1895344 on Days 3-4				
4					
5					
6	Do not take BAY 1895344 on Days 6-21				
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX F TISSUE BIOPSY VERIFICATION

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

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

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

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

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

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

Tissue Type (circle one): **Primary** **Metastatic**

Time point (circle one): **Day -7** **Cycle 1 Day 3 (Irinotecan)** **Cycle 1 Day 6 (Topotecan)**

Site Tissue Taken From: _____

Diagnosis: _____

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

_____ _____
Clinician Signature Date

_____
Clinician Printed Name

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

Version: 1
Effective Date: 9/2019

APPENDIX G NCLN PHARMACODYNAMICS LABORATORY FROZEN BIOPSY COLLECTION PROCEDURE

Title:	Tumor Frozen Needle Biopsy Specimen Collection, Handling and Shipment to EET Biobank				Page 1 of 13
Doc. #:	SOP340567	Revision:	-	Effective Date:	10/08/2021

Laboratory of Human Toxicology & Pharmacology

Applied/Developmental Research Directorate, Leidos Biomedical Research, Inc.

Frederick National Laboratory for Cancer Research

Technical Reviewer: Li Li Date: Li Li -S (Affiliate) Digitally signed by Li Li -S (Affiliate) Date: 2021.10.08 09:55:19 -04'00'

IQC Approval: Katherine V. Ferry-Galow Date: Katherine V. Ferry-galow -S (Affiliate) Digitally signed by Katherine V. Ferry-galow -S (Affiliate) Date: 2021.10.13 11:00:43 -04'00'

LHTP Approval: Ralph E. Parchment Date: Ralph E. Parchment -S (Affiliate) Digitally signed by Ralph E. Parchment -S (Affiliate) Date: 2021.11.30 11:28:47 -05'00'

DCTD OD Approval: Toby Hecht Date: Toby T. Hecht -S Digitally signed by Toby T. Hecht -S Date: 2021.12.06 11:58:47 -05'00'

Change History

Revision	Approval Date	Description	Originator	Approval
--	10/08/2021	New Document	LL/RA/KFG	KFG

Please check for revision status of the SOP at

http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

and be sure to use the current version.

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1.0 PURPOSE

Standardize the method for collecting, handling, and shipping frozen needle tumor biopsies toEET Biobank to enable measurement of pharmacodynamic (PD) markers following treatmentwith anticancer agents.

2.0 SCOPE

This procedure applies to all personnel involved in the collection and handling of frozen needletumor biopsies for use in PD marker assays during clinical trials. The goal of this SOP and associated training is to ensure consistency in tumor needle biopsy collection and handling between clinical sites.

3.0 ABBREVIATIONS

DCTD	=	Division of Cancer Treatment and Diagnosis
EET Biobank	=	NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank, also referred to as the Nationwide Biorepository or ETCTN Biorepository
FNLCR	=	Frederick National Laboratory for Cancer Research
ID	=	Identification / Identifier
IQC	=	Internal Quality Control
LHTP	=	Laboratory of Human Toxicology and Pharmacology
PADIS	=	Pharmacodynamics Assay Development & Implementation Section
PD	=	Pharmacodynamic
SOP	=	Standard Operating Procedure

4.0 INTRODUCTION

Specimen handling, shipping, and storage procedures (pre-analytical variables) can have a significant impact on the reliability of biomarker measurements in the laboratory. Following detailed steps for sample collection and handling procedures and recording any deviations fromthis procedure allow retrospective identification of artifactual changes in biomarker readout andincreases the reliability of the data and validity of the analytical results.

5.0 ROLES AND RESPONSIBILITIES

Laboratory Director/Supervisor The Laboratory Director/Supervisor directs laboratory operations, supervises technical personnel and reporting of findings, and is responsible for the proper performance of all laboratory procedures. Oversees the personnel who follow the SOPs in the laboratory and is responsible for ensuring the personnel are certified and have sufficient experience to handleclinical samples.

Certified Assay Operator and/or PK/PD Support Lab Personnel

An assay operator and/or PK/PD Support Lab personnel may be a Laboratory Technician/Technologist, Research Associate, or Laboratory Scientist who has been trained by DCTD personnel on this SOP. Working under the guidance of the Laboratory Director/Supervisor, this person performs laboratory procedures and examinations in accordance with thecurrent SOP(s), as well as any other procedures conducted by alaboratory, including maintaining equipment and records and performing quality assurance activities related to performance.

5.1 It is the responsibility of the Laboratory Director/Supervisor to ensure that all personnel have documented training and qualification on this SOP prior to the actual handling and processing of samples from clinical trial patients. The Laboratory Director/Supervisor is responsible for ensuring the assay operator running the SOP has sufficient experience to handle and analyze clinical samples. To become proficient with this SOP, sites are highly encouraged to reach out to NCI_PD_Support@mail.nih.gov for additional training materials.

5.2 It is the responsibility of the assay operator to confirm scheduled specimen collection time points, pre-print all labels, request access to **NCI Medidata Rave** (ETCTN Specimen Tracking System), check documentation for accuracy, request sample shipping kits from the EET Biobank and verify that the required collection tubes, supplies, and equipment are available for successful collection and handling of biopsy samples.

5.3 It is the responsibility of the assay operator to conduct the specimen collection and handling procedures following this SOP and complete the required tasks and associated documentation. The Biopsy Collection Record (Appendix 1) must be completed for each patient sample collection and filed with the study patient's other records.

5.4 The responsible personnel are to check the DCTD Biomarkers Web site (http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm) to verify that the latest SOP version is being followed.

6.0 MATERIALS AND EQUIPMENT REQUIRED

6.1 Stopwatch, total time in minutes and seconds required

6.2 1.5-mL Sarstedt o-ring screw cap, conical bottomed tubes (Sarstedt, Cat#: 72.703.416)

6.3 Disposable, fine-tipped tweezers (e.g., VWR, Cat#: 83009-010). Tweezer tips need to easily fit to the bottom of a 1.5-mL Sarstedt tube

6.4 Printable microcentrifuge tube labels or BSI labeling system

6.5 81-place freezer boxes (e.g., Fisher Scientific, Cat#: 12-565-182)

6.6 Thermoflask cooler or polystyrene foam container

6.7 Ice bucket

6.8 Liquid nitrogen or dry ice/ethanol bath

6.9 -80°C freezer (or colder)

6.10 Specimen shipping kit from EET Biobank

7.0 OPERATING PROCEDURES

7.1 This SOP uses **NCI Medidata Rave** for sample tracking, please review the following training videos for **NCI Medidata Rave** before you start:

7.1.1 General RAVE training:
https://www.youtube.com/watch?app=desktop&v=ZRX0lSqs5zo

7.1.2 Label Printing training:
https://www.youtube.com/watch?app=desktop&v=9_Q6_k-KHHs

7.2 Sample Shipping Kits

Sample shipping kits should be requested prior to enrolling the first biopsy patient fromEET Biobank by emailing BPCBank@nationwidechildrens.org. For current customers,the kits can be requested through the EET Biobank (kit management system: https://kits.bpc-apps.nchri.org/Auth/Login?ReturnUrl=%2f. Please allow 5-7 business days for kit shipment.

7.3 Labels

7.3.1 Prepare enough pre-printed specimen labels in **NCI Medidata Rave** by following steps 7.3.1.1- 7.3.1.5:

7.3.1.1 Log into **NCI Medidata Rave** and go to **Enrollment** folder and confirm the **Histology and Disease** form is complete.

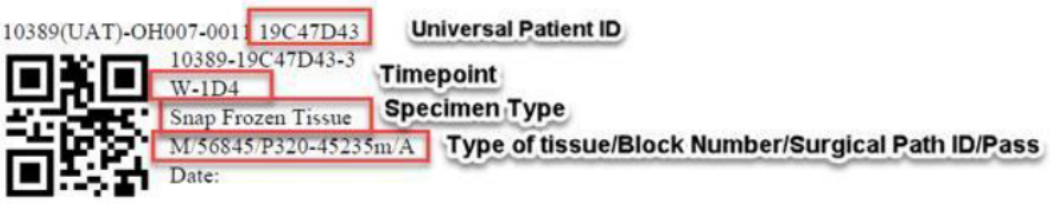
7.3.1.2 Go to **All Specimens** folder.

7.3.1.3 Complete the **Specimen Consent** form.

7.3.1.4 Complete the **Specimen Tracking Enrollment** form for each specimen.

7.3.1.5 Complete the **Print Labels** form. Labels will be sent to user's email address. For tissue specimens, apply appropriately coded label to each pass of the biopsy (see below).

Note: Five labels will be printed by default when you enter "**1**" in the "**How many labels are needed**" field. The first four will be designated with A, B, C and D to represent different passes of the biopsy procedure. Please use those accurately to label the specimens; pass A should be for the first pass, B for the second etc. The fifth labelwill have no pass designation and can be used on reports to be uploaded into RAVE. See an example of pre-printed label for frozen tissue biopsy below.



7.4 Tumor Needle Biopsy Collection and Handling

7.4.1 The research nurse is to notify the laboratory of scheduled PD sample collections, preferably giving at least 24 hours of notice. Arrive at the biopsy collection site early enough to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of frozen specimens from the procedure area to the laboratory, where they will be placed into storage at -80ºC (or colder).

7.4.2 Prior to biopsy, the lesion should be assessed as to whether or not the biopsy should be performed and yield a successful outcome. Fill out the **Pre-Biopsy Lesion Score** form in **NCI Medidata Rave** using inputs from interventional radiologists and/or oncologists.

7.4.3 Bring all necessary lab supplies to the biopsy collection site, including: disposable tweezers, a minimum of four 1.5-mL Sarstedt tubes pre-cooled on liquid nitrogen or dry ice/ethanol in an insulated bucket (Sarstedt tubes will be provided in the sample shipping kit from EET Biobank; please use one tube for each whole biopsy core), the label with no pass designation to give to the research nurse for the patient record, and a printout of Appendix 1.

Note: Pre-chill additional 1.5-mL Sarstedt tubes for specimen collection in casethe interventional radiologist collects additional passes, or if one of the tubes is compromised prior to collection.

7.4.4 The total time elapsed between biopsy collection and placement into the pre-chilled tube is of **key importance** to biomarker analysis; this time should be documented in **NCI Medidata Rave** for each biopsy pass. **It is important to note that all biopsies should be frozen within 2 minutes of collection.** The interventional radiologist will eject the biopsy onto a sterile slide (for optimal analyte recovery the slide should be pre-chilled). Start a stopwatch at this point (or note the time in Appendix 1) and immediately walk the slide to the sample preparation table for transfer to the pre-chilled Sarstedt tube.

7.4.5 Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath (stop the stopwatch at this point). **Note:** DO NOT let the tubes tip over in the liquid nitrogen or dry ice/ethanol bath.

7.4.6 Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of **minutes and seconds** (Appendix 1).

7.4.7 Note the specific needle type used and location of each biopsy pass collected (*e.g.*, spleen, large left upper quadrant splenic mass) (Appendix 1).

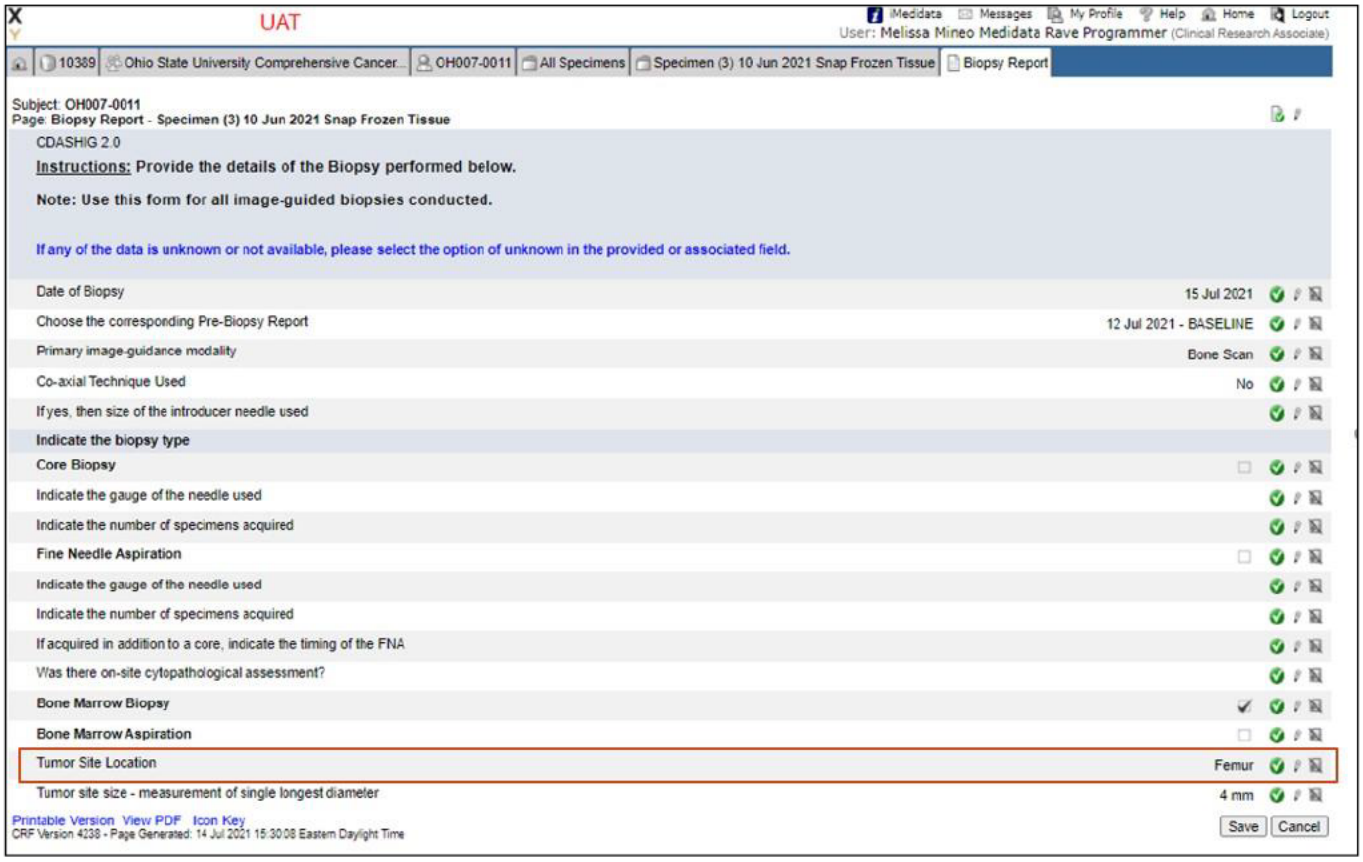
7.4.8 Note the protocol biopsy timepoint in Appendix 1.

7.4.9 Return to the sample processing laboratory and transfer the frozen biopsy specimen(s) to -80°C (or colder) for storage until shipment to the EET Biobank.

7.4.10 After biopsy collection, complete sample tracking documentation in **NCI Medidata Rave** according to notes recorded in Appendix 1.

7.4.11 Fill out **Biopsy Report** form in the **All Specimen** folder.

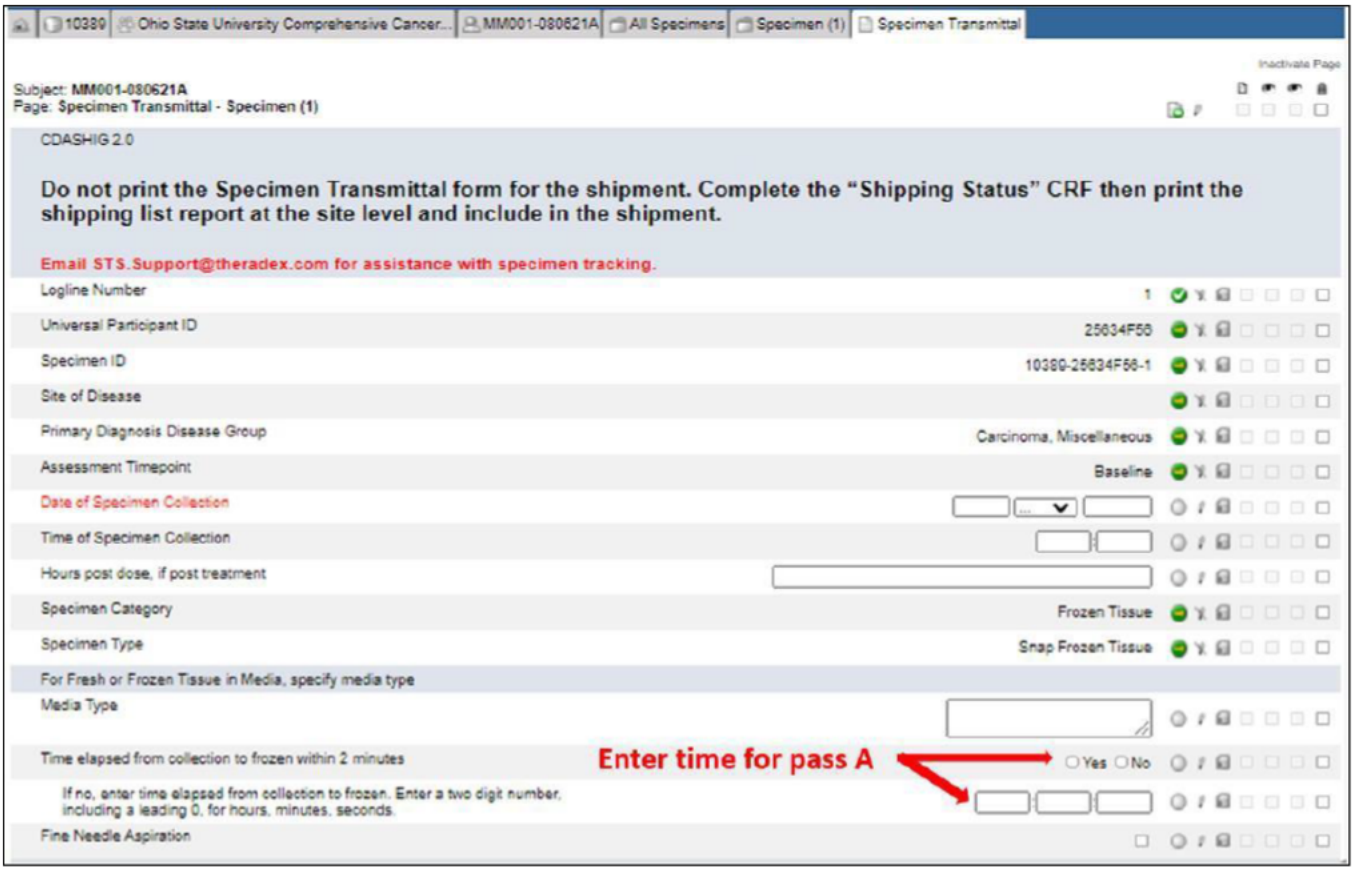
Note: It is very important to record the site of the biopsy to the **Tumor SiteLocation** field as shown below.



7.4.12 Complete the **Specimen Transmittal** form in the All Specimen folder.

Note: It is important to fill out the time from collection to frozen for each pass inthe **Specimen Transmittal** form by following the instructions below.

Pass A time will be recorded in the appropriate fields as shown below:



Times elapsed for passes B, C and D will be recorded in the **Comment** field nearthe bottom of the Specimen Transmittal form as shown below. Biopsy passes notcollected will also be recorded in the **Comment** field as shown below.

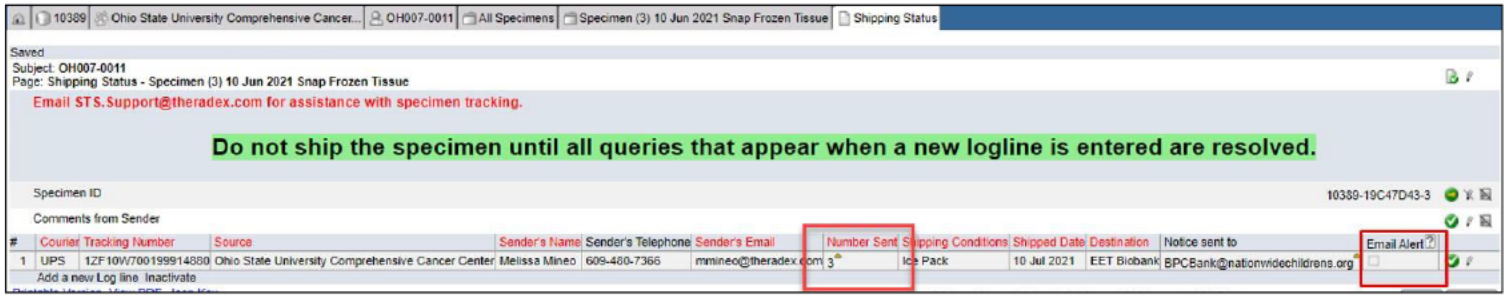
8.0 SHIP TO EET BIOBANK

8.1 When specimens are ready to be shipped, complete shipment documentation in **NCI Medidata Rave.**

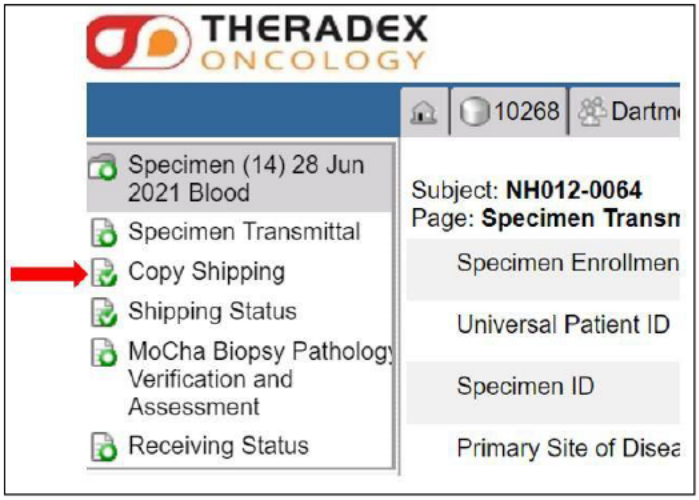
8.1.1 Complete the **Shipping Status** form.

8.1.1.1 Each field in the **Shipping Status** form should be completed as shown below and **Number Sent** (circled below) should equal the number of biopsy passes in the shipment.

8.1.1.2 **Email Alert** (circled below) is only checked for the last specimen in a shipment if multiple specimens are shipped together.

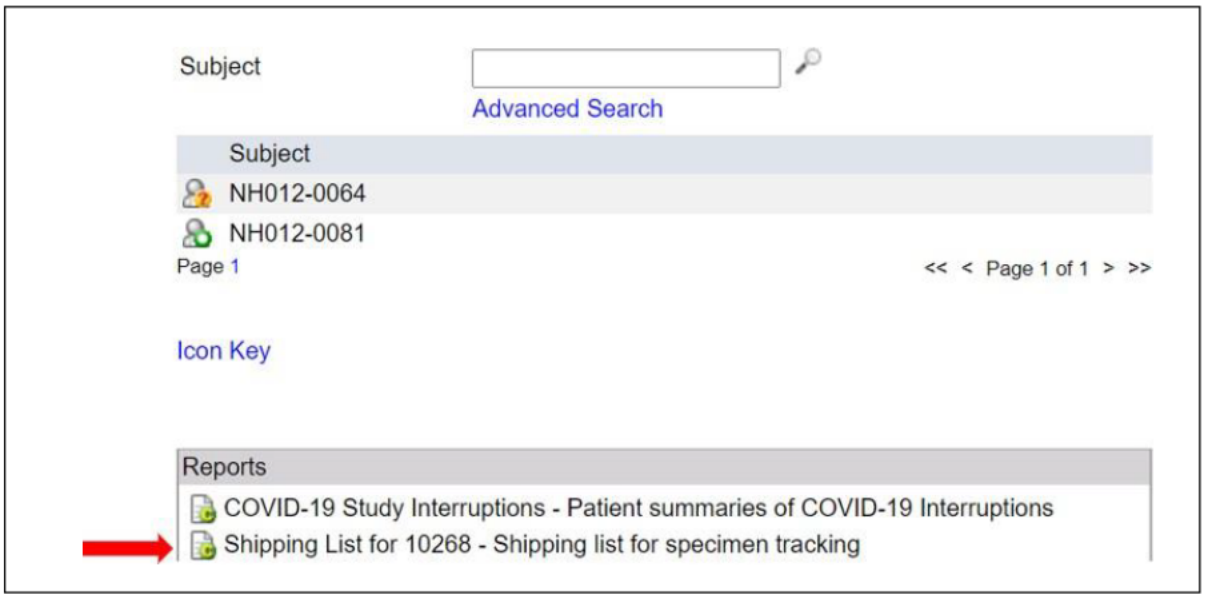


8.1.2 If there are other specimens to be shipped with the frozen biopsies, use the **Copy Shipping** utility form (shown below) in the other specimens' folder.



8.1.3 Print the **Shipping List** report and place it in the box with the specimens.

8.1.3.1 The **Shipping List** report is found in the report panel at the bottom of the window at the site level (an example shown below) since specimens from multiple patients can be included in a single shipment.



8.1.3.2 Shipment should include a hard copy (printed copy) of the **Shipping List**. An example is shown below.

Shipping List

Protocol: 10389 - UAT
Site: Ohio State University Comprehensive Cancer Center
Shipping Date: 10 Jul 2021
Tracking Number: 1ZF10W700199914880

Contact Info: Melissa Mineo
609-480-7366
mmineo@theradex.com

Please include a hardcopy of the pathology and any other relevant report in the shipment.

Protocol-Patient ID / Universal Pat. Id / Specimen ID	TimePoint	Category / Type	Samples Sent	Tissue	Sample Site	Collection Date/Time / Processed Date/Time / Frozen in 2 min/Elapsed	Comments
10389-OH007-0011 19C47D43 10389-19C47D43-1	Baseline	Blood Blood	1		General Blood Draw	21 Jun 202109:00 N/A	
10389-OH007-0011 19C47D43 10389-19C47D43-2	Archival	Formalin Fixed Paraffin Embedded Tissue FFPE Block	1	Metastatic	Esophagus	09 Jan 202115:00 N/A	
10389-OH007-0011 19C47D43 10389-19C47D43-3	Week -1 Day 4 (Expansion Cohort Only)	Frozen Tissue Snap Frozen Tissue	3	Metastatic	Esophagus	10 Jun 202111:10 N/A No/00:03:25	Pass B time to frozen: 02:20 ; Pass C time to frozen: 00:50

8.1.3.3 Shipment should also include a hard copy of the **TISSUE BIOPSY VERIFICATION** form found in the appendices of corresponding protocols.

8.2 Specimen shipment to EET Biobank

8.2.1 Follow the **Shipping Specimens from Clinic Site to the EET Biobank/ETCTN Biorepository** section of the clinical protocol for general instructions of sample shipment to EET Biobank.

8.2.2 Frozen biopsies should be shipped in kits provided by EET Biobank. The shipping container sent with kit contents should be used to ship specimens to EET Biobank. **Note:** It's important to include sufficient dry ice to keep the biopsy frozen for at least 96 hours.

8.2.3 Frozen specimens may be shipped on Monday through Thursday to the following address:

EET Biobank
The Research Institute at Nationwide Children's Hospital700 Children's Drive,
WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897

Note: FedEx Priority Overnight service is the required shipping method. TheEET Biobank FedEx account will not be provided to submitting institutions.
Sites are responsible for all costs for shipments to the EET Biobank, so theovernight express shipment should be billed directly to the shipping institution/site.

8.3 Useful contacts for Specimen Collection, Handling and Shipment:

8.3.1 Send all questions related to this SOP or PD- assay support questions to: NCI_PD_Support@mail.nih.gov

8.3.2 Send all technical questions about the Specimen Tracking System to: STS.Support@theradex.com

8.3.3 EET Biobank queries (kit inquiries and sample shipping): BPCBank@nationwidechildrens.org

APPENDIX 1: BIOPSY COLLECTION RECORD

Note: This document lists important information to be recorded during the biopsy collection process forlater documentation in **NCI Medidata Rave.** The completed document should be filed with the study patient's other records at a predetermined location according to local policy for managing clinical trial information. Please **do not** include the document in the shipment to EET Biobank**.**

Certified Assay Operator: _____

Facility/Clinic Collecting Specimens: _____

Clinical Protocol Number: _____

Patient ID: _____

1. **Biopsy Collection Information:**

Note: Information collected in the table below will be entered in Medidata RAVE.

Note: Record times using military time (24-h designation); for example, specify 16:15 to indicate 4:15PM.

	Pass A	**Pass B**	**Pass C**	**Pass D**
Specimen ID				
Protocol timepoint of biopsy (Cycle, Day, and Hours post dose, if post treatment)				
Needle type				
Site of biopsy (complete for all passes or note "same" for replicate cores)				
Required: Time elapsed from collectionto placement in tube	min sec	min sec	min sec	min sec
Date biopsy collected				
Time biopsy collected	:	:	:	:
Time biopsy placed in tube	:	:	:	:

2. Notes, including any deviations from the SOP:

APPENDIX H PHARMACOKINETICS (PK) SHEET TOPOTECAN DAY 1

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), topotecan (T)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 1 Topotecan (T) infusion (nominal 30 min) T Dose (mg/m2):_____			
pre sample			
T infusion **start**			
5 min post T start			
15 min post T start			
25 min post T start (~5 min prior to EOI)			
T infusion **end**			
5 min post **END** T			
15 min post **END** T			
30 min post **END** T			
1 h post **END** T			
2 h post **END** T			
4 h post **END** T			
6 h post **END** T			

APPENDIX I PHARMACOKINETICS (PK) SHEET TOPOTECAN DAY 2

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), topotecan (T)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 2 Topotecan (T) infusion (nominal 30 min) T Dose (mg/m2):_____ BAY Dose (mg) _____			
pre sample			
T infusion **start** **=time of BAY dose**			
5 min post T start			
15 min post T start			
25 min post T start (~5 min prior to EOI)			
T infusion **end**			
5 min post **END** T			
15 min post **END** T			
30 min post **END** T			
1 h post **END** T			
2 h post **END** T			
4 h post **END** T			
6 h post **END** T			

APPENDIX J PHARMACOKINETICS (PK) SHEET TOPOTECAN DAY 3

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), topotecan (T)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 3 Topotecan (T) infusion (nominal 30 min) T Dose (mg/m2):_____ BAY Dose (mg) _____			
BAY dose time (2nd dose, D2 PM)			Ask patient / retrieve from diary from night before = D2 PM dose
pre sample			
T infusion **start**			

APPENDIX K PHARMACOKINETICS (PK) SHEET TOPOTECAN DAY 4

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), topotecan (T)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 4 Topotecan (T) infusion (nominal 30 min) T Dose (mg/m2):_____			
pre sample			
T infusion **start**			

APPENDIX L PHARMACOKINETICS (PK) SHEET IRINOTECAN COHORT #1 DAY 1-2

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), irinotecan (IR)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 1-2 Irinotecan (IR) infusion (nominal 90 min) IR Dose (mg/m2):_____ BAY Dose (mg) _____			
pre sample			
IR infusion **start** **=time of BAY dose**			
30 min post BAY			
1 h post BAY			
1 h 20 min post BAY / IR start (~10 min prior to EOI)			
IR infusion **end**			
2 h post BAY			
4 h post BAY			
6 h post BAY			
8 h post BAY			(If feasible to obtain)
BAY dose time (2nd dose, D1 PM)			Ask patient / retrieve from diary
~24 h post 1st BAY dose =pre 3rd dose (D2 AM)			
BAY dose time (3rd dose; D2 AM)			

APPENDIX M PHARMACOKINETICS (PK) SHEET IRINOTECAN COHORT #1 DAY 3

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), irinotecan (IR)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 3 Irinotecan (IR) infusion (nominal 90 min) IR Dose (mg/m2):_____ BAY Dose (mg) _____			
BAY dose time (4th dose, D2 PM)			Ask patient / retrieve from diary
~48 h post 1st BAY dose ~12 h post 4th BAY dose			

APPENDIX N PHARMACOKINETICS (PK) SHEET IRINOTECAN COHORT#2 DAY 1

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), irinotecan (IR) - cohort #2

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 1 Irinotecan (IR) infusion (nominal 90 min) IR Dose (mg/m2):_____			
pre sample			
IR infusion **start**			
30 min post IR start			
1 h post IR start			
1 h 20 min post IR start (~10 min prior to EOI)			
IR infusion **end**			
30 min post IR end			
2h 30 min post IR end			
4h 30 min post IR end			

APPENDIX O PHARMACOKINETICS (PK) SHEET IRINOTECAN COHORT#2 DAY 2-3

NCI 10402 (BAY 1895344 (BAY), topotecan (T), irinotecan (IR) in Plasma): BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Advanced Solid Tumors, Phase I with Expansion Cohorts

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~3-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA),** mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also (through (a copy of) this completed form).*

Note the start and stop times of infusions and dose times in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion or dose, a green arrow indicates which time-point starts the clock on subsequent blood draws.

BAY 1895344 (BAY), irinotecan (IR) - cohort #2

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 2-3 Irinotecan (IR) infusion (nominal 90 min) IR Dose (mg/m2):_____ BAY Dose (mg) _____			
pre sample			
IR infusion **start** **=time of BAY dose**			
30 min post BAY			
1 h post BAY			
1 h 20 min post BAY / IR start (~10 min prior to EOI)			
IR infusion **end**			
2 h post BAY			
4 h post BAY			
6 h post BAY			
8 h post BAY			(If feasible to obtain)
~24 h post 1st BAY dose =pre 2nd dose (D3 AM)			
BAY dose time (2nd dose, D1 PM)			Ask patient / retrieve from diary