NCI Protocol #: 10211
Version Date: December 2, 2022

SUMMARY OF CHANGES – Protocol

For Protocol Amendment 9 to A Phase 2 Single-Arm Study of M6620 in Combination with Irinotecan in Patients with Progressive TP53 Mutant Gastric and Gastro-Esophageal Junction Cancer: This protocol is being amended:

- The PI, Dr. Das, is leaving Vanderbilt. We are transferring the study to Dr. Jordan Berlin
- We addressed all CTEP recommendations per review on September 14, 2022

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Local Protocol #: VICCNCIGI10211

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The changes reflect revisions from vAugust 17, 2022 v.December 2, 2022

#	Section	Page	Change
1.	TITLE	1	OLD TEXT: *Version Date:*- ~~August 17, 2022~~ NEW TEXT: Version Date: December 2, 2022 RATIONALE: Updated protocol header so document version date
2.	TITLE	1	Updated PI contact information
3.	7.2.2	43	Please remove the newly created section titled: Change from M6620 CAEPR version 1.4 (older) to version 2.0. These changes only need to be listed in the summary of changes. **PI Response:** Updated as requested.
4.	8.1.1	48	For M6620, please update the storage conditions to: Storage: Store intact vials protected from light inside cardboard boxes at room temperature, below 25°C (77°F), do not freeze ~~with excursions allowed between 15 and 30°C (59 and 86°F)~~. If a storage temperature excursion is identified, promptly return M6620 to ~~between 15 and~~ ~~30°C~~ below 25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. **PI Response:** Updated as requested.

NCI Protocol #: 10211

Local Protocol #: VICCNCIGI10211

ClinicalTrials.gov Identifier: NCT03641313

TITLE: A Phase 2 Single-Arm Study of M6620 in Combination with Irinotecan in Patients with Progressive TP53 Mutant Gastric and Gastro-Esophageal Junction Cancer

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Amendment 9/ Version 2.3/ Version Date: 17 August 2022

SCHEMA

This is a phase II single arm, multicenter study accessing the efficacy of M6620 in combination with irinotecan in patients with progressive metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma harboring a TP53 mutation. Patients with TP53 mutations only in exons 2 and 4-11, will be eligible for the trial. Mutations conferring eligibility can be determined from any next generation sequencing (NGS) assay.

The trial will follow the Flow Schema as below (Figure 1):

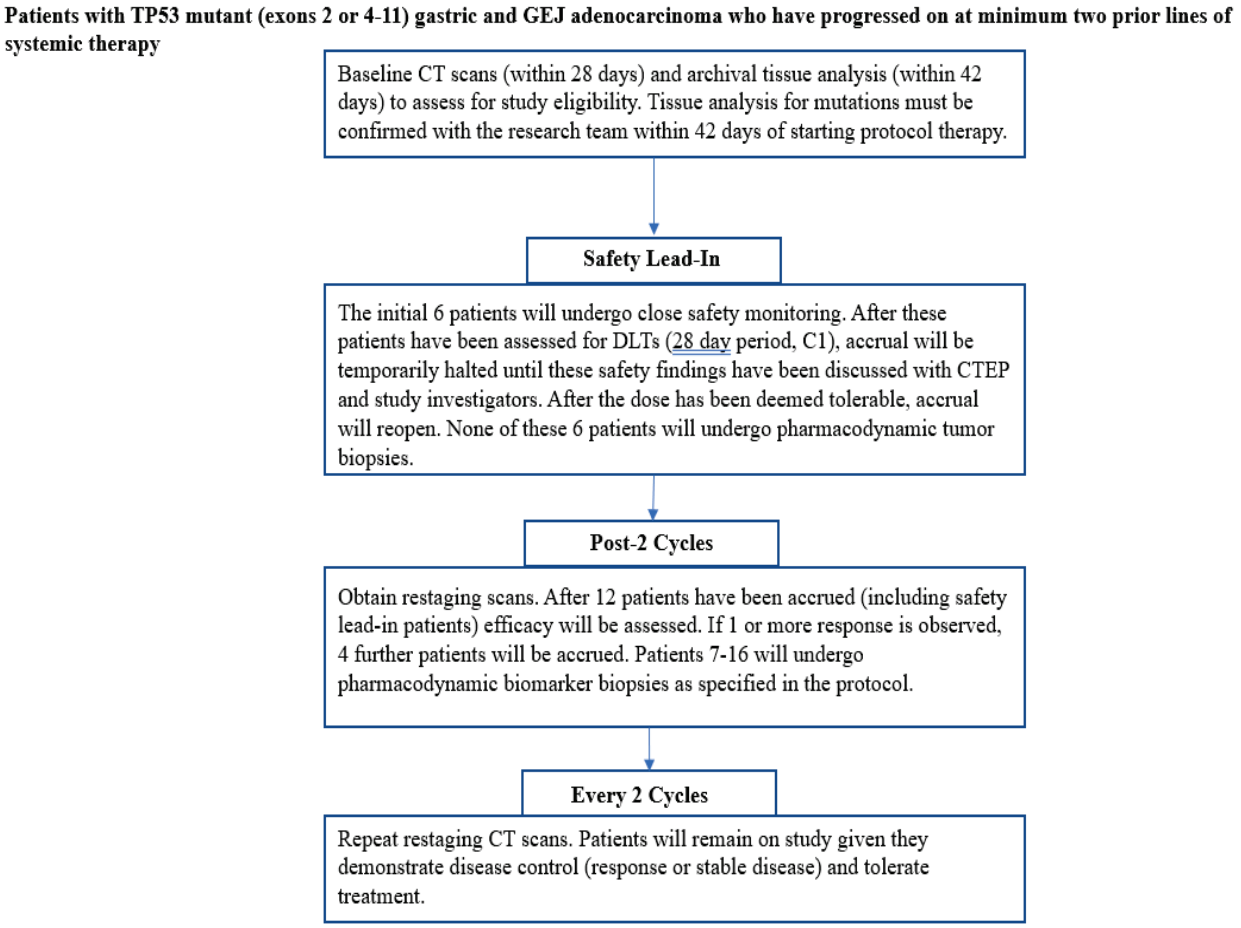

Figure 1. Flow Schema

The first 6 patients will be closely monitored for safety after being treated at a starting M6620 dose of 270 mg/m^2 in combination with irinotecan (180 mg/m^2). The starting dose has been established as tolerable from NCI #9938. Dose limiting toxicities (DLTs) will be assessed in the 28-day period following C1D1 of treatment in these patients. A DLT is defined as grade 4 hematologic toxicity lasting ≥ 7 days, febrile neutropenia consisting of ≥ grade 2 fever and grade 4 neutropenia, grade 4 diarrhea despite supportive measures, any other non-hematologic toxicity ≥ grade 3 occurring in cycle 1 of treatment or the inability to meet C2 treatment parameters within 4 weeks of C1D15. No on-treatment tumor biopsies will be obtained in the patients

enrolled in the safety lead-in and thus M6620 **will not** be omitted on C1D1 as it will for the subsequent 9 patients undergoing pharmacodynamic biomarker assessment.

Irinotecan will be administered via intravenous infusion over 90 minutes, and M6620 will be administered via intravenous infusion over 60 minutes immediately following irinotecan on days 1 and 15. Only on C1D1 will the treatment schedule deviate as M6620 will be omitted for the patients undergoing research biopsies. Treatment cycles repeat every 28 days. Patients will continue treatment in the absence of disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination.

The primary endpoint of study is the objective response rate (ORR). Assuming a 10% type I error and 80% power, Simon's minimax 2-stage design requires 16 efficacy-evaluable patients. If 0 patients in the first 12 treated do not demonstrate a response, stop early for futility. If 3 or more patients experience an ORR among 16 efficacy-evaluable patients, declare the experimental combination worthy of further study.

Secondary endpoints are duration of response (DOR), time to progression (TTP), progression-survival (PFS), and overall survival (OS) in the whole cohort. Exploratory endpoints are ORR, DOR, TTP, PFS, and OS in sub-cohorts based on first-line platinum sensitivity and presence of other DNA damage response defects (DDRD). In patients undergoing research biopsies, tissue samples will be collected 24 hours (+/- 3 hours) post-irinotecan infusion on C1D2 and 24 hours (+/- 3 hours) post-M6620 infusion on C2D2.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- Determine ORR superiority (target 25%) in TP53 mutant patients with progressive metastatic or unresectable gastric/GEJ cancer who receive M6620 and irinotecan compared to ORR (5%) in historical control patients treated with single agent irinotecan alone.

1.2 Secondary Objectives

- Determine DOR, TTP, PFS, and OS superiority in TP53 mutant gastric/GEJ cancer patients who receive M6620 and irinotecan compared to these measures in historical control patients treated with irinotecan alone.

- Perform the following correlative studies in 9 patients:

    - γ-H2AX, KAP1 p-Ser 824 and p-ATR analysis from biopsies collected at 24 hours (+/- 3 hours) post-irinotecan infusion on C1D2 and at 24 hours (+/- 3 hours) post-M6620 on C2D2.

1.3 Exploratory Objectives

- Determine ORR, DOR, TTP, PFS, and OS in patients with other concomitant DDRD, such as mutations in BRCA1, BRCA2, MRE11, RAD50, RAD51, RAD52, RAD54L, NBN, ATM, H2AX, PALB2, RPA, BRIP1, BARD1, ATR, ATRX, CHK1, CHK2, MDM2, MDM4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, treated with the experimental combination.

- Determine whether patients with first line platinum sensitivity (PFS > 3 months) demonstrate improved ORR, DOR, TTP, PFS, and OS compared to patients who were platinum insensitive (PFS < 3 months).

2. BACKGROUND

2.1 *Study Disease*

Gastric and gastro-esophageal junction (GEJ) cancer remains a major global health concern and is the third leading cause of annual cancer associated mortality (Torr et al., 2016). Unfortunately, many patients present with advanced disease where palliative systemic therapy (chemotherapy and more recently, immunotherapy) is the primary treatment option rather than curative surgery. 5-year survival rates are <5% in these patients (SEER, database 2018) and naturally there remains a grave need to add new therapeutics for patients in this setting. One such avenue for drug development is targeting salvage DNA repair pathways in cancer cells. Cancer cells rely on

these pathways to retain functional genomic integrity in the face of faulty DNA replication and DDRD. This reliance creates therapeutic opportunities to combine cytotoxic chemotherapy with salvage repair pathway inhibitors.

DDRD have already been shown in gastric adenocarcinoma patients to predict sensitivity to DNA repair inhibitors such as PARP inhibitors. In a randomized phase II study of 124 progressive adenocarcinoma patients treated with olaparib and paclitaxel versus paclitaxel alone, those with ATM serine/threonine kinase (ATM) deficits had a marked OS benefit from the combination compared to all treated patients (Bang et al., 2015). The tumor suppressor gene TP53 is a downstream effector of ATM and is the most frequently mutated gene across all human cancer. It is mutated in 30-70% of gastric and GEJ adenocarcinoma patients with most mutations falling within exon 2 and exons 4-11 (Bass et al., 2014). Cancer cells with mutations in TP53 tend to depend on ataxia telangiectasia and Rad3-related protein kinase (ATR) as a primary mediator of DNA damage. ATR is normally activated by single strand interruptions associated with replication stress however its activity can also be triggered by pharmacologic stressors including topoisomerase (Top1) inhibitors, anti-metabolic agents or ionizing radiation. Upon activation, ATR activates Chk1, a cell cycle-kinase whose downstream effects lead to cell cycle arrest in S-phase or the G2-M checkpoint (Zeman et al., 2014).

2.2 CTEP IND Agent

2.2.1 M6620

M6620 (VRT-0768079) is a highly potent and selective ATP-competitive inhibitor of ATR, [redacted] (Investigator's Brochure, 2017). In comparison, M6620 was >100-fold weaker inhibitor of ATM (Ki=34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-dependent protein kinase (DNA-PK) (Ki>4 mcM), mTOR (Ki>1 mcM), and PI3K-gamma (Ki=0.22 mcM) (Fokas et al., 2012). [redacted] The starting dose of M6620 will be 270 mg m^{-2} as determined from NCI #9938.

Effect of M6620 on DNA Damage Response (DDR) signaling and DNA damage

M6620 potentiated the activity of multiple DNA-damaging agents in numerous cancer cell lines from a range of indications（Investigator's Brochure, 2017). Concurrent treatment of cancer cell lines with M6620 and various DNA-damaging agents led to sustained M6620-dose-dependent decreases in levels of chemotherapy-induced $CHK1pS^{345}$, a major substrate of ATR (Fokas *et al*., 2012; Hall *et al*., 2014). In the presence of DNA damage, primarily DSBs, histone H2AX is phosphorylated at serine 139 to produce γH2AX ($H2AXpS^{139}$). Although all three DDR regulatory kinases, ATM, ATR, and DNA-PK phosphorylate H2AX to γH2AX, they are variably activated during different DNA-damage repair mechanisms (*e.g*., HR repair, non-homologous end joining [NHEJ] repair, base excision repair due induced by stalled replication

forks, *etc*.) (Kuo and Yang, 2008). In addition, for the efficient DNA-damage repair, the DDR regulatory kinases must be able to access damaged sites in the chromatin environment. ATM has been shown to phosphorylate the heterochromatin protein KAP1 at serine 824 (KAP1pS^{824}) in response to DNA damage (White *et al.*, 2012). Exposure of lung cancer cell lines as well as primary tumors to M6620 in combination with DNA-damaging agents enhanced levels of the DNA-damage markers, *i.e*., γH2AX and KAP1pS^{824}, as compared to DNA-damaging agent alone (Hall *et al*., 2014). Sequential treatment of cells with DNA-damaging agent followed 15 h later by M6620 resulted in an initial inhibition of phospho-CHK1 (for 1 to 2 h) (Investigator's Brochure, 2017). However, over time, phospho-CHK1 re-appeared despite continued exposure to M6620. The rebound of phospho-CHK1 has been attributed to non-specific phosphorylation by an undefined kinase. However, despite the transient inhibition of phospho-CHK1, the sustained accumulation of the DNA damage markers was observed. Together these data suggest that disruption of ATR-mediated DDR signaling by M6620 leads to sustained accumulation of DNA damage in cancer cells exposed to DNA-damaging agents. It has been suggested that the failure to repair chemotherapy-induced DNA damage in the presence of M6620 is the driver of enhanced cytotoxicity in cancer cells. These data support using the DNA-damage markers as pharmacodynamic markers of M6620 activity.

M6620-mediated radiosensitivity of pancreatic ductal adenocarcinoma cells was associated with inhibition of HR repair (Fokas *et al*., 2012). M6620 caused increased persistence of γH2AX levels both *in vitro* and *in vivo*. Adding M6620 to gemcitabine and ionizing radiation (IR) dramatically enhanced antitumor effects, with early and late apoptosis and abrogation of IR-induced G2 checkpoint in cell culture experiments. It has been suggested that by promoting strong S-phase arrest, chemoradiation may further increase dependence of tumor cells on ATR-mediated homologous recombination (HR) repair of DNA double strand breaks (DSBs) and for survival.

Nonclinical studies

In vitro antitumor activity

[redacted]

[redacted]

In addition, significant radiosensitization effects by M6620 were observed against two human pancreatic cancer cell lines with mutant KRAS and mutant p53 (MiaPaCa-2 and PSN1) (P<0.05), but not against non-cancerous fibroblast cell lines (Fokas *et al*., 2012). In addition, M6620 profoundly sensitized pancreatic tumor cells to gemcitabine-based chemoradiation.

[redacted] This suggests that the functional status of the ATM pathway is a contributing factor in the cellular response to the inhibition of ATR.

Of note, the response/TP53 status relationship was unclear in the panel of heterogeneous cancer cell lines exposed to M6620 + chemotherapy (Hall *et al.*, 2014). Although not significant, there was a trend of causality between response and p53 status (P=0.08) for M6620 combined with cisplatin. Furthermore, no clear relationship between cellular response to M6620 + cisplatin and TP53 status was observed in seven primary lung tumors.

In vivo antitumor activity

The *in vivo* activity of M6620 was tested in multiple mouse xenograft models derived from human lung cancer cell lines and primary human tumor cells (Hall *et al.*, 2014; Investigator's Brochure, 2017). M6620 potentiated antitumor effects of cisplatin, gemcitabine, irinotecan, and IR in a dose- and schedule-dependent manner. Antitumor efficacy correlated with inhibition of phospho-CHK1 and an increase in DNA-damage markers. This supports ATR inhibition as a

primary mechanism of action for M6620. Single-agent M6620 had no significant effect on tumor growth in the experimental models. M6620 was generally well tolerated at efficacious doses in combination with DNA-damaging agents. Some body weight loss and enhanced changes in specific peripheral blood cell populations were observed with intensive and sustained dosing of M6620 in combination with cisplatin. This effect could be attributed to an increased growth arrest, which was observed *in vitro* in normal cells for combinations of M6620 with DNA-damaging agents. This effect was reversed when ATR activity was restored. M6620 sensitized pancreatic tumor xenografts to the cytotoxic effects of gemcitabine-based chemoradiation (Fokas *et al*., 2012). The combination treatment was effective even at gemcitabine doses with no single-agent activity. M6620 administered in combination with gemcitabine + IR was well tolerated.

[redacted]

[redacted]

Nonclinical Pharmacokinetics

[redacted]

[redacted]

[redacted]

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Clinical Studies

[redacted]

[redacted]

[redacted]

Clinical Efficacy

[redacted] A summary of preliminary activity is as follows:

- M6620 + gemcitabine in advanced solid tumors: Among 48 patients, 4 (one each NSCLC, head and neck cancer, breast cancer, and unknown primary cancer) had partial response (PR) and 29 patients had stable disease (SD). In an additional cohort of 18 patients with advanced NSCLC, 3 had PRs and 15 had SD.
- M6620 + cisplatin in advanced solid tumors: Among 26 patients, 4 (1 each $BRCA2^{+}$ ovarian cancer, epithelioid mesothelioma, TNBC, neuroendocrine prostate cancer) had PRs, and 15 patients had SD. In an additional cohort of 18 patients with advanced TNBC, 7 had PR and 6 had SD.
- M6620 + carboplatin in advanced solid tumors refractory to standard therapy: Among 21 evaluable patients, 1 had PR (ovarian cancer) and 14 had SD.
- M6620 + carboplatin or M6620 + cisplatin in platinum-resistant advanced SCLC: There were no objective responses observed among nine evaluable patients and 4 had SD.
- M6620 + gemcitabine + cisplatin in advanced solid tumors: Of 7 evaluable patients, 1 had PR (CRC) and 4 had SD.
- M6620 + carboplatin + paclitaxel in advanced solid tumors refractory to standard therapy: Among 8 evaluable patients, 2 had PR (1 each adenosquamous carcinoma of the cervix and melanoma) 3 had SD.

Safety summary from studies with M6620 as single agent or in combination with cytotoxic therapy (Investigator's Brochure, 2017)

Infusion-related reactions (local or systemic), nausea, and vomiting are considered adverse drug reactions (ADRs) for M6620, and myelosuppression events are considered ADRs for M6620 in combination with carboplatin.

- [redacted]
- [redacted]
- [redacted]

- Nausea and vomiting have occurred commonly in patients receiving M6620 monotherapy. Many of the affected subjects experienced these events on the same day as M6620 was administered, and there was some suggestion of a dose response.

- Hematologic AEs in subjects who received M6620 in combination with carboplatin have included neutropenia, thrombocytopenia, and febrile neutropenia.

- M6620 has not been assessed in developmental and reproductive toxicity studies at this stage of development. However, M6620 inhibits DNA-damage repair and it will be administered in conjunction with cytotoxic chemotherapy; thus, the potential for teratogenicity should be M6620 considered high. Patients on M6620 studies must take stringent measures to avoid fathering or bearing children while on study drug and for 6 months after discontinuation of M6620. Refer to the M6620 clinical study protocols for specific contraceptive requirements.

Guidance on prior and concomitant medications (Investigator's Brochure, 2017)

Because the drug interaction profile of M6620 has not been fully characterized, caution should be used when co-administering medications with M6620. [redacted]

2.3 Irinotecan

Top1 inhibitors, such as irinotecan, have long been cornerstones of therapy for gastrointestinal malignancies including colon, pancreatic, esophageal, gastric and GEJ cancer. Top1 is a key enzyme in the DNA repair process and stabilizes partially unwound double helixes during DNA replication. The enzyme generates single stranded breaks and creates unstable intermediate complexes known as Top1 Cleavage Complexes (Top1cc) (Zeman et al., 2014). Top1 inhibitors prevent the reversal of unstable Top1cc intermediates and DNA re-ligation. Persistence of these cleavage complexes results in replication fork collisions, interruption of transcription complexes, replication stress and ultimately double stranded breaks.

Single agent irinotecan monotherapy is utilized largely in the third-line setting for gastric/GEJ adenocarcinoma patients and produces at best, an overall response rate (ORR) of 7% (Makiyama et al. 2018). We realize using this ORR as a historical comparator for our experimental treatment arm in TP53 mutant patients represents a generalization. However, as there are no prior studies which have determined ORR of later-line single agent irinotecan in TP53 mutant gastric/GEJ

patients, we do not have any other viable options with this study design. A meta-analysis from Xu *et al.* suggests TP53 mutant gastric cancer patients may have a more robust response to chemotherapy (in the first-line setting) with platinum agents or platinum plus irinotecan however no trials assessing single agent irinotecan or later-line irinotecan were included in the analysis (Xu et al., 2014). A colon cancer trial from Netter *et al.* found no differential benefit from FOLFIRI in TP53 mutant patients compared to TP53 WT patients, however this was again a first-line trial and a different patient population (Netter et al., 2015). We are combining irinotecan with the ATR inhibitor M6620 in progressive TP53 mutant gastric and GEJ adenocarcinoma patients on our trial. The combination of ATR inhibitors with other replication stress inducers, including other Top1 inhibitors, are being explored in several other early phase clinical trials (Thomas et al., 2017; O'Carrigan et al., 2016).

2.4 Rationale

Preclinical activity of M6620 against ATR has been demonstrated in the esophageal cancer cell lines OE21, OE33 and FLO-1 (first two squamous, latter adenocarcinoma). OE21 cell lines were treated with M6620 and then exposed to hypoxic conditions to stimulate ATR activity. In response to hypoxia, phosphorylated Chk1 levels initially increased. These levels decreased after exposure to M6620. Specificity of the inhibitor was demonstrated by treating OE21 cell lines with either M6620 or the ATM inhibitor KU-55933. M6620 decreased Chk1 dependent phosphorylation of the site S473 on the down-steam KAP-1 protein but not phosphorylation of the site S824 which is predominantly phosphorylated by ATM. OE21 and FLO-1 cells were exposed to increasing dosage of cisplatin (.5 uM, 1 uM) and carboplatin (20 uM, 40 uM, 60 uM) plus M6620 versus a control DMSO solution. In each scenario, addition of the ATR inhibitor significantly reduced cell viability compared to chemotherapy alone (Leszcznyska et al., 2016).

The combination of M6620 with SN-38 (active metabolite of irinotecan) was explored in colorectal cancer cell line studies with COLO205. In vitro experiments suggested synergism between the two agents at concentrations of M6620 as low as 80 nanomolar; M6620 increased the IC50 of SN-38 nearly eight-fold. This was then tested in xenograft colon cancer mice models. Mice were treated with intraperitoneal irinotecan, oral M6620, or the combination. While M6620 had no impact on tumor growth when dosed as a single agent at 60 mg/kg it demonstrated significant anti-tumor activity when dosed in combination with irinotecan at 20 mg/day. The combination produced a greater and more sustained reduction in tumor volume than single-agent irinotecan at 40 mg/day (Figure 1). There was no signal for greater toxicity with the combination compared to the higher dose of irinotecan as a similar drop in body weight was noted in mice who received either treatment (Josse et al., 2014).

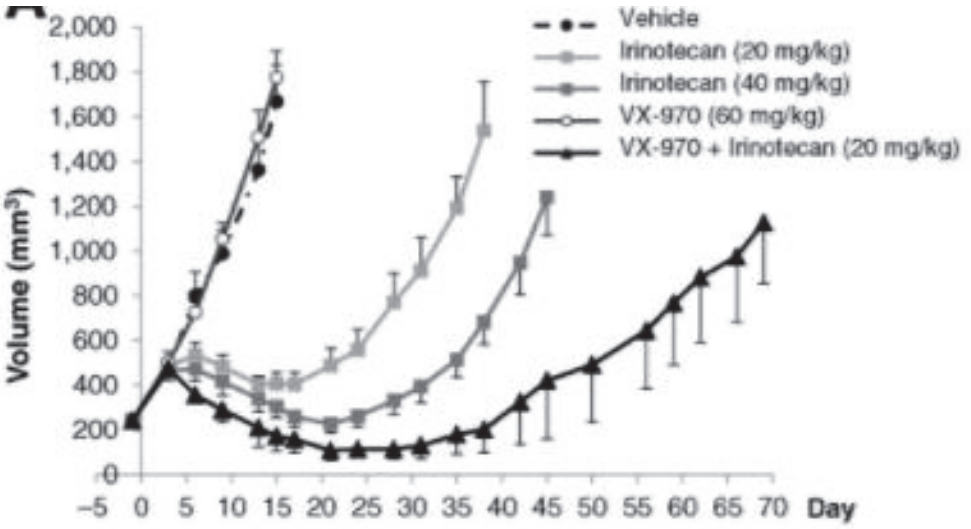


Figure 1: Xenograft model where mice bearing COLO205 tumors were treated with vehicle, irinotecan, M6620 or the combination of M6620 and irinotecan. VX-970 is another name of M6620.

Additional pre-clinical data suggests cancer cell lines with deficits in the ATM and TP53 pathway are particularly sensitive to ATR inhibitors. Min et al. assessed response to the ATR inhibitor AZD 6738 in gastric cancer cell lines. In their experiments, SNU-601 and SNU-484 were chosen as the model cell lines of resistance and sensitivity, respectively. The authors explored why the two cells lines had such disparate sensitivity to AZD 6738 and found ATM-Chk2 axis proteins downregulated in SNU-601 cells compared to levels in SNU-484 cells. Knocking down ATM expression in SNU-484 with siRNA or an ATM inhibitor resensitized the cells to ATR inhibition (Min et al., 2017). Kwok et al. looked at CLL cell lines in vitro and in vivo xenograft mice models and found ATM and TP53 deficient cell lines were markedly more sensitive than their wild-type counterparts to AZD 6738 (Figure 2). Further, AZD 6738 sensitized these deficient cell lines to chemotherapy with agents such as fludarabine, bendamustine and chlorambucil (Kwok et al., 2016). Ma et al demonstrated this same principle in triple negative breast cancer (TNBC) mouse models. In their experiments three TNBC mouse model xenografts were generated: one wild-type (WU-BC3) and two TP53 mutants (WU-BC4 and WU-BC5). These models were treated with irinotecan and a Chk1 inhibitor (UCN-01 or AZD7762) as single agents or in combination. The combination therapy induced apoptosis and tumor death in WU-BC4 and WU-BC5 models but not in WU-BC3. Knocking out TP53 however, sensitized WU-BC3 tumors to the combination therapy (Ma et al., 2012). Manic et al. also demonstrated that TP53 deficient cell lines were particularly susceptible to ATR-Chk1 axis inhibition in RAS mutant colorectal cancer stem cells (CSCs). In their experiments, CSCs with siRNA induced TP53 knockdown were sensitive to the Chk1 inhibitor LY2606368 (Manic et al., 2017).

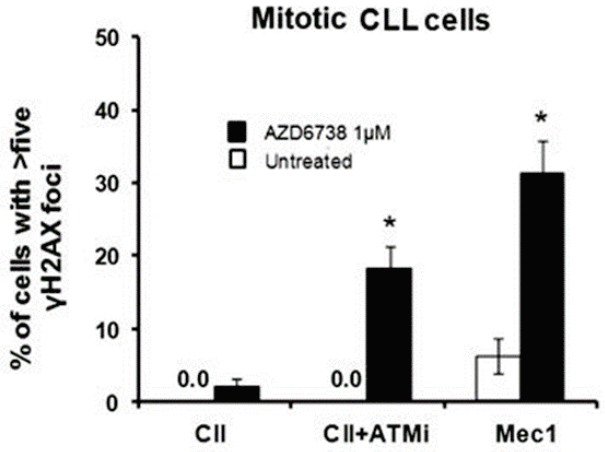


Figure 2: Assessing DNA damage by y-H2AX induction in WT CLL, WT CLL w/ATM inhibitor and Mec1 TP53 deficient CLL lines post addition of AZ6738.

As demonstrated by the preclinical data above, targeting the ATR axis in TP53 mutant patients represents a promising opportunity to enhance cancer cell death. There is an ongoing phase I trial NCT02595931 determining the optimal dose of M6620 in combination with irinotecan in refractory solid tumor patients. We will use the recommended phase II dose (RP2D) from this trial as the treatment dose for patients on our study. Thomas et al. recently reported the phase I results from M6620 and the Top1 inhibitor topotecan in advanced solid tumor patients and demonstrated safety at the MTD as well as signals of efficacy (Thomas et al., 2017). Our primary aim is to demonstrate that TP53 mutant patients will achieve an ORR of 20% with the experimental combination. Secondary aims include demonstrating duration of response (DOR), time to progression (TTP) and overall survival (OS) benefit of the combination in patients on study compared to TTP and OS in historical controls treated with single agent irinotecan. Exploratory aims include assessing the relationship of other DDRD gene mutations and sensitivity to first line platinum therapy with response to M6620 plus irinotecan.

In the 9 patients (median 3 prior lines of treatment) who have been treated thus far on study 10211 with irinotecan plus M660, median PFS was 3.91 (95% CI 2.63 – NR) months and median OS has not yet been reached (95% CI 4.81 – NR) (10-month OS rate > 60%) (Figure 3). For context, in second-line prospective studies of irinotecan monotherapy in patients with gastric and GEJ adenocarcinoma, median PFS was 2-2.1 months and 10-month OS rates were 30% (Lee et al. 2019, Sym et al. 2013). Of the 9 patients, 3 patients have achieved disease control for more than 5 months (with 1 patient currently with stable disease for 11 months), with 1 patient achieving an objective response which was maintained for 7 months (Table 1). The median PFS observed thus far in patients treated with study 10211 approximates the PFS observed with ramucirumab plus paclitaxel (median PFS 4.4 months in RAINBOW trial) which currently represents the second-line treatment standard for patients with gastric and GEJ adenocarcinoma (Wilke et al. 2014). Observing this level of activity in the third-line and beyond setting is unusual for patients with this disease and suggests the study combination may possess meaningful later-line clinical activity in this disease population. If this study meets its primary endpoint, the

subsequent randomized phase II study would compare irinotecan plus M6620 versus either TAS-102 or irinotecan in patients with third-line and beyond gastric and GEJ adenocarcinoma (stratified by TP53 tumor status). TAS-102 represents the current third-line treatment standard for this patient population and garnered FDA approval based upon the results of the TAGS study; median PFS and OS in patients with gastric and GEJ adenocarcinoma treated with the drug were 2 months and 5.7 months, respectively (Shitara et al. 2018).

Beyond the anti-tumor activity observed with irinotecan plus M6620, the study combination appears to be well tolerated. No DLTs were observed in the first 6 patients treated on the study during the establishment of the safe dose. No grade 4 adverse events have occurred in patients in the interim analysis and the most common grade 3 adverse events include anemia (1 case), neutropenia (1 case), diarrhea (1 case), leukopenia (1 case) and vomiting (1 case). Most adverse events experienced by patients were grade 1/2 in nature and in line with the adverse event profile of irinotecan.

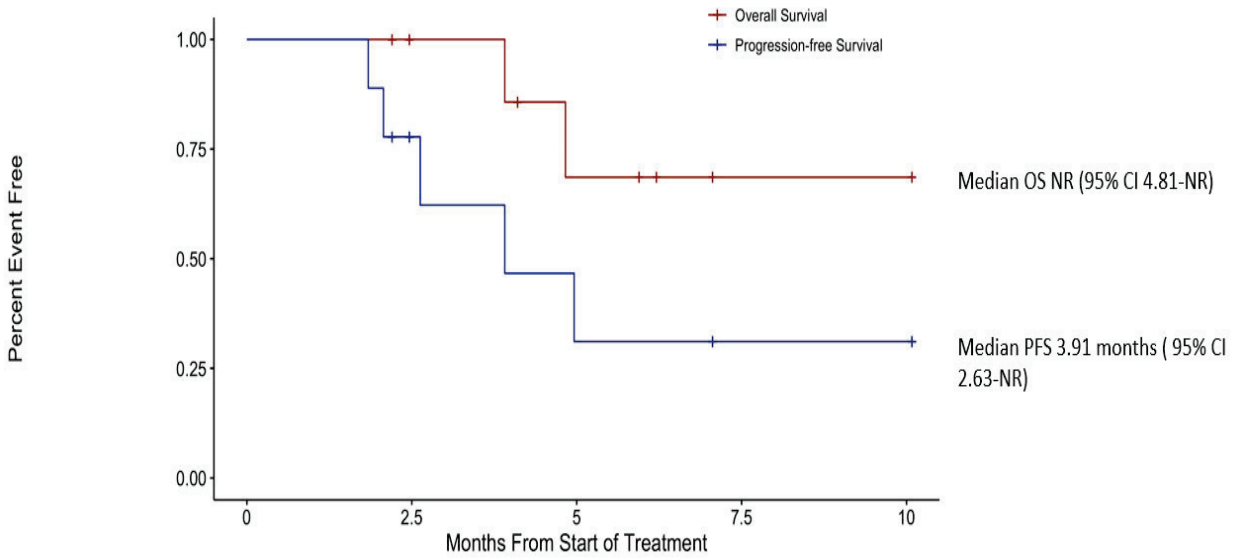


Figure 3: PFS and OS data from 9 patients in interim analysis of study 10211.

Abbreviations: NR, not reached; CI, confidence interval

Table 1: Response data from 9 patients in interim analysis of study 10211.

[redacted]

2.5 Correlative Studies Background

A: TP53 and DDRD Genes:

Mutations in TP53 (exons 2 and 4-11) are a prerequisite for enrollment onto the study and will be ascertained from archived tissue through any CLIA certified NGS assay. Although we will be illustrating how the FoundationOne/FoundationOne Cdx, the dominant NGS assay used at our institution, reports our mutations of interest, this applies to any CLIA certified NGS assay. Results from the FoundationOne/FoundationOne Cdx assay are clearly presented in a synthesized report that specifies the codon (thus identifying the exon) a specific TP53 mutation falls within. Concomitant mutations in other DDRD genes are also reported in a similar manner. Some of these DDRD mutations we feel could improve the likelihood of response with the experimental therapy include BRCA1, BRCA2, MRE11, RAD50, RAD51, RAD52, RAD54L, NBN, ATM, H2AX, PALB2, RPA, BRIP1, BARD1, ATR, ATRX, CHK1, CHK2, MDM2, MDM4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, and FANCL. These genes have been validated across assays and play important roles in homologous recombination (from published literature in breast and ovarian cancer) and the ATR axis (from data cited in the pre-clinical rationale above) (Walsh, 2015).

B: Tissue Based Biomarkers of DNA Damage and Inhibition of ATR Mediated Signaling:

γ-H2AX is phosphorylated histone which is a well validated marker of DNA damage. From a variety of pre-clinical studies (including Min et al. mentioned above), it has been shown to accumulate at sites of DNA double stranded breaks (Kuo et al., 2008; Ivashkevich et al., 2012). P-ATR is a marker for direct ATR pathway activation and signaling. This has been demonstrated in cell line models from several laboratories including the Cortez laboratory at Vanderbilt (Nam

et al., 2011). KAP1 is a heterochomatin protein which is phosphorylated by ATM at the Ser 824 residue following DNA damage. It often co-localizes with γ-H2AX at DNA damage foci however is not dependent on ATR for phosphorylation, carrying potential to serve as a marker of generalized DNA damage in the setting of ATR inhibition (White at al., 2012). Changes in tissue levels of γ-H2AX, KAP1 p-Ser 824 and p-ATR will be measured in the initial nine patients enrolled on the first stage of the study. Because we do not know a priori what the baseline levels of γ-H2AX, KAP1 p-Ser 824 and p-ATR are in TP53 mutant patients with gastric and GEJ adenocarcinoma, we have sent tissue from 4 archived TP53 mutant gastric/GEJ patients (16 slides) to PADIS for measurement of these levels. These baseline levels are currently being quantitated and will help us determine what degree of change in the markers-of-interest constitutes a significant change in study patients. Patients will undergo core biopsies (endoscopically of primary site or percutaneously of metastatic site) on C1D2 24 hours (+/- 3 hours) post-irinotecan infusion and on C2D2 at 24 hours (+/- 3 hours) post-M6620, for tissue ascertainment. Tissue will be prepared and sent to the PADIS laboratory for quantification and analysis. Our hypothesis is we will see a differential pattern of dynamic changes in levels of each between responding and progressing patients. We believe responding patients will demonstrate significant declines in γ-H2AX (post-irinotecan, levels should peak while post-M6620, this signal should be knocked down) and p-ATR levels, and increases in KAP1 p-Ser 824 levels, while progressing patients will demonstrate less robust changes. Multiplex immunofluorescence assays will be utilized to quantify levels of γ-H2AX, p-ATR and KAP1 p-Ser 824. Tumor biopsy specimens will be NBF fixed and paraffin embedded. Specimens will be loaded into the Bond-Max processing module. The module will stain the slides in an automated fashion with a biotinylated γ-H2AX, p-ATR and KAP1 p-Ser 824 monoclonal antibodies as the recorder and streptavidin Alexa fluor 488 coated antibodies as the detector. The slides will then be stained with DAPI prior to image processing. Image capture will be performed through the software provided by the imaging system manufacturer. This same software will perform quantification of γ-H2AX, p-ATR and KAP1 p-Ser 824 (Redon et al., 2010; Kinders et al., 2010).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed progressive metastatic or unresectable gastric or GEJ adenocarcinoma

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have progressed after or been intolerant of at least two lines of systemic therapy. Patients with HER2 positive gastric and GEJ adenocarcinoma must have progressed on trastuzumab plus chemotherapy in the first line setting. Patients with microsatellite unstable (MSI-H) tumors must have received prior immunotherapy with pembrolizumab.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of M6620 in combination with irinotecan in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 Both men and women of all races and ethnic groups are eligible for this trial.

3.1.6 ECOG performance status ≤1 (Karnofsky ≥60%, see Appendix A).

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥ 9 g/dL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal; if liver involvement ≤ 5x ULN
– creatinine clearance	≥45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.8 Patients must have a TP53 mutation (only those known hot-spot mutations that fall within exon 2 or exons 4-11 will be accepted) determined from available archived tumor tissue that has been subjected to NGS through FoundationOne/FoundationOneCDx or a similar assay performed in a CLIA-certified laboratory. Investigators from other sites, who have potential patients who meet study eligibility, will send copies of NGS reports from these patients via Medidata Rave case reports to the Responsible Study Coordinator (contact information on Title Page). Our research team will review each report to ensure each patient possesses the mutations of interest. Similar review will happen for each patient we enroll on the study at our institution. Case reports from all screened patients will be centrally available on the Rave study database

3.1.9 Nine patients must be willing to undergo endoscopic or CT guided tumor biopsies for mandatory correlative studies. If the biopsy is deemed not safe by the treating physician, the patient may still enroll given that the other eligibility criteria are met.

3.1.10 The effects of M6620 on the developing human fetus are unknown. For this reason and because DNA-damage response (DDR) inhibitors, as well as irinotecan, are known to be teratogenic, women of child-bearing potential and men able to father children who have female partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after trial participant's final dose of M6620 or irinotecan (whichever agent is completed last). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

3.2.1 Patients with early stage untreated or resectable gastric adenocarcinoma.

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 previously received irinotecan.

3.2.4 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1, except alopecia) that was administered more than four weeks prior to starting study therapy.

3.2.5 Patients who are receiving any other investigational agents.

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

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to M6620 or irinotecan.

3.2.8 [redacted] and irinotecan and its active metabolite, SN-38, are metabolized by CYP3A4 and UGT1A1, respectively; therefore, concomitant administration with strong inhibitors of CYP3A4 (*e.g*., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir) or inducers of CYP3A4 (*e.g*. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) should be avoided. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. APPENDIX C (Patient Drug Information Handout and Wallet Card) should be provided to patients. 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.

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

3.2.10 Pregnant women are excluded from this study because M6620 as a DNA-damage response (DDR) inhibitor may have 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 M6620*,* breastfeeding should be discontinued if the mother is treated with M6620. These potential risks also apply to irinotecan.

3.2.11 HIV-positive patients are excluded unless they have an undetectable viral load and are able to use anti-viral agents that do not interact with CYP3A4 (or regimens with agents that are not major inhibitors of cytochrome P450 enzymes).

3.2.12 History of other malignancy within 36 months prior to enrollment. Patients with local cancers of any type, provided no recurrence over this timeframe, are eligible.

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.

This clinical trial will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol to address the study objectives in a population representative of

patients with solid organ tumors treated by any of the participating institutions. (See Planned Enrollment Table in Section 13.2).

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 act 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

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 emailing the email address above 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 Federal wide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted 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 on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your 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*, and protocol number *10211*,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via 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.

4.2.3 Checking **Site** Registration Status

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

- Click on *Regulatory* at the top of your screen
- Click on *Site Registration, and*
- Enter your 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 above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

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 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 Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a 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. Please print this confirmation for your records.

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 calendar 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. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Irinotecan	Benztropine 1 mg PO, ondansetron 12 mg IV, Dexamethasone 8 mg IV 30 minutes prior to chemo	180 mg/m^2 in 250 cc D5W	IV over 90 minutes **before** M6620	Day 1 and 15	28 days (4 weeks)
M6620	No scheduled pre-medications prior to M6620 unless there was an infusion reaction with the first dose (see below).	270 mg/m^2 [redacted]	IV over 60 minutes, immediately ** after irinotecan	Day 1** and 15	

The exception to this is during C1 when M6620 is omitted on D1 **only for those patients undergoing on-treatment biopsies for pharmacodynamic assessment.

The doses of irinotecan and M6620 administered will be determined by calculating the patient's body surface area (BSA) based on the patient's weight in kilograms measured pre-dose on each day of dosing (and the patient's height measured at baseline).

If the patient's weight on the day of dosing differs by > ±10% from the weight used to calculate the dose, then doses of irinotecan and M6620 must be recalculated prior to administration.

Unless otherwise specified (e.g. by established institutional practice), all doses may be rounded up (or down) to the nearest milligram; and a ±5% variance in the calculated total dose will be allowed for ease of dose administration.

Every effort should be made to target infusion timings to be as close to scheduled duration as possible. But given the variability of infusion pumps, time windows of ± 10 minutes for the duration of scheduled infusions are permitted. (Additionally, prolongation of infusion duration for the purpose of managing suspected or actual adverse event such as infusion reaction will not be considered a protocol deviation.)

5.1.1 M6620

Infuse over 60 minutes using an infusion set [redacted]

Systemic infusion-related reactions to M6620 may include signs or symptoms such as pruritus, flushing, chills/rigors, urticaria/rash, headache, bronchospasm/dyspnea, and hypotension or hypertension, among others. [redacted]

If any subject develops pruritus, flushing, or any other symptom suggestive of a systemic infusion reaction, standard measures may be employed to manage these symptoms (e.g., antihistamines and/or steroids not prohibited by the protocol). The effectiveness of desensitizing measures to prevent either recurrence or first occurrence of systemic

infusion reactions to M6620 has not been shown; nonetheless, standard desensitizing measures prior to subsequent administrations of M6620 may be employed as long as they are not prohibited by protocol, for example:

- Premedication with 200 mg hydrocortisone approximately 60 minutes before infusion, and 10 mg of chlorpheniramine or equivalent antihistamine approximately 30 minutes before infusion.
- Alternative antihistamine and steroid combinations may be considered.
- If standard measures to limit symptoms of an infusion reaction are insufficient, then the infusion time may be extended beyond 60 minutes but no longer than 90 minutes.

Local infusion-related reactions to M6620, sometimes described as infusion site reactions, may include signs or symptoms such as infusion site erythema, swelling or pain.

The IV catheter through which M6620 is infused should be monitored for evidence of erythema, tenderness, or induration. An infusion site reaction may be non-serious, or it may be serious requiring immediate intervention, and should be managed according to standard of care.

To minimize the possibility of phlebitis, M6620 should be administered through a large-bore catheter into a large-caliber peripheral vein. The IV infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth. If any subject develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the patient cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein).

5.1.2 Irinotecan

Consistent with the irinotecan product label in combination with any overriding established institutional practice, it is recommended that patients receive premedication with antiemetic agents prior to administration of irinotecan:

- In clinical studies (of the weekly dosage schedule), the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT^3 blocker (e.g., ondansetron or granisetron).
- Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan.
- Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed.
- Unless contraindicated, prophylactic administration of 1 mg of oral benztropine should be given to all patients to prevent immediate severe cholinergic symptoms-

such as rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping; bradycardia may also occur. If patients continue to experience symptoms, therapeutic administration of atropine (e.g. 0.25mg to 1mg intravenous or subcutaneous atropine) should be considered.

Both early (occurring during or shortly after irinotecan infusion) and late diarrhea (generally occurring >24 hours after administration of irinotecan) have been observed.

Whereas early diarrhea is usually transient and infrequently severe, late diarrhea may be prolonged and can be life threatening. Late diarrhea may lead to dehydration, electrolyte imbalance, or sepsis; and late diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. In clinical studies using weekly irinotecan dosing, Grade 3-4 late diarrhea occurred in 23-31% of patients. The median time to onset of late diarrhea was 11 days with weekly dosing, and 5 days with 3-week dosing (Prescribing Information, April, 2016).

Prior to initiation of irinotecan, patients should be informed that they may experience diarrhea and should have loperamide readily available to begin treatment for late diarrhea. Patients should be counseled on loperamide use; for example, a loperamide regimen might include the following:

- Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal.
- Loperamide 4 mg at the first onset of diarrhea, followed by 2 mg with each loose motion until diarrhea-free for at least 12 hours (maximum dosage: 16 mg/24 hours).
- Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. Hold loperamide if constipation develops.
- During the night, the patient may take 4 mg of loperamide every 4 hours.
- Adjunct anti-diarrheal therapy is permitted and should be recorded when used.
- Diphenoxylate-atropine may be used in cases of loperamide resistance.

5.2 General Concomitant Medication and Supportive Care Guidelines

M6620 is contraindicated in patients with a known hypersensitivity to any component of the drug product. [redacted]. Because there is a potential for interaction of M6620 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 C (Patient Drug Information Handout and Wallet Card) should be provided to patients.

Because the drug interaction profile of M6620 has not been fully characterized, caution should be used when coadministering medications with M6620.

[redacted]

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.

Prophylactic use of hematopoietic growth factors is allowed per the treating physician's discretion after cycle 1.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may 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).

5.4 Duration of Follow Up

Patients will be in safety follow-up for a minimum of 30 days after final dose irinotecan or M6620 (whichever dose occurs last) or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Each patient will be followed for survival every 2 months (±14 days) after the patient's final treatment with M6620 or irinotecan (whichever occurs last) until death, termination of the trial, patient withdraws consent, or for a maximum of 1 year after a patient's final treatment with M6620/irinotecan – whichever comes first. Survival contact may be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

6. DOSING DELAYS/DOSE MODIFICATIONS

As needed for management of irinotecan-related toxicity, the dose reduction levels for irinotecan are as follows:

Dose Level	Irinotecan Dose
Starting Dose	180 mg/m^2
-1	150 mg/m^2
-2	120 mg/m^2

For patients known to be homozygous for the UGT1A1*28 allele, a reduction in the starting irinotecan dose by at least one dose level should be considered by the patient's study physician.

As needed for management of M6620-related toxicity, the dose reduction levels for M6620 are as follows

Dose Level	M6620 Dose
Starting Dose	270 mg/m^2
-1	240 mg/m^2

-2	210 mg/m^2

Beginning with Cycle 2, Day 1: On the day(s)† of treatment, the following criteria must be met before administering any cycle's 1st dose of irinotecan or 1st dose of M6620 (both of which are intended for Day 1 of each cycle):

- Absolute neutrophil count (ANC) ≥ 1,000/mcL.
- Platelets ≥ 100,000/mcL.
- Creatinine within normal institutional limits; or
  ≥ 45 mL/min/1.73m^2 for patients with creatinine level above institutional normal.
- Total bilirubin within normal institutional limits.
- AST (SGOT) and ALT (SGPT) ≤ 2.5 x institutional upper limit of normal (ULN); or
  if liver involvement, then ≤ 5 x ULN.
- Treatment-related diarrhea is Grade 0 or Grade 1
- Serum potassium within normal institutional limits (may be corrected with K repletion).

Within each cycle, the patient's study physician may additionally elect to require any or all of these conditions in order to administer that cycle's 2nd dose of irinotecan and/or M6620 (both of which are scheduled for Day 15 of each cycle).

† If a cycle's 1st dose of irinotecan and the cycle's 1st dose of M6620 occur on <u>different</u> days (e.g. in a setting of AE management, in which one agent is held, while the other agent is administered), then the above criteria and below dose modifications are separately applicable to the cycle's 1st dose of the one agent on the earlier day, and then to cycle's 1st dose of the other agent on the later day.

Beginning with Cycle 2, Day 1: Dose modification according to the below tables and clarifications will be performed on the day(s) of treatment prior to administering any cycle's 1st dose of irinotecan or 1st dose of M6620 (both of which are intended for Day 1 of each cycle):

- Dose modification of irinotecan is based on the nadir toxicity observed in the interval between initiation of sequential doses of irinotecan. Dose modification of M6620 is based on the nadir toxicity observed in the interval between initiation of sequential doses of M6620.
- Dose modification (e.g. holds or reductions) of irinotecan will be based on toxicity

attributed by the patient's study physician as possibly, probably, or definitely related to irinotecan. (For events deemed by the patient's study physician as unlikely or unrelated to irinotecan, dose modification of irinotecan is not required; but may be optionally elected.)

- Dose modification (e.g. holds or reductions) of M6620 will be based on toxicity attributed by the patient's study physician as possibly, probably, or definitely related to M6620. (For events deemed by the patient's study physician as unlikely or unrelated to M6620, dose modification of M6620 is not required; but may be optionally elected.)
- If dosing of either irinotecan or M6620 is individually held, tolerated treatment with the other agent may be administered as monotherapy – i.e. separable dosing is permitted.
- Patients requiring a dose delay of >2 weeks beyond the date of intended dosing should permanently discontinue the delayed agent. (As treatment is intended for every two weeks, a dose delay of 2 weeks facilitates a total of 4 weeks between treatments.) Regardless of the reason for holding study treatment, the maximum allowed duration of treatment interruption is 4 weeks. If >28 days separates sequential doses of irinotecan or M6620, then the respective agent must be permanently discontinued.
- If one agent (irinotecan or M6620) is permanently discontinued, tolerated treatment with the other agent may continue per protocol.
- If a patient experiences multiple adverse events and there are conflicting management recommendations, the study physician should use the recommended dose adjustment that reduces the dose to the lowest level.
- Dose re-escalation is not allowed.
- A minimum of 11 days must separate sequential doses of irinotecan. A minimum of 11 days must separate sequential doses of M6620.
- For toxicities not mentioned below, especially laboratory abnormalities deemed not clinically significant by the patient's study physician, dose reduction is not required and will be at the study physician's discretion.
- At any time, a more conservative course of dose modification may be elected (e.g. if a modification indicates holding until improvement to Grade 1, the study physician may instead elect to hold until resolution to Grade 0).
- Although these dose modifications are applicable to treatment(s) administered on Day 1 of each *new* cycle (i.e. beginning with and including Day 1 of Cycle 2), the patient's study physician may optionally elect to also apply these modifications to the second dose within any *existing* cycle (e.g. Day 15 dosing during any cycle, including Cycle 1).
- Dose modifications do not apply to the following toxicities, even if related: alopecia, anemia, alkaline phosphatase levels, electrolyte disturbances (if able to be corrected), and nausea /vomiting if antiemetics have not been maximized.

Nausea	**Management of Irinotecan**	**Management of M6620**
≤ Grade 1	No change in dose.	No change in dose.

Nausea	**Management of Irinotecan**	**Management of M6620**
Grade 2	Hold* until ≤ Grade 1, then resume at same dose level.	Hold* until ≤ Grade 1, then resume at same dose level.
Grade 3	Hold* until < Grade 2, then resume at one dose level lower, if indicated.**	Hold* until < Grade 2, then resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2, then resume at 2 dose levels lower.***	Hold* until < Grade 2, then resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > 2 dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: Antiemetics.		

Vomiting	**Management of Irinotecan**	**Management of M6620**
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	Hold* until ≤ Grade 1, then resume at same dose level.	Hold* until ≤ Grade 1, then resume at same dose level.
Grade 3	Hold* until < Grade 2, then resume at one dose level lower, if indicated.**	Hold* until < Grade 2, then resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2, then resume at 2 dose levels lower.***	Hold* until < Grade 2, then resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > 2 dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		
Recommended management: Antiemetics.		

Diarrhea	**Management of Irinotecan**	**Management of M6620**
≤ Grade 1	No change in dose; alternatively, hold* until resolved to baseline, then resume at same dose level.	No change in dose; alternatively, hold* until resolved to baseline, then resume at same dose level.
Grade 2	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 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.***	Hold* until resolved to baseline, then resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > 2 dose reductions should go off protocol therapy. ***Patients requiring > 1 dose reduction should go off protocol therapy.		

Diarrhea	**Management of Irinotecan**	**Management of M6620**
Baseline defined as the most immediately known status prior to initiating study treatment on Cycle 1, Day 1. Recommended management: Loperamide antidiarrheal therapy. Example loperamide dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for at least 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Neutropenia (neutrophil count decreased)	**Management of Irinotecan**	**Management of M6620**
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	Hold* until ≤ Grade 1, then resume with no change in dose.	Hold* until ≤ Grade 1, then resume with no change in dose.
Grade 3	Hold* until ≤ Grade 1, then resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 1, then resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ Grade 1, then resume at 2 dose levels lower.***	Hold* until ≤ Grade 1, then resume at 2 dose levels lower.***
Febrile Neutropenia****	Hold* until resolved, then resume at 2 dose levels lower.***	Hold* until resolved, then resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >2 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 one hour.		

Thrombocytopenia (platelet count decreased)	**Management of Irinotecan**	**Management of M6620**
≤ 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 /mm^3, 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 /mm^3, then resume at one dose level lower, if indicated.**	Hold* until platelets ≥ 100,000 /mm^3, then resume at one dose level lower, if indicated.**

Thrombocytopenia (platelet count decreased)	**Management of Irinotecan**	**Management of M6620**
Grade 4	Hold* until platelets ≥ 100,000 /mm^3, then resume at 2 dose levels lower.***	Hold* until platelets ≥ 100,000 /mm^3, then resume at 2 dose levels lower.***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >2 dose reductions should go off protocol therapy. ***Patients requiring >1 dose reduction should go off protocol therapy.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The Rave CTEP-AERS Integration will determine if the following list of AEs (Section 7.2) and the characteristics of an observed AE (Sections 7.3 and 7.4) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Rave-CTEP-AERS Integration

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

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

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

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

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

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A

report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

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

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

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

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

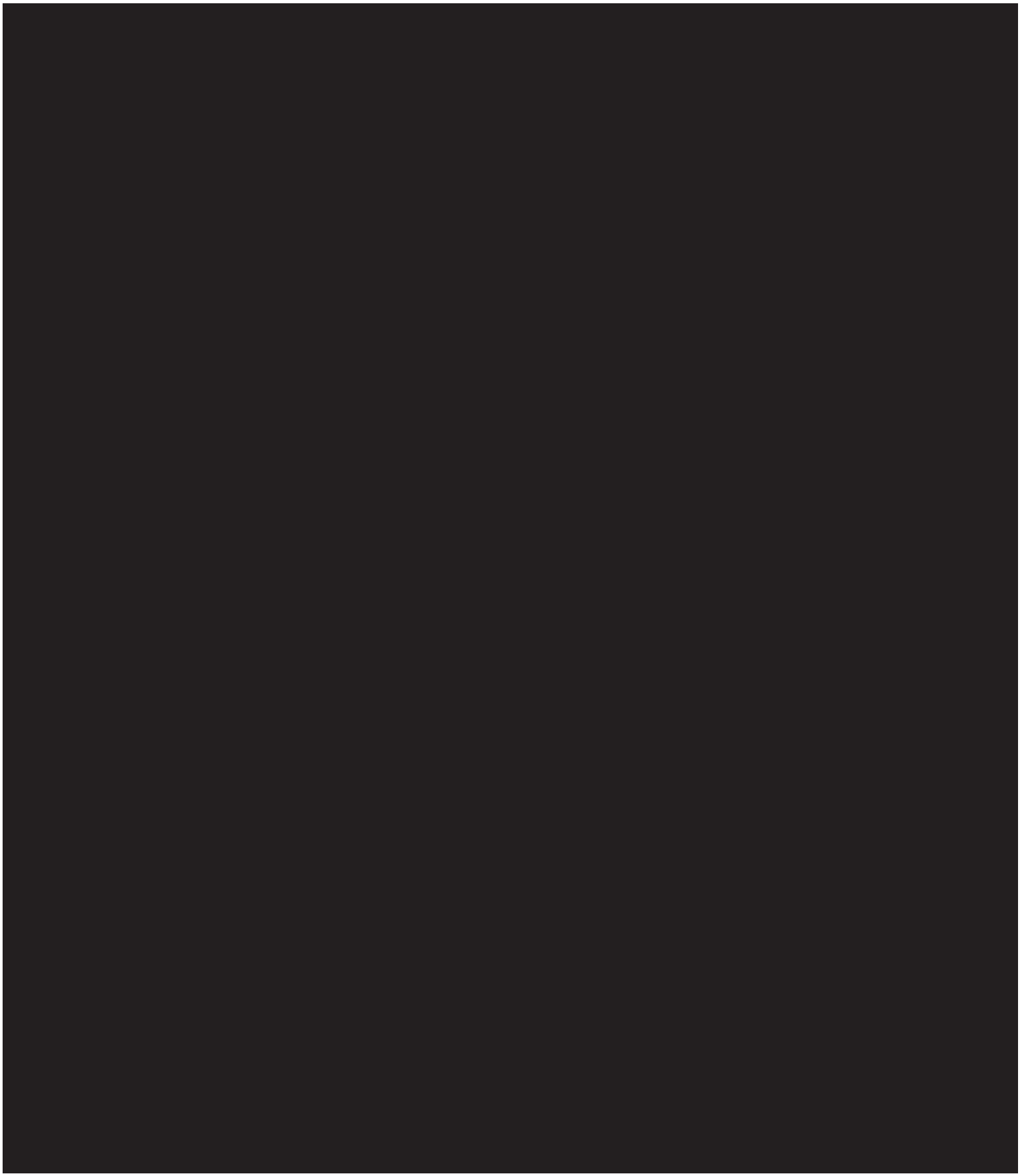
- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

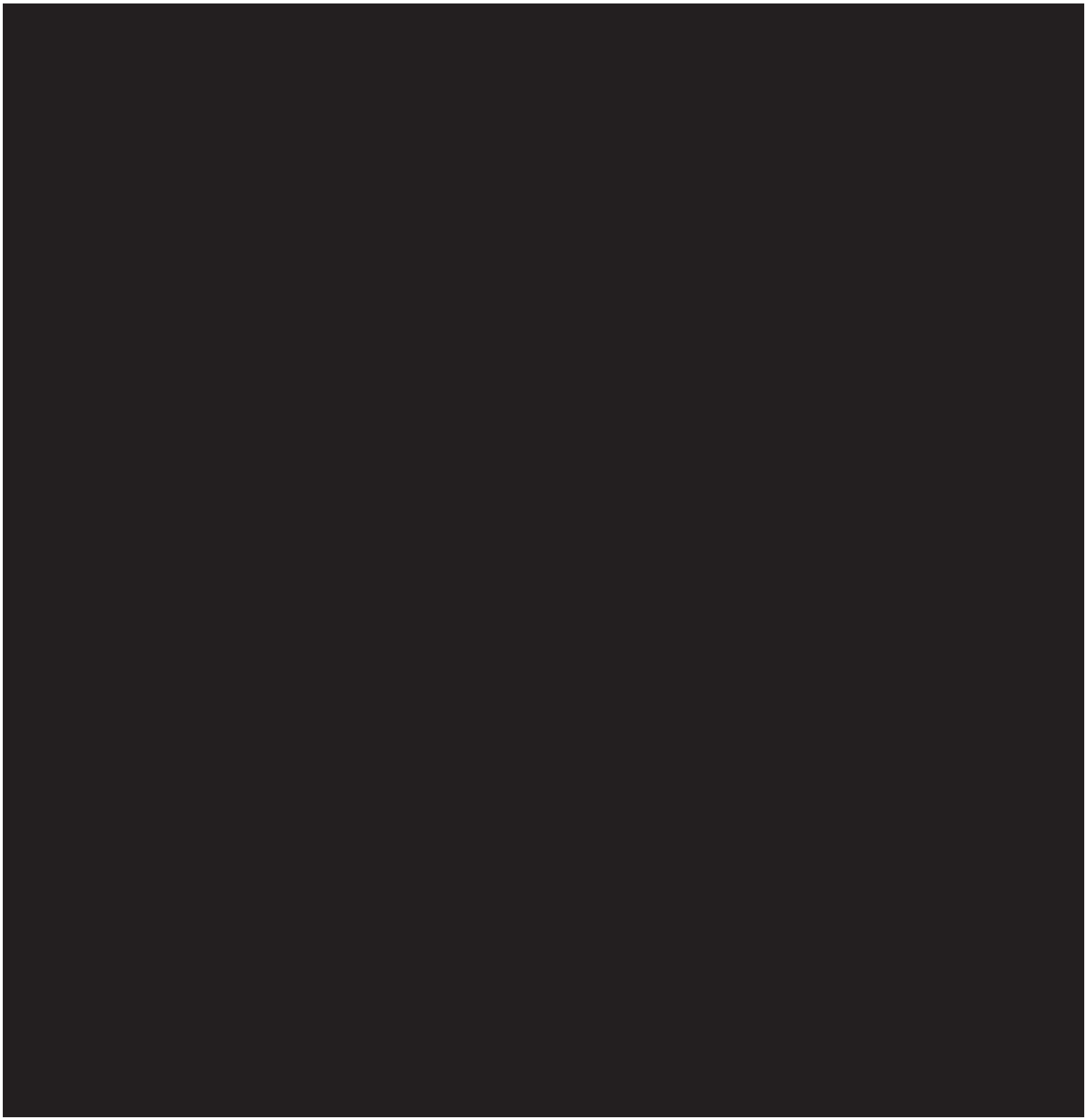
7.2 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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.

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.

7.2.1 CAEPRs for CTEP IND Agent(s)





7.2.2 Adverse Event List(s) for 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.

7.3 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 (starting April 1, 2018) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **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.

7.3.1 Distribution of Adverse Event Reports

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

7.3.2 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. 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.

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.3 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE System Organ Class (SOC)	Adverse Event	Grade	≥24h Hospitalization[a]	Attribution[b] to Irinotecan	Comments
GI	Diarrhea	2	Regardless	Related	Expected with chemotherapy
Bone Marrow	Pancytopenia[c]	2	Regardless	Related	Expected with chemotherapy
GI	Nausea/Vomiting	2	Regardless	Related	Expected with chemotherapy

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.
[b] Possibly, probably or definitely related to irinotecan.
[c] Including one or more of the following: Neutropenia, leukopenia (including lymphocytopenia), anemia, and thrombocytopenia.

7.4 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.

Adverse events will also be reported to EMD Serono:
Fax: +1 (781) 681-2961 or E-mail: usdrugsafety@emdserono.com

Specifying:

- Protocol Number and/or Title
- Subject Number

- Site Number/PI Name
- SAE/Onset Date Relevant follow-up information should be submitted to EMD Serono Drug Safety as soon as it becomes available.

7.5 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.

7.6 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.

7.7 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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 M6620 (NSC 780162)

Other Names: VRT-0768079, MSC2527093A, VX-970

Classification: ATR inhibitor

Molecular Formula: $C_{24}H_{25}N_5O_3S$ **M.W.:** 463.55 Da

Mode of Action: Ataxia telangiectasia mutated and Rad3-related (ATR) kinase is an apical regulator of checkpoint pathways triggered by DNA damage. The DNA damage response (DDR) is regulated by ATR kinase and ataxia telangiectasia mutated (ATM) kinase, which are recruited to distinct DNA damage structures. M6620 disrupts ATR-mediated DNA damage response signaling and leads to sustained accumulation of DNA damage in cancer cells co-treated with DNA-damaging agents.

Description: The drug substance for M6620 is the free base.

How Supplied: M6620 is supplied by Merck KGaA/EMD Serono, Inc. [redacted]

Route of Administration: Intravenous (IV) infusion.

Method of Administration: Prior to administration the solution should be given one hour at ambient temperature to warm up if stored refrigerated following preparation. Infuse over 60 minutes using an infusion set [redacted] The infusion time may be extended beyond 60 minutes (as tolerated) but no more than 90 minutes if standard procedures to limit symptoms of an infusion reaction are insufficient or if the total volume of the infusion exceeds 600 mL. To minimize the possibility of phlebitis, M6620 should be administered through a large bore catheter into a large caliber peripheral vein or central venous access.

Patient Care Implications: Monitor for infusion site reactions, irritation, and phlebitis for at least 30 minutes following infusion. M6620 absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 should take protective measures to minimize sun exposure. Women of childbearing potential and men should use appropriate contraception while on study drug and for 6 months after discontinuation of M6620.

Potential Drug Interactions: M6620 is primarily metabolized by [redacted]

Availability

M6620 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

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.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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's Brochure Availability
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.

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
- 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 and 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 Irinotecan

Product description: 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.

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: All patients are scheduled to receive irinotecan as a 90 minute intravenous infusion on Day 1 and Day 15 of each 28-day cycle. Irinotecan will be administered consistent with established local procedures and the package insert:

- The irinotecan Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), irinotecan injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

Agent Ordering: Each site will obtain irinotecan from commercial supply.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Several biomarker correlative studies will be performed on this study:

- Archival tumor must be assayed for TP53 mutations prior to enrollment in the study using any NGS CLIA certified assay.
- Archival tumor will also be assessed for additional mutations in DNA Damage Response Deficiency (DDRD) genes (see below) via the NGS CLIA certified assay used to determine TP53 mutational status.
- Paired tumor biopsies (from 9 patients) will be collected at 24 hours (+/- 3 hours) post-irinotecan on C1D2 and at 24 hours (+/- 3 hours) post-M6620 on C2D2 to quantify DNA damage and validate on-target inhibition. Expression levels of γ-H2AX, KAP1 p-Ser 824 and p-ATR will be quantified.

The biomarker table is listed below:

Biomarker Name[a] AND Lead PI and Site	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
TP53 Mutation (exons 2 and 4-11) Any CLIA certified NGS assay	NGS CLIA: Yes	Integral To identify candidates eligible for the trial.	Tissue (Archival)	M	Insurance
DDRD (BRCA1, BRCA2, MRE11, RAD50, RAD51, RAD52, RAD54L, NBN, ATM, H2AX, PALB2, RPA, BRIP1, BARD1, ATR, ATRX, CHK1, CHK2, MDM2, MDM4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL) Any CLIA certified NGS assay	NGS CLIA: Yes	Exploratory To identify patient sub-group who may derive further benefit from the experimental therapy. List of genes generated from well validated homologous recombination genes (from ovarian literature) and ATR axis mutations.	Tissue (Archival).	M	Insurance

Biomarker Name[a] AND Lead PI and Site	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
γH2AX, pNBS1 IFA with βCATN segmentation Dr. Kate Ferry-Galow NCLN PD Assay Laboratory at MD Anderson	Multiplexed Immuno-Fluorescence Assay	Integrated To demonstrate the on-target effect of the ATR inhibitor. Post irinotecan on C1D1 we would anticipate levels of γ-H2AX to be at their peak while 24 hours after M6620 on C2D2 we would expect to see levels of γ-H2AX nadir.	Tumor Tissue 24 hours (+/- 3 hours) post-irinotecan on C1D2 and 24 hours (+/- 3 hours) post-M6620 on C2D2.	M	CTEP
KAP1 p-Ser 824 and p-ATR Dr. Ralph Parchment at PADIS, Frederick National Laboratory for Cancer Research (FNLCR)	Multiplexed Immuno-Florescence Assay	Exploratory To demonstrate on target effects of the therapy on ATR mediated signaling specifically and DNA damage globally. In responding patients, we would anticipate seeing declines in p-ATR and rises in KAP1 p-Ser 824 between C1 and C2 biopsies.	Tumor Tissue 24 hours (+/- 3 hours) post-irinotecan on C1D2 and 24 hours (+/- 3 hours) post-M6620 on C2D2.	M	CTEP

The correlative schedule is included in the table below:

Time Point	**Specimen/Report and Quantity**	**Send Specimens/Reports to:**
1st time point: Screening		
	• *TP53 mutation and DDRD laboratory report*	*Responsible Study Coordinator via Medidata RAVE or by email*
2nd time point: C1D2 post-irinotecan within 24 (± 3 hour) hours post-irinotecan		
	• *1-2 tissue cores snap-frozen for γ-H2AX, KAP1 p-Ser 824 and p-ATR analysis.*	**PADIS, Frederick National Laboratory for Cancer Research (FNLCR)**
3rd time point: C2D2 within 24 hours (± 3 hour) post-M6620 infusion		
	• *1-2 tissue cores snap-frozen for γ-H2AX, KAP1 p-Ser 824 and p-ATR analysis.*	**PADIS, Frederick National Laboratory for Cancer Research (FNLCR)**

9.1 Integral Laboratory or Imaging Studies

9.1.1 TP53 Mutation

Mutations in TP53 are a prerequisite for enrollment onto the study and will be ascertained via any CLIA certified NGS assay. Only mutations in exons 2 and 4-11 will be accepted given the possible disparate prognosis of non-hotspot TP53 mutant gastric cancer patients compared to those with hotspot mutations (Tahara et al., Oncotarget 2016).

9.1.1.1 Collection of Specimen(s)

Collection of tissue (whether fresh or archival) should follow your institutional procedures and policies.

Acceptable samples for testing:

- Formalin-fixed paraffin embedded (FFPE) specimens including core-needle biopsies only.

9.1.1.2 Handling of Specimens(s)

- Use standard fixation methods to preserve nucleic acid integrity. 10% neutral-buffered formalin for 6–72 hours is industry standard. DO NOT use other fixatives (e.g., Bouins, B5, AZF, Holland's).
- Do not decalcify. When decalcification is required, EDTA is recommended. Do not use strong acids (e.g., hydrochloric acid, sulfuric acid, picric acid).

9.2 Integrated Correlative Studies

9.2.1 γ-H2AX

γ-H2AX is a well validated marker of DNA damage. We will be assessing it to look at the on-target effect of M6620. The biomarker should peak after administration of irinotecan on C1D1. When we check levels at 24 hours post-M6620 infusion on C2D2 this signal should be effaced given the inhibition of γ-H2AX phosphorylation by the ATR inhibitor. We believe responding patients will demonstrate a greater decline in phosphorylated γ-H2AX levels than patients who do not respond to the combination.

9.2.2.1 Collection of Specimen(s)

In 9 patients, mandatory tumor biopsies (core biopsy only) will be collected at the following time points:

- C1D2 at 24 hours (+/- 3 hours) post-irinotecan
- C2D2 at 24 hours (+/- 3 hours) post-M6620 infusion

Multiplexed immunofluorescence assays (IFA) will be performed on the biopsies in collaboration with the PADIS, Frederick National Laboratory for Cancer Research (FNLCR) and NCLN PD Assay Laboratory at MD Anderson. This panel includes γH2AX and pNBS1 biomarkers with

βCATN segmentation. Additional biomarker such as KAP1 p-Ser 824 and p-ATR could be evaluated depending on the results of ɣH2AX, pNBS1 IFA with βCATN segmentation assay. We will test the hypothesis that declines in γ-H2AX from post-irinotecan levels are a measure of the on-target effect of M6620.

9.2.2.2 Handling of Specimens(s)

In accordance with SOP340507, biopsy specimens are collected into pre-chilled 1.5mL Sarstedt, O-ring screw cap tubes (VWR, Cat#: 83009-010) and then flash frozen in liquid nitrogen or a dry ice/ethanol bath. It is imperative that biopsies are flash frozen within 2 minutes of collection in order to preserve key pharmacodynamic biomarkers.

Biopsies for PD analyses will be shipped on dry ice to the PADIS laboratory after both the pre-dose and the post-dose timepoints have been collected. Store all frozen biopsies at -80ºC or lower until shipment.

9.2.2.3 Shipping of Specimen(s)

Frozen biopsy samples from participating sites are shipped and delivered to FNLCR PD Central Receiving using the following delivery address:

Attention: Dan Danner NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick Frederick, MD 21701
Phone: 301 846-5748

Please Note: Do not ship frozen biopsy specimens on Fridays and one day prior to any Federal holiday, FNLCR receiving is closed and unable to receive samples weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Email the NCI-F PADIS group at NCI_PD_Support@mail.nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. PADIS needs to be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s), and these must be noted on the sample shipping manifest (Appendix 2) and batch record (Appendix 1). One batch record is completed per patient's biopsy specimens with all required information noted. If shipping multiple patient biopsies, one shipping manifest can be completed including all patient specimens within the shipment.

Please contact Amy Pantella at 301-846-6747 or Rachel Andrews at 301-846-1951 (email: NCI_PD_Support@mail.nih.gov) for any shipping or protocol inquiries.

9.2.2.4 Site(s) Performing Correlative Study

The ɣH2AX, pNBS1 IFA with βCATN segmentation assay will be performed at the NCLN PD Assay Laboratory at MD Anderson.

9.3 Exploratory Correlative Studies

9.3.1 DDRD Mutations

DDRD Mutations will be ascertained from the CLIA certified NGS assays used to determine eligibility for the study based on TP53 mutational status.
Concomitant mutations in other DDRD genes which we feel could improve the likelihood of response with the experimental therapy include BRCA1, BRCA2, MRE11, RAD50, RAD51, RAD52, RAD54L, NBN, ATM, H2AX, PALB2, RPA, BRIP1, BARD1, ATR, ATRX, CHK1, CHK2, MDM2, MDM4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, and FANCL. These genes have been validated across assays to play important roles in homologous recombination (from published literature in breast and ovarian cancer) and the ATR axis (from data cited in the pre-clinical rationale above) (Walsh, 2015).

Collection and handling as per specifications listed for TP53 under 9.1.1.1 and 9.1.1.2

9.3.1.1 Assessment of KAP1 p-Ser 824 and p-ATR

P-ATR is a marker for direct ATR pathway activation and signaling. This has been demonstrated in cell line models from several laboratories including the Cortez laboratory at Vanderbilt (Nam et al., 2011). KAP1 p-Ser 824 is an ATR independent marker of DNA damage which co-localizes with γ-H2AX at DNA damage foci. Changes in tissue levels of p-ATR and KAP1 p-Ser 824 will be measured in the initial nine patients enrolled on the first stage of the study. We anticipate seeing differential patterns of dynamic changes in these levels between responding and progressing patients. We believe responding patients will demonstrate greater levels of rise in KAP1 p-Ser 824 and greater levels of decline in p-ATR in tumor tissue than progressing patients.

9.3.1.2 Collection of Specimen(s)

In 9 patients, mandatory tumor biopsies will be collected at the following time points:
- C1D2 at 24 hours (+/- 3 hours) post-irinotecan
- C2D2 at 24 hours (+/- 3 hours) post-M6620 infusion

Depending on the results of γH2AX, pNBS1 IFA with βCATN segmentation assay, multiplexed immunofluorescence assays (IFA) could be performed on biopsies in collaboration with the PADIS, Frederick National Laboratory for Cancer Research (FNLCR)Laboratories. As noted above, this panel includes KAP1 p-Ser 824 and p-ATR.

9.3.1.3 Handling of Specimens(s)

In accordance with SOP340507, biopsy specimens are collected into pre-chilled 1.5mL Sarstedt, O-ring screw cap tubes (VWR, Cat#: 83009-010) and then flash frozen in liquid nitrogen or a dry ice/ethanol bath. It is imperative that biopsies are flash frozen within 2 minutes of collection in order to preserve key pharmacodynamic biomarkers.
Biopsies for PD analyses will be shipped on dry ice to the PADIS laboratory after both the pre-dose and the post-dose timepoints have been collected. Store all frozen biopsies at -80ºC or lower until shipment.

9.3.1.4 Shipping of Specimen(s)

Frozen biopsy samples from participating sites are shipped and delivered to FNLCR PD Central

Receiving using the following delivery address:
Attention: Dan Danner NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick Frederick, MD 21701
Phone: 301 846-5748
Please Note: Do not ship frozen biopsy specimens on Fridays and one day prior to any Federal holiday, FNLCR receiving is closed and unable to receive samples weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Email the NCI-F PADIS group at NCI_PD_Support@mail.nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. PADIS needs to be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s), and these must be noted on the sample shipping manifest (Appendix 2) and batch record (Appendix 1). One batch record is completed per patient's biopsy specimens with all required information noted. If shipping multiple patient biopsies, one shipping manifest can be completed including all patient specimens within the shipment.

Please contact Amy Pantella at 301-846-6747 or Rachel Andrews at 301-846-1951 (email: NCI_PD_Support@mail.nih.gov) for any shipping or protocol inquiries.

9.3.1.5 Site(s) Performing Correlative Study

Multiplexed immunofluorescence assays (IFA) for KAP1 p-Ser 824 and p-ATR will be performed at PADIS, Frederick National Laboratory for Cancer Research (FNLCR).

10. STUDY CALENDAR

	Pre-Study	Cycle 1				Cycles2+				Off Study[5]
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	
Irinotecan		A		A		A		A		
M6620		B[9]		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[1]	X	X		X		X		X		X
Height	X									
Weight	X	X		X		X		X		X
Performance status	X	X		X		X		X		X

CBC w/diff, plts	X	X		X		X		X		X
Serum chemistry[2]	X	X		X		X		X		X
EKG[3]	X									
Adverse event evaluation		X----------X								X
Tumor measurements	X	Tumor measurements repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.								X
Radiologic evaluation	X	Radiologic measurements performed every 8 weeks. Confirmatory scans obtained no sooner than 4 weeks after initial documentation of an objective response.								X[6]
B-HCG	X[4]					X				
Endoscopic or CT-guided Tissue Biopsy[7]		X				X				
TP53 Tumor Mutation[8]	X									

A: Irinotecan: Dose as assigned; 90 minute IV every 2 weeks.
B: M6620: Dose as assigned; 60 minute IV every 2 weeks (immediately after irinotecan). Monitor patients at least 30 minutes post M6620 for infusion-related reactions and other potentially life-threatening adverse events.
1: Vital signs including heart rate (HR), blood pressure (BP) and temperature (oral or tympanic); done at least once on days of treatment prior to dosing (before initiation of any pre-medication). Additional vitals and post-treatment monitoring as clinically indicated.
2: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium; LDH and phosphorous.
3: Single EKG tracing at baseline; additionally as clinically indicated.
4: Serum pregnancy test (women of childbearing potential) performed day 1 of every cycle.
5: Off-study evaluation 30 to 37 days after final dose of irinotecan or M6620 (whichever dose occurs last).
6: Only if previous radiologic evaluation was done >28 days prior to discontinuing study treatment.
7: Fresh biopsy of primary lesion amenable to a safe endoscopic approach or percutaneous biopsy from metastatic site on C1D2 (at 24 hours (+/- 3 hours) post-irinotecan) and on C2D2 (at 24 hours (+/- 3 hours) post-completion of M6620). The same lesion will be biopsied during these two time points. Only 9 patients will undergo these biopsies. The first 6 patients enrolled on the study will not undergo tumor biopsies.
8: Documentation of *TP53* (p53) tumor mutation within 42 days prior to Cycle 1, Day 1 from NGS sequencing of available archival tissue. Sponsor must review and confirm documentation within 42 days of Cycle 1, Day 1. This time window does not refer to collection and assay of tissue.
9: Only for patients undergoing pharmacodynamic research biopsies, M6620 is omitted on Cycle 1 Day 1.

Baseline evaluations are to be conducted within 14 days (2 weeks) prior to start of protocol therapy, unless otherwise indicated. Scans and x-rays must be done within 28 days (4 weeks) prior to the start of therapy.

Time windows:

- On Cycle 1, Day 1: Physical Exam, Performance Status, CBC, and Serum Chemistry need not be repeated if already resulted ≤ 3 days prior to first dose of protocol therapy. On subsequent cycles, Physical Exam, Performance Status, CBC, and Serum Chemistry can be performed ≤ 2 days prior to dose administration.
- In the absence of delayed dosing (e.g. due to an AE), every reasonable effort should be made to remain on a consistent dosing interval of 14 days between infusions of irinotecan/M6620. However, for purpose of accommodating holidays, weekends, bad weather, scheduling limitations, etc., Day 15 treatment days beginning with and including Cycle 1, Day 15 may occur up to every 14 ±3 days. (A minimum of 11 days must separate sequential doses of irinotecan. A minimum of 11 days must separate sequential doses of M6620.)

- Similarly, in the absence of delayed dosing (e.g. due to an AE), every reasonable effort should be made to remain on a consistent schedule of 4-Week (28-day) cycles; but for purpose of accommodating holidays, weekends, bad weather, scheduling limitations, etc., subsequent cycles (i.e. Cycles 2+) may occur up to every 28 days (4 weeks) plus 1-7 days.
- Baseline evaluation of disease status by radiologic evaluation ≤ 28 days prior to initiating protocol treatment on Cycle 1, Day 1. *Re-scanning to occur every 8 weeks* (minus 1-6 days) after initiating protocol treatment on Cycle 1, Day 1. (The minus 1-6 day scan window is intended for flexibility in scheduling re-scans *during Week 4 of every Even cycle* – i.e. between Days 22-28 of Even cycles – prior to initiation of scheduled treatment on Day 1 of every Odd cycle.)

Scanning on the same day as Day 1 of an Odd cycle is discouraged but allowed, provided scan results receive appropriate RECIST review prior to initiating the new Odd cycle of study treatment (e.g. first re-scan is discouraged, but permitted on Cycle 3, Day 1, prior to irinotecan/M6620 treatment scheduled for later that same day). Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease (PD), a radiologic evaluation is to be performed as soon as possible; and in the event of a Complete or Partial Response (CR/PR), confirmatory imaging is to be performed no earlier than 28 days after the first assessment of CR/PR.

Prior to initiating study treatment, all patients must have metastatic or unresectable gastric/GEJ cancer with demonstrated evidence from a recognized laboratory, indicating that a primary lesion or metastatic site contains mutation of TP53 (p53). Only those mutations falling within exon 2 or exons 4-11, will confer eligibility. The NGS report for all potential patients will be sent via a case report form through Medidata Rave to the Responsible Study Coordinator who will ensure these reports are stored centrally in the study database (on Rave). Our research team will review each case report to ensure a patient meets eligibility based on the presence of an eligibility-conferring TP53 mutation in his/her NGS panel. The first 9 patients will also undergo repeat tumor biopsies on C1D1 post-irinotecan infusion and C2D2 within 24 hours post-M6620 infusion; the same lesion will be biopsied during these two time points.

Subsequent to informed consent, an expanded screening window of up to 42 days (six weeks) prior to Cycle 1, Day 1 is applicable for any TP53 testing necessary to obtain standard-of-care results (e.g. FoundationOne).

Prior to initiating treatment, the screening team must have documentation that available archival specimens or fresh specimen [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site have both been requested from a local or outside facility. Physical possession, however, of requested tissue or waiting for histological analysis or confirmation that an acquired specimen contains tumor tissue sufficient for analysis is not initially a requirement prior to starting study treatment. However, as the study enrolls, if insufficient collective tissue from all patients ultimately becomes an anticipated risk to the study-

wide analysis, the sponsor-investigator may require the confirmed presence of sufficient baseline tissue prior to initiating study treatment.

Note: If a patient has a fresh biopsy done within 6 weeks for baseline TP53 eligibility testing, additional tissue for correlative research will need to be collected from the consenting patient (given he or she is among first 9) during a later procedure (i.e we will still require patient to get biopsies at 24 hours (+/- 3 hours) post-irinotecan infusion on C1D2 and at 24 hours (+/- 3 hours) post-M6620 on C2D2).

If a patient consents to a fresh baseline biopsy, but the patient's lesion is deemed inaccessible to safe biopsy, the patient may still be allowed to enroll if otherwise eligible, subsequent to discussion with and advance written permission from the sponsor-investigator.

At any time during the study (i.e. after signing consent, and until initiation of survival follow-up), if additional biopsy is performed as standard-of-care, then a sample of the tissue, if available, may be requested for research purposes.

A woman of childbearing potential is defined as any female who has experienced menarche who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as ≥12 months of spontaneous amenorrhea in a woman over 45 years of age in the absence of alternative biological or physiological cause.

If the patient's postmenopausal status is considered for childbearing potential with respect to study-required contraception, then postmenopausal status in females <62 years of age must be confirmed with a serum follicle-stimulating hormone (FSH) level >40 mIU/mL (or within local laboratory reference range for postmenopausal women).

If a patient discontinues the study for reason other than progressive disease confirmed by radiologic evaluation (e.g. adverse event), then imaging involving sites of known or suspected disease should be continued every 8 weeks (± 7 days) for 6 months and then approximately every 10 weeks (± 4 weeks) thereafter, relative to date(s) of prior scanning, until disease progression is confirmed by imaging. (Note: If the patient initiates treatment in another clinical trial, then any continuing scans done for this trial may terminate.)

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks, regardless of any dosing delays or interruptions. In addition to a baseline scan, confirmatory scans should also be obtained 8 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.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with M6620 and irinotecan.

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.

11.1.2 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.

11.1.3 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.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 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	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

11.1.5 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.

11.1.6 Progression-Free Survival

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

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 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 duration of this study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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.

12.2 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:

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

Rave role requirements:

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

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

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

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave 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.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 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).

12.3 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.

12.4 CTEP Multicenter Guidelines

N/A

12.5 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 another Agent, each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single arm, two-stage phase II clinical trial to test the efficacy, with respect to the objective response rate, of M6620 plus Irinotecan compared to an historical objective response rate estimated from patients treated with Irinotecan alone.

13.1.1 Endpoints

Primary Endpoint. The primary endpoint for the phase II clinical trial is the objective response rate (ORR) according to RECIST 1.1 response criteria.

Secondary Endpoints: PFS is defined as the time from study enrollment to disease progression or death for any reason. OS is defined as the time from study enrollment to death for any reason. DOR is the period-of-time from when patients achieve their best response (CR or PR) to when they progress or die for any reason. All patients will be followed for survival for up to 1 year. Patients lost-to-follow-up or alive and progression-free at the end of the follow-up period will be censored for PFS. Patients lost-to follow-up or alive at the end of the follow-up period will be censored for OS.

13.1.2 Patient population

Efficacy: All patients enrolled who receive any dose of M6620 or Irinotecan.

Safety: All patients enrolled who receive any dose of M6620 or Irinotecan.

13.1.3 Study Design

This phase II study will test the hypothesis that the ORR in patients treated with M6620 plus Irinotecan will experience an ORR of 5% or less using Simon's two-stage minimax design. This design minimizes the maximum sample size for a one arm study. The one-sided type I error rate is 10% and 16 patients provide at least 80% power to reject the null hypothesis that the ORR is less than or equal to 5% if the true ORR of this tandem regimen is 25% or greater. In stage 1 assessment for futility, the study will be stopped due to lack of efficacy if no patients experience an ORR in the first 12 patients treated. Otherwise, the study will continue to full accrual of 16 patients. Study accrual will be temporarily suspended at two points in stage I: after 6 patients have received M6620 plus irinotecan and undergone close safety monitoring (DLT assessment in 28-day period post cycle 1 day 1) and after the first 12 patients have completed their first 8-week post-treatment response assessment.

We will reject the null hypothesis ($p<10\%$) and recommend this tandem of drugs for evaluation in more definitive studies if 3 or more patients experience an objective response among 16 efficacy-evaluable patients. Assuming low efficacy ($<=5\%$) the probability of terminating this trial early is 54% with an expected sample size of 13.8 evaluable patients.

13.2 Sample Size/Accrual Rate

The total sample size is 16 efficacy-evaluable patients. Up to 18 patients will be accrued, assuming a 10% attrition rate, in order to enroll 16 efficacy-evaluable patients. It is expected that 2 eligible patients will be enrolled per month.

The enrollment of the proposed study is not biased in terms of sex/gender, race, and ethnicity. All patients, regardless of sex/gender, race, or ethnicity, with TP53 mutant gastric or GEJ cancer is eligible to enroll.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	1	1	0	0	**2**
White	5	7	1	1	**14**
More Than One Race	0	0	0	0	**0**
Total	**7**	**9**	**1**	**1**	**18**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Stratification Factors

None.

13.4 Analysis of Secondary Endpoints

Continuous variables (e.g., age, γ-H2AX expression) will be summarized using the minimum, 25th, 50th (median), 75th, and maximum values as well as the mean and standard deviation where appropriate. Categorical and ordinal variables (e.g. gender, DDRD status) will be summarized as frequency counts and percent of study group. DOR, TTP, and OS will be estimated using the method of Kaplan and Meier. 95% confidence intervals for all point estimates of effect sizes (odd ratios, hazard ratios, differential pre-post biomarker expression) among subgroups will be estimated.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with M6620 and irinotecan.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable,

insufficient data) [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database].

All of the patients who met the eligibility criteria at study enrollment, received at least one dose of study medication, and have at least one follow-up response evaluation will be included in the primary analysis of the response rate. Treatment will be considered to have failed in patients in response categories 4-9 (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific. Patients who do not have a follow-up response evaluation will be replaced.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals should also be provided.

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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: CTEP MULTICENTER GUIDELINES

Not applicable.

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

Patient Name:	**Diagnosis:**	**Trial #:** 10211
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):** M6620

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.

[redacted]

[redacted]

[redacted]

- 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.
- 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.

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

leidos
Leidos Biomedical Research, Inc.

APPENDIX D; PADIS SOP 34057

Title:	Tumor Frozen Needle Biopsy Specimen Collection and Handling				Page 1 of 11
Doc. #:	SOP340507	Revision:	G	Effective Date:	6/19/2019

Laboratory of Human Toxicology & Pharmacology Applied/Developmental Research

Directorate, Leidos Biomedical Research, Inc.

Frederick National Laboratory for Cancer Research

Technical Reviewer: Corey Evans Date: Corey J. Evans -S (Affiliate) Digitally signed by Corey J. Evans -S (Affiliate) Date: 2019.06.20 13:47:37 -04'00'

NCTVL Reviewer: Jiuping Ji Jiuping Ji -S (Affiliate) (Affiliate) Digitally signed by Jiuping Ji -S Date: 2019.07.05 10:34:23 -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: 2019.07.22 14:46:16 -04'00'

LHTP Approval: Ralph E. Parchment Date: Ralph E. Parchment -S (Affiliate) Digitally signed by Ralph E. Parchment -S (Affiliate) Date: 2019.08.02 13:09:35 -04'00'

DCTD OD Approval: Toby Hecht Date: Toby T. Hecht -S Digitally signed by Toby T. Hecht -S Date: 2019.08.02 16:29:51 -04'00'

Change History

Revision	Approval Date	Description	Originator	Approval
G	6/19/2019	Minor updates to collection and shipping procedures.	KFG	REP
F	2/11/2015	Updated contact shipping address and process for advance notification of shipments.	KFG	REP
E	7/3/2013	Updated tube-type to 1.5-mL conical bottom screw cap tubes to allow for broader use in DCTD assays and minimize the need to transfer biopsies during sample extraction steps. Decreased maximum time from biopsy collection to freezing to 2 minutes.	YAE	REP
D	1/8/2013	Update handling in surgical suite including details on halving of biopsy. Record total time elapsed from biopsy collection to freezing.	YAE, MM	JJ
C	12/29/2010	Update sample snap freeze to dry ice/ethanol bath or liquid nitrogen.	YAE	JJ
B	7/24/2009	Updated SOP format and prepared for publication to the DCTD Biomarkers Web site	YAE	JJ
A	10/13/2006	Revision with New Shipping Address	YZ	JJ
--	8/25/2006	New Document	YZ	JJ

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.**

14. TABLE OF CONTENTS

15. 1.0 PURPOSE

Standardize the method for collecting and handling frozen needle tumor biopsies to enable specimen usefor measurement of pharmacodynamic (PD) markers following treatment with anticancer agents.

16. 2.0 SCOPE

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

17. 3.0 ABBREVIATIONS

DCTD	=	Division of Cancer Treatment and Diagnosis
ELISA	=	Enzyme-Linked ImmunoSorbent Assay
FNLCR	=	Frederick National Laboratory for Cancer Research
ID	=	Identification / Identifier
IQC	=	Internal Quality Control
LHTP	=	Laboratory of Human Toxicology and Pharmacology
NCTVL	=	National Clinical Target Validation Laboratory
PADIS	=	Pharmacodynamics Assay Development & Implementation Section
PD	=	Pharmacodynamic
SOP	=	Standard Operating Procedure

18. 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 from this procedure allows retrospective identification of artifactual changes in biomarker readout and increases the reliability of thedata 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 sufficientexperience to handle clinical samples.

Certified Assay Operator and/or PK/PD Support Lab Personnel — A Certified Assay Operator and/or PK/PD Support Lab personnel may be a Laboratory Technician/Technologist, Research Associate, or Laboratory Scientist who has been certified through DCTD training onthis SOP. Works under the guidance of the Laboratory Director/Supervisor. This person performs laboratory procedures and examinations in accordance with the current SOP(s), as well as any other procedures conducted by a laboratory, 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 Certified Assay Operator running the SOP has sufficient experience to handle and analyze clinical samples.

5.2 It is the responsibility of the Certified Assay Operator and/or PK/PD Support Lab personnel to confirm scheduled specimen collection time points, pre-print all labels and data collection sheets in advance, check documentation for accuracy, and verify that the required collection tubes, supplies, and equipment are available for successful collection and handling of biopsy samples.

5.3 The Certified Assay Operator and/or PK/PD Support Lab personnel responsible for conducting the specimen collection and handling procedures are to follow this SOP and complete the required tasks and associated documentation. The Batch Record (Appendix 1) must be completed in ***real-time*** for each experimental run, with each page ***dated and initialed***, and placed with the clinical sample information.

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 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 Wet ice
6.10 -80°C freezer (or lower)
6.11 Biohazard specimen bags
6.12 Insulating Styrofoam shipping container

7.0 OPERATING PROCEDURES

7.1 Record the name and certification number of the Certified Assay Operator and/or PK/PD Support Lab personnel performing the SOP, the facility/clinic collecting the specimens, the Patient/Sample ID, the primary diagnosis, and the clinical protocol number in the Batch Record (Appendix 1).

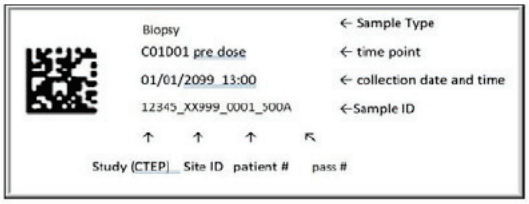
o The Batch Record for this SOP is sufficient for collection of a **single** set of biopsy samples collected from a single patient at a single timepoint. If collecting biopsy samples for morethan one patient, prepare a separate Batch Record for each patient.

7.2 Labels

7.2.1 Prepare enough pre-printed specimen labels for each whole or halved biopsy sample to be collected and frozen as defined in the Pharmacodynamic/Correlative Study section of the Clinical Protocol; be sure to coordinate with the clinical center if they prepare the labels for sample collection. If two passes are collected from one tumor, the labels would be identical except that the specimen ID would be followed by a letter A/B to designate pass number. The specimen ID includes the CTEP protocol number followed by a unique patient identifier and a specimen series ID.

NCI tumor biopsy specimen IDs for PD sampling are series 500 with consecutivenumbers identifying the collection time point as defined in the Clinical Protocol.

Sample pre-printed label for all frozen-tissue biopsy tubes:



7.2.2 Of the pre-printed labels prepared for each sample, one label will go on each 1.5-mL Sarstedt tube, one on the Batch Record (Appendix 1), and the last will be given to the research nurse to place into the patient record sheet. **Note:** be sure that no patient identifiable information is shown on the labels.

7.3 Tumor Needle Biopsy Collection and Handling

7.3.1 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 specimens to the laboratory for placement at -80ºC (or lower) after collection.

7.3.2 Bring all necessary lab supplies including: disposable tweezers, a minimum of two 1.5-mL Sarstedt tubes (one for each whole biopsy core) pre-cooled on liquid nitrogen ordry ice/ethanol in an insulated bucket, and one pre-printed specimen label to give to the research nurse for the patient record.

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

7.3.3 The total time elapsed between biopsy collection and placement into the pre-chilled tube is of **key importance** to biomarker analysis; 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 (or note the time) at this point (Appendix 1, Section 1) and immediately walk the slide to the sample preparation table.

7.3.4 In the Batch Record (Appendix 1, Section 1), indicate if a full or halved biopsy, as defined in the Pharmacodynamic/Correlative Study section of the Clinical Protocol, is prepared.

7.3.4.1 For whole biopsies: Uncap an empty, pre-chilled 1.5-mL Sarstedt tube and, using disposable tweezers, pick up the freshly collected needle biopsy with the tweezers at one end, and touch the opposite end of the biopsy to the inner surface of the prechilled 1.5-mL Sarstedt tube. This should attach the tissue to the tube, allowing it to be dropped into the tube while releasing the tissue from the tweezers without sticking. Dispose of the tweezers in the appropriate biohazardous waste container(s).

7.3.4.2 For halved biopsies: Use 1-2 disposable tweezers and cut/shear the biopsy in half cross-wise while it is on the slide (do not pull or stretch the biopsy longitudinally). Use the tweezers to transfer the halved biopsies to sterile pre-chilled tubes as indicated above.

7.3.5 Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath. **Note:** DO NOT let the tubes tip over in the dry ice/ethanol bath.

7.3.6 Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of **minutes and seconds** elapsed in the Batch Record (Appendix 1, Section 1).

7.3.7 Note the specific location of each biopsy pass collected (*e.g.*, spleen, large left upper quadrant splenic mass) and a description of the appearance of the biopsy (*e.g.*, large whole core or small, fragmented core) in the Batch Record (Appendix 1, Section 1).

7.3.8 Note the biopsy timepoint (Appendix 1, Section 1).

7.4 If biopsy procedure details can be obtained from the interventional radiologist or research nurse, record them in the Batch Record (Appendix 1, Section 2). Some information may not be available until a later time from the clinical staff.

During **first-in-human** PD sample collection studies, information such as type of anesthesia andtime-lag between biopsy needle withdrawal and sample freezing need to be tracked in order to determine the optimal sample collection procedure for the clinical community.

7.5 Return to the sample processing laboratory and transfer the frozen biopsy specimen(s) to -80°C (or lower) for storage until shipment to the PD processing laboratory. Record the date and time specimens are placed at -80ºC (or lower; Appendix 1, Section 3).

7.6 Review and finalize the Batch Record and document **ANY** and **ALL** deviations from this SOP in the Batch Record (Appendix 1, Section 5).

7.7 The Laboratory Director/Supervisor should review the Batch Record and sign to affirm the data contained within are correct (Appendix 1, Section 6).

8.0 SHIP TO FNLCR FOR ANALYSIS (OPTIONAL)

If shipping to a location other than FNLCR, use the following steps as a guide.

8.1 Sites are required to create a FedEx shipping label to accommodate the variable dry ice weight of the shipment package. Use only FedEx Priority Overnight Shipping. FNLCR PD Support will provide a FedEx account number to cover the cost of the shipment via NCI_PD_Support@mail.nih.gov.

8.1.1 By linking the FNLCR FedEx account number provided to the biopsy shipment, FNLCR PD Support can closely monitor the shipment and cover all shipping costs, and appropriate notification can be provided to pertinent staff of expected sample shipment arrival.

8.1.2 Please send all shipments via FedEx Priority Overnight shipping to the FNLCR PD Specimen Central Receiving address listed below:

Attention: Dan DannerNCI-F/FNLCR
1073 Beasley Street, Building 1073Fort Detrick
Frederick, MD 21701
Phone: (301) 846-5748

8.2 Once a tumor biopsy has been collected from a patient and placed at -80ºC (or lower), FNLCR PD Specimen Central Receiving should be notified that the specimens are ready for shipment. Preferably, if additional biopsies will be taken from the same patient (post-dose timepoint[s]), the biopsies are to be stored in a local freezer at -80ºC (or lower), and shipped together as a full set in one shipment.

8.3 Send an e-mail to FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) to advise that biopsy samples are being prepared for shipment. State "*Protocol Name* PD Specimens Ready for Shipment" in the subject line. Request a confirmation e-mail that personnel will be available on the expected delivery date and time. Personnel are generally available to receive frozen shipments Tuesday through Friday, exclusive of government holidays. If needed, FNLCR PD Central Receiving can be contacted directly at (240) 344-5697 (Rachel Andrews) or (301) 401-8070 (Amy Pantella).

8.4 Use the PD Sample Shipping Manifest template in Appendix 2 to generate a shipping list containing pertinent sample information.

8.5 Make a copy of the Shipping Manifest and specimen Batch Records so that one copy can be sent to FNLCR with the biopsy samples and one copy can be maintained at the collection site for internal records.

8.6 Day of Shipment

8.6.1 Just prior to shipment, place specimen tubes into a biohazard specimen bag then in an insulating Styrofoam shipping container. The insulating Styrofoam shipping containers are required to have dimensions of ***at least*** 14″×11″×9″ (length, width, height) with a ***minimum*** of 20 pounds of added dry ice. Sufficient dry ice is imperative to maintain the samples at -20°C for at least 72 hours. Expect 10 pounds of dry ice to sublimate per day during transit. Add additional dry ice to the required 20 pounds if shipping is anticipated to be longer than 24 hours.

8.6.2 All weekly processing specimens are recommended to ship out on Mondays through Thursdays via FedEx Priority Overnight (excluding any day before a federal holiday).

8.6.3 **Verify** that the contents of the package match the Shipping Manifest and sign and date the bottom of both copies of the Shipping Manifest. Place one copy of the Shipping Manifest inside the shipping box along with copies of the completed Batch Records for all specimens.

8.6.4 Seal the box and print and attach the shipping address onto the outside of the shipping container; be sure the container is labeled as containing biohazardous specimens.

8.6.5 Record the shipping date, time, tracking number, and shipping information in the Batch Record (Appendix 1, Section 4).

8.6.6 E-mail FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) a shipment notification. State "*Protocol Name* PD Specimen Shipment" in the subject line and reference the tracking number in the e-mail. Please notify FNLCR PD Specimen Central Receiving of any issues or protocol deviations as soon as possible and provide written notes on the Batch Record.

8.6.7 Once specimens arrive at the receiving laboratory, they should be immediately placed at -80ºC (or lower) pending delivery to the processing laboratory for protein extraction.

19. APPENDIX 1: BATCH RECORD

Place PD SpecimenLabel Here

A **separate** Batch Record should be started for **each patient sample set**.

Note: A pre-dose and post-dose sample from the same patient would have the same Patient ID, but different Specimen ID numbers.

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

Certified Assay Operator: _____

Certification Number: _____

☐ Check here if PK/PD Support Lab Personnel

Facility/Clinic Collecting Specimens: _____

Clinical Protocol Number: _____

Patient ID: _____

Primary Diagnosis: _____

1. Biopsy Collection

1st Pass		2nd Pass	3rd Pass	4th Pass
Specimen ID				
Site of Biopsy (complete for all passes or note "same" for replicate cores)				
Description of Biopsy (*e.g.*, large intact core or small and fragmented core)				
Biopsy Timepoint (Cycle, Day, and Hours post dose, if post treatment)				
Biopsy size prepared for PD or histological analysis:	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved
Required: Time elapsed from collection to placement in tube	min sec	min sec	min sec	min sec
Time biopsy collected (opt)	:	:	:	:
Time biopsy placed in tube (opt)	:	:	:	:

2. Biopsy Procedure Details

Specimen ID	
Time local anesthesia administered	:
Dose of local anesthetic	mg
Name of local anesthetic used (from Research Nurse)	
Time of skin incision	:
Needle Type (*e.g.*, Temno)	
Needle diameter	gauge
Needle Length	cm
Time guide needle introduced	:
Time guide needle placement confirmed	:
Time biopsy needle introduced	:

3. Biopsy Storage

Date/time biopsy specimen(s) placed at -80°C (or lower) _____/__/_____ _____:_____ _____ºC

4. Shipping to FNLCR (optional)

Date and time samples shipped _____ _____:_____

Tracking information _____

****Attach copy of Shipping Manifest**

5. Notes, including any deviations from the SOP:

6. Laboratory Director/Supervisor Review of Batch Record

Laboratory Director/Supervisor:_____(PRINT)

_____(SIGN)

Date: ____/____/_____

BATCH INITIALS:_____ DATE: _____

DCTD Standard Operating Procedures (SOP)

Title:	Tumor Frozen Needle Biopsy Specimen Collection and Handling				Pag
Doc. #:	SOP340507	Revision:	G	Effective Date:	6/

20. APPENDIX 2: PD SAMPLE SHIPPING MANIFEST

From: **Phone:** **E-mail:**	**PD Sample Shipping Manifest**	

In Package	Item No	Patient/ Specimen ID	Clinical Protocol	Description	Primary Diagnosis	Site of Biopsy	Time Point Scheduled
	Example	*1234-xx999-1023-500*	*12-C-0000*	*Full biopsy*	*Melanoma*	*Right forearm*	*Pre-dose D1*
	Example	*1234-xx999-1023-501*	*12-C-0000*	*Half biopsy*	*Melanoma*	*Right forearm (same lesion)*	*Cycle 1, D8*
	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						

Verification of Contents **Signature**

Date

Contents Verified Collection Laboratory

_____

/

/

Contents Verified FNLCR PD Central Receiving

_____

/

/

BATCH INITIALS:_____ DATE: _____