PROTOCOL

A Phase 1b multicenter study of TAS-102 in combination with irinotecan in patients with advanced recurrent or unresectable gastric and gastroesophageal adenocarcinoma after at least one line of treatment with a fluoropyrimidine and platinum containing regimen

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Study Drug: Trifluridine/tipiracil (TAS-102) [Lonsurf©]

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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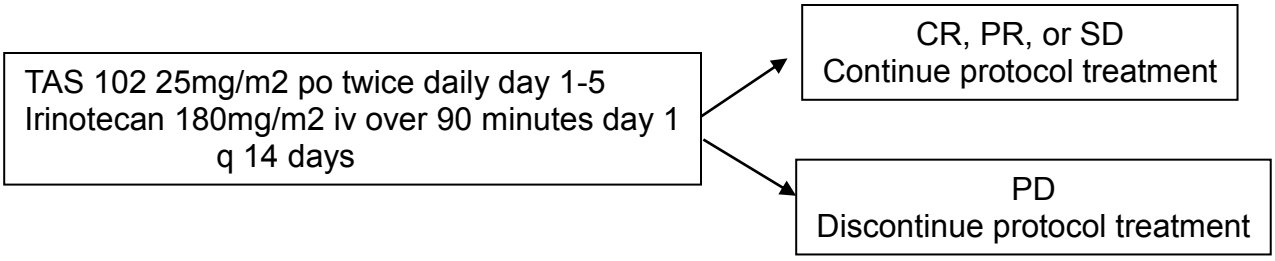
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PFS-6	Progression Free Survival at 6 months
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TAS-102	Trifluridine/tipiracil
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase 1b multicenter study of TAS102 in combination with irinotecan in patients with advanced recurrent or unresectable gastric and gastroesophageal adenocarcinoma after at least one line of treatment with a fluoropyrimidine and platinum containing regimen
Short Title	TAS-102 and irinotecan in 2L+ gastric and gastroesophageal adenocarcinomas
Protocol Number	UCI 18-125
Phase	1b
Methodology	Open label, single arm
Study Duration	3 years
Study Center(s)	multi-center; 2-3 study sites
Objectives	Primary objective: To determine the feasibility and estimate the efficacy of trifluridine and tipiracil (TAS102) in combination with irinotecan in patients with advanced gastric and gastroesophageal adenocarcinoma (GC) Primary Endpoint: 6 months progression-free survival (PFS-6) Secondary Objective: efficacy, safety, Secondary Endpoint: overall survival, objective response rate, adverse events
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	• Histologically proven unresectable or recurrent gastric or gastroesophageal adenocarcinoma • At least one prior chemotherapy regimen including a fluoropyrimidine and/or platinum agent • Age ≥ 18 years • Performance status (Eastern Cooperative Oncology Group) of 0 to 2 • Adequate bone marrow function (ANC≥ 1,500/mcL); and platelet count≥ 80,000/mcl • Adequate liver function (total serum bilirubin level within normal institutional limits and serum transaminases<3 X ULN or ≤5 X ULN if liver metastasis is present); • Adequate renal function (serum creatinine level < 1.5 X upper limit of normal) • An expected survival period of >3 months
Study Product(s), Dose, Route, Regimen	Trifluridine/tipiracil (TAS-102) 25 mg/m2 p.o. days 1-5 Irinotecan 180 mg/m2 i.v. day 1 Every 14 days

Study Duration	The study will consist of a screening period of up to 28 days, a treatment period (14 days cycles), and follow up every 3 months until death or up to 18 months after the last patient is enrolled, whichever occurs first. Subjects will be allowed to continue treatment on study until disease progression, unacceptable toxicity or withdrawal of consent.
Statistical Methodology	Main objective is to describe the feasibility of the combination regimen and estimate PFS-6. If the PFS-6 is less than 35%, futility will be declared. If the PFS-6 is 35% or greater, the study is positive.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Gastric cancer is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide[1]. The incidence of GC varies with different geographic regions, with over 70% of GCs occurring in developing countries[2]. Gastric cancer often presents as advanced disease upon diagnosis, comprising approximately 40% of newly diagnosed cases in the United States (US) and Europe, and approximately 20% in Japan and Korea, where early detection is common[2].

Gastric cancer, including GEJ carcinoma, is a heterogeneous disease with several established risk factors, including environmental, genetic, and behavioral risks. There has been a steady decline in GC mortality attributable to dietary and lifestyle changes worldwide and to decreasing infection with Helicobacter pylori, which is considered the main cause of GC/GEJ in Asian countries[3]. However, the incidence of GEJ tumors has increased considerably due to increases in risk factors such as obesity and gastroesophageal reflux disease[1].

Gastroesophageal junction cancer anatomically straddles the distal esophagus and proximal stomach. Due to its anatomic location and given that, like GC, the majority of GEJ tumors are adenocarcinomas, GEJ tumors are frequently grouped together with GC. Adenocarcinoma is further classified into 2 distinct types: intestinal (well-differentiated) or diffuse (undifferentiated)[4].

Until optimal, tumor-specific treatment strategies are defined, advanced and metastatic GEJ cancer is treated and managed in a similar fashion to GC[5]. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium [S1]) are generally considered as first-line (1L), standard-of-care treatment options in metastatic GC and GEJ cancer across geographic regions[6][7]. These platinum/fluoropyrimidine combinations are also generally accepted as active comparators in Phase 2 or Phase 3 randomized studies by health authorities worldwide[2]. The different biological characteristics and treatment approaches among regions result in different survival outcomes, with median overall survival (mOS) durations of 12 to 14 months in Asian countries and 8 to 11 months in the United States (US) and Europe[6][7].

While these cytotoxic agents are clinically active, with a 30% to 50% objective response rate (ORR) in the 1L GC treatment setting, this clinical activity is accompanied by significant toxicity. Grade 3/4 toxicities up to 77% have been reported for doublet regimens and > 80% for triplet regimens[8][9][10][11]. Hematological toxicity is the major problem; Grade 3/4 neutropenia has been reported in approximately 40% of participants treated with platinum doublets, and has increased to 82% when docetaxel was added on. Renal toxicity and neuropathy are the main reasons for discontinuation of platinum treatment. Gastrointestinal complaints are also common. Additionally, despite ORRs of

30% to 50%, chemotherapy has resulted in few participants achieving complete response (CR).

Since it is increasingly unlikely to induce longterm remission in patients by a first-line treatment only, a potential way could be to expand the lines of treatment from the first- to the second-line and beyond[12]. Indeed, currently roughly 50% of patients progressing after firstline maintain acceptable general conditions and are still good candidates to receive further therapies[12]. Also, the benefit of second-line chemotherapy has been convincingly established in randomised trials[13][14][15], and more recently, the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) ramucirumab has shown to improve survival either as single agent over BSC[16] or combined with paclitaxel over paclitaxel alone in pretreated patients[17].

Monochemotherapy versus BSC

Three are the landmark phase III randomised trials that successfully explored the role of second-line monochemotherapy in patients with GC.

The German Arbeitsgemeinschaft Internistische Onkologie trial compared a 3-week schedule of irinotecan 250 mg/m² (escalated up to 350 mg/m² depending on toxicity) with BSC in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 who had received prior fluoropyrimidine/platinum combination and whose disease progressed during or within 6 months following first line[18]. Although the study was terminated prematurely due to poor accrual, among 40 enrolled patients the median OS was significantly longer in the irinotecan arm than in the BSC arm (4 vs 2.4 months, HR=0.48, p=0.023). The UK COUGAR-2 trial enrolled 168 patients to receive either docetaxel 75 mg/m² every 3 weeks plus BSC for a maximum of six cycles or BSC alone[19]. The median OS was improved with docetaxel compared with BSC (5.2 vs 3.6 months, HR=0.67, p=0.01). Despite a higher incidence of grade 3–4 neutropenia, infection and febrile neutropenia, patients receiving docetaxel experienced less pain, nausea, vomiting and constiption and decreased dysphagia and abdominal pain.

A Korean trial tried to answer the question about the optimal cytotoxics to be used in second line[20]. In this study, 202 patients with ECOG PS 0–1 and failing one or two prior chemotherapy lines were randomised in a 2:1 ratio to either salvage chemotherapy (docetaxel 60 mg/m² every 3 weeks or irinotecan 150 mg/m² every 2 weeks upon investigator's choice) or BSC. The administration of second-line chemotherapy resulted in a significant improvement in OS compared with BSC (5.3 vs 3.8 months, HR=0.657, p=0.007), while no survival difference was recorded between docetaxel and irinotecan (5.2 vs 6.5 months, p=0.116). Even side effects were similar in both treatment arms.

A meta-analysis of patient-level data from the abovementioned trials including a total of 410 patients underscored the median OS gain of roughly 2 months for second-line monochemotherapy as compared with BSC, with a significant reduction in the risk of death by 37% (HR=0.63, p<0.0001). This benefit was conferred by both irinotecan and docetaxel and was of similar magnitude through patients of different ethnic origin[21]. Of note, when we consider these results we have to remind that the docetaxel benefit is limited to a 3-week schedule at a higher dose, while the weekly lower dose regimen did not seem to yield a similar advantage[15].

On the contrary, a weekly paclitaxel regimen provided an OS comparable to that achieved with irinotecan in 219 patients refractory to standard first-line treatment (9.5 vs 8.4 months, HR=1.13, p=0.38)[14].

Combination chemotherapy versus monochemotherapy

Unlike the first-line setting, combination chemotherapy failed to demonstrate a survival benefit over single.-agent in pretreated AGC. In a small Korean phase II trial, irinotecan monotherapy was as effective as FOLFIRI in terms of ORR (17.2% vs 20%, p=0.525), PFS (2.2 vs 3.0 months, p=0.481) and OS (5.8 vs 6.7 months, p=0.514); grade 3–4 toxicity was also superimposable between treatment arms[13]. In another Japanese phase III study comparing biweekly irinotecan (60 mg/m²) plus cisplatin (30 mg/m²) to biweekly irinotecan alone (150 mg/m²) in 130 patients refractory to S1-based first-line chemotherapy, PFS was significantly prolonged in the combination arm (3.8 vs 2.8 months, HR 0.68, p=0.0398) but OS did not[22]. A meta-analysis of 10 randomised trials confirmed that doublet chemotherapy does not significantly improve OS compared with single agent, while resulting in more grade 3–4 myelosuppression, diarrhoea and fatigue, suggesting monochemotherapy as standard of care in this setting[23].

Ramucirumab: single agent and combinatorial approach

In spite of negative results coming from first-line trials, the therapeutic exploitation of angiogenesis turned out to be effective in second line. Ramucirumab, a fully human immunoglobulin IgG1 monoclonal antibody targeting VEGFR-2, has been shown to significantly improve survival in two pivotal international phase III double-blind, placebo-controlled trials. In the REGARD trial, 355 patients whose disease progressed within 4 months of fluoropyrimidine or platinum-containing first-line chemotherapy or within 6 months of completion of adjuvant therapy, and with an ECOG PS of 0–1, were randomised in a 2:1 ratio to either ramucirumab 8 mg/kg or placebo, intravenously every 2 weeks.16 Patients receiving ramucirumab had an improvement in both OS (5.2 vs 3.8 months, HR=0.776, p=0.047) and PFS (2.1 vs 1.3 months, HR=0.48, p<0.0001), with a reduction in the risk of death by 22% compared with placebo[16]. Also, the disease control rate was significantly higher in the experimental arm (49% vs 23%), although objective responses were infrequent with ramucirumab. The survival benefit remained significant after adjusting for main prognostic variables such as PS, tumour location and peritoneal disease. The efficacy of ramucirumab alone was comparable to that reported in phase III trials of second-line chemotherapy, with a more favourable toxicity profile.

Similarly, in the RAINBOW trial, which is the largest second-line trial in GC, the addition of ramucirumab to weekly paclitaxel significantly prolonged either median OS (9.6 vs 7.4 months, HR=0.807, p=0.017) or PFS (4.4 vs 2.9 months, HR=0.635, p<0.0001) when compared with paclitaxel monotherapy in 665 patients[17]. A decrease in the risk of death by 19% was seen and a significantly greater proportion of patients attained an objective response in the combination group than in the single-agent group (28% vs 16%, p=0.0001). These results are noteworthy especially in the light of poor risk feature of patients enrolled as demonstrated by the rate of peritoneal metastases higher than 40% in both the experimental and control arms. In a preplanned subgroup analysis, Asian patients derived less survival benefit than non-Asian. A dilution effect by poststudy discontinuation treatment as well as difference in pharmacokinetics has been advocated to explain this discrepant outcome. Interestingly, the survival benefit was achieved while maintaining patient quality of life, delaying symptom worsening and functional status deterioration[24]. The toxicity of ramucirumab was tolerable and, as expected, higher in the combination regimen. In the single-agent trial the most common AE was an increased risk of grade 3 or higher hypertension (8% vs 3%), while when combined with paclitaxel, ramucirumab resulted in significantly increased rates of grade 3–4 neutropenia (40.7% vs 18.8%), though this did not translate into higher incidence of febrile neutropenia. Antiangiogenic class side effects such as proteinuria, bleeding and gastrointestinal

perforations were mainly infrequent, mild in grade and more commonly noted in the combination arm.

Thirdline and later lines of therapy

Until recently, no randomized trials with cytotoxics were available to show a survival benefit in 3L+ patients with mGAC. The TAGS trial was a global phase 3 study of adult patients with mGC who had received ≥ 2 prior regimens of chemotherapy. Patients were randomized 2:1 to receive FTD/TPI (35 mg/m2 BID on days 1–5 and 8–12 of each 28-day cycle) or placebo, plus best supportive care. Median overall survival was 5·7 months (95% CI 4·8-6·2) in the trifluridine/tipiracil group and 3·6 months (3·1 -4·1) in the placebo group (hazard ratio 0·69 [95% CI 0·56 -0·85]; one-sided p=0·00029, two-sided p=0·00058)[25].
ATTRACTION-2 was a randomized, double-blind, placebo-controlled, phase 3 trial done at 49 clinical sites in Japan, South Korea, and Taiwan in 493 patients with 2+ lines of prior treatment who were randomized to nivolumab or placebo[26]. The study met it's primary endpoint of overall survival (HR 0.63, p<0.0001).
KEYNOTE-059 was a global, open-label, single-arm, multicohort study in patients with 2+ lines of prior treatment[27]. Treatment consisted of pembrolizumab 200mg every 3 weeks. ORR was the primary endpoint and ranged from 6.4% (PD-L1 negative population) to 15.5% (PD-L1 positive population). Median response duration was reported as 16.3 months in patients with PD-L1 positive tumors.

Therefore, the medical unmet need in 2L+ mGAC patients are more efficacious options for patients who have significant peripheral neuropathy from 1L platinum based chemotherapy and thus are not candidates for a taxane based regimen in 2L. Similarly, patients who progress on 2L taxane based regimens have few standard options.

1.2 Study Agent(s) Background and Associated Known Toxicities

TAS-102 is an orally available combination drug of an antineoplastic thymidine-based nucleoside analogue, 1M FTD, and 0.5 M TPI. TPI inhibits degradation of FTD by TPase. Following uptake into cells through nucleoside transporters, FTD is converted to its monophosphate F3dTMP by thymidine kinase. After further phosphorylation steps, its triphosphate F3dTTP is incorporated into DNA as substitute for thymidine triphosphate (Figure 1)[28].

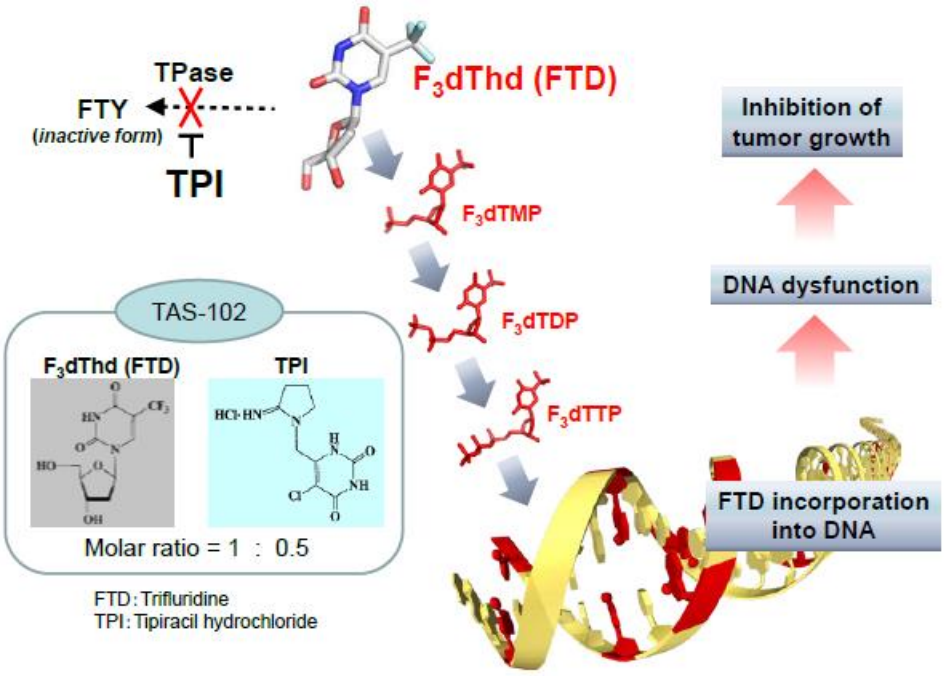


Figure 1 Mechanism of Antitumor Activity of TAS-102

- **Optimal Regimen of TAS-102**

  Comparison of antitumor effect between daily and intermittent administration (Study No. M96-029)

  TAS-102 was administered daily, intermittently, or weekly to mice implanted with human colorectal carcinoma cell line. TAS-102 was more effective, and without severe toxicity, with daily administration than with intermittent or once weekly administration. These data suggest that daily administration is the appropriate administration schedule of TAS-102.

  Comparison of antitumor effect between once daily and divided daily dose administration (Study No. 03-04-004)

  TAS-102 was administered once, twice, or three times a day for 2 weeks to mice implanted with human breast cancer cell line. TAS-102 exhibited an antitumor effect with administration at twice daily and three times daily, but not with once daily (single) administration. Moreover, the amount of FTD incorporation into tumor DNA was enhanced by divided dosing of TAS-102[29]. Based on these results, divided daily dosing is the appropriate schedule for TAS-102 administration orally.

- **Antitumor Profiles of TAS-102**

  Antitumor effect of TAS-102 against tumors insensitive to 5-FU-based anti-cancer agents (Study No. 03-04-005)

  An experiment with human gastric carcinoma xenograft mice was performed to confirm the efficacy of TAS-102 against tumors insensitive to 5-FU. TAS-102 150 mg/kg/day (TID), S-1 8.3 mg/kg/day, or capecitabine 539 mg/kg/day were

administered for 14 days. Only the TAS-102 treatment group showed significant antitumor activity without any body weight loss. These results suggest that TAS-102 is significantly effective against tumors insensitive to 5-FU.

Antitumor effects of TAS-102 against 5-FU resistant human cancer xenografts compared with those of 5-FU or UFT (Experiment Nos. M95-058, 059, 061, 062, 065, and 066)

The antitumor effects of TAS-102 against 5-FU resistant human cancer cell sublines were evaluated in nude mice xenografts and compared with those of intravenous 5-FU, continuous infusion of 5-FU, and oral UFT (tegafur-uracil) therapies at toxicologically similar doses, at which each modality gave a similar body weight decrease to the mice. TAS-102 and UFT were administered orally once daily for 14 days. 5-FU was administered using i.v. injections (15 mg/kg/day) or via a mini-osmotic pump (20 mg/kg/day) in mice for 14 days. TAS-102 was significantly more effective against human cancer cell sublines with acquired-resistance to 5-FU than both 5-FU and UFT.

Antitumor effect of TAS-102 against human colorectal carcinoma with low sensitivity to bevacizumab and cetuximab (Study No. M01-2007-0015)

The antitumor effect of TAS-102 against human colorectal carcinoma xenograft was evaluated in nude mice and compared with those of bevacizumab and cetuximab. TAS-102 was administeredtwice daily for 14 days and bevacizumab and cetuximab were administered twice weekly for 2 weeks. TAS-102 was significantly effective against tumor that showed low sensitivity to bevacizumab and cetuximab.

Antitumor effect of TAS-102 against small-cell lung carcinoma (Study Nos. 03-10-005, M01-2008-0016, and 10-09-087)

The antitumor effect of TAS-102 was evaluated in mice implanted with human small-cell lung carcinoma xenograft, and compared with the antitumor efficacy of cisplatin (CDDP) and S-1. In the Lu-24 xenograft model, 75 mg/kg/day TAS-102 exhibited antitumor efficacy similar to that of CDDP. The antitumor efficacy of TAS-102 in doses greater than 150 mg/kg/day was superior to that of CDDP. In the Lu-134 xenograft model, S-1 and CDDP showed antitumor efficacy but could not arrest tumor growth. TAS-102 exhibited high antitumor efficacy and suppressed tumor growth even after termination of drug administration. These results suggest that TAS-102 might be effective against small-cell lung carcinoma.

Consecutive suppression of tumor regrowth after the end of TAS-102 administration (Study No. M01-2006-0027)

Since it was shown that FTD remains in DNA after FTD removal (Study No. 03-02-017), the FTD in DNA may continue to have antitumor efficacy after the end of administration. The extent of tumor regrowth after TAS-102 administration was compared with that after other antitumor drugs. Mice implanted subcutaneously with human colorectal carcinoma were given TAS-102, 5-FU, Taxol, CDDP or CPT-11. TAS-102 exhibited continued suppression of tumor regrowth even after the end of its administration.

Prolongation of life span in tumor-bearing mice by administration of TAS-102 (Study No. M01-2008-0013)

TAS-102, CPT-11, and cetuximab were administered to mice implanted intraperitoneally with human colorectal carcinoma to estimate the effect of suppression of tumor regrowth by FTD on prolongation of life span. The survival period in the TAS-102 administration group was longer than that in the other drug administration groups. The observed survival benefit of TAS-102 is considered to result from FTD's characteristic of suppressing tumor growth.

- **Combination Therapy**

Antitumor efficacy of two-week administration with two-week discontinuation and one-week administration with one-week discontinuation of TAS-102 combined with CPT-11 (Study No. 12TB02)

The antitumor efficacy of TAS-102 and CPT-11 combination therapy was evaluated using a nude mouse subcutaneous transplantation model of human colorectal cancer and the toxic effects of the combination therapy were investigated. The results of the analysis demonstrated significantly enhanced antitumor efficacy in all of the combined administration groups. A maximum decrease in body weight of approximately 25% was observed in both combination therapy groups. Diarrhea was observed in 6 of 6 animals in the two-week TAS-102 and CPT-11 combination group, while no animals in the two-cycle one-week TAS-102 and CPT-11 combination administration group developed diarrhea. These results suggest that two-week TAS-102 and CPT-11 combination therapy and two-cycle one-week TAS-102 and CPT-11 combination therapy enhances the antitumor efficacy of TAS-102. The body weight loss observed after 1 week of TAS-102 administration was less than that observed after 2 weeks of TAS-102 administration.

Induction of immunogenic cell death (ICD) in combination treatment of TAS-102/oxaliplatin and anti-tumor efficacy of TAS-102 with oxaliplatin/anti-PD-1 antibody using murine colorectal carcinoma (Study No. PHA-95005-001)

The immunogenic properties of the TAS-102 combined with oxaliplatin were assessed in murine microsatellite stable CT26 colon carcinoma. In vitro, TAS-102 in combination with oxaliplatin is able to induce expression of ICD markers including calreticulin (CRT) exposure, high-mobility group box 1 (HMGB1) and ATP release compared to control. CRT exposure and HMGB1 release were significantly increased as compared to oxaliplatin alone. Notably, in vivo, the triple combination TAS-102/oxaliplatin/anti-PD-1 led to significantly increased survival of the mice as compared to TAS-102/oxaliplatin ($p<0.0001$) and TAS-102/anti-PD-1 ($p<0.001$). These results suggest that TAS-102 combined with oxaliplatin is an inducer of ICD.

Effect of TAS-102 in combination with an immunotherapy drug for treatment of mouse colorectal cancer (CMT-93 cell line) (Study No. 15PB10)

In mice, subcutaneously implanted with the mouse colorectal cancer cell strain CMT-93, the TAS-102 150 mg/kg/day monotherapy group, anti-mouse PD-1 antibody 0.1 mg/body monotherapy group, and the TAS-102 150 mg/kg/day + anti-mouse PD-1 antibody 0.1 mg/body combination therapy group all showed significant anti-tumor effect compared with the control group. Moreover, the combination therapy group showed a significant anti-tumor effect compared with either of the monotherapy groups (Figure 2). In addition, the toxicity was in the permissible range in all groups. The above results suggested that the combination treatment of TAS-102 + anti-mouse PD-1 antibody produced a stronger anti-tumor effect than the TAS-102 or

anti-mouse PD-1 antibody monotherapies. Moreover, as toxicity was in the permissible range, similar effects can be expected clinically.

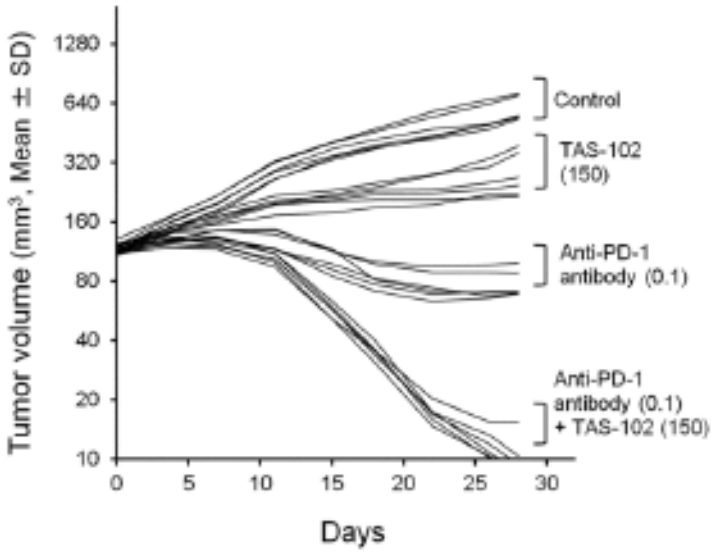


Figure 2: Effect of TAS-102 in combination with an immunotherapy drug for treatment of mouse colorectal cancer (CMT-93 cell line) (Study No. 15PB10)

- **Secondary Pharmacology**

  The inhibitory effects of FTD, FTY and TPI against a typical receptor panel were screened in Study No. AB31436.

  A total of 87 receptors, enzymes and channels were evaluated including: ATPase, cholinesterase, cyclooxygenase, monoamine oxidase, peptidase, phosphodiesterase, protein kinase, adenosine, adrenergic, androgen, angiotensin, bradykinin, calcium channel, cannabinoid, chemokine, cholecystokinin, dopamine, endothelin, estrogen, gamma-aminobutyric acid, glucocorticoid, glutamate, glycine, histamine, leukotriene, melanocortin, muscarinic, neuropeptide, nicotinic, opiate, platelet activating factor, potassium channel, peroxisome proliferator-activated receptor, progesterone, serotonin, sodium channel, tachykinin, transporters, vasopressin.

  No significant interaction between FTD, TPI, FTY and the receptors, enzymes and channels tested has been reported up to the tested concentration of 10μM, which is in excess of the free maximum concentration of FTD, FTY and TPI in human plasma upon dosing with TAS-102 according to the clinical dosing regimen. It can thus be anticipated that no secondary pharmacological effects will occur.

- **Safety Pharmacology**

  In the core battery of safety pharmacology studies of TAS-102, no effects on the central nervous system, respiratory system, or in vivo cardiovascular system were observed. FTD and TPI had no effects on hERG current in vitro (Table 1).

  Table 1 Summary of Safety Pharmacology Studies

Study No.	GLP Compliant	Evaluation Item	Test System	Test Article and Dose	Significant Changes
B040836	Yes	Central nervous system	Rat / Crj:CD(SD)IGS	TAS-102 (FTD+TPI): 0+0, 27.2+12.8, 108.8+51.2, 435+205 mg/kg	Not observed
B040837	Yes	Respiratory system	Rat / Crj:CD(SD)IGS	TAS-102 (FTD+TPI): 0+0, 27.2+12.8, 108.8+51.2, 435+205 mg/kg	Not observed
B040835	Yes	Cardiovascular system	Cynomolgus monkey	TAS-102 (FTD+TPI): 0+0, 6.8+3.2, 27.2+12.8, 108.8+51.2 mg/kg	Not observed
B050268	Yes	hERG Assay	HEK293 cells	FTD: 0, 3, 30, 300 μM	Not observed
B050270	Yes	hERG Assay	HEK293 cells	TPI: 0, 1, 10, 100 μM	Not observed

- **Pharmacokinetics and Metabolism in Animals**

The pharmacokinetic profile of TAS-102 has been investigated in rats and monkeys. The absorption, distribution, metabolism, and excretion of FTD and TPI were studied after oral dosing of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI at a dose of 50 mg FTD/kg and 23.6 mg TPI/kg in rats. The absorption, metabolism, and excretion were also studied after oral dosing at a dose of 10 mg FTD/kg and 4.71 mg TPI/kg in monkeys. Toxicokinetics of TAS-102 were investigated at dose levels of 15 to 450 mg/kg in rat and 1.25 to 20 mg/kg in monkey in multiple studies.

- **Absorption**

- **Single-dose Studies**

The plasma concentrations of FTD, FTY, and TPI were increased with increasing dose after oral administration of TAS-102 to rats at 15 to 450 mg/kg/day of TAS-102 (Study No. B-3687).

The extent of absorption of FTD and TPI that was calculated from the sum of excretion ratios of the radioactivity in the urine and expired air after oral administration of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI to non-fasting male rats was more than 76% and 15% for FTD and TPI, respectively (Study Nos. AE-2350-2G and AE-2350-3G).
The plasma concentrations of FTD, FTY, and TPI were increased with increasing dose after oral administration of TAS-102 to monkeys at 1.5 to 20 mg/kg/day of TAS-102 (Study No. B-6227).

The extent of absorption of FTD and TPI that was estimated from the excretion ratios of the radioactivity in the urine after oral administration of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI to fasting male monkeys was at least 79.4% and 27.3% for FTD and TPI, respectively (Study No. AE-6930-G).

- **Repeat-dose Studies**

The Cmax and AUC0-24 of FTD, FTY, and TPI were generally similar after the first dose and after repeated oral administration of TAS-102 to rats at doses of 15 to 450 mg/kg/day daily for 2 weeks (Study No. B-3687).

No effect of repeated administration and no sex differences were observed on the Cmax of FTD, FTY, and TPI after oral administration of TAS-102 to rats at 50 to 450 mg/kg/day daily for 4 weeks (Study No. B-3906).

There was no marked difference in Cmax and AUC0-24 of FTD, FTY, and TPI in plasma after the first administration and after repeated oral administration of TAS-102 to male and female monkeys at doses of 1.25 to 20 mg/kg/day daily for 13 weeks (Study No. B-6227).

- **Other Absorption Studies**

The absorption site of FTD and TPI in the rat digestive tract was investigated by an in situ loop method using TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI. FTD was highly absorbed from the middle to distal portion of the small intestine, although its absorption was observed throughout the whole gastrointestinal tract. TPI was absorbed throughout the whole small intestine, but its absorption through stomach and colon was much lower than through other segments (Study No. 12DA13).

- **Distribution**

- **In vitro Plasma Protein Binding**

The protein bindings of FTD at 0.5 to 50.0 µg/mL concentrations in rat, mouse, dog, monkey, and human plasma were in the range of 57.1% to 72.3%, 70.0% to 82.5%, 37.8% to 45.4%, 87.8% to 91.5%, and 96.7% to 97.3%, respectively. Thus, species differences were observed on plasma protein binding of FTD. FTD bound mainly to human serum albumin. On the other hand, plasma protein bindings of TPI at 0.05 to 5.0 µg/mL concentrations were below 8% in all species tested (Study Nos. AE-2350-2G and AE-2350-3G).

- **Tissue Distribution**

Whole body autoradiography was performed on 1 animal after oral administration of TAS-102 with [14C]-FTD to non-fasting male rats. At 30 min after dosing, the whole body autoradiogram showed that the levels of radioactivity in the kidney and stomach were higher than those in the other tissues. The levels of radioactivity in the heart, liver, lung, adrenal gland, pancreas, mandibular gland, bone marrow, pineal body, and spleen were low and comparable to that in the blood. The other tissues showed lower levels than blood. At 72 hr after administration, a trace level of radioactivity was found only in the thymus (Study No. AE-2350-3G).

Whole body autoradiography was performed on 1 animal after oral administration of TAS-102 with [14C]-TPI to non-fasting male rats. At 1 hr after dosing, the whole body autoradiogram showed that the levels of radioactivity in the intestine and kidney were higher than those in the other tissues. The levels of radioactivity in the pancreas, liver, fat, stomach, and lung were low and comparable to that in the blood. The other tissues showed lower levels than blood. At 72 hr after administration, a trace level of radioactivity was found only in the intestinal contents (Study No. AE-2350-2G).

Tissue distribution and elimination of radioactivity after oral administration of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI to pigmented rats were similar to those in albino rats. Radioactivity did not remain in the melanin-containing tissues.

- **Blood/Plasma Concentration Ratio**

  Blood/plasma concentration ratios (Rb) of FTD in rat, monkey, and human were in the range of 0.701 to 0.788, 0.628 to 0.678, and 0.596 to 0.619, respectively. Meanwhile Rb of TPI in rat, monkey, and human was in the range of 0.776 to 0.865, 0.634 to 0.680, and 0.581 to 0.661, respectively. FTD and TPI mainly distributed to plasma in rat, monkey, and human. There was no marked species difference on Rb (Study No. 11DA34).

- **Placental and Embryo-fetal Transfer**

  Radioactivity transfer to all fetus tissues was observed after administration of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI to pregnant rats. FTD, TPI and/or their metabolites transfer to the fetus across placenta (Study No. AE-6932-G).

- **Excretion into Milk**

  Radioactivity excretion into milk was observed after administration of TAS-102 with [14C]-FTD or TAS-102 with [14C]-TPI to nursing rats. Therefore, FTD, TPI and/or their metabolites are excreted into milk (Study No. AE-6933-G).

- **Metabolism**

- ***In vivo* Metabolism**

  FTY and an unknown metabolite, HFP1, were identified in rat plasma after oral administration of TAS-102 with [14C]-FTD. The structure of HFP1 was not identified. The major metabolite for FTD was FTY (Study No. AE-2350-3G).

  FTD and the metabolites, FTY, α-trifluoromethylureidopropionic acid (F3MUPA), and FTD glucuronides, were detected in monkey plasma collected at 1 hour after oral administration of TAS-102 with [14C]-FTD at a dose of 10 mg/kg to monkeys (Study No. AE-6930-G). Another metabolite, α-trifluoromethyl-β-alanine (F3MBA) was detected 6 hours and 12 hours after the administration. FTD, FTY, F3MUPA and FTD glucuronides were detected in monkey urine collected by 6 hours after administration.

  Only one metabolite of TPI, 6-hydroxymethyluracil (6-HMU), was identified in rat plasma after administration of TAS-102 with [14C]-TPI (Study Nos. AE-2350-2G and AE-4140).

  TPI and an unknown metabolite, T-Peak5, were detected in monkey plasma at 2 hours after administration of TAS-102 with [14C]-TPI at 10 mg/kg (Study No. AE-6930-G). Another metabolite, T-Peak3, was detected by 12 hours after the administration. TPI, T-Peak4, and imino-oxidated TPI were detected in monkey urine collected by 6 hours after the administration. Other metabolites included T-Peak2 and uracil. In addition, 6-HMU was also detected. The structures of T-Peak1, T-Peak2, T-Peak3, T-Peak4, and T-Peak5 could not be identified.

  FTD was predominantly metabolized to FTY, and further transformed to ring-opening metabolites. FTD glucuronides were also detected in monkeys. TPI was largely non-metabolized, with a number of minor biotransformation products observed. All metabolites of FTD or TPI observed in human clinical samples were also present in animal species.

- ***In vitro* Metabolism**

  TPI is a specific inhibitor of TPase, which was shown to almost completely inhibit the metabolism of FTD in tissue crude extracts from human breast cancer and colon cancer.9 The mode of inhibition of human TPase by TPI is competitive inhibition, and the Ki is 0.017 µmol/L.

  Fukushima et al. reported the impact of TPI on the conversion from FTD to FTY using crude extracts from various animal tissues[30]. This report suggests a species-specific inhibition of the conversion of FTD to FTY in the small intestines of human and monkey. The inhibitory effect of TPI on the metabolism of FTD in monkey was similar to that in human[30].

- **Elimination and Excretion**

- **Elimination**

  In non-fasting male rat plasma, amount (%) of FTD, FTY, and HFP1 at 1 hr after administration of TAS-102 with [14C]-FTD was 9.9%, 81.9%, and 3.7%, respectively. In rat urine at 0-24 hr, the excretion of FTD, FTY, and HFP1 was 13.8%, 36.8%, and 6.9% of the dose, respectively. Urinary excretion of FTD (13.8%) accounted for a minor portion of absorbed FTD (at least 76%, which was the sum of total radioactivity excreted into urine and expired air). Therefore, the main elimination route of FTD was metabolism (Study No. AE-2350-3G).

  In non-fasting male rat plasma, the amount (%) of TPI and 6-HMU at 2 hr after administration of TAS-102 with [14C]-TPI was 75.5% and 15.8%, respectively. In rat urine (0-24 hr), the excretion of TPI and 6-HMU was 9.9% and 3.3% of the dose, respectively. Urinary excretion of TPI (9.9%) accounted for a major portion of absorbed TPI (at least 15%, which was the sum of total radioactivity excreted into urine and expired air). Therefore, the main elimination route of TPI was excretion into urine (Study No. AE-2350-2G).

  In male monkey plasma, the amount (%) of FTD and its metabolites (FTY, F3MUPA, and FTD glucuronides [F-Peak 3a and F-Peak 3b]) at 1 hr after administration of TAS-102 with [14C]-FTD at 10 mg/kg were as follows: FTD, 56.2%; FTY, 26.1%; F3MUPA, 1.4%; and FTD glucuronides, 5.3%. These data show that FTY was the primary metabolite (Study No. AE-6930-G). Another metabolite, F3MBA, was detected 6 hrs and 12 hrs after the administration at 1.6% and 0.8%, respectively. In male monkey urine collected for 6 hr after the administration, the amount (%) of FTD, FTY, F3MUPA and FTD glucuronides were as follows: FTD, 41.4%; FTY, 43.0%; F3MUPA, 2.8%; and FTD glucuronides, 2.5%. These data indicate that FTY is the major metabolite found in urine.

  In male monkey plasma, the amounts (%) of TPI and an unknown metabolite, T-Peak5, at 2 hrs after administration of TAS-102 with [14C]-TPI at 10 mg/kg were 67.9% and 3.8%, respectively (Study No. AE-6930-G). In male monkey urine collected for 6 hrs after administration, the amounts (%) of TPI, T-Peak4, and imino-oxidated TPI were 85.7%, 1.0%, and 1.1%, respectively. These results suggest that TPI is the primary component in plasma and urine.

- **Excretion**

After oral administration of TAS-102 with [14C]-FTD to non-fasting male rats, the excretion of radioactivity in the urine, feces, and expired air was 60.6%, 20.6%, and 15.8% of the dose, respectively, up to 168 hr (total excretion 96.9%). After oral administration of TAS-102 with [14C]-FTD, the excretion of radioactivity in the bile was 0.4% of the dose up to 48 hr after dosing. Therefore, absorbed FTD and its metabolites were mainly excreted into urine (Study No. AE-2350-3G).

After oral administration of TAS-102 with [14C]-TPI to non-fasting male rats, the excretion of radioactivity in the urine, feces, and expired air was 14.3%, 83.4%, and 0.4% of the dose, respectively, up to 168 hr (total excretion 98.0%). After oral administration ofTAS-102 with [14C]-TPI, the excretion of radioactivity in the bile was 0.2% of the dose up to 48 hr after dosing. Therefore, absorbed TPI and its metabolites were mainly excreted into urine (Study No. AE-2350-2G).

After oral administration of TAS-102 with [14C]-FTD to fasting male monkeys, the excretion of radioactivity in the urine and feces was 79.4% and 3.8% of the dose, respectively, up to 168 hr (Study No. AE-6930-G).

After oral administration of TAS-102 with [14C]-TPI to fasting male monkeys, the excretion of radioactivity in the urine and feces was 27.3% and 68.1% of the dose, respectively, up to 168 hr (Study No. AE-6930-G).

- **Toxicology**

- **Single-dose Toxicity**

The single-dose (acute) oral toxicity of TAS-102 was investigated in the rat and dog. Dose levels (FTD equivalent) were 250, 500, 1000 and 2000 mg/kg.

In the rat study, diarrhea was observed on the day of administration in the 250 mg/kg and above groups, but it recovered on the following day. Body weights in the 1000 mg/kg group were lower than those in the control group on the day after administration, but thereafter, the values were similar to those in the control group. In the 2000 mg/kg group, 1/5 male and 4/5 females died on the day after administration or 2 days after administration. In this group, necrosis of glandular epithelial cells in the glandular stomach and intestines, erosion in the glandular stomach, deposition of basophilic material in the lamina propria mucosae in the glandular stomach, and necrosis of lymphocytes in the small intestine were observed (Study No. B-3685).

In the dog study, animals at all dose levels demonstrated varying degrees of emesis for mainly up to 4 hr post dose. The severity of emesis was dose-related. Soft or liquid feces were observed in animals at all dose levels. Body weight loss and decreased food consumption were observed primarily during the first treatment week in the 500 mg/kg and above groups. In animals treated at 250 mg/kg, decreased food consumption was also noted during the first 2 to 3 days after treatment, but the effect was less pronounced than in other groups. One male dog treated at 2000 mg/kg was sacrificed moribund 7 days after treatment. In the moribund animal, vomitus, soft feces, reduced appetite, lung lesions, dark areas in the colon/ileum, and thickening of the wall in the duodenum/jejunum were observed (Study No. 87931).

The lethal dose was 2000 mg/kg in both species. The main target organ of single dose toxicity seemed to be the digestive tract in rats and dogs.

- **Repeat-dose Toxicity**

- **Rat Studies**

  TAS-102 was administered orally to rats at dose levels (FTD equivalent) of 15, 50, 150 and 450 mg/kg/day in a 2-week study; 50, 150 and 450 mg/kg/day in a 4-week study; and 5, 15, 50 and 150 mg/kg/day in a 13-week study; and 10, 30, 100 and 280 mg/kg/day in a 26-week study.

  In the 2-week study, no treatment-related changes were observed at the dose levels of 15 and 50 mg/kg/day and there were no mortalities in any dose group. In the 150 mg/kg/day and above groups, necrosis of the glandular epithelial cells in the small intestine, and follicular atrophy of the mesenteric and submandibular lymph nodes were observed. Furthermore, in the 450 mg/kg/day group, decreased body weight gains and food consumption, decreased leukocyte counts and reticulocyte ratio, decreased spleen and thymus weights, and atrophy of the thymus were observed. The main target organs seemed to be the lymphatic-hematopoietic system and digestive tract (Study No. B-3687).

  In the 4-week study, no treatment-related changes were observed in the 50 mg/kg/day group. In the 150 mg/kg/day and above groups, decreased body weight gains and food consumption, increased drug-induced crystal in the urine sediment, erosion of the glandular stomach, necrosis of glandular epithelial cells in the intestine, increased extramedullary hematopoiesis of the spleen, increased ovary weights, and increased small corpus luteum were observed. Furthermore, in the 450 mg/kg/day group, decreases in osmotic pressure and excretion of sodium, potassium, and chloride in the urine were observed; hematological changes included decreases in leukocyte and erythrocyte counts, reticulocyte ratio, hemoglobin, hematocrit and fibrinogen, and increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH); blood chemistry changes included decreases in total protein and γ-globulin, and increases in total cholesterol and total bilirubin; pathological changes included atrophy in the thymus, spleen and lymph nodes, and hypoplasia in the bone marrow. After a 4-week recovery period, various changes relating to the undernourished state were observed and considered to be caused by poor intake of food due to fractured incisors and malocclusion, and one male dosed at 450 mg/kg/day eventually died. However, abnormalities of the incisors, such as degeneration or disarrangement in the ameloblasts/papillary cells/odontoblasts, would be expected to only occur in the rodents with continuously growing teeth but not in humans. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. B-3906).

  In the 13-week study, no treatment-related changes were observed in the 5 and 15 mg/kg/day groups and no mortalities were observed in any dose group. In the 50 mg/kg/day and above groups, decreased leucocyte counts and increased MCH, increased apoptotic bodies in the glandular epithelial cells of the small intestine and fatty infiltration in the bone marrow were observed. Furthermore, in the 150 mg/kg/day group, decreased erythrocyte counts, increased MCV and atrophy in the thymus were observed. Abnormalities of the incisors, such as disarrangement of the odontoblasts, were observed in the 50 mg/kg/day and above groups. After a 9-week recovery period, TAS-102 induced changes were considered reversible. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. 07CA07).

  In the 26-week study, no toxic changes were observed in the 10 and 30 mg/kg/day groups and no mortalities were observed in the 100 mg/kg/day and less groups. In

the 280 mg/kg/day group (2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period), treatment-related deaths or moribundity occurred in 3 males and 3 females of 26 animals /sex/group including the satellite animals between Days 90 and 176. Dose-related changes were observed mainly in the hematopoietic-lymphatic system, small intestine and incisors in the 100 and 280 mg/kg/day groups. Increased ovary weights were observed in all female dose groups; however, they were not accompanied by related histopathological findings. After a 9-week recovery period, TAS-102 induced changes were considered reversible. The main target organs appeared to be the lymphatic-hematopoietic system and small intestine (Study No. B-8020).

- **Monkey Studies**

  TAS-102 was administered orally to monkeys at dose levels (FTD equivalent) of 1.9, 7.5, 30 and 120 mg/kg/day in a 2-week study; 6.25, 25 and 100 mg/kg/day in a 4-week study; and 1.25, 5 and 20 mg/kg/day in a 13-week study.

  In the 2-week study, no treatment-related changes were observed in males at dose levels of 1.9 mg/kg/day. Decreased leukocyte counts were observed in all TAS-102 groups excluding the males administered 1.9 mg/kg/day. In the 30 mg/kg/day and above groups, soft/liquid feces, salivation, typhlitis, colitis, cryptal necrosis in the colon and cecum, and lymphoid atrophy in the spleen were observed. Furthermore, in the 120 mg/kg/day group, emesis, watery contents in the large intestine, villous atrophy in the small intestine, lymphoid atrophy in the lymph nodes, and bone marrow hypocellularity were observed. One male monkey dosed at 120 mg/kg/day was euthanized on Day 8 due to deteriorating condition. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. 87936).

  In the 4-week study, no treatment-related changes were observed in the 6.25 mg/kg/day group and no mortalities were observed in any dose group. In the 25 mg/kg/day and above groups, soft/liquid feces, dehydration, decreases in leukocyte counts, erythrocyte counts, hemoglobin and hematocrit, small thymus, raised/discoloration/dark areas in the cecum, lymphoid atrophy, and inflammation in the digestive tract were observed. Furthermore, in the 100 mg/kg/day group, emesis, decreased body weight and food consumption, increased platelet counts and mean corpuscular hemoglobin concentration (MCHC), decreased thymus weight, bone marrow hypocellularity, decreased myeloid/erythroid (M/E) ratio due to increased erythroid series, and abnormal nuclear maturation of bone marrow cells were observed. In addition, increases in blood urea nitrogen, creatinine and alanine aminotransferase (ALT) were observed as well as increases in excretion of creatinine, potassium and chloride in the urine. After a 4-week recovery period, TAS-102 induced changes were considered reversible. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. 87941).

  In the 13-week study, no treatment-related changes were observed in the 1.25 mg/kg/day TAS-102 group. In the 5 mg/kg/day and above groups, decreases in body weight, food consumption, leukocyte counts and erythrocyte counts, and an increase in fibrinogen were observed. Furthermore, in the 20 mg/kg/day group, soft/liquid feces, decreased hemoglobin and hematocrit, inflammation in the rectum and atrophy in the spleen were observed. One female monkey dosed at 20 mg/kg/day was euthanized on Day 85 due to being moribund; this monkey showed remarkable changes in hematology, blood chemistry and histopathology which reflected the damage in the lymphatic-hematopoietic system and digestive tract as described

above. After a 9-week recovery period, TAS-102 induced changes were considered reversible. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. B-6227).

- **Dog Study**

  TAS-102 was administered orally to dogs at dose levels (FTD equivalent) of 17, 50 and 150 mg/kg/day in a 2-week study.
  All TAS-102 groups showed emesis, soft/liquid/reduced feces, decreased body weight and food consumption, decreased leukocyte counts, glandular/cryptal necrosis in the digestive tract, bone marrow hypocellularity, and lymphoid atrophy in the thymus, lymph nodes, spleen and intestine. These changes were more severe and occurred earlier in the higher-dose group. In the 50 mg/kg/day and above groups, decreased locomotor activity, weakness, tremors, hypothermia and blood chemical abnormalities were observed; all animals in these groups died or were euthanized on Day 5 to Day 8 due to being moribund. The main target organs appeared to be the lymphatic-hematopoietic system and digestive tract (Study No. 87935).

- **Genotoxicity**

  A series of studies were performed to investigate the genotoxicity of TAS-102. TAS-102 was found to be mutagenic when tested in the in vitro reverse mutation assay using Salmonella typhimurium (TA100, TA1535, TA98 and TA1537) and Escherichia coli (WP2uvrA). In TA100, TA1535 and WP2uvrA, the number of revertant colonies induced by TAS-102 exceeded twice the number in solvent control (physiological saline), or there were dose-dependent increases in the number of revertant colonies with and without S9 mix. In TA98 and TA1537, however, the number of revertant colonies was not twice or more than in the vehicle control group with and without S9 mix, and there was no dose-dependent increase in the number of revertant colonies. These results indicate that TAS-102 induces base pair substitution type mutation (Study No. 00CA11).

  The in vitro potency for chromosomal aberration was investigated using Chinese hamster lung cells. Significant increases in the incidence of cells having structural chromosomal aberrations were observed in the TAS-102 treatment groups under conditions with and without S9 mix. No significant increases in the incidence of cells having numerical chromosomal aberrations were observed in any TAS-102 treatment groups under any treatment condition. These results indicate that TAS-102 is clastogenic (Study No. 00CA12).

  The micronucleus test was performed using bone marrow cells in mice. Significant increases in the frequency of micronucleated polychromatic erythrocyte (MNPCE) were observed in all TAS-102 groups. These results indicate that TAS-102 has in vivo inducing clastogenicity potency (Study No. 01CA15).

- **Reproductive and Developmental Toxicity**

  TAS-102 was tested in male and female fertility studies and in an embryo-fetal development study in rats. Dose levels (FTD equivalent) were 50, 150 and 450 mg/kg/day in the male fertility study and 15, 50 and 150 mg/kg/day in the female fertility study and embryo-fetal development study.

In the male fertility study (Study No. R-908), male parental animals exhibited suppressed body weight gain and decreased food consumption in the 150 mg/kg/day and above groups and dark red spots in the glandular stomach in the 450 mg/kg/day group. No effects on fertility and early embryonic development were noted with respect to day until copulation, copulation index, conception rate, number of corpora lutea, number of implantation, implantation index, number of live embryos or viability index of embryos in any group.

In the female fertility study (Study No. R-904), female parental animals exhibited suppressed body weight gain in the 50 mg/kg/day and above groups and decreased food consumption in the 150 mg/kg/day group. As for effects on fertility, increased numbers of corpora lutea and implantation were noted in the 150 mg/kg/day group. As for effects on embryonic development after implantation, decreased viability index of embryos was noted in the 150 mg/kg/day group.

In the embryo-fetal development study (Study No. 04CA18), female parental animals exhibited suppressed body weight gain in the 50 mg/kg/day and above groups and decreased food consumption in the 150 mg/kg/day group. One female in the 150 mg/kg/day group aborted at Day 21 of gestation. As for effects on embryo-fetal development, decreased fetal weights and delayed ossification in fetus were noted in the 50 mg/kg/day and above groups. The 150 mg/kg/day group exhibited increases in the rate of post implantation loss and the rate of fetuses with anomalies of external (mainly, kinked tail), viscera (mainly, malpositioned subclavian branch, retroesophageal subclavian and left umbilical artery), and skeleton (main sites with anomalies: vertebrae from cervix to tail, sternebrae and ribs).

- **Other Toxicity Studies**

- **Phototoxicity Tests**

  Two in vitro phototoxicity tests of FTD and TPI were conducted using Balb/3T3 clone A31 cells derived from mouse embryo. FTD and TPI did not induce phototoxic response in Balb/3T3 clone A31 cells in these tests (Study Nos. B110945 and B110946).

- **Combination Toxicity Study of TAS-102 and CPT-11 in Rats**

  A combination toxicity study of TAS-102 and CPT-11 in rats was conducted to compare the toxicity between 1- and 2-week interval regimens of TAS-102 in combination with CPT-11. TAS-102 was administered once a day using either a 1-week on/1-week off regimen or a 2-week on/2-week off regimen for four weeks. CPT-11 was administered twice at an interval of two weeks. Dose levels (FTD equivalent) were 0, 150, 300 and 450 mg/kg of TAS-102, and 0 and 60 mg/kg of CPT-11 (Study No. 12CB12).

  Prone position, panting and loose stool were observed in male rats receiving 60 mg/kg CPT-11.

  Just before the second CPT-11 administration, significant decreases relative to control in body weight, food consumption, leukocyte counts, neutrophil counts, monocyte counts, hemoglobin, hematocrit and reticulocyte counts were noted in the 2-week on/2-week off regimen groups compared with 1-week on/1-week off regimen groups. Neutrophil counts recovered just before the second CPT-11 in the 1-week on/1 week off regimen groups. Maximum percent differences in the body weight,

leukocyte counts and lymphocyte counts tended to be more decreased in the 2-week combination regimen group than those in the 1-week combination regimen group. The other percent differences from the control were comparable between 1-week and 2-week regimens. No differences in the reversibility of the combination toxicity were noted between 1-week and 2-week regimens. Based on these results, the 1-week on/1-week off TAS-102 regimen was considered to be more tolerable in combination with CPT-11 administration, with milder toxicities compared to the 2-week on/2-week off TAS-102 regimen.

- **CLINICAL STUDIES**

- **Phase 1 Pharmacokinetic Study of TAS-102 in Combination with CPT-11 and Bevacizumab (Study TPU-TAS-102-109)**

Study TPU-TAS-102-109 is an ongoing Phase 1, open-label, non-randomized, dose-escalation study of TAS-102 administered in combination with irinotecan in western (US) patients with advanced gastrointestinal tumors who are refractory to at least one line of chemotherapy for metastatic disease and for whom no curative therapy exists. The study consists of a dose-escalation phase (Part 1) to determine the MTD of TAS-102 in combination with irinotecan. Subjects are assigned to sequential dose-levels of TAS-102 in combination with irinotecan. TAS-102 (starting dose of 20 mg/m2/dose) is administered orally BID from Day 1 through Day 5 followed by a recovery period from Day 6 through Day 14. CPT-11 is co-administered as an IV infusion with TAS-102 on Day 1 of the 14-day treatment cycle. Once the MTD for TAS-102 and irinotecan combination is established, patients will be enrolled in an expansion phase (Part 2) to further evaluate the safety, PK, and preliminary efficacy of the MTD. The protocol was subsequently amended to investigate the safety of TAS-102 and irinotecan at the MTD when administered in combination with bevacizumab (expansion phase of study).

As of 24 July 2017, a total of 50 patients received study treatment (26 patients have received TAS-102 + CPT-11 and 24 patients have received TAS-102 + CPT-11 + bevacizumab); 24 SAE cases and have been reported for 17 patients.

The MTD of TAS-102 was determined as 25mg/m2/dose in combination with CPT-11 at 180mg/m2. The study enrolled 24 patients in expansion and further enrollment was discontinued as the study reached its objective of the following:

1. Defining the MTD for the triple combination and
2. Demonstrating the preliminary ORR in 24 patients with mCRC.

When evaluating the ORR of the enrolled patients as well the data maturity, the Supporter and Principal Investigator determined that the enrolled patients number should suffice to evaluate the overall safety as well as efficacy of the triplet combination.

- **Phase 3 Study in Gastric Cancer (Study TO-TAS-102-302)**

  This was a multinational, double-blind, two-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 (35 mg/m2/dose BID) plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer who have previously received at least 2 prior regimens for advanced disease. Eligible patients were randomized (2:1) to receive TAS-102 + BSC (experimental arm) or placebo + BSC (control arm) and stratified by region (rest of world vs. Japan), ECOG performance status (0 vs. 1), and prior treatment with ramucirumab (yes vs. no).

  Between Feb 24, 2016, and Jan 5, 2018, 507 patients were enrolled and randomly assigned, 337 to the trifluridine/tipiracil group and 170 to the placebo group. Median overall survival was 5·7 months (95% CI 4·8–6·2) in the trifluridine/tipiracil group and 3·6 months (3·1–4·1) in the placebo group (hazard ratio 0·69 [95% CI 0·56–0·85]; one-sided p=0·00029, two-sided p=0·00058). Grade 3 or worse adverse events of any cause occurred in 267 (80%) patients in the trifluridine/tipiracil group and 97

(58%) in the placebo group. The most frequent grade 3 or worse adverse events of any cause were neutropenia (n=114 [34%]) and anaemia (n=64 [19%]) in the trifluridine/tipiracil group and abdominal pain (n=15 [9%]) and general deterioration of physical health (n=15 [9%]) in the placebo group. Serious adverse events of any cause were reported in 143 (43%) patients in the trifluridine/tipiracil group and 70 (42%) in the placebo group. One treatment-related death was reported in each group (because of cardiopulmonary arrest in the trifluridine/tipiracil group and because of toxic hepatitis in the placebo group).

This Phase 3 study was initiated based on the results of an Investigator-initiated Phase 2 study of TAS-102 conducted in Japanese patients with metastatic gastric cancer who had failed standard chemotherapies including fluoropyrimidines, platinum and any of the taxanes or irinotecan (EPOC1201)[31]. Common Grade 3 or 4 AEs included neutropenia (69.0%), leukopenia (41.4%), anemia (20.7%) and anorexia (10.3%). Only 2 (6.9%) patients discontinued treatment due to adverse events. No treatment-related deaths were observed. The disease control rate was 65.5% (95% CI: 45.7, 82.1). Median PFS was 2.9 months and median OS was 8.7 months.

- **Phase 1 Dose-finding Study of TAS-102 in Combination with Oxaliplatin (Study CL1-95005-001)**

This is an ongoing Phase 1, open-label, non-randomized, dose-escalation study of TAS-102 administered in combination with oxaliplatin (and with bevacizumab or nivolumab in expansion part) in patients with metastatic colorectal cancer who are refractory to at least one line of chemotherapy for metastatic disease. The study consists of a dose-escalation phase (Part 1) to determine the MTD of TAS-102 in combination with oxaliplatin. TAS-102 (starting dose of 25 mg/m²/dose) is administered orally BID from Day 1 through Day 5 followed by a recovery period from Day 6 through Day 14. Oxaliplatin is co-administered as an IV infusion with TAS-102 on Day 1 of the 14-day treatment cycle. Once established, the MTD will be confirmed in 6 additional patients to define the recommended dose (RD). Then patients will be enrolled in an expansion phase (Part 2) to further evaluate the safety, PK, and preliminary efficacy of TAS-102 in combination with oxaliplatin and either bevacizumab or nivolumab. The expansion part will be divided into 2 cohorts: i) a cohort of up to 35 evaluable patients will receive bevacizumab in addition to the combination of TAS-102 and oxaliplatin administered at the RD, ii) a cohort of up to 35 evaluable patients will receive nivolumab in addition to the combination of TAS-102 and oxaliplatin administered at the RD. The inclusion in one or another cohort will be done at the discretion of the investigator and patients will be recruited simultaneously. It will not be possible to cross over onto the other cohort.

As of 24 July 2017, 15 patients have received TAS-102 plus oxaliplatin. No patients have received bevacizumab or nivolumab; 15 SAE cases have been reported. The dose escalation is still ongoing, and the MTD is not defined yet.

- **Phase 2 Study of TAS-102 in Combination with Bevacizumab (Study CL2-95005-002)**

This study is an open-label, randomised, non-comparative Phase 2 study evaluating TAS-102 (35 mg/m²/dose BID) plus bevacizumab and capecitabine plus bevacizumab in the first-line treatment of patients with unresectable metastatic colorectal cancer who are non-eligible for intensive therapy (TASCO1 study). Patients are randomly assigned (1:1) to TAS-102 plus bevacizumab or capecitabine plus bevacizumab and stratified by RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) and country.

Evaluation of efficacy includes PFS based on investigator assessment on radiologic images, ORR, duration of response (DR), DCR and OS.

As of 24 July 2017, the enrollment is completed and a total of 153 patients have been enrolled (77 patients have received TAS-102 + bevacizumab and 76 patients have received capecitabine + bevacizumab); 181 SAEs have been reported for 76 patients.

This Phase 2 study was initiated based on the results of an Investigator Initiated Phase I/II dose-finding study of TAS-102 in combination with bevacizumab for mCRC refractory to standard therapies (C-TASK FORCE) conducted in Japanese patients.212223 Twenty-five patients were enrolled from February to July 2014. The recommended Phase II dose was determined to be TAS-102 35 mg/m2 BID on Days 1-5 and Days 8-12 in combination with bevacizumab 5 mg/kg on Days 1 and 15, every 4 weeks. The most common Grade ≥3 AEs were neutropenia (72%), leukopenia (44%), febrile neutropenia (16%), anaemia (16%), thrombocytopenia (12%), and hypertension (8%). The study met its primary endpoint: the centrally assessed PFS rate at 16 weeks was 42.9% (80% CI: 27.8-59.0%). Median OS (at final cutoff date for analysis) was 11.4 months (IQR 7.4 – 15.6).

1.3 Other Agents

- **Irinotecan (CPT-11) [Camptosar®]**

- **Mechanism of Action**

  Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan hydrochloride or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

- **Pharmacodynamics**

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold; however, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan. The precise contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

- **Pharmacokinetics**

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m2 determined in two clinical studies in patients with solid tumors are summarized in Table 2:

Table 2. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Table 9. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z (L/m^2)	CL ($L/h/m^2$)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8* ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4* ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7† ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0† ±4.3

Cmax - Maximum plasma concentration
AUC0–24 - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
t1/2 - Terminal elimination half-life
Vz - Volume of distribution of terminal elimination phase
CL - Total systemic clearance
*
Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
†
Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

- **Distribution**

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

- **Metabolism**

Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In vitro

studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro.

- **Excretion**

The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m2) to 50% (300 mg/m2).

- **Effect of Age**

The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC0–24 for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan.

- **Effect of Gender**

The pharmacokinetics of irinotecan do not appear to be influenced by gender.

- **Effect of Race**

The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

- **Effect of Hepatic Impairment**

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made.

- **Effect of Renal Impairment**

The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, caution should be undertaken in patients with impaired renal function. CAMPTOSAR is not recommended for use in patients on dialysis.

- **Drug Interactions**

Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the pharmacokinetics of irinotecan.

- **NONCLINICAL TOXICOLOGY**

- **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan Cmax and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m2 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). Neither irinotecan nor its active metabolite SN-38 was mutagenic in the in vitro Ames assay.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits; however, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg and in dogs at 0.4 mg/kg. In separate studies in rodents, this dose produced an irinotecan Cmax and AUC about 5 and 1 times, respectively, of the corresponding values in patients administered 125 mg/m2 weekly. In dogs this dose produced an irinotecan Cmax and AUC about one-half and 1/15th, respectively, of the corresponding values in patients administered 125 mg/m2 weekly.

- **CLINICAL STUDIES**

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent. When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies of combination and single-agent use are described below.

- Metastatic Colorectal Cancer

First Line Therapy in Combination with 5-FU/LV: Studies 1 and 2

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-

FU/LV, with or without irinotecan. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) <500/mm3, even in the absence of fever or diarrhea. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever or if ileus developed.

In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 3.

Table 3. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly × 4 every 6 weeks	**Bolus 5-FU/LV daily × 5 every 4 weeks**	**Irinotecan weekly × 4 every 6 weeks**	**Irinotecan + Infusional 5-FU/LV**	**Infusional 5-FU/LV**
Number of patients	231	226	226	198	187
Demographics and treatment administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median age in years (range)	62 (25–85)	61 (19–85)	61 (30–87)	62 (27–75)	59 (24–75)
Performance status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median time from diagnosis to randomization (months, range)	1.9 (0–161)	1.7 (0–203)	1.8 (0.1–185)	4.5 (0–88)	2.7 (0–104)
Prior adjuvant 5-FU therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median duration of study treatment* (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)*					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed objective tumor response rate† (%)	39	21 (p<0.0001)‡	18	35	22 (p<0.005)‡
Median time to tumor progression§ (months)	7.0	4.3 (p=0.004)§	4.2	6.7	4.4 (p<0.001)§
Median survival (months)	14.8	12.6 (p<0.05)§	12.0	17.4	14.1 (p<0.05)§

* Study 1: N=225 (irinotecan/5-FU/LV),N=219 (5-FU/LV),N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV),N=186 (5-FU/LV)
† Confirmed ≥ 4 to 6 weeks after first evidence of objective response
‡ Chi-square test
§ Log-rank test

Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities).

Second-Line Therapy After 5-FU-Based Treatment

4 Weekly Doses on a 6-Week Cycle: Studies 3, 4, and 5

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m2, but the 150-mg/m2 dose was poorly tolerated (due to high rates of grade 4 late diarrhea and febrile neutropenia). Study 3 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 4 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 4 received a starting dose of 125 mg/m2. Study 5 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 5 was 125 mg/m2 but was reduced to 100 mg/m2 because the toxicity seen at the 125-mg/m2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m2. The majority of responses were observed within the first two cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m2 was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

Once-Every-3-Week Dosage Schedule

Single Arm Study: Study 6

Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the

treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m2 given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Studies: Studies 7 and 8

Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In Study 7, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In Study 8, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m2 for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 7 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the Study 8 received one of the following 5-FU regimens: (1) LV, 200 mg/m2 IV over 2 hours; followed by 5-FU, 400 mg/m2 IV bolus; followed by 5-FU, 600 mg/m2 continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m2/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m2 IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m2/day every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-based therapy (p=0.035). In Study 7, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 8, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations (p=0.001 for Study 7 and p=0.017 for Study 8). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 7, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care (p=0.002).

Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

1.4 Rationale

In 2L+ mGC/GEJ, taxanes with or without ramucirumab, irinotecan, and pembrolizumab in select patients (PD-L1 positive in 3L+ or MSI-high in 2L+) are recommended treatment options[17][16]. Irinotecan has been tested in multiple single arm and randomized trials in 2L+ mGC, with reported ORR in the 15-29% range and median PFS of 2-3 months[32][13]. The largest current randomized phase 3 trial in 2L mGC was the RAINBOW trial, demonstrating an improvement in mOS, mPFS and ORR with the combination of paclitaxel plus ramucirumab vs paclitaxel alone[17]. Despite these advances, outcomes for advanced GC remain poor with a mOS of 9.6 months and PFS-6 of only 36%[17]. Until recently, no randomized phase 3 trial demonstrated a survival benefit in 3L+ mGC. The TAGS trial randomized 507 patients with 3L+ mGC in 2:1 ratio to either TAS102 or placebo and showed a significant improvement in mOS from 3.6 months to 5.7 months (HR 0.69, P= 0.0003)[25]. One of the clinical challenges of 2L treatment with taxanes after 1L platinum containing regimens (in the U.S. mainly oxaliplatin) is the development and worsening of peripheral neuropathy, which often leads to dose reductions, treatment delays, and reduced QoL for patients. In the RAINBOW trial, 46% of patients in the combination arm developed neuropathy, 8% of which were grade 3. The WJOG 4007 trial compared irinotecan with paclitaxel in 2L mGC and found no difference in survival[14]. Thus, irinotecan can be regarded as one possible current standard option for 2L mGC. Early phase trials have evaluated the feasibility of TAS102 in combination with irinotecan +/- bevacizumab in patients with advanced colorectal adenocarcinoma. Doi et al completed a 3+3 dose escalation study and established a recommended dose of 50mg/m2/day (corresponding to 25mg/m2 bid) on days 1-5 and 8-12 with irinotecan 150mg/m2 on days 1 and 15 of a 28 day cycle[33]. More recently, TAS102 was combined with irinotecan and bevacizumab in mCRC in a modified dosing schedule (TAS102 at 25mg/m2 bid day 1-5, irinotecan 180mg/m2 day 1, bevacizumab 5mg/kg day 1, given every 14 days). The authors did not report any new safety signals, and encouraging activity in a cohort of heavily pretreated patients [Varghese AM et al. J Clin Oncol 36, 2018 (suppl; abstr 3546)].

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the efficacy of trifluridine and tipiracil (TAS102) in combination with irinotecan in patients with advanced gastric and gastroesophageal adenocarcinoma

2.2 Secondary Objectives

2.2.1 To describe the adverse events associated with trifluridine and tipiracil (TAS102) in combination with irinotecan in patients with advanced gastric and gastroesophageal adenocarcinoma

2.2.2 In patients with measurable disease, to describe any preliminary evidence of anti-tumor activity by assessment of objective response as determined by RECIST v1.1 in patients with advanced gastric and gastroesophageal adenocarcinoma

2.3 Endpoints

The primary endpoint is 6 months progression-free survival (PFS-6).
The secondary endpoints are rates of drug-related grade 3-5 adverse events experienced within the first 8 weeks (2 cycles) of study treatment. These will be assessed via NCI's CTCAE v5.0 toxicity criteria. Other secondary endpoints are best objective response rate by RECIST v1.1 in patients with measurable disease and overall survival.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed gastric or gastroesophageal adenocarcinoma

3.1.2 Must have locally advanced, recurrent, or metastatic disease not amenable to curative intent surgery.

3.1.3 Must have progressed, or not tolerated, at least one line of treatment with a platinum and/or fluoropyrimidine containing regimen. At least one cycle of combination chemotherapy including a platinum (oxaliplatin, cisplatin, carboplatin) and/or fluoropyrimidine (capecitabine or 5-Fluorouracil) based regimen for advanced disease. Combination regimens with platinum/fluoropyrimidine containing a taxane and or a checkpoint inhibitor are allowed. Patients progressing within six months of perioperative chemotherapy or definitive chemoradiation for localized disease are eligible. Patients who have exhausted all other standard of care options are also eligible.

3.1.4 Age ≥ 18 years
Because no dosing or adverse event data are currently available on the use of TAS-102 in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.5 Performance status: *ECOG performance status ≤2 (Appendix A).*

3.1.6 Life expectancy of greater than 3 months

3.1.7 Adequate organ and marrow function as defined below:

- leukocytes	≥ 3,000/mcL
- absolute neutrophil count	≥ 1,500/mcL
- platelets	≥ 80,000/mcl
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SPGT)	≤ 3 X institutional upper limit of normal or ≤ 5 X if liver metastases are present
- creatinine	< 1.5 X upper limit of normal

3.1.8 The effects of TAS-102 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because topoisomerase inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8.1 A female of child-bearing potential is any woman (regardless of

sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.9. Ability to swallow tablets

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

3.2 Exclusion Criteria

3.2.1 Patients who have had major surgery within 4 weeks, or chemotherapy or radiotherapy within 2 weeks prior to Cycle 1 Day 1.

3.2.2 All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to grade 1 or baseline

3.2.3 Patients may not be receiving any other investigational agents.

3.2.4 Patients with known brain metastases due to poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to TAS-102, irinotecan or other agents used in study.

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

3.2.7 Prior treatment with irinotecan or TAS-102

3.2.8 History of another primary cancer within the last 3 years with the exception of non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in-situ.

3.2.9 Inability to comply with study and follow-up procedures as judged by the Investigator

3.2.10 Patients who are pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

3.3 **Inclusion of Women, Minorities, Vulnerable Populations** Both men and women and members of all races and ethnic groups are eligible for this trial. Non-English speaking, deaf, hard of hearing and illiterate individuals are eligible for this trial.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Patients will be treated with TAS-102 25mg/m2 p.o. twice daily on days 1-5 and irinotecan 180mg/m2 i.v. on day 1 every 14 days. If ANC <1500/uL on day 1 of a cycle, then G-CSF will be added on day 6 for three days. Institutional standards should be followed in determining whether the subject's body weight at baseline or beginning of each cycle should be used to determine the TAS-102 dosage. Doses must be re-calculated for patients who experience a ≥ 10% change in weight from baseline. Other dose re-calculations for changes in body weight < 10% are permitted per institutional standards.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
TAS-102	None	25 mg/m^2 twice daily	PO taken within 1 hour after completion of morning and evening meals	Days 1-5	2 weeks (14 days)
Irinotecan	Dexamethasone in NS 0.9% IVPB 20MG over 20min , give 30min prior to irinotecan Palonosetron injection 0.25mg IV push over 30 sec , give 30min prior to irinotecan Atropine 0.25mg s.c. every 4 hours prn cholinergic reactions Supportive care for infusion reactions per institutional guidelines	180 mg/m^2 in 250 cc D5W over 90 min	IV	Day 1	

4.1.2 Concomitant Medications

If needed for neutropenia, patients will be taught to self-inject G-CSF at home.

Odansetron 8mg tablets and diphenoxylate hydrochloride and atropine sulfate (Lomotil®) 2.5mg/0.025mg tablets will be prescribed to manage associated nausea/vomiting and diarrhea/cramping at home.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5.5). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Dose Modification Table

Dose Level	Agent	Dose
1 (starting dose)	TAS-102	25 mg/m2
1 (starting dose)	Irinotecan	180 mg/m2
-1 (20 % reduction)	TAS-102	20 mg/m2
-1 (20% reduction)	Irinotecan	144 mg/m2
-2 (40% reduction)	Irinotecan	108 mg/m2

Hematological Toxicities

Hematological Toxicity Dose Reductions for Agent A		
ANC	**Platelets**	**Action**
≥ 1,500/μL	80,000/μL	None.
1000-1499/μL	50,000-79,000/μL	*-1st Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 3 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Resume at same dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 5 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Restart next treatment at 20% reduced dose (TAS-102 20mg/m2 and irinotecan 144mg/m2). *-3rd Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 7 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Restart next treatment at 40% reduced dose (irinotecan 108mg/m2) and discontinue TAS-102.

		-4th Occurrence: Discontinue protocol therapy.
500-999/μL	25,000-49,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 5 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Restart next treatment at 20% reduced dose (TAS-102 20mg/m2 and irinotecan 144mg/m2). *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 7 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Restart next treatment at 40% reduced dose (irinotecan 108mg/m2) and discontinue TAS-102. *-3rd Occurrence*: Discontinue protocol therapy.
<500/μL	<25,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 75,000/μL. Do not replace missed doses. If reason for dose delay was neutropenia, give G-CSF s.c. for 7 days (300mcg for weight <75kg or 480mcg for weight ≥75kg). Restart next treatment at 20% reduced dose (TAS-102 20mg/m2 and irinotecan 144mg/m2). *-2nd Occurrence*: Discontinue protocol therapy.

Non-hematological Toxicities:
Treatment may be delayed up to 4 weeks due to intolerable toxicities grade >1 based on investigator discretion. Imaging studies will need to be performed based on protocol schedule (i.e. not delayed due to dose delay).

Non-hematological Toxicity Dose Reductions		
NCI CTC Grade	**TAS-102**	**Irinotecan**
0-2	No change from original starting dose	No change from original starting dose
3	Hold until resolved to ≤ Grade 2, then reduce **to dose level -1, 20mg/m2**	Hold until resolved to ≤ Grade 2, then reduce **to dose level -1, 144mg/m2**
Second episode of grade 3 or 4 toxicity	Discontinue TAS-102	Hold until resolved to ≤ Grade 2, then reduce **to dose level -2, 108mg/m2**
Third episode of grade 3 or 4 toxicity	Remove subject from trial	Remove subject from trial

4.3 Concomitant Medications/Treatments

TAS-102

Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme. Tipiracil is not metabolized in either human liver or hepatocytes. *In vitro* studies indicated that trifluridine, tipiracil, and FTY did not inhibit the

CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5. *In vitro* studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

Irinotecan

Strong CYP3A4 Inducers
Exposure to irinotecan or its active metabolite SN-38 is substantially reduced in adult and pediatric 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.

Strong CYP3A4 or UGT1A1 Inhibitors
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 and its active metabolite SN-38. Coadministration of Cirinotecan 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.

4.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression as defined radiographic progression by RECIST v1.1 criteria OR death OR symptomatic progression as clinically determined by the treating physician
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Treatment held for more than 28 days
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Patients will be followed every 3 months until death or 18 months after the last patient is enrolled, whichever occurs first. Follow-up after removal from treatment is every 3 months (either clinic visit or phone call).

4.6 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.6 apply. Notify UCI CFCCC via secure email (fdayyani@hs.uci.edu and uci18125@hs.uci.edu), and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.7 Patient Replacement

Patients will not be replaced

5.0 STUDY PROCEDURES

Telemedicine Visits

In-person visits are the preferred study visit method for collection of the assessments and procedures. Study visits conducted by phone or videoconferencing technology (i.e., "virtual" or "telemedicine" visits), including adverse event assessments for patients, may be substituted for protocol-required in-person visits, if the site investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit.

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained as long as these assessments are completed within 28 days prior to registration.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated per protocol. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Screening Confirmation

Patient information should be entered into Oncore within 1 business day of consent. Sites are responsible for assigning subject ID. Sites will be assigned a unique site code. Subject IDs should follow a format with the unique site code followed by the sequential patient ID. For example, Site Code-Sequential Number (i.e. for UCI's first patient the subject ID will be 01-01, UCD's first patient will be 02-01). (Refer to Oncore SOP for Oncore data entry instructions)

5.1.3 Medical history

Complete medical, oncology and surgical history, history of infections

5.1.4 Demographics

Age, gender, race, ethnicity

5.1.5 Review subject eligibility criteria

5.1.6 Review previous and concomitant medications

5.1.7 Physical exam

5.1.8 Vital signs

Temperature, pulse respirations, blood pressure, weight and height (height only at screening)

5.1.9 ECOG Performance status

Refer to Appendix A

5.1.10 Hematology

Complete blood count with differential (CBC)

5.1.11 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.12 Tumor Markers (Optional)

Carcinoembryonic antigen (CEA) and cancer-related antigen 19-9 (CA 19-9).

5.1.13 Pregnancy test (for females of child bearing potential)

See section 3.1.8.1 for definition.

5.1.14 Tumor assessment

To be performed with computed tomography of the chest (preferred with iv contrast) and abdomen/pelvis (preferred with iv contrast and oral contrast). CT abdomen/pelvis may be replaced with MRI Abdomen/pelvis (preferred with iv contrast) per clinical judgement of the treating physician. Additional imaging is indicated at baseline if there is clinical suspicion for other organ involvement (i.e. MRI or CT brain and bone scan).
Imaging is to be performed at baseline within 28 days of starting treatment

5.2 Registration Procedures for participating sites only

Prior to confirmation of registration the below items must be emailed via secure email to the initiating site for review and approval.

1. Redacted source documentation required to confirm eligibility (including but not limited to):
    a. Pathology report
    b. Physical exam including ECOG, medical and oncology history
    c. All screening labs
2. Signed eligibility criteria

All items must be emailed via secure email to (fdayyani@hs.uci.edu and uci18125@hs.uci.edu) UCI CFCCC at least 3 business days before planned treatment start date.

Upon receipt of all required documents, UCI CFCCC will provide confirmation of registration. Subjects may not begin study treatment without confirmation of registration.

5.3 Procedures During Treatment

5.3.1 Prior to Each Treatment Cycle

- Physical exam, vital signs
- ECOG Performance status
- Hematology
- Serum chemistries

- CEA and CA 19-9 (optional) – every 4 weeks
- Adverse events
- Study drug accountability
- Review previous and concomitant medications

Site must maintain an accurate and timely record of dispensing of study drug to subject, and receipt of all study drug and pill diaries.

5.3.2 Within 30 days after treatment termination

- Physical exam, vital signs
- ECOG Performance status
- Hematology
- Serum chemistries
- Adverse events
- Review previous and concomitant medications

5.3.3 Tumor Assessments

- To be completed every 8 weeks (+/- one week) during first year of treatment and every 3 months (+/- one week) after the first year until patient comes off treatment

5.4 Follow-up Procedures

Patients will be followed every three months after completion of (or early withdrawal from) study treatment until death or up to 18 months after the last patient is enrolled, whichever comes first.

- Review of systems and determination of live status if the visit is done in clinic during the patient's standard visit. If conducted by phone, only a determination of live status is needed. A review of systems is not needed if conducted by phone.

5.5 Time and Events Table

If baseline evaluations are conducted within 1 week prior to C1D1 administration of protocol therapy, those assessments do not need to be repeated. Scans must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Baseline -28 to -1 days	C1D1 +/- 2 days	At every cycle (14 days) +/- 1 days Administration of irinotecan -1/+4 days	q 8 Weeks for first year, q 3 months after the first year +/- 1 week	Off Treatment	Follow-up (q 3 months until death or up to 18 months after last patient is enrolled, whichever occurs first) +/- 14 days
Assessment						

Informed Consent	X					
History and PE***	X	X	X		X	
Baseline medical and oncology history	X					
Concomitant Medications	X	X	X		X	
Performance Status	X	X	X		X	
Adverse Events		X	X		X	
Tumor Measurements	X			X		
CT CAP or CT chest/MRI Abd/Pelvis	X			X		
CBC / CMP	X	X	X		X	
CEA and CA 19-9 (optional)**	X		X (every 4 weeks)			
Pregnancy Test*	X					
Review of systems						X****
Study Drug Accountability			X		X	

*Urine or serum pregnancy test is done according to local institutional standard and should be obtained ONLY in women of child-bearing potential.
**This is an optional component and should only be collected if done according to local institutional standards.
*** includes vital signs
****This is only done when patients come in for their standard visit. If the visit is conducted by phone, only determination of live status is needed. A review of systems is not needed when the visit is done by phone.

5.6 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.6.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.6.2 Patient withdraws consent (termination of treatment and follow-up);

5.6.3 Patient is unable to comply with protocol requirements;

5.6.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.6.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.6.6 Treating physician judges continuation on the study would not be in the patient's best interest;

5.6.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.6.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.6.9 Lost to follow-up. If a research subject cannot be located to document survival after 3 attempts including 1 mailed certified letter, the subject may be considered "lost to follow-up."

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

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

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.

6.1.2 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 with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all 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 3 lesions per organ and 6 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 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 or absence of each should be noted throughout follow-up.

6.1.3 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 28 days 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 when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. MRI is also acceptable in certain situations (e.g. for body scans). Scans will be done within 28 days prior to cycle 1 and after that every 8 weeks (+/- 7 days) for the first year, then every 3 months after the first year until end of treatment.

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.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): 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

6.1.4.3 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	

Any	PD*	Yes or No	PD	no prior SD, PR or CR
Any	Any	Yes	PD	

* 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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.5 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 recurrent 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.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression *or death, whichever occurs first.*

Progression is defined as death, radiographic progression as defined in 6.1.4.3, or clinical deterioration attributed to disease progression as judged by the investigator.

6.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

Known hypersensitivity to irinotecan or its excipients. TAS-102 has no known contraindications.

7.1.2 Special Warnings and Precautions for Use

In Study 1, LONSURF (TAS-102) caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Based on animal studies and its mechanism of action, LONSURF (TAS-102) can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m2 twice daily.

Diarrhea and Cholinergic Reactions: Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and may be accompanied by cholinergic symptoms. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can occur. Monitor and replace fluid and electrolytes. Treat with loperamide. Use antibiotic support for ileus and fever. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs.

Myelosuppression: Manage promptly with antibiotic support. Interrupt CAMPTOSAR and reduce subsequent doses if necessary.

Patients with Reduced UGT1A1 Activity: Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

Hypersensitivity: Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if this occurs.

Renal Impairment/Renal Failure: Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

Pulmonary Toxicity: Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred. Interrupt for new or progressive dysnpnea, cough, and fever pending evaluation. If IPD diagnosed, discontinue and institute appropriate treatment as needed.

Embryofetal Toxicity: CAMPTOSAR can cause fetal harm when administered to a pregnant woman.

Patients with Hepatic Impairment: In clinical trials, CAMPTOSAR has not been administered to patients with serum bilirubin > 2.0 mg/dL, or transaminases > 3 times ULN if no liver metastases, or transaminases > 5 times ULN if liver metastases. With the weekly dosage schedule, patients with total bilirubin levels 1.0–2.0 mg/dL had greater likelihood of grade 3–4 neutropenia.

7.1.3 Interaction with other medications

Exposure to irinotecan or its active metabolite SN-38 is substantially reduced in adult and pediatric 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 CAMPTOSAR therapy. Do not administer strong CYP3A4 inducers with CAMPTOSAR 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 CAMPTOSAR 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 CAMPTOSAR therapy. Do not administer strong CYP3A4 or UGT1A1 inhibitors with CAMPTOSAR unless there are no therapeutic alternatives.

7.1.4 Adverse Reactions

TAS-102: Severe Myelosuppression.

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

Serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

Abnormal laboratory values are considered to be AEs only if they are assessed as clinically significant by the investigator.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to the combination of the drugs and entered into OnCore.

7.3 Definitions

7.3.1 Event Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as *any expected or unexpected adverse event* that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before

initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation- a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

7.3.2 Characteristics and Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

- **Expectedness**: AEs can be 'Unexpected' or 'Expected'
  Expected: will be described in the following: Investigational Brochure, package insert, protocol and informed consent, safety profile of other drugs in the same class.
  Unexpected: Not listed in Investigational Brochure or not listed at the specificity or severity that has been observed. Not consistent with the risk information described in the general investigational plan.
  -Unexpected: (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents, such as the protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Attribution of the AE:
  - Definite – The AE is clearly related to the combination of TAS-102 and Irinotecan.
  - Probable – The AE is likely related to the combination of TAS-102 and Irinotecan.
  - Possible – The AE may be related to the combination of TAS-102 and Irinotecan.
  - Unlikely – The AE is doubtfully related to the combination of TAS-102 and Irinotecan.

- Unrelated – The AE is clearly NOT related to the combination of TAS-102 and Irinotecan.

- Start Date
  - Start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator
- Stop Date
  - Stop date of the AE is the date at which the subjects recovered, the event resolved but with sequelae or the subject died.

7.3.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.3.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

Following events do not satisfy criteria for SAE:
Hospitalizations for preplanned procedures
Hospitalization for study-related treatment and procedures

7.3.3.4 Results in persistent or significant disability or incapacity.

7.3.3.5 Is a congenital anomaly/birth defect

7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Reporting Requirements

All unanticipated problems, SAEs, non-compliance, serious or continuing non-compliance, deviations, violations and prospective/planned deviations must be reported to the following entities and entered into OnCore according to the timelines mentioned below. Serious adverse events and adverse events will be collected from the time the research patient begins treatment until 30 days after the end of treatment. All adverse

events/serious adverse events should be followed until resolution or stabilization, or the subject dies or withdraws consent from participation in the study.

Event Type	Coordinating Center/Medical Monitor	UCI IRB	Local IRB	Taiho Oncology*	CFCCC DSMB
Unanticipated Problem	Within 24 hours from date the site is aware of the event, the site should enter this information into OnCore. An email notification should also be sent via email to fdayyani@hs.uci.edu and uci18125@hs.uci.edu.	Within 5 business days submit an Unanticipated Problem Report (UP). Current policy can be found here.	According to local institutional policies and guidelines	Within 24 hours of learning of the event. Submit a MedWatch Form to Taiho via fax (609-750-7371) or email (TAS-102_Safety@taihooncology.com)	Within 5 days from date PI is aware of the event. This information must be reported into OnCore.
AEs and SAEs (non-Unanticipated Problem)	Please refer to section 7.5 for reporting timeframes on AEs and SAEs.	N/A		All other SAEs should be reported within 2 weeks of awareness. Please see section 7.6 below for additional reporting for SAEs.	Please refer to section 7.5 for clarification on reporting timeframes for AEs and SAEs.
Non-compliance	N/A	N/A		N/A	Please refer to section 7.5 for reportable deviations/violations.
Serious or continuing non-compliance	Within 24 hours via email to fdayyani@hs.uci.edu and uci18125@hs.uci.edu	Within 5 business days submit a New Information Report		N/A	Within 5 days from date PI is aware of the event.
Prospective/Planned Deviations	At least 5 business days prior to the event via email to fdayyani@hs.uci.edu and uci18125@hs.uci.edu for approval.	At least 48 hours prior to date the request is needed by. Submit a Prospective Deviation		N/A	At the time of progress review as aggregate reports.

		Request form			
*Patients who become pregnant must be reported along same timelines as SAE. Please reference section 7.6 below in regards additional safety information required to be reported to TAIHO for subjects who become pregnant.					

7.5 Additional Reporting Requirements to CFCCC DSMB and Coordinating Center/Medical Monitor

All adverse events, serious adverse events, violations, deviations and unanticipated problems must be entered into OnCore. All participating institutions must enter the events into OnCore and notifying the coordinator center via email, according to the reporting requirements below.

Adverse Event/ Serious Adverse Events

Event Type	Reporting Timeframe to CFCCC DMSB (Notification is done by entering this information into OnCore within the timelines below)	Reporting Timeframe to Coordinating Center (Notification is done via email to fdayyani@hs.uci.edu and uci18125@hs.uci.edu within the timelines below)
• Unexpected SAE all attributions (unrelated, unlikely, possibly, probably, definite) ▪ Grades 3-5 • Unexpected, Related (possible, probable, definite) AE occurring within 30 days of the last dose of treatment ▪ Grades 3,4	5 business days from date the PI is aware of the event.	Only report if the SAE occurred within 30 days of last dose of treatment. Notification must be 24 hours from date the site is aware of the event.
• Expected AE/SAE, all attributions (unrelated, unlikely, possibly, probably, definite) ▪ Grades 1-5	Progress review as aggregate report. This information must be reported into OnCore.	5 business days from the date the site is aware of the event

Deviations/Violations

Event Type	Reporting Timeframe to CFCCC DSMB	Reporting Timeframe to Coordinating Center (Or other entity monitoring/coordinating the trial)
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points).	5 business days from the date the PI is aware of the event	24 hours from the date the site is aware of the event
Planned deviations (e.g. rescheduling a visit that will be out of window due to holiday)	At the time of progress review as aggregate reports	5 business days from the date the site is aware of the event

Deviation as defined above (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	At the time of progress review as aggregate reports	5 business days from the date the site is aware of the event
All incidents (violations, deviations) that occurred during the study	At the time of progress review, as aggregate reports. Includes violations that were promptly reported (within 5 days) will be included in the aggregate report for review	

7.6 Additional Clinical Reporting Requirements to Taiho

SAE Reconciliation

- Reconciliation shall be performed quarterly as an exchange of Line Listings or other means in English. On a quarterly basis, the institution shall provide to TAIHO a line listing or other means of cumulative SAE received to date. At the end of the Clinical Trial a global reconciliation shall be performed. Please reference contact information when sending this reconciliation. All serious adverse events via a MedWatch Form need to be sent to Taiho Oncology, Inc., via fax: 609-750-7371 or e-mail: TAS-102_Safety@taihooncology.com (please note the underscore between '102' and 'Safety').
- DSUR
    - If requested by Institution, TAIHO shall provide the Institution with the final version of this DSUR report within 15 calendar days after submission to health agencies and ethics committees.
- Pregnancy
    - Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports
        - The Institution will report Exposure During Pregnancy and Lactation, or Paternal Drug Exposure on any Clinical Trial Subject while participating in the Clinical Trial, and following exposure to a TAIHO IMP, to TAIHO (as specified below) using copies of the original Pregnancy Report Form and within two weeks of first becoming aware of the pregnancy or exposure. If the partner of a Clinical Trial Subject becomes pregnant, the Institution may collect information about the pregnancy and birth if the partner agrees.
        - The Clinical Trial Subject will also be followed by the Institution to determine the outcome of the pregnancy (including any premature termination of the pregnancy). Information on the status of the mother and child will be forwarded to TAIHO. The Institution must provide final outcome of pregnancy to TAIHO. If any SAE(s) is observed in Clinical Trail Subject or fetus/child, then SAE(s) must also be reported to TAIHO following SAE Reporting guidelines.
    - Routing of Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports
        - Such reports and Information as outlined above, Including Investigator causality assessments against all concerned TAIHO IMP(s) and English translations where reporting Is from a non-English speaking country, shall be sent:
        - by facsimile to PV CONTACT NUMBER :609-750-7371 OR
        - by e-mail to: TAS-102_Safety@taihooncology.com (please note the underscore between '102' and 'Safety')

8.0 DRUG INFORMATION

8.1 TAS-102

A list of the adverse events and potential risks associated with TAS-102 can be found in Section 7.1.

- Other names for the drug(s):
  trifluridine and tipiracil
  LONSURF

- Classification - type of agent:
  Antimetabolite

- Mode of action:
  TAS-102 is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor.

- Storage and stability:
  - Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
  - LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures. "OSHA Hazardous Drugs". OSHA. (http://www.osha.gov/SLTC/hazardousdrugs/index.html)
  - If stored outside of original bottle, discard after 30 days.

- Protocol dose:
  25mg/m2 twice daily for 5 days every 14 days

- Preparation:
  N/A

- Route of administration for this study:
  Oral

- Incompatibilities:
  None

- Availability:
  Provided by supporter

- Agent Ordering
  Taiho Pharmaceuticals Co., Ltd.
  Sub-site(s) will also order agent from Taiho Pharmaceuticals Co., Ltd. and the agent will ship directly to each site.

- Side effects:
  The most common adverse reactions (≥10%) are anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

- **Agent Accountability**

  Accountability for the study drug at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the study center, use by each patient, and destruction.

These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Taiho.

Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

Patients will receive instructions for home administration of TAS-102 according to the regimen description above. TAS-102 is to be taken within 1 hour after completion of morning and evening meals. If doses of TAS-102 are missed or held, the patient should not make up for the missed doses.

Patients will be given a study medication diary to complete at home for TAS-102. Compliance with the dosing regimen will be assessed based on completion of the drug diary and return of unused drug (or empty bottles).

IMP Destruction
IMP will be destroyed by the sites according to their institutional policies. Destruction logs should be made available to Taiho at the end of the study.
IMP Returns
Taiho will not accept returned IMP.

8.2 Irinotecan

A list of the adverse events and potential risks associated with Irinotecan can be found in Section 7.1.

- Other names for the drug(s):
  CPT-11
  CAMPTOSAR

- Classification - type of agent:
  Topoisomerase I inhibitor

- Mode of action:
  Irinotecan is a derivative of camptothecin that inhibits the action of topoisomerase I. Irinotecan prevents religation of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death.

- Storage and stability:
  - Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

  - The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), 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 CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.

- Protocol dose:
  180 mg/m2 on day 1 every 14 days

- Preparation:
  Dilute in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL according to institutional standards.

- Route of administration for this study:
  Intravenous infusion

- Incompatibilities:
  None

- Availability:
  Commercially available

- Agent Ordering
  Provided locally by the trial site

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

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is a prospective single arm open label multi-institutional study. The primary endpoint is rate of progression free survival at 6 months (PFS-6) after starting treatment. Progression is defined in section 6.1.6.
Secondary endpoints include:

- Overall survival, defined as time from starting treatment to death from any cause.
- Objective response rate in patients with measurable disease as defined in section 6.0
- Safety as described in the adverse events in section 7.0

9.2 Sample Size and Accrual

Based on recently published phase 3 data for advanced GAC, PFS-6 in 2L with optimal treatment is estimated at about 35%[17]. In 3L setting, the largest most contemporary randomized phase 3 trial of TAS-102 vs best supportive care (BSC) defined a PFS-6 of 15% with single agent TAS-102 vs 6% with BSC. The hypothesis is that the combination

of TAS-102 and irinotecan will improve PFS-6 compared to these recent historical controls. To estimate the efficacy, n= 20 patients will be enrolled. If at least n=7 patients have not progressed by 6 months (i.e. observed PFS-6 = 35%), then the observed PFS-6 of 35% will have a one sided lower 95% CI of 17.5%[34]. This means the lower boundary for estimated efficacy is as good as or better than currently available options in 3L setting.

The formula to calculate the lower boundary for the 95% CI is calculated as:

95% confidence interval = effect size ± 1.645 × standard error of the effect size[34]

The assumptions for this study are as follows:

Number of responses to treatment = 7
Number of subjects (N) = 20
Observed proportion (P) = 7/20 = 0.35 (or 35%)
Standard error of the true proportion (SE) = √ [P × (1 − P)]/N = (0.35 × 0.65)/20 = 0.107
Lower boundary 95%CI = P - 1.645 × SE = 0.35 - 1.645 × 0.107 = 0.175

Based on the total number of metastatic GAC seen at UC Irvine (n= 40 in 2017) and UC Davis, it is estimated that up to 5 patients are screened monthly and enrollment is 2 patients per month. Based on these assumptions, accrual goal will be met within 12 months of opening enrollment. Considering a minimum of 6 months of follow-up after the last patient in (to estimate PFS-6), final analysis will be performed up to 18 months after the last patient has started treatment.

9.3 Stopping for Futility:

Efficacy is signaled by at least seven out of 20 being progression-free at six months. Therefore, if none of the first 14 evaluable enrollees is progression-free at six months, futility will be declared.

9.4 Continuous Monitoring for Excess Toxicity:

All participants in trial are monitored for serious toxicity for the duration of their participation in the study. Serious toxicities are given in Section 7. A sequential Pocock-type boundary will inform decisions to continue or stop accrual for excess toxicity, as accrual proceeds (Ivanova, 2005). The table below gives the cumulative number of participants enrolled and the corresponding cumulative number of participants showing serious toxicities that will signal the underlying risk of serious toxicity exceeds 33 percent (5% risk of type-1 error).

Threshold Number of Cumulative Toxicities that Signal Excess Toxicity as a Function of Cumulative Number Enrolled*

Cumulative Number Enrolled	Threshold Number Showing Serious Toxicity to Stop Accrual
1	-
2	-
3	-
4	4
5	5

6	**5**
7	**6**
8	**7**
9	**7**
10	**7**
11	**8**
12	**8**
13	**9**
14	**9**
15	**10**
16	**10**
17	**11**
18	**11**
19	**12**
20	**12**

- Pocock –type boundary with maximum acceptable probability of toxicity set to 33 percent and type-1 risk of five percent (Ivanova, 2005).

9.5 Analyses of Secondary Endpoints and Ad-Hoc comparisons

Participants will be characterized on host and demographic factors, with continuous measures given as means or medians and categorical measires given as percents. Consistent with the phase-II nature of the research, we will examine the data in many ways to illuminate future research priorities. We will estimate survival curves for progression-free and overall survival, and attempt to identify systematic differences between those who respond to treatment and those who do not. Survival will be estimated by Kaplan-Meier methods. If assumptions are met, we will model survival using Cox proportional- hazards, eliminating ties by subtracting a small, randomly generated amount from the observed times . As may be indicated, we will transform data to correspond better to analytic requirements, using logit transforms for percent data and log or some other approach for continuous measures. As the goals of these secondary analyses are to inform decisions about future research, no formal statistical hypothesis-testing will be done, probabilities from statistical tests will augment clinical judgment in interpretation, and we will not regard overall, study-wise, error rates for these secondary analyses.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by their own institution's COI committee. All investigators will follow the University conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 If a blind or illiterate person who cannot read and write is enrolled into the trial, they must be able to understand the implications of the participating in the study and be able to indicate approval or disapproval to the study entry. An impartial third party is required to witness the entire consent process and will also need to sign the consent form along with the subject and consenting investigator. Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to UCI CFCCC.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosure statements for the PI and participating investigators, as necessary
- A copy of the IRB-approved consent form and HIPAA form
- IRB member list with their occupations and institutional affiliations or a general assurance number will be acceptable.
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Signed protocol signature page

10.4 Data Completion

10.4.1 OnCore Date Entry

Data, as indicated by Sponsor, will be entered into OnCore – UC Irvine's Clinical Trial Management system. The Investigator is responsible for ensuring all entries are accurate and correct. The Investigator must maintain accurate source data that support OnCore data entry. All data will be entered as per Sponsor's specification and timeframe.

10.4.2 Recording of Events

All investigator initiated treatment trials require that adverse events, serious adverse events, deviations, and unanticipated problems be entered into the clinical trial management system (CTMS), OnCore. All entries must be entered in OnCore within the timelines specified in section 7.4-7.6 of being aware of the adverse event, serious adverse event, violation, deviation, or unanticipated problem. Adverse events and violations/deviations and adverse events that are unanticipated problems that require

prompt reporting to the DSMB must be entered into OnCore according to the timelines as specified in section 7.4-7.6

10.5 Data and Safety Monitoring/Auditing

10.5.1 Quality Assurance

Quality assurance activities will be conducted as per UC Irvine Chao Family Comprehensive Cancer Center's Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC Data and Safety Monitoring Board in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site by the Quality Assurance Officer. Participating sites may follow their own internal quality assurance policies in order to maintain patient safety and data integrity oversight. The investigator must permit study-related monitoring/auditing and provide access to study-related materials.

10.5.2 Data and Safety Monitoring Plan

This is a **risk level 2 study**, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is a study in which the IND is exempt by the FDA.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, all adverse events, deviations, and violations will be reported promptly to the DSMB for review according to section 7.4.

10.6 Protocol Deviations

All protocol deviations will be reported in accordance with UCI IRB, UCI CFCCC Stern Center policies and the participating site's IRB policies.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Due to restrictions instituted during the COVID-19 pandemic, planned clinic visits may be performed according to local institutional policy for natural disasters or a pandemic.

Whenever possible, on-site clinic visits will be replaced by telemedicine visits between the clinic staff and on-study patients.

Emergency Modifications may be enacted if needed to ensure the safety, and well-being of the study patients. Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. Please refer to Section 7.3 for more information on how protocol deviations and violations are defined. It will also provide instructions on when and who to contact and obtain approval from for prospective deviations. Protocol deviations should also be reported to UCI IRB and DSMB.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

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

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

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

Pill Diary

TAS-102 Patient Pill Diary

Patient Name: _____ **Patient MRN:** _____ **Subject ID:** _____ **Cycle:** _____

Take this number of TAS-102 15mg tablets in morning and evening: _____
Take this number of TAS-102 20mg tablets in morning and evening: _____

Day 1 (Same day as Irinotecan infusion)		Date: _____
Number of tablets taken in morning:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time morning dose taken: _____
Number of tablets taken in evening:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time evening dose taken: _____
Comments:		

Day 2		Date: _____
Number of tablets taken in morning:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time morning dose taken: _____
Number of tablets taken in evening:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time evening dose taken: _____
Comments:		

Day 3		Date: _____
Number of tablets taken in morning:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time morning dose taken: _____
Number of tablets taken in evening:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time evening dose taken: _____
Comments:		

Day 4		Date: _____
Number of tablets taken in morning:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time morning dose taken: _____
Number of tablets taken in evening:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time evening dose taken: _____
Comments:		

Day 5		Date: _____
Number of tablets taken in morning:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time morning dose taken: _____
Number of tablets taken in evening:	15mg TAS-102 tablet: ____tablets taken 20mg TAS-102 tablet: ____tablets taken	Time evening dose taken: _____
Comments:		

TAS-102 Dosing Instructions: 25mg/m² twice daily for 5 days every 14 days.

TAS-102 will be taken **within 1 hour after completion of morning and evening meals.**
If you forget to take a dose, **you should not make up for missed doses.** Take the next dose at the next scheduled time.
Please record the **date and times you take TAS-102.**
Please remember to bring your bottles and Patient Pill Diary to each clinic visit.
If you experience any symptoms, please do not take the dose and contact the Study team.
(Study Coordinator:_____, Phone Number:_____)