Mayo Clinic Cancer Center

Phase II Trial of Trifluridine/Tipiracil (FTD/TPI (TAS-102)) in Biliary Tract Cancers

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Drug Availability
Supplied Investigational Agents: FTD/TPI (TAS-102; Lonsurf®) IND 135110 EXEMPT

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist/Data Manager Phone: [redacted] E-mail: [redacted]
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*No waivers of eligibility allowed

Table of Contents

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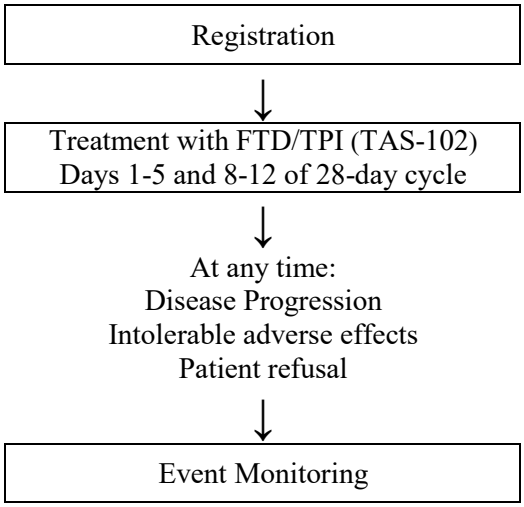
Schema



Cycle = 28 days

Generic name: trifluridine/tipiracil (FTD/TPI; TAS-102)
Brand name(s): Lonsurf®
Mayo Abbreviation: *TBD*
Availability: Mayo Clinic Pharmacy

1.0 Background

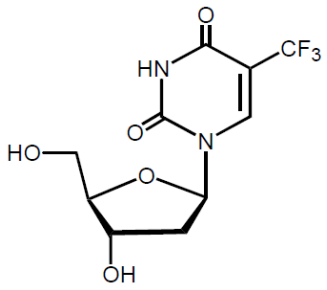
1.1 Biliary Tract Cancer

Biliary tract cancers (BTCs) include malignant intrahepatic and extrahepatic cholangiocarcinomas, gallbladder and ampullary cancers. It is estimated that 11,420 patients will be diagnosed with BTCs in 2016 in United States.(Siegel, Miller et al. 2016) Globally, both the incidence and mortality from BTCs is increasing with much higher incidences in a few regions. Most patients with BTCs present with unresectable or metastatic disease. Even in patients with resectable disease, the recurrences are frequent. The median survival of patients with advanced BTCs is less than 4.5 months.(Glimelius, Hoffman et al. 1996; Sharma, Dwary et al. 2010) Combination gemcitabine and cisplatin has been established as first line standard of care treatment based on the Advanced Biliary Tract Cancer-02 (ABC-02) phase III trial.(Valle, Wasan et al. 2010) Unfortunately, the median overall survival (OS) was less than a year in this trial. There is no FDA approved second line option for patients with advanced BTCs. There is a huge unmet need to develop novel therapies to improve outcome for patients diagnosed with BTCs.

1.2 FTD/TPI (TAS-102; trifluridine/tipiracil)

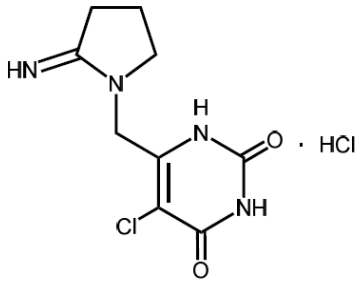
FTD/TPI (TAS-102; Lonsurf; trifluridine/tipiracil) is a novel oral nucleoside consisting of α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1*H*,3*H*)-pyrimidinedione hydrochloride (TPI) at a molar ratio of 1:0·5. The active antitumor component of FTD/TPI is FTD which inhibits thymidylate synthase and is incorporated into DNA in tumor cells.

Trifluridine, an antineoplastic thymidine-based nucleoside analogue, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine, and has the following structural formula:



Trifluridine has a molecular formula C10H11F3N2O5 and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1), and has the following structural formula:



The clinical efficacy and safety of FTD/TPI was evaluated in an international, randomized, double-blind, placebo-controlled study (RECOURSE study) conducted in patients with previously treated metastatic colorectal cancer (CRC). A total of 800 patients were randomized 2:1 to receive trifluridine/tipiracil (n = 534) plus best supportive care (BSC) or matching placebo (n = 266) plus BSC. Patients received 35 mg/m2 trifluridine/tipiracil or matching placebo orally twice daily after meals on Days 1–5 and 8–12 of each 28-day cycle until disease progression or unacceptable toxicity. The primary efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). Patient demographics and baseline characteristics were similar between groups. The median age was 63 years, 61% were male, and 58% and 35% were White and Asian respectively. The RECOURSE study met the efficacy endpoints of significant improvement in OS and PFS compared to placebo in patients with refractory mCRC whose disease had progressed after standard therapies. The median OS was 7.1 months with FTD/TPI compared to 5.3 months in placebo group (Hazard ratio: 0.68; 95% CI: 0.56-0.78). Median PFS was 2 months in FTD/TPI group and 1.7 months in placebo group (Hazard ratio: 0.48; 95% CI: 0.41-0.57). The objective response rate was 1.6%. Common adverse events included fatigue, nausea, vomiting, diarrhea, anorexia and cytopenias. Table 1 lists the common adverse events associated with FTD/TPI.

Table 1: Adverse events (>5%) in the RECOURSE study occurring more commonly than placebo.

Adverse Events	**Trifluridine/tipiracil**		**Placebo**	
	All Grades	**Grade 3-4**	**All Grades**	**Grades 3-4**
Gastrointestinal Disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal Pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decrease appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

Adverse Events	Trifluridine/tipiracil		Placebo	
	All Grades	Grade 3-4	All Grades	Grades 3-4
Blood and lymphatic disorders				
Anemia	77%	18%	33%	3%
Neutropenia	67%	38%	1%	0%
Thrombocytopenia	42%	6%	8%	<1%

1.3 Study Rationale

Fluoropyrimidine-based regimens are frequently utilized for treatment of BTCs despite the fact that they are not FDA approved.(Huggett, Passant et al. 2014; Rogers, Law et al. 2014) On retrospective analysis, fluoropyrimidine based treatments have shown to be associated with improved survival.(Huggett, Passant et al. 2014) However, there are only limited small prospective studies reported utilizing fluoropyrimidines. Single agent 5-fluorouracil has yielded response rates of 10-32% with median OS of approximately 6 months as a first line treatment.(Falkson, MacIntyre et al. 1984; Choi, Choi et al. 2000) Addition of other chemotherapy agents including platinum agents and irinotecan are associated with better response rates at the expense of increase toxicities. However, none of the combination regimens have consistently demonstrated superiority over single agent fluoropyrimidine alone.(Hezel and Zhu 2008) The combination of 5-flourouracil and irinotecan demonstrated a response rate of 10% in a study of 30 patients.(Feisthammel, Schoppmeyer et al. 2007) Another study evaluating the combination of 5-fluorouracil and cisplatin reported response rates of 24% with median survival of 10 months in the first line setting.(Ducreux, Rougier et al. 1998) Capecitabine and cisplatin combination demonstrated median progression free survival ranging from 2.5-3.7 months in untreated advanced BTCs.(Kim, Chang et al. 2003; Hong, Lee et al. 2007) S-1, a combination of tegafur (that is converted to 5-flouorouracil in the liver), 5-chloro-2,4-dihydroxypyridine (inhibitor of dihydropyrimidine dehydrogenase) and potassium oxonate has also shown activity in advanced BTCs as a single agent.(Ueno, Okusaka et al. 2004) These studies suggest there may be a role for fluoropyrimidines in advanced BTCs.

The active antitumor component of FTD/TPI is FTD is incorporated into DNA in tumor cells. FTD has also shown to inhibit thymidylate synthase in tumor xenograft models. The incorporation into DNA is known to have antitumor effects, because inhibition of thymidylate synthase caused by oral FTD rapidly disappears after the drug's elimination. The mechanism of action of FTD/TPI is somewhat dependent on its dosing schedule.(Lenz, Stintzing et al. 2015) Greater inhibition of thymidylate synthase was observed with continuos infusion of FTD than twice daily dosing.(Tanaka, Sakamoto et al. 2014) In contrast, the level of incorporation into DNA was higher with twice-daily oral dosing. Thus, clinically with twice daily dosing schedule of FTD/TPI, incorporation into DNA is the primary mechanism of action for antitumor effects. TPI is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades FTD and helps maintain adequate plasma concentration needed for its activity.

The mechanism of FTD/TPI is thus different from single agent fluoropyrimidine and has shown activity in both fluoropyrimidine sensitive and resistant tumors.(Emura, Nakagawa et al. 2004; Emura, Suzuki et al. 2004)The primary mechanism of resistance to 5-fluorouracil seems to be decrease in activity of orotate phosphoribosyltransferase resulting in decrease in cellular uptake of 5-fluorouracil in the RNA fraction.(Murakami, Kazuno et al. 2000) There is no change in the levels of thymidylate synthase. FTD has demonstrated activity in 5-fluorouracil resistant colorectal and gastric cell lines as

activity of FTD/TPI is not dependent upon orotate phosphoribosyltransferase.(Lenz, Stintzing et al. 2015) Autophagy has also shown to play a role in resistance to 5-fluorouracil but not to FTD.(Bijnsdorp, Peters et al. 2010). These studies suggest that FTD/TPI may have better clinical activity in advanced BTCs than fluoropyrimidine alone.

1.4 Study Design

This is the single arm phase II trial to assess the efficacy of FTD/TPI in advanced, refractory BTCs. The primary end point of this study is 16-week progression-free survival. If 30% of patients remain progression-free at 16-weeks, this trial will be considered a success warranting bigger trials We will accrue 25 evaluable patients using a single stage design. The total sample size of this study is 28 to account for 3 possible non-evaluable subjects.

Patient will receive FTD/TPI at the dose of 35 mg/m^2 on Days 1-5 and 8-12 of 28-day cycle. Patient will receive treatment until disease progression or unacceptable toxicities. Patients will undergo restaging scans every 2 cycles. Subjects will be monitored for adverse events from the beginning of the study drug to 28 days after the last dose. We will collect blood samples for determination of cell free DNA and circulating tumor cells at baseline, after 2 cycles and at progression.

2.0 Goals

2.1 Primary Goal

Determine the efficacy of FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma using progression-free survival at 16 weeks.

2.2 Secondary Goals

2.21 Assess the safety and tolerability of FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma through adverse event monitoring.

2.22 Further explore the efficacy of FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma by overall response rates, progression-free survival, and overall survival.

2.3 Correlative Research

2.31 Determine if circulating tumor cells (CTCs) or cell-free DNA (cfDNA) at baseline correlates with prognosis or response to therapy.

2.32 Determine if change in CTCs or cfDNA correlates with efficacy endpoints.

2.33 Determine if different mutational status of the tumor will affect efficacy endpoints.

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Histological confirmation of advanced biliary tract cancers including cancers originating in gallbladder who have received at least one line of systemic anticancer therapy.
Note: Patients who have either progressed or are intolerant to the prior therapy can be included in this study.

3.13 Measurable disease as defined in Section 11.0.

3.14 ECOG Performance Status (PS) 0 or 1 (Appendix I).

3.15 The following laboratory values obtained ≤21 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Total bilirubin ≤1.5 × upper limit of normal (ULN)
- Aspartate transaminase (AST) or Alanine transaminase (ALT) ≤3 × ULN
- Creatinine ≤1.5 × ULN

3.16 Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

3.17a Provide written informed consent.

3.17b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.17c Willing to provide blood samples for correlative research purposes.

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an agent that has potential genotoxic, mutagenic and teratogenic effects:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception for at least 3 months after the last dose of the study drug

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.24 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.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm ≤21 days prior to registration..

3.26 Receiving any anticancer therapy for biliary tract cancer ≤21 days prior to registration.

3.27 Other active malignancy requiring treatment in ≤6 months prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.

3.28 History of myocardial infarction ≤6 months prior to registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

4.0 Study Schedules

4.1 Test schedule

	Screening	Active Treatment			End of Treatment	
Tests and Procedures	≤21 days prior to registration	D1 of each cycle	D8 of Cycle 1 only	Every 2 cycles	End of Treatment	Safety follow up: 30 days post treatment
window		±7 days	±3 days	±7 days	±7 days	±7 days
History and exam, Wt, PS	X	X	X		X	X
Height	X					
Adverse event assessment	X	X	X		X	X
Pregnancy test[1]	X					
Hematology: CBC with differential	X	X	X		X	X
Chemistry[2]	X	X	X		X	X
CA19-9[3]		X		X[4]	X	
Tumor imaging - CT (chest, abdomen, pelvis) or CT (chest) and MRI (abdomen, pelvis)	X[5]			X[6]	X	
Research blood specimens[7,R]		X			X	
Patient Medication Diary (Appendix II) [8]		X				

Cycle = 28 days; R=Research funded

[1] For persons of childbearing potential only. Must be done ≤7 days prior to registration.
[2] Chemistry: Na, K, albumin, AST, ALT, alkaline phosphatase, total and direct bilirubin, creatinine
[3] Baseline prior to Cycle 1, Day 1, then every two cycles or as clinically indicated
[4] To be performed ≤7 days prior to planned Day 1 of odd numbered cycles (Cycle 3, 5, 7 etc) or as clinically indicated
[5] Can be performed ≤28 days prior registration
[6] To be performed ≤7 days prior to planned Day 1 of odd numbered cycles (Cycle 3, 5, 7 etc) or as clinically indicated
[7] Research blood specimens to be collected on Cycle 1 Day 1 (or any time between registration and Cycle 1 Day 1), Cycle 3 Day 1 and end of treatment (see Section 14.0)
[8] The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 3 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor:

None

6.0 Registration Procedures

6.1 To register a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative studies

A mandatory translational research component is part of this study; the patient will be automatically registered onto this component (Sections 3.17c, 14.0).

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤28 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9 Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

All patients will receive study medication FTD/TPI (TAS-102) in a 28-day treatment cycle. FTD/TPI (TAS-102) is available in 15 and 20 mg tablets. Study medication should be administered as outlined in the protocol.

7.1 Treatment Schedule

Use actual weight or estimated dry weight if fluid retention. BSA needs to be rounded to 2 decimal places. The study medication needs to be stored at the room temperature.

FTD/TPI (TAS-102) is administered in 28-day cycle. The starting dose of FTD/TPI (TAS-102) is 35 mg/m^2. The study drug will be administered on Days 1-5 and 8-12 of 28-day cycle. The treatment regimen consists of following:

Agent	Route	Day	Starting Dose
FTD/TPI (TAS-102)	PO	1-5	35 mg/m^2/dose twice daily
None		6-7	No treatment
FTD/TPI (TAS-102)	PO	8-12	35 mg/m^2/dose twice daily
None		13-28	No treatment

The study drug dose calculation based on BSA is as follows:

FTD/TPI (TAS-102) **dose (twice daily)**	**BSA (m^2)**	**Dosage in mg (twice daily)**	**Tablets per dose**	
			15 mg	**20 mg**
35 mg/m^2	<1.07	35	1	1
35 mg/m^2	1.07-1.22	40	0	2
35 mg/m^2	1.23-1.37	45	3	0
35 mg/m^2	1.38-1.52	50	2	1
35 mg/m^2	1.53-1.68	55	1	2
35 mg/m^2	1.69-1.83	60	0	3
35 mg/m^2	1.84-1.98	65	3	1
35 mg/m^2	1.99-2.14	70	2	2
35 mg/m^2	2.15-2.29	75	1	3
35 mg/m^2	≥2.30	80	0	4

7.2 Self-administration statement

Patients can be instructed in administration techniques and granted treatment independence. Any missed doses will be recorded. Patients will be instructed to:

- Store the study medication at room temperature
- Take the study medication on schedule
- Report any missed doses
- Take study medication within 1 hour after completing morning or evening meals with a glass of water
- If the patient vomits after taking the study medication, the dose should not be replaced.
- Return the unused medication at end of every cycle.
- If a patient forgets to take a dose (morning or evening), the missed dose should not be made up

7.3 Treatment by local medical doctor

Treatment by a local medical doctor (LMD) is not allowed on this study.

8.0 Dosage Modification Based on Adverse Events

For the first two cycles, strictly follow the modifications in this table. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. Under exceptional circumstances, at the investigator discretion (in consultation with principal investigator) dose modifications or treatment interruption or continuation can be considered if it's considered to be in the best interest of a patient. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. The criteria for dose modifications of FTD/TPI (TAS-102) for toxicities will be considered if an adverse event is at least possibly related to FTD/TPI (TAS-102).

NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 4.0* will be utilized for dose modification unless otherwise specified. Upto three dose level reductions are allowed. Once reduced for an adverse event, no increase in dose of TAS-102 will be allowed.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.1 Dose Levels (Based on Adverse Events in Section 8.*2* and 8.3)

8.11 FTD/TPI (TAS-102) dose levels

Dose Level	FTD/TPI (TAS-102)
0*	35 mg/m^2/dose
-1	30 mg/m^2/dose
-2	25 mg/m^2/dose
-3	20 mg/m^2/dose

*Dose level 0 refers to the starting dose.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels –1, –2 and -3) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

8.12 The study drug dose calculation after dose modifications based on BSA is as follows:

FTD/TPI (TAS-102) dose (twice daily)	**BSA (m^2)**	**Dosage in mg (twice daily)**	**Tablets per dose**	
			15 mg	**20 mg**
Dose Level -1 (30 mg/m^2)				
	<1.09	30	2	0
	1.09-1.24	35	1	1
	1.25-1.39	40	0	2
	1.40-1.54	45	3	0
	1.55-1.69	50	2	1
	1.70-1.94	55	1	2

FTD/TPI (TAS-102) dose (twice daily)	BSA (m^2)	Dosage in mg (twice daily)	Tablets per dose	
			15 mg	20 mg
	1.95-2.09	60	0	3
	2.10-2.28	65	3	1
	≥2.29	70	2	2
Dose Level -2 (25 mg/m^2)				
	<1.10	25[1]	2 (PM) [1]	1 (AM) [1]
	1.10-1.29	30	2	0
	1.30-1.49	35	1	1
	1.50-1.69	40	0	2
	1.70-1.89	45	3	0
	1.90-2.09	50	2	1
	2.10-2.29	55	1	2
	≥2.30	60	0	3
Dose Level -3 (20 mg/m^2)				
	<1.14	20	0	1
	1.14-1.34	25[1]	2 (PM) [1]	1 (AM) [1]
	1.35-1.59	30	2	0
	1.60-1.94	35	1	1
	1.95-2.09	40	0	2
	2.10-2.29	45	3	0
	≥2.30	50	2	1

[1]For the total daily dose of 50 mg, patients should take 1 × 20-mg tablet in the morning and 2 × 15-mg tablets in the evening.

8.2 Dose Modifications Based on Interval Adverse Events during the cycle

8.21 For non-specified adverse events the following criteria for dose modification will be used for adverse events occurring during the cycle:

CTCAE Adverse Events[1]	**Action for** FTD/TPI (TAS-102)
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Hold treatment until resolved to ≤Grade 2 Reduce the dose by one dose level

[1] Except for alopecia, clinically insignificant laboratory abnormalities, and inadequately treated nausea, vomiting and diarrhea.

8.22 For specified adverse events following criteria for dose modification will be used for adverse events occurring during the cycle:

CTCAE Adverse Events	**Action for** FTD/TPI (TAS-102)
Neutrophil count decreased <500/mm^3	Hold treatment for the duration of the cycle
Platelet count decreased <50,000/mm^3	Hold treatment for the duration of the cycle

G-CSF can be used in this trial at the discretion of treating physician (see Section 9.2)

8.3 Dose Modifications at the Time of Retreatment (Beginning of new cycle)

8.31 The dose modification guidelines for FTD/TPI (TAS-102) for non-specified adverse events on **Day 1** of each cycle of the treatment is mentioned below:

CTCAE Adverse Events[1]	**Action for** FTD/TPI (TAS-102)
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Delay Treatment until resolve to ≤Grade 2. Reduce the dose by one dose level.

[1] Except for alopecia, clinically insignificant laboratory abnormalities, and inadequately treated nausea, vomiting and diarrhea.

8.32 The dose modification guidelines for FTD/TPI (TAS-102) for specified adverse events on **Day 1** of each cycle of the treatment is mentioned below:

CTCAE { Adverse Events	**Action for** FTD/TPI (TAS-102)
Neutrophil count decreased <1,500/mm^3	Delay treatment by 1 week Reduce dose by one dose level for next treatment only if febrile neutropenia or uncomplicated Grade 4 neutropenia occurs that requires more than one week delay in start of next cycle
Platelet count decreased <75,000/mm^3	Delay treatment by 1 week Reduce dose by one dose level for next treatment only if Grade 4 thrombocytopenia occurs that requires more than one week delay in start of next cycle

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form and submit to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Submit to [redacted] Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure.

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **AEs Experienced Utilizing Investigational Agents / Commercial Agent(s)**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

  or

  http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

  Instructions for completing the MedWatch 3500A:
  http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Gastrointestinal disorders	Nausea	≤Grade 3
	Vomiting	≤Grade 3
	Diarrhea	≤Grade 3
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:
- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 Expedited Reporting Requirements for IND/IDE Agents

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

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

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 for investigational agents or commercial/investigational agents on the same arm.

Submit to Taiho Oncology Inc. Pharmacovigilance contact information for IIT sites to report SAEs (email to #1 preferred):

1. [redacted] (please note the underscore between [redacted])
2. FAX: [redacted]
3. Hotline phone: [redacted] (phone number is only to ask questions, not to report SAEs)

For commercial agents:

Submit form MedWatch 3500A to the FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at 1-800-332-0178 or online at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

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

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Per NIH OBA Appendix M, should a patient die during the study or study follow-up, no matter what the cause, the study doctor will ask the patient's family for permission to perform an autopsy. If permission is granted, a copy of the autopsy report will be sent to the sponsor after all identifying information has been removed. An autopsy will help the researchers learn

more about the safety and efficacy of the treatment. Patients should advise their families about their wishes regarding autopsy.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

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

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for a female patient should be reported **within 24 hours** from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing it to Taiho Pharmacovigilance or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the initial Pregnancy Form must be submitted by faxing an updated Pregnancy Form to Taiho Pharmacovigilance or designee.

If outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to Taiho Pharmacovigilance or designee.

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
Gastrointestinal Disorders	Abdominal Pain	X	X
	Baseline # of stools	X	
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X
General disorders	Fatigue	X	X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Metabolism and nutrition disorders	Anorexia	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Taiho Oncology Additional Event Reporting Instructions

Serious adverse events must be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (including narrative description, medical history and concomitant medications) needs to be provided with careful consideration regarding causality and serious criteria.

After the initial SAE notification to Taiho Pharmacovigilance or designee, follow-up SAE information will be submitted each time that important follow-up information (e.g., diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

All SAEs **within** the follow-up window (e.g., within 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier) established in the protocol will be reported to Taiho Pharmacovigilance or designee.

If serious medical occurrences including deaths **outside** the follow-up window established by the protocol are reported to or observed by the investigator that he/she believes are related to the administration of the investigational product, it is the investigator's responsibility to report this occurrence to Taiho Pharmacovigilance or designee.

10.81 Reporting of Deaths

All deaths occurring through the 30-day follow-up period must be reported to Taiho Pharmacovigilance or designee **within 24 hours**.

1. Death due to disease progression:

Disease progression (radiologic or clinical) with the outcome of death will not be reported as an SAE. However, relevant signs, symptoms and complications of disease progression (radiologic or clinical) must be reported as an AE or SAE if it meets the serious criteria. It should be indicated that the signs, symptoms and complications are related to disease progression.

2. Death due to other causes:

   Deaths due to reasons other than disease progression must be reported as an SAE.

   Death is not an acceptable AE/SAE term. Death is an outcome of an SAE.

When reporting a death, the investigator will be required to identify which of the following best describes the category of death:

- Toxicity for study drugs
- Radiologic disease progression
- Clinical disease progression
- Other causes

10.82 Disease Progression

How to report events related to non-fatal disease progression:

a. Disease progression is not an acceptable AE term. In cases of non-fatal disease progression, the relevant signs, symptoms and complications should be reported as an AE unless they meet the serious criteria. If any of the signs, symptoms and complications meets any of the serious criteria, they should be reported as an SAE. In both cases it should be indicated whether the signs, symptoms and complications are related to disease progression.
b. Radiologic disease progression without relevant signs, symptoms and complications will **not** be reported as an AE or SAE.

10.83 Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for a female patient should be reported **within 24 hours** from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing it to Taiho Pharmacovigilance or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the initial Pregnancy Form must be submitted by faxing an updated Pregnancy Form to Taiho Pharmacovigilance or designee.

If outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to Taiho Pharmacovigilance or designee.

10.84 Medication Errors

A **medication error** is defined as any accidental incorrect administration of a medicinal product. The error may be related to the administration of a wrong medication, nature of the medication, route of administration, dosage or

frequency of the treatment as specified in this protocol (including omission of one or more administrations).

- Medication errors with study drugs and concomitant medication treatment will not be reported unless they result in an AE.
- Medication errors with study drugs that result in an overdose will be reported as an AE.
- Medication errors with study drugs that do not result in an AE should be handled as follows:
  - If it results in the omission of an administration, an incorrect dose (relative to that specified in this protocol), or the administration of more than the prescribed dose (but does not meet the overdose criteria), it will be identified through the recording of study drug accountability data in the CRF and does not need to be reported as an AE.
  - If it results in an overdose, incorrect route of administration, or administration of an incorrect study drug, it will be reported as an AE.

Based on the above criteria, medication errors that are captured as an AE on the CRF should be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of its occurrence following the same process as described for the SAEs even if it does not meet any of the criteria of an SAE.

10.85 Overdose

An overdose with FTD/TPI (TAS-102) for this clinical trial is defined as:

- Taking a dose beyond the recommended dose in 1 day or beyond the recommended total dose in each cycle.

An accidental or intentional overdose with FTD/TPI (TAS-102) regardless of whether it is associated with an AE (even if not fulfilling a seriousness criterion) is to be captured as an AE on the CRF and reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of its occurrence following the same process as described for the SAEs.

There is no known antidote available in case of FTD/TPI (TAS-102) overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

An accidental or intentional overdose for concomitant medication should only be reported if it is associated with an AE.

To Report to Taiho Pharmacovigilance: [redacted]

11.0 Treatment Evaluation

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (*Eisenhauer et al*). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

a) New lesion that has developed after radiation is completed

b) Definite increase in the size of the previously irradiated lesion.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

A subsequent scan must be obtained 8 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

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.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The

BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (CR):All of the following must be true:

a. Disappearance of all target lesions.
b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the

MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.
b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

11.441 For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Prior treatment: 1 vs 2 vs 3+

12.4 Primary site of tumor: Gallbladder vs intrahepatic vs extrahepatic biliary tract cancer

12.5 Degree of differentiation: Well vs moderately vs poorly differentiated vs undifferentiated/anaplastic vs cannot be assessed/unknown

12.6 ECOG performance status: 0 vs 1

12.7 Prior treatment with fluoropyrimidine based regimen: Yes vs no

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.0. Treatment decision during event-monitoring phase is at the discretion of the treating physician.

13.4 Duration of therapy for CR, PR or SD

Patients who achieve a CR, PR or SD will continue to receive treatment per protocol until they develop PD or unacceptable toxicity.

13.5 Definition of Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 4.0 of the protocol.

13.6 Definition of Major Violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4.0 of the protocol.

13.7 Definition of Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.8 Patient removal from study

Patients may be removed from treatment on this study for any of the following reasons:

- Progression of disease
- Noncompliance with study procedures
- Patient’s request to withdraw from the study or refusal of further therapy
- Unacceptable adverse events: A patient may be removed from the study for any complication of treatment that the investigator feels is life threatening
- Investigator discretion
- Dose delay >28 days for treatment related AE NOTE: If a patient has clinical benefit from the study treatment, patient may continue on study at investigator discretion

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Biospecimen	Mandatory or optional	Timing	Correlative science justification	Information on submission
EDTA tube (whole blood)	Mandatory	Serial draws	circulating biomarker work	Section 14.2 and 14.3
Streck cfDNA BCT (whole blood)	Mandatory	Serial draws	cfDNA based studies	Section 14.2 and 14.3
AccuCyte tube (whole blood)	Mandatory	Serial draws	CTC based studies	Section 14.2 and 14.3

14.2 Collection and Processing

14.21 Sample collection should be restricted to Monday – Thursday. However, if the subject can only be seen on a Friday, please contact the Biospecimen Resource Manager for additional instructions (see protocol resource pages for contact information).

14.22 Specimen tube(s) must be labeled with the protocol number, study patient ID number, and the time and date of the blood draw.

14.23 Blood/blood products must be collected and shipped according to specific instructions provided in the kit and the table below.

Collection tube	Volume to collect per tube (number of tubes to collect)	Blood product being processed and submitted	Timepoints			Additional processing required at site	Storage and shipping conditions
			Baseline Cycle 1 Day 1**	Cycle 3 Day 1	End of treatment		
EDTA tube (purple top)	10 mL (1)	Whole blood for DNA, buffy coat, WBCs and plasma*	X	X	X	Yes	Frozen on dry ice
Streck cfDNA BCT tube	10 mL (2)	Whole blood for platelet poor plasma	X	X	X	None	Ship same day at ambient temperature
AccuCyte tube	10 mL (1)	Whole blood for CTCs	X	X	X	None	Ship same day at ambient temperature

* DNA extraction from whole blood to be done at each site

** Baseline samples may be procured any time after registration and prior to treatment on C1D1

14.24 Shipping

14.241 Verify that ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system within 7 days after specimen collection (see Forms Packet).

14.242 Specimens collected in the Streck cfDNA BCT and AccuCyte tubes should be shipped at ambient temperature on the same day they are drawn.

14.243 Specimens collected in EDTA tubes should be processed for DNA from whole blood, a buffy coat back up and plasma aliquots then stored frozen. NOTE: DNA extraction must be done at site where it's collected.

14.244 Samples should be shipped to BAP Freezer Mondays – Thursdays according to kit instructions. Samples should not be sent on weekends or just prior to federal holidays. (If samples can only be shipped on Fridays, please contact the Biospecimen Resource Manager for additional instructions.)

14.25 Processing

BAP Shared Resource will process the specimens.

14.251 Double spun, platelet poor plasma will be derived from the Streck cfDNA BCT tubes using established laboratory processes, and stored at -70ºC by BAP.

14.252 DNA will be extracted from whole blood, and white blood cells and plasma will be derived from remaining blood from the EDTA tubes, divided into aliquots, and stored at -70ºC by BAP according to patient consent information.

14.253 Whole blood collected in the AccuCyte tubes will be provided directly to Dr. Minetta Liu's laboratory at Mayo Clinic Rochester to isolate and retain CTCs.

14.254 As part of ongoing research at the Mayo Clinic, we will retain residual whole blood, white blood cells, CTCs, DNA, and plasma for future research studies, according to patient consent information. Samples will be stored until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented for IRB review and approval.

14.3 Background and Methodology

14.31 ctDNA

Detection of cancer specific mutations from the peripheral blood is an area of active investigation in many different type of cancers. An accumulating body of literature confirms an excellent correlation between mutations found in cancer tissues and mutations detected in cfDNA from the same patients.(Kim, Lee et al. 2015) Changes in cfDNA also correlate well with tumor marker dynamics in serial sampling, suggesting that cfDNA mutant allele fraction changes reflect changes in disease burden over time and treatment. Plasma based DNA mutation detection should therefore provide longitudinal changes in the representative genomic landscape of the malignancy in a non-invasive manner, overcoming the two major limitations of tissue based DNA mutation analysis (invasiveness and limited sampling from a genetically heterogenous tumor).(Diehl, Li et al. 2005; Diehl, Schmidt et al. 2008; Dawson, Tsui et al. 2013)

10 mL whole blood samples will be collected in Streck cfDNA BCT tubes. These specimens will be shipped immediately at ambient temperature to Mayo Clinic Rochester and then processed to aliquots of platelet poor plasma within 7 days of collection using standard protocols. Samples will be stored until we are ready for DNA extraction and mutational analysis.

Mutation analysis will be performed on the baseline cfDNA samples including FGFR and Her-2. Selected mutations identified at baseline will be verified and quantified in all cfDNA samples using ultrasensitive digital droplet PCR based assays.

14.32 CTCs

That CTCs have biologic relevance in epithelial malignancies is

increasingly clear, as their relative abundance in the peripheral blood has strong correlations with disease related outcomes in early stage and advanced breast cancer.(Cristofanilli, Budd et al. 2004; Hayes, Cristofanilli et al. 2006; Liu, Shields et al. 2009; Bidard, Peeters et al. 2014; Liu 2014; Campton, Ramirez et al. 2015)[1-5] Beyond simple enumeration, molecular profiling of these cells may provide clinically relevant predictive information to guide the selection of therapy. Deriving detailed molecular signatures for isolated CTCs may also facilitate drug discovery by assessing the markers unique to progression, such that relapsing patients may be treated for their current molecular disease.

The RareCyte CTC technology is a comprehensive, reproducible and highly sensitive dual-platform for collecting, identifying and analyzing CTCs that does not rely on EpCAM expression for enrichment.[6] The front end AccuCyte system is based fundamentally on the density of CTCs, which is within the range of the buffy coat; a unique separation tube and collector device allow for virtually complete harvesting of the buffy coat into a small volume for application to a microscopic slide without cell lysis or wash steps, a potential source of CTC loss. The follow-up CyteFinder system is an automated scanning digital microscope and image analysis system that presents high-resolution images of candidate cells stained with well-characterized markers before definitive classification as a CTC. Importantly, CyteFinder includes an integrated device (CytePicker™) for CTC retrieval that is mechanically precise, enabling the isolation of DNA derived from single or pooled CTCs advanced genomic analyses including the detection of specific mutations and targeted NGS. The Mayo group has established experience detecting and isolated purified CTCs from breast cancer patients, as well as the capability to design 4- or 6-marker panels to capture specific phenotypic populations of CTCs.

10 mL whole blood samples will be collected in AccuCyte Blood Collection Tubes, which contain the proprietary RareCyte cell preservative. These samples will be shipped immediately at ambient temperature to Mayo Clinic Rochester and then processed through the RareCyte system within 3 days of collection. CTCs will be captured onto glass slides (8 slides per blood sample) for subsequent immunofluorescent staining, selection, and single cell isolation. The markers used for CTC identification will include DAPI or SYTOX orange, cytokeratin, and EpCAM at a minimum. CD45 will be used to distinguish WBCs (CD45 positive) from CTCs (CD45 negative). Pure populations of CTCs will then be isolated and stored for subsequent molecular analyses, as yet to be determined.

15.0 Drug Information

15.1 FTD/TPI (TAS-102; Lonsurf®; Trifluridine (FTD) / Tipiracil hydrochloride (TPI))

15.11 Background

FTD/TPI is an orally available combination drug of an antineoplastic thymidine-based nucleoside analogue, 1M trifluridine (FTD), and 0.5 M tipiracil hydrochloride (TPI). FTD is incorporated into deoxyribonucleic acid of tumor cells following phosphorylation. TPI inhibits degradation of FTD by thymidine phosphorylase.

15.12 Formulation

FTD/TPI contains trifluridine (FTD) and tipiracil (TPI as active ingredients with a molar ratio of 1:0.5. TAS-102 drug products are immediate-released film coated tablets, with two strengths of 15 mg and 20 mg (expressed as FTD). The inactive ingredients of the TAS-102 15 mg and 20 mg tablets are lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, red ferric oxide (only 20 mg tablet), and magnesium stearate.

FTD/TPI (TAS-102) tablet (15 mg) contains 15 mg FTD and 7.065 mg TPI as active ingredients. The appearance is white round tablet.

FTD/TPI (TAS-102) tablet (20 mg) contains 20 mg FTD and 9.42 mg TPI as active ingredients. The appearance is pale red round tablet.

15.13 Preparation and storage

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). If stored outside of original bottle, discard after 30 days

15.14 Administration

Recommended to take within 1 hour after completion of the morning and evening meals.

15.15 Pharmacokinetic information

Protein Binding: Trifluridine: >96% (primarily to albumin); Tipiracil: <8%
Metabolism: Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY)
Half-life elimination: Trifluridine: 2.1 hours (at steady state); Tipiracil: 2.4 hours (at steady state)
Time to peak, plasma: ~2 hours
Excretion: Trifluridine: Urine (<2% [as unchanged drug]; ~19% [as inactive metabolite FTY]); Tipiracil: Urine (~29% [as unchanged drug] .

15.16 Potential Drug Interactions

Caution is required when using drugs that are human thymidine kinase substrates, e.g., zidovudine. Such drugs, if used concomitantly with FTD/TPI, may theoretically compete with the effector of FTD/TPI, i.e., FTD, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative

antiviral agent that is not a human thymidine kinase substrate such as: lamivudine, zalcitabine, didanosine, abacavir, etc.

15.17 **Known potential adverse events:**

Very common known potential toxicities, ≥10%:
Blood and lymphatic: Anemia, leukopenia, neutropenia, thrombocytopenia
Gastrointestinal: Diarrhea, nausea, vomiting
General: Fatigue
Metabolism and nutrition: Decreased appetite

Common known potential toxicities, ≥1% - <10%
Blood and lymphatic: Febrile neutropenia, lymphopenia, monocytosis
Dermatologic: Alopecia, dry skin, Palmar-plantar erythrodysesthesia syndrome, pruritis, rash
Gastrointestinal: Abdominal pain, constipation, oral disorder, stomatitis
General: Malaise, mucosal inflammation, edema, pyrexia
Hepatobiliary: Hyperbilirubinemia
Infections: Lower respiratory tract infection, upper respiratory tract infection
Investigations: Blood alkaline phosphatase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition: Hypoalbuminemia
Nervous System: Dizziness, dysgeusia, headache, peripheral neuropathy
Psychiatric: Insomnia
Renal and urinary: Proteinuria
Respiratory: Cough, dyspnea
Vascular: Flushing

Uncommon known potential toxicities, <1% (Limited to important or life-threatening):
Blood and lymphatic: Pancytopenia
Gastrointestinal: Ascites, colitis, ileus, acute pancreatitis, subileus
General: General physical health deterioration
Infections: Bacterial infection, biliary tract infection, enteritis infection, urinary tract infection
Investigations: Blood lactate dehydrogenase increased
Metabolism and nutrition: Dehydration
Respiratory: Pulmonary embolism

15.18 **Drug procurement**

FTD/TPI (TAS-102) will be provided free of charge by Taiho Oncology.

15.19 **Nursing Guidelines**

15.191 Instruct Patients to take FTD/TPI (TAS-102) within 1 hour after morning or evening meal with a glass of water. Patients will not make up for a missed dose. If a patient vomits after taking the study medication, the dose should not be replaced.

15.192 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.193 GI side effects are common, including nausea, decreased appetite, diarrhea, vomiting, and abdominal pain.

15.194 Cytopenias are common. Monitor CBC w/diff and instruct patients to report any signs or symptoms of infection and/or unusual bruising or bleeding to the study team.

15.195 Rarely Pulmonary embolism has been reported with this agent. Instruct patient to report any shortness of breath or chest pain to study team and/or seek out emergency medical attention.

15.196 Although uncommon, warn patients of the possibility of alopecia.

16.0 Statistical Considerations and Methodology

16.1 Overview

This protocol will assess the efficacy of FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma using a single stage phase II study design. This single arm Phase II trial will assess the 16-week progression-free survival rate (by RECIST v1.1) associated with FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma. We will adopt a PFS rate of 10% as the null hypothesis and PFS rate of 30% as the alternative hypothesis. In addition to response, this study will also evaluate the overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events.

16.11 Primary Endpoint

The primary endpoint for this study is 16-week progression-free survival associated with FTD/TPI (TAS-102) in patients with refractory cholangiocarcinoma.

16.2 Statistical Design:

16.21 Decision Rule

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following single stage design uses 25 patients to test the null hypothesis that the true success proportion in a given patient population is at most 10%. If 5 or fewer successes are observed in the 25 evaluable patients, we will consider this regimen ineffective in this patient population. If 6 or more successes are observed in the 25 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

NOTE: We consider a success to be alive and progression-free by 16 weeks post-registration (i.e. stable disease, partial response, or complete response).

16.22 Sample Size:

The single stage study design to be utilized is fully described in Section 16.21. A maximum of 25 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 28 patients**.**

16.23 Accrual Time and Study Duration

The anticipated accrual rate is approximately 2 patients per month. Therefore, the accrual period for this phase II study is expected to be between 7.5 and 14 months, depending upon whether patients are accrued beyond the first stage. The final analysis can begin approximately 18 months after the trial begins, i.e. as soon as the last patient has been observed for 4 months.

16.24 Power and Significance Level

Assuming that the number of successes is binomially distributed, the significance level is 0.05 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the

probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is . . .	0.1	0.15	0.2	0.25	0.30
then the probability of declaring that the regimen warrants further studies is . .	0.033	0.160	0.383	0.622	0.807

16.25 Other Considerations

Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when patients have been on study for 16 weeks (i.e. received second scan).

16.31 Primary Endpoint

16.311 Definition: The primary endpoint of this trial is the progression-free survival rate. This is defined as the proportion of evaluable patients who are progression-free (stable disease, partial response, complete response) at 16 weeks. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson.

16.316 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.32 Secondary Endpoints

The following endpoints will be evaluated: overall response rate, progression-free survival, overall survival, and adverse events.

16.321 Overall Response Rate (ORR): Overall response rate is defined as the proportion of patients who experience either a partial response or complete response by the given time point. ORR will be reported descriptively and a 95% confidence interval will be reported.

16.322 Progression-Free Survival: Progression-free survival is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on

RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method. The median PFS and 95% confidence interval will be reported. Patients will be censored at the last disease assessment date.

16.323 Overall Survival (OS): Overall survival is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method. The median OS and 95% confidence interval will be reported. Patients will be censored at the date patient was last known to be alive.

16.324 Adverse events: The maximum grade for each type of adverse event by patient will be summarized by frequencies and percentages using CTCAE version 4.0. We will also closely monitor adverse events throughout the study.

16.33 Correlative Research

16.331 To determine if CTCs of cfDNA at baseline will correlate with prognosis or response to therapy.

16.332 To determine if change in CTCs or cfDNA will correlate with efficacy endpoints.

16.333 To determine if different mutations status of the tumor will affect efficacy endpoints.

16.4 Data & Safety Monitoring:

16.41 Review

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- If 3 or more patients in the first 10 treated patients (30% or higher after first 10 patients) experience at least one grade 4+ adverse event at least possibly related to the study treatment
- If one or more patients in the first 10 treated patients (20% or higher after first 10 patients) experience a grade 5 adverse event at least possibly related to the study treatment

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.7 Inclusion of Women and Minorities

16.71 Availability

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 Differential effects

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 Mayo Clinic Population

Based on prior MC studies involving similar disease sites, we expect about 4 % of patients will be classified as minorities by race and about 50 % of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	13	13	26
Ethnic Category: Total of all subjects	**14**	**14**	**28**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	13	13	26
Racial Category: Total of all subjects	**14**	**14**	**28**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See 4.0 Test Schedule and Data Submission Schedule (DSS) for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires baseline supporting documentation of histologic diagnosis and staging of genetic mutations which includes the most recent tumor tissue biopsy pathology report. To submit these materials, they can be uploaded into the Supporting Documentation form in Medidata Rave®. These reports should be submitted within 21 days of registration.

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy. Documentation of tumor genetic mutations is requested at any time, if available.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any data entered into a form will result in that form being marked as "received." However, missing data in each form will be flagged by edit checks in the database.

18.8 Overdue lists

A list of overdue materials is automatically available to each site at any time. In addition, a list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction in the database and respond back to the QAS.

19.0 Budget

19.1 Costs charged to patient

Routine clinical care costs will be the responsibility of the patient and/or the patient's insurance company. This responsibility includes costs associated with surgery and with the administration of standard chemotherapy (carboplatin/paclitaxel or FOLFOX), and radiotherapy. These drugs are commercially available and will be the responsibility of the patient and/or the patient's insurance company.

19.2 Tests to be research funded

- FTD/TPI (TAS-102) will be provided by Taiho Oncology
- Correlative studies
- Collection, processing and storage of blood for research.

19.3 Other considerations

Taiho Oncology will provide a grant to Mayo Clinic to help with costs for the conduct of this study.

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ **Study ID Number** _____

Please complete this diary on a daily basis. Write in the number of pills that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Take your pills twice per day with water within one hour after a meal.

If you experience any health/medical complaints or take any medication other than FTD/TPI (TAS-102), please record this information.

Week of: _____

Study Drug	***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***	
FTD/TPI (TAS-102)	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
15 mg tablets										
20 mg tablets										

Week of: _____
Do not take any TAS-102 this week

Week of: _____

Study Drug	***Day 8***		***Day 9***		***Day 10***		***Day 11***		***Day 12***	
FTD/TPI (TAS-102)	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
15 mg tablets										
20 mg tablets										

Week of: _____
Do not take any FTD/TPI (TAS-102) this week

Week of: _____
Do not take any FTD/TPI (TAS-102) this week

Remember to bring this diary with you to your next appointment along with any FTD/TPI pill bottles (full, empty, or partially filled).

Patient signature: _____

Date: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix III Taiho Tables for Frequency for Serious Adverse Drug Reactions for TAS-102

The baseline frequency for serious adverse drug reactions by MedDRA System Organ Class (Version 18.0) and preferred term in patients receiving FTD/TPI (TAS-102) monotherapy[a] is as below (data taken from TAS-102 Global Investigator's Brochure Ver 7.0 11Oct2016):

MedDRA SOC Preferred Term	**Baseline**[b] (N=769), n (%)
Total Serious Related Advere Events	**60 (7.8)**
Blood and lymphatic system disorders	**32 (4.2)**
Anaemia	10 (1.3)
Disseminated intravascular coagulation	1 (0.1)
Febrile neutropenia	18 (2.3)
Leukopenia	2 (0.3)
Neutropenia	5 (0.7)
Pancytopenia	1 (0.1)
Thrombocytopenia	1 (0.1)
Gastrointestinal disorders	**16 (2.1)**
Abdominal pain	4 (0.5)
Anal fistula	1 (0.1)
Ascite	1 (0.1)
Colitis	2 (0.3)
Constipation	1 (0.1)
Diarrhoea	3 (0.4)
Ileus	2 (0.3)
Nausea	2 (0.3)
Pancreatitis acute	1 (0.1)
Subileus	1 (0.1)
Vomiting	5 (0.7)
General disorders and administration site conditions	**5 (0.7)**
Fatigue	3 (0.4)
General physical health deterioration	1 (0.1)
Malaise	1 (0.1)
Hepatobiliary disorders	**2 (0.3)**
Cholangitis	1 (0.1)
Liver disorder	1 (0.1)
Infections and infestations	**11 (1.4)**
Bacteraemia	1 (0.1)

MedDRA SOC	**Baseline[b]**
Preferred Term	(N=769), n (%)
Infections and infestations (continued)	**11 (1.4)**
Biliary tract infection	1 (0.1)
Cellulitis	1 (0.1)
Endophthalmitis	1 (0.1)
Enteritis infections	1 (0.1)
Lower respiratory tract infection	1 (0.1)
Pelvic infection	1 (0.1)
Pneumonia	4 (0.5)
Pneumonia klebsiella	1 (0.1)
Sepsis	1 (0.1)
Septic shock	1 (0.1)
Urinary tract infection	2 (0.3)
Investigations	**4 (0.5)**
Blood lactate dehydrogenase increased	1 (0.1)
Haemoglobin decreased	1 (0.1)
Neutrophil count decreased	1 (0.1)
Platelet count decreased	1 (0.1)
Weight decreased	1 (0.1)
White blood cell count decreased	2 (0.3)
Metabolism and nutrition disorders	**6 (0.8)**
Decreased appetite	4 (0.5)
Dehydration	3 (0.4)
Hypokalaemia	1 (0.1)
Hyponatraemia	1 (0.1)
Renal and urinary disorders	**1 (0.1)**
Acute kidney injury	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**1 (0.1)**
Pulmonary embolism	1 (0.1)

[a]TAS-102 studies investigating 35 mg/m^2/dose monotherapy in patients with colorectal cancer.
[b]Only includes serious adverse events from protocols completed as of 24 July 2016: J001-10040010, J003-10040030, J004-10040040, TPU-TAS-102-101, TPU-TAS-102-102, TPU-TAS-102-103, TPU-TAS-102-104, TPU-TAS-102-108, TPU-TAS-102-301.

Further adverse events (>5%) in the RECOURSE study are mentioned in section 1.2.

The most frequently reported adverse vents (>10% in either pooled treatment group) reported for patients in the randomized studies (J003-10040030 and TPU-TAS-1-2-301 is as follows (data taken from TAS-102 Global Investigator's Brochure Ver 7.0 11Oct2016):

	Studies J003-10040030 and TPU-TAS-102-301 Combined			
MedDRA SOC	**TAS-102 (N=646), n (%)**		**Placebo (N=322), n (%)**	
Preferred Term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Any adverse event	**635 (98.3)**	**448 (69.3)**	**299 (92.9)**	**146 (45.3)**
Blood and lymphatic system disorder	**311 (48.1)**	**195 (30.2)**	**29 (9.0)**	**11 (3.4)**
Anaemias	216 (33.4)	88 (13.6)	22 (6.8)	7 (2.2)
Neutropenia	156 (24.1)	107 (16.6)	0	0
Gastrointestinal disorders	**502 (77.7)**	**83 (12.8)**	**195 (60.6)**	**37 (11.5)**
Abdominal pain	101 (15.6)	12 (1.9)	46 (14.3)	10 (3.1)
Constipation	92 (14.2)	1 (0.2)	44 (13.7)	3 (0.9)
Diarrhea	213 (33.0)	23 (3.6)	45 (14.0)	1 (0.3)
Nausea	331 (51.2)	15 (2.3)	79 (24.5)	3 (0.9)
Vomiting	186 (28.8)	15 (2.3)	52 (16.1)	1 (0.3)
General disorders and administration site conditions	**457 (70.7)**	**77 (11.9)**	**168 (52.2)**	**38 (11.8)**
Asthenia	97 (15.0)	18 (2.8)	30 (9.3)	8 (2.5)
Fatigue	246 (38.1)	25 (3.9)	82 (25.5)	16 (5.0)
Oedema peripheral	67 (10.4)	2 (0.3)	31 (9.6)	3 (0.9)
Pyrexia	114 (17.6)	6 (0.9)	44 (13.7)	2 (0.6)
Investigations	**399 (61.8)**	**216 (33.4)**	**132 (41.0)**	**44 (13.7)**
Aspartate aminotransferase increased	53 (8.2)	9 (1.4)	34 (10.6)	8 (2.5)
Blood alkaline phosphorase increased	64 (9.9)	21 (3.3)	41 (12.7)	14 (4.3)
Blood bilirubin increased	78 (12.1)	24 (3.7)	27 (8.4)	11 (3.4)
Haemoglobin decreased	85 (13.2)	21 (3.3)	9 (2.8)	3 (0.9)
Neutrophil count decreased	229 (35.9)	142 (22.0)	2 (0.6)	0
Platelet count decreased	125 (19.3)	18 (2.8)	7 (2.2)	0
White blood cell count decreased	232 (35.9)	87 (13.5)	3 (0.9)	0
Metabolism and nutrition disorders	**319 (49.4)**	**58 (9.1)**	**123 (38.2)**	**29 (9.0)**
Decreased appetite	278 (43.0)	24 (3.7)	97 (30.1)	15 (4.7)
Respiratory, thoracic and mediastinal disorders	**169 (26.2)**	**33 (5.1)**	**86 (26.7)**	**18 (5.6)**
Cough	63 (9.8)	2 (0.3)	33 (10.2)	2 (0.6)
Dyspnoea	63 (9.8)	16 (2.5)	34 (10.6)	10 (3.1)