STUDY PROTOCOL
2102-ONC-102

Protocol Title: A Phase 1b/2 Study of FT-2102 in Patients with Advanced Solid Tumors and Gliomas with an IDH1 Mutation

Protocol Number: 2102-ONC-102

Phase: 1b/2

Date of Protocol: 28 January 2020

Version: Version 5 (Amendment 4)

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NCT: NCT03684811

Sponsor: FORMA Therapeutics, Inc.
500 Arsenal Street, Suite 100
Watertown, MA 02472

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (dd/mmm/yyyy):_____

SPONSOR SIGNATURE PAGE

CONTACT INFORMATION

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[redacted]

Protocol No. 2102-ONC-102

A Phase 1b/2 Study of FT-2102 in Patients with Advanced Solid Tumors and Gliomas with an IDH1 Mutation

Protocol History:

Version 1.0	19 June 2018
Version 2.0	26 July 2018
Version 3.0	1 November 2018
Version 4.0	20 June 2019
Version 5.0	28 January 2020

I have read this protocol and approve the design of this study:

[redacted]

SERIOUS ADVERSE EVENT REPORTING

CONTACT FORMA THERAPEUTICS PHARMACOVIGILANCE WITHIN **24 HOURS** OF LEARNING OF ANY **SERIOUS ADVERSE EVENT (SAE)**. IF THE **SAE IS FATAL** OR **LIFE-THREATENING**, FORMA THERAPEUTICS PHARMACOVIGILANCE MUST BE INFORMED **IMMEDIATELY.**

Contact FORMA Therapeutics Pharmacovigilance as described below, and complete a Serious Adverse Event Report Form:

EMAIL OR FAX SAE REPORT FORM TO:	**GLOBAL MEDICAL MONITOR**	**MEDICAL MONITOR ASIA/PACIFIC**
[redacted]	[redacted]	[redacted]

FOR REPORTING OF ALL SAEs, INVESTIGATORS MUST **EMAIL OR FAX** ALL COMPLETED PAGES OF THE SAE REPORT FORM **WITHIN 24 HOURS** TO THE FOLLOWING:

ATTENTION: FORMA Therapeutics Pharmacovigilance

Email: [redacted]

TO DISCUSS AN SAE WITH THE MEDICAL MONITOR, CONTACT [redacted] **OR** [redacted] AT THE NUMBERS PROVIDED ABOVE. **FOLLOW-UP INFORMATION TO SAES MUST BE PROVIDED TO FORMA THERAPEUTICS PHARMACOVIGILANCE WITHIN 24 HOURS OF INVESTIGATOR AWARENESS.**

PROTOCOL SYNOPSIS

Study Title:

A Phase 1b/2 Study of FT-2102 in Patients with Advanced Solid Tumors and Gliomas with an IDH1 Mutation

Protocol Number:

2102-ONC-102

Phase:

1b/2

Study Drugs:

Cohort 1: Glioma

- FT-2102 (FT-2102) single-agent or in combination with 5-azacitidine

Cohort 2: Hepatobiliary Cancers

- FT-2102 single-agent or in combination with a programmed death-1 (PD-1) inhibitor: nivolumab

Cohort 3: Chondrosarcoma

- FT-2102 single-agent or in combination with 5-azacitidine

Cohort 4: Intrahepatic Cholangiocarcinoma (IHCC)

- FT-2102 single-agent or in combination with gemcitabine and cisplatin chemotherapy (GemCis)

Cohort 5: Other Solid Tumors (non-central nervous system [CNS]) with Isocitrate Dehydrogenase 1 (IDH1) Mutations

- FT-2102 single-agent

Study Population:

This study will enroll up to approximately 200 patients across 4 disease-specific cohorts and 1 exploratory cohort in non-CNS solid tumors.

The study will include a Safety Lead-in Period, which will enroll approximately 6 patients with histologically or cytologically-confirmed IDH1 R132X gene-mutated advanced solid tumors and approximately 6 patients with histologically or cytologically-confirmed IDH1 R132X gene-mutated advanced gliomas that have recurred or progressed following standard therapy. Additional patients may be enrolled if different doses or an altered dosing schedule are explored. Patients enrolled during the Safety Lead-in Period who meet the criteria for enrollment into 1 of the 4 disease-specific cohorts outlined below will be counted as part of the Stage 1 evaluation for those disease-specific cohorts at the same dose.

Study Title:

A Phase 1b/2 Study of FT-2102 in Patients with Advanced Solid Tumors and Gliomas with an IDH1 Mutation

Cohort 1 will include 16-46 evaluable patients with relapsed or refractory glioma (per World Health organization [WHO] criteria 2016) with confirmed IDH1 mutation.

Cohort 2 will include approximately 21-78 evaluable patients with relapsed or refractory hepatobiliary tumors with confirmed IDH1 mutation previously treated with an approved therapy for hepatobiliary cancer (HBC).

Cohort 3 will include approximately 16-46 evaluable patients with recurrent, refractory or either locally advanced or metastatic chondrosarcoma with confirmed IDH1 mutation not amenable to complete surgical excision.

Cohort 4 will include approximately 21-77 evaluable patients with advanced, nonresectable or metastatic intrahepatic cholangiocarcinoma with confirmed IDH1 mutation not eligible for curative resection or transplantation.

Cohort 5 will include up to 6 patients with relapsed or refractory other tumors with confirmed IDH1 mutation.

Study Duration:

It is estimated that this study will last approximately 30 months. The expected duration of study treatment for each patient will be approximately 26 weeks.

Patients will remain on study treatment (either single-agent FT-2102 or combination therapy) until disease progression or unacceptable toxicity.

Patients will be followed for safety for 28 days after last dose of study drug or until resolution or stabilization of ongoing adverse events (AEs).

Patients may be followed for survival approximately every 3 months for up to 24 months from first dose of study treatment or for up to 12 months after treatment discontinuation (whichever is longer).

The end of the study will be defined as last patient last visit (LPLV).

Study Centers:

Enrollment is anticipated at approximately 50 global sites (in North America, Europe, and Asia Pacific).

Study Design:

This is a multicenter, Phase 1b/2, open-label, multiple-cohort study examining the efficacy and safety of FT-2102 as a single agent or in combination for the treatment of patients with advanced solid tumors and gliomas with an IDH1 R132X mutation.

The starting dose of FT-2102 is 150 mg twice daily (BID) administered continuously in 28-day cycles; the selection of the starting dose is based on results from a Phase 1 study in patients with hematologic malignancies.

Safety Lead-in Period: Phase 1b

Safety Lead-In, Single-Agent: The study will consist of a Safety Lead-in Period to confirm the safety and tolerability of single-agent FT-2102 150 mg BID administered over 28 days (1 cycle). The Safety Lead-in Period will employ a traditional 3+3 design, whereby 3 patients with any of the specified solid tumors and (Cohorts 2a-5a) or glioma (Cohort 1a) are treated with FT-2102 150 mg BID and monitored for dose-limiting toxicities (DLTs) during the first cycle of study treatment.

- If no dose-limiting toxicities occur in the first 3 patients in either the solid tumor group (Cohorts 2a-5a inclusive) or the glioma group (Cohort 1a), and available pharmacokinetic (PK)/pharmacodynamic (PD) data support the dose, enrollment will continue in the 4 disease-specific cohorts described below.
- If a DLT occurs in the first 3 patients in either group, an additional 3 patients will be treated at that dose level in either the solid tumor group (Cohorts 2a-5a inclusive) or the glioma group (Cohort 1a). If no DLTs occur in these additional 3 patients (ie, <2 DLTs per 6 patients) and available PK/PD data support the dose, enrollment will continue in the 4 disease-specific cohorts described below.
- If there are ≥2 DLTs at the starting dose, 150 mg once daily of FT-2102 will be evaluated following review by the Safety Review Committee (SRC). Likewise, higher doses may be evaluated based upon safety, PK, and PD data as determined by the SRC.

Safety Lead-In Combination: DLTs will be evaluated within the first 3 (or 6) patients of any cohort examining combination therapy to confirm the safety and tolerability of combination therapy administered over 28 days (1 cycle) for Cohort 1b, Cohort 2b, Cohort 3b, and Cohort 4b using a 3+3 design (i.e., up to the first 6 patients in each combination cohort). The cohort will be stopped if there is more than 1 DLT out of the first 6 patients, and additional dose levels will be evaluated as follows:

- If no DLTs occur in the first 3 patients in a combination cohort and available PK/PD data support the dose, enrollment will continue in that disease-specific cohort.
- If a DLT occurs in the first 3 patients in a combination cohort, an additional 3 patients will be treated at that dose level. If no DLTs occur in these additional 3 patients (ie, <2 DLTs per 6 patients) and available PK/PD data support the dose, enrollment will continue in the specific combination cohort.
- If there are ≥2 DLTs at the starting dose, the following dose de-escalations of either the combination agent or FT-2102 will be evaluated following review by the SRC. Following that evaluation, the SRC will evaluate the available safety, PK, and PD data to determine the dose(s) to be used in the combination Phase 2.

FT-2102 + Azacitidine

Dose Level	FT-2102	Azacitidine
-1 (Hematologic DLT)	150 mg BID continuously × 28 days	37 mg/m^2/day intravenous (IV) × 7 days every 28 days
-1 (Non-Hematologic DLT)	150 mg QD continuously × 28 days	75 mg/m^2/day IV × 7 days every 28 days
1 (Starting Dose)	150 mg BID continuously × 28 days	75 mg/m^2/day IV × 7 days every 28 days

FT-2102 + Gemcitabine/Cisplatin

Dose Level	FT-2102	Gemcitabine/Cisplatin
-1 (Any DLT)	150 mg once daily continuously × 28 days	Cisplatin 25 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 on Day 1 and Day 8
1 (Starting Dose)	150 mg BID continuously × 28 days	Cisplatin 25 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 on Day 1 and Day 8

FT-2102 + Nivolumab

Dose Level	FT-2102	Nivolumab
-1 (Any DLT)	150 mg once daily continuously × 28 days	240 mg IV every 2 weeks
1 (Starting Dose)	150 mg BID continuously × 28 days	240 mg IV every 2 weeks

Other Non-CNS Solid Tumors with IDH1 Mutations (n=6, Cohort 5a)

Up to 6 patients with relapsed or refractory non-CNS solid tumors harboring an IDH1 R132X mutation. This cohort will only include treatment with single-agent FT-2102. Due to the diverse population, this is an exploratory cohort without pre-defined efficacy/futility determinations. Aggregate safety data will be monitored by the SRC and if unacceptable toxicity (a DLT) is observed in ≥2 of the first 6 patients, the cohort will be closed for additional enrollment.

Disease-Specific Cohorts: Phase 2

Four disease-specific cohorts will employ a stage-wise design, whereby 8 patients in the first stage of each cohort will be treated with study therapy (either single-agent FT-2102 or in combination with antineoplastic agents) and evaluated for efficacy and safety.

After up to 8 patients in Stage 1 have been evaluated for at least 4 cycles of study treatment, disease-specific efficacy data will be evaluated to determine continued enrollment to Stage 2. Enrollment will continue during the Stage 1 evaluation. If Stage 1 efficacy criteria from any single-agent FT-2102 cohort is not met, then examination of combination therapy may be initiated in a new Simon's 2-stage design.

Safety data from Stage 1 will also be reviewed on an ongoing basis by SRC. Significant safety findings may lead to an early stopping for any cohort and will be considered when deciding to initiate Stage 2 of any cohort.

For the Safety Lead-in Period and Stage 1 of each disease-specific cohort, blood samples for PK and PD will be obtained. Limited PK and PD samples will be obtained during Stage 2.

Overall response is defined as follows:

- **Glioma:** the proportion of patients with a best response of complete response/remission (CR) or partial response/remission (PR) or minor response (MR) (low-grade glioma [LGG])
- **Hepatobiliary cancer:** the proportion of patients with a best response of CR or PR
- **Chondrosarcoma:** the proportion of patients with a best response of CR or PR
- **Intrahepatic Cholangiocarcinoma:** the proportion of patients with a best response of CR or PR

Cohort 1: Glioma (n=16-46)

Cohort 1 will include patients with glioma harboring an IDH1 R132X mutation that is relapsed or refractory. Glioma patients will be initially treated with single-agent FT-2102 (**Cohort 1a**). Cohort 1a will employ a Simon's 2-stage design, in which 8 evaluable patients will be treated with single-agent FT-2102 for a minimum of 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1). If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will initiate with single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + 5-azacitidine) (**Cohort 1b**). Cohort 1b will employ the same Simon's 2-stage design, enrolling 8 evaluable patients in Stage 1 and 15 evaluable patients in Stage 2 with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: Any glioma patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment for single-agent or combination treatment.

Cohort 2: Hepatobiliary Cancer (HBC) (n=21-78)

Cohort 2 will include patients with relapsed/refractory HBC harboring an R132X IDH1 mutation. HBC patients will be initially treated with single-agent FT-2102 (**Cohort 2a**). Cohort 2a will employ

a Simon's 2-stage design, in which 8 evaluable patients will be treated with single-agent FT-2102 for a minimum of 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1). If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will receive single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + PD-1 inhibitor) (**Cohort 2b**). Cohort 2b will employ a new Simon's 2-stage design, whereby 13 evaluable patients will be treated in Stage 1 with combination therapy for a minimum of 4 cycles (cycle=28 days) and assessed for efficacy and safety. If ≥4 clinical response is observed in Stage 1 of Cohort 2b, then Stage 2 (n=42) will initiate with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any HBC patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

Cohort 3: Chondrosarcoma (n=16-46)

Cohort 3 will include patients with relapsed/refractory, locally advanced or metastatic chondrosarcoma harboring an R132X IDH1 mutation. Chondrosarcoma patients will be initially treated with single-agent FT-2102 (**Cohort 3a**). Cohort 3a will employ a Simon's 2-stage design, in which 8 evaluable patients will be treated with single-agent FT-2102 for a minimum of 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1). If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will initiate with single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + 5-azacitidine) (**Cohort 3b**). Cohort 3b will employ the same Simon's 2-stage design, enrolling 8 evaluable patients in Stage 1 and 15 evaluable patients in Stage 2 (n=15) with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any chondrosarcoma patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

Cohort 4: IHCC (n=21-77)

Cohort 4 will include patients with advanced IHCC harboring an R132X IDH1 mutation. IHCC patients will be initially treated with single-agent FT-2102 (**Cohort 4a**). Cohort 4a will employ a Simon's 2-stage design, in which 8 evaluable patients will be treated with single-agent FT-2102 for a minimum of 4 cycles and assessed for efficacy and safety (Stage 1). If ≥2 clinical responses are observed in Stage 1, then Stage 2 (n=14) will initiate with single-agent FT-2102.

If <2 clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + GemCis) (**Cohort 4b**).

Cohort 4b will employ a Simon's 2-stage design, whereby 13 evaluable patients will be treated in Stage 1 with combination therapy for 4 cycles and assessed for efficacy and safety.

If ≥4 clinical responses are observed in Stage 1 of Cohort 4b, then Stage 2 (n=42) will be initiated with combination therapy.

During Stage 1, aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any IHCC patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

Combination therapy in cohorts 1-4 may also be examined in the event that the single agent cohort passes the futility analysis and the enrollment in the single agent cohort is completed following review by the SRC (below).

Safety Review Committee

This study will utilize an SRC, which will meet quarterly at a minimum to review all accumulated data, including safety, PK, PD, and efficacy. The SRC will be composed of a medical representative from the Sponsor, and all Principal Investigators (PIs) or delegates at each of the enrolling sites. The SRC will use all available data to confirm dose decisions and if needed recommend changes to the dosing paradigm.

Dosing Frequency

FT-2102 will initially be administered either as a single agent at 150 mg BID or in combination until disease progression or unacceptable toxicity. In the combination cohorts, FT-2102 150 mg BID will be administered in combination with 5-azacitidine in glioma and chondrosarcoma, with nivolumab in HBC, and with GemCis in IHCC. The SRC will monitor the safety, PK, and PD of both single-agent FT-2102 and combination therapy during Stage 1 of each cohort and may recommend altering the dosing paradigm based on available data. The SRC will conduct an aggregate assessment of PK/PD data as well as a review of the study drug-related AEs to ensure that the combination therapies is safe and well tolerated.

Monitoring of Adverse Events:

Patients will be monitored continuously for toxicity while on study drug. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. If a patient has an AE of a particular severity or an AE assessed as at least possibly related to study drug, then dose modifications will be made according to the guidelines set forth in the study protocol.

DLT Evaluation Period/Definition:

Single-Agent Safety Lead-in

DLTs will be evaluated during the Safety Lead-in Period during the first treatment cycle (28 days) using NCI CTCAE criteria version 4.03 and defined for each part of the study as described below. Drug relatedness will be Investigator -assessed. Grade 3 laboratory abnormalities recorded as an AE, but without clinical sequelae and not requiring treatment, are not considered DLTs. Disease progression is not considered an AE if assessed by Investigator to be unrelated to study agent.

Any DLTs that occur after the Cycle 1 DLT review period will still be considered by the SRC in the evaluation of Stage 1 from the Simon's 2-stage design and for the overall recommended phase 2 dose (RP2D).

DLTs include the following AEs unrelated to underlying disease and considered related to FT-2102:

- Non-hematologic
  - ≥Grade 3 toxicity except: Grade 3 nausea, vomiting, diarrhea, or rash: lasting <72 hours (with optimal medical management)
  - Clinically relevant (i.e. requiring treatment or with clinical sequelae) ≥Grade 3 non-hematologic laboratory finding
- Hematologic
  - ≥Grade 3 thrombocytopenia
  - Grade 4 neutropenia lasting for >7 days
  - ≥Grade 3 febrile neutropenia

Combination Therapy Safety Lead-in

DLTs will also be evaluated during Stage 1 of any cohort examining combination therapy (Cohort 1b, Cohort 2b, Cohort 3b, and Cohort 4b) using a 3+3 design. DLTs will be assessed during the first full treatment cycle of both agents (28 days) using NCI CTCAE criteria version 4.03. Drug relatedness will be Investigator -assessed. Grade 3 laboratory abnormalities recorded as an AE, but without clinical sequelae and not requiring treatment, are not considered DLTs. Disease progression is not considered an AE if assessed by the Investigator to be within the expected tempo of that disease.

Any DLTs that occur after the Cycle 1 review period will still be considered by the SRC in the evaluation of Stage 1 from the Simon's 2-stage design and for the overall recommended phase 2 dose (RP2D).

DLTs include the following AEs unrelated to underlying disease, considered related to FT-2102, and unrelated to the known toxicities of the combination agent(s):

- Non-hematologic
  - ≥Grade 3 toxicity except Grade 3 nausea, vomiting, diarrhea or rash: lasting <72 hours (with optimal medical management)
  - Clinically relevant (i.e. requiring treatment or with clinical sequelae) ≥Grade 3 non-hematologic laboratory finding
- Hematologic
  - Grade 4 thrombocytopenia
  - Grade 3 thrombocytopenia with grade 2 or greater bleeding
  - Grade 4 neutropenia lasting for >7 days
  - Grade 4 febrile neutropenia

Study Objectives:

Primary Objective (Phase 1b)

- Evaluate the safety and tolerability of FT-2102 as monotherapy and confirm the dose to be further examined in expansion cohorts as monotherapy and combination therapy

Secondary Objective (Phase 1b):

- Evaluate the PK of FT-2102 as monotherapy and in combination with other anti-cancer agents
- Evaluate the clinical activity of FT-2102 as a single-agent or in combination in patients with glioma, HBC, chondrosarcoma, and IHCC harboring an IDH1 mutation

Primary Objective (Phase 2)

- Evaluate the clinical activity of FT-2102 as monotherapy or in combination in patients with glioma, HBC, chondrosarcoma, and IHCC harboring an IDH1 mutation

Secondary Objective (Phase 2)

- Evaluate the safety of FT-2102 administered as monotherapy and in combination in patients with glioma, HBC, chondrosarcoma, and IHCC harboring an IDH1 mutation
- Evaluate the PK of FT-2102 as monotherapy and in combination with other anti-cancer agents
- Evaluate additional measures of antitumor activity of FT-2102 as monotherapy and in combination with other anti-cancer agents

Exploratory Objectives (Phase 1b and 2)

- Evaluate potential biomarkers of response, resistance, and/or safety
- Evaluate PD and PK/PD relationship of FT-2102 as a single agent and in combination with chemotherapy or immunotherapy
- Evaluate the biological effects of FT-2102 on tumor tissue, including tumor cells, cerebrospinal fluid (CSF), immune cells, and vasculature
- Assess IDH1 mutations in circulating tumor DNA (ctDNA) and correlate with mutations in tumor tissues
- Evaluate the health-related quality of life (QOL)

Study Endpoints:

Primary Endpoint (Phase 1b):

- DLTs (Safety Lead-in Periods), AEs, and safety laboratory values

Primary Endpoint (Phase 2):

- Objective response rate (ORR) as determined by applicable disease criteria, for disease-specific cohorts

Secondary Endpoints (Phases 1b and 2):

- AEs, and safety laboratory values (Phase 2)
- ORR (Phase 1b only)

- Progression-free survival (PFS), defined as the time from the first dose to disease progression as determined by applicable disease criteria or death due to any cause, whichever is sooner
- Time to progression (TTP), defined as the time from start of treatment until disease specified progression
- Duration of response (DOR), defined as the time from the first response to documented disease progression as determined by applicable disease criteria
- Overall Survival (OS), defined as the time from the first dose to death due to any cause
- Time to Response (TTR), defined as the time from first dose to first response
- AEs and abnormal laboratory findings
- PK parameters derived from plasma/CSF FT-2102 concentrations

Exploratory Endpoints:

- PD and PK/PD in relationship with clinical safety and clinical activity
- Changes in 2-hydroxygluterate (2-HG) levels (PD biomarker) in plasma and tumor tissue (1H magnetic resonance spectroscopy [MRS] and CSF in intracranial gliomas and tumor biopsies for other tumors)
- Characterization of biological effects of FT-2102 on tumor biopsies
- Cancer-associated mutations and/or genetic alterations
- IDH1 mutation in ctDNA
- Health-related QOL patient-reported questionnaire (EQ5D)

Inclusion Criteria:

All patients must meet the following criteria for inclusion:

1. ≥18 years of age
2. Life expectancy of ≥4 months
3. Able to provide tumor tissue sample (archival)
4. Disease, defined as:

   Disease-Specific Cohorts

   - Glioma (Cohort 1)
     - Histologically or cytologically confirmed IDH1 gene-mutated advanced glioma that has recurred or progressed following standard therapy, or that has not responded to standard therapy with measurable disease
     - Glioblastoma multiforme with confirmed IDH1 gene-mutated disease with first or second recurrence with measurable disease
   - HBC (Cohort 2)

- Relapsed/refractory or intolerant to approved standard-of-care therapy (included: hepatocellular carcinoma, bile duct carcinoma, intrahepatic cholangiocarcinoma or other hepatobiliary carcinomas)
- Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria
- Child-Pugh Class A
- Single Agent FT-2102: prior exposure to nivolumab is permitted
- Combination Cohort 2b: patients may not have had prior exposure to nivolumab

- Chondrosarcoma (Cohort 3)
  - Relapsed or refractory and either locally advanced or metastatic and not amenable to complete surgical excision
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per RECIST 1.1 criteria
- IHCC (Cohort 4)
  - Advanced nonresectable or metastatic intrahepatic cholangiocarcinoma not eligible for curative resection or transplantation.
  - Single-Agent/Safety Lead-in of Combination Phase 2: ineligible for standard therapies only
  - Combination Phase 2 (beyond Safety Lead-in): have received no more than 1 cycle of GemCis therapy
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per RECIST 1.1 criteria
- Other tumors (non-CNS) (Cohort 5)
  - Relapsed or refractory to standard-of-care therapy with no other available therapeutic options
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per disease appropriate response criteria

5. Recovered to ≤Grade 2 or baseline toxicity (except alopecia) from prior therapy (per CTCAE v 4.03)
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
7. Adequate bone marrow function
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L without any growth factors in prior 7 days
   - Hemoglobin ≥8.0 g/dL (with or without transfusion support)

     Platelet count ≥75 × 10^9/L (with or without transfusion support); Cohort 4b (GemCis combination): platelet count ≥100 × 10^9/L (with or without transfusion support)

8. Adequate hepatic function
    - Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase) /alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤2.5 × institutional upper limit of normal (ULN). For patients with suspected malignancy related elevations, <5 × ULN.
    - Total bilirubin ≤1.5 × ULN. For patients with suspected malignancy related elevation <3 × institutional ULN. Patients with Gilbert Syndrome ≤3 × ULN.
9. Adequate renal function
    - Creatinine clearance per Cockcroft-Gault equation of ≥60 mL/min
10. For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin (β-hCG) pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women >55 years of age)
11. Willingness of male and female patients who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment, including a period of time after study treatment completed:

- FT-2102 only: 90 days
- Nivolumab (female): 150 days
- Nivolumab (male): 210 days
- Azacitidine: 180 days
- Gemcitabine/Cisplatin: 180 days

Sexually active women using oral contraceptive pills, should also use barrier contraception. Males must agree not to donate sperm while participating in the study and for 90 days after the last dose of the study drug. For males receiving cisplatin, they must agree not to donate sperm while participating in the study and for 2 years following cisplatin.

12. Ability to adhere to the study visit schedule and all protocol requirements
13. Signed and dated IRB/independent ethics committee (IEC)-approved informed consent form before any screening procedures are performed

Exclusion Criteria:

Patients are to be excluded from the study if they meet any of the following criteria:

1. Previous solid organ or hematopoietic cell transplant
2. Less than the minimum time has elapsed from prior anticancer treatment to first dose of study treatment as follows:
    - Small molecule, antibody, or other anticancer therapeutic: 21 days (or 5 half-lives), whichever is shorter. Nitrosoureas or mitomycin C: 6 weeks. For patients enrolling in the Phase 2 (beyond Safety Lead-in with IHCC): 14 days from GemCis therapy.
    - Prior radiation therapy (including radiofrequency ablation): 4 weeks

- Prior stereotactic body radiation therapy: 2 weeks
- Prior chemoembolization or radioembolization: 4 weeks

3. No previous treatment with an IDH1 inhibitor (single agent FT-2102 cohorts only)
4. Congestive heart failure (New York Heart Association Class III or IV) or unstable angina pectoris; previous history of myocardial infarction within one year prior to study entry, uncontrolled hypertension, or uncontrolled arrhythmias
5. History of QT prolongation or baseline QT interval corrected with Fridericia's method (QTcF) >450 ms (average of triplicate readings)

   NOTE: criterion does not apply to patients with a right or left bundle branch block, a cardiology consult is recommended to assure that QTcF is not prolonged.
6. Concomitant medication(s) associated with QTc interval prolongation or Torsades de Pointes (TdP) initiated less than the duration required to reach steady-state plasma concentration (approximately five half-lives) before first dose of study drug (see Appendix 3) (medications used as needed [PRN] (e.g., Zofran) are exempt).
7. Pregnant or nursing women or WCBP not using adequate contraception; male patients not using adequate contraception
8. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ, stage 1, grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years
9. Major surgery within 4 weeks of starting study treatment or not recovered from any effects of prior major surgery (uncomplicated central line placement or fine needle aspirate are not considered major surgery)
10. Receipt of a live vaccine (including yellow fever vaccine) within 30 days of first day of study treatment
11. Patients receiving >6 mg/day of dexamethasone or equivalent
12. Patients with gastrointestinal disorders likely to interfere with absorption of the study medication
13. Known human immunodeficiency virus positivity (HIV)
14. Active infection with hepatitis B or C virus (Hep B or C viral load>100 international units/milliliter or local institutional equivalent)
15. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important medical or psychiatric illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the study. This includes any condition that would be considered a contraindication per local prescribing information to receipt of either azacitidine, nivolumab, gemcitabine or cisplatin based on cohort assigned (combination patients only).
16. PD-1 combination only:

a. Patients with active autoimmune disease

Note: patients with well controlled diabetes or hypothyroidism are eligible

b. Patients with active infections, gastrointestinal tract bleeding, enterocleisis (colon obstruction) and severe colitis are excluded

Statistical Methodology

Sample Size Determination

This study will enroll up to approximately 200 patients.

A single-agent Safety Lead-in Period will be implemented that may enroll approximately 12 patients, which includes approximately 6 patients with glioma and 6 patients with solid tumors. Following successful completion of the Safety Lead-in Period, the study will then enroll 4 disease-specific cohorts examining FT-2102 as either single-agent or in combination. These cohorts include Cohort 1 (glioma) with approximately 16-46 patients; Cohort 2 (HBC) with approximately 21-78 patients; Cohort 3 (chondrosarcoma) with up to 16-46 patients; and Cohort 4 (IHCC) with approximately 21-77 patients. There will be a fifth cohort of IDH1 mutant solid tumors, non-CNS with up to 6 patients, single-agent only.

Cohort 1a, Cohort 2a, Cohort 3a (single-agent FT-2102)

Cohorts 1a, 2a, and 3a will employ an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 5% ORR and alternative hypothesis of 25% ORR. Stage 1 of each single-agent cohort will evaluate 8 patients for efficacy over 4 treatment cycles; if there are 1 or more responses, Stage 2 will initiate with additional 15 patients. If there are 4 or more responses out of the total 23 patients, the null hypothesis of 5% ORR will be rejected. If there is no response in Stage 1 with single-agent FT-2102, combination therapy may be evaluated.

Cohort 4a (single-agent FT-2102)

Cohort 4a employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 8% ORR and alternative hypothesis of 35% ORR. Stage 1 will evaluate 8 patients and if there are 2 or more responses Stage 2 will initiate with additional 14 patients. If there are 5 or more responses out of the total 22 patients, the null hypothesis of 8% ORR will be rejected. If there is 0 or 1 response in Stage 1 with single-agent FT-2102, combination may be evaluated.

Combination Cohorts (1b, 2b, 3b, 4b)

If there is no response in Stage 1 with single-agent FT-2102 combination cohorts may be examined.

Cohort 1b and Cohort 3b

For Cohorts 1b and 3b (combination therapy), an optimal Simon's 2-Stage design will be implemented with a 1-sided alpha of 0.025, 80% power, with a null hypothesis of 5% ORR and alternative hypothesis of 25% ORR. Stage 1 of each cohort will evaluate 8 patients for efficacy over 4 treatment cycles; if there are 1 or more responses, Stage 2 will initiate with additional 15 patients. If there are 4 or more responses out of the total 23 patients, the null hypothesis of 5% ORR will be rejected.

Cohort 2b

Cohort 2b employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 20% ORR and alternative hypothesis of 40% ORR. Stage 1 will evaluate 13 patients for efficacy; if there are 4 or more responses Stage 2 will initiate with an additional 42 patients. If there are 17 or more responses out of the total 55 patients, the null hypothesis of 20% ORR will be rejected.

Cohort 4b

Cohort 4b employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 20% ORR and alternative hypothesis of 40% ORR. Stage 1 will evaluate 13 patients and if there are 4 or more responses Stage 2 will initiate with additional 42 patients. If there are 17 or more responses out of the total 55 patients, the null hypothesis of 20% ORR will be rejected.

Cohort 5a

Cohort 5a, due to the diverse population, this is an exploratory cohort without pre-defined efficacy/futility determinations (n=6).

Analysis Sets

The **DLT-Evaluable Analysis Set** is defined as all patients in the Safety Lead-in Periods (single-agent FT-2102, combination FT-2102 + 5-azacitidine, combination FT-2102 + GemCis, and combination FT-2102 + PD-1 inhibitor, nivolumab) who either experienced a DLT during Cycle 1 or completed at least 75% of the prescribed Cycle 1 dose. This analysis sets will be used to assess the tolerability of FT-2102.

The **Safety Analysis Set** is defined as all patients who received any amount of study drug(s) (FT-2102 and combination agents, if appropriate).

This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation. Safety analysis will be by cohort and by treatment within cohort if more than 1 dose or dosing combination are initiated for a particular indication cohort.

The **Response-Evaluable Analysis Se**t is defined as all patients with measurable disease at baseline who received the study drug(s) specific to the part of their particular cohort (either FT-2102 monotherapy or FT-2102 in combination) and had at least 1 post-baseline response assessment or discontinued the treatment phase due to disease progression (including death caused by disease progression) within 8 weeks (+2-week window) of the first dose of study treatment. This analysis set will be the primary analysis set for efficacy endpoints. All response evaluations will be by cohort, and by treatment within cohort if more than 1 doses or dosing combinations are initiated for a particular indication cohort.

The **PK Analysis Set** is defined as patients from Stage 1 who have received at least one dose of FT-2102 and for whom it is possible to calculate at least one primary PK parameter (e.g. C_{max}, AUC_{last}).

The **Pharmacodynamic Analysis Set** is defined as all patients who received at least one dose of FT-2102 and have completed at least one pharmacodynamic assessment.

Safety Analyses:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher and will be graded according to the NCI CTCAE, v 4.03.

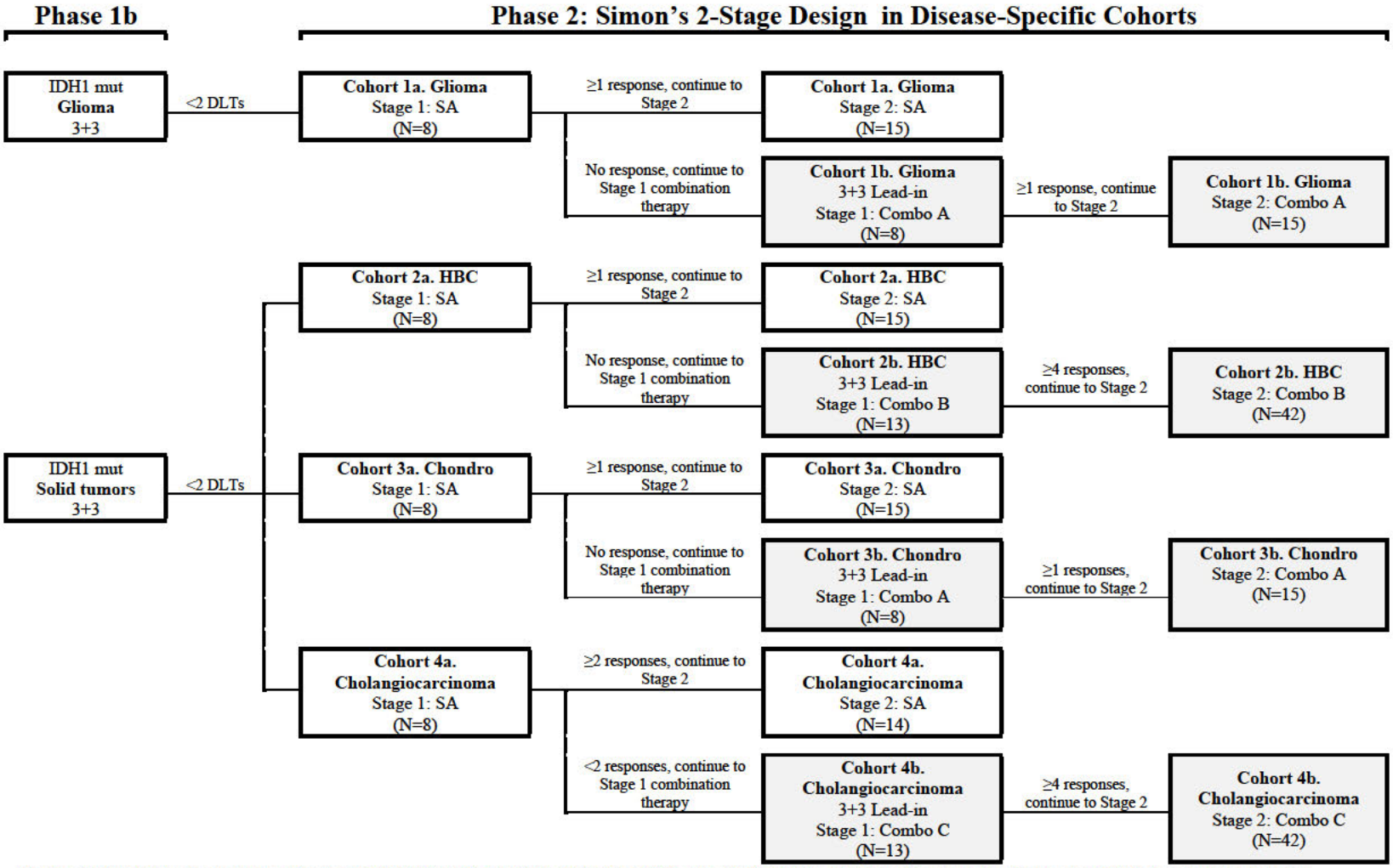
For the Safety Lead-in Periods, the number and type of DLTs experienced by patients will be summarized for each dose level/combination, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to study drug(s).

Summaries of AEs will be based on treatment-emergent AEs (TEAEs). A TEAE is an AE that starts or worsens in the period from the first dose of study treatment to 28 days after the last dose of study drug (any of the combination agents, whichever is later).

TEAEs will be summarized by cohort and dose level and by the frequency of patients experiencing TEAEs corresponding to MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs). Separate tabulations will also be produced for TEAEs assessed as related to study drug(s), TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥Grade 3 in severity. Treatment-emergent serious AEs (SAEs) and SAEs related to study drug(s) will also be tabulated.

Shifts in grade from baseline to the maximum post-baseline grade will be summarized by dose level or treatment group for applicable laboratory data. Laboratory values ≥Grade 3 in severity will be tabulated by dose level or treatment group.

Figure 1: Study Schematic



Combo A=FT-2102 + 5-azacitidine; **Combo B**=FT-2102 + PD-1 inhibitor (nivolumab); **Combo C**=FT-2102 + GemCis; Chondro=chondrosarcoma; DLT=dose limiting toxicity; HBC=hepatobiliary cancer; IHCC=intrahepatic cholangiocarcinoma; mut=mutation; SA=single-agent FT-2102.
Combination therapy in cohorts 1-4 may also be examined in the event that the single agent cohort passes the futility analysis and the enrollment in the single agent cohort is completed

Up to 6 patients with relapsed or refractory non-CNS solid tumors harboring an IDH1 R132X mutation in exploratory Cohort 5a will be treated with single-agent FT-2102.

Table 1: Screening Assessments Checklist[a]

• Informed consent • Inclusion/exclusion criteria • Medical history & demographics • Cancer history • Prior/Concomitant medications & procedures • Full physical examination	• ECOG performance status • ECG (12-lead)[b] • Blood chemistry including CrCl calculation • Hematology and coagulation[c] • Hepatitis B and C[d]	• Urinalysis • Serum β-hCG pregnancy test[e] • Tumor evaluation[f] • AE/SAE assessment[g] • Slides/block of tumor[h] • IDH1 mutation assessment[i] • Child-Pugh Score (HBC only)

a) Screening performed ≤30 days from the first dose (C1D1). See Section 6.1 for details on each study assessment.
b) 12-lead ECG will be conducted following an approximate 10-minute rest period and obtained in triplicate within approximately a 5-minute time period. QTc measurements will use the Fridericia's correction method (QTcF). ECGs will be read locally by the Investigator.
c) CBC includes WBC, Hct, Hb, platelet, differential. Chemistries include: blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), albumin, magnesium, calcium, phosphorus, and prothrombin time (HBC only),
d) All patients will be tested for anti-hepatitis C antibody (anti-HCV) and hepatitis B surface antigen (HbsAg) at Screening. If hepatitis C antibody test is positive, then only patients with hepatitis C RNA <615 IU/L or 100 copies/mL per National Genetics Institute assay or local institutional standard will be eligible.
e) For WCBP, the screening pregnancy test will be serum and must be performed within 7 days prior to the first dose to confirm eligibility.
f) Quantification of baseline disease burden as applicable for disease type. The modality chosen to evaluate each individual patient should be the same throughout the duration of the study. For patients with glioma at sites participating in magnetic resonance spectroscopy, a baseline study should be performed.
g) For all patients, AEs should be monitored from signing of the ICF through 28 days post last dose (whichever is dosed last) or until the patient is determined to be a screen failure. After completion of the initial screening assessments, any new clinically significant findings for enrolled patients will be captured as an AE on the electronic case report form. SAEs for all patients will be reported from the time of the signing of the ICF until 28 days post last dose of FT-2102 or combination therapy agent (whichever is dosed last). At any time after completion of the AE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to any study drug, the event must be reported.
h) Most recent tumor sample, in the form of FFPE block or cut slides, and accompanying pathology report for all patients to be submitted centrally.
i) IDH1 mutation testing and method per local standards. For patients with tumors of unknown IDH1 mutation status, contact Medical Monitor.

Table 2: Schedule of Assessments: Single-Agent FT-2102 (Safety Lead-in, Cohorts 1a, 2a, 3a, 4a, and 5a)

	Cycle 1 (28 days±2)				Cycle 2 & beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1±2	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Safety Measurements											
Con. Medications & Procedures	X	X	X	X	X		X		X	X	
AE/SAE assessment[c]	X	X	X	X	X		X[c]		X	X	
Physical examination[d]	X[d]	X	X	X	X		X[d]		X	X	
ECOG Performance status	X[e]				X				X		
Clinical Laboratory Measurements											
Blood chemistry & hematology[f]	X[e]	X	X	X	X		X[f]		X	X	
AST, ALT, Alk Phos, Bilirubin[g]						C2[g]		C2[g]			
Serum AFP, CA19-9, and CEA (IHCC and HBC)	X	See Table 8									
β-hCG pregnancy test[h]	X[e]				C6/C12				X	X	
Blood sample for circulating tumor DNA	X[i]				X[i]				X[i]		
CSF for PK and 2-HG (Glioma)[j]	X				C3				X		
Urine for 2-HG (Glioma)	X				C3						
Blood for PK/2-HG[k]	D1/D2	See Table 6 or Table 7							X		
12-Lead ECG	X	See Table 6 or Table 7							X		
Tumor tissue & pathology report					X[l]				X[l]		
Study Drug Administration											
FT-2102 oral administration[m]	Continuously BID										

Table 2: Schedule of Assessments: Single-Agent FT-2102 (Safety Lead-in, Cohorts 1a, 2a, 3a, 4a, and 5a)

	Cycle 1 (28 days±2)				Cycle 2 & beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1±2	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Response Assessments											
Disease response assessments	See Table 8										
Quality of Life (EQ5D)	X				C3				X		
Survival[n]											X

AFP=Alpha-fetoprotein; Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA=carcinoembryonic antigen; CSF=cerebrospinal fluid.

a. The Treatment Termination (TT) Visit should occur for any patient who discontinues study treatment. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks, or disease response assessments in the previous 30 days.
b. All patients will have a Safety Follow-up visit approximately 28 (+7) days after the last dose of FT-2102. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At minimum this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit may be required.
c. AEs are collected from signing of informed consent through 28 days post last dose of study drug. At cycle 7 and beyond, if patient is on a stable dose of FT-2102 for at least two cycles, CXD15 AE assessment may be via telephone.
d. Physical exam will include an evaluation of disease-relevant systems and capture of vital signs. At cycle 7 and beyond, if patient is on a stable dose of FT-2102 for at least two cycles, CXD15 PE is at investigator's discretion.
e. Screening evaluations performed within 7 days of Cycle 1 Day 1 (C1D1) can be used and assessments do not need to be repeated at C1D1.
f. On dosing days, sample should be collected prior to dosing. Additional (unscheduled) assessments should be performed as clinically indicated. CBC includes WBC, Hct, Hb, platelet, differential. Chemistries include: blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), albumin, magnesium, calcium, and phosphorus. Prothrombin time/partial thromboplastin time (PT/aPTT) assessed at C1D1 only. At cycle 7 and beyond, if patient is on a stable dose of FT-2102 for at least two cycles, CXD15 labs are at investigator's discretion.
g. Additional liver function testing (AST, ALT, alkaline phosphatase, bilirubin [total and direct]) will be performed on C2D8 (±2) and C2D22 (±2).
h. For WCBP only. May be either urine or serum and performed every 6th cycle while on treatment. The assessment at C1D1 should be serum and within 7 days prior to the first dose
i. Blood (processed for plasma) for circulating tumor DNA pre-dose on C1D1, C3D1 and at time of progression.
j. CSF only if medically feasible and clinically indicated, glioma patents only (on C1D1, may be performed <30 days from C1D1).
k. Blood for PK/2-HG processed for plasma. Note there is a Day 2 visit for PK assessment only (Safety Lead-in and Stage 1 only).
l. Optional tumor tissue if medically feasible at time of any disease response and/or time of disease progression to be submitted centrally at Investigator's discretion if clinically indicated.
m. Patients will receive FT-2102 BID until documented disease progression without clinical benefit or unacceptable toxicity.
n. Survival follow-up assessments will occur every 3 months following documented disease progression or start of a new cancer therapy for 24 months after the first dose of FT-2102 or for 12 months from last dose, whichever is longer. These assessments may be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) will be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

Table 3: Schedule of Assessments: FT-2102 + 5-Azacitidine (Cohort 1b [Glioma] and Cohort 3b [Chondrosarcoma])

	Cycle 1 (28 days±2)				Cycle 2 and beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Safety Measurements											
Con. medications & procedures	X	X	X	X	X		X		X	X	
AE/SAE assessment[c]	X	X	X	X	X		X		X	X	
Symptom-directed Physical examination[d]	X[e]	X	X	X	X		X		X	X	
ECOG Performance status	X[e]				X				X		
Clinical Laboratory Measurements											
Blood chemistry & hematology[f]	X[e]	X	X	X	X		X		X	X	
AST, ALT, Alk Phos, Bilirubin[g]						C2[g]		C2[g]			
β-hCG pregnancy test[h]	X[e]				C6/C12				X	X	
Blood sample for circulating tumor DNA	X[i]				X[i]				X[i]		
CSF for PK and 2-HG (glioma)[j]	X				C3				X		
Urine for 2-HG (glioma)	X				C3				X		
Blood for PK/2-HG[k]	D1/D2	See Table 6 or Table 7							X		
12-Lead ECG	X	See Table 6 or Table 7							X		
Tumor tissue & pathology report					X[l]				X[l]		
Study Drug Administration											
FT-2102 oral administration[m]	Continuously BID										

Table 3: Schedule of Assessments: FT-2102 + 5-Azacitidine (Cohort 1b [Glioma] and Cohort 3b [Chondrosarcoma])

	Cycle 1 (28 days±2)				Cycle 2 and beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Azacitidine[n]	D 1-7				D 1-7						
Response Assessments											
Disease response assessments	See Table 8										
Quality of Life (EQ5D)	X				C3				X		
Survival[o]											X

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen; CSF = cerebrospinal fluid.

a. The Treatment Termination (TT) Visit should occur for any patient who discontinues study treatment. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks, or disease response assessments in the previous 30 days.
b. All patients will have a Safety Follow-up visit approximately 28 (+7) days after the last dose of FT-2102. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At minimum this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit may be required.
c. AEs are collected from signing of informed consent through 28 days post last dose of study drug.
d. Physical exam will include an evaluation of disease-relevant systems and capture of vital signs.
e. Screening evaluations performed within 7 days of Cycle 1 Day 1 (C1D1) can be used and assessments do not need to be repeated at C1D1.
f. On dosing days, sample should be collected prior to dosing. Additional (unscheduled) assessments should be performed as clinically indicated. CBC includes WBC, Hct, Hb, platelet, differential. Chemistries include: blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), albumin, magnesium, calcium, and phosphorus. PT/aPTT assessed at C1D1 only.
g. Additional liver function testing (AST, ALT, alkaline phosphatase, bilirubin [total and direct]) will be performed on C2D8 (±2) and C2D22 (±2).
h. For WCBP only. May be either urine or serum and performed every 6th cycle while on treatment. The assessment at C1D1 should be serum and within 7 days of first dose.
i. Blood for circulating tumor DNA pre-dose on C1D1, C3D1 and at time of progression.
j. CSF only if medically feasible and clinically indicated, glioma patents only (on C1D1, may be performed <30 days from C1D1).
k. Blood for PK/2-HG processed for plasma. Note there is a Day 2 visit for PK assessment only (Safety Lead-in and Stage 1 only).
l. Optional tumor tissue if medically feasible at time of disease response and/or time of disease progression.
m. Patients will receive FT-2102 BID until documented disease progression without clinical benefit or unacceptable toxicity.
n. Patients will receive 5-azacitidine 75 mg/m^2/day IV on Days 1-7 of each cycle 28-day cycle until disease progression or unacceptable toxicity. If the patient has unacceptable toxicity with 5-azacitidine, they may continue with FT-2102 until disease progression or unacceptable toxicity.
o. Survival follow-up assessments will occur every 3 months following documented disease progression or start of a new cancer therapy for 24 months after the first dose of FT-2102 or 12 months after the last dose, whichever is longer. These assessments may be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) will be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

Table 4: Schedule of Assessments: FT-2102 + PD-1 Inhibitor (Nivolumab) (Cohort 2b [HBC])

	Cycle 1 (28 days±2)				Cycle 2 & beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Safety Measurements											
Con. medications & procedures	X	X	X	X	X		X		X	X	
AE/SAE assessment[c]	X	X	X	X	X		X		X	X	
Symptom-directed Physical examination[d]	X[e]	X	X	X	X		X		X	X	
ECOG Performance status	X[e]				X				X		
Clinical Laboratory Measurements											
Blood chemistry & hematology[f]	X[e]	X	X	X	X		X		X	X	
AST, ALT, Alk Phos, Bilirubin[g]						C2[g]		C2[g]			
Serum AFP, CA19-9, and CEA (HBC)	X	See Table 8									
Thyroid-stimulating hormone	X				C6/C12				X		
β-hCG pregnancy test[h]	X[e]				C6/C12				X	X	
Blood sample for circulating tumor DNA	X[i]				X[i]				X[i]		
Blood for PK/2-HG[j]	D1/D2	See Table 6 or Table 7							X		
12-Lead ECG	X	See Table 6 or Table 7							X		
Tumor tissue & pathology report					X[k]				X[k]		
Study Drug Administration											
FT-2102 oral administration[l]	Continuously BID										

Table 4: Schedule of Assessments: FT-2102 + PD-1 Inhibitor (Nivolumab) (Cohort 2b [HBC])

	Cycle 1 (28 days±2)				Cycle 2 & beyond (28±2 days)				Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Nivolumab therapy[m]	X		X		X		X				
Response Assessments											
Disease response assessments	See Table 8										
Quality of Life (EQ5D)	X						C3		X		
Survival[n]											X

AFP = Alpha-fetoprotein; Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen.

a. The Treatment Termination (TT) Visit should occur for any patient who discontinues study treatment. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks, or disease response assessments in the previous 30 days.
b. All patients will have a Safety Follow-up visit approximately 28 (+7) days after the last dose of FT-2102. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At minimum this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit may be required.
c. AEs are collected from signing of informed consent through 28 days post last dose of study drug (through 150 day post last dose of nivolumab).
d. Physical exam will include an evaluation of disease-relevant systems and capture of vital signs.
e. Screening evaluations performed within 7 days of Cycle 1 Day 1 (C1D1) can be used and assessments do not need to be repeated at C1D1.
f. On dosing days, sample should be collected prior to dosing. Additional (unscheduled) assessments should be performed as clinically indicated. CBC includes WBC, Hct, Hb, platelet, differential. Chemistries include: blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), albumin, magnesium, calcium, and phosphorus. PT/aPTT assessed at C1D1 only.
g. Additional liver function testing (AST, ALT, alkaline phosphatase, bilirubin [total and direct]) will be performed on C2D8 (±2) and C2D22 (±2).
h. For WCBP only. May be either urine or serum and performed every 6th cycle while on treatment. The assessment at C1D1 should be serum and within 7 days of first dose.
i. Blood for circulating tumor DNA pre-dose on C1D1, C3D1 and at time of progression.
j. Blood for PK/2-HG processed for plasma.. Note there is a Day 2 visit for PK assessment only (Safety Lead-in and Stage 1 only).
k. Optional tumor tissue if medically feasible at time of disease response and/or time of disease progression.
l. Patients will receive FT-2102 BID until documented disease progression without clinical benefit or unacceptable toxicity.
m. Patients will receive nivolumab 240 mg IV every 2 weeks until documented disease progression or unacceptable toxicity. If the patient has unacceptable toxicity with nivolumab they may continue with FT-2102 until disease progression or unacceptable toxicity.
n. Survival follow-up assessments will occur every 3 months following documented disease progression or start of a new cancer therapy for 24 months after the first dose of FT-2102. These assessments may be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) will be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

Table 5: Schedule of Assessments: FT-2102 + Chemotherapy (GemCis) (Cohort 4b IHCC)

	Cycle 1 (28±7 days)				Cycle 2 to 6 (28±7 days)				Cycle 7 & Beyond (28±2 days)		Treatment Termination (TT)[a]	Safety Follow-up[b]	Survival Follow-up
	D1[a]	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	D1	D15±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Safety Measurements													
Concomitant medications & procedures	X	X	X	X	X		X	X	X	X	X	X	
AE/SAE assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X	
Symptom-directed Physical examination[d]	X[e]	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance status	X[e]				X				X		X		
Clinical Laboratory Measurements													
Blood chemistry & hematology[f]	X[e]	X	X	X	X	X	X		X	X	X	X	
AST, ALT, Alk Phos, Bilirubin[g]						C2[g]		C2[g]					
Serum CA19-9, and CEA	X	See Table 8											
β-hCG pregnancy test[h]	X[e]				X				X		X	X	
Blood for circulating tumor DNA	X[i]				X[i]						X[i]		
Blood sample for PK/2-HG[j]	X	See Table 6 or Table 7									X		
12-Lead ECG	X	See Table 6 or Table 7									X		
Tumor tissue with copy of associated pathology report					X[k]						X[k]		

Table 5: Schedule of Assessments: FT-2102 + Chemotherapy (GemCis) (Cohort 4b IHCC)

	Cycle 1 (28±7 days)				Cycle 2 to 6 (28±7 days)				Cycle 7 & Beyond (28±2 days)		Treatment Termination (TT) [a]	Safety Follow-up [b]	Survival Follow-up
	D1[a]	D8±2	D15±2	D22±2	D1	D8±2	D15±2	D22±2	D1	D15±2	≤7 d from treatment termination	28 (+7) d from last dose	Every 3 months (±2 weeks)
Study Drug Administration													
FT-2102 oral administration[l]	**Continuously BID**												
GemCis Chemotherapy[m]	X	X			X	X							
Response Assessments													
Disease response assessments	**See** Table 8												
Quality of Life (EQ5D)	X				C3								
Survival[n]													X

Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase CEA = carcinoembryonic antigen.

a. The Treatment Termination (TT) Visit should occur for any patient who discontinues study treatment. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks, or disease response assessments in the previous 30 days.
b. All patients will have a Safety Follow-up visit approximately 28 (+7) days after the last dose of FT-2102. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At minimum this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit may be required.
c. AEs are collected from signing of informed consent through 28 days post last dose of study drug.
d. Physical exam will include an evaluation of disease-relevant systems and capture of vital signs.
e. Screening evaluations performed within 7 days of Cycle 1 Day 1 (C1D1) can be used and assessments do not need to be repeated at C1D1.
f. On dosing days, sample should be collected prior to dosing. Additional (unscheduled) assessments should be performed as clinically indicated. CBC includes WBC, Hct, Hb, platelet, differential. Chemistries include: blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), albumin, magnesium, calcium, and phosphorus. Cr Cl to be calculated C1-6, D1. PT/aPTT assessed at C1D1 only.
g. Additional liver function testing (AST, ALT, alkaline phosphatase, bilirubin [total and direct]) will be performed on C2D8 (±2) and C2D22 (±2).
h. For WCBP only. May be either urine or serum and performed every 6th cycle while on treatment. The assessment at C1D1 should be serum and within 7 days of first dose.
i. Blood for circulating tumor DNA pre-dose on C1D1, C3D1 and at time of progression.
j. Blood for PK/2-HG processed for plasma. Note there is a Day 2 visit for PK assessment only (Safety Lead-in and Stage 1 only).
k. Optional tumor tissue if medically feasible at time of disease response and/or time of disease progression
l. Patients will receive FT-2102 BID until documented disease progression without clinical benefit or unacceptable toxicity.
m. Patients will receive GemCis (cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2) on Day 1 and Day 8 of every 28-day cycle for up to 6 cycles. If the patient has unacceptable toxicity with GemCis they may continue with FT-2102 until disease progression or unacceptable toxicity.

n. Survival follow-up assessments will occur every 3 months following documented disease progression or start of a new cancer therapy for 24 months after the first dose of FT-2102. These assessments may be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) will be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

Table 6: Schedule of Pharmacokinetics (PK), PD (2-HG), and Electrocardiogram Assessments (Safety Lead-in, Cohort 5a and Stage 1 of Each Cohort: Single-Agent and Combination)

Cycle	Day	Scheduled timepoint	PK Sample[a]	PD (2-HG)	ECG collection[b]
1	1	Pre-dose	X	X	X
		1 hours (±5 min)	X		
		2 hours (±15 min)	X		
		4 hours (±15 min)	X	X	X
		8 hours (±30 min)	X		X
	2[c], 8, 15, 22	Pre-dose	X	X [d]	X
2	1	Pre-dose	X	X	X
		1 hours (±5 min)	X		
		2 hours (±15 min)	X		
		4 hours (±15 min)	X		X
		8 hours (±30 min)	X		
3 and beyond	1 (±2)	Pre-dose	X	X	X
AE directed	TBC	If needed for treatment-related AE	X		
EoT	--	--	X	X	X

a. An additional blood sample for PK should be drawn if a patient presents with a DLT, including a DLT-like toxicity outside of Cycle 1.

b. At time points for ECG extraction, patients will rest for 10 minutes in a semi-recumbent or supine position. ECGs will be extracted in triplicate within approximately a 5-minute time period at pre and post-dose time points shown above. QTc measurements will use the Fridericia's correction method. All PK samples should be collected after ECG at time points when both are scheduled. ECGs will be read locally by the Investigator.

c. Hold evening dose on C1D1

d. Day 8, 15 and 22 only.

Table 7: Schedule of Pharmacokinetics (PK), PD (2-HG), and Electrocardiogram Assessments (Stage 2 of Each Cohort: Single-Agent and Combination)

Cycle	Day	Scheduled Timepoint	PK Sample[a]	PD (2-HG)	ECG collection[b]
1	1	Pre-dose	X	X	X
3	1	Pre-dose	X	X	X
Random	TBC	If needed based on treatment related AE	X		
EoT	--	--	X	X	X

AE=adverse event; EoT=end of treatment; TBC=to be confirmed.

a. An additional blood sample for PK should be drawn if a patient presents with a DLT, including a DLT-like toxicity outside of Cycle 1.

b. At time points for ECG extraction, patients will rest for 10 minutes in a semi-recumbent or supine position. ECGs will be extracted in triplicate within approximately a 5-minute time period at time points shown above. QTc measurements will use the Fridericia's correction method. All PK samples should be collected after ECG at time points when both are scheduled. ECGs will be read locally by the Investigator.

Table 8: Schedule of Efficacy and Biomarker Assessments (by Cohort)

Cohort	Population	Assessment Criteria	Response Assessment	Tumor Markers	Cycles (Day 1)[b]
1	Glioma	Modified RANO Criteria 2017 and LGG-RANO	Contrast-enhanced MRI (local) and MRS [a] for 2-HG (central)	NA	C3, C5, C7, C9, C12, every 3 cycles thereafter
2	HBC	RECIST v1.1	CT / MRI	Serum AFP, CA19-9, and CEA	C3, C5, C7, C9, C12, every 3 cycles thereafter
3	Chondrosarcoma	RECIST v 1.1	CT / MRI	NA	C3, C5, C7, C9, C12, every 3 cycles thereafter
4	IHCC	RECIST v1.1	CT / MRI	Serum CA19-9, and CEA	C3, C5, C7, C9, C12, every 3 cycles thereafter
5	Other IDH1 Solid Tumors	RECIST v1.1	CT/MRI	NA	C3, C5, C7, C9, C12, every 3 cycles thereafter

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; RANO=revised assessment in neuro-oncology or LGG RANO=low grade glioma revised assessment in neuro-oncology, RECIST=Response Evaluation Criteria in Solid Tumors.

a. MRS at selected US centers only for patients in cohort 1a and 1b.
b. Disease assessment may be performed +/- 7 days but must be prior to starting next cycle.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-HG	2-hydroxygluterate
α-KG	alpha-ketoglutarate
ADL	activities of daily living
AE	adverse event
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
anti-HCV	anti-hepatitis C antibody
API	active pharmaceutical ingredient
AST/SGOT	aspartate aminotransferase
AT	All-Treated
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time zero to the last quantifiable time point
$AUC_{0\text{-INF}}$	area under the plasma concentration-time curve from time zero extrapolated to infinity
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CEC	Central Ethics Committee
CIRB	Central Institutional Review Board
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response/remission
CSF	cerebrospinal fluid
ctDNA	Circulating tumor DNA
DNA	deoxyribonucleic acid
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFD	embryo-fetal developmental
EoT	End of Treatment
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GemCis	gemcitabine and cisplatin
HBC	hepatobiliary cancer
hBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
IHCC	intrahepatic cholangiocarcinoma
IEC	independent ethics committee
INR/PT	international normalized ratio/prothrombin time
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
KPS	Karnofsky Performance Status
LC/MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
LEC	Local Ethics Committee
LFT	liver function test
LGG	low-grade glioma
LPLV	last patient last visit
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response

Abbreviation	Definition
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD-1	programmed death-1
PD	pharmacodynamic
PE	physical examination
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic(s)
PR	partial response/remission
PRN	as needed
PT	Preferred Term
PT/aPTT	Prothrombin time/activated partial thromboplastin time
QOL	quality of life
QTcF	QT interval corrected with Fridericia's method
RANO	Revised Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TdP	Torsades de Pointes
t_{max}	time of maximum observed plasma concentration
TTP	time to progression
TTR	time to response
ULN	upper limit of normal

Abbreviation	Definition
WBC	white blood cell
WCBP	women of childbearing potential
WHO	World Health Organization

1. BACKGROUND

1.1. IDH1 R132X Mutations

Isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) mutations in cancer result in abnormal hypermethylation of histones and DNA and suppression of normal cellular differentiation. The metabolic enzyme IDH1 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). In both hematologic and solid tumor malignancies, IDH1 mutations lead to aberrant accumulation of (R)-2-hydroxyglutarate (2-HG). 2-HG has been proposed to act as an "oncometabolite" that has pleotropic effects on tumorigenesis. Excess production of 2-HG has been shown to inhibit α-KG-dependent enzymes involved in epigenetic regulation, collagen synthesis, and cell signaling, thereby leading to a block in normal differentiation of progenitor cells and the subsequent development of cancer (Gross et al, 2010; Cairns et al, 2013; Losman et al, 2013). Therefore, inhibition of mutated IDH1 in tumor cells and the concomitant decrease in 2-HG production is expected to restore normal cellular differentiation and provide therapeutic benefit in IDH1-mutated cancers.

The identification of frequent mutations in the IDH1 and IDH2 genes in human cancers including glioma, hepatocellular carcinomas, chondrosarcomas and intrahepatic cholangiocarcinoma (IHCC) has provided novel therapeutic targets in these diseases (Yan et al, 2009; Amary et al, 2011; Wang et al, 2013; Lee et al, 2017). IDH mutation specific inhibitors have been shown to reduce aberrantly elevated levels of the oncometabolite 2-HG, resulting in antitumor efficacy in preclinical models (Rohle et al, 2013; Saha et al, 2014). Clinical investigation in patients with IHCC, gliomas and chondrosarcomas are ongoing with several other IDH1 inhibitors. A comparable IDH1 inhibitor, AG-120 has published preliminary data regarding clinical activity in gliomas, chondrosarcomas and IHCC (Tap et al, 2016; Ishii et al, 2017; Mellinghoff et al, 2017).

1.2. FT-2102

1.2.1. Preclinical Summary

[redacted]

[redacted]

1.2.2. Clinical Summary

[redacted]

1.3. Study Rationale

1.3.1. Selection of Patient Populations

Seventy to eighty percent of patients with Grade II-III gliomas bear mutations in IDH1 or IDH2. These IDH mutations have been described to induce a global hypermethylation phenotype (Lu et al, 2012). IDH1 inhibitors have been evaluated in clinical trials with demonstration of preliminary clinical activity (Lowery et al, 2017).

In addition to IDH inhibitors, demethylating agents have demonstrated reduction of methylation and growth inhibition in IDH1 mutant glioma xenografts and patient derived glioma initiator cells (Borodovsky et al, 2013; Turcan et al, 2013). An investigation of single-agent IDH1 inhibitor and combination therapy with a demethylating agent with known safety profile, azacitidine, is proposed in the clinical study.

IDH1 mutations have been reported in a subset of clear cell hepatocellular carcinoma and associated with poor prognosis in a single center investigation (Lee et al, 2017). Histone modification and epigenetic DNA methylation has been demonstrated to repress tumor Th1-type chemokines and subsequently determine effector T-cell trafficking into the tumor microenvironment (Peng et al, 2015). Thus, cancer epigenetic reprograming may remove Th1-type chemokine repressive marks and promote effector T-cell trafficking into the tumor microenvironment and improve the therapeutic efficacy of PD-1 immune checkpoint blockade. The PD-1 inhibitor, nivolumab, has demonstrated clinical activity in advanced hepatocellular carcinoma (El-Khoueiry et al, 2017). The proposed clinical study investigates single-agent FT-2102, then possibly in combination with nivolumab in patients with HBC with the R132X IDH1 mutation.

Mutations of the IDH1/2 genes are present in up to 50% of chondrosarcomas and reported with the enchondromatosis-associated non-hereditary Maffucci and Ollier syndromes, suggesting that the IDH mutation may represent an early tumorigenic event (Amary et al, 2011; Meijer et al, 2012). IDH mutations have been shown to create a hypermethylation phenotype in chondrosarcoma cells which may be reversed with demethylating agents, 5-azacitidine (Lu et al, 2012). The proposed clinical study will evaluate single-agent FT-2102 followed by a combination with 5-azacitidine for patients with relapsed or refractory chondrosarcoma with an IDH1 mutation. For patients with locally advanced or metastatic biliary cancer including IHCC, the current standard of care includes combination chemotherapy with gemcitabine and cisplatin (Valle et al, 2010) with a short duration of progression free survival (PFS; 8.0 months, CI: 6.6-8.6 months) and overall survival (OS) of 11.7 months (CI: 9.5-14.3 months). Other combination agents have been evaluated with comparable PFS and OS (Eckmann et al, 2011). As IDH mutations have been reported to occur in up to 25% of IHCC (Goyal et al, 2015), an evaluation of FT-2102 as a single agent followed by combination with gemcitabine + cisplatin for patients with advanced unresectable IHCC is proposed.

1.4. Determination of Starting Doses and Regimen

1.4.1. Single-Agent FT-2102

Clinical Study 2102-HEM-101 is an ongoing Phase 1/2 investigation in patients with advanced hematologic malignancies with IDH1 mutations. In this study, dose escalation was initiated using FT-2102 as a single agent in AML or MDS patients harboring an IDH1-R132 mutation, as determined by local mutation testing. FT-2102 doses of 150, 300 mg QD and 150 mg BID have been evaluated. FT-2102 is administered orally in continuous 28-day cycles. There were no DLTs observed at any doses and an MTD was not determined. The Phase 1 single-agent study has been completed and a review of available safety data, including all adverse events (AEs) reported in patients treated with the 150 mg BID dose concluded that the safety profile was consistent with that of patients treated in dose escalation; no new safety signals were observed in the expansion cohorts.

Based on this review, in combination with achievement of targeted 2-HG depletion in plasma and preliminary pharmacokinetics (PK), FT-2102 150 mg BID was declared the RP2D for further evaluation in hematologic malignancies (additional details in the IB).

As part of the safety evaluation of the combinations, in each combination cohort, there will be a 3+3 design, safety evaluation of the first patients enrolled in each combination cohort.

1.4.2. FT-2102 in Combination with Azacitidine

There have been extensive evaluations of azacitidine in patients with hematologic malignancies leading to the currently approved dose is 75 mg/m^2/day × 7 days delivered either subcutaneously or intravenously every 28 days (VIDAZA US Prescribing Information). In the Clinical Study 2102-HEM-101, as of 7-April-2018, 26 patients with advanced hematologic malignancies received FT-2102 in combination with azacitidine at 75 mg/m^2/day × 7 days every 28 days (20 patients: FT-2102 at 150 mg BID; 7 patients: FT-2102 at 150 mg QD). When given in combination, when compared to single-agent FT-2102, there were additional gastrointestinal toxicities noted in combination (nausea, constipation, and diarrhea) and electrolyte abnormalities (hypokalemia and hypophosphatemia) which are known toxicities of azacitidine (additional details in IB and azacytidine PI (VIDAZA US Prescribing Information).

Clinical investigations of azacitidine in solid tumors however are quite limited. Jeurgens evaluated the combination of a novel histone deacetylase inhibitor, entinostat, with azacitidine dosed at either 30 mg/m^2/day or 40 mg/m^2/day × 10 days (with a 48-hour interruption at Day 6) in patients with relapsed/refractory non-small cell lung carcinoma. The Investigators concluded that 40 g/m^2/day is a tolerable dose in this small subset of patients (Juergens et al, 2011). A meta-analysis of 11 clinical studies in a total of 694 patients with a variety of solid tumors found response plus stable disease rates of ~35% in breast, colorectal and pancreatic cancers. The authors found that intravenous dosing was supported by the available data (not subcutaneous) and that 67.5 mg/m^2/day correlated favorably with response rates in gastrointestinal (GI), lung and breast cancer (Cowan et al, 2010). Thus, the proposed study will investigate initially in a 3+3 dose confirmation an azacitidine dose of 75 mg/m^2/day for a total of 7 doses permitting a 48-hour window as needed for patient convenience. If there is toxicity at that dose, additional doses will be investigated. If the patient has intolerance to azacitidine, they can continue with FT-2102 as a single agent.

1.4.3. FT-2102 in Combination with Nivolumab

The dose of the PD-1 inhibitor, nivolumab is based upon the Food and Drug Administration (FDA) approved dose for hepatocellular carcinoma, specifically 240 mg IV every 2 weeks. This dose will be the basis for sites where nivolumab is not approved for hepatocellular carcinoma. If the patient is intolerant of nivolumab, they can continue on single-agent FT-2102. Clinical experience to date with FT-2102 includes as a single agent or in combination with azacitidine. Based on the mechanism of action of nivolumab and FT-2102, it is not anticipated that there will be overlapping toxicities, but it is unknown at this time.

1.4.4. FT-2102 in Combination with GemCis

The dose of gemcitabine/cisplatin is based upon the standard of care regimen established by Valle and colleagues (Valle et al, 2010) and a reasonable global standard in a review by Weber and colleagues (Weber et al, 2015): cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2), each administered on Days 1 and 8, every 3 weeks for eight cycles for up to 24 weeks. For patient convenience and data analysis, cycle duration will be 28 days +/- 7 days when gemcitabine/cisplatin is being given with FT-2102. Following completion of the 24 weeks of therapy or if intolerant of either agent, the patient can continue on single-agent FT-2102 with 28-day cycles. Clinical experience to date with FT-2102 includes as a single agent or in combination with azacitidine. Based on the mechanism of action of gemcitabine, cisplatin and FT-2102, it is anticipated that there may be overlapping toxicities (myelosuppression and/or hepatic toxicity) but it is unknown at this time.

2. OBJECTIVES

2.1. Primary Objectives

2.1.1. Phase 1b

- Evaluate the safety and tolerability of FT-2102 as monotherapy and confirm the dose to be further examined in expansion cohorts as monotherapy and combination therapy

2.1.2. Phase 2

- Evaluate the clinical activity of FT-2102 as a monotherapy or in combination in patients with glioma, hepatobiliary cancer (HBC), chondrosarcoma, and IHCC harboring an IDH1 mutation

2.2. Secondary Objectives

2.2.1. Phase 1b

- Evaluate the PK of FT-2102 as single agent and in combination with other anti-cancer agents
- Evaluate the clinical activity of FT-2102 as a single agent or in combination in patients with glioma, HBC, chondrosarcoma, and IHCC harboring an IDH1 mutation

2.2.2. Phase 2

- Evaluate the safety of FT-2102 administered as monotherapy and in combination with other anti-cancer agents in patients with glioma, HBC, chondrosarcoma, and IHCC harboring an IDH1 mutation
- Evaluate the PK of FT-2102 as single agent and in combination with other anti-cancer agents
- Evaluate additional measures of antitumor activity of FT-2102 as a single agent or in combination with other anti-cancer agents

2.3. Exploratory Objectives (Phases 1b and 2)

- Evaluate potential biomarkers of response, resistance, and/or safety
- Evaluate pharmacodynamic (PD) and PK/PD relationship of FT-2102 as monotherapy and in combination with other anti-cancer agents
- Evaluate the biological effects of FT-2102 on tumor tissue, including tumor cells, CSF, immune cells, and vasculature
- Evaluate the biological effects of FT-2102 on tumor tissue, including tumor cells, CSF, immune cells, and vasculature
- Assess IDH1 mutations in ctDNA and correlate with mutations in tumor tissues
- Evaluate the health-related quality of life (QOL)

3. ENDPOINTS

3.1. Primary Endpoints

3.1.1. Phase 1b

- DLTs (Safety Lead-in Periods), adverse event (AEs), and safety laboratory values

3.1.2. Phase 2

- Objective response rate (ORR), as determined by applicable disease criteria, for disease-specific cohorts

3.2. Secondary Endpoints (Phases 1b and 2)

- AEs, and safety laboratory values (Phase 2)
- ORR (Phase 1b only)
- PFS, defined as the time from the first dose to disease progression as determined by applicable disease criteria or death due to any cause, whichever is sooner
- Time to progression (TTP), defined as the time from start of treatment until disease specified progression
- Duration of response (DOR), defined as the time from the first response to documented disease progression as determined by applicable disease criteria
- OS, defined as the time from the first dose to death due to any cause
- Time to Response (TTR), defined as the time from first dose to first response AEs and abnormal laboratory findings
- PK parameters derived from plasma/cerebrospinal fluid (CSF) FT-2102 concentrations

3.3. Exploratory Endpoints (Phases 1b and 2)

- PD and PK/PD in relationship with clinical safety and clinical activity
- Changes in 2-hyroxygluterate (2-HG levels) (PD, biomarker) in plasma and tumor tissue (1H magnetic resonance spectroscopy (MRS) and CSF in intracranial gliomas and tumor biopsies for other tumors)
- Characterization of biological effects of FT-2102 on tumor biopsies
- Cancer-associated mutations and/or genetic alterations
- IDH1 mutation in ctDNA
- Health-related QOL patient-reported questionnaire (EQ5D)

4. STUDY DESIGN

This is a multicenter, Phase 1b/2, open-label, multiple-cohort study examining the efficacy and safety of FT-2102 as a single agent or in combination for the treatment of patients with advanced solid tumors and gliomas with IDH1 R132X mutations.

Please see Figure 1 for an overview of the study. The starting dose of FT-2102 is 150 mg BID administered continuously in 28-day cycles; the selection of the starting dose is based on results from a Phase 1 study in patients with hematologic malignancies.

4.1. Safety Lead-in Period: Phase 1b

4.1.1. Single-Agent

The study will consist of a Safety Lead-in Period to confirm the safety and tolerability of single-agent FT-2102 150 mg BID administered over 28 days (1 cycle). The Safety-Lead-in Period will employ a traditional 3+3 design, whereby 3 patients with any of the solid tumors (Cohorts 2a-5a) and 3 patients with gliomas (Cohort 1a) are treated with FT-2102 150 mg BID and monitored for DLTs during the first cycle of study treatment.

- If no DLTs occur in the first 3 patients in either the solid tumor group (Cohorts 2a-5a) or the glioma group (Cohort 1a), and available PK/PD data support the dose, enrollment will continue in the 4 disease-specific cohorts described below.
- If a DLT occurs in the first 3 patients in either group, an additional 3 patients will be treated at that dose level in either the solid tumor group (Cohorts 2a-5a) or the glioma group (Cohort 1a). If no DLTs occur in these additional 3 patients (ie, <2 DLTs per 6 patients) and available PK/PD data support the dose, enrollment will continue in the 4 disease-specific cohorts described below.
- If there are ≥2 DLTs at the starting dose, 150 mg once daily of FT-2102 will be evaluated following review by the Safety Review Committee (SRC). Likewise, higher doses may be evaluated based upon safety, PK, and PD data as determined by the SRC.

The 3+3 design of the Safety Lead-in period is based on DLT evaluable patients. If a patient enrolls in this phase, but does not qualify as DLT evaluable, that patient will be replaced.

4.1.2. Combination

DLTs will be evaluated within the first 3 (or 6) patients of any cohort examining combination therapy to confirm the safety and tolerability of combination therapy administered over 28 days (1 cycle) for Cohort 1b, Cohort 2b, Cohort 3b, and Cohort 4b using a 3+3 design (ie, up to the first 6 patients in each combination cohort). The cohort will be stopped if there is more than 1 DLT out of the first 6 patients, and additional dose levels will be evaluated as follows:

- If no DLTs occur in the first 3 patients in a combination cohort and available PK/PD data support the dose, enrollment will continue in the that disease-specific cohort.
- If a DLT occurs in the first 3 patients in a combination cohort, an additional 3 patients will be treated at that dose level. If no DLTs occur in these additional 3 patients (ie,

<2 DLTs per 6 patients) and available PK/PD data support the dose, enrollment will continue in the specific combination cohort.

- If there are ≥2 DLTs at the starting dose the following dose de-escalations of either the combination agent or FT-2102 will be evaluated following review by the Safety Review Committee (SRC). Following that evaluation, the SRC will evaluate the available safety, PK and PD data to determine the dose(s) to be used in the combination Phase 2.

If a patient enrolls in this phase, but does not qualify as DLT evaluable, that patient will be replaced.

The dose levels for the combination cohorts are presented in Table 9, Table 10, and Table 11.

Table 9: Dose Levels for FT-2102 + Azacitidine

Dose Level	FT-2102	Azacitidine
-1 (hematologic DLT)	150 mg BID continuously × 28 days	37 mg/m^2/day IV × 7 days every 28 days
-1 (non-hematologic DLT)	150 mg QD continuously × 28 days	75 mg/m^2/day IV × 7 days every 28 days
1 (starting dose)	150 mg BID continuously × 28 days	75 mg/m^2/day IV × 7 days every 28 days

BID=twice daily; DLT=dose limiting toxicity; QD=once daily.

Table 10: Dose Levels for FT-2102 + Gemcitabine/Cisplatin

Dose Level	FT-2102	Gemcitabine/Cisplatin
-1 (any DLT)	150 mg QD continuously × 28 days	Cisplatin 25 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV on Day 1 and Day 8
1 (starting dose)	150 mg BID continuously × 28 days	Cisplatin 25 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV on Day 1 and Day 8

BID = twice daily; DLT = dose limiting toxicity; QD = once daily

Table 11: Dose Levels for FT-2102 + Nivolumab

Dose Level	FT-2102	Nivolumab
-1 (Any DLT)	150 mg QD continuously × 28 days	240 mg IV every 2 weeks
1 (starting dose)	150 mg BID continuously × 28 days	240 mg IV every 2 weeks

BID=twice daily; DLT=dose limiting toxicity; IV=intravenously; QD=once daily.

4.1.3. Safety Review Committee

This study will utilize an SRC, which will meet quarterly at a minimum to review all accumulated data, including safety, PK, PD, and efficacy. The SRC will comprise a medical representative from the Sponsor and all Principal Investigators (PIs) or delegates at each of the enrolling sites. The SRC will use all available data to confirm dose decisions and if needed, recommend changes to the dosing paradigm.

In addition, close monitoring of serious safety events as they are reported are conducted by the Medical Monitor. Serious and non-serious adverse event review is conducted regularly by the Medical Monitor through monthly listing review. Safety events are also reviewed during regular study conduct meetings between the Medical Monitor, the clinical team, pharmacovigilance, and the participating Investigators (the SRC).

These study conduct meetings during the Phase 1 component of this trial include bi-weekly internal review meetings to monitor study progress/safety events and bi-weekly teleconferences with Investigators. For the Phase 2 component, bi-weekly internal meetings will continue and monthly meetings with Investigators are planned.

Periodic safety reviews by FORMA's internal safety group, consisting of the clinical study team, pharmacovigilance, and Medical Monitors not directly involved in the conduct of Study 2102-ONC-102, will also occur. This internal safety group meets at least bi-annually to review safety listings and on an ad hoc basis in response to new safety signals to rapidly assess overall risk to participants. The outcome of these internal safety group meetings, when relevant, is quickly communicated to study Investigators so they may share current risk information with their subjects and collect updated informed consent forms, if appropriate.

4.1.4. Dosing Frequency

FT-2102 will initially be administered either as a single agent at 150 mg BID or in combination until disease progression or unacceptable toxicity. In the combination cohorts, FT-2102 150 mg BID will be administered in combination with 5-azacitidine in glioma and chondrosarcoma, with a programmed death-1 (PD-1) inhibitor in HBC, and with GemCis in cholangiocarcinoma. The SRC will monitor the safety, PK, and PD of both single-agent FT-2102 and combination therapy

during Part 1 of each cohort and may recommend altering the dosing paradigm based on available data. The SRC will conduct an aggregate assessment of PK/PD data as well as a review of the study drug-related AEs to ensure that the combination therapies is safe and well tolerated.

4.2. Disease-Specific Cohorts: Phase 2

Four disease-specific cohorts will employ a Simon's 2-stage-wise design, whereby 8 patients in the first stage of each cohort will be treated with study therapy (either single-agent FT-2102 or in combination with antineoplastic agents) and evaluated for efficacy and safety. After up to 8 patients in Stage 1 have been evaluated for at least 4 cycles of study treatment, disease-specific efficacy data will be evaluated to determine continued enrollment to Stage 2. Enrollment will continue during the Stage 1 evaluation. If Stage 1 efficacy criteria from any single-agent FT-2102 cohort is not met, then examination of combination therapy will be initiated in a new Simon's 2-stage design. Combination therapy in cohorts 1-4 may also be examined in the event that the single agent cohort passes the futility analysis and the enrollment in the single agent cohort is completed.

Safety data from Stage 1 will also be reviewed on an ongoing basis by SRC. Significant safety findings may lead to an early stopping for any cohort and will be considered when deciding to initiate Stage 2 of any cohort. The Simon's 2-stage design is based upon Response Evaluable population. Patients who are not in the Response Evaluable population will not be counted in the numerator or denominator of the number of patients needed in Phase 2.

For the Safety Lead-in Period and Stage 1 of each disease-specific cohort, blood samples for PK and PD will be obtained. Limited PK and PD samples will be obtained during Stage 2.

4.2.1. Cohort 1: Glioma (n=16-46)

Cohort 1 will include patients with glioma harboring an IDH1 R132X mutation that is relapsed or refractory. Glioma patients will be initially treated with single-agent FT-2102 (**Cohort 1a**). Cohort 1a will employ a Simon's 2-stage design, in which 8 patients will be treated with single-agent FT-2102 for 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1).

If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will initiate with single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + 5-azacitidine) (**Cohort 1b**).

Cohort 1b will employ the same Simon's 2-stage design, enrolling 8 evaluable patients in Stage 1 and 15 evaluable patients in Stage 2 with combination therapy.

If ≥1 clinical responses are observed in Stage 1 of Cohort 1b, then Stage 2 (n=15) will be initiated with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any glioma patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment for single-agent or combination treatment.

4.2.2. Cohort 2: HBC (n=21-78)

Cohort 2 will include patients with relapsed/refractory HBC harboring an IDH1 R132X mutation. HBC patients will be initially treated with single-agent FT-2102 (**Cohort 2a**). Cohort 2a will employ a Simon's 2-stage design, in which 8 patients will be treated with single-agent FT-2102 for 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1).

If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will receive single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + PD-1 inhibitor) (**Cohort 2b**).

Cohort 2b will employ a new Simon's 2-stage design, whereby 13 patients will be treated in Stage 1 with combination therapy for 4 cycles (cycle=28 days) and assessed for efficacy and safety.

If ≥4 clinical response is observed in Stage 1 of Cohort 2b, then Stage 2 (n=42) will initiate with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any HBC patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

4.2.3. Cohort 3: Chondrosarcoma (n=16-46)

Cohort 3 will include patients with relapsed/refractory, locally advanced or metastatic chondrosarcoma harboring an IDH1 R132X mutation. Chondrosarcoma patients will be initially treated with single-agent FT-2102 (**Cohort 3a**). Cohort 3a will employ a Simon's 2-stage design, in which 8 patients will be treated with single-agent FT-2102 for 4 cycles (cycle=28 days) and assessed for efficacy and safety (Stage 1).

If ≥1 clinical response is observed in Stage 1, then Stage 2 (n=15) will initiate with single-agent FT-2102.

If no clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + 5-azacitidine) (**Cohort 3b**). Cohort 3b will employ the same Simon's 2-stage design, enrolling 8 patients in Stage 1 and 15 evaluable patients in Stage 2 (n=15) with combination therapy.

If ≥1 clinical responses are observed in Stage 1 of Cohort 3b, then Stage 2 (n=15) will be initiated with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any chondrosarcoma patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

4.2.4. Cohort 4: Cholangiocarcinoma (n=21-77)

Cohort 4 will include patients with advanced cholangiocarcinoma harboring an IDH1 R132X mutation. Cholangiocarcinoma patients will be initially treated with single-agent FT-2102 (**Cohort 4a**). Cohort 4a will employ a Simon's 2-stage design, in which 8 patients will be treated with single-agent FT-2102 for 4 cycles and assessed for efficacy and safety (Stage 1).

If ≥2 clinical responses are observed in Stage 1, then Stage 2 (n=14) will initiate with single-agent FT-2102.

If <2 clinical responses are observed in Stage 1 with single-agent FT-2102, then combination therapy may be examined (FT-2102 + GemCis) (**Cohort 4b**).

Cohort 4b will employ a Simon's 2-stage design, whereby 13 patients will be treated in Stage 1 with combination therapy for 4 cycles and assessed for efficacy and safety.

If ≥4 clinical responses are observed in Stage 1 of Cohort 4b, then Stage 2 (n=42) will be initiated with combination therapy.

During Stage 1 aggregate safety data will be monitored by the SRC. If unacceptable toxicity is observed in Stage 1, then the dose and schedule may be modified by the SRC.

Note: any cholangiocarcinoma patients enrolled in the Safety Lead-in Period will be considered part of Stage 1 enrollment.

4.2.5. Cohort 5a: Other Non-CNS Solid Tumors with IDH1 Mutations (n=6)

Cohort 5a will include patients with relapsed or refractory non-central nervous system (CNS) solid tumors harboring an IDH1 R132X mutation. This cohort will only include treatment with single-agent FT-2102. Due to the diverse population, this is an exploratory cohort without pre-defined efficacy/futility determinations. Aggregate safety data will be monitored by the SRC and if unacceptable toxicity (a DLT) is observed in ≥2 of the first 6 patients, the cohort will be closed for additional enrollment.

4.3. Monitoring of Adverse Events:

Patients will be monitored continuously for toxicity while on study drug. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. If a patient has an AE of particular severity or an AE assessed as at least possibly related to study drug, then dose modifications will be made according to the guidelines set forth in the study protocol.

4.4. DLTs

4.4.1. Single-Agent Safety Lead-in

DLTs will be evaluated during the Safety Lead-in Period during the first treatment cycle (28 days) using the NCI CTCAE version 4.03. DLTs are any of the toxicities outlined in below unrelated to underlying disease and considered related to FT-2102.

Non-hematologic Toxicities:

- ≥Grade 3 toxicity except: Grade 3 nausea, vomiting, diarrhea or rash lasting <72 hours (with optimal medical management)
- Clinically relevant (i.e. requiring treatment or with clinical sequelae) ≥Grade 3 non-hematologic laboratory finding

Hematologic Toxicities:

- ≥Grade 3 thrombocytopenia
- Grade 4 neutropenia lasting for >7 days
- ≥Grade 3 febrile neutropenia

Drug relatedness will be Investigator -assessed. Grade 3 laboratory abnormalities recorded as an AE, but without clinical sequelae and not requiring treatment, are not considered DLTs. Disease progression is not considered an AE if assessed by the Investigator to be unrelated to study agent. Any DLTs that occur after the Cycle 1 DLT review period will still be considered by the SRC in the evaluation of Stage 1 from the Simon's 2-stage design and for the overall RP2D.

4.4.2. Combination Therapy Safety Lead-in

DLTs will also be evaluated during Stage 1 of any cohort examining combination therapy (Cohort 1b, Cohort 2b, Cohort 3b, and Cohort 4b) using a 3+3 design.

DLTs will be assessed during the first full treatment cycle of both agents (28 days) using NCI CTCAE criteria version 4.03. Drug relatedness will be Investigator -assessed. Grade 3 laboratory abnormalities recorded as an AE, but without clinical sequelae and not requiring treatment, are not considered DLTs. Disease progression is not considered an AE if assessed by Investigator to be within the expected tempo of that disease.

Dose-limiting toxicities are any of the toxicities outlined below unrelated to underlying disease and considered related to FT-2102 and unrelated to the known toxicities of the combination agent(s).

Non-hematologic Toxicities:

- ≥Grade 3 toxicity except: Grade 3 nausea, vomiting, diarrhea, or rash lasting <72 hours (with optimal medical management)
- Clinically relevant (i.e. requiring treatment or with clinical sequelae) ≥Grade 3 non-hematologic laboratory finding

Hematologic Toxicities:

- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with grade 2 or greater bleeding

- Grade 4 neutropenia lasting for >7 days
- Grade 4 febrile neutropenia

Any DLTs that occur after the Cycle 1 review period will still be considered by the SRC in the evaluation of Stage 1 from the Simon's 2-stage design and for the RP2D. Patients who experience a DLT may have the opportunity to continue treatment at a lower dose.

4.5. Treatment Discontinuation

Treatment discontinuation is defined as any patient who stops receiving study medication. A patient should be discontinued from study treatment if, in the opinion of the Investigator or Sponsor, it is medically necessary, or if it is the wish of the patient.

All patients who discontinue study treatment should enter Safety Follow-up (see Section 6.5).

Patients may be discontinued from treatment in case of any of the following reasons:

- An AE that requires permanent discontinuation of study treatment
- Disease progression with no evidence of clinical benefit as measured by the appropriate response criteria
- Noncompliance to protocol
- Investigator decision
- Patient becomes pregnant
- Patient death
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal of consent by patient

AEs leading to the discontinuation of study drug will be followed until resolution, resolution to baseline or until the event is considered stable or chronic.

If a patient discontinues study treatment, then an End of Treatment (EoT) Visit should occur within 7 days after the last dose of study drug. Each EoT assessment need not be performed if the patient has had the identical assessment within the previous 2 weeks or previous 30 days for disease response assessments.

All patients will have a Safety Follow-up visit approximately 28 (+7) days after the last dose of study drug. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At a minimum, this visit should include collection of AEs and concomitant medications/procedures.

For combination cohorts, patients who discontinue FT-2102 are considered to have discontinued study treatment. Patients who discontinue azacitidine, nivolumab, or GemCis are allowed to continue FT-2102 until disease progression.

4.6. Study Withdrawal and Study Completion

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients will be withdrawn from the study in case of any of the following reasons:

- Patient lost to follow-up
- Termination of the study by Sponsor
- Voluntary withdrawal by patient

If the patient withdraws consent from the overall study participation (and not just study treatment), no further evaluations should be performed, and no attempts should be made to collect additional data.

A patient is considered to have completed the study if they receive at least one dose of study drug and they are followed for survival for 24 months or if they died during the treatment or survival follow up period. For interim data analyses, patients will be classified as ongoing if they have not died, been lost to follow-up, or withdrawn.

5. STUDY POPULATION

This study will enroll up to approximately 200 patients across 4 disease-specific cohorts and 1 exploratory cohort in non-CNS solid tumors.

The study will include a Safety Lead-in Period, which will enroll approximately 6 patients with histologically or cytologically-confirmed IDH1 R132X gene-mutated advanced solid tumors and approximately 6 patients with histologically or cytologically-confirmed IDH1 R132X gene-mutated advanced gliomas that have recurred or progressed following standard therapy. Additional patients may be enrolled if different doses or an altered dosing schedule are explored. Patients enrolled during the Safety Lead-in Period who meet the criteria for enrollment into 1 of the 4 disease-specific cohorts outlined below will be counted as part of the Stage 1 evaluation for those disease-specific cohorts at the same dose.

Cohort 1 will include approximately 16-46 evaluable patients with relapsed or refractory glioma (per World Health Organization [WHO] criteria 2016) with confirmed IDH1 mutation.

Cohort 2 will include approximately 21-78 evaluable patients with relapsed or refractory hepatobiliary tumors with confirmed IDH1 mutation previously treated with an approved therapy for HBC.

Cohort 3 will include approximately 16-46 evaluable patients with recurrent, refractory or either locally advanced or metastatic chondrosarcoma with confirmed IDH1 mutation not amenable to complete surgical excision.

Cohort 4 will include approximately 21-77 evaluable patients with advanced, nonresectable or metastatic cholangiocarcinoma with confirmed IDH1 mutation not eligible for curative resection or transplantation.

Cohort 5 will include up to 6 patients with relapsed or refractory other solid tumors with confirmed IDH1 mutation.

5.1. Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. ≥18 years of age
2. Life expectancy of ≥4 months
3. Able to provide tumor tissue sample (archival)
4. Disease, defined as:

   Disease-specific Cohorts

   - Glioma (Cohort 1)
     - Histologically or cytologically confirmed IDH1 gene-mutated advanced glioma that has recurred or progressed following standard therapy, or that has not responded to standard therapy with measurable disease, defined as bidimensionally lesions, by T2/FLAIR, with clearly defined margins by CT or MRI scan, with a minimum size of both perpendicular measurements greater than or equal to 10 mm. Axial FLAIR (canthomeatal alignment): 3–5 mm

sections, 1 mm interslice gaps, slice registration preserved as much as possible between sequential studies

- Glioblastoma multiforme with confirmed IDH1 gene-mutated disease with first or second recurrence with measurable disease, defined as bidimensionally lesions (contrast enhancing) with clearly defined margins by CT or MRI scan, with a minimum size of both perpendicular measurements greater than or equal to 10 mm and visible on 2 axial slices which are at least 5mm apart with 0 mm skip.

- HBC (Cohort 2)
  - Relapsed/refractory or intolerant to approved standard-of-care therapy (included: hepatocellular carcinoma, bile duct carcinoma, intrahepatic cholangiocarcinoma or other hepatobiliary carcinomas)
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria
  - Child-Pugh Class A (Appendix 4)
  - Single Agent FT-2102: prior exposure to nivolumab is permitted
  - Combination Cohort 2b: patients may not have had prior exposure to nivolumab
- Chondrosarcoma (Cohort 3)
  - Relapsed or refractory and either locally advanced or metastatic and not amenable to complete surgical excision
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per RECIST 1.1 criteria
- IHCC (Cohort 4)
  - Advanced nonresectable or metastatic cholangiocarcinoma not eligible for curative resection or transplantation.
  - Phase 1b/Safety Lead-in of Phase 2: relapsed or refractory disease
  - Combination Phase 2 (beyond Safety Lead-in): have received no more than 1 cycle of GemCis therapy
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per RECIST 1.1 criteria
- Other tumors (non-CNS) (Cohort 5)
  - Relapsed or refractory to standard-of-care therapy with no other available therapeutic options
  - Histologically or cytologically confirmed IDH1 gene-mutated with measurable disease per disease appropriate response criteria

5. Recovered to ≤Grade 2 or baseline toxicity (except alopecia) from prior therapy (per NCI CTCAE v 4.03)
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
7. Adequate bone marrow function
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without any growth factors in prior 7 days
    b. Hemoglobin ≥8.0 g/dL (with or without transfusion support)

        Platelet count $\geq 75 \times 10^9$/L (with or without transfusion support); Cohort 4b (GemCis combination): platelet count $\geq 100 \times 10^9$/L (with or without transfusion support)
8. Adequate hepatic function
    a. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤2.5 × institutional upper limit of normal (ULN). For patients with suspected malignancy related elevations, <5 × ULN.
    b. Total bilirubin ≤1.5 × ULN. For patients with suspected malignancy-related elevation <3 × institutional ULN. Patients with Gilbert Syndrome ≤3 × ULN.
9. Adequate renal function
    a. Creatinine clearance per Cockcroft-Gault equation of ≥60 mL/min
10. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women >55 years of age)
11. Willingness of male and female patients who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment, including a period of time after study treatment completed:
    - FT-2102 only: 90 days
    - Nivolumab (female): 150 days
    - Nivolumab (male): 210 days
    - Azacitidine: 180 days
    - Gemcitabine/Cisplatin: 180 days

    Sexually active women using oral contraceptive pills, should also use barrier contraception. Males must agree not to donate sperm while participating in the study and for 90 days after the last dose of the study drug. For males receiving cisplatin, they must agree not to donate sperm while participating in the study and for 2 years following cisplatin.
12. Ability to adhere to the study visit schedule and all protocol requirements

13. Signed and dated IRB/independent ethics committee (IEC)-approved informed consent form before any screening procedures are performed

5.2. Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Previous solid organ or hematopoietic cell transplant
2. Less than the minimum time has elapsed from prior anticancer treatment to first dose of study treatment as follows:
   a. Small molecule, antibody, or other anticancer therapeutic: 21 days (or 5 half-lives), whichever is shorter. Nitrosoureas or mitomycin C: 6 weeks. For patients enrolling in the Phase 2 (beyond Safety Lead-in with IHCC): 14 days from GemCis therapy.
   b. Prior radiation therapy (including radiofrequency ablation): 4 weeks
   c. Prior stereotactic body radiation therapy: 2 weeks
   d. Prior chemoembolization or radioembolization: 4 weeks
3. No previous treatment with an IDH1 inhibitor (single agent FT-2102 cohorts only)
4. Congestive heart failure (New York Heart Association Class III or IV) or unstable angina pectoris; previous history of myocardial infarction within one year prior to study entry, uncontrolled hypertension, or uncontrolled arrhythmias
5. History of QT prolongation or baseline QT interval corrected with Fridericia's method (QTcF) >450 ms (average of triplicate readings)

   NOTE: criterion does not apply to patients with a right or left bundle-branch block, a cardiology consult is recommended to assure that QTcF is not prolonged.
6. Concomitant medication(s) associated with QTc interval prolongation or Torsades de Pointes (TdP) initiated <4 weeks before first dose of study drug (see Appendix 3) (medications used as needed [PRN] [e.g., Zofran] are exempt).
7. Pregnant or nursing women or WCBP not using adequate contraception; male patients not using adequate contraception
8. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ, Stage 1, Grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years
9. Major surgery within 4 weeks of starting study treatment or not recovered from any effects of prior major surgery (uncomplicated central line placement or fine needle aspirate are not considered major surgery)
10. Receipt of a live vaccine (including yellow fever vaccine) within 30 days of first day of study treatment
11. Patients receiving >6 mg/day of dexamethasone or equivalent
12. Patients with gastrointestinal disorders likely to interfere with absorption of the study medication

13. Known human immunodeficiency virus (HIV) positivity
14. Active infection with hepatitis B or C virus (Hep B or C viral load >100 international units/milliliter or local institutional equivalent)
15. Unstable or severe, uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important medical or psychiatric illness or abnormal laboratory finding that would, in the Investigator ’s judgment, increase the risk to the patient associated with his or her participation in the study. This includes any condition that would be considered a contraindication per local prescribing information to receipt of either azacitidine, nivolumab, gemcitabine or cisplatin based on cohort assigned (combination patients only).
16. PD-1 combination only:
    a. Patients with active autoimmune disease

    Note: patients with well-controlled diabetes or hypothyroidism are eligible

    b. Patients with active infections, gastrointestinal tract bleeding, enterocleisis (colon obstruction) and severe colitis are excluded

Note: Eligibility criteria waivers will not be granted.

6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the study can be found in the following tables:

Screening Assessments Checklist	Table 1
Schedule of Assessments Single-Agent FT-2102 (Safety Lead-in, Cohorts 1a, 2a, 3a, 4a, and 5)	Table 2
Schedule of Assessments FT-2102 + 5-Azacitidine Cohort 1b [Glioma] and Cohort 3b [Chondrosarcoma])	Table 3
Schedule of Assessments FT-2102 + PD-1 Inhibitor (Cohort 2b [HBC])	Table 4
Schedule of Assessments FT-2102 + Chemotherapy (GemCis) Cohort 4b (IHCC)	Table 5
Schedule of PK and Electrocardiogram (ECG) Assessments (Safety Lead-in and Stage 1 of each Cohort)	Table 6
Schedule of PK and ECG Assessments (Stage 2 of Each Cohort: Single-Agent and Combination)	Table 7
Schedule of Efficacy and Biomarker Assessments (by Cohort)	Table 8

A brief description of each assessment can be found below.

6.1. Screening Assessments

Patients who fail screening criteria may be rescreened later within the initial screening period to confirm eligibility. If rescreening occurs after the initial screening period, sites should contact the study Medical Monitor for approval.

6.1.1. Informed Consent

Patients potentially eligible for participation must sign an informed consent form (ICF) prior to initiating any study-specific procedures. Standard of care assessments that fulfill study eligibility requirements may be performed prior to patient signing the ICF.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential patient and documented in the patient medical record and electronic case report form (eCRF). During the screening period a patient number will be assigned.

6.1.3. Medical History, Demographics, and Cancer History

Each patient's complete medical history will be obtained, including demographics, cancer history, and documentation of all previous treatments and treatment results (ie, best response to previous disease-specific treatments), prior procedures, current medications, and all medications used within 30 days prior to Screening.

6.1.4. Prior/Concomitant Medications and Procedures

At Screening, concomitant/previous medications and procedures will be assessed including all medications/procedures that have occurred within the previous 30 days.

6.1.5. Physical Exam

A full physical exam (PE) will be performed at Screening and will include vital signs (temperature, blood pressure [sitting for 5 minutes], pulse rate, and respiratory rate), height, and weight. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart. All other physical exams performed on study should be symptom-led assessments.

Following Screening, physical examination will be symptom-directed, and will include collection of vital signs. Results from the symptom-directed physical exams will be used for assessment of disease response. Any new clinically significant abnormality from baseline or significant worsening of pre-existing abnormality should be recorded as an AE.

6.1.6. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be assessed at Screening. If the ECOG Performance Status assessed at Screening is performed within 7 days of Cycle 1 Day 1, the Screening assessment can be used and does not need to be repeated at Cycle 1 Day 1 (predose). Refer to Appendix 1 for a sample of the ECOG assessment.

6.1.7. Electrocardiogram

ECGs will be conducted following an approximate 10-minute rest period and obtained in triplicate within approximately a 5-minute time period at the time points outlined in Table 1, Table 6 and Table 7.

6.1.8. Clinical Laboratory Tests

The following laboratory parameters will be measured at Screening (Table 1) and throughout the treatment period (Table 2, Table 3, Table 4, and Table 5), and will be analyzed locally:

- A serum β-hCG pregnancy test should be collected at Screening, within 7 days prior to the first dose for all women of child bearing potential. Subsequent pregnancy tests during the treatment period may be either urine or serum.
- Hematology laboratory parameters include hemoglobin, hematocrit, white blood cell (WBC) count with differential to include an ANC, and platelet count.
- Blood chemistry laboratory parameters include: albumin, total protein, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or carbon dioxide), blood

urea nitrogen (BUN) or urea, creatinine, magnesium, and glucose. Liver function tests include serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase.

- Weekly liver function testing is required through Cycle 2.
- Patients with hepatobiliary and cholangiocarcinoma only: alpha feto protein (AFP), carcinoembryonic antigen (CEA), and CA 19-9 (pre-dose and on treatment per Table 8).
- PT/aPTT will be assessed in all patients at C1D1 only.

Unscheduled assessments should be performed as clinically indicated and recorded in the eCRF.

Clinically significant laboratory findings at Screening should be recorded as medical history.

For Cycle 1 Day 1 (predose), hematology and blood chemistry (including liver function tests) evaluations may be performed within 7 days prior to study treatment, and these results can be used in place of the Cycle 1 Day 1 results.

Clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be reported as AEs (see Section 8.1.1 for definition of an AE).

6.1.9. Additional Screening Laboratory Measurements

At Screening, the following assessments will be performed to determine eligibility:

Hepatitis: All patients will be tested for anti-hepatitis C antibody (anti-HCV) and hepatitis B surface antigen (HBsAg) at Screening. Reflex Hepatitis C RNA if antibody test is positive, then only patients with hepatitis C RNA <615 IU/L or 100 copies/ml per National Genetics Institute assay or local institutional standard will be eligible.

6.1.10. Urinalysis

Complete urinalysis with qualitative analysis for protein (dipstick) should be performed at Screening as outlined in Table 1 and will be analyzed locally.

6.1.11. Tumor Evaluation

Quantification of baseline disease burden should be performed at Screening and as outlined in the Schedule of Assessments as applicable for disease type under study. The modality chosen to evaluate each individual patient should be the same throughout the duration of the study.

Please see Section 6.3 for more information on disease-specific tests to be performed at Screening and on study.

6.1.12. Tumor Biopsy

Most recent tumor sample, in the form of formalin-fixed, paraffin-embedded (FFPE) block or cut slides and accompanying pathology report for all patients will be collected as described in the Lab Manual. Optional fresh tumor biopsies at times of disease assessment or at relapse will be requested as described in Table 2, Table 3, Table 4, and Table 5.

6.1.13. Adverse Events

For all patients, non-serious AEs should be monitored from the time of the first dose of study drug through the post-treatment follow-up visit or 28 days after the last dose of FT-2102, whichever is later. After the patient is enrolled, all AEs will be captured on the eCRF.

All SAEs for all patients will be reported from the time of the signing of the ICF until the post-treatment follow-up visit or 28 days after the last dose of FT-2102, whichever is later, or until the patient has been deemed to be a screen failure. At any time after completion of the AE reporting period (ie, 28 days post last dose of FT-2102), if an Investigator becomes aware of an SAE that the Investigator considers to be related to any study drug, the event must be reported.

All Adverse Events of Special Interest (AESI), as defined in Section 8.2.3, will be reported from first dose of study drug through 28 days after the last dose of FT-2102.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.2. Safety Assessments

6.2.1. Concomitant Medication and Therapies

At every clinic visit, assessment of any change in concomitant medications or procedures since the last visit will occur. Dose, reason, start and stop date of corticosteroid use in patients with CNS tumors should be specified in the eCRF.

6.2.2. Adverse Events

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.3. Response Assessment Procedures

For all parts of the study, response and progression will be determined by Investigator assessment using the appropriate response criteria per disease at the time points shown in Table 8. Additional imaging and response evaluation based upon clinical evidence of progression is at the discretion of the Investigator.

These evaluations will be conducted until the patient experiences progressive disease or discontinues the study. See Section 6.3.1 for more information regarding the disease-specific response procedures and response criteria.

6.3.1. Response Evaluation Criteria

Please see Appendix 2 for more details.

6.3.1.1. Glioma

For patients with low grade glioma the LGG-RANO criteria will be used for disease evaluation with confirmation of a sustained response for a minimum of 4 weeks. For patients with high grade glioma the RANO, 2011 criteria will be used for disease evaluation with confirmation of a sustained response for a minimum of 4 weeks.

6.3.1.2. Chondrosarcoma

Response will be determined by RECIST 1.1 (Eisenhauer et al, 2009) with confirmation of a sustained response for a minimum of 4 weeks.

6.3.1.3. HBC

Response will be determined by RECIST 1.1 (Eisenhauer et al, 2009) with confirmation of a sustained response for a minimum of 4 weeks.

6.3.1.4. Cholangiocarcinoma

Response will be determined by RECIST 1.1 (Eisenhauer et al, 2009) with confirmation of a sustained response for a minimum of 4 weeks.

6.3.1.5. Other Solid Tumors

Response for patients with other solid tumors will be assessed with their appropriate response criteria, most often RECIST 1.1 (Eisenhauer et al, 2009). If a patient enrolls into this cohort with lymphoma, they will be assessed via the Cheson criteria (Cheson, 2014).

6.4. Other Study Procedures

6.4.1. Study Drug Administration

Detailed instructions on administration of FT-2102 can be found in Section 7.1.

6.4.2. Pharmacokinetic Sampling

PK sample collection time points are shown in Table 6 and Table 7. Plasma samples will be analyzed for FT-2102 concentrations using a validated high-performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

The date and time of each sample collection and date and time of the prior study drug dose must be recorded for all collected samples. When FT-2102 is given with another combination agent (nivolumab, azacitidine, gemcitabine/cisplatin) time zero is when the FT-2102 is administered.

An additional PK sample, beyond those listed in Table 6 and Table 7, may be requested (when feasible) at the time of any unusual safety event (i.e., an AE different in type and severity from that which is expected in the setting of FT-2102 use).

Refer to the 2102-ONC-102 Laboratory Manual for details on processing, storage, and shipment of PK samples.

6.4.3. Pharmacodynamic Sampling

Refer to the 2102-ONC-102 Laboratory Manual for PD sample handling procedures and shipping requirements.

6.4.4. Biomarker Assessments

Blood and CSF, and urine (glioma only) will be collected for biomarkers as described in Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7. CSF to be collected per investigator's discretion and if clinically necessary.

6.4.5. Tumor Biopsy

Optional fresh tumor tissue biopsies will be performed at the time points outlined in Table 2, Table 3, Table 4, and Table 5.

See the 2102-ONC-102 Laboratory Manual for instructions on fixation and processing of tumor tissue.

6.4.6. Lumbar Puncture

For patients undergoing a lumbar puncture for clinical care, a sample of CSF is being requested. This is an optional procedure and only for those patients undergoing the procedure as part of clinical care.

See the 2102-ONC-102 Laboratory Manual for instructions on volume and tubes.

6.4.7. Quality of Life (EQSD)

The EQ5D Quality of Life Assessment will be performed as outlined in Table 2, Table 3, Table 4, and Table 5.

6.4.8. Magnetic Resonance Spectroscopy for 2-HG

Imaging will be collected at selected US sites for patients with glioma to evaluate 2-HG levels via magnetic resonance spectroscopy. Details will be provided in an imaging manual provided to sites. Data will be collected at baseline and at time of disease assessments.

6.4.9. Additional Exploratory biomarkers

Samples collected during the study will be banked for up to 25 years. Any material left over will be used to conduct research related to FT-2102.

6.5. Safety Follow-up Visit

All patients will have a Post-Treatment Follow-up visit 28 days after discontinuation of study treatment. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. Patients continuing to experience toxicity at this point following the discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination in the clinical judgement of the Investigator that no further improvement is expected.

6.6. Safety Follow-up

Survival follow-up assessments will occur every 3 months following documented disease progression or start of a new cancer therapy until the last patient is off treatment. These assessments may be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) will be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

6.7. Concomitant Medications

6.7.1. Prohibited: Other Anticancer Therapy or Investigational Agents

During the study treatment period, patients are not to receive any additional anticancer therapy or other investigational agents.

6.7.2. Other Concomitant Therapies

Any other medication which is considered necessary for the patient's welfare, including antimicrobial prophylaxis, may be given at the discretion of the Investigator.

6.7.2.1. Concomitant Medications to Use with Caution

Co-administration of FT-2102 with strong CYP3A4 inducers significantly reduces FT-2102 systemic exposure, therefore co-administration is not recommended and investigators should consider alternative medications.

FT-2102 exhibits CYP3A4 induction potential in vitro and may impact the PK of co-administered sensitive CYP3A4 substrates through increased clearance. Medications that are sensitive substrates of CYP3A4 should not be used while taking FT-2102.

If the patient's clinical condition requires a medication of concern, the clinical condition should be reviewed with the study Medical Monitor. Refer to Appendix 5 for a list of strong CYP3A4 inducers and sensitive substrates.

6.7.2.2. Concomitant Medications Prohibited

During study treatment and for three months following FT-2102, receipt of live vaccines is prohibited (including the yellow fever vaccine). Annual influenza vaccine is permitted.

Concomitant medication(s) associated with known risk of Torsades de Pointes (TdP) are prohibited (see Appendix 3). Medications used as needed [PRN] [e.g., Zofran] are permitted. Concomitant medications that would be contraindicated with any of the combination agents are prohibited during the trial, based on approved prescribing information. For example, highly nephrotoxic agents with cisplatin.

6.8. Precautions

6.8.1. Differentiation Syndrome

Differentiation syndrome has been observed in patients participating in the hematologic malignancy protocol ongoing study and has also been reported in patients with AML/MDS receiving another therapy targeting the IDH1-R132 mutation (Birendra et al, 2016) or receiving azacitidine (Laufer et al, 2015). It would be unlikely to occur in patients with solid tumors. If there are unexplained fevers, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion, with or without hyperleukocytosis (Frankel et al, 1992), FT-2102 should be held and consideration given to prompt initiation of dexamethasone 10 mg IV every 12 hours. Discussion with the Medical Monitor would be required to reinitiate FT-2102.

6.8.2. Hepatic Injury

[redacted] adverse events potentially associated with liver injury have been identified as AESI. These AESI, as defined in Section 8.2.3, regardless if serious or non-serious, must be reported to FORMA Therapeutics Pharmacovigilance within 24 hours of knowledge of event as described in Section 8.2.3.

Patients should be monitored for any new or unusual symptoms suggestive of liver injury unrelated to the patient's primary malignancy. Symptoms may include anorexia, nausea, fatigue, right upper abdominal discomfort or vomiting, dark urine or jaundice. In the event of the development of any new clinical signs or symptoms of hepatic dysfunction, the following clinical investigation is recommended with additional action based upon the patient's clinical presentation and at the treating investigator's discretion.

a. Evaluation of international normalized ratio/prothrombin time (INR/PT), albumin, total bilirubin, direct and indirect bilirubin, amylase, lipase, AST, ALT, gamma glutamyl transpeptidase, complete blood count with differential and alkaline phosphatase

If there is evidence of new liver injury, the following actions should occur:

a. Report the AE per Section 8.2.3
b. Consider obtaining FT-2102 serum levels if aberrant dosing is suspected
c. Obtain tests for viral and other infectious etiologies of hepatitis (including hepatitis A, B, C, D and E) and tests for autoimmune hepatitis
d. Consideration of diagnostic imaging (hepatic ultrasound or MRI) and hepatic biopsy if the patient's clinical status permits
e. Obtain detailed history of symptoms and concurrent or prior disease, concomitant medications including herbal and dietary supplements, alcohol use, recreational drugs (e.g., cannabidiol or tetrahydrocannabinol) and special diets
f. Review medical history to include non-alcoholic steatohepatitis (fatty liver), cardiovascular disease, diabetes, alcoholism or autoimmune disease
g. Evaluate and discontinue if feasible, all hepatic injury-inducing concomitant medications (prescription and over-the-counter) and other hepatic injury-inducing agents (e.g., ethanol)
h. Consider gastrointestinal or hepatology consult
i. Frequent monitoring of AST, ALT, alkaline phosphatase, albumin, INR/PT, and total bilirubin should be initiated. Frequency would be, at minimum, twice per week until asymptomatic and the patient has returned to baseline or Grade 1 toxicity.

Restarting FT-2102 after suspected liver injury:

a. Once the AE returns to Grade 0-1 or baseline, resume treatment with FT-2102 at 150 mg once daily.
b. For the next 28 days, while dosing at 150 mg once daily, AST, ALT and total bilirubin should be monitored at minimum twice per week for the first 2 weeks and then weekly if no recurrence of elevations are observed.
c. If the AE recurs at 150 mg once daily, the patient will be discontinued from study treatment.

d. If after a minimum of 28 days of 150 mg once daily, the AST, ALT and total bilirubin have not elevated to Grade 2 or greater and no other symptoms have been reported, then FT-2102 may be re-escalated to the starting dose, if applicable.
e. Frequent monitoring (at least twice per week) is required upon re-escalation, if applicable, and may be decreased after patient has been on the escalated dose for at least 28 days without an increase in the AST, ALT and total bilirubin.

Patients on active treatment with FT-2102 should be informed to promptly notify study staff if they develop any clinical symptoms of jaundice and to avoid personal habits (excessive ethanol consumption, over-the-counter hepatic injurious medications, herbal medications [e.g., cannabidiol or comparable products]) that may cause additional risk of hepatic injury.

6.8.3. Phototoxicity

A phototoxic potential was demonstrated for FT-2102 in a standard in vitro assay system. Until the photosafety of FT-2102 has been adequately demonstrated in vivo, photosafety risk in the clinical setting will be managed by the use of light-protective measures. Patients should be instructed to avoid extensive sun exposure, phototherapy, or use of a tanning salon within a prudent amount of time prior to and following trial participation.

6.8.4. Childbearing Potential

For all patients of childbearing potential, all methods of contraception, including abstinence, must be in use from the time of consent through the final study visit, and for 90 days after the last dose of study drug. Patients who are not sexually active during the Screening Period must agree to the contraceptive requirements if they become sexually active with a partner of the opposite sex during the study and for the following time periods after study treatment completed:

- FT-2102 only: 90 days
- Nivolumab (female): 150 days
- Nivolumab (male): 210 days
- Azacitidine: 180 days
- Gemcitabine/Cisplatin: 180 days

Unique situations that may not fall within these specifications may be discussed with the Forma Therapeutics Medical Monitor on an individual basis. Investigators are advised to discuss with each patient their options regarding cryopreservation of sperm or ova prior to initiation of therapy per local institutional standard as the treatment may increase the risks of infertility.

Female patients will be considered of childbearing potential after the onset of their first menstrual period. Female patients who are documented as being of nonchildbearing potential (postmenopausal or having undergone surgical sterilization) are exempt from this requirement. Female patients will be considered postmenopausal if they have had 12 months of consecutive spontaneous amenorrhea or less than 12 months of consecutive spontaneous amenorrhea and a serum FSH level >40 mIU/mL at Screening. Female patients will be considered surgically sterile if they are post-hysterectomy, 6 months post-surgical bilateral oophorectomy, or 6 months post-tubal ligation. The effects of FT-2102 on conception, pregnancy, and lactation are unknown.

6.8.4.1. Contraception Guidelines

Acceptable methods of contraception under this protocol are listed below. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Male patients who can father a child must agree to use 1 highly effective method of contraception, which includes:

- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the patient.
- If a male patient confirms that his female partner(s) is not of childbearing potential (i.e., postmenopausal or post-surgical sterilization, as defined above) or is using a highly effective method of contraception, this is acceptable as the only means of contraception.

Examples of highly effective methods of contraception for male patients' female partner(s) include:

- Hormonal contraceptives
- Intrauterine device (IUD)

Alternatively, two effective methods of contraception can be utilized and may include:

- The use of a male condom with spermicide with a female occlusive cap (such as a diaphragm or cervical cap) with spermicide

Male patients with documented infertility or surgical sterilization (performed at least six months before the first dose of study drug) are exempt from the contraception requirement. Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens on ultrasound before the first dose of study drug (Day 1).

Female patients who are considered of childbearing potential must agree to use a highly effective method of contraception, which may include:

- IUD
- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the patient.
- If a female patient confirms that her male partner(s) has been confirmed to be clinically sterile, this method is acceptable as the only means of contraception.

Alternatively, effective double-barrier contraception may be used, to include:

- The use of a male condom with spermicide with a female occlusive cap with spermicide (such as a diaphragm or cervical cap)

Hormonal contraceptives are not considered an effective method of birth control for female patients participating in this study. Male condoms with female condoms should not be used together.

6.8.4.2. Guidance Against Donating Sperm or Ova

Male patients are prohibited from donating sperm and female patients of childbearing potential are prohibited from donating ova during the study and for 90 days after the final dose of study drug. For males receiving cisplatin, they must agree not to donate sperm while participating in the study and for 2 years following cisplatin.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. FT-2102

7.1.1. Dosage

[redacted]

Dose reductions and discontinuations for FT-2102 in individual patients may be made based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor (see Section 7.5).

7.1.2. Administration

FT-2102 will be administered 150 mg BID until documented disease progression or unacceptable toxicity as follows:

- as a single agent and in combination with 5-azacitidine to patients with glioma in Cohort 1 and patients with chondrosarcoma in Cohort 3.
- as a single agent and in combination with a PD-1 inhibitor to patients with hepatobiliary cancers in Cohort 2
- as a single agent and in combination with GemCis in patients with IHCC in Cohort 4
- as a single agent in patients with other non-CNS solid tumors with IDH1 mutations in Cohort 5.

FT-2102 will be administered as a fixed dose. Patients should make all attempts to take FT-2102 capsules at the same time on scheduled dose days. Capsules may be taken with 240 mL of water. Capsules should be ingested at least 2 hours after a meal or at least 30 minutes prior to their next meal. Guidance on the timing of FT-2102 capsule ingestion relative to meals may be modified by the Sponsor based on the clinical experience with FT-2102. If a patient vomits at any time after dosing, the dose of FT-2102 should not be re-administered. The minimum amount of time between consecutive doses of FT-2102 is 8 hours.

Doses of FT-2102 that are omitted for AEs or for any other reason should not be replaced or made up at the end of the dosing period. The site personnel will train the patients and their caregivers on procedures for drug administration. The pharmacist or study nurse will provide the patients with the correct amount of drug for the subsequent dosing period.

Patients will be supplied with the correct number of capsules for the number of doses to be taken prior to the next scheduled visit.

7.1.3. Storage

FT-2102 capsules shall be stored according to storage conditions provided on the drug product label.

7.2. 5-azacitidine

Azacitidine is supplied as a lyophilized powder in 100 mg single-use vials containing no preservative and is packaged in cartons of one vial.

7.2.1. Dosage

The dose of 5-azacitidine will 75 mg/m^2 daily for on Days 1-7 of each cycle (VIDAZA US Prescribing Information). Patient should be premedicated for nausea and vomiting per local institutional standard of care. Cycles should be repeated every 4 weeks (28 days). Treatment may be continued as long as the patient continues to derive clinical benefit. If the patient experiences unacceptable intolerance to azacitidine, patients can continue with FT-2102 as a single agent following discussion with Medical Monitor.

7.2.2. Administration

Azacitidine will be administered intravenously (IV) daily for 7 days in combination with FT-2102 to patients with glioma in Cohort 1 and patients with chondrosarcoma in Cohort 3 in combination with FT-2102. If an Investigator or patient wishes to use subcutaneously dosing, that is permitted (same dose and same schedule). The FT-2102 is administered prior to the azacitidine. Azacitidine when given as an IV infusion should be completed within one hour of reconstitution per local standard of care.

7.2.3. Storage

Unreconstituted vials of azacitidine must be stored according to storage conditions provided in the VIDAZA® package insert. Please see Pharmacy manual for storage, preparation and handling Azacitidine should be reconstituted aseptically with 4 mL of sterile water for injection. The resulting suspension will contain azacitidine 25 mg/mL (10 mg/ml for IV preparation is acceptable). Azacitidine will be administered via subcutaneous injection or intravenous infusion at approximately the same time on scheduled dose days, in accordance with the azacitidine dosing instructions (VIDAZA US Prescribing Information). Patients may have up to a 48-hour drug holiday for weekends during the 7 days of azacitidine.

7.3. PD-1 Inhibitor (Nivolumab)

Nivolumab is supplied as a solution: 40 mg/4 mL, 100 mg/10 mL, or 240 mg/24 mL solution in a single-dose vial depending on applicable regional approvals

7.3.1. Dosage

Nivolumab will be administered intravenously (IV) every 2 weeks (day 1 and 15 +/- 2 days). The recommended dose of nivolumab is 240 mg administered as an intravenous infusion over 60 minutes or local institutional standard.

If the patient experiences unacceptable intolerance to nivolumab, patients can continue with FT-2102 as a single agent following discussion with Medical Monitor.

7.3.2. Administration

Nivolumab will be administered via an IV infusion every 2 weeks, in combination with FT-2102 in patients with hepatobiliary cancers in Cohort 2. The FT-2102 is administered prior to the nivolumab.

7.3.3. Storage

Un-reconstituted vials of nivolumab must be stored according to storage conditions provided in the OPDIVO® package insert. Please see Pharmacy manual for storage, preparation and handling.

7.4. Gemcitabine/Cisplatin (GemCis)

7.4.1. Dosage

Patients will receive GemCis (cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2) IV on Day 1 and Day 8 of every 28-day (±7 days) cycle for up to 6 cycles. FT-2102 will be given concurrently days 1-28 of each cycle. Following completion of 6 cycles or intolerance to GemCis, patients can continue with FT-2102 as a single agent. FT-2102 is administered prior to cisplatin/gemcitabine. Cisplatin should be given as an 1 hour infusion with appropriate hydration (e.g., 1 liter of 0.9% saline including cisplatin, 20 mmol of potassium chloride, and 8 mmol of magnesium sulfate over 1 hour followed by 500 ml of 0.9% saline over 30 minutes) followed by administration of gemcitabine as a 30-minute infusion. Pre-medications (anti-emetics and pre-hydration) per local standard of care. Total duration of all medications and infusions would be 2-3 hours.

7.4.2. Administration

GemCis will be administered in combination with FT-2102 in patients with IHCC in Cohort 4.

7.4.3. Storage

Gemcitabine is provided in 10-mL or 50-mL size sterile single-use vials containing 200 mg or 1000 mg, respectively, of white to off-white, lyophilized powder. Please see Pharmacy manual for storage, preparation and handling.

Cisplatin Injection (1 mg/mL) is supplied either as 50 mg per 50 mL (50 mL fill in 100 mL vial) or 100 mg per 100 mL (100 mL fill in 100 mL vial). Please see Pharmacy manual for storage, preparation and handling. .

7.5. Dose Holds, Modifications, and Discontinuations

Patients will be monitored continuously for toxicity while on study treatment. Toxicity severity will be assessed using the NCI CTCAE v. 4.03. If a patient has an AE related to FT-2102, dose interruptions/holds with possible modifications may occur as described below.

7.5.1. Dose Holds and Modifications

Dose modifications apply only to patients beyond a DLT period, either single-agent or in combination. If patients have a DLT, study agent should be stopped.

For patients beyond a DLT period: a dose may be withheld up to 28 days for toxicity. Doses withheld for > 28 days may result in discontinuation from the study, unless approved by the medical monitor. For azacitidine, nivolumab, gemcitabine and cisplatin, all dose modifications outside of DLT periods are at the discretion of the treating investigator and the following are provided as guidelines.

7.5.1.1. FT-2102

Dose modifications are required if any of the following toxicities occur and are judged by the Investigator as related to study drug (i.e., assessed as unrelated to disease, intercurrent illness, or concomitant medications):

If in the opinion of the Investigator, the patient experiences any of the study drug-related toxicities outlined in Table 12, FT-2102 dose(s) will be held until recovery of the toxicity to ≤Grade 1. Dose modification guidelines for liver function test (LFT) abnormalities are presented in Table 13.

Table 12: FT-2102 Recommended Dose Modifications for Toxicities Unrelated to Liver Function Abnormalities

Hematologic Toxicities [a]	
Grade 0-1	Maintain dose level.
Grade 2	Maintain dose level. After Cycle 1, for Grade 2 AEs that prevent the patient from dosing, withhold FT-2102 until the AE recovers to Grade 0-1 and then resume treatment at the same dose level.
Grade 3	Maintain dose level. After Cycle 1, for Grade 3 AEs that prevent the patient from dosing withhold FT-2102 until the AE recovers to Grade 0-2 and then resume treatment at the same dose level. If dose reduction is clinically indicated, contact Medical Monitor
Grade 4	Hold FT-2102 until the AE recovers to Grade 0-2 or baseline AE level, whichever is worse, then resume treatment with FT-2102 at 150 mg once daily. If the AE recurs at 150 mg once daily, the patient will be discontinued from study treatment.
Non-hematologic Toxicities[a]	
Grade 0-1	Maintain dose level.
Grade 2	Maintain dose level. After Cycle 1, for Grade 2 AEs that prevent the patient from dosing, withhold FT-2102 until the AE recovers to Grade 0-1 and then resume treatment at the same dose level.
Grade 3	Hold FT-2102 until the AE recovers to Grade 0-1 or baseline AE level, whichever is worse[a], then resume treatment with FT-2102 at 150 mg once daily. If the AE recurs at 150 mg once daily, the patient will be discontinued from study treatment. Contact Medical Monitor if resumption of FT-2102 at full dose is clinically indicated.
Grade 4	Discontinue treatment[b]

AE=adverse event.
a. In the event of Grade 3 nausea, vomiting, diarrhea, or rash, the patient can continue at the same dose if the patient is responsive to treatment measures within 72 hr.
b. A patient with a Grade 4 AE may resume treatment at 150 mg once daily if the AE recovers to Grade 0-1 or baseline and if in the opinion of the Investigator and Sponsor, the patient can be monitored for recurrence of AE.

Table 13: FT-2102 Recommended Dose Modifications for Liver Function Abnormalities

Laboratory Abnormality	Action to be Taken with FT-2102
AST or ALT or total bilirubin is Grade 3	Hold FT-2102
AST or ALT is > 3 times the ULN and patient has signs and symptoms of a hypersensitivity reaction not related to underlying disease [e.g., fatigue, nausea, vomiting, RUQ pain or tenderness, fever, rash and/or eosinophilia (>5%)]	Hold FT-2102
For patient with elevated AST or ALT or total bilirubin at baseline: AST or ALT > 2 times baseline AND > 3.0 times ULN OR AST or ALT > 8.0 times ULN- whichever is lower- combined with total bilirubin > 2 times baseline AND > 2 times ULN	Hold FT-2102
AST or ALT is > 3 times the ULN and the total bilirubin is > 2 times ULN and Alkaline phosphatase < 2 times ULN in the absence of a clear alternative explanation	Permanently discontinue FT-2102
AST or ALT or total bilirubin is Grade 4	Permanently discontinue FT-2102

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RUQ = right upper quadrant; ULN = upper limit of normal.

Escalation of FT-2102 following any dose reduction:

Patients who have a dose reduction due to a toxicity may be eligible for a dose increase back to the dose level prior to the reduction (ie, the starting dose) if the patient has tolerated the reduced dose for a minimum of 28 days without any grade 2 or greater toxicities.

Dose confirmation phases:

During Cycle 1 in the dose confirmation stages of the study (single- agent and combination), patients who do not receive their scheduled dose due to drug toxicity (dose hold) will have that counted towards the criteria for a DLT. Dose-reductions will not occur in Cycle 1.

7.5.1.2. 5-Azacitidine

Dosage Adjustment Based on Hematology Laboratory Values

For subsequent doses, if the ANC has not recovered to $\geq$1x 10^9/L **AND** platelet $\geq$50 x 10^9/L within 14 days of completion of 5-azacitidine, subsequent courses should be modified per table below:

Counts		***% Dose in the Next Course***
ANC $\times 10^9$/L	Platelets $\times 10^9$/L	
$\leq$1.0	$\leq$50.0	50%
>1.0	>50.0	100%

ANC = absolute neutrophil count.

Dosage Adjustment Based on Serum Electrolytes and Renal Toxicity

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course.

7.5.1.3. PD-1 Inhibitor (Nivolumab)

Dose modifications for nivolumab toxicities per OPDIVO® package insert (OPDIVO US Prescribing Information) are presented in Table 14. Additional modifications and use of corticosteroids are per local standard of care for PD-1 inhibitors should be discussed with Medical Monitor.

Table 14: Dose Modifications for Nivolumab Toxicities

Adverse Reaction	Severity	Dose modification
Colitis (diarrhea)	Grade 2	Hold dose and resume when Grade 1 or less
	Grade 3 or greater	Discontinue
Pneumonitis	Grade 2	Hold dose and resume when Grade 1 or less
	Grade 3 or greater	Discontinue
Hepatitis	If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Hold dose and resume when returns to baseline
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Discontinue
Hypophysitis	Grade 2 or 3	Hold dose and resume when Grade 1 or less
	Grade 4	Discontinue
Adrenal insufficiency	Grade 2	Hold dose and resume when Grade 1 or less
	Grade 3 or greater	Discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Hold dose and resume when Grade 1 or less
	Grade 4 hyperglycemia	Discontinue
Nephritis and renal dysfunction	Grade 2 or 3	Hold dose and resume when Grade 1 or less
	Grade 4	Discontinue
Skin	Grade 3 or suspected Stevens-Johnson or toxic epidermal necrolysis	Hold dose and resume when Grade 1 or less
	Grade 4	Discontinue
Encephalitis	Grade 2	Hold dose and resume when Grade 1 or less
	Immune mediated encephalitis	Discontinue

Table 14: Dose Modifications for Nivolumab Toxicities

Adverse Reaction	Severity	Dose modification
Other*	Grade 3 first occurrence	Hold dose and resume when Grade 1 or less
	Grade 3 subsequent	Discontinue
	Persistent Grade 2 lasting 12 weeks or longer	Discontinue
	Grade 4	Discontinue
*For first occurrence Grade 3 myocarditis or Grade 3 infusion reaction, treatment will be permanently discontinued		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

7.5.1.4. Gemcitabine

7.5.1.4.1. Dose Modifications for Hematologic Adverse Reactions

Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines below (adapted from Gemzar US Prescribing Information).

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	% of Full Dose
≥1500	And	≥100,000	100
500-1499	Or	50,000-99,999	75
<500	Or	<50,000	Hold

7.5.1.4.2. Dose Modifications for Non-Hematologic Adverse reactions

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) non-hematologic toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

7.5.1.5. Cisplatin

Ototoxicity: Monitoring for hearing loss is at the discretion of the treating investigator and dose modifications per local standard of care for high frequency hearing loss.

Hematopoietic toxicity: Dose modifications for subsequent cycles of cisplatin are as follows:

Total White Blood Cell Count (× 10^6/L)		**Absolute Granulocyte Count (× 10^6/L)**		**Platelet Count (× 10^6/L)**	**% of Full Dose**
≥4000	And	≥1500	And	≥100,000	100
any	Or	500-1499	Or	50,000-99,999	75
any	Or	<500	Or	<50,000	Hold

Nephrotoxicity: Dose modifications are as follows:

Creatinine Clearance	**% of Full Dose**
46—60 mL/min	75
<=45 mL/min	Discontinue

7.5.1.6. Continuing Single Agent FT-2102 in lieu of Combination Therapy

If a patient is unable or unwilling to continue treatment with the combination agent (s) at any time, they may continue participation in the study taking FT-2102 alone, at the discretion of the Investigator. Doses held during a cycle will not be made up. Patients who discontinue treatment must be monitored per study procedure and assessment schedule, unless they withdraw consent. Any patient who requires an additional dose reduction below 150 mg once daily will be permanently discontinued from study drug.

7.6. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of investigational product (FT-2102) received and comparing it with the accompanying drug order form.

All unused FT-2102 will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any study drug at the clinical trial site per site procedures, or if necessary, all FT-2102 will be returned to the Sponsor, or its designee. Disposition of all study drug should be documented, including any study drug is lost or damaged.

7.7. Assignment to Treatment

All patients will receive open-label FT-2102, or FT-2102 in combination, at a dose and regimen based on the study design (see Section 4).

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with study participation, whether or not considered related to study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition, as well as clinically significant changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (e.g., diabetes, hypertension) means that it has increased in CTC grade as compared to baseline. A pre-existing condition that has not worsened during the study is not considered an AE.

8.1.2. Definition of Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization.
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE
    - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is considered an important medical event
    - If an AE does not meet one of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of "Important medical event." Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization.

8.2. Procedures for Recording, and Reporting Adverse Events

8.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through 28 days after the last dose of FT-2102 (and for 150 days following last dose of nivolumab if applicable). All AEs occurring in treated patients will be recorded in the eCRF from the time of first dose through 28 days (and for 150 days following last dose of nivolumab if applicable). after the last dose of FT-2102. An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

All SAEs occurring from the signing of ICF through 28 days after the last dose of FT-2102 (and for 150 days following last dose of nivolumab if applicable) will be processed as outlined in Section 8.2.2.

All AESIs, as defined in Section 8.2.3, from first dose of study drug through 28 days after the last dose of FT-2102 will be processed as outlined in Section 8.2.3.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or non-serious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to each study drug
- Action taken with each study drug as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (e.g., for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (e.g., sepsis secondary to pneumonia, both events should be recorded).

The signs and symptoms of progressive disease that meet the AE criteria should be reported as specific AEs, and not as disease progression.

8.2.1.1. Relationship to Study Drug

The Investigator must assess whether the AE may be related to each study drug or study mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study patient's medical record).

- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of FT-2102, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of FT-2102, there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of FT-2102, there is a plausible mechanism for the event to be related to the study product and causes other than FT-2102 have been ruled out and/or the event re-appeared on re-exposure to FT-2102.

8.2.1.2. Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI CTCAE v. 4.03. Toxicities that are not specified in NCI CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: it is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.1.2 above.

8.2.1.3. Abnormal Laboratory and Electrocardiogram Values

The Investigator is responsible for reviewing clinical laboratory test and ECG results and determining whether an abnormal value in a patient represents a clinically significant change from patient's baseline value. In general, abnormal laboratory findings and ECGs without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. In general, an abnormal laboratory test and ECG results should be reported as an AE if the laboratory result:

- Requires an adjustment or discontinuation of study drug

- Requires treatment or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

8.2.1.4. Medication Errors, Misuse, and Abuse of Study Drug

Overdose, medication error, misuse, and abuse are defined as follows:

- Overdose: refers to the administration of a quantity of study drug given per administration or cumulative, which is above the maximum dose according to the protocol.
- Medication error: refers to an unintentional error in dispensing or administration of study drug not in accordance with the protocol
- Off-label use: relates to situations where the study drug is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where the study drug is intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to the study drug because of one's professional or non-professional occupation

Overdoses, medication errors, abuse, or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

8.2.2. Reporting of Serious Adverse Events

An SAE Report Form will be completed and submitted to FORMA Therapeutics Pharmacovigilance within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug, from the time of signing ICF through 28 days after the last dose of FT-2102 (and for 150 days following last dose of nivolumab if applicable).

Please refer to the SAE Report Form and completion guidelines on where and how to submit the form.

The initial SAE report form must be as complete as possible, including details of the current illness and SAE, and an assessment of the relationship between the event and study drug. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to study drug by the Investigator, occurring more than 28 days after the last dose of FT-2102 (and for 150 days following last dose of nivolumab if applicable) the SAE must be reported as described above.

8.2.2.1. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor will determine expectedness of FORMA product for each reported SAE based on the appropriate reference safety information per local requirements.

The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Sponsor or designee shall notify any applicable Central Institutional Review Boards (CIRBs) and Central Ethics Committees (CECs) of serious, related, and unexpected AE(s), or significant risks to patients, per country requirements.

The Investigator will notify the appropriate IRB/Local Ethics Committees (LECs) of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with FORMA or IRBs/LECs.

8.2.3. Reporting of Adverse Events of Special Interest

As described in Section 6.8.2, adverse events potentially associated with liver injury have been identified as AESI. These AESI (regardless if serious or non-serious) include the following:

a. All events of Grade 2 or higher elevations in ALT, AST, or total bilirubin in patients with normal LFTs at baseline; in patients with elevated LFTs at baseline, one Grade shift or higher in ALT, AST, or total bilirubin;
b. Any hepatic adverse event, e.g., acute hepatitis, cholestatic hepatitis, cholestasis, or hepatic insufficiency

AESI occurring from time of first dose through 28 days after last dose must be reported as outlined below:

a. Report to FORMA Therapeutics Pharmacovigilance within 24 hours of knowledge of event
b. If the event meets both AESI and SAE criteria, complete both the SAE and AESI form
c. If the event is non-serious, complete the AESI form alone

Relevant forms (AESI, SAE, or both) should be submitted via fax ([redacted]) or email [redacted] to FORMA Therapeutics Pharmacovigilance.

8.2.4. Pregnancy and In Utero Drug Exposure

FT-2102 has not been evaluated in pregnant or nursing women. Thus, pregnant women or women of childbearing potential who are not using effective contraception are excluded from this study (see Section 6.8.4 for instructions on birth control and pregnancy testing).

Pregnancies occurring in patients, or partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment through 90 days after the patient's last dose of study drug. If a pregnancy occurs in a patient, study drug must be discontinued immediately. The pregnant woman should be referred to an

obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to FORMA Therapeutics Pharmacovigilance within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Report Form.

The Investigator will follow the pregnant patient (or pregnant partner of male patient) until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information on the Pregnancy Report Form.

If the pregnant patient (or pregnant partner of a male patient) experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (ie, report the event to FORMA Therapeutics Pharmacovigilance within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to FORMA Therapeutics Pharmacovigilance. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to FORMA Therapeutics Pharmacovigilance.

Please refer to the Pregnancy Report Form and associated completion guidelines on where and how to submit the form.

8.2.5. Disease Progression

If progression of the underlying disease (i.e., the condition being treated with study drug) might be reasonably anticipated given the nature and severity of the underlying disease, then progression of the underlying disease per se will not constitute an AE. However, if the progression of the underlying disease meets the criterion for "serious" categorization of AEs (e.g., the underlying disease results in death or hospitalization), then the progression of underlying disease should be reported as an SAE (Section 8.1.2).

9. STATISTICAL METHODS

Details of the statistical methods for this study will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the statistical methods outlined in the protocol; however, any major modification will also be reflected in a protocol amendment.

9.1. Sample Size

This study will enroll up to approximately 200 patients.

A single-agent Safety Lead-in Period will be implemented that may enroll approximately 12 patients, which includes approximately 6 patients with glioma and 6 patients with solid tumors. Following successful completion of the Safety Lead-in Period, the study will then enroll 4 disease-specific cohorts examining FT-2102 as either a single agent or in combination. These cohorts include Cohort 1 (glioma) with approximately 16-46 patients; Cohort 2 (HBC) with up to approximately 21-78 patients; Cohort 3 (chondrosarcoma) with approximately 16-46 patients; and Cohort 4 (IHCC) with approximately 21-78 patients. There will be a fifth cohort of R132X IDH1 mutant solid tumors, non-CNS with up to 6 patients, single-agent only.

Cohort 1a, Cohort 2a, Cohort 3a (single-agent FT-2102)

Cohorts, 1a, 2a and 3a will employ an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 5% and alternative hypothesis of 25%. Stage 1 of each of these cohorts will evaluate 8 patients for efficacy over 4 treatment cycles; if there are 1 or more responses, Stage 2 will initiate with additional 15 patients. If there are 4 or more responses out of the total 23 patients, the null hypothesis of 5% will be rejected. If there is no response in Stage 1 with single-agent FT-2102, or if the null hypothesis is not rejected at the end of Stage 2, combination therapy may be evaluated.

Cohort 4a (single-agent FT-2102)

Cohort 4a employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 8% and alternative hypothesis of 35%. Stage 1 will evaluate 8 patients and if there are 2 or more responses Stage 2 will initiate with additional 14 patients. If there are 5 or more responses out of the total 22 patients, the null hypothesis of 8% will be rejected. If there is 0 or 1 response in Stage 1 with single-agent FT-2102, or if the null hypothesis is not rejected at the end of Stage 2, combination may be evaluated.

Combination Cohorts (1b, 2b, 3b, 4b)

If there is no response in Stage 1 with single-agent FT-2102 combination cohorts may be examined.

Cohort 1b and Cohort 3b

For Cohorts 1b and 3b (combination therapy), an optimal Simon's 2-Stage design will be implemented with a 1-sided alpha of 0.025, 80% power, with a null hypothesis of 5% and alternative hypothesis of 25%. Stage 1 of each cohort will evaluate 8 patients for efficacy over 4 treatment cycles; if there are 1 or more responses, Stage 2 will initiate with additional 15 patients. If there are 4 or more responses out of the total 23 patients, the null hypothesis of 5% will be rejected.

Cohort 2b

Cohort 2b employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 20% and alternative hypothesis of 40%. Stage 1 will evaluate 13 patients for efficacy; if there are 4 or more responses Stage 2 will initiate with an additional 42 patients. If there are 17 or more responses out of the total 55 patients, the null hypothesis of 20% will be rejected.

Cohort 4b

Cohort 4b employs an optimal Simon's 2-Stage design with a 1-sided alpha of 0.025, power of 80%, null hypothesis of 20% and alternative hypothesis of 40%. Stage 1 will evaluate 13 patients and if there are 4 or more responses Stage 2 will initiate with additional 42 patients. If there are 17 or more responses out of the total 55 patients, the null hypothesis of 20% will be rejected.

Cohort 5

Cohort 5, due to the diverse population, this is an exploratory cohort without pre-defined efficacy/futility determinations (n=6).

9.2. Analysis Sets

9.2.1. Dose-Limiting Toxicity-Evaluable Analysis Set

The **DLT-Evaluable Analysis Set** is defined as all patients in the Safety Lead-in Periods (single-agent FT-2102, combination FT-2102 + 5-azacitidine, combination FT-2102 + GemCis and combination FT-2102 + PD-1 inhibitor) who either experienced a DLT during Cycle 1 or completed at least 75% of the prescribed Cycle 1 dose. This analysis sets will be used to assess the tolerability of FT-2102

9.2.2. Safety Analysis Set

The **Safety Analysis Set** is defined as all patients who received any amount of study drug(s) (FT-2102 and combination agents, if appropriate).

This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation. Safety analysis will be by cohort and by treatment within cohort if more than 1 dose or dosing combination are initiated for a particular indication cohort.

9.2.3. Response-Evaluable Analysis Set

The **Response-Evaluable Analysis Se**t is defined as all patients with measurable disease at baseline are included in the Safety Analysis Set and had at least 1 post-baseline response assessment or discontinued the treatment phase due to disease progression (including death caused by disease progression) within 8 weeks (+2-week window) of the first dose of study treatment. This analysis set will be the primary analysis set for efficacy endpoints. All response evaluations will be by cohort, and by treatment within cohort if more than 1 doses or dosing combinations are initiated for a particular indication cohort.

9.2.4. Pharmacokinetics Analysis Set

The PK analysis set is defined as all patients who received at least one dose of FT-2102 and had at least one measurable concentration.

9.2.5. Pharmacodynamics Analysis Set

The Pharmacodynamics analysis set is defined as all patients who received at least one dose of FT-2102 and have completed at least one pharmacodynamic assessment.

9.3. Background Characteristics

9.3.1. Patient Disposition

The number and percentage of patients in each disposition category (e.g., enrolled, included in each Analysis Set, completing a given number of treatment cycles, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by cohort.

9.3.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by cohort for the Safety Analysis Set: sex, race, age, type of cancer, tumor stage (tumor-node-metastases), ECOG performance status, time elapsed since cancer diagnosis, and prior anti-cancer therapies. Additional parameters may be provided in the SAP.

9.4. Study Drug Exposure and Compliance

Total number of cycles is defined as the maximum number of treatment cycles that a patient receives. Total cumulative dose (mg) is the sum of the actual doses that the patient receives across cycles. Total planned dose (mg) is the sum of the planned doses. The total number of days on treatment, total number of cycles, total cumulative dose (mg), total planned dose (mg) will be summarized.

The study drug exposure will be summarized based on the Safety Analysis Set by cohort and dose level.

9.5. Efficacy Analyses

All analysis in this section will be based on patients in the Response-Evaluable Analysis Set unless otherwise specified.

Best response will be summarized as determined by applicable disease criteria, for disease specific cohorts (see Appendix 2 for definitions). RANO (LGG) for low-grade glioma, RANO for high-grade glioma, RECIST 1.1 for cholangiocarcinoma, HBC and other solid tumors.

ORR is defined as follows:

- Glioma: the proportion of patients with a best response of CR or PR or MR (LGG)
- HBC: the proportion of patients with a best response of CR or PR

- Chondrosarcoma: the proportion of patients with a best response of CR or PR
- Cholangiocarcinoma: the proportion of patients with a best response of CR or PR

It will be summarized by cohort and tabulated with 90% confidence interval estimated using Clopper-Pearson method.

Time to event data will be analyzed using Kaplan-Meier (KM) methods for each cohort. The median time will be tabulated along with the 95% confidence intervals. The estimated probability of survival over time will be plotted as KM curves for each cohort (or by disease type and by treatment).

For time to event variables, the following is considered:

- PFS will be defined for all patients in the Response Evaluable Analysis Set. It is the time between first dose of study drug and disease progression, death from any cause, or start of other (non-protocol study drug) new anticancer therapy, whichever occurs first. For a patient with none of these events before the end of study follow-up, PFS will be censored on the date of the last follow-up examination.
- TTR will only be defined for patients who achieve a response (CR/ PR). It is the time between the first dose of study drug and documentation of the first response by applicable disease criteria.
- DOR will be defined only for patients who achieve a response. It is the time between documentation of the response by appropriate disease assessment until the date of progression or any new anticancer therapy, whichever is earlier. For patients who die without documentation/report of disease progression, DOR will be censored on the date of death, regardless of cause, or any other new anticancer therapy (non-protocol study drug), whichever is earlier. For patients with no report of disease progression by the end of the follow-up data collection, DOR will be censored on the date of the last follow-up examination. Since DOR is patient to the competing risk of death without progression, estimates of the cumulative incidence of progression will be reported for each cohort. Similarly, the duration of overall response will also be analyzed.
- OS will be defined based on the Safety Analysis Set. It is the time from study entry until death from any cause. For patients who are not known to have died by the end of study follow-up, OS will be censored on the date the patient was known to be alive. Patients who are lost to follow up with be censored on the last date the patient was known to be alive. The percentage of patients who are alive will be estimated at selected landmark timepoints such as 3 months, 6 months, etc.
- TTP will be defined for all patients in the Response Evaluable Analysis Set. It is the time between first dose of study drug and disease progression. Death from any cause or start of other (non-protocol study drug) new anticancer therapy are censoring events. For a patient with none of these events before the end of study follow-up, TTP will be censored on the date of the last follow-up examination.

Additional efficacy analyses will be specified in the SAP.

9.6. Safety Analyses

The Safety Analysis set will be used to evaluate all safety endpoints unless the endpoints are applicable to only selected patients, e.g., DLT.

9.6.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher and will be graded according to the NCI CTCAE, version 4.03.

A TEAE is an AE that begins or worsens in the period from the first dose of study treatment to 28 days after the last dose of FT-2102.

Summaries of AEs will be based on TEAEs. TEAEs will be summarized separately for each cohort and dose by the number of patients experiencing TEAEs corresponding to MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs) by highest grade.

Separate tabulations will also be produced for TEAEs assessed as related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥Grade 3 in severity. Common AEs will be summarized by MedDRA PT from most to least common. Treatment-emergent SAEs and SAEs related to study drug will also be tabulated. A summary of non-serious TEAEs will also be produced.

9.6.2. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units.

A summary of hematology, chemistry, and coagulation laboratory parameters will be performed using descriptive statistics on the raw values and change from baseline by dose group, disease, and nominal visit.

Shifts in Grade from baseline to the maximum post-baseline grade will be summarized by treatment group for applicable laboratory data. Laboratory values ≥Grade 3 in severity will be tabulated by treatment group.

A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

9.6.3. Electrocardiogram

A summary of raw values and change from baseline values by dose group and disease for each scheduled visit will be provided for ECG parameters.

QTc intervals based on Fridericia's correction method will be summarized by dose. The number and percentage of patients will be presented for each of the following categories of QTcF intervals (≤480 ms, >480 to ≤500 ms, >500 ms). The number and percentage of patients will also be presented for each of the following categories of changes from baseline >30 to ≤60 ms, >60 ms).

9.7. Pharmacokinetic Analyses

PK analyses will be conducted on patients in the PK Analysis Set. PK parameters based on the actual sample collection times will be determined using standard noncompartmental methods. The PK parameters to be assessed include, but are not necessarily limited to:

C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the last quantifiable time point
$AUC_{0\text{-INF}}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity (may be estimated when sufficient data allows)
$t_{1/2}$	Terminal elimination half-life (may be estimated when sufficient data allows)

Evaluations of PK data will include accumulation upon multiple-dose administration, PK/PD relationship, and exposure/QTc analysis.

9.8. Pharmacodynamic Analyses

Pharmacodynamic analyses will be descriptive in nature. In general, pharmacodynamic parameters will be summarized by cohort and nominal visit Summary tabulations may be produced if data from a sufficient number of patients are collected.

10. STUDY ADMINISTRATION

10.1. Good Clinical Practice Statement

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

10.2. Informed Consent

FORMA or its designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

10.3. Patient Confidentiality

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by FORMA or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of FORMA, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the patient's medical history.

The Investigator must ensure that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned patient number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

10.4. Institutional Review Board/Ethics Committee Requirements

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator must submit written approval to FORMA before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/IEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

10.5. Case Report Forms and Source Documentation

eCRFs will be provided for the recording of all data. The Principal Investigator/Sub-Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided.

In place of recording patient data on paper CRFs, which will not be used in this study, site personnel are responsible for entering such data into the Electronic Data Capture (EDC) system in a timely manner. This system has been validated and is compliant with FDA, ICH, and European Union (EU) regulations and guidelines and with Department of Health and Human Services 21 CFR Part 11 rules for electronic records and electronic signatures. No data will be requested other than what is routinely written on paper CRFs.

An audit may be performed at any time during or after completion of the clinical study by Sponsor personnel or their designee. All study-related documentation must be made available to the designated auditor.

10.6. Sponsor Monitoring

Before the first patient is enrolled into the study, a representative of FORMA will visit the study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to the protocol and the responsibilities of FORMA

During the conduct of the study, a representative of FORMA will have regular contact with the clinical trial site, and have regular visits to the clinical trial site to:

- Provide information and support the PI
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

10.7. Data Monitoring Committee

There will be no formal Independent Data Monitoring Committee.

10.8. Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

10.9. Study or Clinical Site Termination

FORMA, or designee, reserves the right to terminate the study or a clinical trial site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of FORMA to suspend or discontinue testing the study treatment
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical trial site to FORMA or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, FORMA and the Investigator(s) will assure that adequate consideration is given to the protection of the patients' interests.

10.10. Duration of the Study, Expected Duration of Patient Participation, and End of Study

Patients assigned to receive FT-2102 will continue this treatment until documented disease progression or unacceptable toxicity.

The end of the study will be defined as last patient last visit (LPLV).

10.11. Records Retention

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, study drug inventory, IRB, and Sponsor correspondence pertaining to this study must be kept on file. All study documents must be kept secured for a period of 2 years after marketing applications are approved for FT-2102, or until 2 years after shipment and delivery of the study drug for investigational use if discontinued or as long as required by local regulations in any country participating in the trial, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing or relocating study records for any reason.

10.12. Publications

Publication by the clinical trial site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

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12. APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group: http://www.ecog.org/general/perf_stat.html
As published in Oken et al, 1982

APPENDIX 2. RESPONSE CRITERIA

LGG/RANO (van den Bent et al, 2011)

Complete response

Complete response requires all the following criteria compared with the baseline scan:

1. Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely)
2. no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement;
3. patients must be off corticosteroids or only on physiological replacement doses; and
4. patients should be stable or improved clinically

Partial response

Partial response requires all of the following criteria compared with the baseline scan:

1. greater than or equal to 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline;
2. no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with
3. radiation effects, and no new or increased enhancement; and
4. patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Minor response

Minor response requires the following criteria compared with baseline:

1. a decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared with baseline;
2. no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement; and
3. patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Stable disease

Stable disease is present if the changes do not qualify for complete, partial, or minor response, or progression and requires:

1. stable area of non-enhancing abnormalities on T2 or FLAIR imaging;
2. no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement; and
3. patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Progression

Progression is defined by any of the following:

1. development of new lesions or increase of enhancement (radiological evidence of malignant transformation);
2. a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events;
3. definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose; or
4. failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.

RANO (Wen et al, 2010):

Complete Response

Complete response requires all of the following with a confirming scan at least 4 weeks later. In the absence of the confirming scan, the response will be considered stable disease:

1. complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; and
2. no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; and
3. patient must be off corticosteroids or on physiologic replacement doses only, and
4. stable or improved clinically.

Partial Response

Partial response requires all of the following (In the absence of a confirming scan at least 4 weeks later, this response will be considered only stable disease):

1. ≥50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; and
2. no progression of nonmeasurable disease; and
3. no new lesions; and
4. stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and
5. patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically.

Stable Disease

If the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following:

1. stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status.

(In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose)

Progression

Progression is defined by any of the following (Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression):

1. ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids;

2. a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; or
3. the appearance of any new lesions; or
4. clear progression of nonmeasurable lesions; or
5. definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression.

*Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

**The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the Karnofsky Performance Status (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

RECIST 1.1 (Eisenhauer et al, 2009):

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as a reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	Sum of diameters increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The sum of diameters must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify.)

APPENDIX 3. DRUGS AFFECTING QTC INTERVAL

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval. Medications that prolong the QT interval and/or have a risk of inducing TdP are listed in Table 15. Additional information can be found at: https://crediblemeds.org/index.php.

Table 15: Drugs that Prolong the QT Interval and/or Have a Risk of Inducing Torsade De Pointes

Aclarubicin (Only on Non-US Market)	Ibutilide
Amiodarone	Levofloxacin
Anagrelide	Levomepromazine (Only on Non-US Market)
Arsenic trioxide	Levomethadyl acetate (Removed from Market)
Astemizole (Removed from Market)	Levosulpride (Only on Non-US Market)
Azithromycin	Mesoridazine (Removed from Market)
Bepridil (Removed from Market)	Methadone
Chloroquine	Moxifloxacin
Chlorpromazine	Ondansetron
Cilostazol	Oxaliplatin
Ciprofloxacin	Papaverine HCl
Cisapride (Removed from Market)	Pentamidine
Citalopram	Pimozide
Clarithromycin	Probucol (Removed from Market)
Cocaine	Procainamide
Disopyramide	Propofol
Dofetilide	Quinidine
Domperidone (Only on Non-US Market)	Roxithromycin (Only on Non-US Market)
Donepezil	Sevoflurane
Dronedarone	Sotalol
Droperidol	Sparfloxacin (Removed from Market)
Erythromycin	Sulpiride (Only on Non-US Market)
Escitalopram	Sultopride (Only on Non-US Market)
Flecainide	Terfenadine (Removed from Market)
Fluconazole	Terlipressin (Only on Non-US Market)
Gatifloxacin (Removed from Market)	Terodiline (Only on Non-US Market)
Grepafloxacin (Removed from Market)	Thioridazine
Halofantrine (Only on Non-US Market)	Vandetanib
Haloperidol	
Ibogaine (Only on Non-US Market)	

Source: www.AZCert.org accessed 19 June 2018

APPENDIX 4. CHILD-PUGH SCORE

Measure	1 point	2 points	3 points	Units
Bilirubin (total)	<2	2-3	>3	mg/dl
Serum albumin	>3.5	2.8-3.5	<2.8	g/dl
INR	<1.8	1.8-2.3	>2.3	NA
Ascites	None	Mild	Severe	NA
Hepatic encephalopathy	None	Grade 1/2	Grade 3/4 (severe)	NA

NA=not applicable.

A: Total score of 5-6

B: Total score of 7-9

C: Total score of 10-15

Source: (Jelic et al, 2010)

Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4[a]	Unarousable coma, no personality/behavior, decerebrate
a. Subjects with clinically active Grade 3 or 4 encephalopathy are excluded.	

Adapted from FDA Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (FDA 2003).

APPENDIX 5. DRUGS THAT ARE SENSITIVE SUBSTRATES OR STRONG INDUCERS OF CYP3A4

Sensitive Substrates:

Alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Strong Inducers:

Carbamazepine, rifampin, ritonavir, enzulatamide, mitotane, phenytoin, phenobarbital and St. John's wort

Additional information can be found at:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1