

NCCN Request for Proposals (RFP): Phase I/II Clinical Trials and Correlative Trials of trifluridine/tipiracil for Gastrointestinal and other Solid Tumors

1.0 Purpose

The National Comprehensive Cancer Network (NCCN) has received a Two Million Dollar research grant from Taiho Oncology, Inc. (hereafter, “Grantor”) to support the performance of clinical and correlative studies of trifluridine/tipiracil (FTD/TPI), in the treatment of gastrointestinal (GI) malignancies and other solid tumors. NCCN will serve as the funding organization. Grants are available only to investigators from NCCN Member Institutions.

2.0 Background

NCCN received a grant from the Grantor for the design and performance of clinical and correlative studies using FTD/TPI to treat GI malignancies and other solid tumors.

Mechanism of Action

Trifluridine/tipiracil (FTD/TPI; also known as TAS-102, Lonsurf®, S 95005) is an orally available combination drug.¹⁻⁵ The active antimetabolite trifluridine is a fluorinated thymidine analog and incorporates into DNA, resulting in inhibition of DNA synthesis and cell proliferation. Tipiracil is a thymidine phosphorylase (TP) inhibitor and prevents degradation of trifluridine. Notably, FTD/TPI is not a pro-drug and has a distinct mechanism of action from 5-fluorouracil (5-FU). The approved dose of FTD/TPI is 35 mg/m² twice daily given days 1-5 and 8-12 every 28 days. It should be administered within 1 hour after morning and evening meals. FTD/TPI is renally excreted and dose modifications may be necessary for individuals with moderate renal impairment. FTD/TPI is not recommended for patients with baseline moderate or severe hepatic impairment.

Clinical Data

FTD/TPI as Monotherapy

The phase 3 RECURSE trial randomized 800 refractory metastatic colorectal cancer (CRC) patients 2:1 to FTD/TPI 35 mg/m² BID or placebo administered on the 4-week schedule.⁶ Included patients were ≥18 years old, ECOG 0-1, had received ≥2 prior regimens for metastatic disease, and were refractory or intolerant to 5-FU, oxaliplatin, irinotecan, bevacizumab, and (if *KRAS* wildtype), anti-epidermal growth factor receptor (EGFR) therapy. Median overall survival (OS) was 7.2 months in the FTD/TPI arm vs. 5.2 months with placebo with a hazard ratio (HR) of 0.69 (95% confidence interval [CI] 0.59-0.81, p<0.0001).⁷ There was an improvement in median progression-free survival (PFS) with FTD/TPI vs. placebo of 2.0 vs. 1.7 months, respectively; HR of 0.48 (0.41-0.57, p<0.001). The observed benefit was not restricted to a particular clinical or molecular subgroup.⁶

The overall incidence of adverse events (AEs) was similar between treatment groups (98.3% and 93.2%, respectively), including the incidence of grade ≥3 AEs (69% and 52%, respectively). The most common grade ≥3 AEs in FTD/TPI (vs. placebo) were neutropenia (38% vs. 0) but with rare febrile neutropenia (4% vs. 0), anemia (18% vs. 3%), thrombocytopenia (5% vs. <1%), decreased appetite (4% vs. 5%), fatigue (4% vs. 6%), and diarrhea (3% vs. <1%).⁶

A study to re-evaluate the efficacy, safety and pharmacokinetic parameters of FTD/TPI at 35 mg/m² BID among Asian patients with advanced gastric cancer (AGC) was conducted.⁸

The primary endpoint was disease control rate (DCR) of >50% after 8 weeks of FTD/TPI 35 mg/m² BID. At the conclusion of the study, DCR was 65.5% (95% CI, 45.7-82.1%). An independent review determined DCR was 51.9% (95% CI, 31.9-71.3%); both results exceeded the primary end-point target. The median PFS and OS were 2.9 months (95% CI, 1.1-5.3 months) and 8.7 months (95% CI, 5.7-14.9 months), respectively. Grade ≥ 3 AEs included neutropenia (69.0%), leukopenia (41.4%), anemia (20.7%) and anorexia (10.3%). No AGC-specific toxicities were detected.

The phase 3 TERRA study randomized 406 Asian patients, with mCRC refractory or intolerant to standard chemotherapies, 2:1 to FTD/TPI 35 mg/m² BID or placebo administered on the 4-week schedule.⁹ Median OS was significantly longer in the FTD/TPI arm (7.8 months [95% CI, 7.1-8.8 months]) vs. placebo (7.1 months [95% CI, 5.9-8.2 months]). Risk of death was significantly lower in the FTD/TPI arm vs. placebo (HR 0.79; 95% CI, 0.62-0.99; log rank $P = .035$), and the incidence of serious adverse events was similar across arms at 23.2% vs. 23.7%, respectively.

The phase 3 TAGS trial randomized 507 refractory gastric and gastroesophageal junction (GEJ) cancer patients 2:1 to FTD/TPI 35 mg/m² BID or placebo administered on the 4-week schedule.¹⁰ Included patients were ≥ 18 years old, ECOG 0-2, had received ≥ 2 prior regimens of a fluoropyrimidine, platinum agent, taxane and/or irinotecan, and, if HER2+, a HER2 inhibitor, as well as were refractory or intolerant to the last prior therapy. The primary endpoint was OS; median OS was 5.7 months in the FTD/TPI arm vs. 3.6 months with placebo with a HR of 0.69 (0.56-0.85, $p=0.0003$). The 12-month OS rate was 21% vs. 13%, respectively. Median PFS was 2.0 vs. 1.8 months, respectively; HR of 0.57 (0.47-0.70, $p<0.0001$) with 6-month PFS of 15% vs. 6%. The incidence of any AE regardless of cause was 97% with FTD/TPI vs. 93% with placebo, with grade ≥ 3 AE in 80% vs. 58%. Specific AEs were similar to what was observed in the RECURSE trial.

FTD/TPI in combination therapy

The TASC0-1 trial was a non-hypothesis testing randomized phase 2 trial of FTD/TPI with bevacizumab ($n=77$) and capecitabine with bevacizumab ($n=76$) in first-line patients with metastatic CRC whom the treating physician deemed not eligible for curative resection or intensive combination chemotherapy with irinotecan or oxaliplatin.¹¹ FTD/TPI was dosed at the approved dose and 4-week schedule with bevacizumab 5 mg/kg IV on days 1 and 15 of the 28-day cycle. PFS (primary endpoint) was 9.2 months in the FTD/TPI + bevacizumab arm vs. 7.8 months in the capecitabine/bevacizumab arm with HR 0.71 (0.48 – 1.06). OS was 18.0 vs. 16.1 months, respectively, HR 0.56 (0.32-0.98). There was no significant increase in hematologic, GI, or other AEs compared to what has been reported for single-agent FTD/TPI. Notably, the incidence of hand-foot syndrome was 3.9% (all grade 1-2) in the FTD/TPI + bevacizumab arm as compared to 53% (12% grade 3-4) in the capecitabine/bevacizumab arm, while grade 3-4 neutropenia was observed in 47% vs. 5% of patients, respectively.

In the phase 1 trial TAS-102-109, FTD/TPI (dose range 20-35 mg/m² BID days 1-5 every 14 days) was evaluated in a standard 3+3 design in combination with irinotecan (dose range 120-180 mg/m² on day 1 of each cycle).^{12,13} Eligible patients had any metastatic GI malignancy that was refractory to at least one prior line of therapy. The majority of patients had CRC (81%) and had prior irinotecan exposure (88% of expansion phase patients). Two dose-limiting toxicities (DLTs) were observed at the FTD/TPI 30 mg/m² and irinotecan 180 mg/m² dose level, thus FTD/TPI 25 mg/m² + irinotecan 180 mg/m² was used in the expansion phase ($n=24$) in combination with bevacizumab 5 mg/kg. Expansion phase

treatment-related grade ≥ 3 AEs were reported in 66.7% of patients. There were no treatment discontinuations due to AEs and no treatment related deaths. Three partial responses (PR) were observed in the expansion phase, two of which had received prior irinotecan. The DCR was 67% with doublet therapy in dose escalation and 84% with triplet therapy (FTD/TPI + irinotecan + bevacizumab) in dose expansion. The median PFS was 7.9 months (95% CI, 5.1-13.4).

FTD/TPI has also been explored in combination with oxaliplatin in a phase I trial with standard 3+3 design.¹⁴ The MTD was FTD/TPI 35 mg/m² BID and oxaliplatin 85 mg/m². Expansion cohort A added bevacizumab 5 mg/kg to the doublet (n=6), while expansion cohort B added nivolumab 3 mg/kg to FTD/TPI + oxaliplatin (n=6). The most common grade 3–4 treatment-related AE was neutropenia. Treatment interruptions due to AEs were reported in 3 patients (25.0%), mainly for neutropenia. Oxaliplatin-related neurotoxicity grade ≥ 2 was observed in two patients and led to oxaliplatin discontinuation for one patient. No immune-related AE due to nivolumab were observed.¹⁵

3.0 Scope and Aims

The overall aim is to develop innovative studies to determine the role of FTD/TPI in the treatment of GI malignancies and other solid tumors. Successful proposals submitted in response to this RFP will be useful in guiding further development of trifluridine/tipiracil. Correlative work to identify predictive markers is welcome.

Studies must utilize dosages and dosing based on already known safety data for the drug. Specifically, as a single agent, the dose of FTD/TPI should be the approved dose of 35 mg/m² BID. In combinations, the range of 25 – 35 mg/m² BID can be used. Frequency of FTD/TPI dosing, either as a single agent or in combination, can be on a 2-week schedule (days 1-5 every 14 days) or a 4-week schedule (days 1-5, 8-12 every 28 days). Of note, FTD/TPI should not be crushed and proposals should focus on patient populations that are able to reliably swallow pills. Prior gastrectomy does not exclude patient participation (PK data will be provided, if requested).

Broad strategic areas of priority interest for this RFP are associated with:

- Use of FTD/TPI in combination with other cytotoxic chemotherapeutic agents, targeted agents, and/or immunotherapy agents. There should be sufficient rationale behind the proposed study drug combination.
- Use of FTD/TPI as a radiosensitizing agent.
- Use of FTD/TPI in early lines of therapy for metastatic disease.

While proposals for any disease site are welcome, the areas of research emphasis for this RFP include:

- Colorectal cancer
 - Combination therapy with chemotherapy except for the specific triplet of oxaliplatin, bevacizumab and FTD/TPI. If there is interest in a combination with irinotecan, additional data on prior experience with this combination will be provided.
 - Combination therapy with EGFR inhibitors.
 - Study of microsatellite stable (MSS) colon cancer with FTD/TPI with PD1/PDL1 will not be of interest.

- Proposals focused on maintenance therapy in metastatic CRC or neoadjuvant therapy in rectal cancer are not of interest.
- Esophageal and gastric cancer
 - This includes combination with other therapies, especially with neoadjuvant radiation and/or with immunotherapy.
 - Proposals combining ramucirumab with FTD/TPI on the 4-week schedule are not of interest, while combinations with ramucirumab and FTD/TPI on a 2-week schedule are welcome.
- Hepatocellular carcinoma
- Biliary cancer
 - Combination therapy is encouraged, while FTD/TPI as monotherapy is not of interest.
- Pancreatic cancer
 - This includes combinations with oxaliplatin and/or irinotecan, but not with liposomal irinotecan.
 - FTD/TPI as monotherapy or in combination with gemcitabine and nab-paclitaxel are not of interest.
- Anal cancer
 - Proposals using monotherapy in 3rd or later line will be considered.
 - Combination with curative intent radiation therapy is not of interest.
- Breast cancer
 - Combination or monotherapy.
- Head and neck cancer
 - Including combination with radiation therapy.

Specific exclusions from this RFP include:

- Neuroendocrine tumor.
- Evaluation of quality of life is welcome as a secondary endpoint, but not as a primary endpoint.
- PK studies are not of interest.

Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined clinical strengths of members, particularly in the case of uncommon tumors. Although the submitting investigator must be from an NCCN Member Institution, participating institutions do not need to be an NCCN Member Institution. This can also include cross-institutional collaboration for the conduct of correlative studies.

The NCCN Request for Proposals Development Team (RFPDT) developed this Request for Proposals (RFP) with a formalized review procedure to accept applications and select the proposals of highest scientific merit. The NCCN RFPDT oversaw the development of the RFP and an NCCN Scientific Review Committee, composed of some members of this group and other NCCN clinical leaders, will perform the review of applications. Preference may be given to proposals for specific patient subsets of high unmet need.

Proposals duplicative of completed, ongoing, or planned studies will not be considered. Ongoing studies are listed at the end of RFP. If you wish for additional information or have questions, please e-mail Patricia Esposito at esposito@nccn.org with the subject line, "2019 Taiho Project".

4.0 Study Time Frames

All approved clinical studies are expected to commence, which is defined as the first patient receiving the first dose of study drug(s), no later than ten (10) months after notice of study approval and are to complete accrual within two (2) years of commencement. A manuscript must be submitted to NCCN for review no later than nine (9) months after the primary study endpoint is achieved. Studies will be funded as described in Section 9.0 and should be designed with subject number commensurate with study timeframes and funding.

Studies for rarer cancers or those that require a large numbers of patients for statistical power must be multi-institutional. Network appropriate studies will be considered as long as submitting PI is from an NCCN Member Institution.

Accepted studies will be held to the following time frames:

Phase I studies are expected to meet primary objective within 2 years of commencement.

Single-arm Phase II studies are expected to explore new approaches that can be tested in larger confirmatory studies if positive results are obtained. It is expected that these studies will meet the primary objective within 2 years of commencement. To meet this goal, single-arm Phase II trials are encouraged to be multi-institutional. Data management and monitoring of studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity, if the study involves multi-institutional participation.

Correlative laboratory studies are expected to be completed within the same time frame as the corresponding clinical trial.

Larger randomized Phase II studies already supported through other mechanisms which will be completed within 2 years (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data.

Randomized Phase II multi-institutional studies are expected to be completed within a 2-year time frame. Multi-institutional data management and monitoring of these studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity.

All studies will require documentation of the feasibility of accruing the targeted study population; studies may be multi-institutional.

5.0 Proposals

In order to respond to the RFP, investigators must submit a proposal to NCCN in the format delineated below, which will be evaluated by the NCCN Scientific Review Committee (SRC).

Proposals are required to be submitted electronically to the NCCN research portal at https://nccn.envisionpharma.com/ienv_nccn and include letters of support from the governing groups of the institution verifying:

- 1) Office of Sponsored Research approval
- 2) Department Chair/Division approval
- 3) Institutional budgetary review and approval
- 4) For clinical trials, the priority status of the research stating if there are competing trials. If there are competing trials, please verify that this trial will have a higher priority.
- 5) Documentation to support feasibility of clinical trials with at least one of the following:
 - Letter from Institution's Feasibility Committee if applicable
 - Documentation by previous studies and accrual (if available, publications and abstracts)
- 6) Letter(s) of support from participating institutions including name of PI at participating institution and their feasibility

Letters should be addressed to Wui-Jin Koh, MD, CMO, National Comprehensive Cancer Network, 3025 Chemical Road, Suite 100, Plymouth Meeting, PA 19462.

Proposals will provide concise documentation of the research plan. The proposal is expected to contain sufficient information to allow the reviewers to fully assess the scientific rigor of the proposed study. A full research project plan may be submitted as a supplemental attachment. A robust review of the statistical plan will be conducted.

Proposals should contain detailed information regarding the following areas:

- 5.1 Clinical/Non-Clinical Research
 - A. General Information: Title/Type of Support/Subsite(s)
 - B. Investigators and institutional affiliations
 - C. Concept information
 - i. Enrollment/Design/Phase
 - ii. Estimated time of completion
 - iii. Overview/Hypothesis
 - iv. Background/Rationale
 - D. Scientific summary
 - i. Primary/Secondary objectives
 - ii. Inclusion/Exclusion criteria
 - iii. Study population
 - iv. Statistical analysis
 - v. Treatment plan
 - vi. References
 - E. Oncology analysis
 - i. Tumor Type/Stage
 - ii. Correlative study information
 - iii. Outcome measures
 - iv. Feasibility documentation
 - F. Request for product: Formulation Dosage/Quantity
 - G. Planned publications: Journal/Congress/Anticipated Dates
- 5.2 Budget using NCCN template (within iEnvision)
 - A. Breakdown by major cost categories

- B. Justification of major costs with enough detail to demonstrate how funding for major elements in the study will be allocated
- C. Salaries are capped at the current NIH salary cap
- D. No travel or publication costs will be covered

5.3 Ancillary Documentation

- A. An NCI format BioSketch of the Principal Investigator
- B. An appendix of supportive literature may be provided

6.0 Proposal Requirements

6.1 Submission

All proposals must be submitted electronically using the directions below and are due by **11:59 PM (EST) on January 7, 2019**. No exceptions will be granted.

1. Please use the link below to register in the system:
https://nccn.envisionpharma.com/ienv_nccn
2. Select "Register for New Account" in the upper right corner of the page, above the "Log In" button
3. Complete all fields (Note: Fields with an asterisk are required)
4. You will receive a confirmation email. Click on the link in the email to activate your account.
5. Enter your name and password (Note: Your user name is your email address. Do not copy and paste.)
6. Set up your security questions
7. Submit your study
 - i. RFP ID: TRIF
 - ii. Primary compound: trifluridine/tipiracil
8. Refer to "Requestor User Manual" located under the question mark on the upper right side of the screen for additional instructions

For technical assistance with the iEnvision system, please contact iEnvision_general_request@envisionpharmagroup.com.

Studies that have safety issues, are already well-funded concepts, or are not consistent with the strategy for investigation as written in this RFP will not be reviewed by the SRC.

For questions or issues, please call Patricia Esposito at (215) 690-0560. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of FTD/TPI in order to avoid the submission of a proposal that is already a well-studied concept.

6.2 Requirements

6.2.1 Human Biological Specimens: All specimens must be obtained under informed consent and IRB approval appropriate for the study. Compliance with all federal regulations is required.

6.2.2 IRB:

6.2.2(a) Draft protocols will be reviewed by NCCN and the Grantor **prior** to IRB review. A copy of the draft protocol must be submitted to NCCN within 4 weeks after the study approval letter. The protocol must be consistent with the approved proposal and all reviewer comments must be addressed.

6.2.2(b) All investigators will submit protocols for IRB review and document approval to NCCN prior to study activation and all collaborators will furnish evidence of IRB approval. It is expected that IRB review and approval be completed **within 150 days** following NCCN notification of funding for the project.

6.2.3 IACUC review and approval: All investigators conducting animal experiments will submit research project plans for IACUC review and document approval to NCCN prior to study activation. It is expected that IACUC review and approval be completed **within 90 days** following NCCN notification of funding for the project.

6.2.4 Serious Adverse Event Reporting: All serious adverse events will be reported to NCCN and the Grantor in addition to regulatory authorities.

6.2.5 Institutional Monitoring: All studies will be internally monitored in accordance with appropriate committees (e.g. institutional Data Safety and Monitoring Plan in the case of human studies). A copy of the Data Monitoring Plan for the study must be submitted to NCCN prior to NCCN approval of study activation.

6.2.6 IND:

6.2.6(a) Investigators are required to hold INDs for studies but will be allowed to cross-reference a filing to Grantor's IND. Investigators are encouraged to apply to the FDA for IND exemption if studies meet all criteria according to 21 CFR 312.2(b). A copy of the FDA approval letter for IND exemption must be submitted to NCCN before study drug will be released.

6.2.6(b) If FTD/TPI is studied in combination with an investigational agent from another pharmaceutical company, or an agent used outside of its indication, the investigator must provide documentation of that company's commitment to provide drug for the investigation as well as the agreement of that company to allow presentation and publication of results and allow cross-filing or filing of a new IND. **This documentation must be provided to NCCN along with the proposal.**

6.2.6(c) Proposals using an experimental diagnostic imaging agent that will require an IND must outline how regulatory issues will be handled in order to meet the required study time frame.

6.2.7 Progress Reports: Investigators will provide interim progress reports to NCCN detailing the progress of studies quarterly, and upon study completion. These reports will be used administratively for funding

purposes. If study progress or accrual lags behind the expected rate, the SRC may be asked for suggestions to improve study progress, or alternatively, to terminate the study and any further funding.

6.2.8 Specimen Transmittal: If specimens are to be transported extramurally for collaborative laboratory studies, all institutional requirements for safety and confidentiality will be met.

6.2.9 Abstracts and Publications: Abstracts for presentation at scientific meetings and all publications of study results will be submitted to NCCN and Grantor for review related to protection of company's intellectual property and confidential information **prior to any submission**. Abstracts must be submitted at least 10 days prior to submission and manuscripts at least 30 days prior to submission. Grantor may delay publication and disclosure of the manuscript or abstract for up to an additional sixty (60) days so as to seek patent protection of intellectual property rights.

6.2.10 NCCN Multi-Institutional Studies: Collaborative studies between NCCN Member Institutions are encouraged. For these studies, the proposal feasibility section should provide information about data management, statistical analysis, and specimen handling issues. Additional funding may be provided for centralized data management and monitoring by the applying institution.

6.2.11 NCCN institutions and investigators will be responsible for conducting all studies in accordance with the applicable research plan, GCP Guidelines, and all applicable laws and regulations. NCCN institutions and investigators will be responsible for all data collection, statistical analysis and safety reporting.

6.2.12 Investigators must provide reasonable assurance that submitted studies will be able to reach completion within the time frames specified in Section 4.0.

6.2.13 Final protocols must be consistent with approved proposals. Funds will be rescinded if there are significant changes without prior NCCN approval. There will be no exceptions.

6.2.14 The Principal Investigator (PI) listed on the protocol must be the same PI listed on the proposal submission unless approved by NCCN.

7.0 Drug Supply

FTD/TPI will be supplied by Grantor for all approved and funded studies.

If FTD/TPI is studied in combination with an investigational agent from another pharmaceutical company, or an agent is used outside of its indication, the investigator must provide documentation of that company's commitment to provide drug for the investigation as well as the agreement of that company to allow presentation and publication of results, and allow cross-filing or filing of a new IND.

8.0 Selection Criteria

Proposals will be judged based on the following criteria:

1. Scientific value
2. Research experience of the Principal Investigator
3. Soundness of study design
4. Feasibility including reasonable assurance of achieving intended full accrual
5. Budgetary reasonableness
6. Statistics

The Grantor has the ability to reject any study with safety issues or if it is an already studied concept.

9.0 Funding

NCCN and its member institutions have an agreement to include a maximum of 25% indirect/overhead costs for trials funded by the NCCN. Direct funding will include all costs including investigators' salaries. For example, \$80,000 direct costs and \$20,000 indirect/overhead costs for a total grant of \$100,000. Any funds in excess of the limits stipulated in this section for direct funding will require detailed justification and review.

Phase I and Single-arm Phase II clinical trials will be funded at a cost of up to \$300,000 (total costs including direct costs and 25% indirect/overhead costs) per trial. Multi-institutional data management and monitoring of these studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity.

The Correlative Laboratory studies section of the clinical trial will be funded up to a total cost of \$100,000, including up to 25% indirect/overhead costs.

Larger Randomized Phase II trials already supported through other mechanisms (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data. Correlative studies for larger randomized trials will be funded up to \$100,000.

Funding should not exceed \$500,000. Clinical study maximum \$300,000 + correlative study maximum \$100,000 + multi-institutional funding maximum \$100,000 = \$500,000
MAXIMUM funding

Funding will be disbursed to approved studies as follows:

Phase I trials:

- 15% after IRB approval and dosing of first study subject;
- Based on the per study subject costs, after the initial 15% of funding has been accounted for based on study subject accrual, funds will be awarded on a quarterly basis for eligible study subjects enrolled in a study, based on the per study subject rate up to a maximum of an additional 65% of the funding; and
- 20% of funds will be awarded after submission of a final report or manuscript for publication.

Phase II trials and correlative study(ies):

- 15% after IRB approval and dosing of first study subject;
- Based on the per study subject costs, after the initial 15% of funding has been accounted for based on study subject accrual, funds will be awarded on a quarterly basis for eligible study subjects enrolled in a study, based on the per study subject rate up to a maximum of an additional 65% of the funding; and
- 20% of funds will be awarded after submission of a final report or manuscript for publication.

Phase I/II trials with 2-stage design with early stopping rules:

- 15% of total requesting funding (based on maximum number of anticipate study subjects) after IRB approval and dosing of the first study subject;
- Remainder of per study subject funding for number of study subjects in the first stage after all study subjects are accrued to the first stage of a study (total funding for a number of study subjects in first stage less the initial payment);
- Total per study subject funding for the number of study Subjects in the second stage less final payment after all study subjects are accrued to the second stage up to a maximum of an additional 65% of the funding; and
- 20% of total requested funding (based on maximum number of anticipated study subjects) after submission of a final report or manuscript for publication.

Multi-center randomized phase II study(ies):

- 15% after IRB approval and dosing of first study subject;
- Based on the per study subject costs, after the initial 15% of funding has been accounted for based on study subject accrual, funds will be awarded on a quarterly basis for eligible study subjects enrolled in a study, based on the per study subject rate up to a maximum of an additional 65% of the funding;
- 20% after submission of a final report or manuscript for publication; and
- Any additional funding will be disbursed to the coordinating center for data management and monitoring. These funds will be delegated at the discretion of the lead Principal Investigator and may include outsourcing of data management and/or monitoring to an independent research organization.

The goal is to have rapid submission of a manuscript so as to have the data available to the wider scientific community.

Studies that do not meet the time frame requirements as stipulated in Section 4.0 will have funds rescinded and will be required to return any and all unused funds previously disbursed.

10.0 Study Agreement

A study agreement will be signed between NCCN and each submitting institution.

If an institution requires a separate contract with another pharmaceutical company for a study, that contract must be fully executed by the time of final contract execution with NCCN.

All aforementioned points between NCCN and the participating institution must be strictly adhered to.

11.0 References

1. Global Investigator's Brochure for TAS-102. Version G 8.0. Final Release Date: 14 October 2017
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4. Heidelberger C, Chaudhuri NK, Danneberg P, et al: Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature* 179:663-6, 1957
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7. Mayer R, Ohtsu A, Yoshino T, et al: TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the phase 3 RECURSE trial. Presented at the Gastrointestinal Cancers Symposium, San Francisco, CA, 2016
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9. Xu J, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study. *J Clin Oncol*. 2017;35 [Epub ahead of print].
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11. Lesniewski-Kmak K, Moiseenko V, Saunders M, et al: Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): Results of the primary analysis, ESMO World GI Congress. Barcelona, Spain, 2018
12. Varghese AM, Cardin DB, Hersch J, et al. A Phase 1 dose-escalation study of trifluridine/tipiracil in combination with irinotecan in patients with advanced gastrointestinal tumors. Poster presented at the AACR Annual Meeting 2018; Chicago, Illinois, USA; April 14-18, 2018.
13. Varghese AM, Cardin DB, Hersch J, et al. A phase 1 expansion study of trifluridine and tipiracil in combination with irinotecan and bevacizumab in patients with metastatic colorectal cancer. Poster presented at 2018 *American Society of Clinical Oncology (ASCO) Annual Meeting*, June 1–5, 2018, Chicago, IL, USA.
14. Hollebecque A, Calvo A, Andre T, et al: Phase I multicenter, open-label study to establish the maximum tolerated dose (MTD) of trifluridine/tipiracil (TAS-102) and oxaliplatin combination in patients (pts) with metastatic colorectal cancer (mCRC), Gastrointestinal Cancers Symposium. San Francisco, CA, 2018
15. Calvo A, Dahan L, Hollebecque A, et al. Safety run in evaluation of the phase I trial of trifluridine/tipiracil (FTD/TPI) in combination with oxaliplatin and a monoclonal antibody (bevacizumab or nivolumab) in patients with metastatic colorectal cancer. Poster (470P) at 2018 ESMO Munich, Germany

Investigator Initiated Trials (Ongoing)

Study Title	NCT Number
Safety of TAS-102 in Combination With Temozolomide for Metastatic Pancreatic Neuroendocrine Tumors	NCT02943733
A Phase II Trial of TAS-102 in Previously Treated Unresectable or Metastatic Squamous Cell Carcinoma of the Lung	NCT02920476
A Phase II Trial of TAS-102 (Lonsurf) in Patients With Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma After Progression Through First Line Chemotherapy	NCT02921737
A Phase I/II Study of Trifluridine/Tipiracil (TAS102) in Combination With Nanoliposomal Irinotecan (NAL-IRI) in Advanced GI Cancers	NCT03368963
Phase I Trial of TAS-102 and Concurrent Radiation Therapy for Patients With Locally Recurrent, Unresectable or Metastatic, Rectal Cancer	NCT03297710
Phase Ib/II Study of TAS-102 Plus Radiation Therapy for the Treatment of the Liver in Patients With Hepatic Metastases From Colorectal Cancer	NCT03223779
Phase II Trial of Trifluridine/Tipiracil (FTD/TPI (TAS-102)) in Biliary Tract Cancers	NCT03278106