NCCN Request for Proposals (RFPs): Phase I/II Clinical Trials of Tipiracil/Trifluridine (TAS-102) and/or Futibatinib (TAS-120) for Gastrointestinal Cancers

Date Issued: September 17, 2024

1.0 Purpose

The National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc. are collaborating to offer a new grant opportunity seeking proposals for investigator-initiated research with tipiracil/trifluridine (FTD/TPI) and/or futibatinib. NCCN has received a $2.5 Million research grant from Taiho (hereafter, “Grantor”) to support NCCN Member Institution investigators to conduct novel clinical trials to further evaluate the effectiveness of FTD/TPI and/or futibatinib in the treatment of Gastrointestinal cancer patients. NCCN will serve as the funding organization. Grants are available only to investigators from NCCN Member Institutions.

2.0 Organization Information

National Comprehensive Cancer Network

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 33 leading cancer centers devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, equitable, and accessible cancer care so all patients can live better lives. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. By defining and advancing high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers around the world.

Grantor

The Grantor is Taiho Oncology, Inc. located at 101 Carnegie Center, Suite 101, Princeton, NJ 08540.

3.0 Background

NCCN received a grant from the Grantor for the design and performance of clinical trials using FTD/TPI and/or futibatinib to treat gastrointestinal cancer patients.

3.1 Tipiracil/Trifluridine (FTD/TPI)

Overview

Trifluridine/tipiracil (FTD/TPI; also known as TAS-102, Lonsurf®) is an orally available combination drug.[1-5] It is approved for use in patients with metastatic colorectal cancers as a single agent or in combination with bevacizumab for patients who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF biological therapy, and/or anti-EGFR therapy, if *RAS* wild-type, and in metastatic gastric or gastroesophageal junction cancers who have previously been

treated with at least two prior lines of systemic therapies that include a fluoropyrimidine, platinum, either a taxane or irinotecan, checkpoint inhibitor(s) and an anti-HER2/neu agent, if appropriate. The approved dose of FTD/TPI is 35mg/m^2 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.

Mechanism of Action

The active antimetabolite trifluridine is a fluorinated thymidine analog which incorporates into DNA, resulting in inhibition of DNA synthesis and cell proliferation.[1-5] 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).

Clinical Data

FTD/TPI as Monotherapy

The phase 3 RECOURSE trial randomized 800 refractory metastatic colorectal cancer (CRC) patients 2:1 to FTD/TPI 35 mg/m^2 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), 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/m^2 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/m^2 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 TAGS trial randomized 507 refractory gastric and gastroesophageal junction (GEJ) cancer patients 2:1 to FTD/TPI 35 mg/m^2 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 (0.470.70, 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 RECOURSE trial.

FTD/TPI in combination therapy

The TASCO-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/m^2 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/m^2 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]

The phase 3 SUNLIGHT trial demonstrated the additive effects of FTD/TPI 35 mg/m^2 BID plus bevacizumab 5 mg/kg on days 1 and 15 every 4 weeks vs FTD/TPI

monotherapy based on the combined mechanisms of action of both agents, leading to improvements in OS and PFS for patients with mCRC.[16] 492 patients with histology confirmed unresectable colorectal adenocarcinoma with two prior lines of chemotherapy at most were enrolled. Median OS for FTD/TPI + bevacizumab was 10.8 months, vs 7.5 months with FTD/TPI alone. The combination was associated with a reduction in the risk of progression of 56%, with a median PFS of 5.6 months vs 2.4 months for FTD/TPI alone. It was also associated with a 0.61 Hazard Ratio (HR) with reduction of risk of death of 39%. FTD/TPI plus bevacizumab showed a statistically significant improvement in the time to worsening of ECOG PS to ≥2 compared with FTD/TPI alone, with a median time to worsening of 9.3 months versus 6.3 months, respectively[1]. This was the first trial to demonstrate an improvement in OS refractory metastatic colorectal cancer versus an active control.

A full list of TAS-102 key studies is available as an attachment to this RFP for reference.

3.2 Futibatinib

Overview
The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival of cells and is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Accordingly, dysregulation of this signaling pathway has been associated with many developmental disorders and cancer. An extensive amount of literature indicates that FGF/FGFR is one of the receptor tyrosine kinases most frequently mutated or otherwise abnormally activated in human cancer. Patients with genetic modifications or overexpression of FGF/FGFR frequently suffer from advanced (non-resectable or metastatic) disease manifestations, which are generally incurable due to intrinsic and adaptive multi-drug resistance.[17-21] Therefore, there is a substantial unmet medical need for novel therapies against advanced cancers with FGF/FGFR abnormalities.

More than 50% of patients with non-muscle invasive bladder cancer have an FGFR3 activating mutation or gene translocation.[20] About 15% of patients with cholangiocarcinoma have FGFR2 fusion.[22,23] The FGFR2 activating mutation is found in 12% of endometrial cancers and 10% of patients with breast cancer have FGFR1/2 amplifications. FGFR2 amplifications are found in 10% of gastric cancer patients.[20] Recent nonclinical and clinical research indicates that FGFR is a valid and promising target for cancer therapy.

Mechanism of Action
Futibatinib is a novel, highly selective small molecule pan-FGFR inhibitor. It is the first irreversible, covalent inhibitor of all 4 FGFR isoforms being tested in humans. Other FGFR inhibitors are predominately ATP competitive inhibitors.[24] Furthermore, futibatinib demonstrates activity against FGFR mutants resistant to ATP-competitive inhibitors.

Preclinical Data
Futibatinib is a pan-FGFR inhibitor with IC50 for FGFR1, FGFR2, FGFR3 and FGFR4 of 3.9 nM, 1.3 nM, 1.6 nM and 8.3 nM respectively.[24]

In vitro studies showed that futibatinib inhibited cellular phosphorylation of FGFR, as well as intracellular signaling pathways downstream of FGFRs, thereby selectively inhibiting cell growth of human cancer cell lines harboring FGFR gene abnormalities (gastric, breast, lung, endometrial, and bladder cancers and multiple myeloma). Futibatinib retained inhibitory potency against mutant FGFR2 including the V565I gatekeeper mutation with a similar potency as when compared with wild type. N550H and E566G mutations in the FGFR2 hinge region, which were reported to cause resistance to dovitinib (another FGFR inhibitor currently in clinical testing), were also sensitive to futibatinib. Furthermore, futibatinib showed inhibitory potency against mutant FGFR2, including K660M activating loop mutation. In contrast, inhibitory potencies of tested ATP competitive inhibitors against these FGFR2 mutations were reduced compared with that against wild type.

In vivo studies showed that futibatinib had strong antitumor efficacy in nude mouse or nude rat xenograft models bearing tumors with various FGFR gene abnormalities (FGFR1 or 2 amplification and FGFR3 translocation) when given on a daily dosing schedule. Futibatinib markedly demonstrated antitumor efficacy with intermittent (alternate day or twice weekly) dosing schedules. From these results, the effective doses of futibatinib on alternate day and daily dosing schedules were estimated to be more than 1.5 mg/kg and 0.5 mg/kg, respectively. In a xenograft model (RT 112/84), equivalent antitumor activity was seen for daily and alternate day dosing of futibatinib. In another xenograft model (NCI H1581), daily dosing of futibatinib showed increased antitumor activity compared with alternate day dosing. An intermittent dosing schedule of futibatinib appeared to prevent continuous up regulation of serum phosphate and may mitigate the potential risk of mineralization caused by hyperphosphatemia.

An in vivo study also demonstrated that plasma FGF23 levels might be a useful pharmacodynamic marker of FGFR inhibitors in vivo. Plasma FGF23 levels were significantly increased by futibatinib at doses of more than 0.31 mg/kg/day.

Clinical Data

In a dose-escalation and expansion Phase 1 study, relapsed/refractory solid tumors harboring FGF amplifications or FGFR aberrations (including rearrangements/gene fusions, mutations or amplifications) were enrolled.[25] Prior FGFR inhibitor use was allowed. In the dose escalation phase, two dosing schedules (oral daily dosing with 4, 8, 16, 20 and 24 mg doses and every other day dosing up to 200 mg) were assessed. The maximum tolerated dose and recommended phase 2 dose was determined to be 20 mg daily. The dose of futibatinib used in the expansion phase was 20 mg daily in a 21-days cycle.

In the Phase 2 trial (FOENIX-CCA2) of futibatinib in patients with unresectable or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or rearrangements who have progressed one prior line of therapy, patients received futibatinib 20 mg daily.[26] No prior FGFR inhibitor use was allowed. 103 patients were enrolled. Objective response rate was 41.7% with a disease control rate of 82.5%, with median duration of response of 9.7 months and median OS of 21.7 months. The most frequently reported grade 3 treatment-related adverse event (AE) overall was hyperphosphatemia (a mechanism-based event) in 30% of patients, without clinical complications. Other grade 3 AEs were increased aspartate aminotransferase level (in 7%), stomatitis (in 6%), and fatigue (in 6%). Only 2% of patients discontinued futibatinib due to AEs. No treatment related deaths occurred.

In all, more than 460 patients and healthy volunteers have been treated with futibatinib across all trials. Collectively, safety data from these studies suggest that futibatinib is associated with manageable toxicity in multiple patient populations. The toxicity profile from other studies is consistent with AEs seen in FOENIX-CCA2. Ocular toxicities, which have been reported with other FGFR inhibitors, were observed with low frequency in all trials.

Futibatinib has demonstrated clinical activity in other tumor types as well, including gastric cancer, CNS tumors, urothelial cancer, and breast cancer. There is currently no clinical data on the safety of the combination of futibatinib with chemotherapy, immunotherapy, hormonal therapy or other targeted agents.

4.0 Aim and Eligibility

Aim	Develop innovative trials to help determine the effectiveness of tipiracil/trifluridine and/or futibatinib in the treatment of gastrointestinal cancer patients. It is hoped proposals submitted in response to this RFP will be useful in guiding further development/usefulness of these drugs. Timely dissemination of the final study results to the larger scientific community is paramount.
Geographic Scope	United States
Eligibility Criteria: Investigators from the following organizations may apply	• NCCN Member Institutions • Collaboration among NCCN Member Institutions is strongly encouraged in order to foster interactive sharing of knowledge and expertise, and to utilize the combined clinical strengths of Member Institutions. • Although the submitting investigator must be from a Member Institution, participating institutions do not need to be from an NCCN Member Institution. • Proposal submissions from junior faculty are encouraged. • Trainees may participate as a sub-investigator under appropriate mentorship from a PI at a Member Institution.

5.0 Requirements

Clinical Area:	Gastrointestinal Cancers
Target Audience:	NCCN Member Institutions
Funding Considerations:	• There is $1.9 million available for funding of all projects. • *Please see Section 7.0 for details on maximum per project funding amounts.* • The maximum indirect (overhead) rate is 25% and *must* be included in total grant request amount. • Direct funding will include all costs including investigators' salaries. For example, $80,000 direct costs and $20,000 indirect 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. • Salaries are capped at the current NIH salary cap.

	• No travel or publication editorial or writing assistance costs will be covered. Publication submission fees can be included in the budget. • Applicants are required to disclose additional sources of funding for this project and demonstrate that funding does not overlap. • The decision relative to funding is deferred to the members of the Scientific Review Committee (SRC) as chosen by NCCN SRC and independent of the Grantor.

Areas of research interest/emphasis:	• Phase I/II clinical trials:
	  • FTD/TPI
	  • Combination studies including FTD/TPI in colorectal or gastric cancer, especially with VEGF-inhibitors, immunotherapy, or targeted therapies
	  • Earlier lines of treatment for colorectal cancer patients
	  • Different gastrointestinal tumor types, including cancers other than labeled indications
	  • Futibatinib
	  • Combination studies including futibatinib with chemotherapy, immunotherapy, or targeted monoclonal antibody
	  • Different gastrointestinal tumor types, including but not limited to cancers other than labeled indications
	  • Clinical activity of futibatinib with and without combinations
	• Drug combination studies in gastrointestinal cancers are acceptable if the toxicity profile of the agent is appropriate for combination with FTD/TPI and/or futibatinib. There is a particular interest in agents that have documented single agent activity of the combining drug in the disease being studied so that the contribution of FTD/TPI and/or futibatinib can be determined.
	• If combination studies with agents that are not standard of care are proposed, partnership with other companies to provide drug supply is required.
	• Preference may be given to proposals for specific patient subsets (e.g. young-onset, gender differences, ethnic differences) and those with a high unmet need.
	
	Adverse event reporting is mandatory for all proposals.

Areas excluded or considered out of scope:	Specific areas considered out of scope or excluded include: • Pre-clinical or translational only research • Studies including quality improvement as primary end point

	• Pediatric Studies • Alternative dosing • Pharmacokinetic-Pharmacodynamic analysis only or as primary end point studies • Biomarker only or as primary end point studies • Non-Gastrointestinal cancers *No studies will utilize doses outside the range for which safety data is available (i.e., nothing greater than 20 mg daily for futibatinib and 35 mg/m^2 for FTD/TPI).* ***Proposals with safety concerns or that are duplicative of completed, ongoing, or planned studies will not be considered. Previously funded trials utilizing FTD/TPI and/or futibatinib are included in Appendix A.***
Study Timeframes for Approved Studies:	• Commencement (defined as first patient receiving first dose of study drug): *no later than ten (10) months* of notice of study approval. • Complete accrual: *within two (2) years* of commencement. • Reporting/Dissemination of results in Manuscript Form: *no later than nine (9) months* after study endpoint achieved. *Please note that manuscript must be submitted to NCCN and Grantor for review prior to submission for publication consideration. • Studies will be funded as described in Section 7.0 and should be designed with subject number commensurate with study time frames and funding. • Studies for rarer cancers or those that require large numbers of patients for statistical power must be multi-institutional. Network affiliate 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 two 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 two 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.

	Randomized Phase II multi-institutional studies are expected to be completed within a two-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 as well as meeting the primary endpoint within the allotted timeframe.*** *Studies that do not meet the timeframe requirements may have funds rescinded and will be required to return any and all unused funds previously disbursed.*
Selection Criteria:	Proposals will be judged based on the following criteria: • Scientific value and innovation; • Research experience of the Research Team; • Soundness of study design; • Statistical rigor; • Feasibility including reasonable assurance of achieving intended full accrual; and • Appropriateness of budgetary request and full justification of all direct and indirect expenses. *The GRANTOR may reject any study with potential safety issues or if it is an already studied concept.*
Drug Supply:	Futibatinib and tipiracil/trifluridine will be supplied by Grantor for all approved and funded studies. If the proposal requires a second investigational drug, a letter of commitment for provision of that drug by the supplier must be submitted with the proposal.
Key Dates:	RFP Release date: September 17, 2024 Proposal Submission deadline: November 12, 2024 (Please note submission deadline is 5:00 PM Eastern Time) Anticipated Grant Award Notification Date: December 20, 2024 Protocol Draft: Due within 30 calendar days after award notification Commencement of Study: Within 10 months after award notification Study completion: 2 years after commencement Manuscript Draft: Within 9 months after completion
Questions:	If you have questions regarding this RFP, please direct them in writing to Nicole Zion, Senior Manager, Clinical Research, at Zion@nccn.org with the subject **"NCCN Taiho Gastrointestinal RFP"**.

6.0 Review and Approval Process

The NCCN Request for Proposals Development Team (RFPDT) has developed a Request for Proposals (RFP) with a formalized review procedure to accept applications and select the proposals of highest scientific merit. The NCCN RFPDT has overseen the development of the RFP and a NCCN Scientific Review Committee composed of this group will perform the review of applications. All reviews, evaluations and award decisions are independent of Grantor.

Applicants will be notified via email with the notification of funding status by the dates noted above.

Proposals duplicative of completed, ongoing, or planned studies will not be considered. Previously funded trials utilizing tipiracil/trifluridine and futibatinib can be found in Appendix A. If you wish for additional information or have questions, please e-mail Nicole Zion, Senior Manager, Clinical Research, at Zion@nccn.org or call 215-690-0230.

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.

7.0 Funding

NCCN and its Member Institutions have an agreement to include a maximum of 25% indirect 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 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 $400,000 (total costs including direct costs and 25% indirect 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 of up to $100,000 may be requested to support the additional resources required for managing and monitoring of sub-sites.

Total funding not to exceed $500,000. Clinical study maximum $400,000 + multi-institutional funding maximum $100,000 = $500,000 MAXIMUM funding.

Funding will be disbursed to approved studies as follows:

Phase I trials:

- 15% of total award for such study 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 manuscript for publication.

Phase II 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% after submission of a manuscript for publication.

Phase II trials with 2-Stage Design with Early Stopping Rules:

- 15% of total requested funding (based on maximum number of anticipated study subjects) after IRB approval and dosing of first study subject;
- Remainder of per Study Subject funding for the number of study subjects in the first stage after all study subjects are accrued to the first stage of a study (total funding for the number of study subjects in first stage less the initial payment) up to a maximum of an additional 65% of the funding;
- 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; and
- 20% of total requested funding (based on maximum number of anticipated study subjects) after submission of a 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.

Studies that do not meet the time frame requirements as stipulated in Section 5.0 will have funds rescinded and will be required to return any and all unused funds previously disbursed.

8.0 Proposals

In order to respond to the RFP, investigators will submit a proposal in the format delineated below to NCCN, 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 a letter 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) 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 Crystal S. Denlinger, MD, CEO, National Comprehensive Cancer Network, 3025 Chemical Road, Suite 100, Plymouth Meeting, PA 19462.

Proposals will provide concise documentation of the research plan and should be the equivalent of no more than 10 pages. 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 an attachment but the required information in iEnvision must also be completed. A robust review of the statistical plan will be conducted.

Proposals should contain detailed information regarding the following areas:

8.1 Clinical Trials

A. General Information: Title/Type of Support/Subsite(s)
   - Select "**TAI1**" for RFPID
   - Select "**Funding and Product**" for Type of Support

B. Investigators and institutional affiliations
   - Include academic title and rank

C. Site Information
   - Primary and sub-site information as applicable

D. Concept information
   - Enrollment/Design/Phase
   - Estimated time of completion
   - Overview/Hypothesis
   - Background/Rationale

E. Scientific summary
   - Primary/Secondary objectives
   - Primary/Secondary endpoints
   - Inclusion/Exclusion criteria
   - Study population
   - Sample size/Statistical analysis
   - Treatment plan
   - References

F. Oncology analysis
   - Tumor Type/Stage/Body systems

- Select “no” from dropdown box
- Outcome measures
- Feasibility documentation
- Letter of Support

G. Request for product: Formulation Dosage/Quantity

H. Planned publications: Journal/Congress/Anticipated Dates

8.2 **Requested Funding Information** (See iEnvision User Manual for additional instructions)

A. Complete the **NCCN Budget Template** (attached) and submit the **full budget** via the attachments folder.
   - Breakdown costs by major cost categories
   - Provide justification of major costs with enough detail to demonstrate how funding for major elements in the study will be allocated
   - Salaries are capped at the current NIH salary cap
   - No travel or writing/editing publication costs will be covered

B. Complete the remainder of the Funding Page:
   - Total direct and indirect costs (see instructions)
   - Requested currency (US Dollar)
   - Overhead %
   - Amount Requested
   - Additional sources of funding

8.3 Required Documentation for Combination Treatment
<u>This documentation must be provided to NCCN along with the proposal or it will not be considered for funding.</u>

1. Documentation is required if tipiracil/trifluridine or futibatinib are to be studied in combination with an agent from another pharmaceutical company, used outside its indication or obtained as standard of care.
2. If tipiracil/trifluridine or futibatinib will be studied in combination with an investigational/approved agent, obtained from a pharmaceutical company, the investigator must provide letter stating the following:
   i. The company’s commitment to provide drug for the investigation;
   ii. The agreement of that company to allow presentation and publication of results, and
   iii. The agreement of that company to allow cross-filing or filing of a new IND.
3. If tipiracil/trifluridine or futibatinib will be studied in combination with an agent used outside of its indication, the investigator must provide documentation of how they are obtaining the drug.

8.4 Ancillary Documentation

A. Curriculum Vitae (CV) for the Principal Investigator

B. An appendix of supportive literature may be provided
C. Any additional information to support proposal submission

9.0 Proposal Submission Process

9.1 Submission

All proposals must be submitted electronically using the directions below and are due by **5:00 PM (EST) on November 12, 2024.** No exceptions will be granted.

A. Please use the link below to register in the system:
    i. https://nccn.envisionpharma.com/ienv_nccn
B. Select "Register for New Account" in the upper right corner of the page, above the "Log In" button
C. Complete all fields (Note: Fields with an asterisk are required)
D. You will receive a confirmation email. Click on the link in the email to activate your account.
E. Enter your username and password (Note: Your username is your email address. Do not copy and paste.)
F. Set up your security questions
G. Submit your study

For technical assistance with the iEnvision system, please contact helpdesk@envisionpharmasupport.com

For questions or issues, please email Nicole Zion at zion@nccn.org with the subject line **"NCCN Taiho Gastrointestinal RFP"**. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of FTD/TPI and futibatinib in order to avoid the submission of a proposal that is already a well-studied concept.

10.0 Additional Terms and Conditions

10.1 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.

10.2 Protocol and IRB submission:

10.2(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.

10.2(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.

10.3 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.

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

10.5 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.

10.6 IND:

10. 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.

10.6(b) 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.

10.7 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.

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

10.9 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.

10.10 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.

10.11 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.

10.12 Investigators must provide reasonable assurance that submitted studies will be able to reach completion within the time frames specified in Section 5.0.

10.13 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.

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

11.0 Study Agreement

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

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

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

12.0 References

1. Global Investigator's Brochure for TAS-102. Version G 16.0. Final Release Date: 10May2024
2. Lenz HJ, Stintzing S, Loupakis F: TAS-102, a novel antitumor agent: a review of the mechanism of action. Cancer Treat Rev 41:777-83, 2015
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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 RECOURSE trial. Presented at the Gastrointestinal Cancers Symposium, San Francisco, CA, 2016
8. Bando H, Doi T, Muro K, et al. A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201).

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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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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
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27. Global Investigator's Brochure for TAS-120. Version10.0. Final Release Date: 28 March 2023

APPENDIX A

Drug Name	Study Title	Country	Tumor Type	Indication	Status	NCT#
ASTX660	A phase 1 study of ASTX660 in combination with standard of care FOLFOX chemotharapy in metastatic colorectal cancer	UK	GI	Metastatic colorectal cancer	Active, not enrolling yet.	
ASTX660	Preoperative study of ASTX660 in combination with (short or long course) chemoradiation in rectal cancer	France	GI	Rectal Cancer	Active	NCT05912075
TAS-120	A phase II platform trial of futibatinib in combination with (chemo) immunotherapy in colorectal cancer and other solid tumor entities – FUTURE platform trial	Europe	GI	CRC	Approved	
TAS-120	Investigating therapeutic sequences with FGFR inhibitors in patients with iCCA	Italy	GI	iCCA	Approved	
TAS-120	The PLATON – Platform for Analyzing Targetable Tumor mutations	Europe	GI	Cholangiocarcinoma	Active	NCT04484636
FTD-TPI	A Phase I/II Study of Trifluridine/Tipiracil (TAS102) in Combination with Nanoliposomal Irinotecan (MM398) in advanced GI cancers	USA	GI	GI cancers	Active, not recruiting	NCT03368963
FTD-TPI	Phase I/II study of TAS-102 plus radiation therapy in GI tumors	USA	GI	CRC with hepatic metastases	Active, not recruiting	NCT03223779
FTD-TPI	SHORT Trial: Short course Radiation and TAS 102 (SHORT) in rectal cancer	USA	GI	CRC	Active, not recruiting	NCT04417699
FTD-TPI	Neoadjuvant Trifluridine/Tipiracil (Lonsurf) with Concurrent Radiation in Previously Untreated Resectable Stage II and Stage III rectal cancer	USA	GI	Rectal cancer	Active	NCT04104139
FTD-TPI	Ramucirumab plus TAS-102 for patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma: an investigator-initiated, randomized noncomparative	USA	GI	Gastric or GEJ adenocarcinoma	Active	NCT04660760
FTD-TPI	Proof of concept study of ctDNA guided change in treatment for refractory minimal residual disease in colon adenocarcinomas	USA	GI	Colon adenocarcinoma	Active	NCT04920032
FTD-TPI	A Phase I Study of Trifluridine/Tipiracil plus the Poly (ADP) Ribose Polymerase Inhibitor Talazoparib in Advanced Cancers	USA	GI	Pancreas	Active	NCT04511039
FTD-TPI	TAS 102 in ctDNA Defined Relapsed Minimal Residual Disease in Colorectal Cancer After Completion of Adjuvant Chemotherapy	USA	GI	CRC	Active	NCT05343013