**A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression through First Line Chemotherapy**

UF-STO-PANC-003; UF-GI-006

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| Protocol Version Number | Protocol Version Date | Affected Section(s) | Summary of Revisions Made |
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| **2.0** | **19November2019** | **Cover Page** | Updated study staff, added keywords, minor edits |
| | | **Throughout** | Minor edits for spelling, grammar, and clarification |
| | | **Definitions** | PDO changed to PMO |
| | | **Signature pages** | **Removed:**<br>Pre-filled information<br>**Added:**<br>Subsite signature page |
| | | **Synopsis** | **Added:**<br>Funding Source<br>**Updated:**<br>Inclusion/exclusion criteria<br>Study enrollment period and duration |
| | | **1.4 Rationale for Regimen/Doses/Schedule** | **Removed:**<br>~~Subjects who have received radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be assessable. Subjects must be willing to use contraception; are neither pregnant nor lactating; have an anticipated life expectancy of at least 3 months; have normal end-organ function and limited comorbidities~~. |
| | | **2 Objectives and Endpoints** | **Added**:<br>The primary endpoint, PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.<br><br>Definition of treatment compliance (% of completion of the treatment) |
| | | **3.2 Inclusion Criteria** | **Removed:**<br>~~Histologic or cytologic confirmed adenocarcinoma of the pancreas~~.<br><br>~~Documented radiologic progression on or intolerance to first or second line chemotherapy which was prescribed for metastatic pancreatic adenocarcinoma or locally advanced unresectable disease . Intolerance is defined as any sign or symptom from chemotherapy~~ |

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| | | ~~that resulted in stopping the treatment prematurely before progression of disease or the subject's desire to stop chemotherapy treatment without evidence of progression.~~<br><br>~~Subjects of childbearing potential must be using an effective means of contraception including but not limited to barrier methods, birth control, intrauterine devices.~~<br>~~Histologic diagnosis of pancreatic adenocarcinoma that has been treated previously with one or two lines of chemotherapy.~~<br>~~Previous surgery and/or radiotherapy to a non-target lesion may have been performed up to 4 weeks prior to the date the subject signs the informed consent form , but there must be evidence of disease progression radiographically or intolerance to first or second line chemotherapy.~~<br>~~Subjects must have provided written informed consent and be willing to comply with all study-related procedures.~~<br><br>**Added:**<br>Clinical diagnosis of confirmed of adenocarcinoma of the pancreas, with pathologic confirmation of adenocarcinoma.<br>Subjects must have measurable disease per RECIST 1.1 criteria.<br><br>Refractory or intolerant to 1 or 2 prior regimens of standard chemotherapy for metastatic or locally advanced pancreatic cancer.<br>a. Patients who have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy, or<br>b. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.<br><br>**Updated:**<br>Subjects on anticoagulation need to have no evidence of uncontrolled bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to the date the subject ~~signs the informed consent form~~starts study drug.<br><br>Metastatic or locally advanced unresectable disease. Subjects without clear evidence of distant metastatic disease will be presented at multidisciplinary tumor board for discussion of disease resectability. |

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| | | AST and ALT equal to or less than 3 times the upper limit of normal for patients without hepatic involvement, or AST and ALT equal to or less than 5 times the upper limit of normal for patients with hepatic involvement<br><br>Absolute neutrophil count ≥1500/ $mm^3$<br><br>Platelet count ≥75,000/ $mm^3$ |
| | **3.3**<br>**Exclusion Criteria** | **Removed:**<br>~~Decline using effective means of contraception if sexually active~~<br><br>~~No history of an invasive malignancy within the five years prior to initiating therapy on this protocol. Subjects may have prior in situ carcinomas (such as of the breast or cervix), non-melanoma skins cancers, Rai Stage 0 chronic lymphocytic leukemia or monoclonal gammopathy of uncertain significance and still otherwise qualify for enrollment on this protocol~~<br><br>~~Radiotherapy to the target lesion within 2 weeks of the date the subject signs the informed consent form~~<br><br>~~Major surgery within 4 weeks of the date the subject signs the informed consent form (the surgical incision should be fully healed prior to study medication administration).~~<br><br>~~Antineoplastic, biologic or anti-cancer treatment within prior 3 weeks. A 3 week washout period will be required prior to beginning study treatment if subjects have received anti-cancer treatment within this time frame.~~<br><br>~~Lingering NCI-CTCAE toxicity grade 2 or higher from prior cancer treatments (excluding anemia, alopecia, skin pigmentation, and platinum induced neurotoxicity) > 28 days after the date the subject signs the informed consent form~~<br><br>~~Subjects with severe hepatic enzyme impairment manifesting as total bilirubin greater than 1.5mg/dL or greater than 3 times the upper limit of normal of AST or ALT.)~~<br><br>~~Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years of carcinoma-in-situ deemed cured by adequate treatment~~ |

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| | | ~~Women or men of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after the last dose of study drug.~~<br><br>**Added:**<br>Intervention for ascites or pleural effusions within 4 weeks before first dose of study drug<br><br>Previous surgery and/or radiotherapy may have been performed 2 or more weeks prior to the date the subject starts study treatment, provided that it was to a non-target lesion and there is still evidence of target lesion disease progression radiographically or intolerance to first or second line chemotherapy.<br><br>Major surgery within 4 weeks before first dose of study drug (the surgical incision should be fully healed prior to drug administration).<br><br>Any anticancer therapy within 3 weeks before first dose of study drug (with the exception of bevacizumab, which must not have been taken within 4 weeks before first dose of study drug).<br><br>Extended field radiation within 4 weeks before first dose of study drug or limited field radiation within 2 weeks before first dose of study drug.<br><br>Any investigational agent received within prior 4 weeks before first dose of study drug<br><br>Subjects must not have more than one active malignancy at the time of enrollment (Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included).<br><br>Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).<br><br>**Updated:** |

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| | | Myocardial infarction or ischemia within the 6 months before ~~Cycle 0 Day 0~~ first dose of study drug<br><br>Known untreated or unstable brain metastases or leptomeningeal disease<br><br>Active infection ~~(ie, body temperature > or equal to 38 degree C due to infection)~~ |
| | **4.**<br>**Registration Procedures** | **Updated** :<br>All consented subjects must be entered into~~registered with~~ the University of Florida's Clinical Trial Management System (OnCore)~~UF Health Cancer Center~~ prior to assignment of a subject identification number. ~~participation in this trial.~~ The study team must submit the completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO: PMO@cancer.ufl.edu) or their assigned Project Manager.~~The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center~~ Unsigned eligibility checklists or eligibility packets with missing or incomplete information may be returned to the study team. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial. Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.~~ Unsigned or incomplete forms will be returned to the site. Once documents are received, the designated Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.~~ |
| | **5.1**<br>**Treatment Schedule/Administration** | **Removed:**<br>~~All participants will have histologic or cytologic confirmed metastatic or locally advanced unresectable pancreatic adenocarcinoma with measurable disease that was previously treated with and progressed or were intolerant to first or second line chemotherapy which was prescribed for metastatic pancreatic adenocarcinoma or locally advanced unresectable disease. Intolerance is defined as any sign or symptom from chemotherapy that resulted in~~ |

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| | | ~~stopping the chemotherapy treatment prematurely before progression of disease or the subject's desire to stop treatment without evidence of progression~~<br><br>~~TAS-102 must only be administered on Days 1 through 5 and Days 8 through 12 of each cycle even if doses are missed or held for any reason during Days 1 through 12.~~<br><br>~~Extension of TAS-102 treatment into the recovery period (Days 6 and 7; Days 13 through 28) is not permitted.~~<br><br>~~Any missed doses reported by the subject should be recorded in the subject's source documents. Subjects should not take additional doses to make up for missed or held doses.~~<br><br>**Added:**<br>The patient must be instructed in the handling of study medication as follows:<br>• To store the study medication at room temperature<br>• To only remove from the study medication kit the amount of tablets needed at the time of dosing<br>• Not to remove doses in advance of the next scheduled dosing<br>• To make every effort to take doses on schedule<br>• To take study medication within 1 hour after completing a meal (morning and evening meals) with a glass of water per the dose schedule<br>• If the patient vomits after taking study medication, the patient should not take another dose.<br>• To keep study medication in a safe place and out of reach of children<br>• To bring all used and unused study medication kits to the site at each visit<br><br>Any missed doses reported by the subject should be recorded in the subject's source documents. Subjects should not take additional doses to make up for missed or held doses.<br><br>**Updated:**<br>Treatment must begin within 28 days of the date the subject is entered into the CTMS (OnCore).<br><br>Upon confirmation of eligibility and provision of subject study number, subjects will receive TAS-102 at the following dose and schedule. |

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| | | Complete blood count (CBC) with differential will be checked on the first day of each cycle, every 28 days, or within 72 hours of each cycle upon completion of Cycle 1 to accommodate subjects with long travel distance and on Day 15 of each cycle to monitor for development of anemia and neutropenia. In the absence of significant treatment-related abnormalities, and documentation of an ANC greater than or equal to 1500/ $mm^3$ and platelet count of greater than or equal to 75,000/ $mm^3$ treatment cycles will continue every 28 days until subject intolerance, subject discontinuation, or disease progression. ~~All subjects experiencing toxicities will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy. Use of granulocyte colony stimulating factor and packed red cell transfusions can be considered to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors. A maximum of three dose reductions in decrements of 5 mg per square meter are allowed for toxicity to a minimum dose of 20mg/$m^2$. Do not escalate dose once it has been reduced.~~ Tumor status will be assessed every two cycles. ~~Participants will continue on therapy until the development of unacceptable toxicity, disease progression, or participant desire to discontinue protocol therapy.~~ |
| | **5.2**<br>**Dose Calculations** | **Removed:**<br>~~TAS-102 is to be taken within 1 hour of completion of morning and evening meals.~~<br><br>~~Days 1 through 5: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5.~~<br><br>~~Days 8 through 12: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12~~ |
| | **5.3**<br>**Concomitant Therapy** | **Updated**:<br>Use of anti-neoplastic or anti-tumor ~~agents~~ therapies not part of the study ~~therapy~~treatment, including surgery, chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study. Use of erythropoietin stimulating agents ~~are~~ is also not permitted. ~~Study participants may receive additional investigational antineoplastic therapies upon completion of their participation in this protocol.~~ Use of concurrent investigational agents is not permitted. |

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| | | Any therapy or medication (except study drugs), administered from ~~screening~~ first dose of study drug until 30 days after the last dose of either study drug, is considered a concomitant therapy or medication. |
| | **5.3.1**<br>**Allowed Concomitant Therapy** | **Removed**:<br>~~Use of granulocyte colony stimulating factor and packed red cell transfusions can be considered to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors.~~<br><br>**Added**:<br>Use of granulocyte colony stimulating factor and packed red cell transfusions are permitted to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors<br>Updated:<br>Subjects may continue on their chronic medications. Subjects on anticoagulation need to have no evidence of bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to first dose of study drug ~~trial enrollment~~. |
| | **5.3.2**<br>**Prohibited Concomitant Therapy** | **Added**:<br>Cancer-related surgery<br><br>**Updated**:<br>*NOTE: Radiation therapy to a symptomatic solitary lesion may be considered on an exceptional case by case basis after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of strictly palliative radiation therapy to a single symptomatic lesion will not be considered clinical progression for the purposes of determining PFS.* |
| | **5.4.1**<br>**Dose Modification Explained** | **Added**:<br>Table 2: TAS-102 Dose Modification Table<br><br>**Updated**:<br>Subjects are permitted dose reduction(s) to a minimum dose of 20 mg/m$^2$ (40 mg/m$^2$/day) in 5 mg/m$^2$ (10 mg/m$^2$/day) steps. A maximum of three dose reductions in decrements of 5 mg |

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| | | per square meter are allowed for toxicity to a minimum dose of 20mg/$m^2$. Do not escalate dose once it has been reduced. Refer to Table 2 located in this sub-section. |
| | **5.4.2 Non-Hemotologic Toxicity** | **Updated:** If there is any uncertainty about continuing study medication or resuming study medication in a subject with Grade ≥3 non-hematologic toxicities, the case must be discussed with the UFHCC Data and Safety Integrity Committee (DISC)~~Sponsor's Medical Monitor~~ prior to continuing treatment. |
| | **6.2 Study Treatment Discontinuation** | **Removed:** ~~It is unlikely that the trial itself will require a premature termination. However, the trial will be stopped prematurely (prior to completion of accrual, protocol therapy, and follow-up) for safety reasons, if the therapy at Dose level 0 is intolerable in the first six subjects, requiring dose reduction to the dose level -1. If this occurs, the protocol will be amended to allow for a more tolerable dosing of TAS102. Intolerability will be defined as the occurrence of the following dose-limiting toxicities~~ **Updated**: Study treatment will be withheld under the following circumstances:<br>• Grade 4 neutropenia (ANC less than 500/$mm^3$ or febrile neutropenia) ~~lasting > 7 days~~, until ANC is resolved to greater than 1500/$mm^3$ or febrile neutropenia is resolved<br>• Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding (platelets less than 50,000/$mm^3$), until platelet count resolved to greater than or equal to 75,000/$mm^3$<br>• ~~Grade 3 or 4 nausea or vomiting lasting > 48 hours and is uncontrolled by aggressive antiemetic therapy~~<br>• ~~Grade 3 or 4 diarrhea lasting > 48 hours and is unresponsive to antidiarrheal medication~~<br>• Other grade 3 or 4 non-hematologic toxicity until the adverse reaction has resolved to Grade 0 or 1~~resulting in a > 2 week delay in the initiation of the next cycle~~<br>A subject will be discontinued from protocol therapy under the following circumstances:<br>• ~~Any therapy or medication (except study drugs), administered from screening until 30 days~~ Any adverse event which, in the Investigator's opinion, requires termination of the study medication. |

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| | | • Disease progression, unless at the discretion of the Principal Investigator (in collaboration with any co-sponsors or collaborators) determines continued treatment with study drug is appropriate.<br>• Substantial non-compliance (>25% of missed doses with the exception of dose delays and dose modifications per protocol, or ~~accounting for~~ dose-related instructions from research team staff due to adverse events), with the requirements of the study.<br>• The subject presents with a beta-HCG test consistent with pregnancy and is confirmed to be pregnant.. Pregnancy will be reported along the same timelines as a serious adverse event.<br>• The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with the study or its results.<br>The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status and progression (as applicable) after the End of Treatment Visit. ~~after the Final Visit~~.<br><br>Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study who receive study drug~~,~~ ~~even for a brief period of time~~. Subjects who discontinue following entry study consent will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die ~~during the trial or~~ within 30 days of ~~stopping~~ receiving study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee (DISC). |
| | **7.1**<br>**Study Schedule of Events** | **Removed**:<br>~~Pretreatment and On-treatment measurements:~~<br>~~All screening procedures should be completed within 28 days of treatment except for serum pregnancy testing which should be completed within 7 days of treatment.~~ |

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| | | ~~History & Physical, Vital Signs, ECOG PS, CMP, CBC w Diff and CA19-9 are not required to be repeated at treatment initiation if they were completed within 7 days prior to Cycle 1 Day 1.~~ |
| | **7.3**<br>**On-Study Evaluations** | **Removed**:<br>~~For the Day 15 CBC w/Diff to be collected each cycle, notify the investigator if any of the following are observed in the lab results:~~<br>~~– Absolute neutrophil count less than or equal to 500 µL (consider G-CSF; to be performed at the provider's discretion);~~<br>~~– Platelets less than 50 thousand/mm$^3$ (transfuse if 10 thousand/mm$^3$ or less); or~~<br>~~- Hemoglobin less than 7 g/dL (consider PRBC transfusion; to be performed at the providers' discretion).~~ |
| | **7.5**<br>**Follow Up/Survival** | **Updated:**:<br>Follow-up evaluations may consist of the interim medical history, physical examination, imaging, CBC, or comprehensive metabolic panel. Any X-rays, CT or MRI scans, or other studies (such as PET scans, bone scans, biopsies, etc.) will be done as clinically indicated and up to the discretion of the treating physician.<br><br>After this one-year follow-up period is over, subjects will continued to be followed for survival until death, withdrawal, or lost to follow up. ~~If subjects are entered onto another study protocol, they will no longer be followed.~~ If subjects are lost to follow-up, every effort will be made at least quarterly to attempt to locate that subject and to determine their health status. ~~Evaluations may consist of the interim medical history, physical examination, imaging, CBC, comprehensive metabolic panel Any X-rays, CT or MRI scans, or other studies (such as PET scans, bone scans, biopsies, etc.) will be done as clinically indicated and up to the discretion of the treating physician.~~ For subjects that come off protocol for reasons other than progressive disease, then CT or MRI scans will be performed every 8 weeks to document disease progression. until disease progression is shown or another anti-cancer therapy is initiated. ~~Vital statistics may be assessed and recorded every 3 months after the completion of study treatment~~ |
| | **10.2**<br>**Period of Observation** | **Updated**:<br>Following the subject's written consent to participate in the study, all SAEs must be collected, ~~including those thought to be associated with protocol-specified procedures.~~ |
| | **10.3** | **Removed**:<br>~~10.3 Procedures for Eliciting Adverse Events~~ |

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| | **Documenting and Reporting of Adverse Events by Investigator** | ~~A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:~~<br>~~• "How have you felt since your last clinical visit?"~~<br>~~• "Have you had any new or changed health problems since you were last here?"~~<br><br>~~Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken with the study drug in response to the event.~~ |
| | **10.4.1**<br>**Serious Adverse Events** | **Added:**<br>Institution SAE and Pregnancy Reporting Information<br><br>SAEs and pregnancies must be reported to the UFHCC CRO Project Management Office (PMO), or assigned designee at:<br><br>Email: pmo@cancer.ufl.edu<br><br>As well as entered in OnCore, the study CTMS.<br><br>**Updated**:<br>At the time of the annual DSUR (data-lock point), a list of all AEs which led to discontinuation, subjects with fatal events, and demographic information for all subjects exposed to TAS-102 must all be submitted to Taiho.<br><br>UFHCC PMO and DISC Reporting Requirements<br><br>Serious adverse events (SAE's) must be d~~ocumented on an SAE report form and emailed~~ reported to UFHCC Project Management Office (PMO; pmo@cancer.ufl.edu) and entered into OnCore within 24 hours of discovery of the event. If only limited details are known, these should be reported within that time frame and follow up reports can be submitted for elaboration, clarifications, or corrections. Any email correspondence must be kept in the trial file at the study site. The site investigator is responsible for informing the IRB and/or |

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| | | the Regulatory Authority of the SAE as per local requirements. SAEs must also be reported to the UFHCC DISC Safety Team within **5 days** of discovery of the event. The original copy of the SAE Report and any email correspondence must be kept within the Trial Master File at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.<br><br>Follow-up information will be submitted to the UFHCC PMO (pmo@cancer.ufl.edu), stating that this is a follow-up to a previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. PMO will confirm that the event and any necessary follow-ups are reported to the UFHCC Data and Safety Integrity Committee (DISC), Taiho Oncology, and any other regulatory authorities as required. ~~Follow-up information will be emailed or faxed to the UFHCC using the SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation. The UFHCC Protocol Development Office (PDO) must also be notified of the SAE by email at PDO@cancer.ufl.edu within 24 hours of awareness of the event.~~ |
| | **10.5**<br>**IND Safety Reports Unrelated to the Trial** | **Updated:**<br>IND safety reports not occurring on this trial but involving the study intervention ~~(outside SAEs)~~ received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. |
| | **11.3**<br>**Methods and Timing for Assessment and Recording Safety Variables** | **Removed:**<br>~~Death as a result of disease progression endpoints are only to be assessed as efficacy measures and not as AEs or SAEs unless the events that led to death met the serious criteria.~~<br><br>**Updated**:<br>The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on the CRF and reported to Taiho in accordance with protocol instructions and clinical trial agreement. |

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| | **12.1**<br>**Sample Size Determination** | **Removed:**<br>~~Assuming at least the last evaluable subject derives benefit from the anticipated maximal number of six cycles, the length of the entire study will be approximately 24 months.~~<br><br>**Updated**:<br>This is a pilot phase II single-arm study, with a primary endpoint of progression-free survival (PFS) to evaluate efficacy of TAS-102. And Additional obhective of the study is to evaluate the feasibility and safety of a regimen of daily TAS-102 administered to subjects with metastatic or unresectable pancreatic adenocarcinoma after progression through or intolerance to first- or second-line chemotherapy. The primary efficacy analysis will be an intent-to-treat comparison of the PFS curve with a reference historical control. From past studies3, the median PFS and/or time to progression (TTP) for subjects with metastatic or unresectable pancreatic adenocarcinoma in the second line of treatment is variable ranging from 6 weeks to 22 weeks. Assuming exponential distributions on PFS on both current study population and the referent population, a sample size of 333 evaluable subjects who will receive the same level of dose will ensure to have at least 80% power to detect an improvement of 3 weeks of median PFS (i.e. from 6 weeks to 9 weeks). The sample size and power derivations were based on one-sample log rank test by Wu (2015)[14] at one-sided significance level of 0.10. It is assumed that the survival time distributions of both groups (historical and this proposed experiment groups) are approximately the Weibull distribution with a shape parameter of ~1.0. Accounting for about ~10% ineligible/inevaluable subjects, the total number of subjects to be accrued to this cohort will be 37, which is expected to be completed within 24 months. Assuming at least the last evaluable subject derives benefit from the anticipated maximal number of 6 cycles, the length of the entire treatment study will be approximately 30 months.<br><br>~~The remaining 27 subjects will also be closely monitored for TAS-102 related toxicities continuously. The study will be temporarily closed for detailed review if the number of observed adverse events listed in the definition of intolerability in section 6.2 is greater than or equal to the corresponding boundary (as shown in the following Table 79). The actual power (based on exact binomial test) of declaring the investigational treatment is too toxic are approximately 88.5%, 66.2%, 35.4% and 11.9% when the true toxicity rates are 44%, 36%, 28% and 20%, respectively.~~<br><br>~~Table 7. Pocock boundaries for toxicity monitoring for the remaining 27 subjects~~ |

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| | | ~~# of evaluable subjects~~ ~~2~~ ~~3-4~~ ~~5-7~~ ~~8-10~~ ~~11-13~~ ~~14-17~~ ~~18-20~~ ~~21-24~~ ~~25-27~~<br>~~Pocock boundary~~ ~~2~~ ~~3~~ ~~4~~ ~~5~~ ~~6~~ ~~7~~ ~~8~~ ~~9~~ ~~10~~<br><br>A subject is considered eligible for toxicity evaluation if they have received at least one dose of TAS-102. ~~A subject will be considered eligible for evaluation of activity if they have received two cycles of therapy as planned.~~ |
| | **12.2**<br>**Analysis of Baseline and Demographic Characteristics** | **Updated**:<br>The analysis of demographic characteristics (age, gender, ethnicity) and baseline characteristics, including weight change, performance status, and histologic subtype, will be primarily descriptive due to the small subject numbers. ~~However, they will be compared between the treatment arm and historical controls to determine if there is any imbalance, which might skew the results of the subject outcomes.~~ <u>All data will be summarized using descriptive statistics (mean/variance, median/range, frequency/proportion) along with graphical illustration as needed.</u> ~~Continuous variables will be compared to historical controls using the Wilcoxon rank sum test, and discrete outcomes will be compared using the exact Chi-square test.~~ |
| | **12.3**<br>**Primary and Secondary Endpoint Efficacy Analysis** | **Updated:**<br>The primary endpoint to this study will be to determine progression-free survival following TAS-102 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated.<br>A secondary endpoint of this study will be overall survival/<u>TTP</u> following treatment with TAS-102. Kaplan-Meier estimates and survival curves ~~of overall survival rates~~ will be calculated. <u>Other</u> secondary endpoints include response rates, clinical benefit rate (CR + PR + SD), toxicities, ~~and~~ reversibility of toxicities, <u>and compliance with intended treatment</u>) will also be estimated along with exact 95% binomial confidence intervals.<br><u>No multiplicity will be adjusted for the secondary endpoints. All data analysis will be conducted in reproducible fashion and the results will be reported regardless of the statistical significance.</u> |
| | **13.1**<br>**Data Integrity and Safety Committee** | **Removed~~:~~**<br>~~The PI will summarize and provide DISC with all pertinent data related to the level of risk assigned by SRMC. This protocol summary will include a minimum of the following:~~ |

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| | | • ~~The UF IRB assigned protocol number, UFHCC assigned protocol number, protocol title, PI name, data coordinator name or primary study coordinator, regulatory coordinator name, and statistician.~~<br>• ~~Date of initial UF IRB approval, date of most recent consent UF IRB approval/revision, date of UF IRB expiration, study status, and phase of the study.~~<br>• ~~Study target accrual and study actual accrual.~~<br>• ~~Protocol objectives with supporting data and list of number of study participants who have met each objective.~~<br>• ~~Measures of efficacy.~~<br>• ~~Early stopping rules with supporting data and a list of the number of study participants who have met the early stopping rules.~~<br>• ~~Summary of toxicities and protocol deviations.~~<br>• ~~Summary of any recent literature which may affect the safety or ethics of the trial.~~ |
| | **13.2**<br>**~~On-site~~ Data Monitoring** | **Updated**:<br>UFHCC (University of Florida Health Cancer Center) Quality Assurance team and/or project management officers will perform remote monitoring and may make monitoring ~~UFHCC monitors will make monitoring~~ visits to the trial sites periodically during the trial to determine if sites are complying with the protocol. Source documents will be reviewed for completion and validated against with data submitted electronically via the Electronic Data Capture. . The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies. As part of the responsibilities assumed by conducting the study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol. |
| | **13.3**<br>**Principal Investigator (PI) Responsibilities** | **Removed:**<br>~~As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.~~<br>**Added**:<br>Per IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB. |

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| | | Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements, as outlined in the UFHCC Guidance: Principal Investigator Responsibilities and Oversight. |
| | **15.1**<br>**Good Clinical Practice** | **Updated:**<br>All potential serious breaches must be reported to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu, who will then report the breach to the UFHCC DISC) and the IRB of record ~~UF Health Cancer Center Data Integrity and Safety Committee (DISC) immediately~~. |
| | **15.2**<br>**Institutional Review Board** | **Removed:**<br>~~The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year~~. |
| | **15.6**<br>**Protocol Amendments** | **Added**:<br>Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will sent out to the applicable study teams, prior to implementing the amendment.<br><br>On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and UFHCC CRO PMO (pmo@cancer.ufl.edu) are notified within 5 business days with a full justification and description of the event. |
| | **15.7**<br>**Case Report Forms** | **Removed:**<br>~~An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.~~<br><br>**Added**:<br>The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document protocol-required outcomes for safety |

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| | | monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.<br>All protocol data is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC. |
| | **16**<br>**Compliance with Laws and Regulations** | **Removed:**<br>~~Protocol Development Officer or assigned designee. All studies must be registered no later than 21 days after enrollment of the first participant. The Protocol Development Officer will maintain the responsibility of updating trials registered with ClinicalTrials.gov; per the FDA's updating requirements of information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study.~~<br><br>**Updated**:<br>All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Project Management Officer or assigned designee. All studies must be registered prior to enrollment of the first participant. The Protocol Management Officer or assigned designee will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study. The PMO will determine if registration and updates to the NCI CTRP are required. |

**A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression through First Line Chemotherapy**

UF-STO-PANC-003; UF-GI-006

PI: Jennifer Duff, MD

| Protocol Version Number | Protocol Version Date | Affected Section(s) | Summary of Revisions Made |
|---|---|---|---|
| **2.0** | **19November2019** | **Cover Page** | Updated study staff, added keywords, minor edits |
| | | **Throughout** | Minor edits for spelling, grammar, and clarification |
| | | **Definitions** | PDO changed to PMO |
| | | **Signature pages** | **Removed:**<br>Pre-filled information<br>**Added:**<br>Subsite signature page |
| | | **Synopsis** | **Added:**<br>Funding Source<br>**Updated:**<br>Inclusion/exclusion criteria<br>Study enrollment period and duration |
| | | **1.4 Rationale for Regimen/Doses/Schedule** | **Removed:**<br>~~Subjects who have received radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be assessable. Subjects must be willing to use contraception; are neither pregnant nor lactating; have an anticipated life expectancy of at least 3 months; have normal end-organ function and limited comorbidities~~. |
| | | **2 Objectives and Endpoints** | **Added**:<br>The primary endpoint, PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.<br><br>Definition of treatment compliance (% of completion of the treatment) |
| | | **3.2 Inclusion Criteria** | **Removed:**<br>~~Histologic or cytologic confirmed adenocarcinoma of the pancreas~~.<br><br>~~Documented radiologic progression on or intolerance to first or second line chemotherapy which was prescribed for metastatic pancreatic adenocarcinoma or locally advanced unresectable disease . Intolerance is defined as any sign or symptom from chemotherapy~~ |

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| | | ~~that resulted in stopping the treatment prematurely before progression of disease or the subject's desire to stop chemotherapy treatment without evidence of progression.~~<br><br>~~Subjects of childbearing potential must be using an effective means of contraception including but not limited to barrier methods, birth control, intrauterine devices.~~<br>~~Histologic diagnosis of pancreatic adenocarcinoma that has been treated previously with one or two lines of chemotherapy.~~<br>~~Previous surgery and/or radiotherapy to a non-target lesion may have been performed up to 4 weeks prior to the date the subject signs the informed consent form , but there must be evidence of disease progression radiographically or intolerance to first or second line chemotherapy.~~<br>~~Subjects must have provided written informed consent and be willing to comply with all study-related procedures.~~<br><br>**Added:**<br>Clinical diagnosis of confirmed of adenocarcinoma of the pancreas, with pathologic confirmation of adenocarcinoma.<br>Subjects must have measurable disease per RECIST 1.1 criteria.<br><br>Refractory or intolerant to 1 or 2 prior regimens of standard chemotherapy for metastatic or locally advanced pancreatic cancer.<br>a. Patients who have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy, or<br>b. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.<br><br>**Updated:**<br>Subjects on anticoagulation need to have no evidence of uncontrolled bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to the date the subject ~~signs the informed consent form~~starts study drug.<br><br>Metastatic or locally advanced unresectable disease. Subjects without clear evidence of distant metastatic disease will be presented at multidisciplinary tumor board for discussion of disease resectability. |

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| | | AST and ALT equal to or less than 3 times the upper limit of normal for patients without hepatic involvement, or AST and ALT equal to or less than 5 times the upper limit of normal for patients with hepatic involvement<br><br>Absolute neutrophil count ≥1500/ $mm^3$<br><br>Platelet count ≥75,000/ $mm^3$ |
| | **3.3**<br>**Exclusion Criteria** | **Removed:**<br>~~Decline using effective means of contraception if sexually active~~<br><br>~~No history of an invasive malignancy within the five years prior to initiating therapy on this protocol. Subjects may have prior in situ carcinomas (such as of the breast or cervix), non-melanoma skins cancers, Rai Stage 0 chronic lymphocytic leukemia or monoclonal gammopathy of uncertain significance and still otherwise qualify for enrollment on this protocol~~<br><br>~~Radiotherapy to the target lesion within 2 weeks of the date the subject signs the informed consent form~~<br><br>~~Major surgery within 4 weeks of the date the subject signs the informed consent form (the surgical incision should be fully healed prior to study medication administration).~~<br><br>~~Antineoplastic, biologic or anti-cancer treatment within prior 3 weeks. A 3 week washout period will be required prior to beginning study treatment if subjects have received anti-cancer treatment within this time frame.~~<br><br>~~Lingering NCI-CTCAE toxicity grade 2 or higher from prior cancer treatments (excluding anemia, alopecia, skin pigmentation, and platinum induced neurotoxicity) > 28 days after the date the subject signs the informed consent form~~<br><br>~~Subjects with severe hepatic enzyme impairment manifesting as total bilirubin greater than 1.5mg/dL or greater than 3 times the upper limit of normal of AST or ALT.)~~<br><br>~~Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years of carcinoma-in-situ deemed cured by adequate treatment~~ |

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| | | ~~Women or men of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after the last dose of study drug.~~<br><br>**Added:**<br>Intervention for ascites or pleural effusions within 4 weeks before first dose of study drug<br><br>Previous surgery and/or radiotherapy may have been performed 2 or more weeks prior to the date the subject starts study treatment, provided that it was to a non-target lesion and there is still evidence of target lesion disease progression radiographically or intolerance to first or second line chemotherapy.<br><br>Major surgery within 4 weeks before first dose of study drug (the surgical incision should be fully healed prior to drug administration).<br><br>Any anticancer therapy within 3 weeks before first dose of study drug (with the exception of bevacizumab, which must not have been taken within 4 weeks before first dose of study drug).<br><br>Extended field radiation within 4 weeks before first dose of study drug or limited field radiation within 2 weeks before first dose of study drug.<br><br>Any investigational agent received within prior 4 weeks before first dose of study drug<br><br>Subjects must not have more than one active malignancy at the time of enrollment (Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included).<br><br>Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).<br><br>**Updated:** |

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| | | Myocardial infarction or ischemia within the 6 months before ~~Cycle 0 Day 0~~ first dose of study drug<br><br>Known untreated or unstable brain metastases or leptomeningeal disease<br><br>Active infection ~~(ie, body temperature > or equal to 38 degree C due to infection)~~ |
| | **4.**<br>**Registration Procedures** | **Updated** :<br>All consented subjects must be entered into~~registered with~~ the University of Florida's Clinical Trial Management System (OnCore)~~UF Health Cancer Center~~ prior to assignment of a subject identification number. ~~participation in this trial.~~ The study team must submit the completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO: PMO@cancer.ufl.edu) or their assigned Project Manager.~~The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center~~ Unsigned eligibility checklists or eligibility packets with missing or incomplete information may be returned to the study team. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial. Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.~~ Unsigned or incomplete forms will be returned to the site. Once documents are received, the designated Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.~~ |
| | **5.1**<br>**Treatment Schedule/Administration** | **Removed:**<br>~~All participants will have histologic or cytologic confirmed metastatic or locally advanced unresectable pancreatic adenocarcinoma with measurable disease that was previously treated with and progressed or were intolerant to first or second line chemotherapy which was prescribed for metastatic pancreatic adenocarcinoma or locally advanced unresectable disease. Intolerance is defined as any sign or symptom from chemotherapy that resulted in~~ |

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| | | ~~stopping the chemotherapy treatment prematurely before progression of disease or the subject's desire to stop treatment without evidence of progression~~<br><br>~~TAS-102 must only be administered on Days 1 through 5 and Days 8 through 12 of each cycle even if doses are missed or held for any reason during Days 1 through 12.~~<br><br>~~Extension of TAS-102 treatment into the recovery period (Days 6 and 7; Days 13 through 28) is not permitted.~~<br><br>~~Any missed doses reported by the subject should be recorded in the subject's source documents. Subjects should not take additional doses to make up for missed or held doses.~~<br><br>**Added:**<br>The patient must be instructed in the handling of study medication as follows:<br>• To store the study medication at room temperature<br>• To only remove from the study medication kit the amount of tablets needed at the time of dosing<br>• Not to remove doses in advance of the next scheduled dosing<br>• To make every effort to take doses on schedule<br>• To take study medication within 1 hour after completing a meal (morning and evening meals) with a glass of water per the dose schedule<br>• If the patient vomits after taking study medication, the patient should not take another dose.<br>• To keep study medication in a safe place and out of reach of children<br>• To bring all used and unused study medication kits to the site at each visit<br><br>Any missed doses reported by the subject should be recorded in the subject's source documents. Subjects should not take additional doses to make up for missed or held doses.<br><br>**Updated:**<br>Treatment must begin within 28 days of the date the subject is entered into the CTMS (OnCore).<br><br>Upon confirmation of eligibility and provision of subject study number, subjects will receive TAS-102 at the following dose and schedule. |

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| | | Complete blood count (CBC) with differential will be checked on the first day of each cycle, every 28 days, or within 72 hours of each cycle upon completion of Cycle 1 to accommodate subjects with long travel distance and on Day 15 of each cycle to monitor for development of anemia and neutropenia. In the absence of significant treatment-related abnormalities, and documentation of an ANC greater than or equal to 1500/ $mm^3$ and platelet count of greater than or equal to 75,000/ $mm^3$ treatment cycles will continue every 28 days until subject intolerance, subject discontinuation, or disease progression. ~~All subjects experiencing toxicities will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy. Use of granulocyte colony stimulating factor and packed red cell transfusions can be considered to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors. A maximum of three dose reductions in decrements of 5 mg per square meter are allowed for toxicity to a minimum dose of 20mg/$m^2$. Do not escalate dose once it has been reduced.~~ Tumor status will be assessed every two cycles. ~~Participants will continue on therapy until the development of unacceptable toxicity, disease progression, or participant desire to discontinue protocol therapy.~~ |
| | **5.2**<br>**Dose Calculations** | **Removed:**<br>~~TAS-102 is to be taken within 1 hour of completion of morning and evening meals.~~<br><br>~~Days 1 through 5: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5.~~<br><br>~~Days 8 through 12: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12~~ |
| | **5.3**<br>**Concomitant Therapy** | **Updated**:<br>Use of anti-neoplastic or anti-tumor ~~agents~~ therapies not part of the study ~~therapy~~treatment, including surgery, chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study. Use of erythropoietin stimulating agents ~~are~~ is also not permitted. ~~Study participants may receive additional investigational antineoplastic therapies upon completion of their participation in this protocol.~~ Use of concurrent investigational agents is not permitted. |

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| | | Any therapy or medication (except study drugs), administered from ~~screening~~ first dose of study drug until 30 days after the last dose of either study drug, is considered a concomitant therapy or medication. |
| | **5.3.1**<br>**Allowed Concomitant Therapy** | **Removed**:<br>~~Use of granulocyte colony stimulating factor and packed red cell transfusions can be considered to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors.~~<br><br>**Added**:<br>Use of granulocyte colony stimulating factor and packed red cell transfusions are permitted to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors<br>Updated:<br>Subjects may continue on their chronic medications. Subjects on anticoagulation need to have no evidence of bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to first dose of study drug ~~trial enrollment~~. |
| | **5.3.2**<br>**Prohibited Concomitant Therapy** | **Added**:<br>Cancer-related surgery<br><br>**Updated**:<br>*NOTE: Radiation therapy to a symptomatic solitary lesion may be considered on an exceptional case by case basis after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of strictly palliative radiation therapy to a single symptomatic lesion will not be considered clinical progression for the purposes of determining PFS.* |
| | **5.4.1**<br>**Dose Modification Explained** | **Added**:<br>Table 2: TAS-102 Dose Modification Table<br><br>**Updated**:<br>Subjects are permitted dose reduction(s) to a minimum dose of 20 mg/m$^2$ (40 mg/m$^2$/day) in 5 mg/m$^2$ (10 mg/m$^2$/day) steps. A maximum of three dose reductions in decrements of 5 mg |

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| | | per square meter are allowed for toxicity to a minimum dose of 20mg/$m^2$. Do not escalate dose once it has been reduced. Refer to Table 2 located in this sub-section. |
| | **5.4.2 Non-Hemotologic Toxicity** | **Updated:** If there is any uncertainty about continuing study medication or resuming study medication in a subject with Grade ≥3 non-hematologic toxicities, the case must be discussed with the UFHCC Data and Safety Integrity Committee (DISC)~~Sponsor's Medical Monitor~~ prior to continuing treatment. |
| | **6.2 Study Treatment Discontinuation** | **Removed:** ~~It is unlikely that the trial itself will require a premature termination. However, the trial will be stopped prematurely (prior to completion of accrual, protocol therapy, and follow-up) for safety reasons, if the therapy at Dose level 0 is intolerable in the first six subjects, requiring dose reduction to the dose level -1. If this occurs, the protocol will be amended to allow for a more tolerable dosing of TAS102. Intolerability will be defined as the occurrence of the following dose-limiting toxicities~~ **Updated**: Study treatment will be withheld under the following circumstances:<br>• Grade 4 neutropenia (ANC less than 500/$mm^3$ or febrile neutropenia) ~~lasting > 7 days~~, until ANC is resolved to greater than 1500/$mm^3$ or febrile neutropenia is resolved<br>• Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding (platelets less than 50,000/$mm^3$), until platelet count resolved to greater than or equal to 75,000/$mm^3$<br>• ~~Grade 3 or 4 nausea or vomiting lasting > 48 hours and is uncontrolled by aggressive antiemetic therapy~~<br>• ~~Grade 3 or 4 diarrhea lasting > 48 hours and is unresponsive to antidiarrheal medication~~<br>• Other grade 3 or 4 non-hematologic toxicity until the adverse reaction has resolved to Grade 0 or 1~~resulting in a > 2 week delay in the initiation of the next cycle~~<br>A subject will be discontinued from protocol therapy under the following circumstances:<br>• ~~Any therapy or medication (except study drugs), administered from screening until 30 days~~ Any adverse event which, in the Investigator's opinion, requires termination of the study medication. |

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| | | • Disease progression, unless at the discretion of the Principal Investigator (in collaboration with any co-sponsors or collaborators) determines continued treatment with study drug is appropriate.<br>• Substantial non-compliance (>25% of missed doses with the exception of dose delays and dose modifications per protocol, or ~~accounting for~~ dose-related instructions from research team staff due to adverse events), with the requirements of the study.<br>• The subject presents with a beta-HCG test consistent with pregnancy and is confirmed to be pregnant.. Pregnancy will be reported along the same timelines as a serious adverse event.<br>• The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with the study or its results.<br>The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status and progression (as applicable) after the End of Treatment Visit. ~~after the Final Visit~~.<br><br>Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study who receive study drug~~,~~ ~~even for a brief period of time~~. Subjects who discontinue following entry study consent will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die ~~during the trial or~~ within 30 days of ~~stopping~~ receiving study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee (DISC). |
| | **7.1**<br>**Study Schedule of Events** | **Removed**:<br>~~Pretreatment and On-treatment measurements:~~<br>~~All screening procedures should be completed within 28 days of treatment except for serum pregnancy testing which should be completed within 7 days of treatment.~~ |

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| | | ~~History & Physical, Vital Signs, ECOG PS, CMP, CBC w Diff and CA19-9 are not required to be repeated at treatment initiation if they were completed within 7 days prior to Cycle 1 Day 1.~~ |
| | **7.3**<br>**On-Study Evaluations** | **Removed**:<br>~~For the Day 15 CBC w/Diff to be collected each cycle, notify the investigator if any of the following are observed in the lab results:~~<br>~~– Absolute neutrophil count less than or equal to 500 µL (consider G-CSF; to be performed at the provider's discretion);~~<br>~~– Platelets less than 50 thousand/mm$^3$ (transfuse if 10 thousand/mm$^3$ or less); or~~<br>~~- Hemoglobin less than 7 g/dL (consider PRBC transfusion; to be performed at the providers' discretion).~~ |
| | **7.5**<br>**Follow Up/Survival** | **Updated:**:<br>Follow-up evaluations may consist of the interim medical history, physical examination, imaging, CBC, or comprehensive metabolic panel. Any X-rays, CT or MRI scans, or other studies (such as PET scans, bone scans, biopsies, etc.) will be done as clinically indicated and up to the discretion of the treating physician.<br><br>After this one-year follow-up period is over, subjects will continued to be followed for survival until death, withdrawal, or lost to follow up. ~~If subjects are entered onto another study protocol, they will no longer be followed.~~ If subjects are lost to follow-up, every effort will be made at least quarterly to attempt to locate that subject and to determine their health status. ~~Evaluations may consist of the interim medical history, physical examination, imaging, CBC, comprehensive metabolic panel Any X-rays, CT or MRI scans, or other studies (such as PET scans, bone scans, biopsies, etc.) will be done as clinically indicated and up to the discretion of the treating physician.~~ For subjects that come off protocol for reasons other than progressive disease, then CT or MRI scans will be performed every 8 weeks to document disease progression. until disease progression is shown or another anti-cancer therapy is initiated. ~~Vital statistics may be assessed and recorded every 3 months after the completion of study treatment~~ |
| | **10.2**<br>**Period of Observation** | **Updated**:<br>Following the subject's written consent to participate in the study, all SAEs must be collected, ~~including those thought to be associated with protocol-specified procedures.~~ |
| | **10.3** | **Removed**:<br>~~10.3 Procedures for Eliciting Adverse Events~~ |

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| | **Documenting and Reporting of Adverse Events by Investigator** | ~~A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:~~<br>~~• "How have you felt since your last clinical visit?"~~<br>~~• "Have you had any new or changed health problems since you were last here?"~~<br><br>~~Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken with the study drug in response to the event.~~ |
| | **10.4.1**<br>**Serious Adverse Events** | **Added:**<br>Institution SAE and Pregnancy Reporting Information<br><br>SAEs and pregnancies must be reported to the UFHCC CRO Project Management Office (PMO), or assigned designee at:<br><br>Email: pmo@cancer.ufl.edu<br><br>As well as entered in OnCore, the study CTMS.<br><br>**Updated**:<br>At the time of the annual DSUR (data-lock point), a list of all AEs which led to discontinuation, subjects with fatal events, and demographic information for all subjects exposed to TAS-102 must all be submitted to Taiho.<br><br>UFHCC PMO and DISC Reporting Requirements<br><br>Serious adverse events (SAE's) must be d~~ocumented on an SAE report form and emailed~~ reported to UFHCC Project Management Office (PMO; pmo@cancer.ufl.edu) and entered into OnCore within 24 hours of discovery of the event. If only limited details are known, these should be reported within that time frame and follow up reports can be submitted for elaboration, clarifications, or corrections. Any email correspondence must be kept in the trial file at the study site. The site investigator is responsible for informing the IRB and/or |

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| | | the Regulatory Authority of the SAE as per local requirements. SAEs must also be reported to the UFHCC DISC Safety Team within **5 days** of discovery of the event. The original copy of the SAE Report and any email correspondence must be kept within the Trial Master File at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.<br><br>Follow-up information will be submitted to the UFHCC PMO (pmo@cancer.ufl.edu), stating that this is a follow-up to a previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. PMO will confirm that the event and any necessary follow-ups are reported to the UFHCC Data and Safety Integrity Committee (DISC), Taiho Oncology, and any other regulatory authorities as required. ~~Follow-up information will be emailed or faxed to the UFHCC using the SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation. The UFHCC Protocol Development Office (PDO) must also be notified of the SAE by email at PDO@cancer.ufl.edu within 24 hours of awareness of the event.~~ |
| | **10.5**<br>**IND Safety Reports Unrelated to the Trial** | **Updated:**<br>IND safety reports not occurring on this trial but involving the study intervention ~~(outside SAEs)~~ received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. |
| | **11.3**<br>**Methods and Timing for Assessment and Recording Safety Variables** | **Removed:**<br>~~Death as a result of disease progression endpoints are only to be assessed as efficacy measures and not as AEs or SAEs unless the events that led to death met the serious criteria.~~<br><br>**Updated**:<br>The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on the CRF and reported to Taiho in accordance with protocol instructions and clinical trial agreement. |

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| | **12.1**<br>**Sample Size Determination** | **Removed:**<br>~~Assuming at least the last evaluable subject derives benefit from the anticipated maximal number of six cycles, the length of the entire study will be approximately 24 months.~~<br><br>**Updated**:<br>This is a pilot phase II single-arm study, with a primary endpoint of progression-free survival (PFS) to evaluate efficacy of TAS-102. And Additional obhective of the study is to evaluate the feasibility and safety of a regimen of daily TAS-102 administered to subjects with metastatic or unresectable pancreatic adenocarcinoma after progression through or intolerance to first- or second-line chemotherapy. The primary efficacy analysis will be an intent-to-treat comparison of the PFS curve with a reference historical control. From past studies3, the median PFS and/or time to progression (TTP) for subjects with metastatic or unresectable pancreatic adenocarcinoma in the second line of treatment is variable ranging from 6 weeks to 22 weeks. Assuming exponential distributions on PFS on both current study population and the referent population, a sample size of 333 evaluable subjects who will receive the same level of dose will ensure to have at least 80% power to detect an improvement of 3 weeks of median PFS (i.e. from 6 weeks to 9 weeks). The sample size and power derivations were based on one-sample log rank test by Wu (2015)[14] at one-sided significance level of 0.10. It is assumed that the survival time distributions of both groups (historical and this proposed experiment groups) are approximately the Weibull distribution with a shape parameter of ~1.0. Accounting for about ~10% ineligible/inevaluable subjects, the total number of subjects to be accrued to this cohort will be 37, which is expected to be completed within 24 months. Assuming at least the last evaluable subject derives benefit from the anticipated maximal number of 6 cycles, the length of the entire treatment study will be approximately 30 months.<br><br>~~The remaining 27 subjects will also be closely monitored for TAS-102 related toxicities continuously. The study will be temporarily closed for detailed review if the number of observed adverse events listed in the definition of intolerability in section 6.2 is greater than or equal to the corresponding boundary (as shown in the following Table 79). The actual power (based on exact binomial test) of declaring the investigational treatment is too toxic are approximately 88.5%, 66.2%, 35.4% and 11.9% when the true toxicity rates are 44%, 36%, 28% and 20%, respectively.~~<br><br>~~Table 7. Pocock boundaries for toxicity monitoring for the remaining 27 subjects~~ |

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| | | ~~# of evaluable subjects~~ ~~2~~ ~~3-4~~ ~~5-7~~ ~~8-10~~ ~~11-13~~ ~~14-17~~ ~~18-20~~ ~~21-24~~ ~~25-27~~<br>~~Pocock boundary~~ ~~2~~ ~~3~~ ~~4~~ ~~5~~ ~~6~~ ~~7~~ ~~8~~ ~~9~~ ~~10~~<br><br>A subject is considered eligible for toxicity evaluation if they have received at least one dose of TAS-102. ~~A subject will be considered eligible for evaluation of activity if they have received two cycles of therapy as planned.~~ |
| | **12.2**<br>**Analysis of Baseline and Demographic Characteristics** | **Updated**:<br>The analysis of demographic characteristics (age, gender, ethnicity) and baseline characteristics, including weight change, performance status, and histologic subtype, will be primarily descriptive due to the small subject numbers. ~~However, they will be compared between the treatment arm and historical controls to determine if there is any imbalance, which might skew the results of the subject outcomes.~~ <u>All data will be summarized using descriptive statistics (mean/variance, median/range, frequency/proportion) along with graphical illustration as needed.</u> ~~Continuous variables will be compared to historical controls using the Wilcoxon rank sum test, and discrete outcomes will be compared using the exact Chi-square test.~~ |
| | **12.3**<br>**Primary and Secondary Endpoint Efficacy Analysis** | **Updated:**<br>The primary endpoint to this study will be to determine progression-free survival following TAS-102 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated.<br>A secondary endpoint of this study will be overall survival/<u>TTP</u> following treatment with TAS-102. Kaplan-Meier estimates and survival curves ~~of overall survival rates~~ will be calculated. <u>Other</u> secondary endpoints include response rates, clinical benefit rate (CR + PR + SD), toxicities, ~~and~~ reversibility of toxicities, <u>and compliance with intended treatment</u>) will also be estimated along with exact 95% binomial confidence intervals.<br><u>No multiplicity will be adjusted for the secondary endpoints. All data analysis will be conducted in reproducible fashion and the results will be reported regardless of the statistical significance.</u> |
| | **13.1**<br>**Data Integrity and Safety Committee** | **Removed~~:~~**<br>~~The PI will summarize and provide DISC with all pertinent data related to the level of risk assigned by SRMC. This protocol summary will include a minimum of the following:~~ |

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| | | • ~~The UF IRB assigned protocol number, UFHCC assigned protocol number, protocol title, PI name, data coordinator name or primary study coordinator, regulatory coordinator name, and statistician.~~<br>• ~~Date of initial UF IRB approval, date of most recent consent UF IRB approval/revision, date of UF IRB expiration, study status, and phase of the study.~~<br>• ~~Study target accrual and study actual accrual.~~<br>• ~~Protocol objectives with supporting data and list of number of study participants who have met each objective.~~<br>• ~~Measures of efficacy.~~<br>• ~~Early stopping rules with supporting data and a list of the number of study participants who have met the early stopping rules.~~<br>• ~~Summary of toxicities and protocol deviations.~~<br>• ~~Summary of any recent literature which may affect the safety or ethics of the trial.~~ |
| | **13.2**<br>**~~On-site~~ Data Monitoring** | **Updated**:<br>UFHCC (University of Florida Health Cancer Center) Quality Assurance team and/or project management officers will perform remote monitoring and may make monitoring ~~UFHCC monitors will make monitoring~~ visits to the trial sites periodically during the trial to determine if sites are complying with the protocol. Source documents will be reviewed for completion and validated against with data submitted electronically via the Electronic Data Capture. . The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies. As part of the responsibilities assumed by conducting the study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol. |
| | **13.3**<br>**Principal Investigator (PI) Responsibilities** | **Removed:**<br>~~As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.~~<br>**Added**:<br>Per IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB. |

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| | | Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements, as outlined in the UFHCC Guidance: Principal Investigator Responsibilities and Oversight. |
| | **15.1**<br>**Good Clinical Practice** | **Updated:**<br>All potential serious breaches must be reported to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu, who will then report the breach to the UFHCC DISC) and the IRB of record ~~UF Health Cancer Center Data Integrity and Safety Committee (DISC) immediately~~. |
| | **15.2**<br>**Institutional Review Board** | **Removed:**<br>~~The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year~~. |
| | **15.6**<br>**Protocol Amendments** | **Added**:<br>Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will sent out to the applicable study teams, prior to implementing the amendment.<br><br>On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and UFHCC CRO PMO (pmo@cancer.ufl.edu) are notified within 5 business days with a full justification and description of the event. |
| | **15.7**<br>**Case Report Forms** | **Removed:**<br>~~An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.~~<br><br>**Added**:<br>The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document protocol-required outcomes for safety |

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| | | monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.<br>All protocol data is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC. |
| | **16**<br>**Compliance with Laws and Regulations** | **Removed:**<br>~~Protocol Development Officer or assigned designee. All studies must be registered no later than 21 days after enrollment of the first participant. The Protocol Development Officer will maintain the responsibility of updating trials registered with ClinicalTrials.gov; per the FDA's updating requirements of information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study.~~<br><br>**Updated**:<br>All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Project Management Officer or assigned designee. All studies must be registered prior to enrollment of the first participant. The Protocol Management Officer or assigned designee will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study. The PMO will determine if registration and updates to the NCI CTRP are required. |

# A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression through First Line Chemotherapy

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| **Protocol Number:** | UF-STO-PANC-003; UF-GI-006 |
| **IRB#:** | IRB201601319 |
| **External Identifier:** | IIT-USA-0115 (Taiho) |
| **Coordinating Center:** | University of Florida |
| **Principal Investigator:** | Jennifer M. Duff, MD<br>University of Florida<br>1600 SW Archer Road<br>Gainesville, FL 32608-1135<br>Telephone: 352-548-6000 x4454<br>Fax: 352-548-6463<br>Email: jennifer.duff@medicine.ufl.edu |
| **Statistician:** | Ji-Hyun Lee, DrPH |
| **Protocol Manager:** | pmo@cancer.ufl.edu |
| **Clinical Phase:** | Phase II |
| **IND Status:** | Exempt |
| **Investigational Agent:** | TAS-102 (Lonsurf®) |
| **Date of Original Protocol:** | 23Jan2017 |
| **Date of Current Protocol:** | 19November 2019 |
| **Version of Current Protocol:** | 2.0 |
| **Keywords:** | pancreatic adenocarcinoma, chemotherapy, metastatic pancreatic cancer |

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**ABBREVIATIONS**

| | |
|---|---|
| AE | adverse event |
| ALT | alanine transaminase (also SGPT) |
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate transaminase (also SGOT) |
| AUC | area under curve |
| BCG | Bacillus Calmette-Guérin |
| BID | twice daily |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| CA | cancer antigen |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CL | Clearance |
| CMP | comprehensive metabolic panel |
| CR | complete remission |
| CRF | case report form |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DISC | Data Integrity and Safety Committee |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOB | date of birth |
| DSUR | Drug Safety Update Report |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EGFR | epidermal growth factor receptor |
| FDA | Food and Drug Administration |
| FDG-PET | fluorodeoxyglucose-positron emission tomography |
| FSH | follicle stimulating hormone |
| FU | fluorouracil |
| GCP | Good Clinical Practice |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |

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|---|---|
| IU | International Unit |
| IV | intravenous |
| m | meter(s) |
| mg | milligram(s) |
| mL | milliliter(s) |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NYHA | New York Heart Association |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PMO | Project Management Office |
| PFS | progression free survival |
| PI | principal investigator |
| PO | orally or by mouth |
| PR | partial remission |
| PRBC | packed red blood cells |
| PS | performance status |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| RBC | red blood cells |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase (also AST) |
| SGPT | serum glutamic pyruvate transaminase (also ALT) |
| $T_{max}$ | time to maximum plasma concentration |
| TTP | time to progression |
| UF | University of Florida |
| UFHCC | University of Florida Health Cancer Center |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |

**Protocol Signature Page**

**A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression Through First Line Chemotherapy**

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|---|---|---|
| Principal Investigator: | | |
| | Signature of Investigator | Date |
| | Printed Name of Investigator | |
| | Name of Facility | |
| | Location of Facility (City/State) | |
| | By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies. | |

**Protocol Signature Page**

**A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression Through First Line Chemotherapy**

Site Principal Investigator:

| | |
|---|---|
| Signature of Investigator | Date |
| Printed Name of Investigator | |
| Name of Facility | |
| Location of Facility (City/State) | |

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

## STUDY SCHEMA

### Chemotherapy

TAS-102 (Lonsurf®) 35 mg/m$^2$ PO BID on days 1-5 and 8-12

Cycles repeated every 28 days

**PROTOCOL SYNOPSIS**

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|---|---|
| **Title:** | A Phase II Trial of TAS-102 (Lonsurf®) in Patients with Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma after Progression Through First Line Chemotherapy |
| **Funding Source:** | Taiho Oncology |
| **Objectives:** | To evaluate the efficacy, safety, and feasibility of TAS-102 in previously treated metastatic and locally advanced unresectable pancreatic adenocarcinoma after progression through or intolerance to first or second line chemotherapy |
| **Study Schema: Drugs / Doses / Length of Treatment** | Days 1 through 5: TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5. TAS-102 is to be taken within 1 hour of completion of morning and evening meals.<br><br>Days 6 through 7: Rest<br><br>Days 8 through 12: TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12. TAS-102 is to be taken within 1 hour of completion of morning and evening meals.<br><br>Days 13 through 28: Rest<br><br>Treat subjects on protocol until progression of disease on the study drug or intolerance after pre-specified dose reductions or subject desire to come off treatment |
| **Endpoints:** | **Primary Endpoint:**<br>• The progression free survival (PFS) defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.<br><br>**Secondary Endpoints**:<br>• The objective response rate (ORR) by RECIST 1.1 criteria<br>• The Clinical Benefit Rate (CR + PR + SD)<br>• The time to progression (TTP)<br>• Overall survival (OS)<br>• The safety profile and tolerability in this population<br>• Compliance with intended treatment |

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| **Study Design:** | Open-label, non-randomized, sequentially enrolling single arm phase II trial |
| **Accrual Goal:** | 33 subjects |
| **Inclusion Criteria:** | o Clinical diagnosis of adenocarcinoma of the pancreas, with pathologic confirmation of adenocarcinoma.<br>o Subjects must have measurable disease per RECIST 1.1 criteria.<br>o Metastatic or locally advanced unresectable disease. Subjects without clear evidence of distant metastatic disease will be presented at multidisciplinary tumor board for discussion of disease resectability.<br>o Refractory or intolerant to 1 or 2 prior regimens of standard chemotherapy for metastatic or locally advanced pancreatic cancer.<br>a. Patients who have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy, or<br>b. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study<br>o TAS102 will be planned to start after disease progression on first or second line chemotherapy, provided any prior chemotherapy-related toxicities have resolved to less than or equal to Grade 1 or baseline within 28 days of the date the subject signs the informed consent form. Grade 2 or greater toxicities including alopecia, skin pigmentation, and platinum induced neurotoxicity/neuropathy are acceptable for starting on trial, as these toxicities do not preclude treatment with TAS-102<br>o ECOG Performance Status of 0-2<br>o Capacity to understand and sign the informed consent document<br>o Able to take medications orally<br>o Life expectancy $\geq$ 12 weeks<br>o Age $\geq$18 years<br>Subjects of childbearing potential must be using an<br>o Subjects on anticoagulation need to have no evidence of uncontrolled bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to the date the subject starts study drug.<br>o Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid |

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| | pregnancy throughout the study and for at least 3 months after the last dose of study drug to minimize the risk of pregnancy. Prior to signing the informed consent form, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.<br>o WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:<br>▪ Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or<br>▪ For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.<br>o Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 3 months following the last dose of study drug.<br>o Baseline laboratory values (bone marrow, renal, hepatic) must include:<br>▪ Adequate bone marrow function:<br>-Absolute neutrophil count ≥1500/$mm^3$<br>-Platelet count ≥75,000/ $mm^3$<br>-HGB equal to or greater than 7g/dL<br>▪ Renal function:<br>-Serum creatinine ≤ 1.5 mg<br>▪ Hepatic function:<br>-Total bilirubin ≤ 1.5 mg/dL<br>-AST and ALT equal to or less than 3 times the upper limit of normal for patients without hepatic involvement, or AST and ALT equal to or less than 5 times the upper limit of normal for patients with hepatic involvement<br>-Serum calcium ≤ 12 mg/dl |
| **Exclusion Criteria:** | • Pregnant or lactating females<br>• Previously taken TAS-102<br>• Myocardial infarction or ischemia within the 6 months before first dose of study drug<br>• Uncontrolled, clinically significant dysrhythmia |

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| | • Intervention for ascites or pleural effusions within 4 weeks before first dose of study drug<br>• Previous surgery and/or radiotherapy may have been performed 2 or more weeks prior to the date the subject starts study treatment, provided that it was to a non-target lesion and there is still evidence of target lesion disease progression radiographically or intolerance to first- or second-line chemotherapy.<br>• Major surgery within 4 weeks before first dose of study drug (the surgical incision should be fully healed prior to drug administration).<br>• Any anticancer therapy within 3 weeks before first dose of study drug (with the exception of bevacizumab, which must not have been taken within 4 weeks before first dose of study drug).<br>• Extended field radiation within 4 weeks before first dose of study drug or limited field radiation within 2 weeks before first dose of study drug.<br>• Any investigational agent received within prior 4 weeks before first dose of study drug<br>• Subjects must not have more than one active malignancy at the time of enrollment (Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included).<br>• Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).<br>• Any co-morbid condition that, in the view of the attending physician, renders the subject at high risk from treatment complications including but not limited to chronic infections, uncontrolled diabetes, congestive heart failure according to the NYHA criteria, untreated brain metastases, liver or renal failure, gastrointestinal hemorrhage.<br>• Known untreated and unstable brain metastases or leptomeningeal disease<br>• Active infection<br>• Prisoners or subjects who are involuntarily incarcerated or subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. |

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| **Efficacy Assessments:** | Mid cycle monitoring:<br>CT or MRI of thorax, abdomen, and pelvis (may be obtained up to one calendar week prior to first day of each odd numbered cycle) |
| **Statistical Considerations:** | The analysis of demographic characteristics (age, gender, tobacco abuse history and ethnicity) and baseline characteristics, including weight change, performance status, and histologic subtype, will primarily be descriptive.<br><br>Kaplan-Meier estimates and survival curves for PFS, TTP and overall survival will be calculated. Secondary endpoints include response rates, clinical benefit rate (CR + PR + SD), toxicities and reversibility of toxicities) will also be estimated along with exact 95% binomial confidence intervals |
| **Estimated Enrollment Period:** | 30 months |
| **Estimated Last Subject Enrollment Date:** | June 15, 2020 |

# 1. INTRODUCTION

## 1.1 Background

Metastatic pancreatic adenocarcinoma carries a dismal prognosis with median survival rates of 3-6 months in those untreated. Over the past decade, despite oncologic advancements, there has been little influence on the long-term survival of these patients. Single agent gemcitabine was primarily used to improve disease related symptoms associated with advanced pancreatic adenocarcinoma, but it had minimal impact on survival. Over the last five years, more aggressive combination chemotherapy regimens such as gemcitabine and nab-paclitaxel and FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) have emerged proving more efficacious compared to gemcitabine alone and yielding a survival advantage. The MPACT study compared gemcitabine and nab-paclitaxel to gemcitabine alone in patients with untreated metastatic pancreatic adenocarcinoma and demonstrated a significant increase in survival with the combination regimen (8.5 months in the gemcitabine plus nab-paclitaxel arm versus 6.7 months in the gemcitabine arm; HR 0.72 (95% CI: 0.62, 0.84); $p < 0.0001$)[1]. The PRODIGE study assessed first line treatment with FOLFIRINOX versus gemcitabine demonstrating improved survival with multi-agent chemotherapy. The median overall survival was 11.1 months compared to 6.8 months in the gemcitabine arm (HR for death, 0.57; $p<0.001$)[2]. In November 2015, the FDA approved nanoliposomal irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin as second line therapy for metastatic pancreatic adenocarcinoma in patients that had progressed following a gemcitabine based regimen. The addition of nanoliposomal irinotecan to 5-FU and leucovorin demonstrated a 2 month survival benefit compared to those treated with 5-FU and leucovorin alone[3]. Prior to this study, there was little objective evidence supporting second-line therapy offering patients a survival advantage. A few trials (mainly phase II) that studied treatment in the second line setting suggested limited benefit in select patients[4-6]. Indeed, consensus national guidelines now consistently support the role of second line therapy for otherwise fit patients (NCCN Guidelines as reference) and for patients whose performance status remains optimal, third line treatment can be considered. Despite the clinical use of these therapies, the median survival for patients with metastatic pancreatic adenocarcinoma continues to be less than 1 year substantiating the need for more effective treatments.

TAS-102 (Lonsurf®) is a combination drug of an oral nucleoside, trifluridine, and thymidine phosphorylase inhibitor, tipiracil hydrochloride. The nucleoside incorporates into DNA eliciting an anti-tumor effect and the thymidine phosphorylase inhibitor prevents enzymatic breakdown of the drug resulting in increased trifluridine bioavailability. It was FDA approved for use in patients with refractory metastatic colorectal cancer after progression on two or more standard chemotherapy regimens[8]. TAS-102 demonstrated a survival benefit despite all patients having being treated previously with 5-FU, which supports an alternative mechanism of action overcoming chemoresistance. TAS-102's efficacy is currently being investigated in other gastrointestinal cancers, specifically, metastatic gastric cancer refractory to standard therapies. Given the cross reactivity of many chemotherapy agents along the GI cancer spectrum (i.e., antimetabolites, platinums, topoisomerase inhibitors), the mechanism of action and chemical backbone of TAS-102 make it an attractive option to explore this agent in advanced pancreatic adenocarcinoma.

This protocol intends to study the activity and tolerability of TAS-102 in the treatment of metastatic or locally advanced unresectable pancreatic adenocarcinoma after progression on or intolerance to first or second line chemotherapy.

1.2 TAS-102 (Lonsurf®) Cancer Therapy

*Each treatment cycle will be 28 days in duration. One treatment cycle consists of the following:*

Days 1 through 5: TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5. TAS-102 is to be taken within 1 hour of the morning and evening meal.

Days 6 through 7: Rest

Days 8 through 12: TAS-102 (35 mg/m$^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12. TAS-102 is to be taken within 1 hour of the morning and evening meal.

Days 13 through 28: Rest
Subjects should take study medication (TAS-102) with a glass of water within 1 hour after completion of their morning and evening meals.

1.3 Clinical Experience

TAS-102 is FDA approved for the treatment of metastatic colon cancer after progression on multiple lines of therapy including EGFR inhibitors in KRAS/NRAS wild-type patients. It has not yet been studied in pancreatic adenocarcinoma.

1.4 Rationale for Regimen/Doses/Schedule

The study will use the same dose of TAS-102 that is FDA approved for the use in metastatic colon cancer. It has previously been shown to be efficacious in patients that have been treated with 5-fluorouracil.

## 2. OBJECTIVES AND ENDPOINTS

2.1 Primary

- To determine progression free survival (PFS). The primary endpoint, PFS, is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.

2.2 Secondary objectives and endpoints

- To determine the objective response rate (ORR) by RECIST 1.1 criteria

- To determine the Clinical Benefit Rate (CR + PR + SD)
- To determine the time to progression (TTP)
- To determine overall survival (OS)
- To determine the safety profile and tolerability in this population
- To determine compliance with intended treatment (% of completion of the treatment)

## 3. SELECTION OF SUBJECTS

### 3.1 Number of Subjects

A total of 33 patients with metastatic or locally advanced unresectable pancreatic adenocarcinoma after progression through first line chemotherapy.

### 3.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

- Clinical diagnosis of confirmed of adenocarcinoma of the pancreas, with pathologic confirmation of adenocarcinoma.
- Subjects must have measurable disease per RECIST 1.1 criteria.
- Metastatic or locally advanced unresectable disease. Subjects without clear evidence of distant metastatic disease will be presented at multidisciplinary tumor board for discussion of disease resectability.
- Refractory or intolerant to 1 or 2 prior regimens of standard chemotherapy for metastatic or locally advanced pancreatic cancer.
  a. Patients who have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy, or
- b. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.TAS102 will be planned to start after disease progression on first- or second-line chemotherapy, provided any prior chemotherapy-related toxicities have resolved to less than or equal to Grade 1 or baseline within 28 days of the date the subject signs the informed consent form. Grade 2 or greater toxicities including alopecia, skin pigmentation, and platinum induced neurotoxicity/neuropathy are acceptable for starting on trial, as these toxicities do not preclude treatment with TAS-102
- ECOG Performance Status of 0-2
- Capacity to understand and sign the informed consent document
- Able to take medications orally
- Life expectancy $\geq$ 12 weeks as predicted by the treating oncologist's clinician judgement
- Age $\geq$18 years
- Subjects on anticoagulation need to have no evidence of uncontrolled bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to the date the subject starts study drug.
- Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 6 months after the last dose of study drug to minimize the risk of pregnancy. Prior to signing the informed consent

form, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

- WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:
    - Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
    - For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.
- Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 3 months following the last dose of study drug.
- Baseline laboratory values (bone marrow, renal, hepatic) must include:
    - Adequate bone marrow function:
        - Absolute neutrophil count ≥1500/ $mm^3$
        - Platelet count ≥75,000/ $mm^3$
        - HGB equal to or greater than 7g/dL
    - Renal function:
        - Serum creatinine ≤ 1.5 mg
    - Hepatic function:
        - Total bilirubin ≤ 1.5 mg/dL
        - AST and ALT equal to or less than 3 times the upper limit of normal for patients without hepatic involvement, or AST and ALT equal to or less than 5 times the upper limit of normal for patients with hepatic involvement
        - Serum calcium ≤ 12 mg/dl

3.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

- Pregnant or lactating females
- Previously taken TAS-102
- Myocardial infarction or ischemia within the 6 months before first dose of study drug
- Uncontrolled, clinically significant dysrhythmia
- Intervention for ascites or pleural effusions within 4 weeks before first dose of study drug
- Previous surgery and/or radiotherapy may have been performed 2 or more weeks prior to the date the subject starts study treatment, provided that it was to a non-target lesion and there is still evidence of target lesion disease progression radiographically or intolerance to first- or second-line chemotherapy.
- Major surgery within 4 weeks before first dose of study drug (the surgical incision should be fully healed prior to drug administration).
- Any anticancer therapy within 3 weeks before first dose of study drug (with the exception of bevacizumab, which must not have been taken within 4 weeks before first dose of study drug).

- Extended field radiation within 4 weeks before first dose of study drug or limited field radiation within 2 weeks before first dose of study drug.
- Any investigational agent received within prior 4 weeks before first dose of study drug Subjects must not have more than one active malignancy at the time of enrollment (Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included).
- Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
- Any co-morbid condition that, in the view of the attending physician, renders the subject at high risk from treatment complications including but not limited to chronic infections, uncontrolled diabetes, congestive heart failure according to the NYHA criteria, untreated brain metastases, liver or renal failure, gastrointestinal hemorrhage.
- History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.
- Known untreated or unstable brain metastases or leptomeningeal disease
- Active infection
- Prisoners or subjects who are involuntarily incarcerated orsubjects who are compulsorily detained for treatment of either a psychiatric or physical illness.
- Subjects demonstrating an inability to comply with the study and/or follow-up procedures.

### 3.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups will be eligible for this trial. Men and women will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will be actively recruited to participate. Only adults (age $\geq$18 years of age) capable of providing their own consent will be eligible.

## 4. REGISTRATION PROCEDURES

All consented subjects must be entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number. The study team must submit the completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO: PMO@cancer.ufl.edu) or their assigned Project Manager. Unsigned eligibility checklists or eligibility packets with missing or incomplete information may be returned to the study team. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial. Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.

## 5. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

### 5.1 Treatment Schedule/Administration:

Treatment must begin within 28 days of the date the subject is entered into the CTMS (OnCore). Upon confirmation of eligibility and provision of subject study number, subjects will receive TAS-102 at the following dose and schedule. The number of tablets of each strength that are needed for the 35 mg/m$^2$ dose per BSA level is shown in Table 1.

**Table 1. Dose Calculations Based off BSA**

| **TAS-102 Dose (2x daily)** | **BSA[a] ($m^2$)** | **Dosage in mg (2x daily)** | **Total daily dose (mg)** | **Tablets per dose** | |
|---|---|---|---|---|---|
| | | | | 15 mg | 20 mg |
| **35 mg/m$^2$** | < 1.07 | 35 | 70 | 1 | 1 |
| | 1.07 - 1.22 | 40 | 80 | 0 | 2 |
| | 1.23 - 1.37 | 45 | 90 | 3 | 0 |
| | 1.38 - 1.52 | 50 | 100 | 2 | 1 |
| | 1.53 - 1.68 | 55 | 110 | 1 | 2 |
| | 1.69 - 1.83 | 60 | 120 | 0 | 3 |
| | 1.84 - 1.98 | 65 | 130 | 3 | 1 |
| | 1.99 - 2.14 | 70 | 140 | 2 | 2 |
| | 2.15 - 2.29 | 75 | 150 | 1 | 3 |
| | ≥2.30 | 80 | 160 | 0 | 4 |
| | | | | | |

a Calculate body surface area (BSA) to 2 decimal places.

*Each treatment cycle will be 28 days in duration. One treatment cycle consists of the following:*

Days 1 through 5: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5.

Days 6 through 7: Rest

Days 8 through 12: TAS-102 (35 mg/$m^2$/dose) orally 2 times daily with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12.

Days 13 through 28: Rest

The patient must be instructed in the handling of study medication as follows:

- To store the study medication at room temperature
- To only remove from the study medication kit the amount of tablets needed at the time of dosing
- Not to remove doses in advance of the next scheduled dosing
- To make every effort to take doses on schedule
- To take study medication within 1 hour after completing a meal (morning and evening meals) with a glass of water per the dose schedule
- If the patient vomits after taking study medication, the patient should not take another dose.
- To keep study medication in a safe place and out of reach of children

To bring all used and unused study medication kits to the site at each visit
Any missed doses reported by the subject should be recorded in the subject's source documents.
Subjects should not take additional doses to make up for missed or held doses.

Complete blood count (CBC) with differential will be checked on the first day of each cycle, every 28 days, or within 72 hours of each cycle upon completion of Cycle 1 to accommodate subjects with long travel distance and on Day 15 of each cycle to monitor for development of anemia and neutropenia. In the absence of significant treatment-related abnormalities, and documentation of an ANC greater than or equal to 1500/ $mm^3$ and platelet count of greater than or equal to 75,000/ $mm^3$ treatment cycles will continue every 28 days until subject intolerance, subject discontinuation, or disease progression. Tumor status will be assessed every two cycles.

5.2 Dose Calculations

Refer to 'Table 1. Dose Calculation Table Based off BSA" in Section 5.1.

5.3 Concomitant Therapy

Use of anti-neoplastic or anti-tumor therapies not part of the study treatment, including surgery, chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study. Use of erythropoietin stimulating agents is also not permitted. Use of concurrent investigational agents is not permitted.

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within 3 weeks prior to screening, regardless of indication, should be recorded

Any therapy or medication (except study drugs), administered from first dose of study drug until 30 days after the last dose of either study drug, is considered a concomitant therapy or medication. However, if another course of anticancer therapy is initiated prior to the 30-day follow-up period visit, a record of concomitant medications will no longer be performed. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, expected duration, and frequency of treatment. Assessment and documentation of concomitant medications will be done at each visit.

### 5.3.1 Allowed Concomitant Therapy

Subjects may continue on their chronic medications. Subjects on anticoagulation need to have no evidence of bleeding and be on a stable anticoagulation dose for at least 2 weeks prior to first dose of study drug.

Use of granulocyte colony stimulating factor and packed red cell transfusions are permitted to maintain adequate bone marrow function according to institutional standards. If no standards are in place for the use of growth factors, then follow the 2015 ASCO Clinical Practice Guidelines for use of WBC growth factors

### 5.3.2 Prohibited Concomitant Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Hormonal anticancer therapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than the study drug in this trial
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed

- Erythropoietin stimulating agents
- Radiation therapy
- Cancer-related surgery

*NOTE: Radiation therapy to a symptomatic solitary lesion may be considered on an exceptional case by case basis after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of strictly palliative radiation therapy to a single symptomatic lesion will not be considered clinical progression for the purposes of determining PFS.*

## 5.4 Dose Modifications

Doses will be reduced or modified if AEs are observed according to the criteria described below.

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 4.0.3 (CTCAE) will be used to grade adverse event toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

### 5.4.1 Dose Modification Explained

Subjects are permitted dose reduction(s) to a minimum dose of 20 mg/m$^2$ (40 mg/m$^2$/day) in 5 mg/m$^2$ (10 mg/m$^2$/day) steps. A maximum of three dose reductions in decrements of 5 mg per square meter are allowed for toxicity to a minimum dose of 20mg/m$^2$. Do not escalate dose once it has been reduced. Refer to Table 2 located in this sub-section.

**Table 2: TAS-102 Dose Modification Table**

| TAS-102 Dose (2x daily) | BSA ($m^2$) | Dosage in mg (2x daily) | Total daily dose (mg) | Tablets per dose | | Cards per Cycle | |
|---|---|---|---|---|---|---|---|
| | | | | 15 mg | 20 mg | 15 mg | 20 mg |
| **Level 1 Dose Reduction: From 35 mg/$m^2$ to 30 mg/$m^2$** | | | | | | | |
| **30 mg/$m^2$** | < 1.09 | 30 | 60 | 2 | 0 | 2 | 0 |
| | 1.09 - 1.24 | 35 | 70 | 1 | 1 | 1 | 1 |
| | 1.25 - 1.39 | 40 | 80 | 0 | 2 | 0 | 2 |
| | 1.40 - 1.54 | 45 | 90 | 3 | 0 | 3 | 0 |
| | 1.55 - 1.69 | 50 | 100 | 2 | 1 | 2 | 1 |
| | 1.70 - 1.94 | 55 | 110 | 1 | 2 | 1 | 2 |
| | 1.95 - 2.09 | 60 | 120 | 0 | 3 | 0 | 3 |
| | 2.10 - 2.28 | 65 | 130 | 3 | 1 | 3 | 1 |
| | ≥ 2.29 | 70 | 140 | 2 | 2 | 2 | 2 |
| **Level 2 Dose Reduction: From 30 mg/$m^2$ to 25 mg/$m^2$** | | | | | | | |
| **25 mg/$m^2$** | < 1.10 | 25[a] | 50[a] | 2 (PM)[a] | 1 (AM)[a] | 2 | 1 |
| | 1.10 - 1.29 | 30 | 60 | 2 | 0 | 2 | 0 |
| | 1.30 - 1.49 | 35 | 70 | 1 | 1 | 1 | 1 |
| | 1.50 - 1.69 | 40 | 80 | 0 | 2 | 0 | 2 |
| | 1.70 - 1.89 | 45 | 90 | 3 | 0 | 3 | 0 |
| | 1.90 - 2.09 | 50 | 100 | 2 | 1 | 2 | 1 |
| | 2.10 - 2.29 | 55 | 110 | 1 | 2 | 1 | 2 |
| | ≥ 2.30 | 60 | 120 | 0 | 3 | 0 | 3 |
| **Level 3 Dose Reduction: From 25 mg/$m^2$ to 20 mg/$m^2$** | | | | | | | |
| **20 mg/$m^2$** | < 1.14 | 20 | 40 | 0 | 1 | 0 | 1 |
| | 1.14 – 1.34 | 25[a] | 50[a] | 2 (PM)[a] | 1 (AM)[a] | 2 | 1 |
| | 1.35 – 1.59 | 30 | 60 | 2 | 0 | 2 | 0 |
| | 1.60 – 1.94 | 35 | 70 | 1 | 1 | 1 | 1 |
| | 1.95 – 2.09 | 40 | 80 | 0 | 2 | 0 | 2 |
| | 2.10 – 2.34 | 45 | 90 | 3 | 0 | 3 | 0 |
| | ≥ 2.35 | 50 | 100 | 2 | 1 | 2 | 1 |

[a] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.
BSA=body surface area (calculate to 2 decimal places)

### 5.4.2 Non- Hematologic Toxicity

Refer to Table 3 located in this sub-section.

These toxicities can be AEs or laboratory abnormalities such as hepatobiliary or renal laboratory findings.

**Table 3: TAS-102 Dose Modification Schedule for Non-hematologic Toxicities**

| **Grade[a]** | **Dose Hold/Resumption within a 28-day Treatment Cycle** | **Dose Adjustment for Next Cycle** |
|---|---|---|
| **Grade 1 or 2** | | |
| **Any occurrence** | Maintain treatment at the same dose level | None |
| **Clinically concerning or treatment-related Grade 3[b] or higher** | | |
| 1st, 2nd, or 3rd occurrence | Suspend treatment until Grade 0 or 1 | Reduce by 1 dose level from the previous level |
| 4th occurrence | Discontinue treatment | Discontinue treatment |

a Note: For toxicities (AEs or laboratory abnormalities) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin), subjects may continue on study medication at the same dose without reduction or interruption at the discretion of the Investigator (irrespective of grade).
b Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication. If there is any uncertainty about continuing study medication or resuming study medication in a subject with Grade ≥3 non-hematologic toxicities, the case must be discussed with the UFHCC Data and Safety Integrity Committee (DISC) prior to continuing treatment.

5.4.3 Hematologic Toxicity

Obtain complete blood cell counts prior to and on Day 15 of each cycle.

Do not initiate the cycle of LONSURF® until:

- Absolute neutrophil count (ANC) is greater than or equal to 1,500/mm$^3$ or febrile neutropenia is resolved
- Platelets are greater than or equal to 75,000/mm$^3$
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold LONSURF® for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm$^3$ or febrile neutropenia
- Platelets less than 50,000/mm$^3$
- Grade 3 or 4 non-hematological adverse reactions

After recovery, resume LONSURF® after reducing the dose by 5 mg/m$^2$/dose from the previous dose level, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm$^3$) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm$^3$) that results in more than 1-week delay in start of next cycle

- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

# 6 TREATMENT DISCONTINUATION

## 6.1 Removal of Subjects From Study

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals.

Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.

## 6.2 Study Treatment Discontinuation

Study treatment will be withheld under the following circumstances::

- Grade 4 neutropenia (ANC less than 500/$mm^3$ or febrile neutropenia), until ANC is resolved to greater than 1500/$mm^3$ or febrile neutropenia is resolved
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding (platelets less than 50,000/$mm^3$), until platelet count resolved to greater than or equal to 75,000/$mm^3$
- Other grade 3 or 4 non-hematologic toxicity, until the adverse reaction has resolved to Grade 0 or 1

A subject will be discontinued from protocol therapy under the following circumstances:

- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the Principal Investigator (in collaboration with any co-sponsors or collaborators) determines continued treatment with study drug is appropriate.
- Substantial non-compliance (>25% of missed doses with the exception of dose delays and dose modifications per protocol, or dose-related instructions from research team staff due to adverse events), with the requirements of the study.
- The subject presents with a beta-HCG test consistent with pregnancy and is confirmed to be pregnant. Pregnancy will be reported along the same timelines as a serious adverse event.
- The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with the study or its results.

- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to follow-up.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status and progression (as applicable) after the End of Treatment Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study who receive study drug. Subjects who discontinue following study consent will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die within 30 days of receiving study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee (DISC).

### 6.3 Replacement of Subjects

Subjects lost to follow up along with other clinical variables without values are considered as missing data. We are not planning to do missing data imputation. These subjects will not be replaced on the trial unless they were lost to follow-up prior to receiving a single dose of the study drug.

## 7 STUDY PROCEDURES

### 7.1 Study Schedule of Events

See Table 4 located in this section.

**Table 4: Study Schedule and Procedures**

| Evaluation | Screening[a] | Treatment Phase[l] (1 cycle = 28 days) | | | End of treatment (within 30 days post last dose) | Follow Up |
|---|---|---|---|---|---|---|
| | | Before each cycle (within 3 days) | D15 of each cycle (± 3 days) | Odd # cycles (± 7 days) | | |
| History & Physical | X | X | | | X | X[i] |
| Performance Status | X | X | | | X | |
| Vital Signs[b] | X | X | | | X | |
| AE Assessment | X | X | | | X | X[j] |
| Concomitant Meds | X | X | | | X | X[k] |
| ECG[c] | X | | | | | |
| Pregnancy test[d] | X | | | | | |
| Urine analysis | X | | | | | |
| CMP[e,f] | X | X | | | X | |
| Magnesium | X | X | | | X | |
| CBC w/Diff[e] | X | X | X[m] | | X | |
| PT/INR[g] | X | | | | | |
| CA19-9 | X | X | | | | |
| CT or MRI[h] | X | | | X | | X |
| Survival Status | | | | | | X |

a. All screening procedures should be completed within 28 days of treatment except for serum pregnancy testing which should be completed within 7 days of treatment. History & Physical, Vital Signs, ECOG PS, CMP, CBC w Diff and CA19-9 are not required to be repeated at treatment initiation if they were completed within 7 days prior to Cycle 1 Day 1.
b. Vital signs include height, weight, blood pressure, pulse, temperature and pain level (subjective 1-10 self-reported scale). Height should be obtained at screening only.
c. ECGs will be obtained at screening. Subjects who are placed on QT prolonging medications while on study should have ECGs performed at regular intervals (interval timing is at the discretion of the treating investigator).
d. Pregnancy testing will be done for all females of childbearing age at Screening prior to TAS-102 initiation. Standard-of-care pregnancy testing will be conducted any time clinical signs present for potential pregnant state, e.g., amenorrhea, other physical signs, or symptoms of pregnancy.
e. Laboratory testing may be performed up to 72 hours prior to day 1 of the next cycle of therapy.
f. CMP: Na, K, Cl, $CO_2$, Glucose, BUN, Creatinine, Ca, Albumin, Total Bilirubin, Alk Phos, Total Protein, AST, ALT.
g. PT/INR should be followed closely for subjects on warfarin.
h. CT of the chest, abdomen and pelvis or CT of the chest and MRI of the abdomen and pelvis are allowed. Consistent imaging modality should be used throughout the study. Imaging should be performed every 8 weeks (+/- 7 days) beginning with Cycle 3 until disease progression.
i. H&P is required at 30 days (+ 7 days) following the last dose of study drug. Additional H&Ps are required as needed to follow ongoing AEs.
j. Adverse events should be followed for 30 days after the last dose of protocol therapy or until the initiation of subsequent treatment. AEs continuing > 30 days should be monitored until resolution.
k. Subjects or providers should be contacted every 3 months to assess survival status and subsequent therapies.
l. TAS-102 (Lonsurf®) is administered orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.
m. For CBC w/diff to be obtained at Day 15 of each cycle, notify the investigator if any of the following parameters are observed in the lab results: 1) ANC ≤ 500 µL, 2) platelets < 50 thou/$mm^3$, or 3) Hgb < 7 g/dL.

7.2 Screening Evaluations

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated.

All screening procedures should be completed within 28 days of treatment except for serum pregnancy testing which should be completed within 7 days of treatment. History & Physical, Vital Signs, ECOG PS, CMP, CBC w Diff and CA19-9 are not required to be repeated at treatment initiation if they were completed within 7 days prior to Cycle 1 Day 1.

7.3 On-Study Evaluations

Please refer to Table 3 located in section 7.1.

7.4 End of Treatment/Off Therapy Measurements (within 30 days post-last dose)

Subjects will be treated until progression of disease, study drug intolerance that is not resolved or amendable to dose reduction, or subject desires to go off study.

Interim history and physical examination, including vital signs and performance status
Review of concomitant medications
Laboratory studies:

- CBC with differential count
- Comprehensive metabolic panel
- Magnesium
- CA 19-9

7.5 Follow up/Survival

Please refer to Table 4 located in Section 7.1.

For the purpose of this study, subjects will be seen in follow-up at least every three months until one year after the completion of study treatment. Follow-up evaluations may consist of the interim medical history, physical examination, imaging, CBC, or comprehensive metabolic panel. Any X-rays, CT or MRI scans, or other studies (such as PET scans, bone scans, biopsies, etc.) will be done as clinically indicated and up to the discretion of the treating physician.

After this one-year follow-up period is over, subjects will be continued to be followed for survival until death, withdrawal, or lost to follow up. If subjects are lost to follow-up, every effort will be made at least quarterly to attempt to locate that subject and to determine their health status.

For subjects that come off protocol for reasons other than progressive disease, then CT or MRI scans will be performed every 8 weeks to document disease progression. until disease progression is shown or another anti-cancer therapy is initiated.

# 8 CRITERIA FOR DISEASE EVALUATION

Tumor response will be assessed using RECIST 1.1[i] criteria.

## 8.1 Tumor Measurement Using RECIST 1.1 Criteria

Measurable disease: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions: lesions that can be accurately measured in at least one dimension (the longest diameter), and with a minimum size of 10 mm by CT scan, or 10 mm by caliper measurement during clinical exam, or 20 mm by chest X-ray.

- A malignant lymph node may be considered pathologically enlarged and measurable if it is ≥ 15 mm in short axis by CT scan.
- A lytic or mixed blastic-lytic bone lesion, with identifiable soft tissue component which is evaluable by CT or MRI, may be considered as measurable lesion if the soft tissue component meets the criteria for measurable lesions.
- Cystic metastases may be considered as measurable lesions if they meet the criteria for measurable lesions, however, non-cystic lesions, if present, are preferred as target lesions.
- Tumor lesions in an area previously subjected to loco-regional treatment, may be considered measurable if there has been demonstrated progression.

Non-measurable lesions: all other lesions, including simple cysts, small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and other truly non-measurable lesions. These include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not measurable by reproducible imaging techniques; blastic bone lesions.

All measurements should be recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes), and ≥ 10 mm diameter using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended. Whenever possible, imaging evaluation should be preferred over clinical exam.

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint. The measurability of lesion by CT scan is based on the assumption that CT slice thickness is ≤ 5 mm.

8.2 Baseline Documentation of Target and Non-target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present' 'absent', or in rare cases 'unequivocal progression'. Multiple non-target lesions involving the same organ may be recorded as a single item.

8.3 Response Criteria

**Evaluation of target lesions**

Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.

Partial Response (PR): at least a 30% decrease in the sum of diameters of the target lesions taking as reference the baseline sum diameters.

Progression (PD): at least a 20% increase in the sum of diameters of the target lesions taking as reference the smallest sum on study, and an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on the study.

**Evaluation of non-target lesions**

Complete Response (CR): disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological (< 10 mm short axis).

Non-complete response (non-CR)/non-progression (non-PD): persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD): unequivocal appearance of one or more new malignant lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by a review panel (or study chair/primary investigator).

**Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 5 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When subjects have non-measurable (therefore non-target) disease only, Table 6 should be used.

**Table 5. Evaluation of Best Overall Response: Subjects with Target Disease, with or without Non-target Disease**

| Target Lesion | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| PR | Non-PD or not at all evaluate | No | PR |
| SD | Non-PD or not at all evaluated | No | SD |
| Not at all evaluated | Non-PD | No | Inevaluable |
| PD | Any | Yes or No | PD |

**Table 5. Evaluation of Best Overall Response: Subjects with Target Disease, with or without Non-target Disease**

| Target Lesion | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

**Table 6. Evaluation of Best Overall Response: Subjects with Non-target Disease Only**

| Non-target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/ non-PD | No | Non-CR/ non-PD[a] |
| Not all evaluated | No | Inevaluable |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

[a]'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status. FDG-PET may be used to upgrade a response to a CR in a manner

similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

8.4 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR or CR must be confirmed by repeat measurements that should be performed no less than 4 weeks after the criteria for response are first met. In this trial, as overall response rate is a secondary endpoint, confirmation of response in the form of a PR or CR will occur 8 weeks after the criteria for response are first met, since restaging imaging per the protocol will be performed every other chemotherapy cycle (ie every 8 weeks).

In randomized trials or studies where the primary endpoints are stable disease or progression, confirmation of response is not required. Elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, particularly in studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

## 9 STUDY DRUG INFORMATION

9.1 Study Drug Name TAS-102 (Lonsurf®)

9.1.1 Drug Supply TAIHO Oncology, Inc.

9.1.2 Contraindications: none

9.1.3 Special Warnings and Precautions for Use

**Myelosuppression**
In Study 1, LONSURF® caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF®-treated patients received granulocyte-colony stimulating factors.
Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF® and more frequently as clinically indicated. Withhold LONSURF® for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/$mm^3$. Upon recovery, resume LONSURF® at a reduced dose.

**Embryo-Fetal Toxicity**

Based on animal studies and its mechanism of action, LONSURF® can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m$^2$ twice daily.
Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF®.

9.1.4 Adverse Event Profile

**Table 7. Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1** Occurring More Commonly (>2%) than in Patients Receiving Placebo**

| **Adverse Reactions** | **LONSURF® (N=533)** | | **Placebo (N=265)** | |
|---|---|---|---|---|
| **All Grades** | **Grades 3-4** | **All Grades** | **Grades 3-4** | |
| **Gastrointestinal disorders** | | | | |
| Nausea | 48% | 2% | 24% | 1% |
| Diarrhea | 32% | 3% | 12% | <1% |
| Vomiting | 28% | 2% | 14% | <1% |
| Abdominal pain | 21% | 2% | 18% | 4% |
| Stomatitis | 8% | <1% | 6% | 0% |
| **General disorders and administration site conditions** | | | | |
| Asthenia/fatigue | 52% | 7% | 35% | 9% |
| Pyrexia | 19% | 1% | 14% | <1% |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 39% | 4% | 29% | 5% |
| **Nervous system disorders** | | | | |
| Dysgeusia | 7% | 0% | 2% | 0% |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 7% | 0% | 1% | 0% |

**Study 1: a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF® as a single agent at a dose of 35 mg/m$^2$/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF® therapy was 12.7 weeks

# 10 ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Adverse Event

The term "adverse event" includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories "serious" and "non-serious."

### 10.1.2 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s) and not listed in the current TAS-102 Global IB.

**NOTE:** The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

**Clarification of the difference in meaning between "severe" and "serious"**

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse event per CTCAE is generally considered severe AE. This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

#### 10.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

### 10.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected.

Collection of all SAEs must continue for 30 days after the last administration of the investigational product or until the start of new anti-tumor therapy, whichever comes first. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information at screening. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until 30 days following the last dose of study treatment (i.e., the Follow-up Visit). However, if another course of anti-cancer therapy is initiated prior to the 30-day follow-up period visit, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

## 10.3 Documenting and Reporting of Adverse Events by Investigator

All adverse events must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

### 10.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

**Not Related:** There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

**Probably Not Related:** There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

**Possibly Related:** The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.

**Probably Related:** When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

**Related:** When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re-administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

#### 10.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4.0.3. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories (see Table 8):

**Mild** (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

**Moderate** (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

**Severe** (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

**Life-threatening** (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

**Death** (Grade 5) – the event resulted in death

**Table 8.** ***Adverse Event Grading (Severity) Scale***

| *Grade* | *Severity* | *Alternate Description* [a] |
|---|---|---|
| *1* | *Mild (apply event-specific NCI-CTCAE grading criteria)* | *Transient or mild discomfort (< 48 hours); no interference with the subject's daily activities; no medical intervention/therapy required* |
| *2* | *Moderate (apply event-specific NCI-CTCAE grading criteria)* | *Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required* |
| *3* | *Severe (apply event-specific NCI-CTCAE grading criteria)* | *Considerable interference with the subject's daily activities; medical intervention/therapy required; hospitalization possible* |
| *4* | *Very severe, life threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)* | *Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable* |
| *5* | *Death related to AE* | |

*Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE.*
*Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI-CTCAE listing.*

### 10.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

**None** – No action was taken with regard to the study drug as a result of the adverse event.

**Interrupted** – Study drug was stopped due to the adverse event, but was later resumed at the same dose.

**Dose decreased** – The dose of study drug was decreased as a result of the adverse event.

**Permanently discontinued** – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry:

Discontinued > dose decreased > therapy interrupted.

#### 10.3.4 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

**Resolved without sequelae** – The subject fully recovered from the adverse event with no observable residual effects.

**Resolved with sequelae** – The subject recovered from the adverse event with observable residual effects.

**Not resolved** – The adverse event was present at the time of last observation.

**Death** – The subject died as a result of the adverse event.

### 10.4 Immediately Reportable Events

#### 10.4.1 Serious Adverse Events

Taiho Reporting Requirements

All SAEs, as well as events of overdose, medication error, pregnancy (whether serious or non-serious), to Taiho Oncology pharmacovigilance or designee within 24 hours of awareness. SAEs will be reported to Taiho Oncology either by e-mail at TAS-102_Safety@taihopui.com or via fax at (609) 750-7371. Any SAE inquiries to Taiho Oncology may be done by hotline phone at (609) 750-5303. **NOTE:** The hotline phone number is for inquiries only and not to report SAEs.

At the time of the annual DSUR (data-lock point), a list of all AEs which led to discontinuation, subjects with fatal events, and demographic information for all subjects exposed to TAS-102 must all be submitted to Taiho.

UFHCC PMO and DISC Reporting Requirements

Serious adverse events (SAE's) must be reported to UFHCC Project Management Office (PMO; pmo@cancer.ufl.edu) and entered into OnCore within 24 hours of discovery of the event. If only limited details are known, these should be reported within that time frame and follow up reports can be submitted for elaboration, clarifications, or corrections. Any email correspondence must be kept in the trial file at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. SAEs must also be reported to the UFHCC DISC Safety Team within **5 days** of discovery of the event. The original copy of the SAE Report and any email correspondence must be kept within the Trial Master File at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be submitted to the UFHCC PMO (pmo@cancer.ufl.edu), stating that this is a follow-up to a previously reported SAE and giving the date of the original report.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. PMO will confirm that the event and any necessary follow-ups are reported to the UFHCC Data and Safety Integrity Committee (DISC), Taiho Oncology, and any other regulatory authorities as required.
All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

| Institution SAE and Pregnancy Reporting Information |
| --- |
| SAEs and pregnancies must be reported to the UFHCC CRO Project Management Office (PMO), or assigned designee at:<br><br>Email: pmo@cancer.ufl.edu<br><br>As well as entered in OnCore, the study CTMS. |

### 10.4.2 Other Events Requiring Immediate Reporting

Pregnancies, overdoses, and medication errors should be documented and reported per the SAE reporting guidelines in section 10.4.1 above.

#### 10.4.2.1 Pregnancy

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

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

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

All pregnancies, regardless of outcome, must be also reported to the UFHCC PMO (pmo@cancer.ufl.edu) and DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome

#### 10.4.2.2 Overdose

An overdose with TAS-102 is defined as:

- Taking a dose beyond the recommended dose in one day or beyond the recommended total dose in each cycle.
- An accidental or intentional overdose with TAS-102 regardless of whether it is associated with an AE (even if not fulfilling a seriousness criterion)

These events are to be captured as an AE on the eCRF and reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the Investigator first becomes aware of its occurrence following the same process as described for the SAEs.

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

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

Although overdose (dose variance of >10%) and cancer are not always serious by regulatory definition, these events should also be reported to the UFHCC PMO (pmo@cancer.ufl.edu) and DISC in an expedited manner. In case the overdose did not result in any adverse event, the Investigator should report this as "overdose, no adverse event" on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

#### 10.4.2.3 Medication Error

A medication error is defined as any accidental incorrect administration of a medicinal product. The error may be related to the administration of a wrong medication, nature of the medication, route of administration, dosage or frequency of the treatment as specified in this protocol (including omission of one or more administrations).

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

recording of study drug accountability data in the eCRF and does not need to be reported as an AE.
- If it results in an overdose, incorrect route of administration, or administration of an incorrect study drug, it will be reported as an AE.

Based on the above criteria, medication errors that are captured as an AE on the eCRF should be reported to UFHCC PMO (pmo@cancer.ufl.edu) and Taiho Pharmacovigilance or designee **within 24 hours** from the time the Investigator first becomes aware of its occurrence following the same process as described for the SAEs even if it does not meet any of the criteria of an SAE.

### 10.5 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the study intervention received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

## 11 ASSESSING SAFETY

### 11.1 Specfications of Safety Analysis

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Death as a result of disease progression is only to be assessed as efficacy measures and not as AEs or SAEs unless the events that led to death met the serious criteria.

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific AE, e.g., mild (Grade 1), moderate (Grade 2), or severe (Grade 3) myocardial infarction. "Serious" is a regulatory definition (see previous definition) and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

### 11.2 Safety Analysis

Subjects will be examined and graded each cycle for subjective/objective evidence of developing toxicity according to NCI-CTCAE version 4.03 toxicity criteria. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal, and incidence of serious adverse events. Subjects will have laboratory values assessed prior to and on Day 15 of each cycle.

Adverse event data and corresponding toxicity grades during treatment and during long-term follow-up will be summarized in the form of tables. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by subjects will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for the overall subject group and by dose levels. Dose-toxicity curves will be fitted to the final data to estimate the toxicity rates of each dose levels.

### 11.3 Methods and Timing for Assessment and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on the CRF and reported to Taiho in accordance with protocol instructions and clinical trial agreement.

### 11.4 Type and Duration of Follow-up of Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to their resolutions, or until the investigator assesses them as stable at the time of the 30-day safety follow-up, or the subject is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE or SAE CRF page and in the subject's medical record to facilitate source data verification.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

## 12. STATISTICAL METHODS

The following sub-sections provide an overview of the statistical considerations and analyses.

### 12.1 Sample Size Determination

This is a pilot phase II single-arm study, with a primary endpoint of progression-free survival (PFS), to evaluate efficacy of TAS-102. Additional objective of the study is to evaluate the feasibility and safety of a regimen of daily TAS-102 administered to subjects with metastatic or unresectable pancreatic adenocarcinoma after progression through or intolerance to first- or second-line chemotherapy. The primary efficacy analysis will be an intent-to-treat comparison of the PFS curve with a reference historical control. From past studies[3], the median PFS and/or time to progression (TTP) for subjects with metastatic or unresectable pancreatic adenocarcinoma in the second line of treatment is variable ranging from 6 weeks to 22 weeks. Assuming exponential distributions on PFS on both current study population and the referent population, a sample size of 33 evaluable subjects who will receive the same level of dose will ensure to have at least 80% power to detect an improvement of 3 weeks of median PFS (i.e. from 6 weeks to 9 weeks). The sample size and power derivations were based on one-sample log rank test by Wu (2015)[14] at one-sided significance level of 0.10. It is assumed that the survival time distributions of both groups (historical and this proposed experiment groups) are approximately the Weibull distribution with a shape parameter of ~1.0. Accounting for about ~10% ineligible/inevaluable subjects, the total number of subjects to be accrued to this cohort will be 37, which is expected to be completed within 24 months. Assuming at least the last evaluable subject derives benefit from the anticipated maximal number of 6 cycles, the length of the entire treatment study will be approximately 30 months.

A subject is considered eligible for toxicity evaluation if they have received at least one dose of TAS-102.

12.2 Analysis of Baseline and Demographic Characteristics

The analysis of demographic characteristics (age, gender, ethnicity) and baseline characteristics, including weight change, performance status, and histologic subtype, will be primarily descriptive due to the small subject numbers. All data will be summarized using descriptive statistics (mean/variance, median/range, frequency/proportion) along with graphical illustration as needed.

12.3 Primary and Secondary Endpoint Efficacy Analysis

The primary endpoint to this study will be to determine progression-free survival following TAS-102 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated.

A secondary endpoint of this study will be overall survival/TTP following treatment with TAS-102. Kaplan-Meier estimates and survival curves will be calculated. Other secondary endpoints include response rates, clinical benefit rate (CR + PR + SD), toxicities, reversibility of toxicities, and compliance with intended treatment will also be estimated along with exact 95% binomial confidence intervals.

No multiplicity will be adjusted for the secondary endpoints. All data analysis will be conducted in reproducible fashion and the results will be reported regardless of the statistical significance.

## 13 DATA AND SAFETY MONITORING

### 13.1 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center Data Integrity and Safety Committee (UFHCC DISC) in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise, the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

In compliance with the UFHCC data and safety monitoring plan, the PI will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC (Scientific Review and Monitoring Committee) review, which occurs prior to initial IRB approval.

UFHCC investigator-initiated protocols will be classified into one of the following categories of risk:

Level 1 – Low risk non-therapeutic interventional trials.
Level 2 – Moderate risk therapeutic (i.e., drug, biologic, or device) trials using FDA approved or commercially available compounds or interventions.
Level 3 – High risk therapeutic trials (i.e., investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
Level 4 – Complex trials involving very high risk to subjects and a high-level complexity (i.e., first in human or gene transfer studies).

### 13.2 Data Monitoring

UFHCC (University of Florida Health Cancer Center) Quality Assurance team and/or project management officers will perform remote monitoring and may make monitoring visits to the trial sites periodically during the trial to determine if sites are complying with the protocol. Source documents will be reviewed for completion and validated against with data submitted electronically via the Electronic Data Capture. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies. As part of the responsibilities assumed by conducting the study, the Principal Investigator (PI) agrees to

maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

### 13.3 Principal Investigator (PI) Responsibilities

Per IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB.

Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements, as outlined in the UFHCC Guidance: Principal Investigator Responsibilities and Oversight.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

## 14 EMERGENCY PROCEDURES

### 14.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

### 14.2 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

## 15 ADMINISTRATIVE CONSIDERATIONS

### 15.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu, who will then report the breach to the UFHCC DISC) and the IRB of record. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

### 15.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, adverse events and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

### 15.3 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

### 15.4 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject.

The PI will retain the original signed consent document in the site study binder or in each subject's study file. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

### 15.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health Data Integrity and Safety Committee, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

### 15.6 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will sent out to the applicable study teams, prior to implementing the amendment.

On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and UFHCC CRO PMO (pmo@cancer.ufl.edu) are notified within 5 business days with a full justification and description of the event.

15.7 Case Report Forms

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document protocol-required outcomes for safety monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.

All protocol data is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC. Record Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

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

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

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

## 16 COMPLIANCE WITH LAWS AND REGULATIONS

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the International Conference on Harmonization and GCP:

http://www.fda.gov/oc/gcp/guidance.html; Declaration of Helsinki: http://www.fda.gov/oc/health/helsinki89.html; Code of Federal Regulations, Title 21: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch. cfm]

All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Project Management Officer or assigned designee. All studies must be registered prior to enrollment of the first participant. The Protocol Management Officer or assigned designee will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study. The PMO will determine if registration and updates to the NCI CTRP are required.

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