A Phase II Trial of TAS-102 in Previously Treated Unresectable or Metastatic Squamous Cell Carcinoma of the Lung

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ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (also SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (also SGOT)
AUC	area under curve
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance
CR	complete remission
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IV	intravenous
LDH	lactic dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MTD	maximum tolerated dose
PCR	polymerase chain reaction
PD	pharmacodynamics
PDO	Protocol Development Office
PK	pharmacokinetics
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (also AST)
SGPT	serum glutamic pyruvate transaminase (also ALT)
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

Protocol Signature Page

A Phase II Trial of TAS-102 in Previously Treated Unresectable or Metastatic Squamous Cell Carcinoma of the Lung

Principal Investigator:

Signature of Investigator	Date
Dennie V. Jones, Jr., MD	
Printed Name of Investigator	
University of Florida	
Name of Facility	
Gainesville, Florida	
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 SYNOPSIS

Title:	A Phase II Trial of TAS-102 in Previously Treated Unresectable or Metastatic Squamous Cell Carcinoma of the Lung
Rationale:	One of the oldest antineoplastic agents available, 5-FU, has some activity against NSCLC. Capecitabine is an oral prodrug which is converted into 5-FU and its active metabolites, and has modest activity against NSCLC in combination with carboplatin. To date, there have only been three reports of the oral 5-FU prodrug UFT (uridine and ftorafur) administered to patients with NSCLC. In two small series a, low response rate was observed, although low doses of UFT were used. In the third trial, UFT was administered as post-surgical adjuvant therapy, and was associated with a statistically significant increase in 5-year survival. S-1 is a separate 5-FU prodrug which has activity in non-small cell lung cancer, and is approved in Japan for the treatment of NSCLC, either alone or in combination with a platinum based therapy. S-1 is composed of tegafur (the 5-FU prodrug); 5-chloro-2, 4-dihydroxypyridine (CDHP), which reversibly inhibits 5-FU degradation by dihydropyrimidine dehydrogenase (DPD); and potassium oxonate which blocks the phosphorylation of 5-FU within the gastrointestinal tract and reduces gastrointestinal toxicities. TAS-102 is an oral drug which consists of a combination of trifluridine and tipiracil hydrochloride. Trifluridine is phosphorylated by thymidine kinase into its active form intracellularly, where is causes DNA strand termination and breaks, leading to its cytotoxic activity. Tipiracil hydrochloride inhibits thymidine phosphorylase, which then prevents the degradation of trifluridine. This drug was recently approved for the treatment of 5-FU-resistant colorectal cancers, and it has demonstrated activity in vitro against a broad spectrum of human tumor cell lines, including non-small cell lung cancer, especially the squamous cell variant. To date, there are no reports of a clinical evaluation of this agent in NSCLC, as is proposed here. This protocol will evaluate squamous cell NSCLC; nonsquamous cell NSCLC (adenocarcinomas, large cell carcinomas, and poorly differentiated p63-negative carcinomas) will not be evaluated in this protocol due to the potential for differential expression of thymidine kinase and thymidine phosphorylase by histology and the preclinical evidence for a lower level of cytotoxicity in those histologic variants. The dire outcome of patients with unresectable and/or metastatic non-small cell lung cancer with currently available therapies justifies the evaluation of new agents to determine their potential clinical benefit in this disease.
Study Schema: Drugs / Doses / Length of Treatment	Upon confirmation of eligibility and provision of written informed consent, subjects will receive TAS-102 (Lonsurf®) at its FDA-approved dose and schedule, 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) 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 until disease progression or unacceptable toxicity. Doses will be rounded to the nearest 5 mg increment. Additional doses will not be taken to make up for missed or held doses. Subjects will be monitored weekly during the first cycle for tolerance, and tumor status will be assessed every other cycle. Participants will continue on therapy until the development of unacceptable toxicity, disease progression, or participant desire to discontinue protocol therapy.
Objectives:	**Primary Objective:** • To determine the percentage of subjects who achieve an objective response by RECIST criteria **Secondary Objectives:** • To evaluate the qualitative and quantitative toxicities, and reversibility of toxicities, of this treatment by NCI CTC Version 4.0.3 criteria • To determine the progression-free survival, in months, of subjects receiving TAS-102 for the treatment of unresectable or metastatic recurrent squamous cell lung cancers • To determine the percentage of subjects who derive clinical benefit (objective response + stable disease) • To determine the median duration of responses in months • To determine the overall survival in months • To determine the percentage of expression of thymidine kinase and thymidine phosphorylase
Study Design:	Non-randomized, open label, sequentially enrolling phase II study with a Simon two-step enrollment design.
Accrual Goal:	Up to 30 subjects
Inclusion Criteria:	Patients must fulfill all of the following criteria to be eligible for study entry: Those who will be eligible will be all patients with unresectable and/or metastatic squamous cell non-small cell lung cancer who have disease which has been previously treated with an FDA- or NCCN-approved platinum doublet. Patients who have not received such therapy must have medical reasons for not receiving such therapy. Those who have a molecularly targetable genetic mutation in their tumor must have also received the appropriate specific therapy for that mutation. All will be appropriate candidates for chemotherapy treatment. All patients will have an ECOG performance status of $\leq$2 at the time of the initiation of therapy, adequate end-organ function, no severe comorbid disease, and ability to provide informed consent.

	Subjects must meet all of the additional following criteria to be eligible for study participation: A. ECOG Performance Status ≤ 2 B. Life expectancy ≥ 12 weeks C. Male or female, age ≥18 years D. Patients of childbearing potential must be using an effective means of contraception. E. Histologic diagnosis of squamous cell lung cancer that is been treated adequately in the metastatic or unresectable setting with a platinum doublet chemotherapy regimen, and now has evidence of disease progression. Patients may have also received additional chemotherapy, such as an immune checkpoint inhibitor or no more than one additional cytotoxic agent (thus participants may have received between one to three prior lines of therapy for metastatic or unresectable disease) F. Those patients who have received platinum-based doublet therapy in the neoadjuvant or adjuvant setting will only be eligible if they have experienced disease progression after their last dose of cytotoxic chemotherapy G. For patients who have a neoplasm for which there currently exists a targeted therapy (such as to EGFR activating mutations, or ALK or ROS1 gene rearrangements) must have received all such targeted therapies and either exhibited progressive disease through such treatments, or have been shown to be intolerant of such therapies, prior to enrollment on this study H. Baseline laboratory values (bone marrow, renal, hepatic): o Adequate bone marrow function: ▪ Absolute neutrophil count ≥1000/μL • Potential subjects with benign ethnic neutropenia, often seen in African Americans and Afro-Caribbean men and women, may be enrolled after discussion with the PI, provided they have no other disqualifying features and no evidence of medical consequences of their neutropenia, such as repeated infections) ▪ Platelet count ≥100,000/μL o Renal function: ▪ Serum creatinine ≤ 2.0 mg o Hepatic function: ▪ Bilirubin ≤1.5x normal o Serum calcium ≤ 12 mg/dl

	I. 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 study enrollment, 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. J. 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. K. Subjects must have provided written informed consent and be willing to comply with all study-related procedures.
Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. Pregnant or lactating females B. Patients with a mixed histology NSCLC, such as adenosquamous carcinoma, where the squamous component is <50% of the assessed lesion C. Patients with a mixed histology where there are ANY small cell elements D. Patients who have not received and progressed through, have not refused, or have not been intolerant of, a commonly utilized platinum-doublet therapy (cisplatin or carboplatin paired with docetaxel, paclitaxel, nab-paclitaxel, gemcitabine, vinorelbine, etoposide or irinotecan) administered for the treatment of unresectable or metastatic lung cancer E. Patients who have not received the appropriate prior targeted therapy for their lung cancer

	F. Any invasive malignancy treated within the prior 3 years prior to Cycle 1, Day 1 G. Myocardial infarction or ischemia within the 6 months before Cycle 1, Day 1 H. Uncontrolled, clinically significant dysrhythmia, or prolonged QT segment I. Uncontrolled malignant disease in the CNS (previously treated disease is eligible, provided it has been radiographically stable for at least four weeks) J. Radiotherapy within the 2 weeks before Cycle 1, Day 1. If any radiation has been administered to the target lesion there must be evidence of growth by radiographic assessments or physical examination K. Surgery within the 2 weeks before Cycle 1, Day 1 L. Any co-morbid condition that, in the view of the attending physician, renders the patient at high risk from treatment complications M. Subjects unwilling to use an acceptable method to avoid pregnancy for the entire study period and for at least 24 weeks after the last dose of study drug. N. 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. O. Prisoners or subjects who are involuntarily incarcerated. P. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. Q. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.
Efficacy Assessments:	**Each week of first cycle (days 1, 8, 15 and 22):** Weight and performance status Physical exam Laboratory studies • CBC with differential count • Comprehensive metabolic panel, serum magnesium **First and 15th day of each subsequent cycle:** Weight and performance status Physical exam Laboratory studies • CBC with differential count

	• Comprehensive metabolic panel, serum magnesium **First day of every odd-numbered cycle (beginning at Cycle 3):** • CT or MRI of thorax and abdomen, or PET/CT (may be obtained up to one calendar week prior to first day of each odd numbered cycle)
Statistical Considerations:	This is a pilot phase II study, so we are interested in evaluating the feasibility and safety of a regimen of daily TAS-102 administered to subjects with squamous cell lung cancer. To minimize the number of subjects exposed, the sample size will be determined by the anticipated response rate. A response rate of 20% or above to TAS-102 will be of interest in subjects with previously-treated squamous cell lung cancer. Initially, 14 subjects will be evaluated for response, and if none of the 14 evaluable subjects experiences a partial or complete response, then the study will be terminated. If the true response rate is 20%, the chance of rejection error is less than 5%. However, in the event of one response among the first 14 subjects, further accrual will continue to a total of 30 evaluable subjects to estimate the response rate more precisely with a standard error of no more than 9%. 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 also received two cycles of therapy as planned.
Estimated Enrollment Period:	It is estimated that accrual to the first level (14 subjects) will be completed within nine months. If the study is fully accrued (30 subjects) and at least the last such subject derives benefit from the anticipated maximal number of six cycles, then the length of the entire enrollment and treatment period will be approximately 24 months.
Estimated Study Duration:	Approximately 30 months

1. INTRODUCTION

1.1 **Background**

Invasive cancer is the second most common cause of cancer death in both men and women in the United States. The data from the American Cancer Society projected 1,658,370 cases of cancer in 2015, with approximately 589,430 deaths; nearly 1 in 4 deaths will be due to cancer. While prostate and breast cancers are more common in men and women, respectively, lung cancer is still a far more lethal malignancy in either sex, with a five-year survival rate that is less than 15%. Surveillance, Epidemiology, and End-Results (SEER) database estimates for 2016 indicate that lung cancer will account for 224,390 new lung cancer cases, or 13.3% of all invasive cancer cases (not including non-melanoma skin cancer or in situ carcinomas), and there will be 158,080 lung cancer deaths, or 26.5% of all deaths. In men 33% of all deaths from cancer are going to be due to lung cancer, while in women, 5% of all cancer-related deaths are due to lung cancer.

Approximately 70% of patients with unresectable non-small cell lung cancer (NSCLC) who receive and progress through frontline chemotherapy will be eligible for second line treatments. Any of the agents which are available for frontline therapy can be used in the salvage setting; crizotinib and ceritinib (for ALK gene translocations), AZD9291 (Tagrisso, for EGFR T790M mutation positive lesions), erlotinib, ramicirumab, docetaxel, and pemetrexed (in non-squamous cell carcinoma) are FDA-approved in the salvage setting based upon their demonstrated survival benefit in randomized phase III trials. All untargeted agents appear to be roughly equivalent in terms of clinical benefit, which is admittedly modest, with response rates <10%, clinical benefit rates of approximately 50%, and overall survivals of approximately 6 months. However, when agents are matched to their molecular targets, both response rates and progression-free and overall survivals tend to improve significantly. Still, a substantial number of patients may not benefit from the agents in the salvage treatment setting, thus it is critical to identify those patients who stand to benefit the most.

One of the oldest antineoplastic agents available, 5-FU, has some activity against NSCLC. Capecitabine is an oral prodrug which is converted into 5-FU and its active metabolites, and has modest activity against NSCLC in combination with carboplatin. To date, there have only been three reports of the oral 5-FU prodrug UFT (uridine and ftorafur) administered to patients with NSCLC. In two small series a, low response rate was observed, although low doses of UFT were used. In the third trial, UFT was administered as post-surgical adjuvant therapy, and was associated with a statistically significant increase in 5-year survival. S-1 is a separate 5-FU prodrug which has activity in nonsmall cell lung cancer, and is approved in Japan for the treatment of NSCLC, either alone or in combination with a platinum. S-1 is composed of tegafur (the 5-FU prodrug); 5-chloro-2, 4-dihydroxypyridine (CDHP), which reversibly inhibits 5-FU degradation by dihydropyrimidine dehydrogenase (DPD); and potassium oxonate which blocks the phosphorylation of 5-FU within the gastrointestinal tract and reduces gastrointestinal toxicities. TAS-102 is an oral drug which consists of a combination of trifluridine and tipiracil hydrochloride. Trifluridine is phosphorylated by thymidine kinase into its active form intracellularly, where is causes DNA strand termination and breaks, leading to its cytotoxic activity. Tipiracil hydrochloride inhibits thymidine phosphorylase, which then prevents the degradation of trifluridine. This drug was recently approved for the treatment of 5-FU-resistant colorectal cancers,

and it has demonstrated activity in vitro against a broad spectrum of human tumor cell lines, including nonsmall cell lung cancer, especially the squamous cell variant. To date, there are no reports of a clinical evaluation of this agent in NSCLC, as is proposed here. This protocol will evaluate squamous cell NSCLC; nonsquamous cell NSCLC (adenocarcinomas, large cell carcinomas, and poorly differentiated p63-negative carcinomas) will not be evaluated in this protocol due to the potential for differential expression of thymidine kinase and thymidine phosphorylase by histology and the preclinical evidence for a lower level of cytotoxicity in those histologic variants. The dire outcome of patients with unresectable and/or metastatic nonsmall cell lung cancer with currently available therapies justifies the evaluation of new agents to determine their potential clinical benefit in this disease.

2. OBJECTIVES

2.1 Primary

- To determine the percentage of subjects who achieve an objective response by RECIST criteria

2.2 Secondary

- To evaluate the qualitative and quantitative toxicities, and reversibility of toxicities, of this treatment by NCI CTC Version 4.0.3 criteria
- To determine the progression-free survival, in months, of subjects receiving TAS-102 for the treatment of unresectable or metastatic recurrent squamous cell lung cancers
- To determine the percentage of subjects who derive clinical benefit (objective response + stable disease)
- To determine the median duration of responses in months
- To determine the overall survival in months

3. SELECTION OF SUBJECTS

3.1 Number of Subjects

This protocol will enroll up to a maximum of 30 subjects.

3.2 Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible for study entry:

Those who will be eligible will be all patients with unresectable and/or metastatic squamous cell non-small cell lung cancer who have disease which has been previously treated with an FDA- or NCCN-approved platinum doublet. Patients who have not received such therapy must have medical reasons for not receiving such therapy. Those who have a molecularly targetable genetic mutation in their tumor must have also received the appropriate specific therapy for that mutation. All will be appropriate candidates for chemotherapy treatment. All patients will have an ECOG performance status of ≤2 at the time of the initiation of therapy, adequate end-organ function, no severe comorbid disease, and ability to provide informed consent.

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

A. ECOG Performance Status ≤ 2
B. Life expectancy ≥ 12 weeks
C. Male or female, age ≥18 years
D. Patients of childbearing potential must be using an effective means of contraception.
E. Histologic diagnosis of squamous cell lung cancer that is been treated adequately in the metastatic or unresectable setting with a platinum doublet chemotherapy regimen and now has evidence of disease progression.Patients may have also received additional chemotherapy, such as an immune checkpoint inhibitor or no more than one additional cytotoxic agent (thus participants may have received between one to three prior lines of therapy for metastatic or unresectable disease).
F. Those patients who have received platinum-based doublet therapy in the neoadjuvant or adjuvant setting will only be eligible if they have experienced disease progression after their last dose of cytotoxic chemotherapy
G. For patients who have a neoplasm for which there currently exists a targeted therapy (such as to EGFR activating mutations, or ALK or ROS1 gene rearrangements) must have received all such targeted therapies and either exhibited progressive disease through such treatments, or have been shown to be intolerant of such therapies, prior to enrollment on this study
H. Baseline laboratory values (bone marrow, renal, hepatic):
    a. Adequate bone marrow function:
        i. Absolute neutrophil count ≥1000/μL
            1. Potential subjects with benign ethnic neutropenia, often seen in African Americans and Afro-Caribbean men and women, may be enrolled after discussion with the PI, provided they have no other disqualifying features and no evidence of medical consequences of their neutropenia, such as repeated infections)
        ii. Platelet count ≥100,000/μL
    b. Renal function:
        i. Serum creatinine ≤ 2.0 mg
    c. Hepatic function:
        i. Bilirubin ≤1.5x normal
    d. Serum calcium ≤ 12 mg/dl
I. 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 study enrollment, 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:
J. Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or

K. 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.
L. 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.
M. Subjects must have provided written informed consent and be willing to comply with all study-related procedures.

3.3 **Exclusion Criteria**

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

A. Pregnant or lactating females
B. Patients with a mixed histology NSCLC, such as adenosquamous carcinoma, where the squamous component is <50% of the assessed lesion
C. Patients with a mixed histology where there are ANY small cell elements
D. Patients who have not received and progressed through, have not refused, or have not been intolerant of, a commonly utilized platinum-doublet therapy (cisplatin or carboplatin paired with docetaxel, paclitaxel, nab-paclitaxel, gemcitabine, vinorelbine, etoposide or irinotecan) administered for the treatment of unresectable or metastatic lung cancer
E. Patients who have not received the appropriate prior targeted therapy for their lung cancer
F. Any invasive malignancy treated within the prior 3 years prior to Cycle 1, Day 1
G. Myocardial infarction or ischemia within the 6 months before Cycle 1, Day 1
H. Uncontrolled, clinically significant dysrhythmia, or prolonged QT segment
I. Uncontrolled malignant disease in the CNS (previously treated disease is eligible, provided it has been radiographically stable for at least four weeks)
J. Radiotherapy within the 2 weeks before Cycle 1, Day 1. If any radiation has been administered to the target lesion there must be evidence of growth by radiographic assessments or physical examination
K. Surgery within the 2 weeks before Cycle 1, Day 1
L. Any co-morbid condition that, in the view of the attending physician, renders the patient at high risk from treatment complications
M. Subjects unwilling to use an acceptable method to avoid pregnancy for the entire study period and for at least 24 weeks after the last dose of study drug.
N. 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.
O. Prisoners or subjects who are involuntarily incarcerated.
P. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

Q. 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 and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

All subjects must be registered with the UF Health Cancer Center prior to participation in this trial. 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 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. 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**

All participants will have unresectable, previously-treated squamous cell NSCLC who have previously been treated with a platinum doublet (or have refused such prior therapy); those who have a molecularly targetable genetic mutation in their tumor must have also received the appropriate specific therapy for that mutation.

Both men and women of all races and ethnic groups will be eligible for this trial. This study was designed to include women and minorities, but will not be designed to measure differences of intervention effects. 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.

Eligible subjects will include those with radiographically-staged locally advanced or metastatic NSCLC who have received any prior therapy for the lesion(s). Patients who receive radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be assessable; be willing to use contraception; are neither pregnant nor lactating; are greater than 18 years old and have an anticipated life expectancy of at least 12 weeks; have normal end-organ function and limited comorbidities, and are able to provide written informed consent.

Upon confirmation of eligibility and provision of written informed consent, subjects will receive TAS-102 (Lonsurf®) at its FDA-approved dose and schedule, 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) 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 until disease progression or unacceptable toxicity. Doses will be rounded to the nearest 5 mg increment. Additional doses will not be taken to make up for missed or held doses. Subjects will be monitored weekly during the first cycle for tolerance, and tumor status will be assessed every other cycle. Participants will continue on therapy until the development of unacceptable toxicity, disease progression, or participant desire to discontinue protocol therapy. There is no set maximum of cycles, as patients who have responded and who are tolerating this regimen may continue it until withdrawal of consent, disease progression, development of undue toxicity, or death.

Those whose disease is responding systemically but who develop CNS metastases as their only site of progression will have protocol therapy temporarily held for the delivery of brain radiotherapy (whole brain and/or gamma knife) and then resume protocol therapy.

5.2 **Concomitant Therapy**

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

Use of any additional anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy; these are not permitted while participating in this study. TAS-102 had minimal or no effect on the QTc interval; the drug was administered to 42 patients with advanced solid tumors with the recommended dosage regimen, but it had no large effect (i.e. > 20 ms) in the mean QTc interval when compared to placebo and no evident exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc greater than 500 msec and 1 of 42 patients (2.4%) had a QTc increase from baseline greater than 60 msec. The components of TAS-102 is not metabolized by the cytochrome P450 system, thus strong CYP inhibitors or inducers are not expected to have any effect on the metabolism of this drug. Study participants may receive additional investigational antineoplastic therapies upon completion of their participation in this protocol. Use of concurrent investigational agents is not permitted.

Any therapy or medication (except study drugs), administered from screening until 28 days after the last dose of either study drug, is considered a concomitant therapy or medication. However, if another course of anti-cancer therapy is initiated prior to the 28-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.
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

- Chemotherapy not specified in this protocol
- Investigational agents other than the study drug in this trial
- Radiation therapy

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 palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

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.

5.3 Dose Modifications

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 4 (CTCAE) will be used to grade toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

The starting dose of TAS-102 is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) 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 until disease progression or unacceptable toxicity. Doses will be rounded to the nearest 5 mg increment. Study medication will be administered on a 4 week schedule. Doses will be delayed or reduced for clinically significant (Grade 3-4) hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

5.3.1 Dose Modification Table

Dose level 0 (standard starting dose)	35 mg/m^2 po bid
Dose level – 1	30 mg/m^2 po bid
Dose level – 2	25 mg/m^2 po bid

Intrapatient dose reduction and dose interruption will be permitted once a patient has experienced drug-related toxicity provided that the criteria for patient withdrawal from study treatment have not been met. All intrapatient dose reductions are relative to the lowest dose of the current cycle.

For all toxicities, doses of TAS-102 will be modified based upon Day 1 and Day 15, complete blood cell counts. Day 1 TAS-102 dosing for each cycle will be held 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, TAS-102 will be withheld 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 TAS-102 after reducing the dose by 5 mg/m^2/dose (as above) 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 baseline in subjects with benign ethnic neutropenia) 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

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade. In the case of two or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment. If more than 3 dose reductions are required, TAS-102 will be discontinued. Do not escalate dose after it has been reduced.

5.3.2 Non- Hematologic Toxicity

For Grade 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to Grade 1 or less (or to baseline), then reinstituted (if medically appropriate) at a one level dose reduction. Nausea and vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy. All agents should be dose reduced in cases where either agent may be the cause of a given toxicity. Patients must meet pre-treatment laboratory criteria (as specified in the inclusion criteria) at Day 1 of each cycle to receive therapy administration. Patients will not be eligible for further treatment if resolution of toxicities requires a greater than 3-week delay in the start of the next cycle (five weeks from the start of the prior cycle).

5.3.3 Hematologic Toxicity

Grade 1, 2 and 3 myelosuppression (neutropenia, thrombocytopenia), with recovery to pre-treatment lab criteria as specified in the inclusion criteria, does not require dose modification. Grade 3 or 4 lymphopenia does not require dose reduction. Patients with a febrile Grade 4 neutropenia >7 days or Grade 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period) or Grade 4 thrombocytopenia >7 days should be retreated after recovery at a one-dose level reduction during subsequent cycles. If any of these toxicities recurs, the patient should be dose reduced again in all subsequent cycles after recovery to pre-treatment lab criteria as specified in the inclusion criteria. Patients will not be eligible for further treatment if resolution of toxicities requires a greater than 2-week delay in the start of the next cycle. Patients who need two dose level reductions of TAS-102 will discontinue from the study.

5.4 **Supportive Care Guidelines**

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Bisphosphonates or denosumab are allowed for patients with bone metastases.

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 patients will be maintained by the study site.

6.2 **Criteria For Study Treatment Discontinuation**

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) continued treatment with study drug is appropriate.
- Substantial non-compliance (>25% of missed doses accounting for delays and dose modifications per protocol or instructions from research team staff for AEs), with the requirements of the study.
- The patient presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The patient 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 results.
- The development of a second malignancy that requires treatment, which would interfere with this study.

- The patient is lost to follow-up.
- Interruption in study drugs administration for greater than 21 days (see Dose Modification section).
- 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 patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient 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 patients are followed up for survival status after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all patients participating in the study, even for a brief period of time. Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients 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 patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee.

6.3 **Replacement of Subjects**

Subjects will be replaced if they have not received any doses of study drug prior to their continuing participation in the protocol for any reason, or if the patient wishes to discontinue participation in the protocol, but is not discontinued for disease progression, toxicity, or any of the reasons listed in section 6.2.

6.4 **Study Discontinuation**

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 patients, requiring dose reduction to Dose level -1.

7. STUDY PROCEDURES

7.1 **Study Schedule of Events**

Day of Protocol	Baseline[2]	Day 1 Each Cycle	Day 15 Each Cycle	Day 1, odd cycles (beginning with Cycle 3)	Off Treatment	Follow Up
Studies:						
H&P[1] / PS / VS & TOX	**X**	**X**			**X**	**X**
CBC w/ Diff.	**X**	**X**	**X**		**X**	**X**
CMP	**X**	**X**			**X**	**X**
UA and Pregnancy Test	**X**					
Diagnostic Imaging Scan / TA[3]	**X**			**X**		**X**
ECG	**X**					
Concomitant Medications	**X**	**X**	**X**		**X**	**X**
Adverse Events	**X**	**X**	**X**		**X**	**X**
Treatment:						
TAS-102(Lonsurf®) [4]		**X**				

1) Abbreviations: H&P=History and Physical examination; PS=ECOG performance status; VS=vital signs (blood pressure, temperature, pulse and respiratory rates, weight and height); TOX=toxicity assessment; CBC/diff=complete blood count and white blood cell differential; CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, uric acid); UA=urinalysis; Pregnancy test only for women of childbearing potential. For the first cycle, the H&P, toxicity assessment, CBC and CMP are repeated weekly (Days 1, 8, 15 and 22).
2) Baseline studies are repeated on day 1 if there are more than 14 days between baseline and day 1. The radiographic assessment must be repeated if there are more than 21 days between baseline and day 1.
3) TA= Tumor assessment by RECIST Criteria by diagnostic CT scan, PET/CT scan and/or MRI scan. Scans are to be done within one calendar week prior to Day 1 of every odd-numbered cycle (beginning with Cycle 3).
4) TAS-102 (Lonsurf®) is initially dosed as 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) 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. Doses will be rounded to the nearest 5 mg increment.
Follow up evaluations are also performed as appropriate clinically

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.

Height, weight and performance status
Physical exam
Concomitant medication collection
Laboratory studies:

- CBC with differential count

- Comprehensive metabolic panel, serum magnesium
- ECG
- Urine pregnancy test (females of potential child-bearing status only)
- CT or MRI of thorax and abdomen, or PET/CT

7.3 On-Study Evaluations

Each week of first cycle (days 1, 8, 15 and 22):

Weight and performance status
Physical exam
Concomitant medication collection
Adverse event collection
Laboratory studies

- CBC with differential count
- Comprehensive metabolic panel, serum magnesium

First day of each cycle (within 3 days):

Weight and performance status
Physical exam
Concomitant medication collection
Adverse event collection
Laboratory studies

- CBC with differential count
- Comprehensive metabolic panel, serum magnesium

Day 15 of each cycle:

Concomitant medication collection
Adverse event collection
Laboratory studies

- CBC with differential count

First day of every odd-numbered cycle (beginning with Cycle 3):

- CT or MRI of thorax and abdomen, or PET/CT (must be obtained within one calendar week prior to first day of each odd numbered cycle)

7.4 End of Treatment

Patients should be seen in the clinic or contacted by telephone to determine if any serious or non-serious adverse events have occurred within 28 days (± 3 days) of termination of TAS-102 dosing.

Patients will be followed for 28 days after completion of the last course of any therapy for the documentation of adverse events and concomitant medications.

Off-therapy measurements:

a. Toxicity assessment, interim medical history and physical examination
b. Laboratory studies:
   CBC with differential count
   CMP

7.5 **Follow up/Survival**

Patients will be seen in follow-up at least every three months for the first three years after the initiation of therapy, or the date of death, whichever occurs first. Patients who are alive after three years will have follow up every six months for years four and five, then annual follow ups until date of death, or lost to follow up. Those patients who are lost to follow up will have every effort by telephone and mail to contact them for at least one month past their first missed clinic visit, with at least four documented attempts at contact to be made during that time.

Evaluation will consist of an interim medical history and a physical examination. Additional studies, such as labs (CBC and CMP), and any X-rays, or CT, PET/CT, bone scans or MRI scans used in evaluation of response will be repeated as clinically indicated. Other studies, such as, biopsies, will be performed as clinically indicated.

8. CRITERIA FOR DISEASE EVALUATION

8.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their dose of any of the three drugs in this study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are considered measurable only if they have demonstrated growth after completion of the radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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 longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy or Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess response. There are no validated tumor markers for NSCLC, and none are being evaluated here.

Cytology or Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. 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. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.2 **Response Criteria**

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on 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 in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal 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). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients 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.

For Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

9. STUDY DRUG INFORMATION

9.1 Study Drug Name

9.1.1 Identification

TAS-102; Trifluridine (FTD) / Tipiracil hydrochloride (TPI); Lonsurf® (Taiho Oncology, Princeton, NJ)

Active Drug Substance

Trifluridine (FTD)
Chemical Name: 2'-deoxy-5-(trifluoromethyl) uridine (IUPAC)
Code Name: FTD, F3TdR, F3dThd
Generic Name: Trifluridine
Chemical Formula: $C_{10}H_{11}F_3N_2O_5$
Molecular Weight: 296.20
Description: White crystals or crystalline powder
Solubility: Soluble in water, sparingly soluble in 2-propanol

Tipiracil Hydrochloride (TPI)
Chemical Name: 5-chloro-6-[(2-iminopyrrolidin-1-yl) methyl] pyrimidine-2,4(1*H*,3*H*)-dione monohydrochloride (IUPAC)
Code Name: TPI, TAS-1-462
Generic Name: Tipiracil hydrochloride
Chemical Formula: $C_9H_{11}ClN_4O_2 \cdot HCl$
Molecular Weight: 279.12
Description: White crystals or crystalline powder
Solubility: Soluble in water, very slightly soluble in ethanol and practically insoluble in diethyl ether

9.1.2 Packaging and Labeling

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

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

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

Packaging type: blister package with desiccant in aluminum pouch

Storage condition: room temperature (between 59°F to 86°F /15°C to 30°C)

Stability: TAS-102 tablets (15 mg and 20 mg) are stable at 25°C 60% relative humidity (RH) for 36 months and 40°C 75%RH for 6 months in blister packaging with desiccant in aluminum pouch.

9.1.3 Drug Supply

Drug for this protocol will be supplied by the manufacturer, Taiho Oncology.

9.1.4 Storage, Handling and Dispensing

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). TAS-102 is a cytotoxic drug. Follow applicable special handling and disposal procedures. If stored outside of original bottle, discard after 30 days.

9.1.5 Drug Ordering and Accountability

9.1.6 Contraindications

There are no known specific contraindications to receiving TAS-102, until or unless the subject displays intolerable toxicities upon initiation of therapy.

9.1.7 Special Warnings and Precautions for Use

Severe Myelosuppression TAS-102 has been associated with severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%), including a low fatality rate (0.2%) due to neutropenic infection. It has been recommended to obtain complete blood counts prior to and on Day 15 of each cycle of TAS-102 and more frequently as clinically indicated.

Embryo-Fetal Toxicity Based on animal studies and its mechanism of action, TAS-102 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/m2 twice daily. While the FDA-approved label advises that pregnant women be told of the potential risk to the fetus, such patients will be ineligible for participation in this protocol.

9.1.8 Interactions with Other Medications

No pharmacokinetic drug-drug interaction studies have been conducted with TAS-102.

9.1.9 Adverse Event Profile

Derived from the TAS-102 Investigator's Brochure, October 14, 2015

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Any Adverse Events	448(69.3)	635(98.3)	146(45.3)	299(92.9)
Blood and Lymphatic System Disorders	195(30.2)	311(48.1)	11 (3.4)	29 (9.0)
Anaemia	88(13.6)	216(33.4)	7 (2.2)	22 (6.8)
Disseminated Intravascular Coagulation	1 (0.2)	2 (0.3)	0	0
Erythropenia	0	1 (0.2)	0	0
Febrile Neutropenia	25 (3.9)	25 (3.9)	0	0
Granulocytopenia	1 (0.2)	1 (0.2)	0	0
Iron Deficiency Anaemia	1 (0.2)	1 (0.2)	0	0
Leukocytosis	0	0	1 (0.3)	2 (0.6)
Leukopenia	13 (2.0)	29 (4.5)	0	0
Lymphadenopathy	0	0	0	2 (0.6)
Lymphopenia	3 (0.5)	6 (0.9)	2 (0.6)	2 (0.6)
Monocytopenia	0	1 (0.2)	0	0
Monocytosis	0	1 (0.2)	0	0
Neutropenia	107(16.6)	156(24.1)	0	0
Neutrophilia	0	0	0	1 (0.3)
Pancytopenia	1 (0.2)	1 (0.2)	0	0
Splenomegaly	0	1 (0.2)	0	0
Thrombocytopenia	11 (1.7)	37 (5.7)	1 (0.3)	1 (0.3)
Cardiac Disorders	5 (0.8)	26 (4.0)	3 (0.9)	12 (3.7)
Acute Myocardial Infarction	2 (0.3)	2 (0.3)	0	0
Angina Pectoris	0	1 (0.2)	0	0
Arrhythmia	0	0	0	1 (0.3)
Atrial Fibrillation	0	3 (0.5)	0	1 (0.3)
Atrial Flutter	0	1 (0.2)	0	0
Atrioventricular Block	0	1 (0.2)	0	0
Bradycardia	0	1 (0.2)	0	0
Bundle Branch Block Right	0	2 (0.3)	0	0
Cardiac Tamponade	0	0	1 (0.3)	1 (0.3)
Cardio-Respiratory Arrest	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Conduction Disorder	0	1 (0.2)	0	0
Myocardial Ischaemia	0	0	1 (0.3)	1 (0.3)
Palpitations	0	4 (0.6)	0	2 (0.6)
Pericardial Effusion	1 (0.2)	2 (0.3)	0	0
Sinus Bradycardia	1 (0.2)	2 (0.3)	0	0
Sinus Tachycardia	0	5 (0.8)	0	3 (0.9)
Tachycardia	0	2 (0.3)	0	4 (1.2)
Ventricular Arrhythmia	0	1 (0.2)	0	2 (0.6)
Congenital, Familial and Genetic Disorders	0	0	0	1 (0.3)
Hydrocele	0	0	0	1 (0.3)
Ear and Labyrinth Disorders	0	12 (1.9)	0	1 (0.3)
Ear Pain	0	2 (0.3)	0	0
Hearing Impaired	0	0	0	1 (0.3)
Hypoacusis	0	2 (0.3)	0	0
Tinnitus	0	2 (0.3)	0	0
Vertigo	0	6 (0.9)	0	1 (0.3)
Endocrine Disorders	0	0	0	1 (0.3)
Cushingoid	0	0	0	1 (0.3)
Eye Disorders	3 (0.5)	25 (3.9)	0	7 (2.2)
Cataract	2 (0.3)	4 (0.6)	0	0
Conjunctival Haemorrhage	0	0	0	1 (0.3)
Conjunctivitis	0	6 (0.9)	0	0
Diabetic Retinal Oedema	0	1 (0.2)	0	0
Diplopia	0	1 (0.2)	0	0
Dry Eye	0	1 (0.2)	0	0
Eye Pain	0	0	0	1 (0.3)
Eye Pruritus	0	1 (0.2)	0	0
Eyelid Bleeding	0	0	0	1 (0.3)
Eyelid Oedema	0	1 (0.2)	0	0
Glaucoma	0	1 (0.2)	0	0
Lacrimation Increased	0	2 (0.3)	0	0
Ocular Icterus	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Ocular Surface Disease	0	3 (0.5)	0	0
Photophobia	0	1 (0.2)	0	0
Photopsia	0	0	0	1 (0.3)
Uveitis	0	1 (0.2)	0	0
Vision Blurred	1 (0.2)	3 (0.5)	0	3 (0.9)
Visual Acuity Reduced	0	1 (0.2)	0	0
Visual Impairment	0	1 (0.2)	0	0
Vitreous Floaters	0	0	0	1 (0.3)
Gastrointestinal Disorders	83(12.8)	502(77.7)	37(11.5)	195(60.6)
Abdominal Discomfort	0	2 (0.3)	0	2 (0.6)
Abdominal Distension	2 (0.3)	25 (3.9)	2 (0.6)	19 (5.9)
Abdominal Hernia	0	1 (0.2)	0	1 (0.3)
Abdominal Pain	12 (1.9)	101(15.6)	10 (3.1)	46(14.3)
Abdominal Pain Lower	1 (0.2)	4 (0.6)	0	2 (0.6)
Abdominal Pain Upper	1 (0.2)	40 (6.2)	1 (0.3)	12 (3.7)
Abdominal Rigidity	0	0	0	1 (0.3)
Abdominal Tenderness	0	2 (0.3)	0	0
Abnormal Faeces	0	2 (0.3)	0	0
Anal Fistula	1 (0.2)	3 (0.5)	0	0
Anal Inflammation	0	1 (0.2)	0	1 (0.3)
Aphthous Stomatitis	0	1 (0.2)	0	1 (0.3)
Ascites	6 (0.9)	22 (3.4)	8 (2.5)	14 (4.3)
Breath Odour	0	1 (0.2)	0	0
Buccal Polyp	0	1 (0.2)	0	0
Cheilitis	0	5 (0.8)	0	1 (0.3)
Colitis	1 (0.2)	2 (0.3)	0	0
Constipation	1 (0.2)	92(14.2)	3 (0.9)	44(13.7)
Dental Caries	0	1 (0.2)	0	0
Diarrhoea	23 (3.6)	213(33.0)	1 (0.3)	45(14.0)
Dry Mouth	0	11 (1.7)	0	4 (1.2)
Dyspepsia	0	18 (2.8)	0	2 (0.6)
Dysphagia	1 (0.2)	3 (0.5)	1 (0.3)	3 (0.9)
Enterocolitis Haemorrhagic	0	1 (0.2)	0	0
Faecal Incontinence	0	1 (0.2)	0	1 (0.3)
Flatulence	0	6 (0.9)	0	3 (0.9)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Gastric Ulcer	0	1 (0.2)	0	0
Gastritis	0	6 (0.9)	0	0
Gastrointestinal Disorder	0	0	0	1 (0.3)
Gastrointestinal Haemorrhage	0	0	1 (0.3)	2 (0.6)
Gastrointestinal Pain	0	1 (0.2)	0	0
Gastrointestinal Sounds Abnormal	0	0	0	1 (0.3)
Gastrooesophageal Reflux Disease	0	7 (1.1)	0	1 (0.3)
Gingival Bleeding	0	2 (0.3)	0	0
Gingival Pain	0	1 (0.2)	0	1 (0.3)
Glossitis	0	2 (0.3)	0	0
Haematemesis	0	1 (0.2)	2 (0.6)	2 (0.6)
Haematochezia	0	5 (0.8)	0	1 (0.3)
Haemorrhoids	0	3 (0.5)	1 (0.3)	3 (0.9)
Hiatus Hernia	0	1 (0.2)	0	0
Ileus	6 (0.9)	6 (0.9)	4 (1.2)	5 (1.6)
Ileus Paralytic	2 (0.3)	2 (0.3)	0	0
Impaired Gastric Emptying	0	2 (0.3)	0	0
Intestinal Obstruction	2 (0.3)	3 (0.5)	1 (0.3)	1 (0.3)
Intestinal Perforation	0	1 (0.2)	1 (0.3)	1 (0.3)
Large Intestinal Obstruction	3 (0.5)	3 (0.5)	1 (0.3)	1 (0.3)
Lip Pain	0	1 (0.2)	0	0
Lower Gastrointestinal Haemorrhage	0	2 (0.3)	0	2 (0.6)
Mechanical Ileus	2 (0.3)	2 (0.3)	0	0
Mouth Ulceration	1 (0.2)	1 (0.2)	0	0
Nausea	15 (2.3)	331(51.2)	3 (0.9)	79(24.5)
Oesophageal Ulcer	0	0	1 (0.3)	1 (0.3)
Oesophagitis	0	4 (0.6)	0	0
Oral Dysaesthesia	0	0	0	1 (0.3)
Pancreatitis Acute	0	1 (0.2)	0	0
Perianal Erythema	0	1 (0.2)	1 (0.3)	1 (0.3)
Periodontal Disease	0	4 (0.6)	0	1 (0.3)
Peritoneal Haemorrhage	2 (0.3)	2 (0.3)	0	0
Proctalgia	1 (0.2)	5 (0.8)	0	0
Rectal Haemorrhage	0	7 (1.1)	1 (0.3)	1 (0.3)
Rectal Perforation	1 (0.2)	1 (0.2)	0	0
Rectal Stenosis	0	0	0	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Rectal Tenesmus	0	2 (0.3)	0	0
Rectal Ulcer	0	1 (0.2)	0	0
Reflux Gastritis	0	1 (0.2)	0	0
Retching	0	1 (0.2)	0	0
Sigmoiditis	1 (0.2)	1 (0.2)	0	0
Small Intestinal Obstruction	6 (0.9)	7 (1.1)	1 (0.3)	2 (0.6)
Stomatitis	2 (0.3)	59 (9.1)	0	22 (6.8)
Subileus	1 (0.2)	3 (0.5)	1 (0.3)	1 (0.3)
Tooth Disorder	0	1 (0.2)	0	1 (0.3)
Toothache	0	1 (0.2)	0	3 (0.9)
Upper Gastrointestinal Haemorrhage	0	0	1 (0.3)	1 (0.3)
Varices Oesophageal	0	0	1 (0.3)	1 (0.3)
Vomiting	15 (2.3)	186(28.8)	1 (0.3)	52(16.1)
General Disorders and Administration Site Conditions	77(11.9)	457(70.7)	38(11.8)	168(52.2)
Asthenia	18 (2.8)	97(15.0)	8 (2.5)	30 (9.3)
Axillary Pain	0	0	0	1 (0.3)
Chest Discomfort	0	1 (0.2)	0	0
Chest Pain	0	13 (2.0)	0	3 (0.9)
Chills	0	10 (1.5)	0	7 (2.2)
Cyst	0	1 (0.2)	0	0
Device Occlusion	0	0	0	1 (0.3)
Disease Progression	1 (0.2)	1 (0.2)	0	0
Face Oedema	0	3 (0.5)	0	1 (0.3)
Fatigue	25 (3.9)	246(38.1)	16 (5.0)	82(25.5)
Feeling of Body Temperature Change	0	1 (0.2)	0	0
Gait Disturbance	0	1 (0.2)	0	0
General Physical Health Deterioration	18 (2.8)	21 (3.3)	12 (3.7)	15 (4.7)
Hernia Pain	0	1 (0.2)	0	0
Hyperpyrexia	1 (0.2)	1 (0.2)	0	1 (0.3)
Hypothermia	0	1 (0.2)	0	0
Inflammation	0	2 (0.3)	0	0
Influenza Like Illness	0	26 (4.0)	0	2 (0.6)
Injection Site Extravasation	0	1 (0.2)	0	0
Localised Oedema	0	4 (0.6)	0	3 (0.9)
Malaise	4 (0.6)	34 (5.3)	1 (0.3)	10 (3.1)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Medical Device Discomfort	0	1 (0.2)	0	0
Mucosal Inflammation	2 (0.3)	30 (4.6)	0	12 (3.7)
Multi-Organ Failure	1 (0.2)	1 (0.2)	0	0
Non-Cardiac Chest Pain	0	2 (0.3)	0	0
Obstruction	0	0	1 (0.3)	1 (0.3)
Oedema	1 (0.2)	5 (0.8)	0	3 (0.9)
Oedema Peripheral	2 (0.3)	67(10.4)	3 (0.9)	31 (9.6)
Pain	4 (0.6)	11 (1.7)	0	3 (0.9)
Performance Status Decreased	0	0	1 (0.3)	1 (0.3)
Pyrexia	6 (0.9)	114(17.6)	2 (0.6)	44(13.7)
Spinal Pain	0	1 (0.2)	0	0
Tenderness	0	1 (0.2)	0	0
Thrombosis in Device	0	1 (0.2)	0	0
Xerosis	0	1 (0.2)	0	0
Hepatobiliary Disorders	36 (5.6)	58 (9.0)	18 (5.6)	28 (8.7)
Bile Duct Obstruction	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Bile Duct Stenosis	2 (0.3)	3 (0.5)	0	1 (0.3)
Biliary Dilatation	2 (0.3)	2 (0.3)	0	0
Cholangitis	2 (0.3)	7 (1.1)	1 (0.3)	1 (0.3)
Cholangitis Acute	1 (0.2)	1 (0.2)	0	0
Cholecystitis	1 (0.2)	1 (0.2)	0	0
Cholelithiasis	0	0	0	1 (0.3)
Cholestasis	1 (0.2)	1 (0.2)	0	0
Deficiency of Bile Secretion	0	2 (0.3)	0	0
Gallbladder Enlargement	0	1 (0.2)	0	0
Hepatic Failure	3 (0.5)	3 (0.5)	8 (2.5)	8 (2.5)
Hepatic Function Abnormal	1 (0.2)	1 (0.2)	0	1 (0.3)
Hepatic Pain	0	2 (0.3)	2 (0.6)	3 (0.9)
Hepatomegaly	2 (0.3)	4 (0.6)	0	2 (0.6)
Hepatotoxicity	1 (0.2)	1 (0.2)	0	0
Hyperbilirubinaemia	11 (1.7)	20 (3.1)	4 (1.2)	7 (2.2)
Jaundice	4 (0.6)	6 (0.9)	2 (0.6)	5 (1.6)
Jaundice Cholestatic	5 (0.8)	5 (0.8)	1 (0.3)	2 (0.6)
Liver Disorder	1 (0.2)	2 (0.3)	0	0
Portal Hypertension	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Portal Vein Thrombosis	0	1 (0.2)	0	1 (0.3)
Immune System Disorders	0	2 (0.3)	2 (0.6)	2 (0.6)
Allergy to Arthropod Sting	0	1 (0.2)	0	0
Anaphylactic Reaction	0	0	1 (0.3)	1 (0.3)
Anaphylactic Shock	0	0	1 (0.3)	1 (0.3)
Hypersensitivity	0	1 (0.2)	0	0
Infections and Infestations	43 (6.7)	171(26.5)	15 (4.7)	49(15.2)
Abdominal Infection	0	1 (0.2)	0	0
Adenoviral Upper Respiratory Infection	0	1 (0.2)	0	0
Alpha Haemolytic Streptococcal Infection	0	0	0	1 (0.3)
Anal Infection	0	1 (0.2)	0	0
Anorectal Infection	0	1 (0.2)	0	0
Bacteraemia	2 (0.3)	2 (0.3)	1 (0.3)	1 (0.3)
Bacterial Infection	0	0	1 (0.3)	1 (0.3)
Bacteriuria	0	1 (0.2)	0	0
Biliary Tract Infection	5 (0.8)	10 (1.5)	2 (0.6)	3 (0.9)
Bronchitis	1 (0.2)	8 (1.2)	0	2 (0.6)
Bronchopneumonia	0	1 (0.2)	1 (0.3)	1 (0.3)
Candidiasis	0	1 (0.2)	0	1 (0.3)
Catheter Site Infection	1 (0.2)	1 (0.2)	0	0
Cellulitis	1 (0.2)	2 (0.3)	0	0
Clostridium Difficile Infection	0	1 (0.2)	0	0
Cystitis	0	6 (0.9)	0	0
Device Related Infection	1 (0.2)	4 (0.6)	2 (0.6)	2 (0.6)
Ear Infection	1 (0.2)	2 (0.3)	0	0
Enteritis Infectious	1 (0.2)	1 (0.2)	0	0
Enterocolitis Infectious	0	0	0	1 (0.3)
Escherichia Urinary Tract Infection	1 (0.2)	1 (0.2)	0	0
Eye Infection	1 (0.2)	1 (0.2)	0	0
Folliculitis	0	1 (0.2)	0	1 (0.3)
Fungal Infection	0	2 (0.3)	0	0
Gastroenteritis	0	2 (0.3)	0	0
Gingival Infection	0	2 (0.3)	0	0
Gingivitis	0	1 (0.2)	0	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Haemophilus Infection	1 (0.2)	1 (0.2)	0	0
Hepatic Infection	0	1 (0.2)	0	1 (0.3)
Herpes Zoster	1 (0.2)	9 (1.4)	0	0
Hordeolum	0	1 (0.2)	0	1 (0.3)
Infection	2 (0.3)	7 (1.1)	1 (0.3)	3 (0.9)
Influenza	0	4 (0.6)	0	0
Keratitis Herpetic	0	1 (0.2)	0	0
Kidney Infection	0	0	1 (0.3)	1 (0.3)
Laryngitis	0	1 (0.2)	0	0
Liver Abscess	1 (0.2)	1 (0.2)	0	0
Lower Respiratory Tract Infection	2 (0.3)	5 (0.8)	0	0
Lung Infection	1 (0.2)	2 (0.3)	1 (0.3)	1 (0.3)
Nail Infection	0	1 (0.2)	0	1 (0.3)
Nasopharyngitis	0	23 (3.6)	0	4 (1.2)
Oesophageal Candidiasis	0	1 (0.2)	0	0
Oral Candidiasis	0	3 (0.5)	0	0
Oral Fungal Infection	0	1 (0.2)	0	1 (0.3)
Oral Herpes	0	3 (0.5)	0	2 (0.6)
Paronychia	0	2 (0.3)	0	1 (0.3)
Pelvic Infection	2 (0.3)	2 (0.3)	0	0
Periodontitis	0	0	0	1 (0.3)
Peritonitis Bacterial	1 (0.2)	1 (0.2)	0	0
Pharyngitis	1 (0.2)	4 (0.6)	0	0
Pneumonia	7 (1.1)	9 (1.4)	1 (0.3)	4 (1.2)
Pneumonia Klebsiella	1 (0.2)	1 (0.2)	0	0
Pneumonia Staphylococcal	2 (0.3)	2 (0.3)	0	0
Purulent Discharge	0	1 (0.2)	0	0
Pyelonephritis	1 (0.2)	1 (0.2)	0	0
Respiratory Tract Infection	0	1 (0.2)	0	1 (0.3)
Rhinitis	0	1 (0.2)	0	1 (0.3)
Scrotal Infection	0	1 (0.2)	0	0
Sepsis	3 (0.5)	3 (0.5)	0	0
Septic Shock	2 (0.3)	2 (0.3)	0	0
Sinusitis	0	4 (0.6)	0	0
Skin Infection	0	1 (0.2)	0	1 (0.3)
Soft Tissue Infection	0	0	0	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Staphylococcal Infection	0	0	0	1 (0.3)
Streptococcal Bacteraemia	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Subcutaneous Abscess	0	1 (0.2)	0	0
Tinea Pedis	0	1 (0.2)	0	0
Tooth Abscess	0	1 (0.2)	0	1 (0.3)
Tooth Infection	0	0	0	1 (0.3)
Trichophytosis	0	1 (0.2)	0	0
Upper Respiratory Tract Infection	0	21 (3.3)	0	4 (1.2)
Urinary Tract Infection	4 (0.6)	19 (2.9)	3 (0.9)	6 (1.9)
Vaginal Infection	0	0	0	1 (0.3)
Viral Upper Respiratory Tract Infection	0	1 (0.2)	0	0
Vulvovaginal Candidiasis	0	0	0	1 (0.3)
Vulvovaginal Mycotic Infection	0	1 (0.2)	0	0
Injury, Poisoning and Procedural Complications	3 (0.5)	30 (4.6)	1 (0.3)	8 (2.5)
Animal Bite	0	1 (0.2)	0	0
Burn Oesophageal	0	1 (0.2)	0	0
Compression Fracture	0	0	0	1 (0.3)
Contrast Media Reaction	0	1 (0.2)	0	0
Contusion	0	7 (1.1)	0	0
Extradural Haematoma	1 (0.2)	1 (0.2)	0	0
Fall	0	6 (0.9)	0	0
Femoral Neck Fracture	1 (0.2)	1 (0.2)	0	0
Foot Fracture	0	0	0	1 (0.3)
Fracture	1 (0.2)	1 (0.2)	0	0
Injury	0	1 (0.2)	0	0
Laceration	0	0	0	1 (0.3)
Medication Error	0	6 (0.9)	0	0
Overdose	0	4 (0.6)	0	0
Post Procedural Haemorrhage	0	1 (0.2)	0	0
Procedural Pain	0	1 (0.2)	1 (0.3)	2 (0.6)
Procedural Site Reaction	0	1 (0.2)	0	0
Radiation Skin Injury	0	0	0	1 (0.3)
Spinal Fracture	0	1 (0.2)	0	0
Sunburn	0	0	0	1 (0.3)
Thoracic Vertebral Fracture	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Tracheal Haemorrhage	0	0	0	1 (0.3)
Tracheal Obstruction	0	1 (0.2)	0	0
Wound	0	3 (0.5)	0	0
Wrist Fracture	0	1 (0.2)	0	0
Investigations	216(33.4)	399(61.8)	44(13.7)	132(41.0)
Activated Partial Thromboplastin Time Prolonged	0	1 (0.2)	0	0
Alanine Aminotransferase Increased	3 (0.5)	35 (5.4)	3 (0.9)	21 (6.5)
Aspartate Aminotransferase Decreased	0	1 (0.2)	0	0
Aspartate Aminotransferase Increased	9 (1.4)	53 (8.2)	8 (2.5)	34(10.6)
Bilirubin Conjugated Increased	5 (0.8)	6 (0.9)	0	1 (0.3)
Blood Albumin Decreased	1 (0.2)	31 (4.8)	2 (0.6)	12 (3.7)
Blood Alkaline Phosphatase Increased	21 (3.3)	64 (9.9)	14 (4.3)	41(12.7)
Blood Bilirubin Increased	24 (3.7)	78(12.1)	11 (3.4)	27 (8.4)
Blood Calcium Decreased	2 (0.3)	10 (1.5)	0	4 (1.2)
Blood Chloride Decreased	0	0	0	1 (0.3)
Blood Cholinesterase Decreased	0	1 (0.2)	1 (0.3)	1 (0.3)
Blood Creatine Increased	0	1 (0.2)	0	0
Blood Creatine Phosphokinase Increased	0	2 (0.3)	0	0
Blood Creatinine Increased	1 (0.2)	23 (3.6)	2 (0.6)	12 (3.7)
Blood Fibrinogen Increased	0	2 (0.3)	0	0
Blood Glucose Decreased	0	1 (0.2)	0	0
Blood Glucose Increased	1 (0.2)	2 (0.3)	0	0
Blood Lactate Dehydrogenase Increased	2 (0.3)	24 (3.7)	3 (0.9)	19 (5.9)
Blood Phosphorus	1 (0.2)	1 (0.2)	0	0
Blood Potassium Decreased	1 (0.2)	8 (1.2)	1 (0.3)	2 (0.6)
Blood Potassium Increased	1 (0.2)	8 (1.2)	1 (0.3)	2 (0.6)
Blood Sodium Decreased	2 (0.3)	16 (2.5)	2 (0.6)	5 (1.6)
Blood Urea	0	1 (0.2)	0	0
Blood Urea Decreased	0	1 (0.2)	0	0
Blood Urea Increased	0	6 (0.9)	0	3 (0.9)
Blood Uric Acid Increased	1 (0.2)	2 (0.3)	0	0
Blood Urine Present	0	3 (0.5)	0	1 (0.3)
C-Reactive Protein Increased	2 (0.3)	17 (2.6)	2 (0.6)	5 (1.6)
Carbohydrate Antigen 19-9 Increased	0	1 (0.2)	0	0
Carcinoembryonic Antigen Increased	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Eastern Cooperative Oncology Group Performance Status Worsened	0	0	1 (0.3)	1 (0.3)
Electrocardiogram QT Prolonged	0	1 (0.2)	0	0
Eosinophil Count Decreased	0	1 (0.2)	0	1 (0.3)
Eosinophil Count Increased	0	0	0	1 (0.3)
Gamma-Glutamyltransferase Increased	20 (3.1)	29 (4.5)	10 (3.1)	14 (4.3)
Glucose Urine Present	0	3 (0.5)	0	0
Haematocrit	0	1 (0.2)	0	0
Haematocrit Decreased	0	37 (5.7)	0	4 (1.2)
Haemoglobin Decreased	21 (3.3)	85(13.2)	3 (0.9)	9 (2.8)
Hepatic Enzyme Increased	0	0	1 (0.3)	1 (0.3)
International Normalised Ratio Increased	2 (0.3)	5 (0.8)	1 (0.3)	1 (0.3)
Lymphocyte Count Decreased	21 (3.3)	63 (9.8)	5 (1.6)	12 (3.7)
Lymphocyte Count Increased	1 (0.2)	1 (0.2)	0	0
Monocyte Count Decreased	0	2 (0.3)	0	0
Monocyte Count Increased	0	9 (1.4)	0	0
Monocyte Percentage Increased	0	1 (0.2)	0	0
Neutrophil Count Decreased	142(22.0)	229(35.4)	0	2 (0.6)
Neutrophil Count Increased	0	6 (0.9)	0	5 (1.6)
Palpatory Finding Abnormal	0	1 (0.2)	0	0
Platelet Count Decreased	18 (2.8)	125(19.3)	0	7 (2.2)
Platelet Count Increased	0	1 (0.2)	0	1 (0.3)
Protein Total Decreased	0	4 (0.6)	0	0
Protein Urine Present	0	20 (3.1)	0	6 (1.9)
Qrs Axis Abnormal	0	1 (0.2)	0	0
Red Blood Cell Count Decreased	0	39 (6.0)	0	2 (0.6)
Serum Ferritin Increased	0	1 (0.2)	0	0
Tandem Gait Test Abnormal	0	1 (0.2)	0	0
Transaminases Increased	0	0	0	1 (0.3)
Troponin Increased	0	1 (0.2)	0	0
Urine Analysis	0	1 (0.2)	0	0
Urine Output Decreased	0	1 (0.2)	0	0
Urobilinogen Urine Increased	0	4 (0.6)	0	1 (0.3)
Weight Decreased	1 (0.2)	64 (9.9)	0	28 (8.7)
Weight Increased	0	7 (1.1)	0	4 (1.2)
White Blood Cell Count Decreased	87(13.5)	232(35.9)	0	3 (0.9)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
White Blood Cell Count Increased	1 (0.2)	7 (1.1)	0	8 (2.5)
White Blood Cells Urine Positive	0	1 (0.2)	0	1 (0.3)
Metabolism and Nutrition Disorders	59 (9.1)	319(49.4)	29 (9.0)	123(38.2)
Acidosis	0	0	1 (0.3)	1 (0.3)
Cachexia	0	1 (0.2)	1 (0.3)	2 (0.6)
Decreased Appetite	24 (3.7)	278(43.0)	15 (4.7)	97(30.1)
Dehydration	3 (0.5)	16 (2.5)	3 (0.9)	10 (3.1)
Diabetes Mellitus	1 (0.2)	3 (0.5)	1 (0.3)	1 (0.3)
Failure to Thrive	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Glucose Tolerance Impaired	1 (0.2)	1 (0.2)	0	0
Gout	0	2 (0.3)	0	0
Hypercalcaemia	0	1 (0.2)	1 (0.3)	1 (0.3)
Hyperglycaemia	8 (1.2)	17 (2.6)	0	9 (2.8)
Hyperkalaemia	1 (0.2)	8 (1.2)	2 (0.6)	8 (2.5)
Hypermagnesaemia	0	0	0	1 (0.3)
Hypernatraemia	0	1 (0.2)	0	0
Hypertriglyceridaemia	0	0	1 (0.3)	1 (0.3)
Hyperuricaemia	0	2 (0.3)	0	1 (0.3)
Hypoalbuminaemia	4 (0.6)	24 (3.7)	2 (0.6)	10 (3.1)
Hypocalcaemia	1 (0.2)	9 (1.4)	0	3 (0.9)
Hypochloraemia	0	0	0	1 (0.3)
Hypocholesterolaemia	0	1 (0.2)	0	0
Hypoglycaemia	0	1 (0.2)	0	0
Hypokalaemia	12 (1.9)	20 (3.1)	2 (0.6)	5 (1.6)
Hypomagnesaemia	0	4 (0.6)	0	0
Hyponatraemia	7 (1.1)	16 (2.5)	4 (1.2)	14 (4.3)
Hypophosphataemia	4 (0.6)	4 (0.6)	1 (0.3)	1 (0.3)
Hyposideraemia	0	1 (0.2)	0	0
Malnutrition	0	2 (0.3)	0	0
Musculoskeletal and Connective Tissue Disorders	16 (2.5)	150(23.2)	8 (2.5)	64(19.9)
Arthralgia	2 (0.3)	30 (4.6)	0	10 (3.1)
Arthritis	0	1 (0.2)	0	0
Back Pain	9 (1.4)	52 (8.0)	2 (0.6)	21 (6.5)
Bone Pain	2 (0.3)	5 (0.8)	1 (0.3)	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Fasciitis	0	1 (0.2)	0	0
Flank Pain	0	3 (0.5)	1 (0.3)	2 (0.6)
Groin Pain	2 (0.3)	4 (0.6)	0	0
Intervertebral Disc Degeneration	0	1 (0.2)	0	0
Intervertebral Disc Protrusion	0	1 (0.2)	0	0
Joint Swelling	0	2 (0.3)	0	1 (0.3)
Muscle Atrophy	0	0	0	1 (0.3)
Muscle Spasms	0	7 (1.1)	0	3 (0.9)
Muscular Weakness	1 (0.2)	5 (0.8)	0	0
Musculoskeletal Chest Pain	0	6 (0.9)	0	5 (1.6)
Musculoskeletal Discomfort	0	2 (0.3)	0	0
Musculoskeletal Disorder	0	2 (0.3)	0	0
Musculoskeletal Pain	1 (0.2)	20 (3.1)	1 (0.3)	8 (2.5)
Musculoskeletal Stiffness	0	0	0	1 (0.3)
Myalgia	0	16 (2.5)	0	9 (2.8)
Myopathy	0	1 (0.2)	0	0
Neck Pain	0	7 (1.1)	0	2 (0.6)
Osteoarthritis	0	1 (0.2)	0	0
Osteosclerosis	0	1 (0.2)	0	0
Pain in Extremity	1 (0.2)	20 (3.1)	3 (0.9)	8 (2.5)
Pain in Jaw	0	1 (0.2)	0	0
Rotator Cuff Syndrome	0	1 (0.2)	0	0
Scoliosis	0	1 (0.2)	0	0
Sensation of Heaviness	0	1 (0.2)	0	1 (0.3)
Spinal Osteoarthritis	0	1 (0.2)	0	0
Tendon Pain	0	1 (0.2)	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	8 (1.2)	51 (7.9)	9 (2.8)	35(10.9)
Adenocarcinoma	1 (0.2)	1 (0.2)	0	0
Cancer Pain	2 (0.3)	12 (1.9)	1 (0.3)	4 (1.2)
Lymphangiosis Carcinomatosa	0	0	1 (0.3)	2 (0.6)
Malignant Ascites	0	0	1 (0.3)	1 (0.3)
Malignant Pleural Effusion	0	0	0	1 (0.3)
Metastases to Central Nervous System	0	0	1 (0.3)	1 (0.3)
Metastases to Liver	0	0	0	1 (0.3)
Metastases to Peritoneum	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Metastasis	0	0	0	1 (0.3)
Skin Papilloma	0	1 (0.2)	0	0
Tumor Associated Fever	0	3 (0.5)	0	3 (0.9)
Tumor Haemorrhage	0	1 (0.2)	0	0
Tumor Necrosis	0	0	0	1 (0.3)
Tumor Pain	5 (0.8)	32 (5.0)	5 (1.6)	23 (7.1)
Urethral Cancer	0	0	0	1 (0.3)
Nervous System Disorders	13 (2.0)	140(21.7)	11 (3.4)	61(18.9)
Akathisia	0	2 (0.3)	0	0
Ataxia	0	1 (0.2)	0	0
Balance Disorder	0	0	0	1 (0.3)
Brain Compression	0	0	1 (0.3)	1 (0.3)
Brain Oedema	3 (0.5)	5 (0.8)	1 (0.3)	1 (0.3)
Burning Sensation	0	1 (0.2)	0	0
Cognitive Disorder	0	0	2 (0.6)	2 (0.6)
Coma	0	0	1 (0.3)	1 (0.3)
Convulsion	2 (0.3)	2 (0.3)	0	2 (0.6)
Depressed Level of Consciousness	0	1 (0.2)	0	0
Dizziness	0	21 (3.3)	0	9 (2.8)
Dysaesthesia	0	2 (0.3)	0	0
Dysarthria	0	0	0	1 (0.3)
Dysgeusia	0	42 (6.5)	0	9 (2.8)
Encephalopathy	1 (0.2)	1 (0.2)	0	0
Epiduritis	1 (0.2)	1 (0.2)	0	0
Haemorrhage Intracranial	0	0	1 (0.3)	2 (0.6)
Headache	0	39 (6.0)	0	15 (4.7)
Hemiparesis	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Hepatic Encephalopathy	0	0	1 (0.3)	1 (0.3)
Hyperaesthesia	0	1 (0.2)	0	0
Hypersomnia	0	1 (0.2)	0	0
Hypoaesthesia	0	1 (0.2)	0	0
Hypotonia	0	1 (0.2)	0	0
Lethargy	0	1 (0.2)	0	0
Loss of Consciousness	1 (0.2)	1 (0.2)	0	0
Monoparesis	0	0	1 (0.3)	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Monoplegia	0	0	1 (0.3)	1 (0.3)
Myoclonus	0	1 (0.2)	0	0
Nerve Root Compression	1 (0.2)	1 (0.2)	0	0
Neuralgia	0	1 (0.2)	0	1 (0.3)
Neurological Decompensation	0	0	1 (0.3)	1 (0.3)
Neuropathy Peripheral	0	3 (0.5)	0	2 (0.6)
Neurotoxicity	0	2 (0.3)	0	2 (0.6)
Paraesthesia	0	8 (1.2)	0	5 (1.6)
Parosmia	0	2 (0.3)	0	0
Partial Seizures	0	0	0	1 (0.3)
Peripheral Motor Neuropathy	1 (0.2)	3 (0.5)	0	1 (0.3)
Peripheral Sensory Neuropathy	1 (0.2)	15 (2.3)	0	9 (2.8)
Peroneal Nerve Palsy	0	0	0	1 (0.3)
Presyncope	0	1 (0.2)	0	0
Psychomotor Skills Impaired	0	0	1 (0.3)	1 (0.3)
Radiculitis	0	1 (0.2)	0	0
Restless Legs Syndrome	0	1 (0.2)	0	0
Sciatica	0	4 (0.6)	0	0
Somnolence	1 (0.2)	9 (1.4)	0	3 (0.9)
Speech Disorder	0	1 (0.2)	0	0
Spinal Cord Compression	1 (0.2)	1 (0.2)	0	0
Syncope	0	1 (0.2)	0	0
Tremor	0	1 (0.2)	0	0
Vasogenic Cerebral Oedema	0	0	0	1 (0.3)
Vocal Cord Paresis	0	1 (0.2)	0	0
Psychiatric Disorders	0	55 (8.5)	0	48(14.9)
Agitation	0	1 (0.2)	0	1 (0.3)
Anxiety	0	17 (2.6)	0	8 (2.5)
Claustrophobia	0	0	0	1 (0.3)
Confusional State	0	3 (0.5)	0	2 (0.6)
Delirium	0	1 (0.2)	0	1 (0.3)
Depression	0	5 (0.8)	0	5 (1.6)
Disorientation	0	1 (0.2)	0	0
Emotional Disorder	0	1 (0.2)	0	0
Feeling of Despair	0	1 (0.2)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Hallucination, Visual	0	1 (0.2)	0	0
Insomnia	0	28 (4.3)	0	30 (9.3)
Nightmare	0	1 (0.2)	0	0
Panic Attack	0	0	0	1 (0.3)
Restlessness	0	1 (0.2)	0	1 (0.3)
Sleep Disorder	0	1 (0.2)	0	0
Renal and Urinary Disorders	13 (2.0)	79(12.2)	10 (3.1)	34(10.6)
Atonic Urinary Bladder	0	0	0	1 (0.3)
Bilirubinuria	0	0	0	1 (0.3)
Chromaturia	0	2 (0.3)	0	2 (0.6)
Cystitis Noninfective	0	1 (0.2)	0	0
Dysuria	0	8 (1.2)	0	3 (0.9)
Glycosuria	0	1 (0.2)	0	0
Haematuria	1 (0.2)	12 (1.9)	3 (0.9)	6 (1.9)
Hydronephrosis	3 (0.5)	7 (1.1)	2 (0.6)	3 (0.9)
Hydroureter	0	1 (0.2)	0	0
Incontinence	0	1 (0.2)	0	1 (0.3)
Leukocyturia	0	2 (0.3)	0	0
Micturition Disorder	0	0	0	1 (0.3)
Micturition Urgency	0	2 (0.3)	0	0
Nephrolithiasis	1 (0.2)	1 (0.2)	0	0
Nephropathy	1 (0.2)	1 (0.2)	0	0
Nocturia	0	0	0	1 (0.3)
Pollakiuria	0	7 (1.1)	0	0
Polyuria	0	1 (0.2)	0	0
Postrenal Failure	1 (0.2)	1 (0.2)	0	0
Prerenal Failure	0	0	1 (0.3)	1 (0.3)
Proteinuria	0	22 (3.4)	0	5 (1.6)
Renal Colic	0	1 (0.2)	0	1 (0.3)
Renal Failure	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Renal Failure Acute	6 (0.9)	6 (0.9)	0	0
Renal Failure Chronic	0	1 (0.2)	0	1 (0.3)
Renal Impairment	0	1 (0.2)	1 (0.3)	1 (0.3)
Ureteric Haemorrhage	0	1 (0.2)	0	0
Ureteric Obstruction	0	0	1 (0.3)	2 (0.6)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Ureteric Stenosis	0	0	0	1 (0.3)
Urethral Pain	0	1 (0.2)	0	0
Urinary Bladder Haemorrhage	0	1 (0.2)	0	0
Urinary Incontinence	0	4 (0.6)	0	1 (0.3)
Urinary Retention	0	6 (0.9)	1 (0.3)	4 (1.2)
Urinary Tract Obstruction	2 (0.3)	4 (0.6)	1 (0.3)	1 (0.3)
Urinary Tract Pain	0	1 (0.2)	0	1 (0.3)
Reproductive System and Breast Disorders	1 (0.2)	12 (1.9)	1 (0.3)	5 (1.6)
Menstrual Disorder	0	1 (0.2)	0	0
Metrorrhagia	0	2 (0.3)	0	0
Oedema Genital	0	1 (0.2)	0	0
Pelvic Pain	1 (0.2)	4 (0.6)	1 (0.3)	1 (0.3)
Penis Disorder	0	0	0	1 (0.3)
Testicular Pain	0	0	0	1 (0.3)
Vaginal Haemorrhage	0	2 (0.3)	0	2 (0.6)
Vulvovaginal Dryness	0	1 (0.2)	0	0
Vulvovaginal Pain	0	1 (0.2)	0	0
Vulvovaginal Pruritus	0	1 (0.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders	33 (5.1)	169(26.2)	18 (5.6)	86(26.7)
Acute Respiratory Failure	0	0	1 (0.3)	1 (0.3)
Aspiration	0	1 (0.2)	0	0
Atelectasis	0	1 (0.2)	0	0
Bronchial Obstruction	0	1 (0.2)	0	0
Bronchospasm	0	0	0	1 (0.3)
Cough	2 (0.3)	63 (9.8)	2 (0.6)	33(10.2)
Dysphonia	0	10 (1.5)	0	6 (1.9)
Dyspnoea	16 (2.5)	63 (9.8)	10 (3.1)	34(10.6)
Dyspnoea Exertional	0	3 (0.5)	0	2 (0.6)
Emphysema	0	0	0	1 (0.3)
Epistaxis	0	13 (2.0)	0	6 (1.9)
Haemoptysis	1 (0.2)	4 (0.6)	0	0
Hiccups	0	3 (0.5)	0	0
Hypoventilation	0	0	0	1 (0.3)
Hypoxia	1 (0.2)	3 (0.5)	0	2 (0.6)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Interstitial Lung Disease	1 (0.2)	1 (0.2)	0	0
Lung Infiltration	0	0	0	1 (0.3)
Nasal Congestion	0	2 (0.3)	0	0
Obstructive Airways Disorder	0	1 (0.2)	0	0
Oropharyngeal Pain	0	8 (1.2)	0	5 (1.6)
Pharyngeal Inflammation	0	3 (0.5)	0	0
Pleural Effusion	3 (0.5)	9 (1.4)	3 (0.9)	8 (2.5)
Pleuritic Pain	0	0	1 (0.3)	1 (0.3)
Pneumonia Aspiration	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Pneumonitis	0	1 (0.2)	0	0
Productive Cough	0	6 (0.9)	0	2 (0.6)
Pulmonary Congestion	0	0	1 (0.3)	1 (0.3)
Pulmonary Embolism	9 (1.4)	9 (1.4)	0	0
Pulmonary Oedema	1 (0.2)	1 (0.2)	0	0
Rales	0	1 (0.2)	0	1 (0.3)
Respiratory Arrest	0	0	1 (0.3)	1 (0.3)
Respiratory Disorder	0	1 (0.2)	0	0
Rhinitis Allergic	0	3 (0.5)	0	0
Rhinorrhoea	0	4 (0.6)	0	0
Sinus Disorder	0	1 (0.2)	0	0
Sputum Increased	0	1 (0.2)	0	0
Upper Respiratory Tract Inflammation	0	1 (0.2)	0	0
Wheezing	0	4 (0.6)	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	2 (0.3)	149(23.1)	2 (0.6)	55(17.1)
Acne	0	1 (0.2)	0	0
Alopecia	0	38 (5.9)	0	3 (0.9)
Blister	0	1 (0.2)	0	0
Decubitus Ulcer	1 (0.2)	2 (0.3)	0	0
Dermatitis	0	1 (0.2)	0	0
Dermatitis Acneiform	0	2 (0.3)	0	1 (0.3)
Dry Skin	0	23 (3.6)	0	11 (3.4)
Ecchymosis	0	1 (0.2)	0	0
Eczema	0	2 (0.3)	0	0
Eczema Asteatotic	0	0	0	1 (0.3)

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Erythema	0	2 (0.3)	0	2 (0.6)
Erythema Multiforme	0	2 (0.3)	0	0
Exfoliative Rash	0	12 (1.9)	0	3 (0.9)
Hyperhidrosis	0	3 (0.5)	0	6 (1.9)
Hyperkeratosis	0	1 (0.2)	0	0
Milia	0	1 (0.2)	0	0
Nail Bed Inflammation	0	1 (0.2)	0	0
Nail Disorder	0	5 (0.8)	0	4 (1.2)
Nail Ridging	0	1 (0.2)	0	0
Night Sweats	0	3 (0.5)	0	1 (0.3)
Onychoclasis	0	2 (0.3)	0	0
Onychomadesis	0	0	0	1 (0.3)
Palmar-Plantar Erythrodysaesthesia Syndrome	0	13 (2.0)	0	6 (1.9)
Petechiae	0	2 (0.3)	0	0
Photosensitivity Reaction	0	1 (0.2)	0	1 (0.3)
Pruritus	0	28 (4.3)	1 (0.3)	15 (4.7)
Purpura	0	0	0	1 (0.3)
Rash	0	20 (3.1)	1 (0.3)	6 (1.9)
Rash Maculo-Papular	0	6 (0.9)	0	3 (0.9)
Seborrhoea	0	0	0	1 (0.3)
Skin Exfoliation	0	1 (0.2)	0	1 (0.3)
Skin Hyperpigmentation	0	0	0	1 (0.3)
Skin Ulcer	0	1 (0.2)	0	2 (0.6)
Urticaria	1 (0.2)	2 (0.3)	0	2 (0.6)
Surgical and Medical Procedures	0	1 (0.2)	0	0
Stoma Care	0	1 (0.2)	0	0
Vascular Disorders	11 (1.7)	57 (8.8)	15 (4.7)	29 (9.0)
Arteriosclerosis	0	1 (0.2)	0	0
Axillary Vein Thrombosis	0	0	0	1 (0.3)
Deep Vein Thrombosis	1 (0.2)	3 (0.5)	2 (0.6)	2 (0.6)
Embolism	0	1 (0.2)	2 (0.6)	2 (0.6)
Flushing	0	4 (0.6)	0	1 (0.3)
Haematoma	0	2 (0.3)	0	0

(Table continues)

MedDRA SOC Preferred Term	TAS-102 (N=646), n (%) CTC Grade >=3	 All Grades	Placebo (N=322), n (%) CTC Grade >=3	 All Grades
Hot Flush	0	7 (1.1)	0	4 (1.2)
Hyperaemia	0	0	0	1 (0.3)
Hypertension	8 (1.2)	22 (3.4)	10 (3.1)	18 (5.6)
Hypotension	2 (0.3)	7 (1.1)	0	1 (0.3)
Hypovolaemic Shock	0	0	1 (0.3)	1 (0.3)
Intra-Abdominal Haematoma	0	0	1 (0.3)	1 (0.3)
Jugular Vein Thrombosis	0	1 (0.2)	0	0
Orthostatic Hypotension	0	2 (0.3)	0	0
Pallor	0	2 (0.3)	0	0
Pelvic Venous Thrombosis	0	1 (0.2)	0	0
Peripheral Coldness	0	1 (0.2)	0	0
Periphlebitis	0	1 (0.2)	0	0
Superior Vena Cava Syndrome	0	1 (0.2)	0	0
Thrombosis	0	1 (0.2)	0	0
Venous Thrombosis Limb	0	1 (0.2)	0	0

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 (eg, 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, including those thought to be associated with protocol-specified procedures. 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 4.03. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

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.

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

Serious adverse events (SAE's) must be documented on a SAE Report Form must be emailed 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 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.

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; not to report SAEs.

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

10.4.2 Other Events Requiring Immediate Reporting

All pregnancies, regardless of outcome, must be reported to the UFHCC DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome.

Although overdose (dose variance of >25%) and cancer are not always serious by regulatory definition, these events should also be reported to the 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.

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

10.5 IND Safety Reports Unrelated to this Trial

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. STATISTICAL METHODS

11.1 Sample Size Determination

This is a pilot phase II study, so we are interested in evaluating the feasibility and safety of a regimen of daily TAS-102 administered to subjects with squamous cell lung cancer. To minimize the number of subjects exposed, the sample size will be determined by the anticipated response rate. A response rate of 20% or above to TAS-102 will be of interest in subjects with previously-treated squamous cell lung cancer. Initially, 14 subjects will be evaluated for response, and if none of the 14 evaluable subjects experiences a partial or complete response, then the study will be terminated. If the true response rate is 20%, the chance of rejection error is less than 5%. However, in the event of one response among the first 14 subjects, further accrual will continue to a total of 30 evaluable subjects to estimate the response rate more precisely with a standard error of no more than 9%. 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 also received two cycles of therapy as planned.

Based upon the numbers of subjects seen at the University of Florida Cancer Center clinics and our accrual to other similar studies, it is estimated that accrual to the first level (14 subjects) will be completed within nine months. If the study is fully accrued (30 subjects) and at least the last such subject derives benefit from the anticipated maximal number of six cycles, then the length of the entire study will be approximately 24 months.

11.2 Analysis of Endpoints/Efficacy

The primary endpoint to this study will be to document the objective rate of response by RECIST Criteria, version 1.1 of the participants in this trial which will be estimated along with exact 95% binomial confidence intervals.

The secondary endpoints of this study will be to determine the rate of development of toxicities, and the reversibility of toxicities of this regimen; the Objective Response Rate (by RECIST Criteria); the Clinical Benefit Rate (objective response + disease stability rate); the median duration of response in months, and the median Overall Survival.

A secondary endpoint of this study will be progression-free survival following TAS-102 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated. Secondary endpoints include clinical benefit rate (CR + PR + SD), toxicities and reversibility of toxicities) will also be estimated along with exact 95% binomial confidence intervals.

11.3 Analysis of Demographic and Baseline Characteristic

The analysis of demographic characteristics (age, gender, tobacco abuse history and ethnicity) and baseline characteristics, including weight change, performance status, and histologic subtype, will be primarily descriptive. 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 patient outcomes. These endpoints will be primarily descriptive in nature due to the small patient numbers; however, these results will be compared against historical US controls. Continuous variables will be compared to historical controls using either a two-sample t-test or Wilcoxon rank sum test depending on normality assumptions, and discrete outcomes will be compared using either Chi-square or Fisher's exact tests.

11.4 Analysis of Safety Data

Patients will be examined and graded each cycle for subjective/objective evidence of developing toxicity according to NCI-CTC version 4.03 toxicity criteria. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal, and incidence of serious adverse events. Patients will have laboratory values assessed weekly during the first cycle, and in the absence of grade 3 or 4 toxicity, will subsequently have laboratory monitoring every cycle from cycle 2 onward. In the absence of significant treatment-related abnormalities, in subsequent courses patients will not require weekly laboratory evaluation, but will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy. All patients experiencing toxicities

will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy.

All patients who received study drug will be included in the safety analysis of this combination regimen. 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 patients 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 patients 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 patient group and by dose levels. Dose-toxicity curves will be fitted to the final data to estimate the toxicity rates of each dose levels.

12. DATA AND SAFETY MONITORING

12.1 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) Data Integrity and Safety Committee (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

12.2 On-site 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 verification of agreement with data as submitted via the data collection system. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by 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.

12.3 Principal Investigator Responsibilities

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.

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.

13. EMERGENCY PROCEDURES

13.1 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.

13.2 Emergency Identification of Investigational Products

This is an unblinded, nonrandomized study. Thus, there will be no need for unmasking procedures, and the identification of the investigational product can be made by simple inquiry to the investigational pharmacy of UF Shands.

13.3 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.

14. ADMINISTRATIVE CONSIDERATIONS

14.1 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 UF Health Cancer Center Data Integrity and Safety Committee (DISC) immediately. 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.

14.2 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 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, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

14.3 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.

14.4 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. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

14.5 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 DISC, 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.

14.6 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol.

14.7 Case Report Forms

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.

14.8 Record Retention

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 patient 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.

15. 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 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.

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