A Phase II study of TAS 102 in Combination with Ramucirumab in Advanced, Refractory Gastric or Gastroesophageal Junction (GEJ) adenocarcinoma

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Protocol Synopsis

Title	**A Phase II study of TAS 102 in Combination with Ramucirumab in Advanced, Refractory Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma**
Clinical study phase	Phase II
Study Agents	TAS 102 PO Ramucirumab IV

Background	Gastric cancer is the second most lethal form of cancer worldwide. Patients with advanced gastric cancer experience a 5 year survival rate <10% even with multimodality therapy representing a clear unmet need for improved treatment. Tumor angiogenesis plays an essential role in cancer growth and metastasis, and therapies targeting tumor angiogenesis are used in a variety of malignancies. In advanced gastric and GEJ adenocarcinoma, ramucirumab (a monoclonal antibody against VEGFR2) has demonstrated clinical activity and has been approved as second line therapy. However, the clinical benefit and impact on tumor control is modest and transient with 8% of objective response rate and 2 months of progression free survival. The acquired tumor resistance to anti-angiogenic therapy has been well established and is hypothesized to occur through several mechanisms including the upregulation of proangiogenic factors. Dual anti-angiogenic therapy has thus been proposed as tumors can not only develop resistance to one anti-angiogenic pathway but can exhibit multiple angiogenic pathways at the outset. The efficacy of dual antiangiogenic blockade such as bevacizumab plus sorafenib, a vascular disrupting agent (OXi4503) plus bevacizumab and a PDGFR inhibitor (SU6668) plus a VEGFR2 inhibitor (semaxinib) has been confirmed in preclinical and clinical studies. TAS 102 is an oral cytotoxic agent with two active components; trifluridine which inhibits tumor cell growth by being incorporated into DNA during DNA synthesis and tipiracil which inhibits the metabolism of trifluridine, thereby prolonging its ability to exert effect. Tipiracil also inhibits platelet derived endothelial cell growth factor (PDEGF) which plays a key role with VEGF in tumor angiogenesis. The combination of a cytotoxic agent with an antiangiogenic agent has demonstrated a significant anticancer activity in multiple cancers by increasing drug accessibility secondary to normalization of the tumor vasculature and by enhanced direct cytotoxicity of cancer cells and endothelial cells. As there are known synergy of dual antiangiogenic therapy, and the combination of a cytotoxic agent with an antiangiogenic agent, the combination of TAS 102 with ramucirumab may potentially produce a synergistic tumor response by complete inhibition of tumor angiogenesis through the blockade of two major tumor angiogenic factors (VEGF and PDEGF) and by enhanced delivery of cytotoxic trifluridine to tumor through normalization of poorly organized, tortuous and hyperpermeable tumor vasculature. We hypothesize that a combination of TAS 102 and ramucirumab might increase efficacy without causing unmanageable toxicity.

Rationale	We hypothesize that the combination of ramucirumab and TAS102 will be a safe and effective in metastatic gastric and GEJ adenocarcinoma by dual angiogenic inhibition of PDEGF and VEGF and by classic cytotoxic activity of trifluridine.
Study objectives	*Primary Objective* To determine the 6 month overall survival in patients with advanced, refractory gastric or gastroesophageal junction (GEJ) adenocarcinoma receiving TAS 102 in combination with ramucirumab. *Secondary Objectives* 1. To determine the frequency and severity of adverse events and tolerability of TAS 102 plus ramucirumab in patients with advanced, refractory gastric or GEJ adenocarcinoma 2. To determine the objective response rate of TAS 102 in combination with ramucirumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 3. To determine the progression free survival in patients with advanced, refractory gastric or GEJ adenocarcinoma receiving TAS 102 in combination with ramucirumab. *Exploratory Objectives* 1. To evaluate potential correlations between blood biomarkers and clinical outcome using a multiplex assay evaluating circulating angiogenic biomarkers

Indication	Patients with advanced, refractory gastric or GEJ adenocarcinoma
Diagnosis and main criteria for inclusion	• Age ≥18 years of age. • Histologically confirmed diagnosis of gastric or GEJ adenocarcinoma • Measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Stage IV or recurrent disease is required. • Patients must have received at least 1 line of prior treatment for advanced/metastatic gastric or GEJ adenocarcinoma. • ECOG Performance Score 0 or 1 • Adequate bone marrow, liver and renal function as assessed by the following: o Hemoglobin > 8.0 g/dl o Absolute neutrophil count (ANC) > 1,000/mm3 independent of growth factor support o Platelet count > 100,000/mm3 o Total bilirubin < 1.5 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin o AST, ALT and Alkaline Phosphatase ≤2.5 times the ULN (≤5 x ULN for patients with liver involvement) o Creatinine clearance ≥ 30 ml/min
Study design	This is a single institutional phase II single arm two-stage design trial using the combination of TAS 102 and ramucirumab in advanced, refractory gastric or GEJ adenocarcinoma. Patients will enter daily use of study medication (TAS 102) in a medication diary for a measure of compliance (Appendix B)
Number of subjects	25
Plan for statistical analysis	Overall survival (OS) will be defined as the time from starting on trial to date of death due to any cause. The final analysis will be conducted after the follow-time of the last patient exceeds 6 months. OS at 6 months is the primary endpoint of the trial and will be estimated using the Kaplan-Meier method. The two-sided 95% confidence interval (CI) for median OS will be computed using log-log transformation. The sample size was determined based on the Simon's two-stage minimax design. With one-sided 10% of type I error rate and 90% power, a sample of evaluable 25 patients will be evaluated (P_0: 0.45, P_1: 0.7); 15 in first stage and additional 10 patients in second stage. If 7 or more out of 15 survive 6 months or more, the study goes on the second stage. The experimental treatment will be deemed to have good activity if ≥15 out of 25 patients survive 6 months or more. We will continue to recruit patients during interim analysis

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1. Introduction

1.1 Background

Gastric cancer is the third leading cause of global cancer related death worldwide with approximately one million new cases diagnosed each year[1]. In 2017, 28,000 new cases of gastric cancer and 10,960 deaths are predicted in the United States[2]. In spite of the significant advances in treatment modalities including radiation therapy, surgery and chemotherapy, the overall clinical outcome for patients with advanced gastric cancer is poor with median overall survival of 4-6 months[3]. The treatment of patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma is quite challenging. Although chemotherapy regimens including docetaxel, capecitabine, irinotecan, cisplatin and oxaliplatin have showed significant survival benefit in advanced gastric cancer[4], a majority of patients experience disease progression within 6 months and die within 1 year of systemic treatment[5]. Recent clinical studies demonstrated that chemotherapy combined with trastuzumab significantly improved clinical outcome in patients with human epidermal receptor 2 (HER-2) overexpressing gastric or GEJ adenocarcinoma[6]. Unfortunately, HER-2 overexpressing tumors represent approximately 20% of the total number of gastric and GEJ adenocarcinoma[6,7]. Therefore, there is a significant unmet need for new therapeutic approach to improve clinical outcome of patients with the advanced gastric and GEJ adenocarcinoma.

1.2 Angiogenesis

Angiogenesis is essential for tumor growth and metastasis. The increase in the tumor size and the functional abnormality of tumor vasculature result in tumor necrosis and tissue hypoxia which stimulates angiogenesis by induction of VEGF expression[8]. The binding of VEGF to VEGF receptors (VEGFR) regulates the angiogenesis signaling. Among 3 major receptors including VEGFR1, VEGFR2 and VEGFR3, VEGFR2 plays a key role in angiogenesis because it is widely considered to be the primary receptor mediating angiogenesis, whereas VEGFR1 and VEGFR3 are classically involved in other pathways such as monocyte chemotaxis, hematopoietic stem cell survival and lymphangiogenesis[9]. Several studies demonstrated that VEGFR2 inhibition reduced tumor growth and vascularity[10], and the expression of VEGFR2 correlated with the vessel count and the stage of disease in gastric cancer[11]. In addition, circulating VEGF levels are associated with increased tumor aggressiveness and reduced survival in patients with gastric cancer[12,13].

In contrast to normal vessels, tumor capillaries are tortuous, blunt-end and chaotic in their organization[14], and blood flow does not reach each region of the tumor equally. Notably, the blood flow abnormalities induced by tumor angiogenesis decrease anticancer activity of radiation, chemotherapy and immunotherapy by limiting delivery of oxygen and cytotoxic drugs to cancer cells and by limiting access of immune effector cells in tumors[15,16].

Therefore, tumor angiogenesis is essential not only for tumor progression and metastasis but also for resistance to anticancer therapy.

1.3 Ramucirumab

Ramucirumab, a human IgG1 monoclonal antibody against VEGFR2, prevents ligand binding and receptor mediated pathway activation in endothelial cells. Several studies have shown that VEGFR2 is the main mediator of several physiological and pathological effects including proliferation, migration, survival and permeability of endothelial cells in tumor angiogenesis[17]. Based on the importance of VEGFR2 in tumor angiogenesis, antibodies targeting VEGFR2 (ramucirumab) was developed, and ramucirumab and its murine version, DC-101 showed to inhibit angiogenesis and the growth of several mouse and human tumors in preclinical studies[18], providing evidence that the blockade of VEGFR2 is an effective strategy for the treatment of human cancer.

Clinical Experience

Clinical Pharmacokinetics
Ramucirumab Fab fragments has high binding affinity (0.1nmol/L) to VEGFR2 effectively blocking VEGF binding (50% inhibitory concentration=1-2nmol/L) and causing inhibition of VEGF induced intracellular calcium mobilization and endothelial cell migration, mitogenesis and proliferation in vitro[19]. Ramucirumab has been evaluated in human subjects in multiple studies at doses ranging from 2mg/kg to 16mg/kg. A mean half-life of ramucirumab is 14-15 days and at doses of ≥8mg/kg, the clearance profile of ramucirumab remains relatively stable[20], indicating saturation of the VEGFR2 mediated clearance pathway. Maximum tolerated dose is 13mg/kg once weekly[21]. Given the pharmacokinetics, 8mg/kg every 2 weeks is used for metastatic gastric or GEJ adenocarcinoma.

Clinical Efficacy
In a phase III study, ramucirumab demonstrated significant prolongation of median overall survival (OS) compared with placebo (5.2 vs 3.8 months) and improved 6 month overall survival rates from 31.6% to 41.8% in the second-line setting of advanced gastric and GEJ adenocarcinoma[22]. Another phase III study showed that ramucirumab plus paclitaxel was associated with high objective response (28% vs 16%), improved median PFS (4.4 vs 2.9 months) and median OS (9.6 vs 7.4 months) compared with paclitaxel in refractory advanced gastric and GEJ adenocarcinoma[23]. Based on the two phase III studies, ramucirumab alone or combined with paclitaxel has been approved for the treatment of advanced gastric and GEJ adenocarcinoma following first-line therapy.

Clinical Safety
Ramucirumab is generally well tolerated. The most common adverse events are fatigue, abdominal pain, decreased appetite, hypertension, vomiting and anemia.
The warnings and precautions for ramucirumab include: hemorrhage, arterial thrombotic events, gastrointestinal perforation, hypertension, reversible posterior leukoencephalopathy syndrome, wound healing impairment and bone marrow suppression.

1.4 TAS 102

TAS 102 is a novel oral cytotoxic agent which consists of trifluridine which inhibits tumor cell growth by being incorporated into DNA during DNA synthesis and tipiracil which inhibits the metabolism of trifluridine. Trifluridine is a thymidine based nucleoside analogue that is metabolized to the triphosphate metabolite, which is then incorporated into DNA, resulting in cell cycle arrest and cell death by inhibition of DNA synthesis and function. Trifluridine retains antitumor activity in 5-FU resistant tumor cells[24]. However, trifluridine is rapidly degraded to its inactive form in the intestines and the liver (first-pass effect), and tipiracil (another component of TAS 102) helps to maintain adequate trifluridine plasma concentration by inhibition of thymidine phosphorylase (known as platelet derived endothelial cell growth factor). In addition to enhancement of trifluridine's bioavailability by reducing its degradation, tipiracil possesses antiangiogenesis by inhibition of platelet derived endothelial cell growth factor (PDEGF) which plays a key role with VEGF in tumor angiogenesis[25]. PDEGF protects cancer cells from hypoxia- or chemotherapy- induced apoptosis by inhibition of mitochondrial release of cytochrome C, upregulation of BCL-2 and BCL-XL, suppression of the phosphorylation of p38 MAPK and inactivation of caspase 3 and 9[26]. PDEGF also plays an essential role in tumor invasiveness and metastasis by enhancing the expression of genes involved in the epithelial to mesenchymal transition program such as MMP-1, MMP-7, MMP-9, urokinase-type plasminogen activator and VEGF[27,28]. Thus, by inhibiting PDEGF, tipiracil may have multiple anticancer properties independent of its synergism with trifluridine.

Pre-Clinical Experience

Preclinical studies demonstrated that TAS 102, the combination of trifluridine and tipiracil had increased plasmatic trifluridine levels and enhanced tumor growth inhibitory activity compared with trifluridine alone[29]. Interestingly, trifluridine and TAS 102 showed antitumor activity in cancer cells and xenograft models in both 5-FU naïve and 5-FU resistant tumor cells[30]. Inhibition of neovascular formation by tipiracil was also confirmed in a gelatin-sponge mouse model[29].

Clinical Experience

Clinical Pharmacokinetics
TAS 102 has been tested in multiple clinical trials with doses ranging from 30mg/m^2/day to 160 mg/m^2/day (trifluridine dose). MTD was 70mg/m^2/day when given twice a day on days 1-5 and 8-12 of a 28 day cycle[31]. Postprandial administration is recommended for TAS 102 because trifluridine's area under the curve is not changed by food but the maximum concentration of trifluridine decreases in neutrophils with postprandial administration[32]. Half-life of trifluridine and tipiracil is 2.1 hours and 2.4 hours, respectively. Given the pharmacokinetics, 35mg/m^2 twice daily within 1 hour of completion of morning and evening meals on days 1 to 5 and days 8 to 12 of a 28 day cycle is used for metastatic colorectal cancer. TAS 102 is not metabolized by cytochrome P450 (CYP) enzymes.

Clinical Efficacy
TAS 102 has been FDA approved for the treatment of metastatic colorectal cancer based on

prolongation of median OS (7.1 vs 5.3 months) compared with placebo in a phase III study[33]. In a recent phase II study, TAS 102 was evaluated in patients with refractory advanced gastric cancer[34]. The median PFS and OS were 2.9 months and 8.7 months, respectively with disease control rate of 65.5% in the study.

Clinical Safety
The most common adverse events are anemia, neutropenia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting and abdominal pain. Grade 3 or higher neutropenia has been observed in 34% with 2% of febrile neutropenia, and there was no grade 5 toxicity related neutropenia in a randomized phase III study of TAS 102[35]. Interestingly, neutropenia caused by TAS 102 was associated with improved disease control rate and improved progression free survival in several studies[36,37].
The warnings and precautions for TAS 102 include: bone marrow suppression, gastrointestinal toxicity, hepatic impairment and renal impairment.

1.5 Rationale

The combination of TAS 102 and ramucirumab may potentially produce a synergistic tumor response by complete inhibition of tumor angiogenesis through the blockade of two major tumor angiogenic factors (VEGF and PDEGF) and enhanced delivery of cytotoxic trifluridine to tumor through normalization of poorly organized, tortuous and hyperpermeable tumor vasculature.

Dual antiangiogenic therapy has been proposed as tumors can not only develop resistance to one anti-angiogenic pathway but also exhibit multiple angiogenic pathways at the outset. The efficacy of dual antiangiogenic blockade such as bevacizumab plus sorafenib, a vascular disrupting agent (OXi4503) plus bevacizumab and a PDGFR inhibitor (SU6668) plus a VEGFR2 inhibitor (semaxinib) has been confirmed in preclinical and clinical studies[38], although toxicity remains a concern.

The combination of a cytotoxic agent with an antiangiogenic agent has demonstrated a significant anticancer activity in multiple cancers including gastric cancer, colorectal cancer, non-small cell lung cancer and ovarian cancer. The proposed mechanisms of benefit from the chemotherapy plus antiangiogenesis include 1) normalization of the tumor vasculature by altering vascular permeability and increasing drug accessibility[39], 2) synergistic effects leading to enhanced direct cytotoxicity of cancer cells and/or endothelial cells[40] and 3) decreased chemoresistance by alteration of cell proliferation pathway such as MAPK[41] and Wnt/β-catenin signaling[42]. The combination of TAS 102 with VEGF inhibition (bevacizumab) was evaluated in preclinical and clinical studies, and the combination showed superior antitumor efficacy to TAS 102 alone by increasing trifluridine accumulation[43,44]. In addition, TAS 102 (35 mg/m^2 twice a day) was safely combined with bevacizumab (5mg/kg every 2 weeks) without dose limiting toxicities in a phase1/2 study[44].

As there are known synergy of dual antiangiogenic therapy and the combination of a cytotoxic agent with an antiangiogenic agent in preclinical and clinical studies, we hypothesize that TAS 102 added to ramucirumab will lead to a disease response and improve survival in refractory metastatic gastric and GEJ adenocarcinoma.

2. Study Objectives

Primary Objective

To determine the 6 month overall survival in patients with advanced, refractory gastric and GEJ adenocarcinoma receiving TAS 102 in combination with ramucirumab.

Secondary Objectives

1. To determine the frequency and severity of adverse events and tolerability of TAS 102 plus ramucirumab in patients with advanced, refractory gastric and GEJ adenocarcinoma
2. To determine the efficacy of TAS 102 in combination with ramucirumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
3. To determine the progression free survival in patients with advanced, refractory gastric and GEJ adenocarcinoma receiving TAS 102 in combination with ramucirumab.

Exploratory Objective

1. To explore potential correlation between blood biomarkers and clinical outcome using a multiplex assay evaluating circulating angiogenic biomarkers (see 12.1 Correlative study)

3. Study Design

This is a single institutional phase II single arm, two-stage trial using ramucirumab and TAS 102 in subjects with advanced, refractory gastric or GEJ adenocarcinoma. In the first stage, 15 patients will be accrued. If 7 or more out of 15 survive 6 months or more, an additional 10 patients will be accrued for a total of 25 patients. TAS 102 and ramucirumab will be concurrently administered with ramucirumab 8mg/kg every 2 weeks (Q2W) and TAS 102 at doses of 35 mg/m^2 twice a day (Details on 5.1). After 2 cycles (1 cycle=28 days), response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Primary endpoint is 6 month overall survival. We will continue to recruit patients during interim analysis. Although no dose limiting toxicities of TAS 102 plus bevacizumab which has almost same mechanisms of action and safety profiles as ramucirumab were observed in a previous phase 1/2 study [44], unexpected toxicities can occur with this combination. Therefore, we will closely monitor first 6 patients for first 28 days. If none or one of these patients has a dose limiting toxicity, we will continue without dose adjustment. If ≥ 2 patients has a dose limiting toxicity, the dose will be decreased to level -1 (TAS 102: 30mg/m^2 twice a day and ramucirumab: 8mg/kg Q2W, details in table 1), and 6 additional patients will be enrolled at dose level -1. If none or one of these patients has a dose limiting toxicity at dose level -1 for first 28 days, we will use dose level -1. If ≥ 2 patients has a dose limiting toxicity at dose level -1, the study will be terminated. First 6 or 12 patients depending on dose limiting toxicities will be used for primary and secondary objectives. Dose limiting toxicity is defined as a grade 3 or higher non-hematological toxicity excluding controllable nausea, vomiting, hypertension, diarrhea, transient electrolyte abnormalities and alopecia; grade 4 neutropenia

lasting 7 days or more; grade 3 or higher febrile neutropenia; grade 4 thrombocytopenia.

4. Eligibility

4.1 Inclusion Criteria

1. Histologically confirmed diagnosis of gastric and GEJ adenocarcinoma
2. Measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Stage IV or recurrent disease is required. An irradiated lesion is considered evaluable only if it has shown enlargement since the completion of last radiation.
3. Patients must have received and progressed with prior therapy. Prior therapy with ramucirumab is not allowed. Patients must have recovered from the toxic effects of the previous anti-cancer chemotherapy (with the exception of alopecia).
4. ECOG Performance Score 0 or 1
5. Estimated life expectancy > 3 months
6. Adequate bone marrow, liver and renal function as assessed by the following:
   - o Hemoglobin > 8.0 g/dl
   - o Absolute neutrophil count (ANC) > 1,000/mm3 independent of growth factor support
   - o Platelet count > 100,000/mm3
   - o Total bilirubin < 1.5 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
   - o AST, ALT and Alkaline Phosphatase ≤2.5 times the ULN (≤5 x ULN for patients with liver involvement)
   - o Creatinine clearance ≥ 30 ml/min

7. Patients must not have had chemotherapy, major surgery, monoclonal antibody therapy or experimental therapy within the 28 days prior to the start of TAS 102 administration.
8. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
9. Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 4 months for both females and males after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
10. Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other study requirements.

4.2 Exclusion Criteria

1. Subjects with active CNS metastases are excluded. If CNS metastases are treated and subjects are at neurologic baseline for at least 2 weeks prior to enrollment, they will be eligible but will need a Brain MRI prior to enrollment.

2. Women who are pregnant or breast-feeding

3. Prior therapy with ramucirumab, bevacizumab, regorafenib or TAS 102.

4. Previous or concurrent cancer within 3 years prior to treatment start EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1 (tumor invades lamina propria)].

5. Uncontrolled hypertension (systolic BP>140 mm Hg or diastolic BP>90 mmHg on repeated measurement despite optimal medical management).

6. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.

7. Persistent proteinuria ≥ Grade 3 on repeated measurement

8. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

9. Subjects with an arterial thrombotic or thromboembolic event within 12 months of informed consent.

10. Ascites, pleural effusion, or pericardial fluid requiring drainage in the last 4 weeks
11. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
12. Clinically significant cardiovascular disease such as unstable angina, uncontrolled or symptomatic arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or history of myocardial infarction within 6 months prior to first dose with study drug

13. Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine.

14. Child-Pugh B cirrhosis (or worse) or a history of hepatic encephalopathy

15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

16. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.

17. Major surgery or a wound that has not fully healed within 4 weeks of enrollment.

18. Patients who need anticancer chemotherapy other than the study drugs during the study or within 4 weeks of study enrollment. Anti-cancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

19. Patients who need hormonal therapy during the study or within 2 weeks of first study enrollment.

20. Patients who need radiotherapy to target lesions during study or within 2 weeks of enrollment.

21. Patients who had bone marrow transplant or stem cell rescue.

22. Patients who need investigational drug therapy outside of this trial during or within 4 weeks of first study treatment.

4.3 Withdrawal of Subjects from Study

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Pregnancy. Pregnancies will be reported to Taiho within 24 hours of having knowledge of the event. Pregnancy will not be reported as an SAE but the subject must be withdrawn from the trial immediately. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up.
- Death.

All subjects who discontinue should comply with protocol specified follow-up and survival procedures. The ONLY exception to this requirement is when a subject withdraws consent for all

study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form page.

Subjects **may be** withdrawn from study treatment for the following reasons:

- The subject is non-compliant with TAS 102 administration, ramucirumab administration, or trial procedures; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to TAS 102 or ramucirumab.
- The development of a second cancer.
- Development of an illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 3 or 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Any subject with progression of disease will come off of treatment except for patients deriving clinical benefit as deemed by the principal investigator with a maximum of 24 months on therapy. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

4.3.1 Screen Failures/Dropouts/Replacements

A subject who discontinues study participation prematurely for any reasons except death, disease progression and severe toxicity is defined as a dropout.

A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

Subjects who withdraw from treatment (for any reason) may be replaced.

4.3.2 Patient Replacement

Dropout (see 4.3.1 for definition of "dropout") patients will need to be replaced.
Patients will be replaced if they come off treatment without any response evaluation for reasons other than drug related AE or disease progression.

5. Treatment Plan

5.1 Drug Administration

Ramucirumab
Ramucirumab is provided as a liquid solution at a concentration of 10mg/ml in either 100mg (10ml) or 500mg (50ml) single dose vials. The drug product is stored as a liquid solution in a refrigerator at 2°C to 8°C until time of use. Ramucirumab is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion following dilution and preparation. After withdrawal of the required volume of ramucirumab from the vials, it can be further diluted with only 0.9% sodium chloride in an intravenous infusion container to a final volume of 250ml. The diluted ramucirumab can be administerd via infusion pump over 60 minutes (±15minutes) through a separate infusion line. When patients develop infusion reaction, we will follow 5.1.1.2.1 infusion related reaction management. The diluted ramucirumab solutions may be stored at room temperature for up to 4 hours or at 2 to 8°C for up to 24 hours.

TAS 102
TAS 102 should be administered orally twice a day within 1 hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The tablets should be swallowed whole with water and should not be broken, or chewed.

TAS-102 15 mg/7.065 mg (trifluridine/tipiracil hydrochloride) and 20 mg/9.42 mg (trifluridine/tipiracil hydrochloride) film coated tablets. The film coated tablets can be printed or unprinted.
TAS 102 tablets are supplied in a blister card containing 20, 40 or 60 tablets.
Keep TAS 102 out of the sight and reach of children.

TAS 102 should be stored according to the storage conditions indicated on the label. The recommended storage condition for TAS 102 is 15°C to 23°C (59°F to 86°F).
Each patient will enter daily use of TAS 102 in a medication diary (Appendix B) for a measure of compliance. A dairy card will be issued and returned at each cycle.

Treatment
Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 8. Dose delays for TAS 102 and ramucirumab are described in Section 5.1.6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. The dose of TAS is 35mg/m^2 (trifluridine dose) twice a day, taken orally. The dose of ramucirumab is 8mg/kg IV every 2 weeks. Each cycle will last for 4 weeks.

Arm	Ramucirumab Dose	TAS 102*
1	8 mg/kg q2wk	35mg/m^2 BID

*To be given PO on days 1-5 and 8-12 of every 28 day cycle

TAS102 (35mg/m^2) twice a day was safely administered with anti-VEGF therapy (bevacizumab)

in a recent a phase 1/2 study[44]. Based on the data, each subject will receive TAS 102 35mg/m^2 twice a day and ramucirumab 8mg/kg Q2W continuously. Since unexpected toxicities can occur with this combination, we will closely monitor first 6 patients for first 28 days. If none or one of these patients has a dose limiting toxicity, we will continue without dose adjustment. If ≥ 2 patients has a dose limiting toxicity, the dose will be decreased to level -1 (TAS 102: 30mg/m^2 twice a day and ramucirumab: 8mg/kg Q2W, details in table 1), and 6 additional patients will be enrolled at dose level -1. If none or one of these patients has a dose limiting toxicity at dose level -1 for first 28 days, we will use dose level -1. If ≥ 2 patients has a dose limiting toxicity at dose level -1, the study will be terminated. First 6 or 12 patients depending on dose limiting toxicities will be used for primary and secondary objectives. Dose limiting toxicity is defined as a grade 3 or higher non-hematological toxicity excluding controllable nausea, vomiting, hypertension, diarrhea, transient electrolyte abnormalities and alopecia; grade 4 neutropenia lasting 7 days or more; grade 3 or higher febrile neutropenia; grade 4 thrombocytopenia.

5.1.1 Management (dose Modifications and dose delays) for Treatment-Related Toxicity

All toxicities will be graded according to National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) (NCI CTCAE v 5). The study investigator will determine if either or both medications should be held.

Dose reductions for AEs related to TAS 102 are permitted dose reductions to a minimum dose of 20mg/m^2 twice a day in 5mg/m^2 steps. After dose reduction, escalation of dose is not allowed.

Table 1. TAS 102 dose modifications

TAS 102 dose (BID)	BSA (m^2)*	Dosage in mg (BID)	Total daily dose (mg)	Tablets per dose	
				15mg	20mg
Starting dose					
35mg/m^2	<1.07	35	70	1	1
	1.07-1.22	40	80	0	2
	1.23-1.37	45	90	3	0
	1.38-1.52	50	100	2	1
	1.53-1.68	55	110	1	2
	1.69-1.83	60	120	0	3
	1.84-1.98	65	130	3	1
	1.99-2.14	70	140	2	2
	2.15-2.29	75	150	1	3
	≥2.30	80	160	0	4
Level 1 dose reduction: from 35mg/m^2 to 30mg/m^2					
30mg/m^2	<1.09	30	60	2	0
	1.09-1.24	35	70	1	1
	1.25-1.39	40	80	0	2
	1.4-1.54	45	90	3	0
	1.55-1.69	50	100	2	1

	1.70-1.94	55	110	1	2
	1.95-2.09	60	120	0	3
	2.10-2.28	65	130	3	1
	≥2.29	70	140	2	2
Level 2 dose reduction: from 30mg/m^2 to 25mg/m^2					
25mg/m^2	<1.10	25	50	2 (PM)¶	1 (AM)¶
	1.10-1.29	30	60	2	0
	1.30-1.49	35	70	1	1
	1.50-1.69	40	80	0	2
	1.70-1.89	45	90	3	0
	1.90-2.09	50	100	2	1
	2.09-2.29	55	110	1	2
	≥2.30	60	120	0	3
Level 3 dose reduction: from 25mg/m^2 to 20mg/m^2					
20mg/m^2	<1.14	20	40	0	1
	1.14-1.34	25	50	2 (PM)¶	1 (AM)¶
	1.35-1.59	30	60	2	0
	1.60-1.94	35	70	1	1
	1.95-2.09	40	80	0	2
	2.10-2.29	45	90	3	0
	≥2.29	50	100	2	1

* Calculate BSA to 2 decimal places.
¶ At a total daily dose of 50mg, patients should take 1 x 20mg tablet in the morning and 2 x 15mg tablets in the evening.

Dose reductions of ramucirumab will be allowed only for proteinuria with 6 mg/kg for first episode of proteinuria (> 2 g/24 hours) and with 5 mg/kg for second episode of proteinuria (> 2 g/24 hours). Only dose delay will be allowed for the other AEs related to ramucirumab.

Table 2. Ramucirumab dose modifications

Starting dose	8mg/kg
Level 1 dose reduction	6mg/kg
Level 2 dose reduction	5mg/kg

Dose modifications will not be required for AEs that are clearly not attributed to TAS 102 or ramucirumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

If a subject experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required.

5.1.1.1 Management for Treatment-Related Toxicity of TAS 102

5.1.1.1.1 Non-hematologic toxicities of TAS 102

Table 3. Non-hematologic toxicity management

Grade¶	Dose hold/resumption within a 28-day treatment cycle	Dose adjustment for next cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3* or higher		
1st, 2nd or 3rd occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment

¶ At the discretion of the investigator, patients may continue on study medication at the same dose without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life-thereating (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin).

* Except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medication. Moreover, if grade 4 non-hematotoxicity that is related to the protocol therapy is observed, protocol therapy is to be discontinued. However, in case of adverse events, which can clearly be judged to have derived from the primary disease, depending on the judgement of the investigator (subinvestigator) protocol therapy can be continued. In this case, the reason for this judgement must be recorded in the medical records, etc. (For example: Grade 3 cancer pain that is associated with the primary disease, Grade 3 weight loss that is associated with the primary disease, etc.)

5.1.1.1.2 Hematologic toxicities of TAS 102

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table 2.

Uncomplicated neutropenia or thrombocytopenia ≤ grade 3 does not require a reduction in dose of study medication. Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a >1 week delay of the start of the next cycle should start the next cycle with dose reduction in 5mg/m^2 step. If toxicity remains despite 4 dose reductions or at a minimum dose (15mg/m^2 twice a day), discontinue TAS 102.

Table 4. Hematologic toxicity management

Parameter	Hold Criteria		Resumption Criteria*	Dose adjustment for next cycle
	Conventional Units	SI units		
Neutrophils	<500/mm^3	<0.5x10^9/L	≥1500/mm^3 (IU: ≥1.5x10^9/L)	Details below¶
Platelets	<50,000/mm^3	<50x10^9/L	≥75,000/mm^3 (IU: ≥75x10^9/L)	Details below¶

* These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met. Both conventional and SI (International System) units are presented in CTCAE v. 5.

¶ 1) ≤ Grade 3 neutropenia or thrombocytopenia

- If there are no complications (such as fever, infection or hemorrhage), there is no need to reduce the dose of TAS 102
- If there are complications, the necessity of reducing dose should be considered also with regard to safety.
- For neutropenia, pegfilgrastim or filgrastim can be administered at investigator's discretion.

2) Grade 4 neutropenia or thrombocytopenia

- When there are no complications, but initiation of the next cycle is delayed by more than one week, dose should be reduced by 1 level (Table 1) when starting next cycle (dose is not reduced when administered on the same weekday). If initiation is not delayed by more than one week, the next cycle can be initiated at the same dose level.
- If there are complications, in consideration of the safety of the patient, dose should be reduced by 1 level (Table 1) when starting the next cycle.
- For neutropenia, pegfilgrastim or filgrastim can be administered at investigator's discretion.

5.1.1.1.3 Dose resumption timing of TAS 102

If the patient recovers from the toxicities to the resumption criteria defined above during the 2-week treatment period (treatment Days 1 through 5, 8 through 12), and no dose reduction is required, study drug therapy may be resumed during that cycle.

If a dose reduction is required, study drug therapy should be resumed at the start of the next cycle at the appropriate dose level according to instructions provided in Table 1 and 2. If the study drug dose is reduced, it must not be increased for subsequent cycles.

If the toxicities that are defined above recover during the recovery period (Days 13 through 28), start the next cycle on schedule at the appropriate dose level according to instructions provided in Table 1, 3 and 4.

If the toxicities that are defined above do not recover during the treatment or rest period, the start of the next cycle can be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If resumption criteria are met by this maximum 28-day delay, start the next cycle at the appropriate dose level according to instructions provided in Table 1, 3 and 4. Patients who

require more than a 28-day delay in the scheduled start date of the next cycle will have study medication discontinued.

5.1.1.2 Management for Treatment-Related Toxicity of ramucirumab

Adverse events of concern which may be related with ramucirumab include are infusion-related reactions, hypertension, arterial or venous thromboembolic events, bleeding (hemorrhagic) events, proteinuria, cardiac events, gastrointestinal perforation, anemia, surgery and wound healing liver injury/liver failure, and reversible posterior leukoencephalopathy syndrome (RPLS). Listed below are guidelines on how to manage these toxicities. Dose reductions of ramucirumab will be allowed only for proteinuria with 6 mg/kg for first episode of proteinuria (2-3 g/24 hours) and with 5 mg/kg for second episode of proteinuria (2-3 g/24 hours) (details on table 2 and **5.1.1.2.4**). Only dose delay will be allowed for the other AEs related to ramucirumab.

5.1.1.2.1 Infusion related reactions

For the treatment of infusion related reaction, institutional protocol can be used. If there is no institutional protocol, the following can be used for treatment of ramucirumab infusion-related reactions.

Grade	Management
Grade 1	• Slow the infusion rate by 50% • Monitor the patient for worsening of condition • For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V.; additional premedication may be administered at the investigator's discretion
Grade 2	• Stop the infusion • Administer diphenhydramine hydrochloride 50 mg I.V., acetaminophen 650 mg orally for fever and oxygen • Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours • Monitor the patient for worsening of condition • For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V.; additional premedication may be administered at the investigator's discretion

Grade 3	• Stop the infusion and disconnect the infusion tubing from the patient • Administer diphenhydramine hydrochloride 50 mg I.V., dexamethasone 8-10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated • Patients who have a Grade 3 infusion-related reaction will be discontinued from study
Grade 4	• Stop the infusion and disconnect the infusion tubing from the patient • Administer diphenhydramine hydrochloride 50 mg I.V., dexamethasone 8-10 mg I.V. (or equivalent), and other medications/treatment as medically indicated. • Give epinephrine or bronchodilators as indicated • Hospital admission for observation may be indicated • Patients who have a Grade 4 infusion-related reaction will be discontinued from study

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8-10 mg I.V.; then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V., acetaminophen 650 mg orally, and dexamethasone 8-10 mg I.V. (or equivalent)

5.1.1.2.2 Hypertension

- If patients develop hypertension during the study, they should be treated with antihypertensive medications according to standard medical practice.
- The following are treatment guidelines for ramucirumab related hypertension

Grade	Management
Grade 1 or 2	○ If the hypertension is not associated with symptoms, continue ramucirumab and initiate antihypertensive therapy ○ If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy
Grade 3	○ For Grade 3 hypertension not associated with symptoms, continue ramucirumab with more intensive antihypertensive therapy. If systolic BP remains ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg > 2 weeks after initiation of additional antihypertensive therapy, hold ramucirumab while continuing appropriate antihypertensive therapy ○ If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate

	antihypertensive therapy
Grade 4	○ Patients with Grade 4 hypertension (life-threatening consequences, eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (> 160 mm Hg systolic or > 100 mm Hg diastolic for > 4 weeks) despite (> 2 oral agents at MTD) will be discontinued from study therapy.

5.1.1.2.3 Thromboembolic events

- Investigators should perform all testing required to fully characterize arterial or venous thrombotic/vascular events.
- Ramucirumab should be discontinued in the event of any Grade 3-4 arterial thromboembolic event or any Grade 3-4 venous thromboembolic event that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy.
- At the investigator's discretion, ramucirumab may be continued in this setting of an incidentally diagnosed asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy.
- In the event that a patient experiences a Grade 4 pulmonary embolism or a Grade 3-4 venous thromboembolic event that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy, the patient will not receive further ramucirumab and be discontinued from study therapy.
- Ramucirumab should also be discontinued, and a patient will be discontinued from study therapy in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

5.1.1.2.4 Proteinuria

If, while on ramucirumab, a patient has proteinuria ≥ 2+ per a dipstick or routine urinalysis test, ramucirumab will continue as scheduled, and a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment in 2weeks.

- The following are treatment guidelines for ramucirumab related proteinuria

Proteinuria	Management
< 2g/24hours urine	• Continue on ramucirumab at the same dose without interruption
2-3g/24hours urine (first episode)	• Hold ramucirumab for 2 weeks • Repeat a 24-hour urine collection prior to next infusion. • Resume ramucirumab at a reduced dose level (6 mg/kg every 2 weeks) once the protein level returns to < 2 g/24 hours.
2-3g/24hours urine (second episode)	• Hold ramucirumab for 2 weeks • Repeat a 24-hour urine collection prior to next infusion. • Resume ramucirumab at a reduced dose level (5 mg/kg every 2 weeks) once the protein level returns to < 2 g/24 hours.
2-3g/24hours urine (third episode) or >3g/24hours urine	• Discontinue ramucirumab

5.1.1.2.5 Hemorrhagic events

Serious hemorrhagic adverse events have been reported from clinical studies investigating ramucirumab.

- The following are treatment guidelines for ramucirumab related hemorrhage

Grade	Management
Grade 1 or 2	• Continue ramucirumab
Grade 3 or 4	• Discontinue ramucirumab

5.1.1.2.6 Gastrointestinal perforation events

An infrequent incidence of gastrointestinal perforations has been associated with some antiangiogenic therapeutic agents. These events may be associated with extensive abdominal/peritoneal disease burden. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. Ramucirumab should be discontinued in the setting of any gastrointestinal perforation.

5.1.1.2.7 Reversible posterior leukoencephalopathy syndrome (RPLS)

- Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes. The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits. Magnetic resonance imaging (MRI) represents the most reliable method for the diagnosis. Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported.
- Because hypertension is an identified risk for ramucirumab, investigators should control BP. In addition, investigators should consider a diagnosis of RPLS in the setting of seizures, headache, nausea, delirium, visual changes, and/or other unexplained neurological symptoms, especially in combination with hypertension and MRI findings of hyperintensity on T2-weighted and fluid-attenuated inversion recovery images
- If the diagnosis of RPLS is confirmed, ramucirumab DP should be permanently discontinued.

5.1.1.2.8 Cardiac events

- Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in this study.
- Ramucirumab should be discontinued in the event of any Grade 3-4 events consistent with CHF.

5.1.1.2.9 Surgery and impaired wound healing

- Surgery and impaired wound healing have been observed with some antiangiogenic agents.
- Ramucirumab will not be administered to patients who have undergone major surgery within 28 days or have undergone central venous access device placement within 7 days prior to ramucirumab adminstration.
- Patients with postoperative and other nonhealing wound complications are excluded, as are patients for whom major surgical procedures are planned.

5.1.1.2.10 Liver injury/liver failure

- Patients with Child-Pugh B cirrhosis (or worse), any degree cirrhosis, a history of hepatic encephalopathy, clinically meaningful ascites from cirrhosis, new occurrence of hepatic encephalopathy and/or hepatorenal syndrome from liver cirrhosis. Ramucirumab should be discontinued following a new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

5.2 Concomitant therapy

• All patients should be maintained on the same medications throughout the study period, as medically feasible;
• The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded;
• Administration of pegfilgrastim or filgrastim following initiation of protocol therapy is at investigator's discretion for all patients;
• Administration of erythropoietin or darbopoietin is allowed;
• Administration of bisphosphonates is permitted at the investigator's discretion
• Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion
• Patients must be instructed not to take any additional medications (including herbal supplements and over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded;
• In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics or steroids).
• Premedication is recommended before ramucirumab administration (including first dose). Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at the investigator's discretion.

5.2.1 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy, immunotherapy or biological therapy not specified in this protocol
- Investigational agents other than TAS 102 or ramucirumab
- Radiation therapy

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.3 Blinding

This is an open-label trial. There will be no randomization or blinding.

5.4 Drug Logistics and Accountability

All study drugs will be stored at the investigational site in accordance with good clinical practice (GCP) and GMP requirements and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiration dates can be found in Dr. Kim's study file; the site-relevant elements, of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drugs and will use the study drugs only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drugs must be properly documented according to Moffitt Cancer Center protocol.

6. Visit schedule and Assessments

6.1 Screening First Visit

Screening examinations will only be performed after having received the subject's written informed consent.

The following examinations will be performed within 28 days prior to the first treatment:

- Written subject informed consent to be obtained prior to any screening assessments.
- Complete medical history and physical examination, including demographics, surgery, therapies, medications, smoking, alcohol history, co-existing diseases, allergies, NYHA classification, vital signs (heart rate, respiration rate, temperature, and BP), weight and review of systems.
- Baseline toxicities / AEs
- ECOG Performance Status Assessment
- 12-lead ECG
- Radiologic assessment: CT scan or MRI with tumor measurement and disease assessment of non-measurable disease
- Coagulation (PT-INR and aPTT)
- Hematology (hemoglobin, HCT, RBC, WBC count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), creatine kinase, lipase, amylase, glucose, calcium phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), total protein and albumin
- Urinalysis
- Hepatitis and HIV test
- Serum pregnancy test (if applicable)
- Radiologic assessment tests (CT scan or MRI) performed up to 4weeks prior to

obtaining informed consent can be used for screening purposes.

6.2 Cycle 1 Day 1

- History and assessment to include physical examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin
- Screening hematology, platelet count and chemistry can be used for cycle 1 day 1 if screening tests are done within 5 days of cycle 1 day 1.
- Issue a new diary card (Appendix B)
- Urinalysis

6.3 Cycle 1 Day 15

- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin

6.4 Subsequent cycles (Cycle X Day 1)

- History and assessment to include brief examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin
- UA (if dipstick or routine urinalysis indicates proteinuria $\geq$ 2+, a 24-hour urine collection must be obtained in 2 weeks before next dose of ramucirumab)
- Return an old diary card and issue a new diary card

6.5 Subsequent cycles (Cycle X Day 15)

- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils,

bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin

6.6 After every 3rd cycle (Cycle 3 Day 1, Cycle 6 Day 1, etc.)

- Tumor measurement/disease assessment according to RECIST 1.1 (please see Appendix B)
- History and assessment to include brief examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin
- UA (if dipstick or routine urinalysis indicates proteinuria ≥ 2+, a 24-hour urine collection must be obtained in 2 weeks before next dose of ramucirumab)
- Return an old diary card and issue a new diary card

6.7 End of Treatment Visit and Follow up

End of Treatment Visit

- History and assessment to include brief examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, LDH, glucose, calcium, phosphate, magnesium, bicarbonate, sodium)
- UA
- Tumor measurement/disease assessment according to RECIST 1.1 (please see Appendix B) may be conducted if it has not been performed within the last 4 weeks.

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer

treatment should also be followed and recorded.

Survival Follow-up
Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase for 6 months and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.8 Calendar

	Screening within 28 days of C1D1[m]	**Cycle 1 Day 1 ± 3 days and subsequent cycles**	**Cycle 1 day 15 ± 3 days**	**Cycle X day 1 ± 5 day**	**Cycle X day 15 ± 5 day**	**End of treatment visit[n]**	**Safety follow-up**	**Survival follow-up**
Complete History/Physical[a]	X							
History & Assessment [b]		X	X	X		X	X	
Toxicity Notation		X	X	X		X	X	
ECOG	X	X	X	X		X		
ECG	X							
Tumor Measurement/ Disease Assessment[c]	X			X		X		
Hematology[d]	X	X	X	X	X	X		
Chemistry[e]	X	X	X	X	X	X		
Coagulation[f]	X							
Urinalysis[g]	X	X		X		X		
24hr urine protein[h]			X	X	X	X		
Hepatitis and HIV Screening[i]	X							
Serum	X							

Pregnancy, if applicable [j]								
Survival f/u [k]								X
Diary – Issued/Returned [l]		X		X				

a. *Complete medical history and physical examination* including demographics, surgery, therapies, medications, smoking, alcohol history, co-existing diseases, allergy, NYHA classification, vital signs (heart rate, respiration rate, temperature and BP), height, weight and review of systems.
b. *History and assessment* including brief examination, vital signs and review of systems. Note all toxicities and adverse events, using CTCAE version 5.
c. Tumor assessment using CT or MRI (at investigator's discretion) will be collected at screening, after every 3 cycles, and as clinically indicated. Tumor response will be assessed using RECIST 1.1 criteria**.** Tumor measurement/disease assessment should be performed within 7 days at the beginning of every 3rd cycle.
d. Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count.
e. ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, creatine kinase, lipase, amylase glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), total protein and albumin.
f. PT-INR and aPTT.
g. Urinalysis including blood, glucose, protein, specific gravity. If dipstick or routine urinalysis indicates proteinuria ≥ 2+, a 24-hour urine collection must be obtained in 2 weeks.
h. If necessary
i. Hepatitis B surface antigen, surface antibody, core antigen and Hepatitis C antibody
j. Pregnancy test will be performed at baseline for WOCBP and then only as clinically indicated
k. Can be performed over the phone. After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 3 months for up to two years or death.
l. A diary card will be issued on day 1 of each cycle and the issued diary card will be returned on subsequent cycle
m. Radiologic tests (CT scan or MRI) performed up to 4 weeks prior to obtaining informed consent can be used for screening purposes.

n. Restaging imaging only to be performed if not done within the last 4 weeks

7. Assessment types

7.1 Pre-Treatment Assessments

The nature of the study and the associated potential risks will be explained to all study candidates and a signed informed consent must be obtained before any study-specific Pre-Treatment procedures are performed. Pre-Treatment assessments must be completed and reviewed within 21 days prior to the start of study drug treatment to ensure eligibility for study entry

Pre-Treatment evaluations will include inclusion/exclusion criteria evaluation, demographic data collection, ECOG performance status, NYHA classification, medical and surgical history collection, vital signs, complete physical examination (including height and weight), 12-lead ECG, biochemistry, hematology and urinalysis, pregnancy test (urine or serum β- hCG in women of childbearing potential only), and tumor assessments

7.2 Efficacy

Response and progression will be evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (see Appendix A). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

7.3 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring of vital signs, and physical condition as shown in corresponding tables.

8. Safety monitoring and reporting

8.1 Adverse Events

8.1.1 Definitions

A serious adverse event is an undesirable sign, symptom or medical condition which:

1. Is fatal or life-threatening.
2. Requires or prolongs hospitalization.
3. Results in persistent or significant disability/incapacity.
4. Constitutes a congenital anomaly or a birth defect.
5. Is medically significant, may jeopardize the subject and may require medical or surgical

intervention to prevent one of the outcomes listed above.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study treatment.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

Full information from serious adverse events as well as adverse events concerning medication errors and overdose will be reported to Taiho Drug Safety or Designee**. This can be performed by faxing it to Taiho or designee at (609) 750-7371 or via e-mail at TAS-102_Safety@taihopui.com (please note the underscore between '102' and 'Safety').**

In addition to the above, fatal events will also be documented by a separate death form, instead of reporting them as AE CTCAE grade.

Events not considered to be serious adverse events are hospitalizations for the:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Only the serious adverse event occurring after the patient has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

Progression of the cancer under study is not considered an adverse event.

8.2 Safety Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology

Criteria for Adverse Events version 5.0 (CTCAE v5) that is available at:
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Protocol Monitoring Committee (PMC);
The PMC monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

Investigators of studies which are designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable.

8.2.1 Internal Monitoring Plan

Data will be captured in OnCore, Moffitt's Clinical Trials Database.
Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

8.3 Reporting of Serious Adverse Events

All AEs will be recorded on the appropriate CRF. The Investigator will also identify the date of onset, date of resolution, seriousness, outcome, and the relationship to study drug. Every effort should be made to determine the cause of each AE and whether or not it is related to the study drugs. The relationship of the AE to the study drug must be rated and recorded following the guidelines outlined in the CTCAE v5. All the AEs will be reviewed by the Principal Investigator of the study. The 2 categories for AE grading are:

1. **Definite**
2. **Probable**
3. **Possible**
4. **Unlike**
5. **Unrelated**

The definition of serious adverse events (SAEs) is given in Section 8.1.1.

Each serious adverse event must be followed up until resolution or stabilization, by submission

of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

To ensure patient safety, each serious adverse event must be reported to Dr. Kim expeditiously. Moffitt Cancer Center will report SAEs by completing an SAE report in OnCore, the electronic data capture system. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to Taiho Drug Safety or Designee within 24 hours from the time that the investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (including narrative description, medical history and concomitant medications) needs to be provided with careful considerations regarding causality and serious criterion. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

Taiho Drug Safety: (email or by fax). **This can be performed by faxing it to Taiho or designee at (609) 750-7371 or via e-mail at TAS-102_Safety@taihopui.com (please note the underscore between '102' and 'Safety').**

The Investigator may report serious adverse events (SAEs) as described below.

A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be faxed to:

PPD/PVG
United States and Canada: Toll-Free Fax: 1-888-529-3580
Rest of World: Toll-Free Fax: 93581-888-529-3580 (will automatically connect to

PVGs toll-free safety fax number (1-888-529-3580)

8.4 Pregnancies

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Principal Investigator. Within 24 hours of the Investigator becoming aware, the pregnancy must be reported to Taiho Drug Safety or Designee using the Pregnancy Form New and/or corrected information regarding the pregnancy obtained after submitting the initial Pregnancy Form must be submitted by faxing an updated Pregnancy Form to Taiho Pharmacovigilance or designee. **This can be performed by faxing it to Taiho or designee at (609) 750-7371.**

9. Statistical Methods and Data Analysis

9.1 Definition of Study Endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability
- Tumor response by RECIST 1.1 (Secondary)
- Exploratory biomarkers and cytokine multiples assay (Exploratory)

9.2 Determination of sample size

The primary objective of this study is overall survival at 6 months. Overall survival (OS) will be defined as the time from starting on trial to date of death due to any cause. Dropouts/screen failures defined in section 4.3.1. Patients will be considered inevaluable for the primary endpoint of 6 months of overall survival if they are not able to complete first cycle or if they are lost follow-up prior to 6 months from starting on trial except death. Inevaluable patients will be replaced. The study will test the null hypothesis of ≤45% of OS at 6 month against the alternative of ≥70% of OS at 6 month. The sample size was determined based on the Simon's two-stage minimax design. With one-sided 10% of type I error rate and 90% power, a sample of evaluable 25 patients will be evaluated; 15 in first stage and additional 10 patients in second stage. If 7 or more out of 15 survive 6 months or more, the study goes on the second stage. The experimental treatment will be deemed to have good activity if ≥15 out of 25 patients survive 6 months or more. We will continue to recruit patients during interim analysis

9.3 Statistical analysis

Overall survival (OS) is defined as the time from starting on trial to date of death due to any cause and progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever comes first. The final analysis will be conducted after the follow-time of the last patient exceeds 6 months. The primary endpoint of the study is OS at 6 month. The experimental treatment will be deemed to have good activity if ≥15 out of 25 evaluable patients survive 6 months or more. OS will be estimated using the Kaplan-Meier method and the two-sided 95% confidence interval (CI) for median OS will be computed using log-log transformation.

The secondary endpoints in this study include toxicity, PFS and the objective response rate (ORR) defined as (complete response (CR) + partial response (PR)) using RECIST 1.1 criteria (Appendix A). ORR will be reported with 95% CI computed by the Clopper-Pearson method. The frequency and severity of adverse events and tolerability of the regimen will be summarized using descriptive statistics. PFS with 95% CI will be estimated. As exploratory objective, the association between biomarkers and clinical outcomes (ORR, OS and PFS) will be examined using multiple logistic regression and the multivariable Cox regression model. A p-value of <0.05 will be considered statistically significant. Frequency and severity of adverse events will be summarized using descriptive statistics.

10. Data Recording

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

10.2 Data Management and Monitoring/Auditing

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and

verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/ amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

10.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.4 Emergency Modifications

Moffitt Cancer Center and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior H. Lee Moffitt Cancer Center or their respective institution's approval/favorable opinion.

For Institutions Relying on Moffitt's IRB:

For any such emergency modification implemented, a Moffitt IRB modification form must be completed by Moffitt Research Personnel within five (5) business days of making the change.

10.5 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 all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

11. Ethical and Legal Aspects

11.1 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Taiho. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Taiho approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and properly documented.

11.2 Subject Information and Consent

Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Taiho, and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

2. For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent form. The investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

11.3 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.

12. Appendix

APPENDIX A: RECIST Criteria for Measuring Tumor Response Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer et al., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ramucirumab or TAS 102.

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.)

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 ≥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 might be considered measurable if the lesion has increased in size since the radiation.

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/pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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.

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. 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.

<u>Response Criteria Evaluation of Target Lesions</u>

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 progression.)

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).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

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 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
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first

APPENDIX B: Medication Diary

Day & date	Time of morning dose	What dose and how many tables and dose?	Time of evening dose?	What dose and how many tables and dose?	List adverse effects / changes in health and level of intensity	List any other medication taken
e.g. 01 Mar 04	*e.g.* 07:30	*e.g.* x 15mg-1 x 20mg-1	*e.g.* 19:00 or 7 pm	*e.g.* x 15mg-1, x 20mg-1	*e.g.* As explained by study doctor and see *** below	*e.g.* 2 "Name" tablets; time and reason.
1		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
2		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
3		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
4		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
5		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
6	X	X	X	X		
7	X	X	X	X		
8		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
9		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
10		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
11		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
12		□ 15mg-_ □ 20mg-_		□ 15mg-_ □ 20mg-_		
13	X	X	X	X		
14	X	X	X	X		
15	X	X	X	X		
16	X	X	X	X		
17	X	X	X	X		

18	X	X	X	X		
19	X	X	X	X		
20	X	X	X	X		
21	X	X	X	X		
22	X	X	X	X		
23	X	X	X	X		
24	X	X	X	X		
25	X	X	X	X		
26	X	X	X	X		
27	X	X	X	X		
28	X	X	X	X		

**** Please assess the intensity of the problem or adverse event as follows:
Mild = aware of sign or symptom, but it is easily tolerated
Moderate = discomfort sufficient to cause interference with normal activities
Severe = it is incapacitating, with inability to perform normal activities.

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