Georgetown Lombardi Comprehensive Cancer Center
Washington, DC

An Open-label, Multi-center, Phase 2 Study of Switch Maintenance with TAS-102 plus Bevacizumab Following Oxaliplatin or irinotecan-based fluoropyrimidine-containing Induction Chemotherapy in Patients with Metastatic Colorectal Cancer (ALEXANDRIA Study)

Georgetown IRB # 2015-0959

Principal Investigator:
John L. Marshall, MD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
3800 Reservoir Road, NW
Washington, DC 20057
Telephone (202) 444-2144
Fax (202) 444-1229
E-Mail: marshalj@georgetown.edu

Co- Investigators:
Marwan Fakih, MD
City of Hope Comprehensive Cancer Center
1500 E Duarte St
Duarte, CA 91010
Email: mfakih@coh.org
Tel: 626-256-4673 extension 63087
Fax: 626-301-8233

Sameh Mikhail MD
Ohio State University
James Comprehensive Cancer Center
320 West 10th Avenue
Columbus, OH, 4320
Email: Mikhail.18@osu.edu
Tel: 614-293-9863
Fax: 614-293-4372

A. Ruth He, MD, PhD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
3800 Reservoir Road, NW
Washington, DC 20057
Telephone (202) 444-2198
Fax (202) 444-9429
E-Mail: arh29@georgetown.edu

Michael J. Pishvaian, MD, PhD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
3800 Reservoir Road, NW
Washington, DC 20057

Protocol version date 17 July 2017

Georgetown Lombardi Comprehensive Cancer Center
Washington, DC

Telephone (202) 444-2144
Fax (202) 444-9429
E-Mail: pishvaim@georgetown.edu

Louis Weiner, MD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
(E501 Research Building)
3800 Reservoir Road, NW
Washington, DC 20057
Telephone (202) 687-2110
Fax (202) 687-6402
E-Mail: weinerl@georgetown.edu

David J. Perry, MD
Washington Cancer Institute at MedStar Washington Hospital Center
110 Irving St. NW
Washington, DC 20010
Telephone (202) 877-2844
Fax (202) 877-4072
Email: david.j.perry@medstar.net

Pallavi Kumar, MD
Harry and Jeanette Weinberg Cancer Institute at Franklin Square
9103 Franklin Square Drive,
Baltimore, MD 21237
Telephone (443) 777-7147
Fax (443) 777-2090
Email: pallavi.p.kumar@medstar.net

Asma Dilawari, MD
MedStar Montgomery Medical Center
18109 Prince Philip Dr., Suite B100
Olney, MD 20832
Telephone (301) 774-8962
Fax (301) 774-8963
Email: asma.a.dilawari@gunet.georgetown.edu

Biostatistician:
HongKun Wang, PhD
Biostatistics and Bioinformatics Shared Resource,
Lombardi Comprehensive Cancer Center
Building D
Georgetown University Medical Center
4000 Reservoir Road, NW
Washington D.C. 20057
Telephone (202) 687-0830
Fax (202) 687-2581
E-Mail: hw87@georgetown.edu

Responsible
Research nurse: Holly DiFebo, BSN Phone: 202-687-5760

Georgetown Lombardi Comprehensive Cancer Center
Washington, DC

Investigational Drug: TAS-102

Development phase: Phase II
Document Status: Final

IND Number: 129102
IND Holder Name: N/A - Exempt

Funding Source: Taiho Oncology, Inc.

Initial version: 01 September 2015
Amended-1: **10 October 2015**
Amended-2: **25 January 2016**
Amended-3: **09 February 2016**
Amended-4: **18 May 2016**
Amended-5: **17 July 2017**

Research Office

Georgetown Lombardi Comprehensive Cancer Center
Clinical Research Management Office
3900 Reservoir Road
Pre-Clinical Sciences Building, LR-3
Washington, DC 20007

Georgetown Lombardi Comprehensive Cancer Center
Washington, DC

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: John Marshall, MD

PI Signature: _____

Date: July 17, 2017

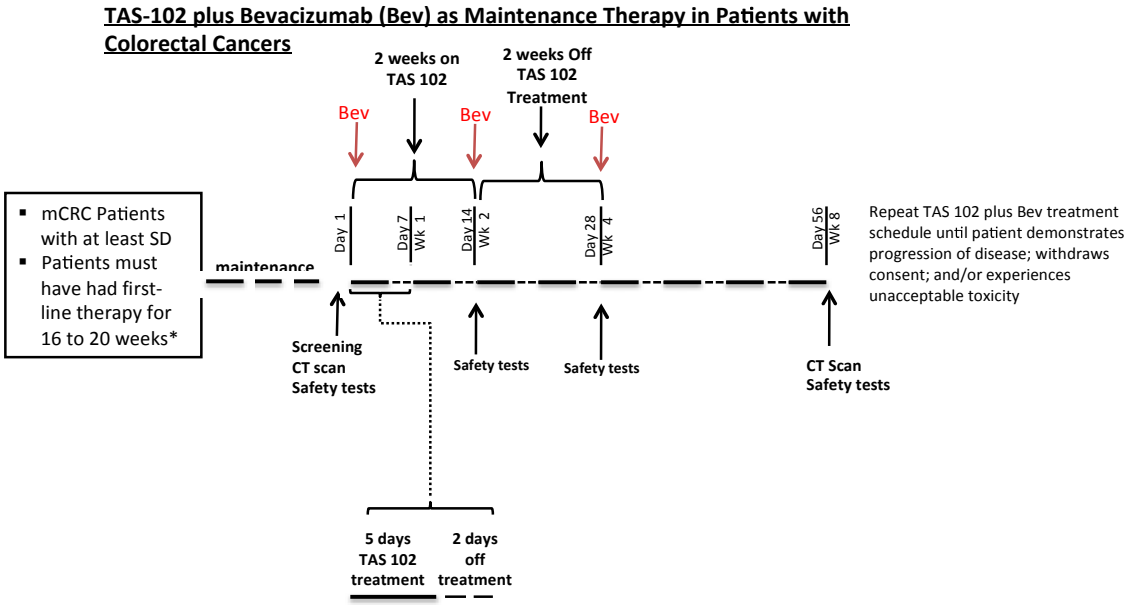
TABLE OF CONTENTS

LIST OF ABBREVIATIONS

5-FU	5-fluououracil
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DDC	Duration of disease control
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FTD	Trifluridine
G-CSF	Granulocyte colony-stimulating factor
HR	Hazard ratio
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
iwCLL	International Workgroup on Chronic Lymphocytic Leukemia
LAFB	Left anterior fascicular block
mCRC	Metastatic colorectal cancer
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFA	Progression-free survival
PR	Partial response
RBBB	Right bundle branch block
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious AE
SD	Stable disease
SI	International System
TPI	Tipiracil hydrochloride
TS	Thymidylate synthase
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
UPR	unanticipated problems involving risk to subjects or others

VEGF	Vascular endothelial growth factor

STUDY SCHEMA



TAS-102: 35 mg/m^2 BID PO d1-5, 8-12 every 28 days
Bevacizumab 5 mg/kg IV administered every 14 days

Primary end point: PFS
Safety tests: Blood draw, physical exam, performance status (every 14 days (2 weeks) for the first month and every month thereafter)
CT Scan: Every 8 weeks

**first-line therapy: oxaliplatin, or irinotecan-based fluoropyrimidine-containing chemotherapy and bevacizumab

STUDY SUMMARY

Title	An Open-label, Multi-center, Phase 2 Study of Switch Maintenance with TAS-102 plus Bevacizumab Following Oxaliplatin and/or irinotecan-based fluoropyrimidine-containing Induction Chemotherapy in Patients with Metastatic Colorectal Cancer
Short Title	Phase II study of TAS-102 plus bevacizumab switch maintenance therapy in patients with mCRC
Protocol Number	
Phase	Phase 2
Methodology	Open-label, single arm, prospective study
Study Center(s)	Multicenter
Objectives	Primary objectives are to estimate the efficacy (progression-free survival by RECIST). Secondary objectives: Safety and tolerability of switch maintenance therapy with TAS-102 plus bevacizumab in patients with advanced colorectal cancer following induction chemotherapy.
Number of Subjects	45
Diagnosis and Main Inclusion Criteria	Diagnosis: Histologically proven, unresectable, evaluable metastatic colorectal cancer. Key inclusion criteria: 1. Prior first-line therapy with Oxaliplatin and/or irinotecan-based fluoropyrimidine-containing chemotherapy for 16 to 20 weeks plus bevacizumab 2. Stable disease (or better) 3. ECOG 0 to 1 4. Age ≥ 18
Study Product, Dose, Route, Regimen	Study Drug: TAS-102 (trifluridine and tipiracil hydrocholoride) and bevacizumab Dosing Details: ➢ Starting dose of TAS-102 (LONSURF) is 35 mg/m2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. ➢ Bevacizumab 5 mg/kg intravenously every 14 days. ➢ The treatment cycle repeats every 28 days.
Duration of administration	Patients may take TAS-102 plus bevacizumab until they exhibit progression of disease, withdraw consent, or experience unacceptable toxicity.
Reference therapy	This is a single arm study. All patients receive the same study treatment
Statistical Methodology	Time-to-event endpoints measured using the Kaplain-Meier method.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Colorectal cancer is the second leading cause of cancer death in the United States (1). At least 50% of patients develop metastases and most of these patients have unresectable tumors. Although significant advances in the treatment of metastatic colorectal cancer have led to improvements in median survival of at least 2 years, over 40,000 patients still

die of colorectal cancer each year (2). Treatment of patients with metastatic colorectal cancer (mCRC) requires a comprehensive strategy that encompasses several lines of chemotherapy, salvage surgery, maintenance therapy, and treatment-free intervals.

For decades, 5-fluorouracil (5-FU) was the only treatment option for patients with mCRC (3-5). This has changed markedly over the last decade, with the approval of irinotecan, oxaliplatin, and three humanized monoclonal antibodies that target vascular endothelial growth factor (VEGF; bevacizumab) and the epidermal growth factor receptor (EGFR; cetuximab and panitumumab). Most recently, aflibercept and regorafenib, in addition to orally active fluoropyrimidines (capecitabine, S-1, UFT) have also become available (6).

1.1.1 First-Line Treatment in mCRC

The standard first-line treatment for inoperable mCRC is combination chemotherapy (usually FOLFOX, FOLFIRI or FOLFOXIRI) (7-13). The VEGF inhibitor, bevacizumab, may be given along with these combinations, and cetuximab or panitumumab are also options in this same setting (dependent on RAS status of the mCRC). Although it is well established that patients benefit more from access to all active agents rather than from a particular treatment sequence of specific regimens used as individual "lines" of therapy, the best way to combine these agents is not yet well defined.

It is acknowledged that for the majority of patients with mCRC, chemotherapy treatment will be palliative and not curative. Hence, the treatment goals are to prolong overall survival with the least possible side effects and to maintain quality of life for as long as possible (14-16). In other words, for patients without symptomatic disease (i.e., the majority of patients), induction of tumor response is not as essential as is delaying tumor progression for as long as possible. In the palliative setting, objective response rate is not the best indicator of treatment benefit. Thus, achieving stable disease as the best response to therapy is considered a reasonable treatment strategy.

1.1.2 Duration of First-Line Chemotherapy

The optimal duration of initial chemotherapy for unresectable disease that does not progress is controversial. Historically, when 5-FU was the only treatment alternative, patients generally stayed on treatment until disease progression or they developed unacceptable toxicity. This typically meant that patients were treated for four to six months (the median progression-free survival [PFS] duration) and then were placed on supportive care alone until they died (median duration of survival approximately one year). However, with the recent change in the therapeutic landscape of mCRC and introduction of the newer agents, there is an urgent need for a better-defined optimal duration of therapy.

Compared with 5-FU alone, newer combinations are more effective (median survival durations now consistently approach two years); however, they are also more toxic. This is especially true for oxaliplatin-containing regimens, which cause cumulative neurotoxicity. Therefore, to improve the clinical benefit of first-line treatment for patients before disease progression, several strategies have emerged that attempt to reduce toxicity while maintaining efficiency.

For example, intermittent therapy—‘stop-and-go strategies”—to best response followed by a chemotherapy "holiday" has been attempted using regimens that contain oxaliplatin, a drug that is associated with dose-limiting neurotoxicity (17). With this approach, patients who respond to an initial oxaliplatin-based regimen discontinue treatment with the drug (a “holiday”) *before* the onset of severe neurotoxicity (usually after three to four months of therapy).

Another strategy that has recently emerged is the concept of maintenance therapy, of which there are two categories: continuation maintenance and switch maintenance therapy. With continuation maintenance therapy, the chemotherapy that is part of a defined number of cycles of combination induction therapy, usually with a targeted agent, is continued in the absence of disease progression as a single agent with or without the targeted agent. In switch maintenance, a different agent is initiated after a predetermined number of cycles of a combined chemotherapeutic induction regimen in the absence of disease progression.

1.2 Maintenance Therapy in Metastatic Colorectal Cancer

The strategy of maintenance therapy is still an evolving one and remains under investigation. Several trials have investigated the role of maintenance therapy in metastatic colorectal cancer using various designs, induction treatments, and maintenance therapies.

1.2.1 Continuation Maintenance Therapy in mCRC

1.2.1.1 Maintenance Therapy with Targeted Agents

Recent studies have evaluated maintenance therapy without chemotherapy with the rationale that targeted therapies can delay tumor progression with fewer side effects than chemotherapy.

1.2.1.2 Maintenance Therapy with Bevacizumab Alone

The role of maintenance Bevacizumab alone has been studied in several trials, most of which used different comparator arms.

1.2.1.2.1 MACRO Trial

In the Spanish MACRO trial (18), patients received six cycles of first-line XELOX plus bevacizumab followed by randomization to continued unchanged therapy or bevacizumab maintenance therapy alone until progression or treatment intolerance. The primary endpoint was median PFS with a noninferiority limit of 7.6 months (i.e. hazard ration [HR] = 1.32), assuming 10 months as median PFS in the control arm. Median PFS was 10.4 months in the continuous arm (control) and 9.7 months in the bevacizumab maintenance arm (investigational), with a HR of 1.11 (0.89–1.37). The authors concluded that the noninferiority of bevacizumab versus XELOX plus bevacizumab could not be confirmed. This result, could not justify use of bevacizumab alone as effective maintenance therapy.

1.2.1.2.2 SAKK 41-06 Trial

In the Swiss SAKK 41-06 trial (19), 262 patients with mCRC were randomized after first-line bevacizumab-containing chemotherapy to maintenance with bevacizumab or completely stopping antitumor therapy after four to six months. The primary endpoint was time to progression (TTP). Like the MACRO trial, the trial failed to achieve its primary endpoint of non-inferiority for TTP with the projected upper limit of the 95 percent confidence interval for TTP exceeding the preset limit. The median TTP was 4.1 for bevacizumab continuation versus 2.9 months for no continuation (HR 0.74, 95% CI 0.57-0.95).

It is important to note that the current experts' opinion is not pursuing bevacizumab alone for maintenance therapy for patients who have no disease progression after an initial course of bevacizumab plus oxaliplatin-containing chemotherapy.

1.2.1.3 Maintenance Therapy with Cetuximab Alone

Maintenance therapy with cetuximab alone was evaluated in the NORDIC VII study (20). Overall survival for patients treated with continuous cetuximab and a chemotherapy-free interval was similar to that for patients with continuous chemotherapy with or without cetuximab.

1.2.1.4 Maintenance Therapy using Targeted Agents in Combination with Cytotoxic Therapy, Compared with Observation Alone

The role of maintenance of fluoropyrimidine therapy plus bevacizumab versus bevacizumab or observation alone has been studied in two large phase III trials with slightly different designs:

1.2.1.4.1 CAIRO-3 Trial

CAIRO3 trial (21) is a phase III trial that randomly assigned 558 patients who were not progressing during induction treatment with cap, oxaliplatin, and bev (CAPOX-B) and were not eligible for potentially curative metastasectomy, to continued (maintenance) therapy with capecitabine (625 mg/m2 twice daily every day) plus bevacizumab (7.5 mg/kg every three weeks) or observation (no further treatment) alone [21]. Upon first progression (PFS1) on their respective "therapies", patients in both arms were treated with XELOX plus bevacizumab until the second progression (PFS2), which was calculated from the time of randomization. Maintenance therapy, compared with observation alone, was associated with a significantly longer PFS1 (median 8.5 versus 4.1 months, HR 0.43, p<0.0001), PFS2 (11.7 versus 8.5 months, HR 0.67, p<0.0001), and time to second progression (defined as time to progression or death on any treatment following PFS1; 19.8 versus 15.0 months, HR 0.67, p<0.0001). However, there was no statistically significant overall survival benefit (median 21.7 versus 18.2 months, HR 0.87, p = 0.16).

1.2.1.4.2 AIO KRK 0207 Trial

Another trial is the German AIO KRK 0207 trial (22). Similar to CAIRO-3 trial results, a benefit was gained from continued fluoropyrimidine plus bevacizumab treatment when compared with observation alone. Patients without progressive disease following six months of initial induction therapy with oxaliplatin plus a fluoropyrimidine (16% capecitabine, the rest fluorouracil/leucovorin) and bevacizumab were randomly assigned to maintenance with the same fluoropyrimidine plus bevacizumab, bevacizumab alone, or observation only. The primary endpoint was the "time to failure of strategy" (TFS), which included the duration of maintenance plus the time from reinduction after first progression to a second disease progression. The trial was powered to demonstrate noninferiority with a noninferiority margin set at 3.5 months, corresponding to a hazard ratio (HR) of 1.42. In a preliminary report, the median TFS in the fluoropyrimidine plus bevacizumab and observations arms was not significantly different (6.8 and 6.1 months, respectively). However, the observation arm was not noninferior to fluoropyrimidine plus bevacizumab combination (HR 1.22, 95% CI 0.96 to 1.57) because the upper limit of the 95% confidence interval exceeded the threshold set for non-inferiority (1.42). In patients with *RAS and BRAF* mutations, the doublet was favored; however, single-agent bevacizumab was no better than no maintenance at all.

1.3 Switch Maintenance Therapy

Maintenance therapy with a fluoropyrimidine plus bevacizumab is a widely accepted strategy, having been shown to prolong progression-free survival, largely based on the results of the CAIRO 3 study, which provides the best evidence so far for the magnitude of benefit that maintenance treatment can be achieved in metastatic colorectal cancer. On the other hand, switch maintenance, when a different agent is initiated after a predetermined number of cycles of combined chemotherapeutic induction therapy in the absence of disease progression, is being investigated. Several therapeutic approaches of switch maintenance treatment are currently being explored in mCRC. For instance **RAVELLO study,** which is a randomized, double-blind, placebo-controlled, multi-center, phase III study designed to evaluate efficacy and safety of regorafenib as maintenance treatment after first line therapy.

Here we propose a novel design with the use of a novel compound, TAS-102, as switch maintenance therapy plus continuation of bevacizumab in patients with mCRC after induction therapy with standard first-line treatment.

1.4 Study Agent(s) Background and Associated Known Toxicities

1.4.1 TAS-102

TAS-102 is a novel nucleoside antitumor agent consisting of trifluridine and tipiracil hydrochloride. Trifluridine is the active component of TAS-102 and is directly incorporated into DNA, leading to DNA dysfunction. However, when trifluridine is taken orally it is largely degraded to an inactive form. Tipiracil hydrochloride prevents the degradation of trifluridine. This mechanism of action is different from that of a fluoropyrimidine, oxaliplatin, and irinotecan.

TAS-102 is a novel nucleoside antitumor agent consisting of a thymidine-based nucleoside analogue (trifluridine; FTD), the active component, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI). TAS-102 is in clinical development in the treatment of patients with mCRC who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and an anti-EGFR therapy.

Trifluridine, an antineoplastic antimetabolite, is a thymidylate synthase (TS) inhibitor. Based on preclinical data, FTD also appears to be incorporated into deoxyribonucleic acid (DNA), thereby providing a second mechanism of action for antitumor activity. Preliminary results suggest that when FTD is incubated with cancer cells at a high concentration for short time periods, it is passively incorporated into the DNA fraction of the cell, and that such behavior of FTD is different from the primary cytotoxic mechanism of 5-FU and 2'-deoxy-5 fluorouridine (FdUrd), i.e., inhibition of TS. When FTD is taken orally it is largely degraded to an inactive form.

TPI inhibits degradation of FTD by thymidine phosphorylase (TP). The bioavailability of FTD after oral administration is extremely low due to first-pass effects by the enzyme TP, which results in the rapid degradation of FTD to an inactive form, 5-trifluoromethyluracil (FTY). Co-administration of TPI, which inhibits TP, increased the area under the concentration-time curve (AUC) of FTD by 100-fold at a ratio of 0.5 M TPI to 1 M FTD (TAS-102) in a study in monkeys. The in vivo potency of TAS-102 is increased with divided oral daily dosing, which was shown to maximize FTD incorporation into DNA.

TAS-102 was approved in Japan on 24 March 2014 for the treatment of patients with unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies), and was marketed in Japan on 26 May 2014 under the trade name of

Lonsurf®. License applications are under preparation in the US and European Union (EU) / European Economic Area (EEA).

1.4.2 Safety in Phase 1-3 Trials

As of July 24, 2014, 1449 patients participated in Taiho sponsored TAS-102 trials globally. The adverse events presented below include adverse events reported from those participants. However, the adverse events shown below are not a complete list because rare events of a non-severe nature were not listed; however, rare events of a severe nature are listed. The list includes events that both may or may have not been related to TAS-102. Though many of the adverse events reported were mild to moderate in nature, some adverse events may become severe and life-threatening and could potentially worsen, leading to death.

a. Likely, occurring in > 20% (all grades) of participants:

- GI: Nausea, vomiting, diarrhea
- Blood: Leucopenia, neutropenia, anemia
- General: Fatigue
- Metabolism: Loss of appetite
- Infection: Infections e.g. blood, lung, pelvis, eye, urinary tract, intestinal tract, skin, liver/biliary tract

b. Common, occurring in 3-20% (all grades) of participants:

- GI: Stomatitis, constipation, abdominal pain, indigestion
- Blood: Thrombocytopenia
- Skin: Alopecia, rash (changes in the color or texture of the skin, possible blistering and peeling)
- Renal: Proteinuria
- Nervous: Dysgeusia, headache
- Musculoskeletal: Back pain, arthralgia
- General: Pyrexia, asthenia
- Metabolism: Hypoalbuminemia
- Psych: Anxiety
- Hepatobiliary: Elevated liver enzymes, e.g. AST, ALT, bilirubin

c. Rare but severe, occurring in < 3% (grade 3 and above) of participants:

- Cardiac: Myocardial infarction, myocardial ischemia, chest pain, bradycardia, tachycardia
- Hepatobiliary: Hepatic failure, jaundice
- Renal: Acute renal failure, hematuria
- Nervous: Effects on cognitive or nerve function, seizure, decreased level of consciousness, thromboembolism
- GI: Colitis, intestinal fistula, small or large bowel obstruction, ascites, hemorrhage, intestinal ulcer

- Respiratory: Pulmonary emboli, dyspnea, respiratory arrest, pneumonitis, epistaxis
- Metabolism: Gout, dehydration
- Vascular: Fainting, DVT, hypotension, blood clotting disorder, hot flushes, septic shock
- Nervous: Dizziness, paresthesia
- Musculoskeletal: Myalgia
- General: Flu like symptoms

Please refer to the current version of the Investigator's Brochure for further information.

1.4.3 Phase III Study in Colorectal Cancer

Recently published in NEJM; the RECOURSE trial was a global, randomized, double-blind, placebo-controlled Phase 3 comparison trial evaluating the efficacy and safety of orally administered TAS-102 in patients with refractory mCRC (24). The trial enrolled 800 patients in the US, Europe, Australia and Japan, who received at least two prior regimens of standard chemotherapy for mCRC which was to include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy for patients with KRAS wild-type tumors, and were refractory to, or failed, those chemotherapies. Patients were randomized (2:1) to receive TAS-102 (35 mg/m2) twice daily, or placebo twice daily plus best supportive care. The primary objective of the RECOURSE trial was improvement in overall survival (OS) versus placebo. [24]

TAS-102 treatment demonstrated statistically significant overall survival (OS) and progression-free survival (PFS) benefit in all prospectively defined subgroup analyses, including prior therapy with regorafenib. The OS in TAS-102 group was 7.1 months vs. 5.3 month in placebo group. TAS-102 had a significantly higher disease control rate (44% vs. 16%) and the hazard ratios for OS and PFS were 0.68 ($p < 0.0001$) and 0.48 ($p < 0.0001$), respectively, both favoring TAS-102.

1.5 Rationale

Maintenance therapy with a fluoropyrimidine plus bevacizumab is a widely accepted strategy, having been shown to prolong progression-free survival, largely based on the results of the CAIRO 3 study, which provides the best evidence so far for the magnitude of benefit that maintenance treatment can be achieved in metastatic colorectal cancer. Thus CAIRO 3 provides very valuable guidance for how to optimize a treatment approach in clinical practice.

TAS-102, an oral cytotoxic agent that consists of two active pharmaceutical ingredients: the nucleoside analog trifluridine (trifluorothymidine; a cytotoxic antimetabolite that has potential antiangiogenic effects related to inhibition of platelet-derived endothelial growth factor) and the potent thymidine phosphorylase inhibitor, tipiracil, which inhibits the metabolism of trifluridine.

As shown above the efficacy of TAS 102 was suggested in a Japanese randomized placebo-controlled phase II trial of 172 patients with refractory mCRC, where TAS-102 significantly prolonged median overall survival (9 versus 6.6 months). Benefit was then confirmed in a subsequent phase III trial (RECOURSE) of 800 patients with metastatic colorectal cancer (mCRC) who were refractory to or intolerant of fluoropyrimidines,

irinotecan, oxaliplatin, bevacizumab, and anti-EGFR agents (if wild-type KRAS). TAS-102 treatment demonstrated statistically significant overall survival (OS) and progression-free survival (PFS) benefit in all prospectively defined subgroup analyses, including prior therapy with regorafenib. The OS in TAS-102 group was 7.1 months vs. 5.3 month in placebo group. TAS-102 had a significantly higher disease control rate (44% vs. 16%) and the hazard ratios for OS and PFS were 0.68 ($p < 0.0001$) and 0.48 ($p < 0.0001$), respectively, both favoring TAS-102.

In preclinical models, TAS-102 with bevacizumab demonstrated enhanced activity against CRC cells compared with either drug alone.
Subsequently a phase I/II study (C-TASK FORCE) was conducted to determine the recommended phase II dose and evaluate the efficacy, safety and pharmacokinetics of this combination in patients with mCRC refractory to standard therapies. The result of this study was recently presented at the 2015 ASCO Annual Meeting (J Clin Oncol 33, 2015 (suppl; abstr 3544)); demonstrating that the combination of TAS-102 (35 mg/m2 BID on days 1–5 and 8–12 every 4 weeks) with bevacizumab (fixed dose 5 mg/kg q2weeks) showed promising antitumor activity with acceptable toxicity profile.

Therefore, TAS-102 plus bevacizumab maintenance therapy is a rational treatment to achieve the goal of disease control in patients with metastatic disease who have responded favorably to induction therapy. TAS-102 has shown activity in the refractory setting with respect to objective tumor response, DCR, PFS and OS. We therefore hypothesize that TAS 102 plus bevacizumab maintenance therapy will achieve disease control in the maintenance setting after fluoropyrimidine-based therapy that might be superior to fluoropyrimidine maintenance strategy given the different mechanism of antitumor effect and favorable toxicity profile. If we obtain a strong signal of activity then a future trial comparing TAS-102 against a fluoropyrimidine (with or without bevacizumab) would be considered.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To estimate the efficacy (progression-free survival [PFS] by RECIST) of TAS-102 plus bevacizumab maintenance therapy in patients with advanced stage colorectal cancer following induction chemotherapy.

2.2 Secondary Objectives

1. To investigate the safety and tolerability of TAS-102 plus bevacizumab maintenance therapy following induction chemotherapy in patients with mCRC

2. To estimate in patients with mCRC, treated with maintenance TAS-102 plus bevacizumab maintenance therapy following induction chemotherapy, the:

   - Objective response rate (ORR) overall
   - Disease control rate (DCR = CR + PR + SD at 8 months)
   - Overall survival (OS)
   - Time to disease progression (TTP)
   - Duration of disease control (DDC)

2.3 Endpoints

2.3.1 Primary endpoint: Progression-Free Survival

2.3.2 Secondary endpoints:

ORR, DCR, OS, TTP, DDC, Safety and Toxicity

3.0 PATIENT ELIGIBILITY

3.1.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria in order to participate in this study.

3.1.1 Written informed consent in accordance with federal, local, and institutional guidelines

3.1.2 Age ≥ 18 years.

3.1.3 Patients with histologically proven, unresectable, evaluable metastatic colorectal cancer, by RECIST criteria

3.1.4 Patients must have had 16 to 20 weeks of first-line therapy with oxaliplatin, and/or irinotecan-based flurorpyrimidine-containing chemotherapy plus Bevacizumab

3.1.5 Patients must have stable disease (or better) during the initial induction chemotherapy with first-line chemotherapy.

3.1.6 No progressive disease at the time of initiation of maintenance therapy

3.1.7 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (see Appendix 1)

3.1.8 Adequate organ and marrow function as defined below:

- absolute neutrophil count	≥ 1,500/mm^3
- platelets	≥ 75,000/mm^3
- total bilirubin	<1.5 times the upper limit of normal (ULN), except patients with Gilbert's syndrome who must have a total bilirubin of <3 times ULN
- AST(SGOT)/ALT(SPGT)	≤ 3.0 times ULN
- creatinine	≤ 1.5 mg/dL

3.1.9 For subjects with liver metastases, AST and ALT ≤ 5 X the upper normal limit of institution's normal range, and Non-fasting bilirubin 1.5 - 3.0 X the upper normal limit of institution's normal range are acceptable.

3.1.10 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Because of the potential for genotoxicity, male patients with female partners of reproductive potential should be advised to avoid getting their partners pregnant during the treatment and for at least 3 months after final dose.

3.1.11 Patient must start maintenance therapy at least 14 days after the last administered induction chemotherapy but no later than 30 days.

3.1.12 Providers must try to provide formalin-fixed, paraffin-embedded (FFPE) tumor tissue block for central confirmation of RAS and BRAF mutation status, and molecular subtyping.

3.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Patients whose tumors have progressed on first-line treatment

3.2.2 Patients with active concurrent malignancy, other than superficial, non-invasive squamous cell carcinoma of the skin or uterine cervix, within the past three years. An active concurrent malignancy will be defined as one currently requiring cancer-directed treatment, or deemed by the treating physician as likely to require such treatment within a six-month period from time of screening.

3.2.3 Women who are pregnant or lactating

3.2.4 Unstable cardiovascular function that includes and may not be limited to:

1) Symptomatic myocardial ischemia, or
2) Uncontrolled clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), or
3) Congestive heart failure (CHF) of NYHA Class 3, or
4) Myocardial infarction (MI) within 3 months.

3.2.5 Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.

3.2.6 Patients with active CNS malignancy. Asymptomatic small lesions are not considered active. Treated lesions may be considered inactive if they are stable for at least 3 months.

3.2.7 Persistent proteinuria $\geq$ Grade 3 NCI-CTCAE v4.0 (> 3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample).

3.2.8 Patients with obstructed gastrointestinal tract or uncontrolled vomiting.

3.2.9 Patients with serious psychiatric or medical conditions that could interfere with treatment.

4.0 TREATMENT PLAN

The study will be conducted at the Georgetown Lombardi Comprehensive Cancer Center, City of Hope Comprehensive Cancer Center, and the Ohio State University James Comprehensive Cancer Center.

4.1 Treatment Dosage and Administration

Patient must start maintenance therapy at least 14 days after the last administered induction chemotherapy but no later than 30 days.

Study medications should be administered as outlined in the protocol; however, the Investigator always has the right to deviate from the established rules for dose reduction at his/her discretion if he/she believes a more conservative approach is needed in the management of related or unrelated AEs.

4.2 Administration Schedule

4.2.1 Bevacizumab

- Bevacizumab 5 mg/kg IV over 30 minutes (or as per institutional guidelines) every 14 days
- The dose of bevacizumab is to be recalculated should the patients weight change by 10% or more.
- Repeat cycles every 28 days until progression until withdrawal of consent or unacceptable toxicity.

4.2.2 TAS-102

The starting dose of TAS-102 (LONSURF) is 35 mg/m2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.

Patients will be instructed to swallow the required number of tablets at approximately the same time on each day. Patients will be instructed to wash their hands before and after taking the drug. Patients will continue to take TAS-102 until they demonstrate progression of disease using standard RECIST criteria or until withdrawal of consent or unacceptable toxicity.

If at the beginning of any treatment cycle, a patient's body weight has decreased by $\geq$10% from baseline, the patient's body surface area (BSA) must be recalculated and the study medication dosage adjusted.

The initial BSA for each patient will be calculated using the following DuBois formula (25) (all BSA calculations are rounded to 2 decimal places):

$$BSA\ (m^2) = ([Body\ Weight\ (kg)]^{0.425} \times [Height\ (cm)]^{0.725} \times 0.007184$$

Please note the following:

- Dose escalations (on a mg/m^2 basis) are not recommended at any time.
- Up to 3 dose reductions of study medication are allowed.

- Up to a 28-day delay in the start of the next treatment cycle is allowed.

  Study medication should be administered as outlined in the protocol. The Investigator always has the right to deviate from the established rules for dose reduction at his/her discretion if he/she believes a more conservative approach is needed in the management of related or unrelated AEs.

  If study treatment discontinuation criteria have been met but there is strong evidence of clinical benefit to justify continuation of dosing with the study medication on protocol, this decision should be made by the Investigator, together with the patient, and noted in the patient's chart.

4.2.3 Study Medication Regimen

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

Day 1 and Day 15: Bevacizumab 5 mg/kg IV over 30 minutes (or as per institutional guidelines).

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

Days 6 through 7: Rest

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

Days 13 through 28: TAS 102 Holiday

Patients should take study medication (TAS-102) with a glass of water within 1 hour of completion of their morning and evening meals.

4.2.4 Administration

4.2.4.1 Bevacizumab

A fixed bevacizumab dose (5 mg/kg) will be given on Days 1 and Days 15 of each cycle.

4.2.4.2 TAS-102

The study medication tablet calculation is presented in Table 1, which shows the number of tablets that are needed per calculated BSA.

- TAS-102 should be given only on Days 1 through 5 and Days 8 through 12 of each cycle even if doses are missed or held for any reason during Days 1 through 12. Any interruptions or missed doses of drug should be noted by the patient and/or physician. Do not take additional doses to make up for missed or held doses

- Extension of TAS-102 treatment into days 6 and 7 or into the holiday period (Days 13 through 28) is not permitted.
- TAS-102 (LONSURF) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

TABLE 1

NUMBER OF TAS-102 TABLETS PER DOSE

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

[a] Calculate BSA to 2 decimal places.

4.2.4.3 Instruction to Patients for Handling Study Medication (TAS-102)

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

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

4.3 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (Section 5.4). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.3.1 Dose Reduction Doses

Study medication dose reductions to be applied in case of toxicity and the number of tablets for each calculated BSA are described in Table 2. Recommended dose reduction(s) occur in 5mg/m^2 steps.

TABLE 2

TAS-102 DOSE MODIFICATIONS					
TAS-102[a] Dose (2x daily)	BSA[b] (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
Level 1 Dose Reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 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 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[c]	50[c]	2 (PM)[c]	1 (AM)[c]
	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
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 – 1.34	25[c]	50[c]	2 (PM)[c]	1 (AM)[c]
	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 – 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

[a] If the study medication dose is reduced, it should not be increased for subsequent cycles.
[b] Calculate BSA to 2 decimal places.
[c] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

If dose modification fails to result in achieving minimal criteria to safely resume treatment, the Investigator may discontinue study medication.

Should the toxicities that require dose reduction recur after dose reduction to 20mg/m^2, study medication may be discontinued.

4.3.2 Hematological Toxicity Dose Reductions for TAS-102

No bevacizumab dose modifications (or delays) will be necessary for hematologic toxicity. However, for patients' convenience and scheduling purposes, the decision of whether to continue or to hold bevacizumab when TAS 102 is held due to hematologic toxicities should be made by the Investigator.

Recommendations for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Tables 3 and 4. Note that for all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria in Table 4 and section 4.2.3.1 are met.

Patients who experience Grade 4 neutropenia or thrombocytopenia that results in a > 1 week delay of the start of the next cycle should start the next cycle at a reduced (by 1 step) dose level as described in Table 2. If the delay is ≤ 1 week, the patient should start the next cycle at the same dose level.

Uncomplicated neutropenia or thrombocytopenia ≤ Grade 3 does not require a reduction in dose of study medication. Patients who experience uncomplicated Grade≥ 3 neutropenia or thrombocytopenia should be considered for administration of hematopoietic growth factors, or for a dose reduction in the next cycle or both, depending on the severity of the complication (Table 2).

Within a treatment cycle, withhold TAS-102 (LONSURF) for any of the following:

- **ANC <500/mm^3 or febrile neutropenia**
- **Platelets <50,000/mm^3**
- **Grade 3 or 4 non-hematologic adverse reactions**

Do not initiate the cycle of TAS-102 (LONSURF) until:

- **Absolute neutrophil count (ANC) ≥1,500/mm^3 or febrile neutropenia is resolved**
- **Platelets ≥75,000/mm^3**
- **Grade 3 or 4 non-hematologic adverse reactions are resolved to Grade 0 or 1**

After recovery, resume TAS-102 (LONSURF) after reducing the dose by 5 mg/m^2/dose from the previous dose level, if the following occur:

- **Febrile neutropenia**
- **Uncomplicated Grade 4 neutropenia (which has recovered to ≥1,500/mm^3) or thrombocytopenia (which has recovered to ≥75,000/mm^3) that results in >1 week delay in start of next cycle**
- **Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication**

A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily. Do not escalate* TAS-102 (LONSURF) *dose after it has been reduced

TABLE 3

TAS-102 DOSE HOLD CRITERIA FOR HEMATOLOGIC TOXICITIES RELATED TO MYELOSUPPRESSION		
	Hold Criteria	
Parameter	**Conventional Units**	**SI Units**
Neutrophils	≤500/mm^3	≤0.5 x 10^9/L

Platelets	≤50,000/mm^3	≤50 x 10^9/L
**Both conventional and SI (International System) units are presented in NCI CTCAE v. 4.03.		

TABLE 4

TAS-102 RESUMPTION CRITERIA FOR HEMATOLOGIC TOXICITIES RELATED TO MYELOSUPPRESSION		
	Resumption Criteria	
Parameter	**Conventional Units**	**SI Units**
Neutrophils	≥1500/mm^3	≥1.5 x 10^9/L
Platelets	≥75,000/mm^3	≥75 x 10^9/L
**Both conventional and SI (International System) units are presented in NCI CTCAE v. 4.03.		

4.3.3 Non-hematological Toxicity Dose Reductions (for both study drugs)

Recommendations for study medication dosing modifications for treatment-related non-hematologic toxicities are provided in Table 5.

TABLE 5

Non-hematological Toxicity Dose Reductions		
NCI CTC Grade[a]	Dose Hold/ Resumption within a 28-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3[b] or Higher		
1st, 2nd, or 3rd occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment
[a] 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-threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin). [b] Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.		

4.3.3.1 Hypertension (Dose delays for bevacizumab only)

Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice	
• Grade 1< (SBP 120-139 mmHg or DBP 80-89 mm Hg)	• Consider increased BP monitoring; start anti-hypertensive medication if appropriate
• Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	• Begin anti-hypertensive therapy and continue agent
• Grade 2 symptomatic< (SBP 140-160 mmHg or DBP 90-100 mm Hg) <	• Start or adjust anti-hypertensive medication
• Grade 3< (≥ SBP 160 mmHg or ≥ DBP 100 mmHg <	• Hold agent until symptoms resolve **AND** BP < 160/90mmHg
• Grade 4< (Hypertensive crisis or malignant hypertension)	• Discontinue agent

Patients who hold or discontinue bevacizumab due to hypertension may continue other protocol treatment.

4.3.3.2 Venous Thrombotic Events

Patients should be carefully monitored for evidence of thromboembolic disease during treatment.

4.3.3.2.1 Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Hold bevacizumab. Bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on stable dose of low molecular weight heparin prior to restarting bevacizumab treatment;
- The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels);
- The patient must not have had hemorrhagic events while on study.

4.3.3.2.2 Grade 4 or for recurrent/worsening venous thromboembolic events despite full anticoagulation after resumption of bevacizumab: Discontinue bevacizumab.

4.3.3.3 Arterial Thrombotic Events

1. For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue bevacizumab. Patients may continue other protocol treatment.

2. For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue bevacizumab. Patients may continue other protocol treatment.

3. For Grade 3 cardiac ischemia/infarction, discontinue bevacizumab. Patients may continue other protocol treatment.

4. For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol treatment.

4.3.3.4 Left Ventricular Dysfunction

4.3.3.4.1 Grade 3 LV dysfunction: Symptomatic CHF responsive to intervention

- Discontinue bevacizumab and TAS 102.

4.3.3.4.2 Grade 4 LV dysfunction: Poorly controlled refractory CHF; intervention such as ventricular assist device or heart transplant is indicated.

- Discontinue all protocol treatment.

4.3.3.5 Hemorrhage/bleeding

4.3.3.5.1 For Grade 3 hemorrhage/bleeding, permanently discontinue bevacizumab and hold other protocol treatment; once hemorrhage or bleeding resolves, other protocol treatment may be continued at the treating physician's discretion

4.3.3.5.2 For Grade 4 hemorrhage/bleeding, discontinue all protocol treatment.

4.3.3.6 Proteinuria (Dose delays for bevacizumab only)

4.3.3.6.1 If nephrotic syndrome (Grade 4 proteinuria) occurs, discontinue bevacizumab. Urine protein should be checked every four weeks.

4.3.3.7 Dose Resumption Timing for TAS-102

If the patient recovers from the toxicities to the resumption criteria defined above during the 14-day treatment period (treatment days 1 through 5 and 8 through 12), with no dose reduction being required, TAS-102 therapy may be resumed (continued) during that cycle. If a dose reduction is required, study medication therapy should be resumed at the start of the next cycle at the appropriate dose level according to the instructions in Table 2. If the study medication dose is reduced, it should not be increased for subsequent cycles.

If the toxicities that are defined above recover during holiday rest period (days 13 through 28), start the next cycle on schedule at the appropriate dose level according to instructions provided in Table 2. If the toxicities that are defined above do not recover during the treatment or holiday 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, the next cycle should be started at the appropriate dose level according to instructions provided in Table 2.

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

4.4 Supportive Care

4.4.1 All supportive measures consistent with optimal patient care will be given throughout the study.

- Diarrhea Management: For symptoms of diarrhea and/or abdominal cramping that occur at any time during treatment, patients will be recommended to begin taking loperamide. Loperamide should be used at the discretion and instructions of the treating physician.

4.4.2 Pegfilgrastim, epoetin and darbepoetin alfa may be administered at the treating investigator's discretion.

4.5 Concomitant Medications/Treatments

Caution should be taken when using drugs that are human thymidine kinase substrates (e.g., stavudine, zidovudine, telbivudine). Such drugs, if used concomitantly with TAS-102, may theoretically compete with the effector of TAS-102 (i.e., FTD), for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and

consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate such as lamivudine, zalcitabine, didanosine, abacivar, etc.

Hematologic Support
Administer hematologic support as medically indicated (e.g., blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin) according to the institutional site standards.

Management of Diarrhea
Both patients and caregivers should be educated regarding the potential seriousness of chemotherapy-induced diarrhea. They should be instructed to contact the clinical site staff immediately at the first sign of loose stool.

Patients should be provided with loperamide or other standard antidiarrheal therapy and the patient instructed on how to use the therapy at the first sign of diarrhea.

The patient's fluid and electrolyte balance should be monitored, with appropriate intervention as clinically indicated with fluids and electrolyte replacement, antibiotics, and antiemetics.

Infection prophylaxis with oral antibiotics should be considered for patients with persistent diarrhea beyond 24 hours, or coincident with grade $\geq$3 neutropenia as clinically indicated.

Patients should be provided with prophylactic treatment for diarrhea, as clinically indicated.

Management of Nausea/Vomiting: Patients should be provided with antiemetic therapy as clinically indicated.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events (AEs), treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable AEs
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Survival Follow-Up

Patients will ideally be followed until death. After treatment discontinuation, a telephone call will be made to the patient (or the patient's family) every 6 months to inquire about the patient's colon cancer status, general health, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

4.8 Removal of Patients from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.9 Collaboration with other institutions

The study will be conducted in collaboration with the City of Hope Comprehensive Cancer Center, and the Ohio State University James Comprehensive Cancer Center. Dr. John Marshall is the Principal Investigator for the study and will oversee the study including the data gathering, safety and reporting. Dr. Marwan Fakih will be the main study contact at the City of Hope Comprehensive Cancer Center, and Dr. Sameh Mikhail will be the main study contact at the OSU-James Cancer Hospital. Patients will be recruited at all institutions for the study.

Monthly conference calls will be conducted between all institutions to follow up on the progress of the trial. Dr. Marshall will be responsible for coordination of the trial between all institutions. Study coordinators will notify Dr. Marshall upon the accrual of any patients in any institution.

4.9.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, at Lombardi-Georgetown, there will be a dedicated “multi-institutional” research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for Dr. Marshall and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including “remote” screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) Reviewing and confirming all study-related adverse events; 2) Submitting all SAE reports to the Georgetown IRB (The research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the “multi-institutional” coordinator will submit the final report); 3) Gathering and preparing all primary source data for review/audit by Theradex, Inc.

4.9.2 Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 - 48 hours containing the subject number, to the PI, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator (by email [hka10@georgetown.edu]). Patients should not start therapy until both PI and the multi-institutional coordinator have reviewed the patient’s records and confirmed that the patient is indeed eligible for enrollment.

4.9.3 Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

5.0 STUDY PROCEDURES

5.1 Please see time and events table below

5.2 Follow-up Procedures

Follow-up continues for 30 days after the patient has stopped taking TAS-102.
The Safety Follow-up visit can be conducted in person or by a phone call. This visit will be conducted approximately 30 days after the last dose of TAS-102. The investigator or trial staff will ask the patient questions about how he/she is feeling and if he/she has had any hospitalizations or emergency treatment since the last visit to the research site.

6.0 STUDY PROCEDURE

6.1 Time and Events Table

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Unless otherwise noted, a standard window of -1 day to + 2 days will be considered acceptable for all testing and evaluations (will not be considered study deviation).

	Study							
Study Procedure	**Pre-study**	**Treatment**				**End of Treatment / Follow-up**		**Survival Follow-up[16]**
	Treatment day -28 to -1	**All Treatment Cycles[1]**	**q 2 Weeks (1st 4 weeks)**	**Every 4 Weeks (week 5 through end of treatment)**	**Every 8 Weeks**	**End of Treatment[14]**	**Safety Follow-up[15]**	
Signed ICF	X[2]							
Demographics	X							
Medical History	X[3]		X	X				
Histologic/Cytologic Confirmation	X[4]							
Physical Exam and vitals[5]	X	X	X	X		X	X	
ECOG Performance Status[6]	X	X	X			X	X	
Concomitant Medications	X		X	X		X	X	
TSH and coagulation parameters[9]	X							
CEA[9]	X	X				X	X	
Urine protein and creatinine [9]	X					X	X	
Confirm eligibility	X[7]							
Height	X							
Weight	X	X[8]						

Hematology[9]	X	X	X			X	X	
Serum Chemistry[9]	X	X	X			X	X	
Pregnancy Test	X[10]					X[10]	X	
TAS-102 plus BevacizumabTreatment		X[11]						
Tumor Measurements (CT or MRI)	X[12]				X[12]			
ADR/SAE Assessment[13]		X	X			X	X	

1 A treatment cycle is defined as 28 days.
2 Obtain a signed and dated Informed Consent Form (ICF) from the patient prior to initiation of any study procedures and administration of TAS-102.
3 Document a patient's medical history in the patient's medical chart prior to administration of TAS-102.
4 Document histological or cytological confirmation of metastatic colorectal cancer in the patient's medical chart prior to administration of TAS-102.
5 Physical examinations including vital signs, height, weight and BSA should be performed prior to each cycle of study drug administration and/or when clinically indicated according to the clinical standard of care and documented in the patient's medical chart.
6 Performance status evaluations should be performed during the screening process prior to the first dose of TAS-102 (to confirm eligibility) and according to standard of care thereafter.
7 Assessments should be performed to confirm that the patient meets all eligibility requirements prior to administration of TAS-102 plus bevacizumab. Screening is to be completed within 14 days of starting treatment with TAS-102 plus bevacizumab.
8 Prior to each treatment cycle with TAS-102 plus bevacizumab, document patient's weight prior to TAS-102 plus bevacizumab administration as measured according to institutional standard of care.
9 Hematology (cbc with diff including platelets), serum chemistry (Complete Metabolic Panel: NA, K, Cl, CO2, BUN, Creatinine, glucose, Calcium, ALK phos, AST, ALT, Total Bilirubin, Albumin, and Total protein) and CEA assessments should be evaluated prior to each cycle of study drug administration and during each treatment cycle based on the clinical standard of care and/or when clinically indicated. Urine protein and urine creatinine, TSH and coagulation parameters (PT, PTT and INR) to be done at screening.
10 Women of childbearing potential must have a negative pregnancy test (urine) within 7 days prior to starting TAS-102 treatment. Additional pregnancy tests should be done per standard of care.
11 TAS-102 will be administered twice daily (BID) on Days 1 through 5 and 8 through 12 of each treatment cycle and bevacizumab 5 mg/kg IV will be administered on Days 1 and 15. Patients must start maintenance therapy at least 14 days (and no later than 30 days) after the last administered induction chemotherapy. In the event of holidays or inclement weather a window of + 1 day will be considered acceptable for initiation of treatment cycles (will not be considered study deviation).
12 Perform tumor assessments/imaging studies of the chest, abdomen, and pelvis every 8 weeks during treatment unless

otherwise indicated based on the treating physician's judgment. 13 Monitor patients for any untoward medical events (AEs or SAEs) from the first dose of study medication through 30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier. 14 End of Treatment will occur on the day of the last dose of TAS-102 or within 14 days later. 15 Safety follow-up continues for 30 days after the patient has stopped taking TAS-102. 16 Patients will be followed until death. After 30 days follow up visit, a telephone call will be made to the patient (or the patient's family) every 6 months to inquire about the patient's survival status and names of antineoplastic therapies utilized since discontinuation of study treatment.	

6.2 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);
5.5.2 Patient withdraws consent (termination of treatment and follow-up);
5.5.3 Patient is unable to comply with protocol requirements;
5.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;
5.5.6 The treating physician judges continuation on the study would not be in the patient's best interest;
5.5.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious AE [SAE]);
5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
5.5.9 Patient is lost to follow-up
Example language: If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

7.0 Measurement of Effect

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

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).

7.1.2 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 $\geq$ 20 mm with

conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 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 or absence of each should be noted throughout follow-up.

7.1.3 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 28 days 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 when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

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

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

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

7.1.4.3 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
C	CR	No	CR	≥6 wks. confirmation
C	Non-CR/Non-PD	No	PR	≥6 wks. confirmation
P	Non-PD	No	PR	
S	Non-PD	No	SD	documented at least once ≥6 wks. from baseline

P	Any	Yes or	PD	no prior SD, PR or CR
An	PD*	Yes or	PD	
An	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Note: If subjects respond to treatment and are able to have their disease resected, the patients' response will be assessed prior to the surgery.

7.1.5 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 recurrent 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.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment (TAS-102 plus bevacizumab) to time of progression, or patient's death from any cause.

7.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic AEs (**http://ctep.cancer.gov/reporting/ctc.html**) and modified criteria for hematologic AEs (Appendix C). Other Efficacy Parameters

8.0 ADVERSE EVENTS

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be

reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an AE, regardless of its relationship to study drug, will be monitored until:

- the AE resolves or the symptoms or signs that constitute the AE return to baseline (and remain at baseline for 30 days;
- any abnormal laboratory values have returned to baseline for at least 30 days;
- start of new antitumor therapy
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

8.2 Definitions

8.2.1 Definition of Adverse Event

An adverse event is any undesirable experience associated with the use of a medical product in a patient. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.2.2 Severity of Adverse Events

All AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

8.2.3 Serious Adverse Events

A “serious” AE (SAE) is defined in regulatory terminology as any untoward medical occurrence that:

8.2.3.1 Results in death.

If death results from (progression of) the disease, it should be reported as event (SAE) itself.

8.2.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

8.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization.

8.2.3.4 Results in persistent or significant disability or incapacity.

8.2.3.5 Is a congenital anomaly/birth defect

8.2.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as an SAE. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of AE using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the AE using the NCI CTCAE v4.

Step 3: Determine whether the AE is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment and one of the following conditions is true:
  - A positive de-challenge, meaning the event resolves when the drug is stopped.
  - A positive re-challenge, meaning the event reappears when the drug is restarted.
  - The event cannot be reasonable explained by the patient's clinical state and/or other administered therapies..
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment. There is no evidence to suggest a causal relationship between the drug and the AE.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the AE.
Expected events are those that have been previously identified as resulting from administration of the agent. An AE is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known AEs listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

8.4 Reporting Requirements for Adverse Events

The investigators will follow standard guidelines (CTCAE v. 4.0) for reporting of AEs. Serious AE information (whether or not related to TAS-102) as well as reports of pregnancy, overdose, or medication error will be reported. In addition, all grades of adverse drug reactions (ADRs, AEs related to study medication) and any AE that results in treatment discontinuation will be recorded as study data on CRFs.

8.4.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious AEs, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- Investigational Agents: TAS 102
- Commercial Agents: Bevacizumab
- When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.
- Late Phase 2 and Phase 3 Studies
  Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention 1

- The IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR). UPRs are defined as any problem or event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

- The FDA should be notified within 7 calendar days of any unexpected fatal or life-threatening AE with possible relationship to study drug, and 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.4.2 Routine Reporting

- All other AEs- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.5 Premature termination of the study

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

9.0 DRUG INFORMATION

9.1 TAS-102

- *Other names for the drug:* trifluridine (FTD) and tipiracil hydrochloride
- Classification - type of agent: Antitumor nucleoside
- Mode of action:

TAS-102 is a novel nucleoside antitumor agent consisting of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is the active component of TAS-102 and is directly incorporated into DNA, leading to DNA dysfunction. However, when FTD is taken orally it is largely degraded to an inactive form. TPI prevents the degradation of FTD.

FTD, an antineoplastic antimetabolite, is a thymidylate synthase (TS) inhibitor. Based on preclinical data, FTD also appears to be incorporated into deoxyribonucleic acid (DNA). Preliminary results suggest that when FTD is incubated with cancer cells at a high concentration for short time periods, it is passively incorporated into the DNA fraction of the cell, and that such behavior of FTD is different from the primary cytotoxic mechanism of 5-FU and 2'-deoxy-5 fluorouridine (FdUrd), i.e., inhibition of TS.

- *Storage and stability:* TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths (expressed as FTD content):
- The 15mg white, round table contains 15mg FTD and 7.065 mg TPI as active ingredients
- The 20-mg pale-red, round tablet contains 20mg FTD and 9.42 mg TPI as active ingredients.
- Both tablet strengths contain lactose monohydrate, pregelatinized starch, stearic acid,hlypromellose, titanium dioxide, polyethylene glycol, and magnesium stearate. The 20mg tablet also contains red ferric oxide.
- Store below 30°C (86°F)
- Protocol dose: 35mg/m^2/dose
- Route of administration for this study: oral
- *Incompatibilities:* Patients should not receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or endocrine therapy while receiving TAS-102.
- Availability: provided by sponsor; specify if provided free of charge as this has implications for the consent form.)
- *Side effects:* Refer to the package insert for a comprehensive list of AEs. Common side effects include the following: Nausea, vomiting, diarrhea, leukopenia, neutropenia, anemia, fatigue, loss of appetite, infection, constipation,

thrombocytopenia, alopecia, rash, proteinuria, headache, arthralgia, hypoalbuminemia, anxiety, elevated liver enzymes.

9.1.1 Return and Retention of Study Drug (TAS-102)

The drug will be destroyed according to the institution's policy and instructions

9.2 Bevacizumab

Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) is a recombinant monoclonal antibody (mAb) IgG1 antibody that has been developed for humans from murine anti-VEGF mAb A4.6.1. The murine mAb A4.6.1 is specific for human VEGF, binding to all of the known isoforms of the ligand (eg, VEGF121, VEGF165, VEGF181, VEGF206). It is formed through alternative gene splicing, preventing it from binding to VEGFRs on vascular endothelial cells.
Bevacizumab is a standard FDA-approved treatment for colorectal cancer treatment.

a. Very Common Side Effects (reported in ≥10% of patients):

- Epistaxis
- Headache
- Hypertension
- Rhinitis
- Proteinuria
- Dry skin
- Rectal hemorrhage
- Taste alteration
- Lacrimation disorder
- Back pain
- Exfoliative dermatitis

b. Most serious side effects (not likely [not common], but sometimes fatal):

- GI perforation. Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.3% to 3.2% across clinical studies.

- The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients

- Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 0.4% to 6.9%.

c. Other possible serious side effects

- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
    - GI-vaginal fistulae occurred in 8.3% of patients in a cervical cancer trial
    - Hypertension (grade 3–4, 5%–18%)
    - Posterior reversible encephalopathy syndrome (PRES) (<0.5%)

- Infusion reactions: infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients.
- Non-GI fistulae (<1% in trials across various indications; 1.8% in a cervical cancer trial)
- GI fistulae (up to 2% in metastatic colorectal cancer and ovarian cancer patients)
- Arterial thromboembolic events (grade ≥3, 2.6%)
- Proteinuria (nephrotic syndrome, <1%)

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is an open-label single arm, prospective, Phase II study. Study endpoints are defined as follows:

Progression-free survival (PFS): PFS will be defined as the time in days from study entry until progression or death from any cause. Patients who are alive and free of progression on the date of closing follow-up will be censored on the date of the last tumor assessment.

Response rate: Objective response will include RECIST criteria with confirmed classification of complete response (CR) or partial response (PR). Patients who are lost to follow-up without a valid response assessment will be classified as not benefiting.

Clinical benefit: Classification will follow the RECIST criteria and will be defined as successful confirmed classification of stable disease (SD), PR, or CR. Patients who are lost to follow-up without a valid response assessment will be classified as not benefiting.

Overall survival (OS): OS will be defined as the time in days from study entry until death. Patients who are alive on the date of closing follow-up will be censored on date of last contact.

Time to progression (TTP): TTP will be defined as the time in days from study entry until progression. Patients who are free of progression on the date of closing follow-up will be censored on the date of the last tumor assessment. Patients who died without progression will be censored on their date of death.

Duration of disease control (DDC): DDC will be defined as the time in days from the date first noted of stable disease or better until progression or death. Patients who are free of progression on the date of closing follow-up will be censored on the date of the last tumor

assessment. Patients who died without progression will be censored on their date of death.

Objective response rate (ORR) overall: ORR will be defined as the sum of partial responses (PR) plus complete responses (CR). When defined in this manner, ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study.

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

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

Disease control rate (DCR): DCR is defined as complete response + partial response + stable disease at 6 months after treatment initiation.

Overall response rate (ORR): FDA has defined ORR as the sum of partial responses plus complete responses. When defined in this manner, ORR is a direct measure of drug antitumor activity.

10.2 Sample Size and Accrual

The primary efficacy endpoint of this single arm study is progression free survival (PFS) of switch maintenance with TAS-102 plus Bevacizumab following induction chemotherapy. The null hypothesis is that the median PFS with observation alone is less than 5 months (the choice of a median of 5 months for the median of observation was largely based on the result of CAIRO-3 trial (Simkens LH, et al lancet), which is by far the best and strongest evidence we have in this setting). In the CAIRO-3 trial, the observation arm had a median PFS of 4.1 months. The 5 months is chosen to be conservative in calculating the sample size so that the difference of the treatment effect will be smaller which will result in a larger sample size.
The alternative hypothesis is that the new treatment will be able to increase the PFS to 8 month. The sample size calculation is based on the assumption of an exponential distribution of the PFS time. Patients entering the trial are assumed to follow a Poisson distribution. A total of 40 patients will be needed at a 0.05 significance level to provide at least 80% power to test the median PFS difference of 8-month vs 5 month for a 1-sided test, assuming that the accrual time is 18 months and minimum follow-up time is 6 months. Therefore study duration will run for a minimum of 24 months. If we account for a 10% of patient dropout rate, then 45 patients will be needed to enroll to the study. Patients will be followed for a maximum of 5 years (60 months), or until patient death.

10.3 Data Analyses Plans

Descriptive statistics will be used to summarize patients' demographics and all laboratory parameters. Toxicity and AEs will be summarized by the grade and frequency according to the CTCAE for all treated subjects. For patients who will be removed for toxicity, they will be included for summary of the AE but not for the PFS evaluation. To test the null hypothesis of 5 month vs. the alternative of at least 8 month of median PFS, a one-sample log-rank test will be used in which the test statistic will follow a chi-square distribution with 1 degree of freedom. The time-to-event endpoints (PFS, OS, TTP, and DDC) will be estimated using the Kaplan-Meier method. Estimates of the rates (ORR and DCR) will be presented with their 95% confidence intervals.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by IRB. All investigators will follow the University conflict of interest policy.

11.2 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.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Registration Procedures

All patients must be registered with the Georgetown CRMO (Clinical Research Management Office) before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Georgetown University Multi-Site Study Coordinator.
All study documents will be redacted by the local site to remove Protected Health Information as defined by HIPAA, and will be labeled with subject initials and number. These materials will be uploaded by the local site to a secure password-protected cloud-based Georgetown Box portal. Access to Box will be provided by Georgetown-LCCC staff, who will receive and review the source documents and confirm eligibility. The local site will receive written notification from Georgetown-LCCC regarding eligibility.

11.5 Data Management

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study Phase II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

Serious Adverse Events (SAEs) are required to be reported to the IRB as per the local policy. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

11.6 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.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

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

11.6.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

11.6.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Protocol Deviations: Each center should enter policy

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.7 Amendments to the Protocol

Only the Lead PI may amend the protocol. There is only one version of the protocol active at any one time. Should amendments to the protocol be required, the amendments will be originated and documented by the Lead Principal Investigator at Georgetown University. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be approved by the IRB of record at study site prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

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

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

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 CFR parts 50 and 56 of the Code of Federal Regulations and/or the Declaration of Helsinki. 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 at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Investigator oversight across multiple sites will be conducted via regularly occurring conference calls, to include review of enrollment and safety data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

1. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer inst. 2013;105(3):175-201.
2. Arnold D, Stein A. New developments in the second-line treatment of metastatic colorectal cancer: potential place in therapy. Drugs. 2013;73(9):883-891.
3. Scheithauer W, Rosen H, Kornek GV, et al. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ. 1993;306(6880):752-755.
4. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. J Clin Oncol. 1992;10(6):904-911.
5. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systemic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ. 2000;321(7260):531-535.
6. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):303-12
7. De Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without Oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938-2947.
8. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouacil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and Oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. J Clin Oncol. 2006;24:3347-3353.
9. Diaz-Rubio E, Tabernero J, Gómez-España A, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol. 2007;25:4224–4230.
10. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22:229–237.
11. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomised trial. Lancet. 2000;355:1041–1047.
12. Fuchs CS, Marshal JL, Mitchell E, et al. A randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C study. J Clin Oncol. 2007;25:4779–4786.
13. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25(13):1670-1676.
14. Grothey A, Hecrick EE, Mass RD, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. J Clin Oncol. 2008;26(2):183-189.
15. Siena S, Peeters M, Van Cutsem E, et al. Association of progression-free survival with patient-reported outcomes and survival: results from a randomised phase 3 trial of panitumumab. Br J Cancer. 2007;97(11):1469.
16. Giessen C, Laubender RP, Ankerst DP, et al. Progression-free survival as a surrogate endpoint for median overall survival in metastatic colorectal cancer: literature-based analysis from 50 randomized first-line trials. Clin Cancer Res. 2013;19(1):225-235.
17. Yalcin S, Uslu R, Dane F, et al. Bevacizumab (BEV) plus capecitabine as maintenance therapy after initial treatment with BEV plus XELOX in previously untreated patients with metastatic colorectal cancer: mature data from STOP and GO, a phase III, randomized, multicenter study. J Clin Oncol . 2010;30:(suppl; abstr 3565).

18. Díaz-Rubio E, Gómez-España A, Massutí B, et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist. 2012;17(1):15.
19. Koeberle D, Betticher DC, Von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41-06). J Clin Oncol. 2013:31(suppl; abstr 3503).
20. Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and Oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol. 2012;30(15):1755-1762.
21. Koopman M, et al. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC) (abstract). J Clin Oncol. 2014;32(suppl 3; abstr LBA388).
22. Arnold D, Graeven U, Lerchenmuller CA, et al. Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): a phase III non-inferiority trial (AIO KRK 0207) (abstract). J Clin Oncol. 2014;32:5s(suppl; abstr 3503).
23. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomized, placebo-control phase 2 trial. Lancet Oncol. 2012;13:993-1001.
24. Robert J. Mayer, Eric Van Cutsem, Alfredo Falcone, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer N Engl J Med 2015;372:1909-19.

25. DuBois D, Dubois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med.* 1916;17:863-871.

13.0 APPENDICES

APPENDIX A ECOG PERFORMANCE STATUS

Protocol No.

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.	