Document Coversheet

Study Title:

A Phase II Study of TAS-102, Irinotecan, and Bevacizumab in Pre-treated Metastatic Colorectal Cancer (TABAsCO)

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Confidentiality Statement

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1 OBJECTIVES

1.1 Primary Objective

- Determine the median progression free survival (PFS) benefit of FOLFIRI naïve patients treated with TAS-102 + irinotecan + bevacizumab as compared to historic control groups treated with FOLFIRI + bevacizumab

1.2 Secondary Objectives

- Estimate the objective response rate (ORR), median overall survival (OS), and adverse event (AE) profile

2 BACKGROUND

Colorectal cancer remains the 2nd most common cause of cancer related death in the US. Despite improvements in systemic therapy and deeper understanding of patient selection for therapies, after first line therapy, median achieved progression free survival (PFS) stands near 6 months with median overall survival (OS) at 11-13 months (1-3). FOLFIRI with bevacizumab remains a standard second line treatment, with bevacizumab being the most common biologic and FOLFIRI the most common chemotherapy regimen utilized in the second-line setting in the US (4, 5). Second-line treatment with FOLFIRI + an anti-angiogenic agent has typically produced a median PGS in the range of 6-7 months (1-3).While such regimens are clearly active, further gains are desperately needed.

2.1 Study Drugs

2.1.1 TAS-102

Preclinical Studies with TAS-102

TAS-102 (Lonsurf®) consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, with a molar ratio of 1:0.5. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

TAS-102 has a distinct mechanism of action from 5-FU and in preclinical models can overcome 5-FU resistance (6). With a twice daily dosing schedule, DNA incorporation is thought to be the major mechanism of action; the base excision repair (BER) pathway and glycosylation responses also appear to differ from that seen with 5-fu-mediated DNA damage (7). Further, there is additive effect when TAS-102 is combined with irinotecan in 5-FU sensitive and resistant cell lines (8). Interestingly, induction of apoptosis is most efficient *in vitro* when the irinotecan metabolite, SN-38, is administered 24 hours prior to TAS-102(9).

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of TAS-102 can be found in the Investigator's Brochure.

Clinical Studies with TAS-102

In September 2015, TAS-102 was FDA approved for use in refractory metastatic colorectal cancer on the basis of the RECOURSE trial. The Phase III RECOURSE trial randomized 800 patients (2:1) to TAS-102 vs placebo and demonstrated an improvement in median OS (7.1 vs 5.3 mo, HR 0.68; $p < 0.001$) as well as PFS (HR 0.47; $p < 0.001$)(10). The most common side effects seen were marrow suppression (anemia, neutropenia, and thrombocytopenia), fatigue, nausea, vomiting, and anorexia. In light of this, TAS-102 has been introduced into the clinic as a standard of care agent in the refractory setting. Biomarkers predictive of efficacy remain elusive.

As TAS-102 carries potential to overcoming 5-FU resistance due to differing mechanisms of action, initial clinical efforts have been taken to combine TAS-102 with agents commonly used in 1st and 2nd–line therapy. The Phase II TASCO1 study evaluated the potential of a TAS-102 based regimen to outperform classic fluoropyrimidines, capecitabine, when either was combined with bevacizumab. The primary endpoint was PFS. There was a non-significant trend toward superior outcome with TAS-102, as compared to capecitabine, with a median PFS of 9.23 vs 7.82 months (HR 0.71, 95% CI 0.48, 1.06). Interestingly, OS appeared to be improved with TAS-102 in this study, at 18 months vs 16.16 months (HR 0.56, 95% CI 0.32, 0.98), suggesting that TAS-102 may confer greater benefit than capecitabine (11).

This agent has also been combined with oxaliplatin and irinotecan successfully. When combined with irinotecan (180 mg/m2 every 14 days) and bevacizumab (5 mg/kg every 14 days), TAS-102 is able to be safely dosed at 25 mg/m2 twice daily, days 1-5 of a 14 day regimen(12). Given in this fashion, neutropenia, and leucopenia are the most common ≥ grade 3 AEs. Grade 3 diarrhea was noted in 12% of patients, fatigue in 8% and other severe AEs occurring ~ 8% of patients or less. Notably in the expansion cohort of this Phase 1 study where 21/24 (88%) patients had received prior irinotecan, 3 (13%) PRs were observed (2 previously irinotecan exposed) and 17/24 (71%) patients achieved stable disease, with a median PFS of 7.9 months. 1/3 of patients were on study for > 40 weeks. This compares favorably to the second-line TML, VELOUR and RAISE studies, which produced median PFS results of 5.7, 6.9, and 5.7 months, respectively(1-3).

The above cited Phase I data was established within an irinotecan pre-treated population, all but 3 patients having had prior irinotecan. As such, one might expect greater efficacy to be seen in an irinotecan naïve population. To test this hypothesis, we propose a single arm Phase II study of TAS-102, irinotecan and bevacizumab as second-line therapy in individuals with metastatic colorectal cancer who received first-line fluoropyrimidine and oxaliplatin-based therapy.

2.1.2 Irinotecan

Irinotecan is a derivative of camptothecin. Camptothecin interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent relegation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks. Irinotecan is a standard agent used in the treatment of advanced colorectal cancer, with multiple supporting studies in the second-line setting.

2.1.3 Bevacizumab

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression. Bevacizumab has demonstrated efficacy in the second line setting and is a standard option which is considered in combination with chemotherapy (1, 13).

2.2 Rationale for Study Combination

Following first line chemotherapy for metastatic colorectal cancer, as part of second-line chemotherapy, typically the fluoropyrimidine, 5-FU, is continued with a switch of the other agents. In the US, the majority of patients have traditionally received 1st line therapy with FOLFOX + a biologic, making FOLFIRI + bevacizumab a very common second-line treatment. This regimen is expected to confer a PFS of approximately 6 months, with median survival standing in the range of 11-13 months (1-3).

TAS-102 has a distinct mechanism of action from 5-FU and in preclinical models can overcome 5-FU resistance. In limited direct comparisons to classic fluoropyrimidines (capecitabine), there are signs that TAS-102 may possess greater activity. Safety in combining TAS-102 with irinotecan and bevacizumab has already been demonstrated, with encouraging activity beyond what would be expected with FOLFIRI + bevacizumab.

Thus, we hypothesize that in the second-line metastatic setting:

1. TAS-102-based combination therapy (TAS-102 + irinotecan + bevacizumab) will demonstrate greater efficacy than the historic comparator, FOLFIRI (5-FU + Leucovorin + irinotecan) + bevacizumab.
2. The combination will demonstrate a favorable toxicity profile with TAS-102 administered at the previously established regimen-specific MTD of 25 mg/m2 twice daily for 5 days of a 14-day treatment, with standard dose irinotecan and bevacizumab.

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

NOTE: For blood Chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

To be included in this study, participants must meet the following criteria:

1. Age ≥ 18 years old.
2. Advanced colorectal cancer (metastatic or unresectable): Histologically or cytological proven adenocarcinoma of the colon or rectum which is metastatic or otherwise incurable.
3. Prior treatment with a fluoropyrimidine (5-FU or capecitabine) and oxaliplatin in the metastatic/unresectable setting **OR**, recurrence within 12 months of adjuvant therapy with a regimen that included oxaliplatin.

4. Have an ECOG Performance Status of 0-1. Refer to **Appendix A**.
5. Have the following clinical laboratory values:
    - Hemoglobin ≥ 9 g/dL
    - Absolute neutrophil count ≥ 1500/mm^3
    - Platelet count ≥ 100,000/mm^3
    - Creatinine < 1.5 ULN or if ≥ 1.5 x ULN CRCL ≥ 30 mL/min (by Cockroft-Gault)
    - Bilirubin < 1.5 x ULN
    - AST/ALT ≤ 2.5 x ULN or ≤ 5 x ULN if with hepatic metastases
6. Have measurable disease per RECIST 1.1 criteria present.
7. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
8. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix B** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Prior treatment with TAS-102 or irinotecan.
2. Anti-cancer therapy within 2 weeks of the planned first dose of study medication.
3. Unresolved toxicities from prior therapy of > Grade 1, excluding alopecia or similar toxicities which are not deemed to be clinically significant or put the participant at greater risk. Grade 2 neuropathy is permitted.
4. Major surgery within 4 weeks of anticipated start of therapy.
5. Uncontrolled hypertension: systolic blood pressure ≥ 150, diastolic blood pressure ≥ 100.
6. Unstable angina, symptomatic congestive heart failure or cardiac arrhythmia requiring anti-arrhythmic therapy (beta-blockers, calcium channel blockers and digoxin are allowed).
7. Arterial or venous thrombotic or embolic events within 3 months of study initiation, unless well controlled on stable anti-coagulation for ≥ 2 weeks. This excludes uncomplicated catheter associated venous thrombosis.
8. History of cerebrovascular or myocardial ischemia within 6 months of initiation.
9. NCI CTCAE v 5.0 Grade 3 or greater hemorrhage within the past 4 weeks.
10. Proteinuria ≥ 2+, unless 24-hour urine collection demonstrates ≤ 1 g of protein OR spot protein: creatinine demonstrates a ratio of ≤ 1.
11. Untreated brain metastases.
12. History of abnormal glucuronidation of bilirubin (Gilbert's Syndrome).

13. History of second primary malignancy within 3 years prior to enrollment, excluding in-situ cervical carcinoma, non-melanoma skin cancer or malignancy of equivalent risk which is highly unlikely to require systemic treatment in the next 2 years.
14. Have known active infection which would heighten the risk of complications.
15. Pregnant or nursing female participants.
16. Unwilling or unable to follow protocol requirements.
17. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.

Refer to **Appendix C** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

3.4 Special Populations

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Prisoners
- Pregnant women

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 36 evaluable participants are required for the primary analysis. To account for potential dropouts, a total of 42 patients may be accrued. Approximately 20 participants are expected to be accrued at Roswell Park with approximately 20 participants accrued from the accompanying external sites (collectively). Accrual is expected to take 36 months.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified/recruited/screened from patients at the GI clinic at Roswell Park and participating sites and from multi-disciplinary conference discussion.

6 MULTI-SITE RESEARCH

This is a multi-site study. It is the responsibility of the lead investigator to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.

- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to **Appendix D**: Instructions for Multi-Site Studies for additional details.

7 STUDY TIMELINES

Accrual is expected to take 36 months with an additional 24 months of follow-up. The estimated time frame that the analysis of the primary endpoint would be evaluable is approximately 4 years (48 months) after study commencement.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- The primary endpoint is the median progression free survival (PFS) of the study population. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 2 cycles (8 weeks) of therapy.

8.2 Secondary Endpoints

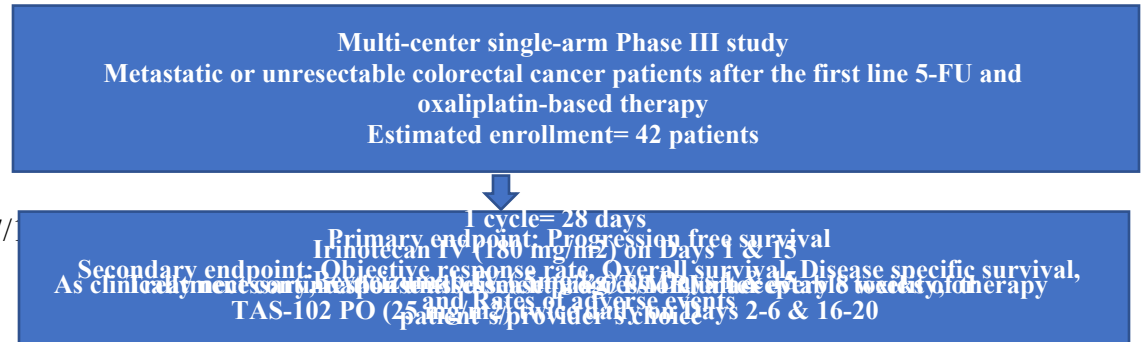
- Objective response rate (ORR) will be tabulated based on RECIST v1.1 criteria.
- Median overall survival (OS) from the date of enrollment to the time of death will be documented.
- Aggregate rates of adverse events as measured by CTCAE v 5.0 will be recorded to objectively measure toxicities of the combination therapy.

9 DESIGN

This is an open-label, non-randomized, multi-center, Phase II study of TAS-102, irinotecan, and bevacizumab in participants with advanced (metastatic or unresectable) colorectal cancer who have received prior treatment with a fluoropyrimidine (5-FU or capecitabine) and oxaliplatin or, who have had a recurrence within 12 months of adjuvant therapy with a regimen that included oxaliplatin. For study purposes, a cycle will be defined as 28 days. Response assessment via CT imaging (or MRI) will be obtained every 8 weeks. Treatment will continue until disease progression, in the absence of unacceptable toxicity or patient/provider choice.

Treatment is intended for an outpatient setting. The study schema is depicted in **Figure 1**.

Figure 1 Study Schema



10 TREATMENT

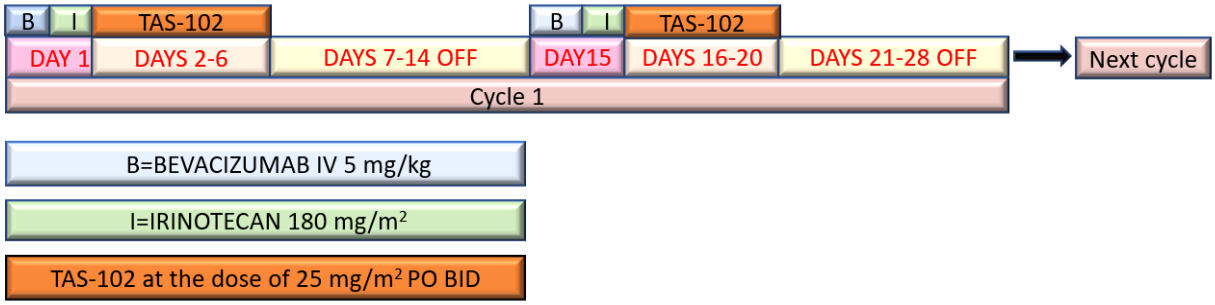
Based upon the presented safety data (NCT01916447) and the pre-clinical data regarding sequencing, the following would be administered every 28 days:

- Irinotecan (180 mg/m^2) IV Day 1 and Day 15 of each treatment cycle
- Bevacizumab* (5 mg/kg) IV Day 1 and Day 15 of each treatment cycle
- TAS-102 (25 mg/m^2) twice daily, orally, on Day 2- Day 6 and Day 16- Day 20 of each cycle

* Use of bevacizumab biosimilars at the same dose is allowed.

Figure 2 provides a graphical representation of the treatment cycle.

Figure 2 Treatment Dosing and Duration



Patients will present for evaluation on Days 1 and 15 of every cycle. Subjects must meet the below criteria (Table 1) to be eligible to proceed with treatment on either of Days 1 or 15 of each cycle. Patients will continue treatment until the development of progressive disease or intolerable toxicity; barring a patient or investigator-related decision to discontinue therapy for other reasons.

Table 1

Criteria for Retreatment before Treatment Initiation
• ANC ≥ 1,500/ mm^3 or febrile neutropenia is resolved
• Platelet count ≥ 75,000/mm^3
• AST and/or ALT CTCAE grade < or equal to five times ULN and Bilirubin < 1.5 X ULN
• Any additional non-hematologic toxicity of Grade ≥ 3 which is potentially attributable to TAS-102 or irinotecan must have resolved to Grade ≤ 1 (or baseline)*

* Patients with bevacizumab related complications which require holding of bevacizumab may continue the other agents, if appropriate.

10.1 Dose Modifications and Treatment Delays

NOTE: Please refer to Table 1 for criteria for retreatment before treatment initiation on Day 1 and Day 15 of each cycle. If patients discontinue one of the medications due to intolerance, they are permitted to and should be advised to continue on treatment with the other agents. For any dose reduction which would decrease irinotecan below 90 mg/m^2 or TAS-102 below 20 mg/m^2 BID, the respective agent should be discontinued altogether. If a toxicity (including those not specifically described below) is deemed to be clearly related to only one drug, dose modification of only that singular drug is permitted. Bevacizumab is administered at a singular dose basis. Thus, qualifying events will result in a hold or discontinuation of therapy rather than dose modification. If any of the 3 agents has to be discontinued for toxicity, patients can remain on treatment with the other 2 (i.e. TAS-102/bevacizumab or irinotecan/bevacizumab or irinotecan/TAS-102). Patients can remain on study if 2 agents have to be discontinued for toxicity (i.e. irinotecan or TAS-102) provided that they continue to derive clinical benefit from participation in the study. Patients who have to stop both irinotecan and TAS-102 will be taken off study.

10.1.1 TAS-102 Dose Modifications for Adverse Reactions

TAS-102 is to be initiated at the recommended dose of 25 mg/m2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food or within one hour of completion of morning and evening meals, on Days 2 through 6 and Days 16 through 20 of each 28-day cycle. Initial dosing calculation based on body surface area (BSA) with dose rounded to the nearest 5 mg increment. Please refer to **Table 2** for calculation of the initial dosage and the number of tablets per dose.

As applicable, this table can be utilized to determine the optimal pill combinations at the time of any dose reductions, as well. In the instance that TAS-102 is dose reduced, simply calculate the new dose based upon the BSA, utilizing the 20 mg/m2 dose level. Round the dose to the nearest 5 mg. The table then provides guidance as to the number and strength of tablets that would be recommended. **Permanently discontinue TAS-102 in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily**. Do not escalate TAS-102 dosage after it has been reduced.

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

- Absolute neutrophil count (ANC) < 500/mm^3 or febrile neutropenia
- Platelets < 50,000/mm^3
- Grade 3 or 4 non-hematologic adverse reaction

Table 2 TAS-102 Initial Dose Calculation

BSA (m^2)	Total Daily dosing (mg: AM + PM)	Dose (mg) administered twice daily	Tablets per dose -15 mg	Tablets per dose-20 mg
<1.07	50[1]	25	2[1]	1[1]
1.07-1.22	60	30	2	0
1.23-1.52	70	35	1	1
1.53-1.68[2]	80	40	0	2

1.69-1.83	**90**	**45**	**3**	**0**
1.84-1.98	**100**	**50**	**2**	**1**
1.99-2.14	**100**	**50**	**2**	**1**
2.15-2.29	**110**	**55**	**1**	**2**
2.30-2.49	**120**	**60**	**0**	**3**
2.5-2.69	**130**	**65**	**3**	**1**
2.7-2.89	**140**	**70**	**2**	**2**
2.9-3.09	**150**	**75**	**1**	**3**
>3.09	**160**	**80**	**0**	**4**

1. Daily total doses lower than 50 mg should not be utilized. At this daily dosing, 20 mg would be administered in the AM and 30 mg in the PM, with the tablet combination described.

2. For participants with BSA > 1.69 m^2, the maximum dose is not to exceed 80 mg (i.e., 80 mg AM and 80 mg PM).

TAS-102 tablets to be taken as whole and not to be crushed.

If a dose is vomited or missed, the dose should not be retaken, and the patient should continue with the next scheduled dose.

Once the dose is established, dosing recalculation is not necessary unless there is a more than 10% change in weight. At the investigator's discretion, dosing may be adjusted for changes of < 10%.

10.1.2 Irinotecan Dose Modifications for Adverse Reactions

Dosage: To be administered at a dose of 180 mg/m^2 as an IV infusion on Days 1 & 15 in conjunction with an antiemetic regimen. A 5HT-3 blocker as well as a corticosteroid is the recommended minimum prior to infusional treatments (e.g. palonosetron 0.25 mg IV or ondansetron 16 mg IV, with dexamethasone 12 mg po). The choice of regimen for nausea prophylaxis is to be per institutional standard of care.

10.1.3 Dose Modifications and Toxicity Management

Table 3 depicts dose levels, which correspond to toxicity-related dose modifications, described in the section(s) below. Permanently discontinue TAS-102 in patients unable to tolerate a dose of 20 mg/m^2 orally twice a day.

Table 3 Dose Levels

Agent	Initial Dose (Level 0)	Level -1	Level -2	Level -3	Level -4
Irinotecan	180 mg/m^2	150 mg/m^2	150 mg/m^2	120 mg/m^2	90 mg/m^2
TAS-102	25 mg/m^2 BID	25 mg/m^2 BID	20 mg/m^2 BID	20 mg/m^2 BID	20 mg/m^2 BID
Bevacizumab	5 mg/kg	No dose reduction	No dose reduction	No dose reduction	No dose reduction

I. Management of Hematologic Toxicities

a. Thrombocytopenia

Table 4 Dose Modifications for Thrombocytopenia

Grade (NCI CTCAE version 5.0)	Treatment Delay	Irinotecan	TAS-102
Grade 1 or LLN - 75,000/mm^3	Hold until platelet count ≥ 75000 /mm^3	Continue at same dose level	Continue at same dose level
Grade 2 or LLN - <75000/mm^3, 1st occurrence	Hold until platelet count ≥ 75000 /mm^3	Continue at same dose level	Continue at same dose level
Grade 2 or LLN - <75000/mm^3, each subsequent occurrence	Hold until platelet count ≥ 75000 /mm^3	Dose reduce by one level (e.g. level -1)	Dose reduce by one level (e.g. level -1)
Grade 3 or <50000-25,000/mm^3 Grade 4 or <25,000/mm^3, each occurrence	Hold until platelet count ≥ 75000/mm^3	Dose reduce by one level (e.g. level -1)	Dose reduce by one level (e.g. level -1)

LLN= Lower limit of normal

b. Neutropenia

Table 5 Dose Modifications for Neutropenia *

Grade (NCI CTCAE version 5.0)	Treatment delay	Irinotecan	TAS-102
Grade 1 or Grade 2 (< 7 days) ANC < LLN - 1000/mm^3	Hold until ANC ≥ 1500/mm^3	Continue at same dose level	Continue at same dose level
Grade 2 ≥ 7 days ANC < LLN – 1000/mm^3	Hold until ANC ≥ 1500/mm^3	Dose reduce by one level (e.g. level -1)	Dose reduce by one level (e.g. level -1)
Grade 3 or ANC < 1000-500/mm^3 Grade 4 or ANC <500/mm^3, each occurrence	Hold until ANC ≥ 1500/mm^3	Dose reduce by one level (e.g. level -1)	Dose reduce by one level (e.g. level -1)

LLN= Lower limit of normal, ANC= absolute neutrophil count

*** If neutropenia grade 2 or higher lasts ≥ 7 days, prophylactic non-pegylated granulocyte stimulating growth factor (G-CSF, i.e. filgrastim or biosimilar) should be considered, to be initiated 24 hours after the last TAS-102 dose (when study treatment dosing restarts).**

c. Febrile Neutropenia

Table 6 Dose Modifications for Febrile Neutropenia*

Febrile Neutropenia	Treatment delay	Irinotecan	TAS-102
1st occurrence	Hold dose until resolved	Dose reduce by one level (e.g. level -1)	Dose reduce by one level (e.g. level -1)
2nd occurrence	Hold dose until resolved	Dose reduce by one level (e.g. level -2)	Dose reduce by one level (e.g. level -2)
3rd occurrence	Hold	Permanently discontinue	Permanently discontinue

* ANC <1000/mm3 with a single temperature of 38.3 degrees C (101 degrees F) or a sustained temperature of >= 38 degrees C (100.4 degrees F) for more than one hour.

In case of febrile neutropenia (1st occurrence), prophylactic non-pegylated G-CSF, i.e. filgrastim or biosimilar) has to be initiated 24 hours after the last TAS-102 dose (when study treatment dosing restarts), unless the patient is already on for prior neutropenia.

II. Management of Non- Hematologic Toxicities

Note: For early-onset diarrhea, diaphoresis or bradycardia resulting from irinotecan infusion, consider the following:

- Atropine, 0.4 mg, subcutaneous, PRN or 0.2 mg, subcutaneous, PRN for a total of up to 1 mg.

a. Diarrhea

Table 7 Dose Modifications for Diarrhea[1]

Grade (NCI CTCAE version 5.0) [2]	Irinotecan	TAS-102
Grade 1 or 2	Continue at same dose level	Continue at same dose level
Intolerable grade 2 Grade 3 or 4: 1st occurrence	Dose reduce to next level (level -1)	Dose reduce to next level (level -1)
Grade 3 or 4: 2nd occurrence	Dose reduce to next level (level -2)	Dose reduce to next level (level -2)
Grade 3 or 4: each additional occurrence [3]	Dose reduce to next level (level -3, etc.) [3]	Dose reduce to next level (level -3, etc.) [3]

1. This table refers to modifications for diarrhea optimally managed with supportive measures. If sub-optimally managed with anti-motility agents, oral hydration, institution of these measures should precede any dose reductions.
2. Grade 1= Increase of <4 stools/day over baseline or mild increase in ostomy output; Grade 2= Increase of 4-6 stools/day over baseline or moderate increase in ostomy output limiting ADLS; Grade 3= Increase of >=7 stools/day needing hospitalization or severe increase in ostomy output limiting ADLS; Grade 4= Life-threatening consequences; urgent intervention indicated
3. Discontinue irinotecan and TAS-102 if dose level -4 is not tolerated (irinotecan at 90 mg/m^2).

b. Other Non- Hematological Toxicities

Table 8 Dose Modifications for Other Non- Hematological Toxicities

Grade (NCI CTCAE version 5.0)	Irinotecan	TAS-102
Grade 1 or 2	Continue at same dose level	Continue at same dose level
Grade 3 or 4: each occurrence*	Delay infusion by 1-2 weeks or until recovered to grade 1 or baseline condition Dose reduce to next level (e.g. level 1)	Delay dose by 1-2 weeks or until recovered to grade 1 or baseline condition Dose reduce to next level (e.g. level 1)
Infusion reaction	Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reactions. Immediately and permanently discontinue drug for serious infusion reactions, requiring medical intervention and/or hospitalization.	n/a

* Note: If it is deemed by the investigator that only 1 of the drugs is responsible for the AE of interest then, only that particular drug need be subjected to the dose modification criteria described herein.

10.1.4 Bevacizumab Specific Dose Modifications for Adverse Reactions

Dosage: Bevacizumab or bevacizumab biosimilar is to be administered as an intravenous (IV) at the dose of 5 mg/kg on Days 1 & 15 over 10 minutes or per institutional policy.

- Do not initiate bevacizumab until at least 28 days following major surgery. Hold bevacizumab until any surgical incision has fully healed.
- Monitor blood pressure at every visit during treatment with bevacizumab. Treat with appropriate anti-hypertensive therapy as per standard of care. Continue to monitor blood pressure at regular intervals in patients with bevacizumab -induced or -exacerbated hypertension after discontinuation of bevacizumab.

Dosing guidance for bevacizumab related toxicities

- **Hypertension**

Table 9 Bevacizumab Dose Modifications for Hypertension

Hypertension*	Occurrence	Bevacizumab management
Grade 2 Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg	Any	Maintain current dose
Grade 3 Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg	Any	Hold until BP is <160/100
Grade 4 including RPLS** or hypertensive encephalopathy or crisis	1st	Discontinue

* Grading as Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.
** Reversible posterior leukoencephalopathy (RPLS) or posterior reversible encephalopathy syndrome (PRES): A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It is an acute or subacute reversible condition.

- **Proteinuria**

Proteinuria will be monitored by urinalysis (UA) dipstick or 24-hour urine on Day 1 of every cycle. UA dipstick values >2+ protein should be confirmed by 24-hour collection and management based upon 24-hour protein values. In lieu of 24-hour urine collection, spot protein: creatinine measurement and calculation may be utilized. Patients may continue therapy while awaiting 24-hour urine protein assessment.

UPC = protein concentration (mg/dL) / creatinine concentration (mg/dL). To obtain urine protein/creatinine (UPC) ratio from random urine sample (i.e., not 24-hour urine):

a. Obtain at least 4 mL of a random urine sample.
b. Determine protein concentration (mg/dL)
c. Determine creatinine concentration (mg/dL)
d. Divide b by c

UPC directly correlates with the amount of protein excreted in the urine per 24 hours (i.e., UPC of 1 should be equivalent to Ig protein in a 24hr urine collection).

Table 10 Bevacizumab Dose Modifications for Proteinuria

Proteinuria	Occurrence	Bevacizumab management
2+ and 3+ proteinuria; urinary protein 2.0- < 3.5 g/24 hrs	1st to 3rd occurrence	Hold until recovery to 24 hr urine protein < 2g, then resume at current dose
	4th occurrence	Discontinue
Urinary protein ≥ 3.5 g/24 hrs; 4+ proteinuria	1st occurrence	Discontinue

- **Hemorrhage**

Table 11 Dose Modifications for Hemorrhage

Hemorrhage*	Occurrence	Bevacizumab management
Grade 2 non-pulmonary or non-CNS	Any	Maintain current dose
Grade 2 pulmonary	Any	Discontinue
Grade 3 or 4	Any	Discontinue
Any grade CNS hemorrhage	Any	Discontinue

* The following terms from NCI CTCAE version 5.0 may be considered for reporting purposes: Vitreous hemorrhage, Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage. Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage. Retroperitoneal hemorrhage, Upper Gastrointestinal hemorrhage, Hepatic hemorrhage, Intraoperative hemorrhage, Postoperative hemorrhage, Tracheal hemorrhage, Intracranial hemorrhage, Renal hemorrhage, Ovarian hemorrhage, Prostatic hemorrhage, Spermatic cord hemorrhage, Testicular hemorrhage, Uterine hemorrhage, Vaginal hemorrhage, Bronchopulmonary hemorrhage, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage.

- **Venous Thromboembolism**

Table 12 Dose Modifications for Venous Thromboembolism (VTE)

Grade*	Occurrence	Bevacizumab management
Grade 2	Any	Maintain current dose
Grade 3**	Any	Hold until stable full -dose anticoagulation is achieved (at least 48 hours), then resume at current dose
Grade 4**	Any	Discontinue

* The following terms from NCI CTCAE version 5.0 may be considered for reporting purposes: Superior vena cava syndrome, Portal vein thrombosis, and Vascular access complication.

**The following criteria must be met by patients who experience a Grade 3 or 4 VTE: (a) No evidence of tumor involving major blood vessels on current CT scan; (b) No use of warfarin; (c) No use of anti-platelet agents during full dose anticoagulation; (d) May use low molecular weight heparin or oral factor Xa inhibitors; (e) No Grade 3 or 4 hemorrhagic event while on anticoagulation; and (f) Clinically stable on a stable dose of low molecular weight heparin or other anticoagulant for at least 48 hours prior to resuming study drug treatment.

- **Arterial Thromboembolism**

Table 13 Dose Modifications for Arterial thromboembolism (ATE)

ATE Toxicity Grade*	Occurrence	Bevacizumab management
Any grade	Any	Discontinue

* The following terms from NCI CTCAE version 5.0 may be considered for reporting purposes: Stroke, Acute coronary syndrome, Myocardial infarction, visceral arterial ischemia, Ischemia Cerebrovascular. This does not apply to pulmonary embolism.

- Besides the above-mentioned points, discontinue bevacizumab for:
    - Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ.
    - Wound dehiscence and wound healing complications requiring medical intervention, unless minor and rapidly resolving, in which case only a hold of dosing is necessary.
- **Hold** bevacizumab for:
    - At least 4 weeks prior to elective surgery. Do not administer Bevacizumab until the wound is fully healed.
    - Severe infusion reactions.

10.2 General Concomitant Medication and Supportive Care

Antiemetic agents would be given on Day 1 and Day 15 of treatment, starting at least 30 minutes before administration of all therapy and for subsequent use as needed. A 5HT-3 blocker as well as a corticosteroid is the recommended minimum prior to infusional treatments (e.g. palonosetron 0.25 mg IV or ondansetron 16 mg IV, with dexamethasone 12 mg po). Additional agents, including NK1 antagonists (e.g. aprepitant), olanzapine, or benzodiazepines may be utilized, as deemed necessary by the investigator. The choice of regimen for nausea prophylaxis is to be per institutional standard of care, considering that this is a moderately emetogenic regimen.

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. Do not administer to patients with serum bilirubin > 2.0 mg/dL, or transaminase > 3 times the upper limit of normal if no liver metastasis, or transaminase > 5 times the upper limit of normal with liver metastasis.

If necessary, growth factor support is permitted during the study protocol. For neutropenia or neutropenic fever, G-CSF should be utilized as stated above in Section 10.1.3 (Dose modifications and toxicity management: I. Management of Hematologic Toxicities). Given the protracted course of administration, non-pegylated agents (e.g. filgrastim) are preferred for use.

10.2.1 Supportive Medications

Management of diarrhea: Patients should have loperamide readily available to begin treatment for late diarrhea. Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. Monitor and replace fluid and electrolytes. Use antibiotic support for ileus, fever, or severe neutropenia.

10.2.2 Permitted Concomitant Medications

Any medications needed to alleviate treatment related side effects or cancer related symptoms are permitted, except for those prohibited below in Section 10.2.3.

10.2.3 Prohibited Concomitant Medications

TAS-102: Caution is required when using drugs that are human thymidine kinase substrates, e.g., zidovudine. 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, abacavir, etc.

Irinotecan: Do not administer irinotecan along with strong CYP3A4 inducers or strong CYP3A4 Inhibitors.

Please refer to **Appendix G** for a list of potentially interacting drugs.

10.3 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity and withdrawal from study, inter-current illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime or, participant withdraws from study.

10.4 Compliance

TAS-102 will be self-administered (in tablet form) BID by the study participant and documented in the provided drug diary. The participant will be asked to bring the diary with him/her to each clinical visit (see **Appendix E**).

11 PROCEDURES INVOLVED

The study-specific assessments are detailed in this section and outlined in **Appendix F** (Schedule of Procedures and Observations). Baseline and/or Screening assessments must be performed

within 14 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of 7 days** unless otherwise noted.

NOTE: For blood Chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

11.1 Participant Randomization and/ or Registration:

Eligibility of each participant will be established prior to registration.

Informed consent MUST be completed prior to receiving any study related procedures.

11.2 Baseline Evaluations

The following will be performed within 2 weeks prior to first dose of study drug:

- Medical history (including all prior anti-tumoral therapy related to their current colorectal cancer diagnosis.
- Physical examination.
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height). Height measured at baseline only.
- ECOG Performance Status (**Appendix A**).
- Concomitant Medications: List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.
- Hematology: (CBC with automated differentials) WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).
- Chemistry (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pregnancy test (urine, serum) in females of childbearing potential.
- Dipstick urine or 24- hour urine collection for total protein assessment.
- ECG/EKG: 12-lead.

A CT/MRI for disease assessment will be performed within 4 weeks prior to the first dose of the study drugs.

11.3 Evaluations Performed on Day 1 and Day 15 of Each Cycle

- Physical examination
- Vital signs
- Concomitant medications
- Adverse events

- Hematology: CBC
- Chemistry: CMP
- Tumor marker: Carcinoembryonic antigen (CEA), to be measured on day 1 of each cycle only.
- Irinotecan (IV) and bevacizumab (IV). **Note**: TAS-102 will be administered orally, BID on Days 2-6 and Days 16-20 of each 28-day cycle.

11.4 Tumor Response Assessment:

- As clinically necessary, response assessment with either a contrast enhanced CT scan or MRI every 8 weeks (± 7 days).

11.5 Evaluations Performed at End of Treatment

The following evaluations will be performed at the end of treatment or at time of treatment discontinuation:

- Physical examination, including vital signs
- ECOG Performance Status
- Hematology: CBC
- Chemistry: CMP
- Concomitant medication: List any ongoing medications with dose changes, as applicable.
- Adverse events

11.6 Post-Treatment Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable).

- Concomitant medications: List any ongoing medications with dose changes, as applicable.
- Adverse events

11.7 Long Term Follow-Up Evaluations

Medical record review will be performed approximately every 6 months for up to 2 years after completion of treatment to assess survival status.

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).
- Death: Date of death will be recorded for those participants who die during f/u after completion of the study treatment.

12 WITHDRAWAL OF SUBJECTS

- Patients who are unable to reasonably comply with study procedures or are putting themselves or the study team at excess risks may be forced to withdraw from the study.
- At their own discretion, subjects may withdraw from the study for any reason.
- Every effort should be made to obtain follow-up imaging studies until progressive disease is noted, in order to document the time to progressive disease.

12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity: treatment related or unrelated
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor decision

13 RISKS TO SUBJECTS

Please refer to the package inserts for a comprehensive description of the potential adverse effects of the three agents utilized in this study.

13.1 TAS-102

The most common adverse reactions or laboratory abnormalities (≥ 10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia

13.2 Irinotecan

Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, alopecia.

13.3 Bevacizumab/Bevacizumab Biosimilar

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

14 POTENTIAL BENEFITS TO SUBJECTS

The patients will receive a treatment that may be more effective than the standard of care in this setting: FOLFIRI (5-FU + leucovorin + irinotecan) and bevacizumab or an anti-EGFR therapy (for RAS wt patients)

15 DATA AND SPECIMEN BANKING

Any clinical data that is associated with the study will be stored on a secured server in the Department of Medicine, will be accessible only by the PI, co-investigators and PI-designated data manager and, will be password protected. All computer entry and networking programs will be done using PIDs only. Any clinical data and/or specimens that are used for future studies will be de-identified before being released from the PI's laboratory.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

16 MEASUREMENT OF EFFECT

16.1 Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (14)[Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

For the purposes of this study, patients should be re-evaluated for response every 8 weeks while on therapy. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Refer to **Appendix H** for a summary of RECIST 1.1 criteria.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not

considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.2 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.5 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.6 Grading and Reporting Adverse Events

17.6.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 5.0. The relationship of event to study drug will be documented by the Investigator as follows:

Unrelated: The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Possible: The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.6.2 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.7 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.7.1 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs that are unexpected and possibly, probably or definitely related must be reported as an Unanticipated Problem. Please refer to **Section 17.10** for details on reporting Unanticipated Problems.

17.8 Investigator Reporting: Notifying Taiho Oncology, Inc.

1 The Principal Investigator at each participating site will monitor the patient for adverse events and fulfil all the reporting requirements to FDA in accordance with Applicable Laws. The Principal Investigator will also inform Taiho Oncology of serious adverse events:

- Unexpected Fatal or Life Threatening Suspected Adverse Reactions: Report to Taiho Oncology, Inc. within 24 hours
- Serious & Unexpected Suspected Adverse Reactions: Report to Taiho Oncology, Inc. within 24 hours
- All other Serious cases (Expected and Related; Expected and Not related; Unexpected and Not related): Report to Taiho Oncology within 2 weeks of awareness

2 All serious adverse events via a MedWatch Form need to be sent to:

Taiho Oncology, Inc.
fax: 609-750-7371 or e-mail: TAS-102_Safety@taihooncology.com
(please note the underscore between '102' and 'Safety')

AND

NCCN at:

ORPreports@nccn.org
or
FAX: (215) -358-7699

3 MedWatch reports must clearly specify SAE term(s) and corresponding investigator causality assessment.

4 Taiho Oncology will send SUSARs to Regulatory Authorities via a MedWatch form within 7 Calendar Days for all fatal/life threatening events and 15 Calendar Days for all other serious events.

17.8.1 Other Reportable Occurrences

For the purposes of this study, other experiences with the TAS-102 shown below should also be reported to Taiho Oncology:

1. Drug exposure during pregnancy and lactation, or paternal drug exposure (see following section)
2. Experience in patients below 18 years of age (depending on Inclusion criteria)
3. Lack of drug effect
4. Unintended beneficial effect
5. Any suspected transmission of an infectious agent by a medicinal product
6. Product quality complaints associated with possible safety issue(s)
7. Drug or food interaction
8. Overdose
9. Medication error
10. Misuse
11. Occupational exposure

17.8.2 Reporting of Exposure during Pregnancy and Lactation, or Paternal Drug Exposure

The Institution will report Exposure During Pregnancy and Lactation, or Paternal Drug Exposure on any subject while participating in the study, and following exposure to TAS-102, to Taiho Oncology (as specified below) using copies of the original Pregnancy Report Form and within two weeks of first becoming aware of the pregnancy or exposure. If the partner of a study subject becomes pregnant, the Institution may collect information about the pregnancy and birth if the partner agrees.

The study subject will also be followed by the Institution to determine the outcome of the pregnancy (including any premature termination of the pregnancy). Information on the status of the mother and child will be forwarded to Taiho Oncology. The Institution must provide final outcome of pregnancy to Taiho Oncology. If any SAE(s) is observed in a study subject or fetus/child, then SAE(s) must also be reported to Taiho Oncology following SAE Reporting guidelines.

Routing of Drug Exposure during Pregnancy and Lactation, or Paternal Drug Exposure Reports

Such reports and Information as outlined above, Including Investigator causality assessments against all concerned Taiho Oncology IMP(s) and English translations where reporting Is from a non-English speaking country, shall be sent:

- By facsimile to PV CONTACT NUMBER :609-750-7371 OR
- By e-mail to: TAS-102_Safety@taihooncology.com (please note the underscore between '102' and 'Safety') AND NCCN at: ORPreports@nccn.org or FAX: (215)-358-7699.

Requesting Follow-up Information:

The institution will provide Taiho Oncology with details of whom Taiho Oncology shall address requests for follow up Information on SAE and pregnancy cases reported from this study, and further agree to update such contact details as necessary. At the time of this Agreement, all such requests should be addressed to: Dr. Christos Fountzilas.

17.9 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.10 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  - The characteristics of the participant population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is deemed Serious per Section 17.7.

17.10.1 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

17.11 FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets ANY of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRSQA@RoswellPark.org.

SAE Reconciliation

Reconciliation shall be performed quarterly as an exchange of Line Listings or other means in English. On a quarterly basis, the institution shall provide to Taiho Oncology, Inc., a line listing or other means of cumulative SAE received to date. At the end of the Clinical Trial a global reconciliation shall be performed. Please reference contact information when sending this reconciliation. All serious adverse events via a MedWatch Form need to be sent to the FDA and to Taiho Oncology, Inc., via fax: 609-750-7371 or e-mail: TAS-102_Safety@taihooncology.com (please note the underscore between "102" and "Safety").

DSUR

If requested by Institution, Taiho Oncology shall provide the Institution with the final version of this DSUR report within 15 calendar days after submission to health agencies and ethics committees.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

19 STATISTICAL PLAN

Design: This is a single-arm Phase II study of TAS-102, irinotecan, and bevacizumab in FOLFIRI naïve patients.

Analysis Cohorts: All patients that receive any treatment will be included in the safety summary. All patients that receive any treatment will be included in the primary and secondary analyses, regardless of the treatment received (intent-to-treat analysis). A sensitivity analysis will be conducted on the set of patients that received their treatment per-protocol.

19.1 Sample Size Determination

The sample size calculations are based on the primary analysis, which evaluates the progression-free survival (PFS) using a one-sided, one-sample log-rank test. Based on published data, we expect the median PFS for the FOLFIRI + bevacizumab to be 6 months. If the proposed TAS-102 + irinotecan + bevacizumab can demonstrate a median PFS of 9 months (hazard ratio [HR] ≈ 0.67), then we'd consider it the superior treatment combination and consider it for further study.

Assuming the above median PFS and that the PFS times are exponentially distributed, PASS (version 15.0.3) indicates a sample size of n=36 subjects would achieve 80.5% power (at $\alpha = 0.1$) to detect such an effect (HR ≈ 0.67).

To account for potential deviations from assumptions and potential dropouts, a total of n=42 patients may be accrued. Accrual is expected to take 36 months with an additional 24 months of follow-up.

19.2 Demographics and Baseline Characteristics

Patient demographic and clinical characteristics will be summarized using the appropriate descriptive statistics.

19.3 Primary Analysis

The primary objective is to evaluate the PFS of FOLFIRI naïve patients treated with TAS-102 + irinotecan + bevacizumab as compared to historic controls group treated with FOLFIRI + bevacizumab. The primary endpoint is PFS, which is treated as bivariate time-to-event data and defined as the time from treatment until disease progression, death due to disease, or last follow-up. Based on previously published studies, we expect the FOLFIRI + bevacizumab to have a median PFS of approximately 6 months. If the TAS-102 + irinotecan + bevacizumab combination

has a median PFS of 9 months (HR≈0.67), then we'd consider it the superior treatment combination and consider it for further study. Therefore, we will test the following hypotheses using a one-sided, one-sample log-rank test:

$$H_o{:}M_{50} = 6 \text{ versus } H_A{:}M_{50} > 6,$$

where $M_{50}$is the true median PFS for patients treated with TAS-102 + irinotecan + bevacizumab. The PFS will be summarized using standard Kaplan-Meier methods, where estimates of the median PFS and 6/12-month PFS rates will be obtained with 90% confidence intervals. The final analysis will be conducted either: 1) 12-months after enrollment of the final subject; or 2) once all subjects have experienced a progression event, whichever occurs earlier.

19.4 Secondary Analysis

The secondary objects are to evaluate objective response, overall and disease-specific survival, and safety and tolerability.

Objective response is treated as a dichotomous variable and will be summarized using frequencies and relative frequencies. Using Jeffrey's prior method, a 90% confidence interval about the true ORR will be obtained for each treatment group.

Overall survival (OS) is treated as bivariate time-to-event data and defined as the time from treatment until death due to any cause or last follow-up. Disease-specific survival (DSS) is treated as bivariate time-to-event data and defined as the time from treatment until death due to disease or last follow-up. OS and DSS will be summarized using standard Kaplan-Meier methods; where estimates of the median survival and 12-month rates are obtained with 90% confidence intervals.

19.5 Safety Analysis

Treatment related adverse events (as per CTCAE v5.0) will be summarized by grade using frequencies and relative frequencies. All patients that receive any treatment will be included in the safety summary

19.6 Interim Analysis

No formal interim analyses or criteria for early termination are planned.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies are reviewed quarterly; Phase II, III and pilot investigator-initiated studies are reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of, or (d) or termination of the study.

21 VULNERABLE POPULATIONS

Not applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable.

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

All study treatment will be administered on an outpatient basis. Participants will be identified/recruited/screened from patients at the Gastrointestinal Clinic at Roswell Park and at the participating site clinics, and from multi-disciplinary conference discussion.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

The gastrointestinal oncology service at Roswell Park sees a large volume of patients with colorectal cancer with approximately 250 new patients per year annually over the last decade. Over this time, at least 30-60 patients per year have presented with metastatic disease at diagnosis and a substantial portion of patients under active surveillance develop recurrent, incurable disease. Dr. Christos Fountzilas is an experienced clinical investigator, having joined Roswell Park Cancer Institute and the GI medical oncology team in 2017. He has previously conducted multiple pharmaceutical run, investigator initiated and NCI-sponsored studies, including one NCCN funded study in refractory mCRC.

In the last 12 months, we had a randomized second-line study open in this setting (NCT02753127) where we enrolled 7 patients over this time. Unfortunately, there were multiple screen-fails due to the relatively stringent inclusion criteria (global rate 30-40%) and randomization is a documented barrier to accrual(15). Thus, we would expect that in a non-randomized study, with more permissive inclusion criteria, we would enroll ≥ 10 patients/year. To complete enrollment swiftly, we would propose enlisting three additional centers in the study, led by experienced investigators: Rutgers Cancer Institute of New Jersey, Moffitt Cancer Center, and Fox Chase Cancer Center/Temple University. In this manner, we would anticipate that analysis of the primary endpoint would be evaluable approximately 4 years (48 months) after study commencement.

27 PRIOR APPROVALS

Not applicable.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-8974.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form

must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32 DRUGS OR DEVICES

Roswell Park will cross-file on the IND for TAS-102.

32.1 TAS-102 (Lonsurf®)

32.1.1 Active Substance and Source

TAS-102 contains FTD and TPI as active ingredients with a molar ratio of 1:0.5. TAS-102 drug products are immediate-released film coated tablets, available in 2 strengths (15 mg and 20 mg tablet, expressed as FTD content). The inactive ingredients of the TAS-102 15 mg and 20 mg tablets are lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, red ferric oxide (only 20 mg tablet), and magnesium stearate.

- TAS-102 tablet (15 mg) contains 15 mg FTD and 7.065 mg TPI (corresponding to 6.14 mg tipiracil) as active ingredients. The appearance is white, round, biconvex film-coated tablets.
- TAS-102 tablet (20 mg) contains 20 mg FTD and 9.42 mg TPI (corresponding to 8.19 mg tipiracil) as active ingredients. The appearance is pale red, round, biconvex film-coated tablets.

32.1.2 Drug Shipment

TAS-102 (Lonsurf®) will be provided by Taiho Oncology, Inc. and shipped to the participating sites.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.1.3 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified and in accordance with the applicable regulatory requirements.

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

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

Drug storage temperature will be maintained and recorded, as applicable.

Refer to the Pharmacy Manual for additional details.

32.1.4 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by the Sponsor exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per

the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Excess drug will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

32.2 Irinotecan

Irinotecan is FDA approved as a second-line therapy for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progresses following initial fluorouracil-based therapy.

Irinotecan will be administered as an intravenous infusion over 90 minutes according to institutional guidelines. Please refer to package insert.

32.3 Bevacizumab/Bevacizumab biosimilar

Bevacizumab and bevacizumab biosimilars are FDA approved for the treatment of Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.

Bevacizumab or bevacizumab biosimilar will be administered as an IV infusion (5 mg/kg) over 10 minutes or per institutional policy.

Please refer to package insert for additional details.

33 REFERENCES

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34 APPENDICES/ SUPPLEMENTS

Appendix A ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix B INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: A Phase II Study of TAS-102, Irinotecan, and Bevacizumab in Pre-treated Metastatic Colorectal Cancer (TABAsCO)

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years old.	
☐	☐	☐	2. Advanced colorectal cancer (metastatic or unresectable): Histologically or cytological proven adenocarcinoma of the colon or rectum which is metastatic or otherwise incurable.	
☐	☐	☐	3. Prior treatment with a fluoropyrimidine (5-FU or capecitabine) and oxaliplatin in the metastatic/unresectable setting **OR**, recurrence within 12 months of adjuvant therapy with a regimen that included oxaliplatin.	
☐	☐	☐	4. Have an ECOG Performance Status of 01. Refer to **Appendix A.**	
☐	☐	☐	5. Have the following clinical laboratory values: • Hemoglobin ≥ 9 g/dL • Absolute neutrophil count ≥ 1500/mm^3 • Platelet count ≥ 100,000/mm^3) • Creatinine < 1.5 ULN or if ≥ 1.5 x ULN with CRCL ≥ 30 mL/min (by Cockroft-Gault) • Bilirubin < 1.5 x ULN • AST/ALT ≤ 2.5 x ULN or ≤ 5 x ULN if with hepatic metastases	
☐	☐	☐	6. Have measurable disease per RECIST 1.1 criteria present.	
☐	☐	☐	7. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	8. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix C INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: A Phase II Study of TAS-102, Irinotecan, and Bevacizumab in Pre-treated Metastatic Colorectal Cancer (TABAsCO)

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Prior treatment with TAS-102 or irinotecan.	
☐	☐	☐	2. Anti-cancer therapy within 2 weeks of the planned first dose of study medication.	
☐	☐	☐	3. Unresolved toxicities from prior therapy of > Grade 1, excluding alopecia or similar toxicities which are not deemed to be clinically significant or put the participant at greater risk. Grade 2 neuropathy is permitted.	
☐	☐	☐	4. Major surgery within 4 weeks of anticipated start of therapy.	
☐	☐	☐	5. Uncontrolled hypertension: systolic blood pressure ≥ 150, diastolic blood pressure ≥ 100.	
☐	☐	☐	6. Unstable angina, symptomatic congestive heart failure or cardiac arrhythmia requiring anti-arrhythmic therapy (beta-blockers, calcium channel blockers and digoxin are allowed).	
☐	☐	☐	7. Arterial or venous thrombotic or embolic events within 3 months of study initiation, unless well controlled on stable anti-coagulation for > 2 weeks. This excludes uncomplicated catheter associated venous thrombosis.	
☐	☐	☐	8. History of cerebrovascular or myocardial ischemia within 6 months of initiation.	
☐	☐	☐	9. NCI CTCAE v 5.0 Grade 3 or greater hemorrhage within the past 4 weeks.	
☐	☐	☐	10. Proteinuria ≥ 2+, unless 24-hour urine collection demonstrates ≤ 1 g of protein OR spot protein: creatinine demonstrates a ratio of ≤ 1.	
☐	☐	☐	11. Untreated brain metastases.	
☐	☐	☐	12. History of abnormal glucuronidation of bilirubin (Gilbert's Syndrome).	
☐	☐	☐	13. History of second primary malignancy within 3 years prior to enrollment, excluding in-situ cervical carcinoma and non-melanoma skin cancer or malignancy of equivalent risk which is highly unlikely to require systemic treatment in the next 2 years.	
☐	☐	☐	14. Have known active infection which would heighten the risk of complications.	
☐	☐	☐	15. Pregnant or nursing female participants.	
☐	☐	☐	16. Unwilling or unable to follow protocol requirements.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	17. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**

If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix D Instructions for Multi-Site (External) Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:
Roswell Park Cancer Institute
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263
Telephone:
Monday - Friday; 7: 00 AM to 3: 30 PM EST
716-845-8084
After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CRS QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

Roswell Park does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park CRS QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and email it to the Roswell Park Network QA Coordinator at CRSNetworkCoordinators@RoswellPark.org.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific; they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** “transfer”, “borrow” or “replace” supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the SAE to SafetyEventReporting@roswellpark.org. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- Roswell Park SAE Source form
- MedWatch 3500A

A complete follow-up report must be sent to the Roswell Park Network QA Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.10**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and emailing it to the Roswell Park Network QA Coordinator.

Appendix E Study Drug Diary

Study No.: _____ **Subject's Name: _____**
Drug Name: _____ **Cycle #: _____**
Medical Record No.: _____

TAS-102 Study Drug Calendar

Please complete this calendar on the days that you take the study drug. The study medication is to be taken whole, with food on Day 2-Day 6 and on Day 16-Day 20 of every 28-day treatment cycle. Fill in the date for each day in the 1st row, write the drug dose that you take each day in the 2nd row, and write the total number of tablets (number of 15 mg tablets and/or number of 20 mg tablets) you take each day in the 3rd and 4th row.

On days you do not take any study drug; please write "0" in drug dose box. If your dose changes record the new dose level.

Start Date: _____ Dose: _____

Number of 15 mg tablets: _____

Number of 20 mg tablets: _____

Take the prescribed number of tablet(s) (15 mg, 20 mg, or combination) each time (AM and PM), about 12 hours apart. Swallow TAS-102 tablets whole, with food or within one hour of completion of morning and evening meals. Do not to retake doses of TAS-102 that are vomited or missed- if this happens; continue with the next scheduled dose

Cycle Day	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
Date														
Dose														
Number of **15 mg tablets** taken	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
Number of **20 mg tablets** taken	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	AM	PM	AM	PM

Cycle Day	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
Date														
Dose														
Number of pills taken	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM

Cycle Day	Day 15		Day 16		Day 17		Day 18		Day 19		Day 20		Day 21	
Date														
Dose														
Number of **15 mg tablets** taken	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
Number of **20 mg tablets** taken	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	AM	PM	AM	PM

Cycle Day	Day 22		Day 23		Day 24		Day 25		Day 26		Day 27		Day 28	
Date														
Dose														
Number of pills taken	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM

Please remember to bring this calendar and your pill bottle (including any unused pills) with you to your next study appointment.

Coordinator's Use Only

$$\%\ Compliance = \left(\frac{Number\ of\ Pills\ Taken}{Number\ of\ Pills\ Scheduled}\right) \times 100$$

$$\_\_\_\_\%\ Compliance = \left(\frac{\quad}{\quad}\right) \times 100$$

Subject's Signature: _____ Date: _____

CRC's Signature: _____ Date: _____

Investigator's Signature: _____ Date : _____

Investigator (printed name): _____

Appendix F Schedule of Procedures and Observations

Time point	Screening[1]	Cycle 1 and additional cycles				Every 8 weeks (±7 days)	End of Treatment/ (± 3 days)	Post-Treatment Follow-Up	
		Day 1	Day 2-6	Day 15	Day 16-20			SafetyFollow-Up[2]	Long Term Follow-Up[3]
Clinical Procedures									
Medical History	X								
Pre-Existing Conditions	X								
Physical Examination[4], including vital signs[5]	X	X		X			X		
ECOG Performance Status	X						X		
Concomitant Medications	X[6]	X		X			X	X	
Adverse Events		X		X			X	X	
Survival Status Assessment									X
Laboratory Procedures									
Hematology[7]	X	X		X			X		
Chemistry[8]	X	X		X			X		
Tumor Marker (CEA)		X							
Dipstick urine or 24 hr urine protein	X	X							
Pregnancy Test (Urine or Serum)	X								
Imaging Procedures									
ECG/EKG (12-lead)	X								
Imaging for Tumor/ Disease Assessment (CT or MRI)[9]	X					X			

Time point	Screening[1]	Cycle 1 and additional cycles				Every 8 weeks (±7 days)	End of Treatment/ (± 3 days)	Post-Treatment Follow-Up	
		Day 1	Day 2-6	Day 15	Day 16-20			SafetyFollow-Up[2]	Long Term Follow-Up[3]
Treatment Regimen/Drug Administration									
TAS-102			X		X				
Irinotecan		X		X					
Bevacizumab*		X		X					

1 Performed within two weeks prior to treatment start (unless otherwise noted).

2 Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug related toxicity (telephone contact is acceptable).

3 Medical record review will be performed approximately every 6 months, for up to 2 years, to ascertain survival status.

4 Research/study-specific assessments should be performed no earlier than two weeks prior to the start of treatment.

5 Vital signs should be performed no earlier than two weeks prior to the start of treatment (temperature, heart rate, respiratory rate, and blood pressure), body weight, and height: Height collected at baseline only.

6 Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.

7 Hematology (CBC with automated differentials): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.

8 Chemistry (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). **NOTE:** For blood Chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

9 Baseline CT imaging (or MRI if necessary) is to be performed up to 4 weeks prior to the start of study treatment. CT imaging (or MRI if necessary) will be performed every 8 weeks ± 7 days while on study treatment, as clinically necessary. Disease evaluation according to RECIST v. 1.1 (See Section 16).

* Or bevacizumab biosimilar

Appendix G Cytochrome p450 Drug Interactions

Table A. Cytochrome p450 inhibitors *

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
Boceprevir Cobicistat Conivaptan Danoprevir and ritonavir, Elvitegravir and ritonavir Lopinavir and ritonavir, Paritaprevir and ritonavir Ombitasvir and/or dasabuvir Saquinavir and ritonavir Telaprevir, tipranavir and ritonavir Nelfinavir Indinavir and ritonavir Grapefruit Juice Itraconazole Ketoconazole Posaconazole Troleandomycin Voriconazole Clarithromycin Diltiazem Idelalisib Nefazodone	Aprepitant Cimetidine Ciprofloxacin Clotrimazole Crizotinib Cyclosporine Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Tofisopam Verapamil	Chlorzoxazone Cilostazol Fosaprepitant Istradefylline Ivacaftor Lomitapide Ranitidine Ranolazine Tacrolimus Ticagrelor

Table B. Cytochrome p450 inducers*

Strong Inducers
Phenytoin, Rifampin

*For more information, please see:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table3-2

Appendix H RECIST 1.1 Criteria

Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. 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. RECIST 1.1 will be used to assess objective tumor response.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Complete Response (CR): Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

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

Stable Disease (SD): Neither a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

Non-Target Lesions

All other small lesions (longest diameter < 10 mm or lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses / abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-Complete Response/Non-Progressive Disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.

Progressive Disease: Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time.

Evaluation of Response

Time point response assessments will be performed every 8 weeks. To determine time point response, refer to **Table 14** and **Table 15** below.

Table 14 Time Point Response Criteria: target (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 15 Time Point Response Criteria: non-target disease only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

The best overall response is the best response recorded from the start of study treatment until the end of treatment, taking into account any requirement for confirmation. In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

Symptomatic Deterioration: Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment includes, but is not limited to, symptoms such as:

- Weight loss > 10% of body weight.
- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of > 1 level on ECOG scale.

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

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

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

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

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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.

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

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The

use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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