Document Coversheet

Study Title: Use of Trifluridine/ Tipiracil (TAS-102) and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma

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Use of Trifluridine/ Tipiracil (TAS-102) and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma

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Confidentiality Statement

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1 OBJECTIVES

1.1 Primary Objective

- Evaluate the pathologic complete response (path CR) rate in participants with esophageal and gastroesophageal junction (GEJ) adenocarcinoma when trifluridine/tipiracil (TAS-102) and oxaliplatin are used as induction chemotherapy prior to surgical resection.

1.2 Secondary Objectives

- Evaluate the 2-year disease-free survival (DFS) and the 2-year overall survival (OS).
- To determinate the safety and tolerability of induction chemotherapy with TAS-102 and oxaliplatin followed by standard chemoradiation and surgery.
- Evaluate the metabolic response to induction chemotherapy with TAS-102 and oxaliplatin in participants with esophageal and gastroesophageal junction (GEJ) adenocarcinoma prior to standard chemoradiation and surgical resection.

1.3 Exploratory Objective

- Correlate circulating tumor DNA (ctDNA) levels with disease recurrence and metabolic response on PET CT.

2 BACKGROUND

Esophageal cancer is a global health problem with an estimated annual incidence of 455,800 and 400,200 annual deaths occurring in 2012 (1). In the US, the majority of the esophageal cancers are adenocarcinoma usually confined to the distal esophagus (2). On the other hand, the incidence of GEJ adenocarcinoma has also increased steadily in the US since the 1970s (2). Esophageal and GEJ adenocarcinoma present as a loco-regional disease in approximately 50% of the cases (3). Typically, a majority of these patients are treated with neoadjuvant chemoradiation followed by surgery. However, despite multimodality treatment, overall survival (OS) at five years is less than 50% (4). It has been shown that achievement of path CR leads to an improved OS (5). However, concurrent chemoradiation produces a path CR in only about 20% patients (3, 6). Therefore, investigators have looked into strategies like induction chemotherapy (IC) before concurrent chemoradiation to improve path CR.

In a randomized Phase II trial to investigate whether induction chemotherapy (IC) using FOLFOX as an induction regimen before chemoradiation can improve path CR in esophageal cancer patients, Ajani et al. (3) concluded that IC neither improves path CR nor overall survival in a significant way. Traditionally, different chemotherapy regimens have been used in this setting: e.g., modified FOLFOX-6 and carboplatin + paclitaxel.

(TAS-102) has a distinct mechanism of action, differing from that of 5-FU. 5-FU leads to cytotoxicity by inhibiting thymidylate synthase (TS) without being directly incorporated into the DNA. Trifluridine, in addition to inhibiting TS, is incorporated into the DNA, causing single- and double-stranded DNA breaks and DNA instability (7). Tipiracil has additional anti-angiogenic properties. Therefore, the combination of TAS-102 has been shown to be active in both 5-FU sensitive and resistant tumors. A randomized Phase 3 study evaluated the efficacy of TAS-102 in refractory advanced gastric or gastroesophageal cancer patients. TAS-102 was found to improve

disease-free survival (PFS) and OS in this heavily pre-treated population (8). Based on the data presented above, we decided to examine the novel combination of TAS-102 and oxaliplatin.

We propose to use a novel combination of Trifluridine/tipiracil (TAS 102) and oxaliplatin as induction chemotherapy in localized esophageal and GEJ adenocarcinoma. This combination has been looked at in a Phase I trial with standard 3+3 design (9). The maximum tolerated dose (MTD) was TAS-102 35 mg/m^2 BID and oxaliplatin 85 mg/m^2.

If the proposed project is successful, it has the potential to introduce a novel treatment approach using a unique induction chemotherapy, which can be further tested concurrently with radiation as well as in the frontline metastatic setting in future clinical trials.

2.1 TAS-102

2.1.1 Preclinical Studies with TAS-102

TAS-102 consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). The 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.

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

2.1.2 Clinical Studies with TAS-102

TAS-102 (LONSURF®) is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

The efficacy of TAS-102 was evaluated in TAGS (NCT02500043) , A Phase 3, international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease (10). In this study, patients (N=507) were randomized 2:1 to receive either TAS-102 (35 mg/m^2 BID on Days 1–5 and 8–12 of each 28-day cycle) plus best supportive care or placebo plus best supportive care. TAS-102 was associated with significantly longer overall survival (compared with placebo) along with significant improvements in disease-free survival, the proportion of patients achieving disease control, and time to deterioration of ECOG performance status.

Please refer to TAS-102 (LONSURF®) Package Insert and Investigator's Brochure for additional details.

2.2 Correlative Studies

The role of ctDNA in gastroesophageal cancer is evolving. Our previous work has used ctDNA to identify therapeutic targets otherwise not detectable from the primary tumor biopsy in gastroesophageal adenocarcinoma (11). Another study found that circulating tumor DNA (ctDNA)

level is prognostic in patients with resectable esophageal cancer (12). Metabolic response on PET has also been found to be predictive of long-term outcome in patients with resectable esophageal cancer, and PET CT is routinely being used in this patient population for re-staging purpose (13). In this study, we propose to collect the ctDNA level at five different time points: at diagnosis, after completion of induction chemotherapy, after completion of chemoradiation, after surgery and at the time of disease recurrence if this occurs. We plan to correlate the ctDNA level with disease recurrence and metabolic response on PET CT. The information obtained from ctDNA in this study may be used in designing future clinical trials as well as identifying new therapeutic targets.

2.3 Study Hypothesis

We hypothesize that induction chemotherapy with a novel combination of Trifluridine/tipiracil (TAS-102) and oxaliplatin before chemoradiation will increase the pathologic complete response (path CR) rate in localized esophageal and GEJ adenocarcinoma. This improved path CR may lead to a survival benefit.

3 INCLUSION AND EXCLUSION CRITERIA

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

3.1 Inclusion Criteria

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

1. Age ≥ 18 years of age.
2. Must have histologically proven loco-regional esophageal or gastroesophageal junction adenocarcinoma.
3. Endoscopic ultrasound (EUS), or clinically determined node-positive disease with any T-stage or T3-T4a with any N stage: Patients with EUS T4b and any M1 cancer **will not** be included.
4. Must have potentially resectable disease.
5. Have an ECOG Performance Status of 0-1. Refer to Appendix A.
6. 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
    - Bilirubin < 1.5 x ULN
    - AST/ALT ≤ 3 x ULN
7. Capacity to take oral tablet(s) without difficulty.
8. Participants of child-bearing potential must agree to use highly effective contraceptive methods (e.g., hormonal plus 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.

9. 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 chemotherapy, thoracic radiotherapy or prior surgical resection for an esophageal tumor.
2. Participants with known metastatic disease.
3. Any concurrent active malignancy that requires active systemic intervention
4. Grade 2 or higher peripheral neuropathy.
5. Participants who have had major surgery or field radiation within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
6. Received an investigational agent within 4 weeks prior to enrollment.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. Grade 3 or higher hypersensitivity reaction to oxaliplatin or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with premedication.
9. Patient previously treated by TAS-102 or history of allergic reactions attributed to compounds of similar composition to TAS-102 or any of its excipients.
10. Hereditary problems of galactose intolerance; e.g., Lapp lactase deficiency or glucose-galactose malabsorption.
11. Pregnant or nursing female participants.
12. Unwilling or unable to follow protocol requirements.
13. 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 in order to prevent any risk to vulnerable populations:

- 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 41 evaluable participants are required for the primary analysis. To account for patients that may be non-evaluable, up to n=45 study subjects may be accrued. Approximately 25 participants are expected to be accrued at Roswell Park, along with approximately 10 participants accrued at each participating external site. Accrual is expected to take 4 years.

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 principal 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 48 months with an additional 12 months of follow-up on study. After completion of 1 year on-study follow-up, the patient will be followed (monitored for survival status) as per standard of care: Year 1-Year 2, every 3-6 months; every 6–12 months for 3–5 years, then annually until disease progression or death, whichever occurs first.

The estimated time frame that the analysis of the primary endpoint would be evaluable is approximately 5 years after study commencement.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- Pathologic complete response rate: The path CR rate will be determined by pathologic examination of resected specimen: complete and partial response to induction chemotherapy followed by standard chemoradiation and surgery

8.2 Secondary Endpoints

- Progression free survival rate (PFS): Evaluate the 2-year disease-free survival rate.
- Overall survival (OS): Evaluate 2-year overall survival rate.
- Toxicities as Assessed by CTCAE v5.0.
- Post-operative complications, 30-day and 90-day post-op mortality.
- Metabolic response as measured by the change in maximum standardized uptake value (SUV max) on PET-CT scans from pre-induction chemotherapy to post-induction chemotherapy. Patients will have a baseline PET CT and a repeat PET will be performed after induction chemotherapy and a blinded reviewer will assess change in SUV max from baseline. Patients with a >35% decrease in SUV max will be categorized as metabolic responders and those with a ≤35% decrease in SUV max will be categorized as metabolic non-responders.

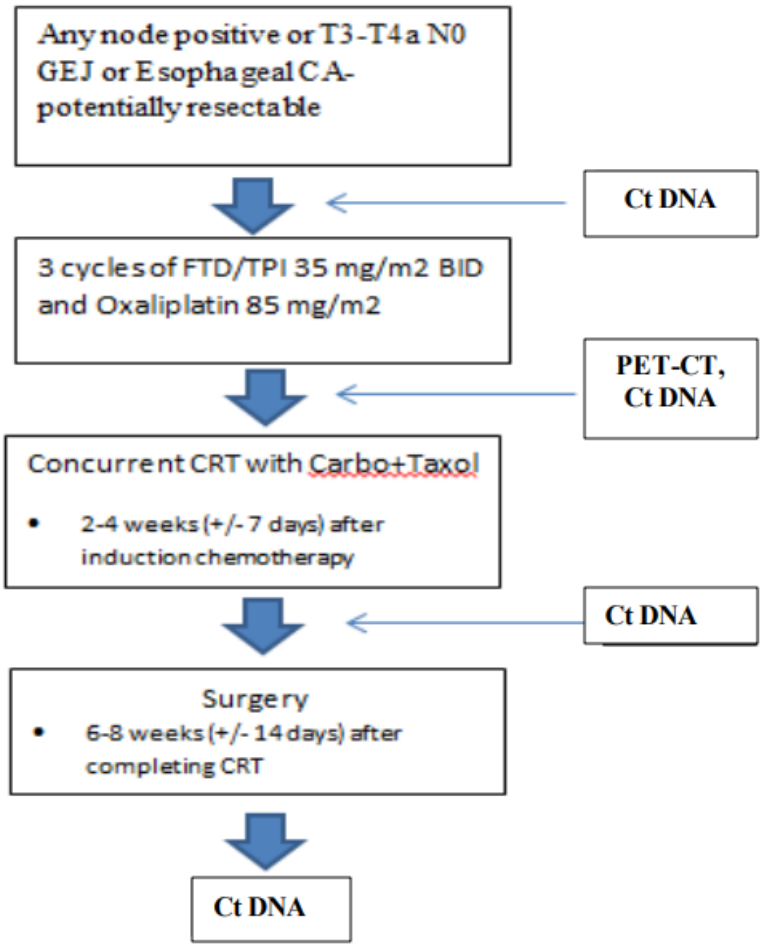
8.3 Exploratory Endpoints

- Circulating tumor DNA (ctDNA) levels will be determined at five time points: at diagnosis, after completion of induction chemotherapy, after completion of chemoradiation, after surgery and at disease recurrence or progression on study. Levels will be compared to disease recurrence and metabolic response on PET CT.

9 DESIGN

This is an open-label, multi-center, Phase 2 study of TAS-102 (trifluridine/tipiracil) administered with oxaliplatin before chemoradiation in participants with adenocarcinoma of the esophagus or GE junction. The study schema is depicted in **Figure 1**.

Figure 1 Study Schema



Patients meeting the inclusion criteria will receive three cycles of TAS-102 (35 mg/m^2 BID) and oxaliplatin (85 mg/m^2) before undergoing concurrent chemoradiation (standard of care radiation dose of 5040 cGY will be utilized at all participating study sites) with weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) for 6 weeks, followed by surgery.

Patients who receive at least one dose of the investigational treatment and eventually go to surgery will be evaluated for path CR (primary analysis), regardless if they discontinue treatment at any point prior to surgery. Patients who discontinue treatment before surgery due to toxicity or disease progression and end up not having surgery will be considered as non-responders. Patients, who discontinue treatment prior to surgery due to any other reason, will be considered non-evaluable for the primary analysis and will be replaced. These patients will be followed for the protocol defined safety/ toxicity period (unless they received no study drug/ procedure that would otherwise require this). They will not have any additional scheduled follow up visits and will not be followed for survival. Once a non-evaluable patient is beyond the safety follow-up window, they will be taken off study in an expedited way.

10 TREATMENT

Treatment is intended for an outpatient setting.

10.1 TAS-102 and Oxaliplatin

Patients meeting the inclusion criteria will receive 3 cycles of TAS-102 and oxaliplatin induction chemotherapy prior to standard of care chemoradiation therapy (standard of care radiation dose of 5040 cGY will be utilized at all participating study sites) with carboplatin and paclitaxel.

For the purpose of this study, 1 cycle= 14 days.

TAS-102 will be administered at the recommended dose of 35 mg/m², BID, orally, on Days 1–5 of every 14-day cycle.

Oxaliplatin will be administered at a fixed dose of 85 mg/m², IV (over 2 hours) on Day 1 only of each cycle. On Day 1, the patient will get oxaliplatin first and then be instructed to take the TAS-102.

Patients will be instructed to swallow TAS-102 tablets whole, with food. Patients are not to retake doses of TAS-102 that are vomited or missed and will be instructed to continue with the next scheduled dose.

10.2 TAS-102 Dose Modifications for Adverse Reactions

Obtain complete blood cell counts prior to treatment on Day 1 of each cycle.

Do not initiate the cycle of TAS-102 until:

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

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

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

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

A maximum of 3 dose reductions are permitted. 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.

10.3 TAS-102: Management of Adverse Effects

Severe Myelosuppression:

Severe and life-threatening (grade 3 or 4) bone marrow suppression (anemia, neutropenia, thrombocytopenia) has occurred, including fatalities (rare) related to neutropenic infection, sepsis, or septic shock. In clinical trials, slightly over 10% of patients received growth factor support.

- Monitor blood counts prior to treatment on Day 1 of each cycle, or more frequently if clinically necessary. May require therapy interruption and/or dose reduction.

Gastrointestinal Toxicity:

Trifluridine/tipiracil is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (14). Nausea, vomiting, diarrhea, and abdominal pain have been commonly reported. Stomatitis may also occur.

- Advise patients to report severe gastrointestinal toxicity to their health care provider.

10.4 Oxaliplatin: Management of Adverse Effects:

Acute toxicities: Longer infusion time (6 hours) may mitigate acute toxicities (e.g., pharyngolaryngeal dysesthesia).

Neurosensory events:

- Persistent (> 7 days) grade 2 neurosensory events:
    - Reduce dose to 75 mg/m^2
- Consider withholding oxaliplatin for grade 2 neuropathy lasting > 7 days despite dose reduction.
- Persistent (> 7 days) grade 3 neurosensory events: Consider discontinuing oxaliplatin.

Gastrointestinal toxicity (grade 3/4) occurring despite prophylactic treatment:

- Delay next dose until recovery from toxicity, then reduce dose to 75 mg/m^2

Hematologic toxicity (grade 4 neutropenia, febrile neutropenia, or grade 3/4 thrombocytopenia):

- Delay next dose until neutrophils recover to $\geq$ 1500/mm^3 and platelets recover to $\geq$ 75,000/mm^3, then reduce dose to 75 mg/m^2.

Pulmonary toxicity (unexplained respiratory symptoms including nonproductive cough, dyspnea, crackles, pulmonary infiltrates): Discontinue until interstitial lung disease or pulmonary fibrosis have been excluded.

Rhabdomyolysis: Discontinue for signs/symptoms of rhabdomyolysis.

Sepsis or septic shock: Withhold treatment.

Cold sensitivity: Patients should be counseled to avoid ice-chips, cold drinks, and exposure to cold water or air as the neurotoxicity seen with oxaliplatin is often exacerbated by cold exposure. The duration of this cold-related neuropathy is not well defined and patients should exercise caution regarding cold exposure during the treatment cycle.

10.5 Management of adverse effects during concurrent chemoradiation with weekly Carbo+Taxol:

Chemotherapeutic toxicity

- Hematologic Related Toxicity
    - If Day 8, 15, 22, 29, and 36 the ANC < 1,000/mm³ or Platelets < 50,000/mm³ or Hemoglobin < 9 g/dL as per the original CROSS regimen: delay chemotherapy by 1 week until recovery above these values.
    - In case of febrile neutropenia (ANC < 0.5/L and fever > 38.5 0C) or in case of severe bleeding or requiring ³ 2 platelet transfusions further chemotherapy will be withheld.
    - Platelets will be transfused if <10,000 or <20,000 and febrile. The cardiac monitoring will be continued until the end of chemoradiation. Baseline EKG and then as needed. Patients will be evaluated as per SOC by radiation oncology. If it is determined that radiation needs to be stopped, patients will come off the study
- Non-hematologic Toxicity

These effects will be graded according to CTC recommendations for grading of acute and sub-acute toxicity.

Reaction	Management of reaction
Renal	
Creatinine < 1.5 x the upper limit of normal at the day of retreatment.	Continue therapy.
Creatinine is > 1.5 x the upper limit of normal.	• Establish intravenous infusion the evening preceding treatment at a rate to correct any volume deficits and produce a urine flow ³ 50 mL/h. • Repeat blood creatinine value in the morning: • < 1.5 x the upper limit of normal → Proceed treatment. • > 1.5 x the upper normal limit →

	Stop chemotherapy.
Gastrointestinal	
Mucositis with oral ulcers or protracted vomiting despite antiemetic premedication.	Delay chemotherapy one week.
Neurologic	
<CTC grade 2.	Continue therapy.
CTC > GRADE 2.	STOP CHEMOTHERAPY.
Cardiac	
Asymptomatic bradycardia or isolated and asymptomatic ventricular extrasystoles.	Continue therapy under continuous cardiac monitoring.
First degree AV block	Continue therapy under continuous cardiac monitoring.
Symptomatic arrhythmia or AV block (except 1st degree) or other heart blocks.	Stop paclitaxel, manage arrhythmia according to standard practice, patient goes off protocol.
Other Major Organ Toxicity	
CTC grade > 2 (with the exception of esophagitis)	Stop therapy, patient goes off protocol treatment.

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

Radiation toxicity

Radiotherapy, especially concurrent with chemotherapy can lead to acute esophagitis. In some cases, medical support and/or a feeding tube will be necessary.

In the event of grade 4 radiation induced esophagitis both chemotherapy and radiotherapy will be withheld until the esophagitis recovered to grade 3.

Other acute complications of the radiation therapy are erythema, cough, nausea, fatigue and weight loss.

In the first weeks to six months after the irradiation radiation pneumonitis or fistula formation can occur.

10.6 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, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime or, participant withdraws from study.

10.7 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 clinic visit (see **Appendix E**)

11 PROCEDURES INVOLVED

The study-specific assessments are detailed in this section and outlined in **Appendix G** (Schedule of Procedures and Observations). Baseline and/or Screening assessments must be performed within 4 weeks 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.

11.1 Participant 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 4 weeks prior to first dose of study drug:

- Medical history with pre-existing conditions
- Physical examination, including vital signs (temperature, heart rate, respiratory rate, and blood pressure), body weight, and height: Height collected at baseline only.
- ECOG Performance Status (**Appendix A**)
- CBC
- CMP
- Pregnancy test for women of childbearing potential (within 7 days of starting induction chemotherapy)
- Blood draw for ctDNA analysis
- 12-lead EKG/ ECG
- Upper endoscopy/ endoscopic ultrasound (EGD with EUS)
- FDG PET/ CT

- Concomitant medications
- Archival or fresh biopsy tissue obtained from EGD (archival will be requested if EGD performed prior to study enrollment; fresh if EGD performed while on study)

11.3 Evaluations Performed on Day 1 of each Induction Cycle

- Physical examination, including vital signs
- CBC
- CMP
- Concomitant medications
- Adverse events

11.4 Evaluations Performed at End of Induction Chemotherapy Treatment

The following evaluations will be performed at the end of Induction Chemotherapy (within 2 weeks) treatment or at time of treatment discontinuation:

- Physical examination, including vital signs
- ECOG Performance Status (Appendix A)
- CBC
- CMP
- Blood draw for ctDNA analysis
- FDG PET/ CT
- Concomitant medications
- Adverse events

11.5 Evaluations performed during chemoradiation (Weeks 2, 4, and 6 ± 1 week after starting chemoradiation)

- Physical examination, including vital signs
- ECOG Performance Status (Appendix A)
- CBC
- CMP
- Concomitant medications
- Adverse events

11.6 Evaluations Performed at End of Chemoradiation (within 4 weeks)

- Physical examination, including vital signs
- CBC
- CMP

- Blood draw for ctDNA analysis
- CT chest, abdomen and pelvis with contrast
- Concomitant medications
- Adverse events

11.7 Evaluations Performed at Time of Surgical Resection

- Physical examination, including vital signs
- CBC
- CMP
- Blood draw for ctDNA analysis
- Pathological assessment of the resected specimen to evaluate complete response
- Concomitant medications
- Adverse events

11.8 Post-Treatment Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 7 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

11.9 Long Term Follow-Up Evaluations

If asymptomatic:

- History and Physical (with vital signs) every 3–6 months for 1 year following surgery.
- A one-time research-related blood draw for ctDNA analysis during the follow-up period (to be determined by the study physician)
- After 1 year following surgery the patient will be followed as per standard of care: Year 1-Year 2, every 3-6 months; every 6–12 months for 3–5 years, then annually until disease progression or death, whichever occurs first.
- Chemistry profile and CBC, imaging studies and upper GI endoscopy and biopsy as clinically indicated will be performed as standard of care follow-up.
- Survival status: At all follow-up timepoints until disease progression or death (telephone contact is acceptable).
- If patient develops disease progression or is a non-responder while still on study and, a biopsy is performed as part of standard of care, FFPE (per section 11.11.2) will be requested for correlative analysis.

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 and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

11.10 Correlative Studies

11.10.1 Blood draw for ctDNA analysis

Blood samples will be collected (on Monday through Thursday only) via venipuncture for ctDNA analysis. Samples will be collected using two, 10 mL Streck Cell-free DNA BCT® tubes.

Samples will be obtained on:

- Baseline
- After completion of induction chemotherapy (within 2 weeks)
- After completion of chemoradiation (within 4 weeks)
- After surgical resection (within 3 days of procedure)
- Disease recurrence or progression on study

Samples will be kept at room temperature prior to processing.

Collect whole blood in Streck Cell-Free DNA BCT® tubes. The Streck collection tubes will be labeled with the participant's initials, participant's study number, clinical study number, protocol time point, and protocol day. Tubes should be filled completely. Immediately after collection, GENTLY INVERT TUBE(s) 10 times to ensure adequate mixing. Inadequate or delayed mixing may result in inaccurate test results.

Samples collected at Roswell Park will be sent at room temperature to the attention of Laboratory Medicine – Protocol Clinical Research Support (pneumatic Station 19) where they will get accessioned for tracking in the source document (external sites will follow their local SOPs for sample tracking). Once sample receipt has been documented, the whole blood samples will be transported on the same day (at ambient temperature) to the Roswell Park Hematologic Procurement Laboratory for processing for plasma and buffy coat (**Appendix H**) and storage until time of analysis.

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.

MULTI-SITE (EXTERNAL) SITES: Follow directions above for whole blood sample collection and processing. The Streck collection tubes will be labeled with the Subject ID #

(unique to External patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The whole blood samples will be shipped out on the **same day** (at ambient temperature) to Roswell Park Comprehensive Cancer Center Hematologic Procurement Laboratory via Fed Express Overnight.

NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Prior to sample shipment, please email the following individuals: linda.lutgen@roswellpark.org and brandon.martens@roswellpark.org.

Roswell Park Comprehensive Cancer Center
Hematologic Procurement Laboratory
Basic Science Bldg., S524
Attn: Linda Lutgen / Brandon Martens
Refer to Study Number– I 443819
Elm & Carlton Streets Buffalo, New York 14263

Tel: 716-845-8098

Address shipments and any questions regarding specimen processing to Linda Lutgen or Brandon Martens (see above for contact information).

11.11 Pathology

11.11.1 Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

Baseline tumor specimens will be collected for all patients. This can be fresh EGD biopsy tissue (collect and process to FFPE block as per site usual procedure) or archival tumor tissue from available EGD tumor biopsies existing in the Paraffin Archive in the Department of Pathology (or sent to the Department from an outside institution):

- One formalin-fixed paraffin embedded (FFPE) tissue block with >25 mm^2 minimum surface area and ≥ 60 microns in total thickness PLUS 1 H&E slide, **OR**
- 10-20 unstained sections at 5-microns each on positively charged slides PLUS one H&E slide is required. Tumor content must be at least 30%.

These de-identified specimens will be labeled with clinical study # (I 443819), study-specific subject ID number, tissue accession number/block ID, Time Point, and serial section # (for slides) and will be sent to the Roswell Park Clinical Research Laboratory Services Office for storage. These samples will be batch shipped, upon PI request, for analysis at the conclusion of the study.

In patients that progress while on study and have a standard of care biopsy performed, fresh or archival tissue will be collected as above, if available.

11.11.2 Fresh Tumor Biopsy at time of Surgical Resection

The following FFPE sections from the surgical resection biopsy performed (following completion of chemoradiation) are required:

- FFPE tumor block and 1 H&E, OR 10-20 unstained serially sectioned (on plus glass) FFPE slides and one adjacent H&E FFPE slide, all at 4µm-5µm thickness.

Tissue samples are to be labeled with clinical study # (I 443819), study-specific ID number, tissue accession number/block ID, protocol time point, and serial section # (for slides) and will be stored in CRLS (S-636, GBSB) and batch shipped, upon PI request, for analysis at the conclusion of the study.

Pathologic complete response rate (pathCR) will be determined by SOC pathologic examination of the tumor specimen obtained following resection.

In patients that have a pathologic complete response (pathCR) with no primary tumor being identified in tissue obtained at time of surgical resection, the following sections of tissue from the most recent neoplastic *pre-treatment* biopsy that exists in the Paraffin Archive in the Department of Pathology (or outside institution) will be requested:

- 10-20 unstained serially sectioned (on plus glass) FFPE slides and one adjacent H&E FFPE slide all at 4µm-5µm thickness.

Tissue samples are to be labeled with clinical study # (I 443819), study-specific subject ID number, tissue accession number/block ID, protocol time point, and serial section # (for slides). The FFPE sections will be stored in CRLS (S-636, GBSB) and batch shipped, upon PI request, for analysis at the conclusion of the study. For Multi-Site (**External Sites**): De-identified tissue samples using study-specific subject ID number and tissue accession# (GCP requires at least 2 identifiers) are to be sent at ambient temperature to Roswell Park Clinical Research Laboratory Services Office (Attn: Protocol Lab Team). The **shipping label** should read as follows:

Roswell Park Comprehensive Cancer Center
Elm & Carlton Streets
Clinical Research Laboratory Services Office
Gratwick Basic Science Building, S-636
Attn: Protocol Lab Team, I 443819 Samples
Buffalo, NY 14263
(716) 845-8917

Email: CRSLabPathTeam@RoswellPark.org

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.

12 WITHDRAWAL OF SUBJECTS

All patients that receive any of the treatment combination will be included in the AE summaries.

Patients without a response assessment who discontinue treatment due to non-treatment (i.e. toxicity) and non-disease (i.e. disease progression) related reasons will be considered non-evaluable for the primary analysis and will be replaced. These patients will be followed for the protocol defined safety/ toxicity period (unless they received no study drug/ procedure that would otherwise require this). They will not have any additional scheduled follow up visits and will not be followed for survival. Once a non-evaluable patient is beyond the safety follow-up window, they will be taken off study in an expedited way.

Patients without a response assessment who discontinue treatment due to a treatment or disease related reason will be considered evaluable for the primary analysis and treated as non-responders.

Stopping Criteria for Toxicity

If study treatment is delayed by at least 3 weeks due to any Grade 3 or Grade 4 toxicity from induction chemotherapy, the patient will be taken off the study and will proceed to chemoradiation as clinically indicated. Once off study, the patient will be followed for the protocol defined safety period [follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug related toxicity, as per Appendix G). Once beyond the safety follow-up window the patients will be taken off protocol and will be considered as non-responders. If 5 or more patients are taken off the study to toxicity during stage 1 of the study, which aims to recruit 22 patients, accrual will stop until further protocol amendments are made.

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
- Noncompliance
- Participant voluntary withdrawal
    - Patient-initiated discontinuation of study therapy: Even after a patient agrees to take part in this study, he or she may stop study therapy or withdraw from the study at any time. If study therapy is discontinued for reasons other than disease progression but the patient still allows the investigator to submit information, continue imaging as per NCCN guidelines until progression or until, at the investigator's discretion, further treatment is begun. Patients will continue to be followed for survival.
    - Patient-initiated withdrawal from the study: If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NCCN), the investigator must provide NCCN with written documentation of the patient's decision to fully withdraw from the study.
- Sponsor decision

In addition to the conditions outlined above, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- The patient develops a serious side effect that he or she cannot tolerate or that cannot be controlled with other medications

- The patient's health gets worse
- The patient is unable to meet the study requirements, or
- New information about the study therapy or other treatments for gastroesophageal cancer becomes available

If study therapy is discontinued for reasons other than progression, continue disease imaging as per NCCN guidelines until disease progression or until, at the investigator's discretion, further treatment is begun. Patients will continue to be followed for survival.

13 RISKS TO SUBJECTS

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 Oxaliplatin

The most common adverse reactions reported (incidence ≥ 40%) are peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue, and stomatitis.

Anaphylactic reactions to oxaliplatin have been reported and may occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis.

13.3 Carboplatin

The most common adverse reactions reporter (incidence (≥ 10%) are:

Pain, hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia, vomiting, abdominal pain, nausea, bone marrow depression, anemia, leukopenia, neutropenia, thrombocytopenia, increased blood alkaline phosphatase, increased blood AST, weakness, decreased creatinine clearance, and increased blood urea nitrogen.

Anaphylactic reactions to carboplatin have been reported and may occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis.

13.4 Paclitaxel

The most common adverse reactions reporter (incidence (≥ 10%) are:

Flushing, ECG abnormality, edema, hypotension, peripheral neuropathy, alopecia, skin rash, nausea, vomiting, diarrhea, mucositis, stomatitis, neutropenia, leukopenia, anemia, thrombocytopenia, hemorrhage, increased blood alkaline phosphatase, increased blood AST hypersensitivity reaction, infection injection site reaction, arthralgia, myalgia, weakness, and increased blood creatinine.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients in clinical trials. Fatal reactions have occurred in patients despite premedication. We will pretreat

all patients with corticosteroids, diphenhydramine, and histamine H_2 antagonists. We will not rechallenge patients who experience severe hypersensitivity reactions to paclitaxel.

14 POTENTIAL BENEFITS TO SUBJECTS

Based on the published data, TAS-102, in addition to its anti-metabolite properties, can induce single- and double-stranded DNA breaks and DNA instability (8). Tipiracil has additional anti-angiogenic properties. It is currently approved by the FDA for treatment of advanced metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. As such, it has the potential to increase the efficacy of standard of care therapy and improve pathologic response rates in localized or locally advanced esophageal or GEJ adenocarcinoma.

Pathologic response to neoadjuvant therapy is a prognostic biomarker for overall survival (15). With current standard treatment, complete pathologic response (path CR) is observed only in 20-25% patients. Our expectation is to improve path CR by 15% with our proposed treatment. Besides, micrometastatic disease is treated earlier using induction chemotherapy and spares those patients from a major surgical approach who are destined to relapse early.

15 DATA AND SPECIMEN BANKING

All blood samples for correlative analysis will be sent to the Roswell Park Hematologic Procurement Laboratory for processing and storage until requested for planned assays at conclusion of the study.

All tumor tissue samples will be sent to Roswell Park Clinical Research Laboratory Services for storage until requested by PI for analysis at the end of the study. Samples will be used for future analysis for other yet to be identified biomarkers that may be related to the clinical outcome of the study population.

Any clinical data that is associated with the samples, will be stored on a secure 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.

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.

All research samples will be utilized for the planned study assays only.

16 MEASUREMENT OF EFFECT

16.1 Solid Tumors

For the purposes of this study, every patient should have a baseline FDG PET-CT scan. Patients should be re-evaluated by a repeat PET-CT within 1 week after completion of induction chemotherapy. In addition, patients should have a chest/abdominal CT scan with contrast and pelvic CT with contrast after completion of the concurrent chemoradiation therapy. After surgery, patients will be followed as per NCCN guidelines.

16.2 Pathologic Complete Response Rate

Pathologic complete response rate (path CR) will be determined by pathologic examination of resected specimen (i.e., complete and partial response to induction chemotherapy followed by standard chemoradiation and surgery). Refer to **Appendix F.**

16.3 PFS and OS

The survival outcomes (PFS and OS) are treated as bivariate time-to-event data. PFS is defined as the time from treatment until disease progression, death from disease, or last follow-up. OS is defined as the time from treatment until death due to any cause or last follow-up. The time to event outcomes will be summarized using standard Kaplan-Meier methods, where estimates of median survival will be obtained with 95% confidence intervals.

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 dates 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 17.10.1** for details on reporting Unanticipated Problems.

17.8 Investigator Reporting: Notifying Taiho Oncology

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 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.

17.9 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.

17.9.1 Other Reportable Events

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

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

17.9.2 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 (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. The Institution must provide final outcome of pregnancy to TAIHO. If any SAE(s) is observed in a study subject or fetus/child, then SAE(s) must also be reported to TAIHO following SAE Reporting guidelines.

<u>Routing of Drug Exposure during Pregnancy and Lactation, or Paternal Drug Exposure Reports</u>

Such reports and Information as outlined above, Including Investigator causality assessments against all concerned TAIHO 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')

Requesting Follow-up Information:

The institution will provide TAIHO with details of whom TAIHO 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. Sarbajit Mukherjee.

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 also 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. Unanticipated problems will be reported to NCCN at same time as Taiho. SAEs may be emailed to ORPreports@nccn.org or faxed to 215-358-7699.

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

The Food and Drug Administration has issued guidance to assist in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. Those recommendations may be found at the link below:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic.

Changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to the sponsor. Since this reflects a protocol deviation to the current protocol practice, documentation of deviations is required. Telephone or video communications with subjects should be utilized at the discretion of the site investigator taking into consideration the guidelines provided above. Besides treatment delay is allowed as per the investigators' discretion as patients are worked-up, treated or hospitalized for COVID-19 or any related illness.

18 DATA MANAGEMENT AND CONFIDENTIALITY

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.

Clinical Data Management activities are performed using CTMS and EDC systems that enable the collection, cleaning and viewing of clinical trial data. CRS Clinical Data Manages designs and develops the study-specific database. 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.

18.1 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.

18.2 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.

18.3 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

19.1 Sample Size Determination

The sample size calculations are based on the primary analysis, which evaluates the one-sided hypotheses about the actual path CR rate using the Simon two-stage minimax design. The historical path CR rate for the standard of care is at most 0.2 (π_0). If the actual path CR rate is $\pi = 0.35$, then the study design ($n=n_1+n_2=22+19=41$ evaluable patients) achieves 80.4% power at a significance level of $\alpha=0.1$. To account for patients that may be non-evaluable, up to n=45 study subjects may be needed.

19.2 Demographics and Baseline Characteristics

Patient characteristics will be summarized using the appropriate descriptive statistics.

19.3 Primary Analysis

The primary outcome is the pathologic CR; which is treated as a dichotomous variable and will be summarized using frequencies and relative frequencies. Historically, the path CR rate in this patient population is approximately 20%. We expect the path CR rate after induction chemotherapy to increase by 15% based on the study by Goodman et al. (13). As such, the following hypotheses will be evaluated using a two-stage minimax design:

H_O: $\pi \leq 0.2$ Versus H_A: $\pi > 0.2$, where π is the actual path CR rate for metabolic responders.

In stage 1, n_1=22 evaluable patients will be enrolled. If there are 4 or fewer path CRs, then the proposed treatment regimen will not be considering promising and the study will be suspended for futility. If there is 5 or more path CRs, an additional n_2=19 evaluable patients will be enrolled in stage 2. If 12 or more response is observed in the total n=41 evaluable patients, then the proposed treatment regimen will be considered promising for further study. Otherwise, the proposed treatment regimen will not be considered promising.

Additionally, the path CR rate will be estimated using an 80% confidence interval obtained using Jeffrey's prior method. Patients without a response assessment who discontinue treatment due to non-treatment (i.e. toxicity) and non-disease (i.e. disease progression) related reasons will be considered non-evaluable for the primary analysis and will be replaced.

19.4 Secondary Analysis

The overall and disease-specific survival will be summarized using standard Kaplan-Meier methods; where estimates of median survival and two-year survival rates will be obtained with 90% confidence intervals.

19.5 Exploratory Analysis

Analysis of the ctDNA samples collected under this protocol will be batched and shipped to Natera, Inc. after processing in-house to be analyzed for ctDNA levels to fulfill the exploratory objective. Samples will be provided to Natera per an executed Research Collaboration Agreement in a de-identified manner.

Shipping instructions for plasma/cfDNA:

Place sample tubes in cryoboxes and then in an insulated shipping box.

- Do not put more than four, 2 inch cryoboxes or two 4-6 inch cryoboxes in one insulated shipping box.
- Fill with a sufficient amount of dry ice (5-10 lbs of dry ice per 24 hour period).
- Use appropriate UN3373 and UN1845 approved shipping containers. Affix appropriate shipping labels to the outside of the box: UN3373 Biological Substance Category B and Dry Ice UN1845.

Ship packages to:

Natera, Inc.

Attn: RUO Operations

201 Industrial Rd., Suite 410

San Carlos, CA 94070

- Fill-out the shipping manifest with all relevant information.
- Please send package tracking information and shipping manifest to:
  - o RnD Samples team (ruoops@natera.com)
  - o cc: Your Alliance Manager Receiving Schedule
- Hours of Operation: Natera accepts delivery of samples Monday through Friday 7:30 a.m.–4:30 p.m. Pacific Time.
- Observed Holidays: The laboratory will be closed during observed holidays. Please contact the courier and laboratory to confirm that deliveries can be made prior to observed holidays.

19.6 Safety Analysis

Toxicities and adverse events (as per CTCAE v5.0) will be summarized by attribution and grade using frequencies and relative frequencies.

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 will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be 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) 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

Previous experience: Sarbajit Mukherjee, MD: Principal Investigator: Dr. Mukherjee has experience in drafting clinical trial proposals, and he is currently a co-principal investigator of an investigator-initiated multicenter Phase 2 clinical trial. Besides, Dr. Mukherjee has previous experience in outside collaborations that led to peer-reviewed publications in high-impact factor journals like Nature Medicine.

Study site: Roswell Park Comprehensive Cancer Center is a nationally and internationally known cancer center with a history of timely completion of clinical trials. The study site does not have competing clinical trials.

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) 845-7405.

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 (or legal guardian) 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

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, by and in accordance with the applicable regulatory requirements.

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 drugs provided, 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 Oxaliplatin

Oxaliplatin will not be supplied by the study and will be paid for by the patient's insurance carrier as part of the standard-of-care treatment.

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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: Use of Trifluridine/ Tipiracil and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Must have histologically proven loco-regional esophageal or gastroesophageal junction adenocarcinoma.	
☐	☐	☐	3. Endoscopic ultrasound (EUS), or clinically determined node-positive disease with any T-stage or T3-T4a with any N stage: Patients with EUS T4b and any M1 cancer **will not** be included.	
☐	☐	☐	4. Must have potentially resectable disease.	
☐	☐	☐	5. Have an ECOG Performance Status of 0-1. Refer to Appendix A.	
☐	☐	☐	6. Have the following clinical laboratory values • Hemoglobin ≥ 9 g/dL • Absolute neutrophil count ≥ 1500/mm3 • Platelet count ≥ 100,000/mm3 • Creatinine < 1.5 ULN • Bilirubin < 1.5 x ULN • AST/ALT ≤ 3 x ULN	
☐	☐	☐	7. Capacity to take oral tablet(s) without difficulty.	
☐	☐	☐	8. 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.	
☐	☐	☐	9. 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: Use of Trifluridine/ Tipiracil and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Prior chemotherapy, thoracic radiotherapy or prior surgical resection for an esophageal tumor.	
☐	☐	☐	2. Participants with known metastatic disease.	
☐	☐	☐	3. Any concurrent active malignancy that requires active systemic intervention.	
☐	☐	☐	4. Grade 2 or higher peripheral neuropathy.	
☐	☐	☐	5. Participants who have had major surgery or field radiation within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.	
☐	☐	☐	6. Received an investigational agent within 4 weeks prior to enrollment.	
☐	☐	☐	7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	8. Grade 3 or higher hypersensitivity reaction to oxaliplatin or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with premedication	
☐	☐	☐	9. Patient previously treated by (TAS-102) or history of allergic reactions attributed to compounds of similar composition to TAS-102 or any of its excipients.	
☐	☐	☐	10. Hereditary problems of galactose intolerance; e.g., Lapp lactase deficiency or glucose-galactose malabsorption.	
☐	☐	☐	11. Pregnant or nursing female participants.	
☐	☐	☐	12. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	13. 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 Comprehensive Cancer Center
CRS Quality Assurance (QA) Office
CRS-QA@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263
Telephone:
Monday - Friday; 7:00 AM to 4:00 PM EST
716-845-3870
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 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 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 (CRS-QA@RoswellPark.org) to the Roswell Park CRS QA 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 CRS QA Coordinator at (CRS-QA@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 CRS 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 CRS 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 OnCore SAE form
- MedWatch 3500A

All serious adverse events via a MedWatch Form need to be sent to the Taiho Oncology, Inc., via fax: 609-750-7371 or e-mail: TAS-102_Safety@taihooncology.com (please note the underscore between '102' and 'Safety').

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

The principal investigator or designee will inform Roswell (via email using both the OnCore SAE form and MEDWATCH 3500A form) within twenty-four (24) hours of first awareness of any event that meets the above criteria. Both forms should include all available information, including a brief narrative describing the SAE, attributions, and any other relevant information. Upload all related (redacted) source information into OnCore along with the completed forms signed by the PI. Forms will be submitted to the CRS QA Office via email to SafetyEventReporting@RoswellPark.org.

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 CRS 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 CRS QA Coordinator at: CRS-QA@RoswellPark.org.

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 1-Day 5 0 of every 14-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. 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 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

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 NCCN Principles of Pathologic Review

Reproduced from: NCCN Guidelines Version 1.2019
Esophageal and Esophagogastric Junction Cancers

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Table 1 Pathologic Review

Specimen Type	Analysis/Interpretation/Reporting[a]
Biopsy	Include in pathology report: • Invasion, if present; high-grade dysplasia in Barrett's esophagus is reported for staging purposes as 'carcinoma in situ (Tis)[b,c,d] • Histologic type[e] • Grade[f] • Presence or absence of Barrett's esophagus
Endoscopic resection	Include in pathology report: • Invasion, if present[b,d] • Histologic type[e] • Grade[f] • Depth of tumor invasion • Vascular/lymphatic invasion • Status of mucosal and deep margins
Esophagogastrectomy, without prior chemoradiation	For pathology report, include all elements as for endoscopic mucosal resection plus: • Location of tumor midpoint in relationship to EGJ[g] • Whether tumor crosses EGJ • Lymph node status and number of lymph nodes recovered
Esophagogastrectomy, with prior chemoradiation	• Tumor site should be thoroughly sampled, with submission of entire EGJ or ulcer/tumor bed for specimens s/p neoadjuvant therapy without grossly obvious residual tumor • For pathology report, include all elements as for resection without prior chemoradiation plus assessment of treatment effect

[a]Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at http://www.cap.org) for reporting pathologic findings is recommended.
[b]For purposes of data reporting, Barrett's esophagus with high-grade dysplasia in an esophageal resection specimen is reported as "carcinoma in situ (Tis)." The term "carcinoma in situ" is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states.[1]
[c]Biopsies showing Barrett's esophagus with suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.[2]
[d]Invasion of a thickened and duplicated muscularis mucosae should not be misinterpreted as invasion of the muscularis propria in Barrett's esophagus.[3]
[e]A specific diagnosis of squamous cell carcinoma or adenocarcinoma should be established when possible for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are stage using the TNM system for squamous cell carcinoma.[1]
[f]Pathologic grade is needed for stage grouping in the AJCC TNM 8th edition.[1]
[g]Midpoint of tumors arising in the proximal 2 cm of the stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[1]

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Assessment of Treatment Response

Response of the primary tumor to previous chemotherapy and/or radiation therapy should be reported. Residual primary tumor in the resection specimen following neoadjuvant therapy is associated with shorter overall survival for both adenocarcinoma[4-6] and squamous cell carcinoma (SCC) of the esophagus.[7]

Although scoring systems for tumor response in esophageal cancer have not been uniformly adopted, in general, three-category systems provide good reproducibility among pathologists.[6,8,9] The modified Ryan scheme in the CAP Cancer Protocol for Esophageal Carcinoma (available at http://www.cap.org)[8,9] should be used. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor. Although the system described by Wu was originally limited to assessment of the primary tumor, it is recommended that lymph nodes be included in the regression score[10] because of the impact of residual nodal metastases on survival.

Table 2

Tumor Regression Score[9]	CAP Cancer Protocol Description
0 (Complete response)	No viable cancer cells, including lymph nodes
1 (Near complete response)	Single cells or rare small groups of cancer cells
2 (Partial response)	Residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells
3 (Poor or no response)	Extensive residual cancer with no evident tumor regression

Reproduced and adapted with permission from Shi C, Berlin J, Branton PA, et al. Protocol for the examination of specimens from patients with carcinoma of the esophagus. In: Cancer Protocol Templates. Northfield, IL: College of American Pathologists; 2017 (available at http://www.cap.org).

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Appendix G Schedule of Procedures and Observations

Time point	Screening[1]	Induction Chemotherapy (IC) Cycle 1-Cycle 3 Day 1 of each cycle	End of IC (within 2 weeks)	During chemoradiation (Weeks 2, 4 and 6 ± 1 week after starting chemoradiation)	End of CRT (within 4 weeks)	At time of Surgical Resection	Follow-Up Safety evaluation[2]	Long Term Follow-Up[3]
Clinical Procedures								
Medical History	X							X
Pre-Existing Conditions	X							
Physical Examination[4] , including vital signs[5]	X	X	X	X	X	X		X
ECOG Performance Status	X		X	X				
Concomitant Medications	X[6]	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	
Survival Status								X
Laboratory Procedures								
Hematology[7]	X	X	X	X	X	X		
Chemistry[8]	X	X	X	X	X	X		
Pregnancy Test (Urine or Blood)	X							
Blood Draw for Correlative Analysis[13]	X		X		X	X		X[9]
Tissue[12]	X[12a]					X[12b]		X[12c]
Imaging Procedures								
ECG/EKG (12-Lead)	X							
EGD with EUS	X							
Imaging for Tumor/ Disease Assessment (FDG PET CT/ CT CAP)	X		X		X			

Time point	Screening[1]	Induction Chemotherapy (IC) Cycle 1-Cycle 3 Day 1 of each cycle	End of IC (within 2 weeks)	During chemoradiation (Weeks 2, 4 and 6 ± 1 week after starting chemoradiation)	End of CRT (within 4 weeks)	At time of Surgical Resection	Follow-Up Safety evaluation[2]	Long Term Follow-Up[3]
Treatment Regimen/Drug Administration								
TAS-102		X[10]						
Oxaliplatin		X[11]						
Carboplatin				X				
Paclitaxel				X				
Radiation				X				

1 Performed within 4 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 If asymptomatic:
→ History and Physical (with vital signs) every 3–6 months for 1 year following surgery.
→After 1 year following surgery the patient will be followed as per standard of care: Year 1-Year 2, every 3-6 months; every 6–12 months for 3–5 y, then annually until disease progression or death, whichever occurs first
→ Chemistry profile and CBC, imaging studies and upper GI endoscopy and biopsy as clinically indicated will be performed as standard of care follow-up

4 Research/study-specific assessments should be performed within 4 weeks (± 2 weeks) prior to the start of treatment.

5 Vital signs (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 Once during the follow-up period (to be determined by study physician): at time of disease recurrence./progression on study. See Section 11.10.1.

10 TAS-102 will be administered at the recommended dose of 35 mg/m², BID, orally, on Days 1–5 of every 14-day cycle.

11 Oxaliplatin will be administered at a fixed dose of 85 mg/m², IV (over 2 hours) on Day 1 only of each cycle. On Day 1, the patient will get oxaliplatin first and then be instructed to take the TAS-102.

12 Refer to Section 11.1
12a. Tissue collection at baseline, either fresh tissue from the esophagogastroduodenoscopy (EGD) if done post-consent, or archival if the EGD was already done prior to study enrollment

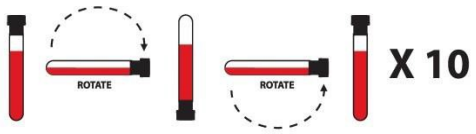
12b. Pathological assessment of the resected specimen to evaluate complete response. FFPE sections from the surgical resection biopsy performed following completion of chemoradiation biopsy will be requested. In patients that have a pathologic complete response (pathCR) with no primary tumor being identified in tissue obtained at time of surgical resection, archival pre-treatment neoplastic tissue will be requested.
12c. In addition to on-trial tissue biopsies, if patient develops disease progression or is a non-responder while still on study and a biopsy is performed as part of standard of care, FFPE (per section 11.11.2) will be requested for correlative analysis.

13 Blood draws for correlative analyses will be drawn on Monday – Thursday only due to Friday overnight shipping restrictions. Refer to Section 11.10.1.

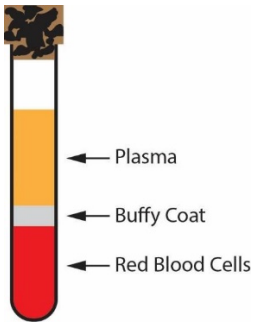
Appendix H Whole Blood Sample Processing

Procedure for the Isolation of Buffy Coat and Plasma from Whole Blood

1. Requirements
    a. Use two (2) Streck Cell-Free DNA BCT tubes (black and tan top) to collect whole blood.
    b. Use aseptic techniques and draw blood from the patient into the Streck BCT tube(s). Make sure to collect full volume to ensure correct blood to anticoagulant ratio.
    c. Immediately after the blood is drawn, thoroughly mix the blood with the anticoagulant by gently inverting the Streck BCT tube(s) ten (x10) times.



    d. Use aseptic techniques to process whole blood.
    e. Store Streck BCT tubes at room temperature (between 18 - 30°C) for a minimum of 1 hour and maximum of 12 hours until processing. Process Streck tubes no more than 7 days after collection. Do not freeze Streck BCT tubes prior to processing.
    f. Note on the case report form date/time of blood collection.
2. Procedure
    a. Centrifuge Streck BCT tube(s) at 3220 x g for 30 minutes at 22°C. Do not use brake to stop centrifuge.
    b. Make sure all blood tube processing is performed under a laminar hood to avoid contamination.
    c. Using a sterile transfer pipette, remove the plasma (yellow-clear liquid) **stopping 5mm** above the buffy coat (the thin gray-white layer) to ensure no aspiration of buffy coat and/or red blood cells/erythrocytes and transfer to a sterile 15 ml centrifuge tube. No cells or debris should be present in the plasma.
    d. Re-centrifuge the 15-ml centrifuge tube <u>using the same or new cap</u> at 3220 x g for 15 minutes at 22°C and using a <u>new</u> sterile transfer pipet, remove the plasma **stopping 5mm** above any debris pellet.



e. Aliquot the plasma from each tube into a 2 mL sterile cryovial (approximately 2). The screw cap polypropylene cryogenic tubes will be labeled with the participant's initials, participant's study number, clinical study number, protocol time point, dose, and protocol day..

f. Immediately freeze the cryovials in a -70°C to -80°C freezer.

g. Store frozen plasma cryovials in a -70°C to -80°C freezer until ready to ship.

h. Using a new sterile transfer pipette, slowly remove the buffy coat (the thin gray-white layer located above the red blood cells/erythrocytes). Avoid aspirating excessive amounts of the red blood cells while collecting the buffy coat.

i. Aliquot the buffy coat from one of the tubes into a 2-mL sterile cryovial. Note: Only one cryovial of buffy coat per case is required.

j. Immediately freeze buffy coat vials in a -70°C to -80°C freezer.

k. Store frozen buffy coat vials in a -70°C to -80°C freezer until ready to ship.

Whole blood samples will be processed and stored at Roswell Park's Hematological Procurement Facility until requested by the Principal Investigator for batch shipping at time of analysis.