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TAS-102 IN COMBINATION WITH OXALIPLATIN (TAS-OX) FOR REFRACTORY METASTATIC COLORECTAL CANCER

Sponsor: Yale Cancer Center

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PROTOCOL SYNOPSIS

Title of study: TAS-102 in Combination with Oxaliplatin (TAS-OX) for Refractory Metastatic Colorectal Cancer.

Study Phase: 1B/II

Study Rationale:

TAS-102 is an oral agent, which consists of a combination of a novel antimetabolite 5-trifluorothymidine (FTD) and a thymidine phosphorylase inhibitor (TPI) that prevents degradation of FTD. It has demonstrated activity in chemorefractory metastatic colorectal cancer (mCRC) patients. In the Japanese randomized phase II trial, TAS-102 improved medial overall survival when compared to placebo (9.0 vs.6.6 months, HR 0.56) in subjects with mCRC refractory to 5-fluorouracil (5-FU), irinotecan and oxaliplatin. Subsequently, a randomized phase III study conducted in 13 countries (RECOURSE trial) confirmed this benefit on overall survival when compared to placebo (7.1 months vs. 5.3 months, HR 0.68) in subjects with refractory metastatic colorectal cancer (CRC) 5.

Oxaliplatin is a third-generation platinum compound, which is active when used together with 5-FU in the treatment of mCRC. FOLFOX chemotherapy, which is frequently combined with anti-angiogenic agent Bevacizumab, is widely accepted as the preferred first-line regimen in the treatment of this disease in the US. Oxaliplatin is also frequently reintroduced in more advanced settings. Reintroduction is seen after progression on maintenance therapy, after resolution of previous treatment limiting neuropathy, after disease recurrence post adjuvant treatment or post metastatectomy. In the control arm of OPTIMOX1 study, oxaliplatin was reintroduced in 27% of subjects. Although patients derive clinical benefit when oxaliplatin is reintroduced, the response rates are not as robust as during initial exposures. Decreased efficacy may be at least in part due to prolonged exposure and resultant resistance to 5-FU, which is a backbone in maintenance and in oxaliplatin containing regimens. Hence, we propose exploring the safety and efficacy of oxaliplatin in combination with an alternative anti-metabolite TAS-102 (TAS-OX).

TAS-102 has demonstrated activity in 5-FU refractory mCRC, so we hypothesize that TAS-OX may serve as an alternative drug combination for patients who have progressed or recurred after FOLFOX, and who are candidates for additional oxaliplatin therapy.

Methodology:

This is a 2-part clinical trial with TAS-102 in combination with oxaliplatin. The first part will be a dose-finding run-in phase. The second part will be a single arm expansion cohort study, which will further evaluate the safety, as well as efficacy, of TAS-OX in the treatment of mCRC. Subjects will be treated with the study drugs until radiological evidence of disease progression or until treatment discontinuation secondary to adverse events.

Objectives and Endpoints:

Part 1: Determination of an optimally tolerated dose (MTD)

Part 2:

Primary:

- Overall Response Rate (ORR)

Secondary:

- Progression Free Survival (PFS)
- Overall Survival (OS)
- Disease Control Rate (DCR)
- Duration of Response
- Safety and Tolerability.

Number of centers & participants:

One center – Yale Cancer Center.

Part 1: 3-18 subjects

Part 2: 30 to 50 subjects will be enrolled in the phase 2 portion of the study according to the Bayesian analysis detailed in the protocol.

Population:

This study will enroll patients with histologically confirmed stage IV colon cancer (AJCC 7th edition) who have progressed after at least 2 lines of standard therapy that included 5-FU, irinotecan and oxaliplatin.

Investigational drugs:

TAS-102 (commercially available)

Oxaliplatin (commercially available)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
DLT	Dose limiting toxicity
C	Celsius
CBC	Complete blood count
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Effective dose
EGFR	Epidermal Growth Factor Receptor
EOT	End of treatment
F	Fahrenheit
FDA	Food and Drug Administration
FTD	Trifluorothymidine
GGT	Gamma glutamyltransferase
HR	Hazard ratio
IC	Inhibitory concentration
ICF	Informed consent form
ILD	Interstitial lung disease
INR	International normalized ratio
IV	Intravenous
Kg	Kilogram
LFT	Liver function tests
M	Molar
MCV	Mean corpuscular volume
mCRC	Metastatic colorectal cancer
Mg	Milligram
MTD	Maximum tolerated dose
NCI	National Cancer Institute

NGS	Next generation sequencing
OAE	Other significant adverse events
PD	Progressive disease
PFS	Progression free survival
PLT	Platelets
PR	Partial response
PT	Prothrombin time
PTT	Partial prothrombin time
QD	Daily
RECIST	Response Evaluation Criteria In Solid Tumor
RR	Response rate
RTK	Receptor tyrosine kinase
SAD	Short axis diameter
SAE	Serious adverse event
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TP	Thymidine phosphorylase
TPI	Tipiracil hydrochloride
TS	Thymidylate synthase
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor

EVALUATION SCHEDULE

Week	0[c]	1	2	3	5	7	9	11	13	15	17+	End [d]
Cycle		1		2	3	4	5	6	7	8	9+	
Oxaliplatin, IV		x		x	x	x	x	x	x	x	x	
TAS-102, PO [h]					Days 1-5 during each 14-day cycle.							
Informed Consent	x											
Demographics	x											
Medical History [f]	x	x		x	x	x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x											
Blood work [a]	x	x	x	x	x	x	x	x	x	x	x	x
Serum CEA [g]		x			x		x		x		x	
AE Evaluation			x	x	x	x	x	x	x	x	x	x
Radiologic Evaluation [b]	x						x				x	

ALL VISITS AND EVENTS WILL BE ALLOWED WITHIN ± 48 HOUR WINDOW

[a.] Complete blood count with differential, albumin, alkaline phosphatase, total bilirubin, bicarbonate, urea or BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium, magnesium. Coagulation tests including PTT and INR at screening; may be repeated if clinically indicated at subsequent visits. Serum or urine pregnancy test (women of childbearing potential) will be obtained at the time of screening.

[b.] CT chest/abdomen/pelvis or PET/CT will be done. Radiological evaluations will be performed every 8 weeks or more frequently if clinically indicated. Restaging scans may be spaced out to every 12 weeks after the first 2 scans on treatment at the discretion of the treating physician.

[c.] Within 14 days of treatment initiation. CT c/a/p scans will be done within 28 days of treatment. Informed consent can be obtained within 28 days of treatment initiation.

[d.] Treatment will be continued until disease progression or intolerable toxicities. End of treatment visit will occur within 28 days after last dose of TAS-102 or prior to their next anti-cancer therapy, whichever happens first.

[e] Vital signs will include measurement of weight, blood pressure, heart rate, temperature, and oxygen saturation. Height will be measured at the time of study enrollment only.

[f] Includes medical, surgical and prior cancer treatment history.

[g] CEA will be checked every 4 weeks (with every other cycle), including on day 1 of cycle 1.

[h] TAS-102 pills are distributed by local pharmacy per Standard of Care (SOC) on Day 1 of each cycle. Subject pill diaries should be completed each cycle.

1. INTRODUCTION

1.1 Colon Cancer

Colon cancer is the third most common cancer in the United States, and it accounts for approximately 9 % of all cancer deaths [1]. More than 100,000 new colon cancer cases were expected to be diagnosed in 2014, with about 20% of these cases having metastatic disease at presentation [1,2]. Unfortunately, only a small number of patients with stage IV disease can be cured with multimodality therapy. Hence, systemic medical therapy is essential in management of these patients. Over the last two decades a number of available systemic treatments for colon cancer have increased significantly. They have improved both quality of life and overall survival, which now exceeds 2 years for stage IV disease [3]. These treatments include conventional chemotherapy agents (fluoropyrimidines, oxaliplatin, and irinotecan), angiogenesis inhibitors (bevacizumab and aflibercept), multitarget oral tyrosine kinase inhibitor (regorafenib), and anti-EGFR antibodies (cetuximab and panitumumab). The optimal sequence for the use of the available drugs is not clear. It is the exposure to all of the active agents that seems to be more important than the order of administration. Hence, the more lines of therapy we can offer to patients, the more benefit patients can derive in terms of their survival and quality of life. Development of alternative/novel treatment options are essential for our ability to treat this disease more effectively.

1.2 TAS-102

1.2.1 Mechanism of Action

TAS-102 is a novel functional antitumor nucleoside. It is a combined form of 1 M trifluridine (FTD; α,α,α-trifluorothymidine) and 0.5 M tipiracil hydrochloride (TPI). FTD is an antineoplastic antimetabolite [4]. It has at two different mechanism of actions. It inhibits thymidylate synthase (TS), and is also incorporated into DNA [4,5]. The latter mechanism is different from the primary cytotoxic mechanism of 5-fluorouracil (5-FU). When FTD is taken orally it is largely degraded to an inactive form by thymidine phosphorylase (TP). This enzyme is present in gastrointestinal tract, liver, and tumor tissue. TPI effectively inhibits TP, and co-administration of TPI with FTD prevents the rapid degradation of FTD in the body. TP has also been shown to play a role in promoting angiogenesis [6]. Hence, TAS-102 may exhibit some of its effects via the potential anti-angiogenic properties of TPI.

1.2.2 Clinical Experience with TAS-102

The safety and efficacy of TAS-102 have been studied in phase 1, 2 and 3 studies, with have been conducted in Japanese and Western populations. These studies established proof of concept, appropriate dosing, and preliminary safety data for TAS-102. As of 24 July 2014, 1449 subjects participated in Taiho sponsored TAS-102 trials globally. Details regarding the early phase studies are included in the Investigator's Brochure for TAS-102.

The efficacy and safety of TAS-102 in the treatment of mCRC subjects have been studied in a Phase 2 trial conducted in Japan and in a global Phase 3 trial (RECOURSE) conducted in the US, Europe, Australia and Japan. In a randomized double-blind Japanese phase 2 trial 169 subjects with metastatic chemorefractory CRC were randomized in a 2:1 fashion to

either TAS-102 or placebo [7]. In this trial, subjects in the TAS-102 group had significantly longer overall survival (OS) when compared to the placebo group (median OS 9.0 vs. 6.6 months; HR 0.56; p=0.0011). Subsequent international randomized phase III study (RECOURSE trial) was conducted in 13 countries. Eight hundred patients with advanced refractory mCRC were randomized 2:1 to TAS-102 or placebo. The results of this trial confirmed TAS-102 associated benefit on overall survival observed in the phase 2 Japanese trial. Median OS in the TAS-102 group was 7.1 months versus 5.3 months in the placebo group (HR 0.68; p<0.0001) [7]. In both of these studies, TAS-102 was well tolerated. Gastrointestinal and hematological toxicities were the most frequently observed toxicities.

The adverse events presented below include adverse events reported from previous trial participants. For subjects in the ongoing trials, no new serious adverse events in addition to those listed below have been reported. However, the side effects shown below are not a complete. Rare events of a non-severe nature are not listed, buy rare events of a severe nature are included below. In addition, the list includes events that may or may not have been related to TAS-102 use.

c. Likely, occurring in > 20% of participants (all grades):
- GI: Nausea, vomiting, diarrhea
- Blood: Leucopenia, neutropenia, anemia
- General: Fatigue, asthenia, malaise
- Metabolism: Decreased/loss of appetite, anorexia
- Infection: Infections e.g. blood, lung, pelvis, eye, urinary tract, intestinal tract, skin, liver/biliary tract

b. Common, occurring in 3 -20% of participants (all grades):
- GI: Stomatitis, constipation, abdominal pain, indigestion
- Blood: Thrombocytopenia
- Skin: Alopecia, rash (changes in the color or texture of the skin, possible blistering and peeling)
- Renal: Proteinuria
- Nervous: Dysgeusia, headache
- Musculoskeletal: Back pain, arthralgia
- General: Pyrexia, asthenia
- Metabolism: Hypoalbuminemia,
- Psych: Anxiety
- Hepatobiliary: Elevated liver enzymes, e.g. AST, ALT, bilirubin

c. Rare but severe, occurring in < 3% of participants (grade 3 and above):
- Cardiac: Myocardial infarction, myocardial ischemia, chest pain, bradycardia, tachycardia
- Hepatobiliary: Hepatic failure, jaundice
- Renal: Acute renal failure, hematuria
- Nervous: Effects on cognitive or nerve function, seizure, decreased level of consciousness, thromboembolism

• GI: Colitis, intestinal fistula, small or large bowel obstruction, ascites, hemorrhage, intestinal ulcer
• Respiratory: Pulmonary emboli, dyspnea, respiratory arrest, pneumonitis, epistaxis
• Metabolism: Gout, dehydration
• Vascular: Fainting, DVT, hypotension, blood clotting disorder, hot flushes, septic shock
• Nervous: Dizziness, paresthesia
• Musculoskeletal: Myalgia
• General: Flu like symptoms

1.2.3 Rationale for Combining TAS-102 and Oxaliplatin.

Oxaliplatin is a third-generation platinum compound, which is active when used in combination with fluoropyrimidines in the treatment of mCRC. FOLFOX chemotherapy, which includes bolus and infusion 5-FU, leucovorin and oxaliplatin, is widely accepted as the preferred first-line chemotherapy backbone in the treatment of mCRC in the US. Oxaliplatin is also frequently reintroduced in more advanced settings. Reintroduction is seen after progression on maintenance therapy, after resolution of previous treatment limiting neuropathy, after disease recurrence post adjuvant treatment or post metastatectomy. Although patients derive clinical benefit when oxaliplatin is reintroduced, the response rates are not as robust as during initial exposures. Decreased efficacy may be at least in part due to prolonged exposure and resultant resistance to 5-FU, which is part of the maintenance and oxaliplatin and irinotecan containing treatment regimens.

In this trial, we propose exploring the safety and efficacy of oxaliplatin in combination with an alternative anti-metabolite, TAS-102 (TAS-OX) in chemorefractory mCRC patients. FTD, an active antimetabolite in TAS-102, has mechanisms of cytotoxicity, which differs from 5-FU, as described above. Hence, the mechanisms underlying 5-FU resistance may not apply to TAS-102. This is probably why TAS-102 was clinically effective for the 5-FU refractory patients in the previous studies [7,8]. In preclinical studies, synergism has been observed when oxaliplatin was combined with FTD [9]. We hypothesize that the combination of TAS-102 with oxaliplatin will serve as a novel clinically relevant treatment strategy for a patient population with limited effective treatment options. If successful, this drug combination can be studied further in earlier settings and in combination with biologics.

1.3 Benefit/risk and ethical assessment

Based on current clinical experience with TAS-102, this drug is well tolerated when used as a single agent. We suggest combining TAS-102 with oxaliplatin as a treatment for patients with chemotherapy refractory mCRC. Patients who have previously been treated with at least 2 lines of therapy that included 5-FU, oxaliplatin and irinotecan will be invited for participation in this trial. Although increased toxicities may be seen when the two drugs are combined, we anticipate that this drug combination will be tolerable and will provide additional efficacy in a patient population with limited treatment options. If this study has promising results, future trials may also explore the use of this drug combination in earlier lines of therapy and in combination with biologics.

2. STUDY OBJECTIVES/ENDPOINTS

2.1 Part 1

The main objective of part 1 of the trial is determination of MTD and Recommended Phase 2 Dose (RP2D) to be used in the expansion cohort in part 2.

2.2 Part 2

Part 2 will evaluate the efficacy of the proposed drug combination in refractory mCRC and further evaluate its safety and tolerability.

Primary Endpoint:

- Overall Response Rate

Secondary Endpoints:

- Progression Free Survival
- Overall Survival
- Disease Control Rate
- Duration of Response
- Safety and Tolerability

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

The study is 2-part phase 1B trial conducted in one center. The study will consist of three study periods: a screening period of 14 days or less, a treatment period, and a safety follow-up period of 28 days after treatment discontinuation.

Part 1 is a dose finding phase with the objective to assess the safety and tolerability of the proposed drug combination and to identify the tolerated dose and a recommended Part 2 dose. Part 1 will enroll an estimated 3-18 subjects depending on the tolerability of the regimen. The second part of the trial will be an open-label expansion study, which will include patients with metastatic chemorefractory CRC who have progressed on at least 2 lines of therapy that included 5-FU, oxaliplatin and irinotecan. Part 2 will obtain further safety data of the proposed drug combination and will evaluate the anti-tumor efficacy and tolerability of TAS-102 and oxaliplatin in this patient population. Part 2 of the trial will enroll up to 50 subjects. In both parts, treatment will continue until radiological evidence of disease progression or development of unacceptable toxicities.

3.2 Part 1 study design

Treatments will be started at level 1 doses (Table 1), which are based on prior clinical experience with the medications studied. Dose escalation will follow a traditional “3+3”

design. Treatments will continue until disease progression according to RECIST 1.1 criteria or development of unacceptable toxicities.

3 + 3 Design:

- A minimum of 3 subjects will be enrolled per dose level.
- If none of the first 3 DLT-evaluable subjects experience a DLT, dose escalation may proceed to the next dose level.
- If 1 of the first 3 DLT-evaluable subjects in a cohort experiences a DLT, additional subjects (up to a total of 6) will be enrolled in that cohort.
- If fewer than one-third of DLT-evaluable subjects in a cohort experience DLTs (e.g., DLTs in fewer than 1 of 3 or 2 of 6 subjects), dose escalation may proceed.
- If one-third or more of DLT-evaluable subjects (e.g., 2 or more of up to 6 DLT-evaluable subjects) in a cohort experience DLTs, the MTD will have been exceeded and dose escalation will cease. Up to 6 DLT-evaluable subjects will be evaluated for DLT at the preceding dose level.
- The highest dose level at which fewer than 2 of 6 DLT-evaluable subjects experience DLTs will be declared the MTD.
- All dose reductions will be permanent.

3.2.1 Treatment Regimen

Each treatment cycle will be 14 days long. Oxaliplatin infusion will be given on day 1 of each cycle. TAS-102 will be taken twice daily on days 1-5 of each cycle. All subjects will be started at dose level 1. Doses will be escalated or de-escalated as outlined in Table 1.

Table 1.

DOSE LEVEL	TAS-102 (mg/m^2) BID, Days 1-5	OXALIPLATIN (mg/m^2) IV, Day 1
1	25	85
2	30	85
3	35	85
-1	25	65
-2	20	65

3.2.2 Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

Dose-limiting toxicity (DLT) is defined as an adverse event (AE) during Cycle 1 that is possibly related to the study drug(s), is clinically significant and/or unacceptable and is judged to be a DLT by the investigator and fulfills any one of the following criterion using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events

(CTCAE) v 4.0. Each subject can be dose reduced a total of 2 times. All dose reductions are permanent.

Definition of DLTs:

- Grade 4 neutropenia with ANC < 500/mm3 lasting longer than 3 days.
- Grade ≥ 3 febrile neutropenia with ANC < 1000/mm3 and temperature > 100.8° F.
- Platelets <25,000/mm3.
- Grade 4 treatment related non-hematologic toxicities excluding alopecia and neuropathy.
- Delay of treatment for > 2 weeks due to toxicity.

3.3 Part 2 study design

The subjects in part 2 will be treated with the drug doses determined in Part 1 of the trial. The dose below the MTD that allows treatment every 14 days most consistently, without further dose delays, will be the Recommended Phase 2 dose. Treatments will continue until disease progression according to RECIST 1.1 criteria or development of unacceptable toxicities.

3.4 Rationale for study design and doses

The study will consist of two parts. First part is a dose finding part since there is no prior experience with the concomitant use of TAS-102 and oxaliplatin. Initial doses of the medications are selected based on past clinical experience. Oxaliplatin is typically given as part of FOLFOX regimen at a dose of 85 mg/m^2. Since this is an approved dose for this combination, dose level 1 will start at this level for oxaliplatin. Oxaliplatin dose may be deescalated as outlined in Table 1 depending on the development of DLTs. In the RECOURSE trial, TAS-102 was used at the dose of 35 mg/m^2 BID on days 1-5 and 8-12 every 4 weeks. Because of concern for overlapping bone marrow toxicities between the two medications, TAS-102 will be started at 25 mg/m^2 and escalated to goal dose level of 35 mg/m^2 if no excess DLTs are observed during the dose escalation “3+3” phase of the study. Each cycle will be 14 days long. Oxaliplatin will be administered on day 1 of each cycle and TAS-102 will be taken on days 1-5 of each cycle, resulting in the same number of days on treatment per 4-week period as was done in the RECOURSE trial. In the Part 2 of the study expansion cohort of subjects with refractory mCRC will be treated with the doses established in part 1.

3.5 Study population

This study will specifically focus on patients with mCRC who have progressed on standard therapy including at least 5-FU, irinotecan and oxaliplatin, bevacizumab (unless contraindicated) and an anti-EGFR antibody, if RAS wild type.

4. PATIENT SELECTION CRITERIA

4.1 Inclusion criteria.

1. Histologically confirmed stage IV colon cancer (AJCC 7th edition) that has progressed after standard therapy that included 5-FU, irinotecan and oxaliplatin. Patients who could not tolerate standard agents because of unacceptable, but reversible, toxicity necessitating their discontinuation will be allowed to participate.
2. Patients who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy will be allowed to count the adjuvant therapy as one chemotherapy regimen.
3. Progression of disease must be documented on the most recent scan.
4. Presence of measurable disease (not required for Phase 1 portion of the trial).
5. RAS mutation and MMR status must be determined (or tissue availability for testing if not already determined)
6. Age 18 years or older.
7. ECOG performance status 0-1.
8. Life expectancy of at least 3 months.
9. Patient with adequate organ function:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Hemoglobin ≥ 9 g/dL
    c. Platelets (PLT) $\geq 75 \times 10^9$/L
    d. AST/ALT $\leq 5 \times$ ULN
    e. Total serum bilirubin of $\leq$1.5 mg/dL (except for Grade 1 hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome).
    f. Albumin ≥ 2.5 g/dL
    g. Serum creatinine $\leq 1.5 \times$ institutional ULN (Cockcroft and Gault formula)
10. Adequate contraception if applicable.
11. Women who are nursing must discontinue nursing prior to enrollment in the program.
12. Ability to take oral medication (i.e. no feeding tube).
13. Patient able and willing to comply with study procedures as per protocol.
14. Patient able to understand and willing to sign and date the written voluntary informed consent form (ICF) at screening visit prior to any protocol-specific procedures.

4.2 Exclusion criteria.

1. Patients who have previously received TAS-102.
2. Grade 2 or higher peripheral neuropathy.

3. Symptomatic CNS metastases requiring treatment.
4. Other active malignancy within the last 3 years (except for non-melanoma skin cancer or a non-invasive/in situ cancer).
5. Pregnancy or breast feeding.
6. Current therapy with other investigational agents.
7. Active infection with body temperature ≥38°C due to infection.
8. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to drug administration).
9. Any anticancer therapy within prior 3 weeks of first dose of study drug.
10. History of allergic reactions attributed to compounds of similar chemical or biologic composition to TAS-102.
11. Current therapy with other investigational agents or participation in another clinical study or any investigational agent received within prior 4 weeks.
12. Grade 3 or higher hypersensitivity reaction to oxaliplatin, or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with pre-medication.
13. Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
14. Extended field radiation within prior 4 weeks of first dose of study drug or limited field radiation within prior 2 weeks of first dose of study drug.
15. Psychological, familial, or sociological condition potentially hampering compliance with the study protocol and follow-up schedule.
16. Involvement in the planning and/or conduct of the study.
17. Previous enrollment in the present study.

5. STUDY CONDUCT

5.1 Treatments

5.1.1 TAS-102

5.1.1.1 Dosing of TAS-102

On Day 1-5 of each cycle TAS-102 (35 mg/m2/dose or MTD) will be taken orally 2 times daily (between 8 and 12 hours) with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5 of each cycle. TAS-102 should only be given on Days 1 through 5 of each cycle even if doses are missed or held for any reason, extension of TAS-102 treatment into Days 6 -14 is not permitted.

The study medication tablet calculation is presented in Table 2, which shows the number of tablets that are needed according to a dose prescribed per calculated BSA. If at the beginning of a treatment cycle, a subject's body weight has decreased by ≥10% from baseline, the subject's body surface area (BSA) must be recalculated and the study medication dosage adjusted.

Table 2.

NUMBER OF TAS-102 TABLETS PER DOSE*

TAS-102 Dose (2x daily)	BSA[a] (m^2) [a]	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
35 mg/m²	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4
30 mg/m²	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
25 mg/m²	< 1.10	25[b]	50[b]	2 (PM)[b]	1 (AM)[b]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
20 mg/m²	< 1.14	20	40	0	1
	1.14 – 1.34	25[b]	50[c]	2 (PM)[b]	1 (AM)[b]
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

[a] Calculate BSA to 2 decimal places.
[b] At a total daily dose of 50 mg, subjects should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.
* Tablets per dose may be provided in different combinations based on availability to attain the same dosage in mg and total daily dose

5.1.1.2 Formulation of TAS-102

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths (expressed as FTD content):

- The 15-mg white, round tablet contains 15 mg FTD and 7.065 mg TPI as active ingredients.
- The 20-mg pale-red, round tablet contains 20 mg FTD and 9.42 mg TPI as active ingredients.

Both tablet strengths contain lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, titanium dioxide, polyethylene glycol, and magnesium stearate. The 20-mg tablet also contains red ferric oxide.

5.1.1.3 Packaging and Storage

TAS-102 15 and 20 mg tablets are commercially available and will be provided by the subject's pharmacy.

5.1.1.4 Food Intake

Subjects should take TAS-102 with a glass of water within 1 hour after completion of their morning and evening meals.

5.1.2 Oxaliplatin

Oxaliplatin will be given as a chemo infusion in 250 ml of 5% dextrose solution over 2 hours on day 1 of each cycle. The starting dose of oxaliplatin will be determined in part 1 of the protocol and will be adjusted as needed based on toxicities observed in expansion cohort. Oxaliplatin dosing will be based on the subject's baseline weight measurement. Weight will be measured on Day 1 of each 2-week treatment cycle. If there is a more than 10% change from the subject's baseline weight measurement, the chemotherapy dose should be recalculated using the new weight.

Supportive medications (e.g., anti-emetics, hydration, antihistamines, corticosteroids) will be administered according to institutional standards and the product package insert.

5.2 Concomitant and post-study treatment(s)

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject from ≤ 7 days prior to the first dose of study drug to the end of treatment visit. All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded during the screening and treatment period, starting from the date of signature of informed consent, and ending at the End of Treatment (EOT) visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

5.3 Restrictions during the study

5.3.1 Administration of other anti-cancer agents

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment, with the exception of bevacizumab with the permission of the PI, if the treating physician feels this is important for the subject's welfare. All standard dosing, management and precautions should be observed. Subjects may continue the use of bisphosphonates for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment. Full details of all of these treatments are recorded in the subject's notes and appropriate section of the eCRF.

5.3.2 Other concomitant treatment

- The subject can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment.
- Live virus and bacterial vaccines should not be administered whilst the subject is receiving study medication and during the 28-day follow up period.
- Caution is required when using drugs that are human thymidine kinase substrates, e.g., stavudine, zidovudine, telbivudine. Such drugs, if used concomitantly with TAS-102, may theoretically compete with the effector of TAS-102, i.e., FTD, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate such as lamivudine, zalcitabine, didanosine, abacavir, etc.
- Administration of hematologic support (e.g., blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin) is allowed as medically indicated according to the institutional site standards.

5.3.3 Pregnancy and Contraception

All subjects must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form. Subjects of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 4 weeks after last dose of study drug(s).

<u>Women of childbearing potential</u>

Females of childbearing potential should use reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g., Depo-provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised

partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males

Male subjects must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. However, where a sexual partner of a male participant is a woman of childbearing potential who is not using effective contraception, men must use a condom during sexual intercourse during the study and for 6 months after discontinuing study treatment. Male subjects should avoid procreation during the trial and for 6 months after discontinuing study treatment.

5.4 Subject enrollment and initiation of investigational product.

Patients who are eligible for the study will be enrolled in the clinical trial after they provide informed consent for study participation. There will be no randomization in this trial. There will be identical enrollment criteria for Part 1 and Part 2 of the study. This is an open label trial. Subjects will continue to receive study treatment until disease progression or development of intolerable toxicities.

5.5 Visits and Assessments

5.5.1 Visit Schedule and Assessments

Week 0 – Screening Visit (within 14 days of treatment initiation)

The following assessments and investigations will be conducted during the visit on Week 0:

- Review eligibility criteria
- Demographic data
- Review cancer history
- Review past medical history and surgical history
- Vital Signs (weight, height, blood pressure, heart rate, temperature, oxygen saturation)
- ECOG performance status determination (Appendix 1)
- Complete physical examination
- Medication reconciliation
- Blood work (complete blood count (CBC), liver function tests (LFT), complete metabolic panel (CMP), magnesium). INR and PTT. See Evaluation Schedule for additional information.
- Pregnancy test for female subjects of childbearing potential
- Obtain informed consent for trial enrollment

Weeks 1, 3, 5, 7, 9, etc. – Cycles 1, 2, 3, 4, 5, etc.

- Vital Signs (weight, blood pressure, heart rate, temperature, oxygen saturation)

- Medication reconciliation
- ECOG performance status determination
- Complete physical examination
- Review occurrence or change of existing conditions
- Review adverse events that have occurred since the previous visit (starting with week 2)
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work (CBC, CMP, LFT. Magnesium)
- CEA will be checked every 4 weeks (with every other cycle), including on day 1 of cycle 1.
- TAS-102 pills provided by local pharmacy per standard of care (SOC)
- Oxaliplatin administration

Week 2: Toxicity assessment during cycle 1

- Vital Signs (weight, blood pressure, heart rate, temperature, oxygen saturation)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination
- Review occurrence or change of existing conditions
- Review adverse events that have occurred since the previous visit
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work (CBC, CMP, LFT, Magnesium)

End of Treatment: Within 28 days of last dose of TAS-102 or prior to their next anti-cancer therapy, whichever happens first

- Vital Signs (weight, blood pressure, heart rate, temperature, oxygen saturation)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination
- Review occurrence or change of existing conditions
- Review adverse events that have occurred since the previous visit

5.5.2 Radiological Evaluations

Subjects will be required to have a restaging scan (CT chest/abdomen/pelvis or PET/CT) within 28 days of treatment initiation. Restaging scans will be obtained every 8 weeks during the study duration. Restaging scans may be spaced out to every 12 weeks after the first 2 scans on treatment at the discretion of the treating physician. Additional scans may be obtained in the event of clinical deterioration or development of new symptoms.

5.6 Treatment compliance

The study medication will be given in accordance with the protocol and the instructions of a site investigator. The appropriate number of TAS-102 tablets for 5 days of treatment will be provided to subjects to be self-administered at home. Subjects will be asked to bring the remaining trial medication to each visit for a compliance check. The remaining tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the subjects should have taken must be documented and explained. A pill diary will be provided and must be completed by the subject for each cycle.

The investigator can withdraw a subject from the study in the event of serious and persistent non-compliance which jeopardizes the subject's safety or render study results for this subject unacceptable. Subjects who do not attend a minimum of 75% of scheduled study visits, unless due to exceptional circumstances, should be evaluated for compliance.

5.6.1 Accountability

The study drugs are both commercially available.

The study personnel will account for all study medications dispensed and returned. Any drug accountability information will be recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms.

5.7 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Subjects who are incorrectly enrolled in the study will be withdrawn from study participation. If study treatments have been initiated, subjects will discontinue study drug and be monitored for development of any toxicity for 28 days following their last dose of study drug.

6. TOXICITY MANAGEMENT

6.1 General Toxicity Management Guidelines

Any toxicity observed during the course of the study should be managed by interruption and/ or dose reduction of the drug if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 28 days on each occasion. If treatment is held > 28 days due to any reason, subject must be removed from protocol treatment.

A new cycle of treatment may begin when the ANC is ≥ 1,500/mcl, the platelet count is ≥ 75,000/mcl, and any treatment-related non-hematological toxicity has resolved to ≤ Grade 2. If toxicity reoccurs following re-challenge with TAS-102 and oxaliplatin, and if further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue treatment. Treatment must be

interrupted after any NCI-CTCAE grade 4 adverse events that are considered to be related to treatment administration except myelosuppression which will be managed with dose modification.

6.1.1 Dosing Modification in Response to Hematologic Toxicities.

For all subjects with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria are met: ANC $\geq$ 1,500/mm^3, the platelet count is $\geq$ 75,000/mm^3.

For subjects who experience neutropenia or thrombocytopenia, TAS-102 should be dose reduced as described in Tables 3 and 3a respectively. If TAS-102 is already at 20 mg/m^2, then oxaliplatin should be reduced by 1 dose level (to 65 mg/m^2), however the doses should not be reduced beyond this. All dose reductions are permanent.

Subjects who experience Grade $\geq$ 3 neutropenia complicated by fever or Grade $\geq$ 3 thrombocytopenia complicated by bleeding should be considered for administration of hematopoietic growth factors as per standard practices, and should undergo a dose reduction as described in Tables 3 and 3a respectively in the next cycle.

For subjects who experience grade 2 neutropenia uncomplicated by fever and are delayed greater than 14 days should be given a growth factor and dose reduced as described in Table 3 when ANC has recovered to 1,500/mm^3. Growth factors should be considered only if a subject's ANC count has not recovered within 14 days of treatment being held.

If hematological abnormalities do not recover to the appropriate level before the start of the next cycle, treatment re-initiation can be delayed until ANC recovery for a maximum of 28 days. If treatment is held > 28 days beyond the intended start of the next cycle (6 weeks from prior dose) due to any reason, the subject must be removed from protocol treatment.

TABLE 3: DOSING GUIDELINES FOR NEUTROPENIA

Neutropenia	Recovery	Re-initiation dose
ANC < 1500/mm^3 to $\geq$ 500/mm^3 **without fevers**	Hold until recovered to $\geq$ 1,500/mm^3	If delay $\leq$ 7 days, no dose modification required. If delay is > 7 days and $\leq$ 14 days, re-initiate at -1 dose level of TAS-102. If delay is > 14 days, re-initiate at -2 dose levels of TAS-102.

Neutropenia	Recovery	Re-initiation dose
ANC < 1000/mm^3 **with single temperature of 101.0 °F or sustained temperature of 100.4 °F for > 1 hour**	Hold until recovered to ≥ 1,500/mm^3 and fever has resolved.	If delay is ≤ 14 days, re-initiate at -1 dose level of TAS-102. If delay is > 14 days, re-initiate at -2 dose levels of TAS-102.
ANC < 500/mm^3	Hold until recovered to ≥ 1,500/mm^3	If delay is ≤ 7 days, re-initiate at -1 dose level of TAS-102. If delay is > 7 days, re-initiate at -2 dose levels of TAS-102.

TABLE 3a: DOSING GUIDELINES FOR THROMBOCYTOPENIA

Thrombocytopenia	Recovery	Re-initiation dose
Platelets <75,000/mm^3 to ≥ 25,000/mm^3 **without bleeding**	Hold until recovered to ≥ 75,000/mm^3	If delay ≤ 7 days, no dose modification required. If delay is > 7 days and ≤ 14 days, re-initiate at -1 dose level of TAS-102. If delay is > 14 days, re-initiate at -2 dose levels of TAS-102.
Platelets < 50,000/mm^3 to ≥ 25,000/mm^3 **with bleeding**	Hold until recovered to ≥ 75,000/mm^3	If delay is ≤ 14 days, re-initiate at -1 dose level of TAS-102. If delay is > 14 days, re-initiate at -2 dose levels of TAS-102.
Platelets < 25,000/mm^3	Hold until recovered to ≥ 75,000/mm^3	Re-initiate at -2 dose levels of TAS-102.

6.1.2 Dosing Modification for Oxaliplatin Induced Neurotoxicity.

For subjects who have persistent grade 2 neurosensory events that do not resolve, oxaliplatin should be reduced to 65 mg/m^2 or next dose level. Oxaliplatin should be discontinued if there are persistent Grade 3 neurosensory events.

6.1.3 Management of Oxaliplatin Hypersensitivity Reactions.

In each case of hypersensitivity reaction, the treating investigator should institute treatment measures according to the best available medical practice. Based on previous experience with oxaliplatin hypersensitivity reactions, the following treatment guidelines may be applicable.

Toxicity Grade	Oxaliplatin Modification
1	Decrease oxaliplatin infusion rate by 50% and monitor closely for any worsening symptoms.
2	Stop oxaliplatin infusion. Administer bronchodilators, oxygen, anti-histamines and H1 blocker, etc. as medically indicated. Resume infusion at 50% of previous rate after allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity. Monitor closely for any worsening symptoms. Institute premedication regimen prior to the next cycle.[a]
3 or 4	Stop oxaliplatin infusion immediately and disconnect infusion tubing from subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically necessary. Discontinue all further oxaliplatin treatment.[b]

[a] Prior to the next oxaliplatin infusion, subjects will be started on long-acting H1 antihistamines and oral dexamethasone (8 mg), which will be taken on the day before oxaliplatin infusion and on the morning of treatment. On the morning of infusion, subjects will also receive 20 mg of oral dexamethasone at the infusion center as part of their premedication regimen. Oxaliplatin infusion rate will be reduced by 50% from baseline. If recurrent grade ≥2 reaction occurs, subjects will be withdrawn from the study.

[b] Subjects with CTCAE Grade ≥3 allergic reaction/hypersensitivity, which can be clearly attributed to oxaliplatin, will be permanently discontinued from the study.

6.1.4 Dosing Modifications in Response to Other Non-Hematologic Toxicities

Grade/Occurrence	Dose Hold/Resumption	Dose Adjustment for Next Cycle
1-2 Any occurrence	Continue without treatment delays. Supportive measures as needed.	None
≥ 3 1st occurrence	Suspend treatment until Grade 0 or 1.	Decrease oxaliplatin by 1 dose level
≥ 3 2nd occurrence	Suspend treatment until Grade 0 or 1.	Decrease TAS-102 by 1 dose level. If TAS-102 already at 20 mg/m2, decrease oxaliplatin by 1 dose level.
≥ 3 3rd occurrence	Discontinue treatment.	Discontinue treatment.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT

7.1 Indications for Treatment Discontinuation

In the absence of significant treatment delays due to adverse events determined to be possibly, probably, or definitely attributed to a study agent (as defined in Section 9.1), treatment may continue indefinitely or until one of the following criteria applies:

- Objective disease progression according to RECIST criteria. Under some circumstances subjects may continue to receive study treatment after radiographic progression per RECIST 1.1 as long as they continue to experience clinical benefit in the opinion of the treating physician.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Severe non-compliance to study protocol as judged by the investigator.
- Subject becomes pregnant.
- Subject is determined to be incorrectly enrolled (i.e., the subject does not meet the required inclusion/exclusion criteria for the study).
- Subject decides to withdraw from the study (the subject is at any time free to discontinue treatment, without prejudice to further treatment).
- General or specific changes in the subject's condition.
- Treatment delay for any reason > 28 days from planned date of treatment.

7.2 Procedures for discontinuation of a subject from investigational product

All reasons for discontinuation of treatment must be documented in the EMR. Any subject discontinuing investigational therapy should be seen at 30 days post treatment discontinuation visit for the evaluations, as outlined in the study schedule, or contacted at least 30 days after discontinuing study medication to collect and /or complete AE information. The subject's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of the study medications, all ongoing or new AEs or SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease, or the subject is lost to follow up.

7.3 Withdrawal from study

Subjects who withdraw from the study before treatment initiation will be replaced by other eligible patients. No subject replacement will take place if withdrawal occurs after treatment has been started.

8. STUDY EFFICACY ASSESSMENTS

Subjects who have received at least 1 cycle of chemotherapy will be included in efficacy assessments. All efficacy assessments will be performed using RECIST criteria. Imaging will be repeated every 8 weeks to evaluate disease response. Restaging scans may be spaced out to every 12 weeks after the first 2 scans on treatment at the discretion of the treating physician. Imaging studies will be repeated prior to eight weeks if a subject develops new symptoms that warrant evaluation or if there is clinical concern for disease progression per discretion of the treating physician.

8.1 Definition of measurable disease and target lesions

8.1.1 Measurable disease

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with callipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimetres (or millimetres). The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. A malignant lymph node is to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in SHORT AXIS (greatest diameter

perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

8.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable, as are previously radiated lesions that have not progressed.

8.1.3 Notes on measurability

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

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

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

8.1.4 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

8.1.5 Non-target lesions

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

8.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

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

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

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

8.3 Response Criteria

8.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all targets extra nodal lesions and the regression of all nodal lesions to < 10 mm SAD.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

8.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	*Unequivocal progression* of existing non-target lesions and/or appearance of one or more new lesions *

**Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.*

8.3.3 Evaluation of overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

8.3.4 Progression free survival

Progression Free Survival (PFS) is defined as the time from the date of start of treatment to the date of first documented progression or any cause of death during the study. Progression will be assessed by a CT scan according to RECIST criteria version 1.1. This criterion will be estimated by the Kaplan-Meier method. Subjects who have not progressed or died at the time of analysis will be censored at the time of their latest follow-up with clinically stable disease. This includes subjects who withdraw consent.

8.3.5 Response rate

Response rate is defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST criteria, version 1.1. A maximum of 5 measurable lesions in total (and up to 2 per organ) representative of all involved organs should be identified as target lesions at baseline and measured through the course of study treatment. Target lesions should be selected based on their size and their suitability for accurate repeated measurements. At baseline, the sum of the diameters (longest diameters (LD) for extra nodal target lesions and short axis diameters (SAD) for nodal lesions) will be calculated and reported as the baseline sum LD. This baseline sum LD will be used as the reference by which to characterize the objective tumor response. All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

9. STUDY SAFETY ASSESSMENTS

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

9.1 Definitions

9.1.1 Adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

9.1.2 Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
- The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Taiho Pharmacovigilance Operations or designee.

9.2 Recording of adverse events

Non-serious adverse events and SAEs will be determined from the time the study drug is given, throughout the treatment period and up to and including the 28-day follow-up period. All grade 2 or higher AEs will be recorded. Grade 1 AEs do not need to be recorded. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 28 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to the Yale Data Safety Monitoring Committee (DSMC) and Yale University Human Investigation Committee (HIC) as per SOPs.). AEs will be recorded per Yale Cancer Center (YCC) SOPs.

All study-related toxicities/ SAEs must be followed until resolution, unless in the Treating Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

9.2.1 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.2.2 Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (e.g. anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

9.2.3 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis during the study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

9.2.4 New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 9.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

9.2.5 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the PI or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

9.2.6 Deaths

All deaths that occur during the study, or within the protocol-defined 28-day post-study follow-up period after the administration of the last dose of study treatment, must be reported

as a serious adverse event as outlined in Section 9.3 within 24 hours from the time site personnel become aware of the death.

When reporting a death in the CRF, it will be required to identify which of the following best describes the category of death:

- Toxicity for study medication.
- Radiological disease progression.
- Clinical disease progression.
- Other causes.

Death should be reported according to YCC SOPs.

9.3 Reporting of serious adverse events

Investigators and other site personnel must inform the Yale DSMC and Yale University HIC per the YCC SOPs on the required forms.

All SAEs meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 710 FR 4: Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events (AEs) Reporting Form as per Human Research Protection Program (HRPP) Policy 710.

The HIC does not require reporting of any other Adverse Event type. A copy of the HRPP Policy 710 Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events is available at:
https://your.yale.edu/sites/default/files/irb_policy_710_reportingupirsosincludingadverseevents.pdf

All SAEs within the safety follow-up window (e.g., within 28 days after the last dose of study medications or until the start of new antitumor therapy, whichever is earlier) established in the protocol will be reported.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the 28-day follow-up period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 28 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA as per their reporting criteria). All study-related toxicities/ SAEs must be followed until resolution, unless in the Treating Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

9.4 Clinical safety assessment

9.4.1 Laboratory safety assessment

Full hematology assessments for safety should be performed during every visit and when clinically indicated. This should include hemoglobin, platelets, mean cell volume (MCV), white blood cells (WBC), absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils). If absolute differentials are not available, % differentials will be provided.

Coagulation profile (activated partial thromboplastin time (aPTT) and international normalized ratio (INR) will be performed at baseline and if clinically indicated.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase (Alk Phos), aspartate transaminase (AST), alanine transaminase (ALT), urea or blood urea nitrogen (BUN), total protein, and albumin should be performed at every visit or more frequently as clinically indicated.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

9.4.2 Physical examination

Complete physical exam will be performed before trial enrollment and during each treatment visit.

9.4.3 Vital signs

Vital signs will be obtained at every clinic visit. Vital signs will include temperature, heart rate, respiration rate, oxygenation, and weight. Height will be measured at the time of study enrollment. Significant abnormalities will be recorded as an AE. Blood pressure and pulse rate will be measured using automated BP measuring devise. Body temperature will be measured in degrees Fahrenheit using an automated thermometer.

9.4.4 ECG

Baseline resting 12-lead ECG will be performed at the time of study enrollment. Repeat ECG will be performed when clinically indicated during the course of the treatment.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the treating investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

9.4.5 Serum or urine pregnancy test

Pregnancy test on blood or urine samples will be performed for pre-menopausal women of childbearing potential within 14 days prior to the start of study treatment. Tests will be performed by the hospital's local laboratory. If results are positive the subject is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

10.2 Subject data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to a regulatory authority, or Institutional Review Board (IRB), to grant access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

10.3 Ethics and regulatory review

10.4 Informed consent

Provision of written Informed Consent will be obtained prior to any study-related procedures. The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects will also be notified that they are free to discontinue from the study at any time. The subject will be given the opportunity to ask questions and allowed time to consider the information provided. The original, signed written Informed Consent Form will be stored for the duration of the study. A copy of the signed written Informed Consent Form will be given to the subject.

10.5 Changes to the protocol and informed consent form

In the event that there are any changes to the protocol, these changes will have to be first reviewed and approved by the Yale University IRB (Human Investigation Committee) via an amendment before any change is implemented. Once approved, subjects will be notified of the protocol changes and will be provided with the updated ICF for their signature, if necessary. Subjects will also be provided with a copy of the updated ICF for their records whenever re-consent is required.

10.6 Audits and inspections

The PI will monitor the clinical trial for safety. The PI will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events will be followed, which are in compliance with 21 CFR 312.32 and 312.22. The clinical trial data consisting of all required observations, AEs, and laboratory data will be entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Center for Clinical Investigation's Yale Data and Safety Monitoring Committee (DSMC) Committee.

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular Weekly Disease Aligned Research Team meetings will be held to discuss ongoing subject treatment and adverse events.

The Principal Investigator will distribute manufacturer provided safety reports and updated Toxicity Lists to Yale University HIC and all relevant personnel involved in the conduct of the study as per their policy (Yale University HRPP Policy 710). The Toxicity List, in addition to the Package Insert, will be used as a reference for reporting any new SAE. Possible

actions taken by the PIs or the Yale DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:

1. Revise consent form
2. Amend the protocol
3. Suspend the protocol

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

The following subject populations will be used in the study:

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the study.
- All treated subjects: All subjects who received at least on dose of study medication.

  Analysis of safety and efficacy will be based on subjects who have received at least 1 cycle of treatment.

11.2 Methods of statistical analyses

11.2.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by dose levels using descriptive statistics.

11.2.2 Efficacy Analyses

Listing of tumor measurements will be provided by subject and study day at each dose level. Response rate will be calculated by dose level. Descriptive statistics will be used to analyze efficacy data using historical data as reference. In a published retrospective analysis, re-challenge with 5-FU and oxaliplatin containing regimen resulted in an 18% response rate[10]. An observed response rate of at least 35% will warrant further trials with the proposed drug combination.

11.2.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class and dose level. Vital signs and clinical laboratory test results will be listed and summarized by dose level. Any significance physical examination findings and results of clinical laboratory test will be listed.

11.3 Determination of sample size

We anticipate that 3-18 subjects will be enrolled in the run-in portion of the study. At most fifty subjects will be enrolled in the phase 2 portion of the study according to the Bayesian analysis plan shown in the table below.

H_0: $p < 0.18$ versus H_a: $p > 0.35$						
n	Max number responders to stop for futility	Min number responders to stop for success	Pr (stop for futility when p=0.18)	Pr (stop for futility when p=0.35)	Pr (stop for success when p=0.18)	Pr (stop for success when p=0.35)
30	5	10	0.5395	0.0233	0.0323	0.6425
35	6	11	0.0951	0.0097	0.0139	0.1034
40	8	12	0.1331	0.0182	0.0125	0.0710
45	9	13	0.0388	0.0057	0.0109	0.0479
50	11	13	0.0937	0.0264	0.0299	0.0521
		Sum:	1- α 0.9003	β 0.0833	α 0.0997	1- β 0.9167

11.4 Data safety and monitoring plan

The principal investigator will be responsible for monitoring the data and assuring protocol compliance. This study is reviewed once per week in the Disease Aligned Research Team meeting. During these meetings, the principal investigator reviews data queries, SAE's, deviations and regulatory issues related to this study. Meeting minutes and attendance logs will only be provided upon request. The principal investigator will also be responsible for conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). The Yale DSMC will be the monitoring committee of record. Either the principal investigator, the IRB or Yale Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

11.5 Important medical procedures to be followed by the investigator

11.5.1 Pregnancy

All outcomes of pregnancy should be reported to the DSMC and IRB per SOPs.

11.5.2 Maternal exposure

If a subject becomes pregnant during the course of the study, TAS-102 and oxaliplatin should be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

12. LIST OF REFERENCES

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13. APPENDIX

Appendix 1. ECOG Performance Status.

ECOG Performance Status	Activity
0	Fully active, able to carry on all pre-disease performance without restrictions.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. 100% confined to bed or chair.