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CLINICAL STUDY PROTOCOL

SHORT: SHOrt course Radiation and TASOX (TAS102 plus Oxaliplatin) chemotherapy in operable rectal cancer, a phase II trial.

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1.0 BACKGROUND

1.1 Current therapy for stage II/III rectal cancer

Tri-modality therapy with chemotherapy, radiation and surgery leads to improved outcomes for stage II/III rectal cancer and neoadjuvant chemotherapy is the current treatment paradigm to reduce toxicity and improve treatment delivery (1). Pre-operative chemotherapy has been shown to be less toxic than similar therapy given post-operatively and result in significantly higher degrees of treatment completion (2,3) and improved overall survival (4).

The optimal chemotherapy regimen for locally advanced tumors is not well-defined and differs for patients with intermediate risk, small tumor with clear circumferential radial margins (CRM), versus those with large, bulky tumors (NCCN and ESMO guidelines). Among patients with resectable tumors, short-course preoperative irradiation (25 Gy in five fractions of 5 Gy) is a standard option for stage II/III tumors and has been shown to be equivalent to chemoradiation (50.4 Gy in 28 fractions of 1.8 Gy, bolus 5-fluorouracil and leucovorin or continuous infusional fluorouracil 225 mg/m(2) per day) (5,6). The Stockholm III study demonstrated that a delay in surgery after short-course radiation is safe and reduces operative morbidity compared to immediate surgery. (7)

While current prospective trials are actively exploring novel treatments for different risk populations of rectal cancer, there are no trials of short-course radiation followed by novel systemic agents. Myerson et al (8) previously reported a 70% rate of downstaging to stage ypT0-2 among 76 patients with stage II-IV rectal cancer treated with short-course pelvic radiation followed by 4 cycles of FOLFOX prior to definitive surgery. In the NRG TNT study (NCT02921256) patients with large (T4, N2) or low tumors and are treated with 8 cycles of intravenous (IV) FOLFOX followed by long-course chemoradiation and are randomized to investigational systemic agents given in combination with long-course chemoradiation.

1.2 Potential Role for Neoadjuvant combination TAS102 plus Oxaliplatin (TASOX).

Single agent TAS102. TAS-102 is a novel type of chemotherapeutic agent being an orally available two-drug combination of a 1M Trifluoridine (FTD, a thymidine-based nucleoside analogue), and 0.5 M Tipiracil Hydrochloride (TPI). Following uptake into cells through nucleoside transporters, FTD is converted to its monophosphate F3dTMP by thymidine kinase. After further phosphorylation steps, its triphosphate F3dTTP is incorporated into DNA as substitute for thymidine triphosphate. In addition to its potent effects as an anti-metabolite as an inhibitor of thymidine synthase, FTD has additional effects causing DNA breaks (9, 10). TPI functions to inhibit degradation of FTD and thereby increases its bioavailability and TPI also exerts antiangiogenic effects by inhibiting thymidine phosphorylase (TP) (10).

Two phase III studies have demonstrated the benefit of TAS102 in patients with metastatic colorectal cancer (mCRC) refractory or not candidates for standard therapy (11,12). Compared to placebo, TAS102 improved overall survival (OS) with a Hazard Ratio of 0.56 (CI 0.44-0.71) in

patients refractory to Fluorouracil, Oxaliplatin and Irinotecan. Therapy was well tolerated and the predominant grade 3/4 toxicities were neutropenia (50%) and anemia (17%) (11). Similar benefits were seen in a more advanced population of patients refractory to 5-Fluorouracil, Oxaliplatin, Irinotecan, Bevacizumab and epidermal growth factor rector inhibitor (EGFRi) therapy with an improvement in OS [Hazard Ratio 0.68 (0.58-0.81)] and similar, predominantly hematologic toxicities. The rate of febrile neutropenia was 4% (12).

In a head-to- head trial against capecitabine, TAS102 was evaluated in TASCO1 (ClinicalTrials.gov number: NCT02743221), a multicentre, randomized, open-label, phase 2 trial (13). Patients with mCRC were randomized to TAS102 plus bevacizumab (TAS102-B) or capecitabine plus bevacizumab (C-B) as first-line therapy. The primary endpoint was progression-free survival (PFS), based on investigator assessment of radiologic images, per RECIST 1.1 criteria. Median PFS was 9.2 months with TAS102-B and 7.8 months with C-B, giving a hazard ratio (HR) of 0.71 (95% confidence interval [CI] 0.48, 1.06) for TAS102-B versus C-B. Preliminary median OS was 18 months with TAS102-B and 16.2 months with C-B giving a HR of 0.56 (95% CI 0.32, 0.98) for TAS102-B versus C-B. In pre-planned sub-group analysis, an enhanced effect of TAS102-B over C-B was seen on PFS was seen in tumors arising in the left colon and rectum, HR 0.5 (95% CI 0.31-0.82).

TASOX, Combination TAS102 and Oxaliplatin: Three phase I studies have established the safety of combination TAS102 and Oxaliplatin in mCRC (14-16) with the recommended dose of TAS102 35 mg/m2 po BID days 1-5 and oxaliplatin IV 85 mg/m2 on day 1 of a q2weekly cycle. In a dose escalation phase I, Hollebecque et al. (14) performed a two-part trial of trifluridine/tipiracil (FTD/TPI) plus oxaliplatin in patients with previously treated mCRC. A total of 17 patients were treated by at least one line of standard chemotherapy and the maximum tolerated dose (MTD) was FTD/TPI 35 mg/m2 BID with oxaliplatin 85 mg/m2. One DLT was reported at the MTD at which the patient experienced grade 3 febrile neutropenia. This patient recovered and continued with a decreased FTD/TPI dose of 30 mg/m2 BID. Patients received a mean of 7.65 treatment cycles and stable disease was achieved in eight patients. One patient previously treated with mFOLFOX6 (folinic acid-fluorouracil-oxaliplatin) achieved a confirmed partial RECIST response.

Calvo et al. (15) reported results from the dose-expansion phase on which 12 patients were administered TAS102 in combination with oxaliplatin with either nivolumab or bevacizumab. TAS102 35 mg/m2 was given BID on Days 1–5, followed q2weekly, in combination with oxaliplatin 85 mg/m2 and either nivolumab 3 mg/kg or bevacizumab 5 mg/kg, all administered on Day 1. The disease control rate was 83.3% in the safety run-in period. Neutropenia was the most common grade 3-4 treatment-related AE reported. Three (25%) patients had AE related treatment interruptions, primarily due to neutropenia. Two patients reported oxaliplatin-related grade $\geq$ 2 neurotoxicity; one patient discontinued oxaliplatin therapy. Treatment-related deaths were not observed. Pharmacokinetic analysis revealed that FTD/TPI did not appear to be affected by co-administration of oxaliplatin.

In a third study (16), TASOX was dose-escalated in a 3+3 fashion starting at TAS102 25 mg/m^2 and escalating to 35 mg/m^2 day 1-5 using a fixed dose of oxaliplatin 85 mg/m^2 on day 1, q2weekly. Eligible patients previously received 5FU, oxaliplatin, irinotecan, appropriate biologics, had measurable disease, usual laboratory parameters, and ECOG PS 0-1. Among 12 patients evaluable for dose limiting toxicity (DLT), no DLTs were observed. Treatment related grade ≥ 3 AEs were neutropenia (n = 4) and thrombocytopenia (n = 1). No AEs resulted in treatment discontinuation. Two patients (dose levels 2 and 3) required dose reductions for prolonged neutropenia. Median number of cycles for all treated patients was 6 ± 4. The disease control rate (DCR) at 8 weeks was 67%. Best response in all evaluable patients was 1 PR (8%) 7 (59%) SD and 4 (33%) PD.

The neoadjuvant benefit of TASOX in rectal cancer is unknown. While the most commonly chosen pre-operative therapy for stage II/III rectal cancer in North America remains capecitabine or 5-fluorouracil in combination with 50.4 Gy radiation, there is a lack of novel systemic agents being evaluated in the curative, neoadjuvant setting. The documented efficacy of TASOX in both early and advanced line therapy for mCRC justifies its application in the neoadjuvant setting where the pathologic and clinical response rate offers an early estimate of treatment benefit.

1.3 Study Overview

The study investigators hypothesize that TASOX can be safely and efficaciously delivered after short course radiation, resulting in significant pathologic downstaging, allowing for an R0 pelvic resection, and providing local control in appropriately selected stage II/III rectal cancer patients treated with contemporary TME-based surgery. It is expected that 3 months (6 cycles) of TASOX at standard doses will allow total neoadjuvant therapy introducing a new systemic agent, a shorter duration of pre-operative radiation and timely delivery of pre-operative systemic therapy. It is anticipated that if this study meets its primary endpoint, the strategy will be prospectively compared to long-course chemoradiation with capecitabine and that the reduced duration of radiation and the introduction of a new systemic agent will improve outcomes for appropriately selected patients with stage II/III rectal cancer.

In this phase II study patients will be treated with short-course preoperative irradiation (25 Gy in five fractions of 5 Gy) followed by 6 (six) 2-week cycles of TASOX followed by total mesorectal excision (TME) for patients with resectable rectal cancer (clinical T3c/dN0, T3c/dN1, T2N1). Eligible study subjects include adults who are candidates for curative intent sphincter-sparing surgery and lack high risk features such as tumor encroaching upon the mesorectal-fascia or low tumors who need an Abdominal-Perineal Resection (APR). The primary measurement of efficacy will be the Neoadjuvant Rectal (NAR) score, a validated surrogate of local and systemic disease control in stage II/III rectal cancer (17).

Figure 1. NAR Score derivation.

$$NAR = \frac{[5\,pN - 3(cT - pT) + 12]^2}{9.61}$$

Fig. 1

Calculation of the neoadjuvant rectal (NAR) score. *cT* is an element of the set {1, 2, 3, 4}, *pT* is in {0, 1, 2, 3, 4}, and *pN* is in {0, 1, 2}. *cT* clinical tumor stage, *pT* pathologic tumor stage, *pN* pathologic nodal stage

The required elements of the NAR score will be prospectively collected as defined in the protocol.

2.0 OBJECTIVES

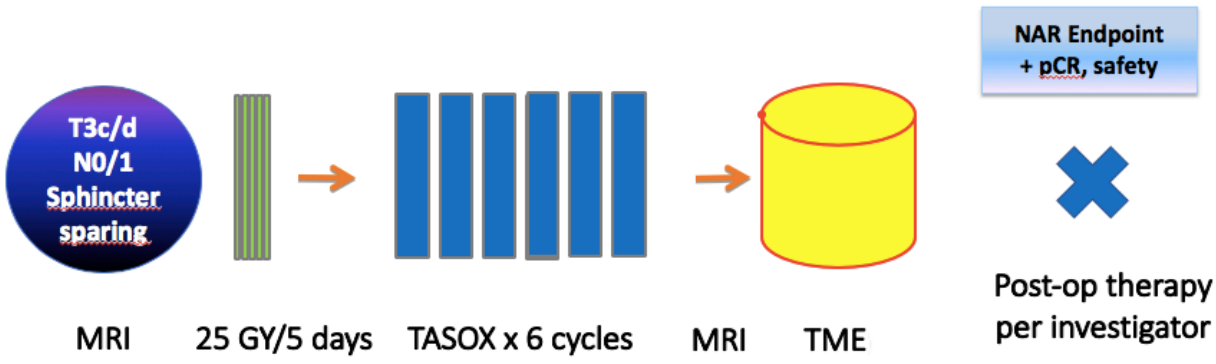
2.1 Primary Objective

The primary objective of this study is to determine whether pre-operative short-course radiation therapy (SRT) and 6 cycles of TASOX offers condensed radiation and total neoadjuvant therapy for intermediate risk rectal cancer. The primary endpoint is to achieve a reduction in Neoadjuvant Response (NAR) score compared to historic controls.

2.2 Secondary Objective

The secondary objective is to describe the adverse event profile and surgery complications among treated subjects.

2.3 Study Schema



3.0 REGISTRATION

3.1 Inclusion Criteria

3.1.1 Age of at least 18 years.
3.1.2 Newly diagnosis of rectal adenocarcinoma.
3.1.3 ECOG Performance Status (PS): 0, 1 or 2.
3.1.4 Candidate for sphincter-sparing surgical resection prior to initiation of neoadjuvant therapy according to the primary surgeon.
3.1.5 Clinical Stage: T1/N1, T2/N1, T3/N1, T3 a/b/c/dN0.
3.1.6 Absence of metastatic disease.

- Clinical staging is based on physical exam by the primary surgeon, CT scan of the chest/abdomen, and pelvic MRI.
- *Node positivity determination:* Entry criteria nodes will be measured in short-axis diameter and for the purposes of study entry will be considered positive if 8 mm or greater in short axis.
- **Radiographic N2** status is estimated as: 4 or more nodes that measure 8mm or more in short-axis.
- **Radiographic N1** status is estimated as: fewer than 4 lymph nodes that measure 8 mm or greater in short axis but 1 or more lymph nodes that measure 8 mm or greater.
- Nodal Metastatic Disease: nodal stations considered suspicious for metastatic disease (M1) for rectal cancer are common iliac, external iliac and inguinal nodes.

3.1.7 Ability to perform a curative intent sphincter-sparing TME resection at diagnosis.
3.1.8 The following laboratory values obtained ≤ 28 days prior to registration.

- Platelet count ≥ 100,000/mm3
- Hemoglobin > 8.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- SGOT (AST) ≤ 3 x ULN
- SGPT (ALT) ≤ 3 x ULN
- Creatinine ≤1.5 x ULN

3.1.9 Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
3.1.10 A patient of child-bearing potential is willing to employ adequate contraception. It includes any of the followings: abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom). See exclusion criterion 3.2.8
3.1.11 Provide informed written consent.
3.1.12 Willing to return to enrolling medical site for all study assessments.

3.2 Exclusion Criteria

3.2.1 Clinical T4 tumors.
3.2.2 Clinical N2 disease estimated as four or more lymph nodes that are ≥8 mm.
3.2.3 Primary surgeon indicates need for abdominoperineal (APR) at baseline.
3.2.4 Tumor is causing symptomatic bowel obstruction or patients who have had a temporary diverting ostomy are ineligible.

3.2.5 Chemotherapy within 5 years prior to registration. (Hormonal therapy is allowable if the disease free interval is ≥ 5 years.)
3.2.6 Any prior pelvic radiation.
3.2.7 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate
- contraception

3.2.8 Co-morbid illnesses or other concurrent disease which, in the judgment of the treating investigator obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
3.2.9 Patients with threatened radial margins, defined as tumors with distance of 1mm or less, or adherent to the mesorectal fascia.

4.0 SCHEDULE OF TESTS

Test & procedures	≤ 28 days pre-registration	≤60 days prior to therapy	Prior to each cycle TASOX, - 3 days[1]	Pre-op visit after completion of cycle 6 TASOX, ie. ≤ 56 days after day 14 , cycle 6[8,10,12]	Post-Surgery 2-8 weeks post - op
History and physical	X		x	x	x
Pulse, BP and temperature	X		x	x	x
ECOG			x	x	x
Weight	X		x	x	x
Height	X				
Adverse Events[10]			x	x	
Hematology[2]	X		x	x	
Chemistry[3]	X		x	x	
CEA	X		x	x	x
Pregnancy test[4]	X		x– cycle #1 only		
Pathology confirmation of rectal adenoca.		x ≤ 90 days			
Rectal exam and proctoscopy[5]		x			
MRI of pelvis[6,8]		x		x [11,8]	
CT Chest or chest Xray [7,8]		x			
CT of abdomen with contrast [7,8]		x			
Documentation of post-operative complications- see Section 6.4.					x

1. Recommendations for timing of therapy:
   - Radiation must commence within 3 weeks of study registration.
   - Chemotherapy with TAS-102 must begin within 1-3 weeks after completion of radiation.

- Patients must have assessment at the time of progressive disease, study withdrawal, or removal.

2. Hematology includes hemoglobin, platelets and absolute neutrophil count (ANC).
3. Chemistry includes SGOT (AST), SGPT (ALT), total bilirubin, creatinine.
4. Urine or serum pregnancy test per institutional standard required for females of childbearing potential ≤ 7 days of registration.
5. Rectal exam and proctoscopy are ideally to be performed by the primary surgeon. Proctoscopy should be performed ≤ 90 days prior to registration or after registration but before the start of treatment. Proctoscopy may be accomplished using rigid proctoscopy or as part of a flexible sigmoidoscopy or colonoscopy.
6. Pelvic MRI Scan, with or without contrast per treating investigator/institutional standards, is to be performed within 60 days prior to treatment start. Use same imaging modality throughout the study.
7. A PET/CT scan may be performed in lieu of a CT scan with contrast, but a CT scan is preferred.
8. Scans do not have to be performed at the trial site; they can be performed at other locations as long as images are available for review. Scan is to be performed within </= 60 days prior to registration. Contrast is preferred but not required for the CT of the chest. Contrast is required for the CT of the abdomen.
9. Recommendation: Surgery should be performed within 10 weeks AFTER the 6th cycle of neoadjuvant TASOX, and restaging investigations should be obtained within 8 weeks (56 days) AFTER day #14, cycle 6.
10. Adverse Events form to be completed at the start of radiation therapy.
11. Pelvic MRI should be booked within 56 days of completion of cycle #6 of TASOX, i.e. within 1-56 days AFTER day #14, cycle 6.
12. Patients that achieve a complete or near complete Clinical Response (cCR or ncCR) may choose to pursue a course of watch and wait with agreement of their treating surgeon. A thorough discussion is recommended with their surgeon concerning the risks and benefits of watch and wait and both they and their physician agree with the intended approach. Patients that pursue a course of watch and wait remain evaluable on study and will be classified as having a ypT0N0 response for the purposes of the NAR score if they do not proceed to TME surgery within 24 months of completing cycle 6, day 14.

5.0 REGISTRATION PROCEDURES

To be completed after eligibility determination and at least 24 hours prior to first day of radiation therapy. It will be done by completing the registration form and emailing the following information to tas-short-communications@providence.org.

All the following information will be required:

- Name of institution.
- Patient initials.

- Age.
- Sex.
- Race.
- Date of diagnosis.
- Informed consent signed date.
- Projected treatment start date. i.e., start date of radiation therapy.

6.0 PROTOCOL TREATMENT

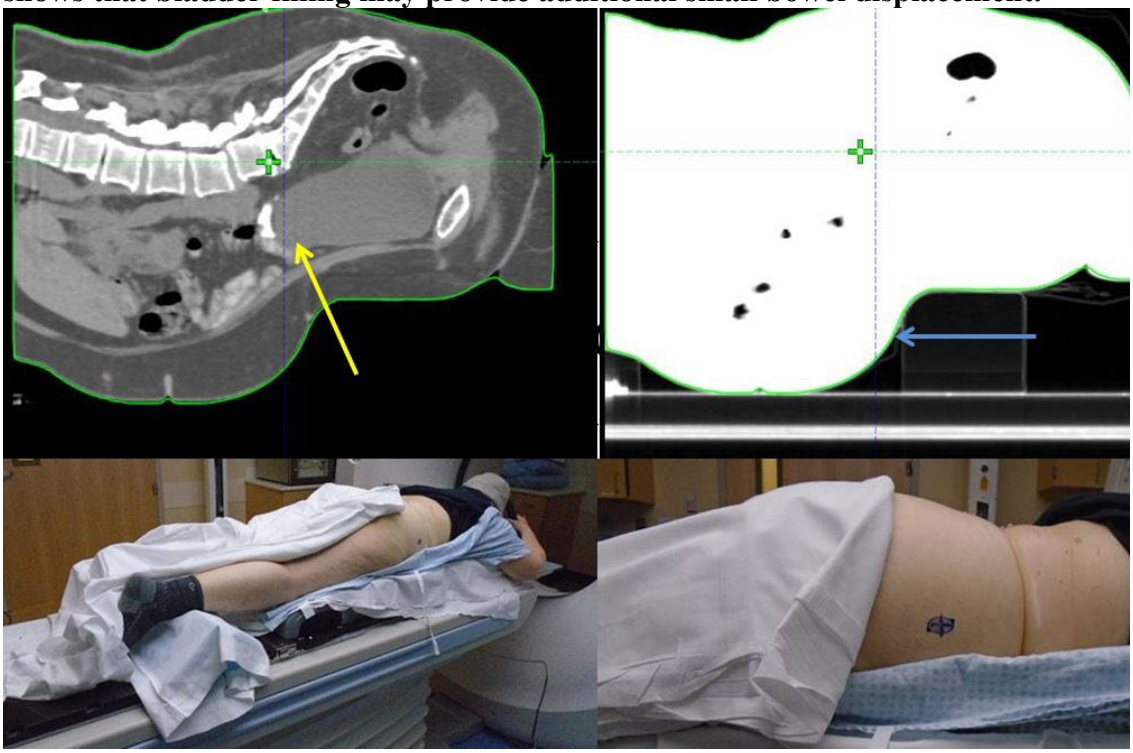
Therapy: Study schema is summarized in Section 2.3. Patients are initially treated with 25 Gy in five fractions of 5 Gy conformal pelvic radiation. Radiation is to be started within 3 weeks of registration. TASOX should be commenced within 3 weeks of radiation completion. Patients are treated with 6 x 14 day cycles of TASOX. Within 4 weeks of the end of cycle #6 of TASOX patients undergo re-staging. Surgery should be performed within 4 weeks AFTER day 14, cycle#6 of TASOX, i.e., 28 days after day 14, cycle 6.

6.1 Radiation Therapy

CT Simulation Techniques

Prone position with use of a bowel displacement device 'belly board' is recommended and may be particularly advantageous for patients with a larger body habitus to improve small bowel sparing (**Figure 2**). At the time of simulation, placement of a radiopaque anal marker may be useful to determine the distance of the disease from the verge for contouring purposes. For males, it is important to pull the external genitalia center and downward. Oral contrast is recommended to be given approximately 30 minutes prior to simulation for better small bowel visualization. If oral contrast is used, the contrast needs to be overwritten to a normal density or planning needs to occur on a pre-contrast scan. Intravenous contrast may be useful in visualizing and contouring the elective nodal vessels, particularly in patients who are thin; however, more commonly, fusion with the patient's CT with contrast staging study is used. For additional small bowel sparing, 16-20 oz of water should be administered PO 30 minutes before the CT for bladder filling,but remember to reproduce the same filling prior to each treatment. Additionally, it is important for the patient to maintain good regular bowel function in order to keep the rectum empty. Once the patient is appropriately positioned, CT images at 2-3 mm intervals from the upper lumbar spine to the mid-femur should be obtained.

Figure 2: Prone CT simulation using a belly board. Blue arrow delineates the gap in the prone belly board that allows for geometric displacement of small bowel. Yellow arrow shows that bladder filling may provide additional small bowel displacement.



Target Volumes

According to the International Commission on Radiological Units 50 guidelines, all target and normal tissue structures are contoured on the planning CT slices. Multiple consensus atlases now exist from the RTOG (18), Australasian Gastrointestinal Trial Group (19) and the EORTC (20) that illustrate target definitions with representative case examples. RTOG also has a pelvic normal tissue contouring atlas (21). When contouring the GTV, one should use all available clinical and radiographic information (digital rectal exam, endoscopy, pelvic MRI, and other imaging as available) including anal verge markers at the time of simulation. Include all macroscopic tumor in the GTV (primary, nodal GTV adjacent to the rectal wall and extramural vascular invasion) on each CT slice and any adjacent normal rectal wall on the same slice. Contouring of the GTV may be aided by registration of the diagnostic MRI (and/or pelvic CT with contrast and/or PET if available) in the treatment planning system. Other large nodal (> 1 cm) disease that either shows increased uptake on PET or has abnormal architecture on CT may also be included in the GTV.

Construction of the clinical target volume (CTV) of the primary tumor (CTV_2500) is performed by an isotropic expansion of 1.0 cm from the GTV. The CTV_2500 should include the entire GTV. This structure should be modified to account for the natural barriers of bone and muscle if the tumor does not involve these structures.

An elective nodal dose volume (CTV_2000) should be constructed that includes the CTV_2500 and all elective nodal CTVs. Elective nodal CTVs include the entire mesorectum, internal iliac, and presacral lymph node regions. The CTV_2000 superior limit should be the more superior of 1 cm above the most superior limit of GTV, or the L5/S1 interspace. This structure should be modified to account for the natural barriers of bone and muscle if tumor does not involve these structures. Common errors in contouring the elective nodal volume include failure to correctly contour the entire extent of the mesorectum. When contouring the CTV_2000 internal iliac lymph node region, a 7 mm isotropic expansion around the vessels should be performed. When contouring the CTV_2000 presacral lymph node region, a 10 mm expansion in front of the sacrum should be performed.

PTV_2500 and PTV_2000 are then constructed by placing a 5 mm isotropic expansion around the CTVs. If daily IGRT cannot be used (kV kV match or CBCT) or if 3-D planning is performed, PTVs should be developed using a 10 mm expansion around the CTVs. In contouring of the normal pelvic organs at risk (OARs), the small bowel, left femoral head, right femoral head, genitalia, bladder, pelvic bones, large bowel, and skin should all be outlined on each axial CT slice. The external contours of all pelvic bones, including iliacs, lumbosacral spine and lower pelvic bones, should be contoured together as a surrogate for pelvic bone marrow. Bowel should be drawn as individual loops without the intertwining mesentery from L3 down. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue. Excellent definitions of normal pelvic organs may be found in the RTOG atlas (Gay 2012). A representative IMRT plan and radiation targets are shown in **Figure 3**.

Although IMRT is preferred, if 3-D is performed, one can perform sequential plans (i.e. initial PTV_2000 over four days followed by a single boost fraction).

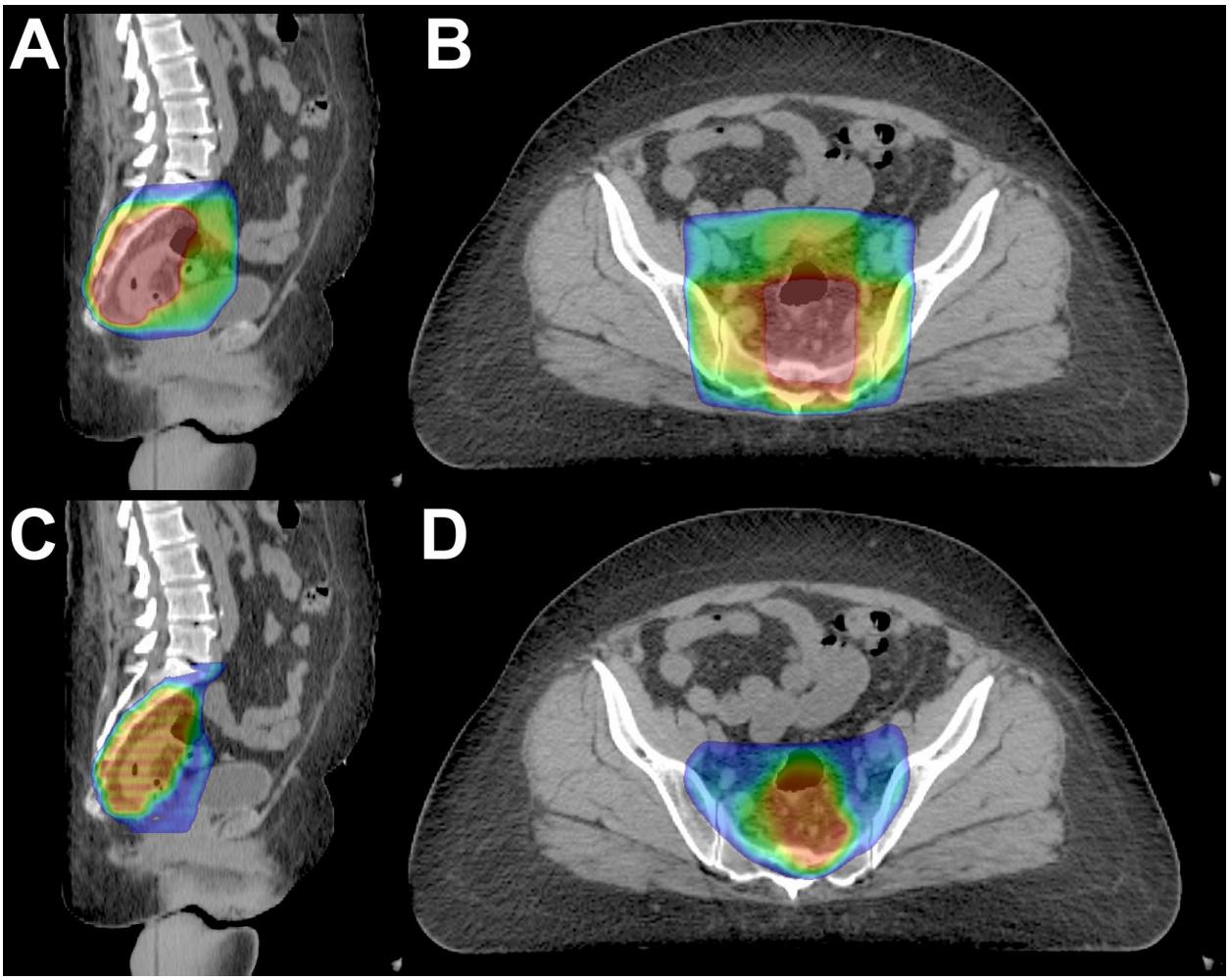


Figure 3. High dose distribution of 3D-CRT vs IMRT planning. This is a patient for whom prone positioning on belly board device did not displace bowel. Sagittal (A and C) and axial (B and D) views of 3D-CRT (A and B) and IMRT (C and D) plans are presented. The IMRT plan demonstrates reduction in high dose region to bowel and bladder. Dose color wash reflects 2000 cGy in blue and 2500 cGy in red.

Dosimetric Planning and Delivery

Conformal radiation with IMRT is preferred using 6MV photon energy and either static field or VMAT, but 3-dimensional 6-18MV photon treatment will be allowed. Proton therapy is not allowed. When using VMAT, consider 270 degree arc fields to avoid a field directly entering the genitalia. IMRT is preferred as planning allows for differential doses to the gross disease, elective nodal regions and the OARs. The OARs used in optimization typically include the small bowel, femoral heads, genitalia, bladder, pelvic bones, and large bowel. In addition, when performing IMRT, all PTVs should spare non-target skin surfaces manually or automatically trimmed by 3-5 mm (unless there is skin involvement). For bone marrow sparing, pelvic bones including the iliac crests, lumbosacral spine, and lower pelvic bones should be contoured

together as a surrogate for pelvic bone marrow. Representative target dose coverage and normal tissue constraints are outlined in **Table 2 and Table 3**.

Treatment planning priorities should be considered in order of decreasing importance:

1. PTV_2500
3. PTV_2000
4. Small bowel
5. Femoral heads
6. Bladder
7. Large bowel

Of note, pelvic bone marrow and genitalia should be kept as low as possible. However, we do not have standard five fraction constraints for these organs.

Table 2. Target Dose and Coverage Parameters

Target	Coverage	Total Dose	Max Point Dose (Gy)
GTV	100% of the volume to 100% of the dose	25 Gy	110% to be within GTV
CTV_2500	98% of the volume to 100% of the dose	25 Gy	110% to be within GTV
PTV_2500	95% of the volume to 95% of the dose	25 Gy	110% to be within GTV
CTV_2000	98% of the volume to 100% of the dose	20 Gy	110%
PTV_2000	95% of the volume to 98% of the dose	20 Gy	105%

Table 3. Normal Organs at Risk Treatment Planning Parameters for Rectal Cancer

Organ at Risk	Suggested Constraints
Small Bowel	V20 < 50cc max point dose 25 Gy
Femoral Head (L)	V20 < 10%
Femoral Head (R)	V20 < 10%
Large Bowel	V20 < 50cc max point dose 27 Gy
Bladder	V20 < 50cc max point dose 27 Gy
Large Bowel	V20 < 50cc max point dose 27 Gy

For IMRT plans, patient specific quality assurance (QA) is highly recommended. QA is performed by delivering the plan onto a phantom or portal imager to measure the 2D/3D dose. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

Image-guided radiation therapy (IGRT): Patients should receive daily KV images for set up and treatment verification. Bone should be used as the surrogate. Corrections should be made for shifts of 3 mm or greater and recorded. Daily cone beam CT images (CBCTs), if available, may also be helpful and strongly recommended to evaluate the relationship of the CTV to the bladder/rectum and to verify male genitalia position.

For IMRT systems where the isocenter is not defined (e.g., tomotherapy), setup verification images may consist of a series of axial CT images (megavoltage or kilovoltage) obtained over at least 5 cm length, to be compared with simulation CT images. It is recommended that there be an option to display target structures on the simulation images. It is also recommended that the setup verification images be obtained at levels where cephalocaudad positioning, as well as transverse positioning, can be verified. Appropriate levels would include either around the mid to upper sacrum or around the upper border of the acetabulae.

Daily doses: PTV_2500 will receive 500 cGy daily x five fractions for a total of 2500 cGy to the gross cancer PTV over 5-7 days. Fractions should be consecutive but may be spread out over two weeks (i.e. over the weekend). The CTV_2000 will simultaneously receive 400 cGy daily x five fractions for a total of 2000 cGy to the elective nodal disease. While IMRT is strongly preferred, 3-D planning with a sequential approach (PTV_2000 over four consecutive fractions followed by the PTV_2500 volume in one treatment as a boost of 500 cGy to the gross cancer PTV) is

allowed. There should be no treatment break. If a treatment break of more than 3 days is needed, please contact the study PI. No bolus should be used.

6.2 Pre-Operative TASOX

6.2.1 TAS102

Each treatment cycle will be 14 days in duration. TAS-102 dosage is calculated according to body surface area.

One treatment cycle consists of the following:

Days 1-5: TAS-102 (35 mg/m^2/dose) orally BID

Days 6-14: Rest

Repeat for a total of 6 cycles.

Study medication should be taken on Days 1-5. If doses are missed or held on those days, the patient should not make up for missed doses.

TAS-102 should be taken with a glass of water within 1 hour after completion of morning and evening meals.

6.2.2 Number of Tablets per Dose

Tablet calculation is presented in **Table 2**. TAS-102 should only be given on Days 1 through 5 of each cycle even if doses are missed or held for any reason during Days 1 through 5.

Table 2: TAS-102 Tablets per Dose

TAS-102 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
35 mg/m^2	< 1.07	35	70	1	1

TAS-102 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
	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

BSA=body surface area (calculate to 2 decimal places)

6.2.3 Instruction to Patients for Handling Study Medication

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

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

6.3 Oxaliplatin

Day 1: Oxaliplatin 85mg/m2 IV in 500 ml of D5W over 2 hours

Days 1-14: see TAS102 schedule.
Repeat for a total of 6 cycles

Oxaliplatin may be administered via peripheral or central IV, per institutional policy.

6.4 Surgical Therapy

Standard surgical therapy with a total mesorectal excision (TME) is to be done within 10 weeks of completion of cycle #6 of chemotherapy with TASOX with staging to be done within 8 weeks after day 14 of cycle 6.

Operative approach will be at the discretion of surgeon, and can include either laparoscopic (or robotic-assisted laparoscopic) or open anterior or low anterior resection with or without temporary fecal diversion. Preoperative antibiotics and bowel preparation are institution specific will be at the discretion of the operating surgeon. The mobilization of the proximal colon and splenic flexure may be performed by laparoscopic, laparoscopic-assisted, robotic-assisted or hand-assisted at the discretion of the surgeon to limit the incision to the lower abdomen. The pelvic dissection should include TME, division of inferior mesenteric vascular pedicle, transection of the specimen, and anastomosis. Anastomosis may be stapled or hand-sewn. Variation in technical approaches will be at the surgeon's discretion as they are impacted by the patient's body habitus, incisions, and tumor location.

Patients that achieve a complete or near complete Clinical Response (cCR or cCR), may choose to pursue a course of watch and wait with agreement of their treating surgeon. A thorough discussion is recommended with their surgeon concerning the risks and benefits of watch and wait and both they and their physician agree with the intended approach. Patients that pursue a course of watch and wait remain evaluable on study and will be classified as having a ypT0N0 response for the purposes of the NAR score if they do not proceed to TME surgery within 24 months of completing cycle 6, day 14.

Surgical Complications

Perioperative and postoperative complications will be collected and submitted; see Section 10.0.

Early complications (within 30 days)

Morbidity and mortality will be closely monitored and recorded using the study data forms with the following definitions:

1. Pulmonary, urinary tract, and intraabdominal infections will be defined by the need for antibiotic treatment and/or interventional radiology drainage.
2. Abdominal wound infections will be defined by the location, extent and severity (i.e. superficial vs. deep space infection) and the need for wound opening and/or surgical intervention. Urinary retention will be defined as the condition of urinary dysfunction that occurs for greater than 5 days following surgery or that requires intervention, including replacement of Foley catheter, surgery, etc
3. Perioperative hemorrhage requiring blood transfusion(s) or reoperation will be considered as a complication. Correction of preoperative anemia will not be included as a complication. The decision to transfuse will be made at the surgeon's discretion.

4. Any documented medical or anesthetic complications that result in patient disability or that requires intervention will be recorded.
5. Problems with healing, function or management of the ostomy that requires intervention or additional hospital stay will be considered complication and recorded.

7.0 RADIOLOGIC IMAGING

The primary interpretation of all imaging studies will occur at each site, and each site will make the initial determination for each patient as to:

1. Study eligibility
2. Initial MRI study adequacy
3. Baseline TNM status
4. Post-treatment T and N status

Estimated Radiographic T Stage (Using AJCC 8th Edition Definitions):
This should be estimated as T1, T2, or T3c/d (ie. T3c, >5 to 15 mm; T3d, >15 mm beyond muscularis propria). T4 tumors are ineligible. See APPENDIX I.

Estimated Radiographic N Stage:
For purposes of achieving consistent interpretation in this protocol:
Node positivity determination: Entry criteria nodes will be measured in short-axis diameter and for the purposes of study entry will be considered positive if 8mm in short axis.
Radiographic N2 status is estimated as: 4 or more nodes that measure 8mm or more in short-axis.
Radiographic N1 status is estimated as: fewer than 4 lymph nodes that measure 8 mm or greater in short axis but 1 or more lymph nodes that measure 10 mm or greater.

Distance of the Tumor from the Mesorectal Fascia Reflection: patients with tumors with a distance of 1mm or less, or adherent to the mesorectal fascia reflection have threatened radial margins and are ineligible.

Presence of Distant Disease:
Nodal stations considered suspicious for metastatic disease (M1) for rectal cancer are: common iliac, external iliac and inguinal nodes.

8.0 SUGGESTED DOSAGE MODIFICATION BASED ON ADVERSE EVENTS

8.1 TASOX chemotherapy

8.1.1 TAS-102 Dose Reduction Levels

Study medication dose reductions in case of toxicity and number of tablets for each calculated BSA are described in **Table 3**. Patients are permitted dose reduction(s) to a minimum dose of 20 mg/m^2 bid(40 mg/m^2/day) in 5 mg/m^2 steps.

Table 3: TAS-102 Dose Reduction Levels and Number of Tablets per Dose

TAS-102 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
Level 1 Dose Reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[1]	50[1]	2 (PM)[1]	1 (AM)[1]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 – 1.34	25[1]	50[1]	2 (PM)[1]	1 (AM)[1]
	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

[1] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

BSA=body surface area (calculate to 2 decimal places)

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

Study medication should be discontinued if toxicities that require dose reduction recur after dose reduction to 20 mg/m^2.

8.1.2 Oxaliplatin Dose Reduction Levels

Dose Modifications levels for oxaliplatin are listed in Table 6:

Table 4: Oxaliplatin dose modification levels

	Starting Dose	Dose Level -1	Dose Level -2
Oxaliplatin	85 mg/m2	65mg/m2	50mg/m2

8.1.3 Dose Hold, Resumption and Modification in Response to Hematologic Toxicities

Criteria for dose HOLD and RESUMPTION in response to hematologic toxicities related to myelosuppression are described in **Table 5 and 6**, respectively.

For all patients with decreases in neutrophils and/or platelets noted in **Table 5**, the next cycle of study treatment should not be started until the resumption criteria in **Table 6** are met; these resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met. **Table 7** and **Table 8** summarize the relative dose reduction requirements for the TASOX regimen.

Table 5: TAS-102 and Oxaliplatin DOSE HOLD CRITERIA for Hematologic Toxicities Related to Myelosuppression

Parameter	Hold Criteria	
	Conventional Units	**SI Units**
Neutrophils	<1,000/mm^3	<1.0 × 10^9/L
Platelets	<50,000/mm^3	<50 × 10^9/L

SI=International System

Table 6: TAS-102 and Oxaliplatin RESUMPTION Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Resumption Criteria[(1)]	
	Conventional Units	**SI Units**
Neutrophils	≥1200/mm^3	≥1.2 × 10^9/L
Platelets	≥75,000/mm^3	≥75 × 10^9/L

(1) These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.
SI=International System

Table 7: Combined dose MODIFICATION for TASOX regimen for Absolute Neutrophil Counts (ANC).

Prior to cycle	ANC SI Units $\times 10^9$/L	Dose level of subsequent cycles	
		Oxaliplatin	TAS102
-If ANC is less than 1.2 within 3 days of day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 4 times. -If ANC is greater than or equal to 1.2 within 4 weeks, proceed with treatment at the dose level noted across the lowest ANC result of the delayed weeks (s) -If ANC remains less than 1.2 after 4 weeks, discontinue treatment.	Greater than or equal to 1.2	Maintain dose level	Maintain dose level
	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	0.5 to less than 1.0	Decrease 1 dose level	Maintain dose level
	Less than 0.5	Decrease 1 dose level	Decrease 1 dose level

Table 8: Combined dose modification for TASOX regimen for Absolute Neutrophil Counts (Plt).

Prior to cycle	Platelets SI Units $\times 10^9$/L	Dose level of subsequent cycles	
		Oxaliplatin	TAS102
-If Plts are less than 75 within 3 days of day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 4 times -If Plts are greater than or equal to 75 within 4 weeks, proceed with treatment at the dose level noted across the lowest Plt result of the delayed weeks(s) If Plts remain less than 75 after 4 weeks, discontinue treatment.	Greater than or equal to 75	Maintain dose level	Maintain dose level
	50 to less than 75	Maintain dose level	Maintain dose level
	10 to less than 50	Decrease 1 dose level	Maintain dose level
	Less than 10	Decrease 1 dose level	Decrease 1 dose level

8.1.4 Dose Modification in Response to Febrile Neutropenia

In the event of febrile neutropenia:

- Interrupt dosing until toxicity resolves to treatment resumption level (**Table 6**).
- When resuming dosing, decrease the dose level by 1 dose level from the previous dose level for both oxaliplatin and TAS102 (as per **Tables 3 and 4**).

8.1.5 Dose Modification in Response to Non-Hematologic Toxicities

In Table 9 dose modifications for non-hematologic toxicities are defined. For grading of neurologic toxicity please see Table 10.

Table 9: TASOX Dose Modification Criteria for Non-hematologic Toxicities

Grade[a]	Dose Hold/Resumption within a 14-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3(1) or Higher		
1st, 2nd, or 3rd occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment

- (1) Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.

Table 10: Oxaliplatin Neurotoxicity Definitions and Dose Modifications

Grade1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Overdose

There is no known antidote available in case of TAS-102 overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

Dosage Forms and Strengths

TAS-102 (15 mg trifluridine/7.065 mg tipiracil hydrochloride) is a white, film-coated tablet. Tablets can be printed or unprinted.

TAS-102 (20 mg trifluridine/9.42 mg tipiracil) is a pale red, film-coated tablet Tablets can be printed or unprinted.

TAS 102 tablets are supplied by way of a pouch containing a 20ct blister card.

9.0 ANCILLARY TREATMENT/SUPPORTIVE CARE

9.1 Concomitant medications and therapies.

All concomitant medications and treatments must be recorded from the time the participant signs the ICF until 28 days after the last dose of study treatment.

Caution is required when using drugs that are human thymidine kinase substrates, e.g., zidovudine. Such drugs, if used concomitantly with TAS-102, may compete with the effector, trifluridine, 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 and abacavir.

- Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme.
- Tipiracil is not metabolized in either human liver or hepatocytes.

9.2 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.3 Blood Products

Blood products are permissible.

9.4 Neulasta and Neupogen

Neulasta and Neupogen should not be started as part of initial therapy and are not usually necessary with TAS102 but may be used.

9.5 Diarrhea

Diarrhea should be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). Use of alternative agents such as Lomotil and tincture of opium is permissible.

10.0 ADVERSE EVENT (AE) REPORTING AND MONITORING

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE v5.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the adverse event must be reported as an expedited report.

The safety reporting period begins after the subject has signed the informed consent and ends 28 days after the last dose of study drug.It is only required that SAEs be reported following consent and prior to radiation therapy initiation, while all AEs (serious and non-serious) be reported thereafter.

10.2 Expected vs. Unexpected

The determination of whether an AE is expected is based on the agent-specific information provided in this protocol. Unexpected AEs are those not listed in the agent-specific information provided in this protocol.

Note: “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Reporting Clinical Safety Data to Taiho

For the purposes of this Agreement an Adverse Event (AE) shall mean any untoward medical occurrence whether thought to have been caused by the study drug(s) or the Clinical Trial procedures or not and Serious Adverse Event (SAE) shall mean any adverse event which is fatal, life threatening, disabling or Incapacitating, requires in-patient hospitalization or prolongs existing hospitalization, Is a congenital anomaly In the off-spring of the patient or which may require Intervention to prevent the previously stated outcomes.

For the purposes of this Clinical Trial, other experiences with the TAIHO Investigational Medicinal Product(s) IMP shown below should also be reported to TAIHO:

A. Drug exposure during pregnancy and lactation, or paternal drug exposure
B. Experience In patients below 18 years of age (depending on Inclusion criteria)
C. Lack of drug effect
D. Unintended beneficial effect

E. Any suspected transmission of an infectious agent by a medicinal product
F. Product quality complaints associated with possible safety issue(s)
G. Drug or food interaction
H. Overdose
I. Medication error
J. Misuse
K. Occupational exposure

10.3.1 Reporting Clinical Safety Information to TAIHO Oncology

a. The Principal Investigator shall monitor the Clinical Trial Subject for adverse events and fulfil all the reporting requirements to FDA in accordance with Applicable Laws. The Principal Investigator shall also inform Taiho Oncology of serious adverse events:
    - *Unexpected Fatal or Life Threatening Suspected Adverse Reactions*- Report to Taiho Oncology within 24 hours
    - *Serious & Unexpected Suspected Adverse Reactions*- Report to Taiho Oncology 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.
b. All serious adverse events are to be reported via a MedWatch Form and are to be sent to the Taiho Oncology, via fax: 609-750-7371 or e-mail: TAS-102_Safety@taihooncology.com (please note the underscore between '102' and 'Safety').
c. MedWatch reports must clearly specify SAE term(s) and corresponding Principal Investigator causality assessment.
d. Taiho Oncology will send SUSARs to Regulatory Authorities via a MedWatch form within 7 Calendar Days for all fatal/life threatening events and 15 Calendar Days for all other serious events.

10.3.2 Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports

The Institution will report Exposure During Pregnancy and Lactation, or Paternal Drug Exposure on any Clinical Trial Subject while participating in the Clinical Trial, and following exposure to a TAIHO IMP, 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 Clinical Trial Subject becomes pregnant, the Institution may collect information about the pregnancy and birth if the partner agrees.

The Clinical Trial 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 Clinical Trail Subject or fetus/child, then SAE(s) must also be reported to TAIHO following SAE Reporting guidelines.

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

Such reports and Information as outlined above, Including Investigator causality assessments against all concerned TAIHO 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 Clinical Trial, and further agree to update such contact details as necessary. At the time of this Agreement, all such requests should be addressed to: Hagen Kennecke, MD

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.

11.0 TREATMENT EVALUATION

11.1 Guidance for radiological tumor evaluation

Repeat non-contrast pelvic MRI to rule out progressive disease and ensure surgical resectability is required as per standard of care recommendations (22). Pelvic MRI should be booked within 56 days of completion of cycle #6 of TASOX, ie within 1-56 days AFTER day #14, cycle 6. Radiographic tumor staging should be performed and reported per the initial, staging MRI. See APPENDIX I for guidance.

11.2 Pathological Tumor Response

Pathology reports for the TME resection must be submitted de-identified reports via email to tas-short-communications@providence.org.

11.3 Definition of Surgical Margin Status

Margins to be considered are:
- Proximal Margins
- Distal Margins
- Radial Margins, synonymously termed circumferential margin.

Margin Positivity: A surgical margin is POSITIVE if the pathologist notes tumor within ≤ 1mm of any edge of the primary tumor specimen.

A surgical margin is NEGATIVE if the pathologist notes that there is NO tumor within > 1mm of any edge of the primary tumor specimen.

11.4 Definition of pathologic stage

Derivation of the Neoadjuvant response (NAR) score requires pathologic staging information from the TME resection specimen staged according to the AJCC8th edition schema:

T describes how far the main (primary) tumor has grown into the wall of the intestine and whether it has grown into nearby areas. Because this information will be ascertained from the surgical pathology report it is denoted with a prefix "p". Because it is ascertained after neoadjuvant treatment, the prefix "y" is also added (e.g., ypT3).
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum
T4b Tumor directly invades or is adherent to other organs or structures
N describes the extent of spread to nearby (regional) lymph nodes based on the rectal resection specimen. The prefix "yp" is added as described for T status.
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1-3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

11.5 Definition of Pathological Complete Response (pCR):

A pCR must include no gross or microscopic tumor identified anywhere within the surgical specimen. This must include no evidence of malignant cells in the primary tumor specimen **and** no lymph nodes that contain tumor.

12.0 POST-OPERATIVE THERAPY

Recommendations for post-operative systemic therapy are not protocol specified and are according to recommendation of the investigator based clinical evidence and NCCN guidelines. Post-operative FOLFOX or 5-Fluorouracil plus Leucovorin/Capecitabine may be recommend taking into consideration clinical and pathologic stage and patient preference.

13.0 TAS102 DRUG INFORMATION

Storage and Handling

- 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) [See USP Controlled Room Temperature].
- TAS102 LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures. "OSHA Hazardous Drugs". OSHA. (http://www.osha.gov/SLTC/hazardousdrugs/index.html)
- If stored outside of original bottle, discard after 30 days.

14.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

14.1 Statistical justification

The primary endpoint will be the Neoadjuvant Response (NAR) Score. This is an established efficacy endpoint for phase II/III rectal cancer trial, offering an early indicator of treatment effectiveness (17). In table I, inclusion criteria, pre-operative therapy and the corresponding pCR rate of published phase II and phase III trials of total neoadjuvant chemotherapy are summarized. The wide range of reported pCR rates is a reflection of treatment efficacy and the pre-treatment tumor stage of eligible patients.

Table 11. Evidence for neoadjuvant chemotherapy in stage II/III rectal cancer.

Study	Inclusion	Preoperative Therapy	N	pCR (95% CI)
Polish II (4)	High Risk T3/T4	5x5 RT →FOLFOX4 x 3	261	16%
RAPIDO (2)	High Risk	CRT 5x5 RT →CAPOX x 6	460 460	Pending (19% full cohort)
Garcia-Aguilar(23)	Stage II/III	CRT CRT →FOLFOX x2 CRT →FOLFOX x4 CRT →FOLFOX x6	60 67 67 65	18% (10-30) 25% (16-37) 30% (19-42) 38% (27-51)

EXPERT-C(24)	High-Risk	CAPOX x 4 → CRT CAPOX Cetux x 4 → CRT	44 46	9% 11%
AVACROSS(25)	High-Risk	CAPOX +Bev x 4 → CRT +Bev	45	36% (22-51%)
GCR-3(1)	High Risk	CAPOX x 4 → CRT	59	14.3% (6.4-26%)
FOWARC(26)	Stage II/III	Inf5FU→CRT→Inf5FU FOLFOX6→CRT-Ox→FOLFOX6	130 141	13.1% 29.1%

High Risk: stage II/III rectal cancer with radiographic high-risk features; 5x5 RT: 25 Gy in five fractions of 5 Gy; CRT: chemoradiation (50.4 Gy in 28 fractions of 1.8 Gy plus fluorouracil based chemotherapy); Cetux: Cetuximab; Bev: Bevacizumab;

14.2 Sample Size

In table 2, the NAR scores of comparable patients enrolled in the phase III R04 study (27) and treated with long-course chemoradiation are presented (personal communications G Yothers). Patients with cT3N0 tumors and similar in stage to those to be enrolled in the proposed concept achieved a NAR score of 14.59 (SD 13.41). Prospective data suggests a 5.8 reduction in NAR score would be a clinically significant improvement in long terms outcomes. (15) For declared target 5.8 NAR reduction from 14.59 to 8.79 a sample size of 24 patients would be required, one-sided alpha=0.1 and beta=0.2 (Power 80.2%). Assuming an ineligibility rate of 10%, the final sample size is **27.**

Patients who pursue a course of watch and wait remain evaluable on study and will be classified as having a ypT0N0 response for the purposes of the NAR score if they do not proceed to TME surgery within 24 months of cycle 6 day 14.

Table 12. pCR and NAR scores in R04 patients.

R04 similar subgroup	**Inclusion**	**Preoperative Therapy**	**N**	**ypT0N0 Rate**	**NAR Score**
	cT1-3 cN any	LRT 50.4/25 plus Fluorouracil	631	18.4%	15.77 SD 14.17
	cT3 Non-Low	"	402	18.4%	16.05 SD 14.32
	cT3 cN0 Non-Low	"	293	20.2%	**14.59** **SD 13.41**

15.0 Oversight and Quality Assurance Plan

Oversight of patient safety will include review of adverse events as well as study progress and outcomes. Patient updates, outcomes, and recruitment and retention of patients will be reviewed on a regular basis by the PI, research nurse, and data coordinator. Deviations will be reviewed during oversight meetings and/or through internal reporting procedures. Aggregate protocol deviations are monitored for trends to be reviewed by the Providence Cancer Institute Clinic and Research Quality Committee. In addition, a "first patient review" is conducted and documented for all clinical trials. This review includes treatment administration, deviations, and SAEs to ensure any compliance and/or safety issues are addressed prior to the enrollment of additional patients.

Study monitoring activities (Quality Control Reviews) are performed by clinical research staff members who have completed specialized training in study monitoring procedures and human subjects' protections. Individuals who perform study monitoring activities do not report to principal investigators or research scientists and may not monitor studies for which they have direct responsibility. Results of study monitoring activities will be reported to applicable study personnel, Clinical Trials Manager and Quality Assurance. Study monitoring activities are conducted regularly and include (but are not limited to) review and verification of the following:

- Eligibility
- Informed Consent process
- Adherence to protocol treatment plan
- Case Report Forms (CRFs)
- Source Documentation
- Adverse Events
- Regulatory Reporting

15.1 Quality Assurance

Quality Assurance (QA) personnel review study monitoring reports and if necessary, determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant patient safety issues are identified. QA will track and trend results from study quality assurance reports as well as associated corrective and preventive actions. QA personnel do not have a direct reporting relationship to the principal investigator and are not responsible for enrollment or coordination of care for study participants.

A review of 20% of the case report forms, per site, will undergo quality assurance review. All quality assurance reviews will include verification of the accuracy and integrity of data entered onto case report forms. Incorrect data will be identified and corrected. The existence of adequate source documents for data will be verified. Each site is responsible for their own implementation of internal monitoring and/or auditing plans for this trial as appropriate. These plans will be revised as necessary during the life of the trial based upon a variety of factors, including but not limited to: protocol amendments, staff turnover, enrollment metrics, and

compliance issues noted. All subsite quality reports will be submitted to the coordinating center quarterly.

16.0 References

1. Ludmir EB, Palta M, Willett CG, Czito BG, Total neoadjuvant therapy for rectal cancer: An emerging option. Cancer. 2017;123(9):1497. Epub 2017 Mar 10.

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APPENDIX I: Baseline staging and post-treatment MRI interpretation.

The following instructions should aid in the consistent interpretation of images. It is recognized that assessment of clinical staging based on imaging is necessarily inexact and involves estimation. Clinical staging should be estimated using the AJCC 8th edition criteria. The criteria set forth below are to foster consistency of interpretation across sites.

T stage coding:
T1
T2
T2/early T3 (including spiculations) is coded T3
T3
T3/possible T4 is coded T4 (not eligible)
T4 (not eligible)

N stage coding:
Estimated radiographic nodal stage will be derived from preoperative imaging procedures using the AJCC 8th edition staging criteria. The total number of nodes to determine stage (N1 = 1-3, N2 = 4 or more) will include mesorectal and superior rectal stations.

Final analysis criteria will be short axis measurement with nodes positive at any size N1=1-3, N2=4 or more. Diminutive nodes (<8mm) are not considered.

Radiographic N1 status is estimated as: fewer than 4 lymph nodes that measure 10 mm or greater in short axis but 1 or more lymph nodes that measure 8 mm or greater.

Radiographic N2 status is estimated as: 4 or more nodes that measure 8mm or more in short-axis (not eligible).

Metastatic nodal disease: Nodal stations considered suspicious for metastatic disease (M1) (AJCC 8th edition) are for rectal cancer: common iliac, external iliac nodes and inguinal nodes. Also bone metastases and peritoneal tumor implants.

Circumferential Radial Margin: Distance of the tumor from the mesorectal fascia reflection (also known as radial margin, also known as CRM or circumferential resection margin).