International Journal of Colorectal Disease (2025) 40:69
https://doi.org/10.1007/s00384-025-04850-9

STUDY PROTOCOL

No operation after short-course radiotherapy followed by consolidation chemotherapy in locally advanced rectal cancer (NOAHS-ARC): study protocol for a prospective, phase II trial

Felipe F. Quezada-Díaz[1] · Aron Bercz[2] · Jose L. Escobar[3] · Nicole Caire[1] · Lucia E. Díaz-Feldman[1] · Erik Manriquez[1] · Gonzalo Carvajal[1]

Accepted: 3 March 2025

Abstract

Purpose Organ preservation through a watch-and-wait (W&W) strategy has become a viable option for select rectal cancer patients with clinical complete responses (cCR) to total neoadjuvant therapy (TNT). This approach limits the morbidity associated with multimodal treatment. However, the optimal treatment strategy and predictors of treatment response are still unresolved. Rectal cancer incidence is rising, particularly in developing countries, and the disease is a major public health concern in Chile. Prior to the no operation after short-course radiotherapy followed by consolidation chemotherapy in locally advanced rectal cancer (NOAHS-ARC) trial, TNT-based treatments and W&W programs had not been implemented in Chile.

Methods/design This single-arm, multicenter, phase II prospective trial, conducted in Santiago, Chile, will enroll patients with stage II/III rectal adenocarcinoma. Treatment involves induction short-course radiotherapy (25 Gy in 5 fractions) followed by consolidation chemotherapy (FOLFOX × 9 or CAPOX × 6 cycles). The response will be assessed 4–8 weeks after chemotherapy completion. Patients achieving cCR will be offered W&W, while those with incomplete responses will undergo total mesorectal excision. The primary endpoint is the rate of complete tumor response, combining pathologic complete responses (pCR) and sustained cCR (> 1 year), compared to a matched cohort treated with neoadjuvant chemoradiation alone. The trial aims to recruit 48 patients, assuming a combined pCR/sustained cCR rate of 12%. Quality of life measures will be assessed, and a biorepository of tissue and plasma samples will be established for future research, alongside serial endoscopic and MRI images.

Discussion NOAHS-ARC seeks to advance organ preservation strategies in rectal cancer while pioneering TNT and W&W protocols in Chile. The study will also focus on functional outcomes and provide valuable data for improving patient care both locally and globally.

Trial registration ClinicalTrials.gov identifier NCT04864067. Registered on April 28, 2021.

Keywords Organ preservation · Watch-and-wait · Nonoperative management · Short-course radiotherapy · Total neoadjuvant therapy

Background

Colorectal cancer (CRC) is the third most common cancer globally, comprising approximately 10% of all oncologic diagnoses annually [1]. Although CRC incidence is greater in developed countries [2], developing countries are anticipated to experience a sharp rise in disease incidence, with an estimated 396,000 new cases per year in Latin America alone by 2030 [3]. In Chile, population studies have reported annual percent increases of up to 4.1% since 1997 [4] and an actuarial 5-year survival rate of 43.2% from 2009 to 2018 [5], rendering it a major public health issue. Consequently,

✉ Felipe F. Quezada-Díaz
ffquezad@gmail.com

[1] Complejo Asistencial Doctor Sotero del Rio, Avenida Concha y Toro #3459, 8150215 Puente Alto, Chile

[2] Department of Surgery, Colorectal Surgery Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[3] Escuela de Medicina. Pontificia Universidad Católica de Chile, Santiago, Chile

Published online: 18 March 2025

CRC has been included in *Garantias Explícitas de Salud* (Explicit Guarantees in Health Programme; GES), which provides Chileans with access to affordable and expedited healthcare for prespecified diseases.

Although population statistics specifically pertaining to rectal cancer in Chile are scarce, the rectum generally comprises one-third of all colorectal malignancies [6]. Locally advanced rectal cancer (LARC), defined as stage II (T3-4, N0) and stage III (T any, N1, or greater) disease, has historically been treated in Chile with a multimodal approach of neoadjuvant long-course chemoradiotherapy (LCRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy. Over the past decade, there has been an international shift in the treatment paradigm of LARC toward total neoadjuvant therapy (TNT) which entails the delivery of systemic chemotherapy and pelvic radiotherapy prior to surgical resection. The adoption of this treatment approach has been supported by both retrospective and prospective studies demonstrating superior treatment responses [7–10] with pathologic complete responses (pCR) achieved in over a quarter of patients [9, 10]. Consequently, the need for radical surgery has been questioned, as TME is associated with significant complications in about 30% of patients, including long-term impacts on bowel, sexual, and urinary function [11]. Indeed, the concept of rectal preservation by means of watch-and-wait (W&W) management is increasingly accepted worldwide as mounting retrospective and prospective evidence supports its efficacy and oncologic safety in appropriately selected patients who achieve a clinical complete response (cCR) [12–25]. Recently published 5-year data from the OPRA trial (NCT02008656) demonstrates that organ preservation is achievable in approximately 50% of patients without compromising oncologic outcomes [16]. Moreover, the treatment sequence of induction chemoradiotherapy followed by consolidation chemotherapy achieved superior organ preservation compared to the inverse sequence. At present day, several randomized control trials are accruing worldwide such as the Janus Rectal Cancer Trial (NCT05610163) in the USA, the ENSEMBLE trial (NCT05646511) in Japan, the ACO/ARO/AIO-18.1 trial (NCT02363374) in Germany, and CCHOWW trial (NCT05000697) in Brazil to further elucidate treatment regimens that optimally facilitate organ preservation.

Given that the demonstration of the safety and feasibility of W&W is an iterative process, the importance of multiple prospective studies cannot be understated. Herein, we report on the details of the Chilean single-arm, phase II trial, no operation after short-course radiotherapy followed by consolidation chemotherapy in locally advanced rectal cancer (NOAHS-ARC, NCT04864067), hypothesizing that the utilization of induction short-course radiotherapy (SCRT) followed by consolidation chemotherapy as an investigational TNT paradigm will achieve superior treatment response (sustained cCR > 1 year or pCR) compared to a matched cohort treated with neoadjuvant LCRT alone. This represents an essential inquiry, as most organ preservation studies to date have been conducted in the context of LCRT. Although SCRT has been demonstrated to be non-inferior to LCRT in multiple prospective studies that entailed surgical resection [10, 26–33], concerns remain regarding the risk of local regrowth following SCRT in the context of organ preservation and TNT approaches [23, 34–36]. Given that SCRT is fundamentally delivered as 25 Gy in 5 Gy fractions, (as opposed to 45–50.4 Gy in 1.8 Gy fractions with LCRT), SCRT may provide practical yet effective treatment for many Chileans who have limited access to healthcare, such as rural communities or public hospitals. Moreover, treatment response is recognized as a prognostic indicator of long-term outcomes [37, 38], but molecular drivers of treatment response remain undefined and the early identification of responders versus non-responders remains an unmet need. Our aim is to assess the efficacy of a standardized SCRT-based TNT model in enhancing treatment response (i.e., pCR/sustained cCR) and to develop a biorepository to identify predictors of response using patient-derived tissue and plasma specimens obtained longitudinally.

Methods/design

Trial design and setting

The NOAHS-ARC trial is a prospective, single-arm phase II trial based in Santiago, Chile, sponsored by *Agencia Nacional de Investigación y Desarrollo* (FONDECYT #11,201,291, trial PI and Chair, F.F. Quezada-Díaz). Patients with locally advanced rectal cancer are recruited from three tertiary hospitals within the Health Service Network. All patients are treated with TNT with the potential for W&W management versus TME, based on the clinical response at the time of reassessment (Fig. 1). This trial was approved by *Comite Etico Cientifico Servicio Salud Metropolitano Sur Oriente* and adhered to the SPIRIT reporting recommendations (Additional file 1). A list of study sites can be obtained at ClinicalTrials.gov (identifier: NCT04864067).

Patient selection

Patients with biopsy-proven stage II (T3-4, N0) and stage III (T any, N1 or greater) mismatch repair proficient adenocarcinoma of the middle/lower rectum (< 7 cm from anal verge, palpable by digital rectal exam, DRE) will be recruited and provide written consent (patient or authorized surrogate) for trial participation (Table 1). At the time of baseline assessment, all patients will undergo a comprehensive evaluation including DRE, flexible sigmoidoscopy with endoscopic

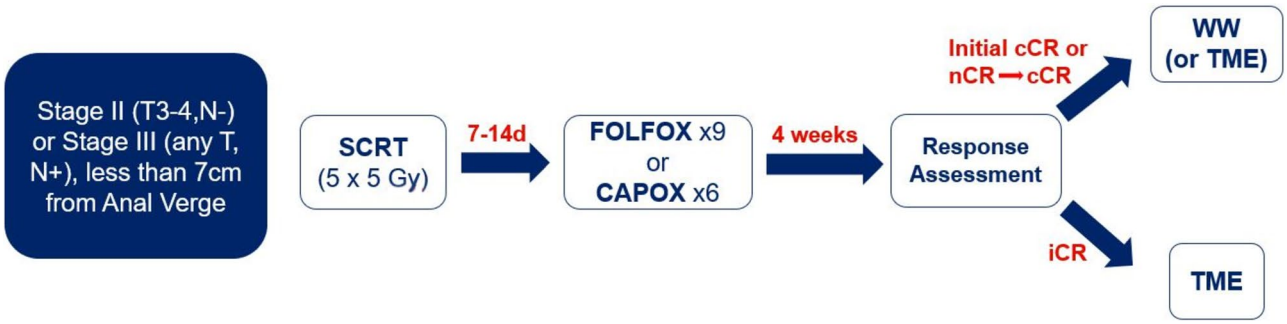

Fig. 1 NOAHS-ARC trial treatment schema

Table 1 Eligibility criteria

Inclusion criteria
• Histologically confirmed rectal adenocarcinoma
• Mismatch repair proficient
• Stage II (T3-4, N-) or III (any T, N +) based on MRI
• Tumor < 7 cm from anal verge (per MRI) and palpable on digital rectal exam
• No prior history of rectal cancer
• Age > 18 years
Exclusion criteria
• Stage IV disease at diagnosis
• Mismatch repair deficient
• Tumor > 7 cm from anal verge (per MRI) or unpalpable tumor on digital rectal exam
• Indication for pelvic exenteration
• ECOG > 1
• Recurrent rectal cancer
• Contraindication to radiotherapy
• Contraindication to chemotherapy
• Contraindication to MRI (i.e., pacemakers)
• Untreated coronary artery disease
• Acute coronary syndrome within the past 12 months
• Congestive heart failure
• Peripheral neuropathy
• Pregnancy or breastfeeding
• Baseline hemoglobin < 8 g/dL
• Baseline white blood cell count < 4000/L
• Baseline platelets < 100,000/L
• Baseline creatinine clearance < 50 mL/min
• Baseline total bilirubin < 5 mg/dL
• Inability to consent or follow-up

biopsies, rectal magnetic resonance imaging (MRI), staging computed tomography (CT) chest/abdomen/pelvis, and bloodwork (Fig. 2). Exclusion criteria include tumors > 7 cm from anal verge (as determined by MRI), unpalpable tumors on DRE, evidence of metastatic disease at diagnosis, anticipated need for pelvic exenteration, age less than 18 years, ECOG > 1, contraindication to radiotherapy or chemotherapy, prior pelvic radiation, active pregnancy or breastfeeding, and failure to follow-up or consent. Comorbidities including untreated coronary artery disease or recent acute coronary syndrome within 12 months, congestive heart failure, and peripheral neuropathy are also grounds for trial exclusion. Additional exclusionary criteria include baseline laboratory values of hemoglobin < 8 g/dL, white blood cell count < 4000/L, platelets < 100,000/L, creatinine clearance < 50 mL/min, and total bilirubin > 5 mg/dL. All trial candidates are discussed by a disease management team prior to inclusion.

Intervention/treatment

After informed consent is obtained, protocol therapy will be initiated with induction SCRT, delivered as 25 Gy in five 5 Gy fractions. Seven to 14 days following the completion of SCRT, consolidation systemic chemotherapy will begin with either 9 cycles of FOLFOX (oxaliplatin 85 mg/m^2 + 5 fluorouracil bolus of 400 mg/m^2 + leucovorin 400 mg/m^2 + 5-fluorouracil infusion of 2400 mg/m^2 in 46 h every 14 days) OR 6 cycles of CAPOX (capecitabine 1000 mg/m^2 every 12 h for 14 days + oxaliplatin 130 mg/m^2 on day 1, every 21 days). Treatment toxicity will be monitored and classified according to CTCAE version 5.0 [39]. In the case of treatment toxicity, the protocol provides explicit guidance to the principal investigator on how to adjust or discontinue chemotherapy. Prior to each chemotherapy cycle, patients will undergo bloodwork including a complete blood cell count, renal function panel, and hepatic function panel.

In addition to the baseline tumor assessment, all patients will undergo re-evaluation by a colorectal surgeon during the

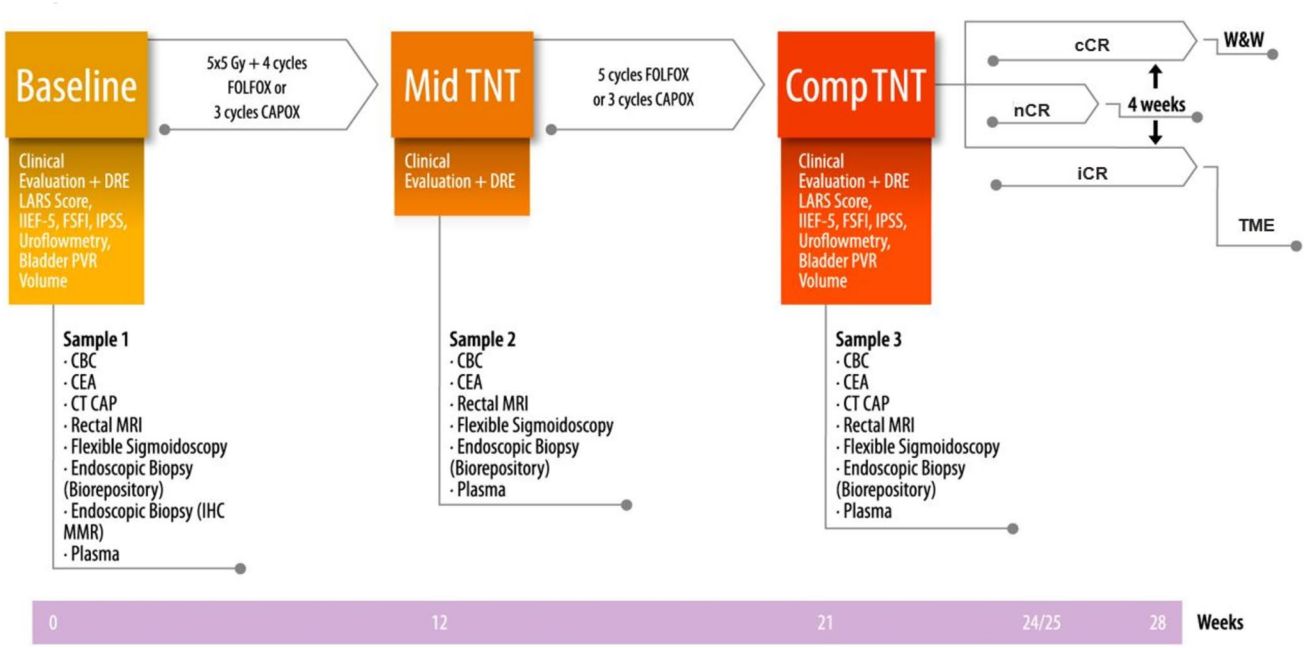

Fig. 2 Schedule of tumor evaluation and data collection

middle of TNT (9 weeks after initiation of chemotherapy) and upon completion of TNT (4 weeks after chemotherapy completion). Importantly, the continued administration of chemotherapy will not be influenced by the response assessment at the mid-treatment evaluation. At each of the three timepoints, patients will be evaluated with DRE, flexible sigmoidoscopy with biopsy, rectal MRI, and bloodwork. CT chest/abdomen/pelvis will be performed at baseline and post-TNT. Four to 8 weeks following TNT completion, a response assessment will be performed by two independent evaluators (PI and surgical staff) and described according to the Memorial Sloan Kettering Regression Schema [40]. In the event of discrepant assessments, the opinion of a third evaluator will be rendered. Patients demonstrating an incomplete clinical response (iCR) will undergo TME. Patients with a cCR will be offered nonoperative management with a W&W strategy or TME. Patients with a near complete response (nCR) will be offered re-evaluation in 4 weeks, after which cCR or iCR will be assigned. Surgical specimens will be processed in a standardized manner and tumor regression grade will be assessed using the American College of Pathologist Scale [41].

Follow-up

All patients will be followed for at least 2 years regardless of whether they were managed with TME or W&W (Fig. 3). TME patients will be followed with (a) clinical exam every 4 months for 2 years, (b) CEA and CBC every 4 months for 2 years, (c) CT chest/abdomen/pelvis at 12 and 24 months, and (d) complete colonoscopy at 12 and 24 months postoperatively. W&W patients will be followed with (a) clinical exam with DRE every 4 months for 2 years, (b) flexible sigmoidoscopy every 4 months for 2 years, (c) CBC and CEA every 4 months for 2 years, (d) CT chest/abdomen/pelvis annually for 2 years, (e) rectal MRI every 6 months for 2 years, and (f) complete colonoscopy annually for 2 years. Local regrowth, defined as any endoscopic or MRI evidence of pelvic tumor recurrence on W&W surveillance following the confirmation of cCR, will require a recommendation for TME. Sustained cCR will be defined as the absence of local regrowth for at least one year following the completion of TNT.

Functional and quality of life measures

Patients will be asked to complete multiple validated questionnaires throughout the treatment course, including at baseline, time of TNT completion, and at 6, 12, and 24 months post-TNT. To evaluate bowel function, the Low Anterior Resection Syndrome (LARS) Score will be used, which has previously been validated in the Chilean population [42]. To assess sexual function, the IIEF-5 score and FSFI score will be used for males and females, respectively. Both scores have been translated and adapted to the Chilean population. The urinary function will be assessed with the IPPS score (male and female) at baseline, time of TNT completion, and 6 months post-TNT. Quality-of-life (QoL) evaluation will be conducted using the EORTC QLQ-C30

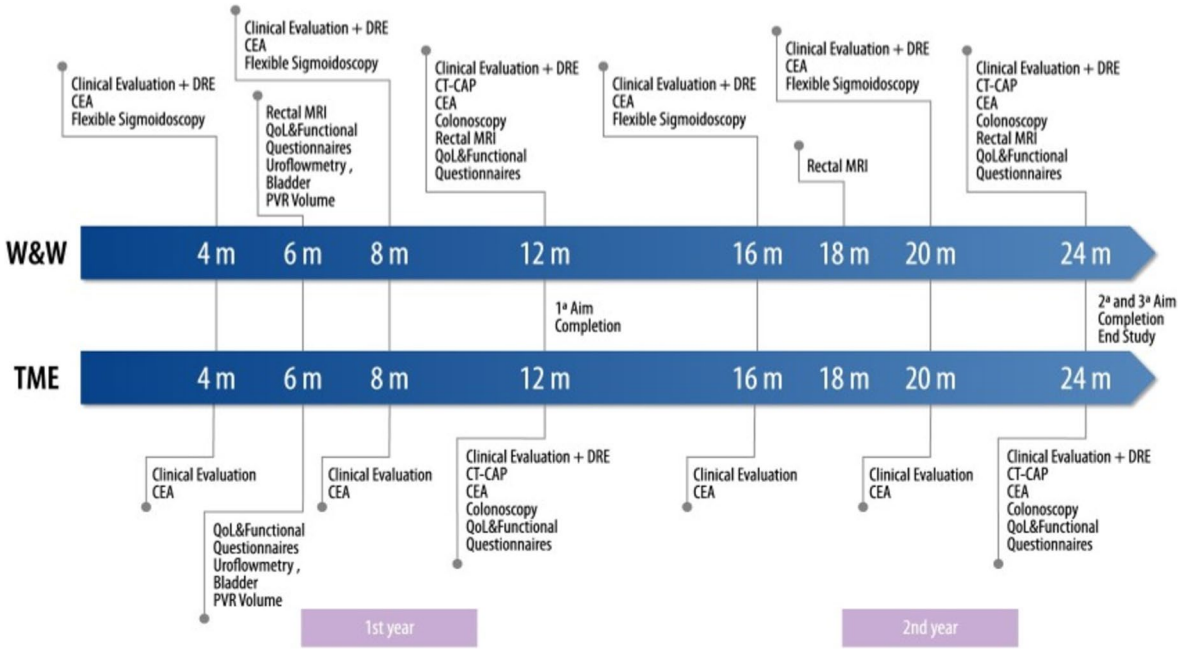

Fig. 3 Surveillance schedule based on the proposed management strategy

version 3.0 questionnaire (Chilean Spanish Version, Additional file 2).

Primary and secondary objectives

The primary outcome of NOAHS-ARC is the rate of complete response, defined as the combined number of cases with pCR and sustained (≥ 1 year) cCR. The rate of complete response will be compared to the pCR rate reported from a matched cohort of patients treated with neoadjuvant chemoradiotherapy followed by TME. Of note, the clinical response will specifically refer to the local (i.e., pelvic) response. Distant metastases will not be considered in the primary endpoint. A secondary outcome is the assessment of quality of life and functional outcomes between W&W and TME patients, using standardized evaluations with validated questionnaires, as described previously. Additionally, secondary outcome measures include the incidence of adverse events during treatment, which will also be compared to the matched cohort.

Data collection and management

All data collected during the trial will be stored in a de-identified and encrypted database, under the jurisdiction of a data monitoring committee (authors FQD, JLE, NC, LDF, EM, and GC). Upon obtaining informed consent, tissue, and blood specimens will be collected longitudinally during the treatment course to establish a biorepository for future correlative and translational analyses (Fig. 4). Endoscopic tissue biopsy specimens will be fixed in paraformaldehyde, rinsed, and placed in ethanol before being set in paraffin blocks and stored at 4℃. Histologic slides will be prepared for pathologic assessment, including baseline analysis for MMR protein expression using immunohistochemistry. Peripheral blood specimens will be collected for standard laboratory monitoring including complete blood count (Beckman Coulter LH780, California, USA) and CEA immunoassay (Roche Analytics E170, Basel, Switzerland). An additional 3 mL peripheral blood sample will be collected in EDTA tubes and centrifuged to isolate plasma, which will be stored at − 80℃ for future circulating tumor DNA (ctDNA) analysis.

Next-generation targeted sequencing techniques such as MSK-IMPACT will be used to analyze key genetic regions of cancer-related genes [43], aiding in the evaluation of targeted therapies and mutations associated with treatment response. Whole exome sequencing (WES) will be utilized as a complementary analysis for broad genetic evaluation beyond those assessed by MSK-IMPACT, potentially identifying new genetic markers relevant to cancer treatment and patient outcomes. Sequencing may be undertaken using plasma or paraffin-embedded tissue samples.

Additionally, an imaging repository will be established using endoscopic photographs/videos and MRI obtained longitudinally during the treatment course. Endoscopic images will be collected via the Exera III capture system (Olympus, Tokyo, Japan). MRI images are obtained via Philips Achieva 1.5 T MRI. An exploratory objective is to correlate and validate the findings of the prospectively banked tissue

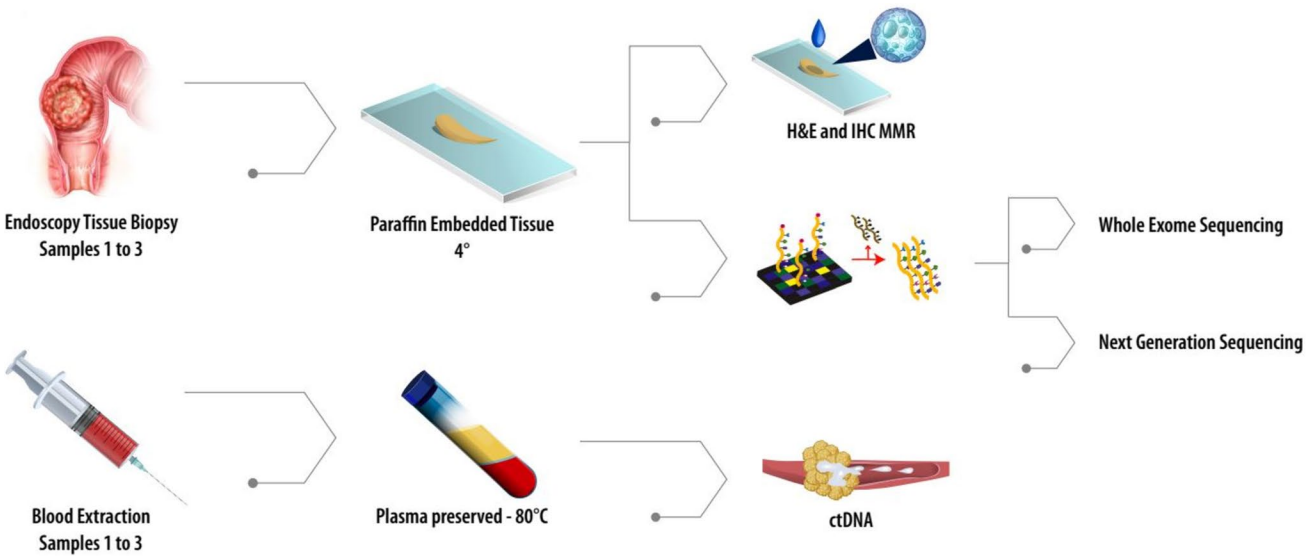

Fig. 4 Anticipated analyses using tissue and blood specimens

and plasma specimens with radiographic, pathologic, and clinical outcomes in collaboration with our translational partners at Memorial Sloan Kettering Cancer Center to identify potential predictors of treatment response.

Statistical methods

For the sample size calculation, a pCR rate of 12% was used based on historical data. The null hypothesis is that the combined pCR/sustained cCR rate is 12%. For an alternative hypothesis where the combined pCR/sustained cCR rate is greater than 12% powered at 30%, a target accrual of 48 evaluable patients will be required to achieve statistical significance with a β-power of 80% and one-sided alpha of 0.05. The principal investigator (FQD) will conduct an interim analysis at 50% of the expected accrual (i.e., $N = 24$ evaluable patients) for safety and data analysis. Lan-DeMets alpha spending function with the O'Brien-Fleming boundary will be used to test for efficacy, with consideration for premature termination of the study due to efficacy if the observed combined pCR/sustained cCR rate exceeds 35.7% (i.e., responders ≥ 9) or if $p < 0.006$. If accrual continues to 48 patients, the null hypothesis will be rejected if the p-value comparing the observed combined pCR/sustained cCR rate to the estimated 12% rate is < 0.044, or if the observed rate is greater than 23.0% (i.e., responders ≥ 12).

Parametric or non-parametric tests will be used for continuous variables, while chi-square and Fisher exact tests will be used for categorical variables. Group analyses will assume a 5% α-error level, utilizing STATA Software for the analysis.

Discussion

The NOAHS-ARC trial adds to the ongoing global dialogue around the optimization of total neoadjuvant treatment strategies while addressing the growing challenge of rectal cancer in Chile, with recognition of the profound impact that rectal cancer can have on an individual patient's quality of life and the economic strain on the individual and the collective healthcare system. Our comprehensive study is a pioneering initiative in Chile, aimed to develop and implement the first standardized TNT protocol in Chile and introduce a dedicated W&W program that promises to enhance patient outcomes by deferring radical surgery for well-selected candidates.

The objectives of the study are multifaceted and ambitious. Foremost, we seek to evaluate the efficacy, safety, and feasibility of a TNT paradigm in the Chilean population. This will serve as a proof of concept, demonstrating the viability and potential for wider adoption and replication of TNT strategies. Given the findings of prior prospective investigations [8–10], we anticipate that our TNT protocol will increase complete response (i.e., pCR and sustained cCR) rates relative to the pCR rate of the historical standard of neoadjuvant chemoradiation alone followed by resection. Furthermore, this study represents one of the first prospective investigations on the oncologic safety and efficacy of SCRT-based TNT in the framework of organ preservation. It will be important to regard our results in the context of additional ongoing prospective trials evaluating SCRT and organ preservation, such as ENSEMBLE (NCT05646511) investigating SCRT with randomization to doublet (CAPOX) or triplet (CAPOXIRI) chemotherapy and ACO/ARO/AIO-18.1

(NCT02363374) randomizing patients to SCRT- and LCRT-based TNT regimens. The current study can serve as a platform for future studies in our unique population where optimization of response and appropriate selection for non-responders will be essential.

Moreover, the study aims to deepen the understanding of the broader impact that rectal cancer can have on each individual patient, particularly how the disease and associated treatments affect patient-reported quality of life. This includes examining the psychological and physical burdens placed on patients and the healthcare infrastructure. Differences in functional and QoL outcomes between patients treated with nonoperative management and TME will be compared longitudinally using previously validated questionnaires, with the hypothesis that nonoperative management will yield improved patient-reported outcomes compared to those patients managed by total mesorectal excision. By closely monitoring compliance and toxicity associated with the protocol treatment, our goal is to develop methods for early detection and prevention of treatment-related adverse effects, mitigating the morbidity associated with the treatment of LARC.

Furthermore, the establishment of a biorepository in our public hospital represents a critical step towards facilitating future research efforts. An exploratory objective of NOAHS-ARC entails the identification of predictive markers of treatment response, which remains a critically unmet need. Given the heterogeneity of treatment responses observed in rectal cancer, we believe that a sensitive biomarker requires the integration of multi-modal data points. To that end, we aim to leverage tissue specimens, plasma specimens, endoscopic images, and MRI images collected longitudinally during the trial, along with histopathologic slides and patient-specific molecular profiling data. These data points will serve as critical inputs for future integrated analyses using artificial intelligence (AI), which has demonstrated promise in revolutionizing oncologic care and delivering targeted therapies [44–47]. Moreover, the repository of tissue specimens may be harnessed to derive rectal cancer organoids, which serve as invaluable platforms for translational research [48]. Research efforts employing AI and organoids may indeed uncover clinical markers or molecular drivers of treatment response, thereby enhancing the selection of patients who will benefit most from treatment intensification or de-intensification strategies and optimization of outcomes. Finally, although the role of ctDNA has been explored for a range of solid malignancies, in the context of rectal cancer, it has yet to be implemented into routine clinical practice. We hypothesize that plasma-based ctDNA analysis may correlate with treatment response and detect disease relapse with a high degree of sensitivity. To that end, we will explore the feasibility of developing a surveillance protocol using ctDNA to monitor for local regrowth/recurrence and determine whether ctDNA can detect local regrowth/recurrence prior to imaging/endoscopic assessments.

In conclusion, NOAHS-ARC is a prospective study that not only seeks to introduce a novel and potentially transformative treatment protocol for LARC in the Chilean population but also aims to lay the groundwork for future advances in the delivery of precision oncologic care. Through extensive longitudinal assessments, consideration for functional and QoL outcomes, and endeavors to identify predictive markers of treatment response, this trial embodies a holistic approach to addressing rectal cancer while seeking to contribute to future scientific progress in our understanding of the biology and underlying features of treatment response in rectal cancer.

Trial status

The NOAHS-ARC trial opened for accrual on June 9, 2021, with an estimated study completion date of May 30, 2025. As of January 1, 2025, 46 patients had been enrolled.

Abbreviations CAPOX: Capecitabine, oxaliplatin; CAPOX-IRI: Capecitabine, oxaliplatin, irinotecan; CEA: Carcinoembryonic antigen; cCR: Clinical complete response; CRC: Colorectal cancer; CT: Computed tomography; CTCAE: Common terminology criteria for adverse events; DRE: Digital rectal exam; ECOG: Eastern cooperative oncology group; FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin; iCR: Clinical incomplete response; LARC: Locally advanced rectal cancer; LCRT: Long-course chemoradiotherapy; MRI: Magnetic resonance imaging; nCR: Clinical near complete response; pCR: Pathologic complete response; SCRT: Short-course radiotherapy; TME: Total mesorectal excision; TNT: Total neoadjuvant therapy; W&W: Watch-and-wait

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00384-025-04850-9.

Acknowledgements We would like to extend our sincere thanks to J. Joshua Smith, MD, PhD, and Paul B. Romesser, MD, from Memorial Sloan Kettering Cancer Center for their invaluable guidance and expertise in clinical trial design. We also wish to thank Qian Shi, PhD from the Mayo Clinic Institute for her guidance and expertise with the statistical methods.

Authors' contributions FQD, AB, JLE, NC, LDF, EM, GC were responsible for protocol writing, manuscript conception, design and drafting. FQD, AB, JLE, NC, LDF, EM, GC were responsible for review, critical assessment of the protocol and writing of the manuscript.

Funding This trial was funded by *Agencia Nacional de Investigacion* and *Fondo Nacional de Desarrollo Científico y Tecnológico* (ANID + FONDECYT) #11201291. The funder had no role in the data collection, management, analysis, interpretation of the study, or writing of this manuscript. AB is supported by an NCI Surgical Oncology T32 Research Training Grant [5T32 CA 9501–34].

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interest The authors declare no competing interests.

References

1. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249. https://doi.org/10.3322/caac.21660
2. Lu B, Li N, Luo C, Cai J, Lu M, Zhang Y et al (2021) Colorectal cancer incidence and mortality: the current status, temporal trends and their attributable risk factors in 60 countries in 2000–2019. Chin Med J 134(16):1941–1951. https://doi.org/10.1097/CM9.0000000000001619
3. Arnold M, Sierra M, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017) Global patterns and trends in colorectal cancer incidence and mortality. Gut 66(4):683–691. https://doi.org/10.1136/gutjnl-2015-310912
4. Sierra MS, Forman D (2016) Burden of colorectal cancer in Central and South America. Cancer Epidemiol 44(1):S74–S81. https://doi.org/10.1016/j.canep.2016.03.010
5. Mondschein S. Estay C, Subiare F, Yankovic N, Von Muhlenbrock C, Berger Z (2022) Colorectal cancer trends in Chile: an observational study. Lancet Oncol 23 (S33). https://doi.org/10.1016/S1470-2045(22)00432-6.
6. Siegel RL, Wagle ND, Cercek A, Smith RA, Jemal A (2023) Colorectal cancer statistics. J Clin 2023(73):233–254
7. Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM et al (2018) Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol 4(6):e180071
8. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N et al (2022) Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). J Clin Oncol 40(15):1681–1692
9. Conroy T, Bosset JF, Etienne PL, Rio E, François E, Mesgouez-Nebout N et al (2021) Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 22(5):702–715
10. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Meershoek-Klein Kranenbarg E et al (2021) Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. Lancet Oncol 22:29–42
11. Downing A, Glaser AW, Finan PJ, Wright P, Thomas JD, Gilbert A et al (2019) Functional outcomes and health-related quality of life after curative treatment for rectal cancer: A population level study in England. Int J Radiat Oncol Biol Phys 103(5):1132–1142
12. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH et al (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240(4):711–7
13. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL et al (2018) Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 391:2537–2545
14. Smith JJ, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A et al (2019) Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 5(4):e185896
15. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM et al (2022) Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol 40(23):2546–2556
16. Verheij FS, Omer DM, Williams H, Buckley JT, Lin ST, Qin LX et al (2023) Long-term results of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: The randomized phase II OPRA trial. J Clin Oncol 42(5):500–506. https://doi.org/10.1200/JCO.23.01208
17. Maas M, Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans PJ, Engelen SME et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Onc 29(35):4633–4640
18. Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JCR et al (2015) High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 16(8):919–927
19. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Sun Myint A et al (2016) Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 17(2):174–183
20. Jimenez-Rodriguez RM, Quezada-Diaz F, Hameed I, Kalabin A, Patil S, Smith JJ et al (2021) Organ preservation in patients with rectal cancer treated with total neoadjuvant therapy. Dis Colon Rectum 64(12):1463–1470
21. Gerard JP, Barbet N, Schiappa R, Magne N, Martel I, Mineur L et al (2023) Neoadjuvant chemoradiotherapy with radiation dose escalation with contact X-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 8(4):356–367
22. Garant A, Vasilevsky CA, Boutros M, Khosrow-Khavar F, Kavan P et al (2022) MORPHEUS phase II-III study: a preplanned interim safety analysis and preliminary results. Cancers 14(15):3665
23. Chin RI, Roy A, Pedersen KS, Huang Y, Hunt SR, Glasgow SC et al (2022) Clinical complete response in patients with rectal adenocarcinoma treated with short-course radiation therapy and nonoperative management. Int J Radiat Oncol Biol Phys 112(3):715–725. https://doi.org/10.1016/j.ijrobp.2021.10.004
24. Kim H, Pedersen K, Olsen JR, Mutch MG, Chin RI, Glasgow SC et al (2021) Non-operative rectal cancer management with short

course radiation followed by chemotherapy: A nonrandomized control trial. Clin Colorectal Cancer 20:e185–e193
25. Nilsson PJ, Ahlberg M, Kordnejad S, Holm T, Martling A (2021) Organ preservation following short-course radiotherapy for rectal cancer. BJS Open (5). https://doi.org/10.1093/bjsopen/zrab093.
26. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93:1215–1223
27. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Krynski J, Polish colorectal study group et al (2016) Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 27:834–842. https://doi.org/10.1093/annonc/mdw062
28. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D et al (2012) Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-tasman radiation oncology group trial 01.04. J Clin Oncol 30:3827–3833
29. Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C et al (2017) Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): A multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 18:336–346
30. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, et al. (2022) Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). J Clin Oncol 40(15):1681–1682
31. Thakur N, Seam RK, Gupta MK, Gupta M, Fotedar V, Vats S et al (2020) A prospective observational study comparing long-course conventional neoadjuvant chemoradiotherapy with short-course radiotherapy followed by consolidation chemotherapy with delayed surgery in locally advanced rectal cancer. South Asian J Cancer 9:80–85
32. Aghili M, Khalili N, Khalili N, Babaei M, Farhan F, Haddad P et al (2020) Short-course versus long-course neoadjuvant chemoradiotherapy in patients with rectal cancer: preliminary results of a randomized controlled trial. Radiat Oncol J 38:119–128
33. Chakrabarti D, Rajan S, Akhtar N, Qayoom S, Gupta S, Verma M, et al (2021) Short-course radiotherapy with consolidation chemotherapy versus conventionally fractionated long-course chemoradiotherapy for locally advanced rectal cancer: randomized clinical trial. Br J Surg. https://doi.org/10.1093/bjs/znab020.
34. Hammarström K, Imam I, Mezheyeuski A, Ekström J, Sjöblom T, Glimelius B (2020) A comprehensive evaluation of associations between routinely collected staging information and the response to (chemo)radiotherapy in rectal cancer. Cancers (Basel) 13(1):16. https://doi.org/10.3390/cancers13010016
35. Pietrzak L, Cencelewicz A, Rutkowski A, Hołdakowska A, Paciorek K, Jankowski M, Polish Colorectal Study Group et al (2022) The utility of short-course radiotherapy in a watch-and-wait strategy for rectal cancer - the need to measure the interval to tumour response assessment from the radiation start. Acta Oncol 61(9):1121–1125. https://doi.org/10.1080/0284186X.2022.2117571
36. Bercz A, Park BK, Pappou E, Nemirovsky D, Sarkar R, Yamner M et al (2024) Organ preservation after neoadjuvant long-course chemoradiotherapy versus short-course radiotherapy. Ann Oncol 35(11):1003–1014. https://doi.org/10.1016/j.annonc.2024.07.729
37. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ et al (2010) Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 11(9):835–844
38. Park IJ, You YN, Agarwal A, Skibber JM, Rodriguez-Bigas MA, Eng C et al (2012) Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 30(15):1770–1776
39. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. (2017). Common terminology criteria for adverse events (CTCAE) version 5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
40. Smith JJ, Chow OS, Gollub MJ, Nash GM, Temple LK, Weiser MR et al (2015) Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer 15:767
41. Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE et al (2005) Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 47(2):141–146
42. Lopez SN, Carrillo K, Sanguineti MA, Azolas RM, Diaz MB, Bocic G et al (2017) Adaptacion transcultural del cuestionario acerca de la funcion intestinal (LARS Score) para su aplicacion en pacientes operados de cancer de recto medio y bajo. Revista chilena de cirugia 69:44–48
43. Cheng DT, Mitchell TN, Zehir A, Shah RH, Benayed R, Syed A et al (2015) Memorial sloan kettering-integrated mutation profiling of actionable cancer targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn 17(3):251–264
44. Luchini C, Pea A, Scarpa A (2022) Artificial intelligence in oncology: current applications and future perspectives. Br J Cancer 126(1):4–9
45. Mansur A, Saleem Z, Elhakim T, Daye D (2023) Role of artificial intelligence in risk prediction, prognostication, and therapy response assessment in colorectal cancer: Current state and future directions. Front Oncol 13:1065402
46. Foersch S, Glasner C, Woerl AC, Eckstein M, Wagner DC, Schulz S et al (2023) Multistain deep learning for prediction of prognosis and therapy response in colorectal cancer. Nat Med 29(2):430–439
47. Wang A, Ding R, Zhang J, Zhang B, Huang X, Zhou H (2023) Machine learning of histomorphological features predict response to neoadjuvant therapy in locally advanced rectal cancer. J Gastroint Surg 27(1):162–165
48. Ganesh K, Wu C, O'Rourke KP, Szeglin BC, Zheng Y, Gabriel Sauve CE et al (2019) A rectal cancer organoid platform to study individual responses to chemoradiation. Nat Med 25(10):1607–1614