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Protocol

Study Protocol: Non-operative management after chemoradiotherapy plus consolidation or sandwich (induction with bevacizumab and consolidation) chemotherapy in patients with locally advanced rectal cancer: A multicentre, randomised phase II trial (NOMINATE trial)

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ABSTRACT

Introduction: Total mesorectal excision (TME) and postoperative adjuvant chemotherapy following neoadjuvant chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer (LARC). However, neoadjuvant CRT has no recognized impact on reducing distant recurrence, and patients suffer from a long-lasting impairment in quality of life (QOL) associated with TME. Total neoadjuvant therapy (TNT) is an alternative approach that could reduce distant metastases and increase the proportion of patients who could safely undergo non-operative management (NOM). This study is designed to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with LARC.

Methods and analysis: NOMINATE trial is a prospective, multicentre, randomised phase II selection design study for patients with clinical stage II or III (T3-T4Nany) LARC ≤5 cm from the anal verge or for those who are candidates for abdominoperineal resection or intersphincteric resection prior to neoadjuvant therapy. Patients will be randomised to either Arm A consisting of CRT (50.4 Gy with capecitabine) followed by consolidation chemotherapy (6 courses of CapeOx), or Arm B consisting of induction chemotherapy (3 courses of CapeOx plus bevacizumab) followed by CRT and consolidation chemotherapy (3 courses of CapeOx). In the case of clinical complete response (cCR) or near cCR, patients will progress to NOM. The primary endpoint is the proportion of patients achieving pathological CR or cCR ≥ 2 years, defined as the absence of local regrowth within 2 years after the start of NOM among eligible patients. Allowing for a drop-out rate of 10%, 66 patients (33 per arm) from 5 institutions will be accrued.

Ethics and dissemination: The study protocol was approved by Wakayama Medical University Certified Review Board in December 2020. Trial results will be published in peer-reviewed international journals and on the jRCT website.

Trial registration number jRCTs051200121

Strength and limitations of this study

- ► This phase II study is the first study of total neoadjuvant therapy and non-operative management to compare the efficacy and safety of consolidation chemotherapy to sandwich chemotherapy using bevacizumab combined with capecitabine-based chemoradiotherapy.
- ► The assessment of a clinical complete response and near clinical complete response will be performed based on pre-defined response criteria, determined at a multi-centre, multi-disciplinary team meeting.
- ► Confirmatory conclusions cannot be drawn from a randomised phase II study.

INTRODUCTION

The current standard treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (CRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy. This multimodality treatment has significantly reduced local recurrence rates to <10%. However, neoadjuvant CRT has failed to reduce distant recurrence or improve disease-free survival (DFS) and overall survival (OS). Despite the adoption of adjuvant postoperative chemotherapy, distant relapse occurs in about 30% of patients at 5 years. Postoperative adjuvant chemotherapy following neoadjuvant CRT has failed to show survival improvement, possibly due to poor compliance to chemotherapy, a longer interval between diagnosis and commencing chemotherapy, and the application of suboptimal regimens.[1] These limitations have led to the development of a total neoadjuvant therapy (TNT) approach, which delivers both radiotherapy and systemic chemotherapy preoperatively in an attempt to treat micrometastases earlier, increase adherence to systemic chemotherapy, and improve DFS. Two recent phase 3 randomised controlled trials investigating TNT (RAPIDO[2] and PRODIGE 23 trial[3]) showed better pathological complete response (pCR) rate and fewer distant metastases in the TNT arm as compared with the standard short-course radiotherapy or CRT arm.

Numerous studies have shown that patients with a pCR have more favourable long-term oncological outcomes in terms of distant and local control,[4] and this has raised the question as to whether TME can be avoided in patients with pCR. Because TME is associated with postoperative complications and late morbidity, such as bowel, sexual, and urinary dysfunction after TME,[5,6] avoiding TME may provide an opportunity to reduce the morbidity and the need of a permanent stoma, and improve quality of life (QOL). In 2004, Habr-Gama et al. for the first time proposed a watch-and-wait (WW) approach or non-operative

management (NOM) for patients with a clinical complete response (cCR) after CRT.[7] Since then, many studies—mainly retrospective observational studies—have shown NOM to be a feasible option for patients with cCR after CRT.[8,9]

TNT has the potential to increase the proportion of patients achieving cCR and thus being eligible for NOM;[10] however, randomised trial data evaluating the efficacy of NOM in the context of TNT are lacking. OPRA was the first randomised phase II trial to address the efficacy of TNT and NOM for patients with cCR or near cCR, with the primary endpoint of 3-year DFS, as compared with standard historical controls managed with CRT and TME followed by adjuvant chemotherapy.[11] In the OPRA trial, 306 patients with LARC were randomised to receive 4 months of 5-Fluorouracil (5-FU), Leucovorin and Oxaliplatin (FOLFOX) or Capecitabine and Oxaliplatin (CapeOx) either before (induction chemotherapy) or after (consolidation chemotherapy) CRT, followed by NOM for patients with cCR or near cCR. Preliminary analyses demonstrated higher 3-year organ preservation rates in the consolidation arm over the induction arm (59% vs 43%).[12] Similarly, in the CAO/ARO/AIO-12 phase II trial, which randomly assigned patients to either induction or consolidation chemotherapy (3 cycles of FOLFOX) before or after oxaliplatin-based CRT followed by TME, demonstrated higher pCR rates in the consolidation arm as compared with the induction arm (25% vs 17%).[13] Given these results, CRT followed by consolidation chemotherapy may enable greater organ preservation, and should be preferentially considered.[14]

On the other hand, several studies have shown that the addition of anti-vascular endothelial growth factor (VEGF) drugs before radiotherapy can enhance the radiation response in LARC.[15,16] In the GEMCAD 1402 randomised phase II trial of induction chemotherapy with 3 months of mFOLFOX6 with or without aflibercept followed by CRT

and TME, patients in the aflibercept arm demonstrated a higher pCR rate than those without aflibercept (22.6% vs 13.8%).[17] In a single-arm phase II trial of 3 months of mFOLFOX6 plus bevacizumab prior to CRT, we reported a pCR rate of 37% with favourable toxicity in a series of 43 patients with poor-risk LARC.[18] Furthermore, a single-arm phase II study of sandwich-like neoadjuvant therapy consisting of one cycle of induction FOLFOX with bevacizumab, followed by CRT with three doses of bevacizumab, and one cycle of consolidation FOLFOX, also reported a high pCR rate (39.1%).[19] Given these results, we hypothesized that sandwich-like therapy of 3 cycles of induction chemotherapy with bevacizumab and 3 cycles of consolidation chemotherapy could provide the advantages of both induction (addressing micrometastatic disease earlier and enhanced CRT response by bevacizumab) and consolidation (greater pCR or NOM rate) therapy arms.

To this end, we designed this randomised phase II trial (NOMINATE trial) of TNT and NOM to compare the efficacy and safety of consolidation chemotherapy (6 cycles of CapeOx) to a sandwich chemotherapy regimen using bevacizumab (3 cycles of CapeOx plus bevacizumab as induction chemotherapy and 3 cycles of CapeOx as consolidation chemotherapy) combined with capecitabine-based CRT.

METHODS AND ANALYSIS

Study design

This is a prospective, multicentre, randomised phase II selection design study to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with LARC. The study flowchart is shown in Figure 1.

Primary endpoint

The primary endpoint is the proportion of patients achieving pCR or cCR ≥ 2 years among eligible patients. pCR is defined as no residual tumor cells in the surgical specimen. cCR ≥ 2 years is defined as the absence of local regrowth within 2 years after the start of NOM.

Secondary endpoints

Secondary endpoints include cCR rate, near cCR rate, rate of NOM, OS, distant metastasis-free survival, locoregional failure-free survival, time to disease-related treatment failure, TME-free survival, permanent stoma-free survival, safety of the treatment, completion rate of the treatment, faecal incontinence according to Wexner score[20] and Low Anterior Resection Syndrome (LARS)-scale[21], and quality of life according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) - C30[22] and CR29[23]. Locoregional failure includes progressive unresectable disease, local R2 resection, and intrapelvic recurrence after TME. Local regrowth after NOM is not considered as locoregional failure when followed by an R0/R1 resection. Disease-related treatment failure is defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal cancer, or treatment-related death.[2] In patients managed by TME, surgical morbidity, R0 resection rate, pathological stage, Dworak tumour regression grade[24] will also be assessed. In patients managed by NOM, local regrowth rate, time to local regrowth, salvage surgery rate in patients with local regrowth, surgical morbidity in salvage surgery, and R0 resection rate in salvage surgery will also be assessed. The grade of adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

Eligibility criteria

Inclusion criteria

1. Histologically confirmed diagnosis of adenocarcinoma of the rectum.

2. Clinical stage II/III (cT3-4 cNany) rectal cancer ≤5 cm from the anal verge or patient is a candidate for abdominoperineal resection or intersphincteric resection prior to neoadjuvant therapy according to the primary surgeon.

3. Clinical stage II (cT3-4N0) or stage III (cT3-4N1-3) by MRI and CT.

4. ECOG PS 0 or 1.

5. Age ≥ 20 years.

6. Adequate organ functions within 28 days prior to entry: neutrophils ≥ 1,500 /mm^3, platelets ≥ 10×10^4 /mm^3, haemoglobin ≥ 9.0 g/dL, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase ≤ 100 IU/L, alanine aminotransferase ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL or Ccr ≥ 60 mL/min/body, urine protein/creatinine < 1.

7. If there is bowel obstruction or strong stricture, stoma is constructed prior to neoadjuvant therapy.

8. Written informed consent is obtained.

Exclusion criteria

1. Patients with a history of a prior malignancy within the past 5 years, except for adequately treated cancer with 5-year relative survival rate ≥ 95%.

2. History of pelvic irradiation.

3. Administration contraindication of capecitabine, oxaliplatin, or bevacizumab.

4. Uncontrolled active infection.

5. Body temperature ≥ 38 ℃ at entry.

6. Possibly pregnant, pregnant, or nursing.

7. Patients with concurrent psychiatric condition or disease that would make them inappropriate candidates for entry into this study in the investigator's judgement.

8. Patients with concurrent serious complication (heart failure, interstitial lung disease or pulmonary fibrosis, uncontrolled diabetes, renal failure, liver failure, hypertension, thrombotic disease, gastrointestinal fistula, among other similarly serious conditions).

9. History of operation ≤ 4 weeks ago or minor operation such as stoma construction ≤ 2 weeks ago.

10. Deficient in mismatch repair (dMMR), as determined by immunohistochemistry and/or microsatellite instability testing using pre-treatment biopsy specimens.

11. Other conditions not suitable for this study in the investigator's judgement.

Sample size calculation

This study uses a "pick the winner" format proposed by Simon et al.[22] The expected baseline proportion of pCR or cCR ≥ 2 years is set at 25%. If the difference in response rate between the treatment arms is at least 10%, 30 patients per arm (total 60 patients) is necessary to select the better treatment with a probability of ≥80%. With consideration for dropouts of 10%, 33 patients per arm (total 66 patients) will be necessary. If there are no differences in response rate between treatment arms, a better treatment will be chosen in terms of secondary endpoints.

Registration and randomization

Patients are registered to the study after confirming the eligibility criteria and written informed consent is obtained. Patients are requested to fill out EORTC QLQ-C30, CR29, and

a questionnaire about faecal incontinence (Wexner score and LARS scale) at registration. After registration, patients are randomly assigned at a 1:1 ratio to the consolidation arm (arm A) or sandwich arm (arm B) using a minimization method balancing on institution, cT (cT3 vs cT4), and cN (cN- vs cN+). Registration, randomization, and collection of patient information will be performed using the Viedoc electronic data capture (EDC) system. Data are anonymized using a unique patient identification number.

Treatment

Arm A consists of CRT (50.4 Gy in 28 fractions and capecitabine 825mg/m^2 bid, day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38) followed by consolidation chemotherapy (6 courses of CapeOx: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day 1, Q3w). Arm B consists of induction chemotherapy (3 courses of CapeOx plus bevacizumab: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day1, bevacizumab 7.5 mg/kg, day 1, Q3w) followed by CRT (same as in Arm A) followed by consolidation chemotherapy (3 courses of CapeOx).

Response assessment

Interval evaluation will be performed twice: after the completion of CRT and after the completion of 3 courses of consolidation chemotherapy in Arm A, and after the completion of induction chemotherapy and after the completion of CRT in Arm B. Final response assessment will be performed after the completion of all neoadjuvant treatments. In the case of cCR or near cCR, patients will progress to NOM, but TME is also permitted if patients hope to undergo radical surgery. In the case of non-CR, patients will progress to TME. Criteria for response assessment are shown in Table 1.[11,25-28] Final response assessment

involves a combination of digital rectal examination, endoscopy, and MRI, and will be discussed at online multidisciplinary-team meetings attended by the principal investigator (PI) and the local investigators.

Follow-up

Patients treated with TME will be followed with measurements of serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9 and will be subjected to chest/abdomen/pelvis CT scan every 6 months for 5 years. Patients treated with NOM will be followed every 3 months for the first 2 years and every 6 months thereafter, as shown in Table 2. In the case of near cCR, patients will be followed every 6-8 weeks for the first 6 months. Salvage TME will be recommended for patients with local regrowth after NOM; if the patient refuses TME, local resection will also be acceptable. If a patient refuses surgical resection of local regrowth, it is considered as locoregional failure.

Statistical analysis plan

The primary analysis will be conducted when 3 years have passed since patient accrual completion. All analyses are based on descriptive data without testing because of the study design. The proportions at the primary endpoint will be estimated using an Clopper-Pearson method for binomial response. The proportions among registered patients or patients who complete the protocol treatment will also be calculated as a reference. An analysis of secondary endpoints will also be performed to complement the results at the primary endpoint, but adjustment of multiplicity will not be performed due to their exploratory nature. Kaplan–Meier method will be used to estimate OS, with 95%CIs calculated by Greenwood's formula. Univariate Cox regression will be used to estimate HRs with 95%CIs associated

with treatment arms. For endpoints with competing risk, such as distant metastasis-free survival, locoregional failure-free survival and an estimation of HRs will be performed using Fine and Grey models. The final analysis will be conducted when 6 years have passed since patient accrual completion.

Interim analysis and monitoring

Interim analysis is planned for possible early trial termination to claim futility. In Simon's optimal two-stage design,[29] when the null hypothesis is a pCR or cCR/near cCR rate of 15% versus the alternative of 30% for each arm, and power and one-sided alpha are set at 80% and 5%, respectively, 19 subjects will be accrued in the first stage. If there are 3 or fewer responders within these 19 subjects, enrolment in that arm will be stopped. If the number of treatment-related deaths reach two for each arm, the registration will be suspended until Data and Safety Monitoring approve the continuation of the trial. The Data Centre (Clinical Research and Medical Development Centre, Cancer Institute Hospital, Japanese Foundation for Cancer Research) will perform central monitoring every 6 months and monitoring reports will be submitted to the Data and Safety Monitoring Committee.

Translational research

Accompanying translational research about the molecular determinants of response to TNT and molecular predictors of successful organ preservation is planned. The specific study protocol for correlative translational research to the NOMINATE trial has been approved by the intuitional review boards of all participating institutions. Tumour tissue and plasma will be collected and stored at different time points after obtaining written informed consent from patients. Next-generation sequencing, such as exome sequencing, RNA sequencing, and

circulating tumour DNA analysis, will be performed.

Ethics and dissemination

Wakayama Medical University Certified Review Board approved this study protocol in December 2020. This trial will be performed in accordance with the Declaration of Helsinki and Clinical Trials Act in Japan. Trial results of the primary and secondary endpoints will be published in peer-reviewed international journals and on the jRCT website (https://jrct.niph.go.jp/), as well as at international and national conferences.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Contributors TA, SE, TS, NI, TK developed the trial concept and wrote the protocol. All authors contributed to refining the protocol and have read and approved the final version.

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Competing interests KY reports honoraria from Chugai Co., Ltd.

Patient consent for publication Not required.

Ethics approval Wakayama Medical University Certified Review Board (CRB5180004).

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Figure Legends

Figure 1 Study flowchart

Table 1 Criteria for response assessment

			cCR	Near cCR	Non-CR
Endoscopy	WL-C	Ulcer	Closed	Closed	Open
		Scar	Linear and flat (white)	Irregular surface (reddish)	Incompletely closed ulcer, residual erosion or white moss
		Protruded tumor nodule	No	No	Yes
		Wall extension	Normal	Decreased	Poor with submucosal tumor-like deformity
	ME	Vessel pattern	Regular circulated/lacy	Lack of uniformity	Calibre change/irregularity
		Surface pattern (Chromoendoscopy)	Uniformly arranged regeneration pits or hypercellular pits	Regenerated pits irregularly arranged	Residual neoplastic pit pattern
DRE			Normal	Smooth induration or minor mucosal abnormalities	Tumor nodules palpable
MRI	T2WI	Tumor bed	Normalized rectal wall or no residual intermediate signal in the tumor bed and fibrotic hypointense signal		Residual intermediate tumor signal (regardless of the percentage of fibrotic hypointense signal)
		Lymph node	Downsizing of involved lymph nodes to a short-axis diameter <5 mm		Partial or no regression of involved lymph nodes with a short-axis diameter ≥5 mm
	DWI (b800 or b1000 images)	Tumor bed	No high signal on high b-value images and no low ADC signal in the tumor bed		Presence of high signal on high b-value images and low ADC signal in the tumor bed

cCR clinical complete response, *near cCR* near clinical complete response, *Non-CR* non-complete response, *WL-C* White light conventional endoscopy, *ME* magnifying endoscopy, *NB*I narrow-band imaging, *DRE* digital rectal examination, *T2WI* T2-weighted images, *DWI* diffusion-weighted images, *ADC* apparent diffusion coefficient.

Table 2 Follow-up protocol for non-operative management

Time from final response assessment	Tumor marker[a]	DRE	MRI[b]	CT[c]	Endoscopy	Adverse events	PROM[d]
3 months[e]	x	x	x		Rectum	x	
6 months	x	x	x	x	Rectum	x	x
9 months	x	x	x		Rectum	x	
1 year	x	x	x	x	Total	x	x
1 year 3 months	x	x	x		Rectum	x	
1 year 6 months	x	x	x	x	Rectum	x	
1 year 9 months	x	x	x		Rectum	x	
2 years	x	x	x	x	Rectum	x	x
2 years 6 months	x	x	x	x	Rectum	x	
3 years	x	x	x	x	Total	x	x
3 years 6 months	x	x	x	x	Rectum	x	
4 years	x	x	x	x	Rectum	x	
4 years 6 months	x	x	x	x	Rectum	x	
5 years	x	x	x	x	Total	x	

[a]Tumor marker includes serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9.

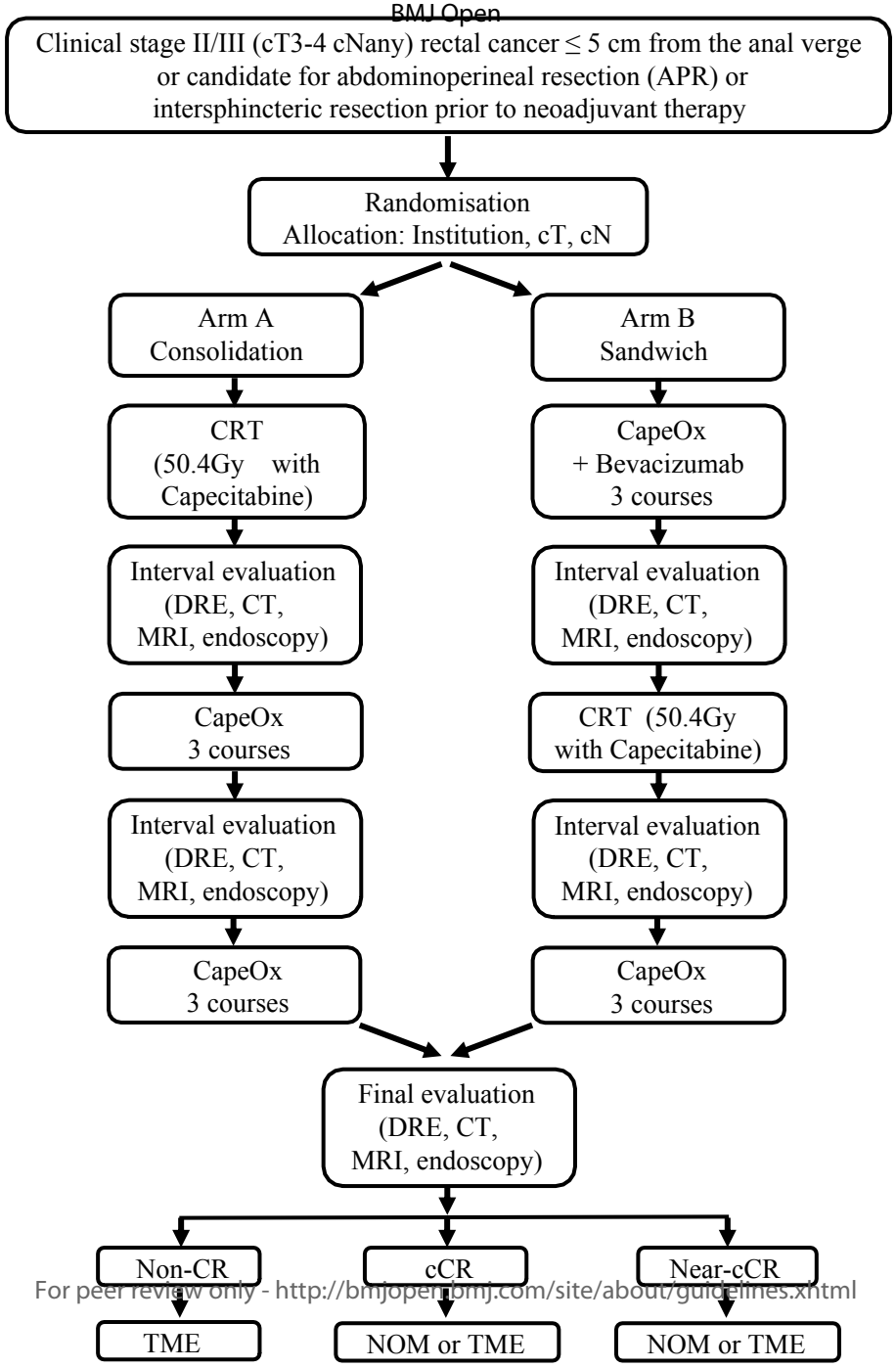
[b]MRI includes pelvic MRI

[c]CT includes chest/abdomen/pelvis CT

[d]PROM includes EORTC QLQ - C30 and CR29, Wexner score, and LARS-scale

[e]Near cCR patients will be followed every 6-8 weeks for the first 6 months

DRE digital rectal examination, *MRI* magnetic resonance imaging, *CT* computed tomography, *PROM* patient-reported outcome measure



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-7
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	13
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	11
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	3-4
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Study Protocol: Non-operative management after chemoradiotherapy plus consolidation or sandwich (induction with bevacizumab and consolidation) chemotherapy in patients with locally advanced rectal cancer: A multicentre, randomised phase II trial (NOMINATE trial)

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Protocol

Study Protocol: Non-operative management after chemoradiotherapy plus consolidation or sandwich (induction with bevacizumab and consolidation) chemotherapy in patients with locally advanced rectal cancer: A multicentre, randomised phase II trial (NOMINATE trial)

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ABSTRACT

Introduction: Total mesorectal excision (TME) and postoperative adjuvant chemotherapy following neoadjuvant chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer (LARC). However, neoadjuvant CRT has no recognized impact on reducing distant recurrence, and patients suffer from a long-lasting impairment in quality of life (QOL) associated with TME. Total neoadjuvant therapy (TNT) is an alternative approach that could reduce distant metastases and increase the proportion of patients who could safely undergo non-operative management (NOM). This study is designed to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with LARC.

Methods and analysis: NOMINATE trial is a prospective, multicentre, randomised phase II selection design study. Patients must have clinical stage II or III (T3-T4Nany) LARC with distal location (≤5 cm from the anal verge or for those who are candidates for abdominoperineal resection or intersphincteric resection). Patients will be randomised to either Arm A consisting of CRT (50.4 Gy with capecitabine) followed by consolidation chemotherapy (6 cycles of CapeOx), or Arm B consisting of induction chemotherapy (3 cycles of CapeOx plus bevacizumab) followed by CRT and consolidation chemotherapy (3 cycles of CapeOx). In the case of clinical complete response (cCR) or near cCR, patients will progress to NOM. Response assessment involves a combination of digital rectal examination, endoscopy, and MRI. The primary endpoint is the proportion of patients achieving pathological CR or cCR ≥ 2 years, defined as the absence of local regrowth within 2 years after the start of NOM among eligible patients. Secondary endpoints include the cCR rate, near cCR rate, rate of NOM, overall survival, distant metastasis-free survival, locoregional failure-free survival, time to disease-related treatment failure, TME-free survival, permanent stoma-free survival, safety of the treatment, completion rate of the treatment, and quality of

life. Allowing for a drop-out rate of 10%, 66 patients (33 per arm) from 5 institutions will be accrued.

Ethics and dissemination: The study protocol was approved by Wakayama Medical University Certified Review Board in December 2020. Trial results will be published in peer-reviewed international journals and on the jRCT website.

Trial registration number jRCTs051200121

Strength and limitations of this study

- ► This phase II study is the first study of total neoadjuvant therapy and non-operative management to compare the efficacy and safety of consolidation chemotherapy to sandwich chemotherapy using bevacizumab combined with capecitabine-based chemoradiotherapy for locally advanced rectal cancer.
- ► This study includes clinical T3-T4NanyM0, mismatch repair-proficient rectal cancer with distal location.
- ► The assessment of a clinical complete response and near clinical complete response will be performed based on pre-defined response criteria.
- ► Patients treated with non-operative management will undergo intensive monitoring as per the follow-up protocol.
- ► Confirmatory conclusions cannot be drawn from this randomised phase II study with relatively small sample size and a limited number of participating centres.

INTRODUCTION

The current standard treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (CRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy. This multimodality treatment has significantly reduced local recurrence rates to <10%. However, neoadjuvant CRT has failed to reduce distant recurrence or improve disease-free survival (DFS) and overall survival (OS). Despite the adoption of adjuvant postoperative chemotherapy, distant relapse occurs in about 30% of patients at 5 years.[1] The benefit of postoperative adjuvant chemotherapy following neoadjuvant CRT remains unclear, possibly due to poor compliance to chemotherapy, a longer interval between diagnosis and commencing chemotherapy, and the application of suboptimal regimens.[2] These limitations have led to the development of a total neoadjuvant therapy (TNT) approach, which delivers both radiotherapy and systemic chemotherapy preoperatively in an attempt to treat micrometastases earlier, increase adherence to systemic chemotherapy, and improve DFS. Two recent phase 3 randomised controlled trials investigating TNT (RAPIDO[3] and PRODIGE 23 trial[4]) showed better pathological complete response (pCR) rate and fewer distant metastases in the TNT arm as compared with the standard short-course radiotherapy or CRT arm.

Numerous studies have shown that patients with a pCR have more favourable long-term oncological outcomes in terms of distant and local control,[5] and this has raised the question as to whether TME can be avoided in patients with pCR. Because TME is associated with postoperative complications and late morbidity, such as bowel, sexual, and urinary dysfunction,[6,7] avoiding TME may provide an opportunity to reduce the morbidity and the need of a permanent stoma, and improve quality of life (QOL). In 2004, Habr-Gama et al. for the first time proposed a watch-and-wait (WW) approach or non-operative management

(NOM) for patients with a clinical complete response (cCR) after CRT.[8] Since then, many studies—mainly retrospective observational studies—have shown NOM to be a feasible option for patients with cCR after CRT.[9,10]

TNT has the potential to increase the proportion of patients achieving cCR and thus being eligible for NOM;[11] however, randomised trial data evaluating the efficacy of NOM in the context of TNT are lacking. OPRA was the first randomised phase II trial to address the efficacy of TNT and NOM for patients with cCR or near cCR, with the primary endpoint of 3-year DFS, as compared with standard historical controls managed with CRT and TME followed by adjuvant chemotherapy.[12] In the OPRA trial, 306 patients with LARC were randomised to receive 4 months of 5-Fluorouracil (5-FU), Leucovorin and Oxaliplatin (FOLFOX) or Capecitabine and Oxaliplatin (CapeOx) either before (induction chemotherapy) or after (consolidation chemotherapy) CRT, followed by NOM for patients with cCR or near cCR. Preliminary analyses demonstrated higher 3-year organ preservation rates in the consolidation arm over the induction arm (59% vs 43%).[13] Similarly, in the CAO/ARO/AIO-12 phase II trial, which randomly assigned patients to either induction or consolidation chemotherapy (3 cycles of FOLFOX) before or after oxaliplatin-based CRT followed by TME, demonstrated higher pCR rates in the consolidation arm as compared with the induction arm (25% vs 17%).[14] Given these results, CRT followed by consolidation chemotherapy may enable greater organ preservation, and should be preferentially considered.[15]

On the other hand, several studies have shown that the addition of anti-vascular endothelial growth factor (VEGF) drugs before radiotherapy can enhance the radiation response in LARC.[16,17] In the GEMCAD 1402 randomised phase II trial of induction chemotherapy with 3 months of mFOLFOX6 with or without aflibercept followed by CRT

and TME, patients in the aflibercept arm demonstrated a higher pCR rate than those without aflibercept (22.6% vs 13.8%).[18] In a single-arm phase II trial of 3 months of mFOLFOX6 plus bevacizumab prior to CRT, we reported a pCR rate of 37% with favourable toxicity in a series of 43 patients with poor-risk LARC.[19] Furthermore, a single-arm phase II study of sandwich-like neoadjuvant therapy consisting of one cycle of induction FOLFOX with bevacizumab, followed by CRT with three doses of bevacizumab, and one cycle of consolidation FOLFOX, also reported a high pCR rate (39.1%).[20] Given these results, we hypothesized that sandwich-like therapy of 3 cycles of induction chemotherapy with bevacizumab and 3 cycles of consolidation chemotherapy could provide the advantages of both induction (addressing micrometastatic disease earlier and enhanced CRT response by bevacizumab) and consolidation (greater pCR or NOM rate) therapy arms. We chose long-course CRT because there was limited data on the use of short-course radiotherapy in NOM.[21]

To this end, we designed this randomised phase II trial (NOMINATE trial) of TNT and NOM to compare the efficacy and safety of consolidation chemotherapy (6 cycles of CapeOx) to a sandwich chemotherapy regimen using bevacizumab (3 cycles of CapeOx plus bevacizumab as induction chemotherapy and 3 cycles of CapeOx as consolidation chemotherapy) combined with capecitabine-based CRT.

METHODS AND ANALYSIS

Study design

This is a prospective, multicentre, randomised phase II selection design study to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with

LARC. The study flowchart is shown in Figure 1.

Primary endpoint

The primary endpoint is the proportion of patients achieving pCR or cCR ≥ 2 years among eligible patients. pCR is defined as no residual tumor cells in the surgical specimen. cCR ≥ 2 years is defined as the absence of local regrowth within 2 years after the start of NOM.

Secondary endpoints

Secondary endpoints include cCR rate, near cCR rate, rate of NOM, OS, distant metastasis-free survival, locoregional failure-free survival, time to disease-related treatment failure, TME-free survival, permanent stoma-free survival, safety of the treatment, completion rate of the treatment, faecal incontinence according to Wexner score[22] and Low Anterior Resection Syndrome (LARS)-scale[23], and quality of life according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) - C30[24] and CR29[25]. Locoregional failure includes progressive unresectable disease, local R2 resection, and intrapelvic recurrence after TME. Local regrowth after NOM is not considered as locoregional failure when followed by an R0/R1 resection. Disease-related treatment failure is defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal cancer, or treatment-related death.[3] In patients managed by TME, surgical morbidity, R0 resection rate, pathological stage, Dworak tumour regression grade[26] will also be assessed. In patients managed by NOM, local regrowth rate, time to local regrowth, salvage surgery rate in patients with local regrowth, surgical morbidity in salvage surgery, and R0 resection rate in salvage surgery will also be assessed. The grade of adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE)

V.5.0.

Eligibility criteria

Inclusion criteria

1. Histologically confirmed diagnosis of adenocarcinoma of the rectum.

2. The lowest part of the tumor ≤5 cm from the anal verge or patient is a candidate for abdominoperineal resection or intersphincteric resection prior to neoadjuvant therapy according to the primary surgeon.

3. Patients must have clinical stage II (cT3-4N0) or stage III (cT3-4N1-3) by MRI and CT.

4. ECOG PS 0 or 1.

5. Age ≥ 20 years.

6. Adequate organ functions within 28 days prior to entry: neutrophils ≥ 1,500 /mm^3, platelets ≥ 10 × 10^4 /mm^3, haemoglobin ≥ 9.0 g/dL, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase ≤ 100 IU/L, alanine aminotransferase ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL or Ccr ≥ 60 mL/min/body, urine protein/creatinine < 1.

7. If there is bowel obstruction or significant stricture, stoma is constructed prior to neoadjuvant therapy.

8. Written informed consent is obtained.

Exclusion criteria

1. Patients with a history of a prior malignancy within the past 5 years, except for adequately treated cancer with 5-year relative survival rate ≥ 95%.

2. History of pelvic irradiation.

3. Administration contraindication of capecitabine, oxaliplatin, or bevacizumab.

4. Uncontrolled active infection.

5. Body temperature ≥ 38 ℃ at registration.

6. Possibly pregnant, pregnant, or nursing.

7. Patients with concurrent psychiatric condition or disease that would make them inappropriate candidates for entry into this study in the investigator's judgement.

8. Patients with concurrent serious comorbidity (heart failure, interstitial lung disease or pulmonary fibrosis, uncontrolled diabetes, renal failure, liver failure, hypertension, thrombotic disease, gastrointestinal fistula, among other similarly serious conditions).

9. History of operation ≤ 4 weeks ago or minor operation such as stoma construction ≤ 2 weeks ago.

10. Deficient in mismatch repair (dMMR), as determined by immunohistochemistry and/or microsatellite instability testing using pre-treatment biopsy specimens.

11. Other conditions not suitable for this study in the investigator's judgement.

Sample size calculation

This study uses a "pick the winner" format proposed by Simon et al.[27] The expected lowest response rate of pCR or cCR ≥ 2 years is set at 25%.[28] If the difference in response rate between the treatment arms is at least 10%, 30 patients per arm (total 60 patients) is necessary to select the better treatment with a probability of ≥80%. With consideration for dropouts of 10%, 33 patients per arm (total 66 patients) will be necessary. If there are no differences in response rate between treatment arms, a better treatment will be chosen in terms of secondary endpoints such as toxicity and safety of the treatment.

Registration and randomization

Patients are registered to the study after confirming the eligibility criteria and written informed consent is obtained. Patients are requested to fill out EORTC QLQ-C30, CR29, and a questionnaire about faecal incontinence (Wexner score and LARS scale) at registration. After registration, patients are randomly assigned at a 1:1 ratio to the consolidation arm (arm A) or sandwich arm (arm B) using a minimization method stratified by institution, cT (cT3 vs cT4), and cN (cN- vs cN+). Registration, randomization, and collection of patient information will be performed using the Viedoc electronic data capture (EDC) system. Data are anonymized using a unique patient identification number.

Treatment

Arm A consists of CRT (50.4 Gy in 28 fractions and capecitabine 825mg/m^2 bid, day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38) followed by consolidation chemotherapy (6 cycles of CapeOx: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day 1, Q3w). Consolidation chemotherapy should start at 3-8 weeks after the last day of radiotherapy. Arm B consists of induction chemotherapy (3 cycles of CapeOx plus bevacizumab: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day1, bevacizumab 7.5 mg/kg, day 1, Q3w) followed by CRT (same as in Arm A) followed by consolidation chemotherapy (3 cycles of CapeOx). CRT should start at 3-6 weeks after the last day of induction chemotherapy, and consolidation chemotherapy should start at 3-8 weeks after the last day of radiotherapy.

Response assessment

Interval evaluation will be performed twice: after the completion of CRT and after the completion of 3 cycles of consolidation chemotherapy in Arm A, and after the completion of

induction chemotherapy and after the completion of CRT in Arm B. Final response assessment will be performed at 4 (- 1/+ 4) weeks after the completion of all neoadjuvant treatments. In the case of cCR or near cCR, patients will progress to NOM, but TME is also permitted if patients hope to undergo radical surgery. In the case of non-CR, patients will progress to TME. Criteria for response assessment are shown in Table 1.[12,29-32] Final response assessment involves a combination of digital rectal examination, endoscopy, and MRI, and will be discussed at online multidisciplinary-team meetings attended by the principal investigator (PI) and the local investigators.

Table 1 Criteria for response assessment

			cCR	**Near cCR**	**Non-CR**
Endoscopy	WL-C	Ulcer	Closed	Closed	Open
		Scar	Linear and flat (white)	Irregular surface (reddish)	Incompletely closed ulcer, residual erosion or white moss
		Protruded tumor nodule	No	No	Yes
		Wall extension	Normal	Decreased	Poor with submucosal tumor-like deformity
	ME	Vessel pattern (NBI)	Regular circulated/lacy	Lack of uniformity	Calibre change/irregularity
		Surface pattern (Chromoendoscopy)	Uniformly arranged regeneration pits	Regenerated pits irregularly arranged	Residual neoplastic pit pattern
DRE			Normal	Smooth induration or minor mucosal abnormalities	Tumor nodules palpable
MRI	T2WI	Tumor bed	Normalized rectal wall or no residual intermediate signal in the tumor bed and fibrotic hypointense signal		Residual intermediate tumor signal (regardless of the percentage of fibrotic hypointense signal)
		Lymph node	Downsizing of involved lymph nodes to a short-axis diameter <5 mm		Partial or no regression of involved lymph nodes with a short-axis diameter ≥5 mm

DWI (b800 or b1000 images)	Tumor bed	No high signal on high b-value images and no low ADC signal in the tumor bed	Presence of high signal on high b-value images and low ADC signal in the tumor bed

cCR clinical complete response, *near cCR* near clinical complete response, *Non-CR* non-complete response, *WL-C* White light conventional endoscopy, *ME* magnifying endoscopy, *NB*I narrow-band imaging, *DRE* digital rectal examination, *T2WI* T2-weighted images, *DWI* diffusion-weighted images, *ADC* apparent diffusion coefficient.

Follow-up

Patients treated with TME will be followed with measurements of serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9 and will be subjected to chest/abdomen/pelvis CT scan every 6 months for 5 years. Patients treated with NOM will be followed every 3 months for the first 2 years and every 6 months thereafter, as shown in Table 2. In the case of near cCR, patients will be followed every 6-8 weeks for the first 6 months. Salvage TME will be recommended for patients with local regrowth after NOM; if the patient refuses TME, local resection will also be acceptable. If a patient refuses surgical resection of local regrowth, it is considered as locoregional failure.

Table 2 Follow-up protocol for non-operative management

Time from final response	**Tumor marker**	**DRE**	**MRI**[b]	**CT**[c]	**Endoscopy**	**Adverse events**	**PROM**[d]
3 months[e]	x	x	x		Rectum	x	
6 months	x	x	x	x	Rectum	x	x
9 months	x	x	x		Rectum	x	
1 year	x	x	x	x	Total	x	x
1 year 3 months	x	x	x		Rectum	x	
1 year 6 months	x	x	x	x	Rectum	x	
1 year 9 months	x	x	x		Rectum	x	
2 years	x	x	x	x	Rectum	x	x
2 years 6 months	x	x	x	x	Rectum	x	
3 years	x	x	x	x	Total	x	x
3 years 6 months	x	x	x	x	Rectum	x	
4 years	x	x	x	x	Rectum	x	
4 years 6 months	x	x	x	x	Rectum	x	
5 years	x	x	x	x	Total	x	

[a]Tumor marker includes serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9.
[b]MRI includes pelvic MRI
[c]CT includes chest/abdomen/pelvis CT
[d]PROM includes EORTC QLQ - C30 and CR29, Wexner score, and LARS-scale
[e]Near cCR patients will be followed every 6-8 weeks for the first 6 months
DRE digital rectal examination, *MRI* magnetic resonance imaging, *CT* computed tomography, *PROM* patient-reported outcome measure

Statistical analysis plan

The primary analysis will be conducted when 3 years have passed since patient accrual completion. All analyses are based on descriptive data without testing because of the study design. The proportions at the primary endpoint will be estimated using an Clopper-Pearson method for binomial response. The proportions among registered patients or patients who complete the protocol treatment will also be calculated as a reference. An analysis of secondary endpoints will also be performed to complement the results at the primary endpoint, but adjustment of multiplicity will not be performed due to their exploratory nature. Kaplan–Meier method will be used to estimate OS, with 95%CIs calculated by Greenwood's formula. Univariate Cox regression will be used to estimate HRs with 95%CIs associated with treatment arms. For endpoints with competing risk, such as distant metastasis-free survival, locoregional failure-free survival and an estimation of HRs will be performed using Fine and Grey models. The final analysis will be conducted when 6 years have passed since patient accrual completion.

Interim analysis and monitoring

Interim analysis is planned for possible early trial termination to claim futility. In Simon's optimal two-stage design,[33] when the null hypothesis is a pCR or cCR/near cCR rate of 15% versus the alternative of 30% for each arm, and power and one-sided alpha are set at 80% and

5%, respectively, 19 subjects will be accrued in the first stage. If there are 3 or fewer responders within these 19 subjects, enrolment in that arm will be stopped. If the number of treatment-related deaths reach two for each arm, the registration will be suspended until Data and Safety Monitoring approve the continuation of the trial. The Data Centre (Clinical Research and Medical Development Centre, Cancer Institute Hospital, Japanese Foundation for Cancer Research) will perform central monitoring every 6 months and monitoring reports will be submitted to the Data and Safety Monitoring Committee.

Translational research

Accompanying translational research about the molecular determinants of response to TNT and molecular predictors of successful organ preservation is planned. The specific study protocol for correlative translational research to the NOMINATE trial has been approved by the intuitional review boards of all participating institutions. Tumour tissue and plasma will be collected and stored at different time points after obtaining written informed consent from patients. Next-generation sequencing, such as exome sequencing, RNA sequencing, and circulating tumour DNA analysis, will be performed.

Ethics and dissemination

Wakayama Medical University Certified Review Board approved this study protocol in December 2020. The first patient was enrolled in March 2021, and the estimated study completion date is November 2030. This trial will be performed in accordance with the Declaration of Helsinki and Clinical Trials Act in Japan. Trial results of the primary and secondary endpoints will be published in peer-reviewed international journals and on the jRCT website (https://jrct.niph.go.jp/), as well as at international and national conferences.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Contributors TA, ES, ST and TK developed the trial concept, wrote the protocol, and drafted the manuscript. NI designed the statistical analyses for the study. AC, MH, TT, TN, ST, SM, SM, KO, TM, YH, TY, TN, KY, MU, HK and YF have made substantial contributions to the conception and design of the work and subsequent protocol revisions. All authors read and approved the final manuscript.

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Competing interests KY reports honoraria from Chugai Co., Ltd.

Patient consent for publication Not required.

Ethics approval Wakayama Medical University Certified Review Board (CRB5180004).

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Figure Legends

Figure 1 Study flowchart

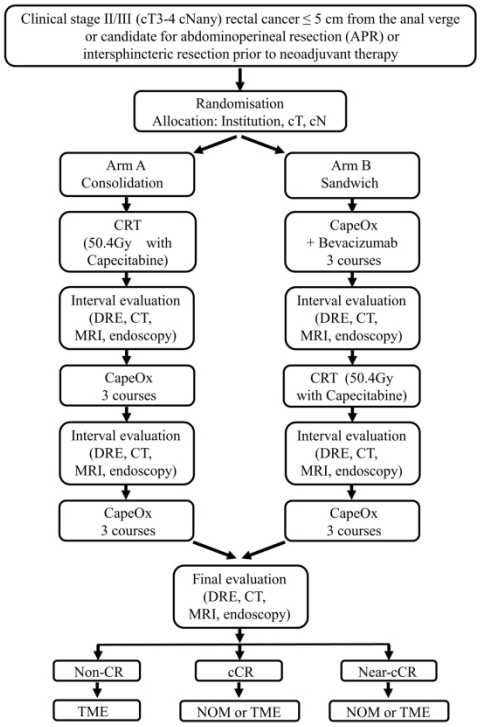

Figure 1

254x190mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NS in this paper (stated in registration)
Protocol version	3	Date and version identifier	NS in this paper (stated in protocol)
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	No sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No sponsor and funders

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NS in this paper (stated in protocol)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NS in this paper (stated in protocol)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NS in this paper (stated in protocol)

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NS in this paper (stated in protocol)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NS
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	NS in this paper (stated in protocol)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NS in this paper (stated in protocol)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	NS in this paper (stated in protocol)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14-15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NS in this paper (stated in protocol)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	No auditing

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NS in this paper (stated in protocol)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NS in this paper (stated in protocol)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NS in this paper (stated in protocol)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NS in this paper (stated in protocol)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No plan

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary information
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Study Protocol: Non-operative management after chemoradiotherapy plus consolidation or sandwich (induction with bevacizumab and consolidation) chemotherapy in patients with locally advanced rectal cancer: A multicentre, randomised phase II trial (NOMINATE trial)

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	Planning and Management Konishi, Tsuyoshi; The University of Texas MD Anderson Cancer Center, Department of Colon and Rectal Surgery
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery
Keywords:	CHEMOTHERAPY, RADIOTHERAPY, Colorectal surgery < SURGERY

Protocol

Study Protocol: Non-operative management after chemoradiotherapy plus consolidation or sandwich (induction with bevacizumab and consolidation) chemotherapy in patients with locally advanced rectal cancer: A multicentre, randomised phase II trial (NOMINATE trial)

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ABSTRACT

Introduction: Total mesorectal excision (TME) and postoperative adjuvant chemotherapy following neoadjuvant chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer (LARC). However, neoadjuvant CRT has no recognized impact on reducing distant recurrence, and patients suffer from a long-lasting impairment in quality of life (QOL) associated with TME. Total neoadjuvant therapy (TNT) is an alternative approach that could reduce distant metastases and increase the proportion of patients who could safely undergo non-operative management (NOM). This study is designed to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with LARC.

Methods and analysis: NOMINATE trial is a prospective, multicentre, randomised phase II selection design study. Patients must have clinical stage II or III (T3-T4Nany) LARC with distal location (≤5 cm from the anal verge or for those who are candidates for abdominoperineal resection or intersphincteric resection). Patients will be randomised to either Arm A consisting of CRT (50.4 Gy with capecitabine) followed by consolidation chemotherapy (6 cycles of CapeOx), or Arm B consisting of induction chemotherapy (3 cycles of CapeOx plus bevacizumab) followed by CRT and consolidation chemotherapy (3 cycles of CapeOx). In the case of clinical complete response (cCR) or near cCR, patients will progress to NOM. Response assessment involves a combination of digital rectal examination, endoscopy, and MRI. The primary endpoint is the proportion of patients achieving pathological CR or cCR ≥ 2 years, defined as the absence of local regrowth within 2 years after the start of NOM among eligible patients. Secondary endpoints include the cCR rate, near cCR rate, rate of NOM, overall survival, distant metastasis-free survival, locoregional failure-free survival, time to disease-related treatment failure, TME-free survival, permanent stoma-free survival, safety of the treatment, completion rate of the treatment, and quality of

life. Allowing for a drop-out rate of 10%, 66 patients (33 per arm) from 5 institutions will be accrued.

Ethics and dissemination: The study protocol was approved by Wakayama Medical University Certified Review Board in December 2020. Trial results will be published in peer-reviewed international journals and on the jRCT website.

Trial registration number jRCTs051200121

Strength and limitations of this study

- ► This phase II study is the first study of total neoadjuvant therapy and non-operative management to compare the efficacy and safety of consolidation chemotherapy to sandwich chemotherapy using bevacizumab combined with capecitabine-based chemoradiotherapy for locally advanced rectal cancer.
- ► This study includes clinical T3-T4NanyM0, mismatch repair-proficient rectal cancer with distal location.
- ► The assessment of a clinical complete response and near clinical complete response will be performed based on pre-defined response criteria.
- ► Patients treated with non-operative management will undergo intensive monitoring as per the follow-up protocol.
- ► Confirmatory conclusions cannot be drawn from this randomised phase II study with relatively small sample size and a limited number of participating centres.

INTRODUCTION

The current standard treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (CRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy. This multimodality treatment has significantly reduced local recurrence rates to <10%. However, neoadjuvant CRT has failed to reduce distant recurrence or improve disease-free survival (DFS) and overall survival (OS). Despite the adoption of adjuvant postoperative chemotherapy, distant relapse occurs in about 30% of patients at 5 years.[1] The benefit of postoperative adjuvant chemotherapy following neoadjuvant CRT remains unclear, possibly due to poor compliance to chemotherapy, a longer interval between diagnosis and commencing chemotherapy, and the application of suboptimal regimens.[2] These limitations have led to the development of a total neoadjuvant therapy (TNT) approach, which delivers both radiotherapy and systemic chemotherapy preoperatively in an attempt to treat micrometastases earlier, increase adherence to systemic chemotherapy, and improve DFS. Two recent phase 3 randomised controlled trials investigating TNT (RAPIDO[3] and PRODIGE 23 trial[4]) showed better pathological complete response (pCR) rate and fewer distant metastases in the TNT arm as compared with the standard short-course radiotherapy or CRT arm.

Numerous studies have shown that patients with a pCR have more favourable long-term oncological outcomes in terms of distant and local control,[5] and this has raised the question as to whether TME can be avoided in patients with pCR. Because TME is associated with postoperative complications and late morbidity, such as bowel, sexual, and urinary dysfunction,[6,7] avoiding TME may provide an opportunity to reduce the morbidity and the need of a permanent stoma, and improve quality of life (QOL). In 2004, Habr-Gama et al. for the first time proposed a watch-and-wait (WW) approach or non-operative management

(NOM) for patients with a clinical complete response (cCR) after CRT.[8] Since then, many studies—mainly retrospective observational studies—have shown NOM to be a feasible option for patients with cCR after CRT.[9,10]

TNT has the potential to increase the proportion of patients achieving cCR and thus being eligible for NOM;[11] however, randomised trial data evaluating the efficacy of NOM in the context of TNT are lacking. OPRA was the first randomised phase II trial to address the efficacy of TNT and NOM for patients with cCR or near cCR, with the primary endpoint of 3-year DFS, as compared with standard historical controls managed with CRT and TME followed by adjuvant chemotherapy.[12] In the OPRA trial, 306 patients with LARC were randomised to receive 4 months of 5-Fluorouracil (5-FU), Leucovorin and Oxaliplatin (FOLFOX) or Capecitabine and Oxaliplatin (CapeOx) either before (induction chemotherapy) or after (consolidation chemotherapy) CRT, followed by NOM for patients with cCR or near cCR. Preliminary analyses demonstrated higher 3-year organ preservation rates in the consolidation arm over the induction arm (59% vs 43%).[13] Similarly, in the CAO/ARO/AIO-12 phase II trial, which randomly assigned patients to either induction or consolidation chemotherapy (3 cycles of FOLFOX) before or after oxaliplatin-based CRT followed by TME, demonstrated higher pCR rates in the consolidation arm as compared with the induction arm (25% vs 17%).[14] Given these results, CRT followed by consolidation chemotherapy may enable greater organ preservation, and should be preferentially considered.[15]

On the other hand, several studies have shown that the addition of anti-vascular endothelial growth factor (VEGF) drugs before radiotherapy can enhance the radiation response in LARC.[16,17] In the GEMCAD 1402 randomised phase II trial of induction chemotherapy with 3 months of mFOLFOX6 with or without aflibercept followed by CRT

and TME, patients in the aflibercept arm demonstrated a higher pCR rate than those without aflibercept (22.6% vs 13.8%).[18] In a single-arm phase II trial of 3 months of mFOLFOX6 plus bevacizumab prior to CRT, we reported a pCR rate of 37% with favourable toxicity in a series of 43 patients with poor-risk LARC.[19] Furthermore, a single-arm phase II study of sandwich-like neoadjuvant therapy consisting of one cycle of induction FOLFOX with bevacizumab, followed by CRT with three doses of bevacizumab, and one cycle of consolidation FOLFOX, also reported a high pCR rate (39.1%).[20] Given these results, we hypothesized that sandwich-like therapy of 3 cycles of induction chemotherapy with bevacizumab and 3 cycles of consolidation chemotherapy could provide the advantages of both induction (addressing micrometastatic disease earlier and enhanced CRT response by bevacizumab) and consolidation (greater pCR or NOM rate) therapy arms. We chose long-course CRT because there was limited data on the use of short-course radiotherapy in NOM.[21]

To this end, we designed this randomised phase II trial (NOMINATE trial) of TNT and NOM to compare the efficacy and safety of consolidation chemotherapy (6 cycles of CapeOx) to a sandwich chemotherapy regimen using bevacizumab (3 cycles of CapeOx plus bevacizumab as induction chemotherapy and 3 cycles of CapeOx as consolidation chemotherapy) combined with capecitabine-based CRT.

METHODS AND ANALYSIS

Study design

This is a prospective, multicentre, randomised phase II selection design study to compare two TNT regimens in the context of NOM for selecting a more optimal regimen for patients with

LARC. The study flowchart is shown in Figure 1.

Primary endpoint

The primary endpoint is the proportion of patients achieving pCR or cCR ≥ 2 years among eligible patients. pCR is defined as no residual tumor cells in the surgical specimen. cCR ≥ 2 years is defined as the absence of local regrowth within 2 years after the start of NOM.

Secondary endpoints

Secondary endpoints include cCR rate, near cCR rate, rate of NOM, OS, distant metastasis-free survival, locoregional failure-free survival, time to disease-related treatment failure, TME-free survival, permanent stoma-free survival, safety of the treatment, completion rate of the treatment, faecal incontinence according to Wexner score[22] and Low Anterior Resection Syndrome (LARS)-scale[23], and quality of life according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) - C30[24] and CR29[25]. Locoregional failure includes progressive unresectable disease, local R2 resection, and intrapelvic recurrence after TME. Local regrowth after NOM is not considered as locoregional failure when followed by an R0/R1 resection. Disease-related treatment failure is defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal cancer, or treatment-related death.[3] In patients managed by TME, surgical morbidity, R0 resection rate, pathological stage, Dworak tumour regression grade[26] will also be assessed. In patients managed by NOM, local regrowth rate, time to local regrowth, salvage surgery rate in patients with local regrowth, surgical morbidity in salvage surgery, and R0 resection rate in salvage surgery will also be assessed. The grade of adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE)

V.5.0.

Eligibility criteria

Inclusion criteria

1. Histologically confirmed diagnosis of adenocarcinoma of the rectum.

2. The lowest part of the tumor ≤5 cm from the anal verge or patient is a candidate for abdominoperineal resection or intersphincteric resection prior to neoadjuvant therapy according to the primary surgeon.

3. Patients must have clinical stage II (cT3-4N0) or stage III (cT3-4N1-3) by MRI and CT.

4. ECOG PS 0 or 1.

5. Age ≥ 20 years.

6. Adequate organ functions within 28 days prior to entry: neutrophils ≥ 1,500 /mm^3, platelets ≥ 10 × 10^4 /mm^3, haemoglobin ≥ 9.0 g/dL, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase ≤ 100 IU/L, alanine aminotransferase ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL or Ccr ≥ 60 mL/min/body, urine protein/creatinine < 1.

7. If there is bowel obstruction or significant stricture, stoma is constructed prior to neoadjuvant therapy.

8. Written informed consent is obtained.

Exclusion criteria

1. Patients with a history of a prior malignancy within the past 5 years, except for adequately treated cancer with 5-year relative survival rate ≥ 95%.

2. History of pelvic irradiation.

3. Administration contraindication of capecitabine, oxaliplatin, or bevacizumab.

4. Uncontrolled active infection.

5. Body temperature ≥ 38 ℃ at registration.

6. Possibly pregnant, pregnant, or nursing.

7. Patients with concurrent psychiatric condition or disease that would make them inappropriate candidates for entry into this study in the investigator's judgement.

8. Patients with concurrent serious comorbidity (heart failure, interstitial lung disease or pulmonary fibrosis, uncontrolled diabetes, renal failure, liver failure, hypertension, thrombotic disease, gastrointestinal fistula, among other similarly serious conditions).

9. History of operation ≤ 4 weeks ago or minor operation such as stoma construction ≤ 2 weeks ago.

10. Deficient in mismatch repair (dMMR), as determined by immunohistochemistry and/or microsatellite instability testing using pre-treatment biopsy specimens.

11. Other conditions not suitable for this study in the investigator's judgement.

Sample size calculation

This study uses a "pick the winner" format proposed by Simon et al.[27] The expected lowest response rate of pCR or cCR ≥ 2 years is set at 25%.[28] If the difference in response rate between the treatment arms is at least 10%, 30 patients per arm (total 60 patients) is necessary to select the better treatment with a probability of ≥80%. With consideration for dropouts of 10%, 33 patients per arm (total 66 patients) will be necessary. If there are no differences in response rate between treatment arms, a better treatment will be chosen in terms of secondary endpoints such as toxicity and safety of the treatment.

Registration and randomization

Patients are registered to the study after confirming the eligibility criteria and written informed consent is obtained. Patients are requested to fill out EORTC QLQ-C30, CR29, and a questionnaire about faecal incontinence (Wexner score and LARS scale) at registration. After registration, patients are randomly assigned at a 1:1 ratio to the consolidation arm (arm A) or sandwich arm (arm B) using a minimization method stratified by institution, cT (cT3 vs cT4), and cN (cN- vs cN+). Registration, randomization, and collection of patient information will be performed using the Viedoc electronic data capture (EDC) system. Data are anonymized using a unique patient identification number.

Treatment

Arm A consists of CRT (50.4 Gy in 28 fractions and capecitabine 825mg/m^2 bid, day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38) followed by consolidation chemotherapy (6 cycles of CapeOx: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day 1, Q3w). Consolidation chemotherapy should start at 3-8 weeks after the last day of radiotherapy. Arm B consists of induction chemotherapy (3 cycles of CapeOx plus bevacizumab: capecitabine 2000 mg/m^2/day, days 1-14, oxaliplatin 130 mg/m^2, day1, bevacizumab 7.5 mg/kg, day 1, Q3w) followed by CRT (same as in Arm A) followed by consolidation chemotherapy (3 cycles of CapeOx). CRT should start at 3-6 weeks after the last day of induction chemotherapy, and consolidation chemotherapy should start at 3-8 weeks after the last day of radiotherapy.

Response assessment

Interval evaluation will be performed twice: after the completion of CRT and after the completion of 3 cycles of consolidation chemotherapy in Arm A, and after the completion of

induction chemotherapy and after the completion of CRT in Arm B. Final response assessment will be performed at 4 (- 1/+ 4) weeks after the completion of all neoadjuvant treatments. In the case of cCR or near cCR, patients will progress to NOM, but TME is also permitted if patients hope to undergo radical surgery. In the case of non-CR, patients will progress to TME. Criteria for response assessment are shown in Table 1.[12,29-32] Final response assessment involves a combination of digital rectal examination, endoscopy, and MRI, and will be discussed at online multidisciplinary-team meetings attended by the principal investigator (PI) and the local investigators.

Table 1 Criteria for response assessment

			cCR	**Near cCR**	**Non-CR**
Endoscopy	WL-C	Ulcer	Closed	Closed	Open
		Scar	Linear and flat (white)	Irregular surface (reddish)	Incompletely closed ulcer, residual erosion or white moss
		Protruded tumor nodule	No	No	Yes
		Wall extension	Normal	Decreased	Poor with submucosal tumor-like deformity
	ME	Vessel pattern (NBI)	Regular circulated/lacy	Lack of uniformity	Calibre change/irregularity
		Surface pattern (Chromoendoscopy)	Uniformly arranged regeneration pits	Regenerated pits irregularly arranged	Residual neoplastic pit pattern
DRE			Normal	Smooth induration or minor mucosal abnormalities	Tumor nodules palpable
MRI	T2WI	Tumor bed	Normalized rectal wall or no residual intermediate signal in the tumor bed and fibrotic hypointense signal		Residual intermediate tumor signal (regardless of the percentage of fibrotic hypointense signal)
		Lymph node	Downsizing of involved lymph nodes to a short-axis diameter <5 mm		Partial or no regression of involved lymph nodes with a short-axis diameter ≥5 mm

DWI (b800 or b1000 images)	Tumor bed	No high signal on high b-value images and no low ADC signal in the tumor bed	Presence of high signal on high b-value images and low ADC signal in the tumor bed

cCR clinical complete response, *near cCR* near clinical complete response, *Non-CR* non-complete response, *WL-C* White light conventional endoscopy, *ME* magnifying endoscopy, *NB*I narrow-band imaging, *DRE* digital rectal examination, *T2WI* T2-weighted images, *DWI* diffusion-weighted images, *ADC* apparent diffusion coefficient.

Follow-up

Patients treated with TME will be followed with measurements of serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9 and will be subjected to chest/abdomen/pelvis CT scan every 6 months for 5 years. Patients treated with NOM will be followed every 3 months for the first 2 years and every 6 months thereafter, as shown in Table 2. In the case of near cCR, patients will be followed every 6-8 weeks for the first 6 months. Salvage TME will be recommended for patients with local regrowth after NOM; if the patient refuses TME, local resection will also be acceptable. If a patient refuses surgical resection of local regrowth, it is considered as locoregional failure.

Table 2 Follow-up protocol for non-operative management

Time from final response	**Tumor marker**	**DRE**	**MRI**[b]	**CT**[c]	**Endoscopy**	**Adverse events**	**PROM**[d]
3 months[e]	x	x	x		Rectum	x	
6 months	x	x	x	x	Rectum	x	x
9 months	x	x	x		Rectum	x	
1 year	x	x	x	x	Total	x	x
1 year 3 months	x	x	x		Rectum	x	
1 year 6 months	x	x	x	x	Rectum	x	
1 year 9 months	x	x	x		Rectum	x	
2 years	x	x	x	x	Rectum	x	x
2 years 6 months	x	x	x	x	Rectum	x	
3 years	x	x	x	x	Total	x	x
3 years 6 months	x	x	x	x	Rectum	x	
4 years	x	x	x	x	Rectum	x	
4 years 6 months	x	x	x	x	Rectum	x	
5 years	x	x	x	x	Total	x	

[a]Tumor marker includes serum carcinoembryonic antigen (CEA) and carbohydrate (CA) 19-9.
[b]MRI includes pelvic MRI
[c]CT includes chest/abdomen/pelvis CT
[d]PROM includes EORTC QLQ - C30 and CR29, Wexner score, and LARS-scale
[e]Near cCR patients will be followed every 6-8 weeks for the first 6 months
DRE digital rectal examination, *MRI* magnetic resonance imaging, *CT* computed tomography, *PROM* patient-reported outcome measure

Statistical analysis plan

The primary analysis will be conducted when 3 years have passed since patient accrual completion. All analyses are based on descriptive data without testing because of the study design. The proportions at the primary endpoint will be estimated using an Clopper-Pearson method for binomial response. The proportions among registered patients or patients who complete the protocol treatment will also be calculated as a reference. An analysis of secondary endpoints will also be performed to complement the results at the primary endpoint, but adjustment of multiplicity will not be performed due to their exploratory nature. Kaplan–Meier method will be used to estimate OS, with 95%CIs calculated by Greenwood's formula. Univariate Cox regression will be used to estimate HRs with 95%CIs associated with treatment arms. For endpoints with competing risk, such as distant metastasis-free survival, locoregional failure-free survival and an estimation of HRs will be performed using Fine and Grey models. The final analysis will be conducted when 6 years have passed since patient accrual completion.

Interim analysis and monitoring

Interim analysis is planned for possible early trial termination to claim futility. In Simon's optimal two-stage design,[33] when the null hypothesis is a pCR or cCR/near cCR rate of 15% versus the alternative of 30% for each arm, and power and one-sided alpha are set at 80% and

5%, respectively, 19 subjects will be accrued in the first stage. If there are 3 or fewer responders within these 19 subjects, enrolment in that arm will be stopped. If the number of treatment-related deaths reach two for each arm, the registration will be suspended until Data and Safety Monitoring approve the continuation of the trial. The Data Centre (Clinical Research and Medical Development Centre, Cancer Institute Hospital, Japanese Foundation for Cancer Research) will perform central monitoring every 6 months and monitoring reports will be submitted to the Data and Safety Monitoring Committee.

Translational research

Accompanying translational research about the molecular determinants of response to TNT and molecular predictors of successful organ preservation is planned. The specific study protocol for correlative translational research to the NOMINATE trial has been approved by the intuitional review boards of all participating institutions. Tumour tissue and plasma will be collected and stored at different time points after obtaining written informed consent from patients. Next-generation sequencing, such as exome sequencing, RNA sequencing, and circulating tumour DNA analysis, will be performed.

Ethics and dissemination

Wakayama Medical University Certified Review Board approved this study protocol in December 2020. The first patient was enrolled in March 2021, and the estimated study completion date is November 2030. This trial will be performed in accordance with the Declaration of Helsinki and Clinical Trials Act in Japan. Trial results of the primary and secondary endpoints will be published in peer-reviewed international journals and on the jRCT website (https://jrct.niph.go.jp/), as well as at international and national conferences.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Contributors TA, ES, ST and TK developed the trial concept, wrote the protocol, and drafted the manuscript. NI designed the statistical analyses for the study. AC, MH, TT, TN, ST, SM, SM, KO, TM, YH, TY, TN, KY, MU, HK and YF have made substantial contributions to the conception and design of the work and subsequent protocol revisions. TA submitted the study.

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Competing interests KY reports honoraria from Chugai Co., Ltd.

Patient consent for publication Not required.

Ethics approval Wakayama Medical University Certified Review Board (CRB5180004).

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Figure Legends

Figure 1 Study flowchart

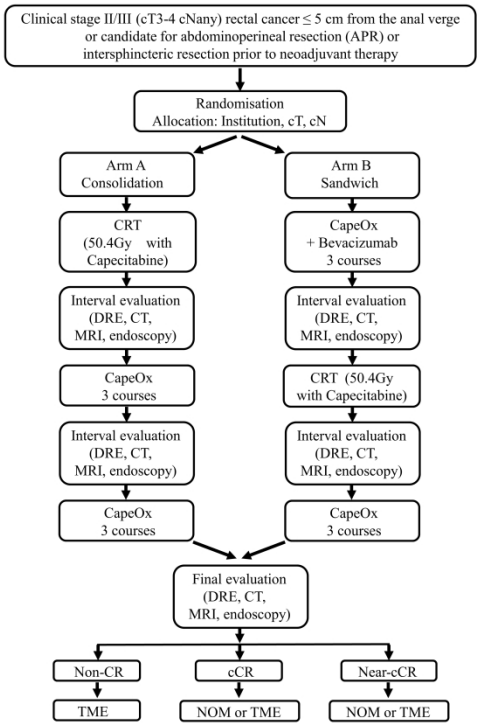

Figure 1

254x190mm (600 x 600 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NS in this paper (stated in registration)
Protocol version	3	Date and version identifier	NS in this paper (stated in protocol)
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	No sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No sponsor and funders

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NS in this paper (stated in protocol)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NS in this paper (stated in protocol)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NS in this paper (stated in protocol)

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NS in this paper (stated in protocol)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NS
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	NS in this paper (stated in protocol)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NS in this paper (stated in protocol)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	NS in this paper (stated in protocol)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14-15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NS in this paper (stated in protocol)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	No auditing

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NS in this paper (stated in protocol)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NS in this paper (stated in protocol)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NS in this paper (stated in protocol)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NS in this paper (stated in protocol)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No plan

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary information
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.