PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Akiyoshi, Takashi; Shinozaki, Eiji; Taguchi, Senzo; Chino, Akiko; Hiratsuka, Makiko; Tominaga, Tetsuro; Nonaka, Takashi; Toda, Shigeo; Matoba, Shuichiro; Matsui, Shimpei; Okabayashi, Koji; Mukai, Toshiki; Hiyoshi, Yukiharu; Yamaguchi, Tomohiro; Nagasaki, Toshiya; Yamaguchi, Kensei; Ueno, Masashi; Kuroyanagi, Hiroya; Fukunaga, Yosuke; Ishizuka, Naoki; Konishi, Tsuyoshi

VERSION 1 – REVIEW

REVIEWER	Frizelle, Frank University of Otago, Department of Surgery
REVIEW RETURNED	18-Aug-2021

GENERAL COMMENTS	Thnak you for undertaking an relvant and intresting study can I make the following suggestions 1. Please put in trial registration number 2. abstract line Methods and analysis (line 12) . remove words "..prior to neoadjuvant therapy". If this is adds nothing and is confusing as patient swill have surgery (if they do) after LCCRT a=/- induction chemo , which some may consider neoadj, so just drop it out. 3. Sample size calculation page 10, reference of Simon et al . It is stated as ref 22 iin text, however , in refences it is 29 . It looks like it should be 22 and the reference in references needs to be changed. also it is not Simon et al , it is just Simon, not et al. (he is the single author of that paper) 4. I think your number needed to treat is to small despite the reference , while I recognise this is a phase two study, and has a control arm, I suspect when you look at other similar studies and other ways to assess numbers needed to treat you might consider increasing the numbers. This is particularly so with your main outcome measures being effectiveness based . 5. Definition of complete clinical response . Most trails looking at CRC are using MRI for follow yup ,looking at the mesorectum, CT for metastatic disease and endoscopy for intraluminal assessment of recurrence - perhaps you are doing that but its not that clear to me that you are. please calcify 6 It might also help in the discussion or introduction to insert why you chose LCCRT as opposed to short course. Looking at clinical

	trials com, I see an increasing number of Short Couse and as you know the RAPIDO is short course

REVIEWER	Price, Timothy The University of Adelaide, Department of Medical Oncology
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	Review undertaken primarily by Dr Annabel Smith 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 2 trial (NOMINATE) Abstract The abstract is missing some salient information. Recommend adding secondary outcomes to abstract (rate of NOM, OS, distant metastasis free survival, locoregional failure free survival) as these will be of interest to the reader when scanning abstract. The abstract should also include detail of the response assessment for cCR given that this is the primary endpoint ie; DRE, endoscopy and MRI. The use of the word “courses” for chemotherapy in line 38,41,43 in abstract and later in protocol is unusual, consider changing to cycles. Introduction: Line 19, distant relapse rate 30% requires reference Line 21, not technically correct, there has been one study showing survival benefit of adjuvant oxaliplatin based chemotherapy following CRT (ADORE) trial. Line 51-55, reads poorly, repeated use of TME, consider removing “after TME” in line 55, as this is implied by ‘post operatively’ The Introduction is otherwise concisely and well written and is appropriate in detail given this is publication of protocol not results Trial Design There is clear trial design and the use of a randomized selection design is appropriate in the context of no prior data to support one experimental arm over the other. Primary and Secondary endpoints are well defined. Participants Regarding patient population first stated in the abstract and then in inclusion criteria 2. The syntax is ambiguous and could be interpreted that a tumour stage 1 suitable for APR could be included. This sentence should be reworded to ensure it is clear the tumour must be clinical stage II/III but that the distance from the anal verge is not strict if the patient is suitable for APR. In exclusion criteria 8 – “Patient with concurrent serious complications” - complication should be replaced with comorbidity or condition Line 60, page 9, exclusion criteria 5. Body temperature >/= 38 degrees at entry” is ambiguous. At entry to what? Screening visit? Does a fever on one day render the patient ineligible completely? There is no mention in inclusion/exclusion about patients who have presented with perforation, this subgroup should be specified as excluded Page 9, Line 36, inclusion criteria 7 – consider changing strong stricture to ‘significant stricture’ Exclusions criteria does not include specifications around proteinuria – which is a contraindication to bevacizumab. This could be encompassed in excl criteria 3.

	Page 11, line 9, consider changing ‘balancing on’ to ‘stratified by’ Sample size calculations: Line 38, There is no reference to justify the selection of 25% as the ‘baseline proportion of pCR or cCR at >/= 2years’. The trials referred to have pCR rates of 30% and OPRA for consolidation it may be as high as 50%. The sample size calculation is partly specified, with description of β and delta but no mention of the prespecified α. Drop out has been accounted for. Line 45-50, recommend specify the secondary end points of interest in the event that primary endpoint will not ‘pick the winner’ - ? other measures of efficacy (OS) ? safety or QoL measures. Interventions Treatment in both arms is well defined. Time intervals between treatment modalities is not specified but would be of interest. Consider adding Follow up: The authors do not discuss how they generated their follow up for NOM patients (Table 2.) or how this approach differs from similar studies. Statistical analysis plan: The authors have not outlined which of the secondary endpoints will be assessed if the primary end point does not ‘pick a winner’ (ie <10% difference between arms).

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1
Comment: Thank you for undertaking a relevant and interesting study can I make the following suggestions.
Response: We appreciate your positive comment.

Comment: Please put in trial registration number.
Response: The trial registration number (jRCTs051200121) was put in the abstract in the original manuscript.

Comment: abstract line Methods and analysis (line 12) . remove words "..prior to neoadjuvant therapy". If this is adds nothing and is confusing as patient swill have surgery (if they do) after LCCRT a=/- induction chemo, which some may consider neoadj, so just drop it out.
Response: As the reviewer pointed out, we deleted words “prior to neoadjuvant therapy”.

Comment: Sample size calculation page 10, reference of Simon et al . It is stated as ref 22 in text, however, in refences it is 29 . It looks like it should be 22 and the reference in references needs to be changed. also it is not Simon et al , it is just Simon, not et al. (he is the single author of that paper).
Response: Thank you for pointing this out. I am sorry, but the reference about the pick the winner format was wrong. The correct reference was Simon et al (new reference number 27).

Comment: I think your number needed to treat is to small despite the reference, while I recognise this is a phase two study, and has a control arm, I suspect when you look at other similar studies and other ways to assess numbers needed to treat you might consider increasing the numbers. This is particularly so with your main outcome measures being effectiveness based.
Response: Thank you for your comment. I agree with the reviewer that the number of patients assessed in our study is relatively small. However, the patient number was determined

statistically based on the Simon's selection design. Our study uses a pick the winner format, and the winner will be selected for further subsequent trial. We consider that it is not feasible to increase the number of patients at present.

Comment: Definition of complete clinical response. Most trails looking at CRC are using MRI for follow up, looking at the mesorectum, CT for metastatic disease and endoscopy for intraluminal assessment of recurrence - perhaps you are doing that but its not that clear to me that you are. please calcify.
Response: Details of definition of complete clinical response and follow-up protocol are summarized in table 1 and table 2.

Comment: It might also help in the discussion or introduction to insert why you chose LCCRT as opposed to short course. Looking at clinical trials com, I see an increasing number of Short Couse and as you know the RAPIDO is short course.
Response: Thank you for your comment. We have added the following sentence to the introduction: "We chose long-course CRT because there was limited data on the use of short-course radiotherapy in NOM.".

Responses to Reviewer 2
Comment: The abstract is missing some salient information. Recommend adding secondary outcomes to abstract (rate of NOM, OS, distant metastasis free survival, locoregional failure free survival) as these will be of interest to the reader when scanning abstract. The abstract should also include detail of the response assessment for cCR given that this is the primary endpoint ie; DRE, endoscopy and MRI. The use of the word "courses" for chemotherapy in line 38,41,43 in abstract and later in protocol is unusual, consider changing to cycles.
Response: Thank you for your comment. As the reviewer pointed out, we have added the following sentence to the abstract: "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.". Regarding response assessment, we have added the following sentence to the abstract:" Response assessment involves a combination of digital rectal examination, endoscopy, and MRI.". Finally, we changed "courses" to "cycles" in the abstract and in the main text.

Comment: Introduction:
Line 19, distant relapse rate 30% requires reference Line 21, not technically correct, there has been one study showing survival benefit of adjuvant oxaliplatin based chemotherapy following CRT (ADORE) trial.
Line 51-55, reads poorly, repeated use of TME, consider removing "after TME" in line 55, as this is implied by 'post operatively'
The Introduction is otherwise concisely and well written and is appropriate in detail given this is publication of protocol not results Trial Design There is clear trial design and the use of a randomized selection design is appropriate in the context of no prior data to support one experimental arm over the other.
Response: We have added the reference to suggest distant relapse rate of about 30%. We have changed the sentence from "Postoperative adjuvant chemotherapy following neoadjuvant CRT has failed to show survival improvement" to "The benefit of postoperative adjuvant chemotherapy following neoadjuvant CRT remains unclear". Finally, we have removed "after TME". Thank you for these suggestions.

Comment: Participants
Regarding patient population first stated in the abstract and then in inclusion criteria 2. The syntax is ambiguous and could be interpreted that a tumour stage 1 suitable for APR could be included. This

sentence should be reworded to ensure it is clear the tumour must be clinical stage II/III but that the distance from the anal verge is not strict if the patient is suitable for APR.
In exclusion criteria 8 – "Patient with concurrent serious complications" - complication should be replaced with comorbidity or condition Line 60, page 9, exclusion criteria 5. Body temperature >/= 38 degrees at entry" is ambiguous. At entry to what? Screening visit? Does a fever on one day render the patient ineligible completely?
There is no mention in inclusion/exclusion about patients who have presented with perforation, this subgroup should be specified as excluded Page 9, Line 36, inclusion criteria 7 – consider changing strong stricture to 'significant stricture'
Exclusions criteria does not include specifications around proteinuria – which is a contraindication to bevacizumab. This could be encompassed in excl criteria 3.
Page 11, line 9, consider changing 'balancing on' to 'stratified by'
Response: Thank you for pointing this out. In the abstract, we have changed the sentence from "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" to "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)". Inclusion criteria 2 and 3 have been changed accordingly.
We have corrected "Patient with concurrent serious complication" to "Patient with concurrent serious comorbidity" in exclusion criteria 8.
We have corrected "Body temperature >/= 38 degrees at entry" to "Body temperature >/= 38 degrees at registration". A fever on one day at screening visit does not render the patient ineligible, and the patient is eligible when the fever goes down at registration and there is no active infection.
We have corrected "strong stricture" to 'significant stricture' in inclusion criteria 7.
Thank you for your suggestion to include the perforation in inclusion/exclusion. However, there was no specific mention about perforation in exclusion in similar studies such as RAPIDO trial and OPRA trial. As our common sense, patients with perforation are not suitable for the study, and its condition corresponds to" Other conditions not suitable for this study in the investigator's judgement" in the exclusion criteria 11. Finally, to change the protocol, it takes a long time to be approved by the central review board.
Regarding proteinuria, we adopt the stricter quantitative test (urine protein/creatinine < 1). It is specified in the inclusion criteria 6.
We have corrected "balancing on" to 'stratified by'.

Comment: Sample size calculations:
Line 38, There is no reference to justify the selection of 25% as the 'baseline proportion of pCR or cCR at >/= 2years'. The trials referred to have pCR rates of 30% and OPRA for consolidation it may be as high as 50%. The sample size calculation is partly specified, with description of β and delta but no mention of the prespecified α. Drop out has been accounted for. Line 45-50, recommend specify the secondary end points of interest in the event that primary endpoint will not 'pick the winner' - ? other measures of efficacy (OS) ? safety or QoL measures.
Interventions
Treatment in both arms is well defined. Time intervals between treatment modalities is not specified but would be of interest. Consider adding Follow up:
The authors do not discuss how they generated their follow up for NOM patients (Table 2.) or how this approach differs from similar studies.
Statistical analysis plan:
The authors have not outlined which of the secondary endpoints will be assessed if the primary end point does not 'pick a winner' (ie <10% difference between arms).
Response: Thank you for your comment, and we have added the reference. In this meta-analysis by Petrelli F et al, the pooled pCR rate was 22.4% (95%CI 19.4%-25.7%), and therefore we selected 25% as the lowest response rate. In our single-arm phase II trial of 3 months of mFOLFOX6

plus bevacizumab prior to CRT, we reported a pCR rate of 37%, but the 95% CI was 24.4%-52.1%. We understand that the OPRA trial reported higher cCR rate, but our study cohort will include patients with high risk-features such as lateral lymph node enlargement, T4b, EMVI, etc, and we consider that lower proportion of pCR or cCR ≥ 2 years than that of OPRA trial is possible.
Based on the Simon's randomized phase II selection design, sample sizes are given without specifying α; the design does not give any testing, assuring 80% probability to select the better treatment if the difference in response rates is at least 10% and the lowest response rate is assumed to be 25%.
If there are no differences in response rate between treatment arms, a better treatment will be chosen considering secondary endpoints comprehensively. We have added "such as toxicity and safety of the treatment" in the sentence.
Regarding the time intervals between treatment modalities, we have added the following sentences: "Consolidation chemotherapy should start at 3-8 weeks after the last day of radiotherapy." "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." "Final response assessment will be performed at 4 (- 1/+ 4) weeks after the completion of all neoadjuvant treatments.".
Regarding follow-up for NOM patients, surveillance protocol is highly variable according to the studies. Clinical assessment and endoscopy are most commonly recommended every 3-4 months for the first 2 years, similar to our protocol. MRI and CT are commonly performed every 6 months for the first year and then yearly thereafter, but our protocol is stricter in terms of the timing of MRI and CT. We intended to detect local regrowth as soon as possible. We did not discuss the follow-up protocol because we consider that this is not the main point of our study.

VERSION 2 – REVIEW

REVIEWER	Frizelle, Frank University of Otago, Department of Surgery
REVIEW RETURNED	17-Nov-2021

GENERAL COMMENTS	This protocol for the NOMINATE trial, which is a phase two trial of TNT for complete clinical response (non operative management) for T3-T4 (any N, M0) rectal cancer.. The intervention is with long course chemoradiotherapy (LCCRT) then chemo (capox) or chemo (capox with bevacizumab) then LCCRT. This trial fills a gap as most trails have focused on short course radiotherapy, yet LCCRT is the most widely used in clinical practise normally when treating rectal cancer. Trials to date on the are attached The primary end point is complete clinical response at 2 years and more., with a variety of secondary end points, including time local region failure -free survival, time to disease related treatment failure. I would suggest that consideration be given to including overall survival as an outcome, though I understand that as a primary outcome this would shift the numbers needed to treated considerable, therefore consideration should eb given to making it a secondary outcome. Patients with relapse are more likely with wait and watch have been reported to develop metastatic disease,(JAMA Oncol. 2019;5(4):e185896. doi:10.1001/jamaoncol.2018.5896) this is an important observation, hence some thought might be given to explore his observation with secondary outcomes as well.

	The other end point that might be considered is the issues around what happens when patients don't get a complete clinical response >50% who have surgery and is the surgery more difficult, patient having more complications etc, with radiation first V chemo first. The are reasons to think that chemo first may am the surgery earlier. As most patients will have surgery, (not get a complete clinical response) tis issue should be considered s well. The sample size is said to be 60 given the parameters, I think on my assessment this looks to low and would suggest that the authors may want to review this. In all the relevant, well designed and with the issues raised above considered, this study should help define the way forward.

REVIEWER	Price, Timothy The University of Adelaide, Department of Medical Oncology
REVIEW RETURNED	14-Nov-2021

GENERAL COMMENTS	Authors have addressed comments adequately.

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 2
Comment: Authors have addressed comments adequately.
Response: We appreciate your positive comment.

Responses to Reviewer 1
Comment: The intervention is with long course chemoradiotherapy (LCCRT) then chemo (capox) or chemo (capox with bevacizumab) then LCCRT. This trial fills a gap as most trails have focused on short course radiotherapy, yet LCCRT is the most widely used in clinical practise normally when treating rectal cancer. Trials to date on the are attached.
Response: Thank you for your comment and file about trials to date.

Comment: The primary end point is complete clinical response at 2 years and more., with a variety of secondary end points, including time local region failure -free survival, time to disease related treatment failure.
I would suggest that consideration be given to including overall survival as an outcome, though I understand that as a primary outcome this would shift the numbers needed to treated considerable, therefore consideration should be given to making it a secondary outcome.
Response: Thank you for your comment. Overall survival is included in secondary endpoints; 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 (page 3 and 8).

Comment: Patients with relapse are more likely with wait and watch have been reported to develop metastatic disease, (JAMA Oncol. 2019;5(4):e185896. doi:10.1001/jamaoncol.2018.5896) this is an important observation, hence some thought might be given to explore his observation with secondary outcomes as well.
Response: Distant metastasis-free survival (DMFS) is included in secondary endpoints; we can explore the difference of DMFS in patients with or without local regrowth managed by NOM.

Comment: The other end point that might be considered is the issues around what happens when patients don't get a complete clinical response >50% who have surgery and is the surgery more difficult, patient having more complications etc, with radiation first V chemo first. The are reasons to think that chemo first may am the surgery earlier. As most patients will have surgery, (not get a complete clinical response) tis issue should be considered s well.
Response: Secondary endpoints include surgical morbidity, R0 resection rate, pathological stage, Dworak tumour regression grade in patients managed by TME,

Comment: The sample size is said to be 60 given the parameters, I think on my assessment this looks to low and would suggest that the authors may want to review this.
Response: I agree with the reviewer that the number of patients assessed in our study is relatively small. However, the patient number was determined statistically based on the Simon's selection design. Our study uses a pick the winner format, and the winner will be selected for further subsequent trial. We consider that it is not feasible to increase the number of patients at present.