Cancer Research Consortium of West Michigan
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FAST FACTS

The NEO-RT Trial: A PHASE 3 RANDOMIZED TRIAL OF NEOADJUVANT CHEMOTHERAPY, EXCISION AND OBSERVATION VERSUS CHEMORADIOTHERAPY FOR EARLY RECTAL CANCER

1.0 Eligibility Criteria

1.1 Histologically confirmed invasive, well-moderately differentiated rectal adenocarcinoma, mismatch repair proficient.

1.2 MRI stage:

a) cT1 not eligible for transanal surgery alone as per NCCN guidelines, (including but not limited to T1 tumours >2 cm in size, positive margin, tumour depth SM3 invasion to the lower third of the submucosal level).

or

b) cT2

1.3 cN0 stage based on pelvic MRI – including absence of radiographic evidence of mesorectal nodal metastasis, tumour deposits or extramural venous invasion (EMVI).

1.4 M0 stage based on no evidence of metastatic disease by CT imaging of chest, abdomen and pelvis.

1.5 Mid to low-lying tumour eligible for transanal excision in the opinion of the treating surgeon.

1.6 Medically fit to undergo radical TME surgery as per treating surgeon's decision.

1.7 Participant is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French or Spanish. The baseline assessment must be completed within required timelines, prior to enrollment. Inability (lack of comprehension in English or French or Spanish, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the participant ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the participant ineligible.

1.8 Age of at least 18 years.

1.9 No contraindications to protocol chemotherapy

1.10 Adequate normal organ and marrow function as defined below (must be done within 30 days prior to enrollment):

- ANC ≥ 1.5 x 109/L
- platelet count ≥100 x 109/L
- bilirubin < 1.5 ULN, excluding Gilbert's syndrome
- Estimated creatinine clearance of ≥ 50 ml/min.

1.11 The patient must have an ECOG performance status of ≤ 2 (or Karnofsky ≥ 60%). Patient consent must be appropriately obtained in accordance with applicable local and regulatory
requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

1.12 Must be accessible for treatment and follow-up. Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, follow-up and response assessments.
Patients must agree to return to their primary care facility or any adverse events which may occur through the course of the trial.

1.13 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method during and for 9 months after completion of chemotherapy. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive
months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or
vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected.

1.14 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

2.0 Ineligibility Criteria

2.1 Pathologic high-risk factors on diagnostic biopsy: high histologic grade (poorly differentiated), mucinous or signet ring histology, lymphatic/vascular or perineural invasion.

2.2 Patients with visible pelvic sidewall nodes on MRI.

2.3 Patients with unequivocal determination of nodal disease that, in the opinion of the investigator, would prohibit protocol therapy administration.

2.4 Previous pelvic radiation for any reason, including brachytherapy alone.

2.5 Patients who have had primary lesion excised prior to enrollment.

2.6 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

2.7 Prior treatment for rectal cancer.

2.8 Patients with known dihydropyrimidine dehydrogenase deficiency (DYPD).

2.9 Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

2.10 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

2.11 Any contra-indications to undergo MRI imaging.

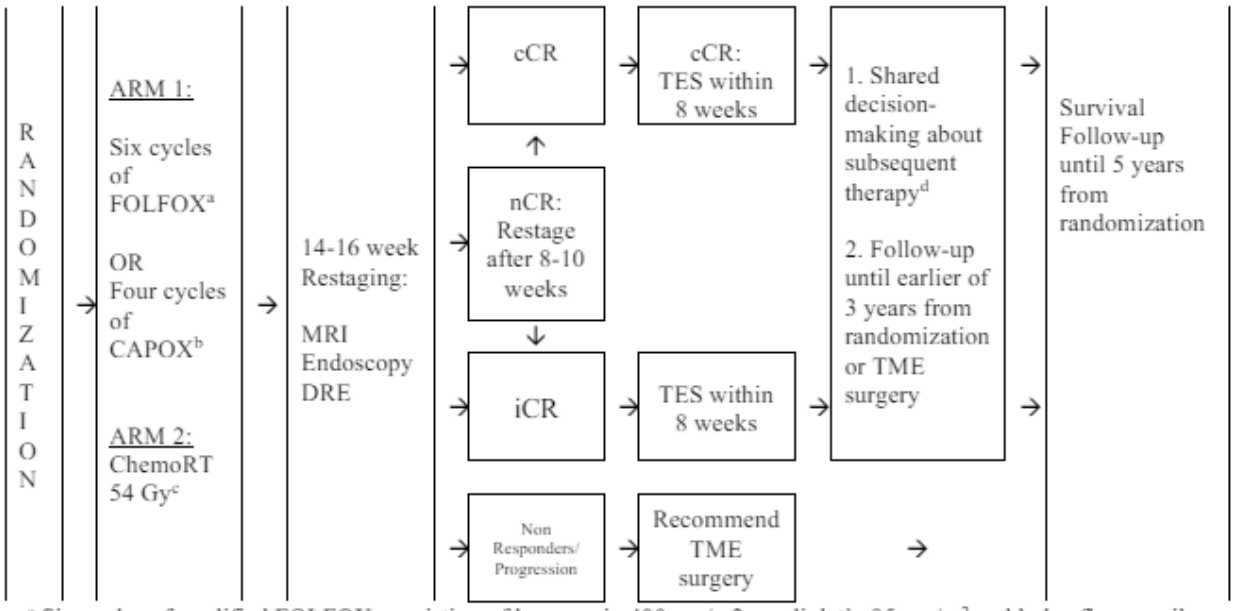
2.12 Presence of anterior lesions above or near peritoneal reflection rendering the patient ineligible for a transanal tumour excision.

TREATMENT SCHEMA

This is an international multi-centre, phase 3 randomized non-inferiority trial comparing induction FOLFOX/CAPOX chemotherapy followed by transanal endoscopic surgery (TES) to chemoradiation (chemoRT) followed by transanal endoscopic surgery (TES) in patients with cT1-T2/N0 pMMR rectal adenocarcinoma.

Stratification:

- Centre
- T stage (T1, T2)
- Gender at birth (male, female)



[a] Six cycles of modified FOLFOX consisting of leucovorin 400 mg/m2, oxaliplatin 85 mg/m^2 and bolus fluoruracil (optional) 400 mg, infusional fluorouracil 2,400 mg/m^2

[b] Capecitabine 1,000 mg/m2 twice daily for 14 days and Oxaliplatin 130 mg/m2 on day 1

[c] Standard dose of infusional 5-Fluorouracil/capecitabine, 54 Gy (27-30 fractions)

[d] See Section 7.5