FULL PROTOCOL TITLE

DYNAMIC-Rectal: Circulating Tumour DNA Analysis Informing Adjuvant Chemotherapy in Locally Advanced Rectal Cancer: A Multicentre Randomised Study

STUDY CHAIRS

Prof Jeanne Tie

Prof Peter Gibbs

PROJECT MANAGER / TRIAL COORDINATOR

Tina Cavicchiolo, Project Manager

DYNAMIC-RECTAL@mh.org.au

LINK TO STUDY

https://gicancer.org.au/clinical-trial/dynamic-rectal/

TRIAL IDENTIFIER

ACTRN12617001560381

COORDINATING CENTRE

WEHI (Walter and Eliza Hall Institute of Medical Research)

FUNDING SOURCES

NHMRC

STUDY CHAIR

Prof Jeanne Tie

Walter and Eliza Hall Institute of Medical Research

FINANCIAL DISCLOSURE

Consultant/Advisory role: Haystack Oncology, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Novartis, MSD, Gilead, Seres Therapeutics, Beigene, Illumina, Daiichi Sankyo

AIM/S

The primary objective of the DYNAMIC-Rectal study is to demonstrate that an adjuvant therapy strategy incorporating ctDNA results in addition to standard pathologic risk will reduce the number of patients receiving adjuvant chemotherapy.

BACKGROUND

Despite guidelines recommending the routine use of adjuvant chemotherapy in locally advanced rectal cancer (LARC), there is little evidence in the modern era to support the routine use of post-operative chemotherapy in patients who received pre-operative chemo-radiotherapy. Although the use of adjuvant FOLFOX appears promising in node-positive disease (ypN+), this comes with a toxicity price and the impact on overall survival yet to be proven. Clearly, better predictors of those patients who actually require adjuvant chemotherapy are needed (e.g. ctDNA-positivity indicating presence of minimal residual disease).

Across multiple colorectal cancer cohorts, our initial studies demonstrated the potential utility of ctDNA as a marker of recurrence risk. The end goal for LARC patients is to integrate ctDNA analysis into routine clinical practice to guide clinical decision making, and most importantly to benefit patients. This initial study is powered to show that a ctDNA-based approach to adjuvant therapy will lead to substantially fewer patients receiving adjuvant therapy, which we believe is the only practical study design with a clinically significant endpoint, within the patient numbers that could be recruited. Importantly, this study will also demonstrate the feasibility of performing such a biomarker-driven study in the rectal cancer population.

STUDY DESIGN

A prospective, multi-centre, randomised study enrolling a total of 408 patients with locally advanced rectal cancer treated with standard neoadjuvant chemo-radiation followed by surgery. Patients will be randomised 1:2 to be treated as per standard of care **(Arm A: SOC)** or according to post-op ctDNA results **(Arm B: ctDNA-informed)**. Patient enrolment will be stratified by participating centre and ypN stage.

The primary endpoint of this study is number of patients receiving adjuvant chemotherapy. Secondary endpoints include: ctDNA results turn-around time; 3-year recurrence free survival; and overall survival.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Aged 18 years of age and over
- Subjects with locally advanced rectal cancer treated with curative intent
- Subjects treated with pre-operative long course chemo-radiation and surgery
- CT scan of chest/abdomen/pelvis prior to commencing pre-operative chemo-radiation demonstrating no metastatic disease
- A tumour sample (from the pre-treatment biopsy or surgery specimen is available for molecular testing within 35 days after surgery)

- Fit for adjuvant (post surgery) chemotherapy.

EXCLUSION CRITERIA

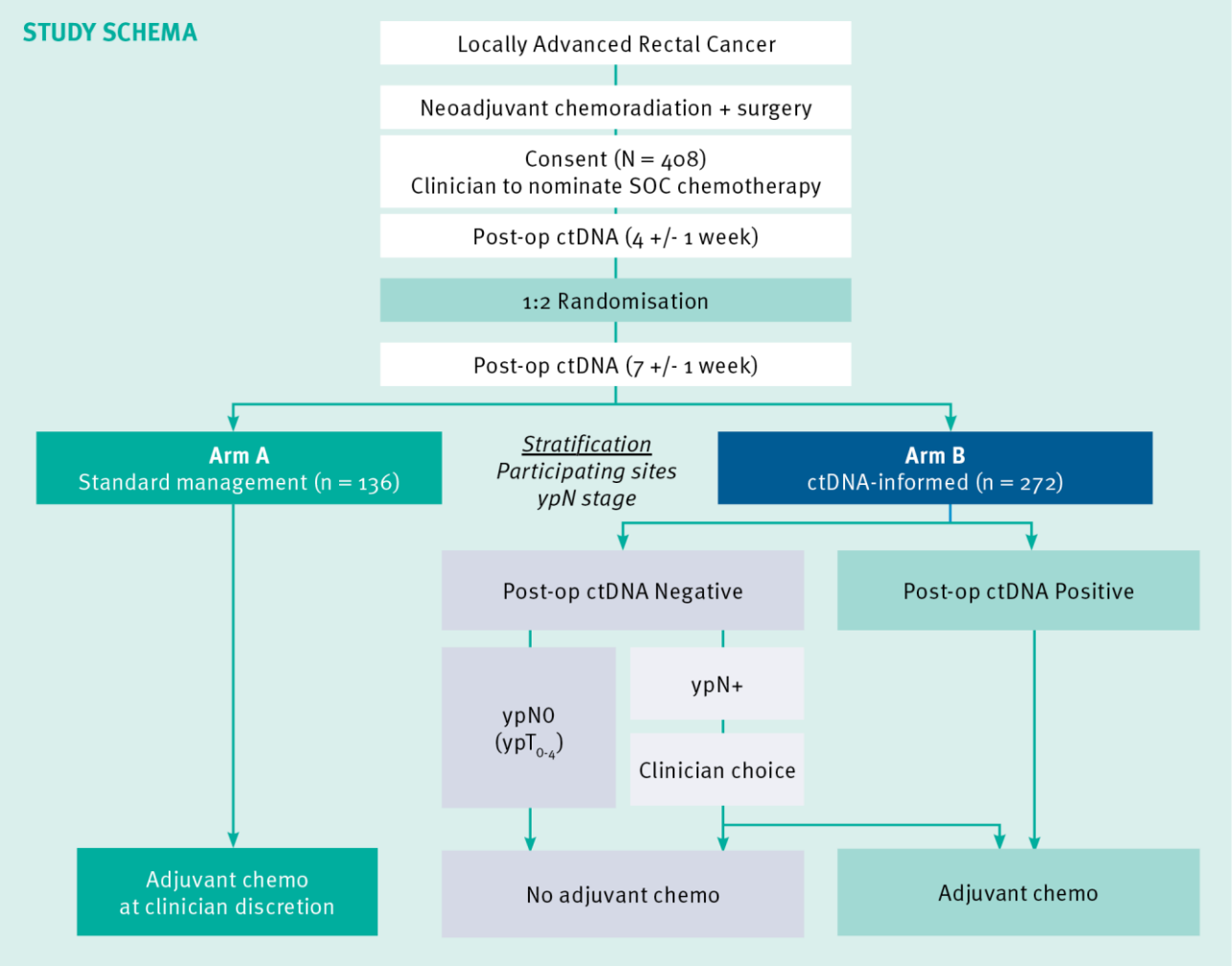
- History of another primary cancer within the last 3 years (with the exception of non-melanoma skin cancer and carcinoma in situ).
- Patients with multiple primary colorectal cancers
- Inadequate bone marrow, kidney and liver function, as determined by blood tests
- Evidence of active infection
- Clinically significant cardiovascular disease
- Medical or psychiatric condition or occupational responsibilities that may preclude compliance with the study requirements.

STUDY UPDATE

- The DYNAMIC-Rectal study received central ethics approval in Australia in September 2017. The first site opened in June 2018 and the first patient was randomised in July 2018. The DYNAMIC-Rectal trial posed no safety concerns following reviews by the IDSMC.
- Study recruitment was closed prematurely in September 2021 due to a significant slowing down in recruitment in the first 6 months of 2021, largely due to the COVID-19 pandemic and also the changing treatment landscape with a move towards total neoadjuvant therapy. A total of 250 patients were enrolled from 37 sites. Patients continue to be followed up on study. The majority of patients will reach 2-year follow up by September 2023.
- Primary analysis planned for Sept 2023, with preliminary results to be presented at ASM.
- Publications – Abstract submission planned for GI ASCO 2024.

TRANSLATIONAL RESEARCH

There are no current proposals for additional translational research, however there are future proposals including the exploration of other liquid biopsy analytes to improve the sensitivity of ctDNA analysis. Specimens collected include blood for: 1) ctDNA analysis and 2) biobank for future research. Work has begun on combining the fear of cancer recurrence data with the DYNAMIC (stage II) trial.


STUDY SCHEMA
Locally Advanced Rectal Cancer
Neoadjuvant chemoradiation + surgery
Consent (N = 408)
Clinician to nominate SOC chemotherapy
Post-op ctDNA (4 +/- 1 week)
1:2 Randomisation
Post-op ctDNA (7 +/- 1 week)
Arm A
Standard management (n = 136)
Stratification
Participating sites
ypN stage
Arm B
ctDNA-informed (n = 272)
Post-op ctDNA Negative
Post-op ctDNA Positive
ypN0
(ypT0-4)
ypN+
Clinician choice
Adjuvant chemo
at clinician discretion
No adjuvant chemo
Adjuvant chemo