SPAR: A RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL OF SIMVASTATIN IN ADDITION TO STANDARD CHEMOTHERAPY AND RADIATION IN PREOPERATIVE TREATMENT FOR RECTAL CANCER. AN AGITG CLINICAL TRIAL

AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

NHMRC Clinical Trials Centre

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Background / Rationale

Retrospective studies show improved outcomes in colorectal cancer patients if taking statins, including overall survival, pathological response of rectal cancer to preoperative chemoradiotherapy (pCRT), and acute and late toxicities of pelvic radiation [1]. Major tumour regression following pCRT has strong prognostic significance and can be assessed in vivo using MRI-based tumour regression grading (mrTRG) or after surgery using pathological TRG (pathTRG) [2].

Study Design

General Aim: To evaluate the effect of simvastatin (SIM) on efficacy and toxicity of pCRT in rectal cancer, and on systemic and local inflammatory responses.

Randomised double-blind placebo-controlled multicentre phase II trial.
222 patients from New Zealand and Australia, randomised 1:1 to Simvastatin or placebo.

Objectives

Primary Objective:

To compare rates of favourable (grades 1-2) mrTRG after pCRT with simvastatin or placebo (mrTRG in 4 ordered categories: 1, 2, 3, 4-5)

Secondary Objectives:

To compare between simvastatin and placebo groups:

- rate of favourable (grades 1-2) pathTRG
- incidence of > G2 acute gastro-intestinal (GI) and non-GI adverse events
- incidence of late GI adverse events
- compliance with pCRT and trial medication
- surgical resection rate post-pCRT
- 3-year local recurrence, DFS and cancer-specific survival
- pathological scores for radiation colitis in irradiated rectum

Tertiary/correlative Objectives:

To determine in total trial population:

- association between mrTRG and pathTRG grouping
- inter-observer agreement between site and central radiologist on mrTRG scoring
- inter-observer agreement between site and central pathologist on pathTRG scoring

To compare between the SIM and placebo groups:

- association between CD3+ and/or CD8+ T-cell infiltrates in tumour in diagnostic biopsies and pathTRG
- intensity and distribution of subsets of infiltrating T-cells in irradiated normal and malignant tissue
- influence of SIM on systemic inflammation, assessed with mGPS and NLR

Eligibility Criteria

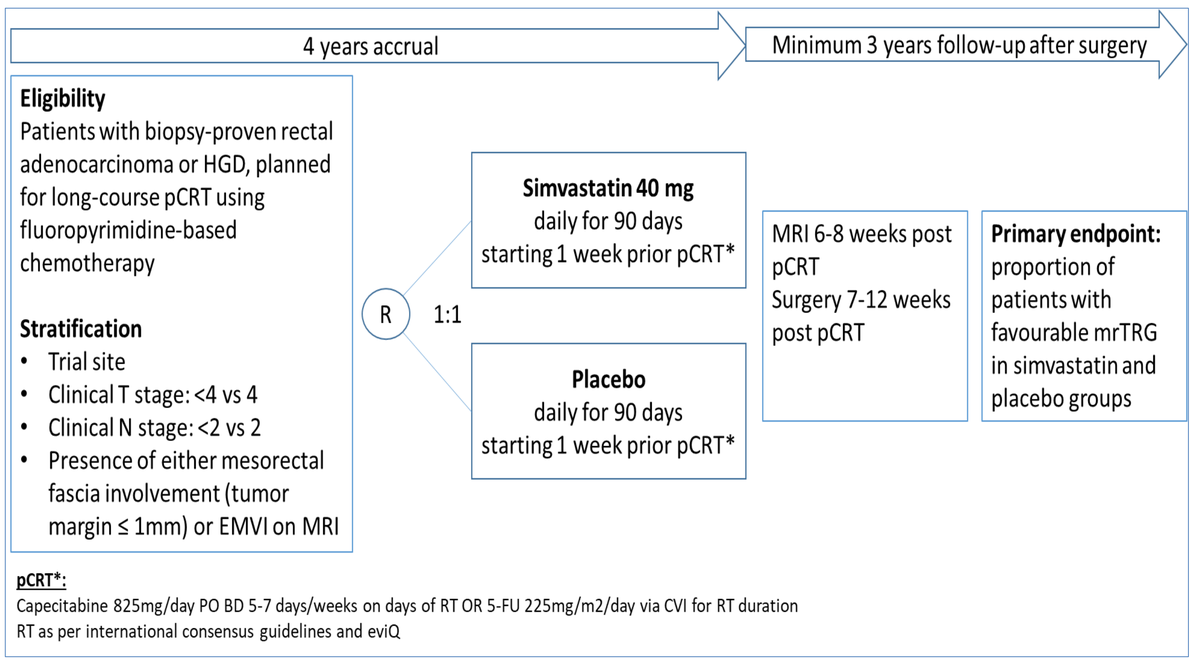
Key Inclusion Criteria

- Adults with biopsy proven rectal adenocarcinoma or high grade dysplasia (HGD)
- Distal border of the tumour is below the peritoneal reflection on MRI
- TNM stage T2-4 N0-2, M0/resectable liver or lung M1 after CT C/A/P and pelvic MRI
- Planned for long-course pCRT using fluoropyrimidine-based chemo
- Radiologically-measureable disease on baseline pelvic MRI
- Adequate bone marrow, liver and renal function
- Diagnostic biopsy of rectal tumour available for histological sub studies

Key Exclusion Criteria

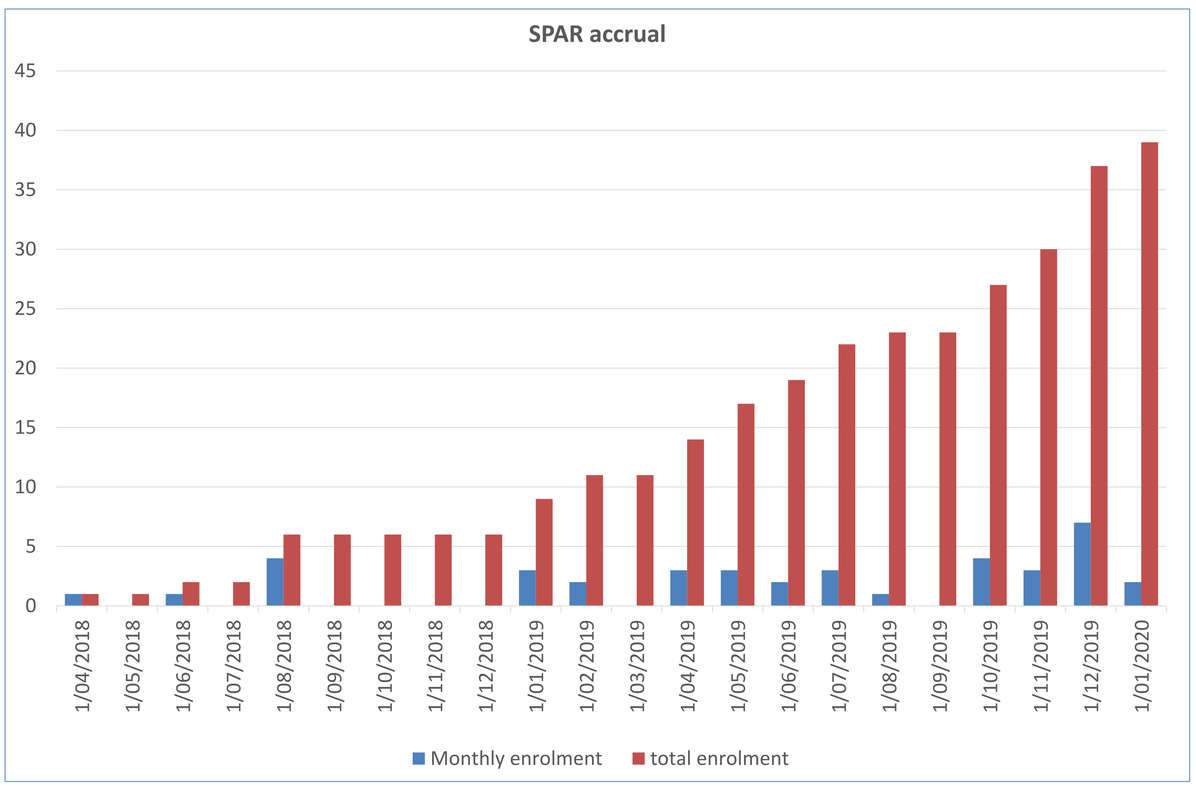
- Contraindications or hypersensitivity to statins, fluoropyrimidine chemotherapy or radiotherapy
- Patients planned to receive oxaliplatin or biological agents (e.g. cetuximab) as part of pCRT
- Taking statins in the 6 weeks before planned start of pCRT
- Predicted life expectancy of less than 3 years
- Prior pelvic or rectal radiotherapy
- History of another malignancy within 5 years prior to registration

Schema



Study Progress

Recruitment commenced in April 2018. SPAR is currently open to recruitment in 15 sites across Australia and New Zealand. 39 participants have been enrolled as at February 2020.



Participating sites	Location	Principal Investigator	Recruitment
Lake Macquarie Private Hospital	NSW	Stephen Ackland	12
Waikato Hospital	NZ	Michael Jameson	8
Calvary Mater Cancer Care	NSW	Swetha Sridharan	4
Royal Brisbane and Women's Hospital	QLD	Matthew Burge	4
ICON - Gold Coast	QLD	Andrew Oar	4
Palmerston North	NZ	Rix Du Plessis	2
Tauranga Hospital	NZ	Elliott Brenman	1
Bankstown-Lidcombe Hospital	NSW	Ray Asghari	1
Port Macquarie Base Hospital	NSW	Stephen Begbie	1
The Queen Elizabeth Hospital	SA	Timothy Price	1
Peter MacCallum Bendigo	VIC	Neetu Tejani	1

Other participating sites: Christchurch Hospital, NZ; Chris O'Brien Lifehouse, NSW; Royal North Shore Hospital, NSW; Mater Cancer Care Centre, QLD.

References

(1) Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut 2010 Nov; 59(11):1572-85.
(2) Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, et al. Magnetic resonance imaging-detected tumour response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011 Oct 1; 29(28):3753-60.

Acknowledgements

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More information: Please send us your questions or comments: SPAR@ctc.usyd.edu.au or visit the AGITG at www.gicancer.org.au. SPAR is listed on the ANZCTR clinical trials registry: #12617001087347