FULL PROTOCOL TITLE

STOPNET: A randomised study of cessation of somatostatin analogues after Peptide Receptor Radionuclide Therapy in Mid-Gut Neuroendocrine tumours

STUDY CHAIRS

Dr Matthew Burge
A/Prof David Wyld
A/Prof David Pattison

PROJECT MANAGER

Sandra Bahamad
research@gicancer.org.au

LINK TO STUDY

https://gicancer.org.au/clinical-trial/stopnet/

TRIAL IDENTIFIER

Trial Identifier Number pending

COORDINATING CENTRE

AGITG In-House Trial Coordination
Canadian Cancer Trials Group (CCTG)

FUNDING SOURCES

Philanthropic funding
Tour De Cure Grant

PRESENTER

Dr Matthew Burge

Royal Brisbane and Women's Hospital

FINANCIAL DISCLOSURE
None to declare.

AIM/S

To estimate the feasibility and outcomes ceasing somatostatin analogue (SSA) inpatients with low and moderately differentiated gut neuroendocrine tumours, who have progressed on SSA therapy, and receive Peptide Receptor Radionuclide Therapy (PRRT) thereafter cease. The co-primary objectives are to estimate 1) the 20-month progression free survival rate after PRRT in patients who cease SSA, as measured by RECIST 1.1.; 2) feasibility as measured by recruitment rate and ability to cease SSA in the investigational arm. Important secondary endpoints include quality of life, health economics and assessment of the psychological impact of SSA cessation.

BACKGROUND

Neuroendocrine tumours commonly originate from the gut and metastasise widely including to the liver, lymph nodes and bones. Originally called “carcinoid tumours”, these low- grade cancers are initially treated with somatostatin analogues (SSA). These analogues treat any carcinoid syndrome and slow tumour growth. Despite SSA therapy, progression usually develops over time. Upon such progression, peptide receptor radionuclide therapy (PRRT) is the next standard therapeutic option and is superior to escalating the SSA dose. After PRRT is initiated, it is unclear if continuing the SSA injections is beneficial. There are reasons to believe it might be necessary to continue SSA, but other reasons to believe they should cease. Given that SSA injections are expensive and associated with side effects, this study investigates the utility of continuing SSA injections after progression on SSA therapy and commencement of PRRT.

STUDY DESIGN

This is a prospective, randomised, non-comparative, open label, multicentre phase II study. Patients meeting the inclusion and exclusion criteria will be randomised, prior to commencing PRRT, to either continue or cease SSA treatment. Randomisation will occur centrally in REDCap by the Hunter Medical Research Institute (HMRI). Randomisation will be 2:1 (the majority being randomised to cease SSA), and will be stratified by:

- WHO Tumour grade:
    - Low Grade – G1 (Ki67<2% and/or mitotic count <2) vs.
    - Intermediate Grade – G2 (Ki67 3-20 % and/or mitotic count 2-20)
- Institution
- Visceral only verse visceral with bone metastases.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Adults 18 years of age and over with well or moderately differentiated mid or hindgut neuroendocrine tumour, metastatic and inoperable, demonstrating progression despite SSA treatment of sufficient disease magnitude to warrant PRRT as determined by the treating clinician and/or the NET Multidisciplinary Team (MDT).
- Ki67 ≤ 20%; mitotic count less than 20 per HPF (i.e., WHO grade 1 or 2).
- Non-functioning NET: SSA treatment must have been commenced primarily for control of tumour growth and not primarily for carcinoid syndrome, as judged by the clinician and/or NET MDT.
    - In addition, non-functioning tumour is defined as:
        - Never had escalation of the SSA treatment dose to control carcinoid symptoms.
        - Never required short acting SSA treatment to control carcinoid symptoms.
        - No significant carcinoid symptoms at study entry - as judged by the clinical team.
        - No significant carcinoid induced valvular heart disease.
- Patient has been receiving growth-controlling doses of SSA for at least 3 months prior to study entry. This is a minimum of 30 mg Octreotide and 120mg lanreotide monthly.
- Uptake on gallium-68 octreotate scan (and FDG PET if required) demonstrating somatostatin receptor expression that is suitable for PRRT as judged by the clinical team.
- PRRT is deemed the most appropriate next treatment step (i.e., patient is inoperable, and liver directed therapies are not preferred).
- ECOG performance status 0 -2.
- Written informed consent. Patients must be willing to either cease or continue SSA, depending on which study arm they are randomised to. Patients must be willing to comply with all other study requirements.
- Adequate renal, hepatic and haematologic function as judged by the treating team.
- Life expectancy of at least 12 months.

EXCLUSION CRITERIA

- This study is for mid-gut and hind-gut NET only. Pancreatic, gastric and lung NETs are excluded.
- Any patient on an SSA dose lower than the standard growth-control dose. Patients must have been on octreotide 30 mg or lanreotide 120 mg for at least 3 months prior to study entry.
- No prior chemotherapy, targeted therapy (e.g., everolimus) or liver directed therapy (including SIRT). Prior external beam radiotherapy is allowed.

- Any contraindication to PRRT, as judged by the clinical treating team. These may include, but are not limited to:
    - Poor renal function
    - Significant valvular heart disease
    - Low albumin level
- No prior PRRT. Patients being considered for re-treatment with PRRT are not eligible.
- Uncontrolled central nervous system metastases. Patients must have completed any surgery or radiation at least 4 weeks prior to registration and must be off corticosteroids for at least 2 weeks.
- Any patient, in the opinion of the investigator, who will not comply with study assessments and follow up visits. These might include any social, psychological, or geographical concerns, including alcohol/drug abuse.
- Any poorly controlled concurrent medical illness that may prevent the patient from complying with study assessments and follow up. This is to be judged by the treating team.
- Any concurrent or prior malignancy that, in the opinion of the treating team, may interfere with study assessments and endpoints.

STUDY UPDATE

STOPNET is the first Commonwealth Neuroendocrine Tumour research collaborative (CommNETS) branded trial, a collaboration between AGITG and the Canadian Cancer Trials Group (CCTG). STOPNET is internationally led by AGITG and coordinated via the AGITG In House Trial Coordination. STOPNET was approved as the first trial to be coordinated by AGITG in July 2022. Currently in start-up and lead ethics submission preparation underway for November 2023. Trial anticipated to open in Q1 2024. Recruitment target of 52 participants globally over a 24-month recruitment period; CCTG to contribute 26 participants to sample size. Stage 1 of the trial is fully funded by AGITG philanthropic funding and a Tour de Cure grant. Medical Research Future Fund (MRFF) Clinical Trial Activity grant application submitted 28 June 2023 to fund stage 2 of the study, outcome announced in November 2023. CCTG awarded Canadian Neuroendocrine Tumour Society (CNETS) grant to commence start-up activities in Canada. CCTG have submitted a Canadian Institutes of Health Research (CIHR) grant and North American Neuroendocrine Tumour Society (NANETS) grant, pending outcomes.

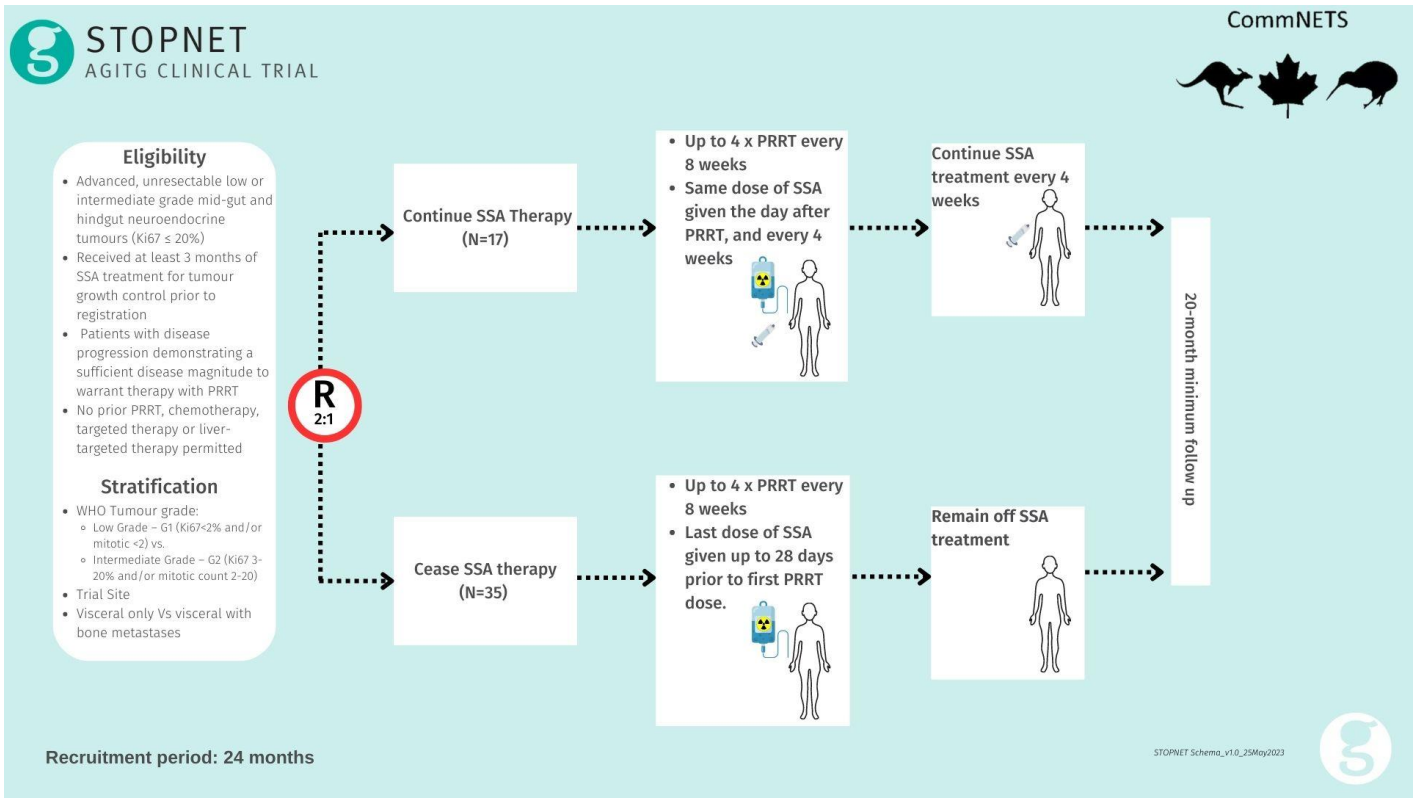
TRANSLATIONAL RESEARCH

Translational research studies will include identifying biomarkers that are potentially prognostic and/or predictive of treatment response, resistance, and safety (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to:

- Define and validate NET tissue and circulating biomarkers using miRNA-based machine-learning approaches and extracellular RNA-based Fuzzy Inference System approaches.

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, a definitive list of biomarkers to be tested remains to be determined.

SCHEMA


STOPNET
AGITG CLINICAL TRIAL
CommNETS
Eligibility
Advanced, unresectable low or intermediate grade mid-gut and hindgut neuroendocrine tumours (Ki67 ≤ 20%)
Received at least 3 months of SSA treatment for tumour growth control prior to registration
Patients with disease progression demonstrating a sufficient disease magnitude to warrant therapy with PRRT
No prior PRRT, chemotherapy, targeted therapy or liver-targeted therapy permitted
Stratification
WHO Tumour grade:
Low Grade – G1 (Ki67<2% and/or mitotic <2) vs.
Intermediate Grade – G2 (Ki67 3-20% and/or mitotic count 2-20)
Trial Site
Visceral only Vs visceral with bone metastases
R
2:1
Continue SSA Therapy (N=17)
Up to 4 x PRRT every 8 weeks
Same dose of SSA given the day after PRRT, and every 4 weeks
Continue SSA treatment every 4 weeks
Cease SSA therapy (N=35)
Up to 4 x PRRT every 8 weeks
Last dose of SSA given up to 28 days prior to first PRRT dose.
Remain off SSA treatment
20-month minimum follow up
Recruitment period: 24 months
STOPNET Schema_v1.0_25May2023