FULL PROTOCOL TITLE

NABNEC: A Randomised Phase II Study Of nab-Paclitaxel In Combination With Carboplatin As First Line Treatment Of Gastrointestinal Neuroendocrine Carcinomas

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LINK TO STUDY

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

TRIAL IDENTIFIER

ACTRN12616000958482

COORDINATING CENTRE

NHMRC Clinical Trials Centre, University of Sydney

FUNDING SOURCES

National Health and Medical Research Council (NHMRC)

PRESENTER

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FINANCIAL DISCLOSURE

None to declare.

AIM/S

The primary aim of NABNEC is to establish if the carboplatin and nab-paclitaxel combination is an effective and tolerable chemotherapy treatment for grade 3 advanced gastrointestinal NECs. Full analysis will be available early next year but primary results will be presented here. Plans for a separate publication of the functional imaging endpoints are in progress.

BACKGROUND

Neuroendocrine carcinomas (NEC, WHO 2010 grade 3 or PanNET, WHO 2017 grade 3), comprising small cell NEC and large cell NEC, are aggressive rare cancers and are generally rapidly fatal. They arise commonly in the gastrointestinal system. There have been a few retrospective studies, but no randomised, prospective controlled trials conducted to establish gold standard chemotherapy for advanced gastrointestinal NECs. The combination of etoposide and carboplatin has been the historical standard of care by extrapolation from small cell lung cancer trials. Paclitaxel and carboplatin are active in gastrointestinal NECs but there is no data on the role of nab-paclitaxel. This randomised study aims to determine the role of these therapies in clinical practice and to prospectively study the biology and imaging characteristics of NEC.

STUDY DESIGN

NABNEC began as an open label centrally 2:1 randomised multicentre phase II trial. The study treatments were:

Experimental arm: IV nab-paclitaxel (100 mg/m^2) weekly and carboplatin (Area Under Curve [AUC]=5) every 3 weeks.

Control arm: IV carboplatin AUC=5 on Day 1 and etoposide 100mg/m^2 on Days 1-3 every 3 weeks. The sample size is 58 patients. A protocol amendment in February 2020 closed the control arm of the study after 12 patients had been randomised to this arm to reach an achievable statistically relevant trial result. There were a total of 48 patients enrolled onto the experimental arm of the trial.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Unresectable advanced and/or metastatic histologically proven (WHO/ENET) Grade 3 NEC with Ki-67>20%
- Mixed Tumours are eligible
- Tumour sufficiently FDG-avid on initial PET staging (SUVmax≥ 3.5)
- Measurable disease
- ECOG performance status 0-2
- Adequate haematological, renal and hepatic function.

EXCLUSION CRITERIA

- Primary neuroendocrine cancer not gastro-intestinal in origin

- Suspected pulmonary origin of the neuroendocrine tumour
- Known hypersensitivity to nab-paclitaxel
- Severe existing cardiovascular, hepatic, neurologic or renal conditions
- Active infection of chronic active hepatitis B, C or HIV.

STUDY UPDATE

The trial closed to recruitment on 31 December 2021. A total of 60 patients were recruited exceeding the recruitment target of 58 patients. There were 18 sites open to recruitment. The trial closed to treatment and follow up on 31 December 2022. As at 31 December 2022 there was 1 patient on treatment, 6 in follow up, 48 deceased, 3 completed 3 years of follow up, 1 lost to follow up and 1 withdrawn. The patient on treatment continued after trial closure with compassionate access nab-paclitaxel provided by Specialised Therapeutics Australia. Data cleaning is close to completion and analysis has commenced.

The primary results of the trial will be presented at this meeting. There are plans to present a trial abstract at ASCO GI January 2024. Publication planning has commenced. Planning on translational research publications have also commenced.

BARRIERS TO RECRUITMENT

The main barriers to study recruitment were the cancer being a rare cancer, difficulty obtaining timely FDG PET-CT in some hospitals and unwell patients needing to start treatment promptly. To improve recruitment, the study team allowed some flexibility with baseline scan dates and the study protocol was amended in February 2020 to remove the control arm. In April 2021, the NABNEC Trial Management Committee made the decision to extend the recruitment period by 6 months until 31 December 2021. An ethically approved trial promotion video was used on social media and stakeholder websites. The promotional video in conjunction with several other recruitment initiatives including monthly emails to sites helped to boost recruitment and reach the recruitment target.

INTERIM ANALYSIS

The interim analysis for futility was conducted in November 2018 and the independent review committee recommended the study continue as per protocol.

STRATEGIES EMPLOYED TO INCREASE EQUITY, DIVERSITY AND INCLUSION, DATA FOR PATIENTS ENROLLED FROM DIFFERENT BACKGROUNDS

Participants from different backgrounds, including Aboriginal, Torres Strait Islander and Culturally and Linguistically Diverse (CALD) communities will be included in the data collected from this study. Efforts to increase data from these populations include Community Outreach liaison at treating hospitals, working with interpreters at treating hospitals where possible and adapting our consent forms to be more inclusive through the CTC's Equity, Diversity and Inclusion in Trials initiatives.

TRANSLATIONAL RESEARCH

Donation of blood and archival tumour tissue for translational research is optional for participants. Serial bloods were collected at four timepoints: baseline, C4D1, C10D1, and progressive disease (PD).

Planned or ongoing studies include:

- Tissue biomarker studies of: cell proliferation (Ki67), adhesion (E-, F-, Beta-catenin), metastasis
- (F-actin, integrins), molecular fingerprinting (mRNA analyses)
- Circulating tumour cells (CTCs) – enumeration, molecular characterisation and generation of cell lines
- Molecular analyses of circulating tumour cells and tissue of a subset of participants.

Centrally analysed baseline Ga-DOTATATE and FDG PET scans at specified time points:

- Analysis is underway and has been completed for 2/3 of the trial scans.

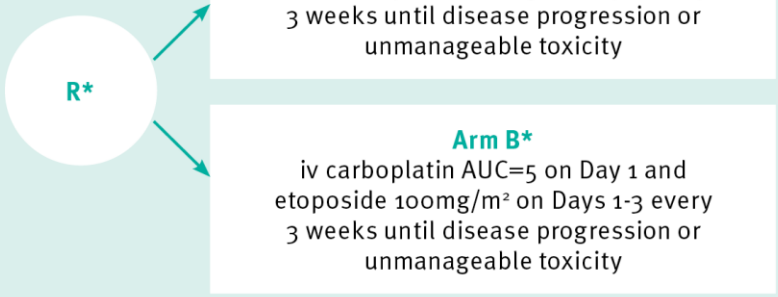
Quality of Life questionnaire data will also be analysed and reported in future publications.

STUDY SCHEMA

Eligibility
Adults with advanced and/or metastatic non-resectable gastrointestinal NECs, including both small cell and large cell-NEC

Stratification
Stratified by study site, Ki-67 (‹55% v ≥ 55%), primary site (pancreatic vs non-pancreatic) and FDG-PET uptake and/or avidity (‹10% v ›10%)

Duration of accrual: 4.5 years *Duration of follow-up: up to 3 years*



Endpoints
Primary endpoint
Objective tumour response rate

Secondary endpoints
Progression free survival
Overall survival
Safety
Quality of life

Tertiary/correlative endpoints
Biomarker analyses of blood and tissue
Mutational and DNA metylation profiling
FDG-PET imaging
^{68}GA-octreotate PET/CT imaging

** Protocol version 3.0 (25 November 2019) amended to cease randomisation and close the control arm, all future patients are recruited to the experimental arm (Arm A) only*