FULL PROTOCOL TITLE

INTEGRATE IIa: A Randomised Phase III Double-Blind Placebo-Controlled Study of regorafenib in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)

STUDY CHAIRS

Prof Nick Pavlakis

Prof David Goldstein

PROJECT MANAGER / TRIAL COORDINATOR

Ashley Douglas

Chelsea Bassett

Monet Potter

integrateii.study@sydney.edu.au

LINK TO STUDY

https://gicancer.org.au/clinical-trial/integrate-ii/

TRIAL IDENTIFIER

ACTRN12616000420448

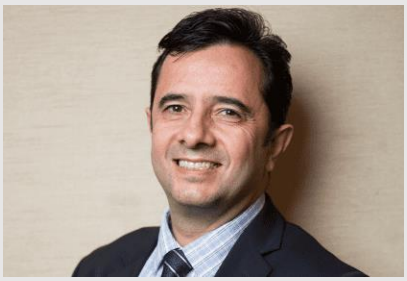
COORDINATING CENTRE

NHMRC Clinical Trials Centre (CTC)

FUNDING SOURCES

Bayer HealthCare Pharmaceuticals Inc

PRESENTER



Prof Nick Pavlakis

Royal North Shore Hospital

FINANCIAL DISCLOSURE

None to declare.

AIM/S

INTEGRATE IIa was a randomised, placebo controlled multicentre international Phase II trial that evaluated the activity or Regorafenib versus placebo in Advanced Gastro-Oesophageal Cancer (AGOC).

The primary objective was overall survival (death from any cause), while secondary objectives include progression free survival, objective tumour response rates, quality of life, safety, pharmacokinetics, and investigation of the prognostic/predictive role of circulating biomarkers.

BACKGROUND

Refractory AGOC has limited options. Five-year survival for AGOC is <7% and, medium overall survival remains less than 1 year. Regorafenib is an oral multi-kinase inhibitor with a distinct profile, targeting angiogenic, stromal and oncogenic receptor tyrosine kinases.

STUDY DESIGN

INTEGRATE IIa was a double-blind placebo-controlled phase 3 trial comparing regorafenib and best supportive care (BSC) vs placebo and BSC for subjects with confirmed evaluable metastatic/locally advanced AGOC on a 2:1 randomisation, stratified by tumour location, geographic region (Asia vs rest of world), prior VEGF inhibitors, in patients who failed ≥ 2 prior therapies.

Primary endpoint was overall survival (OS), with OS among Asian sub-population a key secondary objective. Treatment efficacy on OS was tested first in the pooled INTEGRATE I + INTEGRATE IIa cohort and, if significant, then in the INTEGRATE IIa cohort. Secondary endpoints included PFS, objective response rate, safety and quality of life (QoL).

ELIGIBILITY CRITERIA

Eligible patients were aged 18 years or older with metastatic or locally recurrent confirmed adenocarcinoma or undifferentiated carcinoma which had arisen in gastro-oesophageal junction (GOJ) or stomach, with evaluable disease according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1).

Other key inclusion criteria included failure or intolerance to a minimum of two lines of prior anti-cancer therapy for recurrent/metastatic disease which must have included at least one platinum agent and one fluoropyrimidine analogue and have Eastern Co-operative Oncology Group (ECOG) performance status of 0-1 and adequate organ function. Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy was considered as first line treatment when patients relapsed or progressed within 6 months of completing this treatment. Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, was also considered a line of treatment. Known HER2-positive participants must have received prior trastuzumab.

Key exclusion criteria included uncontrolled metastatic disease to the central nervous system; poorly-controlled hypertension (systolic blood pressure >140mmHg or diastolic pressure> 90mmHg despite optimal medical management); any prior anti-vascular endothelial growth factor (VEGF) targeted therapy using small molecule VEGF TKIs (e.g. apatinib/rivoceranib) -prior anti-VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) were permitted; treatment with any previous drug therapy within two weeks prior to first dose of study treatment, including any

investigational therapy; arterial thrombotic or ischaemic events, such as cerebrovascular accident, within 6 months prior to randomization; history of another malignancy within two years prior to randomisation; known, uncontrolled malabsorption syndromes.

STUDY UPDATE

Regorafenib was found to improve survival compared with placebo in advanced refractory AGOC, offering a new treatment option.

INTEGRATE IIa results were presented at ASCO GI 2023 – 20 January 2023.

251 patients were enrolled in INTEGRATE IIa: 157 from Asia, and 94 Rest of World; 169 assigned to regorafenib and 82 to placebo. No significant heterogeneity was seen between INTEGRATE I + INTEGRATE IIa studies on OS. Pooled analysis of OS showed a HR of 0·70 (95% CI:0·56 to 0·87; p= 0·001; 361 events). In INTEGRATE IIa alone, OS HR was 0·68 (95%CI: 0·52 to 0·90; p=0·006; 238 events), with 12-month survival rate of 19% (regorafenib) vs 6% (placebo). After pre-planned adjustment for multiplicity, there were no statistically significant differences across region or other pre-specified subgroups. Regorafenib improved PFS (HR=0·53; 95% CI: 0·40 – 0·70; p<0.0001) and delayed deterioration in global QoL (HR 0·68; 95% CI: 0·52-0·89; p = 0·0043). Toxicity is consistent with previous reports.

PUBLICATIONS

- Lyn Ley Lam, Nick Pavlakis, Kohei Shitara, Katrin M Sjoquist, Andrew J Martin, Sonia Yip, Yoon-Koo Kang, Yung-Jue Bang, Li-Tzong Chen, Markus Moehler, Tanios Bekaii-Saab, Thierry Alcindor, Christopher J. O'Callaghan, Niall C. Tebbutt, Wendy Hague, Howard Chan, Sun Young Rha, Keun-Wook Lee, Val Gebski, Anthony Jaworski, John Zalcberg, Timothy Price, John Simes, David Goldstein, on behalf of the INTEGRATE investigator Study Team. INTEGRATE II: Randomised Phase III Controlled Trials of Regorafenib Containing Regimens Versus Standard of Care in Refractory Advanced Gastro-Oesophageal Cancer (AGOC): a study by the Australasian Gastro-Intestinal Trials Group (AGITG). BMC Cancer, 2023 23:180 https://doi.org/10.1186/s12885-023-10642-7
- INTEGRATE IIa results publication submitted to the *Lancet* (outcome pending)

TRANSLATIONAL RESEARCH

Archival tumour tissue and serial bloods at 4 timepoints (C1D1, C2D1 C4D1 and end of treatment) were collected from all participants. These will be used to identify biomarkers that are prognostic/predictive for study endpoints relating to survival, response, and safety. A regorafenib pharmacokinetic sub-study may also be conducted to explore any variation between patient populations from different geographical regions. Other translational research studies will be guided by exploratory study results of the earlier INTEGRATE trial.

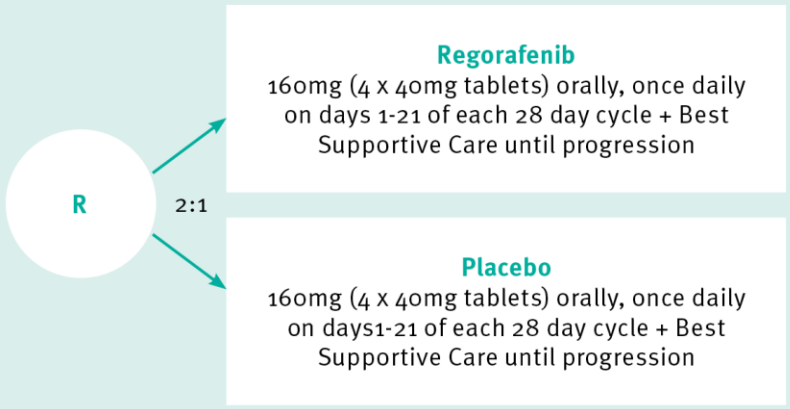
STUDY SCHEMA

Eligibility

- Metastatic or locally recurrent gastro-oesophageal cancer
- Adenocarcinoma or undifferentiated carcinoma
- Failed or intolerant to a minimum of two lines of prior anti-cancer therapy

Stratification

- Location of tumour (GOJ vs gastric)
- Geographic region (Asia vs Rest of World)
- Prior VEGF inhibitors (Y/N)



Endpoints

Overall survival (Primary)
Progression free survival (PFS)
Objective tumour response rate (RR)
Quality of life (QoL)
Safety
Biomarkers
Pharmacokinetics (PK)