FULL PROTOCOL TITLE

INTEGRATE IIb: A Randomised Phase III Open Label Study of regorafenib + nivolumab vs standard chemotherapy in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)

STUDY CHAIRS

Prof Nick Pavlakis

Prof Kohei Shitara

Prof David Goldstein

PROJECT MANAGER / TRIAL COORDINATOR

Ailsa Langford, Project Manager

Chelsea Bassett, Trial Coordinator

Monet Potter, Trial Coordinator

integrateii.study@sydney.edu.au

LINK TO STUDY

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

TRIAL IDENTIFIER

NCT04879368

COORDINATING CENTRE

The University of Sydney, NHMRC Clinical Trials Centre

FUNDING SOURCES

Bayer HealthCare Pharmaceuticals Inc

PRESENTER

Prof Nick Pavlakis

Royal North Shore Hospital

FINANCIAL DISCLOSURE

None to declare.

AIM/S

To determine if the regorafenib and nivolumab combination (RegoNivo) improves overall survival compared with current standard chemotherapy options in refractory Advanced Gastro-oesophageal Carcinoma (AGOC).

BACKGROUND

AGOC has a poor prognosis, and there is no established standard treatment following failure of first- and second-line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in the INTEGRATE Phase II trial. The INTEGRATE II Phase III trial commenced aiming to determine if regorafenib improves overall survival in refractory AGOC. The INTEGRATE II study was amended in December 2019 into two separate trials; INTEGRATE IIa (Regorafenib v placebo; presented at ASCO 2023, publication submitted) and IIb.

Immune checkpoint inhibitors enhance anti-tumour T-cell activity through the inhibition of immune checkpoints such as the programmed death-1 (PD-1) receptor. Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of PD-1, shown to be effective in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens in the ATTRACTION-2 study. Biologic rationale exists for synergy between anti-angiogenic therapy (anti-VEGF and others) and anti-PD-1/PD-L1 therapy through changes in the tumour microenvironment. The regorafenib and nivolumab combination (RegoNivo) showed manageable toxicity and encouraging activity in patients with refractory advanced gastric cancer in a Phase Ib trial, including in patients having received prior nivolumab. Current practice in countries participating in INTEGRATE IIb has evolved to use chemotherapy in 3rd and subsequent lines of therapy in fit patients. Agents with demonstrated activity in the 2nd line setting (vs Best supportive Care alone) are utilised, including taxanes (paclitaxel and docetaxel), irinotecan, and oral trifluridine/tipiracil (TAS 102).

With the shift in practice in AGOC resulting in use of multiple lines of therapy, the use of new immunotherapy agents, and the promising activity of RegoNivo, the INTEGRATE IIb amended trial was commenced to compare the effectiveness of RegoNivo in pre-treated patients with AGOC compared to the current standard chemotherapy.

STUDY DESIGN

A randomised phase III, open label trial with 2:1 (RegoNivo: standard chemotherapy) randomisation and stratification by:

1. Geographic region (Asia vs. Rest of World)
2. Prior VEGF inhibitors (Yes vs No)
3. Prior immunotherapy (Yes vs No)

Both arms will receive Best Supportive Care (BSC).

STATISTICAL CONSIDERATIONS

A sample of 450 participants randomised in a 2:1 ratio (RegoNivo: chemotherapy) and followed until 380 deaths occur (e.g. over a 24 month recruitment period plus an additional follow-up period of at least 12 months) provides 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05.

ELIGIBILITY CRITERIA

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial.

KEY INCLUSION CRITERIA

1. Adults (18 years or over) with metastatic or locally recurrent gastro-oesophageal cancer which:
    a. Has arisen in any primary gastro-oesophageal site (oesophago-gastric junction (GOJ) or stomach); and
    b. Is of adenocarcinoma or undifferentiated carcinoma histology; and
    c. Is evaluable according to RECIST 1.1 by CT scan performed within 21 days prior to randomisation.
    d. Has failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy for recurrent/metastatic disease which must have included at least one platinum agent and one fluoropyrimidine analogue.
    e. HER2+ve participants must have received trastuzumab
2. ECOG Performance Status of 0 or 1
3. Ability to swallow oral medication.

KEY EXCLUSION CRITERIA

1. Known allergy to the investigational product drug class or excipients in regorafenib
2. Poorly controlled hypertension
3. Participants with known uncontrolled malabsorption syndromes
4. Any prior anti-VEGF targeted therapy using small molecule VEGF TKIs. Prior anti-VEGF targeted monoclonal antibody therapies are permitted
5. Arterial thrombotic or ischaemic events within 6 months prior to randomization
6. Venous thrombotic events and pulmonary embolism within 3 months prior to randomization
7. Any haemorrhage or bleeding event › Grade 3 within 4 weeks of randomization
8. Uncontrolled metastatic disease to the central nervous system
9. Abnormal thyroid function (TSH outside normal range)

STUDY UPDATE

The INTEGRATE IIb study opened to recruitment in May 2021 and has now reached 80% recruitment. As of the September 2023, there are 24 Australian sites open and 389 participants enrolled globally into the study. Recruitment in each regions is as follows; Australia (96 pts), Korea (131 pts – recruitment now closed), Japan (77 pts), Taiwan (8 pts), Germany (72 pts) and USA (5 pts). Sites in Italy, France, Belgium and Spain are likely to open in Q4 2023. Site Monitoring schedules have returned in Australia following the pandemic and all second monitoring visits are on target to be completed by the end of 2023. Recruitment is expected to close following Q2 2024.

Protocol: Current Protocol Amendment v8.0 dated 24Apr2022.

RECRUITMENT

Globally 389/450 randomised participants.

- **Barriers**
  - COVID-19 pandemic did impact upon accrual, but study currently remains on target to accrue in the expected time frame.
  - Feedback from sites: Many patients did not reach 3rd line due to decline in PS. Patients with advanced gastro-oesophageal cancer who have failed at least 2 lines of therapy are usually fairly unwell and sites are advising that some of these patients may not want to undergo further treatment.

The INTEGRATE IIb study has enrolled globally across Europe, Asia, USA and Australia, covering a diverse patient population. To monitor equity, diversion and inclusion in Australia, data has been evaluated on the ethnicity of Australian patients enrolled to date, with varying ethnic backgrounds including South African, Australian Aboriginal, Bosnian, Burmese, Caucasian, Chinese, English, European, Greek, Indonesian, Italian, Japanese, New Zealander, Korean, Macedonian, Papua New Guinean and Polish. Study participants with well controlled disease after two months treatment with Nivolumab are allowed to have Nivolumab administered every 28 days as oppose to every 14 days which can reduce the travel requirements for remote patients. Patients are able to complete QOLs in any of the approved available languages to assist access for non-English speaking participants.

SAFETY

At the AGITG IDSMC extraordinary Meeting held Thursday, 21st July 2022 the Independent Data and Safety Monitoring Committee found that after review of the Integrate IIB's safety interim analysis report there was no safety signals to change or modify the trial. The IDSMC recommend for the trial to continue as planned and have no safety concerns.

PUBLICATIONS

- Lam LL, Pavlakis N, Shitara K, Sjoquist KM, Martin AJ, Yip S, Kang YK, Bang YJ, Chen LT, Moehler M, Bekaii-Saab T, Alcindor T, O'Callaghan CJ, Tebbutt NC, Hague W, Chan H, Rha SY, Lee KW, Gebski V, Jaworski A, Zalcberg J, Price T, Simes J, Goldstein D. 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 Feb 22;23(1):180. doi: 10.1186/s12885-023-10642-7

- Nick Pavlakis, Kohei Shitara, Katrin Sjoquist, Andrew Martin, Anthony Jaworski, Sonia Yip, Do-Youn Oh, Markus Moehler, Li-Tzong Chen, Tanios S. Bekaii-Saab, John Simes, David Goldstein. INTEGRATE IIb: A Randomised Phase III Open Label Study of regorafenib + nivolumab vs standard chemotherapy in Refractory Advanced Gastro-Oesophageal Cancer (AGOC). ASCO GI Cancers Symposium; 20-22 January 2022; San Francisco & Online.
- Pavlakis N, Shitara K, Sjoquist K, Martin A, Jaworski A, Yip S, Oh D, Moehler M, Chen L, Bekaii-Saab T, Simes J, INTEGRATE II: A Randomised Phase III Open Label Study of regorafenib + nivolumab vs standard chemotherapy in Refractory Advanced Gastro-Oesophageal Cancer (AGOC) An international study led by the Australasian Gastrointestinal Trials Group (AGITG). ESMO, Sep 2021

TRANSLATIONAL RESEARCH

Archival tumour tissue and serial bloods for translational research will be collected from all patients at up to 4 time points: C1D1, C2D1, at the time of week 8 CT scan, and end of treatment. These will be used to explore biomarkers that are prognostic/predictive for study endpoints relating to survival, response, and safety.

- A regorafenib pharmacokinetic sub study will also be conducted using blood collection at three time points: C1D15, C2D1, C2D15 (patients on RegoNivo arm, pre- and post-Rego dose) from selected hospital sites.
- Peripheral blood mononuclear cells from serial bloods are being collected from selected patients (Europe) for analyses of immune-related biomarkers.
- Other translational research studies will be guided by exploratory study results of the earlier INTEGRATE II trial.

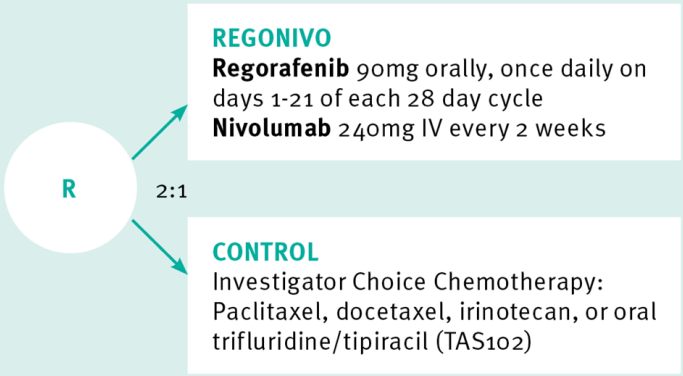
STUDY SCHEMA

Eligibility:

- Metastatic or locally recurrent gastro-oesophageal cancer
- Adenocarcinoma or undifferentiated carcinoma
- Failed or intolerant to at least 2 lines of prior anti-cancer therapy which must have included at least a platinum agent & a fluoropyrimidine analogue as single agents or in combination

Stratification:

- Geographic region (Asia vs Rest of World)
- Prior VEGF inhibitors (Y vs N)
- Prior Immunotherapy (Y vs N)



Endpoints

Overall survival (Primary)
Progression free survival (PFS)
Objective tumour response rate (OTRR)
Disease Control Rate (DCR)
Quality of life (QoL)
Safety
Pharmacokinetics
Biomarkers
Immune therapy predictors:
IHC, PDL1, CPS, Tissue TMB, Blood