INTEGRATE II: Regorafenib in Gastric Cancer Lay Summary

Full Title: Randomized Phase 3 Study of Regorafenib in refractory Advanced Oesophago-Gastric Cancer (AOGC)

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1. Study Background
   There currently exist few effective treatment options for patients with Advanced Gastro-Oesophageal Cancer (AOGC) that has returned after surgery or where it is incurable (metastatic) at diagnosis. Chemotherapy can be effective at first, but once the cancer has become resistant to this the options for treatment are limited. A second course of a different chemotherapy (docetaxel or irinotecan) can prolong survival, but not all patients are fit to receive this treatment. For those who do receive a second course their cancer will eventually become resistant (or “refractory”) to these drugs. In both of these situations there are currently no accepted treatment options that have been shown to be effective against the cancer and tolerable for patients. Better treatment options are urgently needed.

   Regorafenib (BAY 73-4506) is a ‘multi-targeted therapy’ that targets a number of different signals in the cell that cause the cancer cell to grow and produce blood vessels. The investigators had previously completed a smaller trial called Integrate. This trial has demonstrated efficacy in AOGC and could potentially become a new standard of care after other therapeutic agents have stopped working. This trial Integrate II is being done to confirm the findings in the smaller trial in a larger population. In other cancers such as colon cancer and GIST, Regorafenib is being used when other drugs have ceased to work.

2. Rationale for the study
   The aim of this study is to confirm the activity seen in the smaller trial Integrate and determine if it could become a new standard of care after other treatments no longer have activity on the patient’s gastric cancer.

3. Proposed study design
   A phase III randomised trial with 2:1 (regorafenib: placebo) randomization (see schema).

   In total it is planned to recruit 460 patients from sites in Australia, New Zealand, Asia, North America and potentially Europe over 2 years (340 to receive Regorafenib; 120 to receive placebo). Half of these patients would be from Asia as there might potentially be a difference in outcome depending on ethnicity. (230 to be recruited from that region)

   Regorafenib (or placebo) is taken as 4 tablets once per day for the first 21 days, every 4 weeks. The effectiveness of treatment will be evaluated by CT scan every 8 weeks until cancer progresses.
The participants would not be aware of which drug they have taken whether it is placebo or regorafenib. If the participants’s medical oncologist determines there is cancer progression based on clinical judgement or radiological imaging the patient will stop the study drug. The participant’s medical oncologist would determine if the participant is suitable for ongoing therapy. The participant will be actively observed until he/she passes away either from the cancer or other reason.

Translational studies will be conducted to explore which patients might receive the greatest benefit from this treatment based on (i) biomarkers – particular characteristics that can be measured in the tissue and blood of patients: (ii) drug levels to see how the patient’s body processes the drug (pharmacokinetic analysis). Patients who agree to participate in these studies will be asked to contribute tumour tissue that have previously been taken (the patient will not need to undergo an additional biopsy for the purposes of the trial) and additional samples of blood for research (at approximately 3 time points) at the same time blood is collected for their standard blood tests.

4. Please indicate if there are any restrictions to the study.

Patients must have received prior chemotherapy with 2 different courses for metastatic/incurable (Advanced) Gastro-Oesophageal Cancer. The cancer can have arisen in the lower 1/3 of the oesophagus (Gastro-Oesophageal Junction) or anywhere in the stomach, providing it is comprised of adenocarcinoma or undifferentiated cell types. The cancer must also be able to be evaluated on CT scan.

Patients with significant medical problems that might put them at risk of serious side effects from this treatment will be excluded.

5. Quality of life issues

Quality of life is a secondary endpoint of this study and patients would be asked to fill in a standardised questionnaire called EORTC QLQ-C30 to evaluate their quality of life.

The major side effects that could impact upon quality of life include –

- High blood pressure requiring treatment – risk about 1/3
- Severe Blisters to the skin of the palms and soles – risk about 1/5
- Marked Rash – risk about 1/10
- Intense Diarrhoea – risk about 1/20
- Altered blood chemicals – risk about 1/7

6. Health Economics

The cost effectiveness of this drug is another secondary endpoint of this study. The health economics component will assess whether the clinical benefit and possible improvement in the quality of the patient’s life offset the costs they potentially incur due to the limitations of funding available for increasingly expensive therapeutic options.
SCHEMA

Adult patients with AOGC (adenocarcinoma or undifferentiated) who have failed or were intolerant of 2 lines of prior chemotherapy known to have effect on gastric cancer

RANDOMISATION

Stratification by
- Location of tumour (OGJ vs Gastric)
- Geographic region (Asia vs Rest of World)
- Prior ramucirumab (drug that has a similar action to regorafenib)

REGORAFENIB
(BAY 73-4506)
160 mg orally (4 tablets), once daily on days 1-21 of a 28 day cycle
plus best supportive care (BSC)

PLACEBO
Orally with 4 matched tablets, once daily on days 1-21 of a 28 day cycle
plus best supportive care (BSC)

Disease progression

- Follow up every 2 months to determine survival
- Further treatment at investigator’s discretion