



The University of Sydney



# ALT GIST

**A randomised phase II trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (GIST)**

**NHMRC CTC Protocol number CTC 0122/AGITG AG1013GST**

**International Study Chair: Professor Heikki Joensuu**

**ANZ Study Chair: Associate Professor Desmond Yip**

**Protocol version. 1.0, 1<sup>st</sup> July 2014**

**International Sponsor:** Australasian Gastro-Intestinal Trials Group (AGITG)  
119-143 Missenden Road  
Camperdown NSW 2050

This study is collaboration between the AGITG, NHMRC Clinical Trials Centre (NHMRC CTC), European Organisation for Research and Treatment of Cancer (EORTC) and Scandinavian Sarcoma Group (SSG).

**ANZ Coordinating and International Data Centre:**

NHMRC Clinical Trials Centre  
92-94 Parramatta Road  
Camperdown NSW 2050  
Telephone: 61-2-9562-5000  
Fax: 61-2-9565-1863  
Email: [ALTGIST@ctc.usyd.edu.au](mailto:ALTGIST@ctc.usyd.edu.au)

**CONFIDENTIAL**

# ALT GIST

**Senior Statistician**

Professor Val Gebski

**CTC Clinical Lead**

Dr Katrin Sjoquist

Region	Coordinating Centre	Clinical Lead	Coordinating Centre Lead
ANZ	NHMRC CTC	A/Prof. Desmond Yip	Ms Cheryl Friend
Europe	EORTC	Prof Jean Yves Blay	Ms Anne Kirkpatrick
Scandinavia	SSG	Prof Heikki Joensuu	Dr Mikael Eriksson

## Protocol Development Working Party

The following individuals also contributed to the design and development of this protocol:

Name	Position	Organisation
Dr Wendy Hague	Director of Clinical Trials	NHMRC CTC
Dr Danielle Ferraro	Research Fellow – AGITG trials	NHMRC CTC
Ms Nicole Wong	Associate Oncology Program Manager	NHMRC CTC
Dr Sonia Yip	Translational Research Fellow	NHMRC CTC

# ALT GIST

## Table of Contents

LIST OF ABBREVIATIONS .....	5
SYNOPSIS AND SCHEMA .....	6
1. BACKGROUND.....	10
2. REGORAFENIB .....	11
3. AIM AND OBJECTIVES .....	11
4. DESIGN .....	12
5. SUBJECT POPULATION .....	12
5.1. Target Population .....	12
5.2. Inclusion criteria .....	12
5.3. Exclusion criteria.....	13
6. STUDY ENROLMENT .....	14
6.1. Screening .....	14
6.2. Registration .....	14
6.3. Randomisation.....	14
7. TREATMENT PLAN.....	14
7.1. Administration of study treatments.....	14
7.2. Dose modifications .....	15
7.2.1. Dose levels .....	16
7.2.2. Treatment-Emergent Hypertension .....	18
7.2.3. Treatment Related Hepatic Toxicity .....	20
7.3. Concomitant Medications/Treatments .....	21
7.3.1. Recommended .....	21
7.3.2. Permitted.....	22
7.3.3. Use with caution.....	22
7.3.4. Prohibited .....	22
7.3.5. Concomitant medication reporting .....	23
7.4. Treatment discontinuation.....	23
7.5. Subsequent treatment .....	23
8. ASSESSMENT PLAN .....	24
8.1. Schedule of assessments .....	24
8.2. Assessment phase definitions and special circumstances .....	26
8.2.1. Baseline.....	26
8.2.2. During treatment.....	26
8.2.3. End of treatment .....	27
8.2.4. 30 day safety assessment .....	27
8.2.5. Follow-up after treatment.....	27
8.2.6. After study is closed .....	27
9. OUTCOMES, ENDPOINTS AND OTHER MEASURES .....	27
9.1. Progression free survival at 24 months (disease progression or death) .....	27
9.2. Objective tumour response rate at 16 weeks .....	27
9.3. Clinical benefit rate at 16 weeks .....	28
9.4. Complete response rate .....	28
9.5. Time to treatment failure .....	28
9.6. Adverse Events (worst grade according to NCI CTCAE v4.03).....	28
9.7. Overall survival .....	28
9.8. Rate of patients having macroscopically complete removal of all residual disease by surgery .....	28
9.9. Change in PET imaging during washout period of regorafenib and imatinib in those taking part in the PET substudy.....	28
9.10. Biomarkers.....	29
10. SAFETY REPORTING.....	29
10.1. Definitions .....	29

# ALT GIST

10.2. Reporting of Serious Adverse Events (including SUSARs) .....	30
10.3. Pregnancy .....	31
11. CENTRAL REVIEW AND BIOSPECIMEN COLLECTION .....	31
11.1. Central Biospecimen Collection.....	31
11.2. Central Imaging Collection .....	32
12. TREATMENT INFORMATION .....	32
12.1. Description of Study Products .....	32
12.2. Supply of Study Product .....	32
12.3. Drug Accountability .....	32
13. STATISTICAL CONSIDERATIONS .....	33
13.1. Sample Size .....	33
13.2. Statistical Analysis .....	33
13.3. Compliance Assessment .....	33
14. STUDY ORGANISATION .....	33
14.1. Trial Management Committee(s) .....	34
14.2. Independent Safety and Data Monitoring Committee.....	34
15. ADMINISTRATIVE ASPECTS .....	34
15.1. Ethics and regulatory compliance .....	34
15.2. Confidentiality .....	34
15.3. Protocol amendments .....	35
15.4. Data Handling and Record Keeping .....	35
15.5. Audit and Inspection.....	35
15.6. Clinical Study Report.....	35
16. REFERENCES.....	36
17. LIST OF APPENDICES .....	37
Appendix 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 .....	38
Appendix 2. Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1) .....	39

# ALT GIST

## LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood Pressure
CBR	Clinical benefit rate
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CTC	NHMRC Clinical Trials Centre
DNA	Deoxyribonucleic acid
EGFR	Epidermal Growth Factor receptor
FDA	Food and Drug Administration
GIST	Gastrointestinal Stromal Tumour
GP	General Practitioner
HREC	Human Research Ethics Committee
HIV	Human immunodeficiency virus
IDSMC	Independent Data, Safety Monitoring Committee
INR	International Normalised Ratio
ISC	International Steering Committee
NYHA	New York Heart Association
PET	Positron emission tomography
PDGFRA	Platelet-derived growth factor receptor alpha
PFS	Progression Free Survival
PD	Progressive Disease
PR	Partial Response
SAE	Serious adverse event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake values
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TKI	Tyrosine Kinase inhibitor
ULN	Upper limit of normal

# ALT GIST

## SYNOPSIS AND SCHEMA

### PROTOCOL SYNOPSIS

#### Background

Despite highly active current treatment for metastatic gastrointestinal stromal tumour (GIST) with the use of imatinib, most people will ultimately relapse and die of multifocal metastatic disease. Using an alternating regimen of imatinib and regorafenib with brief drug free intervals may allow tumour stem cells to re-enter the cell cycle and become susceptible once more to drug therapy. Regorafenib, a multi-targeted tyrosine kinase inhibitor (TKI) with activity against angiogenic, stromal and oncogenic receptor tyrosine kinases, has demonstrated activity in the treatment of GIST and is FDA approved for third line therapy of advanced GIST.

#### General aim

To determine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST.

#### Primary objective (endpoint)

- PFS at 24 months as calculated from the time from either (i) randomization (if patients have not yet commenced treatment) or (ii) commencement of therapy (if patients are randomized during the first cycle of imatinib) to the date of progression as determined by RECIST v1.1

#### Secondary objectives (endpoints)

- Objective tumour response rate following 2 cycles of treatment
- Clinical benefit rate (SD + PR + CR) following 2 cycles of treatment
- CR rate
- Time-to-treatment failure
- Safety/toxicity/tolerability
- Overall survival

#### Exploratory objectives (endpoints)

To explore the relationship between study endpoints and:

- Change in PET imaging during washout period of regorafenib and imatinib (in subset of participants at selected centres)
- Imatinib plasma levels at 3 and 11 weeks after commencement of treatment in both arms, and in Arm B regorafenib plasma levels 7 and 15 weeks after commencement of treatment
- Circulating biomarkers as prognostic and/or predictive markers including, but not limited to:
  - Circulating serum/plasma growth factor and cytokine levels (multiplex assay)
  - KIT/PDGFRA mutations in circulating blood DNA ('liquid biopsy')

# ALT GIST

- DNA load

- Tumour tissue biomarkers including, but not limited to, proteins relating to PDGFR signalling and angiogenesis
- Rate of patients having macroscopically complete removal of all residual disease by surgery

## Design

Prospective, randomised, open label phase II trial, stratified by participating site, previous adjuvant therapy (prior vs none), and previous imatinib for metastatic disease for less than 21 days.

## Population

The target population is adults with histologically confirmed, measurable metastatic GIST, who have received no prior treatment for metastatic disease. Patients who are currently taking, and have had up to 21 days of uninterrupted treatment with 400mg daily of imatinib are eligible to participate in this study.

## Study treatments

Patients will be randomised to receive either:

Arm A – imatinib 400mg orally daily continuously (control arm);  
or

Arm B – alternating 28-day periods of imatinib 400mg orally daily for 21 to 25 days followed by a washout (drug free) period of 3 to 7 days, then regorafenib 160mg orally daily for 3 weeks followed by a 7 day washout (drug free) period.

Treatment will continue until disease progression or prohibitive adverse events as detailed in the protocol.

## Assessments

- Clinic visits (including laboratory tests) will be required at baseline, prior to each cycle of treatment and at the end of study treatment visit. During Cycles 1, 2 and 3, clinic visits will occur prior to commencing each new agent (4 weekly) including blood tests for haematological, hepatic and renal function. .
- Additional liver function tests will be performed weekly during the first 2 cycles of regorafenib treatment for those patients in the alternating arm (Arm B) of the study.
- Imaging will be performed at baseline (within 21 days prior to commencing treatment) and every 8 weeks for the first year on trial, and then every 12 weeks until disease progression or death, timed from the date of the commencement of treatment.
- Blood samples for biomarker studies will be collected at baseline and every 4 weeks for the first 3 cycles of treatment; and then every 8 weeks for the first year on trial; and then every 12 weeks until progression or cessation of study treatment (up to 24 months).
- Blood for drug plasma level will be collected on the last

## ALT GIST

day of taking imatinib in both Arm A and Arm B, as well as on the last day of taking regorafenib in Arm B, in cycles 1 and 2.

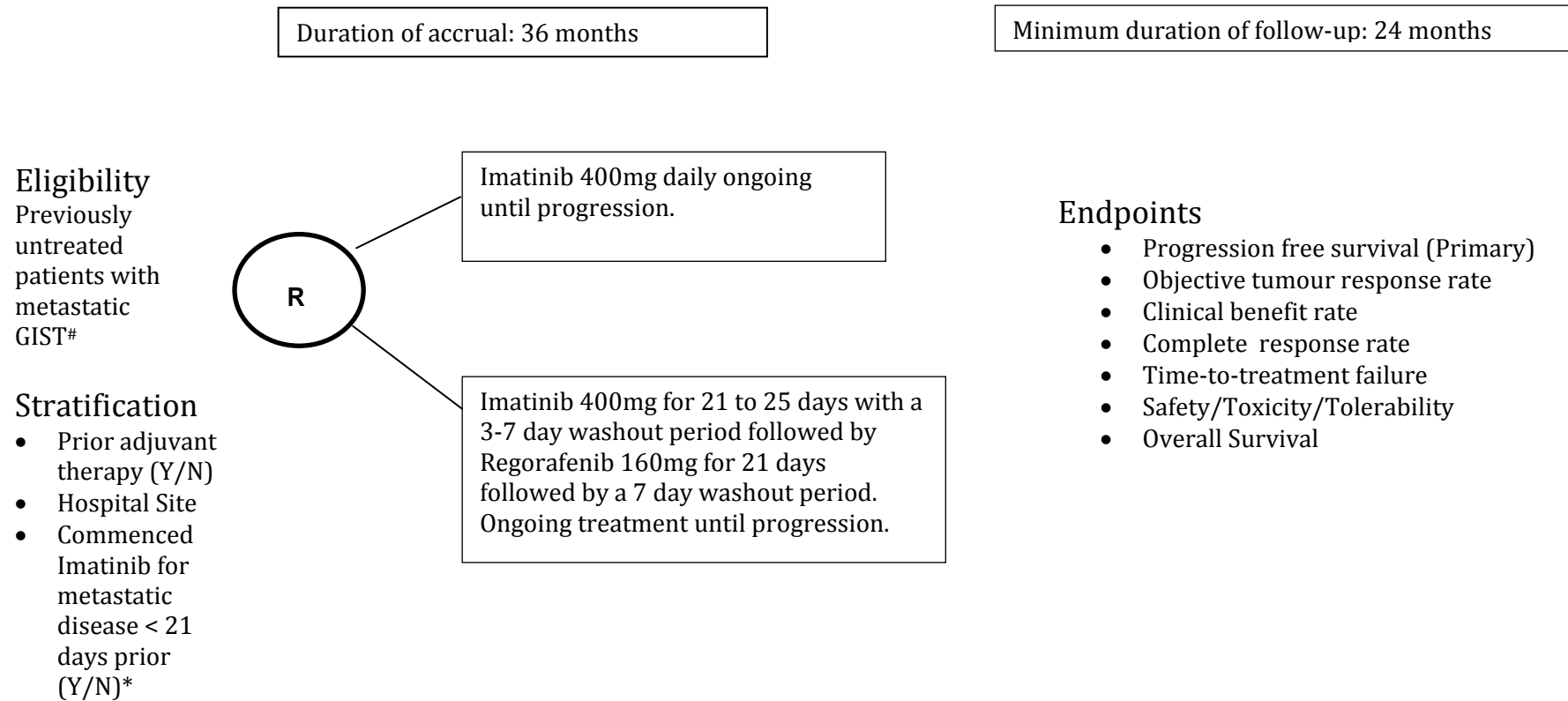
- For those involved in the PET substudy, 2 PET scans will be performed, one at the commencement of the drug washout period and one at the conclusion of the drug washout period during cycle 3.

### Statistical considerations

In order to demonstrate a relative increase in progression free survival at 24 months from the date of randomisation from an expected 78% to 88%, with 80% power and 95% confidence based on A'Hern's adjustment to Fleming's design, approximately 110 evaluable participants will be required in each arm. Thus, it is proposed to enrol 240 participants into the trial, allowing for approximately a 10% drop-out rate. Currently 80% of participants are expected to achieve a clinical benefit at 24 months (CBR – rate of complete or partial response, or stable disease). A secondary outcome would be to determine whether a minimum 25% relative increase of the CBR (from 80% to 85%) in the experimental cohort can be attained. The study will be open to recruitment for 36 months while follow-up will continue until the last enrolled participant has been followed for a minimum of 24 months timed from the date of commencement of treatment.



# Study Schema



## NOTE:

Cycles are 8 weeks in length for both arms.

# Not suitable for surgery with curative intent

\* Patients who have already commenced imatinib may be randomized at any time in the first 21 days of treatment. For these patients, the number of days that imatinib has already been taken for will be **included** in the treatment period (ie this prior treatment will count towards the total days of imatinib in cycle 1).

## 1. BACKGROUND

While modern treatment of metastatic gastrointestinal stromal tumour (GIST) with imatinib is highly active with clinical benefit rates of over 80%, most people will ultimately relapse. Two large pivotal randomized trials of 400mg versus 800mg of imatinib conducted in Europe/Scandinavia/Australasia and North America respectively (1, 2), demonstrated the median progression free survival (PFS) was approximately two years. However more recent data suggests that the median PFS is longer than this in patient populations with a small tumour burden at the time of imatinib initiation (3). Nevertheless clinical experience and longer follow up has confirmed that relatively few people are cured, with most people eventually dying of multifocal disease progression.

In these circumstances, tumours may express varying mechanisms of resistance to imatinib (4) as well as second generation tyrosine-kinase inhibitors (TKI), due either to the acquisition of secondary mutations in *KIT* (5) or potentially the selection of pre-existing drug-resistant clones (6). The emergence of resistance to imatinib occurs despite initial response rates of well over 70% in the more sensitive tumours carrying mutations in exon 11 of *KIT*.

Given the exquisite sensitivity of GIST cells to imatinib *in vitro* (7), and the dramatic clinical effect of imatinib administered to people in the first-line setting (8), particularly in tumours carrying mutations in *KIT* exon 11 (representing approximately 65% of all patients), it is unclear why complete responses are comparatively rare and the cure rate so low, with the vast majority of people dying with advanced disease.

A potential explanation for this observation relates to the presence of GIST stem cells – Bardsley et al have identified progenitors for Interstitial Cells of Cajal (ICC) which act as stem cells for GIST. These cells expressed Cd44 (in a similar manner to some other cancer stem cells) and Cd34, and were capable of self-renewal and differentiation. They formed malignant tumours that expressed GIST markers when spontaneously transformed stem cells were implanted in nude mice. These stem cells had innately low *KIT* expression, and were thus resistant to in-vitro blockade by *KIT* inhibitors. The progeny cells however rely on *KIT* signalling for their survival and differentiation (9). We hypothesise that by eliminating the selective pressure of continued pharmacologic therapy - which encourages the proliferation of resistant clones - by temporarily discontinuing treatment ('washout period'), and using a second TKI such as regorafenib, with established activity in GIST (10), response rates and survival times may improve for patients with this malignancy.

Incorporating a brief TKI- free interval (washout period) into the treatment schedule may allow dormant cells to become active again, and quiescent stem cells responding to higher than pre-treatment levels of stem cell factor (a ligand for the extracellular domain of *KIT*, known to increase during treatment for metastatic GIST (11)) may also re-enter the cell cycle. This cell re-activation should result in even greater tumour apoptosis with the subsequent recommencement of TKI therapy.

Tumour cells harbouring secondary mutations that expand predominantly because of this selective pressure may also regress during a brief period free of TKI exposure, and become more susceptible to therapy.

Given the above rationale, it is predicted that with the addition of a second targeted agent, regorafenib (a drug with very substantial activity, at least in the third-line setting in GIST (10)) after a drug-free

# ALT GIST

period, residual tumour cells may be eradicated and some partial responders will be converted into complete responders.

## 2. REGORAFENIB

Regorafenib (12) is a TKI with inhibitory activity against VEGFR1-3, bFGFR, PDGFRA, Tie 2, BRAF, CRET RaFi p38 MAPK and KIT with an IC<sub>50</sub> *in vitro* of approximately 10nM. In a randomised, placebo controlled phase 3 trial in 199 patients who had failed at least 2 previous lines of therapy for GIST, there was a statistically significant reduction in the risk of progression in the regorafenib arm compared to the placebo arm (median PFS 4.8 vs. 0.9 months, HR 0.27)(13). During the double blind phase of the same trial, the most common grade 3 or higher adverse events recorded in the regorafenib arm were hypertension (23%), hand-foot syndrome (20%), and diarrhoea (5%). Dose modifications were required more frequently in the regorafenib arm compared to the placebo arm, but the rate of permanent treatment discontinuation due to adverse events in the regorafenib arm (6%) was similar to that in the placebo group (8%).

These strategies for improving response to therapy (treatment-free periods and addition of a second active agent) are incorporated in the design of this pragmatic trial, which aims to increase the PFS rate and ultimately increase the cure rate for advanced GIST.

The purpose of this study is to determine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST. If this strategy proves beneficial it has the potential to change treatment in this setting.

## 3. AIM AND OBJECTIVES

General aim	To determine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST.
Primary objective (endpoint)	<ul style="list-style-type: none"><li>▪ PFS at 24 months as calculated from either the date of (i) randomization (if patients have not yet commenced treatment) or (ii) commencement of therapy (if patients are randomized during the first cycle of imatinib)</li></ul>
Secondary objectives (endpoints)	<ul style="list-style-type: none"><li>▪ Objective tumour response rate at 2 cycles after randomisation</li><li>▪ Clinical benefit rate (SD + PR + CR) following 2 cycles of treatment</li><li>▪ CR rate</li><li>▪ Time to treatment failure</li><li>▪ Safety/toxicity/tolerability</li><li>▪ Overall survival</li></ul>
Tertiary and correlative objectives	<p>To explore the relationship between study endpoints and:</p> <ul style="list-style-type: none"><li>▪ Change in PET imaging during washout period of regorafenib and imatinib (in subset of participants at selected centres)</li><li>▪ Arm A: Imatinib plasma levels at 4 and 12 weeks after</li></ul>

# ALT GIST

commencement of treatment. Arm B: Imatinib plasma levels at 3 and 11 weeks after commencement of treatment and regorafenib plasma levels 7 and 15 weeks after commencement of treatment.

- Circulating biomarkers as prognostic and/or predictive markers including but not limited to:
  - Circulating serum/plasma growth factor and cytokine levels (multiplex assay)
  - KIT/PDGFRA mutations in circulating blood DNA ('liquid biopsy')
  - DNA load
- Tumour tissue biomarkers including, but not limited to, proteins relating to EGFR and PDGFR signalling and angiogenesis.
- Rate of patients having macroscopically complete removal of all residual disease by surgery

## 4. DESIGN

Prospective, randomised, open label phase II trial, with randomisation 1:1 and stratification by site, receipt of previous adjuvant therapy (prior vs none), and receipt of imatinib for metastatic disease for less than 21 days.

## 5. SUBJECT POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the regional site coordinating centre prior to registration.

### 5.1. Target Population

Eligible participants with metastatic GIST (not suitable for surgery with curative intent), with no previous treatment for metastatic disease.

### 5.2. Inclusion criteria

1. Adults (over 18 yrs) with histologically confirmed GIST. In CD-117-negative cases DOG-1 must be positive or a *KIT*/*PDGFRA* mutation must be present.
2. Unresectable, metastatic disease.
3. No prior TKI for metastatic disease, with the exception of those patients who have had up to 21 days of uninterrupted treatment on 400mg daily of imatinib.
4. Imatinib therapy given as an adjuvant treatment and completed at least 3 months prior to entry into this trial is permitted. Patients who have progression of GIST while on adjuvant therapy are not eligible for this trial.
5. ECOG performance status 0-2
6. Measurable disease by RECIST version 1.1. (Note: Participants with only peritoneal disease will be eligible only if they have lesions measurable in two dimensions and have at least 1 lesion which is  $\geq 2$  cm in size).

## ALT GIST

7. Adequate bone marrow function (Haemoglobin  $\geq 9.0\text{g/dL}$ , platelet count  $\geq 100 \times 10^9/\text{L}$ , and absolute neutrophil count  $\geq 1.5 \times 10^9/\text{L}$ ).
8. Adequate liver function (Serum total bilirubin  $\leq 1.5 \times \text{ULN}$ , INR  $\leq 1.5$ , and ALT, AST, ALP  $\leq 2.5 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  for participants with liver metastases). Lipase level must be  $\leq 1.5 \times \text{ULN}$ .
9. Adequate renal function (Creatinine clearance  $> 50\text{ml/min}$ ) based on either the Cockcroft Gault formula, 24 hour urine or Glomerular Filtration Rate (GFR scan); and serum creatinine  $\leq 1.5 \times \text{ULN}$ .
10. Tumour tissue available for central review.
11. Willing and able to comply with all study requirements, including treatment timing and/or nature of required assessments.
12. Study treatment both planned and able to start within 14 days of randomisation.
13. Signed, written informed consent.

### 5.3. Exclusion criteria

1. Concurrent GI illness which may prevent absorption of imatinib or regorafenib – please note that prior gastrectomy or bowel resection does not exclude patients from this study.
2. Use of other investigational drugs within 4 weeks prior to enrolment.
3. Known sensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
4. Participants receiving therapeutic doses of warfarin.
5. Presence of brain metastases.
6. The presence of *PDGFR* D842V mutation or other mutation known to cause imatinib resistance.
7. Inability to swallow tablets.
8. Arterial thrombotic or ischaemic events, such as cerebrovascular accident or pulmonary embolism within 6 months prior to randomisation; or major venous thrombotic events requiring use of an anticoagulant such as warfarin within 6 months prior to randomisation.
9. Poorly controlled hypertension (systolic blood pressure  $> 140\text{ mmHg}$  or diastolic pressure  $> 90\text{ mmHg}$  despite optimal medical management).
10. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomisation, or non healing wound, ulcer or fracture.
11. Congestive cardiac failure (NYHA  $\geq$  grade 2), unstable angina or new onset angina within the previous 3 months, or AMI within the previous 6 months. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
12. Haemorrhage or bleeding event  $\geq$  Grade 3 according to CTCAE v4.0 within 4 weeks prior to randomisation.
13. Ongoing infection of  $>$  Grade 2 according to CTCAE v4.0.
14. Active hepatitis B or C or HIV, or chronic hepatitis B or C requiring treatment with antiviral therapy. Testing for these is not mandatory unless clinically indicated.
15. Interstitial lung disease with ongoing signs and symptoms.
16. Persistent proteinuria of  $\geq$  Grade 3 ( $>3.5\text{g}/24\text{ hours}$ ) according to CTCAE v4.0
17. Other significant medical or psychiatric condition judged by the investigator to interfere with protocol requirements.
18. Use of biological response modifiers such as granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to randomisation.
19. Patients taking strong cytochrome P (CYP) CYP3A4 inhibitors (eg clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinovir,

# ALT GIST

telithromycin, voriconazole) or strong CYP3A4 inducers (eg carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort).

20. History of another malignancy within 5 years prior to registration. Patients with a past history of adequately treated carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or superficial transitional cell carcinoma of the bladder are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment.
21. Pregnancy, lactation, or inadequate contraception. Women must be post menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Women of childbearing potential and men must agree to use adequate contraception before entering the trial until at least 8 weeks after the last study drug administration.

## 6. STUDY ENROLMENT

### 6.1. Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed. Entry to the study is conditional on the outcome of the *DOG-1* or *KIT/PDGFRA* mutational status.

### 6.2. Registration

Registration will be done according to the instructions in the Study Manual. Once the registration process has been completed, the participant will be assigned a participant study number. Individuals may only be registered once in this trial.

Written confirmation of registration will be provided to the site.

Requests for registration will only be accepted from authorised investigators at sites that have all requisite approvals in place. Registration should be done only after all screening assessments have been performed and the responsible investigator has verified the participant's eligibility.

### 6.3. Randomisation

Randomisation occurs once all the inclusion criteria has been met.

Once the registration and randomisation processes have been completed as per the instructions in the Study Manual, the patient will be assigned a subject study number, a treatment arm, and written confirmation of successful randomisation will be provided to the site.

Individuals may only be registered and randomised once in this trial.

## 7. TREATMENT PLAN

### 7.1. Administration of study treatments

Participants randomised to standard therapy (Arm A) will receive 400mg (1 x 400mg tablet) orally daily of imatinib, with no washout periods.

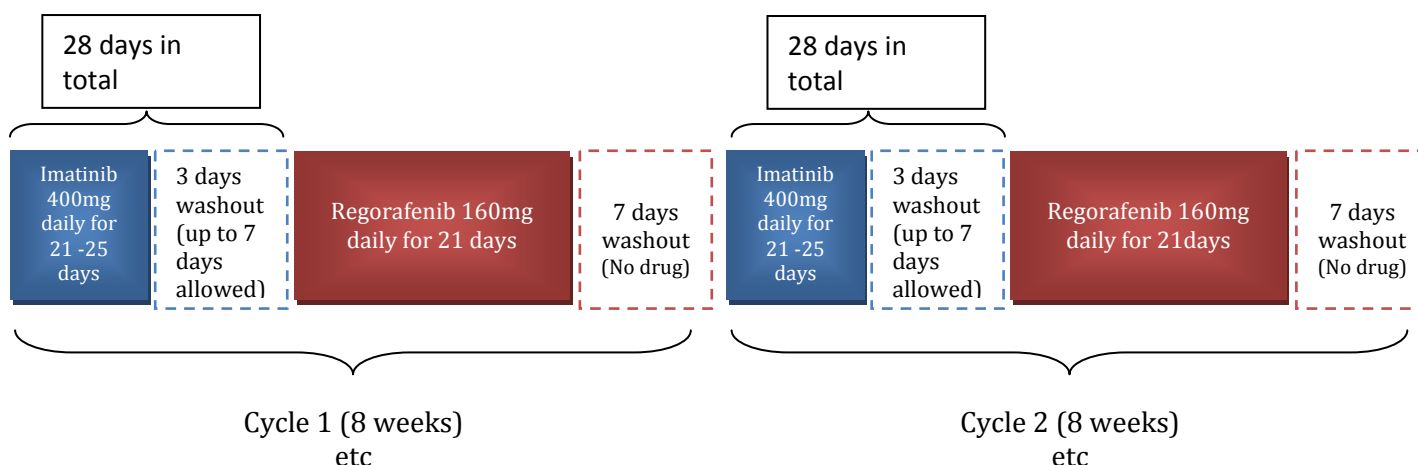
Those randomised to the experimental alternating arm (Arm B) will receive:

Imatinib 400mg (1 x 400mg tablet) orally daily for 21 to 25 days, then a 3 - 7 day washout period (no drug). A 3 day washout period is mandated, but up to 7 days break is allowed to maximise tolerability

# ALT GIST

of the regimen, at the discretion of the site investigator. In total, the days taking imatinib plus the washout period must be 28 days. This is followed by regorafenib 160 mg (4 x 40mg tablets) orally daily for 21 days, then a 7 day washout period. This combination of imatinib, regorafenib and intervening washout periods will constitute 1 cycle of study treatment (imatinib plus washout period 28 days in total; regorafenib 3 weeks on, 1 week off; cycle duration 8 weeks in total). See diagram below.

Missed or vomited tablets cannot be compensated for by treatment at a later date and/or time.



Even in participants with a complete response, treatment will continue until progressive disease (PD) or prohibitive adverse events are documented. Participants who cease treatment after receiving at least 2 years of therapy from the time of commencing treatment will not be considered to have failed treatment for toxicity reasons. Surgery will be permitted for participants whose cancer becomes operable during trial treatment at the discretion of the treating team, and participants will be able to continue on study treatment and will continue to be followed for progression free survival post operatively. For patients undergoing surgery, regorafenib should be ceased at least 2 weeks prior to surgery, and recommenced on the basis of clinical judgement.

Treatment after progression will be according to clinician preference and local institutional guidelines. Crossover from either arm to single agent regorafenib will not be permitted as part of the study.

## 7.2. Dose modifications

### Dose escalation:

Regorafenib dosages will not be increased above 160mg daily.

Dose escalation of imatinib up to 800mg daily will be allowed in both arms for those participants with an identified *KIT* exon 9 mutation. It is recommended in this situation that the patient be escalated first to 600mg for at least 2 weeks prior to further escalation to 800mg. The timing of dose escalation for *KIT* exon 9 mutation patients during the trial is at the discretion of the site investigator.

### Dose reductions and delays:

Instructions for treatment delays and dose modifications for adverse events are specified below. In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until

# ALT GIST

the adverse event has resolved to G0-1, at the investigator's discretion unless otherwise specified. Day 1 treatment may be delayed for a maximum of 28 days. If the adverse event has not resolved to G0-1 after this delay, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events with differing recommendations, then the modification that results in the longest delay and lowest dose should be used.

Dose modification guidelines differ for each arm of the study (see below). For Arm A, dose modifications are provided for adverse events thought to be attributable to imatinib (Table 2). For Arm B, dose modifications are provided for adverse events specific to regorafenib (hand-foot syndrome, hypertension and hepatic dysfunction)- see Tables 3-5, and separately for general adverse events thought related to either regorafenib or imatinib (including nausea, haematologic abnormalities, fatigue) – see Table 5.

## 7.2.1. Dose levels

Table 1:

DRUG	Units	STARTING DOSE	LEVEL				
			-2	-1	0 START	+1	+2
Imatinib	mg	400	200	300	400	600 <sup>a</sup>	800 <sup>a</sup>
Regorafenib	mg	160	80	120	160	----	----

- a. Only patients with *KIT* exon 9 mutations are permitted to have imatinib dose escalations above 400mg.

**In Arm A** (standard therapy arm), dose modifications for adverse events thought to be related to imatinib are shown below:

Table 2:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-haematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade ≤1, then resume at same dose level. If event recurs, withhold dose until toxicity is grade ≤1 and reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.	Withhold dose until toxicity is grade ≤1, then reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.
Haematologic (excluding anaemia **)	Continue at the same dose level.	Continue at the same dose level	Withhold dose until neutrophils ≥1.0 and platelets ≥100, then	Withhold dose until neutrophils ≥1.0 and platelets ≥100, then



## ALT GIST

			resume treatment at the same dose level. If event recurs, withhold dose until neutrophils $\geq 1.0$ and platelets $\geq 100$ , and reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.	reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.
--	--	--	---	---

**\*\***No dose modifications are required for Grade 1–4 anaemia however transfusion is permitted.

**In Arm B** (alternating therapy arm) for events specifically related to regorafenib (skin toxicity, treatment emergent hypertension, and hepatic dysfunction), see tables below:

Dose modifications for skin toxicity including Hand-foot skin reaction.

Table 3:

Skin Toxicity Grade	Occurrence	Dose Modification <sup>a</sup>
Grade 1: Numbness, dysaesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the participant's normal activities.	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the participant's normal activities.	1st occurrence	Decrease dose by one dose level and immediately institute supportive measures. If there is no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1 <sup>c</sup> .
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one dose level <sup>c</sup> .
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one additional dose level <sup>b,c</sup> .
	4th occurrence	Discontinue study treatment permanently.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the participant to be unable to work or perform activities of daily living.	1st occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one dose level.

## ALT GIST

	2nd occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one additional dose level <sup>b</sup> .
	3rd occurrence	Discontinue study treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the Investigator.

b. Participants requiring > 2 dose level reductions should discontinue protocol therapy permanently.

**If there is no recovery after a delay of 28 days, treatment will be discontinued permanently.**

For participants who require a dose reduction for grade 2 or 3 rash or hand-foot skin reaction, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose without the reappearance of rash or hand-foot skin reaction > grade 1.

### **7.2.2. Treatment-Emergent Hypertension**

The dose modification schedule for treatment-emergent hypertension during study drug dosing should be followed. Participants' Blood Pressure (BP) measurements will be monitored and appropriate treatment to effectively control hypertension is required.

(Table on next page).

# ALT GIST

Table 4:

NCI-CTCAE v4.03 Grade	Definition	Anti-Hypertensive Therapy	Regorafenib dosing
Grade 2	Systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP $\leq$ 90 mmHg - If BP previously within normal limits, start anti-hypertensive monotherapy - If participant already on anti-hypertensive medication, titrate up the dose.	Continue regorafenib. If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP $\leq$ 90 mmHg <sup>a</sup> . When regorafenib is restarted, continue at the same dose level
Grade 3	Systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 100 mmHg OR More than one anti-hypertensive medication or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP $\leq$ 90 mmHg - Start anti-hypertensive medication AND/OR - Increase current anti-hypertensive medication AND/OR - Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP $\leq$ 90 mmHg, and if symptomatic, until symptoms resolve <sup>a</sup> . When regorafenib is restarted, continue at the same dose level If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level <sup>b</sup> . If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level <sup>c</sup>
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)		Discontinue study treatment permanently

a. Participants requiring a delay of 28 days will be permanently discontinued.

b. If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the Investigator's discretion.

c. Participants requiring > 2 dose level reductions will be permanently discontinued.

# ALT GIST

## 7.2.3. Treatment Related Hepatic Toxicity

For participants with observed worsening of serum liver tests considered related to study drug (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring recommendations in the below table should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in participants with Gilbert's syndrome.

Table 5:

Observed Elevations	1st Occurrence	Restart	Recurrence
AST and/or ALT $\leq$ 5x ULN ( $<$ G3)	Continue dosing, with weekly monitoring of liver function until transaminases return to $<$ 3x ULN ( $\leq$ G1) or baseline.		
ALT and/or AST $>$ 5x ULN ( $\geq$ G3)	Interrupt dosing, with weekly monitoring until transaminases return to $<$ 3x ULN or baseline.	If the potential benefit for reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: Reduce 1 dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST $>$ 20x ULN ( $\geq$ G4)	Discontinue		
ALT and/or AST $>$ 3X ULN ( $\geq$ Grade 2) with concurrent bilirubin $>$ 2 X ULN	Discontinue treatment and measure serum liver tests weekly until resolution. Exception: Patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		

NOTE: ALT, AST, and bilirubin must be obtained at baseline and monitored weekly for the first 2 cycles even if values are normal. The investigators may use investigational site or local laboratory AST, ALT, and bilirubin values for subject treatment decisions for day 8, 15 and 22 of regorafenib treatment for Cycles 1 and 2

ALT = alanine aminotransferase, AST = aspartate aminotransferase, NCI-CTCAE v 4.03 = National

Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0, ULN = upper limit of normal.

In **Arm B**, for all other events related to either imatinib or regorafenib (excluding skin toxicity, treatment emergent hypertension, and hepatic dysfunction), see table below:

(Table on next page).

# ALT GIST

Table 6:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-haematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade $\leq 1$ , then resume at same dose level. If event recurs, withhold dose until toxicity is grade $\leq 1$ and reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.	Withhold dose until toxicity is grade $\leq 1$ , then reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.
Haematologic (excluding anaemia)	Continue at the same dose level.	Continue at the same dose level	Withhold dose until neutrophils $\geq 1.0$ and platelets $\geq 100$ , then resume treatment at the same dose level. If event recurs, withhold dose until neutrophils $\geq 1.0$ and platelets $\geq 100$ , and reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.	Withhold dose until neutrophils $\geq 1.0$ and platelets $\geq 100$ , then reduce dose for next cycle by 1 level. Dose reduce by 1 further level for further grade 3 or higher toxicity.

## 7.3. Concomitant Medications/Treatments

All therapies which are considered necessary for the participant's welfare, and which are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the treating clinician.

### 7.3.1. Recommended

The following medications and treatments are recommended in this study for the prevention and treatment of skin rash including hand-foot skin reaction in those on the alternating arm (Arm B):

Before initiating treatment:

- Check condition of hands and feet

During treatment:

- Avoid pressure points and protect tender areas by use of cushion inserts and well-padded footwear
- Avoid items that rub, pinch, or create friction

# ALT GIST

- Foot soaks with tepid water and Epsom salts
- Suggest a manicure/pedicure, when indicated
- Recommend pumice stone use for callus or 'rough spot' removal
- Use socks/gloves to cover moisturising creams once applied

Use of creams:

- Apply non-urea based skin-hydrating creams liberally.
- Keratolytic creams: Use sparingly and only to affected (hyperkeratotic) areas.
- Urea-based creams, Salicylic acid 6%, Alpha hydroxy acid (AHA) based creams: Concentrations of approximately 5-8% provide gentle chemical exfoliation. Apply liberally two times each day.
- Topical analgesics like lidocaine 2% should be considered for pain control.
- Topical corticosteroids should be considered for participants with grade 2 or 3 hand-foot skin reaction.

## **7.3.2. Permitted**

The following medications and treatments are permitted in this study:

- Corticosteroids
- Other palliative treatments, such as non-emergency surgery provided the circumstances of which have previously been discussed with the Study Chair (or Delegate).
- Other concomitant therapies considered necessary for the participant's well being may be prescribed at the Investigator's discretion including antiemetics, antidiarrhoeals, anti-inflammatory agents, and analgesics.
- Treatment with non-conventional therapies (for example herbs or acupuncture) and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints in the opinion of the Investigator.
- Bisphosphonates
- Prophylactic or therapeutic treatment with heparin as required.

## **7.3.3. Use with caution**

Participants taking narrow therapeutic index medications (e.g.: quinidine, cyclosporine, and digoxin) should be monitored proactively.

## **7.3.4. Prohibited**

The following medications should not be used during this study:

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors (including tyrosine kinase inhibitors), immunotherapy, hormonal therapy for cancer, and experimental or unapproved therapies
- Bone marrow transplant or stem cell rescue
- Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to randomisation. Note: G-CSF may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the Investigator; however, they may not be substituted for a required dose reduction. Routine use of G-CSF is not encouraged.
- Radiotherapy
- All traditional/alternative medicines with an anti-cancer indication, including Traditional Chinese Medicine (TCM).

# ALT GIST

- Strong cytochrome P (CYP) CYP3A4 inhibitors (eg clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinovir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg carbamazepine, phenobarbitol, phenytoin, rifampicin, St John's wort).
- Grapefruit juice

Subjects who require treatment with any of these agents will need to discontinue study treatment, this should be discussed with the Study Chair prior to use..

## **7.3.5. Concomitant medication reporting**

Concomitant medications will not be recorded during the study, except for medications being taken at the onset of serious adverse events or medications known to interact with the study medications.

## **7.4. Treatment discontinuation**

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease (PD) is documented by a site investigator.
- Unacceptable toxicity as determined by the patient or site investigator or as defined in section 7.2.
- Delay of day 1 treatment for >28 days due to treatment-related adverse events. For delays >28 days due to reasons other than treatment-related adverse events, please contact the regional co-ordinating centre to discuss treatment continuation.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Required use of a concomitant treatment that is not permitted, as defined in section 7.3.4.
- Failure to comply with the protocol. If a patient has failed to attend scheduled assessments in the study, the clinician must attempt to determine the reason(s).
- The patient declines further study treatment.

The reasons for discontinuing treatment will be documented in the subject's medical record and eCRF.

Follow up of subjects who stop study treatment should continue according to this protocol (see section 8.1).

## **7.5. Subsequent treatment**

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

## ALT GIST

### 8. ASSESSMENT PLAN

#### 8.1. Schedule of assessments

Assessments must be completed within 3 days of the assessment due date (unless otherwise specified in the footnotes)

Parameter	Baseline (up to 90 days prior to rando)	Baseline part 1 <sup>a, b</sup>	C1 Wk1 D1 (note permitted windows <sup>c, d</sup> )	C1 Wk4 D1	C2 and C3 Wk1 D1	C2 and C3 Wk4 D1	C4 Wk1 D1 and ongoing cycles	30 day safety assessment	Follow-up (12 weekly)
Informed consent	x								
Pregnancy test		x							
Clinical <sup>e</sup>			x	x	x	x	x		
Additional BP monitoring (Arm B) <sup>f</sup>				x	x	x			
Mutation status if not previously determined <sup>g</sup>	x								
Biochem <sup>h</sup>			x	x	x	x	x		
Haem <sup>i</sup>			x	x	x	x	x		
Dipstick urine <sup>j</sup>			x		x		x		
ECG		x							
Imatinib plasma level <sup>k</sup> Arm A and B				x Arm A C1 Wk4 D1 Arm B C1 Wk3 (on last day of imatinib administration)	x Arm B C2 Wk3 ( on last day of imatinib administration)	x Arm A (C2 Wk4 D1 )			
Regorafenib plasma level (Arm B) <sup>l</sup>				C1 Wk7 (on last day of regorafenib)		C2 Wk7 (on last day of regorafenib)			
Blood for research <sup>m</sup>		x	x C1 Wk1 D1 (prior to the commencement of study treatment, Baseline 2)	x Arm A: C1 Wk4 D1 Arm B C1 Wk3 on last day of imatinib administration) Arm B: C1 Wk7 (on last day of regorafenib administration)	x Arm B; C2 Wk3 (on last day of imatinib administration)	x Arm A (C2 Wk4 D1 ) Arm B C2 Wk7 (on last day of regorafenib administration)	x C4 Wk1 D1 C8 Wk1 D1		x At relapse
Disease status								x	x
CT scan <sup>n</sup>		x			x		x		
PET scan (substudy) <sup>o</sup>					x (on last day of regorafenib / imatinib administration and before 1 <sup>st</sup> dose of imatinib / regorafenib)				

NB: 1 cycle in continuous treatment arm = 8 weeks of imatinib:

1 cycle in alternating arm = 3 weeks of imatinib, 1 week washout, 3 weeks of regorafenib, 1 week washout



# ALT GIST

- a – for patients who have already commenced treatment, up to 42 days prior to randomisation.
- b – for patients who have not yet commenced treatment, up to 21 days prior to randomisation
- c - for patients who have already commenced treatment, up to 35 days prior to randomisation.
- d – for patients who have not yet commenced treatment, up to 14 days prior to randomisation
- e – clinical assessment including vital signs, blood pressure, physical examination, ECOG PS, adverse event monitoring during treatment
- f – for patients on the alternating regimen (Arm B), weekly blood pressure measurements are required from the commencement of regorafenib in cycle 1 until the completion of cycle 2
- g – analysis of tumour mutation status needs not to be completed before registration
- h - biochemistry including serum creatinine, urea, LFT, lipase, calcium, magnesium, phosphate. Liver function testing must also be performed weekly in the alternating treatment arm (Arm B) during regorafenib use for the first 2 cycles. INR should be checked at baseline and then as clinically indicated.
- i – full blood count including differential cell count
- j – dipstick urinalysis using standard urine test strip is required on D1 of each cycle. If abnormal, further investigations should be conducted as clinically appropriate
- k – blood collected for drug (imatinib) level testing. Refer to Biological Sampling Handbook for details of collection and processing.
- l- blood collected for drug (regorafenib) level testing. Refer to Biological Sampling Handbook for details of collection and processing.
- m – blood for translational research will be collected at these timepoints. Documentation of compliance with treatment during the preceding cycle should be documented in the eCRF. Refer to Biological Sampling Handbook for details of collection, processing and storage.
- n– for the first 12 months, CT scans are performed 8 weekly after which CT scans are performed 12 weekly. Imaging of the brain should be undertaken if clinically indicated. CT scans should continue as per the protocol until PD.
- o – only in those Arm B patients enrolled in the PET substudy, and timing based on second randomisation to either PET scans during imatinib washout period, or regorafenib washout period. PET scans to be performed at the completion of regorafenib or imatinib tablets (depending on allocated arm) in the first cycle (or up to 2 days prior) and before the commencement of the subsequent imatinib or regorafenib cycle (or up to 2 days prior).

### **8.2. Assessment phase definitions and special circumstances**

#### **8.2.1. Baseline**

Some patients in this study may have already commenced treatment with imatinib, while others will be treatment naive. For those already receiving imatinib, Baseline part 1 procedures must be performed within 42 days. For all other patients procedures must be performed within 35 days of randomisation.

For those who are treatment naive, Baseline part 1 procedures must be performed within 21 days, and procedures must be performed within 14 days of randomisation for all other patients

#### **8.2.2. During treatment**

- Clinical assessment (including vital signs, blood pressure, physical examination, ECOG PS, adverse event monitoring), full blood count (including differential cell count), biochemistry (including serum creatinine, urea, LFT, lipase, calcium, magnesium, phosphate) to be performed at the following timepoints;
  - C1 Wk1 and 4 D1
  - C2 and C3 Wk1 and Wk4 D1
  - C4 onward Wk1 D1
- All participants who are on regorafenib should have their blood pressure monitored weekly from the commencement of regorafenib in cycle 1 until the end of cycle 2. During this time, participants must attend the clinic weekly for their blood pressure to be taken. Alternatively, the weekly blood pressure measurements can be done by GPs, or using home blood pressure monitors if available. Blood pressure readings collected by the patient at home or by their GP will need to be communicated to the study site for appropriate management. Recommendations for anti-hypertension management will be provided in the Study Manual
- Liver function testing must also be performed weekly in the alternating treatment arm (Arm B) during regorafenib use for the first 2 cycles. INR should be checked at baseline and then as clinically indicated.
- Dipstick urinalysis using standard urine test strip is required on day 1 of each cycle. If abnormal, further investigations should be conducted as clinically appropriate.
- Patients on Arm A blood collection for drug (imatinib) level testing to be performed on cycle 1 week 4 and cycle 2 week 4. For patients on the alternating regimen (Arm B) blood collected for drug (imatinib) level testing to be performed on cycle 1, week 3 (on last day of imatinib administration) and cycle 2 week 3 (on last day of imatinib administration). blood collected for drug (regorafenib) level testing to be performed on cycle 1 week 7 (on last day of regorafenib) and cycle 2 week 7 (on last day of regorafenib).
- Blood for translational research will be collected at the following timepoints;
  - Baseline
  - C1 Wk1 D1 (prior to the commencement of study treatment, baseline 2)
  - For Arm A: C1 Wk4 and C2 Wk4.
  - For Arm B: C1 Wk3 (on the last day of imatinib administration) C1 Wk7 (on the last day of regorafenib administration)
  - For Arm B: C2 Wk3 (on the last day of imatinib administration) and C2 Wk7 (on the last day of regorafenib administration)
  - C4, and 8 Wk1 D1
  - Upon relapse

# ALT GIST

- For the first 12 months, CT scans are performed 8 weekly after which CT scans are performed 12 weekly.
- Patients enrolled in the PET substudy - PET scans to be performed at the completion of regorafenib or imatinib tablets (depending on allocated arm) in the first cycle (or up to 2 days prior) and before the commencement of the subsequent imatinib or regorafenib cycle (or up to 2 days prior)

## **8.2.3. End of treatment**

No additional investigations are required for this trial at the time of treatment cessation.

## **8.2.4. 30 day safety assessment**

A safety assessment should be performed to include any adverse events occurring within 30 days (+/- 7 days) after the last dose of study treatment.

## **8.2.5. Follow-up after treatment**

Subjects who stop study treatment prior to the time recommended in the protocol will continue follow-up visits.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, state-based cancer registries and/or the national mortality registry.

## **8.2.6. After study is closed**

The study will be closed after data required for the primary objective has been collected and analysed. Collection of long term outcomes, for example survival data, will continue after the main study is closed, using a simple follow-up CRF, monitoring of central registries, or contact with treating clinicians.

# **9. OUTCOMES, ENDPOINTS AND OTHER MEASURES**

## **9.1. Progression free survival at 24 months (disease progression or death)**

Progression free survival is defined as the time from either (i) randomization (if patients have not yet commenced treatment) or (ii) commencement of therapy (if patients are randomized during the first cycle of imatinib). PFS at 24 months will be the proportion of patients potentially not progressing at 24 months. Disease progression is defined according to RECIST 1.1 (see appendix).

## **9.2. Objective tumour response rate at 16 weeks**

Tumour evaluation using the RECIST Version 1.1 guidelines will be used to determine response status (i.e. complete response, partial response, stable disease, and progressive disease) at each assessment time point. The OTRR will be calculated by summing the number of participants assessed as having a complete or partial response within the first 16 weeks from randomisation, and dividing this by the total number of participants evaluable for response.

# ALT GIST

## **9.3. Clinical benefit rate at 16 weeks**

The clinical benefit rate will be calculated by summing the number of participants assessed as having a complete response, partial response or stable disease within the first 16 weeks from randomisation, and dividing this by the total number of participants evaluable for response (according to RECIST Version 1.1) within the first 16 weeks.

## **9.4. Complete response rate**

The complete response rate will be calculated by summing the number of participants assessed as having a complete response and dividing this by the total number of participants evaluable for response (according to RECIST Version 1.1).

## **9.5. Time to treatment failure**

Time to treatment failure is defined as the time from either (i) randomization (if patients have not yet commenced treatment) or (ii) commencement of therapy (if patients are randomized during the first cycle of imatinib) to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death.

## **9.6. Adverse Events (worst grade according to NCI CTCAE v4.03)**

The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.03) will be used to classify and grade the intensity of adverse events after each treatment cycle.

## **9.7. Overall survival**

Overall survival is defined as the interval from either (i) randomization (if patients have not yet commenced treatment) or (ii) commencement of therapy (if patients are randomized during the first cycle of imatinib) to date of death from any cause, or the date of last known follow-up alive.

## **9.8. Rate of patients having macroscopically complete removal of all residual disease by surgery**

This is defined as the rate of patients who proceed to surgery with the aim of resecting all remaining macroscopic disease.

## **9.9. Change in PET imaging during washout period of regorafenib and imatinib in those taking part in the PET substudy**

The PET substudy aims to primarily evaluate the change in PET response during washout periods for regorafenib and imatinib. PET scans will be performed in a subgroup of participants enrolled to alternating treatment (Arm B) at selected centres. These patients will be further randomised to have PET scans either during the imatinib washout period, or during the regorafenib washout period. At these selected centres, PET scans will be conducted in addition to regular imaging studies. In the substudy, PET will be carried out on 2 occasions in each group. For those randomised to PET scans during the imatinib washout period, a PET scan will be performed immediately following the last dose of imatinib (or up to 2 days prior) of Cycle 3, and before the first regorafenib dose (or up to 2 days prior) of Cycle 3. For those randomised to PET scans during the regorafenib washout period, a PET scan will

# ALT GIST

be performed immediately following the last regorafenib dose of Cycle 3 (or up to 2 days prior) and on the first day of the subsequent imatinib cycle prior to the first dose of imatinib (i.e. Cycle 4 day 1 or up to 2 days prior). The change between the PET standardised uptake values (SUV) of the scan performed at the commencement of the drug washout period and the PET SUV of the scan performed at the conclusion of the drug washout period will be assessed.

## 9.10. Biomarkers

This will include investigations of how regorafenib and imatinib may work in people with GIST, biological mechanisms of action as well as studies that may help to understand the pathogenic course of this cancer and related diseases.

Planned tissue biomarker analyses may include but are not limited to: *KIT*/PDGFRA mutation analysis and other proteins relating to PDGFR signalling.

Planned analysis of blood collected for research may include but not be limited to:

- circulating serum/plasma growth factor and cytokine levels (multiplex assay)
- imatinib plasma levels and in Arm B regorafenib plasma
- circulating tumour cells and
- *KT*/PDGFR mutations in circulating blood DNA
- circulating DNA load

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

## 10. SAFETY REPORTING

### 10.1. Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

# ALT GIST

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

- (i) The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- (ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the drugs, imatinib or regorafenib caused the AEs, i.e. there is evidence to suggest a causal relationship between the drug and the event.

For the purposes of this study, the following adverse events are not reported as SAEs:

- Hospitalisations related to disease progression
- Hospitalisations for management of pain related to disease
- Any elective surgery not related to cancer treatment
- Surgery for complete resection of residual disease
- Deaths related to disease progression
- Elective hospitalisation to simplify study procedures

## ***10.2. Reporting of Serious Adverse Events (including SUSARs)***

**For AGITG sites:** The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trial Centre (CTC) within 1 working day of the investigator becoming aware of the event using the SAE form. All SAEs must be reported up to 30 days from the end of study intervention.

SAE reports should be reported to the CTC as per the procedure documented in the Study Manual.

# ALT GIST

The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC.

The investigator must notify their local HREC as required.

The study sponsor/CTC will submit 'reportable safety events' to the TGA in Australia, and to the lead centre to provide to the regulatory authorities in other participating countries for which the CTC is responsible.

The following information will be recorded for each Serious Adverse Event:

- Event description including classification according to NCI CTCAE 4.03
- Severity / Worst Grade
- Attribution to study intervention
- Expectedness (listed in IB/product information),
- Action taken with study intervention
- Type of SAE (e.g. hospitalisation)
- Outcome of SAE including end date if recovered

## **10.3. Pregnancy**

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The local co-ordinating centre must be notified within 1 working day using the SAE form and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the investigator and the regional co-ordinating centre. The partner should be counselled and followed as described above.

## **11. CENTRAL REVIEW AND BIOSPECIMEN COLLECTION**

### **11.1. Central Biospecimen Collection**

Formalin-fixed paraffin-embedded (FFPE) diagnostic tumour tissue is required from all participants and will be collected for:

- pathology quality control and
- translational research (including potential future translational research relevant to this study).

The tissue will be from archival tumour material – no additional biopsy of the participant is required. Representative FFPE tissue will be collected by sites and sent to a central laboratory for analysis. Refer to the Biological Sampling Handbook for the details of collection, processing and shipping procedures.

Blood for research will be collected from consenting participants at multiple time points and will be processed for blood components including, but not limited to serum and plasma. Processed samples will then be sent to a central laboratory for analysis. Refer to the Biological Sampling Handbook for the details of collection, processing and shipping procedures.

# ALT GIST

## **11.2. Central Imaging Collection**

Central review of CT reports will occur retrospectively and will be used for final endpoint classification for the study. A subset of CT scans may be collected on CD/DVD so these can be reviewed centrally.

Refer to the Study Manual for collection requirements

## **12. TREATMENT INFORMATION**

### **12.1. Description of Study Products**

The regorafenib 40 mg tablet is coated, not divisible, grey-orange-red, oval (length 16 mm, width 7 mm, thickness 4.9-5.6 mm) and 472 mg each in total weight. The packaging configuration is 30 tablets and a 3g desiccant capsule per bottle of regorafenib 40 mg.

Tablets are in an immediate-release dosage form with rapid dissolution characteristics under in vitro test conditions.

The regorafenib 40 mg tablet contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide E171 (color index 77891), macrogol/PEG 3350, lecithin (soy), iron oxide yellow E172 (color index 77491), and iron oxide red E172.

Regorafenib tablets will be packaged separately in high-density polyethylene (HDPE) bottles with a white child-resistant closure and induction seal. Each bottle includes a desiccant. The bottles will have a label affixed containing study identification, quantity of tablets, and other details as required by local regulations. Once the drug has been received, it must be kept in a secure, dry location at a temperature not above 25 °C (77 °F).

Imatinib is manufactured as 100mg and 400mg tablets packaged in polyethylene bottles. The bottles will have a label affixed containing study identification, quantity of tablets, and other details as required by local regulations. Once the drug has been received, it must be kept in a secure, dry location at a temperature not above 30 °C.

The tablets contain imatinib, and the excipients microcrystalline cellulose, crospovidone, hypromellose, anhydrous colloidal silica, magnesium stearate, iron oxide yellow CI 77492, iron oxide red CI 77491, macrogol 4000, and talc.

### **12.2. Supply of Study Product**

Bayer will be providing regorafenib for the study and the regional co-ordinating centre will arrange for the delivery of the investigational product to sites. Imatinib will be supplied according to usual hospital practice.

### **12.3. Drug Accountability**

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.



# ALT GIST

## 13. STATISTICAL CONSIDERATIONS

### 13.1. *Sample Size*

This is a randomized Phase II design to investigate the efficacy/activity of an alternating regimen of 21-25 days of imatinib followed by a 3-7-day gap for washout followed by 21 of regorafenib and a 7-day gap for washout. The control group will be a regimen of continuous imatinib in a 56 day cycle. In order to demonstrate a relative increase in progression free survival at 24 months from the date of randomisation or commencement of imatinib (if the participant had already commenced treatment), based on A'Hern's adjustment of Fleming's design, approximately 110 evaluable participants in the alternating group will provide 80% power with a 2-sided 95% confidence each to rule out a 24 month expected PFS rate of 78% in favour of 88%. Allowing for a 1:1 randomisation, it is proposed to enrol 240 participants into the trial, allowing for approximately a 10% drop-out rate. Currently 80% of participants are expected to achieve a clinical benefit at 24 months (CBR – rate of complete or partial response, or stable disease). A secondary outcome would be to determine whether a minimum 25% relative increase of the CBR (from 80% to 85%) in the experimental cohort can be attained. Other secondary outcomes are rates of objective tumour response, complete response, adverse events, time to treatment failure and overall survival.

### 13.2. *Statistical Analysis*

Analyses will include all patients who were randomised. Treatment activity will be assessed by the proportion, together with the 95% confidence interval, of patients not having progressed at 24 months as determined by the method of Kaplan-Meier. For patients who have already commenced imatinib treatment prior to randomization, the time to progression will be defined as the interval from the time of commencement of this treatment (cycle 1) to documented progression or last follow-up. For patients not on imatinib therapy prior to randomisation, the time to progression will be defined as the interval from the time of randomization to documented progression or last follow-up.

Similarly definitions apply the time-to event endpoints of overall survival and time to treatment failure. Treatment failure is defined as the first event before 24 months of death, disease progression and unacceptable toxicity causing study treatment to cease or patient preference to cease therapy. For purposes of treatment failure, only events in the first 24 months will be considered. Patients not experiencing a treatment failure within 24 months will be censored at 24 months. While there will not be any formal comparisons between the two groups, exploratory comparative analyses may be performed. For time-to-event outcomes, these will include univariate logrank and multivariate proportional hazards comparisons. Other exploratory analyses will also be performed as appropriate.

### 13.3. *Compliance Assessment*

After 15 participants are enrolled in the experimental arm and have received at least 2 cycles of treatment, an interim analysis examining the dose intensity of imatinib and regorafenib will be performed. Modifications to the protocol will be considered if more than 10 patients have not received more than 75% of the planned cumulative doses in the experimental arm. This would be inconsistent with a 50% compliance rate. While the interim analysis is being performed, the study will continue recruiting.

## 14. STUDY ORGANISATION

# ALT GIST

This trial is conducted as an intergroup collaboration between the Australasian Gastrointestinal Trials Group (AGITG), the Scandinavian Sarcoma Group (SSG), and the Soft Tissue Sarcoma Group of the European Organisation for Research and Treatment of Cancer (EORTC).

SSG/EORTC will oversee the management of the study in Scandinavia and Europe and AGITG/NHMRC CTC in ANZ. Interpretation of data and publication will be a joint collaboration. Randomisation, database development, management and statistical analysis will be conducted at the NHMRC CTC on behalf of the AGITG.

## **14.1. Trial Management Committee(s)**

A locally formed Trial Management Committee (TMC) in each region will monitor the progress of the study and review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). A member from the TMC will represent each region on the International Steering Committee (ISC).

## **14.2. Independent Safety and Data Monitoring Committee**

The AGITG Independent Data, Safety and Monitoring Committee (IDSMC) will closely monitor the trial for safety and toxicity. While no formal interim analysis is planned the IDSMC may review outcome data (PFS and OS) if it is felt appropriate. The IDSMC will pay particular attention to the rate of participant drop-out from trial (especially in the experimental arm) for reasons of toxicity or participant/clinician preference.

The IDSMC will provide independent assessment of patient safety and trial progress, making recommendations to the TMC about the continuation of the trial based on data made available by the trial statistician. Additionally, the IDSMC will review all SUSARS in a timely manner after appropriate authorities have been notified as detailed in section 9.

## **15. ADMINISTRATIVE ASPECTS**

### **15.1. Ethics and regulatory compliance**

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

### **15.2. Confidentiality**

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the relevant coordinating centre and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement. No personal information that reveals the patient identity will be

# ALT GIST

entered into the CRFs or the study database. The patients will be provided a study code (subject number) that links the patient identity to the information stored in the study database.

## **15.3. Protocol amendments**

Changes and amendments to the protocol can only be made by the International Steering Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

## **15.4. Data Handling and Record Keeping**

All trial data required for the monitoring and analysis of the study will be recorded on the CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

- a. Subject's name, contact information and protocol identification.
- b. The date that the subject entered the study.
- c. A statement that informed consent was obtained (including the date).
- d. Relevant medical history
- e. Dates of all subject visits and results of key trial parameters.
- f. Occurrence and status of any adverse events.
- g. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 15 years following completion of the study.

## **15.5. Audit and Inspection**

This study may be subject to audit or inspection by representatives of the collaborative group or the CTC/SSG/EORTC or Bayer Healthcare Pharmaceutical or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA)).

## **15.6. Clinical Study Report**

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication.

# ALT GIST

The ISC will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol in the Group name with subsequent publications of data subsets in individual names based on contribution. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. All publications (including substudies) must receive prior written approval from the ISC prior to submission.

## 16. REFERENCES

1. Verweij J, Casali P, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high dose imatinib: randomised trial. *Lancet*. 25 September 2004; 364 (9440):1127 – 1134
2. Blanke CD, Rankin C, Demetri GD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol*. Feb 1 2008; 26(4):626-32
3. von Mehren M. Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST) (abstract). *J Clin Oncol* 2011; 29(15\_Suppl): Abstract 10016.
4. Sleijfer S, Wiemer E, Seynaeve C et al. Improved insight into resistance mechanisms to imatinib in gastrointestinal stromal tumors: a basis for novel approaches and individualization of treatment. *Oncologist*. June 2007; 12(6):719-26.
5. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005; 11:4182-90.
6. Desai J, Shankar S, Heinrich MC. Clonal Evolution of Resistance to Imatinib in Patients with Metastatic Gastrointestinal Stromal Tumors. *Clin Cancer Res*. 15 September 2007; 13:5398 - 5405
7. Heinrich MC, Griffith DJ, Druker BJ et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood*. 2000; 96:925-32
8. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002; 347: 472-80
9. Bardsley MR, Horvath VJ, Asuzu DT, et al. Kit<sup>low</sup> stem cells cause resistance to Kit/platelet-derived growth factor  $\alpha$  inhibitors in murine gastrointestinal stromal tumors. *Gastroenterology* 2010; 139: 942–52
10. George S, Wang Q, Heinrich M et al. Efficacy and Safety of Regorafenib in Patients With Metastatic and/or Unresectable GI Stromal Tumor After Failure of Imatinib and Sunitinib: A Multicenter Phase II Trial. *J Clin Onc*. May 21 2012; 30(19): 2401-07
11. Bono P, Krause A, von Mehren M et al. Serum KIT and KIT ligand levels in patients with gastrointestinal stromal tumors treated with imatinib. *Blood*. 15 April 2004; 103(8):2929-35
12. Wilhelm S, Dumas J, Adnane L et al. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer*. 1 July 2011; 129(1):245-55
13. Demetri G, Reichardt P, Kang YK et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 295 -302
14. A'Hern, R. Sample size tables for exact single-stage phase II designs. *Stat in Med* 2001; 20: 859-866.

# ALT GIST

## 17. LIST OF APPENDICES

**Appendix 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03**

**Appendix 2. Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1)**

# ALT GIST

## ***Appendix 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03***

Link: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

# ALT GIST

## Appendix 2. Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1)

These instructions are based on the guidelines recommended in Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

### 1 Evaluable for response

All participants who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Participants on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

### 2 Disease and lesion definitions

**2.1 Measurable Disease.** Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm with chest x-ray, and as  $\geq 10$  mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component  $\geq 10$  mm by CT scan). *Malignant lymph nodes* must be  $\geq 15$  mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

**2.2 Non-measurable Disease.** All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

**2.3 Target Lesions.** When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of  $\geq 15$  mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

**2.4 Non-target Lesions.** All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

### 3 Response Definitions

# ALT GIST

All participants will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

**Complete Response (CR):** Disappearance of all *target* and *non-target* lesions and normalisation of any specified tumour markers. Pathological lymph nodes must have short axis measures < 10mm (**Note:** continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol.

**Partial Response (PR):** At least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol.

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of  $\geq 5$ mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

**Table 1:** Integration of Target, Non-target and New lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response*	Best Response for this category also requires
<i>Target lesions <math>\pm</math> non target lesions</i>				
CR	CR	No	CR	Normalisation of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once $\geq 4$ wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
<i>Non target lesions ONLY</i>				



# ALT GIST

No Target	CR	No	CR	Normalisation of specified tumour markers AND lymph nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
<p><u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>”. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.</p> <p>*Confirmation of a complete or partial response will be undertaken based on the results of the next scan performed (i.e. no additional scans to those presented in the Schedule of Assessments in Section 6.1 are required).</p>				

## 4 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

## 5 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomised studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

## 6 Methods of Measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

**6.1 Clinical Lesions.** Clinical lesions will only be considered measurable when they are superficial and  $\geq 10\text{mm}$  as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

**6.2 Chest X-ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions  $\geq 20\text{ mm}$  on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

## ALT GIST

6.3 CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

6.4 Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

6.5 Endoscopy, Laparoscopy. The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

6.6 Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a participant to be considered in complete response.

6.7 Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.