INTEGRATE II

Randomised Phase III Controlled Trials of Regorafenib containing regimens versus standard care in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)

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The INTEGRATE II platform is an international collaboration led by the AGITG and the NHMRC CTC, University of Sydney evaluating regorafenib containing regimens in advanced gastro-oesophageal cancer

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CONFIDENTIAL

INTEGRATE II

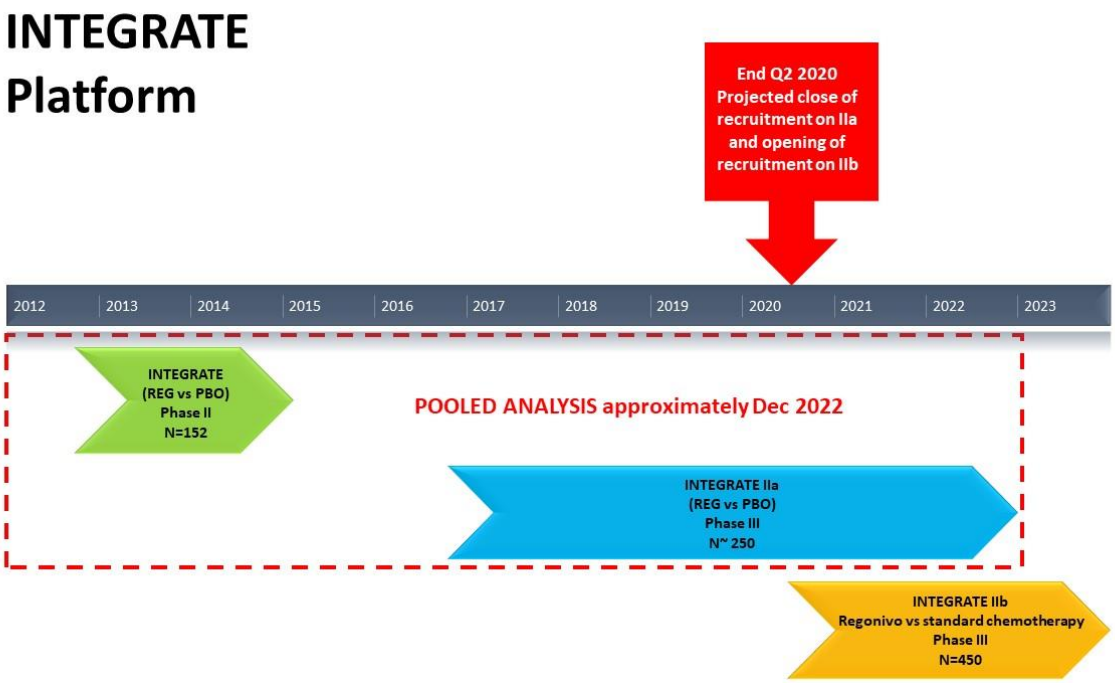
Overview

Advanced Gastro-oesophageal Carcinoma (AGOC) has a poor prognosis, and there is no established standard treatment following failure of first and second line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in the INTEGRATE randomised phase II trial. INTEGRATE II is currently a randomised phase III trial to determine if regorafenib improves overall survival in refractory AGOC.

Nivolumab, a human IgG4 monoclonal antibody inhibitor of PD-1, has been shown to be effective in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of previous chemotherapy regimens. A recent early phase Ib trial of nivolumab with regorafenib has shown promising activity and manageable toxicity with the combination, including in patients receiving prior nivolumab.

With the shift in practice in AGOC resulting in use of additional lines of therapy, and new immunotherapy agents, together with promising activity from the combination of regorafenib & nivolumab, it is proposed to amend the current trial. **INTEGRATE IIb** – will compare the effectiveness of the combination of regorafenib & nivolumab in pre-treated patients with AGOC to current standard therapy (i.e.: chemotherapy).

The current INTEGRATE II trial – now referred to as **INTEGRATE IIa** – will continue to recruit eligible patients up until this protocol amendment has been approved at each site, at which time INTEGRATE IIa recruitment will cease at that site and INTEGRATE IIb recruitment will commence. It is estimated a total of approximately 250 patients will be recruited to INTEGRATE IIa.



General Aim: To determine if regorafenib regimens improve overall survival in refractory AGOC

Design: A platform randomised phase III trial with regorafenib regimens versus standard care:

INTEGRATE II

INTEGRATE IIa:

Randomisation: Regorafenib + Best Supportive Care vs placebo (PBO) + Best Supportive Care in 2:1 randomisation

Primary Objective (Endpoint): To determine the effect of regorafenib on overall survival (OS) (death from any cause) in the overall study population.

Population: The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant to a minimum of 2 lines of prior anti-cancer therapy which have included a platinum agent & a fluoropyrimidine analogue.

Study Treatments: Participants will self-administer 160mg (4x40mg) of regorafenib or matching placebo orally on days 1-21 of each 28 day treatment cycle until disease progression or prohibitive adverse events as per protocol. Both treatment groups will receive Best Supportive Care (BSC).

Statistical Considerations: A sample of 250 participants randomised in a 2:1 ratio (REG: PBO) is expected to contribute 221 OS events to a pooled analysis with the previous INTEGRATE trial (which had 123 OS events). The conditional power (conditional on the known INTEGRATE trial results) of this proposal to detect a hazard ratio (HR) for OS of 0.67 is estimated to be over 90%. Based on 221 events, INTEGRATE IIa on its own will have 80% power to detect HR of 0.67.

INTEGRATE IIb:

Randomisation: Regorafenib + Nivolumab (RegoNivo) + Best Supportive Care vs Investigator Choice Chemotherapy + Best Supportive Care in 2:1 randomisation

Primary Objective (Endpoint): To determine the effect of RegoNivo on overall survival (OS) (death from any cause) in the overall study population.

Population: The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant to a minimum of 2 lines of prior anti-cancer therapy which have included a platinum agent & a fluoropyrimidine analogue.

Study Treatments: Participants in the RegoNivo arm will self-administer 90mg (3x30mg) of regorafenib days 1-21 of each 28-day treatment cycle and receive intravenous nivolumab 240 mg day 1 of 14 days until disease progression or prohibitive adverse events as per protocol. Participants in the **control arm** will receive investigator choice chemotherapy with any of the following agents: taxane, irinotecan or oral trifluridine/tipiracil (TAS102). Both treatment groups will receive Best Supportive Care (BSC).

Statistical Considerations: A sample of 460 participants randomised in a 2:1 ratio (RegoNivo: chemotherapy) and followed until 380 deaths occur provides at least 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05.

Protocol Structure: The amended protocol follows which contains **discrete sections** for INTEGRATE II, now called **INTEGRATE IIa (or IIa)**, and **INTEGRATE IIb (or IIb)**.

INTEGRATE IIa
This section outlines the ongoing management of patients already enrolled or to be recruited at existing INTEGRATE IIa sites. IIa sites will continue to follow this protocol until INTEGRATE IIb is

locally approved and activated at their site by the global coordinating centre. The main changes to INTEGRATE IIa relate to the *amended sample size and revised analysis plans.*

INTEGRATE IIb

New sites/regions not currently active on IIa – will activate to IIb once all required approvals have been obtained and the global coordinating centre has activated the site to IIb.

Existing IIa sites – will continue to enrol to IIa until required approvals have been obtained and global coordinating centre has activated the site to IIb.

Discrete IIa & IIb sections (marked by distinct headers) are followed by sections common to both IIa/IIb *except where noted*.

INTEGRATE II

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Abbreviations

AE	Adverse Event
ANC	Absolute Neutrophil Count
AGOC	Advanced Gastro-Oesophageal Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood Pressure
BSC	Best Supportive Care
CF	Cisplatin + Fluorouracil
CX	Cisplatin + Capecitabine
CR	Complete Response
CRF	Case report form
CS1	Cisplatin + S-1
CT	Computed tomography (scan)
CTC	NHMRC Clinical Trials Centre, University of Sydney
CTCAE	Common Terminology Criteria for Adverse Events
D	Docetaxel
DNA	Deoxyribonucleic acid
E	Epirubicin
ECOG	Eastern Cooperative Oncology Group
F	Infusional 5-FU
FFPE	Formalin-fixed paraffin–embedded
FNAB	Fine-needle aspirate biopsy
GC	Gastric adenocarcinoma
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular Filtration Rate
HDPE	High-Density Polyethylene
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HREC	Human Research Ethics Committee
IDSMC	Independent Data Safety Monitoring Committee
INR	International Normalised Ratio
irAE	Immune-related Adverse Event
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
MUGA	Multiple-Gated Acquisition Scan
GOJ	Gastro-oesophageal Junction
OS	Overall survival
OTRR	Objective tumour response rate
PBO	Placebo
PD	Progressive Disease
PD-1	programmed cell death 1 receptor

PD–L1	PD-1 ligand
PFS	Progression free survival
PK	Pharmacokinetics
PPT	Partial Thromboplastin Time
PR	Partial response
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
REG	Regorafenib
RR	Response rate
SAE	Serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFT	Thyroid function test
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase inhibitor
TMC	Trial Management Committee
TMG	Trial Management Group
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
X	Capecitabine

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INTEGRATE IIa

INTEGRATE IIa

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

NOTE:
INTEGRATE IIa protocol should only be used as follows:

- **Sites currently activated on the INTEGRATE II (now called "INTEGRATE IIa" or "IIa") study**
- **Sites that will activate on IIa prior to activating on the INTEGRATE IIb (IIb) study**
- **For patients randomised to IIa, or on treatment/in follow-up on this protocol**
- **Active IIa sites will continue to randomise patients to IIa until the site**
  - **Has all local approvals in place for IIb**
  - **Has received training for IIb protocol & data systems**
  - **Has received IIb supplies (ie: lab kits)**
  - **Has been activated by the global coordinating centre**
- **<u>Recruitment for IIa will cease at the site once it activates to IIb</u>**
- **New sites participating on IIb only – please proceed to p42**

INTEGRATE IIa

1. IIa SYNOPSIS & SCHEMA

1.1. SYNOPSIS

Background	Advanced Gastro-oesophageal Carcinoma (AGOC) has a poor prognosis, and there is no established standard treatment following failure of first and second line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in INTEGRATE
General Aim	To determine if regorafenib improves overall survival in refractory AGOC
Design	A randomised phase III, double-blind, placebo-controlled trial with 2:1 (regorafenib : placebo) randomisation and stratification by: 1. Location of tumour (GOJ vs. gastric) 2. Geographic region (Asia vs. Rest of World) 3. Prior VEGF inhibitors (Yes vs No)
Primary Objective (Endpoint)	To determine the effect of regorafenib on: 1. Overall survival (OS) (death from any cause) in the overall study population.
Secondary Objectives (Endpoints)	To determine the effect of regorafenib on: 2. Overall survival (death from any cause) in the Asian sub-population. 3. Progression free survival (PFS) (disease progression or death) 4. Objective tumour response rate (OTRR) (partial or complete response (PR or CR)) 5. Quality of life (QoL)(scores from participant-completed questionnaires) 6. Safety (rates of adverse events)
Tertiary/Correlative Objectives	5. To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) 6. To evaluate regorafenib PK in patient populations from different geographical regions (PK levels)
Population	The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant to a minimum of 2 lines of prior anti-cancer therapy which have included a platinum agent & a fluoropyrimidine analogue.

INTEGRATE IIa

Study Treatments

Participants will self-administer 160mg (4x40mg) of regorafenib or matching placebo orally on days 1-21 of each 28 day treatment cycle until disease progression or prohibitive adverse events as per protocol. Both treatment groups will receive Best Supportive Care (BSC).

Assessments

- Clinic visits (including laboratory tests) will be required at baseline, every 2-4 weeks during treatment, and at the end of treatment. Weekly assessment of blood-pressure and liver function tests (LFTs) will be required during the first 4 weeks on treatment, then fortnightly to week 8, then on D1 each cycle thereafter.
- Cardiac function will be assessed within 90 days prior to randomisation, and then only if clinically indicated during treatment.
- Urinalysis will be performed at baseline and then on day 1 of each treatment cycle.
- Participants will be assessed 4 weekly until disease progression, and then for survival status 8 weekly until death.
- Imaging will be performed at baseline, then 8 weekly until disease progression or death, timed from the date of randomisation.
- Blood for biomarkers will be collected at C1D1, C2D1, C4D1 and end of treatment. Additional blood for PK to be collected on C1D15, C2D1 and C2D15 at selected centres only.
- Health-related QoL will be obtained at baseline (C1D1 prior to dosing), then on a 4 weekly basis continuing up to (and including) the visit where disease progression is established.

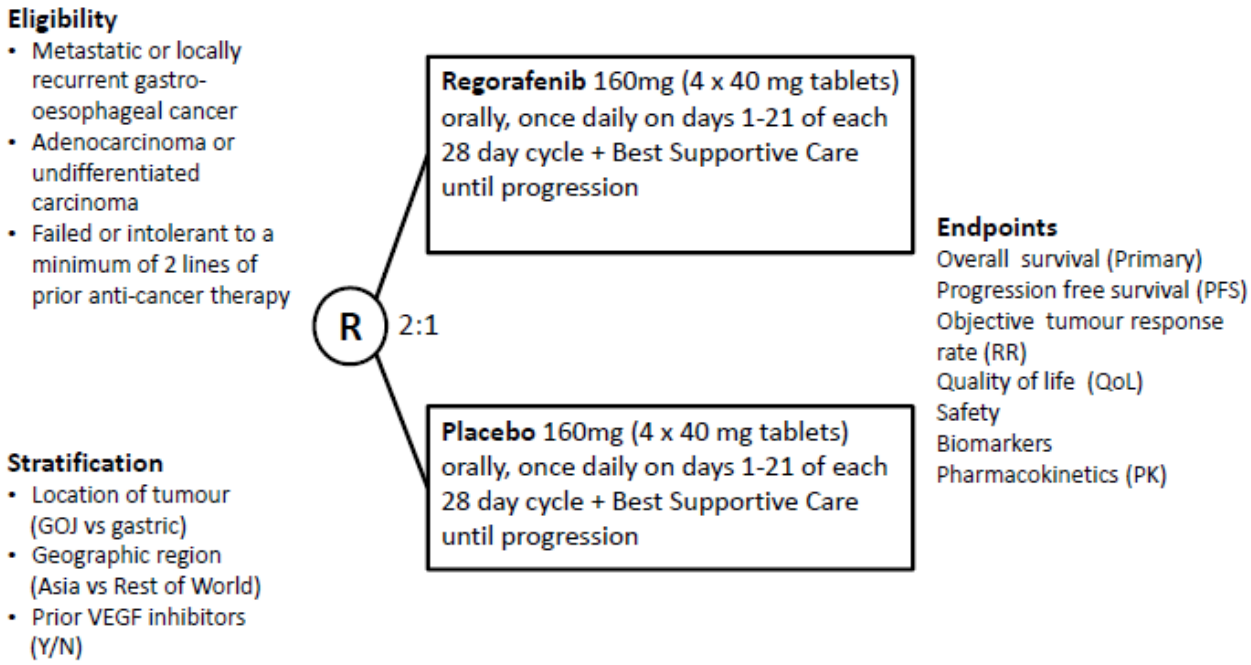
Statistical Considerations

250 participants randomised in a 2:1 ratio (REG: PBO) is expected to yield 221 OS events. These events will contribute to a pooled analysis with the previous INTEGRATE trial (which had 123 OS events). The conditional power (conditional on the known INTEGRATE trial results) of the pooled analysis to detect a hazard ratio (HR) for OS of 0.67 is estimated to be at least 90%. Based on 221 events, INTEGRATE IIa on its own will also have 80% power to detect HR of 0.67.

A sequential closed testing procedure (with alpha set to 5%) will be applied to the following null hypotheses of no treatment effect in the:

- Pooled cohort ($H0_1$)
- INTEGRATE IIa cohort ($H0_2$)
- Asian region pooled cohort ($H0_3$)
- Asian region INTEGRATE IIa cohort ($H0_4$)

1.2. IIa SCHEMA



2. IIa BACKGROUND

2.1. Epidemiology & Current Treatment of Gastric Cancer

Gastric adenocarcinoma (GC) is the fifth most common cancer worldwide (~6.8% of cancers in 2012) but the third leading cause of cancer death (8.8% of cancer deaths) (1). There is a tenfold variation in incidence between the highest and lowest risk regions, with the highest incidence being recorded in East Asia, Eastern Europe, and Central and South America (1). Despite significant progress, the mortality remains high in countries such as Korea and Japan (13/100,000 and 12.4/100,000 respectively) (2). In Australia, there are approximately 1900 new cases of GC reported each year (1.9% of all cancers) with GC representing 2.8% of total cancer deaths (3).

Five-year survival for advanced gastro-oesophageal cancer (AGOC) is <7% and, median overall survival (OS) remains less than 1 year (4). In people with AGOC and good performance status, chemotherapy improves overall survival and quality of life (QoL) compared with best supportive care (BSC) alone (Hazard Ratio (HR) 0.37, 95% confidence interval (CI) , 0.24-0.55)(4). Two drug combination chemotherapy regimens improve patient outcomes in AGOC compared with single agent chemotherapy (HR for survival of 0.82, 95% CI,0.74-0.90, in favour of combination chemotherapy) (4), although the preferred regimen varies widely across the world.

The current standard first-line chemotherapy treatment of AGOC has regional differences, but usually includes a fluoropyrimidine and a platinum agent. In Asia, a doublet regimen with flurouracil or S1 or capecitabine with a platinum agent, such as cisplatin or oxaliplatin remains the standard of care first line (5). In Europe and the USA, fluoropyrimidine and platinum-based combinations with or without the addition of a third drug, typically docetaxel (D) or epirubicin (E), are the most widely used chemotherapy combinations for first-line AGOC (6).Other treatment approaches have included the use of newer fluoropyrimidines and platinum agents. Two trials established the non-inferiority of capecitabine (X) to infusional 5-FU (F) and oxaliplatin (O) to cisplatin (C), respectively in the combination regimens CX, OX, ECX, EOX and EOF (7, 8). A similar finding with the fluorouracil analogue S-1 has also been reported (9). In a meta-analysis, capecitabine-containing chemotherapy resulted in longer OS and improved response rate (RR) compared with the 5-FU combinations (HR of Survival 0.87, p=0.02) (10). A recent French Intergroup Phase II study also confirmed efficacy

with FOLFIRI in the first line setting (11). In Australia, current practice typically follows that of the United Kingdom with the standard chemotherapy regimens for AGOC being platinum-based combinations: ECF, ECX or EOX, or CF, OX or FOLFOX in people who cannot tolerate triplet therapy. Recently, the FLOT regimen of fluorouracil, oxaliplatin and docetaxel has shown promising activity in both neoadjuvant and metastatic settings (12, 13).

After failure of first line treatment for AGOC, patient performance status can often decline rapidly. However, second-line chemotherapy is now established as a standard care option in appropriately selected patients, based on three randomized studies, each of which demonstrated a survival advantage with chemotherapy over best supportive care alone, using taxanes (paclitaxel and docetaxel) or irinotecan ((14). A meta-analysis of these studies demonstrated a HR for OS of 0.73 (95% CI, 0.58-0.96), and in patients with performance status 0-1 the HR was 0.57 (95% CI, 0.36-0.91 (15). There is limited but increasing evidence, particularly in Asian countries, for third line chemotherapy in advanced gastric cancer, with studies using paclitaxel, docetaxel and irinotecan all reporting some clinical benefit (16-19).

2.2. **Targeted Therapies for AGOC**

Attempts to improve outcomes for treatment in AGOC have focused on targeting growth factor signaling pathways (such as HER2, mTOR and tumour angiogenesis). HER2 positivity has been reported in around 15-20% of OG cancers although positivity rates differ according to tumour location and histological subtype (20). As in breast cancer, HER2 positivity has been correlated with poorer outcomes and more aggressive disease. In the first line setting, an international phase III randomised trial of trastuzumab in HER2-positive AGOC/GOJ (ToGA trial) recently demonstrated a significantly improved median OS with trastuzumab in combination with chemotherapy (CX or CF) compared with chemotherapy alone (13.8 vs. 11.1 months; HR 0.74; p=0.0046), and improved median PFS (6.7 vs. 5.5 months; HR 0.71; p=0.0002) (21). Trastuzumab is considered standard of care in patients known to be HER2-positive, although it may not be available in all countries.

In the second-line treatment of AGOC, a number of agents have demonstrated activity in phase II trials, although with modest benefit (RR 16-29%, median PFS 2-4 months)(22). A recent phase III study of everolimus, an inhibitor of the PI3K/Akt/mTOR pathway, failed to demonstrate a significant improvement OS compared with placebo. Although a statistically significant improvement in PFS was demonstrated in the intervention (everolimus) group, the difference in median PFS was only 0.27 months (1.68 months with EVE vs. 1.41 months with PBO (HR 0.66; 95% CI, 0.56-0.78; p<0.0001) (23).

Another molecular target of interest in AGOC is the MET receptor signaling pathway. MET is amplified in approximately 2% to 10% of gastric adenocarcinomas but expressed by immunohistochemistry in 40-50% of cases (24). Two agents targeting MET signaling in advanced gastric cancer (rilotumumab and onartuzumab) recently reported the outcome from phase III trials in the treatment of advanced gastric cancer. Unfortunately both studies failed to meet their primary survival endpoints (24, 25).

The most recent class of therapy to be explored in AGOC are the immune checkpoint inhibitors, which have shown great promise in melanoma, lung cancer and other solid tumours. Of particular interest are the checkpoint inhibitors focused on programmed cell death 1 receptor (PD-1) and PD-1 ligand (PD–L1) (26). Many kinds of tumours express PD-L1 on the cell surface and down-modulate T-cell activity by binding PD-L1 to PD-1. Therefore, antibodies directed against PD-1 or PD-L1 can reverse this T-cell suppression and produce tumour response (27)Although still preliminary, this approach may play an important role in gastric cancer. Data from key recently reported clinical trials of immunotherapy are summarized below.

ATTRACTION-2, a phase III trial of Nivolumab (a human IgG4 monoclonal antibody which blocks the PD-1 receptor) versus placebo, showed improved overall survival benefit in patients having received at least two prior chemotherapy regimens. Median overall survival was 5.32 months with nivolumab vs 4.14 months with placebo (HR 0.63 , 95%CI 0.51-0.78; p<0.0001) in the Asian population (the study was conducted in Japan, South Korea and Taiwan). The survival benefit was independent of PD–L1 positivity (28).

Pembrolizumab, a PD-1 antibody, was approved by FDA for patients who progressed following two or more prior lines of therapy including fluoropyrimidine and platinum-containing chemotherapy based on the KEYNOTE-059 study .This phase II study in PD-L positive tumours (defined as immunohistochemistry score for PD-L1 $\geq$ 1%) demonstrated 15.5% ORR (95%CI,10.1-22.5),with 2% patients achieving complete remission (95% CI,0.4-5.8) (29)

Preliminary data has also been presented from the JAVELIN study using avelumab, an anti-PD-L1 antibody, in Japanese patients with advanced gastric or gastro-oesophageal junction cancer (30). Clinical activity was demonstrated with a 65% disease control rate in their cohort. In another phase 1b study using pembrolizumab (PD-1 inhibitor) in patients with advanced gastric cancer, the 6 month overall survival rate was 69% (31)

Data from numerous additional international trials evaluating the efficacy of checkpoint inhibitors in AGOC are ongoing or maturing, including evaluation of combinations with chemotherapy, and maintenance therapy. The ultimate place for the best use of immunotherapy agents for patients with AGOC awaits results from these studies.

2.3. **Rationale for Therapies Targeting Vascular Endothelial Growth Factor (VEGF) in AGOC**

2.3.1. Potential Prognostic and Predictive value of VEGF

VEGF is identified as a critical regulator of both normal and pathological angiogenesis (32). VEGF produces a number of biological effects including endothelial cell mitogenesis and migration and also induction of proteinases that lead to remodeling of the extracellular matrix, increased permeability of the vasculature, and maintenance of survival of newly formed blood vessels (32).

VEGF is expressed in tumour tissue and peripheral blood, and exists as VEGF isoforms (A, B, C, D) and receptors- VEGFR-1 (also known as Flt-1) and VEGRF-2 (Flk/FDR) (33). Expression of total VEGF or its individual isoforms and VEGF receptors may be performed by measuring RNA levels (using reverse transcription-polymerase chain reaction (RT-PCR)) or protein levels (e.g. using immunohistochemistry (IHC) on tissue, or enzyme-linked immunosorbent assay (ELISA) on blood-derivatives). A number of Investigators have explored the relationship between expression of VEGF and its receptors, either as total levels or individual isoforms, in both tumour tissue and circulating in peripheral blood of people with various cancers including colorectal (34), pancreatic and gastroesophageal junction (35) and breast and gynaecological cancers (36).

Circulating VEGF levels have been demonstrated to be prognostic in a variety of cancers, and may be predictive of benefit from treatments that inhibit signalling through the VEGF pathway. Quantification of total serum VEGF by ELISA has been shown to be reliable in mesothelioma (37) and renal cancer (38). In these cohorts, higher levels of VEGF have been associated with poorer prognosis. A recent combined analysis of phase III studies in metastatic colorectal, non-small cell lung and renal cell cancers demonstrated the prognostic value of circulating total VEGF levels, with high levels correlating with shorter PFS and OS (39).

A small cohort study in GC examined circulating levels of the VEGF isoforms A, C, & D, and VEGFR 1 & 2. These investigators did not find any significant prognostic value for any of the VEGF isoforms or their receptors, except for VEGFR-1 where high levels were associated with a poorer OS (40).

This study was limited by its cohort design and small sample size. Another study of 181 case controlled people with advanced GC found that serum VEGF per platelet count was correlated with poorer OS (41). High pre-operative serum VEGF levels were also found to be correlated with recurrence and poorer OS after R0 resection for GC (42).

Studies of VEGF expression in gastric tumour tissue have shown interesting results. A meta-analysis of 11 observational studies (1,194 people) showed that high expression of VEGF in gastric tumour tissue correlated with poorer OS in Asian people with GC (43). A study in the Ukraine found that in 105 people with GC, people with high levels of expression of VEGF and microvessel density as well as strong tumour hypoxia had lower OS (44) .Other studies have examined the expression of isoforms of VEGF in gastric tumour tissue. A cohort study found that in 107 people, an increased VEGF-A expression in gastric tumour tissue was closely correlated with poor prognosis and survival (45). While high VEGF-D expression has been found to be associated with distant metastasis (46) and lymphatic metastases (47) and a significant prognostic factor for relapse-free survival, it has not been shown to be associated with better OS (46, 47). In a study of 204 people undergoing curative gastrectomy, expression of both VEGF-C and VEGFR3 were prognostic factors for poorer OS and associated with lymph-node metastasis (48). Over-expression of VEGF in tumour specimens from people with AGOC has been associated with more rapid progression and poorer prognosis (49, 50).

The relationship between VEGF gene polymorphisms and GC risk remains unclear with most studies being relatively small. A cohort study of 503 people showed that the VEGF-460T > C polymorphism was correlated with poorer disease-free survival in people with curatively resected early stage GC (51). A later study in 150 case controlled people with GC found that the VEGF +1612 G/A gene polymorphisms may be associated with GC in Chinese Han participants (52). A case controlled meta-analysis of 30 studies found that carriers of the VEGF 1612G had an 85% reduction of GC risk compared with those carrying a VEGF 1612G >A homozygote mutation in 2 studies (53). Other cohort studies show a correlation between VEGFR 634CC/CG carriers and poorer survival (54, 55).

As in most other cancers, VEGF and angiogenesis expression or pathway upregulation is of poor prognostic significance in GC. The important area of uncertainty is whether there is a predictive angiogenic pathway marker that can identify the people and or subgroups that may benefit most from anti-angiogenic therapy. Candidates include any of the aforementioned VEGF pathway measures, however the potential predictive (versus prognostic) value of these and other candidate biomarkers should be examined in a prospective, randomised clinical trial.

The identification of a predictive biomarker for anti-VEGF/anti-angiogenic therapy benefit in any cancer has remained elusive (56). Analysis of possible predictive factors for efficacy of bevacizumab in the AVAGAST study found that patients with high baseline plasma VEGF-A levels showed a trend toward improved overall survival, as did patients with low baseline tissue expression of neuropilin-1 (57). An analysis of circulating VEGF-A levels in four phase III trials of bevacizumab in colorectal cancer, lung cancer, and renal cell carcinoma found that circulating VEGF-A was prognostic for outcome but not predictive for bevacizumab based treatment benefit (58) . A novel VEGF-A ELISA assay with higher sensitivity to shorter, more soluble VEGF-A isoforms, including VEGF110 and VEGF121 was used as being most sensitive (58) . In a detailed analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer in the CORRECT trial, in univariate analyses, plasma von Willebrand factor was associated with regorafenib and PFS, while plasma Tie1 was associated with regorafenib and OS (59).

Other angiogenic pathways of interest in AGOC include the FGF signaling pathway. Basic FGF (bFGF) has been shown to be expressed in gastric cancer, correlating with measures of tumour vascularity, supporting a role of bFGF in the angiogenesis of the gastric cancers (60). FGFR2 amplification in gastric cancer has also been reported (61). The molecular understanding of gastric cancer changed with the publication of the findings of a study by the Cancer Genome Atlas Research Network in 2014. It was proposed that gastric cancer be categorized into four key molecular phenotypes (tumours positive for Epstein–Barr virus, microsatellite unstable tumours, genomically

stable tumours, and tumours with chromosomal instability) in order to help stratify patients for targeted therapies. How these different phenotypes behave in response to existing therapies is unknown. Differential expression of angiogenesis-related genes (VEGFA and FGF2) has been demonstrated in human gastric cancers with and those without high-frequency microsatellite instability (62).

An exploratory analysis of the distribution of these molecular phenotypes in the INTEGRATE II study population and their association with angiogenic biomarkers may assist in identifying which patient sub-populations benefit most from regorafenib.

2.3.2. Evidence for Therapies Targeting VEGF

A randomised phase III trial of bevacizumab (anti-VEGF monoclonal antibody) in combination with chemotherapy (CX) in AGOC (AVAGAST) demonstrated significant improvement in the secondary efficacy endpoints of PFS (6.7 months vs. 5.3 months; HR 0.80; p=0.0037) and ORR (46% vs. 37%; p=0.0315) with bevacizumab, but did not meet the primary endpoint of OS (63). Phase II studies of the multi-targeted VEGF receptor tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib have shown some activity in AGOC (64, 65).

More recently, studies have reported positive outcomes with the VEGF receptor (R) -2 monoclonal antibody ramucirumab and the VEGFR-2 tyrosine kinase inhibitor (TKI) apatinib. Two studies evaluated the efficacy of ramucirumab in previously treated AGOC – the RAINBOW study of ramucirumab and paclitaxel vs. paclitaxel alone (66), and the REGARD study of ramucirumab or placebo (67). The RAINBOW study demonstrated improved OS with the ramucirumab/paclitaxel combination compared with paclitaxel alone (median 9.6 months [95% CI 8·5-10·8] vs 7.4 months [95% CI 6·3-8·4], HR 0.807 [95% CI 0·678-0·962]; p=0.017 (66), and the REGARD study demonstrated improved OS of ramucirumab as monotherapy compared with placebo (median OS 5.2 months v 3.8 months (HR 0.776, 95% CI 0.603-0.98; p=0.47) (67). In both trials, ramucirumab was tolerated.

In a placebo-controlled randomized Phase II study in Chinese patients, apatinib showed improved progression-free survival and OS in heavily pre-treated patients with metastatic gastric cancer who had experienced treatment failure with two or more chemotherapy regimens (68). The median OS was 2.50 months (95% CI: 1.87-3.70 months) for placebo versus 4.83 months (95% CI: 4.03 -5.97 months) and 4.27 months (95% CI: 3.83-4.77 months) for apatinib (850 mg daily and 425 mg bid respectively), p=0.0017 (68). The survival benefit of apatinib 850 mg daily was confirmed in a subsequent placebo controlled Phase III trial in Chinese patients, with median OS 195 days versus 140 days; HR 0.71; 95% CI (0.54-0.94); p<0.016 (69).

2.4. **Rationale for Use of regorafenib (BAY73-4506)**

Regorafenib (BAY 73-4506) is an oral multi-kinase inhibitor with a distinct profile, targeting angiogenic (VEGFR, bFGF, TIE-2), stromal (PDGFR-β) and oncogenic (RAF, RET and KIT) receptor tyrosine kinases. A recent phase II study in imatinib and sunitinib refractory Gastrointestinal Stromal Tumours (GISTs) showed promising activity (73% clinical benefit (pooled RR and SD)) (70). Three international phase III studies of regorafenib have been completed in refractory GIST and refractory metastatic colorectal cancer. The GRID study in refractory GIST demonstrated improved progression free survival (71), whilst the global CORRECT study and the Asia only CONCUR study in refractory metastatic colorectal cancer both demonstrated improvements in overall survival (72, 73). Similarly, a second line study of regorafenib in hepatoma has shown an overall survival gain from 7.8 to 10.6 months vs placebo (74).

There is no established standard treatment for refractory AGOC after failure of second line therapy, nor any alternative treatments for people for whom second line chemotherapy is not appropriate.

INTEGRATE IIa

Ramucirumab only has data supporting its use in second line as monotherapy in patients unsuitable for chemotherapy and has only recently been approved in the US and EU. Apatinib is the only agent with evidence for benefit beyond second line therapy but only in Chinese patients, thus, there remains a strong clinical need for more therapies in patients with AGOC.

INTEGRATE was a randomized placebo controlled multicentre international (ANZ, Korea, Canada) Phase II trial that evaluated the activity of regorafenib versus placebo in AGOC (75) Regorafenib was effective in prolonging PFS 11.1 wks (95% CI: 7.7–13.3) vs. placebo 3.9 wks (3.7 - 4.0), HR 0.40, p<0.0001. A trend in overall survival was observed with regorafenib (Median OS 25 wks (95% CI: 18.9-29.6) vs. placebo 19.4 wks (95% CI: 14.9–22.7), HR 0.74, p=0.11, allowing for the fact 29/50 (58%) of placebo patients crossed over to receive regorafenib at progression. Pre-specified analyses found the regorafenib effect greater in Korea than ANZ/Can (HR 0.12 v 0.61, p=0.0009) but consistent across age, NLR (neutrophil:lymphocyte ratio), primary site, lines of CT, peritoneal metastases (mets) presence, number of metastatic sites, and baseline VEGF-A. Regorafenib was well tolerated, with expected spectrum of toxicities (75).

The findings from INTEGRATE provide a strong signal for activity of regorafenib in AGOC and raise the interesting question about possible differential efficacy by geographic region. The trend toward a survival benefit is seen as a strong signal for overall clinical benefit, particularly given the fact 58% of placebo patients crossed over at disease progression to receive regorafenib, thus diluting the ability to demonstrate an effect of regorafenib on survival. Consequently, in order to confirm this survival benefit, the design of INTEGRATE IIa cannot allow crossover of placebo patients to receive regorafenib. There currently exists no randomised trial evidence to support a survival benefit from 3rd or subsequent line systemic therapies in AGOC, hence a placebo control in this setting remains appropriate.

The purpose of the INTEGRATE IIa Phase III study is to determine whether regorafenib is effective in prolonging survival in patients with refractory AGOC overall and in the Asian sub-population.

3. IIa AIM AND OBJECTIVES

General Aim	To determine if regorafenib improves overall survival in refractory AGOC
Primary Objective (Endpoint)	To determine the effect of regorafenib on: 1. Overall survival (death from any cause) in the overall study population.
Secondary Objectives (Endpoints)	To determine the effect of regorafenib on: 2. Overall survival (death from any cause) in the Asian sub-population. 3. Progression free survival (PFS)(disease progression or death) 4. Objective tumour response rate (OTRR)(partial or complete response (PR or CR)) 5. Quality of life (QoL)(scores from participant-completed questionnaires) 6. Safety (rates of adverse events)
Tertiary/Correlative Objectives	6. To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) 7. To evaluate regorafenib PK in patient populations from different geographical regions.

4. IIa DESIGN

A randomised phase III, double blind, placebo-controlled trial with 2:1 (regorafenib:placebo) randomisation and stratification by:

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

5. IIa SUBJECT POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the NHMRC CTC prior to randomisation.

5.1. Target Population

The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant to a minimum of 2 lines of prior anti-cancer therapy which have included a platinum & fluoropyrimidine analogue.

5.2. Inclusion Criteria

1. Adults (18 years or over) with metastatic or locally recurrent gastro-oesophageal cancer which:
    a. has arisen in any primary gastro-oesophageal site (oesophago-gastric junction (GOJ) or stomach); *and*
    b. is of adenocarcinoma or undifferentiated carcinoma histology; *and*
    c. is **evaluable** according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1) by computed tomography (CT) scan performed within 21 days prior to randomisation. A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrolment; *and*
    d. has failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy for recurrent/metastatic disease which must have included at least one platinum agent and one fluoropyrimidine analogue. Note: Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy will be considered as first line treatment where people have relapsed or progressed within 6 months of completing treatment; Radiosensitising chemotherapy given solely for this purpose concurrent with palliative radiation will not be considered as a line of treatment. *Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, will be considered a line of treatment*.
    e. HER2-positive participants must have received trastuzumab

2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 1).
3. Ability to swallow oral medication.
4. Adequate bone marrow function (Platelets ≥100x10^9/L; Absolute Neutrophil Count (ANC) ≥1.5x10^9/L and Haemoglobin ≥ 9.0g/dL).
5. Adequate renal function (Creatinine clearance >50 ml/min) based on either the Cockcroft-Gault formula (Appendix 2), 24-hour urine or Glomerular Filtration Rate (GFR) scan; and serum creatinine ≤1.5 x Upper Limit of Normal (ULN).
6. Adequate liver function (Serum total bilirubin ≤1.5 x ULN, and INR ≤ 1.5 x ULN, and Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) ≤2.5 x ULN (≤ 5 x ULN for participants with liver metastases)).
   Participants being treated with an anti-coagulant, such as warfarin or heparin, will be

allowed to participate provided that no prior evidence of an underlying abnormality in these parameters exists.

7. Adequate cardiac function (Left Ventricular Ejection Fraction (LVEF) ≥ 50% or above the lower limit of normal (LLN) for the Institution (whichever is lower).
   Cardiac function should be assessed within 3 months prior to randomisation, but after completion of any anthracycline-containing chemotherapy.
8. Willing and able to comply with all study requirements, including treatment, timing, and/or nature of required assessments and follow-up.
9. Study treatment both planned and able to start within 7 days after randomisation (note: subjects randomised on a Friday should commence treatment no earlier than the following Monday)
10. Signed, written informed consent.

5.3. Exclusion Criteria

1. Known allergy to the investigational product drug class or excipients in the regorafenib
2. Poorly-controlled hypertension (systolic blood pressure >140mmHg or diastolic pressure> 90mmHg despite optimal medical management).
3. Participants with known, uncontrolled malabsorption syndromes
4. Any prior anti-VEGF targeted therapy using small molecule VEGF TKIs (e.g. apatinib). Prior anti-VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) are permitted.
5. Treatment with any previous drug therapy within 2 weeks prior to first dose of study treatment. This includes any investigational therapy.
6. Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to randomisation.
7. Concurrent treatment with strong CYP3A4 inhibitors or inducers.
8. Palliative radiotherapy, unless more than 14 days have elapsed between completion of radiation and the date of registration, and adverse events resulting from radiation have resolved to< Grade 2 according to CTCAE V4.03
9. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization
10. Arterial thrombotic or ischaemic events, such as cerebrovascular accident, within 6 months prior to randomization.
11. Venous thrombotic events and pulmonary embolism within 3 months prior to randomization
12. Any haemorrhage or bleeding event ≥ Grade 3 according to CTCAE v4.03 within 4 weeks prior to randomization.
13. Non-healing wound, ulcer, or bone fracture.
14. Interstitial lung disease with ongoing signs and symptoms
15. Clinical hyperthyroidism or hypothyroidism. Note: non-clinically significant abnormal TFTs (abnormal TSH and abnormal T3 and/or abnormal T4) considered to be due to sick euthyroid syndrome is allowed.
16. Persistent proteinuria of ≥ Grade 3 according to CTCAE v4.03 (equivalent to ≥ 3.5g of protein over 24 hours, measured on either a random specimen or 24 hour collection)
17. Uncontrolled metastatic disease to the central nervous system. To be eligible, CNS metastases should have been treated with surgery and/or radiotherapy and the patient should have been receiving a stable dose of steroids for at least 2 weeks prior to randomization, with no deterioration in neurological symptoms during this time.
18. History of another malignancy within 2 years prior to randomization. Participants with the following are eligible for this study:

a) curatively treated cervical carcinoma in situ,
b) non-melanomatous carcinoma of the skin,
c) superficial bladder tumours (T1a [Non-invasive tumour], and Tis[Carcinoma in situ]),
d) treated thyroid papillary cancer

19. Any significant active infection, including chronic active hepatitis B, hepatitis C, or HIV. Testing for these is not mandatory unless clinically indicated. Participants with known Hepatitis B/C infection will be allowed to participate providing evidence of viral suppression has been documented and the patient remains on appropriate anti-viral therapy.
20. Serious medical or psychiatric condition(s) that might limit the ability of the patient to comply with the protocol.
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 randomization. Men must have been surgically sterilized or use a barrier method of contraception.

5.4. 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. Study-specific screening investigations are those performed for the purpose of screening for the study that would not have normally been performed as part of routine care.

5.5. Randomisation

~~The process of enrolling an eligible person to participate in the study is randomisation.~~ Participant screening is used to confirm eligibility, while randomisation is the process by which participants are assigned to a treatment arm. Randomisation occurs via the ALMAC IXRS™ (IVRS) system.

Randomisation can only occur at sites that have received ethics approval and been activated in the IXRS system by the NHMRC CTC. Randomisation must not occur until eligibility has been confirmed by the investigator and the participant is ready to be randomised, and should be performed according to the instructions in the Study Manual.

Once the randomisation process has been completed, the participant will be assigned to a treatment arm, and confirmation of randomisation including study number will be provided to the site. Participants may only be randomised once in this trial. NOTE: Subjects randomised on a Friday should commence treatment dosing no earlier than the following Monday. Subjects should not commence treatment dosing on the weekend.

Current INTEGRATE IIa sites will continue to randomise eligible participants to INTEGRATE IIa until such time as all required regulatory/ethics approvals are in place for INTEGRATE IIb, required trial supplies are at site, training has been completed, and site is ready to activate on INTEGRATE IIb. Once INTEGRATE IIb opens to recruitment at a site, enrolment to INTEGRATE IIa will cease at that site. Patients enrolled in INTEGRATE IIa who remain on treatment/in follow up when their site opens to INTEGRATE IIb will continue on treatment/in follow up per the INTEGRATE IIa protocol. When INTEGRATE IIa closes at any site following the final analysis, all patients remaining on therapy at that time and judged by the investigator to still be deriving clinical benefit will continue on that treatment until progression or intolerance.

6. IIa TREATMENT PLAN

6.1. Administration of IIa Study Treatments

6.1.1. IIa Regorafenib

Regorafenib is the experimental intervention in this study. Regorafenib or matching placebo will be self-administered by participants at 160mg (4 x 40mg tablets) orally once daily on days 1-21 of each 28 day cycle until progression or prohibitive toxicity as defined by the protocol. It is recommended that regorafenib (or matching placebo) be taken as whole tablets with water after a light breakfast. Missed or vomited tablets cannot be compensated for by treatment at a later date and/or time.

6.1.2. Best Supportive Care (BSC)

Both treatment groups will receive BSC, which includes any intervention to preserve the comfort and dignity of study participants. For the purposes of this study, details on the nature of interventions that are considered as part of BSC are listed in Section 6.3.

6.2. IIa Dose Modifications

Instructions for treatment delays and dose modifications for adverse events are specified below. Adverse events are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 (Appendix 3).

In general, treatment should be withheld during adverse events of severity Grade 3-4, and not restarted until the adverse event has resolved to Grade 0-2, except where otherwise specified. Day 1 treatment may be delayed for a maximum of 28 days. If the adverse event has not resolved to Grade 0-2 after delaying day 1 treatment for 28 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

If commencement of a planned cycle (i.e.: Day 1 of treatment) is delayed, the first day of treatment of that cycle is still referred to as Day 1.

When an interruption is required *after a treatment cycle has commenced*, the clock does not stop – the dosing interval is always 21 days followed by a 7 day rest, beginning from day 1 of treatment. Withheld treatment days should not be rescheduled or made up. For example, if after 7 days of treatment, a patient requires an interruption of 7 days, the day that the patient recommences treatment is still called day 14 (not day 8).

Treatment may only be recommenced during the **treatment phase** of a cycle (day 1 to day 21). If the patient recovers and would be suitable for treatment during the non-treatment phase of a cycle (day 22 – day 28), treatment should not be recommenced until the Day 1 of the next planned cycle.

Specified dose reductions apply to all subsequent doses of study drug unless otherwise specified. If a patient experiences several adverse events with differing recommendations, then the most conservative modification (i.e.: results in the longest delay and lowest dose) should be used.

Only two dose level reductions are permitted. Treatment should be discontinued if not tolerated at dose level -2, according to the conditions outlined below. If a dose reduction has been performed, dose re-escalation for that participant can be considered, unless contrary to Sections 6.2.1, 6.2.2 and 6.2.3, (up to the maximal 160 mg daily dose) at the discretion of the treating Investigator providing that the toxicity(ies) has resolved to baseline.

Table 6.1 IIa Regorafenib Dose Levels

Dose Level 0 (Starting Dose)	160 mg po od	4 x 40mg tablets of regorafenib or matching placebo
Dose Level -1	120 mg po od	3 x 40mg tablets of regorafenib or matching placebo
Dose Level -2	80 mg po od	2 x 40mg tablets of regorafenib or matching placebo

6.2.1. Prevention of, and Dose-Modification for, Skin Toxicity including Hand-Foot Skin Reaction

Table 6.2 IIa Dose modifications for skin toxicity including Hand-foot skin reaction.

Skin Toxicity Grade	Occurrence	Dose Modification[a]
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	Consider decreasing 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[c].
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level[c].
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level[b,c].
	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 resuming treatment, decrease dose by one dose level[c].
	2nd occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level [b,c].
	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.
c. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the Investigator. 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 re-escalated 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.

6.2.2. Treatment-Emergent Hypertension

The dose modification schedule for treatment-emergent hypertension during study drug dosing should be followed (see Table 6.3 below). Participants' Blood Pressure (BP) measurements will be monitored and appropriate treatment to effectively control hypertension is required.

All participants should have their blood pressure monitored weekly during the first 4 weeks of treatment, then fortnightly to week 8, and on D1 of each cycle thereafter. D1 & D15 blood pressures will be taken during the clinic visit; D8 & D22 blood pressures may be taken at a GP's office or using a home blood pressure monitor if available. Blood pressure readings collected by a GP, or using a home BP monitor, will be recorded in a blood pressure diary and provided to the study site at each visit for appropriate management. Recommendations for anti-hypertension management will be provided in the Study Manual.

Table 6.3 IIa Dose modifications for treatment-emergent hypertension

NCI-CTCAE v4.03 Grade	**Definition**	**Anti-Hypertensive Therapy**	**Regorafenib/Placebo Dosing**
Grade 1	Pre-hypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None	Continue regorafenib/placebo. Consider more frequent blood pressure monitoring at Investigator's discretion
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 ≤ 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/placebo. If symptomatic, hold regorafenib/placebo until symptoms resolve AND diastolic BP ≤ 90 mmHg [a]. When regorafenib/placebo is restarted, continue at the same dose level
Grade 3	Systolic BP ≥ 160 mmHg or diastolic BP ≥100 mmHg OR More than one anti-hypertensive medication required OR more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mmHg - Start anti-hypertensive medication AND/OR - Increase current anti-hypertensive medication AND/OR - Add additional anti-hypertensive medications.	Hold regorafenib/placebo until diastolic BP ≤ 90 mmHg, and if symptomatic, until symptoms resolve [a]. When regorafenib/placebo 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 [b]. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level [c]
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 Investigator's discretion.
c. Participants requiring > 2 dose level reductions will be permanently discontinued.

6.2.3. 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 Table 6.4 should be followed.

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

Table 6.4: IIa Dose modifications/interruption for ALT[a] and/or AST[a] increases related to study drug

NCI-CTCAE v4.03[a]	1st occurrence	Restart	Reoccurrence
Baseline G0 → G1 or Baseline G1 → G2	Treat on time and check AST and ALT[d] 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.	N/A	Treat on time and check AST and ALT[d] 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks
Baseline G0 → G2	Delay until ≤ G1 and check AST and ALT[d] 2x/week. If there is a concomitant rise in bilirubin of ≥ 2x ULN[a], discontinue study treatment at the first occurrence[c, e].	Reduce 1 dose level and check AST and ALT[d] 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[b]	Discontinue regorafenib/placebo permanently[c]
Baseline any grade → G3	Delay until ≤ G1 if baseline was G0 or G1 OR until G2 if baseline was G2. Check AST and ALT[d] 2x/week. If ALT or AST >8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation of regorafenib/placebo at the first occurrence[c, e].	Reduce 1 dose level and check AST and ALT[d], 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks [b]	Discontinue regorafenib/placebo permanently[c]
Baseline any grade → G4	Discontinue regorafenib/placebo permanently[c]		

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal

b. If all values remain stable for 2 full cycles, dose re-escalation may be considered at discretion of investigator. After re-escalation AST, and ALT[d] should be checked 2x/week for 2 weeks, followed by weekly assessments for at least 4 weeks

c. In case of discontinuation, AST and ALT[d] should be checked 2x/week for 2 weeks, followed by weekly assessments until recovery to baseline

d. Bilirubin should be checked with AST/ALT however, dose modifications/interruptions for isolated bilirubin increases related to study drug should be as per table 6.5

e. Patients with known Gilberts syndrome experiencing a rise in bilirubin with < = 2x ULN and other liver function abnormalities are exceptions and can be observed to see if bilirubin changes are transient.

6.2.4. Other IIa Adverse Events not listed above

Table 6.5 below outlines dose modifications for all other adverse events deemed to be related to regorafenib/placebo not previously mentioned (excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities). If, after surgery, there is evidence of wound dehiscence, regorafenib/placebo should be discontinued.

Table 6.5 IIa Dose modifications for all other adverse events deemed to be related to regorafenib/placebo

NCI CTCAE v4.03 Grade	Dose Delay	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	No delay	No change	No change
Grade 3	Delay until ≤ Grade 2 [a]	Reduce 1 dose level	Dose escalation not allowed outside of specific recommendations in 6.2.1, 6.2.2, & 6.2.3
Grade 4	Delay until ≤ Grade 2[a]	Reduce by 1 dose level	Permanent discontinuation can be considered at treating Investigator's discretion.

[a] If no recovery after a delay of 28 days, regorafenib/placebo will be permanently discontinued.

6.3. IIa Concomitant Medications/Treatment

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 Investigator.

6.3.1. Recommended

The following measures are recommended for prevention and treatment of skin rash including hand-foot skin reaction:

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
- 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.

6.3.2. Permitted

- Corticosteroids
- Stent insertion for gastric outlet obstruction, providing that the position of the stent will not compromise response evaluation and there is no evidence of disease progression in all other sites. Stent insertion under other circumstances while receiving study treatment should be discussed with the Study Chair (or Delegate) via NHMRC CTC.

- Radiotherapy is allowed for the symptomatic treatment of non-evaluable bone lesions where there is no evidence of disease progression in other sites.
- Other palliative treatments, such as radiation to a bleeding primary tumour or non-emergency surgery, provided the circumstances of which have previously been discussed with the Study Chair (or Delegate) via NHMRC CTC.
- For non-emergency surgery, study treatment should be stopped at least 2 weeks prior to and 2 weeks following major surgery. The decision to resume study treatment should be based on physician judgement of adequate wound healing. Study treatment should be discontinued in patients with wound dehiscence.
- 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
- Participants who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate as per the inclusion criteria. Note: Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be affected by regorafenib. Close monitoring of at least weekly evaluations are recommended to be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care.
- Antiviral therapy required for viral suppression of Hepatitis B and/or C provided no contraindications exist (as outlined under section 6.3.3 Use with Caution or 6.3.4 Prohibited)

6.3.3. Use With Caution

Pharmacokinetic data from a clinical probe substrate study indicated that regorafenib may be given concomitantly with substrates of CYP2C19 (e.g. omeprazole), CYP2C8 (e.g. rosiglitazone), CYP2C9 (e.g. S-warfarin) without a clinically meaningful drug interaction. Specific caution should be employed when considering or administering a concomitant medication that is metabolized by the phase II glucuronosyl transferases UGT1A1 and 1A9. Studies have shown regorafenib may increase systemic exposure to UGT1A1 and 1A9 substrates. A list of CYP substrates, inhibitors, and inducers is provided at the following website: http://medicine.iupui.edu/clinpharm/ddis/.

- Participants taking narrow therapeutic index medications (e.g.: quinidine, cyclosporine,) should be monitored proactively. Co-administration of regorafenib with digoxin has no effect on plasma digoxin.

6.3.4. Prohibited

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors (including tyrosine kinase inhibitors), immunotherapy, hormonal therapy, and experimental or approved therapies
- Bone marrow transplant or stem cell rescue
- Concomitant palliative radiation therapy is not allowed, except as described as Best Supportive Care under Section 6.3.2.
- Strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, St John's wort) are not permitted. Co-administration of strong CYP3A4 inhibitors/inducers may lead to increased toxicity of regorafenib.
- Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF). 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 substitute for a required dose reduction. Routine use of G-CSF is not encouraged.

- Surgery for complications of disease or treatment, unless meets criteria as described under section 6.3.2;
- All traditional/alternative medicines with an anti-cancer indication, including Traditional Chinese Medicine and other investigational treatments.

6.3.5. Concomitant Medication Reporting

Concomitant medications will not be recorded during the study, except for medications being taken at the occurrence of any serious adverse events (SAEs) or medications known to interact with the study drugs.

6.4. Regorafenib/Placebo Treatment Compliance

Participant medication compliance will be determined at each clinic visit by tablet return review out of the sight of the participant, and the participant counselled appropriately if significant non-compliance is determined.

6.5. Unblinding

6.5.1. Emergency Unblinding

Unblinding is not generally necessary for the management of a participant with an adverse event (i.e.: emergency unblinding), and as it has an impact on the study's validity, it is strongly discouraged. However, if required, it should be done after discussion with the Study Chair (or Delegate) by contacting the INTEGRATE IIa emergency unblinding number on page 2 of the protocol.

6.6. Treatment Discontinuation

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

- Progressive disease (PD) according to RECIST Version 1.1 is documented by a site Investigator.
- Unacceptable toxicity as determined by the participant or Site Investigator or as defined in Section 6.2.
- Delay of day 1 treatment for >28 days, or > 2 dose level reductions required due to treatment-related adverse events. For delays >28 days due to due to reasons other than treatment-related adverse events, please contact the NHMRC CTC to discuss treatment continuation.
- The Investigator determines that continuation of treatment is not in the participant's best interests.
- Occurrence of an exclusion criterion affecting participant safety, e.g. pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in Section 6.3.4
- Failure to comply with the protocol e.g. repeatedly failing to attend scheduled assessments. If a participant has failed to attend scheduled assessments in the study, the Investigator must determine the reasons and document the circumstances as completely and accurately as possible in the medical records and CRF.
- The participant declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the participant's medical record. Follow up of participants who stop study treatment should continue according to the INTEGRATE IIa protocol.

6.7. Subsequent Treatment

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

7. IIa ASSESSMENT PLAN

7.1. IIa Schedule of Assessments

	Screening / Baseline	Treatment Period Assessments must be completed within a window of +/- 3 days of the assessment due date (unless otherwise specified in 7.2 – Details of assessments, or a footnote to this table)				Follow-Up
		Cycles 1-2 (1 Cycle = 28 days)		Cycles 3+	End of Treatment Visit	
Procedure / Assessment	Up to 14 days prior to randomisation unless otherwise indicated	Day 1*^	Day 15	Day 1*	Within 30 days of last dose of study drug	Every 8 weeks from last scan date
Clinic Assessment:						
Informed Consent (Main and Optional Translational components)	X[1]					
Medical History: Prior medical and anticancer therapy	X[2]					
Physical Assessment: Vital Signs (T,P,Resp), ECOG PS	X	X		X		
Adverse Events (at the **end** of each cycle for the previous cycle)		X[3]		X	X	(X[4])
Participant Status		X		X		X
Cardiac Monitoring:						
Cardiac Function (GCBPS/MUGA or Echo)	X[1]	See 7.2.2				
Blood Pressure	X	See 7.2.1		X		
Blood Tests:						
Haematology: Full blood count with 5-cell differential count	X	X	X	X		
Biochemistry: Creatinine, uric acid, sodium, potassium, chloride, electrolytes corrected serum calcium, phosphate, albumin, glucose	X	X	X	X		
Biochemistry: Liver function tests (Bilirubin (total and direct), AST, ALT, ALP, GGT)	X	See 7.2.4		X		
Biochemistry: Thyroid function tests (TFT: TSH, free T4, free T3 at each assessment)	X	X		X		
Tumour Marker (CA19-9, LDH)[5]	X[2]	See 7.2.4 with each CT until PD				
Coagulation Panel: PT/PT-INR, PTT	X	X	X	X		
Hepatitis B & C Serology and/or HIV Testing	X[2]					
Serum Pregnancy Test	X[6]					
Blood for Translational Research (see 7.2.4)		C1D1, C2D1		C4 D1 only	X	
Blood for PK (at selected sites)[8] (see 7.2.4)		C1D15, C2D1[7], C2D15				
Urinalysis:						

	Screening / Baseline	Treatment Period Assessments must be completed within a window of +/- 3 days of the assessment due date (unless otherwise specified in 7.2 – Details of assessments, or a footnote to this table)				Follow-Up
		Cycles 1-2 (1 Cycle = 28 days)		Cycles 3+	End of Treatment Visit	
Procedure / Assessment	Up to 14 days prior to randomisation unless otherwise indicated	Day 1*^	Day 15	Day 1*	Within 30 days of last dose of study drug	Every 8 weeks from last scan date
Spot urine for protein:creatinine ratio	X					
Dipstick		X		X		
Imaging:						
CT (Chest, Abdomen and Pelvis) (see 7.2.2)	X[2]	every 8 weeks from date of randomisation to PD				
Quality of Life (QoL):						
EORTC QLQ-C30, STO22, Patient D.A.T.A Form, EQ-5D-5L (until PD)		X		X	X	X(8-weekly until PD)
Other:						
Concomitant Medications	Concomitant medications will not be recorded, except those administered within 30 days of a serious adverse event report. Concomitant medications used to treat an SAE will not be recorded					

* D1 assessments should be conducted prior to commencing dosing.
^Subjects should not commence C1 treatment dosing *on a weekend*. Subjects randomised on a Friday should commence treatment dosing no earlier than the following Monday
[1] Up to 90 days prior to randomisation
[2] Up to 21 days prior to randomisation
[3] Commencing C2D1
[4] Ongoing AE's at the End of Treatment visit should continue to be assessed in follow-up until resolved to baseline
[5] Window of +/-7 days around each CT applies
[6] Within 7 days prior to randomisation
[7] Window of +/-3 days not permitted for C2D1 sample only (must be drawn on D1 or up to +3 days only – see 7.2.4)
[8] Where a scheduled PK sample collection (and clinic visit) fall on a public holiday refer to Section 7.2.4

7.2. Details of IIa Assessments

7.2.1. Clinical Assessment

Day 1 assessments must be conducted prior to dosing. **Baseline blood tests do not need repeating prior to C1D1 unless clinically indicated.** BP should be monitored weekly for the first 4 weeks of treatment, then 2-weekly until week 8. After 8 weeks of treatment, BP monitoring can be reduced to Day 1 of each treatment cycle. D8 & D22 blood pressures may be taken at the clinic, at a GPs office or using a home blood pressure monitor if available. Blood pressure readings collected by a GP, or using a home BP monitor will be recorded in a blood pressure diary and provided to the study site at each visit for appropriate management

7.2.2. Imaging

Eligibility and baseline tumour assessment will be determined by a CT scan performed within 21 days prior to randomisation. This should be performed as close to randomisation as possible. Tumour assessments must be performed thereafter at 8 week intervals (+/- 3 days), as appropriate, regardless of delays in study drug administration, until disease progression. The timing of tumour assessments is considered **from date of randomisation**. A repeat CT is not required prior to Day 1 Cycle 1. Brain imaging is only required if clinically indicated.

Cardiac function should be assessed within 90 days prior to randomisation, but after completion of anthracycline-containing chemotherapy. Repeat measurements of LVEF should be performed as clinically indicated while on treatment.

7.2.3. Quality of Life

Quality of Life questionnaires (i.e.: QLQ-C30, STO22, Patient D.A.T.A. Form, EQ-5D-5L) should be completed at baseline (i.e.: C1D1 prior to dosing), every 4 weeks thereafter during treatment, and at the time of disease progression. For patients who end treatment before disease progression, QoLs will be collected every 8 weeks during follow-up until disease progression. Where necessary, translations of these questionnaires into the primary local language will be made available. Refer to INTEGRATE II eCRF completion guidelines (section 9.11) for further detail on administration of QOL's, tips for minimizing missing data, etc.
Note: Patient D.A.T.A Form to be completed by English-speaking participants only (no translations available).

7.2.4. Blood & Urine Collection

Weekly Liver Function Tests (LFTs) are required for first 4 weeks of treatment, then 2-weekly to week 8, and then on day 1 of all subsequent cycles of treatment. The weekly LFTs can be done at a laboratory other than the randomising site, however, it is recommended that if there is a clinically significant result, the test should be repeated at the randomising site. Study sites must ensure that all LFTs are documented in the participant's study file as source data.

Tumour Markers CA19-9 and LDH are to be assessed at the same time as CT imaging (+/- 7 days) until disease progression – refer to 7.2.2 for timing of tumour assessments by CT imaging.

TSH/T3/T4 are required at baseline AND for all subsequent assessments as per 7.1. Thyroid function tests are not required on Day 15 of each treatment cycle.

Testing for chronic active hepatitis B, hepatitis C or HIV is not mandatory unless clinically indicated.

A serum pregnancy test must be performed within 7 days prior to randomisation for women of childbearing potential.

Blood for translational research is to be collected from all patients at 4 timepoints: C1D1, C2D1, C4D1, and end of treatment. For processing and storage procedures, refer to Biospecimen Manual.

Blood collection for pharmacokinetics (PK) collected at three time points: C1D15, C2D1, C2D15 is optional (and collected at selected sites only). At these time points, a blood sample is collected before regorafenib is taken at the site, and another sample collected 1-4 hours after regorafenib has been taken. Participants will be asked to record exact dosing times for the 3 days prior to C1D15 & C2D15 (not C2D1) in a PK diary. **Where a scheduled PK sample collection (and clinic visit) falls on a public holiday:**

- **C1D15 and C2D15**: the visit may be rescheduled either earlier or later (+/- 3 day window is permitted in this instance)
- **C2D1**: the visit must be rescheduled later (only +3 day window is permitted). **Sample collection (and dosing) is not permitted during protocol-mandated 7 day washout at the end of C1**
- collect the PK samples pre/post dose at the rescheduled clinic visit AND
- remind the subject to complete their regorafenib PK diary (date and time of drug, number of tablets) as per instructions ***for the actual 3 days prior to the rescheduled clinic visit***

If a PK sample collection is affected by study treatment interruptions, please contact your Coordinating Centre for further instructions. For processing and storage procedures, please refer to Biospecimen Sampling Manual.

Spot urine, a random urine sample sent to the lab for analysis, which includes protein:creatinine ratio, is required at baseline. If protein excretion is abnormally high, further quantification via a 24 hr. urine or other test should be done as per usual site practice to confirm eligibility (i.e.: < 3.5 g protein over 24 hours). Dipstick urinalysis, using standard urine test strip, is required after commencement of treatment on D1 of each cycle. If abnormal, further investigations should be conducted as clinically appropriate.

7.2.5. Tissue Collection

Submission of available tumour tissue (primary or metastatic) is requested. Refer to the Biospecimen Manual for details as to type of specimen, etc.

7.3. Follow-up After Treatment

Participants will attend an end of treatment visit within 30 days of the last dose of study treatment, and then be followed 8-weekly *from the last CT scan date* for survival for a minimum of 12 months or until death. Ongoing AE's at the end of treatment visit should continue to be assessed at follow-up visits until resolved to baseline.

8. IIa OUTCOMES, ENDPOINTS AND OTHER MEASURES

8.1. Overall Survival (OS)

(Death from any cause)

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive.

8.2. Progression Free Survival (PFS)

(Disease progression or death)

Progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first evidence of disease progression or death, whichever occurs first. A PFS event is defined as the first occasion that either: (i) RECIST criteria for disease progression are met, (ii) a patient is judged to have progressed by the responsible investigator (in the event that no RECIST assessment is available), or (iii) death occurs. Patients who commence non-protocol anti-cancer therapy without prior evidence of progression will be censored at the prior assessment. Patients who are not observed to meet any of the above conditions will be censored at the date of the last assessment.

8.3. **Objective Tumour Response Rate (OTRR)**

The OTRR will be calculated by summing the number of participants in a given arm that are assessed as having a complete or partial response (as per RECIST criteria), and dividing this by the total number of participants in the corresponding arm of the analysis set.

8.4. **Quality of Life (QoL)**

The core EORTC QoL Questionnaire (QLQ-C30) will be used in conjunction with the disease specific module for GC (STO22). The EQ-5D-5L will be used to obtain utility valuations on the health states experienced by participants (The EuroQol Group (2009). Additional items on cancer-specific symptoms will be collected using the Patient Disease And Treatment Assessment (D.A.T.A.) Form for English-speaking participants only (76) (refer to Appendix 6. Quality of Life Questionnaires & Patient D.A.T.A. Forms). The Patient D.A.T.A Form includes relevant items not covered in the other instruments (e.g., rash, light-headedness, headaches, sore hands/feet, drowsiness). These PROs were used together in the preceding phase II trial and were found to be appropriate in this setting (77). Standard scoring methods will be used to derive scales from these instruments for analysis.

8.5. **Safety**

See protocol Section 21.1 for the definition of an adverse event (AE). The NCI Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE) will be used to classify and grade the intensity of adverse events after each treatment cycle.

8.6. **Tertiary/Correlative**

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

Planned biomarker analyses may include but are not limited to:

- Investigation of VEGF-related biomarkers including VEGF, VEGF polymorphisms, circulating VEGF isoforms (VEGF A short isoforms), VEGF family receptors (VEGFR-1, 2, 3) and other proteins downstream of VEGFR, as prognostic and/or predictive markers for those study endpoints relating to survival, response and safety
- Other biomarkers relating to angiogenesis and/or tumourigenesis in blood and tumour including FGF pathway, PDGF, vWF, Tie1 and 2.
- Evaluation of the prevalence and distribution of the four proposed molecular phenotypes of gastric cancer proposed by the Cancer Genome Atlas Research Network (2014), and their association with angiogenic biomarkers and regorafenib activity.
- Regorafenib pharmacokinetics in patients from different geographical regions.

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.

9. IIa STUDY DRUG INFORMATION

9.1. Investigational Product

The following investigational products (IPs) will be used as study treatments:

- INTERVENTION: regorafenib tablets.
- CONTROL: placebo tablets (matching in appearance to regorafenib)

9.1.1. Description of Investigational Product

Regorafenib and matching placebo will be provided by the manufacturer. The regorafenib 40 mg tablet is coated, non-divisible, grey-orange-red, oval-shaped (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 or matching placebo.

The tablets are stored in high-density polyethylene (HDPE) bottles with a desiccant cartridge inside. The tablets must be stored in the original bottle at the temperature indicated on the bottle label (i.e.: not above 25^0C). The bottle must be kept tightly closed after first opening, with the desiccant remaining in the bottle. Once the bottle is opened the tablets must be discarded after 7 weeks.

9.1.2. Supply of Investigational Product

Participating Institutions will be provided with a start-up supply of study medication once the institution has been activated to commence accrual by the Coordinating Centre. In order to maintain the blind, study medication (regorafenib or matching placebo) will be labelled with a unique “kit” number, which will be assigned to a participant at each dispensing visit. Each kit consists of 3 bottles of study medication, or sufficient supply for 1 cycle at the starting dose of 160mg.

9.1.3. Investigational Product Accountability

The Pharmacy at Participating Institutions will maintain a record of
drugs dispensed for each participant and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

10. IIa STATISTICAL CONSIDERATIONS

Due to the shift in practice in AGOC, recruitment to INTEGRATE IIa has been halted. Without breaking the treatment allocation blind, a decision was prospectively made to pool the data from INTEGRATE IIa with INTEGRATE to compensate for the reduced sample size. The sections below explain the statistical considerations associated with both the pooled analyses and INTEGRATE IIa analyses.

A statistical analysis plan for INTEGRATE IIa (including the analyses of data pooled across INTEGRATE and INTEGRATE IIa) has been prepared and contains additional detail on the methods described below.

10.1. Sample Size and Statistical Hypotheses

A sample of 250 participants randomised in a 2:1 ratio (REG: PBO) is expected to yield at least 221 OS events. These 221 events will contribute to a pooled analysis with the previous INTEGRATE trial (which had 123 OS events). The conditional power (conditional on the known INTEGRATE trial results) of the pooled analysis to detect a hazard ratio (HR) for OS of 0.67 is estimated to be over 90%. Based on 221 events, INTEGRATE IIa on its own will also have 80% power to detect HR of 0.67.

To determine the appropriateness of a pooled analysis, heterogeneity of treatment effect on OS across INTEGRATE and INTEGRATE IIa will be tested by fitting a trial-by-treatment interaction term in a Cox proportional hazard regression model (that includes the corresponding main effect terms). The null hypothesis associated with the trial-by-treatment interaction for the OS endpoint will be tested at the two-sided 5% level of significance.

If there is no statistically significant heterogeneity, A sequential closed testing procedure (with two-sided alpha set to 5%) will be applied to the following null hypotheses of no treatment effect in the:

- Pooled cohort ($H0_1$)
- INTEGRATE IIa cohort ($H0_2$)
- Asian region pooled cohort ($H0_3$)
- Asian region INTEGRATE IIa cohort ($H0_4$)

If there is significant heterogeneity between INTEGRATE and INTEGRATE IIa, a sequential closed testing procedure (with alpha set to 5%) will be applied to the following null hypotheses of no treatment effect in the:

- INTEGRATE IIa cohort ($H0_2$)
- Asian region INTEGRATE IIa cohort ($H0_4$)

10.2. Statistical Analysis

The methods described below for the analysis of INTEGRATE IIa data will be adapted as appropriate to perform any analyses of data pooled across INTEGRATE and INTEGRATE IIa. Refer to the statistical analysis plan for further details.

The primary analysis of efficacy endpoints will be performed on the analysis set comprising all randomised patients in accordance with the intention-to-treat analysis principle. The safety population will comprise all randomised participants who received at least one administration of study medication. Participants will be analysed according to the regimen they received for the purposes of the safety analysis.

10.2.1. Analysis of Efficacy Endpoints

The comparison of overall survival (OS) between the two treatment arms will be performed using a log-rank test accounting for stratification factors. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression accounting for stratification factors. PFS will be analysed in a comparable fashion to OS. The OTRR will be compared between randomised groups using a Cochran-Mantel-Haenszel test accounting for stratification factors (or an unstratified exact test given few responses).

A series of subgroup analyses will be performed on OS for the stratification factors used at randomisation, self-reported ethnicity (Asian vs. other), and time since prior immunotherapy (subject to sufficient participant numbers).

The analysis of QoL will follow the methods used for the phase II INTEGRATE trial (77)(75). The primary analysis approach will compare groups on deterioration-free survival (DFS). DFS is defined as the time from randomisation to the first of the following events: a 10-point deterioration in health status from baseline (without subsequent 10-point improvement compared with baseline), disease progression, death, or treatment discontinuation. Two DFS endpoints will be derived using different markers of health status deterioration based on the EORTC QLQ-C30. One will use the Physical Function Scale (DFS_{PF}), and the other used the General Health Scale (DFS_{GHS}). DFS_{PF} and DFS_{GHS} will be analysed in a comparable fashion to OS. A repeated measures model (RMM), specified within the general linear-mixed model framework, will be applied to the scales from the EORTC QLQ-C30, EORTC STO22, and EQ-5D instruments in a secondary analysis. The models will include the

relevant baseline score, treatment allocation, time point, and a treatment allocation-by-time point interaction as covariates. The general linear-mixed model framework accommodates missing post-baseline data and yields valid estimates under the 'Missing At Random' assumption. Information from the Patient D.A.T.A. Forms will be analysed as part of a tertiary analysis. The proportion of patients experiencing symptoms, or impacts on general aspects of QoL, (of at least 3-points intensity on 11 point scale) will be calculated across the post-baseline assessment period, and comparisons between treatment arms will be made using logistic regression adjusting for baseline.

10.2.2. Analysis of Safety Endpoints

A descriptive analysis of the adverse events (AE) data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness.

10.2.3. Analyses for Tertiary/Correlative Objectives

An evaluation of the candidate biomarkers (that may include those listed in Section 8.6) as prognostic and/or predictive factors will be undertaken in a set of exploratory analyses using the appropriate modelling method applicable to each clinical and patient reported endpoint.

10.3. **Timing of Analyses**

INTEGRATE IIa will be unblinded for analysis after 221 events are observed.

INTEGRATE IIb

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

NOTE:

- **Sites may use the IIb protocol provided they**
  - **Have all local approvals in place for IIb**
  - **Have received training for IIb protocol & data systems**
  - **Have received IIb supplies (ie: lab kits)**
  - **Have been activated by the Global Coordinating Centre**
- ***New sites/regions* will open on the IIb study arm once the above criteria have been met**
- **Site currently activated for IIa must continue recruiting to IIa until the above criteria have been met**
- **Patients randomised to IIa will be treated and followed as per the IIa protocol**

11. IIb SYNOPSIS & SCHEMA

11.1. SYNOPSIS

Background

Advanced Gastro-oesophageal Carcinoma (AGOC) has a poor prognosis, and there is no established standard treatment following failure of first- and second-line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in INTEGRATE The INTEGRATE II trial is currently a randomised phase III, controlled trial aiming to determine if regorafenib improves overall survival in refractory AGOC.

Immune checkpoint inhibitors enhance anti-tumour T-cell activity through the inhibition of immune checkpoints such as the programmed death-1 (PD-1) receptor. Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of PD-1, shown to be effective in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens in the ATTRACTION-2 study (28). Biologic rationale exists for synergy between anti-angiogenic therapy (anti-VEGF and others) and anti-PD-1/PD-L1 therapy through changes in the tumour microenvironment (78). The regorafenib and nivolumab combination (RegoNivo) showed manageable toxicity and encouraging activity in patients with refractory advanced gastric cancer in a Phase Ib trial, including in patients having received prior nivolumab (79). Current practice in countries participating in INTEGRATE IIb has evolved to use chemotherapy in 3rd and subsequent lines of therapy in fit patients. Agents with demonstrated activity in the 2nd line setting (vs Best supportive Care alone) are utilised, including taxanes (paclitaxel and docetaxel), irinotecan, and oral trifluridine/tipiracil (TAS 102)(14, 17, 18, 80-82).

With the shift in practice in AGOC resulting in use of multiple lines of therapy, the use of new immunotherapy agents, and the promising activity of RegoNivo, this amended trial is proposed to compare the effectiveness of RegoNivo in pre-treated patients with AGOC to the current standard therapy (i.e.: chemotherapy).

General Aim

To determine if the regorafenib and nivolumab combination (RegoNivo) improves overall survival compared with current standard chemotherapy options in refractory AGOC

Revised Design

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

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

INTEGRATE IIb

Primary Objective (Endpoint)	To determine the effect of RegoNivo on overall survival (OS) (death from any cause) in the overall study population.
Secondary Objectives (Endpoints)	To determine the effect of RegoNivo on: • Overall survival (death from any cause) in the Asian sub-population. • Progression free survival (PFS) (disease progression or death) • Objective tumour response rate (OTRR) (partial or • complete response (PR or CR)) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, and immune-related iRECIST(83) • Quality of life (QoL)(scores from participant-completed questionnaires) • Safety (rates of adverse events)
Tertiary/Correlative Objectives	• To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) • To evaluate regorafenib PK in patient populations from different geographical regions (PK levels)
Population	The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant of a minimum of 2 lines of prior anti-cancer therapy which must have included a platinum agent and a fluoropyrimidine analogue
Study Treatments	Participants in the **RegoNivo arm** will self-administer 90mg (3x30mg) of regorafenib days 1-21 of each 28-day treatment cycle and receive intravenous nivolumab 240 mg day 1 of each 14 day cycle until disease progression or prohibitive adverse events as per protocol. After 2 months, patients whose disease is controlled may have nivolumab administered 480 mg every 28 days. Participants in the **control arm** will receive investigator choice chemotherapy with any of the following agents (see 16.1.2): • taxane (paclitaxel or docetaxel) • irinotecan or • oral trifluridine/tipiracil (TAS102) Both treatment groups will receive Best Supportive Care (BSC).
Assessments	• From 30th April 2025 Integrate IIb will be considered closed for all participants except those receiving RegoNivo treatment. No further protocol assessments or routine follow-up are required for any participants in the control arm (investigator choice chemotherapy) or participants in the RegoNivo arm who are in the follow-

up phase. Participants currently on study treatment in the RegoNivo arm will continue treatment and follow-up according to the revised schedule of assessments in Section 17.1.

- Clinic visits (including biochemistry and haematology tests) will be required at baseline, every 2-4 weeks during treatment, and at the end of treatment. Weekly assessment of blood-pressure and liver function tests (LFTs) will be required during the first 4 weeks on treatment, then fortnightly to week 8, then on D1 each cycle thereafter.
- Urinalysis will be performed at baseline and then on day 1 of each treatment cycle.
- Participants will be assessed 4 weekly until disease progression, and then for survival status 8 weekly until death.
- Imaging will be performed at baseline, then 8 weekly until disease progression or death, timed from the date of randomisation.
- Blood for biomarkers will be collected at C1D1, C2D1, and with tumour markers test at the time of 8-week CT scan. Following local implementation of Protocol v10.0, no further samples will be collected at end of treatment. Additional blood for PK to be collected on C1D15, C2D1, and C2D15 at selected centres only for RegoNivo arm only (optional).
- Health-related QoL will be obtained at baseline (C1D1 prior to dosing), then on a 4 weekly basis continuing up to (and including) the visit where disease progression is established.

Statistical Considerations

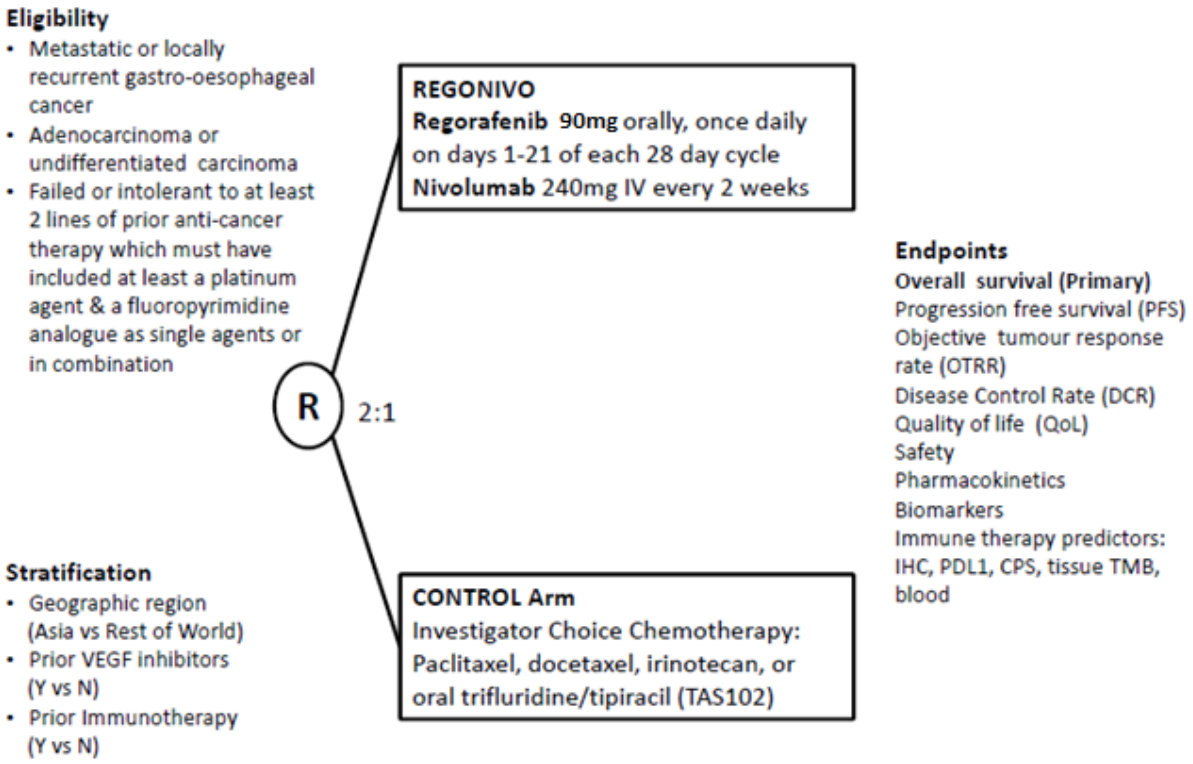
A sample of 460 participants randomised in a 2:1 ratio (RegoNivo: chemotherapy) and followed until 380 deaths occur provides at least 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05 assuming median survival amongst chemotherapy patients is 6 months and allowing for a 2% margin for loss to follow-up. The reference median survival of 6 months is based on the Keynote 061 study and Javelin Gastric 300 study(84, 85).

The design accommodates early stopping for benefit at an interim analysis performed at 2/3 of the required events (using the error spending approach of Lan-DeMets).

The primary objective involves testing the following two null hypotheses at trial completion: (1) no treatment effect on OS in the whole trial cohort ($H_0^{(All)}$); and, (2) no treatment effect on OS in the Asian region cohort ($H_0^{(Asian)}$). A sequenced closed testing procedure will be used to constrain the overall type I error of these two tests to 5%. This will involve first testing $H_0^{(All)}$ at α=5%. If $H_0^{(All)}$ is rejected, then $H_0^{(Asian)}$ will tested and rejected at α=5%. If $H_0^{(All)}$ is not rejected, then $H_0^{(Asian)}$ will not be rejected. Around 50% of the trial cohort is expected to be recruited from Asian regions providing at least 80% power to

detect a HR for OS of 0.60 following this sequential testing procedure.

11.2. SCHEMA



12. IIb BACKGROUND

12.1. Current Treatment of Gastric Cancer

Giving third line chemotherapy is widely practiced for patients with good performance status. In a systemic review and meta-analysis Zheng et al reported the effect of third-line chemotherapy in advanced gastric cancer in 19 studies (86). Six were randomized placebo control or best supportive care control studies with agents such as irinotecan, docetaxel, apatinib and sunitinib. Fourteen studies were non-controlled using FOLFIRI, ith doxorubicin, paclitaxel, doxetaxel with or without sunitinib, irinotecan and tivantinib. They reported better median overall survival and progression free survival with third line chemotherapy when compared to placebo or best supportive care (Hedges's g for OS=0.315±0.077, P<.001; and for PFS=0.382±0.098, P<.001). More recently a randomised phase 3 study of TAS-102 v placebo demonstrated a survival advantage in this pre-treated population (82). The main chemotherapy associated side effects for all of these agents include anaemia, neutropenia, thrombocytopenia, anorexia, fatigue, nausea and vomiting; with most patients able to continue and complete therapy. Despite this data, there is no guideline for the optimal third line chemotherapy as the evidence is limited to studies of small sample size, mostly non-randomized trials, lacking formal quality of life reporting. Furthermore, drug selection in the third line setting depends on drug availability and choice of prior regimen in first and second line.

12.2. Current Targeted Therapies for AGOC

The most recent class of therapy to be explored in AGOC are the immune checkpoint inhibitors, which have shown great promise in melanoma, lung cancer, bladder cancer and other solid tumours. Of particular interest are the checkpoint inhibitors focused on programmed cell death 1 receptor (PD-1) and PD-1 ligand (PD–L1) (26). Although still preliminary, this approach may play an important role in gastric cancer. Data from key recently reported clinical trials of immunotherapy are summarized below in section 12.2.1.2.

12.2.1. Rationale for Therapies Targeting immune checkpoint inhibitors in AGOC

12.2.1.1 Potential Prognostic and Predictive value of PD-1/PD-L1 pathway

Programmed cell death protein 1(PD-1) is present on T cell, B cell, natural killer cell and monocyte surface (87, 88). PD-1 has two main ligands, PD-L1 and PD-L2, both of which are expressed on tumour cells (87, 89). When PD-1 on T cells interact with PD-L1 and PD-L2, T-cells are exhausted, leading to escape immune surveillance (90). Therefore, antibodies directed against PD-1 or PD-L1 can reverse this T-cell suppression and produce tumour response (27)
In gastric-oesophageal cancers, PD-L1 is expressed in 2-63% of tumour cells and 18-64% of immune/inflammatory cells within the tumour microenvironment (30, 91-99). There are mixed data on association of PD-L1 expression and prognosis. Expression of PD-L1 was associated with better survival in some studies (30, 91) but poor prognosis in others (94-97, 99). PD-L1 expression is found to be predictive of response to immunotherapy in non-small cell lung cancer (100, 101). There is limited data on predictive value of PD-L1 in advanced gastric and gastroesophageal junction cancers. Programmed death-1 ligand 1 (PD-L1) expression, which is associated with depth of invasion, tumour size, lymph node metastasis, and a shorter median survival, has been reported in 25–65% of gastric cancers (28, 102-104). In KEYNOTE-012, patients with gastric or gastroesophageal junction tumour showing PD-L1 expression received single agent pembrolizumab (105). They reported higher level of PD-L1 expression to be associated with a trend towards better ORR, PFS and OS (1-sided P=0.10, 0.16, and 0.12, respectively) (105). Similarly, in KEYNOTE-059, ORR was higher in PD-L1 positive when compared to PD-L1 negative patients (15.5% vs 6.4%) (29).

12.2.1.2 Evidence for Therapies Targeting PD-1/PD-L1 pathway

ATTRACTION-2, a phase III trial of Nivolumab (a human IgG4 monoclonal antibody which blocks the PD-1 receptor) versus placebo, showed improved overall survival benefit in patients having received at least two prior chemotherapy regimens. Median overall survival was 5.32 months with nivolumab vs 4.14 months with placebo (HR 0.63, 95%CI 0.51-0.78; p<0.0001) in the Asian population (the study was conducted in Japan, South Korea and Taiwan). The survival benefit was independent of PD–L1 positivity (28).

In CheckMate-032, a phase II study, efficacy and safety of nivolumab and nivolumab plus ipilimumab (ipilimumab and nivolumab was used at two different doses making it a three arm study) was assessed in patients with advanced gastroesophageal cancer (106). The objective response rates were 12% (95% CI, 5% to 23%), 24% (95% CI, 13% to 39%), and 8% (95% CI, 2% to 19%) with nivolumab 3 mg/kg, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg respectively. Twelve months progression free survival rates were 8%, 17% and 10% respectively; 12 months overall survival rates were 39%, 35% and 24% respectively. Therapy related grade ¾ side effects were 17%, 47% and 27% respectively in the three groups. The safety profile was manageable by following protocol-specified AE management algorithms.

Pembrolizumab, a PD-1 antibody, was approved by FDA for patients who progressed following two or more prior lines of therapy including fluoropyrimidine and platinum-containing chemotherapy based on the KEYNOTE-059 study (29).This phase II study in PD-L positive tumours (defined as immunohistochemistry score for PD-L1 $\geq$ 1%) demonstrated 15.5% ORR (95%CI,10.1-22.5),with 2% patients achieving complete remission (95% CI,0.4-5.8)(29) (.

In the JAVELIN study, avelumab, an anti-PD-L1 antibody versus physician's choice of chemotherapy was compared in Japanese patients with advanced gastric or gastro-oesophageal junction cancer (85). Avelumab did not improve OS (median, 4.6 versus 5.0 months; HR=1.1; 95% CI 0.9–1.4; $P = 0.81$), PFS (median, 1.4 versus 2.7 months; HR=1.73; 95% CI 1.4–2.2; $P > 0.99$) or ORR (2.2% versus 4.3%) when compared to chemotherapy. Avelumab however did show a more manageable

side effect profile when compared to chemotherapy (grade ≥3 treatment related adverse events 9.2% versus 31.6% respectively). In another phase 1b study using pembrolizumab (PD-1 inhibitor) in patients with advanced gastric cancer, the 6 month overall survival rate was 69% (31)(Muro 2015).

Subsequently, KEYNOTE-061, a phase III trial compared pembrolizumab with paclitaxel in previously treated advanced gastric and gastro-oesophageal junction tumours having a combined positive score (CPS) of 1 or higher (84). Median overall survival was the same between the two treatment arms (9.1 months with pembrolizumab vs 8.3 months with paclitaxel HR=0.82, 95% CI 0·66–1·03) with pembrolizumab arm showing better safety profile compared to paclitaxel (grade 3-5 treatment related adverse events 14% vs. 35%).

Data from numerous additional international trials evaluating the efficacy of checkpoint inhibitors in AGOC are ongoing or maturing, including evaluation of combinations with chemotherapy, and maintenance therapy. The ultimate place for the best use of immunotherapy agents for patients with AGOC awaits results from these studies.

12.3. **Rationale for Use of regorafenib (BAY73-4506) & nivolumab in combination**

There is no single standard treatment for refractory AGOC after failure of second line therapy, Ramucirumab only has data supporting its use in second line as monotherapy in patients unsuitable for chemotherapy and has only recently been approved in the US and EU. Apatinib is the only agent with evidence for benefit beyond second line therapy but only in Chinese patients (69). Thus, there remains a strong clinical need for more therapies in patients with AGOC. Immunotherapy remains an emerging treatment with modest efficacy and limited availability

The response rate to single agent immune checkpoint inhibitors is around 2.2%-16% (28, 29, 84, 85, 106). This may be due to increase in number of immunosuppressive cells (e.g., myeloid derived suppressor cells (MDSC) and regulatory T cells) and tumor-associated macrophages, as the tumor progresses (107). Similarly, in unpublished data of a case study of gastric cancers, regulatory T cells were increased after treatment in patients with progressive disease when compared to those with stable disease or partial response. This data proposes that efficacy of immune checkpoint inhibitors may improve by inhibiting immunosuppressive cells. Vascular endothelial growth factor (VEGF) is thought to be involved in regulatory T cell, MDSC and tumor-associated macrophage production. Inhibition of VEGF receptor is reported to inhibit immunosuppressive cell production and lead to increase in invasion of tumor by T-cells [OBJ]108-111). In addition inhibition of RAF and MEK inhibitors escalates invasion of tumor by T cells [OBJ][OBJ], 113). Based on these findings it can be suggested that multikinase inhibitors (which have antiangiogenic effect and inhibit RAF) in combination with immune checkpoint inhibitors is promising. In renal cell cancer, a phase I study of pazopanib/sunitinib in combination with nivolumab demonstrated high response rate in pazopanib combination (56%) and sunitinib combination (41%) (114).

Concurrent blockade of PD-1 and vascular endothelial growth factor receptor 2 (VEGFR-2) stimulates synergistic immune mediated tumor kill. The phase I JVDF study assessed safety of pembrolizumab and ramucirumab (anti-VEGFR-2) combination in first line treatment of advanced gastric or gastroesophageal junction cancers (115). This combination demonstrated promising antitumor activity with 51% disease control rate, with median PFS of 2.5 months (95% CI 1.5-4.2), median OS of 5.9 months (95% CI 4.4-10.6) and 6% grade IV adverse events (2% each of anemia, cholestasis and infection with pneumocystis jirovecii).

In the Japanese REGONIVO phase Ib dose-finding/dose expansion study, the combination of regorafenib and nivolumab was assessed in previously treated gastric cancer and colorectal cancers (79). They reported objective response rates of 44% in MSS gastric cancer and 33% in MSS colorectal cancer. There was reduction in $FoxP3^{hi}CD45RA^{-}$Tregs fraction before and after treatment in the tumour samples.
The Japanese REGONIVO Phase Ib trial evaluated escalating doses of regorafenib using the 40 mg formulation escalating dosing from 80 mg to 160 mg daily for 21 days every 28 days using a 3+3

design (79). Dose limiting toxicities (DLTs) were evaluated to determine the maximum tolerated dose (MTD) and recommend dose (RD) for regorafenib to combine with nivolumab. Three DLTs were observed with regorafenib 160 mg (79). No DLTS were observed with 120 or 80 mg regorafenib. The MTD for regorafenib combined with nivolumab was determined as 120 mg, but as frequent grade 3 rashes were observed during the dose-expansion phase of the study, the initial regorafenib dose was further reduced to 80 mg. Of the 25 patients that initially received 120 mg , 21 (84%) required dose reduction during the entire treatment period, most because of palmarplantar erythrodysesthesia or maculopapular rash (79). Using 80 mg regorafenib, 36% of patients experienced grade 1 or 2 skin toxicities. From this, 80 mg was determined to be the optimal dose of regorafenib in combination with nivolumab, which, using the 40 mg tablet formulation allows for one dose level reduction to 40 mg.

A recently reported Phase 1B study of regorafenib combined with pembrolizumab as first line treatment in patients with advanced hepatocellular carcinoma, also confirmed regorafenib 120 mg as the MTD, recommending 80 mg to combine with the PD1 checkpoint inhibitor pembrolizumab (116). Sixteen patients had been treated with the recommended 80 mg regorafenib dose, of which 6 patients are reported to have experienced a grade 3 treatment emergent adverse event attributable to regorafenib in preliminary analysis (116). The study is ongoing with 80 mg regorafenib combined with pembrolizumab.

Since Bayer has developed the 30 mg regorafenib tablet formulation, the proposed starting dose of regorafenib in the INTEGRATE IIB study is 90 mg (11% increase). Due to the high inter-subject PK variability of regorafenib demonstrated clinically (~40% CV), a dose of 90 mg is expected to provide very similar exposure to the currently used combination starting dose of 80 mg, and will permit a first dose reduction to 60 mg using 2 x 30 mg tablets dose level -1 = 33 % reduction. Furthermore, the 60 mg regorafenib dose is supported by plasma sVEGFR2 data, a PD marker of VEGF inhibition, from the phase I dose escalation study by Mross et al (117). This study reported that ≥60 mg dose of regorafenib had higher impact on sVEGFR2 level when compared to doses lower than 60 mg. VEGFR inhibition is one of the proposed mechanisms of regorafenib and IO combination (117).

Regorafenib 90 mg has therefore been chosen as the starting dose for phase III testing in combination with nivolumab.

The purpose of INTEGRATE IIb is to determine whether the combination of regorafenib and nivolumab, when compared with chemotherapy, is effective in prolonging survival in patients with refractory AGOC overall and in the Asian sub-population.

12.4. **Purpose of Protocol Amendment v10.0, 24th February 2025**

The Integrate IIb study closed to recruitment on 30th April 2024 and the required number of events for the primary analysis was met in January 2025. Integrate IIb will be considered closed for all participants from 30th April 2025 *except those receiving RegoNivo treatment*. From 30th April 2025, study specific assessment and follow-up are no longer required for any participants in follow-up in the RegoNivo arm or any participants in the control arm.

For participants still receiving RegoNivo after 30th April 2025, this protocol amendment v10.0 dated 24 February 2025 should be implemented following the required local approvals to allow these participants to continue RegoNivo treatment with a reduced assessment schedule. Ongoing assessments of participant safety, treatment, and disease status will be collected until end of treatment on all participants remaining on RegoNivo treatment in accordance with updated Section 17.1.

13. IIb AIM AND OBJECTIVES

General Aim	To determine if the regorafenib and nivolumab combination (RegoNivo) improves overall survival compared with current standard chemotherapy options in refractory AGOC
Primary Objective (Endpoint)	To determine the effect of RegoNivo on overall survival (OS) (death from any cause) in the overall study population.
Secondary Objectives (Endpoints)	To determine the effect of RegoNivo on: • Overall survival (death from any cause) in the Asian sub-population. • Progression free survival (PFS)(disease progression or death) • Objective tumour response rate (OTRR)((partial or complete response (PR or CR)) according to Response Evaluation Criteria in Solid Tumours (RECIST) version. 1.1, and iRECIST • Quality of life (QoL)(scores from participant-completed questionnaires) • Safety (rates of adverse events)
Tertiary/Correlative Objectives	• To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) • To evaluate regorafenib PK in patient populations from different geographical regions (regorafenib levels).

14. IIb DESIGN

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

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

15. IIb SUBJECT POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the NHMRC CTC prior to randomisation.

15.1. Target Population

The target population is adults with histologically or cytologically confirmed AGOC, with evaluable metastatic or locally advanced disease, who have failed or were intolerant to a minimum of 2 lines of prior anti-cancer therapy which must have included a platinum & fluoropyrimidine analogue.

15.2. Inclusion Criteria

1. Adults (18 years or over) with metastatic or locally recurrent gastro-oesophageal cancer which:

a. has arisen in any primary gastro-oesophageal site (oesophago-gastric junction (GOJ) or stomach); *and*
b. is of adenocarcinoma or undifferentiated carcinoma histology; *and*
c. is **evaluable** according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1) by computed tomography (CT) scan performed within 21 days prior to randomisation. A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrolment; *and*
d. has failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy for recurrent/metastatic disease which must have included at least one platinum agent and one fluoropyrimidine analogue. Note: Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy will be considered as first line treatment where people have relapsed or progressed within 6 months of completing treatment; Radiosensitising chemotherapy given solely for this purpose concurrent with palliative radiation will not be considered as a line of treatment. *Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, will be considered a line of treatment*.
e. HER2-positive participants must have received trastuzumab

2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 1).
3. Ability to swallow oral medication.
4. Adequate bone marrow function (Platelets ≥100x10^9/L; Absolute Neutrophil Count (ANC) ≥1.5x10^9/L and Haemoglobin ≥ 9.0g/dL).
5. Adequate renal function (Creatinine clearance >50 ml/min) based on either the Cockcroft-Gault formula (Appendix 2), 24-hour urine or Glomerular Filtration Rate (GFR) scan; and serum creatinine ≤1.5 x Upper Limit of Normal (ULN).
6. Adequate liver function (Serum total bilirubin ≤1.5 x ULN, and INR ≤ 1.5 x ULN, and Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) ≤2.5 x ULN (≤ 5 x ULN for participants with liver metastases)).
   Participants being treated with an anti-coagulant, such as warfarin or heparin, will be allowed to participate provided that no prior evidence of an underlying abnormality in these parameters exists.
7. Willing and able to comply with all study requirements, including treatment, timing, and/or nature of required assessments and follow-up.
8. Study treatment both planned and able to start within 7 days after randomisation (note: subjects randomised on a Friday should commence treatment no earlier than the following Monday)
9. Signed, written informed consent.

15.3. **Exclusion Criteria**

1. Known allergy to the investigational product drug class or excipients in the regorafenib and/or nivolumab
2. Poorly-controlled hypertension (systolic blood pressure >140mmHg or diastolic pressure> 90mmHg despite optimal medical management).
3. Participants with known, uncontrolled malabsorption syndromes
4. Any prior anti-VEGF targeted therapy using small molecule VEGF TKIs (e.g. apatinib). Prior anti-VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) are permitted.
5. Any prior use of more than one immune checkpoint inhibitor
6. Treatment with any previous drug therapy within 2 weeks prior to first dose of study treatment. This includes any investigational therapy.
7. Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to randomisation.
8. Concurrent treatment with strong CYP3A4 inhibitors or inducers.

9. Palliative radiotherapy, unless more than 14 days have elapsed between completion of radiation and the date of randomisation, and adverse events resulting from radiation have resolved to < Grade 2 according to CTCAE V5.0
10. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization
11. Arterial thrombotic or ischaemic events, such as cerebrovascular accident, within 6 months prior to randomization.
12. Venous thrombotic events and pulmonary embolism within 3 months prior to randomization
13. Any haemorrhage or bleeding event ≥ Grade 3 according to CTCAE v5.0 within 4 weeks prior to randomization.
14. Non-healing wound, ulcer, or bone fracture.
15. Interstitial lung disease with ongoing signs and symptoms
16. Clinical hyperthyroidism or hypothyroidism. Note: non-clinically significant abnormal TFTs (abnormal TSH and abnormal T3 and/or abnormal T4) considered to be due to sick euthyroid syndrome is allowed.
17. Persistent proteinuria of ≥ Grade 3 according to CTCAE v5.0 (equivalent to ≥ 3.5g of protein over 24 hour measured on either a random specimen or 24 hour collection.
18. Uncontrolled metastatic disease to the central nervous system. To be eligible, known CNS metastases should have been treated with surgery and/or radiotherapy and the patient should have been receiving a stable dose of steroids for at least 2 weeks prior to randomization, with no deterioration in neurological symptoms during this time.
19. History of another malignancy within 2 years prior to randomization. Participants with the following are eligible for this study:
    a. curatively treated cervical carcinoma in situ,
    b. non-melanomatous carcinoma of the skin,
    c. superficial bladder tumours (T1a [Non-invasive tumour], and Tis [Carcinoma in situ]),
    d. treated thyroid papillary cancer
20. Any significant active infection, including chronic active hepatitis B, hepatitis C, or HIV. Testing for these is not mandatory unless clinically indicated. Participants with known Hepatitis B/C infection will be allowed to participate providing evidence of viral suppression has been documented and the patient remains on appropriate anti-viral therapy.
21. Patients with acute coronary syndrome (including myocardial infarction and unstable angina), and with a history of coronary angioplasty or stent placement performed within 6 months before enrolment
22. Patients with a ≥ grade 3 active infection according to CTCAE version 5.0
23. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease who require pharmacotherapy. Low dose steroids (e.g. ≤ 10 mg prednisone) are permitted.
24. Patients who require systemic corticosteroids (excluding temporary usage for tests, prophylactic administration for allergic reactions, or to alleviate swelling associated with radiotherapy; if used as replacement therapy e.g. ≤ 10 mg prednisolone or dexamethasone ≤ 2 mg per day) or immunosuppressants, or who have received such a therapy < 14 days prior to randomisation
25. Patients with a seizure disorder who require pharmacotherapy
26. Serious medical or psychiatric condition(s) that might limit the ability of the patient to comply with the protocol.
27. 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 randomization. Men must have been surgically sterilized or use a barrier method of contraception.

15.4. 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. Study-specific screening investigations are those performed for the purpose of screening for the study that would not have normally been performed as part of routine care.

15.5. Randomisation

Participant screening is used to confirm eligibility, while randomisation is the process by which participants are assigned to a treatment arm. Randomisation occurs via the NHMRC Clinical Trial Centre Medidata RAVE™ system.

Sites will only be able to randomise to INTEGRATE IIb after all required regulatory/ethics approvals are in place for INTEGRATE IIb, required trial supplies are at site, training has been completed, access has been granted to the RAVE system and site has been activated by the global coordinating centre. Randomisation must not occur until eligibility has been confirmed by the investigator and the participant is ready to be randomised, and should be performed according to the instructions in the Study Manual.

Once the randomisation process has been completed, the participant will be assigned to a treatment arm, and confirmation of randomisation including study number and allocation will be provided to the site. Participants may only be randomised once in this trial. NOTE: Subjects randomised on a Friday should commence treatment no earlier than the following Monday. Subjects should not commence treatment on the weekend.

16. IIb TREATMENT PLAN

16.1. Administration of IIb Study Treatments

16.1.1. IIb Regorafenib & Nivolumab (Experimental Arm - RegoNivo)

The combination of regorafenib & nivolumab is the experimental intervention in this study. Regorafenib will be self-administered by participants at 90mg (3 x 30mg tablets) orally once daily on days 1-21 of each 28 day cycle until disease progression or prohibitive adverse events as per protocol. It is recommended that regorafenib be taken as whole tablets with water after a light breakfast. Missed or vomited tablets cannot be compensated for by treatment at a later date and/or time.

Nivolumab 240mg will be administered intravenously on day 1 of each 14 day cycle until disease progression or prohibitive adverse events as per protocol, or 2 years maximum treatment duration, whichever is applicable. After 2 months, patients whose disease is controlled may have nivolumab administered 480 mg every 28 days. Nivolumab should be administered as a 30 minute IV infusion (not IV push or bolus injection) through a 0.2 micron to 1.2 micron in-line filter. Nivolumab 100mg/10mL must be diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

When the two study drugs are administered on the same day, regorafenib should be taken first orally, followed by nivolumab infusion. Day 1 treatment of each cycle can be delayed up to **+3 days** in the event of scheduling difficulties or public holidays. Please contact the NHMRC CTC if the anticipated delay is > 3 days.

16.1.2. IIb Investigator's Choice Chemotherapy (Control Arm)

Participants on the control arm will receive investigator choice chemotherapy with any of the following agents:

- taxane (paclitaxel or docetaxel)
- irinotecan or
- oral trifluridine/tipiracil (TAS102)

Table 16.1: Investigator's Choice Chemotherapy

Regimen	Doses
Docetaxel	Docetaxel 60-75 mg/m^2 IV every 21 days (81)
Paclitaxel	Paclitaxel 135-250 mg/m^2 IV on day 1, every 21 days (118) Paclitaxel 80 mg/m^2 IV on days 1, 8, 15 and 21, every 28 days (119) Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15, every 28 days (19)
Irinotecan	Irinotecan 250-300 mg/m^2 IV on days 1, every 21 days(120) Irinotecan 150-180 mg/m^2 IV on days 1 and 15, every 28 days (19) Irinotecan 125 mg/m^2 IV on days 1 and 8, every 21 days (80)
Trifluridine and tipiracil (3rd and subsequent lines)	Trifluridine and tipiracil 35 mg/m^2 (up to 80 mg/dose) PO twice daily on days 1-5 and 8-12. Repeat every 28 days. (82)

The choice of chemotherapy should be documented in the medical record at the time of randomisation to the study. Anti-emetics and pre-chemotherapy medications will be used as per institutional practice. Both treatment groups will receive BSC, which includes any intervention to preserve the comfort and dignity of study participants. For the purposes of the INTEGRATE IIb study, details on the nature of interventions that are considered as part of BSC are listed in Section 16.3.

16.2. IIb Dose Modifications

16.2.1. IIb Regorafenib Dose Modifications

Instructions for treatment delays and dose modifications for regorafenib-related adverse events are specified below. Adverse events are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 (Appendix 3).

In general, treatment should be withheld during adverse events of severity Grade 3-4, and not restarted until the adverse event has resolved to Grade 0-2, except where otherwise specified. Day 1 treatment may be delayed for a maximum of 28 days. If the adverse event has not resolved to Grade 0-2 after delaying day 1 treatment for 28 days, then regorafenib should be discontinued. When treatment with regorafenib is terminated for any reason, the continuation of nivolumab monotherapy is permitted. Treatment should not be delayed or modified for alopecia of any grade.

If commencement of a planned cycle (i.e.: Day 1 of treatment) is delayed, the first day of treatment of that cycle is still referred to as Day 1.

When an interruption is required *after a treatment cycle has commenced*, the clock does not stop – the dosing interval is always 21 days followed by a 7 day rest, beginning from day 1 of treatment. Withheld treatment days should not be rescheduled or made up. For example, if after 7 days of treatment, a patient requires an interruption of 7 days, the day that the patient recommences treatment is still called day 14 (not day 8).

Treatment may only be recommenced during the treatment phase of a cycle (day 1 to day 21). If the patient recovers and would be suitable for treatment during the non-treatment phase of a cycle (day 22 – day 28), treatment should not be recommenced until the Day 1 of the next planned cycle.

Specified dose reductions apply to all subsequent doses of study drug unless otherwise specified. If a patient experiences several adverse events with differing recommendations, then the most conservative modification (i.e.: results in the longest delay and lowest dose) should be used. Only one dose level reduction of regorafenib is permitted. Regorafenib treatment should be discontinued if not tolerated at dose level -1, according to the conditions outlined below. If a dose reduction has been performed, dose re-escalation for that participant can be considered, unless contrary to Sections 16.2.1.1, 16.2.1.2 and16.2.3.1, (up to the maximal 90 mg daily dose) at the discretion of the treating Investigator providing that the toxicity(ies) has resolved to baseline.

Table 16.2 IIb Regorafenib Dose Levels

Dose Level 0 (Starting Dose)	90 mg po od	3 x 30mg tablets of regorafenib
Dose Level -1	60mg po od	2 x 30mg tablet of regorafenib

16.2.1.1 IIb Dose-Modification for Regorafenib-related Skin Toxicity including Hand-Foot Skin Reaction

Table 16.3 IIb Regorafenib Dose modifications for skin toxicity including Hand-foot skin reaction

Skin Toxicity Grade	Occurrence	Regorafenib Dose Modification[a]
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	Consider decreasing 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[c].
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease regorafenib dose by one dose level[c].
	3rd occurrence	Discontinue regorafenib 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 resuming treatment, decrease regorafenib dose by one dose level[c].
	2nd occurrence	Discontinue regorafenib permanently.

a. More conservative management is allowed if judged medically appropriate by the Investigator.
b. Participants requiring > 1 dose level reductions should discontinue regorafenib therapy permanently.
c. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the Investigator. If there is no recovery after a delay of 28 days, regorafenib 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 re-escalated 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.

16.2.1.2 IIb Regorafenib-related Hypertension

The dose modification schedule for treatment-emergent hypertension during study drug dosing should be followed (see Table 16.4 below). Participants' Blood Pressure (BP) measurements will be monitored and appropriate treatment to effectively control hypertension is required.

All participants should have their blood pressure monitored weekly during the first 4 weeks of treatment, then fortnightly to week 8, and on D1 of each cycle thereafter. D1 & D15 blood pressures will be taken during the clinic visit; D8 & D22 blood pressures may be taken at a GP's office or using a home blood pressure monitor if available. Blood pressure readings collected by a GP, or using a home BP monitor, will be recorded in a blood pressure diary and provided to the study site at each visit for appropriate management. Recommendations for anti-hypertension management will be provided in the Study Manual.

Table 16.4 IIb Dose modifications for regorafenib-related hypertension

NCI-CTCAE v5.0 Grade	Definition	Anti-Hypertensive Therapy	Regorafenib Dosing
Grade 1	Pre-hypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None	Continue regorafenib. Consider more frequent blood pressure monitoring at Investigator's discretion
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 ≤ 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 ≤ 90 mmHg [a]. When regorafenib is restarted, continue at the same dose level
Grade 3	Systolic BP ≥ 160 mmHg or diastolic BP ≥100 mmHg OR More than one anti-hypertensive medication required OR More intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 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 ≤ 90 mmHg, and if symptomatic, until symptoms resolve [a]. 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 [b].
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue regorafenib 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 Investigator's discretion.
c. Participants requiring > 1 dose level reductions will permanently discontinue regorafenib

16.2.1.3 Regorafenib-related proteinuria

The dose modification schedule for regorafenib-related proteinuria during study drug dosing should follow the table below (Table 16.5). Participants' urinary protein will be monitored each cycle prior to treatment.
For patients with Grade 2 proteinuria, a urinary protein/ creatinine ratio (uPCR) should be obtained. A 24-hour urinary protein can be considered according to institutional practice, this is not mandatory unless stated otherwise.

Table 16.5- IIb Dose modifications for regorafenib-related proteinuria

Proteinuria Toxicity Grade[a]	Occurrence	Dose modification/ management[b]	
Grade 1: 1+ proteinuria; Urinary protein ≥ULN - <1.0g/ 24 hours	Any	Not required	
Grade 2: 2+ and 3+ proteinuria; Urinary protein 1.0g- <3.5g/ 24 hours Obtain urinary protein (mg/dL)/ creatinine (mg/dL) ratio (uPCR). A 24-hour urinary protein can be considered according to institutional practice.	1st occurrence	**uPCR**	**24-hour urinary protein**
		<2– no dose modification required.	**≤2g** – no dose modification required.
		2-2.4 - withhold regorafenib, repeat test weekly until ≤ Grade 1. Restart regorafenib at the same dose.	**>2g**- withhold regorafenib, repeat test weekly until ≤ Grade 1. Restart regorafenib at the same dose.
		If uPCR **>2.4**, a 24-hour urinary protein should be initiated within 72 hours to verify the grade of proteinuria	
	2nd occurrence	Management as above. Restart regorafenib with one level dose reduction if uPCR ≥2-2.4 or 24-hour urinary protein >2g.	
	3rd occurrence	Discontinue regorafenib permanently if uPCR ≥2 or 24-hour urinary protein >2g.	
Grade 3: 4+ proteinuria; Urinary protein ≥3.5g/ 24 hours	Any	Discontinue regorafenib permanently	

a. 24-hour urine collection takes precedence over dipstick
b. The use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) for the management of proteinuria is allowed if deemed appropriate by the investigator.

16.2.1.4 Other IIb Regorafenib-related Adverse Events not listed above

Table 16.6 below outlines dose modifications for all other adverse events deemed to be related to regorafenib not previously mentioned (excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities). If, after surgery, there is evidence of wound dehiscence, regorafenib should be discontinued.

Table 16.6 Dose modifications for all other adverse events deemed to be related to regorafenib

NCI CTCAE v5.0 Grade	Dose Delay	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	No delay	No change	
Grade 3	Delay until ≤ Grade 2 [a]	Reduce 1 dose level	Dose escalation not allowed outside of specific recommendations in 16.2.1.1, 16.2.1.2, & 16.2.3.1
Grade 4	Discontinue permanently		

[a] If no recovery after a delay of 28 days, regorafenib should be permanently discontinued.

16.2.2 IIb Nivolumab dose modifications

Adverse events (irrespective of severity) associated with nivolumab exposure might be of immunological aetiology. Such adverse events can occur immediately following the commencement of treatment with nivolumab, or several months after completion of treatment. For toxicities and severe or life-threatening adverse events with a causal relationship to nivolumab, nivolumab should be interrupted or terminated in accordance with Table 16.7 below. For guidelines regarding supportive therapy, including the use of corticosteroids, refer to section 16.2.2.1, and the nivolumab investigator brochure (appendix 4 Management Algorithms).

If a delay in nivolumab administration is required when a treatment cycle has commenced, there should be no less than 12 days between nivolumab doses for the 14-day schedule, or no less than 20 days between nivolumab doses for the 28-day schedule. If nivolumab treatment needs to be delayed for more than 12 weeks from last treatment date in the event of toxicity, it should be discontinued permanently. When nivolumab is terminated for any reason, the continuation of regorafenib monotherapy is permitted.

Table 16.7 Criteria for nivolumab interruption and termination for nivolumab-related toxicity

Toxicity	Grade requiring hold	Timing of restart after hold	Instance requiring nivolumab discontinuation
Diarrhoea/colitis	2–3	Resolved to ≤ grade 1	Discontinue permanently if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to ≤10 mg/day of prednisolone within 12 weeks.
	4	Discontinue permanently	
Elevated AST, ALT, and/or bilirubin	Refer to Table 16.9		
Type I diabetes (T1DM: when newly developed) or hyperglycaemia	T1DM or G3–4	Clinically and metabolically stable	Discontinue permanently if not clinically and metabolically stable within 12 weeks of the last dose.
Hypophystitis/ adrenal insufficiency	2–4	Resolved to ≤ grade 1. When endocrine hormone replacement therapy has been initiated.	Discontinue permanently if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to ≤10 mg/day of prednisolone within 12 weeks.
Hyperthyroidism	3	Resolved to ≤ grade 1	Discontinue permanently if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be

			decreased to ≤10 mg/day of prednisolone within 12 weeks.
	4	Discontinue permanently	
Hypothyroidism	Not stipulated	After thyroid hormone replacement therapy has been initiated	
Infusion reaction	2[b]	Resolved to ≤ grade 1	Terminate when toxicity develops despite appropriate pre-treatment.
	3–4	Discontinue permanently	
Pneumonitis	2	Resolved to ≤ grade 1	Terminate if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to ≤10 mg/day of prednisolone within 12 weeks.
	3–4	Discontinue permanently	
Renal impairment or nephritis	2	Resolved to ≤ grade 1	Terminate if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to ≤10 mg/day of prednisolone within 12 weeks.
	3–4	Discontinue permanently	
All other toxicities with a causal relationship	Intolerance or persistent G2	Decision to withdraw and resume nivolumab at the discretion of the investigator	Terminate if the toxicity persists after drug withdrawal and not resolved to ≤ grade 1 within 12 weeks from the last dose.
	G3 or severe	Resolved to ≤ grade 1	Terminate if subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to ≤10 mg/day of prednisolone within 12 weeks.
	4	Discontinue permanently	
Note: In the event that severe or ≥ grade 3 side effects recur or when life-threatening toxicity develops, treatment should be permanently discontinued. a. In patients with liver metastasis and HCC, and grade 2 AST and/or and ALT elevation, treatment should continue. Treatment should be terminated when AST and/or ALT levels continue to be 50% higher than at baseline for ≥ 1 week. b. If the subject recovers from symptoms within 1 hour of dose suspension, the dose should be resumed at an infusion rate of 50% of the initial rate (e.g., 50 mL/h from 100 mL/h). If the subject does not recover from symptoms within 1 hour of dose suspension, the dose should be withdrawn until the symptoms resolve. Pre-treatment should be administered at the time of the next dose. Refer to 16.2.2.2 for details.			

16.2.2.1 Supportive therapy for nivolumab-related adverse events

Supportive therapy to manage suspected nivolumab-related adverse events is listed below. A dose reduction in steroids can exacerbate symptoms, thus, steroid dose should be decreased gradually over a period of time. Additional supportive therapy may be required, thus, efforts should be made to exclude other causes for each adverse event (e.g., metastatic lesions and bacterial and viral infections).

Pneumonitis:

- For grade 2 pneumonitis, systemic corticosteroids should be administered. When symptoms resolve to ≤ grade 1, steroid dose should gradually be decreased over ≥ 4 weeks.
- For grade 3–4 pneumonitis, steroid therapy should be administered immediately via an intravenous infusion. In addition, anti-inflammatory drugs should be administered as required.
- When steroid therapy is prolonged, antibiotics will be administered additionally to prevent opportunistic infections.

Diarrhoea/colitis:

- The presence or absence of signs and symptoms of enteritis (e.g., diarrhoea, abdominal pain, blood or mucus in the stool, presence or absence of accompanying fever), as well as signs and symptoms of intestinal perforation (signs of peritonitis and/or intestinal obstruction) should be verified.
- Patients who develop diarrhoea/colitis should be instructed to maintain adequate oral fluid intake. If oral fluid intake is inadequate, an intravenous infusion of electrolyte-containing solution should be administered. To rule out colitis in the event of ≥ grade 2 diarrhoea, a gastroenterology consultation and endoscopic examination is recommended.
- For grade 2 diarrhoea/colitis lasting ≥ 3 days, oral corticosteroids should be administered.
- For grade 3–4 diarrhoea/colitis lasting ≥ 1 week, an intravenous steroid infusion, followed by high-dose oral steroids should be given.
- When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks.

Hyperglycaemia:

≥ Grade 3 hyperglycaemia accompanied by type-1 diabetes (including diabetic ketoacidosis in the event of newly developed type-1 diabetes), ketosis (ketonuria), and/or metabolic acidosis:

- For grade 3–4 hyperglycaemia accompanied by type-1 diabetes, metabolic acidosis, and/or ketonuria, insulin replacement therapy should be considered.
- Serum glucose level and metabolism test values (e.g.: urinary ketones, glycohaemoglobin, and C-peptides) should be monitored

Hypophystitis:

- For grade 2 hypophystitis, corticosteroids should be administered. When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks. Appropriate hormone replacement therapy may be required due to the gradual reduction in dose.
  For grade 3–4 hypophystitis, an intravenous infusion of corticosteroids, followed by oral corticosteroids should be given. When the symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks. Appropriate hormone replacement therapy may be required due to the gradual reduction in dose.

Adrenal insufficiency:

- For grade 2 adrenal insufficiency, corticosteroids should be administered. When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks. Steroids with mineralocorticoid component may be required.

  For grade 3–4 adrenal insufficiency, an intravenous infusion of corticosteroids, followed by oral corticosteroids should be given. When the symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks. Steroids with mineralocorticoid component may be required.

Hyperthyroidism and hypothyroidism:

Thyroid dysfunction can occur at any time during the dose administration. Changes in thyroid function test values (conducted at the start of investigational drug dosing, then according to routine and clinical evaluations), as well as the presence or absence of signs/symptoms of thyroid dysfunction should be monitored.

- Grade 2 hyperthyroidism (and grade 3–4 hypothyroidism):
  - In hyperthyroidism, nonselective beta-blockers (e.g.: propranolol) are recommended as

the first line treatment.
  - In hypothyroidism, thyroid hormone replacement therapy (e.g.: levothyroxine or liothyronine) are recommended as standard treatment.

- Grade 3–4 hyperthyroidism:
  - Following the intravenous infusion of corticosteroids, oral corticosteroids should be administered. When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks. Appropriate hormone replacement therapy may be required due to the gradual reduction in dose.

Liver impairment:

- For grade 2 liver impairment, liver function tests should be performed frequently until the values return to baseline (weekly tests should be considered).
  - Corticosteroids should be administered via an intravenous infusion or orally.
- For grade 3–4 liver impairment, corticosteroid therapy should be administered for 24–48 h via an intravenous infusion.
- When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks.

Renal impairment and nephritis:

- For grade 2 impairment, corticosteroid therapy should be administered.
- For grade 3–4 impairment, corticosteroid therapy should be administered.
- When the symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks.

16.2.2.2 Nivolumab Infusion reaction management

The signs and symptoms of an infusion reaction normally appear during administration of the drug or immediately after administration, and most patients completely recover within 24 hours of administration. Table 16.8 below lists the countermeasures to take in the event that an infusion reaction associated with nivolumab occurs.

For grade 2, or grade 3-4 immunity-related toxicities (other than those listed above), systemic corticosteroid therapy will be administered at as per management guidelines for immune-related toxicity. When symptoms resolve to ≤ grade 1, the steroid dose should gradually be decreased over a period of ≥ 4 weeks.

Table 16.8: Countermeasures in the event of a nivolumab-related infusion reaction

NCI-CTCAE grade	Countermeasures	Pre-treatment upon the administration of the next and subsequent doses
Grade 1 Mild reaction; does not require infusion suspension or treatment.	Increase vital sign frequency until symptoms are deemed stable by the investigator	None
Grade 2 Suspend infusion; if however, the subject responds immediately to symptomatic treatment	Suspend nivolumab dosing and monitor symptoms. Administer appropriate treatment (e.g.: intravenous transfusion, antihistamines, NSAIDs, acetaminophen, and opioid analgesics).	1.5 h (± 30 min) before nivolumab dosing. administer pre-treatment with the drugs below. Oral diphenhydramine at a dose of 50 mg (or a similar antihistamine).

(e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intravenous transfusion); prophylactic treatment is required within 24 h.	Increase the frequency of monitoring of vital signs until the symptoms of the patient concerned are deemed stable by the attending physician. If the subject recovers from symptoms within 1 h of dose suspension, dosing is resumed at an infusion rate of 50% of the initial rate (e.g.: 50 mL/h from 100 mL/h). If the subject does not recover from symptoms within 1 h of dosing suspension, the dose will be withdrawn until the symptoms recover, and pre-treatment will be administered at the time of the next dose. In patients who develop ≥ grade 2 toxicities despite appropriate pre-treatment, nivolumab treatment will be terminated (no resumption of dosing permitted).	Oral acetaminophen at a dose of 500–1000 mg (or a similar antifebrile agent). Oral or intravenous corticosteroids according to local institutional standards
Grade 3 Prolongation (the subject does not respond quickly to symptomatic treatment and short-term infusion suspension); recurrence despite improving once; hospital admission is required for sequelae (e.g., renal impairment, pulmonary infiltration).	Suspend nivolumab dosing and monitor symptoms. Administer appropriate treatment (e.g.: intravenous transfusion, anti-histamines, NSAIDs, acetaminophen, opioid analgesics, oxygen inhalation, hypertensive drugs, corticosteroids, and epinephrine). Increase the frequency of monitoring of vital signs until the symptoms of the patient concerned are deemed stable by the attending physician. The patient is hospitalized as required.	Discontinue permanently
Grade 4 Life-threatening; administration of hypertensive drugs and artificial respiration is needed.	Discontinue permanently	
During nivolumab dosing, appropriate resuscitation equipment is placed in the room so that the physician can respond quickly.		

16.2.3 IIb Dose Modifications related to both Regorafenib & Nivolumab

16.2.3.1 IIb Dose Modifications for Regorafenib & Nivolumab-Related Hepatic Toxicity

For participants with observed worsening of serum liver tests considered related to study treatment (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring recommendations in Table 16.9 should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in participants with Gilbert's syndrome. Patients with known Gilbert's syndrome experiencing a rise in bilirubin with ≤ 2x ULN and other liver function abnormalities are exceptions should be observed to see if bilirubin changes are transient.

Table 16.9: IIb Dose modifications/interruption for Total Bilirubin and/or ALT/AST increases related to regorafenib & nivolumab

NCI-CTCAE v5.0	Dose modifications/interruption related to regorafenib & nivolumab
G1 ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal AND/OR >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	**Regorafenib** Treat on time and check LFT's at least once per week until the LFT result returns to within normal range **Nivolumab** Continue Nivolumab
G2 >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal AND/OR >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	**Regorafenib** **If treatment emergent G2 T bili and AST/ALT**, continue at same dose & monitor LFT's weekly until T bili and AST/ALT ≤ G1. **Nivolumab** **If treatment emergent G2 T bili and AST/ALT,** delay until toxicity ≤ G1, then restart nivolumab at same dose level. Discontinue nivolumab permanently when the subject does not recover from toxicity within 12 weeks of the last dose
G3 >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal AND/OR >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	**Regorafenib** Discontinue regorafenib until T bili and AST/ALT ≤ G1. When dosing is resumed, it is recommended to reduce dose by 1 level and repeat AST/ALT/T bili once per week for a minimum of 4 weeks. On second reoccurrence, discontinue regorafenib permanently **Nivolumab** On first occurrence, terminate Nivolumab. Re-exposure may be allowed after discussion with the Study Chair (or Delegate) via NHMRC CTC
G4 >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal AND/OR >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	On first occurrence, discontinue both **regorafenib** and **nivolumab** permanently

16.2.4 Chemotherapy dose modifications

Chemotherapy modifications/delays will be according to usual practice/institutional standards. Dose level reductions leading to treatment discontinuation will be according to usual practice/institutional standards.

16.3. Concomitant Medications/Treatment

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 Investigator.

16.3.1 Recommended

The following measures are recommended for prevention and treatment of skin rash including hand-foot skin reaction:

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
- 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.

16.3.2 Permitted

- Corticosteroids permitted if used as replacement therapy for conditions such as hypophystitis or adrenal haemorrhage e.g. 10 mg prednisolone per day.
- Stent insertion for gastric outlet obstruction, providing that the position of the stent will not compromise response evaluation and there is no evidence of disease progression in all other sites. Stent insertion under other circumstances while receiving study treatment should be discussed with the Study Chair (or Delegate) via NHMRC CTC.
- Radiotherapy is allowed for the symptomatic treatment of non-evaluable bone lesions where there is no evidence of disease progression in other sites.
- Other palliative treatments, such as radiation to a bleeding primary tumour or non-emergency surgery, provided the circumstances of which have previously been discussed with the Study Chair (or Delegate) via NHMRC CTC.

- For non-emergency surgery, study treatment should be stopped at least 2 weeks prior to and 2 weeks following major surgery. The decision to resume study treatment should be based on physician judgement of adequate wound healing. Regorafenib should be discontinued in patients with wound dehiscence.
- 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
- Participants who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate as per the inclusion criteria. Note: Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be affected by regorafenib. Close monitoring of at least weekly evaluations are recommended to be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care.
- Antiviral therapy required for viral suppression of Hepatitis B and/or C provided no contraindications exists (as outlined under section 16.3.3 Use with Caution or 16.3.4 Prohibited)

16.3.3 Use With Caution

Pharmacokinetic data from a clinical probe substrate study indicated that regorafenib may be given concomitantly with substrates of CYP2C19 (e.g. omeprazole), CYP2C8 (e.g. rosiglitazone), CYP2C9 (e.g. S-warfarin) without a clinically meaningful drug interaction. Specific caution should be employed when considering or administering a concomitant medication that is metabolized by the phase II glucuronosyl transferases UGT1A1 and 1A9. Studies have shown regorafenib may increase systemic exposure to UGT1A1 and 1A9 substrates. A list of CYP substrates, inhibitors, and inducers is provided at the following website: http://medicine.iupui.edu/clinpharm/ddis/.

Participants taking narrow therapeutic index medications (e.g.: quinidine, cyclosporine,) should be monitored proactively. Co-administration of regorafenib with digoxin has no effect on plasma digoxin.

16.3.4 Prohibited

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors (including tyrosine kinase inhibitors), immunotherapy, hormonal therapy, and experimental or approved therapies
- Bone marrow transplant or stem cell rescue
- Concomitant palliative radiation therapy is not allowed, except as described as Best Supportive Care under Section 16.3.2.
- Strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, St John's wort) are not permitted. Co-administration of strong CYP3A4 inhibitors/inducers may lead to increased toxicity of regorafenib, irinotecan or paclitaxel/docetaxel. CYP2C8 inhibitors (e.g. pazopanib, lapatinib, gemfibrozil and monteleukast) may lead to increased toxicity of paclitaxel. Similarly, human thymidine kinase substrate antivirals (e.g. stavudine, zidovudine, telbivudine etc.) should be avoided as it may decrease efficacy of antiviral agent.
- Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF). 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 substitute for a required dose reduction. Routine use of G-CSF is not encouraged.

- Surgery for complications of disease or treatment, unless meets criteria as described under section 16.3.2;
- All traditional/alternative medicines with an anti-cancer indication, including Traditional Chinese Medicine and other investigational treatments.
- Live vaccines administered <30 days before the initiation of treatment with the investigational drug and during the trial period. Examples of live vaccines are as follows (however, the list is not exhaustive): measles, mumps, rubella, chicken pox/herpes zoster, yellow fever, rabies*, BCG for tuberculosis, and typhoid vaccines*. Inoculation with inactive vaccines (e.g., seasonal influenza vaccines) is permitted; however, the intranasal administration of attenuated influenza vaccines (e.g., Flu-Mist®) is prohibited. (*In Japan, live vaccines are not approved).
- Systemic glucocorticoids for purposes other than treating symptoms caused by notable events with a suspected immunological aetiology. The use of corticosteroids is permitted according to the physiological dose required to alleviate symptoms (e.g., to control symptoms of acute asthma or if used as replacement therapy e.g. ≤10 mg prednisolone or dexamethasone ≤2 mg per day).

16.3.5 Concomitant Medication Reporting

Concomitant medications must be recorded in site source records from baseline until end of treatment.

16.4. Treatment Compliance (Regorafenib tablets)

Participant medication compliance will be determined at each clinic visit by tablet return review out of the sight of the participant, and the participant counselled appropriately if significant non-compliance is determined.

16.5. Treatment Discontinuation

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

- Participants randomised to the control arm who remain on treatment at 30th April 2025. These participants can continue receiving investigator choice chemotherapy via standard of care.
- Progressive disease (PD) according to RECIST Version 1.1 and iRECIST is documented by a site Investigator.
- Unacceptable toxicity as determined by the participant or Site Investigator or as defined in Section 16.2. When regorafenib is terminated for regorafenib-related toxicity, the continuation of nivolumab monotherapy is permitted (refer to section 16.2 for further discussion regarding dose modifications).
- Delay of day 1 treatment for >28 days (12 weeks from last treatment for nivolumab), or > 1 dose level reductions required due to treatment-related adverse events. Dose level reductions in the control arm leading to treatment discontinuation will be according to local institutional standards. For delays beyond the allowed window due to reasons other than treatment-related adverse events, please contact the NHMRC CTC to discuss treatment continuation.
- The Investigator determines that continuation of treatment is not in the participant's best interests.
- Occurrence of an exclusion criterion affecting participant safety, e.g. pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in Section 16.3.4
- Failure to comply with the protocol e.g. repeatedly failing to attend scheduled assessments. If a participant has failed to attend scheduled assessments in the study, the Investigator must

determine the reasons and document the circumstances as completely and accurately as possible in the medical records and CRF.

- The participant declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the participant's medical record. Follow up of participants who stop study treatment should continue according to this protocol.

16.6. Subsequent Treatment

Treatment after discontinuation of study treatment is at the discretion of the participant's clinician. Information regarding subsequent treatments will be collected in the CRF.

Nivolumab may be allowed to continue beyond objective progression if, in the opinion of the investigator, the patient is continuing to receive clinical benefit, and provided the patient is tolerating treatment and well enough to continue. This will be decided on a case by case basis, and should be discussed with the study chairs prior to continuing with nivolumab treatment.

17. IIb ASSESSMENT PLAN

17.1. IIb Schedule of Assessments – Regonivo

Participants in follow-up on the RegoNivo arm will cease study assessments from 30th April 2025 following end of study for Integrate IIb. No further study treatment, protocol assessments or routine follow-up is required for these participants.

Participants continuing RegoNivo from 30th April 2025 will continue per the revised schedule of assessments under protocol v10.0 dated 24th February 2025, as follows.

	Screening / Baseline	**Treatment Period** Assessments must be completed within a window of +/- 3 days of the assessment due date (unless otherwise specified in 17.1.1 – Details of Regonivo assessments or footnote to this table)				**Follow-Up#**
		Cycles 1-2 (1 Cycle = 28 days)		**Cycles 3+**	**End of Treatment Visit**	
Procedure / Assessment	Up to 14 days prior to randomisation unless otherwise indicated	Day 1*^	Day 15	Day 1	Within 30 days of last dose of study drug	Every 8 weeks from last scan date[5]
Clinic Assessment:						
Informed Consent (Main and Optional Translational components)	X[1]					
Medical History: Prior medical and anticancer therapy	X[2]					
Physical Assessment: Vital Signs (T,P,Resp), ECOG PS	X	X		X		
Adverse Events (at the **end** of each cycle for the previous cycle)		X[3]		X	X	(X[4])
Participant Status		X		X		X
Cardiac Monitoring:						
Blood Pressure	X	See 17.1.1.1		X		
Blood Tests:						
Haematology: Full blood count with 5-cell differential count	X	X	X	X		
Biochemistry: Creatinine, uric acid, sodium, potassium, chloride, electrolytes corrected serum calcium, phosphate, albumin, glucose	X	X	X	X		
Biochemistry: Liver function tests (Bilirubin (total and direct), AST, ALT, ALP, GGT)	X	See 17.1.1.4		X		
Biochemistry: Thyroid function tests (TFT: TSH, free T4, free T3 at each assessment)	X	X		X		
Tumour Marker (CA19-9, LDH)[5]	X[2]	See 17.1.1.4 with each CT until PD[9]				
Coagulation Panel: PT/PT-INR, PTT	X	X	X	X		
Hepatitis B & C Serology and/or HIV Testing	X[2]					

INTEGRATE IIb

	Screening / Baseline	Treatment Period Assessments must be completed within a window of +/- 3 days of the assessment due date (unless otherwise specified in 17.1.1 – Details of Regonivo assessments or footnote to this table)				Follow-Up[#]
		Cycles 1-2 (1 Cycle = 28 days)		Cycles 3+	End of Treatment Visit	
Procedure / Assessment	Up to 14 days prior to randomisation unless otherwise indicated	Day 1*^	Day 15	Day 1	Within 30 days of last dose of study drug	Every 8 weeks from last scan date[5]
Serum Pregnancy Test	X[6]					
Blood for Translational Research (see 17.1.1.4)		C1D1, C2D1,		with week 8 CT scan	X	
Blood for PK (at selected sites)[8] (see 17.1.1.4)		C1D15, C2D1[7], C2D15				
Urinalysis:						
Spot urine for protein:creatinine ratio	X					
Dipstick		X		X		
Imaging:						
CT (Chest, Abdomen and Pelvis)	X[2]	every 8 weeks, or per local institutional guidelines, from date of randomisation to PD				
Quality of Life (QoL):						
EORTC QLQ-C30, STO22, Patient D.A.T.A Form, EQ-5D-5L (until PD)		X				X (8-weekly until PD)
Other:						
Concomitant Medications	Concomitant medications will be recorded from baseline to end of treatment.					

* D1 assessments should be conducted prior to commencing treatment

^Subjects should not commence C1 treatment dosing *on a weekend*. Subjects randomised on a Friday should commence treatment dosing no earlier than the following Monday

[#]Participants continuing RegoNivo under protocol v10.0 dated 24th February 2025 who cease study treatment and complete the End of Treatment Visit will be considered off study. No further protocol assessments or routine follow-up is required.

[1] Up to 90 days prior to randomisation

[2] Up to 21 days prior to randomisation. Hepatitis B & C Serology and/or HIV Testing to be completed only if clinical indicated

[3] Commencing C2D1

[4] Ongoing AE's at the End of Treatment visit should continue to be assessed in follow-up until resolved to baseline

[5] Window of +/-7 days applies

[6] Within 7 days prior to randomisation

[7] Window of +/-3 days not permitted (must be drawn on D1 or up to +3 days only)

[8] Where a scheduled PK sample collection (and clinic visit) fall on a public holiday refer to Section 17.1.1.4

[9] Tumour Markers will not be collected for participants continuing RegoNivo under Protocol v10.0 dated 24th February 2025.

17.1.1. Details of Assessments - Regonivo

17.1.1.1 Clinical Assessment

Day 1 assessments must be conducted prior to dosing. **Baseline blood tests do not need repeating prior to C1D1 unless clinically indicated.** BP should be monitored weekly for the first 4 weeks of treatment, then 2-weekly until week 8. After 8 weeks of treatment, BP monitoring can be reduced to Day 1 of each treatment cycle. D8 & D22 blood pressures may be taken at the clinic, at a GPs office or using a home blood pressure monitor if available. Blood pressure readings collected by a GP, or using a home BP monitor will be recorded in a blood pressure diary and provided to the study site at each visit for appropriate management

17.1.1.2 Imaging

Eligibility and baseline tumour assessment will be determined by a CT scan performed within 21 days prior to randomisation. This should be performed as close to randomisation as possible. Tumour assessments must be performed thereafter at 8 week intervals (+/- 7 days), as appropriate, regardless of delays in study drug administration, until disease progression. The timing of tumour assessments is considered **from date of randomisation**. A repeat CT is not required prior to Day 1 Cycle 1. Brain imaging is only required if clinically indicated. CT imaging should be performed with IV and oral contrast except where the use of contrast is contraindicated, in which case a CT without contrast is permitted. Where the reaction to contrast is mild, prophylactic treatment according to usual practice/institutional standards may be considered.

17.1.1.3 Quality of Life

Quality of Life questionnaires (i.e.: QLQ-C30, STO22, Patient D.A.T.A. Form, EQ-5D-5L) should be completed at baseline (i.e.: C1D1 prior to dosing), every 4 weeks thereafter during treatment, and at the time of disease progression. For patients who end treatment before disease progression, QOLs will be collected every 8 weeks during follow-up until disease progression. QOLs will not be collected for participants continuing RegoNivo under Protocol v10.0 dated 24th February 2025. Where necessary, translations of these questionnaires into the primary local language will be made available. Refer to INTEGRATE IIb eCRF completion guidelines for further detail on administration of QOL's, tips for minimizing missing data, etc.
Note: Patient D.A.T.A Form to be completed by English-speaking participants only (no translations available).

17.1.1.4 Blood & Urine Collection

Weekly Liver Function Tests (LFTs) are required for first 4 weeks of treatment, then 2-weekly to week 8, and then on day 1 of all subsequent cycles of treatment. The weekly LFTs can be done at a laboratory other than the randomising site, however, it is recommended that if there is a clinically significant result, the test should be repeated at the randomising site. Study sites must ensure that all LFTs are documented in the participant's study file as source data.

Tumour Markers CA19-9 and LDH are to be assessed at the same time as CT imaging (+/- 7 days) until disease progression – refer to 7.2.2 for timing of tumour assessments by CT imaging. Tumour Markers will not be collected for participants continuing RegoNivo under Protocol v10.0 dated 24th February 2025. TSH/T3/T4 are required at baseline AND for all subsequent assessments as per 17.1. Thyroid function tests are not required on Day 15 of each treatment cycle.

Testing for chronic active hepatitis B, hepatitis C or HIV is not mandatory unless clinically indicated. A serum pregnancy test must be performed within 7 days prior to randomisation for women of childbearing potential.

Blood for translational research is to be collected from all patients at up to 4 time points: C1D1, C2D1, with tumour markers test at the time of week 8 CT scan, and end of treatment (if already collected). No further end of treatment samples will be collected for participants continuing RegoNivo under Protocol v10.0 dated 24th February 2025. For processing and storage procedures, refer to Biospecimen Manual.

Blood collection for pharmacokinetics (PK) is optional (collected at selected sites only, Regonivo arm), at three time points: C1D15, C2D1, C2D15. At these time points, a blood sample is collected before regorafenib is taken at the site clinic visit, and another sample collected 1-4 hours after regorafenib has been taken. Participants will be asked to record exact dosing times for the 3 days prior to C1D15 & C2D15 (not C2D1) in a PK diary. **Where a scheduled PK sample collection (and clinic visit) falls on a public holiday:**

- **C1D15 and C2D15**: the visit may be rescheduled either earlier or later (+/- 3 day window is permitted in this instance)
- **C2D1**: the visit must be rescheduled later (only +3 day window is permitted). **Sample collection (and dosing) is not permitted during protocol-mandated 7 day washout at the end of C1**
- collect the PK samples pre and post dose at the rescheduled clinic visit AND
- remind the subject to complete their regorafenib PK diary (date and time of drug, number of tablets) as per instructions ***for the actual 3 days prior to the rescheduled clinic visit***

If a PK sample collection is affected by study treatment interruptions, please contact your Coordinating Centre for further instructions. For processing and storage procedures, please refer to Biospecimen Sampling Manual.

Spot urine, a random urine sample sent to the lab for analysis, which includes protein:creatinine ratio, is required at baseline. If protein excretion is abnormally high, further quantification via a 24 hr. urine or other test should be done as per usual site practice to confirm eligibility (i.e.: < 3.5 g protein over 24 hours). Dipstick urinalysis, using standard urine test strip, is required after commencement of treatment on D1 of each cycle. If abnormal, further investigations should be conducted as clinically appropriate.

17.2. IIb Chemotherapy Regimens & Schedule of Assessments

Participants on the control arm will end study from 30th April 2025 and continue off-study treatment at the discretion of the investigator. No further study treatment, protocol assessments or routine follow-up is required for these participants.

Chemotherapy Regimens	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Subsequent Cycles
Docetaxel 75mg/m² IV every 21 days	X			X			X		Every 21 days from last dose
Paclitaxel 135-250 mg/m² IV on day 1, every 21 days	X			X			X		Every 21 days from last dose
Paclitaxel 80 mg/m² IV on days 1, 8, 15 and 21, every 28 days	X	X	X	X	X	X	X	X	Weekly
Paclitaxel 80 mg/m² IV on days 1, 8, and 15, every 28 days	X	X	X		X	X	X		Days 1, 8, 15, every 28 days
Irinotecan 250-300 mg/m² IV on days 1, every 21 days	X			X			X		Day 1, every 21 days
Irinotecan 150-180 mg/m² IV on days 1 and 15, every 28 days	X		X		X		X		Days 1, 15 every 28 days
Irinotecan 125 mg/m² IV on days 1 and 8, every 21 days	X	X		X	X		X	X	days 1, 8, every 21 days
Trifluridine and tipiracil 35 mg/m² (up to 80 mg/dose) PO twice daily on days 1-5 and 8-12. Repeat every 28 days.	Days 1-5	Days 8-12			Days 1-5	Days 8-12			Days 1-5, 8-12 every 28 days

	Screening / Baseline	Treatment Period Assessments must be completed within a window of +/- 3 days of the assessment due date (unless otherwise specified in 17.2.1 – Details of chemotherapy assessments or footnote to this table)*									End of Treatment	Follow-up
Procedure / Assessment	Up to 14 days prior to randomisation or as indicated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	**Subsequent Weeks**	Within 30 days of last treatment	Every 8 weeks from last scan date
Clinic Assessment:												
Informed Consent (Main and Optional Translational components)	X[1]											
Medical History: Prior medical and anticancer therapy	X[2]											
Physical Assessment: Vital Signs (T,P,Resp), ECOG PS	X	At the beginning of each cycle*										
Adverse Events		At the end of each cycle for the previous cycle									X	(X[3])
Participant Status		At the beginning of each cycle*										X
Blood Tests:												
Haematology: Full blood count with 5-cell differential count[6]	X	At the beginning of each cycle*										
Biochemistry: Creatinine, uric acid, sodium, potassium, chloride, electrolytes corrected serum calcium, phosphate, albumin, glucose	X	At the beginning of each cycle*										
Biochemistry: Liver function tests (Bilirubin (total and direct), AST, ALT, ALP, GGT)	X	At the beginning of each cycle*										
Biochemistry: Thyroid function tests (TFT: TSH, free T4, free T3)	X											
Tumour Marker (CA19-9, LDH)[4]	X[2]	with each CT until PD										
Hepatitis B & C Serology and/or HIV Testing	X[2]											
Serum Pregnancy Test	X[5]											

Blood for Translational Research (see 17.2.1.4)		C1D1*, C2D1* & with the week 8 CT scan	X	
Imaging:				
CT (Chest, Abdomen and Pelvis)	X[2]	every 8 weeks from date of randomisation to PD[4]		
Quality of Life (QoL):				
EORTC QLQ-C30, STO22, Patient D.A.T.A Form, EQ-5D-5L (until PD)		At the beginning of each cycle until PD	X	X(8-weekly until PD)
Other:				
Concomitant Medications	Concomitant medications will be recorded from baseline to end of treatment.			

* D1 assessments should be conducted prior to commencing treatment
[1] Up to 90 days prior to randomisation
[2] Up to 21 days prior to randomisation
[3] Ongoing AE's at the End of Treatment visit should continue to be assessed in follow-up until resolved to baseline
[4] Window of +/-7 days applies
[5] Within 7 days prior to randomisation
[6] For patients on TAS102, in addition to C1D1 repeat FBC on C1D15

17.2.1. Details of Assessments - Chemotherapy

17.2.1.1 Clinical Assessment

Assessments must be conducted at baseline and prior to each cycle. D1 assessments must be conducted prior to treatment. **Baseline blood tests do not need repeating prior to C1D1 unless clinically indicated.**

17.2.1.2 Imaging

Eligibility and baseline tumour assessment will be determined by a CT scan performed within 21 days prior to randomisation. This should be performed as close to randomisation as possible. Tumour assessments must be performed thereafter at 8 week intervals (+/- 7 days), as appropriate, regardless of delays in study drug administration, until disease progression. The timing of tumour assessments is considered **from date of randomisation**. A repeat CT is not required prior to Day 1 Cycle 1. Brain imaging is only required if clinically indicated. CT imaging should be performed with IV and oral contrast except where the use of contrast is contraindicated, in which case a CT without contrast is permitted. Where the reaction to contrast is mild, prophylactic treatment according to usual practice/institutional standards may be considered.

17.2.1.3 Quality of Life

Quality of Life questionnaires (i.e.: QLQ-C30, STO22, Patient D.A.T.A. Form, EQ-5D-5L) should be completed at baseline (i.e.: C1D1 prior to dosing), at the beginning of each cycle during treatment, and at end of treatment. For patients who end treatment prior to disease progression, QoLs will be collected every 8 weeks during follow-up until disease progression. Where necessary, translations of these questionnaires into the primary local language will be made available. Refer to INTEGRATE IIb eCRF completion guidelines for further detail on administration of QOL's, tips for minimizing missing data, etc.
Note: Patient D.A.T.A Form to be completed by English-speaking participants only (no translations available).

17.2.1.4 Blood Collection

Haematology, biochemistry, and LFT's are assessed at baseline and the beginning of each cycle thereafter. Thyroid function tests are collected at baseline only. **For patients on TAS102, a repeat FBC should be collected on C1D15**

Tumour Markers CA19-9 and LDH are to be assessed at the same time as CT imaging (+/- 7 days) until disease progression – refer to 17.2 for timing of tumour assessments by CT imaging.

Testing for chronic active hepatitis B, hepatitis C or HIV is not mandatory unless clinically indicated. A serum pregnancy test must be performed within 7 days prior to randomisation for women of childbearing potential.

Blood for translational research is to be collected from all patients at 4 time points: **C1D1, C2D1, with tumour markers test at the time of week 8 scan, and at the end of treatment**. For processing and storage procedures, refer to Biospecimen Manual.

17.3. Tissue Collection

Submission of available tumour tissue (primary or metastatic) is requested. Refer to the Biospecimen Manual for details as to type of specimen, etc.

17.4. Follow-up After Treatment

For participants continuing RegoNivo under Protocol v10.0 dated 24th February 2025, following their final dose of study treatment an end of treatment visit is required within 30 days of the last dose of study treatment. They will then be considered off study with no further protocol assessments or routine follow-ups required on study. Participants will return to standard of care with ongoing follow-up via standard institutional practice.

Participants in the control arm will end study from 30th April 2025 with no further protocol assessments required. For participants continuing off-study chemotherapy treatment at investigator discretion, ongoing assessments and follow-up will be per standard institutional practice.

18. IIb OUTCOMES, ENDPOINTS AND OTHER MEASURES

18.1. Overall Survival (OS)

(Death from any cause)

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive.

18.2. Progression Free Survival (PFS)

(Disease progression or death)

Progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first evidence of disease progression or death, whichever occurs first. A PFS event is defined as the first occasion that either: (i) RECIST criteria and iRECIST for disease progression are met, (ii) a patient is judged to have progressed by the responsible investigator (in the event that no RECIST assessment is available), or (iii) death occurs. Patients who commence non-protocol anti-cancer therapy without prior evidence of progression will be censored at the prior assessment. Patients who are not observed to meet any of the above conditions will be censored at the date of the last assessment.

18.3. Objective Tumour Response Rate (OTRR)

The OTRR will be calculated by summing the number of participants in a given arm that are assessed as having a complete or partial response (as per RECIST criteria, and iRECIST), and dividing this by the total number of participants in the corresponding arm of the analysis set.

18.4. Quality of Life (QoL)

The core EORTC QoL Questionnaire (QLQ-C30) will be used in conjunction with the disease specific module for GC (STO22). The EQ-5D-5L will be used to obtain utility valuations on the health states experienced by participants (The EuroQol Group (2009). Additional items on cancer-specific symptoms will be collected using the Patient Disease And Treatment Assessment (D.A.T.A.) Form for English-speaking participants only (Stockler et al. 2007) (refer to Appendix 6. Quality of Life Questionnaires & Patient D.A.T.A. Forms). The Patient D.A.T.A Form includes relevant items not covered in the other instruments (e.g., rash, light-headedness, headaches, sore hands/feet, drowsiness). These PROs were used together in the preceding phase II trial and were found to be appropriate in this setting (77). Standard scoring methods will be used to derive scales from these instruments for analysis.

18.5. Safety

See protocol Section 21 for the definition of an adverse event (AE). The NCI Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE) will be used to classify and grade the intensity of adverse events after each treatment cycle.

18.6. Tertiary/Correlative

This will include investigations of how regorafenib and nivolumab may work in people with AGOC as well as studies that may help to understand the pathogenic course of this cancer and related diseases.

Planned biomarker analyses may include but are not limited to:

- Investigation of VEGF-related biomarkers including VEGF, VEGF polymorphisms, circulating VEGF isoforms (VEGF A short isoforms), VEGF family receptors (VEGFR-1, 2, 3) and other proteins downstream of VEGFR, as prognostic and/or predictive markers for those study endpoints relating to survival, response and safety
- Other biomarkers relating to angiogenesis and/or tumourigenesis in blood and tumour including FGF pathway, PDGF, vWF, Tie1 and 2.
- Evaluation of the prevalence and distribution of the four proposed molecular phenotypes of gastric cancer proposed by the Cancer Genome Atlas Research Network (2014), and their association with angiogenic biomarkers and regorafenib activity.
- Regorafenib pharmacokinetics in patients from different geographical regions.
- Associations between circulating tumour DNA and clinical outcomes
- Associations between autoimmunity and clinical outcomes
- Immunoprofiling including: immune cell infiltration, expression of immune checkpoint molecules including PD-1 and PD-L1
- Tumour mutational burden (TMB)
- Cellular and molecular signatures associated with immune-related adverse events.

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.

19. IIb STUDY DRUG INFORMATION

19.1. Investigational Products

The following investigational products (IPs) will be used as study treatments:

- regorafenib tablets
- intravenous nivolumab vials

19.1.1. Description of Investigational Products

Regorafenib will be provided by the manufacturer. The regorafenib 30 mg tablets are coated, non-divisible, light pink, oval-shaped (length 14 mm, width 7 mm, thickness 4.6-5.3.6 mm) and 355 mg each in total weight. The packaging configuration is 21 tablets and a 3g desiccant capsule per bottle of regorafenib 30 mg.

The tablets are stored in high-density polyethylene (HDPE) bottles with a desiccant cartridge inside. The tablets must be stored in the original bottle at the temperature indicated on the bottle label (i.e.: not above 30^0C) and must not be freezed. The bottle must be kept tightly closed after first opening, with the desiccant remaining in the bottle. Once the bottle is opened the tablets must be discarded after 7 weeks.

Nivolumab is a sterile, non-pyrogenic, single-use, isotonic aqueous solution. Nivolumab will be provided for infusion as vials of 100mg/10mL (10mg/mL). Vials of nivolumab are to be stored at 2-8°C and protected from light, freezing and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

19.1.2. Supply of Investigational Product

Participating Institutions will be provided with a start-up supply of study medication once the institution has been activated to commence accrual by the Global Coordinating Centre. Refer to Investigational Product Handling Manual in study manual for further details.

19.2. Investigational Product Accountability

The Pharmacy at Participating Institutions will maintain a record of investigational drugs dispensed for each participant and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

20. IIb STATISTICAL CONSIDERATIONS

20.1. Sample Size

The planned sample size for the trial has been increased from 450 to 460 patients. The increase in sample size will enable additional patient recruitment from some European countries joining the trial and improve representativeness of the study population. A sample of 460 participants randomised in a 2:1 ratio (RegoNivo:chemotherapy) and followed until 380 deaths occur provides at least 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05 assuming median survival amongst chemotherapy patients is 6 months and allowing for a 2% margin for loss to follow-up. The reference median survival of 6 months is based on the Keynote 061 study and Javelin Gastric 300 study(84, 85). The design accommodates early stopping for benefit at an interim analysis performed at 2/3 of the required events (using the error spending approach of Lan-DeMets).

The final analysis on OS will involve testing the following two null hypotheses: (1) no treatment effect on OS in the whole trial cohort ($H_0^{(All)}$); and, (2) no treatment effect on OS in the Asian region cohort ($H_0^{(Asian)}$). A sequenced closed testing procedure will be used to constrain the overall type I error of these two tests to 5%. This will involve first testing $H_0^{(All)}$ at α=5%. If $H_0^{(All)}$ is rejected, then $H_0^{(Asian)}$ will tested and rejected at α=5%. If $H_0^{(All)}$ is not rejected, then $H_0^{(Asian)}$ will not be rejected. Around 50% of the trial cohort is expected to be recruited from Asian regions providing at least 80% power to detect a HR for OS of 0.60 following this sequential testing procedure. In the event the study is stopped early because $H_0^{(All)}$ is rejected at the interim analysis performed at 2/3 of the required events, tests of other hypotheses, including the test of $H_0^{(Asian)}$, will still use α=5%. This approach has been shown in simulation studies to have no or minimal impact on type I error inflation in a range of circumstances when combined with a sequential closed testing approach (121).

20.2. Statistical Analysis

A statistical analysis plan for INTEGRATE IIb will be prepared and finalised prior to database release for analysis. Note that the objectives, and corresponding analyses, for INTEGRATE IIa will be treated, from a statistical perspective, as secondary to those of INTEGRATE IIb.

The primary analysis of efficacy endpoints will be performed on the analysis set comprising all randomised patients in accordance with the intention-to-treat analysis principle. The safety population will comprise all randomised participants who received at least one administration of study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.

20.2.1. Analysis of Efficacy Endpoints

The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test accounting for stratification factors. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression accounting for stratification factors. The sensitivity of the estimated treatment effect on OS to adjustment for baseline covariates, and stratification factors, will be explored.

A series of subgroup analyses will be performed on OS for the stratification factors used at randomisation. Additional subgroup analyses (e.g. location of tumour, ECOG performance status, time since prior immunotherapy, and other prognostic factors) will be pre-specified in a statistical analysis plan. The evaluation of a treatment effect on OS within the Asian region cohort is of particular interest (See Primary Objective) and will be appropriately conducted to maintain a type I error rate of 5% (using a closed testing procedure).

PFS will be analysed in a comparable fashion to OS. The OTRR will be compared between randomised groups using a Cochran-Mantel-Haenszel test accounting for stratification factors (given a sufficient number of responses is observed).

The analysis of QoL will follow the methods used for the phase II INTEGRATE trial (77). The primary analysis approach will compare groups on deterioration-free survival (DFS). DFS is defined as the time from randomisation to the first of the following events: a 10-point deterioration in health status from baseline (without subsequent 10-point improvement compared with baseline), disease progression, death, or treatment discontinuation. Two DFS endpoints will be derived using different markers of health status deterioration based on the EORTC QLQ-C30. One will use the Physical Function Scale (DFS_{PF}), and the other used the General Health Scale (DFS_{GHS}). DFS_{PF} and DFS_{GHS} will be analysed in a comparable fashion to OS. Mixed Models for Repeated Measures (MMRM) will be applied to the scales from EORTC QLQ-C30, EORTC STO22, and EQ-5D instruments in a secondary analysis. The models will include the relevant baseline score, treatment allocation, time point, and a treatment allocation-by-time point interaction as covariates. MMRM accommodates missing post-baseline data and yields valid estimates under the 'Missing At Random' assumption. Information from the Patient D.A.T.A. Forms will be analysed as part of a tertiary analysis. The proportion of patients experiencing symptoms, or impacts on general aspects of QoL, (of at least 3-points intensity on 11 point scale) will be calculated across the post-baseline assessment period, and comparisons between treatment arms will be made using logistic regression adjusting for baseline.

20.2.2. Analysis of Safety Endpoints

A descriptive analysis of the adverse events (AE) data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness.

20.2.3. Analyses for Tertiary and Correlative Objectives

An evaluation of the candidate biomarkers (that may include those listed in Section 18.6) as prognostic and/or predictive factors will be undertaken in a set of exploratory analyses using the appropriate modelling method applicable to each clinical and patient reported endpoint.

20.3. Timing of Analyses

20.3.1. Interim Analyses

Results of the interim analysis will be reviewed unblinded by the study Independent Data Safety Monitoring Committee (IDSMC) only. The IDSMC will also monitor selected safety endpoints, accrual and event rates.

As INTEGRATE IIB is the first study to formally evaluate the 90 mg regorafenib starting dose in combination with nivolumab, an interim safety analysis is proposed after 50 patients have completed 2 cycles of regorafenib. This safety analysis will be undertaken when a minimum of 8 patients are enrolled from Japan, 16 from rest of Asia and the remainder from USA, Europe and Australasia. The safety data from this cohort will be independently reviewed by the IDSMC, considering the expected event rate with 80 mg regorafenib from the REGONIVO study was as follows: no grade 3 skin toxicities, 36% grade 1-2 events, and the Grade 3-4 event rate with nivolumab alone in a similar target population in the Attraction-2 placebo controlled study was 4% (28, 79). Note that all grade 3 skin toxicities with 120 mg regorafenib in the REGONIVO study were reversible with administration of corticosteroids (79).

As such, based on the adverse event data from the REGONIVO study and the Attraction-2 study (28, 79), if the IDSMC considers the adverse event rate with 90 mg regorafenib and the planned dose reduction schedule to be acceptable, the study will be expanded to full accrual, otherwise an amendment will be considered to the regorafenib dosing schedule.

An interim analysis of overall survival will be conducted when approximately 2/3 of the required number of events have occurred. Consideration will be given to early stopping (or altering aspects of the study for safety reasons) if:

- The results of the interim analysis yield clear evidence of benefit or harm based on using the error spending approach of Lan-DeMets with an O'Brien-Fleming stopping boundary.
- The conditional power of the study is unacceptably low (e.g. <20%) at the time of the interim analysis.
- The accrual/event rate is insufficient to complete the study in a reasonable time frame.
- The rate of serious AEs (grade 3 to 5) in the regorafenib arm is unacceptably high compared to the control arm.
- Medical or ethical reasons emerge affecting continued performance of the study.

20.3.2. Primary Analysis

Assuming the study is not terminated early, the primary analysis is planned to be undertaken once the required number of events have occurred.

Common Sections

The following sections are common to both INTEGRATE IIa & INTEGRATE IIb and should be used for both arms

21. SAFETY REPORTING

21.1. 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).

AEs 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)
  Note: overdoses are only reportable as an AE if an adverse effect presents as a result of the overdose
- 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).
- Any untoward event that occurs after the protocol-specified reporting period, which the Investigator believes may be related to the study drug or device.

AEs must be reported as AEs even if they do not meet SAE criteria. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (Appendix 3), and should be assessed from baseline to 30 days following last treatment dose.

An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the regional or global coordinating centre.

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

- results in death,
- is life-threatening (i.e. the participant 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.

In addition to the above, for the purposes of this study the following adverse events are to be considered serious and must be recorded as SAEs, even if they do not otherwise meet the criteria for seriousness as defined above;

- Intracranial haemorrhage of any grade
- Grade 2 or above cerebrovascular ischaemia
- Grade 2 or above perforation of any site within the gastrointestinal tract

In Australia the following definitions are used for reporting of safety events;

- A SIGNIFICANT SAFETY ISSUE (SSI) is defined as is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. These events may be in addition to the current SAE/SADR/SUSAR reports and generally have a consequence related to patient safety within the current study protocol, which thus requires some type of amendment.
- An URGENT SAFETY MEASURE (USM) is one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken.

Examples include:

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt/termination of a trial for safety reasons
- recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure)

SSIs or USMs do not necessarily meet all criteria to be considered an SAE. For purpose of safety reporting, these events are to be reported as SAE with a note that this concerns an SSI or USM.

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's 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 Participant Information Sheet and Informed Consent Form or elsewhere in the protocol).

An event is causally related if there is a reasonable possibility that the drug caused the AE, 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:

- Hospitalisation for pain control

- Hospitalisation due to progression of disease
- Death due to progressive disease
- Surgery for treatment of disease
- Elective hospitalisation to simplify treatment, elective or study procedures.

21.2. Reporting of SAEs

The Investigator is responsible for reporting all SAEs (including SUSARs) occurring during the study to the NHMRC CTC within 24 hours of the Investigator becoming aware of the event using the study-specific SAE eCRF and procedures documented in the Study Manual, except for those that are identified in the protocol as not needing immediate reportingSAEs must be reported from the first dose of study treatment to 30 days from the last dose of study drug.

The following information will be recorded for each SAE:

- Event description including classification according to NCI CTCAE Version 5.0 (Appendix 3)
- Primary and secondary diagnoses of event
- Severity / Worst Grade
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE including end date if recovered

The following information must also be recorded in relation to the study intervention (ie: related to regorafenib for INTEGRATE IIa, related to regorafenib and/or nivolumab for INTEGRATE IIb)

- Attribution to study intervention
- Expectedness (listed in IB for regorafenib or nivolumab or both as above)
- Action taken with study intervention, including rechallenge (if done)

The Investigator must notify the local HREC of SAEs occurring at their site as required. The NHMRC CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The NHMRC CTC will be responsible for providing individual SAE reports as well as SUSAR reports and SAE line listings to the Lead HREC as required.

The local study sponsor/regional coordinating centre in each country/region will submit 'reportable safety events' to the local regulatory authorities (e.g. TGA in Australia, Medsafe in NZ etc.).

21.3. Pregnancy

In the event of a pregnancy occurring in a participant during the course of a study, the participant must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the treatment (ie: regonivo or chemotherapy) must also be reported to the Investigator. The Investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The NHMRC CTC must be notified within 1 working day using the SAE form in the eCRF and the participant 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 participant in the study and up to 8 months after the completion of the study drug should also be reported to the Investigator, and to the NHMRC CTC using the paper form found in the study manual. The pregnant partner should be counselled and followed as described above.

22. CENTRAL REVIEW AND BIOSPECIMEN COLLECTION

22.1. Central Tissue Collection

Formalin-fixed paraffin–embedded (FFPE) tissue of tumour tissue will be collected for translational research (including future translational research relevant to this study) where available from participants. This tissue may include biopsy of primary tumour, resection, biopsy and/or matched fine-needle aspirate biopsy (FNAB) of metastatic lesion if available. The tissue will be from archival tumour material – no additional biopsy of the participant is required. FFPE tissue will be collected by sites and sent to a central laboratory for translational studies (tertiary/correlative objectives). Refer to the Biospecimen Manual for the details of procedures related to central tissue collection.

22.2. Central Blood Collection

Blood for translational research will be collected from all participants at multiple time points and will be processed then stored at each trial site. Blood for regorafenib PK studies will be collected from consenting patients on the Regonivo arm *at selected sites only*. The processed samples will then be transported at a later date to a central laboratory for translational studies (tertiary/correlative objectives). Refer to Biospecimen Manual for the details of collection, processing and shipping procedures.

22.3. Central Radiology Review

Reports of diagnostic scans will be collected centrally for endpoint confirmation. Refer to the Central Radiology Review manual for further details.

23. STUDY COMMITTEES

The study will be coordinated by the NHMRC CTC and conducted in collaboration with the AGITG as sponsor in Australia and New Zealand. Where necessary, a contract research organisation (CRO) or other group may be engaged as local sponsor and delegated local project management responsibilities (including study coordination and monitoring) in countries outside of Australia and New Zealand. Study coordination, monitoring, data acquisition and management and statistical analysis will be performed by the NHMRC CTC.

23.1. International Trial Management Group (TMG)

The international Trial Management Group (TMG) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The international TMG will consider recommendations from the ISDMC about whether to continue the study as planned, modify (for safety reasons), or stop it, based on the interim analysis or other information.

Each regional coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the international TMG.

23.2. Trial Management Committee (TMC)

The local/regional TMC's, where established, will primarily oversee regional study progress and regularly report to the TMG.

23.3. Independent Data and Safety Monitoring Committee (IDSMC)

This study has an IDSMC provided by the AGITG. Agreed terms of reference for the IDSMC have been developed. The IDSMC is independent of the study, and is comprised of the following representatives:

- Statistician;
- Medical Oncologist;
- Medical Oncologist; and
- Chair (Radiation Oncologist)

The IDSMC meet at least six monthly and provide independent assessment of patient safety and trial progress, making recommendations to the TMC about continuing/modifying the trial.

24. ADMINISTRATIVE ASPECTS

24.1. Ethics and Regulatory Compliance

This study will be conducted according to the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) dated 9 November 2016 and local regulations To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the participant 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 participant. In this circumstance, the NHMRC CTC, Principal Investigator and HREC must be advised immediately.

24.2. 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 NHMRC CTC, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

24.3. Protocol Amendments

Changes and amendments to the protocol can only be made by the Trial Management 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 the trial participant(s).

24.4. Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded in the eCRFs 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 electronically signing key CRFs as indicated.

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

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

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

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

24.5. Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC or their delegates. Monitoring will include centralised review of eCRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring will include monitoring visits to investigational sites during the study for source data verification, review of the Investigator's site file and drug handling records. The NHMRC CTC will be given direct access to source documents, eCRFs and other study-related documents. By signing the informed consent form, the participant gives authorised NHMRC CTC staff direct access to their medical records and the study data.

24.6. Audit and Inspection

This study may be subject to audit or inspection by representatives of the AGITG, Bayer, BMS, NHMRC CTC, or representatives of ethics and regulatory bodies (e.g. Therapeutic Goods Administration (TGA)).

24.7. 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. The Clinical Study Report or summary thereof will be provided to both Bayer/BMS.

24.8. Publication Policy

The Trial Management Committee 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 using the study 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 must receive prior written approval from the TMC prior to submission. Please see Appendix 5.

25. REFERENCES

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26. LIST OF APPENDICES

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26.1. Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status Scoring

Grade	ECOG Performance Status
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: *Oken, M.M. et al. (1982) Am. J. Clin. Oncol. (CCT) 5: 649-655*

26.2. **Appendix 2. Cockcroft-Gault Formula**

Renal function (GFR) may be estimated with the Cockcroft–Gault formula, as follows:

Male participants:

Creatinine clearance (ml/minute) = $\frac{(140 - age) * weight}{0.814 * SerumCr}$

Female participants:

Creatinine clearance (ml/minute) = $\frac{(140 - age) * weight * 0.85}{0.814 * SerumCr}$

Units:
Age in years
Weight in kilograms
Serum creatinine (SerumCr) in micromoles per litre

26.3. Appendix 3. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

26.4. Appendix 4. 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 ≥ 20 mm with chest x-ray, and as ≥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 ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm 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 ≥ 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 ≥ 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 can not 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

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 ≥ 5mm. 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**
Target lesions ± non target lesions				
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 ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	

Non target lesions ONLY				
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	
Note: 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 "*symptomatic deterioration"*. 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. *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).				

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 ≥ 10mm 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 ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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.

26.5. Appendix 5. AGITG Publications Policy

Ratified: 4 April 2019

General Principles

1. The aim of the Publication Policy is to ensure appropriate dissemination of AGITG clinical research programme results to the scientific community and the population at large.

   1.1. The results are categorised as:

   - Reports of primary outcomes of studies
   - Reports of secondary outcomes and analyses of studies
   - Reports of sub-studies.

2. Publication of AGITG data without adhering to this policy is not permitted without the prior written consent of the Chair of the AGITG Scientific Advisory Committee (SAC).
3. AGITG requires an opportunity to **review and approve** all publications (journal article and/or presentation) **prior** to submission to a Journal or Conference.
4. AGITG will be acknowledged in **all** publications (including conference presentations, media releases and abstracts).
5. The AGITG Corporate Governance Committee (CGC) is responsible for approving the Publication Policy.
6. The SAC will ensure compliance with this Publication Policy via internal reports detailing a list of all publications and presentations.
7. AGITG will maintain a current bibliography of all publications notified to the AGITG, CTC Publications Officer and OEC. The bibliography will be published on the AGITG website.

Study Chair and Trial Management Committee (TMC)

1. Ensure timely production of a scientific manuscript at the completion of the trial. If there is a significant delay in the writing of the manuscript, alternate strategies will be explored.

   1.1. **Timeframe for publication** – if the study data is not published **within 3 years** of study closure, the Study Chair will provide the final analysis as a Study Report to the Operations Executive Committee (OEC) and/or AGITG. The Study Report will be publicly available on the AGITG website.

   1.2. **Studies that are published** – a Lay Summary of the publication will be provided by the Study Chair to AGITG. The summary will be made available on the AGITG website following Consumer Advisory Panel (CAP) review and feedback.

2. For studies coordinated by the NHMRC Clinical Trials Centre (CTC), the manuscript will be drafted in liaison with the CTC Associate Oncology Program Manager (AOPM) and Publications Officer.
3. Ensure the manuscript is written by a writing committee, TMC or individuals associated with the study.
4. Suggest a list of authors.
5. Finalise the author list.
6. Ensure all authors have approved the final content of the manuscript before it is submitted to a journal.
7. Suggest a priority list of journals to submit to.
8. Forward the publication to AGITG, AOPM or CTC Publications Officer.

9. Ensure that the OEC monitor the timeliness of the publication of trial results.

Authorship

1. Presentation of the primary results of the main study should include group authorship where possible with a list of specific contributions at the end.
2. AGITG will be acknowledged in all publications (including conference presentations, medial releases and abstracts).
3. As per the ICMJE guidelines (www.icmje.org), an 'author' is considered to be someone who has made substantive intellectual contributions to a published study. Authorship credit should be based on:
   - 3.1. Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data
   - 3.2. Drafting the article or revising it critically for important intellectual content
   - 3.3. Final approval of the version to be published.
   - 3.4. Authors should meet conditions 1, 2 and 3 above.
4. Eligibility for authorship will be based on the following factors:
   - 4.1. Substantial contribution to the trial design and protocol development,
   - 4.2. Substantial contribution to the management and conduct of the trial,
   - 4.3. Substantial contribution to the analysis and interpretation of the data,
   - 4.4. Level of contribution of participants to the study.
5. **Study Chair** or **Co-Chair** should be the first (potentially two) author(s) on the basis that:
   - Study Chair or Co-Chair has ensured the success of the study.
   - Study Chair or Co-Chair has made significant contributions to the scientific ideas on which the study was based and to the writing of the manuscript.
   - Study Chair or Co-Chair is a guarantor of the study.

   5.1. In the event there are two Co-Chairs on a trial, the arrangements for authorship should be determined in consultation with the Trial Management and the Operations Executive committees before commencement of the study.

   5.2. In the event there are Co-Chairs on a trial, every effort should be made to ensure there are opportunities for more than one publication and that both Co-Chairs can have a first-author publication.

   5.3. A Co-Chair who is not the first author should choose whether to be second author or last author.
6. **Statistician** should be a principal author (second, third or fourth author) on the basis that:
   - The Statistician has made a significant contribution to the scientific principles of the study.
   - The Statistician has been a prime contributor to the study design, determination of sample size and scientific conduct of the study (unblinding principles, analysis principles, interpretation of results, compliance, etc.)
   - The Statistician guarantees the scientific integrity of the study.
7. **AGITG-CTC Group Coordinator** should be considered as an author to reflect their contribution throughout the lifecycle of the trial (development, conduct, analysis and publication) for studies coordinated by the NHMRC CTC, if in compliance with the policy criteria.

8. **SAC Chair** should be considered as an author to reflect their contribution throughout the lifecycle of the trial (development, conduct, analysis and publication), if in compliance with the policy criteria.
9. Subsequent authors will comprise clinicians or other scientists who have made scientific or intellectual contributions to the study question or the study conduct and meet the journal's requirements for authorship, including members of the TMC.
10. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
11. Contributors listed in Acknowledgements:
    - Any person who contributes to the success of the study or the progress of the manuscript but does not qualify for authorship should (with his/her permission) be acknowledged in the acknowledgements section.
    - All participating sites and the coordinating centre will be acknowledged in the manuscript.

Sub-studies

1. Various sub-study publications are likely to result from any major trial or study. These may involve a distinct subset of patients or may look at specific features.
2. All sub-studies should:
    - be approved by the TMC and OEC before they are started
    - have draft publications approved as detailed in section 5
    - Acknowledge the AGITG trial involved and any sponsors of the trial.
3. Authorship of sub-studies will follow the general policy as detailed in section 6. The sub-study chair will generally be the primary author.

Intergroup Cooperative Studies

1. If the study is a collaborative (intergroup) trial, authorship should be agreed to in the protocol development phase.
2. Authorship for AGITG led intergroup studies will follow the general policy as detailed in section 6.
3. Authorship for Intergroup studies where AGITG are participating but not leading will follow the publication policy of the lead group. The Australian Principal Investigator in consultation with the Australian TMC will determine authorship for Australian investigators. Authorship will be finalised after discussion with the OEC.
4. The agreement about authorship will be included in the protocol in a section titled 'Publication Policy'.
5. This policy can accommodate such instances provided that:
    - All groups are represented on the trial management committee
    - The Principal Investigator is clearly designated.
6. Manuscripts for AGITG led intergroup studies must be reviewed and scientific content approved by the OEC prior to submission.
7. Manuscripts for intergroup studies where AGITG are participating but not leading must be reviewed and scientific content approved by the OEC. The Australian Principal Investigator should liaise with the OEC to facilitate this process.
8. Reference to this policy on authorship should be included as the publications policy in all intergroup trial protocols in which the AGITG participates.

9. During the development of intergroup protocols, the publication policy should be circulated to the Protocol Development Group to facilitate discussion and resolution on this issue.

Abstracts, Presentations and Posters

1. Study participants are encouraged to write and present abstracts based on the scientific information available from the study.
2. Authorship will follow the general policy as detailed in section 6.
3. Abstracts and other presentations would generally not require OEC approval. However the following procedures are mandatory:

   3.1. Before submission, abstracts to be submitted must be referred to the study Statistician who will ensure that information disclosed is appropriate and will not compromise the main study.

   3.2. The final abstract will be sent by the primary author to the relevant Trial Coordinator or Project Manager for dissemination to the OEC.
4. Copies of submitted abstracts and presented posters, with details of the pertinent scientific meeting, should be provided to the AGITG or CTC Publications Officer by the primary author.

Ownership of Trial Data

1. Study data will usually remain the property of the AGITG (and University of Sydney when the trial is coordinated by NHMRC CTC). Researchers who require use of all or part of the data must obtain approval from the appropriate study chair.
2. Studies conducted jointly with other groups will generally have joint ownership of the data unless agreed to otherwise. Although access to data for research projects by AGITG investigators would not require formal approval from the cooperative groups, professional courtesy would ensure that notification of such projects to these groups is given.
3. Ownership of data generated in trials funded by the pharmaceutical industry will remain with the AGITG (and University of Sydney when the trial is coordinated by NHMRC CTC). The use of data by industry funders will be in accordance with the terms and conditions set out in the funding agreement. Decisions regarding the use of data will be made on an individual trial basis and incorporate the commitment from each party which will be outlined in the funding agreement.
4. In some instances both funders and the AGITG may make agreement for joint ownership after some time period has elapsed, after the termination of the study (for example 2 years). In this period, the AGITG would prepare all its reports and manuscripts. After this period the AGITG would reserve the right to use the data for further analyses in research and teaching without necessarily seeking the approval of the funder.
5. Individual sites retain the ownership of their own patient data (that is, data recorded about patients randomised or registered by investigators at that site).

Funders

1. Funding or other contributions to the study such as drug product will be acknowledged in all publications, presentations and posters.
2. Any financial relationship between the funder, or a funder's competitor, and any author must be disclosed on publications or in the submission letter to the journal.

Disputes

1. Disputes that cannot be resolved by discussion will be referred to an independent sub-group of the SAC for resolution. This committee will be chaired by SAC Chair. In cases where there is a conflict of interest, the committee will be chaired by the SAC Deputy Chair.

Glossary of Terms

Operations Executive:	AGITG Chair, Group Coordinator, CTC Director, CTC Clinical Trial Director, Research Fellow, AGITG Chief Executive Officer, CTC Associate Oncology Program Managers, AGITG Clinical Research Manager.
Study Chair:	A person, or persons, usually clinicians, taking primary responsibility for the conception, conduct, monitoring and completion of the trial or research project.
Statistician:	The statistician taking primary responsibility for the statistical considerations of the trial. Usually the group statistician or his or her designate.
Trial Coordinator:	The person responsible for the running of the trial on a day-to-day basis. Responsibilities include randomisation, documentation, data processing, data cleaning, adverse event monitoring, quality control, liaison with site staff and preparation of reports.
Project Manager:	Used interchangeably with the term Trial Coordinator.
Principal Investigator:	Person identified at each participating institution responsible for the conduct of the trial or research project within that institution.
Reviewed:	Appraised of the content of the manuscript or abstract to ensure that the validity of the trial, the objectives of the group, and the interpretation of the data are maintained.
Commented:	Provided written feedback to the principal investigator, first author or coordinating centre to indicate that the review is complete.
Approved:	Signed off on the manuscript or abstract after review, with or without comment, and conveying this in writing to the principal investigator, first author or coordinating centre.

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

INTEGRATE II

Patient's Disease and Treatment Assessment Form

Patient Initials: ☐☐☐ (*First Middle Last*) Study Number: ☐☐☐ Site Code: ☐☐☐☐☐

Study Phase: ☐ (*Treatment = T, Follow-up = F*) Assessment Number: ☐☐ (*Baseline = 0, Follow-up=: re-start at 1*) Today's Date: ☐☐☐☐☐☐☐☐ (*D D M O N Y Y Y Y*)

Please **circle** one number for each line to best show **how much that aspect troubled you** on average **during the last month**.

	No trouble at all		Mild			Moderate			Severe		Worst I can imagine
1. Pain (all and anywhere)	0	1	2	3	4	5	6	7	8	9	10
2. Fatigue (tiredness)	0	1	2	3	4	5	6	7	8	9	10
3. Poor appetite	0	1	2	3	4	5	6	7	8	9	10
4. Cough	0	1	2	3	4	5	6	7	8	9	10
5. Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
6. Trouble sleeping	0	1	2	3	4	5	6	7	8	9	10
7. Nausea	0	1	2	3	4	5	6	7	8	9	10
8. Vomiting	0	1	2	3	4	5	6	7	8	9	10
9. Diarrhoea	0	1	2	3	4	5	6	7	8	9	10
10. Constipation	0	1	2	3	4	5	6	7	8	9	10
11. Urinary symptoms	0	1	2	3	4	5	6	7	8	9	10
12. Leg swelling	0	1	2	3	4	5	6	7	8	9	10
13. Difficulty walking	0	1	2	3	4	5	6	7	8	9	10
14. Anxiety (feeling worried)	0	1	2	3	4	5	6	7	8	9	10
15. Depression (feeling sad)	0	1	2	3	4	5	6	7	8	9	10
16. Irritability (being cranky)	0	1	2	3	4	5	6	7	8	9	10
17. Trouble concentrating	0	1	2	3	4	5	6	7	8	9	10

Please circle one number for each line to show how you would rate yourself on that aspect on average **during the last month**.

	Best possible		Very Good		Good		Fair		Poor		Very poor	Worst possible
18. Energy	10	9	8	7	6	5	4	3	2	1		0
19. Appetite	10	9	8	7	6	5	4	3	2	1		0
20. Mobility (ability to get around)	10	9	8	7	6	5	4	3	2	1		0
21. Mood	10	9	8	7	6	5	4	3	2	1		0
22. Physical well-being	10	9	8	7	6	5	4	3	2	1		0
23. Emotional well-being	10	9	8	7	6	5	4	3	2	1		0
24. Overall well-being	10	9	8	7	6	5	4	3	2	1		0

Please continue, there are more questions on the next page.

INTEGRATE II

Patient's Disease and Treatment Assessment Form

Patient Initials: ☐☐☐ (*First Middle Last*) Study Number: ☐☐☐ Site Code: ☐☐☐☐☐

Study Phase: ☐ (*Treatment = T, Follow-up = F*) Assessment Number: ☐☐ (*Baseline = 0, Follow-up=: re-start at 1*) Today's Date: ☐☐☐☐☐☐☐☐ (*D D M O N Y Y Y Y*)

Please **circle** one number for each line to best show **how much that aspect troubled you** on average **during the last month**.

	No trouble at all			Mild			Moderate			Severe		Worst I can imagine
25. Drowsiness	0	1	2	3	4	5	6	7	8	9	10	
26. Headaches	0	1	2	3	4	5	6	7	8	9	10	
27. Feeling dizzy or lightheaded	0	1	2	3	4	5	6	7	8	9	10	
28. Dry mouth	0	1	2	3	4	5	6	7	8	9	10	
29. Altered sense of taste	0	1	2	3	4	5	6	7	8	9	10	
30. Sore mouth or throat	0	1	2	3	4	5	6	7	8	9	10	
31. Difficulty swallowing	0	1	2	3	4	5	6	7	8	9	10	
32. Hair loss	0	1	2	3	4	5	6	7	8	9	10	
33. Skin rash	0	1	2	3	4	5	6	7	8	9	10	
34. Sore hands and/or feet	0	1	2	3	4	5	6	7	8	9	10	
35. Numbness or pins and needles	0	1	2	3	4	5	6	7	8	9	10	
36. Fevers	0	1	2	3	4	5	6	7	8	9	10	
37. Hot flashes	0	1	2	3	4	5	6	7	8	9	10	
38. Sweating or sweats	0	1	2	3	4	5	6	7	8	9	10	
39. Problems with sex	0	1	2	3	4	5	6	7	8	9	10	
40. Problems taking tablets	0	1	2	3	4	5	6	7	8	9	10	
41. Problems with needles or injections	0	1	2	3	4	5	6	7	8	9	10	
42. Inconvenience of treatment	0	1	2	3	4	5	6	7	8	9	10	
43. Problems coping with treatment	0	1	2	3	4	5	6	7	8	9	10	
44. Thought of actually having treatment	0	1	2	3	4	5	6	7	8	9	10	
45. Problems looking after myself	0	1	2	3	4	5	6	7	8	9	10	
46. Problems doing what I wanted	0	1	2	3	4	5	6	7	8	9	10	
47. Problems for my friends or family	0	1	2	3	4	5	6	7	8	9	10	

This is the end of the form. Thank you for filling it out.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems with walking around ❑
I have slight problems with walking around ❑
I have moderate problems with walking around ❑
I have severe problems with walking around ❑
I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑
I have slight problems with washing or dressing myself ❑
I have moderate problems with washing or dressing myself ❑
I have severe problems with washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐