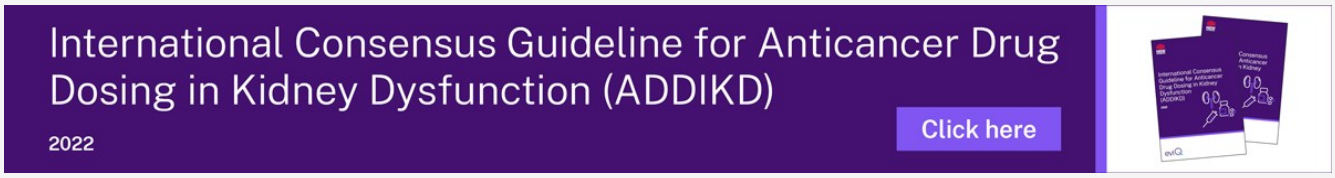
Gastrointestinal stromal cell tumour (GIST) metastatic regorafenib

ID: 1902 v.2 **Endorsed**

Check for clinical trials in this patient group. Link to Australian Clinical Trials website

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Related pages:

- Gastrointestinal stromal cell tumour (GIST) metastatic sUNITinib
- Gastrointestinal stromal cell tumour (GIST) metastatic imatinib
- Gastrointestinal stromal cell tumour (GIST) metastatic ripretinib

Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
Regorafenib	160 mg ONCE a day *	PO	1 to 21 **

*Careful monitoring is required and consideration should be given to starting at 120 mg once a day

**Rest week from day 22 to day 28

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

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Drug status: Regorafenib is TGA registered but not PBS listed

Regorafenib is available as a **40 mg** tablet

Cost: ~ $4,170 per cycle

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Cycle 1 and further cycles

Day 1 to 21

Day 1 to 21		
Regorafenib	160 mg (PO)	ONCE a day after a light breakfast. Careful monitoring is required and consideration should be given to starting at 120 mg once a day

Rest week from day 22 to day 28

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

- Metastatic or unresectable gastrointestinal stromal tumour (GIST) after failure (or intolerance to) imatinib and sunitinib
  - ECOG performance status 0 to 1 only.

Clinical information

Caution with oral anti-cancer drugs	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the COSA guidelines and oral anti-cancer therapy
Emetogenicity minimal or low	No routine prophylaxis required. If patients experience nausea and/or vomiting, consider using the low emetogenic risk regimen. Read more about preventing anti-cancer therapy induced nausea and vomiting
Cardiac toxicity	Patients treated with regorafenib experience an increased incidence of myocardial ischemia and infarction. Withhold regorafenib therapy in those who develop new or acute onset cardiac ischemia or infarction. Reinstituting regorafenib therapy after resolution of acute cardiac ischemic events should occur only if the potential benefits of therapy outweigh the risks of further cardiac damage. Read more about cardiac toxicity associated with anti-cancer drugs
Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing treatment and blood pressure should be monitored regularly and treated, if required. In severe or uncontrolled hypertension, treatment should be withheld until hypertension is controlled. Dose modification or permanent discontinuation may be necessary - refer to dose modification section for specific recommendations.
Hepatotoxicity	Severe hepatotoxicity (including fatal outcomes) has been observed with this treatment. Monitor for abnormal liver function tests (LFTs), jaundice and tiredness. Refer to blood tests and dose modification sections for specific recommendations.
Hand-foot syndrome	Hand-foot syndrome (palmar-plantar erythrodysaesthesia) and rash are common adverse effects with this treatment which generally appear during the first 6 weeks of therapy. Read more about hand food syndrome or palmar plantar erythrodysaesthesia (PPE)
Wound healing	There have been no formal studies on the effects of regorafenib on wound healing. Since VEGF inhibitors are known to impair wound healing, treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. Regorafenib can be resumed after surgery when the wound is considered to be adequately healed. Regorafenib should be discontinued in patients with wound dehiscence.
Gastrointestinal perforation	Gastrointestinal perforation and fistula have been reported in patients treated with regorafenib. Regorafenib should be permanently discontinued in anyone who develops gastrointestinal perforation or fistula.

Haemorrhage	Haemorrhage was reported in 19.3% of patients treated with regorafenib across all clinical trials. Most cases of bleeding events were mild to moderate in severity (Grade 1 and 2: 16.9%). Blood counts and coagulation parameters should be monitored in patients with conditions that predispose to bleeding, and in those treated with anti-coagulants or other medications that increase the risk of bleeding.
Oral mucositis	Oral mucositis may manifest as mouth and tongue ulceration. Early intervention may help to avoid dose alteration or interruption. Topical treatments (alcohol free) are recommended. Read more about oral mucositis and stomatitis
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Reversible posterior leukoencephalopathy syndrome (RPLS)	Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in patients receiving this treatment and may be fatal. Discontinue drug in patients developing RPLS. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)
Blood tests	LFT before initiation and monitor every two weeks during first two months of treatment. Then LFTs monthly and as clinically indicated. FBC, EUC, calcium, magnesium and phosphate at baseline, repeat at week 2, then every 4 weeks. INR as clinically indicated.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is NOT usually recommended for patients receiving this treatment. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol

has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note:

- Dose modifications were required in 72% of patients in the GRID trial (compared to 26% in the placebo group). The following dose modifications have been adapted from the GRID trial.[1]
- The lowest recommended daily dose is 80 mg.

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	No dose modification necessary
less than 30	Regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease

Hepatic impairment	
At baseline:	
Mild	No dose modification necessary
Moderate	Limited data in patients with moderate hepatic impairment
Severe	Regorafenib has not been studied in patients with severe hepatic impairment
During treatment:	
ALT and/or AST and/or bilirubin	
If baseline is Grade 0 and increases to Grade 1 or If baseline is Grade 1 and increases to Grade 2	Continue regorafenib Monitor liver function twice weekly for 2 weeks, then weekly for at least 4 weeks until recovery to baseline
If baseline is Grade 0 and increases to Grade 2	1st occurrence: Delay treatment and monitor liver function twice weekly until toxicity has resolved to Grade 1 or less. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet) and monitor liver function twice weekly for 2 weeks, then weekly for at least 4 weeks. If all values remain stable for two full cycles, dose re-escalation may be considered at the discretion of the treating doctor. 2nd occurrence: Discontinue regorafenib. Continue to monitor liver function until recovery to baseline.
If any baseline grade increases to Grade 3	1st occurrence: Delay treatment and monitor liver function twice weekly until toxicity has resolved to Grade 1 or less (if baseline was Grade 0 or 1) or until Grade 2 (if baseline was Grade 2). When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet) and monitor liver function twice weekly for 2 weeks, then weekly for at least 4 weeks. If all values remain stable for two full cycles, dose re-escalation may be considered at the discretion of the treating doctor. 2nd occurrence: Discontinue regorafenib. Continue to monitor liver function until recovery to baseline. If ALT or AST is 8.0 x ULN or greater, with concurrent rise in bilirubin (any degree) from baseline: 1st occurrence: Consider permanent discontinuation of regorafenib. Continue to monitor liver function until recovery to baseline.
If any baseline grade increases to Grade 4	1st occurrence: Discontinue regorafenib. Continue to monitor liver function until recovery to baseline.

Hand foot syndrome (link to Hand foot syndrome (Palmar-plantar erythrodysaesthesia))	
Grade 1	Continue current dose of regorafenib and immediately institute supportive measures for symptomatic relief, e.g. topical therapy with emollients, moisturisers and keratolytics including urea cream (10-40% depending on severity, e.g. Urederm® cream) or salicylic acid-containing aqueous cream.
Grade 2	1st occurrence: Consider reducing the dose of regorafenib by 40 mg (one tablet) and immediately institute supportive measures for symptomatic relief. If no improvement within 7 days or 2nd occurrence: Interrupt treatment until toxicity resolves to Grade 1 or less. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating doctor. 3rd occurrence: Interrupt treatment until toxicity resolves to Grade 1 or less. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet)*. 4th occurrence: Discontinue treatment.
Grade 3	1st occurrence: Immediately institute supportive measures. Interrupt treatment for a minimum of 7 days, until toxicity resolves to Grade 1 or less. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating doctor. 2nd occurrence: Immediately institute supportive measures. Interrupt treatment for a minimum of 7 days, until toxicity resolves to Grade 1 or less. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet)*. 3rd occurrence: Discontinue treatment.

** Patients requiring more than 2 dose reductions should discontinue regorafenib (as this would result in a dose less than the lowest recommended daily dose of 80 mg).*

Hypertension	
Grade 1	Continue regorafenib Consider increasing the frequency of BP monitoring
Grade 2	Treat hypertension to achieve a diastolic BP of 90 mm Hg or less: - If BP was previously within normal limits, begin antihypertensive monotherapy - If patient is already on antihypertensive therapy, titrate up the dose of antihypertensive agent. If patient is asymptomatic, continue regorafenib at the same dose. If patient is symptomatic, withhold regorafenib until symptoms resolve and diastolic BP is 90 mmHg or less**. When resuming treatment, continue regorafenib at the same dose.
Grade 3	Treat hypertension to achieve a diastolic BP of 90 mm Hg or less: - Commence antihypertensive medication, or - Increase current antihypertensive medication, and/or - Add additional antihypertensive medication(s). Withhold regorafenib until symptoms resolve and diastolic BP is 90 mmHg or less**. When resuming treatment, continue regorafenib at the same dose. If BP is not controlled with the addition of new or more intensive antihypertensive therapy, reduce the dose of regorafenib by 40 mg (one tablet). If BP remains controlled for at least one full cycle, a dose re-escalation may be considered at the discretion of the treating doctor. If Grade 3 hypertension recurs despite regorafenib dose reduction and antihypertensive therapy, reduce the dose of regorafenib by a further 40mg (one tablet)*.

Hypertension	
Grade 4	Discontinue regorafenib.

** Patients requiring more than 2 dose reductions should discontinue regorafenib (i.e. reductions that would result in a dose less than 80 mg).*

*** Patients requiring a delay longer than 4 weeks should discontinue regorafenib.*

Diarrhoea	
Grade 1 or Grade 2	Continue treatment; no dose modification necessary
Grade 3	Delay treatment until toxicity has resolved to Grade 2 or less**. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet). If toxicity remains Grade 2 or less, dose re-escalation may be considered at the discretion of the treating doctor. If dose is re-escalated and toxicity Grade 3 or greater recurs, permanently reduce the dose of regorafenib by 40 mg (one tablet).
Grade 4	Delay treatment until toxicity has resolved to Grade 2 or less**. When resuming treatment, reduce the dose of regorafenib by 40 mg (one tablet). Permanent discontinuation can be considered at the discretion of the treating doctor.

*** Patients requiring a delay longer than 4 weeks should discontinue regorafenib.*

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. References & Disclaimer

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Regorafenib		
	Interaction	**Clinical management**
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of regorafenib possible due to reduced clearance	Avoid combination or monitor for regorafenib toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of regorafenib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to regorafenib
Drugs metabolised by UDP glucuronosyl transferase (UGTs) or undergoing Breast Cancer Resistance Protein (BCRP) or P-gp mediated elimination (e.g. irinotecan, methotrexate, phenytoin, digoxin, dexamethasone, dabigatran, loperamide etc.)	Increased effect/toxicity of these drugs possible due to inhibition of UGTs, BCRP and P-gp by regorafenib resulting in reduced clearance	Caution advised if combination used - monitor for increased effect/toxicity of interacting drugs
Antibiotics, bile acid binding agents (e.g. cholestyramine)	Reduced efficacy of regorafenib possible due to interference with enterohepatic circulation of regorafenib and its metabolites	Caution advised if combination used - monitor for decreased clinical response to regorafenib

General		
	Interaction	**Clinical management**
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual

product information monographs via the TGA website for further information.

Days 1 to 21

This is an oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Treatment - Time out

Regorafenib

- administer orally ONCE a day on **days 1 to 21**
- to be swallowed whole with a glass of water; do not break, crush or chew
- to be taken after a low fat meal (ideally at breakfast) that contains less than 30% fat*
- monitor blood pressure at baseline and repeat weekly for first 6 weeks, then regularly throughout treatment.

Note: missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

*Example of a low fat meal include one cup of cereal, 250 mL or one glass of skimmed milk, one slice of toast with jam, apple juice and one cup of coffee or tea (520 calories, 2 g fat, 17 g protein, 93 g of carbohydrate).

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Discharge information

Regorafenib tablets

- Regorafenib tablets with written instructions on how to take them.

Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash
Palmar-plantar erythrodysaesthesia (PPE) - hand-foot syndrome (HFS)	Bilateral erythema, tenderness, pain, swelling, tingling, numbness, pruritus, dry rash, or moist desquamation and ulceration of the palms and soles. It is also known as hand-foot syndrome (HFS). Symptoms appear to be dose dependent and palms are affected more than soles. Read more about hand-foot syndrome associated with chemotherapy
Oral mucositis	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about oral mucositis
Diarrhoea	Read more about treatment induced diarrhoea
Hypertension	High blood pressure is commonly associated with many anti-cancer drugs. Pre-existing hypertension should be controlled prior to initiation of drugs capable of causing hypertension.
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
Gastrointestinal perforation	A rupture of the wall of the stomach, small intestine or large bowel. Symptoms include acute abdominal pain, tenderness and signs of sepsis.
Haemorrhage	
Fatigue	Read more about fatigue
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia

Late (onset weeks to months)	
Alopecia	Hair loss may occur from all parts of the body. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling

Evidence

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (GRID study) involving 199 patients comparing placebo with regorafenib alone in patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib and sunitinib.[1]

Between January 4 and August 18, 2011, 199 patients were randomised in a 2:1 ratio to receive regorafenib 160mg orally once daily (n=133) or matching placebo (n=66), for the first 3 weeks of each 4 week cycle. All patients also received best supportive care.

The primary end point was progression-free survival (PFS) and secondary end points were overall survival (OS), time to progression (TTP), objective response rate (ORR), disease control rate (defined as rate of complete response or partial response plus stable disease lasting for at least 12 weeks), safety and tolerability.

At disease progression, patients assigned placebo could crossover to receive open-label regorafenib. There was significant crossover (85%) in the placebo group.

Efficacy

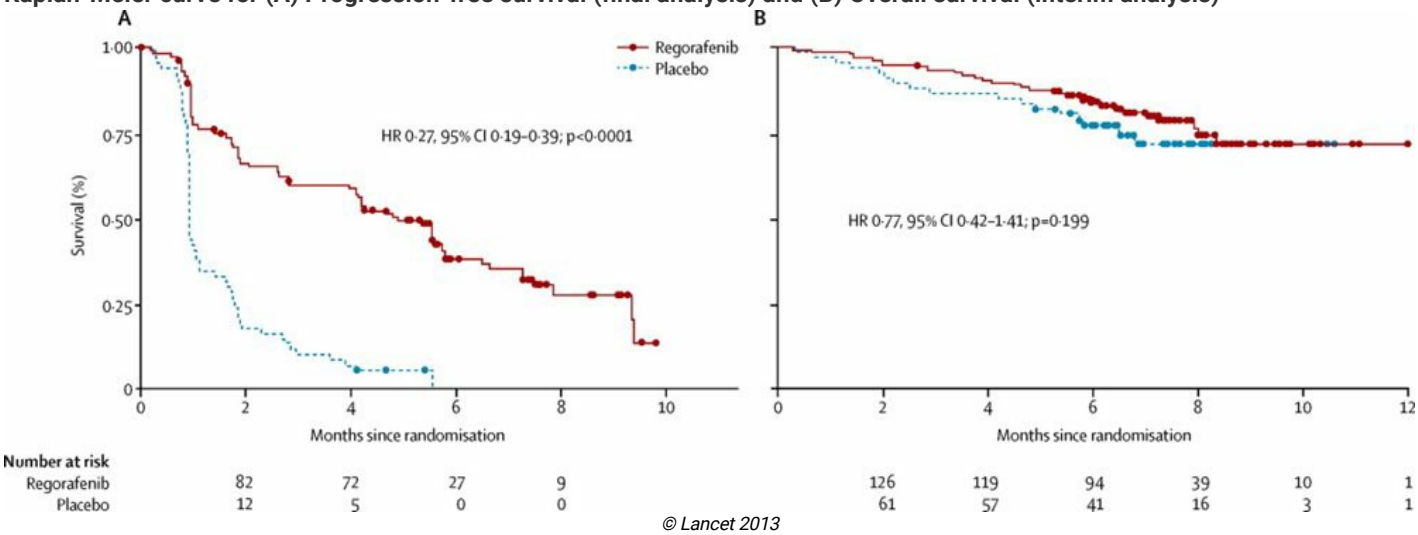
At the time of analysis when the predetermined criteria of 144 PFS events was reached, the median PFS was 4.8 months in the regorafenib group vs 0.9 months in the placebo group (HR=0.27; CI 95% 0.19 to 0.39; p<0.0001), meeting the primary endpoint of the study.[1]

There was no statistically significant difference in OS between the regorafenib and placebo groups (HR 0.77, 95% CI 0.42-1.41; p=0.199), however the proportion of patients who crossed over from the placebo group may account for this.[1]

No patients in either group had a complete response, while 6 out of 133 patients in the regorafenib group and 1 out of 66 patients in the placebo group had a partial response, giving ORRs of 4.5% and 1.5% respectively.[1]

QOL data was not collected in the key evidence and has not been presented.

Kaplan-Meier curve for (A) Progression-free survival (final analysis) and (B) Overall survival (interim analysis)[1]



Toxicity

Drug-related adverse events of any grade were reported in 130 (98%) of the regorafenib-treated patients and 45 (68%) of the placebo patients. The most common adverse event of any grade was hand-foot skin reaction, which occurred in 74 (56%) patients in the regorafenib group and 9 (14%) patients in the placebo group.[1]

Drug-related adverse events of grade 3 or higher were reported in 81 (61%) of the regorafenib-treated patients and 9 (14%) of the placebo patients. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (23%), hand-food skin reaction (20%) and diarrhoea (5%).[1]

Serious adverse events were reported in 38 (29%) patients in the regorafenib group, the most common being abdominal pain (4%), fever (2%) and dehydration (2%). Grade 5 adverse events were reported in 7 (5%) patients in the regorafenib group, two of which were deemed to be drug-related (cardiac arrest and hepatic failure). In the placebo group grade 5 adverse events occurred in 3 (4.5%) of the 66 patients, one of which was deemed to be drug-related (fatigue).

Although dose modifications were more frequent in the regorafenib group (72%) vs placebo group (26%), the occurrence of adverse events that led to permanent discontinuation of treatment was similar between the two groups.[1]

Toxicity[1]

	Regorafenib (N=132*)			Placebo (N=66)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	130 (98%)	77 (58%)	2 (2%)	45 (68%)	5 (8%)	1 (2%)
Hand-foot skin reaction	74 (56%)	26 (20%)	0	9 (14%)	0	0
Hypertension	64 (49%)	30 (23%)	1 (1%)	11 (17%)	2 (3%)	0
Diarrhoea	53 (40%)	7 (5%)	0	3 (5%)	0	0
Fatigue	51 (39%)	3 (2%)	0	18 (27%)	0	0
Oral mucositis	50 (38%)	2 (2%)	0	5 (8%)	1 (2%)	0
Alopecia	31 (24%)	2 (2%)	0	1 (2%)	0	0
Hoarseness	29 (22%)	0	0	3 (5%)	0	0
Anorexia	27 (21%)	0	0	5 (8%)	0	0
Rash, maculopapular	24 (18%)	3 (2%)	0	2 (3%)	0	0
Nausea	21 (16%)	1 (1%)	0	6 (9%)	1 (2%)	0
Constipation	20 (15%)	1 (1%)	0	4 (6%)	0	0
Myalgia	18 (14%)	1 (1%)	0	6 (9%)	0	0
Voice alteration	14 (11%)	0	0	2 (3%)	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

Table 2: **Drug-related adverse events in ≥10% of patients during double-blind treatment period**

References

1 Demetri, G. D., P. Reichardt, Y. K. Kang, et al. 2013. "Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial." Lancet 381(9863):295-302.

Bibliography

De Wit, M., C. B. Boers-Doets, A. Saettini, et al. 2014. "Prevention and management of adverse events related to regorafenib." Support Care Cancer 22(3):837-846.

History

Version 2

Date	Summary of changes
19/12/2016	New protocol taken to Medical Oncology Reference Committee meeting on 21 October 2016. Approved and published on eviQ. Next review in 1 year.
31/05/2017	Transferred to new eviQ website. Version number changed to V.2. Hepatitis B screening changed to NOT recommended.
16/02/2018	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Review in 2 years
25/09/2020	Protocol reviewed electronically by the Medical Oncology Reference committee. Nil changes. Next review in 2 years.
21/12/2021	Changed antiemetic clinical information block to minimal or low, to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5.
20/10/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review 2 years.

First approved: 19 December 2016
Last reviewed: 20 October 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/1902
13 Jul 2023

Patient information - Gastrointestinal stromal cell tumour (GIST) metastatic - Regorafenib

Patient's name:

Your treatment

The treatment schedule below explains how the drug for this treatment is given.

Regorafenib		
This treatment cycle is repeated every 28 days. Your doctor will advise you how long to take the treatment for.		
Day	**Treatment**	**How it is given**
1 to 21	**Regorafenib** (RE-goe-RAF-e-nib*)*	Take orally ONCE a day after a light breakfast (low fat*). Swallow whole with a glass of water, do not break, crush or chew. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.
22 to 28	**Do not** take regorafenib tablets from day 22 to day 28	

*An example of a low fat meal includes one cup of cereal, one glass of skim milk, one slice of toast with jam, apple juice and one cup of tea or coffee.

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38°C or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • you become unwell.	Daytime: Night/weekend: Other instructions:

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get

severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests. Tell your doctor if you are on an anticoagulant (medication used to treat or prevent blood clots) e.g. warfarin. You may need to have additional blood tests.

Surgery and wound healing

This treatment may affect wound healing. Tell your doctor if you are planning to have surgery or have a wound that has not healed.

Other medications given during this treatment

- **Antidiarrhoeals:** you may be given some medication to treat diarrhoea. Your doctor or nurse will tell you how and when to take your antidiarrhoeal medication.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Taste and smell changes	• You may find that food loses its taste or tastes different. • These changes are likely to go away with time. • Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. • Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.
Early (onset days to weeks)	

Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**
Hand-foot syndrome (palmar-plantar erythrodysaesthesia)	• The palms of your hands and soles of your feet may become: ◦ red and hot ◦ swollen ◦ painful and tender ◦ blistered. • The skin in the area may also peel. • Moisturise your hands and feet daily with sorbolene or aqueous cream. • Keep your hands and feet clean and dry. • Avoid hot water, instead use lukewarm water to bathe. • Avoid direct sunlight. • Avoid unnecessary walking, jogging or exercise. • Wear cotton socks and avoid tight-fitting shoes. • **Tell your doctor or nurse as soon as possible if you notice any skin changes on your hands or feet.**
Mouth pain and soreness (mucositis)	• You may have: ◦ bleeding gums ◦ mouth ulcers ◦ a white coating on your tongue ◦ pain in the mouth or throat ◦ difficulty eating or swallowing. • Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks. • Try bland and soft foods. • Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so. • Rinse your mouth after you eat and brush your teeth, using either: ◦ 1/4 teaspoon of salt in 1 cup of warm water, or ◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water • Ask your doctor or nurse for eviQ patient information - Mouth problems during cancer treatment. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
High blood pressure (hypertension)	• You may not have any signs or symptoms if you have high blood pressure. • If it is severe you may get headaches, shortness of breath or feel dizzy. • Your blood pressure will be taken regularly during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the signs or symptoms listed above.**

Liver problems	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**
Bleeding into stomach or bowel	• This side effect is rare, but can be very serious. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of these signs or symptoms:** ◦ **severe stomach pain** ◦ **swollen and hot skin around your stomach** ◦ **bleeding** ◦ **nausea or vomiting** ◦ **fever or chills** ◦ **a fast heartbeat** ◦ **you feel short of breath.**
Bleeding (haemorrhage)	• Tell your doctor or nurse if you have a wound that does not heal. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **unusual bleeding or bruising** ◦ **bright red or black, tarry bowel motions (stools, poo)** ◦ **stomach pain** ◦ **slurred speech** ◦ **shortness of breath** ◦ **a fast heartbeat.**
Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.

Late (onset weeks to months)	
Hair loss (alopecia)	• Your hair may start to fall out from your head and body. • Hair loss usually starts 2 to 3 weeks after your first treatment. • You may become completely bald and your scalp might feel tender. • Use a gentle shampoo and a soft brush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat, scarf or wig. • Protect your scalp from the sun with a hat or sunscreen of SPF 50 or higher. • Moisturise your scalp to prevent itching. • Ask your doctor or nurse about the Look Good Feel Better program

General advice for people having cancer treatment

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council 13 11 20 for cancer information and support

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- CHILL Cancer related hair loss - scalpcooling.org
- eviQ Cancer Treatments Online – eviq.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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