Colorectal metastatic FOLFOXIRI (modified) (fluorouracil leucovorin oxaliplatin irinotecan) and beVACizumab

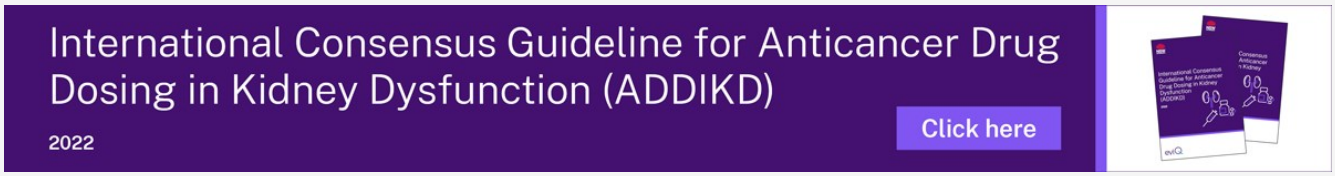
ID: 1715 v.8 **Endorsed** Essential Medicine List

⚠ Fluoropyrimidine overdose or overexposure:
Fluoropyrimidine overdose or overexposure may result in severe or life-threatening toxicity. An antidote is available and is highly effective if given within 96 hours. Read more about fluoropyrimidine overdose or overexposure.

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

Avastin® (bevacizumab) is no longer available on the PBS and alternative biosimilars are now available. The rapid infusion administration instructions for subsequent doses of bevacizumab included in eviQ protocols are based on studies conducted using Avastin® (bevacizumab).

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.



Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
beVACizumab	5 mg/kg	IV infusion	1
Irinotecan	165 mg/m^2	IV infusion	1
Oxaliplatin	85 mg/m^2 #	IV infusion	1
Calcium folinate (Leucovorin)	50 mg *	IV bolus	1
Fluorouracil	3,200 mg/m^2	CIV via pump over 48 hours (equivalent to 1600 mg/m^2/day)	1

Consideration should be given to limiting oxaliplatin to 6 cycles.[1] If oxaliplatin is continued, oxaliplatin should be limited to 12 cycles. Maintenance therapy may be continued in patients who are stable or responding to treatment.

* The dose of calcium folinate (Leucovorin®) has been modified in this protocol from the original clinical trial dose of 200 mg/m² to 50 mg based on reference committee consensus. Refer to discussion on calcium folinate (Leucovorin®) and evidence section for more information.

Frequency: 14 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:
There was an increased incidence of Grade 3 and 4 toxicities observed with this regimen; this protocol should be restricted to

very fit patients with minimal comorbidities. Strategies to minimise toxicity include G-CSF support, thorough patient education and vigilant monitoring for any potential septic episodes (link to patient information - Infection during cancer treatment).

Drug status: All drugs in this protocol are on the PBS general schedule

Cost: ~ $720 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		
Netupitant	300 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with palonosetron)
Palonosetron	0.5 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with netupitant)
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
beVACizumab	5 mg/kg (IV infusion)	in 100 mL sodium chloride 0.9% over 90 minutes (1st dose); if first dose is well tolerated, subsequent doses may be administered over 10 minutes *
Irinotecan	165 mg/m^2 (IV infusion)	in 250 mL to 500 mL glucose 5% over 90 minutes
Oxaliplatin	85 mg/m^2 (IV infusion)	in 250 mL to 500 mL glucose 5% over 2 hours #
Calcium folinate (Leucovorin)	50 mg (IV bolus)	over 1 to 2 minutes **
Fluorouracil	3,200 mg/m^2 (CIV)	via ambulatory infusion pump over 48 hours (equivalent to 1600 mg/m^2/day)
Day 2 and 3		
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food. Note: dexamethasone doses on day 2 and 3 may not be required and may be reduced or omitted at the clinicians discretion. ***

Consideration should be given to limiting oxaliplatin to 6 cycles.[1] If oxaliplatin is continued, oxaliplatin should be limited to 12 cycles. Maintenance therapy may be continued in patients who are stable or responding to treatment.

* It is the consensus of the eviQ reference committee that it is safe to give the initial dose of bevacizumab over 30 minutes.[2] The rapid infusion administration instructions for subsequent doses of bevacizumab are based on studies conducted using Avastin® (bevacizumab). Refer to bevacizumab infusion times for more information.

** The dose of calcium folinate (Leucovorin®) has been modified in this protocol from the original clinical trial dose of 200 mg/m² to 50 mg. A discussion regarding the effect of dosing on outcome can be found in the calcium folinate dose document.

*** Dexamethasone doses on day 2 and 3 may not be required and may be reduced or omitted at the clinicians discretion. Link to Prevention of chemotherapy induced nausea and vomiting.

Frequency: 14 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

- Metastatic colorectal cancer in patients younger than 75 years with WHO performance status of 0 to 1 and/or where a rapid response is the prime goal of therapy (please note that the addition of bevacizumab to chemotherapy was not shown to improve resectability).

Clinical information

Safety alert fluoropyrimidines	Fluoropyrimidines can be administered by different routes and schedules with each method having associated increased risk of certain side effects. Fluoropyrimidine overdose or overexposure is a rare but potentially life threatening side effect of this drug class and can occur by any route of administration. An antidote is available and highly effective if given within 96 hours. Read more about the medication safety alert for infusional fluorouracil and fluoropyrimidine overdose or overexposure
Venous access	Central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with oxaliplatin. Read more about Hypersensitivity reaction
Premedication	Consider atropine 0.3 to 0.6 mg IV or SC prior to irinotecan administration as required to help prevent irinotecan induced cholinergic side effects (atropine should not be used in patients with glaucoma).
Emetogenicity MODERATE	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. A NK1 receptor antagonist and a 5HT3 receptor antagonist in combination with dexamethasone are available on the PBS for primary prophylaxis of oxaliplatin induced nausea and vomiting. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Cardiac toxicity	Cardiac toxicity is a serious complication that can occur during treatment with fluorouracil. Patients treated with fluorouracil, especially those with a prior history of cardiac disease or other risk factors, should be carefully monitored during therapy. Read more about cardiac toxicity associated with anti-cancer drugs
Laryngopharyngeal dysaesthesia associated with oxaliplatin	Sensation of loss of breathing related to oxaliplatin without objective evidence of respiratory distress. Symptoms are often precipitated by exposure to cold. Read more about laryngopharyngeal dysaesthesia associated with oxaliplatin
Diarrhoea (early onset) and cholinergic syndrome	Early onset diarrhoea and other cholinergic symptoms such as rhinitis, hypersalivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping can occur during or within 24 hours of administration of irinotecan. Symptoms may be treated with atropine 0.3 to 0.6 mg IV or SC as needed, repeated up to a maximum dose of 1.2 mg (unless clinically contraindicated). Patients 65 years of age and above should be closely monitored due to a greater risk of early diarrhoea observed in this population. Read more about treatment induced diarrhoea

Diarrhoea (late onset)	Irinotecan induced diarrhoea can be life threatening and requires immediate management. Ensure patients have sufficient antidiarrhoeal (e.g. loperamide) and appropriate instructions should this adverse event occur. Note: If prescribing loperamide, the recommended maximum daily dose of 16 mg of loperamide can be exceeded. Read more about treatment induced diarrhoea
Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency	Rare, life-threatening toxicities such as mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment. Testing for DPD enzyme deficiency is available in Australia but not currently reimbursed. Read more about dihydropyrimidine dehydrogenase (DPD) enzyme deficiency
Severe enteropathy associated with fluoropyrimidine	Severe enteropathy has been reported among patients with stage II/III colon cancer treated with fluoropyrimidine chemotherapy with or without oxaliplatin. Patients treated with fluoropyrimidine should be closely monitored for diarrhoea and aggressively managed. Read more about severe enteropathy associated with fluorouracil in colorectal cancer
Gilbert's syndrome	Patients with Gilbert's syndrome should have their dose of irinotecan reduced. There is no clear dosing strategy; however based on the area under the concentration-time curve of SN-38, Innocenti et al (2006) recommend a 20% dose reduction of irinotecan. Read more about Gilbert's syndrome
Wound healing	Bevacizumab may adversely affect wound healing and should not be initiated in patients with a serious non-healing wound or ulcer. Elective surgery should not be undertaken within 6 weeks from the last dose of bevacizumab. Bevacizumab can be restarted 28 days after surgery provided wound healing is complete. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
Gastrointestinal perforation	Bevacizumab has been associated with serious cases of gastrointestinal (GI) perforation and should be permanently discontinued in patients who develop it.
Haemorrhage	Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis). Bevacizumab should be used with caution in patients at risk of bleeding.
Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing bevacizumab and blood pressure should be monitored during therapy. Commence or adjust antihypertensive medication as clinically indicated.
Proteinuria	Patients may be at increased risk of developing proteinuria when treated with bevacizumab. Baseline urinalysis for proteinuria is recommended prior to commencement of therapy, and as clinically indicated. Routine testing prior to each treatment is no longer recommended, as dose reductions for low/intermediate levels of proteinuria are not recommended. Clinicians are advised to consider evaluating for proteinuria periodically (e.g. every 3 to 4 months) or in patients with clinical concerns (e.g. oedema/unexplained hypoalbuminemia) as treatment interruption may be required if proteinuria is significant (e.g. > 3 g/L). Read more about proteinuria
Reversible posterior leukoencephalopathy syndrome (RPLS)	Bevacizumab should be discontinued in patients who develop reversible posterior leukoencephalopathy syndrome (RPLS). The risk of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)
Thromboembolism	Both arterial and venous thromboembolic events have been observed in patients with this treatment. Therefore, use with caution in patients at increased risk or with a history of thrombotic events (i.e., cerebrovascular and cardiovascular disease)

Peripheral neuropathy	Assess prior to each treatment. If a patient experiences grade 3 or greater, cessation of drug is recommended; review by medical officer before commencing treatment. Read more about peripheral neuropathy Link to chemotherapy-induced peripheral neuropathy screening tool
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
Blood tests	FBC, EUC and LFTs at baseline and prior to each cycle. 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).

The recommendations in this protocol have been based on the trial protocol.[3]

Note:

- All dose reductions are calculated as a percentage of the starting dose.
- The dose of calcium folinate (Leucovorin®) remains fixed at 50 mg and is delayed or omitted if fluorouracil bolus is delayed or omitted.

Haematological toxicity

Haematological toxicity	
ANC x 10^9/L (pre-treatment blood test)	
0.5 to less than 1.0	Delay treatment until recovery and consider adding G-CSF for subsequent cycles
less than 0.5	Delay treatment until recovery and consider adding G-CSF for subsequent cycles If patient is already on G-CSF, reduce irinotecan and oxaliplatin by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider adding G-CSF for subsequent cycles If patient is already on G-CSF, reduce irinotecan and oxaliplatin by 25% for subsequent cycles
Platelets x 10^9/L (pre-treatment blood test)	
75 to less than 100	The general recommendation is to delay, however if the patient is clinically well it may be appropriate to continue treatment; refer to treating team and/or local institutional guidelines
50 to less than 75	Delay treatment until recovery
less than 50	Delay treatment until recovery and reduce irinotecan and oxaliplatin by 25% for subsequent cycles

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	Reduce irinotecan and fluorouracil by 25%
less than 30	Omit oxaliplatin Reduce irinotecan and fluorouracil by 50% or withhold chemotherapy

Hepatic impairment	
Hepatic dysfunction	
Minimal	Reduce irinotecan by 25%
Mild	Reduce irinotecan by 50%
Moderate	Omit irinotecan and reduce fluorouracil by 25% or withhold chemotherapy
Severe	Omit irinotecan and reduce fluorouracil by 50% or withhold chemotherapy
Gilbert's syndrome	Reduce irinotecan by 20%

Peripheral neuropathy	
Grade 2 which is present at the start of the next cycle	Reduce oxaliplatin by 25%; if persistent, reduce oxaliplatin by 50%
Grade 3 or Grade 4	Omit oxaliplatin
Acute laryngo-pharyngeal dysaesthesia	Increase oxaliplatin infusion time to 6 hours

Mucositis and stomatitis	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce fluorouracil by 25% 3rd occurrence: Reduce fluorouracil by 50% 4th occurrence: Withhold chemotherapy
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce fluorouracil by 25%

Mucositis and stomatitis	
	2nd occurrence: Reduce fluorouracil by 50% 3rd occurrence: Withhold chemotherapy
Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce fluorouracil by 50% 2nd occurrence: Withhold chemotherapy

Diarrhoea	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce irinotecan and fluorouracil by 25% 3rd occurrence: Reduce irinotecan and fluorouracil by 50% 4th occurrence: Withhold chemotherapy
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce irinotecan and fluorouracil by 25% 2nd occurrence: Reduce irinotecan and fluorouracil by 50% 3rd occurrence: Withhold chemotherapy
Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce irinotecan and fluorouracil by 50% 2nd occurrence: Withhold chemotherapy

Hand foot syndrome (link to Hand foot syndrome (Palmar-plantar erythrodysaesthesia))	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce fluorouracil by 50% 2nd occurrence: Cease fluorouracil
Grade 3	Cease fluorouracil

Cease bevacizumab if any of the following occur:

- haemorrhagic event grade 3 or greater
- pulmonary embolism, cerebrovascular event or arterial insufficiency
- arterial thromboembolic event
- grade 4 hypertension or persisting grade 3 hypertension
- nephrotic syndrome
- gastrointestinal perforation.

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*

Bevacizumab		
	Interaction	**Clinical management**
Anthracyclines	May enhance the cardiotoxic effect of anthracycline anti-cancer drugs	Monitor for increased cardiotoxicity (e.g. congestive heart failure)
Sunitinib	Microangiopathic haemolytic anaemia	Monitor for haemolytic anaemia, thrombocytopenia, hypertension, elevated creatinine and neurological symptoms
Sorafenib	Increased risk of toxicity, especially hand-foot syndrome	Monitor for increased toxicity
Anti-EGFR monoclonal antibodies (e.g. cetuximab, panitumumab)	Additive toxicity without additional treatment benefit	Avoid combination
Medications known to cause GI perforation (e.g. methylnaltrexone, NSAIDs, steroids)	Additive risk of GI perforation	Avoid combination

Fluorouracil		
	Interaction	**Clinical management**
Folic acid	Increased toxicity of fluorouracil due to stabilisation of its bond to thymidylate synthetase (folic acid is a precursor of folinic acid/leucovorin)	Advise patients not to take folic acid supplements (inc. multivitamins) around the time of receiving treatment with fluorouracil
Metronidazole, tinidazole	Increased toxicity of fluorouracil due to reduced clearance	Avoid combination or monitor for fluorouracil toxicity
Warfarin and other drugs metabolised by CYP2C9 (e.g. warfarin, phenytoin etc.)	Increased effect/toxicity of these drugs due to inhibition of CYP2C9 by fluorouracil resulting in reduced clearance	Avoid combination or monitor for increased effect/toxicity of these drugs (e.g. for bleeding/elevated INR with warfarin, elevated phenytoin serum levels or signs of toxicity such as ataxia, tremor etc.)
Allopurinol	Reduced efficacy of fluorouracil possible due to reduced conversion to the active metabolites	Avoid combination or monitor for reduced fluorouracil efficacy

Irinotecan		
	Interaction	**Clinical management**
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin, grapefruit juice etc.)	Increased toxicity of irinotecan possible due to reduced clearance	Avoid combination or monitor for irinotecan toxicity (Ketoconazole contraindicated and should be discontinued at least 1 week prior to irinotecan)
CYP3A4 and P-gp inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort, dexamethasone etc.)	Reduced efficacy of irinotecan possible due to increased clearance	Avoid combination or monitor for decreased clinical response to irinotecan (St John's wort contraindicated; substituting non-enzyme inducing antiepileptics (e.g. clonazepam, diazepam, lorazepam) at least 1 week prior to irinotecan should be considered)
Atazanavir	Increased toxicity of irinotecan possible due to reduced clearance caused by inhibition of both CYP3A4 and UGT1A1 by atazanavir	Avoid combination or monitor for irinotecan toxicity
Smoking	Reduced efficacy of irinotecan possible due to increased clearance caused by induction of both CYP3A4 and UGT1A1 by smoking	Monitor for decreased clinical response to irinotecan in patients who continue to smoke; no specific dosing recommendations are available

Oxaliplatin		
	Interaction	**Clinical management**
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Neurotoxic drugs (e.g. vincristine, paclitaxel)	Additive neurotoxicity	Monitor closely for neuropathy if combination used

NK-1 antagonist e.g. aprepitant, fosaprepitant, netupitant		
	Interaction	**Clinical management**
Dexamethasone	Increased effects/toxicity of dexamethasone due to inhibition of its metabolism via CYP3A4	Reduce dose of **antiemetic dexamethasone** by approximately 50% when adding a NK-1 antagonist. For protocols that already recommend a NK-1 antagonist, the dose reduction of **antiemetic dexamethasone** has already been taken into account. If **dexamethasone is part of the chemotherapy protocol**, dose reduction as per the product information is not routinely recommended in clinical practice and no additional dexamethasone is required for antiemetic cover.
Warfarin	Reduced anticoagulant efficacy of warfarin due to increased clearance (aprepitant induces CYP2C9). *Note interaction only applicable to aprepitant/ fosaprepitant	INR should be monitored in the 2 week period, particularly at 7 to 10 days following the administration of aprepitant/ fosaprepitant
Combined oral contraceptive	Reduced contraceptive efficacy due to increased clearance. *Note interaction only applicable to aprepitant/ fosaprepitant	Alternative non-hormonal methods should be used during and for 1 month after stopping aprepitant/ fosaprepitant
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of NK-1 antagonist possible due to increased clearance	Avoid combination or monitor for decreased antiemetic effect. Consider using an alternative antiemetic regimen
CYP3A4 inhibitors (e.g. azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of NK-1 antagonist possible due to reduced clearance	Avoid combination or monitor for increased adverse effects of NK-1 antagonist (e.g. headache, hiccups, constipation)
Drugs metabolised by CYP3A4 (e.g. etoposide, imatinib, irinotecan, midazolam, paclitaxel, vinblastine, vincristine etc.)	Increased effects/toxicity of these drugs possible due to inhibition of CYP3A4 by NK-1 antagonist	Avoid combination or monitor for increased toxicity especially with orally administered drugs

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.

Day 1

Approximate treatment time: 6 hours (initial); 5 hours (subsequent)

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

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

Prime IV line(s).

Access TIVAD or CVAD.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Verify dexamethasone taken or administer as prescribed.

Treatment - Time out

Bevacizumab

- Bevacizumab is only compatible with sodium chloride 0.9%, ensure IV lines are flushed with sodium chloride 0.9% pre and post administration.

Prior to administration check:

- blood pressure
- baseline urinalysis for protein and repeat as clinically indicated (link to proteinuria).

Administer bevacizumab:

- via IV infusion
- first dose over 90 minutes
  - the product information recommends giving the first dose over 90 minutes, it is the consensus of the eviQ reference committee that it is safe to give the initial dose of bevacizumab over 30 minutes[2]
- if well tolerated:
  - subsequent doses over 10 minutes (read more about the bevacizumab infusion times)
- observe for hypersensitivity reaction
- flush with ~ 50 mL of sodium chloride 0.9%.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate
- for severe reactions seek medical assistance immediately and do not restart infusion.

Chemotherapy - Time out

Irinotecan

Prior to administration:

- administer atropine premedication if required
- patient vital signs should be closely monitored post atropine administration as atropine can cause tachycardia, heart arrhythmias, hypertension and angina.

Administer irinotecan (irritant):

- via IV infusion over 90 minutes
- protect from light
- flush with ~ 100 mL of sodium chloride 0.9%
- observe patient for cholinergic symptoms
- if patient develops early onset diarrhoea and other cholinergic symptoms (such as rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing) - stop infusion, monitor vital signs and review by medical officer.

Oxaliplatin

- Oxaliplatin is only compatible with glucose 5%, ensure IV lines are flushed with glucose 5% pre and post administration.

Administer oxaliplatin (irritant with vesicant properties):

- via IV infusion over 2 hours
- risk of laryngopharyngeal dysaesthesia
  - patients should not drink cold fluids
- monitor for signs of hypersensitivity
- flush with ~ 100 mL glucose 5%
- if patient has laryngopharyngeal dysaesthesia or a hypersensitivity reaction - stop infusion and obtain medical officer review. If rechallenge indicated, premedicate patient and administer oxaliplatin at a slower rate (up to 6 hours).

Calcium Folinate (Leucovorin)

- administer by IV bolus via a side port of the IV line over 1 to 2 minutes
- flush with ~ 50mL of sodium chloride 0.9%.

Fluorouracil continuous infusion (irritant)

Connect pump containing fluorouracil and administer over the correct time for the amount of drug in the pump:

- ⚠ safety alert issued for administration of infusional fluorouracil
- verify the correct rate of infusion via the ambulatory infusion pump
- read more information about the different ambulatory infusion pumps.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 3

Approximate treatment time: 30 minutes

Safe handling and waste management

Disconnection of ambulatory infusion pump/infusor

Verify the ambulatory infusion pump/infusor is complete.

Disconnect the ambulatory infusion pump/infusor as per recommended procedure for type of pump/infusor.

Read more about ambulatory infusion pumps/infusors.

Deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Antiemetics

- Antiemetics as prescribed.

Antidiarrhoeals

- Antidiarrhoeals (e.g. loperamide) as prescribed with written instructions on how to manage this side effect and 24 hour emergency contact.

Patient information

- Ensure patient receives patient information sheet.

Infusion pumps

- CADD-Legacy® 1 ambulatory infusion pump patient information sheet.
- CADD-Legacy® Plus ambulatory infusion pump patient information sheet.
- CADD® Solis VIP ambulatory infusion pump patient information sheet.
- Elastomeric infusion system 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)	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Laryngopharyngeal dysaesthesia	The sensation of difficulty breathing or an inability to swallow. This is associated with oxaliplatin and can occur during, and for up to 48 hours after treatment. Read more about laryngopharyngeal dysaesthesia
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Diarrhoea and cholinergic syndrome (early onset) associated with irinotecan	Cholinergic syndrome can occur during or shortly after commencing the irinotecan infusion, or within 24 hours of administration of the drug. It is characterised by diarrhoea, rhinitis, hypersalivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. Read more about treatment induced diarrhoea
Taste and smell alteration	Read more about taste and smell changes
Cardiotoxicity	Coronary artery spasm is a temporary, sudden narrowing of one of the coronary arteries that may present at any time during treatment with fluoropyrimidines. It most commonly manifests as angina.

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Diarrhoea (late onset) associated with irinotecan	Late onset of diarrhoea after 24 hours post irinotecan administration can be life threatening and requires immediate treatment. Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
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
Actinic keratoses flare	Pre-existing actinic keratoses (AKs) can become more inflamed and scaly as a result of immunosuppression. Read more about actinic keratoses flare
Ocular changes	Symptoms may include eye pain, blurred vision, blepharitis, uveitis, optic neuritis, tear duct stenosis, conjunctivitis, hyperlacrimation, watery or dry eyes and photophobia.

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
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
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
Peripheral neuropathy	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about peripheral neuropathy
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.
Thromboembolism	Arterial and venous thromboembolic events, including pulmonary embolism, deep vein thrombosis and cerebrovascular accidents can occur. Patients should be carefully assessed for risk factors, and consideration given for antithrombotic prophylaxis in high risk patients.
Epistaxis	Acute bleeding from the nostril(s), nasal cavity, or nasopharynx.
Proteinuria	Read more about proteinuria
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.
Reversible posterior leukoencephalopathy syndrome (RPLS)	A neurological disorder which may present with headache, seizures, lethargy, confusion, blindness and/or other visual and neurological disturbances. Mild to severe hypertension may also occur. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)
Haemorrhage	

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Alopecia - partial	Hair thinning and/or patchy hair loss. 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
Hyperpigmentation	Darkening of an area of skin caused by the overproduction of melanin.
Nail changes	Hyperpigmentation, paronychia, onycholysis, splinter haemorrhage, pyogenic granuloma formation, subungal haematoma and subungal hyperkeratosis are some of the nail changes associated with anti-cancer drugs. Read more about nail toxicities
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs

Evidence

Due to the lack of conclusive evidence to identify the optimum dose of calcium folinate (Leucovorin®), it is the consensus of the eviQ reference committee to adopt flat dosing of calcium folinate (Leucovorin®) as a 50 mg IV bolus when used with bolus 5FU across all colorectal and upper gastrointestinal protocols. A discussion regarding the effect of dosing on outcome can be found in

the calcium folinate (Leucovorin®) dose document.

The evidence supporting this protocol is provided by a phase III, randomised, open-label, multicenter trial (TRIBE) involving 508 patients comparing FOLFIRI plus bevacizumab with FOLFOXIRI plus bevacizumab in patients with untreated metastatic colorectal cancer.[3]

Between July 2008 and May 2011, 256 patients were randomised to receive FOLFIRI plus bevacizumab (bevacizumab 5 mg/kg, irinotecan 180 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400 mg/m^2 bolus followed by 2400 mg/m^2 continuous infusion over 46 hours. Cycles were repeated every 14 days up to 12 cycles) and 252 patients were randomised to receive FOLFOXIRI plus bevacizumab (bevacizumab 5 mg/kg, irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 3200 mg/m^2 continuous infusion over 48 hours. Cycles were repeated every 14 days up to 12 cycles).[3] Maintenance treatment with fluorouracil plus bevacizumab was then continued until disease progression in both arms.

There was a significantly higher proportion of right-sided tumours in the experimental group compared to the control group; all other characteristics were balanced. KRAS and BRAF mutation status was known in 80% of enrolled patients: 39.4% had KRAS mutations, 5.5% had BRAF mutations.

The primary end point was progression-free survival and secondary end points were response rate, overall survival rate, resection rate of metastases, and rate of adverse events.[3]

Efficacy

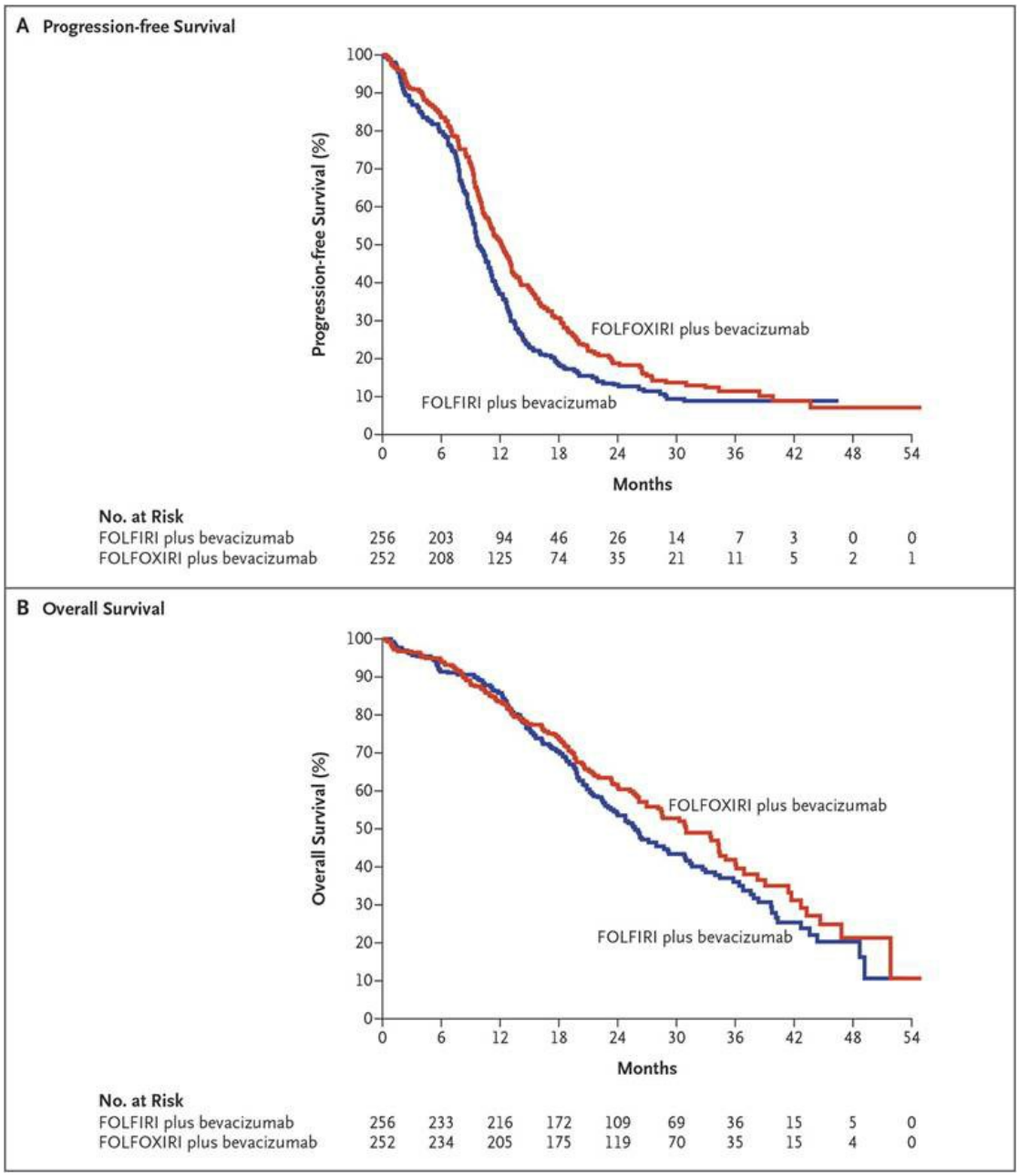
After a median follow up of 32.2 months, the median progression-free survival was 12.1 months for the FOLFOXIRI plus bevacizumab group and 9.7 months for the FOLFIRI plus bevacizumab group (HR=0.75; CI 95% 0.62 to 0.90 ; p=0.003).[3] This PFS benefit was maintained across all subgroups, including both mutant and wild-type KRAS and BRAF, except in those patients who had received prior adjuvant chemotherapy where there was an association with worse PFS on FOLFOXIRI plus bevacizumab compared to FOLFIRI plus bevacizumab (p=0.04).

The objective response rate was 65% in the FOLFOXIRI plus bevacizumab group and 53% in the FOLFIRI plus bevacizumab group (Odds Ratio=1.64; 95% CI 1.15 to 2.35; p= 0.006). Overall survival was longer, but not significantly in the FOLFOXIRI plus bevacizumab group (31.0 vs. 25.8 months; hazard ratio for death=0.79; 95% CI, 0.63 to 1.00; p = 0.054).[3] The rate of R0 resection of metastases was not significantly different between the groups (12% vs. 15%; p=0.33).

Updated but yet unpublished data with a median follow up of 48.1 months confirms the continued PFS advantage (12.3 vs. 9.7 months; HR = 0.77; p=0.006), as well as a significant OS advantage with FOLFOXIRI plus bevacizumab compared to FOLFIRI plus bevacizumab (29.8 vs. 25.8 months, HR = 0.80; p=0.03).[4]

No quality of life data was collected in this trial.

Kaplan-Meier Estimates (A) Progression-free Survival (B) Overall Survival[3]



Toxicity

The incidence of grade 3 or 4 neutropenia, diarrhoea, stomatitis, and neurotoxicity (i.e., peripheral neuropathy) was significantly higher in the FOLFOXIRI plus bevacizumab group than in the FOLFIRI plus bevacizumab group. The rates of serious adverse events were similar in the two groups (19.7% vs. 20.4%; p=0.91); four patients in the control group and 6 patients in the experimental group died as a result of adverse events.[3] There were no significant differences observed in the rates of bevacizumab related toxicity.

Most Common Adverse Events[3] (Grade 3 or 4)	FOLFIRI plus Bevacizumab (n=254) %	FOLFOXIRI plus Bevacizumab (n=250) %	*p*-value
Neutropenia	20.5	50.0	<0.001
Febrile neutropenia	6.3	8.8	0.32
Diarrhoea	10.6	18.8	0.01
Stomatitis	4.3	8.8	0.048
Nausea	3.2	2.8	1.00
Vomiting	3.2	4.4	0.49

Most Common Adverse Events[3] (Grade 3 or 4)	FOLFIRI plus Bevacizumab (n=254) %	FOLFOXIRI plus Bevacizumab (n=250) %	*p*-value
Asthenia	9.1	12.0	0.31
Peripheral neuropathy	0	5.2	<0.001
Hypertension	2.4	5.2	0.11
Venous thromboembolism	5.9	7.2	0.59
Serious adverse events	19.7	20.4	0.91

References

1 Tournigand, C., A. Cervantes, A. Figer, et al. 2006. "OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study." J Clin Oncol. 24(3):394-400.

2 Reidy, D. L., K. Y. Chung, J. P. Timoney, et al. 2007. "Bevacizumab 5 mg/kg can be infused safely over 10 minutes." J Clin Oncol. 25(19):2691-2695.

3 Loupakis, F., C. Cremolini, G. Masi, et al. 2014. "Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer." N Engl J Med 371(17):1609-1618.

4 Cremolini C., F. Loupakis, G. Masi, et al. 2015. " FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (mCRC): Updated survival results of the phase III TRIBE trial by the GONO group." ASCO GI Meeting Abstract. J Clin Oncol 33 (suppl 3; abstr 657)

History

Version 8

Date	Summary of changes
20/10/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. Indications section updated. Version increased to V.8. Next review 2 years.
21/10/2022	Bevacizumab treatment schedule note updated based on reference committee consensus to add that it is safe to give the initial dose of bevacizumab over 30 minutes.

Version 7

Date	Summary of changes
16/11/2021	Pulmonary toxicity added to side effects. Version number changed to V.7.

Version 6

Date	Summary of changes
28/05/2021	Protocol flag added regarding bevacizumab biosimilar and administration time information. Treatment schedule- bevacizumab rapid infusion information added. Drug status - updated to include bevacizumab on PBS general schedule. Patient information- bevacizumab infusion time information updated in 'your treatment' section. Version increased to V.6
27/07/2021	Protocol title updated to "Colorectal metastatic FOLFOXIRI (modified) (fluorouracil leucovorin oxaliplatin irinotecan) and bevaciizumab".

Version 5

Date	Summary of changes
16/12/2020	Treatment schedule note added regarding number of oxaliplatin cycles as per Medical Oncology Reference Committee consensus. Version number increased to V.5. Next review in 2 years.

Version 4

Date	Summary of changes
04/09/2020	Biosimilar drug added to clinical information. Version number changed to V.4.
25/09/2020	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review in 2 years.

Version 3

Date	Summary of changes
27/03/2015	New protocol taken to Medical Oncology Reference Committee meeting.
24/04/2015	Approved and published on eviQ.
15/07/2016	Reviewed by Medical Oncology Reference Committee via email. No changes. Next review in 2 years.
16/10/2016	Patient information sheet updated to include more fluorouracil toxicity symptom warnings.
09/11/2016	The following changes made post Medical Oncology Reference Committee meeting held on 21 October 2016: information in pre-clin, administration and side effect regarding bevacizumab and monitoring for proteinuria changed and recommendations removed from dose modifications. Link to AGTIG and ANZCTR added. Sentence in dose modifications regarding omitting leucovorin if fluorouracil is delayed or omitted changed to specify fluorouracil bolus.
31/05/2017	Transferred to new eviQ website. Version number changed to V.2. Antiemetic change: A NK1 receptor antagonist and a $5HT_3$ receptor antagonist in combination with dexamethasone has been added as available on the PBS for primary prophylaxis of oxaliplatin induced nausea and vomiting. Hepatitis screening changed to not required.
16/02/2018	Protocol reviewed electronically by Medical Oncology Reference Committee. Fluoropyrimidine warning added. Review in 2 years.
10/05/2018	Haematological dose modifications updated as per consensus of the expert clinician group. Fluoropyrimidine safety alert and DPD enzyme deficiency wording in clinical information updated. Version number changed to V.3.
22/06/2018	Antiemetics updated to be in line with international guidelines. Note to dexamethasone added.
25/09/2018	Treatment schedule note and evidence section updated with Leucovorin® dosing information as per reference committee consensus.
10/06/2020	Administration treatment time updated to 6 hours (initial), 5 hours (subsequent). Patient information treatment time updated.

First approved: 24 April 2015
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/1715
16 Jul 2023

Patient information - Bowel cancer metastatic - FOLFOXIRI modified (fluorouracil, leucovorin, oxaliplatin, irinotecan) and bevacizumab

Patient's name:

Your treatment

The treatment schedule below explains how the drugs for this treatment are given.

FOLFOXIRI modified (fluorouracil, leucovorin, oxaliplatin, irinotecan) and bevacizumab			
This treatment cycle is repeated every 14 days. Your doctor will advise you of the number of treatments you will have.			
Day	**Treatment**	**How it is given**	**How long it takes**
1	**Bevacizumab** (*be-vuh-SIZ-uh-mab*) **Irinotecan** (*eye-ri-noe-TEE-kan*) **Oxaliplatin** (*ox-AL-ih-pla-tin*) **Calcium folinate (Leucovorin)** *(loo-koe-VOR-in)* **Fluorouracil** *(Flure-oh-YOOR-a-sill)*	By a drip into a vein	About 6 hours for the first treatment. If no reactions, subsequent treatment may be given over a shorter amount of time
	Fluorouracil *(Flure-oh-YOOR-a-sill)*	By a pump slowly into a vein	For 2 days (46 hours) by pump at home
3	**Disconnect pump**		About 30 minutes

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 • leaking from your pump • you become unwell.	Daytime:..... Night/weekend:..... Other instructions:.....

During your treatment immediately tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

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.

Pumps and central venous access devices (CVADs)

This treatment involves having chemotherapy through a pump. To have this, you will also need a central venous access device (CVAD). Your doctor or nurse will explain this to you. For more information see the eviQ patient information sheets on pumps and CVADs. At home you will need to look at your pump 3 to 4 times a day to check it is working. Your nurse will teach you how to do this.

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.

Treatment with oxaliplatin

You should avoid cold drinks, cold food and ice on the day of and for up to 2 days after treatment with oxaliplatin. If you have cold food or drinks you may get discomfort or tightness in the back of the throat, or the feeling like you cannot breathe or swallow.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Antidiarrhoeals:** you will be given some medication called loperamide to treat the diarrhoea. See the *Side effects* section below for further information about diarrhoea and for instructions on how and when to take the loperamide.

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)

Allergic reaction	• Allergic reactions are uncommon but can be life threatening.
	• **If you feel unwell during the infusion or shortly after it, or:**
	  ◦ **get a fever, shivers or shakes**
	  ◦ **feel dizzy, faint, confused or anxious**
	  ◦ **start wheezing or have difficulty breathing**
	  ◦ **have a rash, itch or redness of the face**
	
	While you are in hospital: Tell your doctor or nurse immediately.
	After you leave: Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.

Breathing or swallowing problems	• You may get discomfort or tightness in the back of the throat, or the feeling like you cannot breathe or swallow. • This can happen during an infusion of oxaliplatin, and for up to 48 hours after. • These symptoms are temporary. • They can be distressing but they are not usually harmful and will disappear. • If symptoms develop, cup your hands over your mouth and breathe normally. The warm air will help relieve the feeling. • Avoid cold temperature, cold drinks and ice cubes before having oxaliplatin and for 2 days after, as this can increase the risk. • **Tell your doctor or nurse as soon as possible if your symptoms don't go away.**
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.**

Diarrhoea (early onset)	• You may get bowel motions (stools, poo) that are more frequent or more liquid (diarrhoea).
	• You may also get:
	  ◦ bloating, cramping or pain
	  ◦ increased saliva, a runny nose or watery eyes
	  ◦ sweating or flushing.
	• These symptoms are caused by the drug irinotecan. They can occur during or shortly after the drug has been given.
	• **Tell your doctor or nurse immediately if you develop any of these symptoms.**

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.

Heart problems	• You may get:
	  ◦ chest pain or tightness
	  ◦ shortness of breath
	  ◦ an abnormal heartbeat
	• Tell your doctor if you have a history of heart problems or high blood pressure.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**

Early (onset days to weeks)	
Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**
Low platelets (thrombocytopenia)	• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising. • Try not to bruise or cut yourself. • Avoid contact sport or vigorous exercise. • Clear your nose by blowing gently. • Avoid constipation. • Brush your teeth with a soft toothbrush. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if you have any bruising or bleeding. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.**
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.

Diarrhoea (late onset)	• You may get bowel motions (stools, poo) that are more frequent or more liquid (diarrhoea). • You may also get bloating, cramping or pain. • These symptoms are caused by the drug irinotecan. This can become very serious and life threatening if not treated quickly and properly. • Take your antidiarrhoea medication, loperamide, as prescribed: When the diarrhoea starts, take 4 mg (this is 2 tablets/capsules), then take one tablet/capsule (2 mg) every 2 hours during the day and 2 tablets/capsules (4 mg) every 4 hours at night while you still have diarrhoea and until the diarrhoea has stopped for 12 hours. You should not take loperamide at these doses for more than 48 hours. • 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 if you get any of the symptoms listed above.** • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have diarrhoea for more than 24 hours, any blood in your bowel motions, or a temperature of 38°C or higher.**
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.**
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.**
Skin changes	• Your skin may become dry, and you may notice changes to areas of your skin that have been exposed to the sun. • Keep your skin moisturised with a cream such as sorbolene or aqueous cream. • Avoid direct sunlight. • Protect your skin from the sun by wearing a wide-brimmed hat, sun-protective clothing, sunglasses and sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you notice any skin changes.**

Eye problems	• You may get:
	  ◦ eye pain
	  ◦ red, sore or swollen eyes
	  ◦ blurred vision
	  ◦ watery or gritty eyes
	  ◦ changes in your eyesight
	  ◦ sensitivity to sunlight.
	• Protect your eyes from the weather (sun and wind) by wearing sunglasses, especially if you have lost your eyelashes.
	• **Tell your doctor or nurse if you get any of the symptoms listed above. Eye drops may help with your symptoms.**

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.**

Skin that is more sensitive to the sun (photosensitivity)	• After being out in the sun you may develop a rash like a bad sunburn. • Your skin may become red, swollen and blistered. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
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.**

Nerve damage (peripheral neuropathy)	• You may notice a change in the sensations in your hands and feet, including:
	  ◦ tingling or pins and needles
	  ◦ numbness or loss of feeling
	  ◦ pain.
	• You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects.
	• Test water temperature with your elbow when bathing to avoid burns.
	• Use rubber gloves, pot holders and oven mitts in the kitchen.
	• Wear rubber shoes or boots when working in the garden or garage.
	• Keep rooms well lit and uncluttered.
	• Ask your doctor or nurse for eviQ patient information – Nerve problems during cancer treatment.
	• Tell your doctor or nurse if you get any of the symptoms listed above.

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.**
Blood clots (thromboembolism)	• Blood clots can occur with this treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **redness, heat or pain in your leg(s)** ◦ **numbness or weakness in your face, arm or leg** ◦ **chest pain** ◦ **sudden shortness of breath** ◦ **dizziness** ◦ **trouble speaking** ◦ **blurred vision** ◦ **severe headache** ◦ **unexplained falls or loss of balance.**
Nose bleeds	• If your nose starts to bleed gently apply pressure on the soft part of nostrils below the bridge of the nose for at least 10 minutes. • It may help to put a cold pack over your forehead or the bridge of the nose. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if your nose will not stop bleeding.**
Kidney changes or damage	• This treatment may cause changes to how your kidneys work. This may cause protein in your urine. • This is not something that you will notice. • You will have blood and urine tests to check that your kidneys are working properly.
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.**
Changes in the way your brain works [reversible posterior leukoencephalopathy syndrome (RPLS)]	• This treatment can have an effect on your brain, but this is rare. • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **headaches or vision problems** ◦ **nausea and vomiting** ◦ **tiredness** ◦ **confusion** ◦ **fits (seizures)** ◦ **high blood pressure.**

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.**

Late (onset weeks to months)	
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Hair thinning	• Your hair may become dry and may break easily. • You may lose some of your hair. • Use a gentle shampoo and a soft hairbrush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat or scarf. • Protect your scalp from the sun with a hat and sunscreen of SPF 50 or higher. • Ask your doctor or nurse about the Look Good Feel Better program (www.lgfb.org.au)
Skin colour changes	• You may have darkening of your skin, especially in areas that are exposed to the sun. • You may also notice darkening of your tongue, gums and over your finger joints. • These skin changes may fade over time. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher.
Nail changes	• Your nails may: ◦ grow more slowly ◦ become darker ◦ develop ridges or white lines ◦ become brittle and flaky • In some cases, you may lose your nails completely. • Keep your nails clean and short. • Avoid things like biting your fingernails, getting a manicure, pedicure or false nails. • Wear gloves when you wash the dishes, work in the garden, or clean the house.
Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment. • You may get: ◦ shortness of breath ◦ fever ◦ dry cough ◦ wheezing ◦ fast heartbeat ◦ chest pain. • Your doctor will monitor how well your lungs are working during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**

General advice for people having cancer treatment

Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - Chemotherapy safety at home.

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 on 13 11 20 for cancer information and support

Bowel cancer information

- Australian Council of Stoma Associations – australianstoma.com.au
- Australian Government Bladder and Bowel – bladderbowel.gov.au
- Australian Government Department of Health & Ageing Stoma appliance scheme – health.gov.au/internet/main/publishing.nsf/Content/Stoma+Appliance+Scheme-1
- Bowel Cancer Australia – bowelcanceraustralia.org
- National Public Toilet map – toiletmap.gov.au
- Recovering after Pelvic Radiation Therapy: A guide for women – https://www.targetingcancer.com.au/useful-resources/recovering-after-pelvic-radiation-therapy-a-guide-for-women/

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

Additional notes:

First approved: 24 April 2015
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/pi/1715
13 Jul 2023