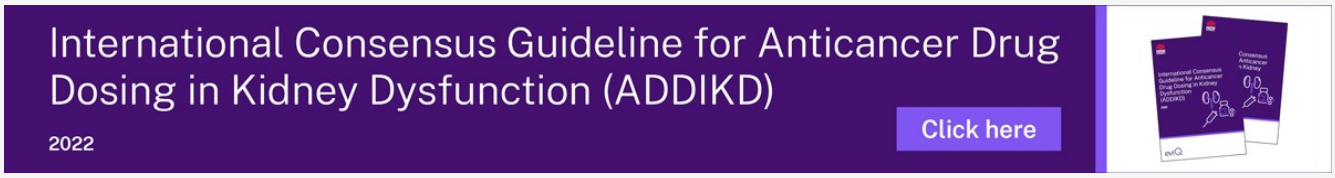
Metastatic trifluridine/tipiracil

ID: 3806 v.1 **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.



Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
Trifluridine/tipiracil	35 mg/m^2 TWICE a day * (Cap dose at 80 mg)	PO	1 to 5 and 8 to 12

* The dose expressed is based on the trifluridine component. For information on number of tablets for starting dose of 35 mg/m² see trifluridine/tipiracil dosing table .

Note: In heavily pre-treated patients consideration may be given to starting at a lower dose due to concerns about myelosuppression in addition to usual fluoropyrimidine toxicities.

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:
Trifluridine/tipiracil consists of a thymidine-based nucleoside analog (trifluridine), and thymidine phosphorylase inhibitor (tipiracil). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Drug status: Trifluridine/tipiracil is PBS authority

Trifluridine/tipiracil is available as **15 mg** and **20 mg** tablets

Cost: ~ $3,160 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 5 and 8 to 12		
Trifluridine/tipiracil	35 mg/m^2 (PO) (Cap dose at 80 mg)	TWICE a day within one hour after completion of a meal

- The dose expressed is based on the trifluridine component. For information on number of tablets for starting dose of 35 mg/m² see trifluridine/tipiracil dosing table .
- In heavily pre-treated patients consideration may be given to starting at a lower dose due to concerns about myelosuppression in addition to usual fluoropyrimidine toxicities.

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population - Colorectal

Indications:

- Metastatic colorectal cancer (CRC) in patients who have been previously treated with, or not considered a candidate for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, and, if RAS wild-type, anti-EGFR therapy.
  - ECOG performance status 0 to 1 only.

Cautions:

- Patients older than 75 years of age.

Indications and patient population - Gastric and gastroesophageal

Indications:

- Metastatic gastric or gastroesophageal junction adenocarcinoma in patients who have been previously treated with two or more lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane- or irinotecan-based treatment.
  - ECOG performance status 0 to 1 only.

Cautions:

- Patients older than 75 years of age.

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
Oral mucositis	Oral mucositis is a common side effect with this treatment and 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
Blood tests	FBC, EUC, LFTs at baseline and prior to each cycle. For cycle 1, consider clinical review and FBC on day 15 and then 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:

- a maximum of 3 dose reductions are permitted to a minimum of 20 mg/m^2 twice daily, or a minimum of 15 mg/m^2 in severe renal impairment.
- do not escalate trifluridine/tipiracil dose after it has been reduced.
- the following dose modification recommendations have been adapted from the product information, study by Mayer et al[1], review by Price et al[2] and by consensus of the reference committee.

Haematological toxicity	
ANC x 10^9/L (pre-treatment blood test)	
1.0 to less than 1.5	Refer to local institutional guidelines; it is the view of the expert clinicians that treatment

Haematological toxicity	
	should continue if patient is clinically well
less than 1.0	Delay treatment until neutrophils are greater than or equal to 1.0 Reduce trifluridine/tipiracil by 5 mg/m^2 for subsequent cycles
Febrile neutropenia	Delay treatment until neutrophils are greater than or equal to 1.0 Reduce trifluridine/tipiracil by 5 mg/m^2 for subsequent cycles
Platelets x 10^9/L (pre-treatment blood test)	
50 to less than 75	Delay treatment until platelets are greater than or equal to 75
less than 50	Delay treatment until platelets are greater than or equal to 75 Reduce trifluridine/tipiracil by 5 mg/m^2 for subsequent cycles

Renal impairment	
Creatinine clearance (mL/min)	
30 to 59	Limited data. Higher incidence of ≥ Grade 3 and serious toxicity, dose delays and reductions than with mild renal impairment. Use with caution and consider dose adjustment.
15 to 29	Reduce starting dose to 20 mg/m^2 twice daily. One dose reduction to a minimum of 15 mg/m^2 twice a day is permitted based on individual safety and tolerability.
less than 15	Trifluridine/tipiracil is not recommended as it has not been studied in patients with end-stage renal disease.

Hepatic impairment	
Hepatic dysfunction:	
Mild	No dose reductions necessary
Moderate	Limited data. Trifluridine/tipiracil is not recommended due to higher incidence of Grade 3/4 hyperbilirubinaemia in patients with moderate hepatic impairment.
Severe	Trifluridine/tipiracil is not recommended as it has not been studied in patients with severe hepatic impairment

Mucositis and stomatitis	
Grade 2	No dose modifications necessary
Grade 3 or 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 trifluridine/tipiracil by 5 mg/m^2 2nd occurrence: Reduce trifluridine/tipiracil by further 5 mg/m^2 3rd occurrence: Reduce trifluridine/tipiracil by further 5 mg/m^2 4th occurrence: Discontinue treatment

Diarrhoea	
Grade 2	No dose modifications necessary
Grade 3 or 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 trifluridine/tipiracil by 5 mg/m^2 2nd occurrence: Reduce trifluridine/tipiracil by further 5 mg/m^2 3rd occurrence: Reduce trifluridine/tipiracil by further 5 mg/m^2 4th occurrence: Discontinue treatment

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*

Trifluridine/tipiracil		
	Interaction	**Clinical management**
Trifluridine and tipiracil are not metabolised by cytochrome P450 enzymes. No formal pharmacokinetic drug interaction studies have been conducted with trifluridine/tipiracil.		
Human thymidine kinase substrate antivirals (e.g. stavudine, zidovudine, telbivudine etc.)	Reduced efficacy of the antiviral agent possible due to competition with trifluridine for activation via thymidine kinases.	Avoid combination or monitor for possible decreased efficacy of antiviral agent. Consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate (e.g. lamivudine, zalcitabine, didanosine, abacavir).

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.	The safety of having vaccinations whilst on this treatment is unknown and is therefore not recommended.

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 5 and 8 to 12

This is an oral treatment

Safe handling and waste management

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.

Pre treatment medication

Administer antiemetics if required

Chemotherapy - Time out

Trifluridine/tipiracil

- administer orally TWICE a day **on days 1 to 5 and 8 to 12**
- to be swallowed whole with a glass of water; do not break, crush or chew
- to be taken within one hour after the end of a meal

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

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

Discharge information

Trifluridine/tipiracil tablets

- Trifluridine/tipiracil tablets with written instructions on how to take them

Antiemetics

- Antiemetics as prescribed.

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

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
Abdominal pain	Dull ache, cramping or sharp pains are common with some anti-cancer drugs. These are caused by either increased or decreased gastrointestinal motility and can be associated with diarrhoea or constipation.
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Diarrhoea	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

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Hyperbilirubinaemia	An abnormal increase in the amount of bilirubin circulating in the blood which may result in jaundice.

Evidence - Colorectal

The evidence supporting this protocol is provided by a phase III, multicentre, international, double-blind, randomised trial (RECOURSE) involving 800 patients comparing TAS-102 (trifluridine/tipiracil) with placebo in patients with refractory stage IV colorectal cancer who have received prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and EGFR targeted therapy. 17-20% of patients in the trial had been previously treated with regorafenib.[1]

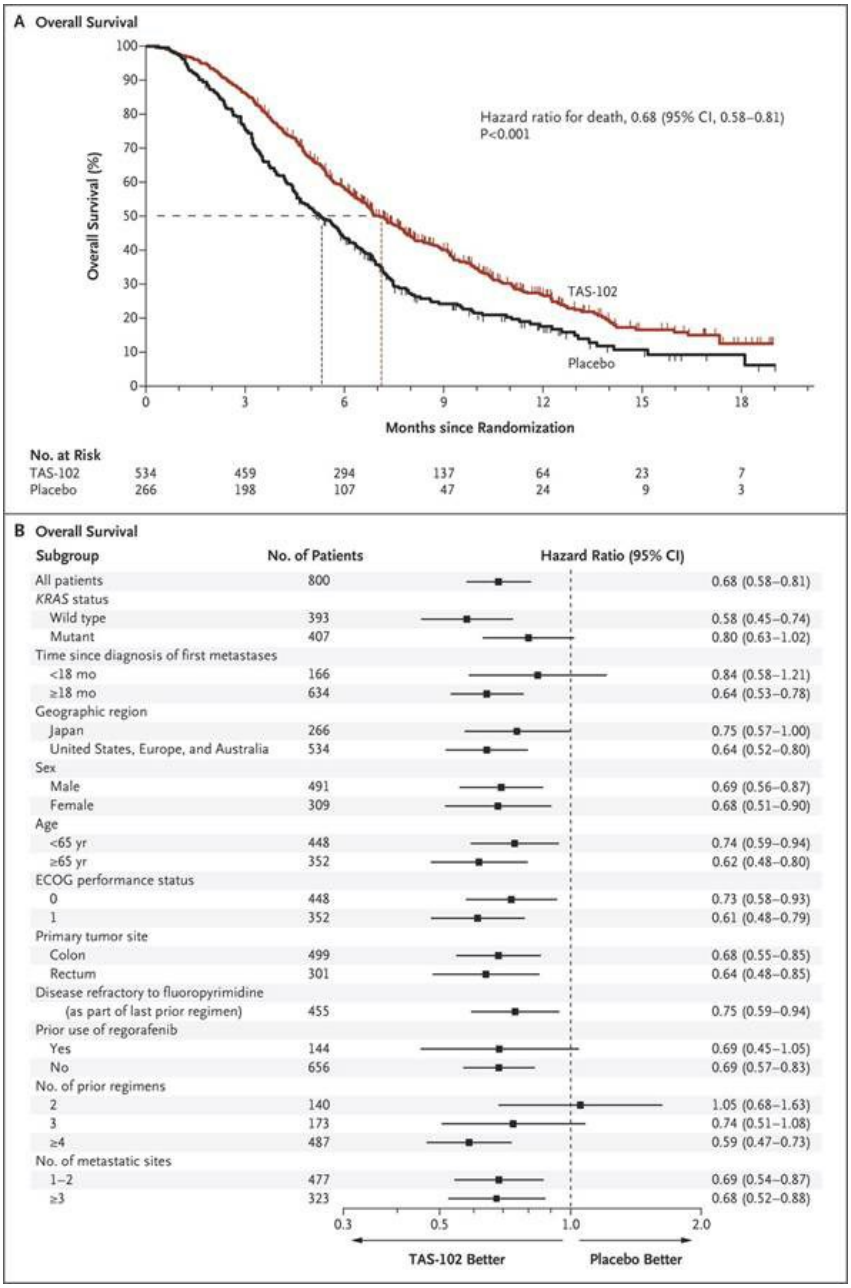
Between June 2012 and October 2013, 800 patients were randomised 2:1 to receive either TAS-102 at 35 mg/m^2 orally twice daily or placebo.

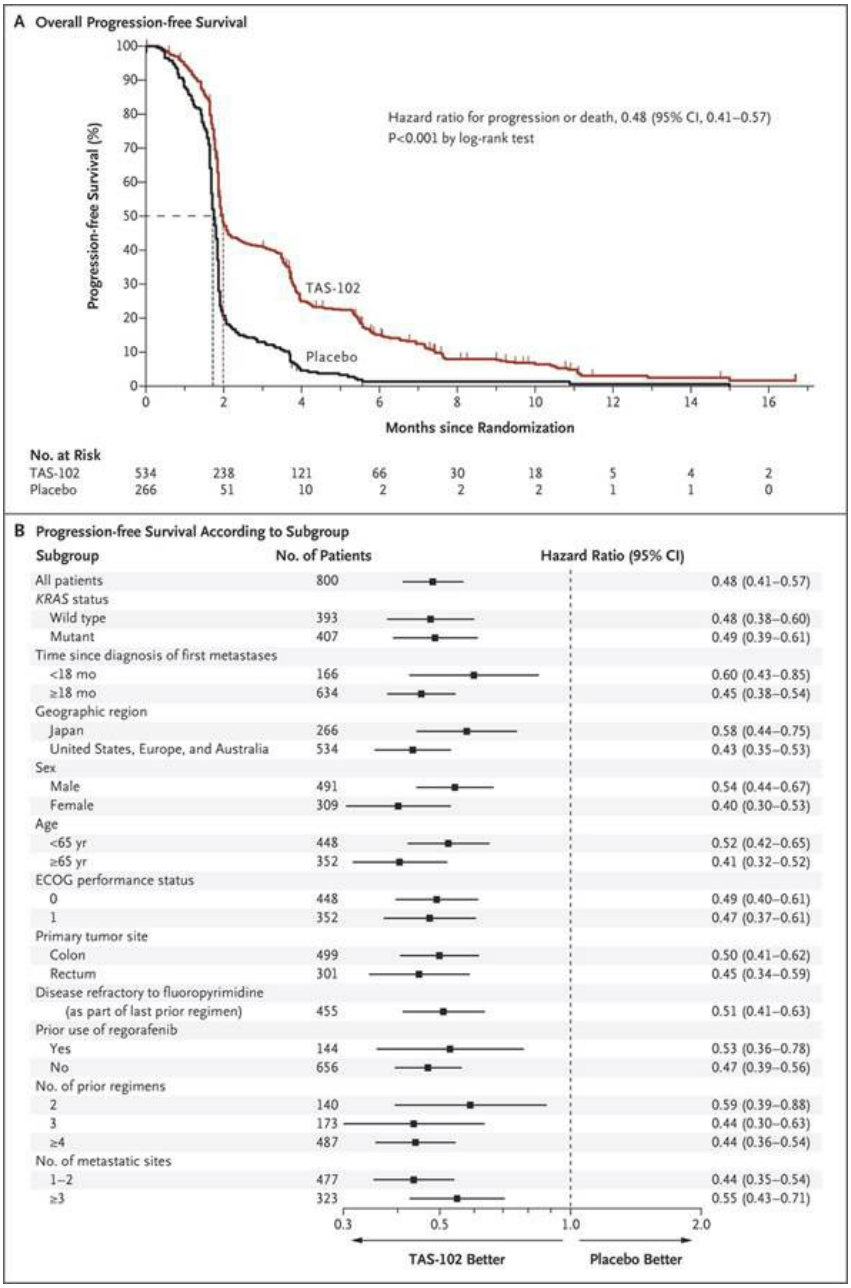
The primary end point was overall survival (OS) and secondary end points were progression free survival (PFS), rate of disease control (DCR), response rate (RR) and safety.

Efficacy

After a median follow up of 11.8 months, the median OS was 7.1 months in the TAS-102 group vs 5.3 months in the placebo group (HR=0.68; 95% CI, 0.58 to 0.81; p<0.001). The median PFS was 2.0 months in the TAS-102 group and 1.7 months in the placebo group (HR=0.48; 95% CI, 0.41 to 0.57; p<0.001). Disease control was achieved in 44% of patients in the TAS-102 group and 16% in the placebo group. Addition of TAS-102 to best supportive care (BSC) resulted in significant delay in deterioration of ECOG performance status compared with addition of placebo to BSC. No formal quality of life data are published.[1]

Kaplan-Meier curves for overall survival and progression-free survival[1]


A Overall Survival
Overall Survival (%)
Hazard ratio for death, 0.68 (95% CI, 0.58–0.81)
P<0.001
TAS-102
Placebo
Months since Randomization
No. at Risk
TAS-102 534 459 294 137 64 23 7
Placebo 266 198 107 47 24 9 3
B Overall Survival
Subgroup | No. of Patients | Hazard Ratio (95% CI)
All patients 800 0.68 (0.58–0.81)
KRAS status
Wild type 393 0.58 (0.45–0.74)
Mutant 407 0.80 (0.63–1.02)
Time since diagnosis of first metastases
<18 mo 166 0.84 (0.58–1.21)
≥18 mo 634 0.64 (0.53–0.78)
Geographic region
Japan 266 0.75 (0.57–1.00)
United States, Europe, and Australia 534 0.64 (0.52–0.80)
Sex
Male 491 0.69 (0.56–0.87)
Female 309 0.68 (0.51–0.90)
Age
<65 yr 448 0.74 (0.59–0.94)
≥65 yr 352 0.62 (0.48–0.80)
ECOG performance status
0 448 0.73 (0.58–0.93)
1 352 0.61 (0.48–0.79)
Primary tumor site
Colon 499 0.68 (0.55–0.85)
Rectum 301 0.64 (0.48–0.85)
Disease refractory to fluoropyrimidine (as part of last prior regimen) 455 0.75 (0.59–0.94)
Prior use of regorafenib
Yes 144 0.69 (0.45–1.05)
No 656 0.69 (0.57–0.83)
No. of prior regimens
2 140 1.05 (0.68–1.63)
3 173 0.74 (0.51–1.08)
≥4 487 0.59 (0.47–0.73)
No. of metastatic sites
1–2 477 0.69 (0.54–0.87)
≥3 323 0.68 (0.52–0.88)
TAS-102 Better
Placebo Better



Toxicity

Drug-related adverse events of grade 3 or higher were reported in 370 (69%) of the TAS-102 treated patients and 137 (52%) of the placebo patients.[1]

The most commonly reported adverse events included haematological (anaemia, neutropenia, and leucopenia) and gastrointestinal (diarrhoea, nausea, and vomiting) events. 9% of the TAS-102 treated patients received granulocyte colony-stimulating factor. There was one reported treatment-related death resulting from septic shock. Other frequently reported side effects included fatigue, anorexia and alopecia.[1]

Though clinically not significant compared to placebo, rare occurrences of cardiac toxicity, pneumonitis, thromboembolism, colitis and bile duct stenosis were reported.[1]

Adverse events[1]

Table 2. Frequency of Adverse Events and Laboratory Abnormalities.*

Event	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any event — no. (%)	524 (98)	370 (69)	247 (93)	137 (52)
Any serious event — no. (%)	158 (30)		89 (34)	
Most common events — no. (%)†				
Nausea	258 (48)	10 (2)	63 (24)	3 (1)
Vomiting	148 (28)	11 (2)	38 (14)	1 (<1)
Decreased appetite	208 (39)	19 (4)	78 (29)	13 (5)
Fatigue	188 (35)	21 (4)	62 (23)	15 (6)
Diarrhea	170 (32)	16 (3)	33 (12)	1 (<1)
Abdominal pain	113 (21)	13 (2)	49 (18)	10 (4)
Fever	99 (19)	7 (1)	37 (14)	1 (<1)
Asthenia	97 (18)	18 (3)	30 (11)	8 (3)
Events associated with fluoropyrimidine treatment — no. (%)				
Febrile neutropenia	20 (4)	20 (4)	0	0
Stomatitis	43 (8)	2 (<1)	17 (6)	0
Hand–foot syndrome	12 (2)	0	6 (2)	0
Cardiac ischemia‡	2 (<1)	1 (<1)	1 (<1)	1 (<1)
Laboratory abnormalities — no./total no. (%)§				
Neutropenia	353/528 (67)	200/528 (38)	2/263 (<1)	0
Leukopenia	407/528 (77)	113/528 (21)	12/263 (5)	0
Anemia	404/528 (77)	96/528 (18)	87/263 (33)	8/263 (3)
Thrombocytopenia	223/528 (42)	27/528 (5)	21/263 (8)	1/263 (<1)
Increase in alanine aminotransferase level	126/526 (24)	10/526 (2)	70/263 (27)	10/263 (4)
Increase in aspartate aminotransferase level	155/524 (30)	23/524 (4)	91/262 (35)	16/262 (6)
Increase in total bilirubin	189/526 (36)	45/526 (9)	69/262 (26)	31/262 (12)
Increase alkaline phosphatase level	205/526 (39)	42/526 (8)	118/262 (45)	28/262 (11)
Increase in creatinine level	71/527 (13)	5/527 (<1)	32/263 (12)	2/263 (<1)

* All adverse events were grading according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the TAS-102 group and in a greater percentage in that group than in the placebo group.
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischemia.
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one postbaseline measurement during treatment.

Evidence - Gastric and gastroesophageal

The evidence supporting this protocol is provided by a phase III multicentre, international randomised trial (TAGS) involving 507 patients comparing trifluridine/tipiracil with placebo in patients with metastatic, non-resectable gastric adenocarcinoma (including adenocarcinoma of the gastroesophageal junction). Patients had received at least two prior therapies, including fluoropyrimidine-, platinum-, and taxane- and/or irinotecan-based regimes. HER2-positive patients must have received prior HER2-targeted therapy if available.[3]

Between February 2016 and January 2018, 337 patients were randomised to receive trifluridine/tipiracil 35 mg/m^2 orally twice daily on days 1 to 5 and days 8 to 12 every 28 days and 170 patients were randomised to receive matching placebo.

The primary end point was overall survival (OS) and the secondary end points were progression-free survival (PFS), safety and tolerability, objective response, disease control rate (DCR), time to deterioration of ECOG status, and health-related quality of life.

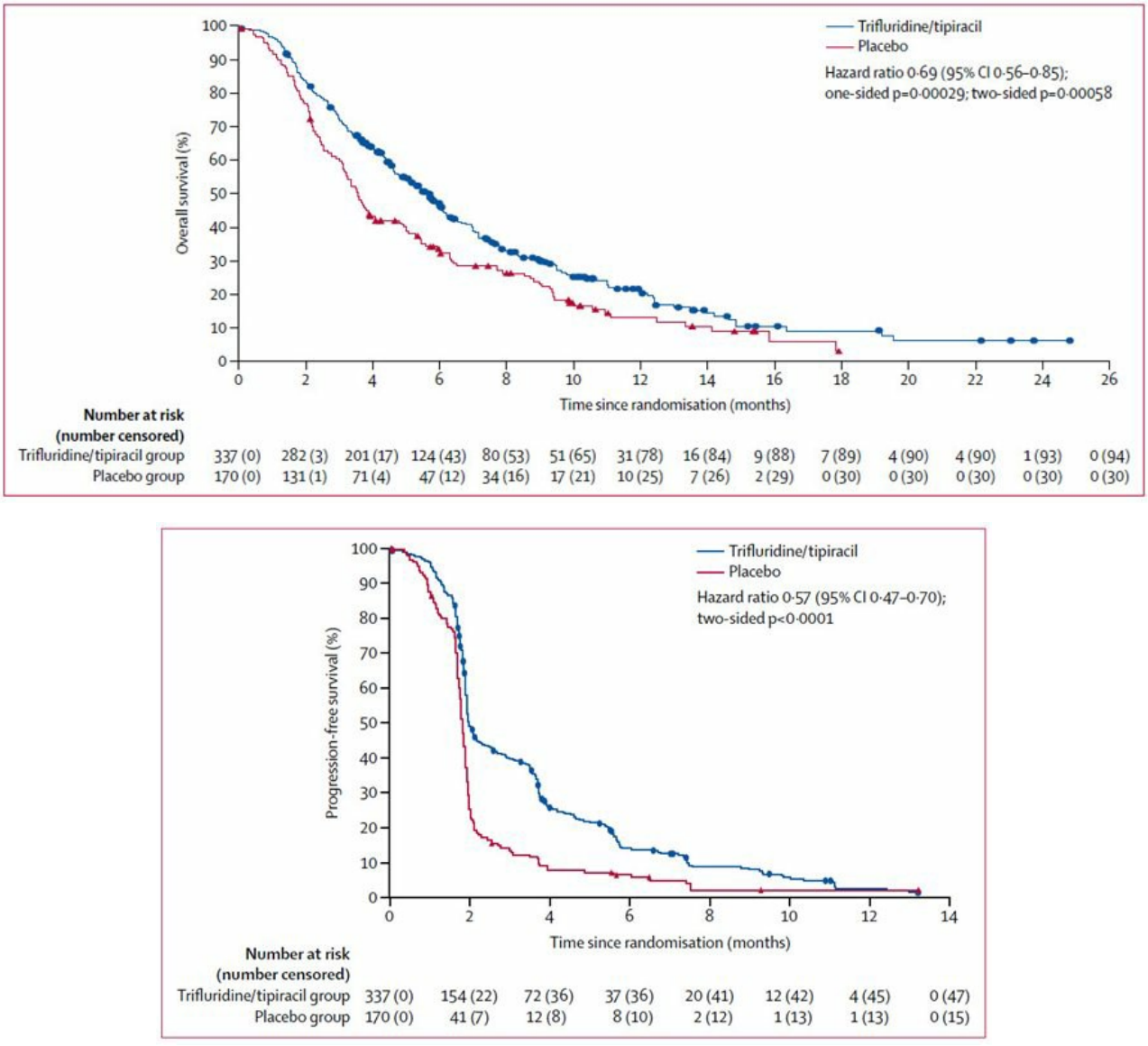
Efficacy

After a median follow up of 10.7 months, the median OS was 5.7 months in the trifluridine/tipiracil group compared to 3.6 months in the placebo group (HR=0.69; 95% CI 0.56 to 0.85; p=0.00058). The 12 month survival rate was 21% versus 13% respectively. The median PFS was 2.0 months in the trifluridine/tipiracil group compared to 1.8 months in the placebo group (HR=0.57; 95% CI 0.47

to 0.70; p<0.0001). The 6 month PFS rate was 15% compared to 6% respectively. Objective responses were noted in 4% of the trifluridine/tipiracil group and 2% in the placebo group. DCR was 44% in the trifluridine/tipiracil group compared to 14% in the placebo group. The time to deterioration of ECOG status score to 2 or higher was significantly longer in the trifluridine/tipiracil group compared to the placebo group.[3]

Quality of life scores were largely stable in both groups.[4]

Kaplan-Meier curves for overall survival and progression-free survival[3]



Toxicity

Grade 3 or worse events occurred in 80% of patients in the trifluridine/tipiracil group compared to 58% in the placebo group. The most common grade 3/4 adverse events in the trifluridine/tipiracil group included neutropenia, anaemia and leucopenia.[3]

Adverse events[3]

	Trifluridine/tipiracil group (n=335)				Placebo group (n=168)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event of any cause*	59 (18%)	172 (51%)	51 (15%)	44 (13%)	60 (36%)	64 (38%)	14 (8%)	19 (11%)
Any treatment-related adverse event	95 (28%)	136 (41%)	39 (12%)	1 (<1%)†	73 (43%)	21 (13%)	0	1 (1%)‡
Most common adverse events of any cause§								
Nausea	114 (34%)	10 (3%)	0	0	48 (29%)	5 (3%)	0	0
Anaemia or decreased haemoglobin concentration	86 (26%)	63 (19%)	1 (<1%)	0	19 (11%)	12 (7%)	1 (1%)	0
Decreased appetite	86 (26%)	28 (8%)	1 (<1%)	0	41 (24%)	9 (5%)	2 (1%)	0
Vomiting	71 (21%)	10 (3%)	2 (1%)	0	31 (18%)	3 (2%)	0	0
Diarrhoea	67 (20%)	8 (2%)	1 (<1%)	0	21 (13%)	3 (2%)	0	0
Fatigue	66 (20%)	23 (7%)	0	0	25 (15%)	10 (6%)	0	0
Neutropenia or decreased neutrophil count	62 (19%)	85 (25%)	29 (9%)	0	7 (4%)	0	0	0
Asthenia	49 (15%)	14 (4%)	2 (1%)	0	29 (17%)	11 (7%)	0	0
Thrombocytopenia or decreased platelet count	49 (15%)	7 (2%)	4 (1%)	0	8 (5%)	0	0	0
Leucopenia or decreased white blood cell count	47 (14%)	28 (8%)	3 (1%)	0	3 (2%)	0	0	0
Abdominal pain	41 (12%)	14 (4%)	0	0	16 (10%)	15 (9%)	0	0
Constipation	41 (12%)	3 (1%)	1 (<1%)	0	16 (10%)	4 (2%)	0	0
Back pain	23 (7%)	2 (1%)	0	0	7 (4%)	4 (2%)	0	0
Increased blood alkaline phosphatase concentrations	21 (6%)	9 (3%)	0	0	9 (5%)	5 (3%)	0	0
Dyspnoea	18 (5%)	6 (2%)	0	0	11 (7%)	4 (2%)	2 (1%)	0
Dysphagia	13 (4%)	6 (2%)	1 (<1%)	0	4 (2%)	4 (2%)	0	0
Ascites	7 (2%)	12 (4%)	0	0	5 (3%)	10 (6%)	0	1 (1%)
General deterioration of physical health	1 (<1%)	4 (1%)	1 (<1%)	17 (5%)	2 (1%)	3 (2%)	1 (1%)	11 (7%)
Hyponatraemia	1 (<1%)	4 (1%)	0	0	1 (1%)	7 (4%)	0	0
Increased γ-glutamyltransferase concentrations	1 (<1%)	2 (1%)	1 (<1%)	0	0	4 (2%)	1 (1%)	0

Data are n (%) and are presented for all treated patients. Adverse events were defined according to the Common Terminology Criteria for Adverse Events. *Adverse event data were missing for accidental overdose (n=1 [<1%]) and drug misuse (n=1 [<1%]) in the trifluridine/tipiracil group and encephalopathy (n=1 [1%]) in the placebo group. †Attributed to cardiopulmonary arrest. ‡Attributed to toxic hepatitis. §Adverse events for which grade 1 or 2 events were reported in 10% or more of patients in either treatment group and adverse events for which grade 3, 4, or 5 events were reported in 2% or more of patients in either treatment group.

References

1 Mayer, R.J., E. Van Cutsem, A. Falcone, et al. 2015. "Randomised trial of TAS-102 for refractory metastatic colorectal cancer." N Engl J Med 372(20):1909-1919

2 Price, T., M. Burge, L. Chantrill, et al. 2020. "Trifluridine/tipiracil: A practical guide to its use in the management of refractory metastatic colorectal cancer in Australia." Asia Pac J Clin Oncol 16 Suppl 1:3-12.

3 Shitara, K., T. Doi, M. Dvorkin, et al. 2018. "Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Oncol 19(11):1437-1448.

4 Tabernero, J., M. Alsina, K. Shitara, et al. 2020. "Health-related quality of life associated with trifluridine/tipiracil in heavily pretreated metastatic gastric cancer: results from TAGS." Gastric Cancer 23(4):689-698.

History

Version 1

ID 3806 Metastatic trifluridine/tipiracil

Date	Summary of changes
18/08/2020	New multi-indication protocol approved electronically by Medical Oncology reference committee. Note that this protocol replaces the existing approved protocol ID 1940.
26/08/2020	Protocol published on eviQ. Next review due in 1 year.
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.
20/01/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. Vaccination clinical information updated. Cautions/exclusions in the indication section changed to cautions. Next review in 2 years.

As ID 3806 Metastatic trifluridine/tipiracil replaces one existing approved protocol, the individual History section is included below for consistency in documentation.

ID 1940 Colorectal metastatic trifluridine/tipiracil version 1	
Date	**Summary of changes**
21/10/2016	New protocol taken to Medical Oncology Reference Committee meeting.
05/02/2018	Approved and published on eviQ.
14/01/2019	Trifluridine/tipiracil dosing table added to treatment schedule.

First approved: 18 August 2020
Last reviewed: 31 December 2021
Review due: 31 December 2023

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/3806
15 Jul 2023

Patient information - Metastatic - Trifluridine/tipiracil

Patient's name:

Your treatment

This treatment may be used to treat different types of cancer. Your doctor will advise you why you are receiving this treatment.

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

Trifluridine/tipiracil		
This treatment cycle is repeated every 28 days. Your doctor will advise you of the number of treatments you will have.		
Day	**Treatment**	**How it is given**
1 to 5 8 to 12	**Trifluridine/tipiracil** *(trye-FLURE-i-deen and tye-PIR-a-sil)*	Swallow tablets whole TWICE a day (morning and evening) within one hour after the end of a meal. 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.
6 to 7 13 to 28	**Do not** take trifluridine/tipiracil tablets from day 6 to 7 and day 13 to 28.	

Trifluridine/tipiracil tablets are available in two tablet strengths, 15 mg and 20 mg. It is important that you take the correct tablets and understand how to take them. Ask your doctor, nurse or pharmacist to complete the table below with the correct number of tablets for you.

Trifluridine/tipiracil	Morning	Evening
Number of 15 mg tablets		
Number of 20 mg tablets		

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	Daytime:..... Night/weekend:.....

- chills, sweats, shivers or shakes
- shortness of breath
- uncontrolled vomiting or diarrhoea
- pain, tingling or discomfort in your chest or arms
- you become unwell.

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.

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 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.**
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.**
Stomach pain	• You may get: ◦ dull aches ◦ cramping or pain ◦ bloating or flatulence (gas). • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have stomach pain that you are unable to control.**
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	• 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.**

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.**

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.**
High blood bilirubin levels (hyperbilirubinaemia)	• 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.**

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.
- 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 - Bowel cancer

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

Where to get more information - Stomach and oesophageal cancer

Telephone support

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

Stomach and oesophageal cancer information

- Pancare Foundation – pancare.org.au

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

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- iCanQuit – iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

Additional notes:

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