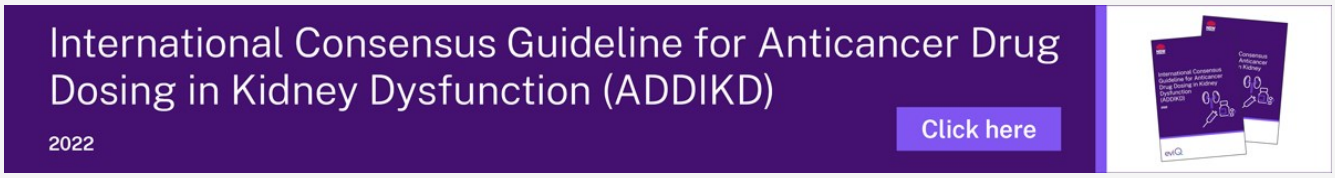
Renal cell metastatic cABOZANtinib

ID: 2027 v.3 **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

Drug	Dose	Route
cABOZANtinib	60 mg ONCE a day *	PO

* For mild to moderate hepatic impairment reduce cabozantinib starting dose to 40 mg once daily.

Continuous until disease progression or unacceptable toxicity

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Drug status: Cabozantinib is PBS authority

Cabozantinib is available as **20 mg, 40 mg** and **60mg** tablets

Cost: ~ $9,290 per month

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.*

Continuous treatment		
cABOZANtinib	60 mg (PO)	ONCE a day on an empty stomach (one hour before food or two hours after food). Swallow whole with a glass of water.

Continuous until disease progression or unacceptable toxicity

Indications and patient population

Indications:

- first line treatment of intermediate- or poor-risk advanced or metastatic clear cell renal cell carcinoma (RCC)

- advanced or metastatic renal RCC with clear cell histology
  - after failure of treatment with a VEGF-targeting tyrosine kinase inhibitor (TKI).

Cautions/exclusions:

- Karnofsky performance status < 70
- hepatic impairment (total bilirubin > 1.5 x ULN). Consider dose of 40 mg once a day in patients with mild to moderate hepatic impairment. Not recommended for patients with severe hepatic impairment.
- severe renal impairment (serum creatinine > 2 x ULN, or calculated creatinine clearance < 30 mL/minute)
- NYHA Class 3 or 4 heart failure
- recent history of severe haemorrhage
- gastrointestinal fistula or perforation
- thrombotic events

Clinical information

- Close monitoring during the first 8 weeks of treatment is recommended, as most adverse events that require dose modification or interruption can occur early in the course of treatment. If grade 1 or 2 diarrhoea or hand-foot syndrome occur early in the course of treatment, then consider dose interruption until recovery.

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
Hand-foot syndrome	Hand-foot syndrome (palmar-plantar erythrodysaesthesia) and rash are common adverse effects with this treatment which generally appear during the first 6 weeks of therapy. Read more about hand food syndrome or palmar plantar erythrodysaesthesia (PPE)
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Thromboembolism	Fatal arterial and venous thromboembolic events have been observed in patients with this treatment. Cabozantinib should be used with caution in patients with increased risk or history of arterial thrombotic events (i.e. cerebrovascular and cardiovascular disease). Cabozantinib should be discontinued for myocardial infarction, cerebral infarction or other serious arterial thromboembolic events.
Haemorrhage	Significant haemorrhagic events have occurred with this treatment. Use with caution in patients with risk of haemorrhage (i.e. CNS metastases, coagulopathy, concurrent anticoagulant or antiplatelet medications etc.)
Gastrointestinal perforation	Serious cases of gastrointestinal (GI) perforation have been reported with this treatment. Use with caution in patients at risk of GI perforation, including patients with inflammatory bowel disease and tumour infiltration of GI tract. Patients should be monitored for signs and symptoms of GI perforation.
Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing treatment and blood pressure should be monitored regularly and treated, if required. In severe or uncontrolled hypertension, treatment should be withheld until hypertension is controlled. Dose modification or permanent discontinuation may be necessary - refer to dose modification section for specific recommendations.
Proteinuria	Patients with a history of diabetes, high blood pressure and kidney disease may be at increased risk of developing proteinuria. Signs of proteinuria include swelling of the feet or the whole body. Treatment interruption may be required if proteinuria is significant (e.g. > 3g/day). Baseline and periodic urinalyses are recommended as clinically indicated. Read more about proteinuria

Hypothyroidism	Thyroid dysfunction in particular hypothyroidism may occur with this treatment. Monitor for signs and symptoms of thyroid dysfunction and manage as clinically appropriate.
ECG abnormalities	Cabozantinib can cause QT interval prolongation. Baseline and periodic electrocardiogram (ECG) monitoring and maintenance of electrolytes (calcium, magnesium and potassium) within normal range is recommended. Cabozantinib should be used with caution in patients at risk or QTc prolongation (i.e. history or QTc interval prolongation, concurrent medications prolonging QTc interval or pre-existing cardiac disease). Read more about drugs that may prolong QTc interval at crediblemeds.org (registration required).
Reversible posterior leukoencephalopathy syndrome (RPLS)	Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in patients receiving this treatment and may be fatal. Discontinue drug in patients developing RPLS. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)
Wound healing	This treatment may impair wound healing and temporary interruption of treatment is recommended in patients undergoing surgical procedures. The cabozantinib product information recommends ceasing 28 days prior to planned surgery, and resuming 10 days after minor surgery (such as minor excision or tooth extraction) and 28 days after major surgery.
Blood tests	FBC, EUC, LFTs and CPM (calcium, phosphate and magnesium) at baseline then 2-weekly for 8 weeks then monthly. TFT at baseline and as clinically indicated.
Hepatitis B screening and prophylaxis	The requirement for routine screening for HBsAg and anti-HBc for patients receiving this treatment is unknown. Clinical judgement and individual patient situations should be taken into consideration. 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).

- Dose modifications are adapted from the clinical trial by Choueiri et al. [1]

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 should continue if patient is clinically well.
0.5 to less than 1.0	Delay treatment until recovery to ≥ 1.0 and recommence cabozantinib as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Consider recommencing cabozantinib at 20 mg, if not tolerated, discontinue treatment
less than 0.5	Delay treatment until recovery to ≥ 1.0 and recommence cabozantinib as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Consider recommencing cabozantinib at 20 mg, if not tolerated, discontinue treatment
Platelets x 10^9/L (pre-treatment blood test)	
25 to less than 50	Delay treatment until recovery to ≥ 50 and recommence cabozantinib as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Consider recommencing cabozantinib at 20 mg, if not tolerated, discontinue treatment
less than 25	Delay treatment until recovery to ≥ 50 and recommence cabozantinib as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Consider recommencing cabozantinib at 20 mg, if not tolerated, discontinue treatment

Renal impairment	
Mild to moderate	No dose modification necessary
Severe	Cease cabozantinib

Hepatic impairment	
Hepatic dysfunction	
Mild to moderate	Reduce cabozantinib starting dose to 40 mg once daily. Throughout treatment: delay treatment until recovery and recommence cabozantinib as follows: 1st occurrence: Reduce cabozantinib to 40 mg (or 20 mg if previously on 40 mg) 2nd occurrence: Discontinue treatment

Hepatic impairment	
Severe	Not recommended

Diarrhoea	
Grade 1 or 2	Continue treatment at same dose, consider dose interruption until recovery if occurs early in the course of treatment. Add anti-diarrhoeal / anti-motility medications as needed
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 cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Discontinue treatment
Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less then consider recommencing cabozantinib with a dose reduction to 40 mg or permanently discontinue

Hand foot syndrome (link to Hand foot syndrome (Palmar-plantar erythrodysaesthesia))	
Grade 1	Consider dose interruption until recovery if occurs early in the course of treatment
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less, commence supportive measures for symptomatic relief and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Discontinue treatment
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less, commence supportive measures for symptomatic relief and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce cabozantinib to 40 mg 2nd occurrence: Reduce cabozantinib to 20 mg 3rd occurrence: Discontinue treatment

Hypertension			
Systolic		**Diastolic**	**Management**
> 150 mm Hg and < 160 mm Hg	or	> 100 mm Hg and < 110 mm Hg	Optimise antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. Reduce cabozantinib treatment to 40 mg if optimal antihypertensive therapy (usually 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic. If symptomatic, discontinue treatment.
≥ 160 mm Hg	or	≥ 110 mm Hg	Reduce cabozantinib treatment to 40 mg and add new or additional antihypertensive medications and/or increase dose of existing medications and monitor closely for hypotension. If optimised antihypertensive therapy (usually 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. Interrupt cabozantinib treatment if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is < 180 mm Hg systolic or > 120 mm Hg diastolic or if symptomatic. Restart cabozantinib treatment at the most tolerable dose and re-escalate cabozantinib dose only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive crisis or hypertensive encephalopathy			Discontinue treatment

Cease cabozantinib if any of the following occur:
Severe haemorrhage Development of unmanageable fistula or gastrointestinal perforation Arterial thromboembolic event (e.g. myocardial infarction, cerebral infarction) Hypertensive crisis or severe hypertension despite optimal medical management Nephrotic syndrome Reversible posterior leukoencephalopathy syndrome

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*

Cabozantinib		
	Interaction	**Clinical management**
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir, verapamil, diltiazem etc.)	Increased toxicity of cabozantinib possible due to reduced clearance	Avoid combination or monitor for cabozantinib toxicity; reduce the dose of cabozantinib if concomitant use cannot be avoided
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of cabozantinib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to cabozantinib; consider increasing the dose of cabozantinib if concomitant use cannot be avoided
Highly protein-bound drugs	Increased free concentrations of cabozantinib and/or highly protein-bound drug	Avoid combination or monitor for cabozantinib toxicity or highly protein-bound drug toxicity
Drugs that may prolong the QTc interval (e.g. azole antifungals, tricyclic antidepressants, antiarrhythmics etc.)	Additive effect with cabozantinib; may lead to torsades de pointes and cardiac arrest	Avoid combination and/or minimise additional risk factors (e.g. correct electrolyte imbalances) and monitor ECG for signs of cardiac arrhythmia

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.

Administration

This is a continuous oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

General patient assessment prior to each treatment.

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

Treatment - Time out

Cabozantinib

- administer orally ONCE a day
- to be swallowed whole with a glass of water; do not break, crush or chew
- to be taken on an empty stomach one hour before food or two hours after food

Note: missed doses should not be taken if it is less than 12 hours until the next dose. If a dose is forgotten or vomited, it should not be replaced.

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

Discharge information

Cabozantinib tablets

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

Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

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

Immediate (onset hours to days)	
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting

Early (onset days to weeks)	
Fatigue	May require dose interruption or reduction if disabling. Read more about fatigue
Diarrhoea	Read more about treatment induced diarrhoea
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
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
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.
Haemorrhage	
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.
Proteinuria	Read more about proteinuria
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)

Evidence

First-line setting (CABOSUN)[2,3]

The evidence supporting use of this protocol is provided by a randomised phase 2 trial involving 157 patients comparing cabozantinib and sunitinib in patients with intermediate- or poor-risk advanced or metastatic clear cell renal cell carcinoma.

Between July 2013 and April 2015, 79 patients were randomised to receive cabozantinib 60 mg daily and 78 patients were randomised to receive sunitinib 50 mg daily for cycles of 4 weeks followed by 2 weeks off.

The primary end point was progression-free survival (PFS). Secondary end points included objective response rate (ORR), overall survival (OS) and safety. The study was not powered for OS. Quality of life was not assessed.[2]

Second-line setting (METEOR)[1,4]

The evidence supporting this protocol is provided by an open label phase 3 randomised trial involving patients with advanced renal cell carcinoma who had progressed on at least one VEGFR-targeting tyrosine kinase inhibitor.[1] In the METEOR trial from August 2013 through to November 2014, a total of 658 patients from 173 centres in 26 countries were randomly assigned in a 1:1 ratio to receive either cabozantinib or everolimus.[1]

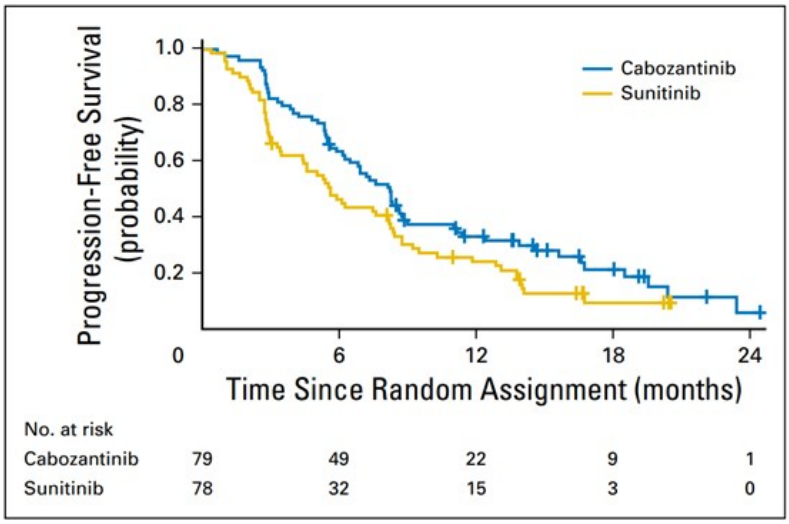
The primary end point was PFS. Secondary end points included OS, ORR, adverse events, and quality of life.[1]

Efficacy

First-line setting

Median PFS with cabozantinib was 8.2 months (95% CI, 6.2 to 8.8) versus 5.6 months (95% CI, 3.4 to 8.1) with sunitinib.

Kaplan-Meier curve for PFS[2]



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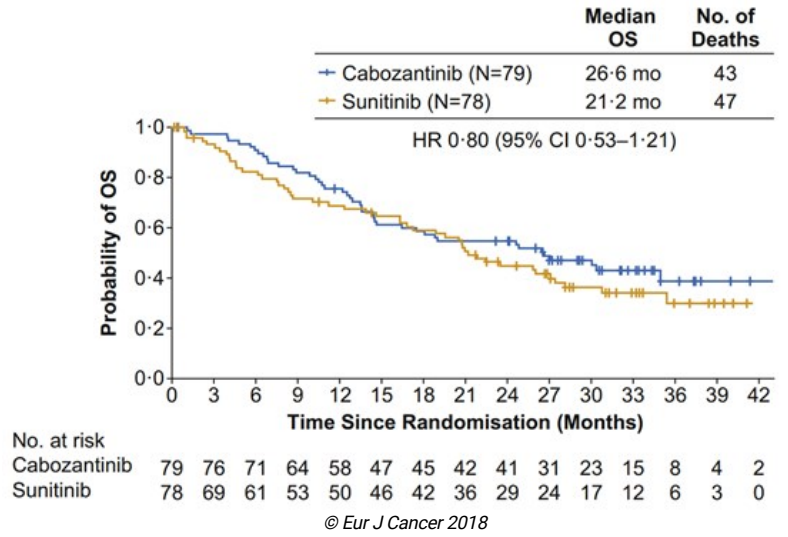
The ORR with cabozantinib was 33% (95% CI, 23 to 44%) compared with sunitinib 12% (95% CI, 5.4 to 21%).[2] An updated analysis at a median follow up of 35.4 months found OS was 26.6 months (95% CI, 14.6 to not estimable) and 21.2 months (95% CI 16.3 to 27.4) respectively (difference not statistically significant, HR 0.80, 95% CI, 0.53 to 1.21).[3]

Kaplan-Meier curve for OS[3]



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A subgroup analysis at a median follow up of 25 months demonstrated improved PFS and ORR benefits for cabozantinib compared with sunitinib across all subgroups, including IMDC risk group, bone metastases, age, and tumour burden.[5]

A post hoc analysis evaluating Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment (Q-TWiST) found that cabozantinib was associated with longer quality-adjusted survival compared with everolimus.[6]

Second-line setting

PFS was significantly prolonged with cabozantinib compared with everolimus (median 7.4 versus 3.8 months). Rate of disease progression or death was 42% lower for cabozantinib versus everolimus (HR 0.58, 95% CI, 0.45 to 0.75; p<0.0001).[1]

Kaplan-Meier curve for PFS[1]

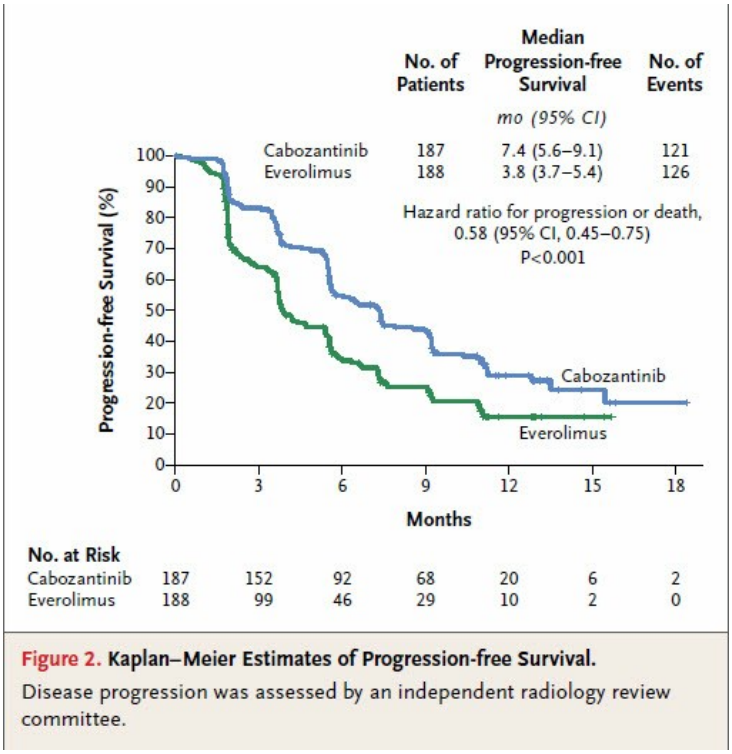
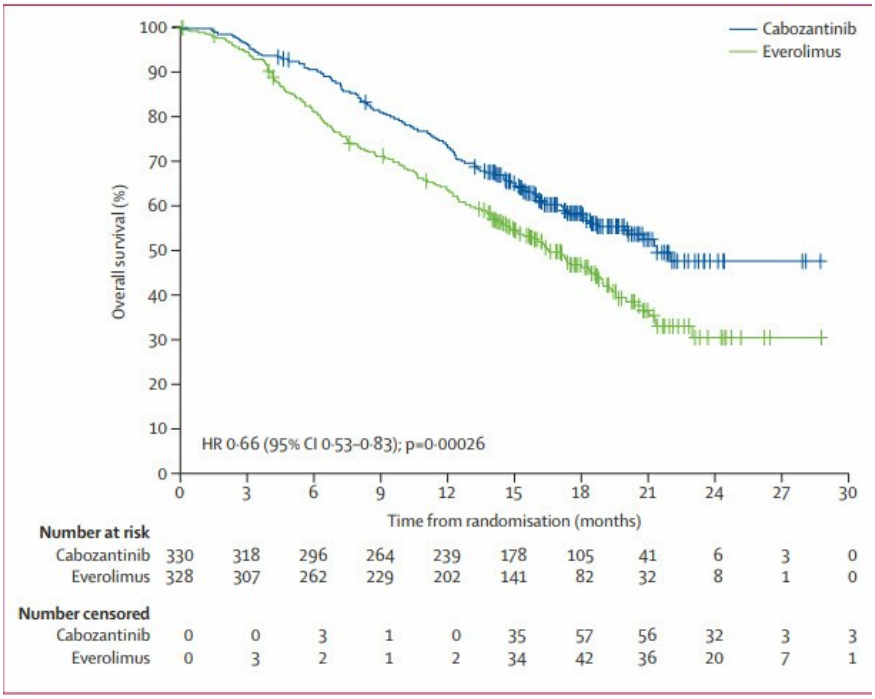


Figure 2. Kaplan–Meier Estimates of Progression-free Survival.
Disease progression was assessed by an independent radiology review committee.

The ORR was significantly higher with cabozantinib than with everolimus (21% versus 5%, p<0.001).[4]

An updated analysis at a median follow-up of 18 months found OS was significantly prolonged with cabozantinib compared with everolimus (median survival 21.4 months versus 16.5 months, HR 0.66; 95% CI, 0.53 to 0.83; p=0.00026).[4]



A subgroup analysis demonstrated improved PFS, OS and ORR for cabozantinib compared with everolimus in patients with bone metastases.[7]

Quality of life was similar for patients allocated to cabozantinib or everolimus, except diarrhoea and nausea were worse for cabozantinib, and shortness of breath was worse for everolimus. The median duration of treatment was 7.6 months among patients who received cabozantinib, and 4.4 months among patients who received everolimus.[4] The median time to deterioration (TTD) was 5.5 months for cabozantinib compared with 3.7 months for everolimus (p<0.001), while the median TTD for patients with bone metastases was 5.6 months versus 1.9 months respectively (p<0.001).[8]

Toxicity

First-line setting

Dose reductions occurred in 46% of patients with cabozantinib vs 35% with sunitinib. The rate of treatment discontinuation due to adverse events was 20% vs 21% respectively.

Treatment related adverse events[2]

Table 3. Adverse Events

	No. (%)			
	Cabozantinib (n = 78)		Sunitinib (n = 72)	
Adverse Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event	77 (98.7)	52 (66.7)	71 (98.6)	49 (68.1)
Fatigue	67 (85.9)	5 (6.4)	59 (81.9)	11 (15.3)
Hypertension	63 (80.8)	22 (28.2)	49 (68.1)	16 (22.2)
Diarrhea	56 (71.8)	8 (10.3)	38 (52.8)	8 (11.1)
AST increased	48 (61.5)	2 (2.6)	23 (31.9)	2 (2.8)
ALT increased	43 (55.1)	4 (5.1)	20 (27.8)	0 (0)
Anorexia	37 (47.4)	4 (5.1)	23 (31.9)	0 (0)
PPES	33 (42.3)	6 (7.7)	24 (33.3)	3 (4.2)
Dysgeusia	32 (41.0)	0 (0)	21 (29.2)	0 (0)
Thrombocytopenia	31 (39.7)	1 (1.3)	45 (62.5)	8 (11.1)
Oral mucositis	28 (35.9)	4 (5.1)	21 (29.2)	4 (5.6)
Anemia	26 (33.3)	1 (1.3)	33 (45.8)	1 (1.4)
Nausea	25 (32.1)	2 (2.6)	28 (38.9)	3 (4.2)
Weight loss	25 (32.1)	3 (3.8)	12 (16.7)	0 (0)
Neutropenia	12 (15.4)	0 (0)	25 (34.7)	3 (4.2)
Leukopenia	9 (11.5)	0 (0)	25 (34.7)	2 (2.8)

NOTE. All-causality adverse events reported in at least 30% of patients in either study group are shown. Patients were counted once at the highest grade for each preferred term. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).
Abbreviation: PPES, palmar-plantar erythrodysesthesia syndrome.

Second-line setting

In the METEOR trial, adverse events amongst patients treated with cabozantinib were significant, requiring dose reductions in 60%, two dose reductions in 19%, dose interruptions in 70%, and discontinuation due to treatment-related adverse events in 9%. Median time to first dose reduction was 55 days, and to first dose interruption was 38 days. The median average daily dose of cabozantinib was 44 mg. The rate of treatment discontinuations due to adverse events not related to renal cell carcinoma was 9%. One treatment-related death occurred in the cabozantinib group.[1]

Treatment related adverse events[1]

Table 2. Adverse Events.*

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any adverse event	331 (100)	226 (68)	321 (>99)	187 (58)
Diarrhea	245 (74)	38 (11)	88 (27)	7 (2)
Fatigue	186 (56)	30 (9)	148 (46)	22 (7)
Nausea	165 (50)	13 (4)	90 (28)	1 (<1)
Decreased appetite	152 (46)	8 (2)	108 (34)	3 (<1)
Palmar–plantar erythrodysesthesia syndrome	139 (42)	28 (8)	19 (6)	3 (<1)
Hypertension	122 (37)	49 (15)	23 (7)	10 (3)
Vomiting	106 (32)	7 (2)	45 (14)	3 (<1)
Weight decreased	102 (31)	6 (2)	40 (12)	0
Constipation	83 (25)	1 (<1)	60 (19)	1 (<1)
Dysgeusia	78 (24)	0	30 (9)	0
Stomatitis	73 (22)	8 (2)	77 (24)	7 (2)
Hypothyroidism	67 (20)	0	1 (<1)	0
Dysphonia	65 (20)	2 (<1)	12 (4)	0
Mucosal inflammation	63 (19)	3 (<1)	73 (23)	11 (3)
Asthenia	62 (19)	14 (4)	50 (16)	7 (2)
Dyspnea	62 (19)	10 (3)	90 (28)	13 (4)
Cough	61 (18)	1 (<1)	107 (33)	3 (<1)
Back pain	56 (17)	7 (2)	47 (15)	7 (2)
Abdominal pain	53 (16)	12 (4)	31 (10)	4 (1)
Rash	50 (15)	2 (<1)	89 (28)	2 (<1)
Pain in arms or legs	47 (14)	3 (<1)	26 (8)	1 (<1)
Muscle spasms	41 (12)	0	16 (5)	0
Dyspepsia	40 (12)	1 (<1)	15 (5)	0
Dry skin	37 (11)	0	32 (10)	0
Headache	37 (11)	1 (<1)	38 (12)	1 (<1)
Arthralgia	36 (11)	1 (<1)	45 (14)	4 (1)
Dizziness	36 (11)	0	21 (7)	0
Peripheral edema	31 (9)	0	72 (22)	5 (2)
Pyrexia	28 (8)	2 (<1)	51 (16)	1 (<1)
Pruritus	25 (8)	0	47 (15)	1 (<1)
Epistaxis	12 (4)	0	46 (14)	0
Pneumonitis	0	0	33 (10)	6 (2)
Laboratory abnormality				
Aspartate aminotransferase increased	58 (18)	6 (2)	18 (6)	1 (<1)
Anemia	56 (17)	18 (5)	122 (38)	50 (16)
Alanine aminotransferase increased	53 (16)	8 (2)	19 (6)	1 (<1)
Hypomagnesemia	52 (16)	16 (5)	5 (2)	0
Proteinuria	41 (12)	8 (2)	30 (9)	1 (<1)
Hypokalemia	38 (11)	15 (5)	21 (7)	6 (2)
Hypophosphatemia	33 (10)	12 (4)	18 (6)	7 (2)
Hypertriglyceridemia	20 (6)	5 (2)	40 (12)	9 (3)
Serum creatinine increased	15 (5)	1 (<1)	35 (11)	0
Hyperglycemia	15 (5)	2 (<1)	62 (19)	16 (5)

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History

Version 3

Date	Summary of changes
22/10/2021	Protocol reviewed at Medical Oncology Reference Committee meeting. Evidence for first and second line settings updated with subgroup analysis and quality of life results. Patient information title changed to "Kidney cancer advanced or metastatic". Version increased to V.3. Next review in 2 years.
21/12/2021	Changed antiemetic clinical information block to minimal or low, to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5.

Version 2

Date	Summary of changes
19/05/2017	New protocol taken to Medical Oncology Reference Committee meeting.
10/07/2018	Approved and published on eviQ. Review 1 year.
02/04/2019	Protocol reviewed at Medical Oncology Reference Committee meeting on 15/03/2019. Indication, drug status and evidence updated to include first-line treatment. Side effects reordered. Evidence for second-line treatment summarised. Patient information updated- your treatment and when to get help changed to less chemotherapy focused information. Version increased to V.2. Next review in 2 years.
28/08/2020	Interactions updated- H2 blockers, proton pump inhibitors and antacids removed.
16/08/2021	Drug status updated.

First approved: 10 July 2018
Last reviewed: 22 October 2021
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https://www.eviq.org.au/p/2027
19 Jun 2023

Patient information - Kidney cancer advanced or metastatic - Cabozantinib

Patient's name:

Your treatment

It is important to understand that cabozantinib is not a traditional chemotherapy drug and has a different way of working. It works by targeting the cancer cells to stop them growing and spreading. The treatment schedule below explains how the drug for this treatment is given.

Cabozantinib		
This treatment is continuous. Your doctor will advise you how long to take the treatment for.		
Day	**Treatment**	**How it is given**
Continuous	**Cabozantinib** (Kab-*oh-zan-ti-nib)*	Take orally ONCE a day with a glass of water, on an empty stomach (one hour before food or two hours after food). Swallow capsules whole, do not break, crush or chew capsules. If you forget to take a capsule and it is less than 12 hours late, take it as soon as you remember. If it is more than 12 hours late, skip that dose and take your normal dose the next time it is due. Do not take an extra dose.

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 suddenly become unwell.

Emergency contact details

Ask your doctor or nurse from your treating team when you should get help and who to contact if you have a problem

Daytime: .....

Night/weekend: .....

Other instructions: .....

.....

.....

Other information about your treatment

Changes to your dose or treatment delays

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

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

Blood tests and monitoring

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low, your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests.

Surgery and wound healing

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

Other medications given during this treatment

- **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)	
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.

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.**
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.**
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.**
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.**
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.**

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.**
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.
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.**

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

Kidney cancer information

- Kidney Cancer Association – kidneycancer.org/

- Kidney Health Australia – kidney.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

Quit smoking information and support

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

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

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