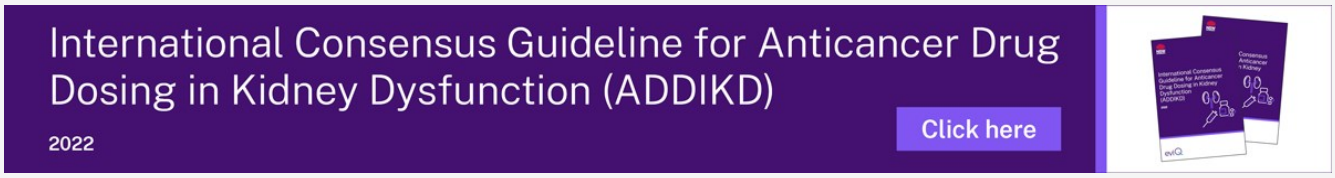
Renal cell metastatic avelumab and aXITinib

ID: 4039 v.2 **Endorsed**

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer using immunological agents. Before commencing immunotherapy treatment in any patient, clinicians should have an understanding of the immune-related adverse events (irAEs) associated with immunotherapy treatment and their management.

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

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



Related pages:

- Renal cell metastatic cABOZANtinib
- Renal cell metastatic ipilimumab and nivolumab (induction)
- Renal cell metastatic pAZOPanib
- Renal cell metastatic sUNITinib
- Renal cell metastatic temsirolimus

Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
Avelumab	800 mg *	IV infusion	1
aXITinib	5 mg TWICE a day #	PO	1 to 14

*In the trial the avelumab dose was 10 mg/kg however the TGA registered dose of avelumab is 800 mg for this indication.[1]

#starting dose; refer to dose modifications for dose escalation schedule.

Frequency: 14 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:
In the first few months after the start of immunotherapy, some patients can experience transient tumour flare (termed "pseudo progression" or an immune response). This may manifest as growth of existing lesions or the development of new lesions prior to later tumour regression. While this is rare (~5%), continuing treatment and performing a second scan 4 to 6 weeks later to confirm progression may be considered, particularly if the patient remains well.

Radiation recall has been observed with PD-L1 inhibitors, consideration should be given to the timing when starting this treatment after a prolonged course of radiation therapy.

Drug status: **Avelumab** and **axitinib** are TGA registered but not PBS listed for this indication

Axitinib is available as **1 mg** and **5 mg** tablets

Cost: ~ $7,960 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.*

Cycle 1 and further cycles

Day 1		
Paracetamol	1,000 mg (PO)	60 minutes before treatment*
Loratadine	10 mg (PO)	60 minutes before treatment*
Avelumab	800 mg (IV infusion)	in 250 mL sodium chloride 0.9% over 60 minutes
aXITinib	5 mg (PO)	TWICE a day (starting dose; refer to dose modifications for dose escalation schedule)
Day 2 to 14		
aXITinib	5 mg (PO)	TWICE a day (starting dose; refer to dose modifications for dose escalation schedule)

*Observe for hypersensitivity reaction. Patients should be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab due to the significant risk of infusion related reaction. Following fourth infusion, premedication for subsequent doses should be administered at the discretion of the treating clinician.

Frequency: 14 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

Indications:

- Advanced or metastatic clear cell renal cell carcinoma (RCC) without prior systemic therapy
  - ECOG performance status 0 to 1.

Cautions/exclusions:

- patients with untreated central nervous system metastases
- moderate or severe hepatic impairment
- end stage renal failure
- NYHA Class 3 or 4 heart failure
- recent history of severe haemorrhage
- gastrointestinal fistula or perforation
- thrombotic events.

Precautions:

If any of these conditions are present, clinical judgement should be used and individual cases discussed with an expert in the field as indicated:

- significant autoimmune disease (e.g. myasthenia gravis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, autoimmune ocular disease)

- organ transplantation
- previous history of viral hepatitis
- HIV/acquired immune deficiency syndrome (AIDS)
- previous radiation to the lungs.

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
Venous access required	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with avelumab. Severe infusion-related reactions have been reported.
Premedication	Premedicate with appropriate antihistamine and paracetamol prior to the first four infusions of avelumab. Further premedication is at the discretion of the treating physician. Premedication should continue if previous mild/moderate infusion related reaction.
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

Immune-related adverse events (irAEs)	Immune-related adverse events (irAEs) can occur early and escalate quickly in patients receiving immune checkpoint inhibitors. irAEs can also occur after discontinuation of treatment. Fatalities have been reported. Management of irAEs is largely based on expert opinion and consensus guidelines. Examples of irAEs with high risk of mortality include: • cardiac toxicity: myocarditis • musculoskeletal toxicity: myositis • neurological toxicity: encephalitis, Guillain-Barré syndrome, myelitis, myasthenia gravis • pulmonary toxicity: pneumonitis • skin toxicity: Steven-Johnson syndrome, toxic epidermal necrolysis. Examples of irAEs in order of frequency include: • Common ◦ endocrinopathies: thyroid dysfunction ◦ gastrointestinal toxicity: diarrhoea ◦ musculoskeletal toxicity: arthralgia, myalgia ◦ skin toxicity: rash, erythema, pruritus • Less common ◦ endocrinopathies: hypophysitis, type I diabetes mellitus ◦ gastrointestinal toxicity: colitis ◦ musculoskeletal toxicity: inflammatory arthritis ◦ ocular toxicity: dry eye ◦ renal toxicity ◦ skin toxicity: vitiligo • Rare ◦ endocrinopathies: primary adrenal insufficiency ◦ gastrointestinal toxicity: pancreatitis ◦ haematological toxicity ◦ musculoskeletal toxicity: vasculitis ◦ ocular toxicity: uveitis, iritis. Proactive monitoring, patient self-monitoring and early reporting of adverse events is critical. Treatment interruptions/discontinuation, consultation with specialist and administration of corticosteroids and/or supportive care is required to minimise the risk of death. Read more about the management of immune-related adverse events (irAEs)
Cardiac toxicity	Tyrosine kinase inhibitors have been associated with cardiac complications of varying degrees and severity. Patients, especially those with pre-existing cardiovascular disease, should have a baseline cardiac assessment including an electrocardiogram (ECG) and biochemistry and be closely monitored; consider an echocardiogram (ECHO) as clinically indicated. Cardiac assessment should then be repeated as clinically indicated or when starting new medication which affects the QT interval. Read more about cardiac toxicity associated with anti-cancer drugs
Thromboembolism	Both arterial and venous thromboembolic events have been observed in patients with this treatment. Therefore, use with caution in patients at increased risk or with a history of thrombotic events (i.e., cerebrovascular and cardiovascular disease)
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. Patients should be monitored for signs and symptoms of GI perforation.

Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing treatment. Baseline blood pressure monitoring and repeated weekly for the first 6 weeks then regularly throughout treatment. 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.
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)
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. 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.
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)
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Wound healing	This treatment may impair wound healing and temporary interruption of treatment is recommended in patients undergoing major surgical procedures. Resume treatment based on clinical judgement of adequate wound healing.
Baseline investigations	Consider ECG and troponin at baseline. There is no clear evidence regarding the efficacy/value of baseline ECG or troponin in patients receiving immune checkpoint inhibitor therapy. Some cancer specialists obtain baseline testing, and others continue this through the initial period of therapy. Consider urinalysis at baseline, particularly in patients with additional risk factors for developing immune-related acute kidney injury.
Blood tests	FBC, EUC, LFTs, serum cortisol, TFTs and BSL at baseline. Repeat FBC, EUC, LFTs and BSL prior to each cycle and serum cortisol and TFTs alternate cycles. Check lipase and amylase if symptomatic of pancreatitis. In the absence of suspicion of immune-related adverse events less frequent monitoring may be applicable, according to institutional guidelines. Evidence for the frequency of routine blood testing with immunotherapies varies within published studies and guidelines. Read more about immunotherapy blood test monitoring recommendations.
Hepatitis and HIV	Hepatitis screening is recommended in all patients who are to receive immune checkpoint inhibitors. Immunotherapy is associated with inflammatory adverse reactions resulting from increased or excessive immune activity and patients are at risk of developing autoimmune hepatitis. It should be used with caution in patients who have a history of chronic hepatic infections (hepatitis B and C), detectable human immunodeficiency virus (HIV) viral load or acquired immune deficiency syndrome (AIDS).
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. The safety of having vaccinations during immunotherapy is unknown. Patients in the clinical trials were typically allowed to receive inactivated and recombinant vaccines but not live vaccines. 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.

Effects of cancer treatment on fertility	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. Studies to evaluate the effects of immune checkpoint inhibitor therapy on fertility have not been performed. Therefore, the effect on male and female fertility is unknown. Limited evidence supports that immune checkpoint inhibitor-related hypogonadism due to orchitis and hypophysitis can impact fertility. Immune checkpoint inhibitors can cause fetal harm when given to pregnant women. A pregnancy test should be considered 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. There is very limited evidence to provide guidance regarding contraception timelines. Some studies have demonstrated PD-1 receptor occupancy for greater than 9 months after anti-PD-1 therapy (Brahmer et al., 2010). As a result, some cancer specialists advise using contraception for at least six months or even as long as two years after treatment finishes. Read more about the effect of cancer treatment on fertility Link to Brahmer et al., 2010

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 .

Axitinib dose modifications

The dose adjustments below relate to axitinib only and are based on the product information, the clinical trial[1] and reference committee consensus.

Dose Escalation	
Patients who tolerate axitinib 5 mg twice daily • with no adverse reactions worse than Grade 2 for two consecutive weeks, • are normotensive (BP 140/90 or lower), • and are not receiving antihypertensives	Increase axitinib to 7 mg twice daily
Patients who tolerate axitinib 7 mg twice daily • with no adverse reactions worse than Grade 2 for two consecutive weeks, • are normotensive (BP 140/90 or lower), • and are not receiving antihypertensives	Increase axitinib to 10 mg twice daily

Dose Levels				
+ 2 dose levels	**+ 1 dose level**	**Starting dose**	**- 1 dose level**	**- 2 dose levels**
10 mg twice daily	7 mg twice daily	5 mg twice daily	3 mg twice daily	2 mg twice daily

Renal impairment
Consider if immune-related adverse event. See Management of immune-related adverse events (irAEs)
No dose modification necessary for mild to severe renal impairment Use with caution in patients with end-stage renal disease (CrCl less than 15 mL/min)

Hepatic impairment	
Hepatic dysfunction	
Consider if immune-related adverse event. See Management of immune-related adverse events (irAEs)	
Mild	No dose modification necessary
Moderate	Reduce axitinib by 50% and round dose to the nearest 1 mg
Severe	No studies done

Mucositis and stomatitis	
Grade 3	Delay treatment until toxicity has resolved to Grade 2 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce axitinib by 1 dose level 2nd occurrence: Reduce axitinib by 2 dose levels 3rd occurrence: Discontinue axitinib
Grade 4	Discontinue axitinib

Diarrhoea	
Consider possibility of TKI-induced or immune-related adverse event. If TKI-induced, would expect resolution within day/s. See Management of immune-related adverse events (irAEs)	
Grade 3	Delay treatment until toxicity has resolved to Grade 2 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: Reduce axitinib by 1 dose level 2nd occurrence: Reduce axitinib by 2 dose levels 3rd occurrence: Discontinue axitinib
Grade 4	Discontinue axitinib

Hand foot syndrome (link to Hand foot syndrome (Palmar-plantar erythrodysaesthesia))	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce axitinib by 1 dose level 3rd occurrence: Reduce axitinib by 2 dose levels 4th occurrence: Discontinue axitinib
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 axitinib by 1 dose level 2nd occurrence: Reduce axitinib by 2 dose levels 3rd occurrence: Discontinue axitinib

Hypertension			
Systolic		**Diastolic**	
Two readings separated by at least 1 hr showing higher than 150 mmHg	or	Two readings separated by at least 1 hr showing higher than 100 mmHg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain axitinib dose If on maximal antihypertensive treatment, reduce by 1 dose level
Two readings separated by at least 1 hr showing higher than 160 mmHg	or	Two readings separated by at least 1 hr showing higher than 105 mmHg	Interrupt dosing and adjust antihypertensive medication When BP controlled at less than 150/100 mmHg, restart axitinib at 1 dose level lower
Recurrent higher than 150 mmHg	or	Recurrent higher than 100 mmHg	Repeat axitinib dose reduction by another

Hypertension			
(two readings separated by at least 1 hr) following previous dose reduction		(two readings separated by at least 1 hr) following previous dose reduction	dose level

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*

Avelumab		
No formal pharmacokinetic drug interaction studies have been conducted with avelumab. Since avelumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.		
	Interaction	**Clinical management**
Immunosuppressants (inc. corticosteroids)	Reduced efficacy of both immunosuppressants and avelumab possible due to pharmacodynamic interaction	It is recommended that patients requiring corticosteroids **prior** to treatment receive the lowest possible dose (preferably no greater than 10 mg prednisolone or equivalent steroid per day). **Once started** on avelumab the use of corticosteroids to treat immune related adverse events (irAEs) does not appear to impact the clinical response to avelumab. In patients requiring ongoing corticosteroids **post management** of an irAE, the dose should be as low as possible. Monitor for signs of organ rejection in transplant recipients.

Axitinib		
	Interaction	**Clinical management**
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir, verapamil, diltiazem etc.)	Increased toxicity of axitinib possible due to reduced clearance	Avoid combination or monitor for axitinib toxicity; reduce axitinib dose approximately by half during concomitant use of strong inhibitor
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of axitinib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to axitinib; consider careful upward titration of axitinib dose if strong inducer cannot be avoided
Drugs metabolised by CYP1A2 (e.g. theophylline etc.)	Increased effect/toxicity of these drugs possible due to inhibition of CYP1A2 by axitinib resulting in reduced clearance	Avoid combination or monitor for increased effect/toxicity of interacting drugs

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

Administration

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

product information monographs via the TGA website for further information.

Day 1 IV

Approximate treatment time: 90 minutes

Handling of monoclonal antibodies and waste management

Safe administration

General patient assessment and immunotherapy patient assessment prior to each treatment.

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

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify premedication taken or administer as prescribed.

Treatment - Time out

Avelumab

Administer avelumab:

- low protein binding 0.2 micron in-line or add-on filter should be used
- via IV infusion over 60 minutes
- observe for infusion-related reactions
- at first signs of infusion-related reaction obtain medical officer review
- flush with ~ 100 mL of sodium chloride 0.9%.

Mild infusion-related reaction:

- decrease the rate of infusion by 50% and monitor closely
- give any further doses with close monitoring.

Moderate infusion-related reaction:

- stop the infusion until symptoms are mild or have resolved
- restart the infusion at 50% of the previous rate
- observe the patient closely for the remainder of the infusion
- give any further doses with close monitoring and premedication

Severe infusion-related reaction:

- stop the infusion
- medical officer review
- permanently discontinue avelumab.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Days 1 - 14 (PO)

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

Axitinib

- administer orally TWICE a day
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with food or on an empty stomach - ensure the doses are taken consistently each time (either with or without food).

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

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

Discharge information

Axitinib tablets

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

Premedication

- Premedication for next cycle of chemotherapy.

Antiemetics

- Antiemetics if required or 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.

There can be an overlap between the immune-related and targeted-therapy-related adverse events with this treatment. Immune-related adverse events (irAEs) can escalate quickly and close monitoring of the patient is required. Immune-related symptoms should improve promptly after the introduction of immunosuppressive therapy. If this does not occur review the diagnosis and seek further specialist advice. Refer to the Management of immune related adverse events document for further information.

Immune related adverse events	
Cardiotoxicity	Cardiotoxicity is a rare but serious side effect, which may manifest as asymptomatic reduction in left ventricular ejection fraction (LVEF), arrhythmia, cardiomyopathy, myocarditis, pericarditis, cardiac fibrosis, hypertension, cardiac ischaemia, congestive heart failure (CHF) and cardiac arrest. Read more about Management of immune related adverse events.
Gastrointestinal toxicity	Colitis, diarrhoea or more bowel movements than usual; blood or mucous in stools; dark, tarry, sticky stools; abdominal pain or tenderness. Read more about Management of immune related adverse events
Haematological toxicity	Autoimmune haemolytic anaemia (AIHA), acquired thrombotic thrombocytopenic purpura (TTP), aplastic anaemia (AA), immune thrombocytopenia (ITP), acquired haemophilia (AH), haemolytic uremic syndrome (HUS) and lymphopenia are rare but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events.
Hepatotoxicity	Transaminase and total bilirubin elevation, jaundice, severe nausea or vomiting, pain on the right side of the abdomen, drowsiness, dark urine, bleeding or bruising more easily than normal, anorexia. Read more about Management of immune related adverse events.
Musculoskeletal toxicity	Inflammatory arthritis, temporal arteritis, arthralgia, myalgia, synovitis, vasculitis, polymyalgia-like syndrome and myositis. Read more about Management of immune related adverse events.
Neurological toxicity	Aseptic meningitis, myasthenia gravis, Guillain-Barre syndrome, encephalitis, meningeal symptoms, optic neuritis, neuropathy and acute inflammatory demyelinating polyneuropathy are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events.
Ocular toxicity	Eye pain, blurred vision, Uveitis/iritis, episcleritis, blepharitis, optic neuritis, tear duct stenosis, conjunctivitis, hyperlacrimation, watery or dry eyes and photophobia. Read more about Management of immune related adverse events.
Other endocrinopathies	Type 1 diabetes mellitus, hypophysitis, hypopituitarism and adrenal insufficiency are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events
Pulmonary toxicity	Radiographic changes, dyspnoea, new or worsening cough, hypoxia, tachycardia, chest pain or fever. Read more about Management of immune related adverse events.
Renal toxicity	Increase in serum creatinine, oliguria, haematuria, peripheral oedema and anorexia. Read more about Management of immune related adverse events.
Skin toxicity	Rash including full thickness, pruritus, skin blisters, ulceration and necrosis. Radiation recall can occur at site of previous radiation therapy. Symptoms include vesiculation, desquamation and ulceration of the skin. Read more about Management of immune related adverse events
Thyroid toxicity	Thyroid toxicity is common with immune checkpoint inhibitors. Hypothyroidism is most frequent however hyperthyroidism can also occur. Read more about Management of immune related adverse events

Non-immune related adverse events immediate (onset hours to days)	
Infusion reaction	Infusion-related reactions were reported commonly during treatment with avelumab. Severe infusion-related reactions have been reported. All patients should receive premedication with an anti-histamine and paracetamol prior to the first 4 infusions of avelumab. Further premedication is at the discretion of the treating physician.
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting

Non-immune related adverse events 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
Oral mucositis	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about oral mucositis
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
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.
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
Arthralgia and myalgia	Generalised joint pain or and/or stiffness and muscle aches, often worse upon waking or after long periods of inactivity. Can improve with movement. May be mild or severe, intermittent or constant and accompanied by inflammation. Read more about arthralgia and myalgia
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash
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	
Cardiotoxicity	Cardiotoxicity may manifest as asymptomatic reduction in left ventricular ejection fraction (LVEF), arrhythmia, cardiomyopathy, hypertension, cardiac ischaemia and congestive heart failure (CHF). The risk of cardiotoxicity is increased by a number of factors, particularly a history of heart disease and electrolyte imbalances. Read more about cardiotoxicity associated with anti-cancer drugs

Non-immune related adverse events late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Alopecia - partial	Hair thinning and/or patchy hair loss. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling

Evidence

The evidence supporting this protocol is provided by a phase III multicentre international trial (Javelin Renal 101) involving 886 patients comparing avelumab plus axitinib with sunitinib.[1]

Between March 2016 and December 2017, 442 patients were assigned to receive avelumab (10 mg/kg on day 1) plus axitinib (5 mg twice daily on a continuous dosing schedule) every 14 days, and 444 assigned to receive sunitinib (50 mg once daily for 4 weeks of a 6-week cycle).

The co-primary endpoint was progression-free survival (PFS) and overall survival (OS) among patients with PD-L1 positive tumours (≥1% of immune cells staining positive within the tumour area of the tested tissue sample) across all IMDC risk groups. Secondary end points included PFS and OS in the overall population, PFS as determined by investigator assessment, objective response rate (ORR), adverse events, pharmacokinetic measures, tumour tissue biomarkers, and patient-reported outcomes.

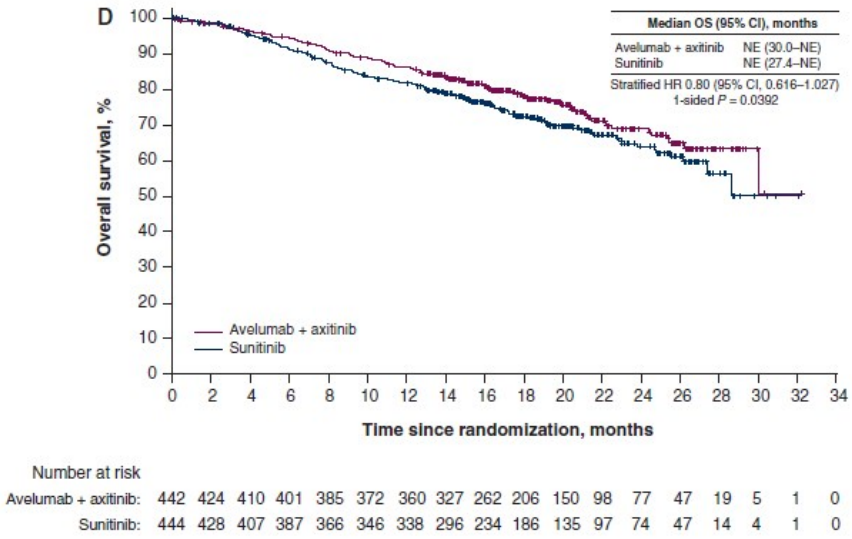
Efficacy

In the overall population, after a median follow up of 10.8 months for avelumab and axitinib and 8.6 months for sunitinib, median PFS was 13.8 months for avelumab and axitinib (95% CI: 11.1 to [could not be estimated]) vs 8.4 months in sunitinib group (95% CI: 6.9 to 11.1) (HR=0.69; 95% CI: 0.56 to 0.84; p<0.001).[1]

At second-interim analysis (median follow up 19 months for OS), median PFS in the overall population was 13.3 (95%CI: 11.1-15.3) in avelumab plus axitinib group versus 8.0 (95%CI: 6.7-9.8) in the sunitinib group (stratified HR= 0.69, 95%CI: 0.574- 0.825, 1-sided P<0.0001).[2] OS data is still immature. Benefit was seen across all IMDC risk groups in ITT analysis.[2]

It is important to note that this combination is supported by improvement in PFS rather than OS to date.

Kaplan-Meier estimates of median OS in the overall population[2]



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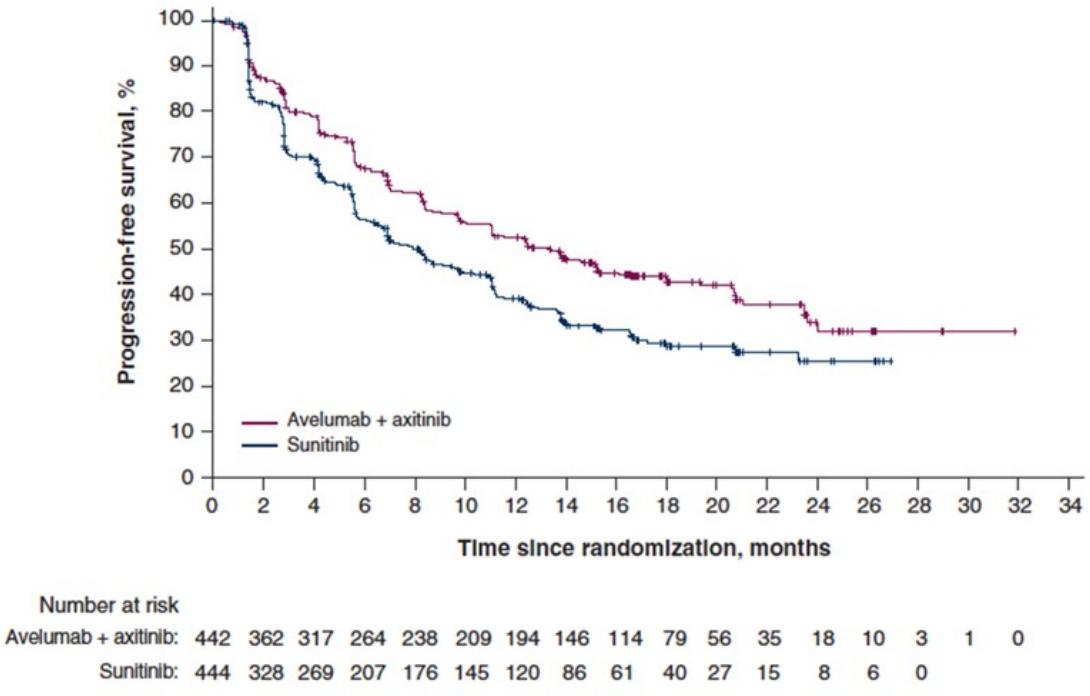
Kaplan-Meier estimates of median PFS in the overall population[2]



End point summary[2]

End point	Overall population	P-value
OS months (95% CI)	A+A: NE (30-NE) S: NE (27.4-NE) HR 0.80	0.0392
ORR % (95% CI)	A+A: 52.5 (47.7-57.2) S: 27.3 (23.2-31.6)	N/A
Median time to response (range) months (95% CI)	A+A: 2.6 (1.2-13.8) S: 3.2 (1.2-11.6)	N/A

Abbreviations: A+A = Avelumab plus axitinib; S = sunitinib, NE = not estimable.

Quality of life data has not been published.

Toxicity

Treatment related adverse events[1]

Table 3. Adverse Events of Any Grade That Occurred during Treatment in 10% or More of Patients or Adverse Events of Grade 3 or Higher That Occurred in 5% or More of Patients in the Overall Population of 873 Patients.

Variable	Avelumab plus Axitinib (N=434)		Sunitinib (N=439)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Patients with any events	432 (99.5)	309 (71.2)	436 (99.3)	314 (71.5)
Diarrhea	270 (62.2)	29 (6.7)	209 (47.6)	12 (2.7)
Hypertension	215 (49.5)	111 (25.6)	158 (36.0)	75 (17.1)
Fatigue	180 (41.5)	15 (3.5)	176 (40.1)	16 (3.6)
Nausea	148 (34.1)	6 (1.4)	172 (39.2)	7 (1.6)
Palmar–plantar erythrodysesthesia syndrome	145 (33.4)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	133 (30.6)	2 (0.5)	14 (3.2)	0
Decreased appetite	114 (26.3)	9 (2.1)	126 (28.7)	4 (0.9)
Hypothyroidism	108 (24.9)	1 (0.2)	61 (13.9)	1 (0.2)
Stomatitis	102 (23.5)	8 (1.8)	103 (23.5)	4 (0.9)
Cough	100 (23.0)	1 (0.2)	83 (18.9)	0
Headache	89 (20.5)	1 (0.2)	71 (16.2)	1 (0.2)
Dyspnea	86 (19.8)	13 (3.0)	57 (13.0)	7 (1.6)
Arthralgia	85 (19.6)	4 (0.9)	50 (11.4)	2 (0.5)
Decreased weight	85 (19.6)	12 (2.8)	30 (6.8)	4 (0.9)
Vomiting	80 (18.4)	4 (0.9)	87 (19.8)	7 (1.6)
Back pain	77 (17.7)	2 (0.5)	65 (14.8)	8 (1.8)
Constipation	77 (17.7)	0	64 (14.6)	0
Increased alanine aminotransferase level	74 (17.1)	26 (6.0)	50 (11.4)	11 (2.5)
Chills	69 (15.9)	1 (0.2)	33 (7.5)	0
Asthenia	64 (14.7)	11 (2.5)	72 (16.4)	13 (3.0)
Increased aspartate aminotransferase level	63 (14.5)	17 (3.9)	52 (11.8)	9 (2.1)
Rash	62 (14.3)	2 (0.5)	49 (11.2)	2 (0.5)
Mucosal inflammation	61 (14.1)	5 (1.2)	61 (13.9)	5 (1.1)
Pruritus	61 (14.1)	0	22 (5.0)	0
Abdominal pain	59 (13.6)	5 (1.2)	43 (9.8)	8 (1.8)
Dysgeusia	57 (13.1)	0	142 (32.3)	0
Pyrexia	56 (12.9)	0	62 (14.1)	1 (0.2)
Infusion-related reaction	53 (12.2)	7 (1.6)	0	0
Pain in extremity	52 (12.0)	1 (0.2)	46 (10.5)	3 (0.7)
Dizziness	51 (11.8)	2 (0.5)	47 (10.7)	3 (0.7)
Oropharyngeal pain	44 (10.1)	0	27 (6.2)	0
Dry skin	43 (9.9)	0	44 (10.0)	0
Edema, peripheral	39 (9.0)	2 (0.5)	45 (10.3)	1 (0.2)
Epistaxis	37 (8.5)	0	49 (11.2)	0
Dyspepsia	35 (8.1)	0	83 (18.9)	0
Anemia	26 (6.0)	7 (1.6)	101 (23.0)	36 (8.2)
Thrombocytopenia	15 (3.5)	1 (0.2)	85 (19.4)	27 (6.2)
Decreased platelet count	8 (1.8)	0	63 (14.4)	22 (5.0)
Neutropenia	6 (1.4)	1 (0.2)	83 (18.9)	35 (8.0)
Decreased neutrophil count	1 (0.2)	0	45 (10.3)	25 (5.7)

References

1 Motzer, R. J., K. Penkov, J. Haanen, et al. 2019. "Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma."

N Engl J Med 380(12):1103-1115.

2 Choueiri, T. K., R. J. Motzer, B. I. Rini, et al. 2020. "Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma." Ann Oncol 31(8):1030-1039.

History

Version 2

Date	Summary of changes
04/03/2022	Protocol updated based on the consensus gained at the immunotherapy reference committee meeting held on 4th of March 2022. The following changes have been made across all immune checkpoint inhibitor protocols: • Clinical information- general irAEs, hepatitis and HIV, and fertility blocks updated. Individual irAE-related blocks removed. New block (baseline investigations) added. • Side effects- preamble wording updated. • Patient information- side effect section preamble wording updated. Pregnancy and breastfeeding block in general advice section updated. Version number increased to V.2.
20/09/2022	Blood tests in clinical information section updated to remove information about CTLA-4 containing regimens.
30/09/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review in 2 years.

Version 1

Date	Summary of changes
22/10/2021	New protocol discussed at Medical Oncology Reference Committee meeting.
11/11/2021	Approved and published on eviQ. Review 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.

First approved: 11 November 2021
Last reviewed: 30 September 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/4039
19 Jun 2023

Patient information - Kidney cancer advanced or metastatic - Avelumab and axitinib

Patient's name:

Your treatment

It is important to understand that avelumab and axitinib are not traditional chemotherapy drugs and have a different way of working. Avelumab is an immunotherapy treatment (also called anticancer drug) that works with your immune system to detect and destroy cancer cells. Axitinib works by targeting the cancer cells to stop them growing and spreading.

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

Avelumab and axitinib

Avelumab is given once every 14 days and axitinib is given continuously. Your doctor will advise you how long to take the treatment for.

Day	Treatment	How it is given	How long it takes
1	**Avelumab** (*a-VEL-ue-mab*)	By drip into a vein	About 90 minutes
Continuous	**Axitinib** (*ax-i-ti-nib)*	Take orally TWICE a day, approximately 12 hours apart with or without food. Swallow whole with a glass of water, do not break, crush or chew tablets. 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.	

Prior to your treatment tell your doctor if you are taking any other medicines (e.g. corticosteroids, immunosuppressive therapy), have or ever had chronic liver infections e.g. hepatitis B (HBV) or C (HCV), human immunodeficiency virus (HIV) or an organ transplant.

When to get help

It is important that you tell your doctor or nurse immediately if you develop any of the symptoms listed below in the side effects section. If you can't contact your doctor or nurse, go to your nearest hospital Emergency Department for help.

Emergency contact details

Ask your doctor or nurse from your treating team who to contact if you have a problem

Daytime:.....

Night/weekend:.....

Other instructions:.....

.....

.....

.....

.....

.....

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

- leaking from the area where the drugs are being given

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

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

You will need to have a blood test before you start treatment and regularly throughout your treatment. Your doctor or nurse will tell you when to have these blood tests.

Other medications given during this treatment

- **Avelumab premedication:** before your treatment with avelumab you will need to take some tablets called a premedication to help prevent you from having a reaction to the avelumab.
- **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.
- **Steroids:** you may be given some steroid tablets to help reduce immune-related side effects. Your doctor or nurse will tell you how and when to take the steroids. You may need to monitor your blood sugar levels closely while you are taking steroids. If you have diabetes, your diabetic medication may need to be adjusted because of the effects of steroids. Speak to your diabetes advisor.

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.

Immunotherapy may cause serious immune reactions against your own body. These are called immune-related adverse events. They may occur during your treatment, or after your treatment has ended. Immunotherapy can affect many parts of your body. Some side effects can cause severe or life threatening conditions, so even mild side effects must be reported immediately. Do not try to treat these symptoms yourself without talking to your doctor or nurse first. You will be given an information pack at the start of your treatment. You will be given an information pack at the start of your treatment. This contains an alert card which you should carry with you at all times. Bring this alert card with you to hospital, especially if you are unwell or attending the emergency department.

This treatment uses both targeted therapy and immunotherapy. These drugs work in different ways, but can cause similar side effects.

Immune related side effects

Heart problems	• You may get: ◦ chest pain or tightness ◦ shortness of breath ◦ swelling of your ankles ◦ an abnormal heartbeat. • Heart problems are uncommon but potentially fatal. If heart problems were to occur, symptoms usually start within the first 3 months of treatment, but can happen at any time even after the treatment has finished. • Tell your doctor if you have a history of heart problems or high blood pressure. • Before or during treatment, you may be asked to have a test to see how well your heart is working. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**
Bowel and stomach inflammation	• You may get: ◦ bowel motions (stools, poo) that are more frequent or more liquid (diarrhoea) ◦ blood or mucous in your stool ◦ dark, tarry, or sticky bowel motions ◦ bloating, cramping, pain or tenderness in your stomach area. • Inform your doctor or nurse immediately if you get diarrhoea • Take your anti-diarrhoeal or steroid medication as directed by your doctor. • Drink plenty of fluids (unless you are on a fluid restriction). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled despite taking anti-diarrhoea medicine, severe stomach pains and bloating, and/or if you feel dizzy or light-headed.**
Blood problems	• Blood problems are infrequent but can be serious. • You may feel dizzy, light-headed, tired, weak and appear more pale than usual. • You may get: • dark, tarry bowel motions (stools, poo) • blood in your urine or not urinating as often • dark-coloured urine • yellowing of the whites of your eyes, and/or your skin • pinpoint red spots on your skin • unexplained bleeding • major bruising • a fever • shortness of breath • a severe headache • confusion • faster heartbeat than normal • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if it has been longer than 12 hours since you have emptied your bladder or if you get any of the symptoms listed above.**

Liver damage	• You may get: ◦ fatigue ◦ severe nausea and vomiting ◦ weight loss ◦ bruising or bleeding more easily ◦ pain or tenderness on the right side of your stomach area ◦ dark coloured urine ◦ yellowing of the whites of your eyes and/or your skin ◦ itchy skin ◦ drowsiness • You will have regular blood tests to check how well your liver is working. • Take your steroid medication as directed by your doctor. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes or skin look yellow, if you have unexplained bruising or bleeding or if you have severe stomach pain.**
Muscle and joint problems	• You may get: • muscle or joint stiffness, especially after a period of rest • muscle weakness • pain in your muscles or joints • joint swelling • tiredness • headaches • Take your pain relief or steroid medication as directed by your doctor. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above.**
Nervous system problems	• Nervous system changes are rare, but can be serious. • You may get: ◦ headaches ◦ fever ◦ stiff neck ◦ confusion or difficulty concentrating ◦ dizziness or drowsiness ◦ loss of consciousness ◦ muscle weakness or pain ◦ numbness or tingling in your hands or feet ◦ jerky movements. • Take your steroid medication as directed by your doctor. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**
Eye problems	• You may get: ◦ eye pain ◦ itchy eyes ◦ red or swollen eyes ◦ blurred or change in vision ◦ change in colour vision ◦ watery or gritty eyes ◦ dry eyes ◦ sensitivity to light. • Protect your eyes from the weather (sun and wind) by wearing sunglasses. • Use your eye drops or take your steroid medication as directed by your doctor. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above.**

Hormone problems	• Hormone changes are infrequent, but can be serious. • You may get: ◦ headaches ◦ tiredness, dizziness or fainting ◦ abnormal heartbeat (faster than usual) ◦ a feeling of being hot or cold more easily ◦ excessive sweating ◦ weight changes ◦ a deepened voice ◦ irregular or absent periods ◦ nausea and vomiting ◦ thirsty and need to urinate more often than normal ◦ high blood sugar levels ◦ pain in your stomach area ◦ muscle pain or weakness ◦ difficulty sleeping ◦ agitated more easily ◦ changes in your mood or behaviour, such as decreased sex drive or irritability. • Take your hormone or steroid medication as directed by your doctor. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you feel confused, weak, dizzy, or faint, or get sudden pain in your lower back or legs.**
Lung problems	• You may get: ◦ shortness of breath ◦ difficulty breathing ◦ faster heartbeat than normal ◦ chest pain ◦ new or worsening cough ◦ fever. • Your doctor will monitor how well your lungs are working during your treatment. • Take your steroid medication as directed by your doctor. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**
Kidney damage	• This treatment can cause changes to how your kidneys work. • You may get: ◦ a feeling of needing to urinate less often than normal ◦ blood in your urine ◦ swollen hands and feet ◦ loss of appetite. • You will have regular blood tests to check how well your kidneys are working. • You may need to drink more fluids while you are having treatment. Your doctor or nurse will tell you if you need to do this. • Take your steroid medication as directed by your doctor. • **Tell your doctor or nurse as soon as possible if you notice that your urine changes colour or you don't need to empty your bladder as often.**

Skin rash	• You may get
	  ◦ a red rash
	  ◦ a bumpy rash
	  ◦ dry and itchy skin
	  ◦ skin peeling or blisters.
	  ◦ if you have had previous radiation therapy to an area this effect may be worse
	• Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream.
	• Avoid scratching your skin.
	• Avoid wearing tight fitting clothing
	• Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher.
	• Take your antihistamine medication or apply your steroid cream as directed by your doctor.
	• **Tell your doctor or nurse as soon as possible if you notice any changes to the rash like pain or pus forming.**

Thyroid problems	Thyroid problems are common with this treatment. The most common problem is an underactive thyroid gland (hypothyroidism), occasionally you may get an overactive thyroid gland (hyperthyroidism).
	• If you have an **underactive** thyroid, you may get:
	  ◦ fatigue and low energy levels
	  ◦ depression
	  ◦ slow heart rate
	  ◦ unexplained weight gain
	  ◦ intolerance to cold temperatures
	  ◦ fatigued and aching muscles
	  ◦ dry, coarse skin
	  ◦ puffy face
	  ◦ hair loss
	  ◦ constipation
	  ◦ problems with concentration
	  ◦ changes in your periods
	• If you have an **overactive** thyroid, you may get
	  ◦ abnormal heartbeat (faster than usual)
	  ◦ a feeling of being hot or cold more easily
	  ◦ excessive sweating
	  ◦ difficulty sleeping
	  ◦ anxiety, nervousness or agitated more easily
	  ◦ diarrhoea
	  ◦ changes in your periods
	• You will have regular blood tests to check how well your thyroid is working.
	• Take your hormone or steroid medication as directed by your doctor.
	• Tell your doctor or nurse if you get any of the symptoms listed above.

Non-immune related side effects 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.**

Non-immune related side effects 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.**
Mouth pain and soreness (mucositis)	• You may have: ◦ bleeding gums ◦ mouth ulcers ◦ a white coating on your tongue ◦ pain in the mouth or throat ◦ difficulty eating or swallowing. • Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks. • Try bland and soft foods. • Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so. • Rinse your mouth after you eat and brush your teeth, using either: ◦ 1/4 teaspoon of salt in 1 cup of warm water, or ◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water • Ask your doctor or nurse for eviQ patient information - Mouth problems during cancer treatment. • **Tell your doctor or nurse if you get any of the symptoms listed above.**

Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
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.**
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.**
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.**
Joint and muscle pain and stiffness	• You may get muscle, joint or general body pain and stiffness. • Applying a heat pack to affected areas may help. • Talk to your doctor or nurse about other ways to manage these symptoms. You may need medication to help with any pain.

Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**
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.**
Heart problems	• You may get: ◦ chest pain or tightness ◦ shortness of breath ◦ swelling of your ankles ◦ an abnormal heartbeat. • Heart problems can occur months to years after treatment. • Tell your doctor if you have a history of heart problems or high blood pressure. • Before or during treatment, you may be asked to have a test to see how well your heart is working. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**

Non-immune related side effects late (onset weeks to months)	
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Hair thinning	• Your hair may become dry and may break easily. • You may lose some of your hair. • Use a gentle shampoo and a soft hairbrush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat or scarf. • Protect your scalp from the sun with a hat and sunscreen of SPF 50 or higher. • Ask your doctor or nurse about the Look Good Feel Better program (www.lgfb.org.au)

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 treatments.
- 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.
- Don't have **any** vaccinations without talking to the doctor who is managing your cancer treatment.
- People you live with should be fully vaccinated, 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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