Hepatic advanced or metastatic atezolizumab and beVACizumab

ID: 3881 v.3 **Endorsed**

⚠ Oesophageal varices:
This treatment is associated with an increased risk of fatal gastro-oesophageal variceal bleeding. Patients must be evaluated for the presence of varices and have them treated as indicated within 6 months prior to initiating this treatment. This treatment should be avoided in patients with varices that are untreated, actively bleeding (including recent bleeding) or at high risk of bleeding, or in patients who have not been assessed for varices within 6 months.

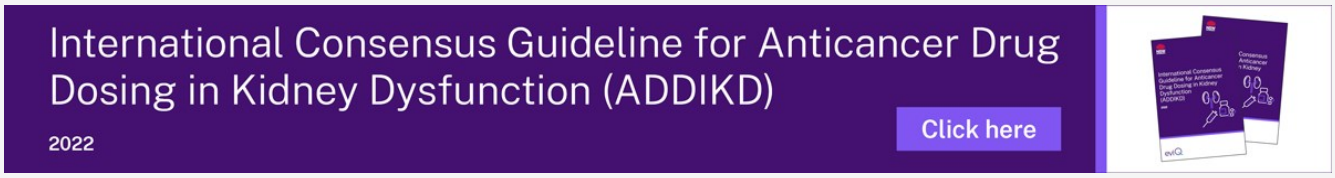
Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer using immunological agents. Before commencing immunotherapy treatment in any patient, clinicians should have an understanding of the immune-related adverse events (irAEs) associated with immunotherapy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

This treatment should be initiated in consultation with a multidisciplinary team including a gastroenterologist and medical oncologist.

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

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

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



Related pages:

- Hepatic advanced soRAFENib
- Hepatic advanced or metastatic leNVAtinib

Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
Atezolizumab	1,200 mg	IV infusion	1
beVACizumab	15 mg/kg *#	IV infusion	1

*If bevacizumab is discontinued consider continuing atezolizumab as monotherapy. Atezolizumab monotherapy alternative dosing schedule 1680 mg every 28 days.[1]

Frequency: 21 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:
In the first few months after the start of immunotherapy, some patients can have a 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 is believed to be deriving clinical benefit.

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: Bevacizumab is on the PBS general schedule

Atezolizumab is PBS authority

Cost: ~ $8,270 per cycle

Treatment schedule - Detail

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

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

Cycle 1 and further cycles

Day 1		
Atezolizumab	1,200 mg (IV infusion)	in 250 mL sodium chloride 0.9% over 60 minutes (1st dose); if first dose is well tolerated subsequent doses may be administered over 30 minutes
beVACizumab	15 mg/kg (IV infusion)	in 100 mL sodium chloride 0.9% over 90 minutes (1st dose); if first dose is well tolerated subsequent doses may be administered over 30 minutes*#

* If bevacizumab is discontinued consider continuing atezolizumab as monotherapy. Atezolizumab monotherapy alternative dosing schedule 1680 mg every 28 days.[1]

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

Frequency: 21 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

Indications:

- Treatment of advanced or unresectable hepatocellular carcinoma (HCC) not amenable to curative or locoregional therapies, who have not received prior systemic therapy
- Barcelona Clinic Liver Cancer (BCLC) stage B or C
- Child-Pugh A classification of liver function
- Oesophagogastroduodenoscopy for varices within the last 6 months
- ECOG performance status 0 or 1.

Cautions:

- Gastro-oesophageal varices that are untreated or incompletely treated, actively bleeding (including recent bleeding) or at high risk of bleeding, or in patients who have not been assessed for varices within 6 months

- Current or recent (within 10 days prior to treatment start) use of full-dose anticoagulants, thrombolytic agents or anti-platelet therapy.

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

Safety alert oesophageal varices	An increased rate of oesophageal variceal bleeding was seen in patients treated with atezolizumab-bevacizumab, in some cases leading to death. Patients should be evaluated for the presence of varices and have varices treated as indicated within 6 months prior to initiating 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
Emetogenicity MINIMAL	No antiemetics should be routinely administered before treatment in patients without a history of nausea and vomiting. If patients experience nausea and/or vomiting, consider using the low antiemetic prophylaxis 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)
Gastrointestinal perforation	Bevacizumab has been associated with serious cases of gastrointestinal (GI) perforation and should be permanently discontinued in patients who develop it.
Haemorrhage	Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis). Bevacizumab should be used with caution in patients at risk of bleeding.
Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing bevacizumab and blood pressure should be monitored during therapy. Commence or adjust antihypertensive medication as clinically indicated.
Proteinuria	Patients may be at increased risk of developing proteinuria when treated with bevacizumab. Baseline urinalysis for proteinuria is recommended prior to commencement of therapy, and as clinically indicated. Routine testing prior to each treatment is no longer recommended, as dose reductions for low/intermediate levels of proteinuria are not recommended. Clinicians are advised to consider evaluating for proteinuria periodically (e.g. every 3 to 4 months) or in patients with clinical concerns (e.g. oedema/unexplained hypoalbuminemia) as treatment interruption may be required if proteinuria is significant (e.g. > 3 g/L). Read more about proteinuria
Reversible posterior leukoencephalopathy syndrome (RPLS)	Bevacizumab should be discontinued in patients who develop reversible posterior leukoencephalopathy syndrome (RPLS). The risk of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)

Thromboembolism	Both arterial and venous thromboembolic events have been observed in patients with this treatment. Therefore, use with caution in patients at increased risk or with a history of thrombotic events (i.e., cerebrovascular and cardiovascular disease)
Wound healing	Bevacizumab may adversely affect wound healing and should not be initiated in patients with a serious non-healing wound or ulcer. Elective surgery should not be undertaken within 6 weeks from the last dose of bevacizumab. Bevacizumab can be restarted 28 days after surgery provided wound healing is complete. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
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 .

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).

Immune checkpoint inhibitor dose modifications

- Dose reduction is not recommended
- No dose adjustment is required in the elderly, mild or moderate renal impairment or mild hepatic impairment. Immune checkpoint inhibitors have not been studied in patients with severe renal impairment or moderate to severe hepatic impairment.

Management of immune-related adverse events (irAEs)

Link to Management of immune-related adverse events (irAEs)

Bevacizumab dose modifications

Renal impairment
No dose modifications necessary

Hepatic impairment
No dose modifications necessary

Cease bevacizumab if any of the following occur:
• haemorrhagic event grade 3 or greater • life threatening venous thromboembolic event, pulmonary embolism, cerebrovascular event or arterial insufficiency • arterial thromboembolic event • grade 4 hypertension or persisting grade 3 hypertension • nephrotic syndrome • gastrointestinal perforation or fistula formation • episode of reversible posterior leukoencephalopathy syndrome (RPLS).

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*

Atezolizumab		
No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab.		
	Interaction	**Clinical management**
Immunosuppressants (inc. corticosteroids)	Reduced efficacy of both immunosuppressants and atezolizumab 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 atezolizumab the use of corticosteroids to treat immune related adverse events (irAEs) does not appear to impact the clinical response to atezolizumab. 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.

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

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

Administration

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

product information monographs via the TGA website for further information.

Day 1

Approximate treatment time: 2.5 hours (initial); 90 minutes (subsequent)

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) with sodium chloride 0.9%.

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Administer antiemetics if required

Treatment - Time out

Atezolizumab

- atezolizumab has a short expiry- 8 hours at room temperature and 24 hours when refrigerated

Administer atezolizumab:

- via IV infusion over 60 minutes for first infusion. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes
- flush with 50 mL of sodium chloride 0.9%

Mild or moderate (grade 1 or 2) infusion-related reaction:

- decrease the rate of infusion and monitor closely
- give any further doses with close monitoring
- premedication with paracetamol and an antihistamine should be considered for further doses

Severe (grade 3 or 4) infusion-related reaction:

- stop infusion immediately
- medical officer review
- permanently discontinue atezolizumab

Bevacizumab

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

Prior to administration check:

- blood pressure
- baseline urinalysis for protein and repeat as clinically indicated (read more about proteinuria)

Administer bevacizumab:

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

Stop infusion at first sign of reaction:

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

Remove IV cannula and/or deaccess TIVAD or CVAD.

Discharge information

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)	
Headache	

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
Diarrhoea	Read more about treatment induced diarrhoea
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Oesophageal varices	Increased risk of gastro-oesophageal variceal haemorrhage. Patients should be evaluated for the presence of varices and have varices treated as indicated within 6 months prior to initiating therapy.
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.
Epistaxis	Acute bleeding from the nostril(s), nasal cavity, or nasopharynx.
Fatigue	Read more about fatigue
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
Haemorrhage	
Proteinuria	Read more about proteinuria
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.
Hypertension	High blood pressure is commonly associated with many anti-cancer drugs. Pre-existing hypertension should be controlled prior to initiation of drugs capable of causing hypertension.
Reversible posterior leukoencephalopathy syndrome (RPLS)	A neurological disorder which may present with headache, seizures, lethargy, confusion, blindness and/or other visual and neurological disturbances. Mild to severe hypertension may also occur. Read more about reversible posterior leukoencephalopathy syndrome (RPLS)

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

Evidence

The evidence supporting this protocol is provided by a phase 3 open-label multicentre international randomised trial (IMbrave150)[3] involving 501 patients comparing atezolizumab plus bevacizumab with sorafenib in patients with unresectable hepatocellular carcinoma and Child-Pugh A classification of liver function who had not previously received systemic treatment. Key exclusion criteria included history of autoimmune disease, untreated or incompletely treated oesophageal or gastric varices and treatment with therapeutic anticoagulation or antiplatelet agents other than low-dose aspirin.

Between March 15, 2018 and January 30, 2019, 501 patients were randomised in a 2:1 ratio to receive either atezolizumab 1200 mg plus bevacizumab 15 mg/kg intravenously every 3 weeks (336 patients) or sorafenib 400 mg orally twice daily (165 patients) until unacceptable toxic effects occurred or there was a loss of clinical benefit.

The primary end points were overall survival (OS) and progression-free survival (PFS) and secondary end points were objective

response rate, duration of response, time to deterioration of quality of life, physical functioning and role functioning.

Atezolizumab-bevacizumab was associated with a longer OS and PFS when compared to sorafenib.

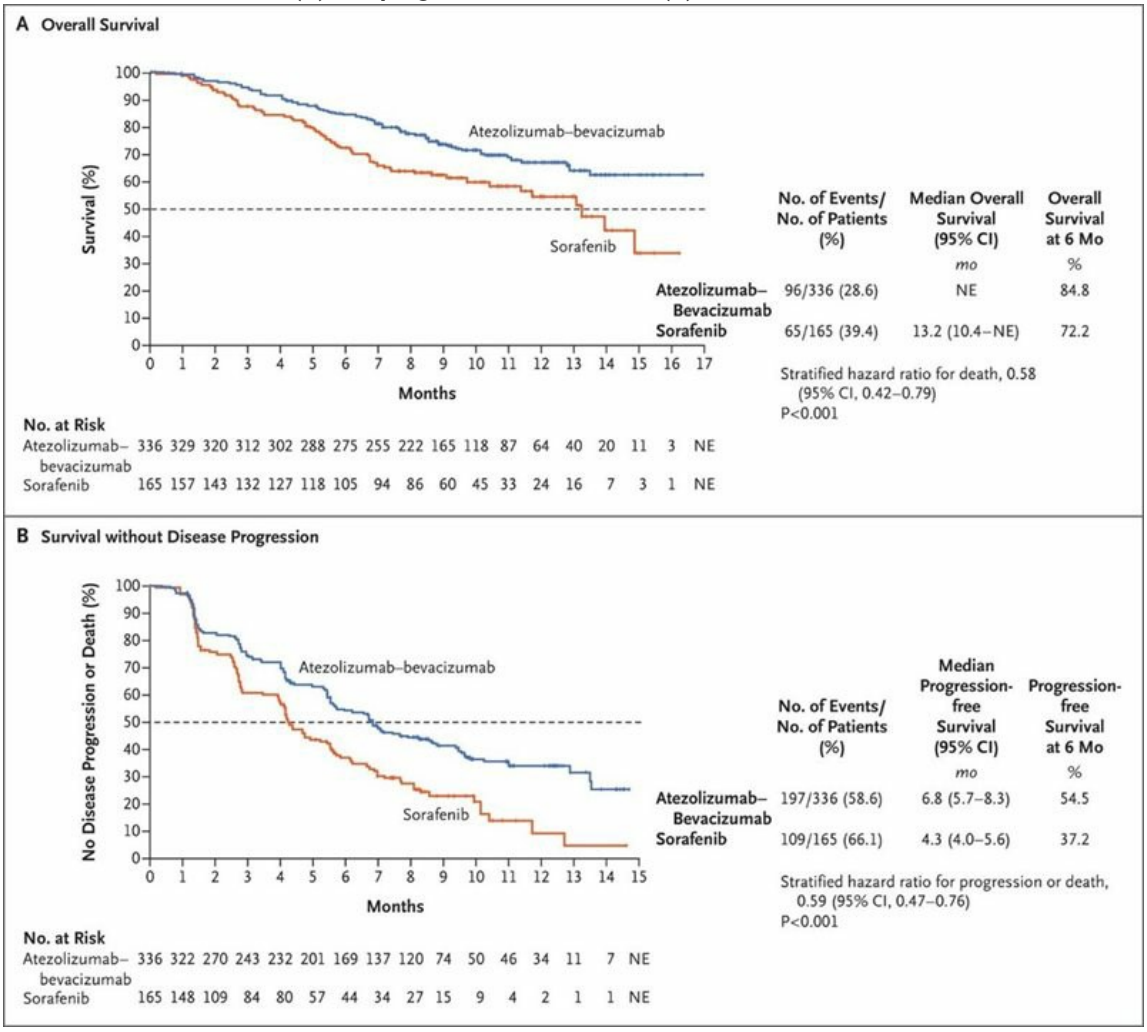
Efficacy

After a median follow up of 8.6 months 28.6% of patients in the atezolizumab–bevacizumab group and 39.4% in the sorafenib group had died (stratified hazard ratio for death, 0.58; 95% confidence interval [CI], 0.42 to 0.79; P<0.001).[3]

Median overall survival was not reached in the atezolizumab–bevacizumab group, and 13.2 months (10.4 – NE) in the sorafenib group. Rates of OS at 12 months were 67.2% in the atezolizumab-bevacizumab group (95% CI, 61.3 to 73.1) vs 54.6% (95% CI, 45.2 to 64.0) in the sorafenib group.[3]

Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001).

Kaplan-Meier curve of overall survival (A) and progression free survival (B)[3]



Secondary efficacy outcomes[3]

Table 2. Secondary Efficacy Outcomes.*

Variable	RECIST 1.1			HCC-Specific mRECIST		
	Atezolizumab–Bevacizumab (N=326)	Sorafenib (N=159)	Difference (P Value)†	Atezolizumab–Bevacizumab (N=325)	Sorafenib (N=158)	Difference (P Value)†
Confirmed objective response — no. (% [95% CI])‡	89 (27.3 [22.5–32.5])	19 (11.9 [7.4–18.0])	15.4 (<0.001)	108 (33.2 [28.1–38.6])	21 (13.3 [8.4–19.6])	19.9 (<0.001)
Complete response — no. (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response — no. (%)	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease — no. (%)	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate — no. (%)§	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease — no. (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated — no. (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing — no. (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff — no./total no. (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

* Included are patients who presented with measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and according to hepatocellular carcinoma (HCC)–specific modified RECIST (mRECIST), as assessed at an independent review facility. CI denotes confidence interval.
† The difference is the between-group difference (atezolizumab–bevacizumab minus sorafenib) in the percentage of patients with confirmed response, expressed in percentage points. The P value was derived from a Cochran–Mantel–Haenszel test. Randomization, which was performed through an interactive voice-response or Web-response system, included as stratification factors geographic region (Asia excluding Japan vs. the rest of the world), alpha-fetoprotein level (<400 ng per milliliter vs. ≥400 ng per milliliter) at baseline, and macrovascular invasion, extrahepatic spread, or both (yes vs. no).
‡ Confirmed objective response was defined as a response (complete or partial) seen at two consecutive tumor assessments at least 28 days apart.
§ The control rate is the sum of complete response, partial response, and stable disease.

Patient-reported quality of life was collected for >80% of patient in this trial. Measures were favourable in the atezolizumab–bevacizumab group, with delayed deterioration of patient-reported quality of life (median time to deterioration, 11.2 months with atezolizumab–bevacizumab vs. 3.6 months with sorafenib; hazard ratio, 0.63; 95% CI, 0.46 to 0.85).[3]

Toxicity

Rates of any adverse events and grade 3 or 4 adverse events were similar across both treatment groups. One or more of the trial drugs was discontinued due to an adverse event in 15.5% of patients in the atezolizumab–bevacizumab group compared with 10.3% in the sorafenib group.[3]

In the atezolizumab-bevacizumab group, there were 15 treatment-related deaths. Of these, 4 were attributable to gastrointestinal or variceal haemorrhage and one was attributed to gastric ulcer perforation. There were 9 treatment-related deaths in the sorafenib group.

Adverse events[3]

Table 4. Adverse Events with an Incidence of More Than 10% in Either Group.

Event	Atezolizumab–Bevacizumab (N=329)		Sorafenib (N=156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion-related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar–plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

References

1 Morrissey, K. M., M. Marchand, H. Patel, et al. 2019. "Alternative dosing regimens for atezolizumab: an example of model-informed drug development in the postmarketing setting." Cancer Chemother Pharmacol 84(6):1257-1267.

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

3 Finn, R. S., S. Qin, M. Ikeda, et al. 2020. "Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma." N Engl J Med 382(20):1894-1905.

History

Version 3

Date	Summary of changes
13/04/2022	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: • Indications and patient populations- previous radiation to the lungs added to precautions.

Date	Summary of changes
	• 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.3.
20/09/2022	Blood tests in clinical information section updated to remove information about CTLA-4 containing regimens.
21/10/2022	Bevacizumab treatment schedule note updated based on reference committee consensus to add that it is safe to give the initial dose of bevacizumab over 30 minutes.

Version 2

Date	Summary of changes
28/05/2021	Protocol flag added regarding bevacizumab biosimilar and administration time information. Treatment schedule - bevacizumab rapid infusion information added. Drug status - updated to include bevacizumab on PBS general schedule. Patient information - bevacizumab infusion time information updated in 'your treatment' section. Version increased to V.2.
20/01/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review 2 years.

Version 1

Date	Summary of changes
23/10/2020	New protocol taken to Medical Oncology Reference Committee meeting.
02/11/2020	Protocol approved and published. Review 1 year.
20/11/2020	The following change have been made across all immune checkpoint inhibitor protocols as approved by the eviQ immunotherapy reference committee: • Treatment schedule - additional note added: radiation recall.

First approved: 2 November 2020
Last reviewed: 31 December 2021
Review due: 31 December 2023

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/3881
14 Jul 2023

Patient information - Liver cancer advanced or metastatic - Atezolizumab and bevacizumab

Patient's name:

Your treatment

It is important to understand that atezolizumab is not a traditional chemotherapy drug and has a different way of working. It is an immunotherapy treatment (also called anticancer drug) that works with your immune system to detect and destroy cancer cells.

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

Atezolizumab and bevacizumab

This treatment cycle is repeated every 21 days. Your doctor will advise you of the number of treatments you will have. If bevacizumab is stopped you may continue treatment with atezolizumab, your doctor will talk to you about this.

Day	Treatment	How it is given	How long it takes
1	**Atezolizumab** (*a-te-zoe-LIZ-ue-mab*) **Bevacizumab** (*be-vuh-SIZ-uh-mab*)	By a drip into a vein	About 2.5 hours for the first treatment. If no reactions, subsequent treatment may be given over a shorter amount of time.

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

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

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

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

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

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

Other information about your treatment

Changes to your dose or treatment delays

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

Blood tests and monitoring

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

Other medications given during this treatment

- **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.

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.

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. 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)	
Headache	• You can take paracetamol if you have a headache. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.**

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.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
Bleeding from the oesophagus (food pipe), stomach or bowel	• This side effect is can be very serious and life-threatening. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of these signs or symptoms:** ◦ **nausea or vomiting** ◦ **vomiting blood** ◦ **severe stomach pain** ◦ **swollen and hot skin around your stomach** ◦ **bleeding** ◦ **black, tarry or bloody stools** ◦ **fever or chills** ◦ **lightheadedness** ◦ **a fast heartbeat** ◦ **shortness of breath.**

Nose bleeds	• If your nose starts to bleed gently apply pressure on the soft part of nostrils below the bridge of the nose for at least 10 minutes. • It may help to put a cold pack over your forehead or the bridge of the nose. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if your nose will not stop bleeding.**
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.**
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.**
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.**
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.
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.**
High blood pressure (hypertension)	• You may not have any signs or symptoms if you have high blood pressure. • If it is severe you may get headaches, shortness of breath or feel dizzy. • Your blood pressure will be taken regularly during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the signs or symptoms listed above.**

Changes in the way your brain works [reversible posterior leukoencephalopathy syndrome (RPLS)]	• This treatment can have an effect on your brain, but this is rare. • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **headaches or vision problems** ◦ **nausea and vomiting** ◦ **tiredness** ◦ **confusion** ◦ **fits (seizures)** ◦ **high blood pressure.**

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.**

General advice for patients having cancer treatment

Blood clot risk

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

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal 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.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

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

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.

- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

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

Quitting smoking

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

Staying active

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

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

Where to get more information

Telephone support

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

General cancer information and support

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

Quit smoking information and support

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

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

Additional notes:

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects. While eviQ endeavours to link to reliable sources that provide accurate information, eviQ and the Cancer Institute NSW do not endorse or accept responsibility for the accuracy, currency, reliability or correctness of the content of linked external information sources. Use of this document is subject to eviQ's disclaimer available at www.eviQ.org.au

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