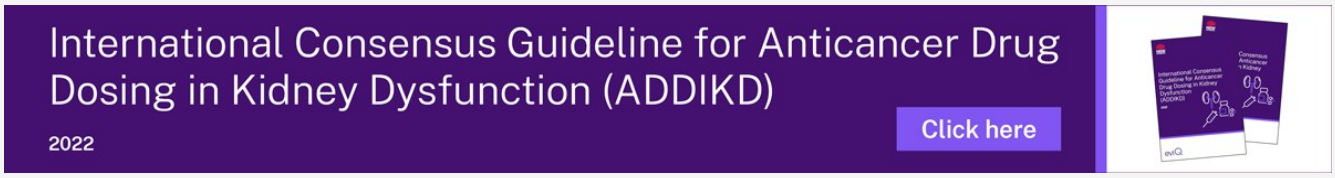
Hepatic advanced or metastatic leNVAtinib

ID: 3603 v.1 **Endorsed**

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

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



Related pages:

- Hepatic advanced or metastatic atezolizumab and beVACizumab

Treatment schedule - Overview

Drug	Dose	Route
leNVAtinib	12 mg ONCE a day	PO

Continuous until disease progression or unacceptable toxicity

Notes:
If bodyweight is < 60 kg, 8 mg ONCE a day (see dose modifications)

Overall management should be in consultation with a multidisciplinary liver cancer team.

Drug status: Lenvatinib is PBS authority

Lenvatinib is available as **4 mg** capsules.

Cost: ~ $7,150 per month

Treatment schedule - Detail

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

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

Continuous treatment		
leNVAtinib	12 mg (PO)	ONCE a day (3 x 4 mg capsules) with or without food

If bodyweight is < 60 kg, 8 mg ONCE a day (see dose modifications)

Continuous until disease progression or unacceptable toxicity

Indications and patient population

Indications:

- monotherapy for advanced (unresectable) hepatocellular carcinoma Child-Pugh class A
- patients must not have previously received a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for hepatocellular carcinoma, or must have developed intolerance to a previous VEGF TKI
- ECOG performance status 0 to 2.

Precautions:

- The pivotal trial only included patients who were Barcelona Clinic Liver Cancer stage B or C, and Child-Pugh class A.
- The pivotal trial excluded patients with Child-Pugh class B or C, ≥ 50% liver occupation, clear invasion of the bile duct or invasion of the main portal vein. Patients with significant cardiovascular disease were also excluded (see evidence).

Clinical information

Caution with oral anti-cancer drugs	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the COSA guidelines and oral anti-cancer therapy
Emetogenicity minimal or low	No routine prophylaxis required. If patients experience nausea and/or vomiting, consider using the low emetogenic risk regimen. Read more about preventing anti-cancer therapy induced nausea and vomiting
Hypertension	Patients treated with lenvatinib may experience an increased incidence of hypertension. Pre-existing hypertension should be adequately controlled prior to commencing treatment and blood pressure should be monitored after 1 week of treatment, then every 2 weeks for the first 2 months and then monthly thereafter. Refer to dose modification section for management of hypertension.
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
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Gastrointestinal perforation	Serious cases of gastrointestinal (GI) perforation have been reported with this treatment. Use with caution in patients at risk of GI perforation (e.g. prior surgery or radiation therapy). Patients should be monitored for signs and symptoms of GI perforation.
Haemorrhage	Serious and sometimes fatal haemorrhagic events have been reported with this treatment. Patients should be monitored for signs and symptoms of severe bleeding. Use with caution in patients with risk of bleeding (ie. coagulopathy, concurrent anticoagulant or antiplatelet medications etc.) In the case of bleeding, dose interruptions, adjustments or discontinuation of therapy may be necessary.
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)

Hepatotoxicity	Severe hepatotoxicity (including fatal outcomes) has been observed with this treatment. Monitor for abnormal liver function tests (LFTs), jaundice and tiredness. Refer to blood tests and dose modification sections for specific recommendations.
Hypothyroidism	Thyroid dysfunction in particular hypothyroidism may occur with this treatment. Monitor for signs and symptoms of thyroid dysfunction and manage as clinically appropriate.
Prolongation of QT interval	This treatment may prolong the QT interval and increase the risk of cardiac arrhythmia. Use with caution in patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking medications that may prolong the QT interval and those with electrolyte disturbances. Risk factors (e.g. electrolyte abnormalities) should be corrected, where possible, prior to commencement of treatment and the concurrent use of drugs that may prolong the QT interval should be avoided. Baseline and periodic monitoring of electrocardiogram (ECG) and electrolytes (potassium, magnesium, calcium) should be considered in patients at high risk of QT prolongation. Read more about drugs that may prolong QTc interval at crediblemeds.org (registration required).
Proteinuria	Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of the treatment. Diabetes, high blood pressure and kidney disease are risk factors for developing proteinuria. Monitor for proteinuria by urine dipstick analysis at baseline and regularly during treatment. If proteinuria is detected, consider 24-hour urinary protein determination. For those who develop moderate to severe proteinuria dose interruptions, adjustments, or discontinuation of treatment may be necessary. Lenvatinib should be discontinued in the event of nephrotic syndrome.
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)
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	Some suggest (Bose et al. 2010- see link to abstract) that antiangiogenic tyrosine kinase inhibitors (TKI's) be interrupted for at least one week (48 hours for agents with short half life) before surgery and not re-initiated until adequate wound healing has occurred. At many institutions, therapy with these agents is held for four weeks after major surgery and for at least two weeks after minor surgery, although there are no prospective data validating this approach. The decision to resume therapy following a major surgical intervention should be based upon clinical judgement of recovery from surgery. Read more about "Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care", Bose et al 2010[1]
Blood test	FBC, EUC, calcium, magnesium, phosphate and TFTs at baseline then monthly or as clinically indicated. LFTs at baseline, then repeat every 2 weeks for first 2 months then monthly or as clinically indicated.
Hepatitis B screening and prophylaxis	The requirement for routine screening for HBsAg and anti-HBc for patients receiving this treatment is unknown. Clinical judgement and individual patient situations should be taken into consideration. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.

Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note:

- Mild to moderate adverse reactions (e.g. Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management.

Dose level	Dose if weight ≥ 60 kg	Dose if weight < 60 kg
Starting dose	12 mg once a day	8 mg once a day
First dose reduction	8 mg once a day	4 mg once a day
Second dose reduction	4 mg once a day	4 mg alternate days
Third dose reduction	4 mg alternate days	

Haematological toxicity	
Platelets x 10^9/L	
50 to 75	Continue treatment at same dose and monitor as clinically indicated
less than 50	Delay treatment until platelets > 50 and restart lenvatinib at a reduced dose

Note: If platelets < 50 prior to commencing treatment, recommend seeking input from a sub-specialist.

Hepatic impairment	
Hepatic dysfunction (at baseline)	
Mild (Child-Pugh A)	No dose modifications necessary
Moderate to severe (Child-Pugh B or C)	No dose modification information available (should not be used for this indication)

Hepatic impairment	
Lenvatinib-induced hepatotoxicity	
Grade 1 or Grade 2	Continue treatment at same dose.
Grade 3 or non-life-threatening Grade 4	Delay treatment until resolved to baseline and restart lenvatinib at a reduced dose
Life-threatening Grade 4	Permanently discontinue treatment

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	No dose modifications necessary
less than 30	No dose modification information available

Hypertension	
Standard antihypertensive therapy should be commenced and/or adjusted to control blood pressure (BP)	
Blood pressure level	**Recommended action**
At baseline:	
Blood pressure ≥ 140/90	Delay commencement of treatment until blood pressure is < 140/90 mmHg
During treatment:	
Systolic BP ≥ 140 mmHg up to < 159 mmHg **OR** diastolic BP ≥ 90 mmHg up to < 99 mmHg	Continue treatment at same dose. Initiate, increase dose of, or add antihypertensive therapy
Systolic BP ≥ 160 mmHg **OR** diastolic BP ≥ 100 mmHg	Delay treatment and initiate, increase dose of, or add antihypertensive therapy. When systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg, restart lenvatinib at a reduced dose

Hand and foot syndrome (link to Hand foot syndrome (Palmar-plantar erythrodysaesthesia)	
Grade 2 or 3	Delay treatment until toxicity has resolved to Grade 1 or less and consider restarting lenvatinib at a reduced dose

Diarrhoea	
Grade 1	Continue treatment at same dose.
Grade 2 or 3	Delay treatment until toxicity has resolved to Grade 1 or less. If early in treatment, restart lenvatinib at a reduced dose. If previously stable on treatment, consider restarting lenvatinib at the same dose.
Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and restart lenvatinib at a reduced dose

Proteinuria	
Grade 3	If urinary protein-to-creatinine ratio is ≥ 3.5, or there is oedema, pleural effusion, ascites or increased serum creatinine, delay treatment until proteinuria has resolved to Grade 1 or baseline: 1st occurrence: restart lenvatinib at same dose 2nd occurrence: restart lenvatinib at reduced dose

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*

Lenvatinib		
	Interaction	**Clinical management**
Drugs that may prolong the QTc interval (e.g. azole antifungals, tricyclic antidepressants, antiarrhythmics etc.)	Additive effect with lenvatinib; may lead to torsades de pointes and cardiac arrest	Avoid combination or minimise additional risk factors (e.g. correct electrolyte imbalances) and monitor ECG for signs of cardiac arrhythmia

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

Administration

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

product information monographs via the TGA website for further information.

Administration

This is a continuous oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

General patient assessment prior to each treatment.

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

Treatment - Time out

Lenvatinib

Prior to administration check:

- blood pressure
- urinalysis for protein

Administer lenvatinib

- administer orally ONCE daily
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food
- capsules may also be dissolved in water or apple juice if patient has swallowing difficulties:
  - place the required number of capsules in a disposable cup and fill with approximately 25 mL of water or apple juice
  - leave the capsules to dissolve (approximately 10 minutes) and then gently stir for at least 3 minutes to dissolve the capsules shells
  - after this the liquid can be swallowed straight away
  - avoid direct contact of the capsules or solution with the skin or mucous membrane. If such contact occurs, wash thoroughly.

Note: if a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose.

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

Discharge information

Lenvatinib capsules

- Lenvatinib capsules with written instructions on how to take them

Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

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

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

Early (onset days to weeks)	
Acneiform rash	A skin rash, characterised by papules and pustules affecting the face and upper body. This is commonly associated with small molecule EGFR inhibitors and some monoclonal antibodies (e.g. cetuximab, panitumumab). Read more about acneiform rash associated with EGFR inhibitors
Haemorrhage	
Diarrhoea	Read more about treatment induced diarrhoea
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.
QT prolongation	This treatment can cause QTc interval prolongation. QTc prolongation can lead to ventricular arrhythmias that may be fatal.
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
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.
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.
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)
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
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
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Constipation	
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
Fatigue	Read more about fatigue
Urinary tract infection	Lenvatinib has been associated with urinary tract infection

Late (onset weeks to months)	
Hypothyroidism	
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 comes from a multicentre, phase 3, randomised, open-label, non-inferiority study of patients with unresectable hepatocellular carcinoma.[2]

Between March 2013 and July 2015, a total of 954 patients were randomised to receive lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight <60 kg) (n=478) or sorafenib 400 mg twice daily (n=476) in 28 day cycles. Most patients were <65 years old (58%), male (84%), Asian (69%), ≥60 kg (69%), ECOG PS 0 (63%), and Barcelona Clinic Liver Cancer stage C (79%).[2]

The primary endpoint was overall survival. Secondary endpoints included progression-free survival, time to progression, objective response rate and quality of life measurements. The study was powered to determine non-inferiority if the upper limit of the two-sided 95% CI for HR was less than 1.08.[2]

Efficacy

After a median follow up of 27.7 months in the lenvatinib group, and 27.2 months in the sorafenib group, lenvatinib showed non-inferiority in terms of overall survival compared to sorafenib. The median overall survival was 13.6 months in the lenvatinib group and 12.3 months in the sorafenib group, with a hazard ratio of 0.92 (95% CI 0.79 to 1.06).[2]

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	..
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..
Masked independent imaging review according to mRECIST				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·7)	HR 0·64 (0·55–0·75)	<0·0001
Time to progression (months)	7·4 (7·2–9·1)	3·7 (3·6–3·9)	HR 0·60 (0·51–0·71)	<0·0001
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..
Disease control rate (%, 95% CI)	353 (73·8%, 69·9–77·8)	278 (58·4%, 54·0–62·8)	..	..
Masked independent imaging review according to RECIST 1.1				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·9)	HR 0·65 (0·56–0·77)	<0·0001
Time to progression (months)	7·4 (7·3–9·1)	3·7 (3·6–5·4)	HR 0·61 (0·51–0·72)	<0·0001
Objective response (%, 95% CI)	90 (18·8%, 15·3–22·3)	31 (6·5%, 4·3–8·7)	OR 3·34 (2·17–5·14)	<0·0001
Complete response	2 (<1%)	1 (<1%)	..	..
Partial response	88 (18%)	30 (6%)	..	..
Stable disease	258 (54%)	250 (53%)	..	..
Durable stable disease lasting ≥23 weeks	163 (34%)	118 (25%)	..	..
Progressive disease	84 (18%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	43 (9%)	..	..
Disease control rate (%, 95% CI)	348 (72·8%, 68·8–76·8)	281 (59·0%, 54·6–63·5)	..	..

Data are presented as median (95% CI) or n (%) unless otherwise indicated. mRECIST=modified Response Evaluation Criteria in Solid Tumours. HR=hazard ratio. OR=odds ratio.

Table 2: Efficacy measures

Both groups had similar baseline scores on quality of life measures (EORTC QLQ-C30 and EORTC QLQ-HCC18), and both groups had declining scores over time. A decline in pain, diarrhoea, nutrition and body image occurred earlier in the sorafenib arm compared to the lenvatinib arm, although the summary scores were comparable.[2]

Toxicity

The most common treatment-related adverse events for lenvatinib were hypertension, diarrhoea, anorexia and weight loss. Of those taking lenvatinib, treatment-related adverse events led to drug interruption in 40% (compared with 32% in the sorafenib arm), dose reduction in 37% (compared with 38%) and withdrawal in 9% (compared with 7%). There were 11 (2%) fatal adverse events in the lenvatinib arm which included hepatic failure (n=3), cerebral haemorrhage (n=3), and respiratory failure (n=2). There were 4 (1%) fatal adverse events in the sorafenib arm, from tumour haemorrhage, ischaemic stroke, respiratory failure and sudden death.[2]

	Lenvatinib (n=476)		Sorafenib (n=475)	
	All grades (%)	Grade 3 or higher (%)	All grades (%)	Grade 3 or higher (%)
Treatment-related treatment-emergent adverse events	94	57	95	49
Palmar-plantar erythrodysaesthesia	27	3	52	11
Diarrhoea	39	4	46	4
Hypertension	42	23	30	14
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	14	0	25	0
Proteinuria	25	6	11	2
Dysphonia	24	<1	57	0
Nausea	20	1	14	1
Abdominal pain	17	2	18	3
Decreased platelet count	18	5	12	3
Elevated aspartate aminotransferase	14	5	17	8
Hypothyroidism	16	0	2	0
Vomiting	16	1	8	1
Constipation	16	1	11	0
Rash	10	0	16	>1
Increased blood bilirubin	15	7	13	5

References

1 Bose, D., F. Meric-Bernstam, W. Hofstetter, et al. 2010. "Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care." Lancet Oncol 11(4):373-382.

2 Kudo, M., R. S. Finn, S. Qin, et al. 2018. "Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial." Lancet 391(10126):1163-1173

History

Version 1

Date	Summary of changes
26/06/2019	New protocol discussed by Medical oncology reference committee (electronically via email)
23/07/2019	Approved and published on eviQ
23/10/2020	Protocol reviewed electronically by the Medical Oncology Reference committee. Link to ID 3042 Hepatocellular carcinoma (HCC) staging: the BCLC score added in indications section. Next review in 2 years.
21/06/2021	Archived: Changed antiemetic clinical information block to moderate to high, to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5 (see row below as 12 mg dose should be minimal or low).
21/12/2021	Changed antiemetic clinical information block to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5.
20/10/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review 2 years.

First approved: 23 July 2019
Last reviewed: 20 October 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/3603
15 Jul 2023

Patient information - Liver cancer advanced or metastatic - lenvatinib

Patient's name:

Your treatment

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

Lenvatinib

This treatment is continuous. Your doctor will advise you how long to take the treatment for.

Day	Treatment	How it is given
Continuous	**Lenvatinib** (*len-va-ti-nib)*	Take orally ONCE a day, at the same time each day, with or without food. Swallow whole with a large glass of water, do not break, crush or chew. If you are unable to swallow the capsule whole they may be dissolved in water and the solution swallowed (see directions in *Other information about your treatment).* If you forget to take a dose, and it is less than 12 hours late, take it as soon as you remember. If it is more than 12 hours late, skip that dose and take your normal dose the next time it is due. Do not take an extra dose. If the capsule is vomited do not take another dose.

When to get help

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

Emergency contact details

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

Daytime: .....

Night/weekend: .....

Other instructions: .....

.....

.....

Other information about your treatment

Changes to your dose or treatment delays

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

Blood tests and monitoring

You may need to have blood tests while you are receiving this treatment. Your doctor or nurse will tell you when to have these blood tests. Tell your doctor if you are on an anticoagulant (medication used to treat or prevent blood clots) e.g. warfarin. You may need to have additional blood tests.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Antidiarrhoeals:** you may be given some medication to treat diarrhoea. Your doctor or nurse will tell you how and when to take your antidiarrhoeal medication.

Instructions for dissolving lenvatinib capsules:

- Lenvatinib capsules should not be crushed, cut or chewed. For patients with swallowing difficulties lenvatinib capsules can be dissolved.
- You (or whoever is dissolving the capsule) should wear disposable gloves and try to minimise touching the capsules.
- Without breaking or crushing, place the lenvatinib capsules(s) whole in a glass with approximately 25 mL of plain drinking water or apple juice. No other liquids should be used.
- The capsules must be left to disintegrate in the liquid for at least 10 minutes and then gently stirred for at least 3 minutes to dissolve the capsules shells.
- After this then drink the liquid straight away.
- Rinse the empty glass with approximately 25 mL of water or apple juice and drink it.
- Do not mix more than one medicine in the glass at the same time.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Early (onset days to weeks)	

Skin rash (acneiform rash)	• You may get an acne-like skin rash. • Your skin may become red and dry. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Do not use over-the-counter acne treatments as these can make the rash worse. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • You may be given medications to prevent the rash. • **Tell your doctor or nurse as soon as possible if you notice any changes to the rash like itching, pain or pus forming**
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.**
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.**
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.**
Heart changes	• You may get chest pain, shortness of breath, an abnormal heartbeat or swelling in your arms or legs. • Before, during or after treatment you may be asked to have tests to see how well your heart is working. • You will also have other blood tests to check your electrolyte levels. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department, if you get any of the symptoms listed above.**
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.**

Bleeding into stomach or bowel	• This side effect is rare, but can be very serious. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of these signs or symptoms:** ◦ **severe stomach pain** ◦ **swollen and hot skin around your stomach** ◦ **bleeding** ◦ **nausea or vomiting** ◦ **fever or chills** ◦ **a fast heartbeat** ◦ **you feel short of breath.**
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.**
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.**
Liver problems	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**

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.**

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.

Constipation	• You may have bowel motions (stools, poo) that are less frequent, harder, smaller, painful or difficult to pass.
	• You may also get:
	  ◦ bloating, cramping or pain
	  ◦ a loss of appetite
	  ◦ nausea or vomiting.
	• Drink plenty of fluids (unless you are fluid restricted).
	• Eat plenty of fibre-containing foods such as fruit, vegetables and bran.
	• Take laxatives as directed by your doctor.
	• Try some gentle exercise daily.
	• **Tell your doctor or nurse if you have not opened your bowels for more than 3 days.**

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.

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.**
Urine infection (UTI)	• You can get a urine infection whilst receiving lenvatinib. • You may get: ◦ pain on passing urine ◦ burning or difficulty in passing urine ◦ the need to pass urine more often • Drink plenty of water • Avoid alcohol and caffeine • **Tell your doctor or nurse as soon as possible, if you get any of the symptoms listed above**

Late (onset weeks to months)	
Slow thyroid gland (hypothyroidism)	• You may: ◦ 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 • You will have regular blood tests to check how well your thyroid is working • **Tell your doctor or nurse if you get any of the symptoms listed above.**
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

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).

- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

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

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

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

Quitting smoking

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

Staying active

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

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

Where to get more information

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

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https://www.eviq.org.au/pi/3603
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