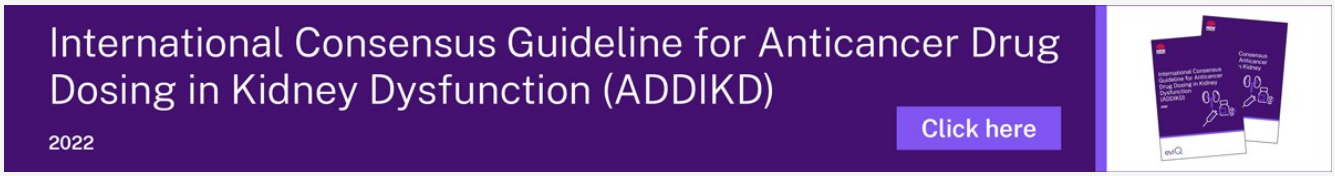
Non small cell lung cancer locally advanced or metastatic brigatinib

ID: 3789 v.1 **Endorsed**

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

Link to Clinical practice guidelines for the treatment of lung cancer

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:

- Non small cell lung cancer locally advanced or metastatic crizotinib SUPERSEDED
- Non small cell lung cancer locally advanced or metastatic alectinib

Treatment schedule - Overview

Cycle 1

Drug	Dose	Route	Day
Brigatinib	90 mg ONCE a day *	PO	1 to 7
Brigatinib	180 mg ONCE a day	PO	8 to 28

Cycle 2 and further cycles

Drug	Dose	Route	Day
Brigatinib	180 mg ONCE a day	PO	1 to 28

* If 90 mg dose well tolerated for 7 days, escalate dose to 180 mg.

Frequency: 28 days

Cycles: **Continuous until disease progression or unacceptable toxicity**

Notes:
Step up dosing of brigatinib over a 7 day period is used to reduce the risk of uncommon early-onset pulmonary events[1]

Drug status: Brigatinib is PBS Authority

Brigatinib is available in **30 mg, 90 mg** and **180 mg** tablets

Cost: ~ $6,800 per month

Treatment schedule - Detail

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

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

Cycle 1

Day 1 to 7		
Brigatinib	90 mg (PO)	ONCE a day

Day 8 to 28		
Brigatinib	180 mg (PO)	ONCE a day

Cycle 2 and further cycles

Day 1 to 28		
Brigatinib	180 mg (PO)	ONCE a day

* If 90 mg dose well tolerated for 7 days, escalate dose to 180 mg

Frequency: 28 days

Cycles: **Continuous until disease progression or unacceptable toxicity**

Indications and patient population

Indications:

- Palliative treatment of anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non small cell lung cancer (NSCLC)
- WHO performance score 0 to 2

Exclusion:

- Congenital long-QT syndrome
- Interstitial lung disease
- Clinically significant uncontrolled cardiovascular disease including significant bradyarrhythmias or hypertension

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

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
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).
Bradycardia	Sinus bradycardia (both symptomatic and asymptomatic) is a known effect of this treatment. The full effect may not develop until several weeks after the start of treatment. Avoid using this treatment in combination with other bradycardic agents (e.g. beta blockers, verapamil, diltiazem, clonidine, digoxin etc) due to increased risk of symptomatic bradycardia (e.g. syncope, dizziness, hypotension). Monthly monitoring of pulse rate and blood pressure is recommended. For patients with existing cardiac disease, measure left ventricular ejection fraction (LVEF) at baseline and as clinically indicated. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia, treatment should be withheld and the use of concomitant medications should be re-evaluated.
Hypertension	Pre-existing hypertension should be adequately controlled prior to commencing treatment and blood pressure should be monitored regularly and treated, if required. In severe or uncontrolled hypertension, treatment should be withheld until hypertension is controlled. Dose modification or permanent discontinuation may be necessary - refer to dose modification section for specific recommendations.
Pulmonary toxicity	This treatment has been associated with severe, life-threatening or fatal interstitial lung disease (ILD)/pneumonitis. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Treatment should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis. Read more about pulmonary toxicity associated with anti-cancer drugs.
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Hepatotoxicity	Severe hepatotoxicity (including drug-induced liver injury) 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.
Blood tests	FBC, EUC, eGFR, LFTs, lipase, amylase and fasting glucose at baseline. Monitor LFTs 2 weekly for the first month then periodically throughout treatment as clinically indicated. Monitor all other bloods regularly throughout treatment as clinically indicated.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is NOT usually recommended for patients receiving this treatment. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy

Vaccinations	Live vaccines should be used with caution in cancer patients. For cancer patients who are not receiving immunosuppressive therapy, there is currently no data as to the safety of giving 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.
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).

Brigatinib dose reduction schedule			
Dose	**Dose reduction levels**		
	First	**Second**	**Third**
90 mg once daily (first 7 days)	reduce to 60 mg once a day	permanently discontinue	not applicable
180 mg once daily	reduce to 120 mg once a day	reduce to 90 mg once a day	reduce to 60 mg once a day

Permanently discontinue brigatinib if unable to tolerate 60 mg once a day. If dose is interrupted for 14 days or longer for reasons other than adverse events, resume at 90 mg once a day for 7 days before increasing to previous dose.

Haematological toxicity	
ANC x 10^9/L (pre-treatment blood test)	
1.0 to less than 1.5	Refer to local institutional guidelines; it is the view of the expert clinicians that treatment should continue if patient is clinically well.
0.5 to less than 1.0	Delay treatment until recovery
less than 0.5 or febrile neutropenia	Delay treatment until recovery and reduce the dose as follows:

Haematological toxicity	
	1st occurrence: Reduce brigatinib to the next lower dose level 2nd occurrence: Reduce brigatinib to the next lower dose level 3rd occurrence: Discontinue brigatinib
Platelets x 10^9/L (pre-treatment blood test)	
50 to less than 100	The general recommendation is to delay, however if the patient is clinically well it may be appropriate to continue treatment; refer to treating team and/or local institutional guidelines.
25 to less than 50	Delay treatment until recovery
less than 25	Delay treatment until recovery and reduce the dose as follows: 1st occurrence: Reduce brigatinib to the next lower dose level 2nd occurrence: Reduce brigatinib to the next lower dose level 3rd occurrence: Discontinue brigatinib

Interstitial lung disease/pneumonitis	
Grade 1	If new pulmonary symptoms occur during the first 7 days of treatment, delay treatment until recovery to baseline then resume at the same dose and do NOT escalate to 180 mg if ILD/pneumonitis suspected If new pulmonary symptoms occur after the first 7 days of treatment, delay treatment until recovery to baseline then resume at the same dose If recurs, permanently discontinue brigatinib
Grade 2	If new pulmonary symptoms occur during the first 7 days of treatment, delay treatment until recovery to baseline then resume at the next lower dose level and do NOT escalate to 180 mg if ILD/pneumonitis suspected If new pulmonary symptoms occur after the first 7 days of treatment, delay treatment until recovery to baseline. If ILD/pneumonitis is suspected then resume at the next lower dose, otherwise resume at the same dose. If recurs, permanently discontinue brigatinib
Grade 3 or 4	Permanently discontinue brigatinib

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	No dose modifications necessary
less than 30	Reduce starting dose to 60 mg once a day for the first 7 days. The dose may be increased to 90 mg once a day based on individual safety and tolerability.

Hepatic impairment	
At baseline	
Mild or moderate	No dose modifications necessary
Severe	Reduce starting dose to 60 mg once a day for the first 7 days The dose may be increased to 120 mg once a day based on individual safety and tolerability
During treatment:	
Transaminases (ALT and AST) +/- Bilirubin	
Grade 1 or Grade 2	No dose modification necessary
Grade 3 or Grade 4 transaminases with total bilirubin 2.0 x ULN or less	Delay treatment until toxicity has resolved to Grade 1 or baseline (3 x ULN or less) and resume brigatinib at next lower dose level

Hepatic impairment	
Grade 2 or greater transaminases with total bilirubin greater than 2.0 x ULN	Permanently discontinue brigatinib

Bradycardia	
Symptomatic bradycardia	Delay treatment until asymptomatic or a resting heart rate of 60 bpm or higher Identify contributing concomitant drugs that may be causing bradycardia and discontinue or dose adjust if possible. If achieved, resume at the same dose. If no concomitant drug is identified or not discontinued or dose adjusted, then resume at the next lower dose level.
Bradycardia with life threatening consequences, urgent intervention required	Delay treatment until asymptomatic or a resting heart rate of 60 bpm or higher Identify contributing concomitant drugs that may be causing bradycardia and discontinue or dose adjust if possible. If achieved, resume at next lower dose level and monitor frequently as clinically indicated. If no concomitant drug is identified permanently discontinue brigatinib If recurs, permanently discontinue brigatinib

Hypertension	
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less then resume at the same dose If recurs, delay treatment until toxicity has resolved to Grade 1 or less then resume at the next lower dose level or permanently discontinue
Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less then resume at the next lower dose level or permanently discontinue If recurs, permanently discontinue brigatinib

Hyperglycaemia	
Grade 3 (13.9 mmol/L or greater)	If adequate hyperglycaemic control cannot be achieved with optimal medical management, delay until adequate hyperglycaemic control is achieved. If hyperglycaemic control is achieved resume dose at next lower dose level or permanently discontinue.

Other adverse reactions	
Grade 3	Delay treatment until toxicity has resolved to baseline, then resume at the same dose If recurs, delay treatment until toxicity has resolved to baseline and resume at next lower dose level
Grade 4	Delay treatment until toxicity has resolved to baseline, then resume at next lower dose level If recurs, delay treatment until toxicity has resolved to baseline and resume at next lower dose level or permanently discontinue

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*

Brigatinib		
	Interaction	**Clinical management**
CYP3A4 inhibitors (e.g. amiodarone, aprepitant, azole antifungals, ritonavir, macrolides, grapefruit juice etc.)	Increased toxicity of brigatinib possible due to reduced clearance	Avoid combination or monitor for brigatinib toxicity. If concomitant use of strong CYP3A4 inhibitors cannot be avoided, reduce brigatinib dose by 50% (i.e. from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A4 inhibitor, brigatinib should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A4 inhibitor.
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of brigatinib possible due to increased clearance	Avoid combination with strong and moderate CYP3A4 inducers
Drugs undergoing P-gp, BCRP, OCT1, MATE1 and MATE2K-mediated elimination (e.g. digoxin, dabigatran, methotrexate etc.)	Increased toxicity of substrate possible due to reduced clearance	Monitor patients closely for drugs with a narrow therapeutic index
Bradycardic agents (e.g. beta-blockers, verapamil, diltiazem, clonidine, digoxin, etc.)	Additive effect with brigatinib	Avoid combination or monitor pulse rate and blood pressure regularly

Note:

- Brigatinib may induce CYP3A and other enzymes and transporters via the same mechanisms e.g. CYP2C. This may reduce the plasma concentration of coadministered drugs that are substrates of these enzymes and transporters. Clinical drug-drug interaction studies with sensitive CYP3A substrates have not been conducted.

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 should be used with caution in cancer patients. For cancer patients who are not receiving immunosuppressive therapy, there is currently no data as to the safety of giving live vaccines. 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.

Pre treatment medication

Administer antiemetics if required

Treatment - Time out

Brigatinib

- administer orally ONCE a day
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food.

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

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

Discharge

Discharge information

Brigatinib tablets

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

Antiemetics

- Antiemetics as prescribed.

Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

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

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

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs
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
Diarrhoea	Read more about treatment induced diarrhoea
Constipation	
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Fatigue	Read more about fatigue
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.
Bradycardia	An abnormally slow heart rate of 60 beats per minute or less can occur with this treatment. Assess baseline cardiac status and history and monitor those with pre-existing cardiac disease.
QT prolongation	This treatment can cause QTc interval prolongation. QTc prolongation can lead to ventricular arrhythmias that may be fatal.

Evidence

First line setting

The evidence supporting the use of brigatinib in the treatment of locally advanced or metastatic ALK-positive non small cell lung cancer (NSCLC) is provided by a phase III open-label multicentre randomised trial ALTA-1L. ALK inhibitor naive patients were treated with either brigatinib or crizotinib.[1]

Between April 2016 and August 2017, 275 patients underwent randomisation to receive oral treatment with either brigatinib 180 mg once daily with a 7 day lead-in at 90 mg (n=137) or crizotinib 250 mg twice daily (n=138).

The primary end point was progression free survival (PFS) and secondary end points included objective response rate (ORR) and intracranial response.

In patients who had not previously been treated with an ALK inhibitor treatment with brigatinib resulted in significantly longer PFS than crizotinib.

Second line setting

The evidence supporting the second line use of brigatinib in the treatment of locally advanced or metastatic ALK-positive non small cell lung cancer (NSCLC) is provided by a phase II open-label multicentre randomised trial - ALTA. Patients who had progressed whilst receiving crizotinib were treated with brigatinib Between June 2014 and September 2015, 222 patients were randomised 112 to receive 90 mg brigatinib once daily (arm A) and 110 to receive 180 mg brigatinib once daily with a seven-day lead in dose of 90 mg brigatinib once daily (arm B) until disease progression or unacceptable toxicity.[2]

The primary end point was investigator assessed confirmed objective response rate (cORR). Secondary end points included duration of response, overall survival (OS), independent review committee (IRC) assessed cORR, PFS, CNS response and

intercranial PFS, safety and tolerability.[2]

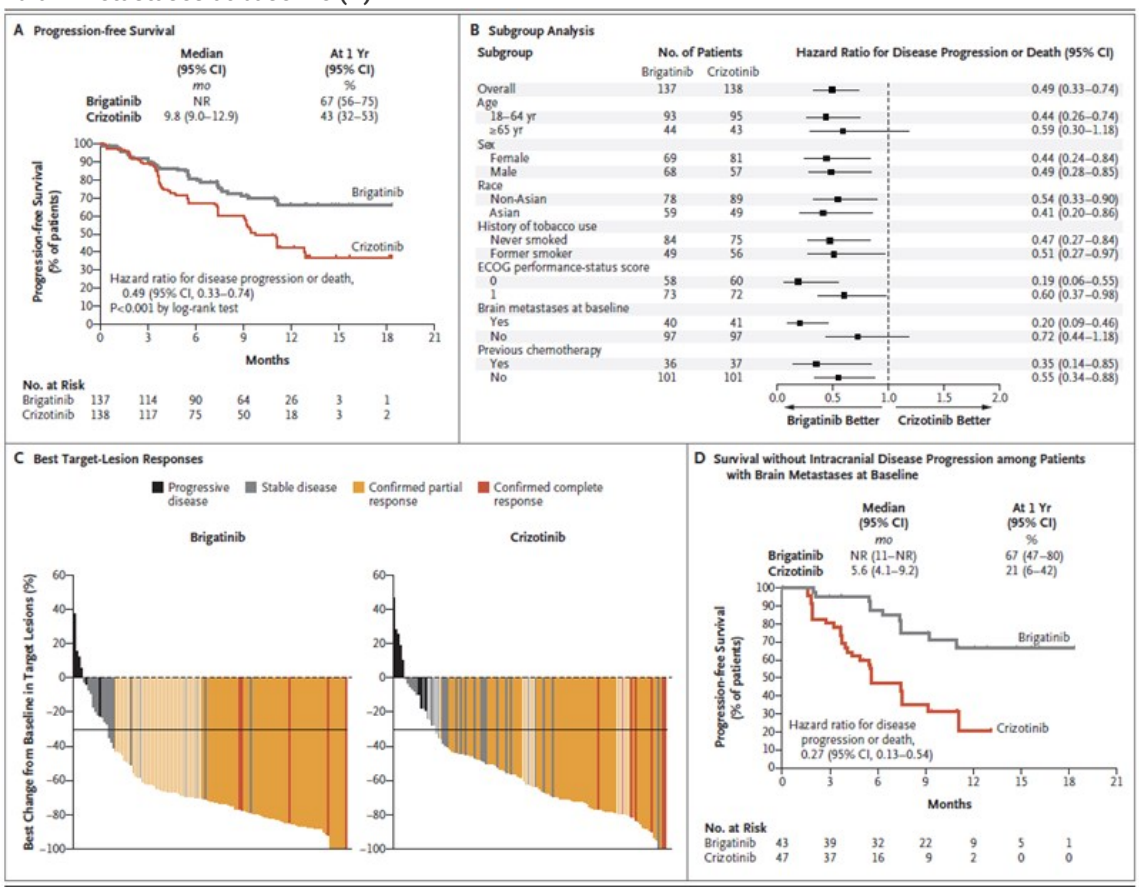
Efficacy

First line setting

After a median follow up of 11.0 months in the brigatinib group and 9.3 months in the crizotinib group, the median 12-month estimated PFS was 67% (95% confidence interval [CI], 56 to 75) in the brigatinib group compared with 43% (95% CI, 32 to 53) in the crizotinib group. Hazard ratio (HR) for progression or death was 0.49 (95% CI, 0.33 to 0.74; p<0.001). Subgroup analysis also favoured brigatinib.[1]

The cORR was 71% (95% CI, 62 to 78) with brigatinib and 60% (95% CI, 51 to 68) with crizotinib.

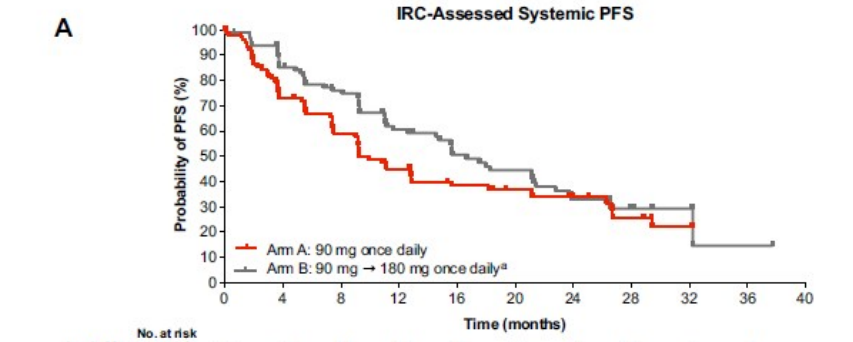
PFS (A), subgroup analysis (B), best target lesion responses (C), survival without intracranial disease progression among patients with brain metastases at baseline (D) [1]



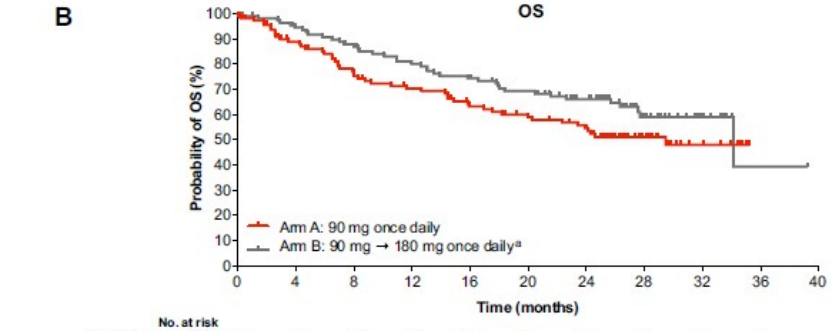
Second line setting

After a median follow up of 19.6 months in arm A and 24.3 months in arm B the investigator assessed cORR (97.5% CI) was 46% (35 to 57%) in arm A and 56% (45 to 67%) in arm B, median duration or response was respectively 12.0 months (95% CI: 9.2 to 17.7) and 13.8 months (95% CI: 10.2 to 19.3). In arm A the IRC-assessed cORR was 51% (95% CI: 41% to 61%) compared with 56% (95% CI: 47% to 66%) in arm B. Median IRC-assessed PFS was 9.2 months (95% CI: 7.4 to 12.8) in arm A and 16.7 months (95% CI: 11.6 to 21.4) in arm B. Median OS was 29.5 months (95% CI: 18.2 to not reached [NR]) in arm A and 34.1 months (27.7 to NR) in arm B.[3]

Kaplan-Meier estimates of IRC-assessed PFS (A) and OS (B)[3]



	Investigator-Assessed		IRC-Assessed	
	Arm A: 90 mg once daily n=112	Arm B: 90 mg→ 180 mg once daily[a] n=110	Arm A: 90 mg once daily n=112	Arm B: 90 mg→ 180 mg once daily[a] n=110
Median PFS, months (95% CI)	9.2 (7.4–11.1)	15.6 (11.1–21.0)	9.2 (7.4–12.8)	16.7 (11.6–21.4)
1-year PFS probability, % (95% CI)	37 (27–46)	58 (47–67)	45 (35–55)	61 (49–70)



	Arm A: 90 mg once daily n=112	Arm B: 90 mg → 180 mg once daily[a] n=110
Median OS, months (95% CI)	29.5 (18.2–NR)	34.1 (27.7–NR)
1-year OS probability, % (95% CI)	70 (61–78)	80 (71–87)
2-year OS probability, % (95% CI)	55 (44–64)	66 (56–74)

Toxicity

The most common adverse events with brigatinib were diarrhoea, increased blood creatine kinase, nausea, cough, hypertension, elevated liver aminotransferase and lipase level, vomiting, constipation, pruritis and rash.[1]

Grade 3 or 4 events occurred with similar incidence in both the brigatinib and crizotinib groups (61% and 55% respectively). Permanent discontinuation secondary to adverse events occurred in 12% of those receiving brigatinib, and 9% of those receiving crizotinib. There were no treatment related deaths.

Adverse events[1]

Table 3. Adverse Events of Any Grade That Differed by More Than 5 Percentage Points in Frequency between Groups.

Event	Brigatinib (N=136)		Crizotinib (N=137)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	132 (97)	83 (61)	137 (100)	76 (55)
Diarrhea	67 (49)	2 (1)	75 (55)	3 (2)
Increased blood creatine kinase level*	53 (39)	22 (16)	21 (15)	2 (1)
Nausea	36 (26)	2 (1)	77 (56)	4 (3)
Cough	34 (25)	0	22 (16)	0
Hypertension	31 (23)	13 (10)	10 (7)	4 (3)
Increased alanine aminotransferase level	26 (19)	2 (1)	44 (32)	13 (9)
Increased lipase level†	26 (19)	18 (13)	16 (12)	7 (5)
Vomiting	25 (18)	1 (1)	54 (39)	3 (2)
Constipation	20 (15)	0	57 (42)	1 (1)
Increased amylase level†	19 (14)	7 (5)	9 (7)	1 (1)
Pruritus	18 (13)	1 (1)	6 (4)	1 (1)
Rash	14 (10)	0	3 (2)	0
Decreased appetite	10 (7)	1 (1)	27 (20)	4 (3)
Dermatitis acneiform	9 (7)	0	2 (1)	0
Dyspepsia	8 (6)	0	18 (13)	0
Epistaxis	8 (6)	0	0	0
Bradycardia	7 (5)	1 (1)	17 (12)	0
Peripheral edema	6 (4)	1 (1)	53 (39)	1 (1)
Dysgeusia	6 (4)	0	26 (19)	0
Upper abdominal pain	6 (4)	1 (1)	18 (13)	2 (1)
Pain in extremity	6 (4)	0	17 (12)	1 (1)
Increased blood creatinine level	3 (2)	0	19 (14)	1 (1)
Neutropenia	2 (1)	0	12 (9)	6 (4)
Pleural effusion	2 (1)	1 (1)	9 (7)	2 (1)
Photopsia	1 (1)	0	28 (20)	1 (1)
Gastroesophageal reflux disease	1 (1)	0	12 (9)	0
Visual impairment	0	0	22 (16)	0
Deep-vein thrombosis	0	0	8 (6)	0

* Myalgia was reported in 6% of patients in the brigatinib group and 4% of patients in the crizotinib group; musculoskeletal pain was reported in 4% and 6% of the patients, respectively. No myalgia or musculoskeletal pain of grade 3 or greater was reported in either group.
† No clinical cases of pancreatitis were reported in either group.

References

1 Camidge, D. R., H. R. Kim, M. J. Ahn et al. 2018. "Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer." N Engl J Med: 379 (21): 2027-2039.

2 Kim, D. W., M. Tiseo, M. J. Ahn, et al. 2017. "Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial." J Clin Oncol 35(22):2490-2498.

3 Huber, R. M., K. H. Hansen, L. Paz-Ares Rodriguez, et al. 2020. "Brigatinib in Crizotinib-Refractory ALK+ NSCLC: 2-Year Follow-up on Systemic and Intracranial Outcomes in the Phase 2 ALTA Trial." J Thorac Oncol 15(3):404-415.

History

Version 1

Date	Summary of changes
04/11/2020	Protocol approved electronically by Medical Oncology Reference Committee and published on eviQ. Review 1 year.
21/12/2021	Changed antiemetic clinical information block to minimal or low, to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5.
20/05/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. EGFR TKI cardiac toxicity clinical information added. Next review in 2 years.

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09 Aug 2023

Patient information - Lung cancer locally advanced or metastatic - Brigatinib

Patient's name:

Your treatment

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

Brigatinib

This treatment is continuous. Your doctor will advise you how long to take the treatment for. You will take a lower dose for the first seven days, if well tolerated your doctor will increase the dose.

Day	Treatment	How it is given
Continuous	**Brigatinib** (*bri-GA-ti-nib)*	Take orally ONCE a day. Swallow the tablet whole with a glass of water at about the same time each day with or without food. If you forget to take a dose, skip that dose and take your normal dose the next time it is due. Do not take a double dose for a missed dose or if a dose is vomited.

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

Other medications given during this treatment

- **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.
- **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.

Side effects

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

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

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

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

Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**
Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment. • You may get: ◦ shortness of breath ◦ fever ◦ dry cough ◦ wheezing ◦ fast heartbeat ◦ chest pain. • Your doctor will monitor how well your lungs are working during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**
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**
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.**

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.**
Extra fluid in the body (fluid retention)	• You may gain weight over a short amount of time. • Your hands and feet may become swollen, appear red or feel hot and uncomfortable. • Wear loose clothing and shoes that are not too tight. • Try not to stand up or walk around too much at one time. • If your ankles or legs get swollen, try raising them. • Make sure that any cuts or areas of broken skin are treated as soon as possible. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above or gain 1 to 2 kg in a week.** • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you become short of breath.**
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.
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.**
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.**

Slow heart rate (bradycardia)	• You may get:
	  ◦ a slow heart rate
	  ◦ dizziness
	  ◦ shortness of breath
	  ◦ fainting.
	• 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.**

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.**

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

Other medical and dental treatment

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

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

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

Pregnancy and breastfeeding

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

Sex life and sexuality

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

Quitting smoking

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

Staying active

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

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

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Lung Foundation Australia on 1800 654 301

Lung cancer information

- Lung Foundation Australia – lungfoundation.com.au
- Lungevity – lungevity.org

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
- Carer Help - carerhelp.com.au
- CHILL Cancer related hair loss - scalpcooling.org
- eviQ Cancer Treatments Online – eviQ.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information

and support to help you quit smoking. Talk to your treating team about any other questions you may have.

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

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