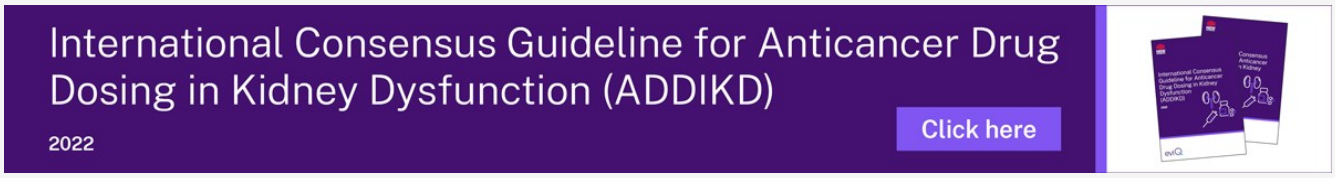
Prostate metastatic denosumab

ID: 1301 v.2 **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:

- Prostate metastatic zoledronic acid

Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
Denosumab	120 mg	Subcut	1

Frequency: 28 days

Cycles: Continuous until unacceptable toxicity

Notes:
The risk of osteonecrosis of the jaw may increase with prolonged use of denosumab.[1]

There is limited evidence to support the safety of denosumab beyond two years, as such it is by expert opinion of the Reference Committee that consideration be given to reduce the frequency to 12 weeks after one to two years of treatment, to reduce risks of cumulative exposure including increased risk of osteonecrosis of the jaw.

Drug status: **Denosumab** is PBS authority

Cost: ~ $460 per month

Treatment schedule - Detail

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

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

Cycle 1 and further cycles

Day 1

Calcium	500 mg (PO)	ONCE a day (daily oral supplement of at least calcium 500 mg is required)
Vitamin D	400 International Units (PO)	ONCE a day (daily oral supplement of at least vitamin D 400 international units is required)
Denosumab	120 mg (Subcut)	Inject subcutaneously into the thigh, abdomen or upper arm
Day 2 to 28		
Calcium	500 mg (PO)	ONCE a day (daily oral supplement of at least calcium 500 mg is required)
Vitamin D	400 International Units (PO)	ONCE a day (daily oral supplement of at least vitamin D 400 international units is required)

Frequency: 28 days

Cycles: Continuous until unacceptable toxicity

Indications and patient population

- Prevention of skeletal related events in patients with bone metastases due to castration-resistant prostate cancer

Clinical information

Dental review	Dental review prior to treatment and 6 monthly dental review during treatment is recommended to minimise risk of osteonecrosis of the jaw. Read more about medication-related osteonecrosis of the jaw (MRONJ)
Severe hypocalcaemia	Severe symptomatic hypocalcaemia (corrected serum calcium < 1.75 mmol/L) including fatal cases have occurred. Signs and symptoms include altered mental status, tetany, seizures and QTc prolongation. Patients with severe kidney dysfunction (eGFR < 30 mL/min/1.73 m^2 or receiving dialysis) or who have undergone thyroid surgery are at increased risk of hypocalcaemia. Daily oral supplements of at least calcium 500 mg and vitamin D 400 International Units is required (unless contraindicated) for the duration of the therapy.
Length of treatment	It is unclear whether continuing the drug is of benefit once a skeletal related event has occurred.
Blood tests	Calcium, magnesium and phosphate at baseline and prior to each cycle or as clinically indicated
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.

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).

Renal impairment
No dose modification necessary

Hepatic impairment
The safety and efficacy of denosumab has not been studied in patients with hepatic impairment

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*

Denosumab

No formal clinical drug interaction studies with denosumab have been conducted.

	Interaction	Clinical management
Drugs that may cause hypocalcaemia (e.g. bisphosphonates, cinacalcet etc.)	Increased risk of hypocalcaemia	Avoid combination or monitor calcium levels closely; ensure calcium and vitamin D supplementation is occurring (unless hypercalcaemic). Denosumab should not be administered concomitantly with bisphosphonates.
Immunosuppressants	Concurrent use with immunosuppressants may result in increased risk of immunosuppression.	Consider therapy modification or monitor for infection

Administration

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

Day 1

Subcutaneous injection

Handling of monoclonal antibodies and waste management

Safe administration

Treatment - Time out

Denosumab

Prior to administration:

- allow refrigerated drug to warm to room temperature for up to 30 minutes prior to administration.

Administer denosumab:

- administer via subcutaneous injection
- rotate sites for each injection (thigh, abdomen, upper arm).

Discharge information

Supplements

- Daily oral supplements of calcium 500 mg and vitamin D 400 International Units are recommended.

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.

Early (onset days to weeks)	
Hypocalcaemia	Abnormally low levels of calcium in the blood.

Delayed (onset months to years)	
Osteonecrosis of the jaw (ONJ)	Exposed, necrotic bone in the maxillofacial region is associated with IV bisphosphonates and denosumab. It can persist for more than 8 weeks. Read more about medication-related osteonecrosis of the jaw

Evidence

The evidence supporting this protocol is provided by a phase 3 multicentre international randomised trial involving 1904 patients comparing denosumab with zoledronic acid alone in patients with castrate resistant prostate cancer.[2]

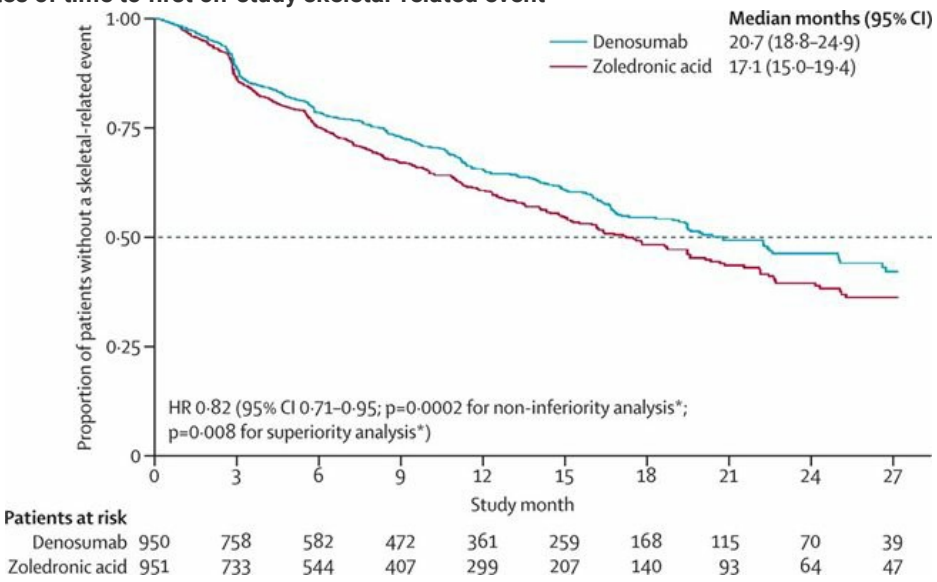
Between May 2006 and October 2009, 950 patients were randomised to receive 120 mg denosumab and 951 patients were randomised to receive 4 mg zoledronic acid (or equivalent creatinine-adjusted dose of zoledronic acid in patients with a baseline creatinine clearance of 60 mL/min) every 4 weeks.[2]

The primary end point was time to first on-study skeletal-related event (noninferiority analysis), and secondary end points were time to first on-study skeletal-related event (superiority analysis) overall survival, investigator-assessed overall disease progression, prostate-specific antigen concentration during the study, and change in bone turnover markers from baseline. Safety endpoints included frequency of treatment-emergent adverse events, changes in routine chemistry and haematology laboratory values, and presence of neutralising anti- denosumab antibodies.[2]

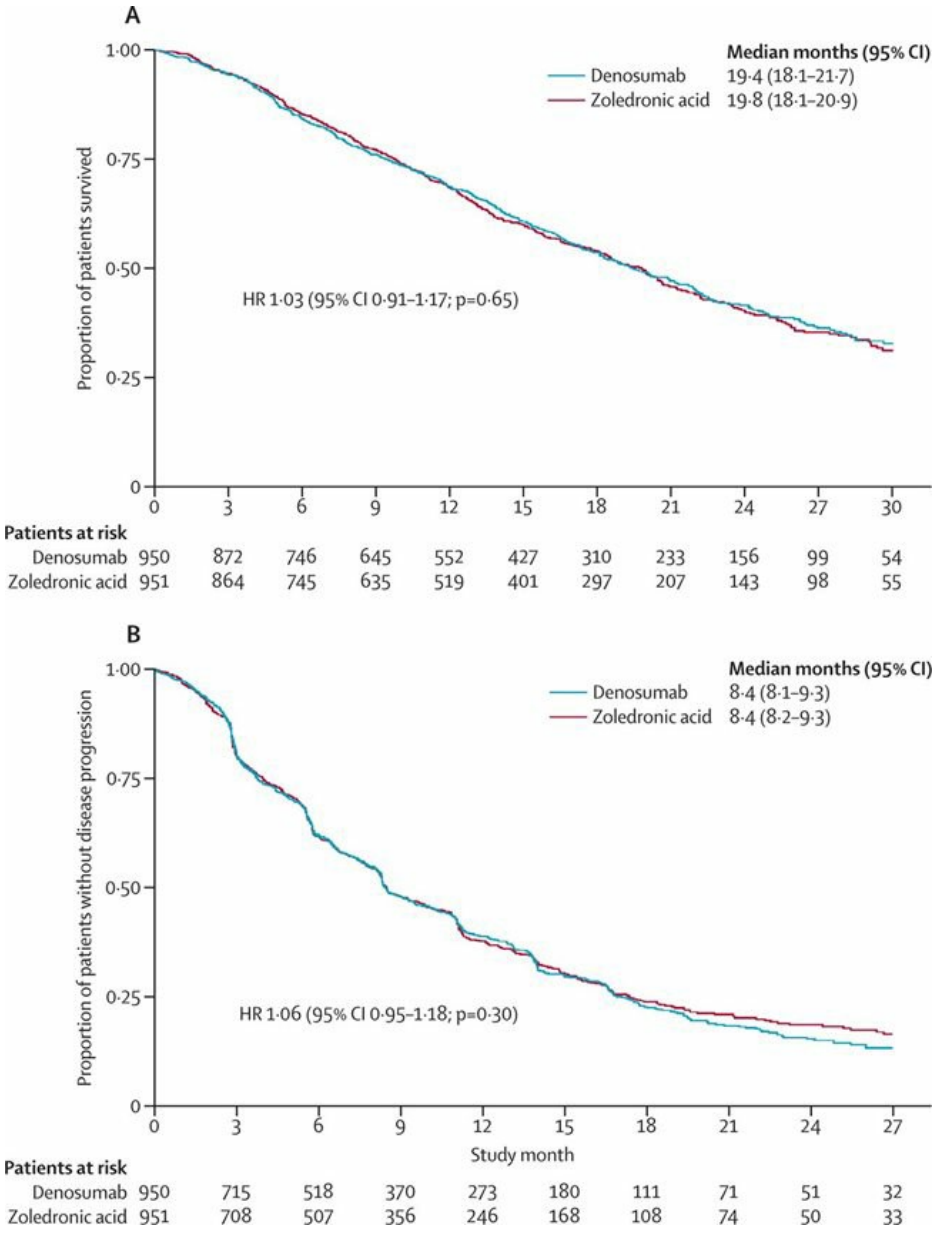
Efficacy

After a median time on study of 12.2 months for the denosumab group and 11.2 months for the zoledronic acid group, the median time to first on-study skeletal-related event was 20.7 months (95% CI 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio 0.82, 95% CI 0.71–0.95; p=0.0002 for non- inferiority; p=0.008 for superiority).[2]

Kaplan-Meier estimates of time to first on-study skeletal-related event[2]



Kaplan-Meier estimates (A) overall survival (B) time to disease progression[2]



Toxicity

Adverse events were recorded in 916 patients (97%) on denosumab and 918 patients (97%) on zoledronic acid, and serious adverse events were recorded in 594 patients (63%) on denosumab and 568 patients (60%) on zoledronic acid. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; p<0.0001). Osteonecrosis of the jaw occurred infrequently (22 [2%] vs 12 [1%]; p=0.09).[2]

Toxicity[2]

	Zoledronic acid (n=945)	Denosumab (n=943)	p value*
Overall safety summary			
Any adverse event	918 (97%)	916 (97%)	1·00
Adverse events occurring with ≥20% frequency in either treatment group			
Anaemia	341 (36%)	337 (36%)	0·89
Back pain	287 (30%)	304 (32%)	0·40
Decreased appetite	274 (29%)	267 (28%)	0·76
Nausea	245 (26%)	272 (29%)	0·16
Fatigue	222 (23%)	257 (27%)	0·06
Constipation	251 (27%)	236 (25%)	0·46
Bone pain	245 (26%)	235 (25%)	0·63
Asthenia	239 (25%)	239 (25%)	1·00
Arthralgia	202 (21%)	194 (21%)	0·69
Pain in extremity	196 (21%)	197 (21%)	0·95
Peripheral oedema	174 (18%)	192 (20%)	0·30
Adverse events leading to treatment discontinuation	138 (15%)	164 (17%)	0·10
CTCAE grade 3 or 4 adverse events	628 (66%)	678 (72%)	0·01
Serious adverse events	568 (60%)	594 (63%)	0·20
Fatal adverse events	276 (29%)	283 (30%)	0·72
Adverse events of interest			
Infectious adverse events†	375 (40%)	402 (43%)	0·21
Cumulative osteonecrosis of the jaw (total)	12 (1%)	22 (2%)	0·09
Year 1	5 (1%)	10 (1%)	..
Year 2	8 (1%)	22 (2%)	..
Hypocalcaemia	55 (6%)	121 (13%)	<0·0001
New primary malignant disease	10 (1%)	18 (2%)	0·13

Data are number (%). CTCAE=Common Terminology Criteria For Adverse Events (version 3.0). *Calculated by Fisher's exact test. †Based on Medical Dictionary for Regulatory Activities (MedDRA; version 12.1) system organ class categorisation of infections and infestations.

Table 4: **Adverse events and adverse events of interest in patients receiving at least one dose of study treatment**

References

1 Stopeck, A. T., A. Lipton, J. J. Body, et al. 2010. "Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study." J Clin Oncol 28(35):5132-5139.

2 Fizazi, K., M. Carducci, M. Smith, et al. 2011. "Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study." Lancet 377(9768):813-822.

History

Version 2

Date	Summary of changes
27/04/2012	New protocol taken to Medical Oncology Reference Committee meeting.
22/06/2012	Approved and published on eviQ.
17/12/2013	Reviewed electronically. Severe hypocalcaemia pre clin and blood tests. Review again 1 year.
09/05/2014	Protocol reviewed electronically by Medical Oncology Reference Committee; no change. Next review in 2 years.
15/05/2015	Skin rash (Dryness, Erythema and Pruritus) side effect removed.
31/05/2017	Transferred to new eviQ website. Protocol version number changed to V.2. Note added informing limited evidence beyond 2 yrs and to consider 12 weekly dosing after one to two years as per expert opinion of the reference committee.
25/03/2019	Protocol reviewed at Medical Oncology Reference Committee meeting on 15/03/2019. No changes. Next review

Date	Summary of changes
	in 5 years.

First approved: 22 June 2012
Last reviewed: 15 March 2019
Review due: 30 June 2024

Patient information - Prostate cancer metastatic - Denosumab

Patient's name:

Your treatment

The treatment schedule below explains how the drug for this treatment is given.

Denosumab			
This treatment cycle is repeated every 28 days. Your doctor will advise you of the number of treatments you will have.			
Day	**Treatment**	**How it is given**	**How long it takes**
1	**Denosumab** (*den-os-u-mab*)	By injection under your skin in your thigh, stomach or arm	About 5 minutes

- denosumab is **not** chemotherapy. It is used to slow down the spread of cancer in the bones and help to prevent changes to the bones that can make them weak

When to get help

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

Treatment delays

There may 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. Your doctor will explain if you need any 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.

Other medications given during this treatment

- **Calcium and vitamin D supplements:** you may be given some calcium and vitamin D tablets. Your doctor or nurse will tell you how and when to take these.

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.

Early (onset days to weeks)	
Low blood calcium levels (hypocalcaemia)	• This may be found from your routine blood tests and treated by your doctor. • If it is severe you may get: ◦ muscle cramps or twitches ◦ numbness or tingling in your fingers, toes or around your mouth ◦ sleepy or drowsy • **Tell your doctor or nurse as soon as possible if you get any of the signs or symptoms listed above.**

Delayed (onset months to years)	
Jaw problems (osteonecrosis of the jaw)	• You may get the following signs or symptoms during treatment, or after you have stopped treatment: ◦ pain, swelling or infection in the gums ◦ loosening of teeth ◦ numbness or heaviness in the jaw ◦ poor healing of gums and sockets, especially after dental treatment • Do your mouth care regularly. • See a dentist before you begin treatment and then for 6 monthly check ups. • Make sure you tell your dentist that you are starting treatment with a bisphosphonate or denosumab. • If you need a tooth removed, talk to your doctor first, as you will need to stop treatment 6 to 8 weeks before the dental work. Only start treatment again when the tooth socket has healed. • **Tell your doctor or dentist immediately if you get any of the symptoms listed above.**

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.
- Vaccinations such as flu and tetanus vaccines are safe to receive while you are having treatment. If you are unsure, check with your doctor before you have any vaccinations.

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 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.

Fathering a child

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that your partner could be pregnant.
- Do not try to 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 fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.

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

Prostate cancer information

- Continence Foundation of Australia – continence.org.au
- Healthy Male Andrology Australia – healthymale.org.au
- National Continence Management Strategy – bladderbowel.gov.au/ncp/ncms
- National Public Toilet Map – toiletmap.gov.au
- Prostate Cancer Foundation of Australia – prostate.org.au
- South Australian Prostate Cancer Clinical Outcome Collaborative – prostatehealth.org.au

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au

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

Quit smoking information and support

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

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

Additional notes:

First approved: 22 June 2012
Last reviewed: 15 March 2019
Review due: 30 June 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/pi/1301
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