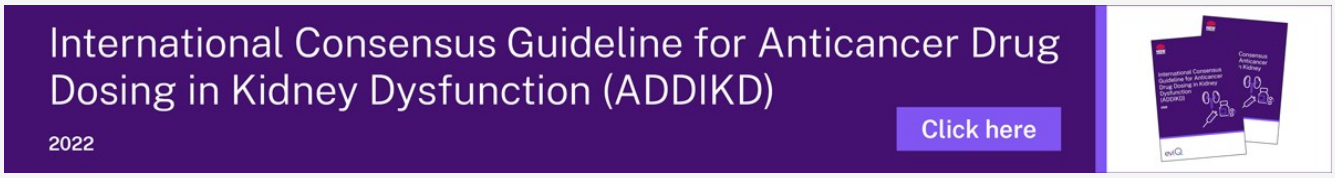
Breast metastatic denosumab

ID: 1300 v.4 **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:

- Breast 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 (there is no information regarding how long denosumab treatment should be continued)

Notes:
The incidence of osteonecrosis of the jaw reported with denosumab is around 2%,[1] and may increase with prolonged use.

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 6 to 12 weeks at clinician discretion, to reduce the risks of cumulative exposure including the increased risk of osteonecrosis of the jaw.

Drug status: Denosumab is PBS authority

Cost: ~ $460 per cycle

Treatment schedule - Detail

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

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

Cycle 1 and further cycles

Day 1		
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 (dose determined by vitamin D level; daily oral supplement of at least 400 international units vitamin D 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 (dose determined by vitamin D level; daily oral supplement of at least 400 international units vitamin D is required)

Frequency: 28 days

Cycles: Continuous until unacceptable toxicity (there is no information regarding how long denosumab treatment should be continued)

Indications and patient population

- Prevention of skeletal related events in patients with bone metastases from breast 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 renal impairment (creatinine clearance < 30 mL/min 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.
Blood tests	Calcium, magnesium, phosphate and vitamin D at baseline. Repeat prior to each cycle or as clinically indicated.

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 .

Renal impairment
No dose modifications 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

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, double-blind, double-dummy trial involving 2,049 patients comparing denosumab and placebo with zoledronic acid and placebo in patients with cytologically confirmed breast adenocarcinoma with radiographic evidence of at least one bone metastasis.[2]

Between April 2006 and December 2007, 1,026 patients were randomised to receive subcutaneous injection of denosumab 120 mg and an intravenous infusion of placebo every 4 weeks, and 1,026 patients were randomised to receive an intravenous infusion (lasting no less than 15 minutes) of zoledronic acid 4 mg and a subcutaneous injection of placebo every 4 weeks.[2]

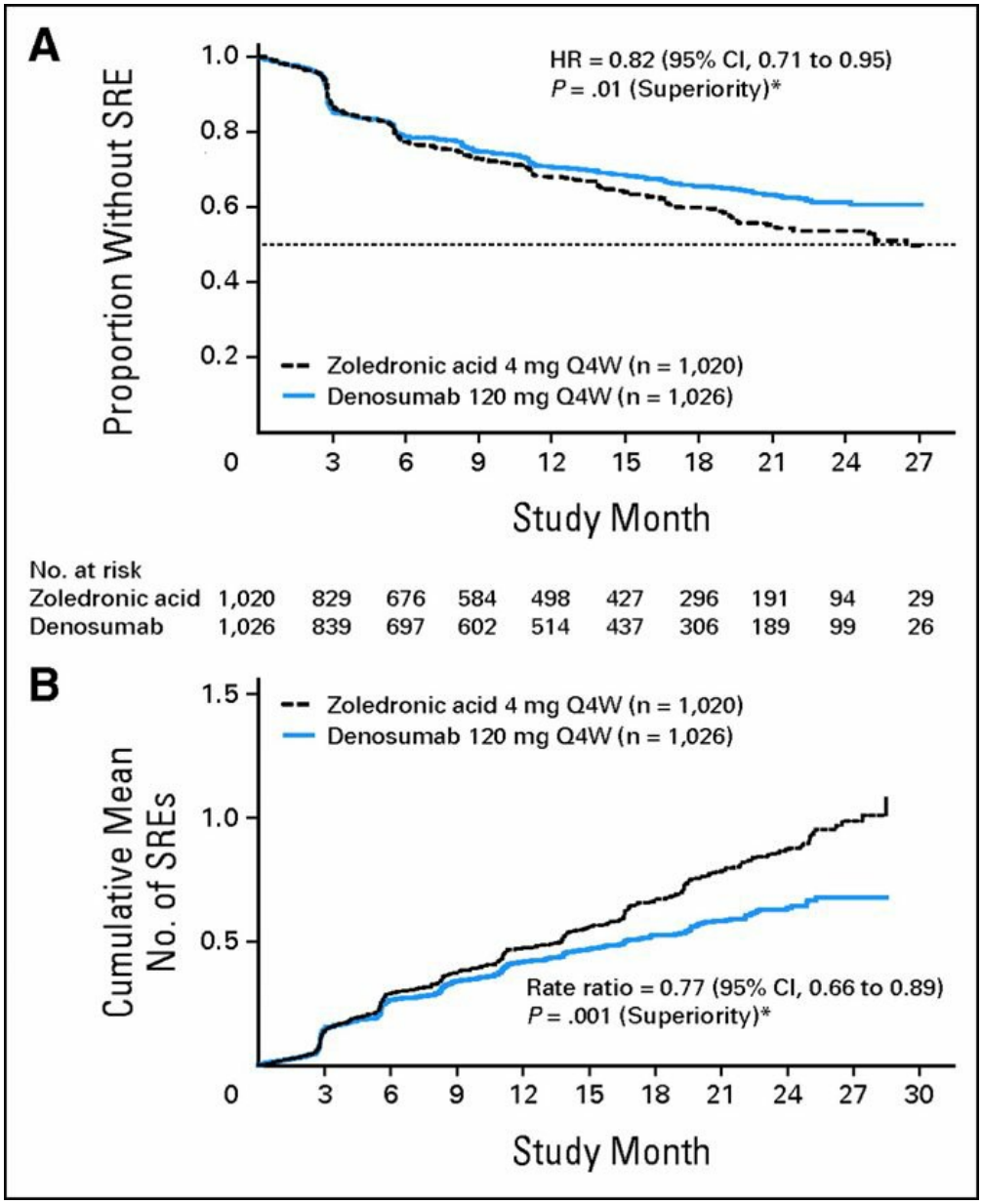
The primary end point was time to first on-study Skeletal Related Event (SRE) (noninferiority analysis), defined as pathologic fracture (excluding major trauma), radiation therapy to bone, surgery to bone, or spinal cord compression. Secondary end points were time to first on-study SRE (superiority analysis) and time to first and subsequent on-study SREs (multiple event analysis). Subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (e.g. surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate SREs.[2]

Safety end points included incidence of treatment-emergent adverse events (AEs), changes in laboratory values, and incidence of anti-denosumab antibodies.[2]

Efficacy

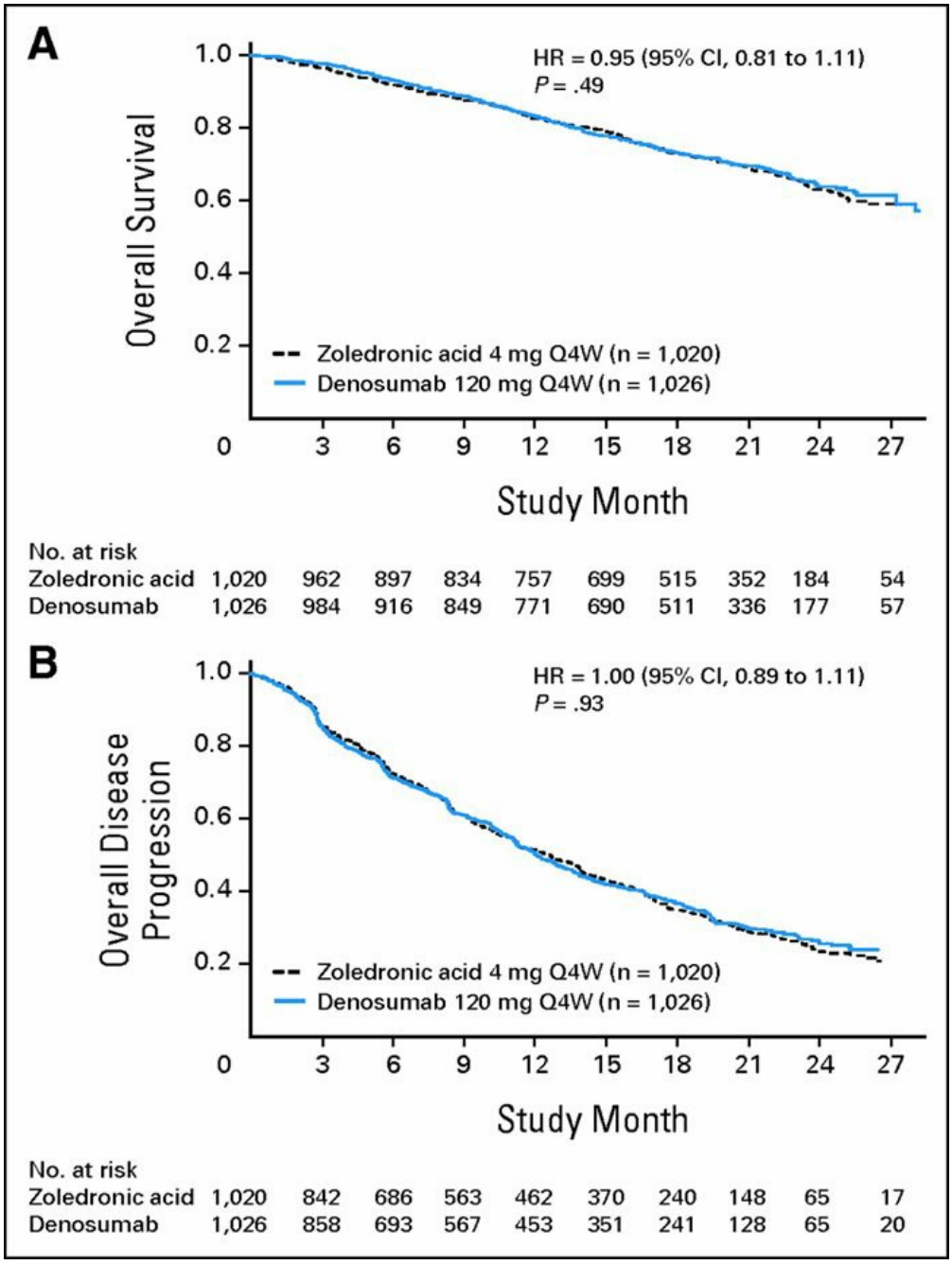
After a median time on study of 17 months, the median time to first on-study SRE was 26.4 months for the zoledronic acid group and has not yet been reached for the denosumab group. (Denosumab significantly delayed time to first on-study SRE by 18% compared with zoledronic acid (HR, 0.82; 95% CI, 0.71 to 0.95; $P < .001$ noninferiority; $P = .01$ superiority).[2]

Kaplan-Meier estimates of (A) time to first SRE and (B) time to first and subsequent SREs[2]



© Journal of Clinical Oncology 2010

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



© Journal of Clinical Oncology 2010

Quality of life (QOL) data was not collected in the key evidence.

Toxicity

Note: 40% of patients were also receiving chemotherapy.[2]

Adverse Event	Zoledronic Acid Q4W (4 mg) (n = 1,013) No.	%	Denosumab Q4W (120 mg) (n = 1,020) No.	%
Adverse events of interest				
Infectious adverse events*	494	48.8	473	46.4
Infectious serious adverse events*	83	8.2	71	7.0
New primary malignancy	5	0.5	5	0.5
Adjudicated positive ONJ†	14	1.4	20	2.0
Resolved	6 of 14	42.9	10 of 20	50.0
Ongoing	1 of 14	7.1	2 of 20	10.0
Continued until death	5 of 14	35.7	5 of 20	25.0
Unknown‡	2 of 14	14.3	3 of 20	15.0
Local infection	9 of 14	64.3	10 of 20	50.0
Surgical treatment	7 of 14	50.0	7 of 20	35.0
Limited surgery	7 of 14	50.0	7 of 20	35.0
Bone resection	0	0	0	0
Acute phase reactions (first 3 days)§	277	27.3	106	10.4
Adverse events potentially associated with renal toxicity¶	86	8.5	50	4.9
Adverse events potentially associated with renal toxicity occurring with ≥ 1% frequency¶				
Increased blood creatinine	41	4.0	31	3.0
Renal failure	25	2.5	2	0.2
CTCAE grade ≥ 3 adverse events potentially associated with renal toxicity	22	2.2	4	0.4
Serious adverse events potentially associated with renal toxicity	15	1.5	2	0.2

Abbreviations: Q4W, every 4 weeks; CTCAE, Common Terminology Criteria of Adverse Events, Version 3.0; ONJ, osteonecrosis of the jaw.

*Based on Medical Dictionary for Regulatory Activities (MedDRA) v12.0 System Organ Class categorization "infections and infestations."

†As of February 2010.

‡Consent withdrawn, lost to follow-up, status unknown at time of death, or current status unknown.

§Defined as flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias, and myalgias that have been associated with intravenous bisphosphonate use, per prescribing information for zoledronic acid.

¶Includes increased blood creatinine, hypercreatininemia, oliguria, renal impairment, proteinuria, renal failure, decreased urine output, decreased creatinine renal clearance, acute renal failure, abnormal renal function test, anuria, increased blood urea, and chronic renal failure.

© Journal of Clinical Oncology 2010

References

1 Saad, F., J. E. Brown, C. Van Poznak, et al. 2012. "Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases." Ann Oncol 23(5):1341-1347.

2 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.

History

Version 4

Date	Summary of changes
27/04/2012	New protocol taken to Medical Oncology Reference Committee meeting.
21/06/2012	Approved and published on eviQ.
30/06/2013	Protocol reviewed by committee via email survey. No changes and next review in 2 years.

Date	Summary of changes
17/12/2013	Electrolyte imbalance replaced by severe hypocalcaemia under clinical information. Blood tests updated.
10/08/2014	Protocol reviewed at reference committee meeting 09/05/14. Added baseline monitoring of vitamin D and repeat calcium level prior to each treatment . Incidence of osteonecrosis of the jaw added. Skin rash side effect removed. Patient information updated. Next review in 2 years.
18/02/2016	Discussion with Medical Oncology Reference Committee Chairs and protocol to be reviewed every 5 years. Next review due in 3 years.
31/05/2017	Transferred to new eviQ website. Version number change to V.3.
23/09/2019	Protocol reviewed at Medical Oncology Reference Committee meeting on 30/08/2019. Treatment schedule note updated to consider 12 weekly dosing after one to two years. Version number change to V.4. Next review in 2 years.
13/08/2021	Protocol reviewed electronically by Medical Oncology Reference Committee. Nil changes. Review in 2 years.
19/08/2022	Treatment schedule note regarding frequency changed from 'reduce the frequency to 12 weeks after one to two years of treatment' to 'reduce the frequency to 6 to 12 weeks at clinician discretion' as per Medical Oncology reference committee consensus.

The information contained in this protocol is based on the highest level of available evidence and consensus of the eviQ reference committee regarding their views of currently accepted approaches to treatment. Any clinician (medical oncologist, haematologist, radiation oncologist, medical physicist, radiation therapist, pharmacist or nurse) seeking to apply or consult this protocol is expected to use independent clinical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. While eviQ endeavours to link to reliable sources that provide accurate information, eviQ and the Cancer Institute NSW do not endorse or accept responsibility for the accuracy, currency, reliability or correctness of the content of linked external information sources. Use is subject to eviQ's disclaimer available at www.eviQ.org.au

First approved: 22 June 2012
Last reviewed: 13 August 2021
Review due: 31 December 2023

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/1300
07 Jun 2023

Patient information - Breast cancer metastatic - Denosumab

Patient's name:

Your treatment

This treatment is not chemotherapy. It is used to reduce the damage caused to the bones by the cancer. It works by helping the bones to heal where damaged and increasing the strength of the bones. By doing this it reduces pain, fractures and the need for radiation therapy to treat bone metastases.

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

Denosumab (Xgeva®)			
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 an injection under the skin in your thigh, stomach or arm	About 5 minutes

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

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.

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 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.

Breast cancer information

- Australasian Lymphology Association – lymphoedema.org.au
- Australasian Menopause Society – menopause.org.au
- Breast Cancer Network Australia – bcna.org.au
- National Breast Cancer Foundation – nbcf.org.au
- YWCA Encore breast cancer exercise program – ywcaencore.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:

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

First approved: 22 June 2012
Last reviewed: 13 August 2021
Review due: 31 December 2023

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/pi/1300
07 Jun 2023