XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

FAKULTAS KEDOKTERAN
UNIVERSITAS TRISAKTI

# "Bridging Outcome of XGEVA Enhancing for Preventing Bone Complications"

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**Fakultas Kedokteran Universitas Trisakti**

# Disclaimer

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- All information presented in these slides are intended for scientific exchange and not to solicit off-label use.
- Please refer to local prescribing information for all drugs mentioned in this presentation for further details before prescribing.
- In Indonesia, **XGEVA** is indicated: for **reducing the risk of skeletal related events** (e.g. pathological fracture, radiation to bone, surgery to bone and spinal cord compression) in adult patients with bone metastases from **solid tumours.**
- Each vial contains 120 mg Denosumab in 1.7 mL solution (70 mg/mL)

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# Burden of Disease Bone Metastases

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# Bone Metastases Risk in Solid Tumors

Patients with **breast, prostate or lung cancer are at the highest risk for developing bone metastases**[1]

~ 7 out of 10

Women with advanced metastatic breast cancer develop bone metastases[2]

~ 7 out of 10

Men with advanced metastatic prostate cancer develop bone metastases[2]

~ 4 out of 10

Patients with advanced metastatic lung cancer develop bone metastases[3]

1. Mundy GR, *Nat Rev Cancer.* 2002;2(8):584-593; 2. Barlev A, et al. *J Manag Care Pharm.* 2010;16(9):693-702; 3. Colemen RE. *Clin Cancer Res.* 2006:12(supl20):6243s-6249s

# Bone Metastases Risk in Solid Tumors

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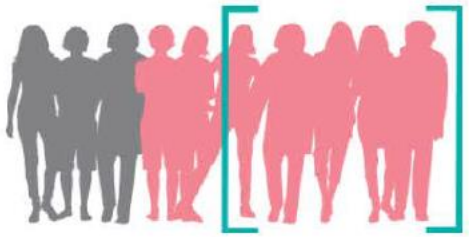
- **Bone metastases** put patients a **risk for bone complications**[1]
- An **initial bone complication increases the risk for additional bone complications**[4]



**64%**

Of women with breast cancer and bone metastases **develop first bone complications**[2]

**49%**

Of men with prostate cancer and bone metastases **develop bone complications**[3]

**69%**

In another study, after experiencing a first bone complication, women with breast cancer and bone metastases suffered a **subsequent bone complication**[4]

1. Van Moos R, et al. *Support Care Cancer. 2016:24(3):1327-1337; 2.* Lipton A, et al. Cancer. 2000:88(5):1082-1090; 3. Saad F, et al. *J Natl cancer Inst* 2004:96(11):897:882; 4. Hussain A, et al. Plos One 13(3):e0193661;

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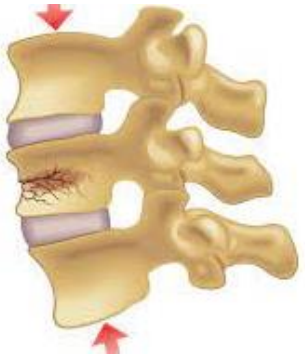
# Bone Complications

- Bone metastases put patients at risk of developing bone complications known as skeletal-related events (SREs)[2-3]
- SREs are defined as one or a combination of the following complication:[1-3]

The most common reason for radiation is **pain palliation**, It is also used to **reduce risk** of bone complications

**Pathologic fracture** can be painful for patients and often do not heal, resulting in bone destruction

**Surgery to bone** may be required to treat pain, pathologic fracture, or other complications



**Spinal cord compression** is considered to be an **oncologic emergency**

1. Lutz ST, et al. Cancer 2007;109:1462-1470; 2. Moore DR, et al. *Pediatrics* Jul 26, 2010; DOI: 10.1542/peds.2009-2826; 3. Wedin R, et al. Acta Orthop Scand Suppl 2010,72:1-29.

# The Risk of SREs is Immediate and Increase Over Time

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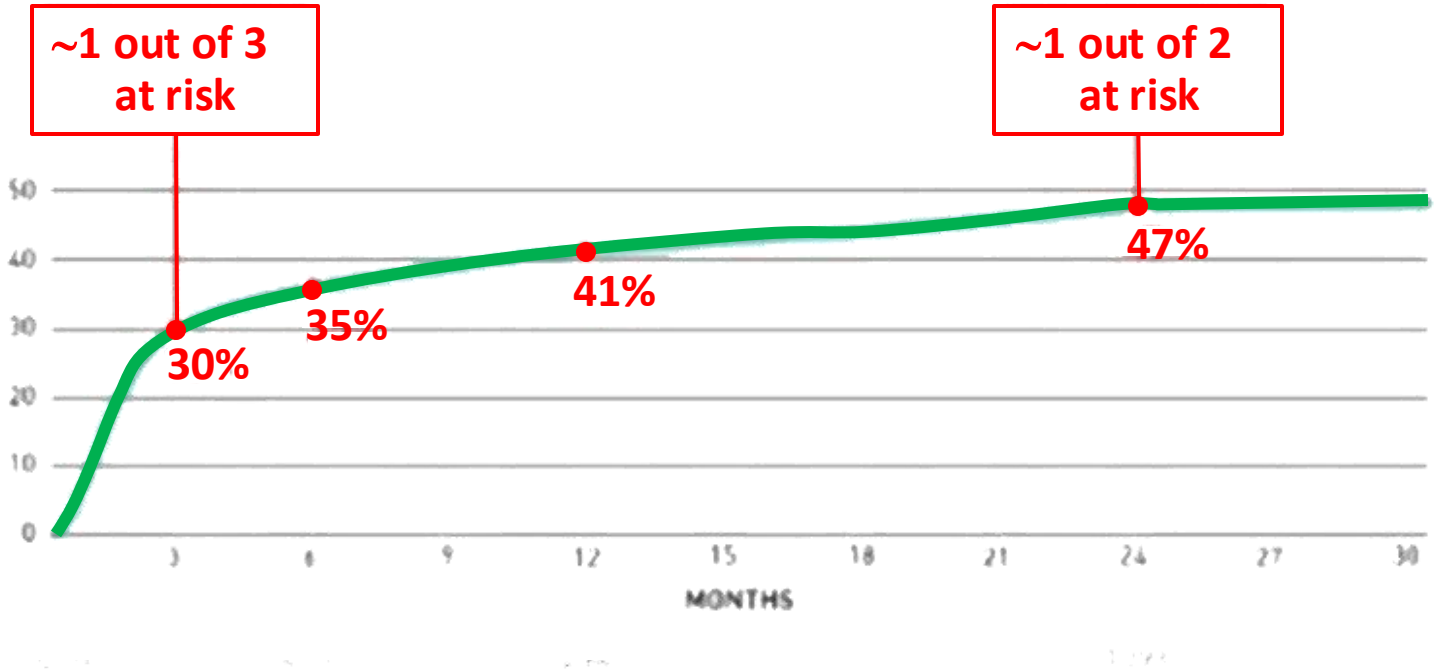
Almost half (47%) of patients experienced at least one bone complication within 2 years of bone metastases diagnosis, regardless of prior bone complication status



# Bone Complication-Related Pain

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- Pain is a common symptom for patients with bone metastases from solid tumors
- Result from a retrospective study which included 176 patients with breast cancer and bone metastases from 2008-2012.

**Patients with bone complications frequently suffered from pain**

**86%** **of patients with bone complications frequently experienced bone pain**

Kuchuk I, et al. J Bone Oncol 2013;2(4):137-144.

# Impact of SRE in Survival

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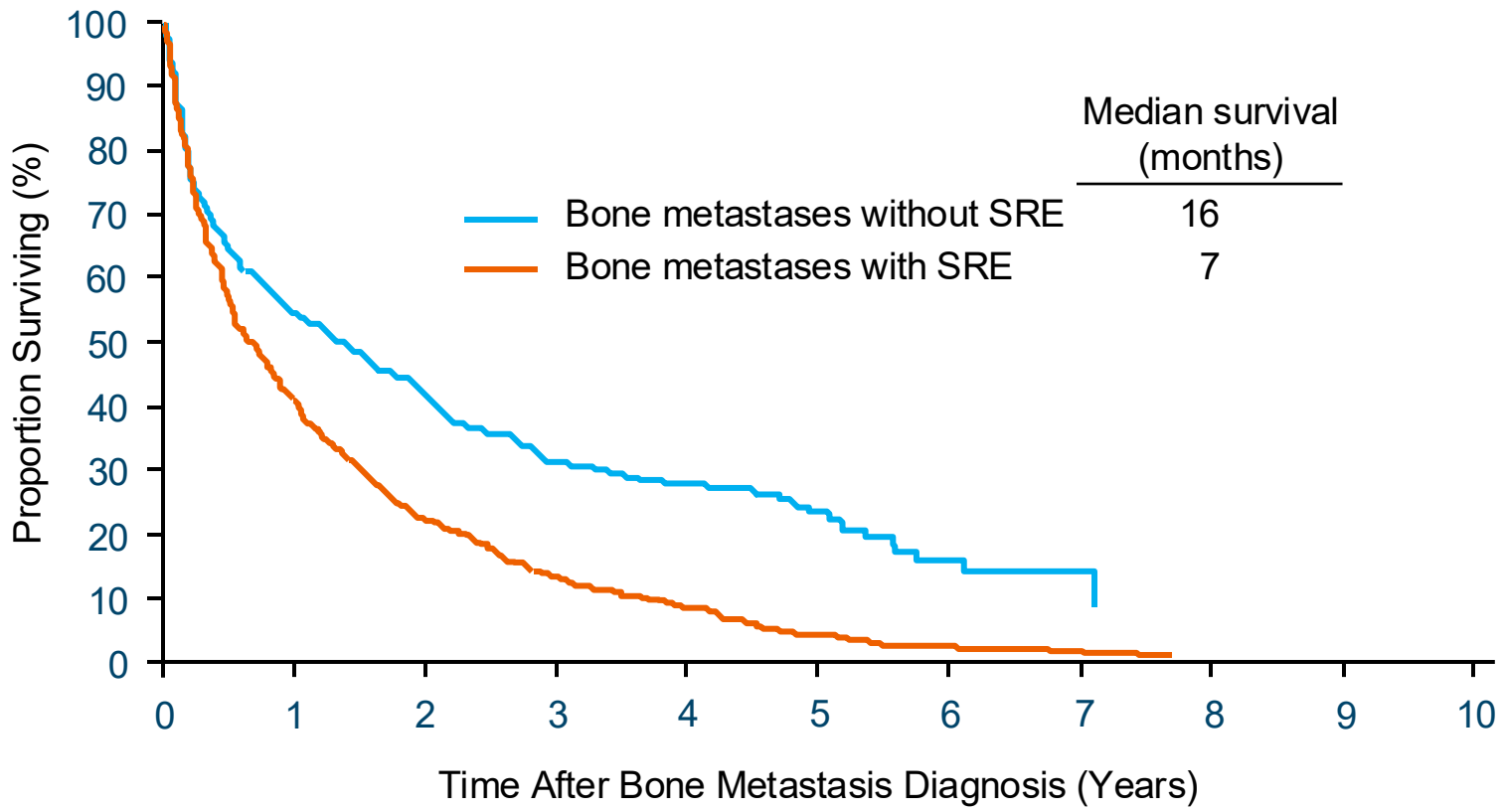
- Breast Cancer Patients with Bone Metastases and **SREs have a Worse Prognosis** than those without SREs



# The burden of SREs

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## Impact on Patients

- Bone pain[1]
- Poorer physical, functional, and emotional status[2]
- Sleep disturbance[3]
- Reduced health-related quality of life (HRQoL)[2]
- Increased hospital visits/stays[4]
- Shorter survival[2]

## Impact on Healthcare Systems

- Increased hospital visits/stays[4]
- Increased treatment costs[3,4]

1. Coleman R. *Clin Cancer Res* 2006;12:6243s-9s; 2. De Puy V, Anstrom K, Castel L, et al. *Support Cancer Care* 2007;15:869-76;
3. Khan L, Uy C, Nguyen J, et al. *J Palliat Med* 2011;14:708-14; 4. Body JJ, Pereira J, Sleeboom H, et al. *Eur J Health Econ* 2016;17:711-21;

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# Bone Targeted Agent: Role of XGEVA in SRE Management

# When should we start bone targeted agent (BTA)?

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At bone mets diagnosis

After pain onset pre-bone complication

After first bone complication


Asymptomatic patients with limited number of bone mets

Symptomatic bone mets but no previous bone complication

Patients who have experienced a bone complication

Coleman, R. et al. Annals of Oncology, Volume 31, Issue 12, 1650 – 1663
Van Moos R, et al. Support Care Cancer 2013;21:3497-3507

# Normal Bone Remodelling

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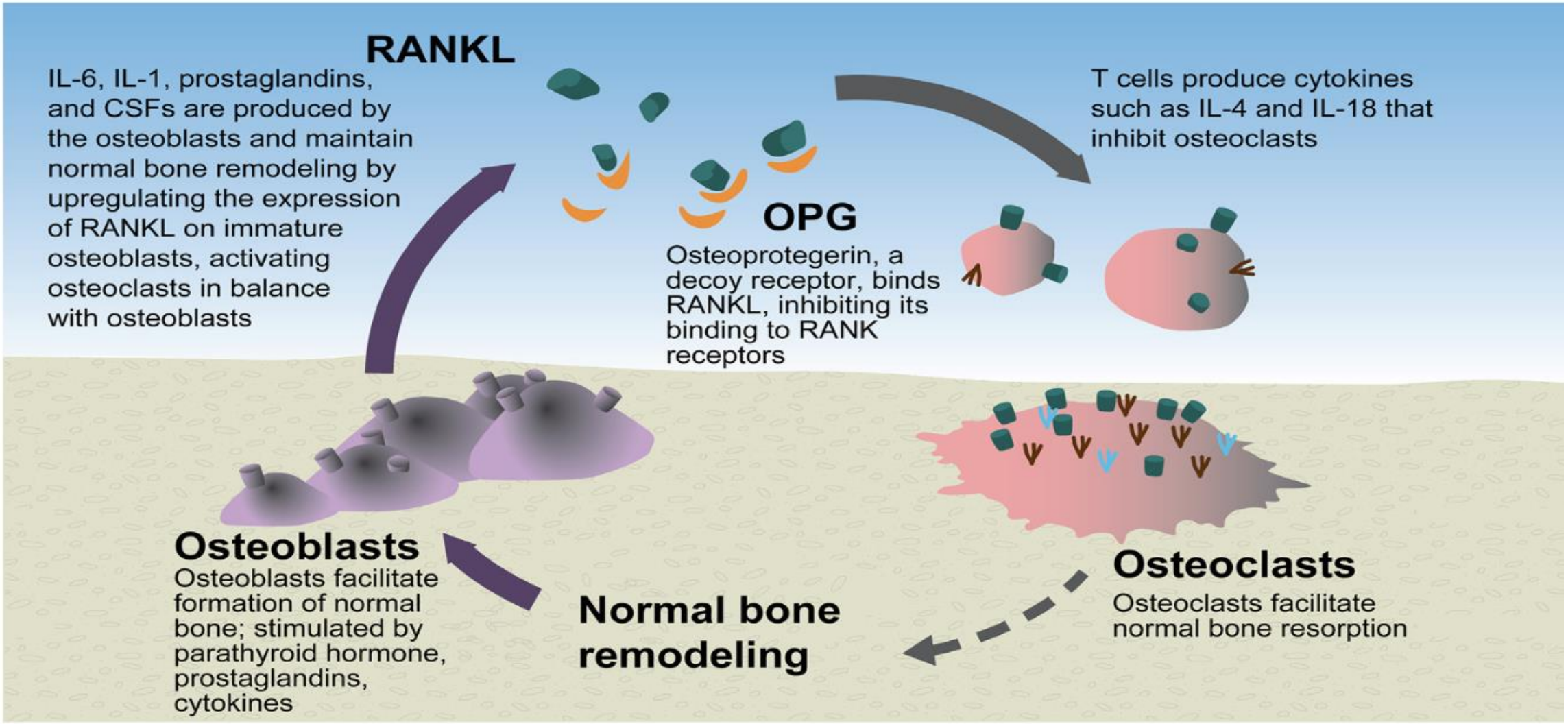

# The Presence of Tumor Cells in Bone Drives a 'Vicious Cycle' of Bone Destruction and Tumor Growth

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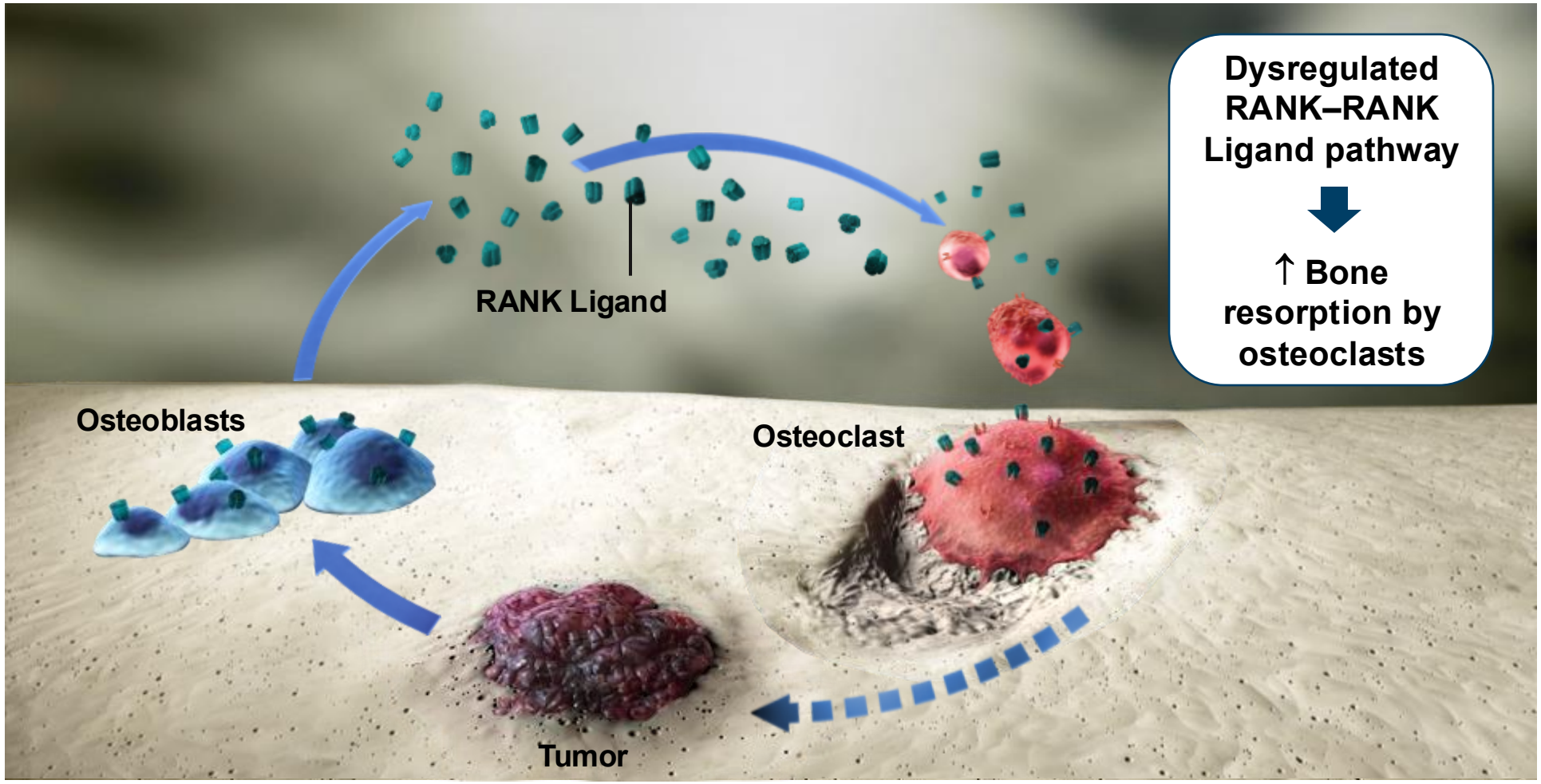


RANK=receptor activator of nuclear factor kappa-B.

Adapted from Roodman GD. *N Engl J Med* 2004;350:1655-64; Mundy GR. *Nat Rev Cancer* 2002;2:584-93.

# XGEVA Binds to RANK Ligand to Break the Vicious Cycle of Bone Destruction and Tumor Growth in Metastatic Bone Disease

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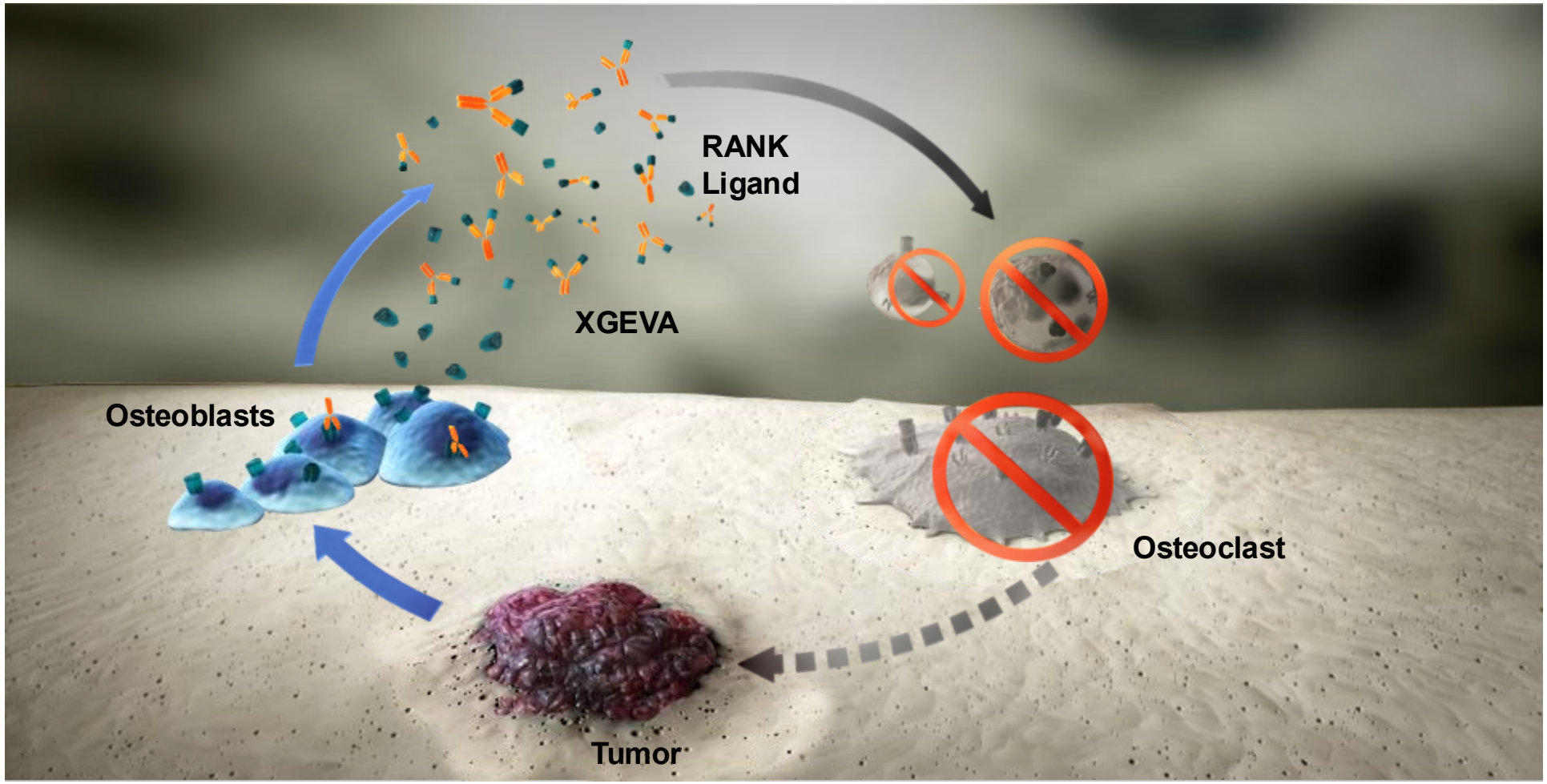


Adapted from Roodman GD. *N Engl J Med* 2004;350:1655-64; Mundy GR. *Nat Rev Cancer* 2002;2:584-93; McClung MR, Lewiecki EM, Cohen SB, et al. *N Engl J Med* 2006;354:821-31.

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# XGEVA Pivotal Study

# Study Design

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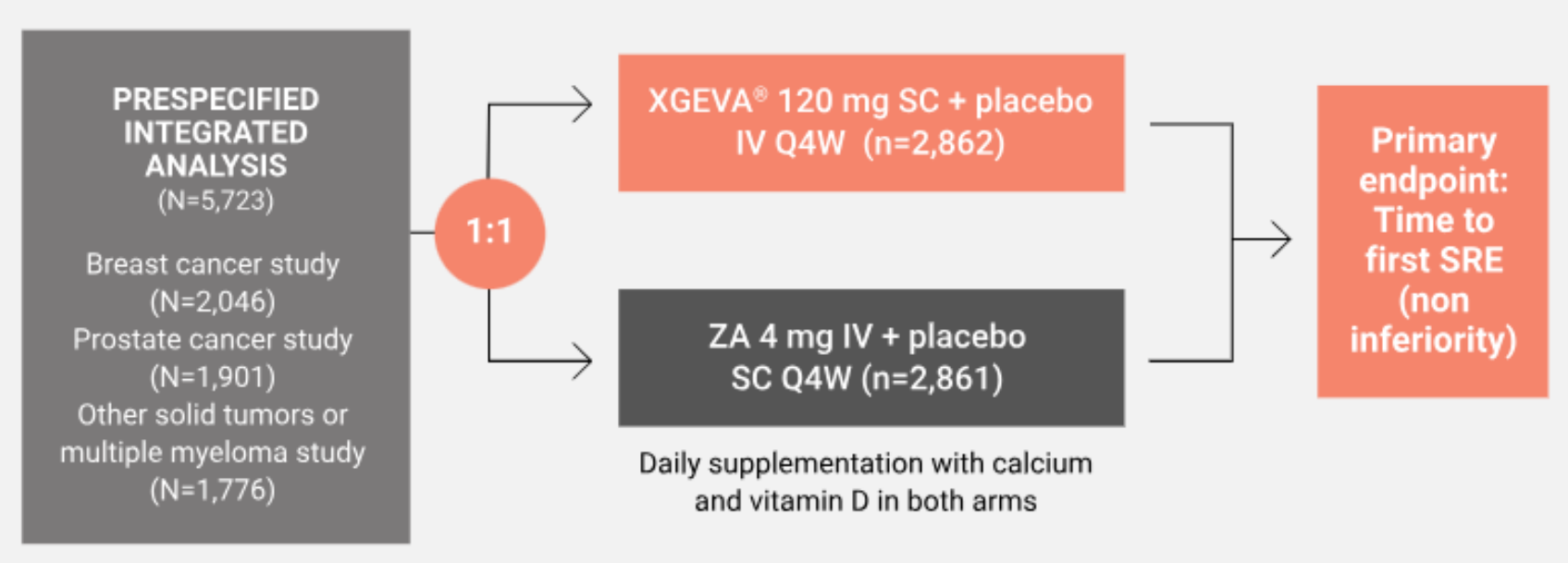
- Evaluated in 3 identically designed head-to-head studies vs ZA including more than **5.600** patients + 2-year open label extension (OLE) phase[2*,3]




Safety and tolerability were also addressed.

**Secondary endpoints**[1,2]

- Time to first on-study bone complication (superiority)
- Time to first and subsequent bone complications (superiority using multiple-event analysis)

If the primary endpoint of non inferiority was met; the superiority test for secondary endpoint was concluded.

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

1. XGEVA® Indonesia Product Information, 2024; 2. Lipton A, et al. Eur J Cancer. 2012;48(16):3082-3092; 3. Stopeck AT, et al. Support Care Cancer. 2016;24(1):447-455.

# Demographic and Baseline Characteristics

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| Baseline characteristics | XGEVA (n=2,862) | ZA (n=2,861) |
|---|---|---|
| Median age, years | 63 | 63 |
| ECOG status 0-1, % | 90 | 89 |
| Creatinine clearance ≥30 and ≤60 mL/min, % | 17 | 17 |
| Presence visceral metastases, % | 42 | 40 |
| Prior skeletal related event, % | 39 | 40 |
| **Primary tumor type, %** | | |
| Breast | 36 | 36 |
| Prostate | 33 | 33 |
| Non-small cell lung | 12 | 12 |
| Multiple myeloma | 3 | 3 |
| Renal | 2 | 2 |
| Small cell lung | 2 | 2 |
| Other | 11 | 10 |

ECOG, Eastern Cooperative Oncology Group

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

Lipton A, et al. Eur J Cancer. 2012;48(16):3082-3092

# Results

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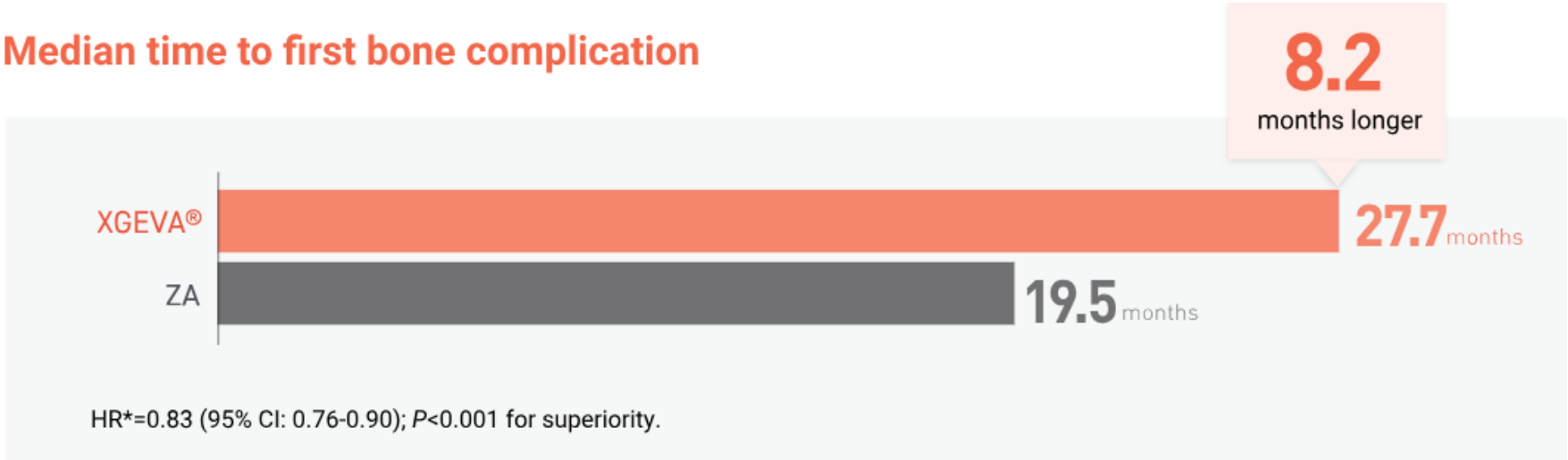
- In a prespecified, integrated analysis XGEVA prevents bone complications for 8.2 months longer than ZA




*HR is defined as the increase or decrease in likelihood of an event of interest (in this case, a bone complication) for one group relative to a comparator group.
CI, confidence interval; HR, hazard ratio.

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

1. XGEVA® Indonesia Product Information, 2024; 2. Lipton A, et al. Eur J Cancer. 2012;48(16):3082-3092

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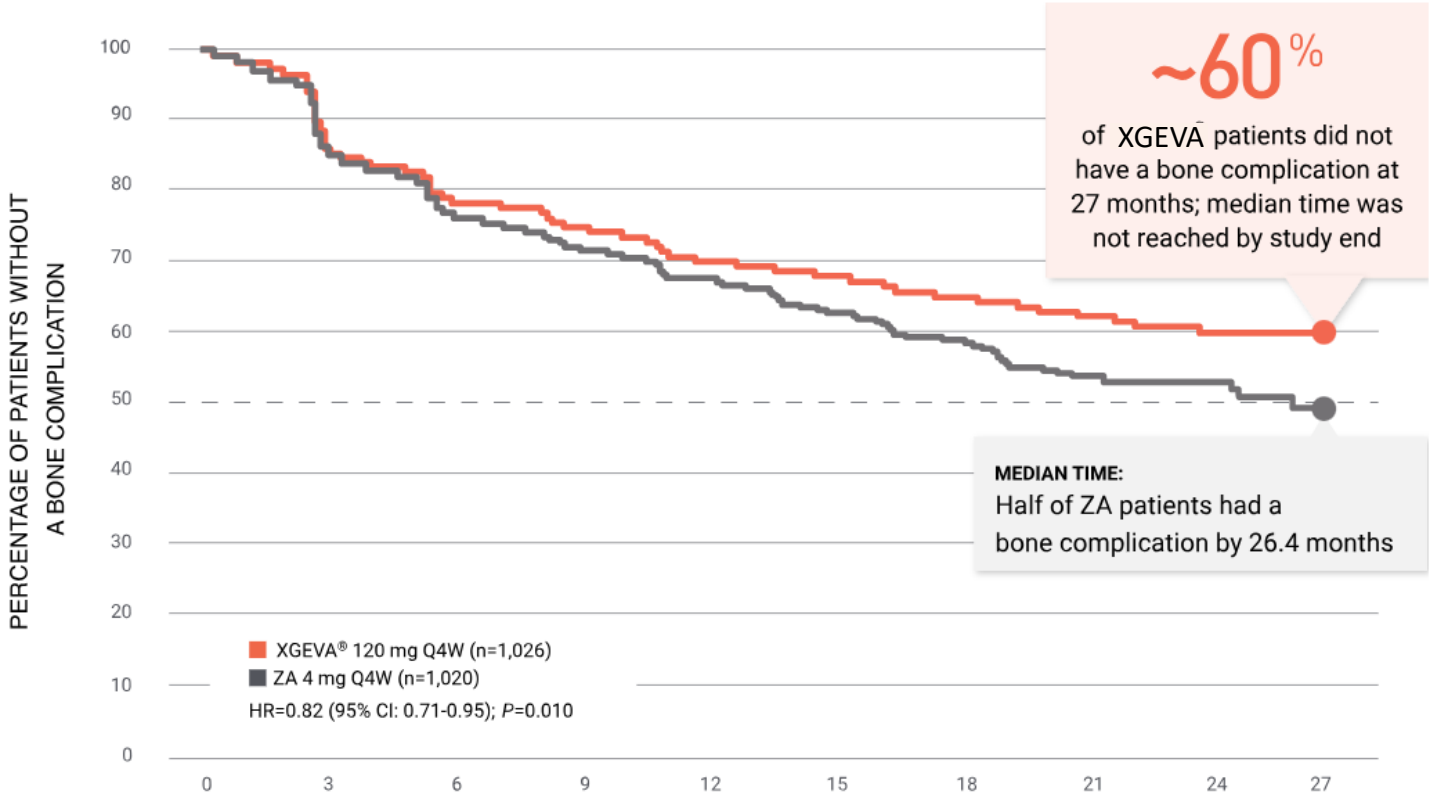
# Breast Cancer with Bone Metastases Data




XGEVA **prevented bone complications for >2 years.**

**18%** risk reduction compared with ZA

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

1. XGEVA® Indonesia Product Information, 2024; 2. Stopeck AT, et al. J Clin Oncol. 2010;28(35):5132-5139.

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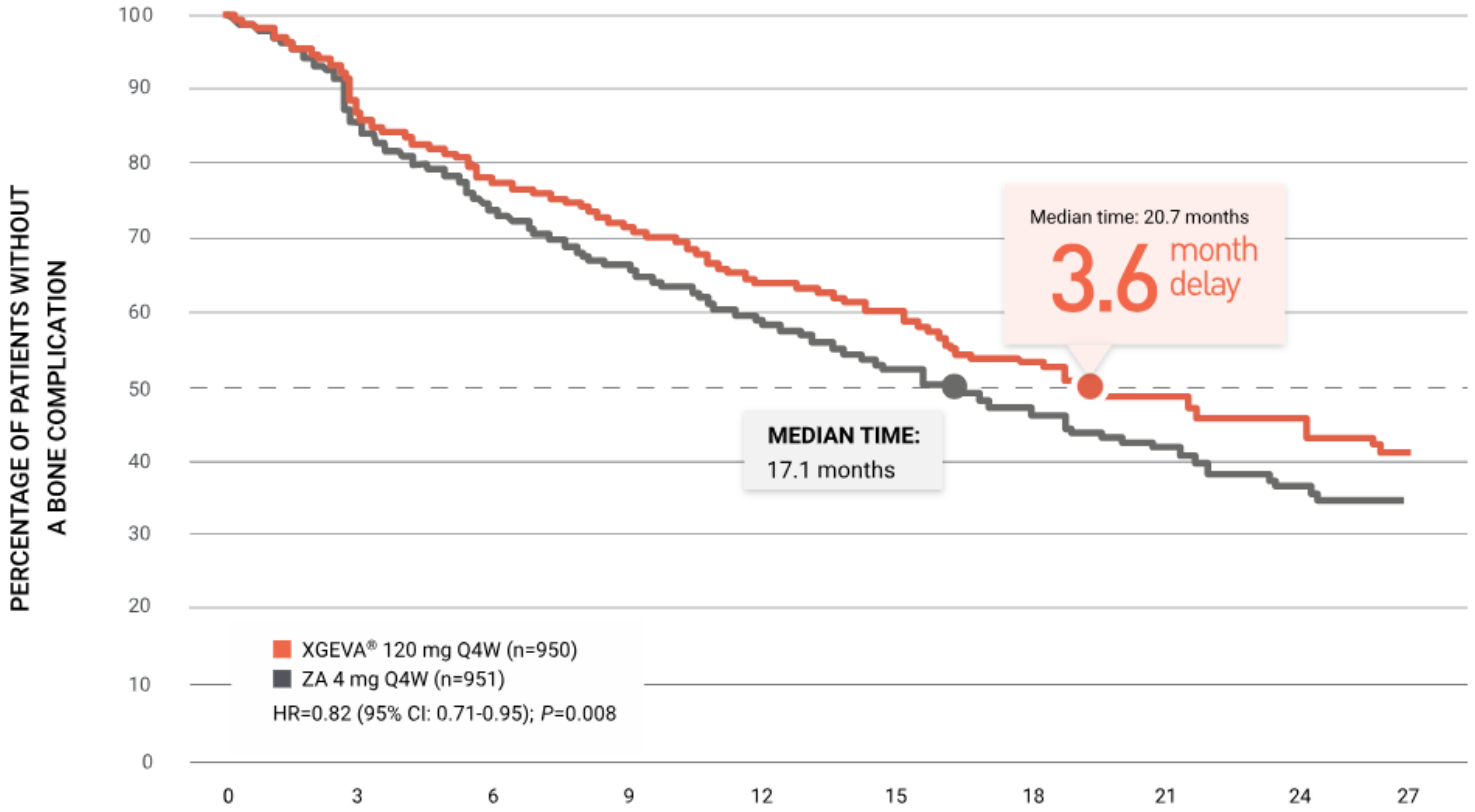
# Prostate Cancer with Bone Metastases Data




XGEVA prevented bone complications for a **median of 20.7 months**.

**18%** risk reduction compared with ZA

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

1. XGEVA® Indonesia Product Information, 2024; 2. Fizazi K, et al. Lancet. 2011;377(9768):813-822.

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# Time to worsening of pain


- Women with breast cancer taking **XGEVA went 3.9 months longer before experiencing moderate to severe pain** than those taking ZA (9.7 months vs 5.8 months; P = 0.002).[1]
- Results for castration-resistant prostate cancer patients: XGEVA (5.8 months) vs ZA (4.9 months) P=0.0024.[2]
- Results for advanced solid tumor-only cancer patients (excluding multiple myeloma): XGEVA (4.7 months) vs ZA (3.7 months) P=0.05.[3]

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

1. Cleeland CS, *Cancer*. 2013;119(4):832-838; 2. Patrick DL, et al. *Support Care Cancer*. 2015;23(4):1157-1168; 3. Henry D, et al. *Support Care Cancer*. 2014;22:679-687

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# Safety Profile

| Adverse Events (AEs), n (%) | SC XGEVA (120 mg) (n=1020) | IV Zoledronic Acid (4 mg) (n=1013) |
|---|---|---|
| **Any AE** | **977 (95.8)** | **985 (97.2)** |
| AEs occurring with ≥20% frequency in either group | | |
| Nausea | 356 (34.9) | 384 (37.9) |
| Fatigue | 301 (29.5) | 324 (32.0) |
| Arthralgia | 250 (24.5) | 291 (28.7) |
| Back pain | 241 (23.6) | 264 (26.1) |
| Pyrexia | 170 (16.7) | 247 (24.4) |
| Bone pain | 186 (18.2) | 238 (23.5) |
| Vomiting | 212 (20.8) | 238 (23.5) |
| Anemia | 192 (18.8) | 232 (22.9) |
| Diarrhea | 231 (22.6) | 207 (20.4) |
| Dyspnea | 222 (21.8) | 190 (18.8) |
| Pain in extremity | 204 (20.0) | 222 (21.9) |
| Headache | 197 (19.3) | 214 (21.1) |
| Constipation | 176 (17.3) | 205 (20.2) |

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

Stopeck AT, Lipton A, Body JJ, et al. *J Clin Oncol* 2010;28:5132-9.

# Osteonecrosis of the jaw (ONJ)

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- **Osteonecrosis of the jaw (ONJ) occurred infrequently**
  - 20 (2.0%) SC XGEVA vs 14 (1.4%) IV zoledronic acid
  - Rates of **ONJ were not statistically significantly different between groups** (*P*=0.39)
- Acute-phase reactions occurring within the first 3 days after treatment were 2.7 times more common with zoledronic acid
- AEs potentially associated with renal toxicity (8.5% vs 4.9%; *P*=0.001) occurred more frequently with zoledronic acid
- Decreases in serum calcium were generally mild, transient and not associated with clinical sequelae

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Stopeck AT, Lipton A, Body JJ, et al. *J Clin Oncol* 2010;28:5132-9.

# Renal Adverse Events

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- Incidence of AEs associated with **renal toxicity was lower in the XGEVA** group (*P*=0.001)
  - XGEVA, n=50 (4.9%)
  - Zoledronic acid, n=86 (8.5%)
- The incidence of renal AEs in XGEVA-treated patients was as expected in patients with advanced cancer and lower than the 6.7% rate of increased serum creatinine reported in the placebo group in the pivotal study of zoledronic acid in patients with solid tumors and bone metastases
- No patients in the XGEVA group and 3 patients (0.3%) in the zoledronic acid group withdrew from investigational product because of renal failure
- **No dose adjustment or dose withholding for renal dysfunction were required for XGEVA**

* In Indonesia, **XGEVA** is indicated: for **reducing the risk of SREs** in adult patients with bone metastases from **solid tumours.**

Martín M, Bell R, Bourgeois H, et al. *Clin Cancer Res* 2012;18:4841-9.;

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# Summary

- Various advanced **cancer** types **can spread to the bone**, which may weaken its integrity, and **lead to incidences of complications (SREs)**
- The presence of bone metastasis and its associated **SRE can be associated with a significant morbidity and mortality risk**
- **XGEVA is the only RANKL inhibitor** that provides superior protection against serious bone problems compared with ZA by **prevent SRE for more than 2 years**, 27.7 months in XGEVA vs 19.5 months in ZA. **Reduce risk of bone complications by 18%.**
- **Patients with XGEVA went 9.7 months without pain worsening**, 3.9 months longer before experiencing severe pain compared to ZA
- XGEVA has a **tolerable safety profile**, and **no need adjust dosing for patients with impaired renal function**

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# THANK YOU