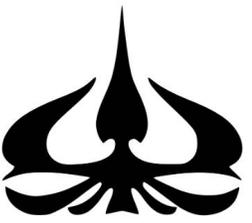


**XGEVA**<sup>®</sup>  
(denosumab) injection  
120 mg/1.7 mL vial



FAKULTAS KEDOKTERAN  
UNIVERSITAS TRISAKTI

# “Bridging Outcome of XGEVA Enhancing for Preventing Bone Complications”

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# Disclaimer

- 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)

# Burden of Disease Bone Metastases

# Bone Metastases Risk in Solid Tumors

Patients with **breast, prostate or lung cancer** are at the highest risk for developing **bone metastases**<sup>1</sup>



~ 7 out of 10

Women with advanced metastatic breast cancer develop bone metastases<sup>2</sup>



~ 7 out of 10

Men with advanced metastatic prostate cancer develop bone metastases<sup>2</sup>

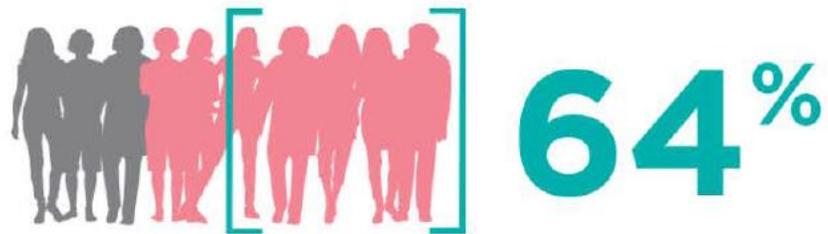


~ 4 out of 10

Patients with advanced metastatic lung cancer develop bone metastases<sup>3</sup>

# Bone Metastases Risk in Solid Tumors

- **Bone metastases** put patients a **risk for bone complications**<sup>1</sup>
- An **initial bone complication** increases the risk for **additional bone complications**<sup>4</sup>



Of women with breast cancer and bone metastases **develop first bone complications**<sup>2</sup>



Of men with prostate cancer and bone metastases **develop bone complications**<sup>3</sup>

**69%**

In another study, after experiencing a first bone complication, women with breast cancer and bone metastases suffered a **subsequent bone complication**<sup>4</sup>

# Bone Complications

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



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



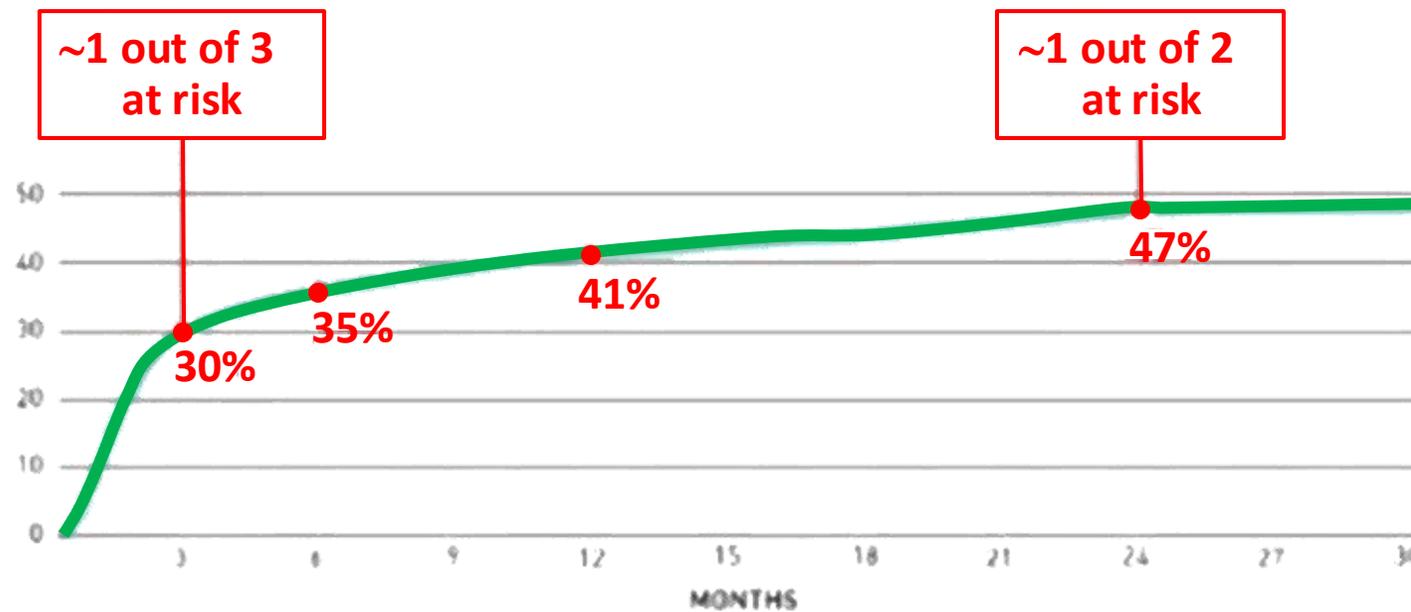
**Surgery to bone** may be required to treat pain, pathologic fracture, or other complications



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

# The Risk of SREs is Immediate and Increase Over Time

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

- 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.



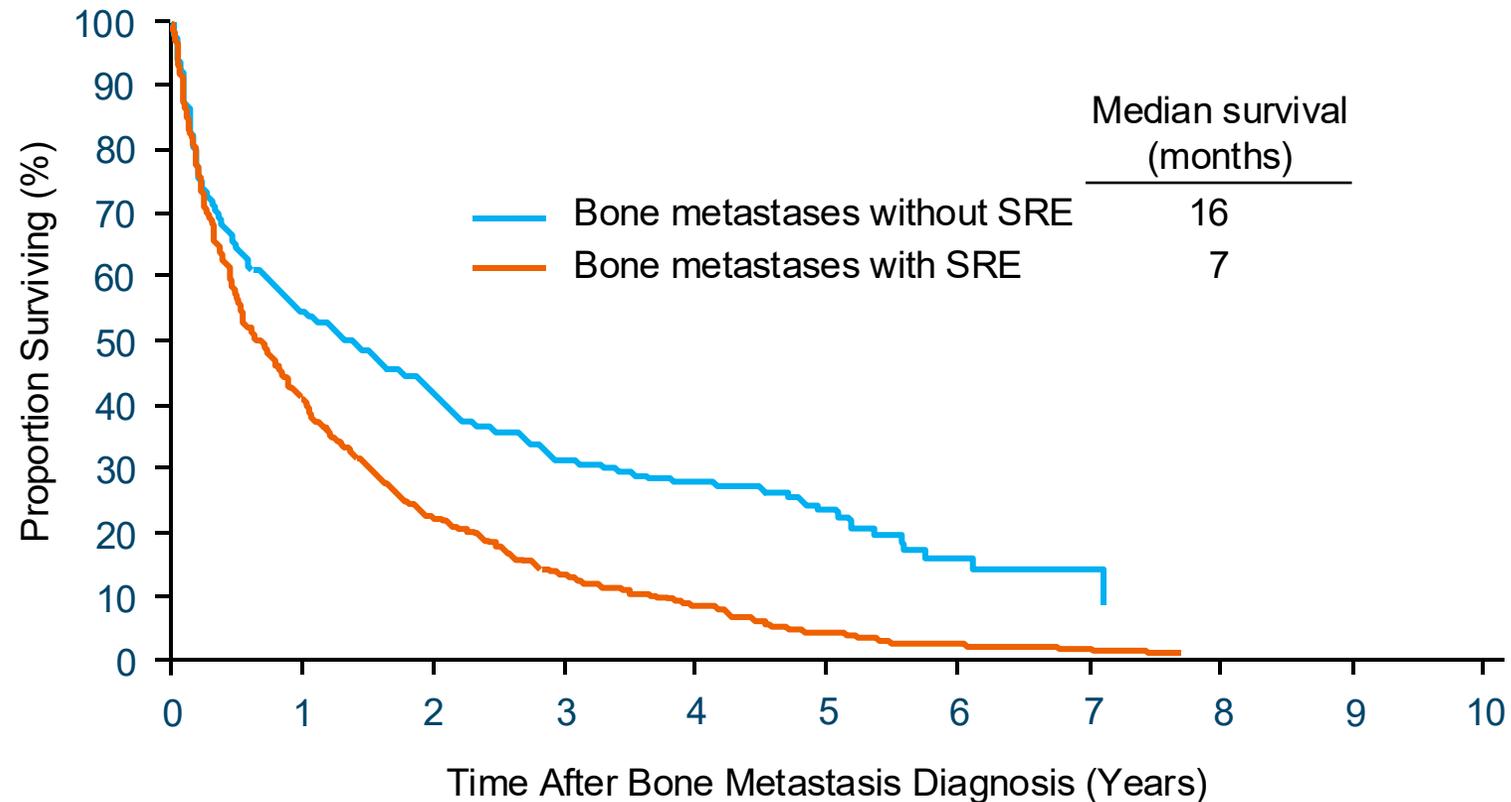
**Patients with bone complications frequently suffered from pain**

**86%**

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

# Impact of SRE in Survival

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



# The burden of SREs

## Impact on Patients

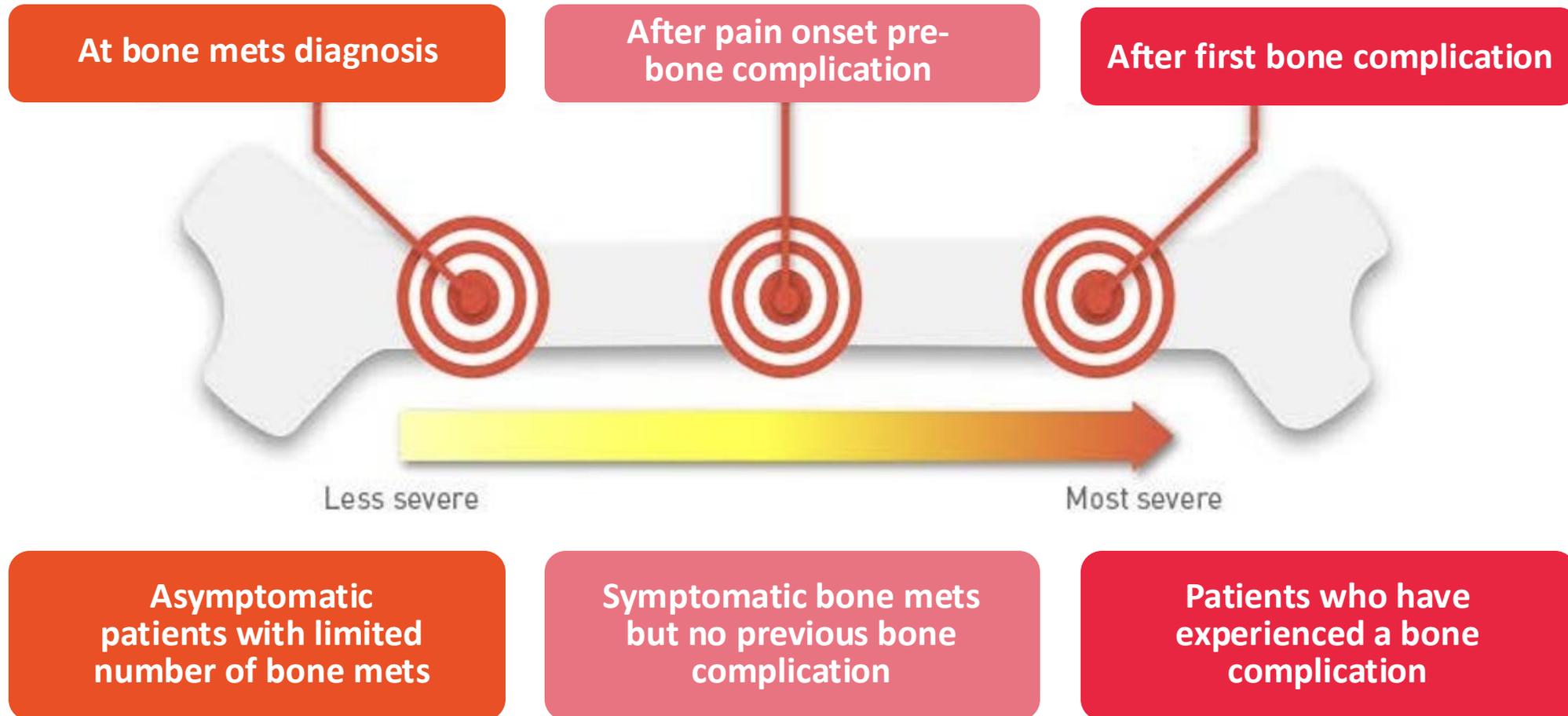
- Bone pain<sup>1</sup>
- Poorer physical, functional, and emotional status<sup>2</sup>
- Sleep disturbance<sup>3</sup>
- Reduced health-related quality of life (HRQoL)<sup>2</sup>
- Increased hospital visits/stays<sup>4</sup>
- Shorter survival<sup>2</sup>

## Impact on Healthcare Systems

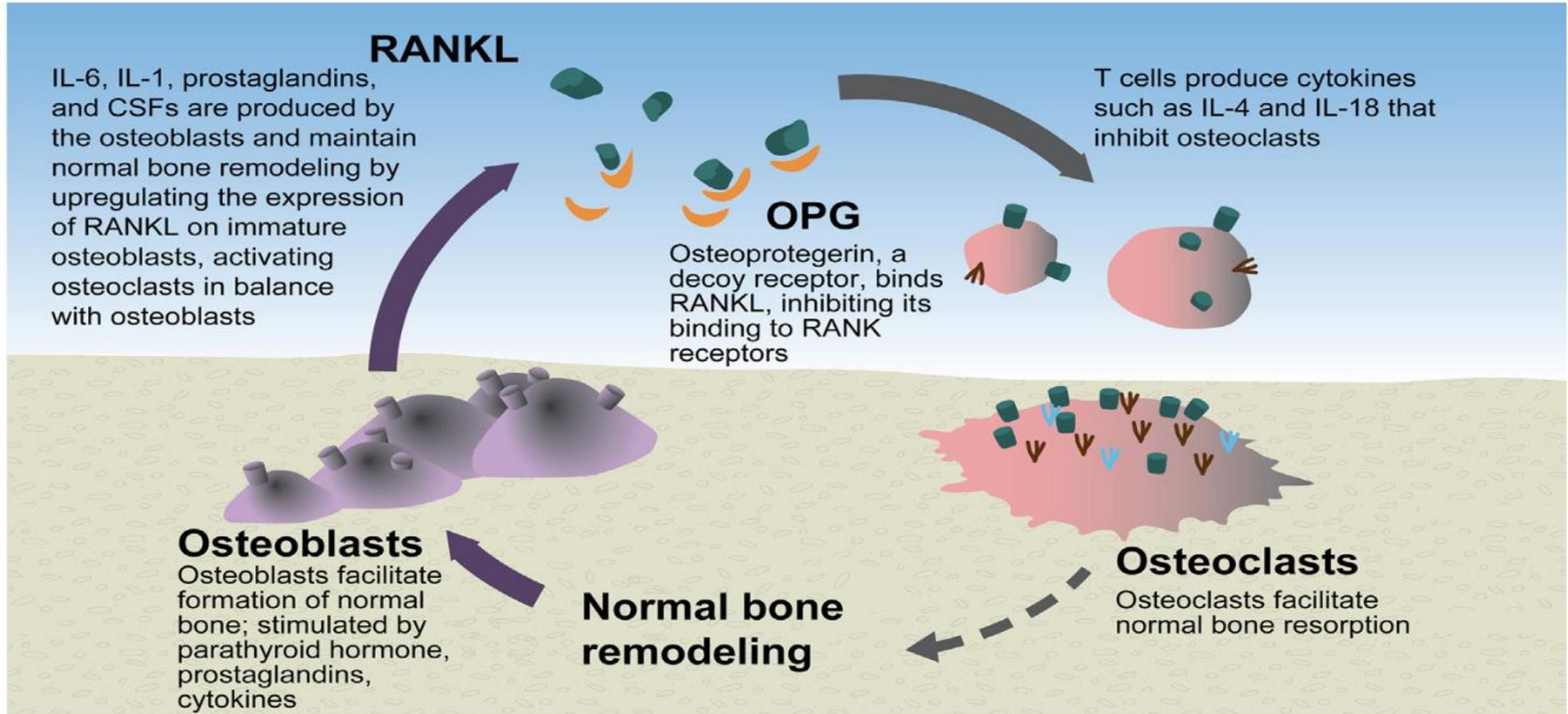
- Increased hospital visits/stays<sup>4</sup>
- Increased treatment costs<sup>3,4</sup>

# Bone Targeted Agent: Role of XGEVA in SRE Management

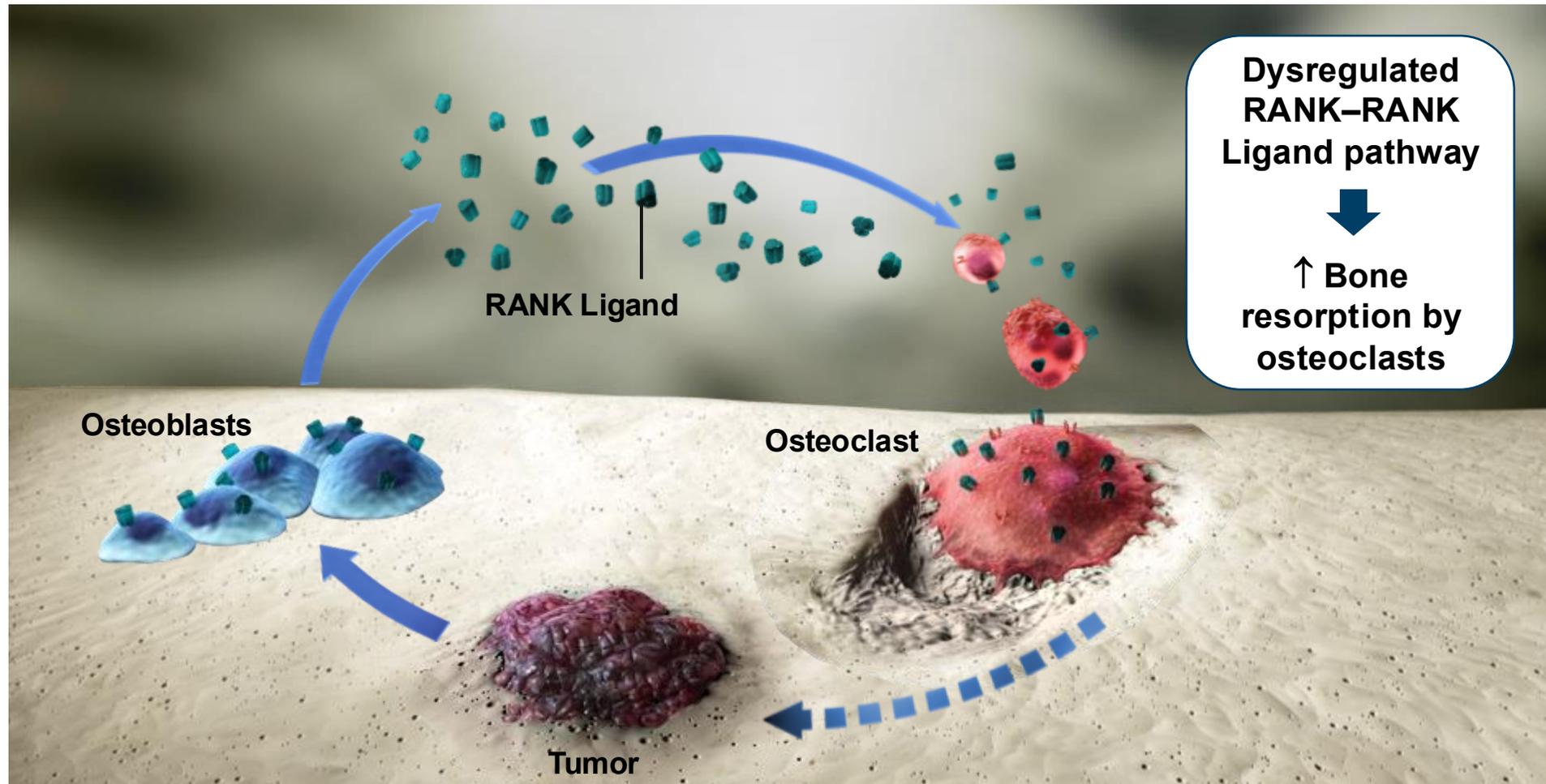
# When should we start bone targeted agent (BTA)?



# Normal Bone Remodelling

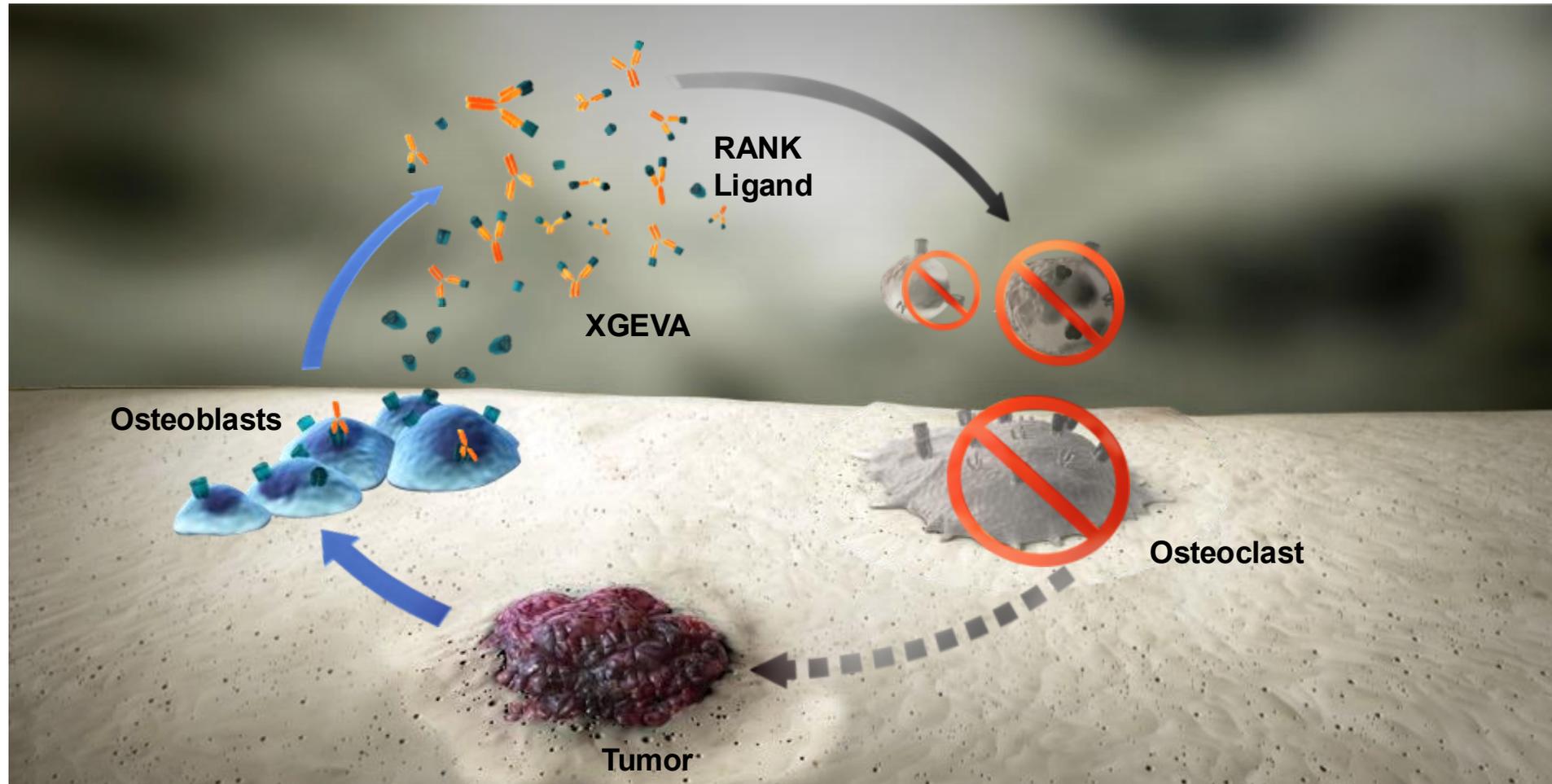


# The Presence of Tumor Cells in Bone Drives a 'Vicious Cycle' of Bone Destruction and Tumor Growth



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

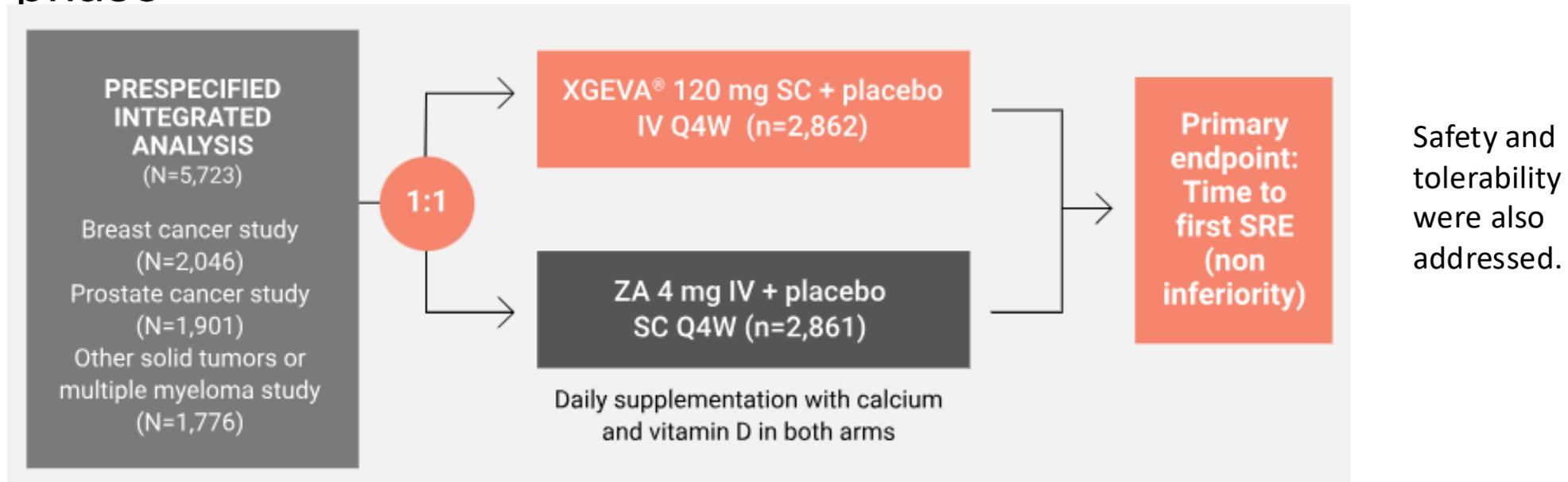
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# XGEVA Pivotal Study

## Study Design

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



### Secondary endpoints<sup>1,2</sup>

- 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**.

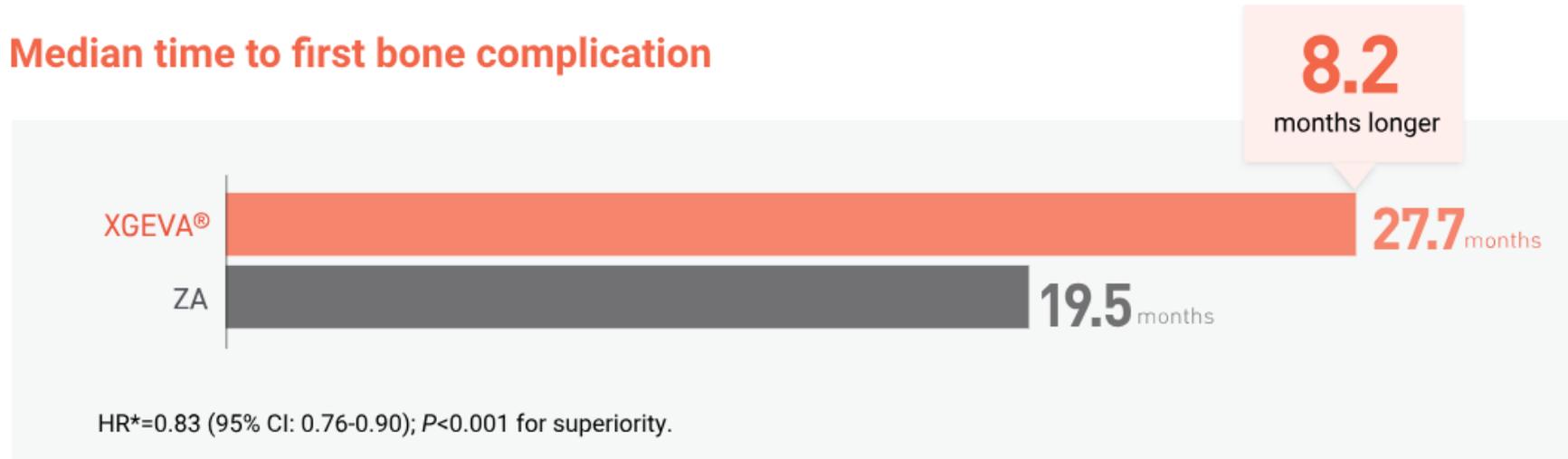
## Demographic and Baseline Characteristics

Baseline characteristics	XGEVA (n=2,862)	ZA (n=2,861)
Median age, years	63	63
ECOG status 0-1, %	90	89
Creatinine clearance $\geq 30$ and $\leq 60$ 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

## Results

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

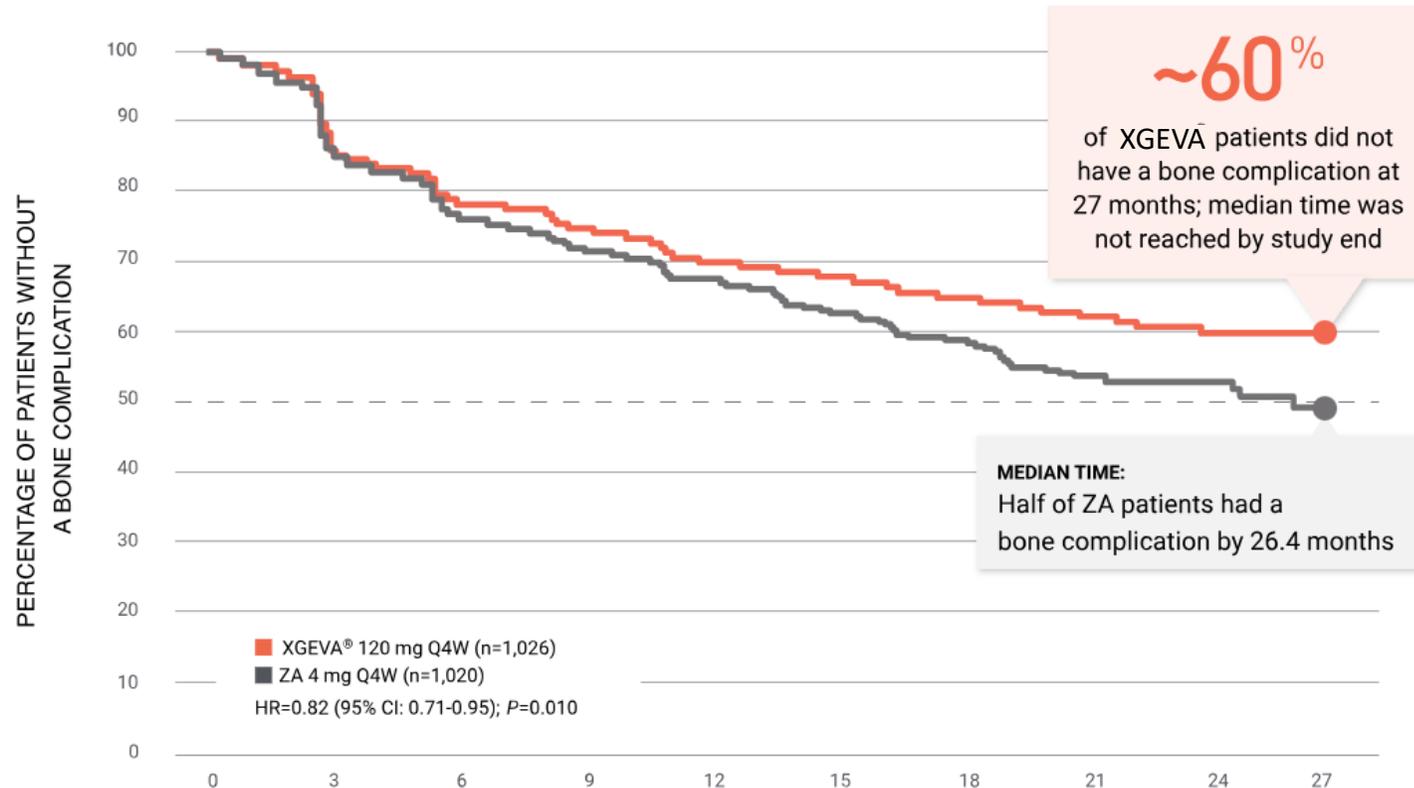
### Median time to first bone complication



\*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**.

## Breast Cancer with Bone Metastases Data

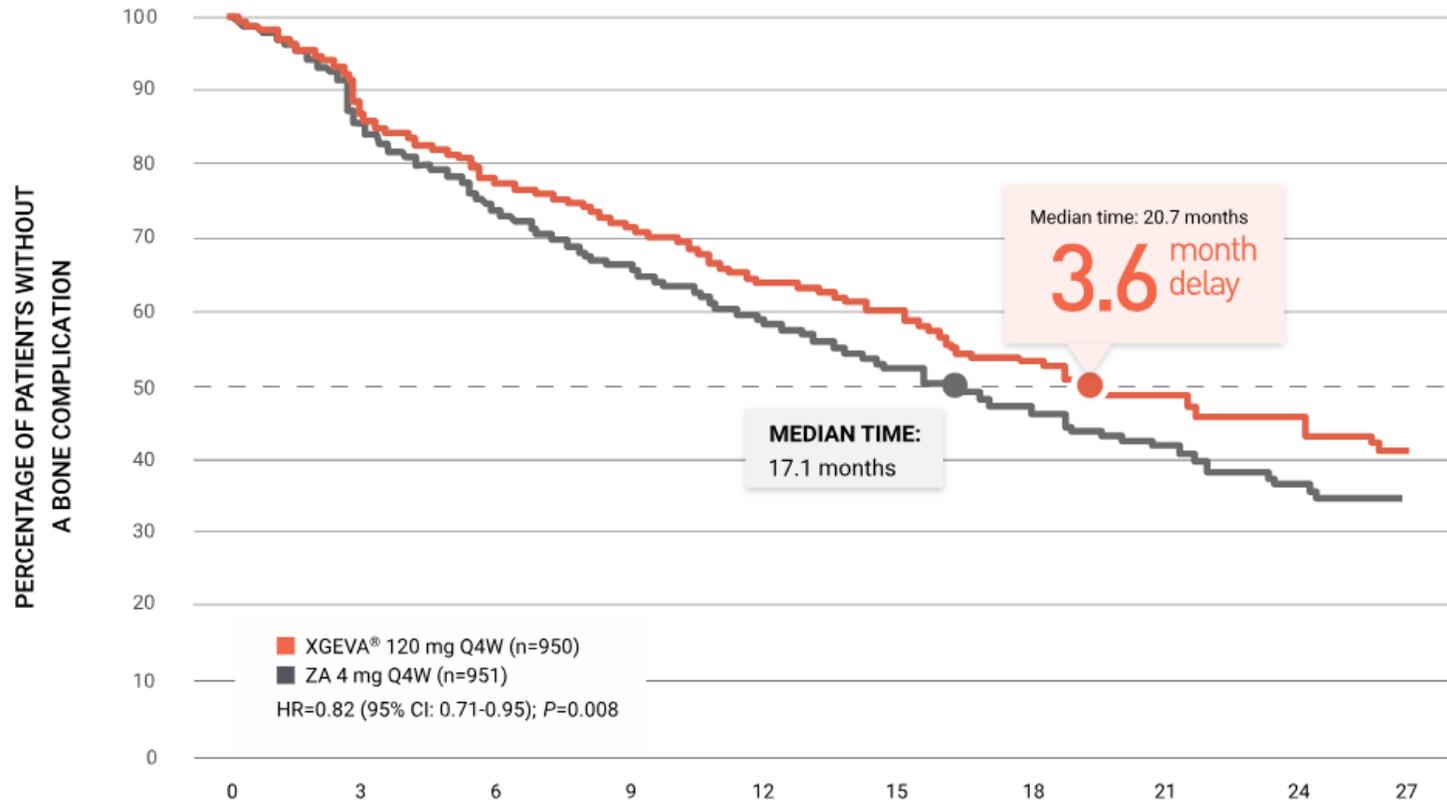


**XGEVA prevented bone complications for >2 years.**

**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**.

## 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**.

## 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).<sup>1</sup>
- Results for castration-resistant prostate cancer patients: XGEVA (5.8 months) vs ZA (4.9 months) P=0.0024.<sup>2</sup>
- Results for advanced solid tumor-only cancer patients (excluding multiple myeloma): XGEVA (4.7 months) vs ZA (3.7 months) P=0.05.<sup>3</sup>

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# Safety Profile

Adverse Events (AEs), n (%)	SC XGEVA (120 mg) (n=1020)	IV Zoledronic Acid (4 mg) (n=1013)
<b>Any AE</b>	<b>977 (95.8)</b>	<b>985 (97.2)</b>
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**.

## Osteonecrosis of the jaw (ONJ)

- **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

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

## Renal Adverse Events

- 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**.

# 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