대한결핵 및 호흡기학회
The Korean Academy of Tuberculosis and Respiratory Diseases

Current Management of Bone Metastasis in Lung Cancer

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강 다 현

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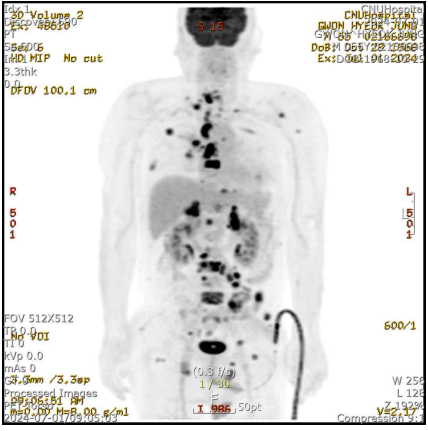
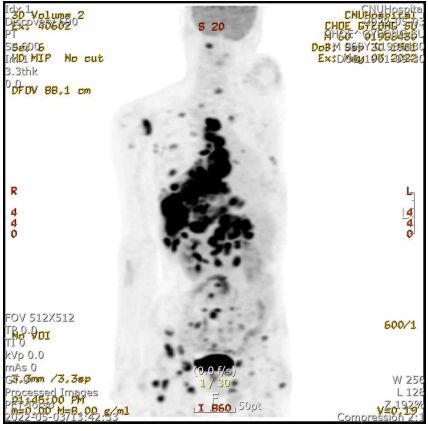
Clinical Cases: Bone Metastasis in Lung cancer

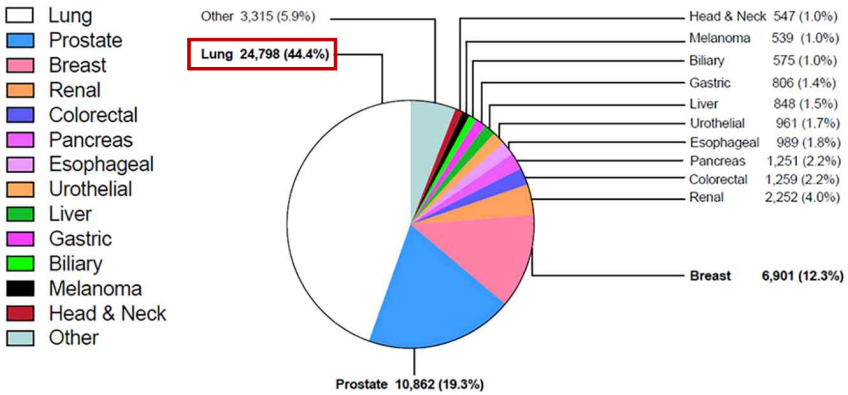


NSCLC



SCLC

Distribution of primary tumor location in patients with bone metastases



Knapp, Brendan J., et al. *Frontiers in Oncology* 14 (2024): 1392667.

Incidence of bone metastases at presentation according to the primary tumor

Tumor Location and Histology	Patients with Bone Metastases	Total Patients	Percentage with Bone Metastases
Lung	24,798	133,396	18.59
Non-Small Cell Lung Cancer	18,123	100,448	18.04
Squamous	2,908	26,539	10.96
Adenocarcinoma	12,930	63,257	20.44
Large Cell	300	1,587	18.90
Other	1,985	9,065	21.90
Small Cell	3,814	15,159	25.16
Carcinoid/Neuroendocrine	419	4,318	9.70
Other	2,442	13,471	18.13

Knapp, Brendan J., et al. *Frontiers in Oncology* 14 (2024): 1392667.

Bone Metastases in Lung Cancer

- **Lung cancer** is the most common primary tumor associated with bone metastases in adults over 25 years
- Bone metastasis is a major cause of death in lung cancer patients
- 30–40% of NSCLC patients eventually **develop bone metastases**
- Advances in targeted therapy and immunotherapy have prolonged OS, potentially increasing the incidence of bone metastases

Roato, Ilaria. *World journal of clinical oncology* 5.2 (2014): 149.

Skeletal-Related Events (SREs)

1 Definition

- **Major complications** of bone metastasis
- **Key indicator** of disease progression & functional decline

2 Core Components

Pathologic Fracture
Structural bone failure due to metastatic weakening

Spinal Cord Compression
Neurological emergency requiring urgent intervention

Radiotherapy to Bone
For pain control or fracture prevention

Surgery to Bone
For stabilization or decompression

3 Clinical Impact

Survival
Significant decrease in overall survival (OS)

Quality of Life
Loss of mobility and functional independence

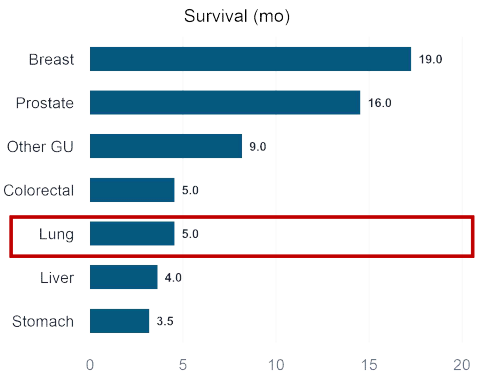
Economic Burden
High healthcare costs and prolonged hospitalization

Bone metastasis and SREs in Korean Cancer Patients

Summary by Cancer Type

Cancer Type	BM (%)	SRE (%)	Time to BM (mo)	Survival after BM
Breast	18.8	43.6	14.9	19 mo
Prostate	17.5	45.9	17.4	16 mo
Lung	13.7	53.4	9.0	5 mo
Other GU	7.1	34.4	22.6	9 mo
Liver	5.7	50.9	16.3	4 mo
Colorectal	4.4	40.2	28.9	5 mo
Stomach	4.1	37.9	23.4	3.5 mo
All	**8.6**	**45.1**	**18.9**	—

Median Survival After Bone Metastasis (months)



Hong, Soojung, et al. *PloS one* 15.7 (2020): e0234927.

Summary: Epidemiology & Burden of Bone Metastasis

18-25%

Bone Metastasis in Lung Cancer

Most common primary tumor associated with BM

SEER data, Systematic meta-analysis (2025)

30–40%

of NSCLC Patients

Eventually develop bone metastases

50-55%

SRE Rate in Lung Cancer

Highest among all cancer types

Korean NHIS data, Danish Cohort, US Medicare data

SREs: Clinical Burden

- **Pathologic fracture, SCC, RT, surgery**
  → affect 45.1% of all BM patients
- **Survival impact**
  → Median survival after BM: 5-10 months in lung cancer
- **Rapid onset**
  → Most SREs occur within 1 month of BM diagnosis

Why Understanding Pathophysiology Matters

- **Growing burden**
  As immunotherapy and targeted therapy prolong survival, BM incidence is expected to rise
- **Unmet need**
  Lung cancer has the highest SRE rate yet shortest survival after BM — early intervention is critical
- **Next section**
  Understanding the vicious cycle and RANKL pathway

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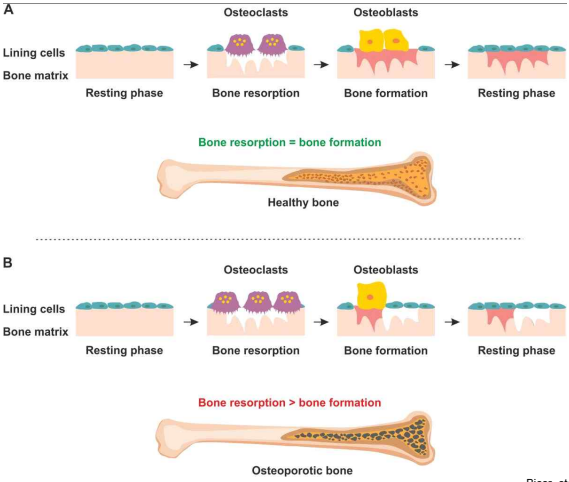
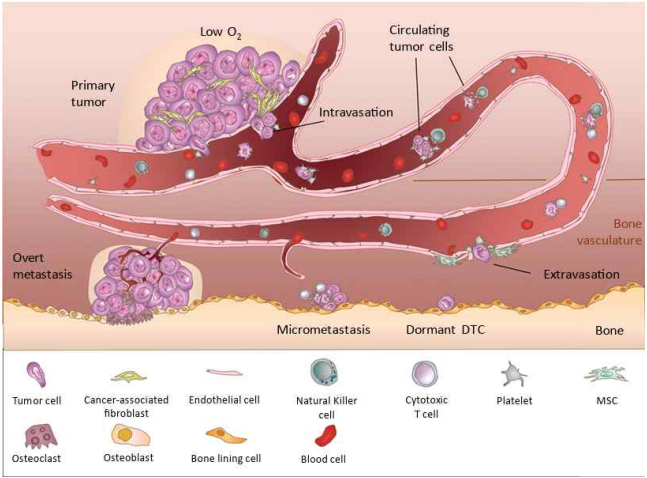
Bone Remodeling



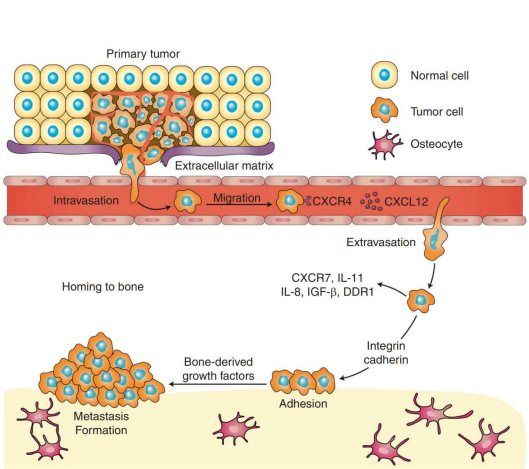
Bicer, etc. *Stem cell research & therapy* 12.1 (2021): 31

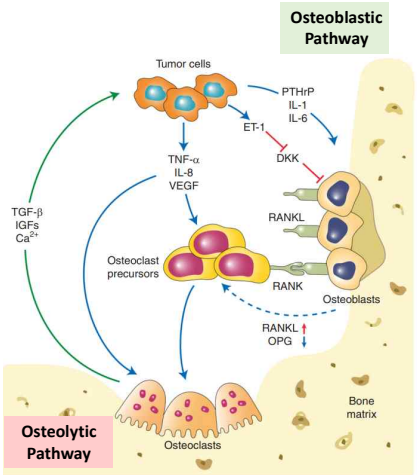
Steps of Bone Metastasis



Zhang, Weijie, et al. *Trends in cancer* 5.2 (2019): 95-110.

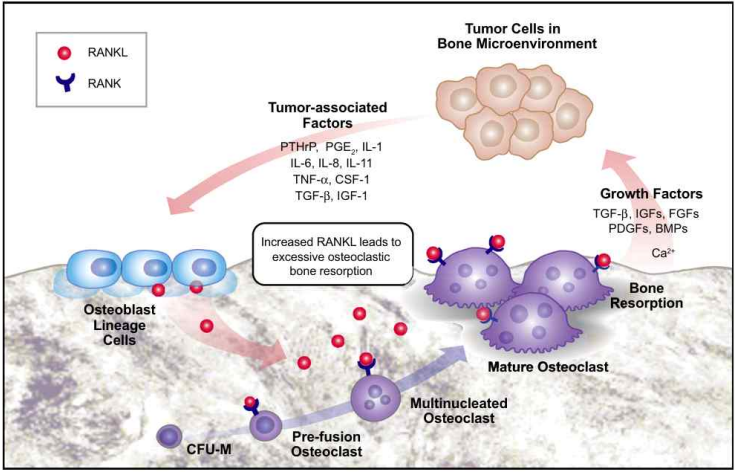
Multistep process of bone metastasis





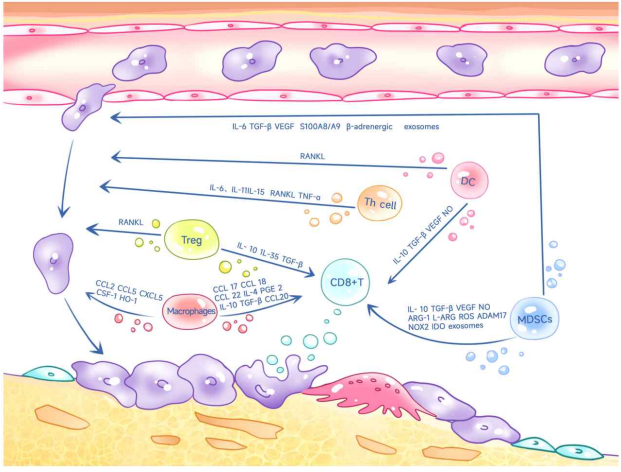
Wang, Manni, et al. *Bone research* 8.1 (2020): 30.

Vicious cycle of bone destruction



Roodman, G. David, and William C. Dougall. *Cancer treatment reviews* 34.1 (2008): 92-101.

Immunosuppressive Bone Microenvironment



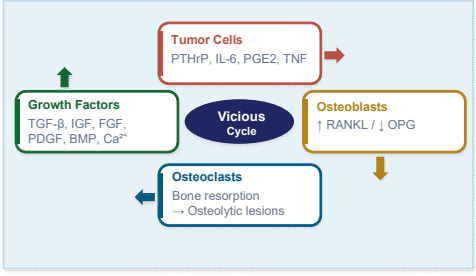
Chen, Shixin, et al. *Frontiers in Immunology* 15 (2024): 1335366.

Summary: Pathophysiology of Bone Metastasis

Metastatic Cascade: From Primary Tumor to Bone

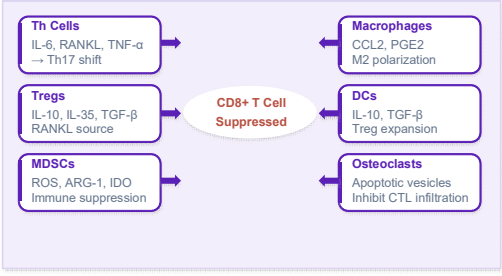
Zhang et al., Trends in Cancer 2019 | Wang et al., Bone Research 2020

1 The Vicious Cycle



Roodman & Dougall, Cancer Treat Rev 2008

2 Immune-Bone Axis



Chen et al., Frontiers in Immunology 2024

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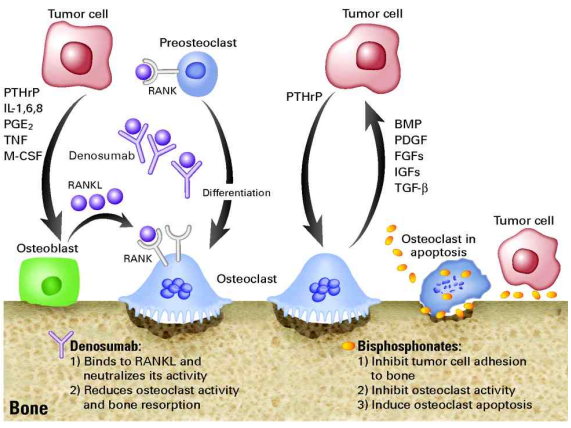
Bone-Modifying Agents (BMAs)

Rationale and Mechanism of Action

Why BMAs Are Essential

- **Bone metastasis = incurable**
  Goal: prevent SREs, control pain, maintain QoL
- **SREs affect 45–55% of BM patients**
  Pathologic fracture, SCC, RT, surgery
- **BMAs reduce SRE risk by 15–30%**
  Delay time to first SRE significantly

Mechanism of Action: RANKL antibody vs. Bisphosphonate



ESMO Clinical Practice Guidelines, Ann Oncol 2020 | Coleman et al., Ann Oncol 2014
Fornier, Monica N. Journal of Clinical Oncology 28.35 (2010): 5127-5131.

Palliative Radiotherapy for Bone Metastases

ASTRO Clinical Practice Guideline 2024

Indications

Pain Control

Most common indication, Pain relief in 60–80% of patients

Fracture Prevention

Impending fracture in weight-bearing bones

Spinal Cord Compression

Emergency RT for neurological preservation

Post-surgical Adjunct

After fixation/decompression for local control

Dose-Fractionation Regimens

Regimen	Dose	Pain Relief	Re-treatment
Single Fraction	8 Gy × 1	Equivalent	20% (higher)
Multi-Fraction	30 Gy / 10 fx 20 Gy / 5 fx	Equivalent	8% (lower)
SBRT (Non-spine)	12–16 Gy × 1	Superior local control	Low
SBRT (Spine)	24 Gy / 2 fx	Superior local control	Low

Fracture risk ↑

ASTRO 2024 Recommendation:

Single fraction 8 Gy is preferred for uncomplicated painful bone metastases — equivalent pain relief with greater convenience

Surgical Intervention for Bone Metastases

Indications, Scoring Systems, and Goals

Surgical Indications

Pathologic Fracture

Long bone fracture requiring stabilization (intramedullary nailing)

Spinal Cord Compression

Decompression + stabilization within 24–48 hours

Spinal Instability

SINS score ≥ 7 (potentially unstable or unstable)

Intractable Pain

Failed conservative management including RT and analgesics

Prognostic Scoring Systems

Revised Tokuhashi Score

6 parameters: PS, extraspinal BM, vertebral BM, visceral mets, primary site, palsy

- 0–8 pts → LE < 6 mo → Conservative tx
- 9–11 pts → LE ≥ 6 mo → Palliative surgery
- 12–15 pts → LE ≥ 12 mo → Excisional surgery

Tomita Score

3 parameters: Primary tumor grade, visceral mets, bone mets

- 2–3 pts → Wide excision
- 4–5 pts → Marginal/intralesional
- 6–7 pts → Palliative surgery
- ≥ 8 pts → Non-surgical

Mirels Score

4 parameters: Site, pain, lesion type, size — Long bone pathologic fracture risk

- ≤ 7 pts → Low risk → Conservative (RT)
- 8 pts → Borderline → Clinical judgment
- ≥ 9 pts → High risk → Prophylactic fixation

Goal:

Pain relief, preservation of ambulatory function, and spinal stability — not cure. Multidisciplinary decision is essential.

Tokuhashi et al., Spine 2005 | Tomita et al., Spine 2001 | Mirels H., Clin Orthop Relat Res 1989 | Fisher et al., Spine 2010 (SINS)

Mirels Scoring System

Prophylactic Fixation of Impending Pathologic Fractures — Long Bones

Scoring Parameters

Variable	1 Point	2 Points	3 Points
Site	Upper extremity	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion Type	Blastic	Mixed	Lytic
Size	< 1/3 diameter	1/3 – 2/3 diameter	> 2/3 diameter
Total Score Range: 4 – 12			

Score Interpretation

Score	Risk Level	Recommendation
≤ 7	**Low Risk**	Conservative (Radiation therapy)
8	**Borderline**	Clinical judgment required
≥ 9	**High Risk**	Prophylactic surgical fixation

Key Points

- Designed for long bone metastases
- Weight-bearing sites & lytic lesions increase fracture risk
- Functional pain indicates structural compromise

Mirels H. Clin Orthop Relat Res. 1989;(249):256-264.

Revised Tokuhashi Scoring System (0–15)

Preoperative Evaluation of Metastatic Spine Tumor Prognosis

Scoring Criteria

Parameter	Criteria	Score
General Condition (KPS)	Poor (10–40%)	0
	Moderate (50–70%)	1
	Good (80–100%)	2
Extraspinal Bone Mets	≥ 3	0
	1–2	1
	0	2
Vertebral Mets	≥ 3	0
	1–2	1
	0 (single)	2
Visceral Mets	Unresectable	0
	Resectable	1
	None	2
Primary Tumor	Lung, Pancreas, Stomach	0
	Liver, Gallbladder, Unknown	1
	Others / Kidney, Uterus	2–3
	Rectum / Thyroid, Breast, Prostate	4–5
Neurologic Status	Complete paralysis	0
	Incomplete paralysis	1

Prognosis & Treatment Strategy

Total Score	Survival	Strategy
0 – 8	< 6 months	Conservative (supportive care)
9 – 11	≥ 6 months	Palliative surgery (decompression)
12 – 15	≥ 12 months	Excisional surgery (curative intent)

Key Points:

- 6 parameters, total 0–15
- Primary tumor type has highest weight (0–5 points)
- Lung cancer scores 0 (worst)
- Accuracy: ~87.9%

Tokuhashi Y, et al. Spine. 2005;30(19):2186-2191.

Tomita Scoring System (2–10)

Surgical Strategy for Spinal Metastases

Scoring Criteria (3 Parameters)

Parameter	Criteria	Score
Primary Tumor Growth Rate	Slow (thyroid, breast, prostate)	1
	Moderate (kidney, uterus)	2
	Rapid (lung, stomach, pancreas)	4
Visceral Metastases	None	0
	Treatable	2
	Untreatable	4
Bone Mets Extent	Solitary (single)	1
	Multiple (same region)	2
	Multiple (multiple regions)	3

Treatment Strategy by Score

Score	Growth	Goal	Surgery Type
2–3	Slow	Long-term local control	Wide / marginal excision
4–5	Moderate	Medium-term local control	Marginal / intralesional
6–7	Fast	Short-term palliation	Palliative surgery
8–10	Very aggressive	Terminal care	Non-surgical (supportive)

Key Points:

- Only 3 parameters — simpler than Tokuhashi
- Lung cancer = rapid growth (4 pts) → high score
- Higher score → less aggressive treatment
- Highest statistical significance in validation

Tokuhashi vs. Tomita — When to Use:

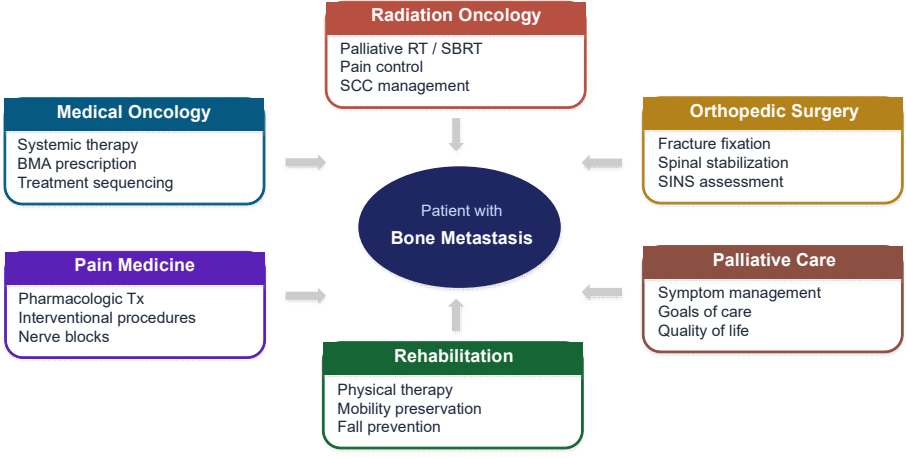
Tokuhashi (6 parameters): More comprehensive, better accuracy (~87.9%), considers neurologic status → Best for overall prognosis estimation

Tomita (3 parameters): Simpler, highest statistical significance → Best for quick surgical decision-making

Tomita K, et al. Spine. 2001;26(3):298-306. | Tokuhashi Y, et al. Spine. 2005;30(19):2186-2191.

Comprehensive Multidisciplinary Care

Patient-Centered Approach to Bone Metastasis Management



ESMO Clinical Practice Guidelines 2020 | NCCN Guidelines: Cancer-Related Bone Disease 2024

Contents

RCTs & RWD: Denosumab vs Zoledronic Acid

Clinical Trials & Real-World Data in Bone Metastases

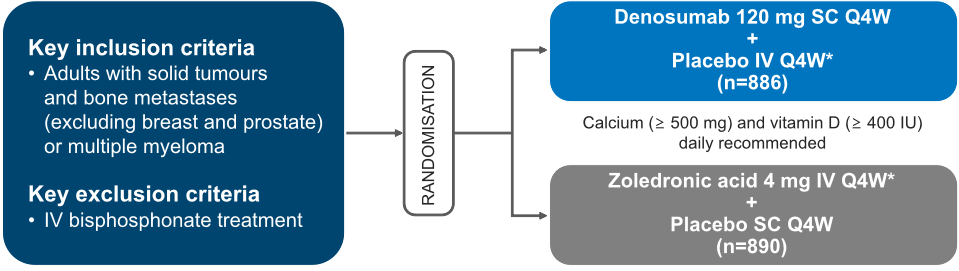
Study	Design	Population	N	Time to 1st SRE	Multiple SREs	Overall Survival
Randomized Controlled Trials						
Henry et al. J Clin Oncol 2011	Phase 3 DB RCT	Solid tumors + MM (excl. breast, prostate)	**1,776**	HR 0.84 (0.71–0.98) Non-inferior **p<0.001** Superiority NS (p=0.06)	RR 0.90 (0.77–1.04) p=0.14 (NS)	No significant difference
Henry et al. Support Care Cancer 2014	Ad hoc (excl. MM)	Solid tumors only (excl. breast, prostate, MM)	**1,597**	HR 0.81 (0.68–0.96) Superior **p=0.017** Median: 21.4 vs 15.4 mo	RR 0.85 (0.72–1.00) **p=0.048**	No significant difference
Scagliotti et al. J Thorac Oncol 2012	Subgroup analysis	Lung cancer with bone mets	**702**	HR 0.84 (0.64–1.10) p=0.20 (NS)	Not reported separately	OS: 8.9 vs 7.7 mo HR 0.80 (0.67–0.95) **p=0.01**
Real-World Data						
Yu et al. BMJ Open Respir Res 2025	Retro-spective cohort	Lung cancer + bone mets (Taiwan)	**302**	Not reported	Not reported	Denosumab: better OS aHR 0.67 (0.50–0.91) **p=0.010**
Aliyev et al. J Clin Med 2025	Retro-spective RWD	Solid tumors + bone mets (multi-cancer)	**382**	SRE: 34.8% vs 51.8% **p<0.001** Breast/Prostate sig. Lung: NS (p=0.484)	Not reported	Not reported
Shiau et al. Clin Oncol 2026	PS-matched cohort (global)	Lung cancer + bone mets (global RWE)	**Large**	SRE: 3.9% vs favoring denosumab	Not reported	Mortality benefit favoring denosumab in subgroup analysis

DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

Green = statistically significant (p<0.05) | Red = not significant

International, randomised, double-blind, active-controlled, phase 3 trial comparing denosumab with zoledronic acid

Study design



Primary endpoint	• Time to first on-study SRE (noninferiority)
Secondary endpoints	• Time to first on-study SRE (superiority) • Time to first and subsequent on-study SRE(s) (superiority)

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.
SRE, skeletal-related event; IV, intravenous; SC, subcutaneous; Q4W, once monthly.
1. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

Bone metastasis in patients with solid tumors or multiple myeloma excluding breast and prostate

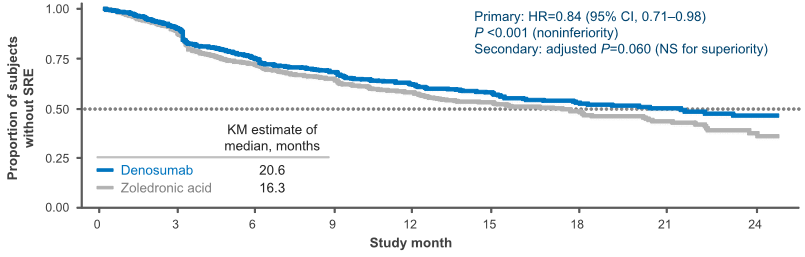
Characteristic	Denosumab (n=886)	Zoledronic acid (n=890)
Male, n (%)	588 (66)	552 (62)
Median age, years	60	61
Primary tumour type		
Non-small-cell lung cancer, n (%)	**350 (39)**	**352 (40)**
Multiple myeloma, n (%)	87 (10)	93 (10)
Other, n (%)	449 (51)	455 (50)
ECOG performance status of 0 or 1, n (%)	748 (84)	728 (82)
Median time from first bone metastasis to randomisation, months	2	2
Previous SRE, n (%)	**440 (50)**	**446 (50)**
Presence of visceral metastases, n (%)	474 (54)	448 (50)

SRE, skeletal-related event; ECOG, Eastern Cooperative Oncology Group.

1. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

Denosumab was noninferior to zoledronic acid in delaying the time to first on-study SRE

Primary endpoint: time to first on-study SRE



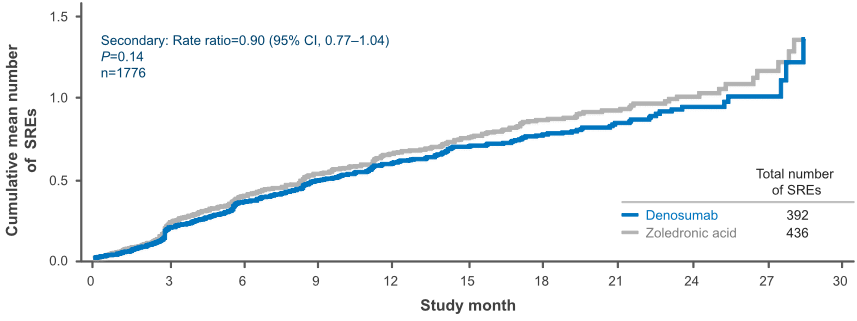
Subjects at risk:

Denosumab	886	582	387	266	202	134	96	55	28
Zoledronic acid	890	578	376	261	194	126	86	47	20

[*]Excluding breast and prostate cancer.
SRE, skeletal-related event; HR, hazard ratio; CI, confidence interval; NS, not significant; KM, Kaplan-Meier.
1. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

Denosumab was not significantly different in reducing the risk of developing multiple SREs

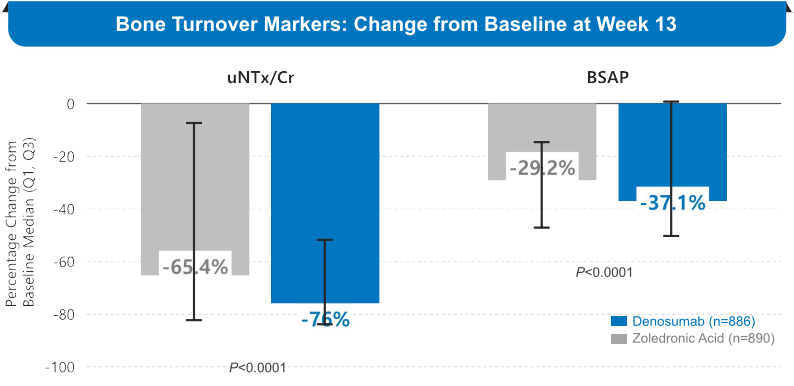
Secondary endpoint: time to first and subsequent on-study SRE†



*Excluding breast and prostate cancer. †Multiple event analysis events that occurred 21 days apart.
SRE, skeletal-related event; CI, confidence interval.

1. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

Patients treated with denosumab experienced a greater suppression of bone turnover markers than with zoledronic acid



*Excluding breast and prostate cancer.
uNTx/Cr, urinary N-telopeptide corrected for creatinine; BSAP, bone-specific alkaline phosphatase.
1. Henry DH, et al. J Clin Oncol. 2011;29:1125–32.

RCTs & RWD: Denosumab vs Zoledronic Acid

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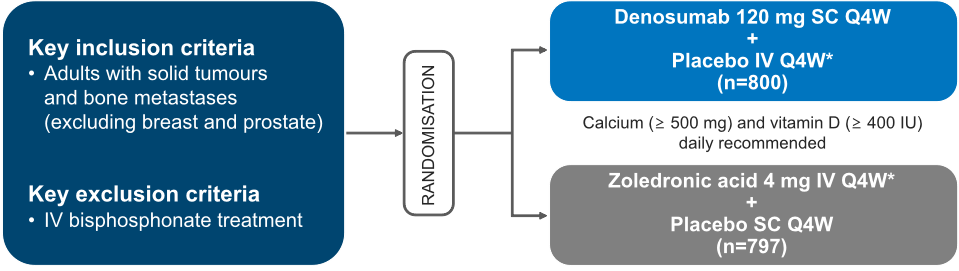
Denosumab non-inferior to ZA for SRE prevention in mixed solid tumors

DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

Green = statistically significant (p<0.05) | Red = not significant

Ad hoc analysis in patients with solid tumors excluding patients with multiple myeloma

Study design



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*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.
SRE, skeletal-related event; IV, intravenous; SC, subcutaneous; Q4W, once monthly.
1. Henry D, et al. Support Care Cancer. 2014;22:679–87.

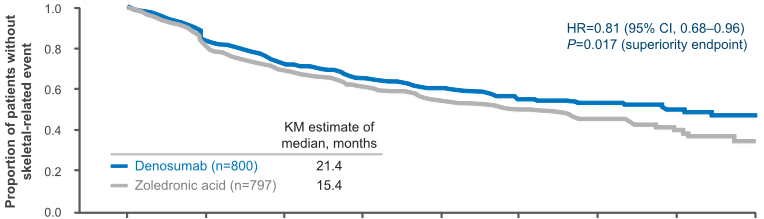
Baseline demographics and disease characteristics were generally well balanced between the two treatment groups

Characteristic	Denosumab (n=800)	Zoledronic acid (n=797)
Male, n (%)	531 (66)	498 (62)
Age years, median (min, max)	59 (18, 89)	61 (22, 87)
ECOG PS 0 or 1, n (%)	678 (85)	654 (82)
Previous SRE, n (%)	379 (47)	381 (48)
Primary tumour types* NSCLC Other	 350 (44) 448 (56)	 352 (44) 445 (56)
Months from initial diagnosis of bone metastases to randomisation, median (Q1, Q3)	1.8 (0.9, 3.8)	1.8 (0.9, 3.9)
Visceral metastases, n (%)	471 (59)	446 (56)

*Based on randomisation.
SRE, skeletal-related event; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.
1. Henry D, et al. Support Care Cancer 2014;22:679–87.

The median time to first on-study SRE was a difference of 6 months, representing a 19% reduction in hazard.

Ad hoc analysis in solid tumours: time to first on-study SRE



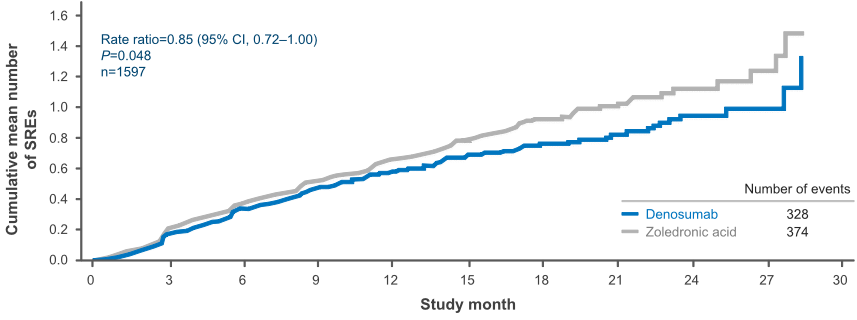
Patients at risk:

Denosumab	800	521	336	225	168	104	70	40	22
Zoledronic acid	797	509	321	216	155	91	55	28	13

[*]Excluding breast and prostate cancer.
SRE, skeletal-related event; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.
1. Henry DH, et al. Support Care Cancer. 2014;22:679–87.

The risk of multiple SREs was reduced by an estimated 15% with denosumab compared with zoledronic acid

Ad hoc analysis in solid tumours: time to first and subsequent on-study SRE*



*Multiple event analysis events that occurred 21 days apart.
SRE, skeletal-related event; CI, confidence interval.

1. Henry DH, et al. Support Care Cancer. 2014;22:679–87.

The effect of denosumab on time to first on-study SRE and multiple SREs was consistent across tumor types including lung cancer.

Ad hoc analysis in solid tumors: outcomes for the most common tumor types

	Time to first on-study SRE			Time to first-and-subsequent SRE		
	Hazard ratio			Rate ratio		
	Pt Est	(95% CI)	*P* value	Pt Est	(95% CI)	*P* value
Non-prostate GU cancers*						
Zoledronic acid 4 mg Q4W (n=125)						
Denosumab 120 mg Q4W (n=102)	0.75	(0.48, 1.15)	0.19	0.81	(0.55, 1.18)	0.27
Renal cancers						
Zoledronic acid 4 mg Q4W (n=85)						
Denosumab 120 mg Q4W (n=70)	0.71	(0.43, 1.17)	0.18	0.75	(0.49, 1.16)	0.19
Lung cancer†						
Zoledronic acid 4 mg Q4W (n=400)						
Denosumab 120 mg Q4W (n=411)	0.87	(0.68, 1.11)	0.26	0.90	(0.71, 1.13)	0.35
Non-small cell lung cancer‡						
Zoledronic acid 4 mg Q4W (n=352)						
Denosumab 120 mg Q4W (n=350)	0.85	(0.65, 1.12)	0.25	0.89	(0.69, 1.15)	0.38
Small cell lung cancer‡						
Zoledronic acid 4 mg Q4W (n=48)						
Denosumab 120 mg Q4W (n=61)	0.92	(0.47, 1.80)	0.80	0.91	(0.52, 1.61)	0.76

*Includes renal, bladder and transitional cell cancers; †data not adjusted for stratification factors; ‡subgroup analysis of patients per actual strata.
SRE, skeletal-related event: Pt Est, point estimate; CI, confidence interval; Q4W, once monthly.
1. Henry DH, et al. Support Care Cancer. 2014;22:679–87.

RCTs & RWD: Denosumab vs Zoledronic Acid

Clinical Trials & Real-World Data in Bone Metastases

Study	Design	Population	N	Time to 1st SRE	Multiple SREs	Overall Survival
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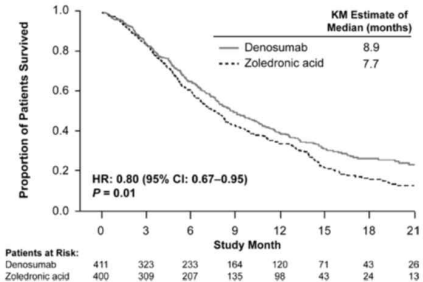
Scagliotti et al. J Thorac Oncol 2012	Subgroup analysis	Lung cancer with bone mets	**702**	HR 0.84 (0.64–1.10) p=0.20 (NS)	Not reported separately	OS: 8.9 vs 7.7 mo HR 0.80 (0.67–0.95) **p=0.01**
Real-World Data						
Yu et al. BMJ Open Respir Res 2025	Retro-spective cohort	Lung cancer + bone mets (Taiwan)	**302**	Not reported	Not reported	Denosumab: better OS aHR 0.67 (0.50–0.91) **p=0.010**
Aliyev et al. J Clin Med 2025	Retro-spective RWD	Solid tumors + bone mets (multi-cancer)	**382**	SRE: 34.8% vs 51.8% **p<0.001** Breast/Prostate sig. Lung: NS (p=0.484)	Not reported	Not reported
Shiau et al. Clin Oncol 2026	PS-matched cohort (global)	Lung cancer + bone mets (global RWE)	**Large**	SRE: 3.9% vs favoring denosumab	Not reported	Mortality benefit favoring denosumab in subgroup analysis

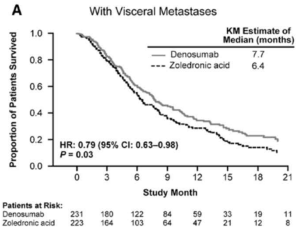
Denosumab: Superior for SRE in solid tumors (+6 mo delay)

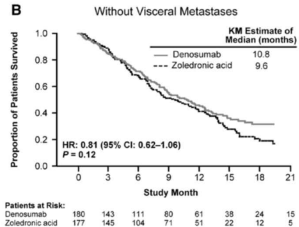
DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

Green = statistically significant (p<0.05) | Red = not significant

Overall Survival Improvement in Patients with Lung Cancer and Bone Metastases Treated with Denosumab Versus Zoledronic Acid

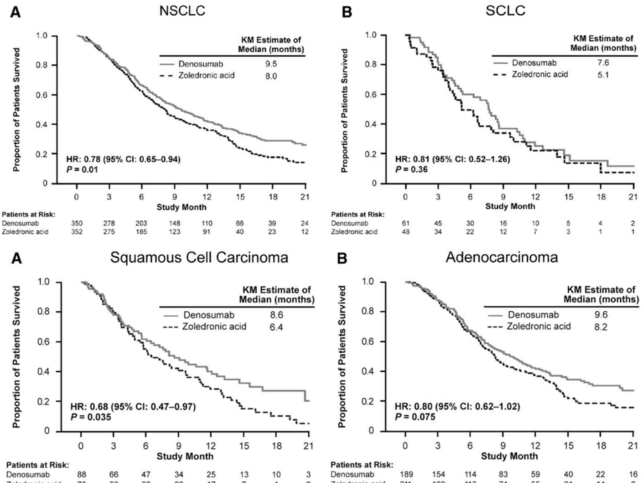






Scagliotti, Giorgio Vittorio, et al. *Journal of Thoracic Oncology* 7.12 (2012): 1823-1829.

Overall Survival Improvement in Patients with Lung Cancer and Bone Metastases Treated with Denosumab Versus Zoledronic Acid



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RCTs & RWD: Denosumab vs Zoledronic Acid

Clinical Trials & Real-World Data in Bone Metastases

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OS benefit (8.9 vs 7.7 mo) with denosumab in lung cancer subgroup

DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

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Denosumab usage is associated with better overall survival of patients with lung cancer and bone metastases: a retrospective cohort study

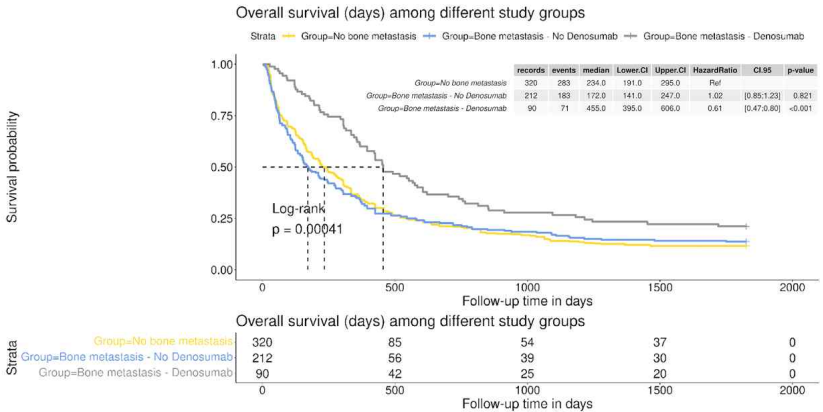

Figure 1 Kaplan-Meier overall survival curves among patients with lung cancer without bone metastases, bone metastases with denosumab treatment and bone metastases without denosumab treatment.

Yu, Chung Chi, et al. *BMJ Open Respiratory Research* 12.1 (2025).

OS according to the number of denosumab treatment cycles

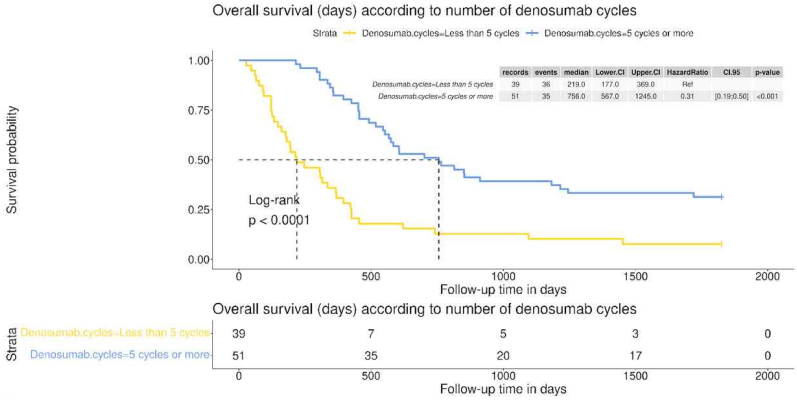

Figure 3 Kaplan-Meier overall survival curves among denosumab-treated patients with lung cancer according to the number of denosumab treatment cycles.

Yu, Chung Chi, et al. *BMJ Open Respiratory Research* 12.1 (2025).

Cox Regression: Factors Affecting Overall Survival

Lung Cancer Patients with Bone Metastases (N=302)

		Univariate			Multivariate		
Factor	**Comparison**	**HR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Age	> 65 vs ≤ 65	1.44	1.12–1.84	**0.004**	1.20	0.90–1.61	0.2
Smoking	Yes vs No	1.52	1.19–1.95	**<0.001**	1.06	0.73–1.53	0.8
Histology	SqCC vs Adeno	2.37	1.53–3.67	**<0.001**	1.26	0.76–2.09	0.4
	Others vs Adeno	1.79	1.23–2.61	**0.002**	0.95	0.60–1.49	0.8
Mutation	EGFR-L858R vs None	0.43	0.31–0.59	**<0.001**	0.87	0.32–2.40	0.8
	EGFR-Ex19Del vs None	0.28	0.20–0.40	**<0.001**	0.76	0.27–2.14	0.6
	Other mutations vs None	0.34	0.22–0.51	**<0.001**	0.70	0.37–1.32	0.3
ECOG	2–4 vs 0–1	2.60	2.02–3.36	**<0.001**	2.17	1.59–2.97	**<0.001**
TKI	Afatinib vs None	0.47	0.34–0.64	**<0.001**	0.24	0.09–0.63	**0.004**
	Erlotinib/Gefitinib vs None	0.40	0.28–0.57	**<0.001**	0.16	0.05–0.44	**<0.001**
	Osimertinib vs None	0.18	0.09–0.34	**<0.001**	0.05	0.02–0.18	**<0.001**
	Others vs None	0.23	0.11–0.49	**<0.001**	0.17	0.06–0.47	**<0.001**
Chemo	Yes vs No	1.42	1.09–1.85	**0.009**	0.32	0.21–0.49	**<0.001**
IO	Yes vs No	0.52	0.28–0.95	**0.034**	0.32	0.16–0.63	**<0.001**
Denosumab	Yes vs No	0.60	0.46–0.79	**<0.001**	0.67	0.50–0.91	**0.010**
Other mets	Yes vs No	1.16	0.91–1.49	0.2	1.44	1.10–1.89	**0.008**

Green highlight = significant in multivariate model ($p < 0.05$). Other metastasis: not significant in UV but significant in MV.

Yu, Chung Chi, et al. *BMJ Open Respiratory Research* 12.1 (2025).

RCTs & RWD: Denosumab vs Zoledronic Acid

Clinical Trials & Real-World Data in Bone Metastases

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Real-World Data						
Yu et al. BMJ Open Respir Res 2025	Retro-spective cohort	Lung cancer + bone mets (Taiwan)	**Denosumab: Independent predictor of better OS (multivariate)**			Denosumab: better OS p=0.010
Aliyev et al. J Clin Med 2025	Retro-spective RWD	Solid tumors + bone mets (multi-cancer)	**382**	SRE: 34.8% vs 51.8% **p<0.001** Breast/Prostate sig. Lung: NS (p=0.484)	Not reported	Not reported
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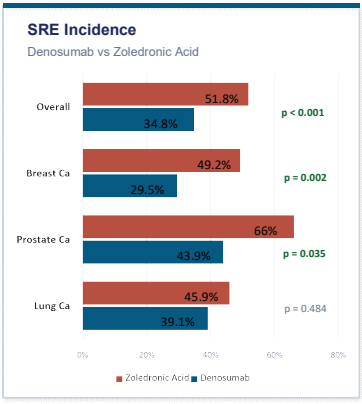
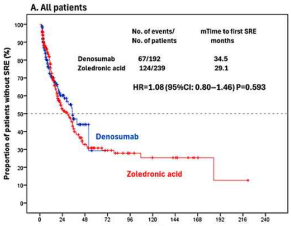
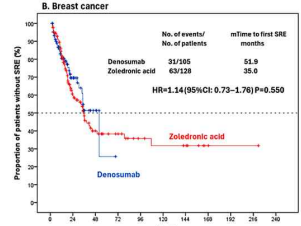
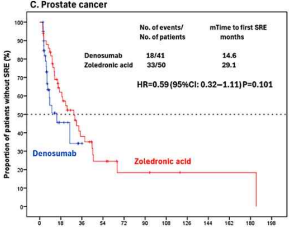
Green = statistically significant (p<0.05) | Red = not significant

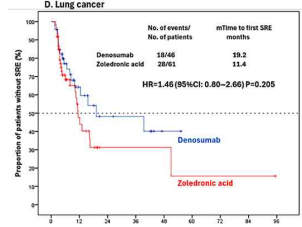
Real world retrospective analysis: Denosumab vs. Zoledronic acid







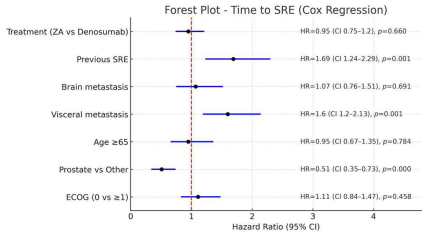


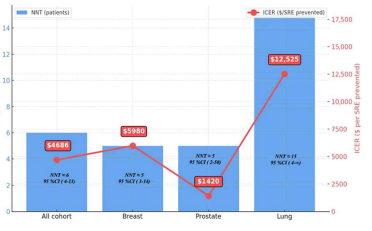


Aliyev, Vali, et al. *Journal of Clinical Medicine* 14.18 (2025): 6469.

Real world retrospective analysis: Denosumab vs. Zoledronic acid

Variables		SRE (+) *n* (%)	SRE (−) *n* (%)	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Age (years)	<65	145 (46.9)	164 (53.1)	Ref.			
	≥65	46 (37.7)	76 (62.3)	0.6 (0.44–1.05)	0.08		
Tumor type	Prostate	51 (56.0)	40 (44.0)	Ref.		Ref.	
	Other	140 (41.2)	200 (58.8)	1.8(1.1–2.9)	0.01	1.9 (1.22–3.19)	0.005
ECOG	0	79 (47.6)	87 (52.4)	Ref.			
	≥1	112 (42.7)	150 (57.3)	0.8 (0.54–1.19)	0.27		
Prior SRE	No	97 (38.8)	153 (61.2)	Ref.		Ref.	
	Yes	94 (55.6)	75 (44.4)	1.6 (1.1–2.3)	0.01	1.6 (1.12–2.49)	0.011
Visceral Met	No	86 (37.9)	141 (62.1)	Ref.			
	Yes	105 (52.2)	96 (47.8)	1.2 (0.81–1.77)	0.34		
Cranial Met	No	170 (43.9)	217 (56.1)	Ref.			
	Yes	21 (46.7)	24 (53.3)	1.1 (0.72–1.76)	0.59		
Treatment	Denosumab	85 (44.3)	107 (55.7)	Ref.		Ref.	
	ZA	106 (44.4)	133 (55.6)	2.0 (1.36–2.97)	0.001	2.0 (1.34–2.98)	0.001





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RCTs & RWD: Denosumab vs Zoledronic Acid

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Green = statistically significant (p<0.05) | Red = not significant

Global Real-World Evidence: Propensity-Matched Cohort Study

TriNetX Global Lung Cancer Cohort (2010–2020; n=52,521; PSM n=2,735 per group)

Primary and secondary outcomes

	No. of patients with outcome (%)		HR (95% CI)[c]	*P* value
	Study group[a]	Control group[b]		
Primary outcome: All-cause mortality (2-year)	1471 (53.8)	1507 (55.1)	0.741 (0.690, 0.797)	<.0001
Secondary outcome: SRE [d] incidence (2-year)	106 (3.9)	204 (7.5)	0.419 (0.331, 0.530)	<.0001

[a] Study group: with denosumab use.
[b] Control group: without denosumab use.
[c] HR (95% CI): hazard ratio (95% confidence interval).
[d] SRE: skeletal-related event, which encompassed pathological fracture, hypercalcaemia, radiotherapy to bone, and cord compression.

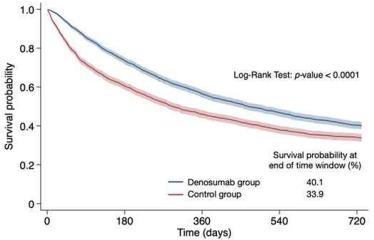


Fig 2. Kaplan–Meier time-to-event curve for the primary outcome.

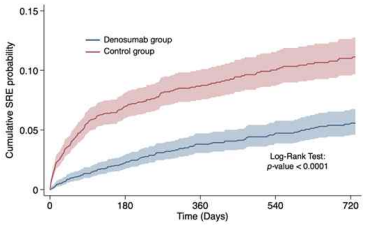
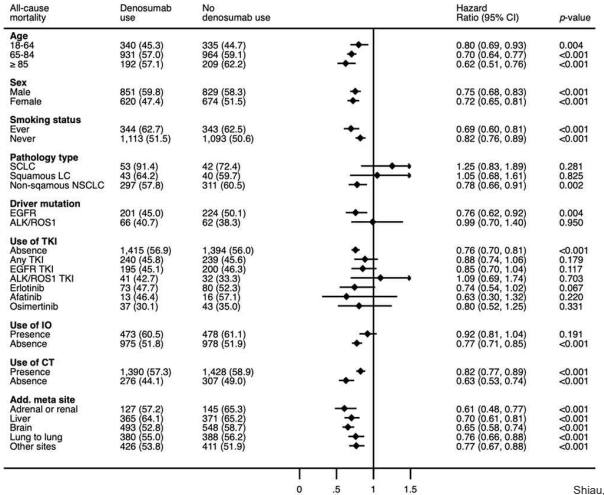


Fig 3. Cumulative probability curve for the secondary outcome.

Global Real-World Evidence: All-Cause Mortality by Subgroup

TriNetX Global Lung Cancer Cohort (2010–2020; n=52,521; PSM n=2,735 per group)

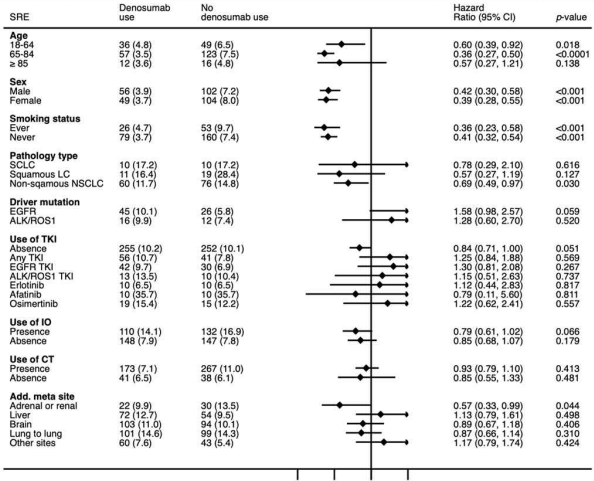


Shiau, Bo-Wen, et al. *Clinical Oncology* (2026): 104067.

Global Real-World Evidence: SRE by Subgroup

TriNetX Global Lung Cancer Cohort (2010–2020; n=52,521; PSM n=2,735 per group)

SRE	Denosumab use	No denosumab use	Hazard Ratio (95% CI)	*p*-value
Age				
18-64	36 (4.8)	49 (6.5)	0.60 (0.39, 0.92)	0.018
65-84	57 (3.5)	123 (7.5)	0.36 (0.27, 0.50)	<0.0001
≥ 85	12 (3.6)	16 (4.8)	0.57 (0.27, 1.21)	0.138
Sex				
Male	56 (3.9)	102 (7.2)	0.42 (0.30, 0.58)	<0.001
Female	49 (3.7)	104 (8.0)	0.39 (0.28, 0.55)	<0.001
Smoking status				
Ever	26 (4.7)	53 (9.7)	0.36 (0.23, 0.58)	<0.001
Never	79 (3.7)	160 (7.4)	0.41 (0.32, 0.54)	<0.001
Pathology type				
SCLC	10 (17.2)	10 (17.2)	0.78 (0.29, 2.10)	0.616
Squamous LC	11 (16.4)	19 (28.4)	0.57 (0.27, 1.19)	0.127
Non-squmous NSCLC	60 (11.7)	76 (14.8)	0.69 (0.49, 0.97)	0.030
Driver mutation				
EGFR	45 (10.1)	26 (5.8)	1.58 (0.98, 2.57)	0.059
ALK/ROS1	16 (9.9)	12 (7.4)	1.28 (0.60, 2.70)	0.520
Use of TKI				
Absence	255 (10.2)	252 (10.1)	0.84 (0.71, 1.00)	0.051
Any TKI	56 (10.7)	41 (7.8)	1.25 (0.84, 1.88)	0.569
EGFR TKI	42 (9.7)	30 (6.9)	1.30 (0.81, 2.08)	0.267
ALK/ROS1 TKI	13 (13.5)	10 (10.4)	1.15 (0.51, 2.63)	0.737
Erlotinib	10 (6.5)	10 (6.5)	1.12 (0.44, 2.83)	0.817
Afatinib	10 (35.7)	10 (35.7)	0.79 (0.11, 5.60)	0.811
Osimertinib	19 (15.4)	15 (12.2)	1.22 (0.62, 2.41)	0.557
Use of IO				
Presence	110 (14.1)	132 (16.9)	0.79 (0.61, 1.02)	0.066
Absence	148 (7.9)	147 (7.8)	0.85 (0.68, 1.07)	0.179
Use of CT				
Presence	173 (7.1)	267 (11.0)	0.93 (0.79, 1.10)	0.413
Absence	41 (6.5)	38 (6.1)	0.85 (0.55, 1.33)	0.481
Add. meta site				
Adrenal or renal	22 (9.9)	30 (13.5)	0.57 (0.33, 0.99)	0.044
Liver	72 (12.7)	54 (9.5)	1.13 (0.79, 1.61)	0.498
Brain	103 (11.0)	94 (10.1)	0.89 (0.67, 1.18)	0.406
Lung to lung	101 (14.6)	99 (14.3)	0.87 (0.66, 1.14)	0.310
Other sites	60 (7.6)	43 (5.4)	1.17 (0.79, 1.74)	0.424



Shiau, Bo-Wen, et al. *Clinical Oncology* (2026): 104067.

RCTs & RWD: Denosumab vs Zoledronic Acid

Clinical Trials & Real-World Data in Bone Metastases

Study	Design	Population	N	Time to 1st SRE	Multiple SREs	Overall Survival
Randomized Controlled Trials						
Henry et al. J Clin Oncol 2011	Phase 3 DB RCT	Solid tumors + MM (excl. breast, prostate)	**1,776**	HR 0.84 (0.71–0.98) Non-inferior **p<0.001** Superiority NS (p=0.06)	RR 0.90 (0.77–1.04) p=0.14 (NS)	No significant difference
Henry et al. Support Care Cancer 2014	Ad hoc (excl. MM)	Solid tumors only (excl. breast, prostate, MM)	**1,597**	HR 0.81 (0.68–0.96) Superior **p=0.017** Median: 21.4 vs 15.4 mo	RR 0.85 (0.72–1.00) **p=0.048**	No significant difference
Scagliotti et al. J Thorac Oncol 2012	Subgroup analysis	Lung cancer with bone mets	**702**	HR 0.84 (0.64–1.10) p=0.20 (NS)	Not reported separately	OS: 8.9 vs 7.7 mo HR 0.80 (0.67–0.95) **p=0.01**
Real-World Data						
Yu et al. BMJ Open Respir Res 2025	Retro-spective cohort	Lung cancer + bone mets (Taiwan)	**302**	Not reported	Not reported	Denosumab: better OS aHR 0.67 (0.50–0.91) **p=0.010**
Aliyev et al. J Clin Med 2025	Retro-spective RWD	Solid tumors + bone mets (multi-cancer)	**382**	SRE: 34.8% vs 51.8% **p<0.001** Breast/Prostate sig. Lung: NS (p=0.484)	Not reported	Not reported
Shiau et al. Clin Oncol 2026	PS-matched cohort (global)	Lung cancer + bone mets (global RWE)	**Large**	**Global RWE supports denosumab benefit (PS-matched)**		Mortality benefit in subgroup analysis

DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

Green = statistically significant (p<0.05) | Red = not significant

Evidence Summary: Denosumab vs Zoledronic Acid

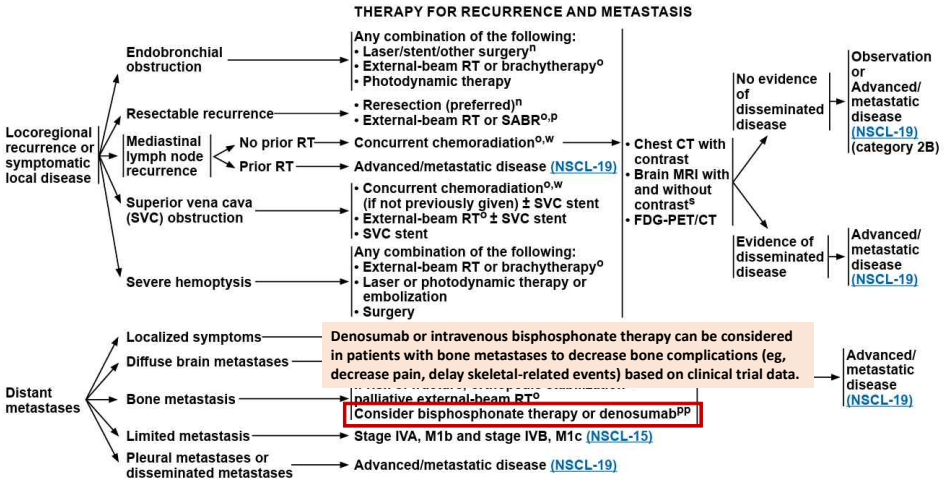
Clinical Trials & Real-World Data in Bone Metastases

Study	Design	Population	N	Time to 1st SRE	Multiple SREs	Overall Survival	Key Finding
Randomized Controlled Trials							
Henry et al. J Clin Oncol 2011	Phase 3 DB RCT	Solid tumors + MM (excl. breast, prostate)	**1,776**	HR 0.84 (0.71–0.98) Non-inferior **p<0.001** Superiority NS (p=0.06)	RR 0.90 (0.77–1.04) p=0.14 (NS)	No significant difference	Denosumab non-inferior to ZA for SRE prevention in mixed solid tumors
Henry et al. Support Care Cancer 2014	Ad hoc (excl. MM)	Solid tumors only (excl. breast, prostate, MM)	**1,597**	HR 0.81 (0.68–0.96) Superior **p=0.017** Median: 21.4 vs 15.4 mo	RR 0.85 (0.72–1.00) **p=0.048**	No significant difference	Denosumab SUPERIOR for SRE in solid tumors (+6 mo delay)
Scagliotti et al. J Thorac Oncol 2012	Subgroup analysis	Lung cancer with bone mets	**702**	HR 0.84 (0.64–1.10) p=0.20 (NS)	Not reported separately	OS: 8.9 vs 7.7 mo HR 0.80 (0.67–0.95) **p=0.01**	OS benefit with denosumab in lung cancer subgroup
Real-World Data							
Yu et al. BMJ Open Respir Res 2025	Retro-spective cohort	Lung cancer + bone mets (Taiwan)	**302**	Not reported	Not reported	Denosumab: better OS aHR 0.67 (0.50–0.91) **p=0.010**	Denosumab independent predictor of better OS (multivariate)
Aliyev et al. J Clin Med 2025	Retro-spective RWD	Solid tumors + bone mets (multi-cancer)	**382**	SRE: 34.8% vs 51.8% **p<0.001** Breast/Prostate sig. Lung: NS (p=0.484)	Not reported	Not reported	Overall SRE lower with denosumab; lung cancer subgroup NS
Shiau et al. Clin Oncol 2026	PS-matched cohort (global)	Lung cancer + bone mets (global RWE)	**Large**	SRE: 3.9% vs favoring denosumab	Not reported	Mortality benefit favoring denosumab in subgroup analysis	Global RWE supports denosumab benefit (PS-matched)

DB=double-blind; RCT=randomized controlled trial; MM=multiple myeloma; RR=rate ratio; NS=not significant; PS=propensity score; RWE=real-world evidence

Green = statistically significant (p<0.05) | Red = not significant

NCCN guideline (2026)



BMA Head-to-Head Comparison

Denosumab vs Zoledronic Acid — Key Clinical Differences

Category	Denosumab	Zoledronic Acid
Class / Target	RANKL monoclonal antibody	Bisphosphonate (osteoclast inhibitor)
Administration	✓ SC (subcutaneous)	IV infusion
Dosing (bone mets)	120 mg q4w	4 mg q4w (or q12w)
Renal function	✓ No dose adjustment needed	⚠ CrCl <30 contraindicated / monitoring req
SRE prevention	✓ Slightly superior (vs ZA)	Effective
Overall survival	No confirmed OS benefit	No confirmed OS benefit
Convenience	✓ Outpatient SC injection	IV infusion required
Cost	More expensive	✓ Relatively cheaper
Hypocalcemia	⚠ More frequent (monitor closely)	✓ Relatively less frequent
ONJ risk	Similar	Similar
Acute phase reaction	✓ None	Flu-like reaction possible

Scagliotti et al., J Clin Oncol 2012 | Stopeck et al., J Clin Oncol 2010 | ESMO Clinical Practice Guidelines 2020

Safety Comparison: Denosumab vs Zoledronic Acid

Adverse Event Profile in Bone Metastases (Integrated Analysis)

Adverse Event	Denosumab	Zoledronic Acid	Clinical Implication
Hypocalcemia (overall)	2.1%	1.1%	Denosumab higher -> Requires Ca/VitD supplement
Hypocalcemia (lung cancer)	8.6%	3.8%	More pronounced in lung cancer subgroup
ONJ	1.8%	1.3% (p=0.13, NS)	Similar incidence No significant difference
ONJ (lung cancer)	<1%	<1%	Very low in both
Acute Phase Reaction	8.7%	20.2%	ZA significantly higher (fever, bone pain, chills)
Renal toxicity	No dose adjustment needed	CrCl <30 contraindicated Dose adjustment required	ZA requires renal monitoring
Long-term safety (up to 5 yrs)	No new safety signals (Stopeck 2016)	Established long-term profile	Both acceptable for long-term use

Denosumab Advantage

Lower acute phase reaction, no renal dose adjustment

SC administration (outpatient convenience)

Zoledronic Acid Advantage

Lower hypocalcemia risk

Lower cost, established long-term safety profile

Lipton et al., Eur J Cancer 2012 | Scagliotti et al., J Thorac Oncol 2012 | Stopeck et al., Support Care Cancer 2016 | Udagawa et al., J Cancer Res Clin Oncol 2017

Hypocalcemia: Incidence & Management

Both BMAs Require Calcium/Vitamin D Supplementation

Incidence by Study

Study	Denosumab	Zoledronic Acid	Difference
Integrated (Lipton 2012)	2.1%	1.1%	Deno higher
Lung cancer (Scagliotti 2012)	8.6%	3.8%	Deno higher
NSCLC (Udagawa 2017)	Gr1: 15, Gr2: 7	Gr1: 18, Gr2: 8	Similar (mostly Gr1-2)
Long-term (Stopeck 2016)	3.8%	2.7%	Deno slightly higher
Breast Ca (Martin 2012)	5.5%	3.4%	Deno higher

Management (Both BMAs)

Pre-treatment

Correct pre-existing hypocalcemia before initiating EITHER BMA

Supplementation

Calcium (>= 500 mg) + Vitamin D (>= 400 IU) daily — required for BOTH denosumab & ZA

Monitoring

Regular serum calcium checks
More frequent monitoring with denosumab (especially lung cancer patients)

Renal consideration

ZA: CrCl <30 contraindicated (switch to denosumab)
Denosumab: no renal dose adjustment needed

Both BMAs carry hypocalcemia risk — denosumab slightly higher but manageable with proper supplementation.

In lung cancer, hypocalcemia rates are higher than overall population for both agents.

Body et al., Eur J Cancer 2015 | Scagliotti et al., J Thorac Oncol 2012 | XGEVA & Zometa Product Information

Osteonecrosis of the Jaw (ONJ)

Shared Risk with Both Antiresorptive Agents

Incidence

Overall (Saad 2012):

Denosumab 1.8% vs ZA 1.3%

p=0.13 (not significant)

Lung cancer (Scagliotti 2012):

<1% in BOTH groups

NSCLC (Udagawa 2017):

Denosumab: 4 (Gr2), ZA: 0

Risk Factors (Shared)

Drug-related:

Duration of antiresorptive therapy

(applies to BOTH agents)

Local factors:

Tooth extraction (79% of cases)

Invasive dental procedures

Concomitant oral disease

Systemic: genetics, other meds

Resolution

Resolution rate:

Denosumab: 40.4%

ZA: 30.2%

Time to resolution:

Denosumab: median 26.8 mo

ZA: median not reached

p=0.024

Denosumab: reversible RANKL inhibition

ZA: accumulates in bone matrix

Benefit-Risk Assessment (Saad 2012)

17 : 1

NNT (SRE prevention): 12.3

NNH (ONJ): 212.2

Key Takeaway

ONJ risk is SIMILAR between denosumab and ZA (no significant difference).

Both agents are antiresorptive -> both carry ONJ risk.

If ONJ occurs, denosumab-related cases resolve faster.

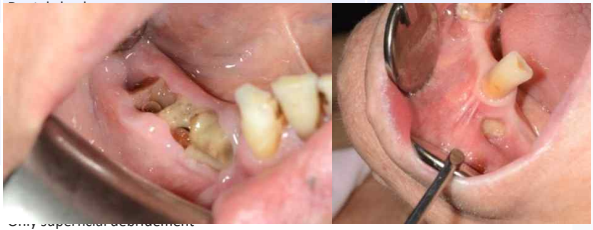
Dental screening before EITHER agent is essential.

Saad et al., Ann Oncol 2012 | Ikesue et al., Support Care Cancer 2021 | Ruggiero et al., J Oral Maxillofac Surg 2022

ONJ: Staging & Management

AAOMS Position Paper — Applies to ALL Antiresorptive Agents

Stage	Description	Management	Severity
At Risk	No apparent necrotic bone in asymptomatic patients	No treatment indicated Patient education	Monitoring
Stage 0	Non-specific symptoms or radiographic findings		
Stage 1	Exposed necrotic bone No pain or infection		
Stage 2	Exposed necrotic bone with pain and/or infection		
Stage 3	Exposed necrotic bone + extracutaneous fistula or osteolysis to inferior border	Antibacterial mouth rinse Pain medication & antibiotics Surgical debridement/resection	Severe



These staging/management guidelines apply equally to denosumab- and bisphosphonate-related MRONJ.

Ruggiero et al., J Oral Maxillofac Surg 2014 | Ruggiero et al., J Oral Maxillofac Surg 2022 | Kyriakidou et al. *British Journal of Medical Practitioners* 2016

Safety Management Protocol

Applies to BOTH Denosumab and Zoledronic Acid

Before BMA Therapy

- Comprehensive dental examination
- Complete invasive dental procedures before starting
- Allow adequate healing time
- Correct hypocalcemia (baseline Ca, VitD levels)

During BMA Therapy

- Ca (>=500mg) + VitD (>=400IU) daily supplementation
- Regular serum calcium monitoring
- Avoid invasive dental procedures if possible
- Maintain good oral hygiene + dental follow-up q3-6mo

Drug-Specific Monitoring

- Denosumab: closer Ca monitoring (higher hypo risk)
- ZA: renal function monitoring (CrCl check before each dose)
- ZA: contraindicated if CrCl <30 mL/min
- If ONJ suspected: conservative management + multidisciplinary consult

Proactive safety management is essential for BOTH agents — not a reason to withhold BMA therapy

ESMO Clinical Practice Guidelines 2020 | AAOMS Position Paper 2022 | XGEVA & Zometa Product Information

Safety Summary & Clinical Decision Factors

	Denosumab	Zoledronic Acid
Hypocalcemia	Higher risk — needs closer monitoring	Lower risk — still requires supplementation
ONJ	Similar risk (1.8%) — faster resolution	Similar risk (1.3%) — slower resolution
Acute Phase Rxn	Significantly lower (8.7%)	Higher (20.2%) — fever, bone pain
Renal Safety	No dose adjustment needed	CrCl <30 contraindicated
Administration	SC q4w (convenient)	IV q4w (infusion required)
Long-term Safety	No new signals up to 5 years	Established long-term profile

Clinical Decision Factors

Choose Denosumab when:

- Renal impairment (CrCl <30)
- Acute phase reaction concern
- Outpatient convenience preferred

Choose Zoledronic Acid when:

- Cost is a primary consideration
- Lower hypocalcemia risk preferred
- Adequate renal function (CrCl >30)

ESMO Clinical Practice Guidelines 2020 | Lipton et al., Eur J Cancer 2012 | Saad et al., Ann Oncol 2012

BMA Therapy: Timing, Duration & Discontinuation

When to Start, How Long to Continue, and What Happens If You Stop

When to Start?

ESMO Recommendation:
Start BMA at diagnosis of bone metastases
regardless of symptoms [I, A]

Rationale:
- SRE risk begins at BM diagnosis
- Early initiation delays 1st SRE
- OS benefit in lung cancer (8.9 vs 7.7 mo, p=0.01)

In Lung Cancer:
- BMA recommended for all patients with bone metastases

Both Denosumab & ZA:
equally recommended at diagnosis

How Long to Continue?

ESMO Guideline:
Continue indefinitely

May consider withholding in:
- Oligometastatic disease
- Low perceived SRE risk
- Durable response to systemic tx

Duration — Unclear:
- No RCT defines optimal duration
- Pivotal trials: median ~17-19 mo
- Extended dosing (q12w) may be considered after 1-2 yrs of q4w

ONJ risk increases with duration:
~5% at >3 years of treatment
-> balance SRE prevention vs ONJ

If Discontinued?

Rebound SRE Risk
After denosumab discontinuation:
- SRE incidence x3.3 higher

Temporal pattern:
- Peak at 12-15 months (IRR 8.7)
- Significant at 6-15 months
- Transient (declines after)

Mechanism:
- Rebound bone resorption
- Osteoclast precursor accumulation during Tx
- ALP elevation at 6 mo predicts subsequent SRE (AUC 0.80)

Fewer doses = higher risk
ZA accumulates in bone -> less rebound concern

Start early at BM diagnosis | Continue as long as possible | If stopping denosumab, consider switching to ZA to mitigate rebound

ESMO Bone Health Guidelines 2020 | Scagliotti et al., J Thorac Oncol 2012 | Yu et al., BMJ Open Respir Res 2025 | Setsu et al., J Bone Oncol 2025

Denosumab + EGFR-TKI: OS Benefit in Real-World Cohort

Ko et al., Cancers 2022 | Retrospective, Multi-institutional (Chang Gung, Taiwan) | N=400 (BM=190)

Study Design

Population:

400 EGFR-mutated NSCLC
190 with bone metastasis (47.5%)
73 received denosumab (38.4%)

1st-line TKI:

Gefitinib / Erlotinib / Afatinib

Bone Metastasis Impact

BM vs No BM:

OS: 21.7 vs 33.0 mo (p<0.001)
MV: HR=1.37 (1.07-1.76, p=0.013)

Initial SRE at diagnosis:

With SRE: 15.4 mo
Without SRE: 23.6 mo (p=0.026)

Denosumab OS Benefit

Denosumab vs No Denosumab:

OS: 26.6 vs 20.1 mo (p=0.015)

Multivariate Analysis:

OS: HR=0.60 (0.41-0.88, p=0.008)
SRE: HR=0.61 (0.37-0.98, p=0.042)

Subgroup Analysis: Denosumab Effect by SRE Status

Subgroup	Endpoint	Result	HR (95% CI)	p-value
Without initial SRE (started denosumab preventively)	SRE-free survival	Denosumab delayed SRE	HR 0.36 (0.19-0.79)	0.009
With initial/pre-existing SRE (started denosumab after SRE)	Overall survival	25.3 vs 12.9 mo	—	0.016
All BM patients	Subsequent SRE incidence	Denosumab reduced SRE	HR 0.53 (0.31-0.90)	0.019

Key Findings

1. **Denosumab independently improved OS in EGFR-mutated NSCLC with BM (HR=0.60, p=0.008)**
2. **Preventive denosumab (before SRE) delayed SRE occurrence (HR=0.36, p=0.009)**
3. **Even in patients with pre-existing SRE, denosumab improved OS (25.3 vs 12.9 mo, p=0.016)**

Denosumab + TKI in EGFR-Mutated NSCLC with Bone Metastasis

Chen et al., Cancer Medicine 2024 — Retrospective Cohort (N=247)

Study Design

Population:
247 EGFR-mutated NSCLC
with bone metastasis

Treatment:
EGFR-TKI (1st/2nd/3rd gen)
± Denosumab / ZA
± Anti-angiogenic therapy (AAT)

Primary endpoint: OS, PFS

Key Results

Bone Metastasis Impact
PFS: 10.5 vs 12.6 mo (p=0.017)
OS: 30.9 vs 49.7 mo (p<0.001)

Denosumab Benefit
Denosumab: independent (+)
prognostic factor for OS

Triple Combination: Denosumab + AAT + Sequential Osimertinib

OS: 60.6 mo vs 27.9 mo (p = 0.028)

→ More than doubling of overall survival with optimized combination strategy

Multivariate Analysis — Independent Prognostic

Factor	HR (OS)	95% CI	p-value
Denosumab use	0.62	0.40–0.95	0.028
Anti-angiogenic therapy	0.61	0.43–0.87	0.006
Sequential osimertinib	0.54	0.35–0.83	0.005

Key Finding

In EGFR-mutated NSCLC with BM, denosumab is an independent positive prognostic factor.
Triple combination (denosumab + AAT + osimertinib) showed remarkable OS benefit (60.6 mo).

Bone Metastasis & Immunotherapy: The Challenge

Why BM Attenuates ICI Efficacy in NSCLC — Zhu et al., Lung Cancer 2022

ICI Efficacy in BM vs Non-BM Patients

PFS: HR = 3.44 (95% CI 1.84–6.42, p < 0.001)
OS: HR = 3.24 (95% CI 1.51–6.97, p = 0.003)
ORR: 21.6% vs 36.7% (p = 0.08)

BM is an independent negative prognostic factor for ICI treatment outcomes in NSCLC

"Cold" Immune Microenvironment in BM

61% of BM patients classified as Immune Subtype A
→ "Cold" phenotype with low immune infiltration

Characteristics:

- Low PD-L1 expression
- Reduced immune cell infiltration
- Diminished IFN-γ signaling

Bisphosphonate Use During ICI Improved Outcomes

Among BM patients receiving ICI, concurrent bisphosphonate use was associated with:

- Improved PFS (HR 0.42, p = 0.048)
- Improved OS (HR 0.30, p = 0.047)

→ Bone-modifying agents may help overcome the immunosuppressive BM microenvironment

Clinical Implication

BM creates an immunosuppressive niche → Bone-targeting agents may serve as immune modulators beyond skeletal protection

RANKL-RANK Axis: Linking Bone Biology & Tumor Immunology

Mechanistic Rationale for Denosumab + ICI Combination — Wang et al., Cancer Control 2026

BM Immunosuppressive Niche

Bone marrow microenvironment is enriched with:

- Regulatory T cells (Tregs)
  → Suppress anti-tumor immunity
- MDSCs
  → Inhibit T cell function
- Tumor-associated macrophages
  → M2 polarization, pro-tumor
- TGF-β from bone resorption
  → Immune evasion signals

RANKL-RANK Pathway in Immunity

RANKL expressed on:
Activated T cells, tumor cells, osteoblasts, bone marrow stroma

RANK expressed on:
Osteoclasts, dendritic cells, tumor cells, immune cells

Key effects of RANKL signaling:

- Promotes osteoclastogenesis
  → Vicious cycle of bone destruction
- Upregulates PD-1 on CD8+ T cells
  → T cell exhaustion
- Enhances Treg differentiation

Denosumab: Immune Modulation

By blocking RANKL:

1. Breaks vicious cycle of bone destruction
2. Downregulates PD-1 on CD8+ T cells
3. Reduces Treg-mediated immunosuppression
4. Restores anti-tumor immune response

→ Potential ICI synergy

Summary

- **RANKL–RANK signaling supports an immunosuppressive niche rich in Tregs, MDSCs, and M2 macrophages in bone microenvironment.**
- **By inhibiting RANKL, denosumab may not only prevent bone destruction but also enhance anti-tumor immunity and synergize with immunotherapy.**

Denosumab + ICI: Clinical Evidence in NSCLC

Summary of Available Clinical Data — Wang et al., Cancer Control 2026

Study	Design	N	ICI Regimen	BMA	Key Outcome	Conclusion
Zhu 2022 (Lung Cancer)	Retrospective Cohort	196	Anti-PD-1/PD-L1 (mono or combo)	Bisphosphonate (ZA or others)	PFS HR 0.42 (p=0.048) OS HR 0.30 (p=0.047) for BMA users	BMA during ICI improved survival in BM patients
Gyawali 2023 (J Immunother)	Retrospective VA cohort	2,737	Anti-PD-1/PD-L1	Denosumab or ZA	Denosumab: OS 12.3 mo ZA: OS 10.8 mo vs No BMA: 7.2 mo	BMA + ICI associated with better OS
Ahern 2018 (Melanoma)	RCT sub-analysis	1,471	Ipilimumab (anti-CTLA-4)	None (RANKL expr.)	High RANKL: better ipilimumab response	RANKL may predict ICI benefit
Liede 2018 (Ann Oncol)	Retrospective Cohort	2,120	Anti-PD-1/PD-L1 or anti-CTLA-4	Denosumab vs none	OS improved with denosumab + ICI (multiple tumors)	Denosumab + ICI synergy signal across tumor types
Wang 2026 (Review)	Systematic Review	—	Various ICI regimens	Denosumab or ZA	Consistent trend of improved outcomes with BMA + ICI	Prospective RCTs needed

Evidence Summary

- **Multiple retrospective studies consistently show improved survival with BMA + ICI combination**
- **Denosumab may have additional immunomodulatory benefit beyond skeletal protection**
- **Limitation: No prospective RCT data yet — all evidence is retrospective or sub-analysis**

BMA Evidence & Drug Selection: Take-Home Messages

1

BMA Clinical Evidence

Denosumab: non-inferior to ZA (RCT), superior in solid tumors (HR 0.81).
Lung cancer OS benefit (Scagliotti: HR 0.80, p=0.01). RWD consistently supports OS improvement.

2

Drug Selection

Denosumab when renal impairment, acute phase reaction concern, SC convenience
ZA when cost priority, adequate renal function. Both recommended (NCCN/ESMO).

3

Safety & Management

Hypocalcemia: Deno slightly higher (manageable with Ca/VitD) | ONJ: similar risk, Deno resolves faster | Acute phase reaction: ZA higher.
Benefit:Risk = 17:1. Dental optimization, Ca/VitD support, Ca and renal function monitoring, and ONJ surveillance

4

Timing & Duration

Start at BM diagnosis (ESMO I,A). Continue indefinitely (consider q12w after 1-2 yrs).
If stopping denosumab: rebound SRE risk (IRR 3.3) -> consider switching to ZA.

5

Beyond Skeletal Protection: TKI/ICI Combination

Triple combo (Deno+AAT+Osi): OS 60.6 mo. Prospective RCTs needed.
RANKL-RANK axis links bone biology and tumor immunology. BMA + ICI/TKI: emerging synergy signal (retrospective).

Denosumab: proven SRE prevention + OS benefit in lung cancer + manageable safety + emerging immune synergy

Thank you
for your attention