

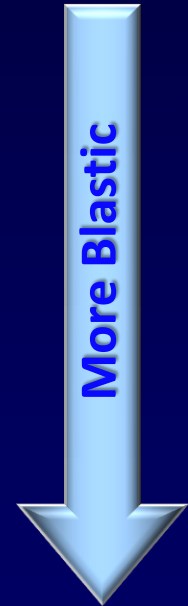
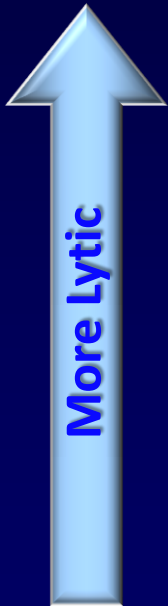
Treatment of Bone Metastases

Mohammad Jahanzeb, MD, FACP

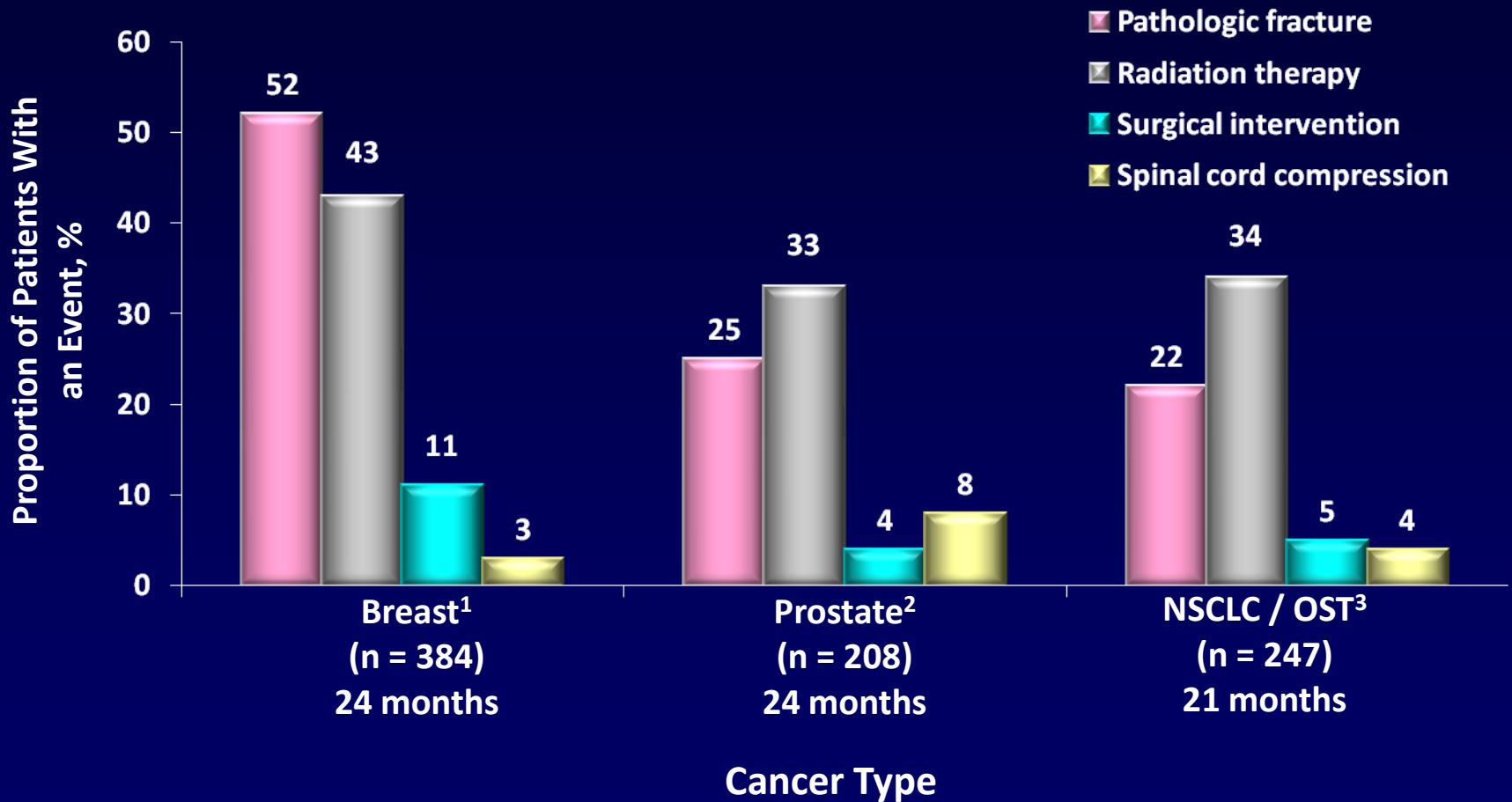
Professor of Clinical Medicine, Hematology-Oncology
Director, UM Sylvester Deerfield Campus
Associate Center Director for Community Outreach
Sylvester Comprehensive Cancer Center
University of Miami, Miller School of Medicine

Metastatic Bone Disease Is Prevalent

	5-Year World Prevalence, thousands ¹	Incidence of Bone Metastases in Cancers, % ²	Median Survival, months ²⁻⁴
Myeloma	144	70 - 95	6 - 54
Renal	480	20 - 25	6 - 12
Melanoma	533	14 - 45	< 6
Bladder	1,000	40	6 - 9
Thyroid	475	60	48
Lung	1,394	30 - 40	< 6
Breast	3,860	65 - 75	19 - 25
Prostate	1,555	65 - 75	12 - 53



SREs Are Prevalent in Patients With Cancer in the Absence of Bone-Targeted Therapy

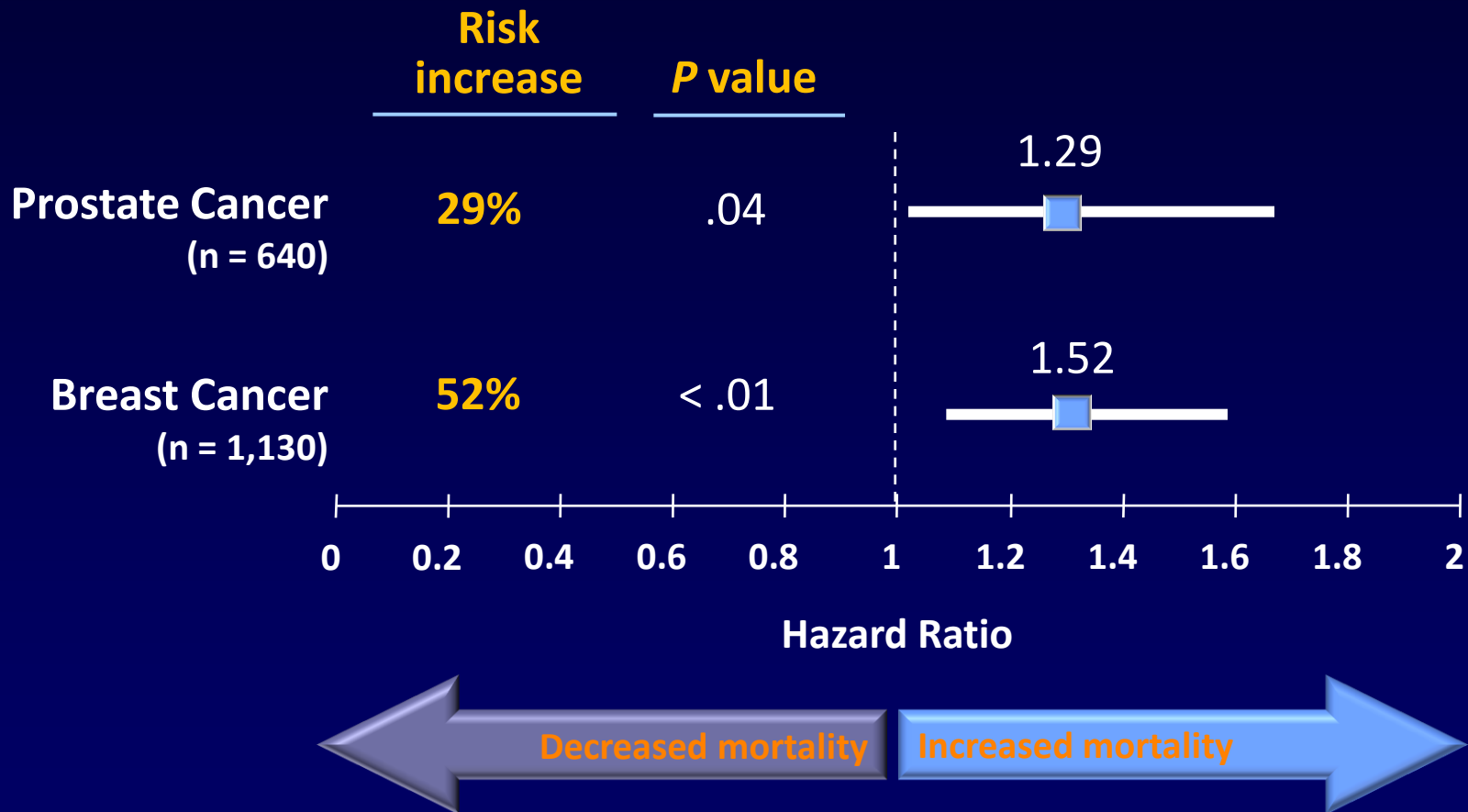


Data results from placebo arms of clinical trials.

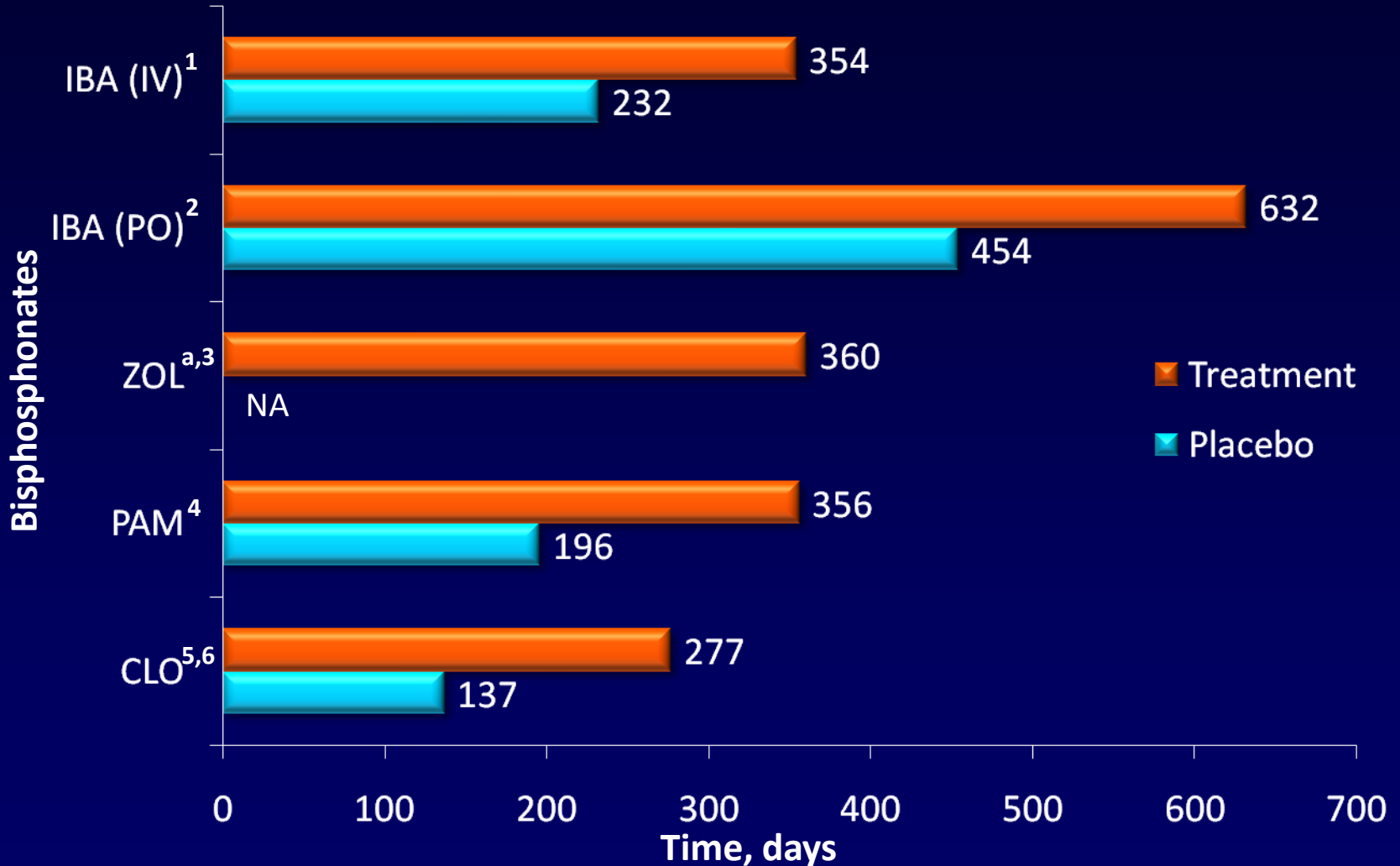
Abbreviations: NSCLC, non-small cell lung cancer; OST, other solid tumors; SRE, skeletal-related event.

1. Lipton A, et al. *Cancer*. 2000;88(5):1082-1090; 2. Saad F, et al. AUA 2003, abstract 1472; 3. Rosen LS, et al. *Cancer*. 2004;100(12):2613-2621.

Pathologic Fractures Negatively Affect Survival



Bisphosphonates Delay Time to First On-Study SRE or New Bone Events

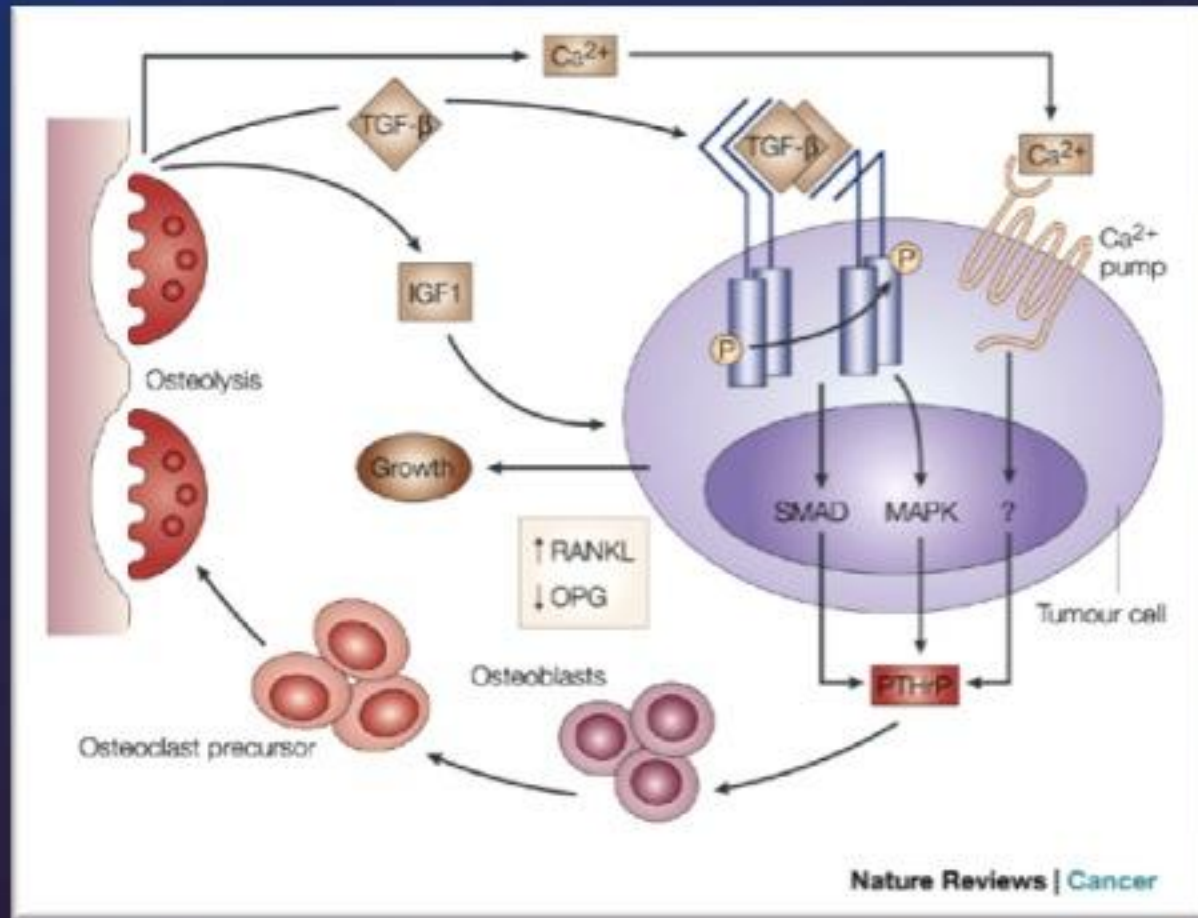


^a Phase III trial of ZOL compared with PAM in patients with bone metastases from breast cancer.

Abbreviations: CLO, clodronate; IBA, ibandronate; IV, intravenous; NA, not applicable; PAM, pamidronate; PO, oral; SRE, skeletal-related event; ZOL, zoledronic acid.

1. Body JJ, et al. *Ann Oncol.* 2003;14(9):1399-1405; 2. Body JJ, et al. *Br J Cancer.* 2004;90(6):1133-1137; 3. Kohno N, et al. *JCO.* 2005;23(15):3314-3321; 4. Lipton A, et al. *Cancer.* 2000;88(5):1082-1090; 5. Paterson AHG, et al. *JCO.* 1993;11(1):59-65; 6. Pavlakis N, Stockler M. In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Bone metastasis: the « vicious cycle » theory



Phase III Trials of Dmab vs ZOL in Patients With Malignant Bone Disease

- Advanced cancer
- ≥18 years of age
- At least 1 bone metastasis
- ECOG 0, 1, or 2
- Adequate organ function

• **3 Multicenter, randomized, double blind trials —**

- **Breast cancer (N = 2,046)**
- **Prostate cancer (N = 1,901)**
- **OST/MM (N = 1,776)**

R

Dmab 120 mg SC* +
placebo IV infusion q 4 wk (n = 1,020)

ZOL 4 mg IV +
placebo SC injection q 4 wk (n = 1,026)

Event-driven analysis for primary endpoint

Primary endpoint: Time to first on-study SRE (non-inferiority trial)

Secondary endpoints: Time to first on study SRE (superiority), time to first and subsequent on-study SREs (superiority), laboratory values, safety, incidence of anti-denosumab antibodies

Dmab vs ZOL: Efficacy Overview

	Breast cancer ^{1,2}		OST and MM ^{2,3}		Prostate cancer ^{2,4}	
	Dmab	ZOL	Dmab	ZOL	Dmab	ZOL
N	1,026	1,020	886	890	950	951
Pts with on-study SRE, %	30.7	36.5	31.4	36.3	35.9	40.6
SRE breakdown, %						
RT	8.0	11.7	13.4	16.2	18.6	21.3
Path Fx	20.7	23.3	13.8	15.6	14.4	15.0
Surgery	1.2	0.8	1.5	2.1	0.1	0.4
SCC	0.9	0.7	2.7	2.4	2.7	3.8
Median time to SRE, mo	NR	26.4	20.5	16.3	20.7	17.1
HR	0.82		0.84		0.82	
P (non-inf.)	< .001		< .001		< .001	
P (superior.)	.010		.060		.008	

Abbreviations: Dmab, denosumab; HR, hazard ratio; Path Fx, pathologic fracture; RT, radiotherapy; SCC, spinal cord compression; SRE, skeletal-related event; ZOL, zoledronic acid.

1. Stopeck AT, et al. *JCO*. 2010;28(35):5132-5139; 2. Xgeva™ (denosumab) injection, for subcutaneous use [package insert]. Thousand Oaks, CA. Amgen Inc. 2010; 3. Henry D, et al. ECCO-ESMO 2009, abstract 20LBA;

4. Fizazi K, et al. ASCO 2010, abstract LBA4507.

FDA-Approved Agents for Prevention of SREs in Metastatic Breast Cancer

Agent	Drug Class	Recommended Dose and Schedule
Zoledronic acid	Bisphosphonate	4 mg IV q3-4w
Pamidronate	Bisphosphonate	90 mg IV q3-4w
Denosumab	RANKL-targeted MAb	120 mg SQ q4w

- **Both American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend all 3 agents^{1,2}**
 - **No agent recommended over another**

Safety of Antiresorptive Therapies

AEs During Antiresorptive Therapy

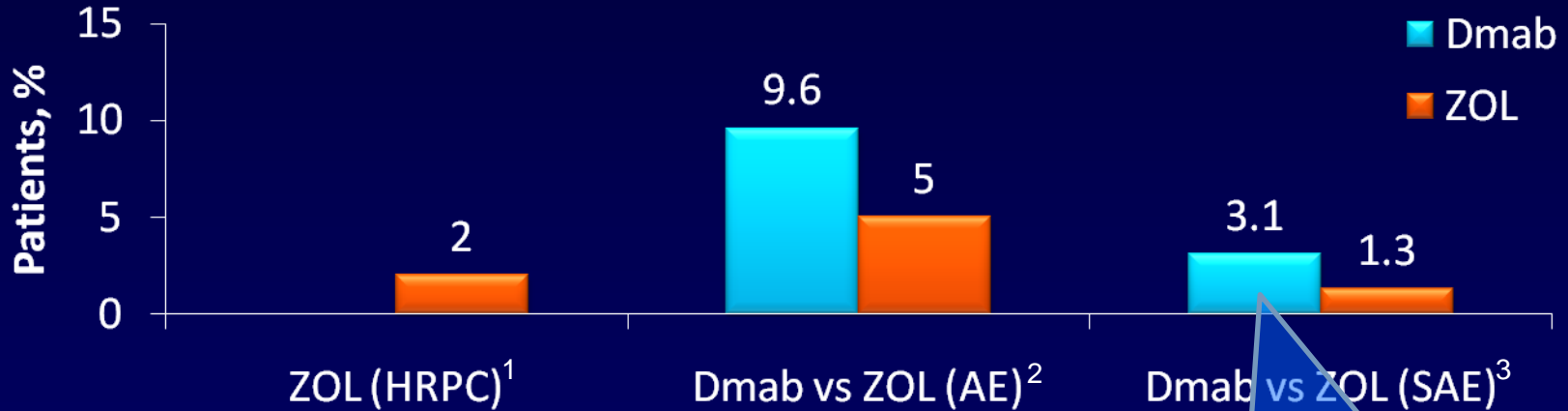
- Common AEs
 - Acute phase reaction (IV BPs)
- Uncommon AEs (all antiresorptive agents)
 - Hypocalcemia
 - Renal adverse events
 - Osteonecrosis of the jaw (ONJ)
 - Rare—ulcers, perforations, and strictures (oral BPs)

Acute-Phase Reaction

- **Transient reaction observed in 15% to 30% of patients after the first infusion of a nitrogen-containing bisphosphonate**
- **Incidence is rare during subsequent infusions**
- **Characterized by**
 - **Mild to moderate pyrexia**
 - **Chills in some cases**
 - **Myalgia**
- **Management**
 - **Preventive or therapeutic analgesics (acetaminophen, ibuprofen)**
 - **Adequate hydration**
 - **Patient education**
- **Typically a self-limiting reaction that peaks at 24 to 48 hrs after infusion and resolves within 3 days**

Uncommon AEs: Hypocalcemia

- Potentially severe electrolyte imbalance associated with bone-directed therapies
- Grade 3/4 hypocalcemia in phase III trials



■ Prevention/management

- Calcium supplementation
- Correction of predisposing factors (eg, hypoparathyroidism)
- **Monitor serum calcium monthly during BP or Dmab treatment**

**Regular (monthly)
serum calcium
monitoring per PI**

Abbreviations: AE, adverse event; BP, bisphosphonate; Dmab, denosumab; HRPC, hormone-refractory prostate cancer; PI, package insert; SAE, serious adverse event; ZOL, zoledronic acid.

1. Saad F, et al. *JNCI*. 2002;94(19):1458-1468; 2. Lipton A, et al. ESMO 2010. Abstract 1249; 3. Xgeva™ (denosumab) injection, for subcutaneous use [package insert]. Thousand Oaks, CA. Amgen Inc. 2010.

Uncommon AEs: Renal Adverse Events

- Uncommon in patients with normal renal function when IV BPs are used per label
- Risk factors
 - Type of bone-targeted therapy
 - Route of administration
 - Dose
 - Schedule
 - Duration of infusion
 - Concomitant medications
 - Underlying disease (eg, end-organ damage in myeloma)

Precautions and Dose Modifications for IV BP Therapy

- Serial monitoring of renal function—before each dose
- Adequate hydration
- Dose modification based on baseline renal function
 - Baseline assessment also needed with Dmab³

ZOLEDRONIC ACID

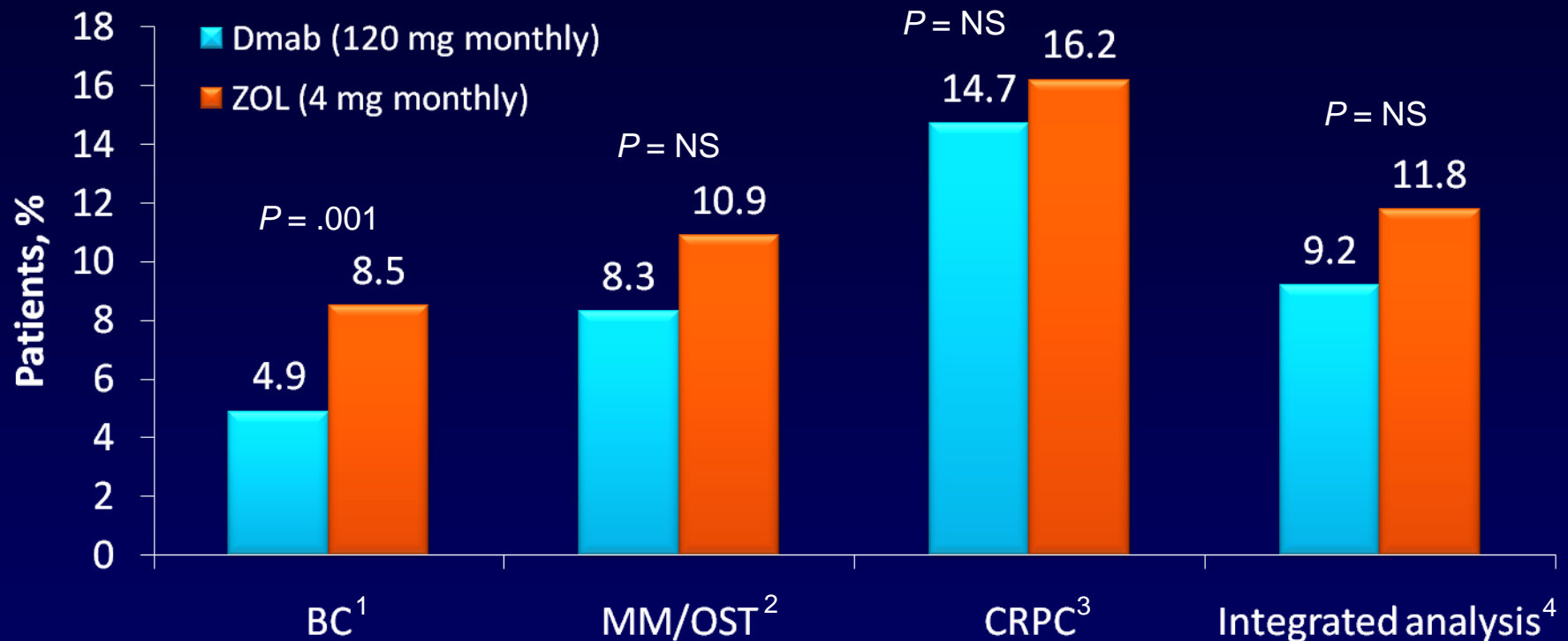
Baseline CrCl, mL/min	Recommended dose, mg	Infusion time, hour
> 60	4.0	0.25
50 - 60	3.5	0.25
40 - 49	3.3	0.25
30 - 39	3.0	0.25

^a If serum creatinine increases, resume therapy only when creatinine returns to within 10% of baseline.

Abbreviations: BP, bisphosphonates; CrCl, creatinine clearance; Dmab, denosumab; IBN, ibandronate; IV, intravenous; ZOL, zoledronic acid.

1. Prescribing information for zoledronic acid. www.zometa.com; 2. Prescribing information for ibandronate. www.emea.europa.eu/; 3. Xgeva™ (denosumab) injection, for subcutaneous use [package insert]. Thousand Oaks, CA. Amgen Inc. 2010.

Renal AEs in Phase III Trials of Dmab in Patients With Malignant Bone Disease



- Renal safety of Dmab in the absence of serum Cr monitoring is not established
 - Dmab has not been tested in advanced cancer patients with $CrCl < 30$ mL/min⁵

Abbreviations: AE, adverse event; BC, breast cancer; Cr, creatinine; CrCl, creatinine clearance; CRPC, castration-resistant prostate cancer; Dmab, denosumab; MM, multiple myeloma; NS, not significant; OST, other solid tumors (not breast or prostate cancer); ZOL, zoledronic acid.

1. Stopeck A, et al. *JCO*. 2010;28(35):5132-5139; 2. Henry D, et al. ECCO-ESMO 2009, abstract 20LBA; 3. Fizazi K, et al. ASCO 2010, abstract LBA4507; 4. Lipton A, et al. ESMO 2010, abstract 1249; 5. Xgeva™ (denosumab) injection, for subcutaneous use [package insert]. Thousand Oaks, CA. Amgen Inc. 2010.

Monitoring Renal Function and Dose Adjustments During IV BP Therapy

- Serum creatinine should be assessed before each cycle
- Dose adjustments for patients with pre-existing renal insufficiency at baseline
- Treatment should be withheld for \uparrow serum creatinine
 - For patients with normal baseline levels, \uparrow of 0.5 mg/dL
 - For patients with abnormal baseline levels, \uparrow of 1.0 mg/dL
- Treatment may resume when serum creatinine is within 10% of baseline value

Monitoring Hypocalcemia During Denosumab Therapy

- FDA warning: *“Severe hypocalcemia can occur in patients receiving Xgeva. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and adequately supplement all patients with calcium and vitamin D”*¹
- Additional FDA recommendations during denosumab treatment¹
 - Monitor baseline renal function
 - Do not administer if CrCl < 30 mL/min
 - Correct pre-existing hypocalcemia
 - Patients with risk factors for hypocalcemia?
- EMA recommendations during denosumab (Prolia) treatment for osteoporosis²
 - Correct pre-existing hypocalcemia
 - All patients should receive calcium and vitamin D supplements
 - Patients with CrCl < 30 mL/min are at risk for hypocalcemia
 - Monitor calcium levels in patients predisposed to hypocalcemia

Abbreviations: CRCL, creatinine clearance; FDA, US Food and Drug Administration.

1. Xgeva™ (denosumab) injection [package insert]. Thousand Oaks, CA: Amgen Inc., 2010; 2. Prolia (denosumab) package leaflet. Amgen Europe B.V., 2010.

Dmab vs ZOL in BC: Adverse Events of Interest¹

Event, n (%)	ZOL (n = 1,013)	Dmab (n = 1,020)
Infectious AEs	494 (49)	473 (46)
Infectious SAEs	83 (8.2)	71 (7.0)
Acute phase reaction (first 3 days)	277 (27)	106 (10)
Potential renal toxicities ^a	86 (8.5)	50 (4.9)
ONJ incidence	14 (1.4)	20 (2.0)
New primary malignancy	5 (0.5)	5 (0.5)
Hypocalcemia	34 (3.4)	56 (5.5)

^a Includes blood creatinine increases, renal failure acute, proteinuria, blood urea increased, renal impairment, urine output decreased, anuria, azotemia, hypercreatininemia, creatinine renal clearance decreased, renal failure chronic, blood creatinine abnormal.

Abbreviations: AE, adverse event; BC, breast cancer; Dmab, denosumab; ONJ, osteonecrosis of the jaw; SAE, serious adverse event; ZOL, zoledronic acid.

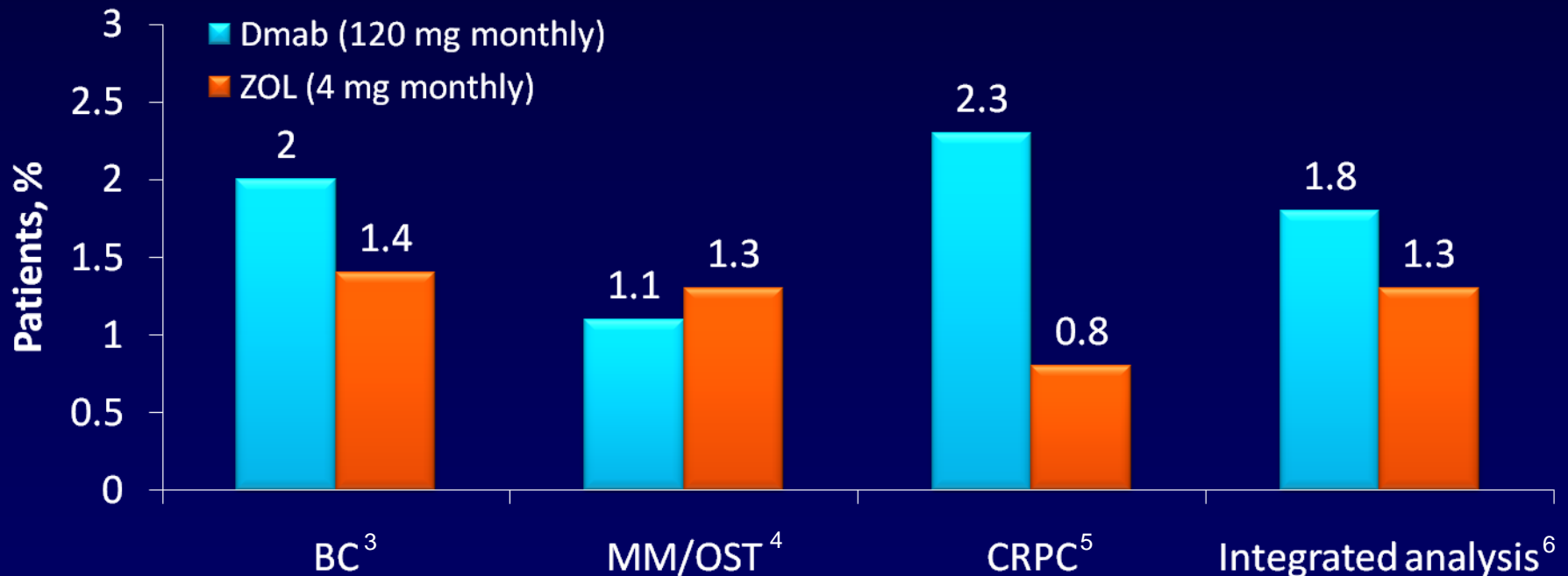
1. Adapted from Stopeck A, et al. *JCO*. 2010;28(35):5132-5139.

Signs and Symptoms of Suspected Osteonecrosis of the Jaw (ONJ)

- Symptoms
 - “Heavy jaw,” a dull, aching sensation
 - Numbness/tingling of the jaw
 - Oral pain
- Signs
 - Rough area on the jawbone
 - Soft-tissue swelling, drainage, or infection
 - Exposed bone in the oral cavity in the absence of healing
 - Sudden change in the health of periodontal tissue
 - Failure of oral mucosa to heal
 - Loosening of teeth

Uncommon AEs: ONJ

- Uncommon condition in cancer patients receiving complex treatment regimens such as BPs, Dmab, sunitinib, and bevacizumab¹⁻⁵



- Similar ONJ rates with Dmab vs ZOL

Abbreviation: AE, adverse event; BC, breast cancer; BP, bisphosphonate; CRPC, castrate-resistant prostate cancer; Dmab, denosumab; MM, multiple myeloma; ONJ, osteonecrosis of the jaw; OST, other solid tumors (not breast or prostate cancer); ZOL, zoledronic acid.

1. Hoff AO, et al. *JBMR* 2008;23(6):826-836; 2. McArthur HL, et al. ASCO 2008, abstract 9588; 3. Stopeck A, et al. *JCO*. 2010;28(35):5132-5139; 4. Henry D, et al. ECCO-ESMO 2009, abstract 20LBA;

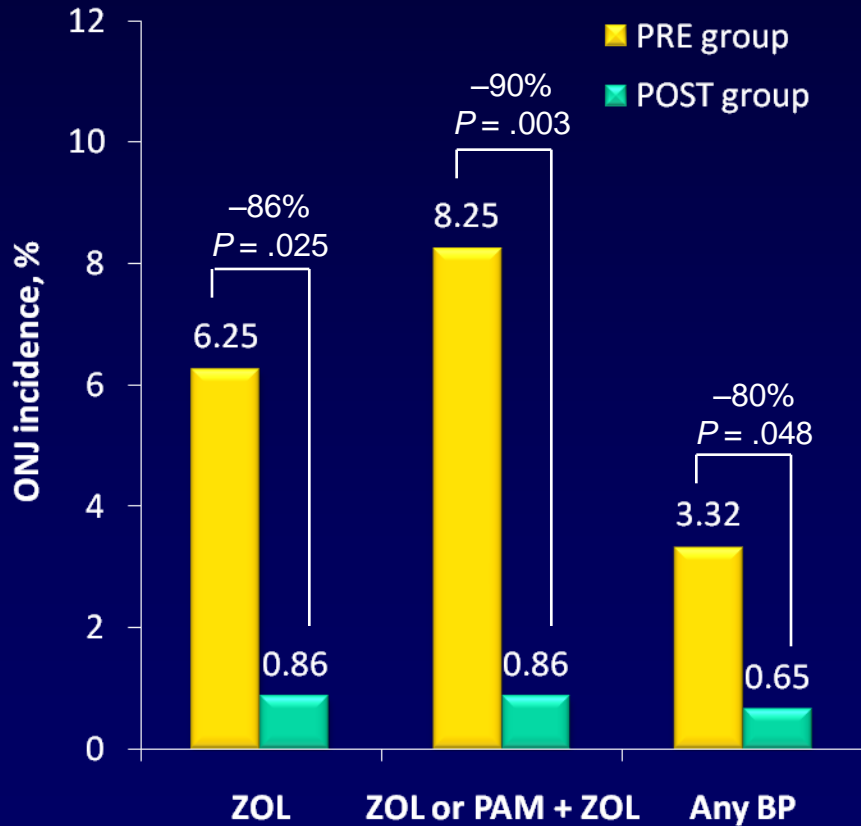
5. Fizazi K, et al. ASCO 2010, abstract LBA4507; 6. Lipton A, et al. ESMO 2010, abstract 1249.

Prevention of ONJ

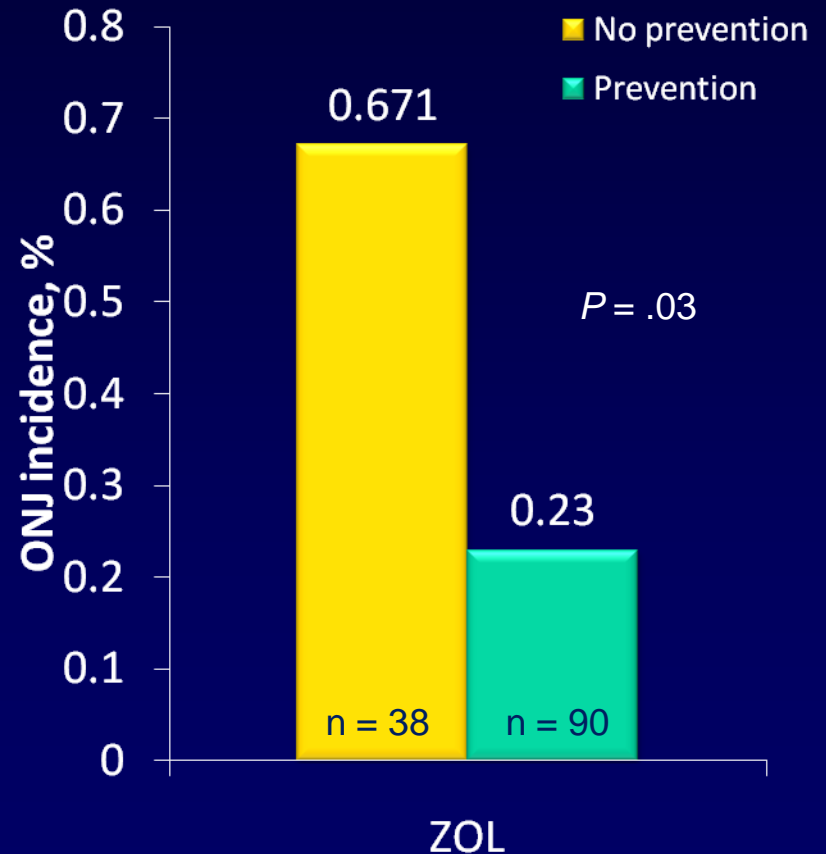
- Prior to treatment with antiresorptive agents^{1,2}
 - Dental exam with appropriate preventive dentistry
 - Remove abscessed and nonrestorable teeth, teeth with severe periodontal disease, and teeth with poor long-term prognosis
 - Functionally rehabilitate salvageable dentition
 - Educate patients on oral hygiene and signs and symptoms of ONJ

Preventive Measures Can ↓ ONJ Incidence

- A retrospective study in cancer patients receiving BPs (N = 966)¹



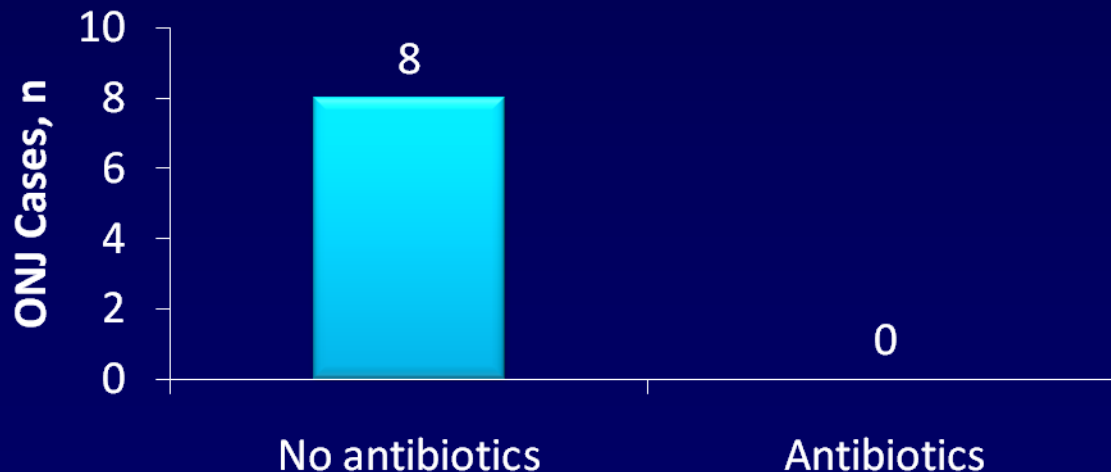
- A retrospective study in cancer patients receiving BPs (N = 128)²



Abbreviations: BP, bisphosphonate; ONJ, osteonecrosis of the jaw; PAM, pamidronate; PRE, pre-implementation of preventive measures; POST, post-implementation of preventive measures; ZOL, zoledronic acid.

Prevention of ONJ

- During antiresorptive treatment^{1,2}
 - Seek dental maintenance care at least every 6 months
 - Avoid invasive dental procedures if possible
 - Maintain good dental hygiene
- Antibiotic prophylaxis ↓ ONJ risk during dental procedures³



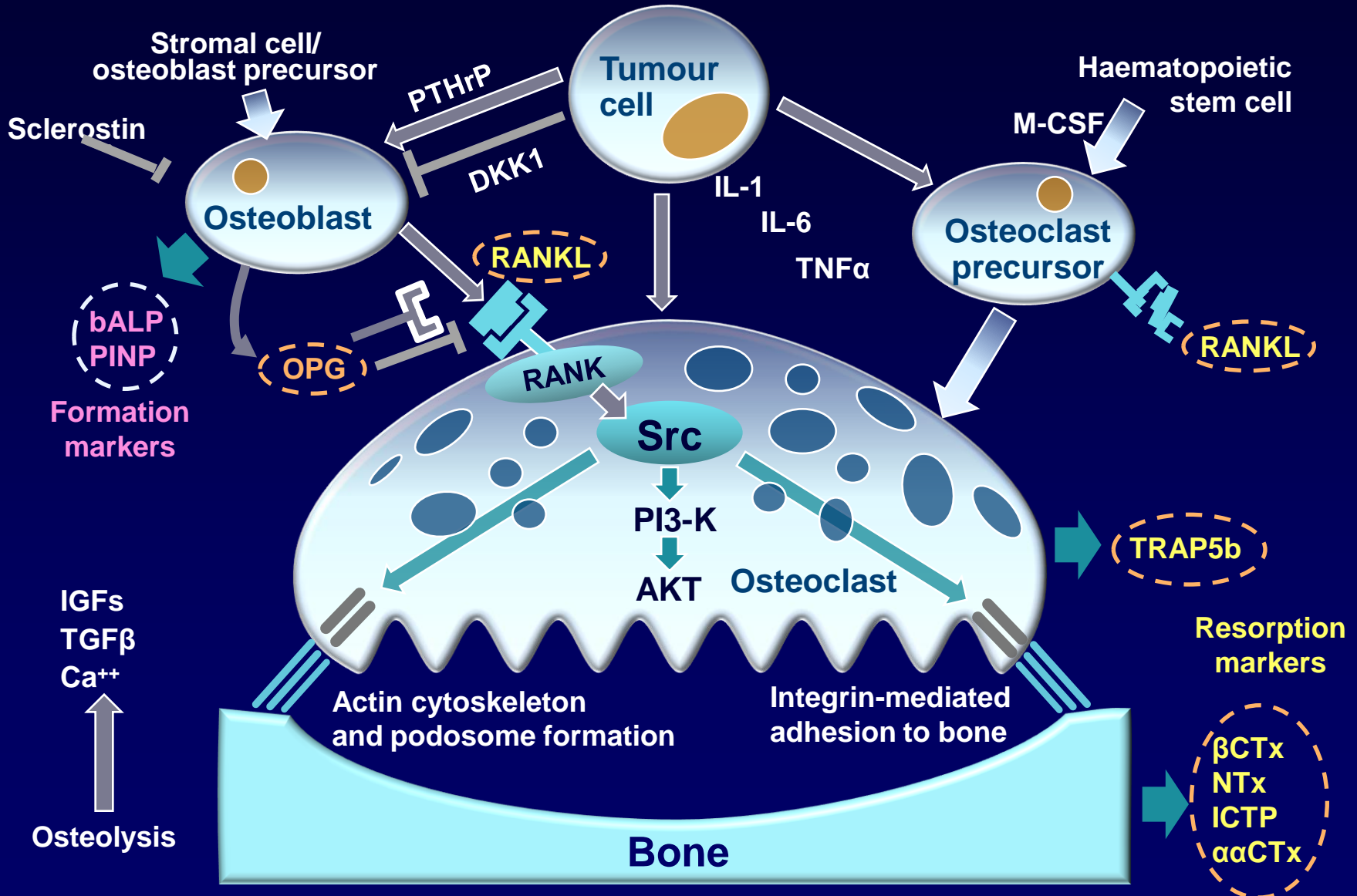
Abbreviation: ONJ, osteonecrosis of the jaw.

1. Weitzman R, et al. *Crit Rev Oncol Hematol*. 2007;62(2):148-152; 2. Mehrotra B, et al. *Hematology ASH Educ Program*. 2006;356-360, 515; 3. Montefusco V, et al. *Leuk Lymph*. 2008;49(11):2156-2162.

Monitoring of Adverse Events During Antiresorptive Therapy

Adverse Event	Monitoring or Management Required		
	IV BP	Oral BP	Dmab
Acute-phase reaction	✓	—	—
Renal adverse events (monitor serum creatinine)	✓	—	?
Hypocalcemia (monitor serum calcium)	—	—	✓
ONJ (monitor oral health)	✓	✓	✓

Src: A Role in Osteoclast Function and Metastatic Bone Disease



Phase II Multicenter Study to Assess Saracatinib Effects on Bone Markers in Cancer Patients With Bone Metastasis

Patients

- Breast or prostate cancer
- Metastatic bone disease
- No prior exposure to bisphosphonates
- Threshold level of bone resorption (urinary NTx ≥ 30 nmol BCE/mmol creatinine)

4 weeks

Saracatinib^a
(175 mg/day PO)
+ Standard of care

Randomization
1:1

Zoledronic acid
(4 mg) single IV
infusion on day 1
+ Standard of care

Endpoints

- Serum β CTx
- Safety
- Serum: bALP, ICTP, PINP, TRAP5b; Urine: NTx/Cr, $\alpha\alpha$ CTx/Cr
- Saracatinib steady-state PK
- Serum: PTH, tALP, calcium, phosphate, RANKL/OPG
- Pain
- PSA
- PK/PD
- Exploratory biomarkers & DNA

- Open label, 4-week treatment period
- Stable hormonal therapy allowed; no concomitant chemotherapy
- Bone markers assessed at baseline and weeks 1, 2, and 4

^a Continuation of therapy beyond 4 weeks if clinical benefit.

Conclusions

- Metastatic bone disease and SREs are substantial concerns in advanced oncology patients
- SREs are associated with ↑ morbidity and ↓ quality of life
 - Pathologic fractures can ↓ survival
- Current treatment options to ↓ SRE risk—
 - Bisphosphonates
 - Denosumab
- Safety Concerns
 - Monitor renal function with IV BPs
 - ↑ Risk of hypocalcemia (monitor serum calcium)
 - Use ONJ preventive measures