

Case #8

Multiple Myeloma: Use of Bisphosphonates

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Bisphosphonate Use in Multiple Myeloma

- **66 yo, previously healthy farmer went to his general practitioner for a routine check-up**
- **Physical exam – no abnormalities**
- **Serum electrophoresis – revealed a monoclonal protein (IgG kappa)**
- **Pt referred to a hematologist who performs additional examinations**

Lab values: Hb: 13.6 g/dL, ESR: 92 mm/h
Creatinine: 1.1 mg/dL,
Calcium: 2.4 mmol/L
TP: 10.2 g/dL, Albumin: 4.2 g/dL
B2M: 2.6 mg/L; CRP: 0.9
IgG: 4270 mg/dL; IgA: <25 mg/dL;
IgM: <17 mg/dL

Bone marrow bx: 24% plasma cells in cytology, 30% in histology.
18% plasma cells in flow cytometry with aberrant immunophenotype (CD138+CD56+CD19-)
Karyotype analysis is normal.

Radiologic exams: No lytic bone lesions

What would you do at this time with the patient?

- 1. Wait and watch**
- 2. Start patient on steroids alone**
- 3. Induction chemotherapy with stem cell harvest after the third course**
- 4. Thalidomide/Dexamethasone therapy**
- 5. Bisphosphonate therapy**

Classification of Monoclonal Gammopathies

- **Monoclonal Gammopathy of Undertermined Significance (MGUS)**
- **Asymptomatic Myeloma**
- **Symptomatic Myeloma**
- **Non-Secretory**
- **Solitary Plasmacytoma of Bone**
- **Extramedullary Plasmacytoma**
- **Plasma Cell Leukemia**

Myeloma-related organ or tissue impairment (Roti) due to the plasma cell proliferative process

- **Calcium levels increased: serum Ca^{++} >0.25 mmol/l above the ULN or >2.75 mmol/l**
- **Renal insufficiency: Cr >173 mmol/l**
- **Anaemia: Hb 2 g/dl below the LLN or Hb <10 g/dl**
- **Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)**
- **Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)**
- * **CRAB (calcium, renal insufficiency, anaemia or bone lesions)**

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- **M-protein in serum <30 g/l**
- **Bone marrow clonal plasma cells <10% and low level of plasma cells infiltration in a trephine biopsy (if done)**
- **No evidence of other B-cell proliferative disorders**
- **No related organ or tissue impairment - no end organ damage, including bone lesions, AL amyloid and the IgM paraprotein-related neurological syndromes would be instances of “MG associated with...”**

Asymptomatic Myeloma (Smoldering Myeloma)

- **M-protein in serum ≥ 30 g/l**
and/or
- **Bone marrow clonal plasma cells $\geq 10\%$**
- **No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms**

Symptomatic Multiple Myeloma

- M-protein in serum and/or urine
- Bone marrow (clonal) plasma cells * or plasmacytoma
- Related organ or tissue impairment (end organ damage, including bone lesions)
- * If flow cytometry is performed, most plasma cells (>90%) will show a 'neoplastic' phenotype

Some patients may have no symptoms but have related organ or tissue impairment

Smoldering Multiple Myeloma

Mayo Clinic 1970 – 1994

	N	%
Serum M-protein \geq 3 g/dl and Bone marrow plasma cells \geq 10%	106	38
Serum M-protein $<$ 3 g/dl and Bone marrow plasma cells \geq 10%	143	52
Serum M-protein \geq 3 g/dl and Bone marrow plasma cells $<$ 10%	27	10
TOTAL	276	100

Smoldering Multiple Myeloma

Progression

	N	%	Expected No. Pts	RR
Multiple Myeloma	157	57	0.3	522
Primary Amyloid (AL)	5	2	0.1	50
Total	162	59		

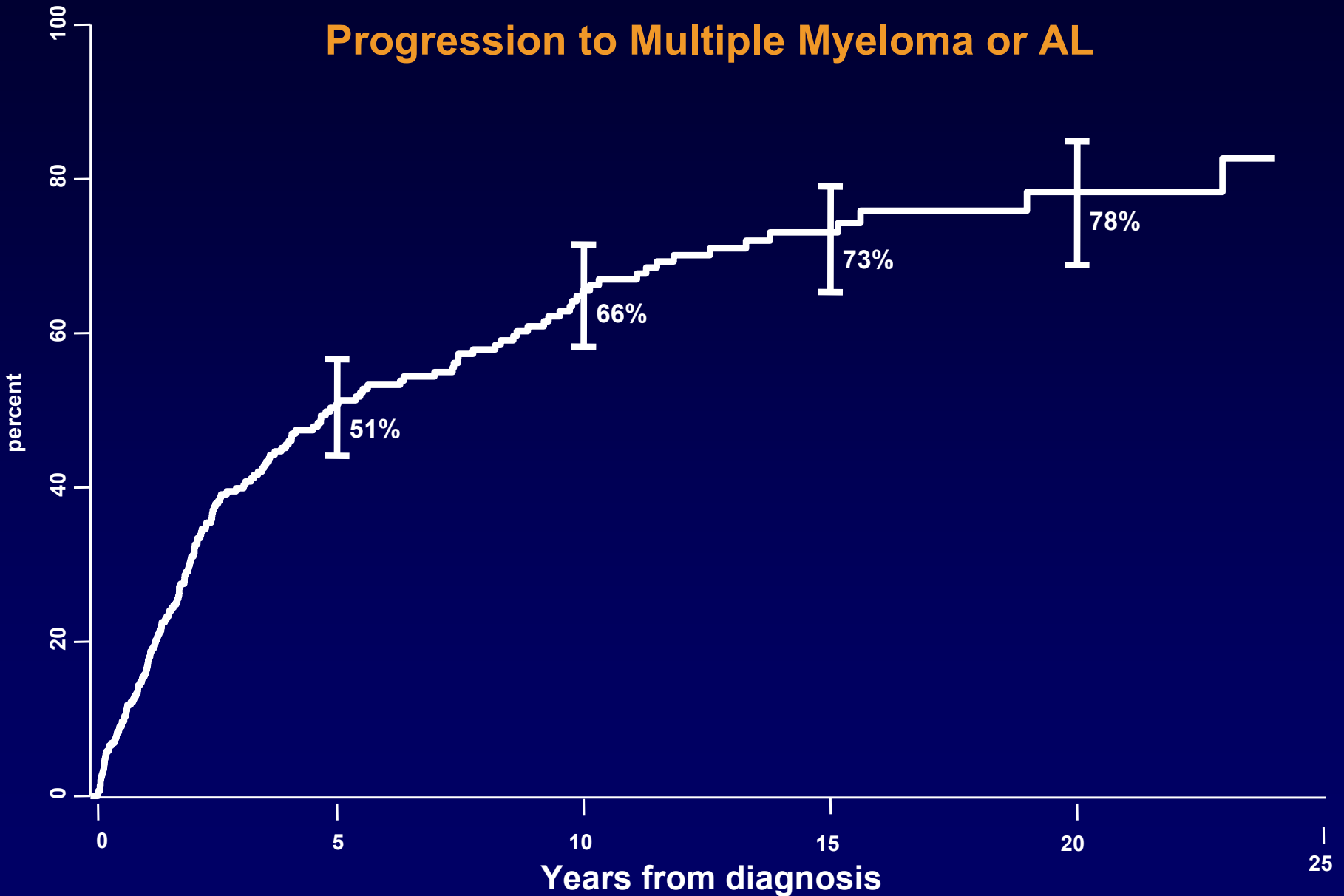
Smoldering Multiple Myeloma

	Time to progression (Median)
Serum M-spike ≥ 30 g/L and Bone marrow plasma cells $\geq 10\%$	2 years
Serum M-spike < 30 g/L and Bone marrow plasma cells $\geq 10\%$	8 years
Serum M-spike ≥ 30 g/L and Bone marrow plasma cells $< 10\%$	19 years
Total (N = 276)	5 years

p = <0.001

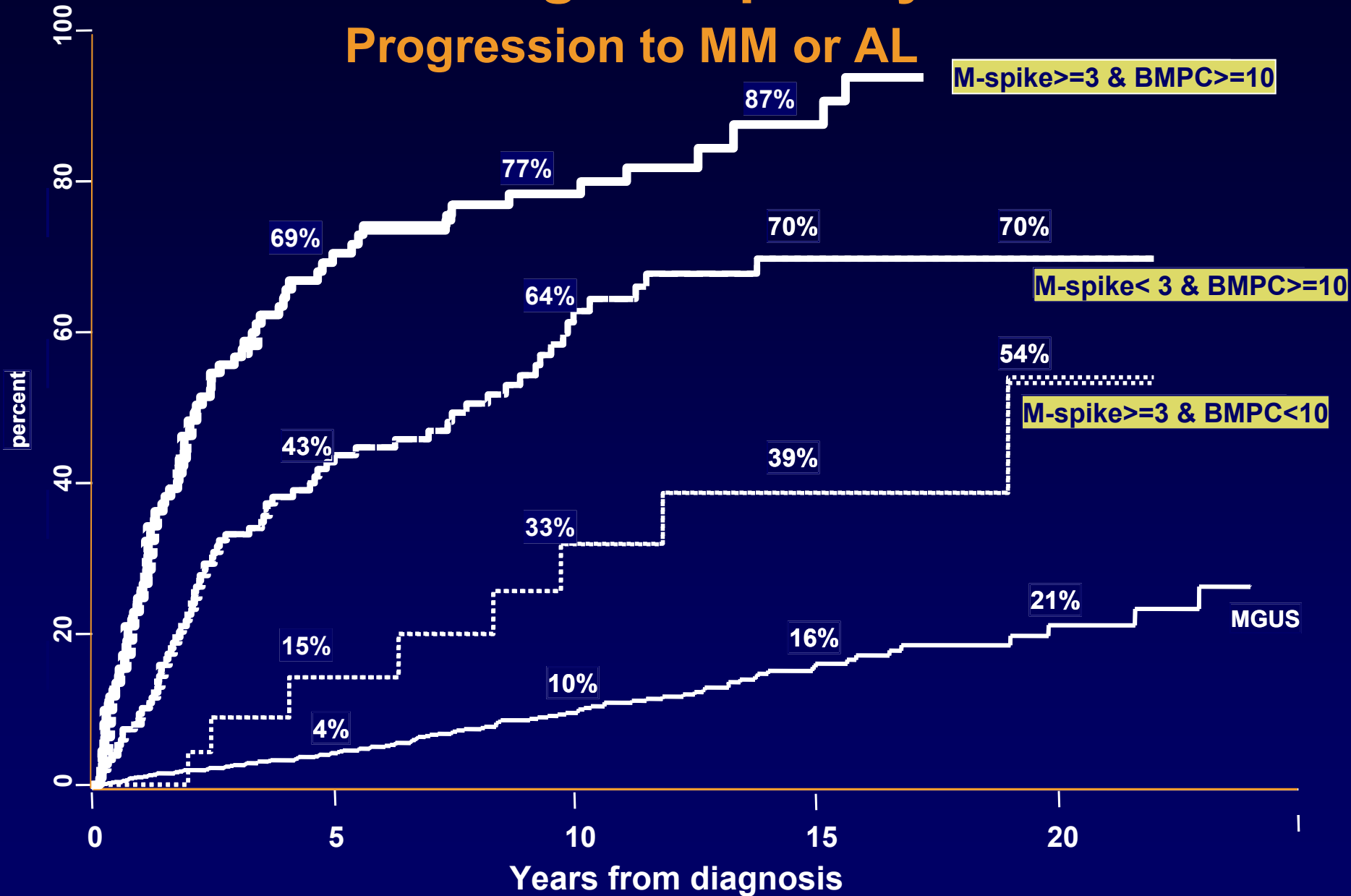
Smoldering Multiple Myeloma

Progression to Multiple Myeloma or AL



Smoldering Multiple Myeloma

Progression to MM or AL

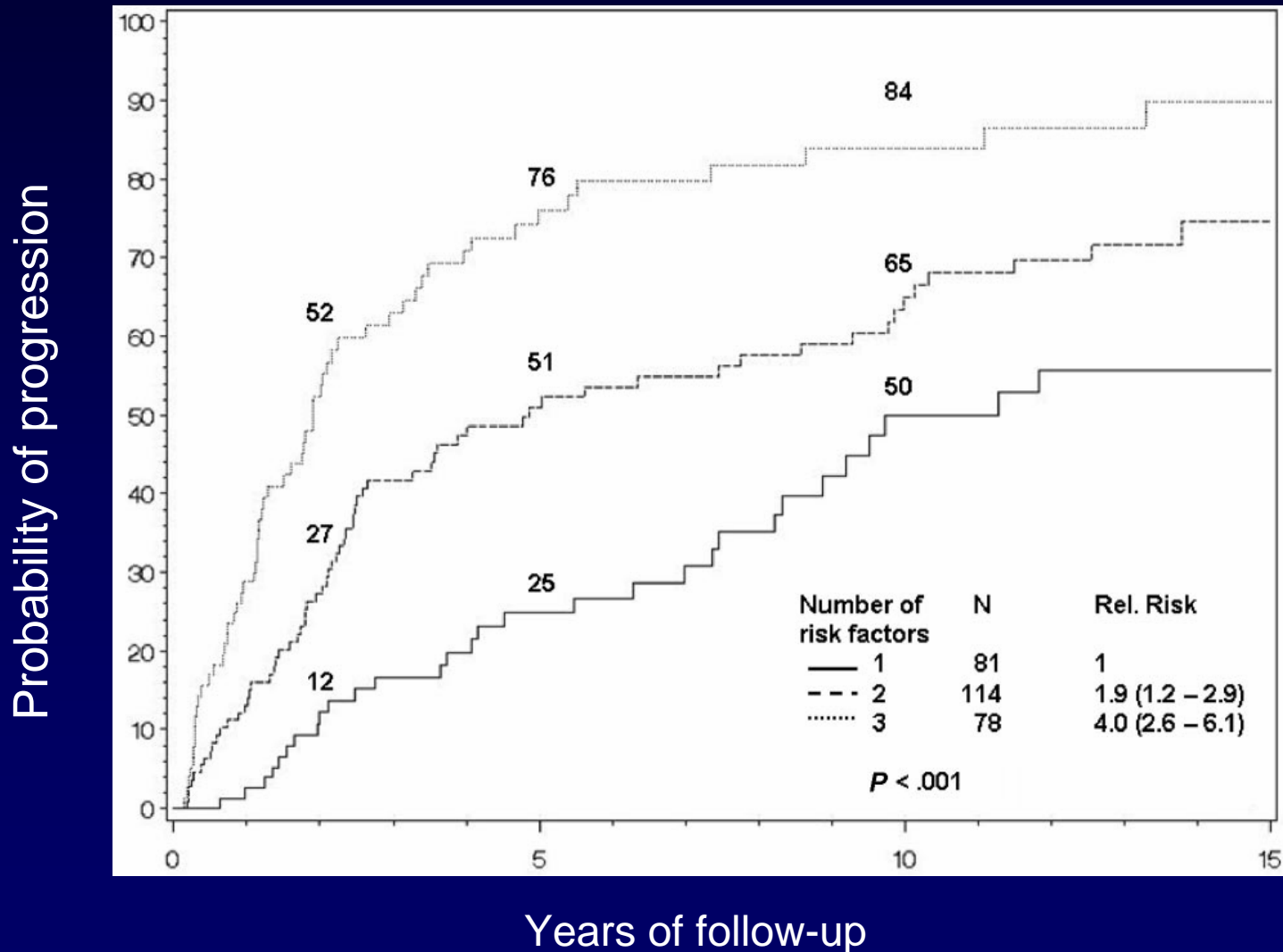


Prognostic Model in Smoldering Myeloma

Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

Prognostic factor	Hazard ratio (95% CI)	P
BM plasma cells >10%	3.1 (1.6-6.3)	< .01
FLC ratio (<0.125 or >8)	1.9 (1.3-2.7)	< .01
Serum M protein >30 g/L	1.9 (1.4-2.6)	< .01

Prognostic Model in Smoldering Myeloma



- **14 months later, pt developed anemia**
 - Plasma cell infiltration in BM – 44%
 - IgG kappa – 7.1 g/dl
- **Treated with EPO and VAD x 3**
- **Achieves 90% reduction of the M-protein**
- **Undergoes SC harvest and treated with HD Melphalan and auto SCT**
- **3 months later, BM shows BM plasma cell percentage of 5%**
- **Started on zoledronic acid 4 mg IV monthly x 24 months**


- **50 months later, pt presents with:**
 - **Hypercalcemia (4.4 mmol/L)**
 - **Creatinine increase to 1.6 mg/dl**
 - **Osteolytic lesions of vertebral spine**
- **Treated with vigorous hydration, furosemide, corticosteroids, and zoledronic acid (4 mg IV)**
- **Once hypercalcemia under control, further tx with thal, dex, cyclophosphamide**

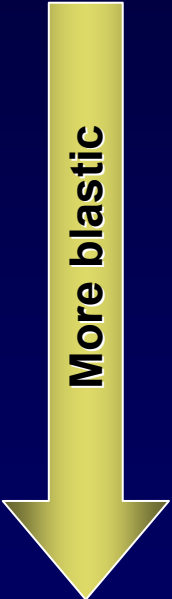
Would you put this patient on a bisphosphonate again?

- 1. Definitely**
- 2. I don't think he is going to benefit**

Metastatic Bone Disease is Prevalent

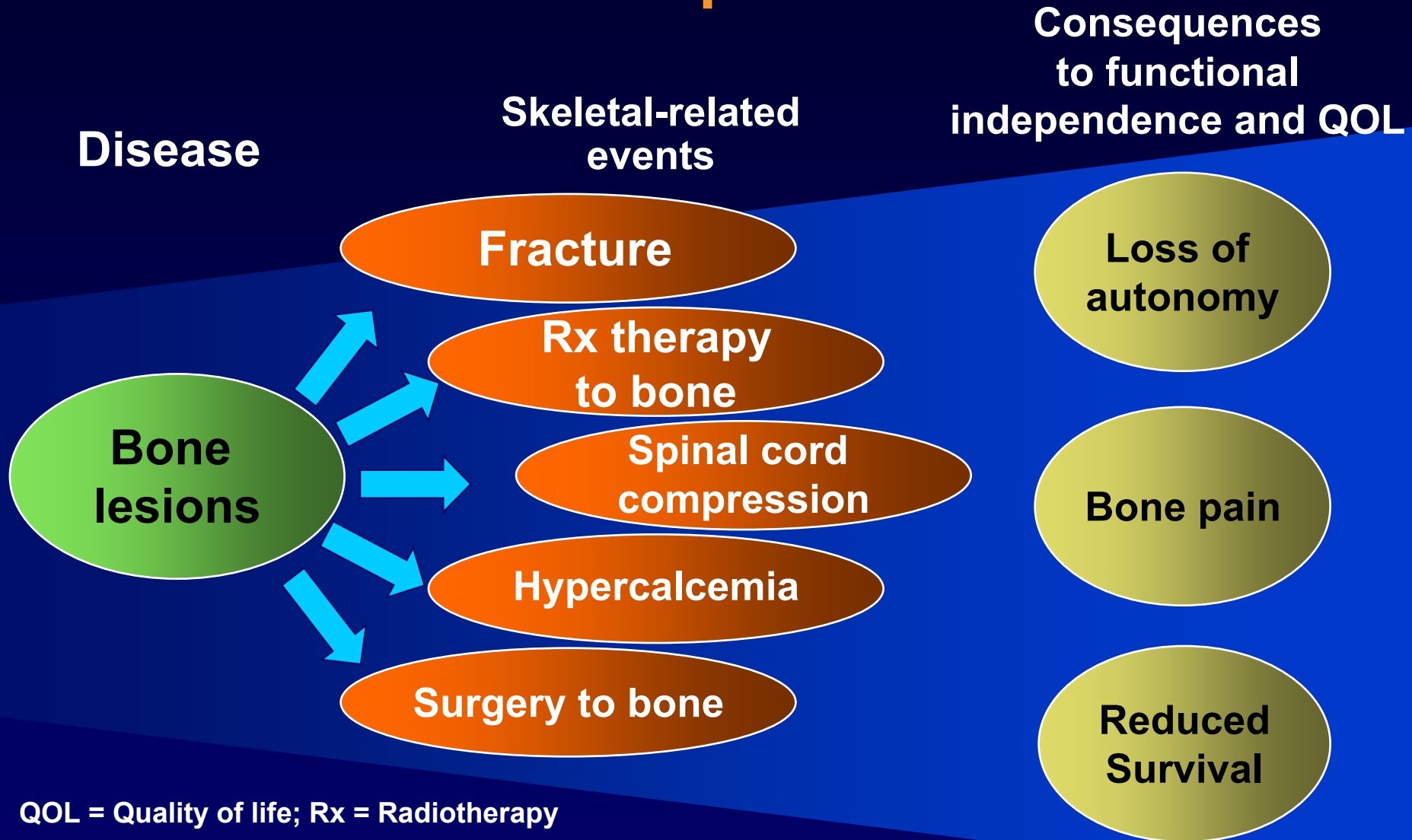
	5-year world prevalence, thousands ¹	Incidence of bone metastases in cancers ²	Median survival, Months ²⁻⁴
Myeloma	144	70 - 95	6 - 54
Renal	480	20 - 25	12
Melanoma	533	14 - 45	6
Bladder	1,000	40	6 - 9
Thyroid	475	60	48
Lung	1,394	30 - 40	6 - 7
Breast	3,860	65 - 75	19 - 25
Prostate	1,555	65 - 75	12 - 53





1. Ferlay J, et al. IARC Globocan 2000. Cancer Incidence, Mortality, and Prevalence. 2. Coleman RE. *Cancer Treat Rev.* 2001;27:165-176. 3. Coleman RE. *Cancer.* 1997;80:1588-1594. 4. Zekri J et al. *Int J Oncol.* 2001;19:379-382.

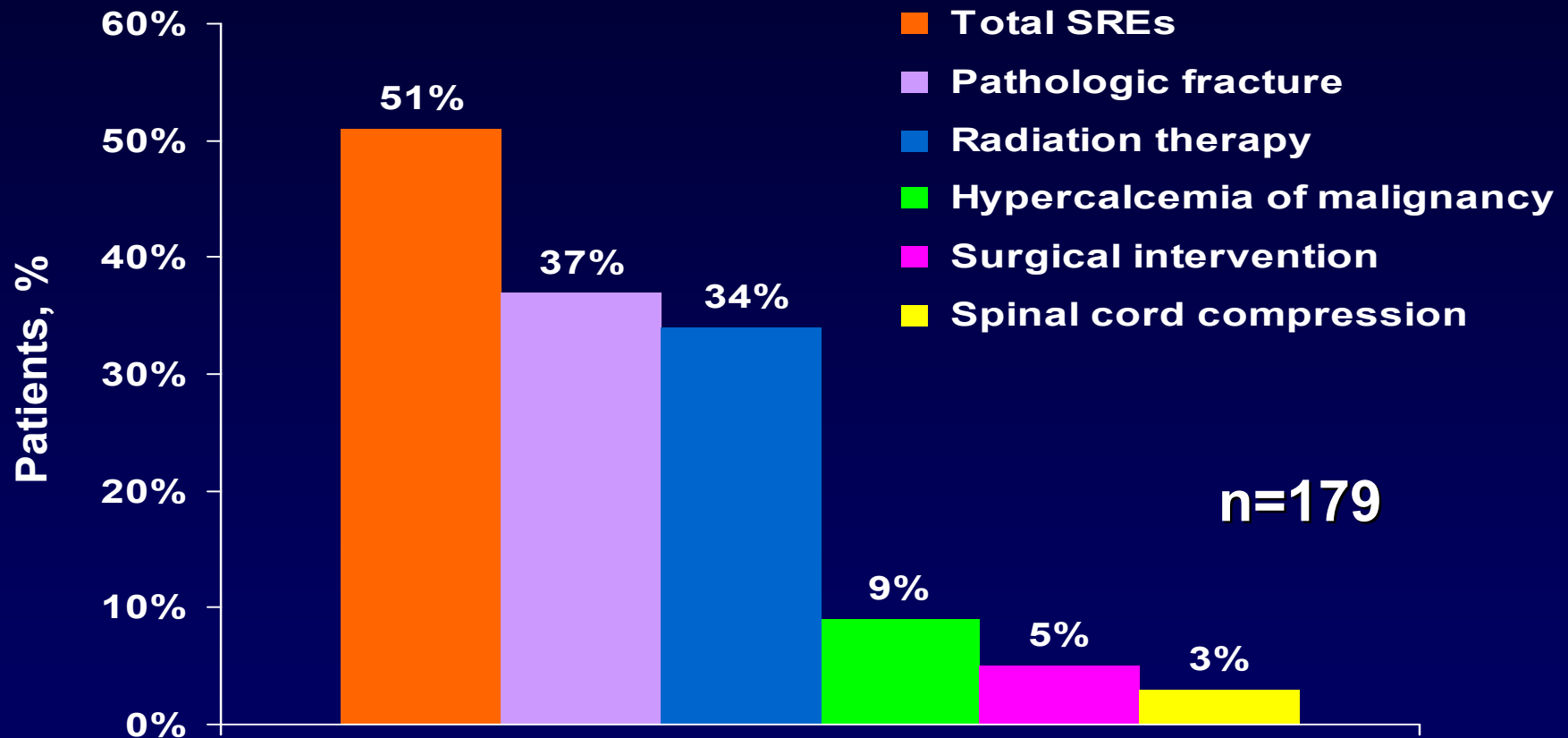
Bone Lesions Have Debilitating Consequences



Skeletal-Related Events (SREs)

- SREs include the following skeletal complications
 - Radiation for bone pain or to treat/prevent pathologic fractures or spinal cord compression
 - Pathologic fracture
 - Spinal cord compression
 - Surgery to bone
 - Hypercalcemia of malignancy (HCM)

Skeletal-Related Events Are a Serious Threat To Multiple Myeloma Patients*



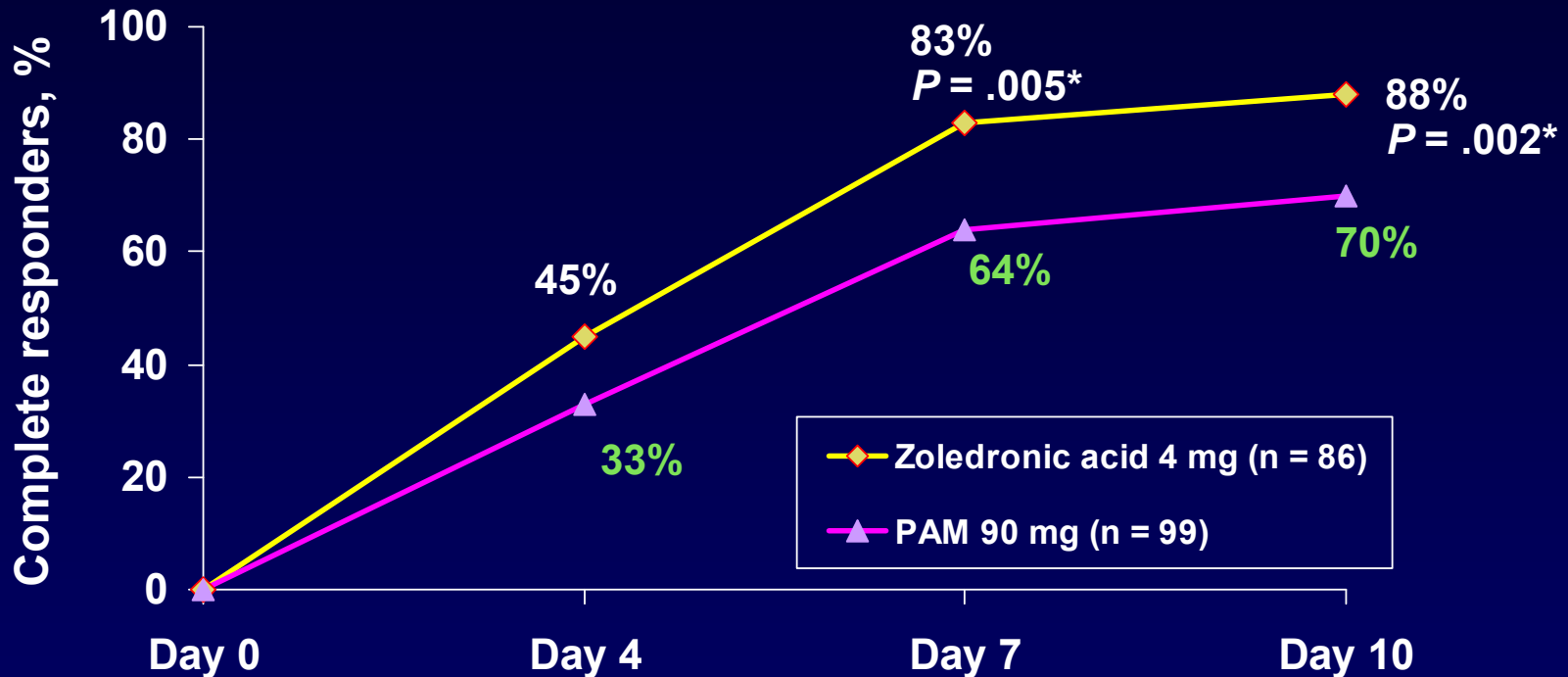
SRE = Skeletal-related event.

*21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.

The Goal of Therapy for Bone Lesions

- Preserve patient's functional independence and QOL by
 - Preventing skeletal-related events (SREs)
 - Prevent the **first** SRE
 - Delay the onset of the first SRE
 - Prevent the **recurrence** of SRE
 - Palliating and controlling bone pain
 - Reduce the need for analgesics and palliative radiotherapy

Zoledronic Acid Produced a Faster and Stronger Response Rate Than PAM for HCM

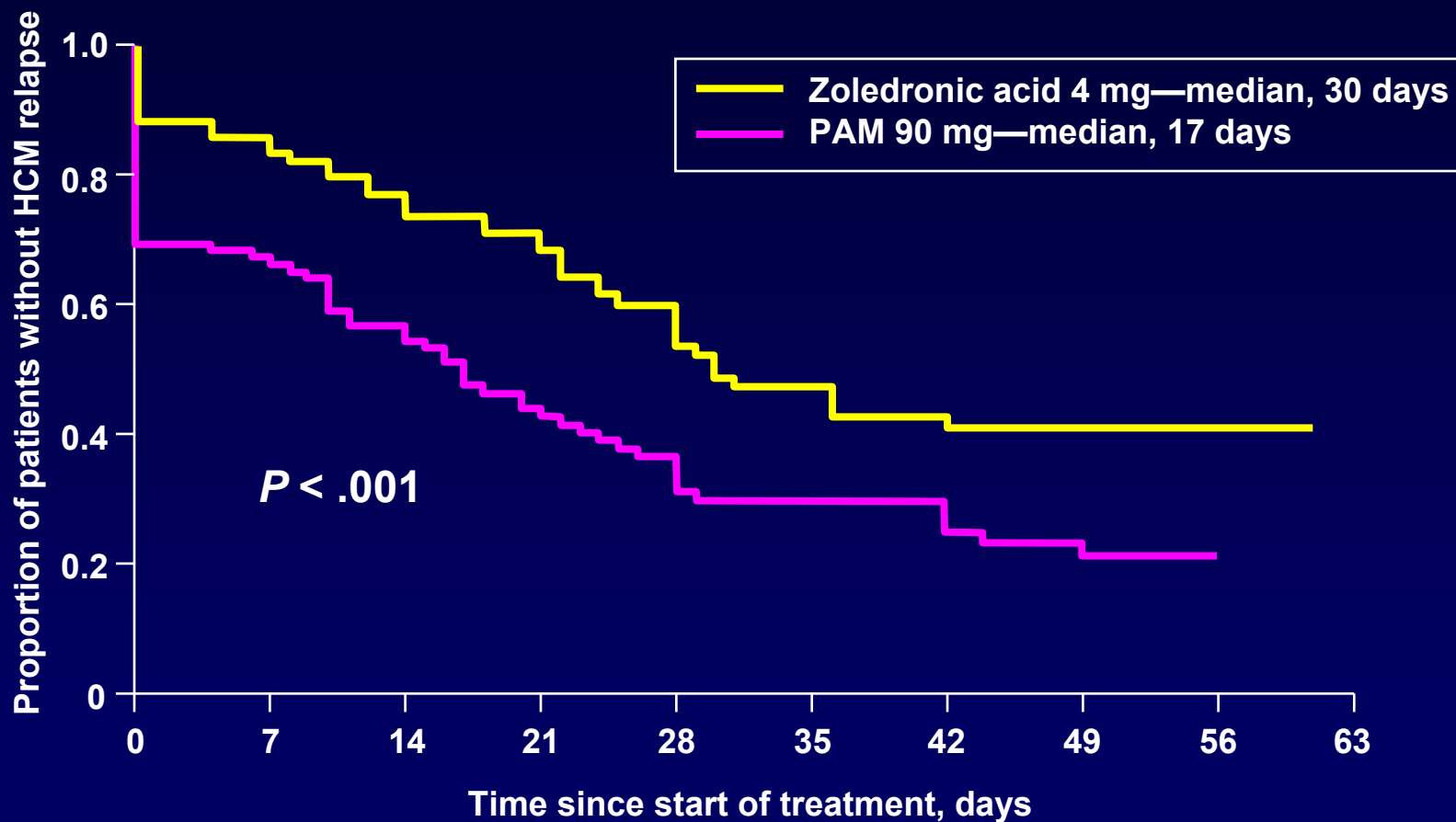


Pooled Protocols 036 and 037—complete response rate: normalization of corrected serum calcium ≤ 10.8 mg/dL (≤ 2.7 mmol/L)

PAM = Pamidronate.

*Denotes statistical significance versus pamidronate.

Zoledronic Acid Produced a Longer Time to Relapse Compared With PAM in HCM



Zoledronic Acid Was at Least as Efficacious as PAM in the Multiple Myeloma Stratum

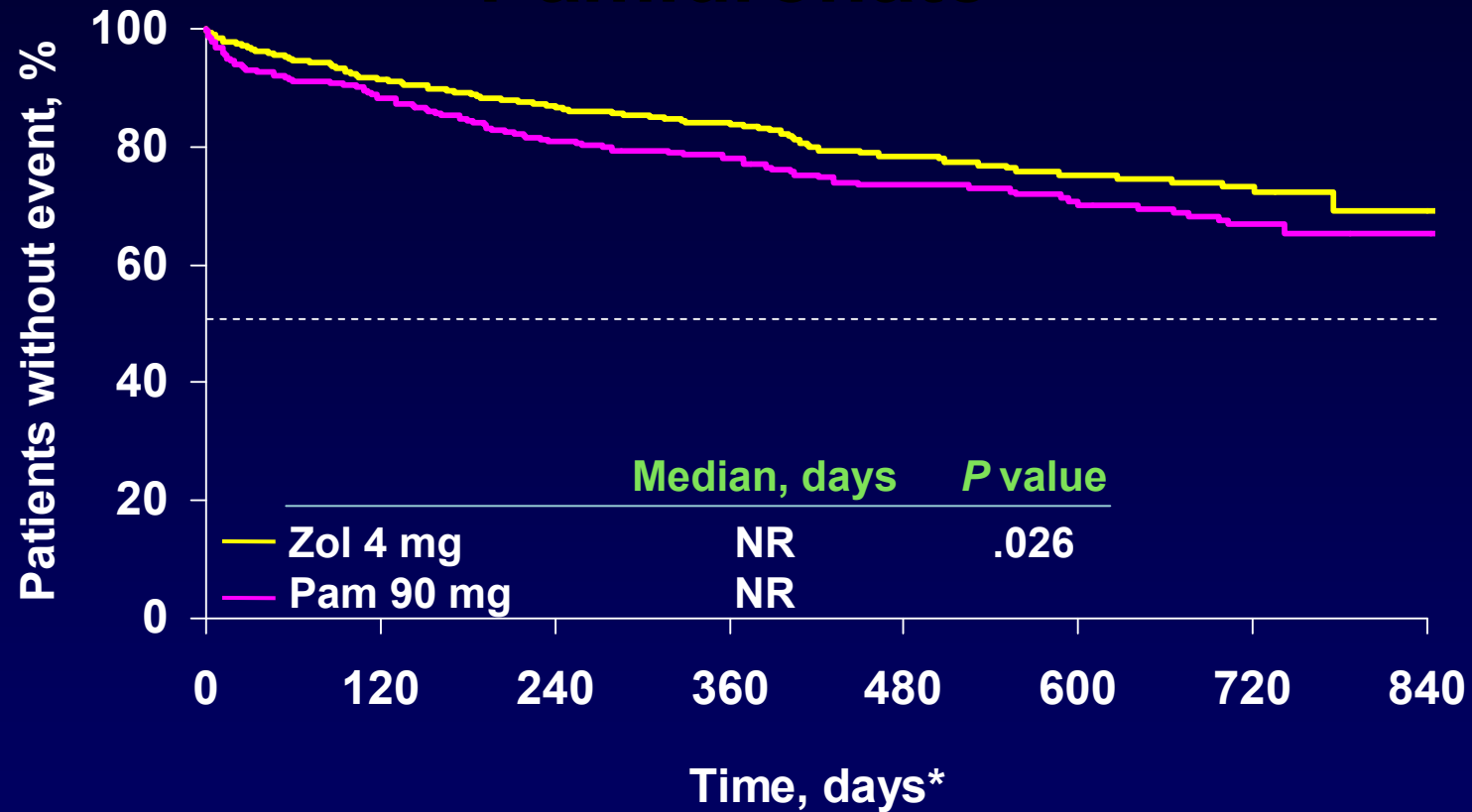
	Proportion with SRE, %*	Median time to SRE, days*	Multiple event analysis, risk ratio*
Zoledronic acid 4 mg	50	380	0.932
Pamidronate 90 mg	55	286	—
<i>P</i> value†	.368	.539	.593

*HCM is included as an SRE.

†Zoledronic acid 4 mg versus pamidronate.



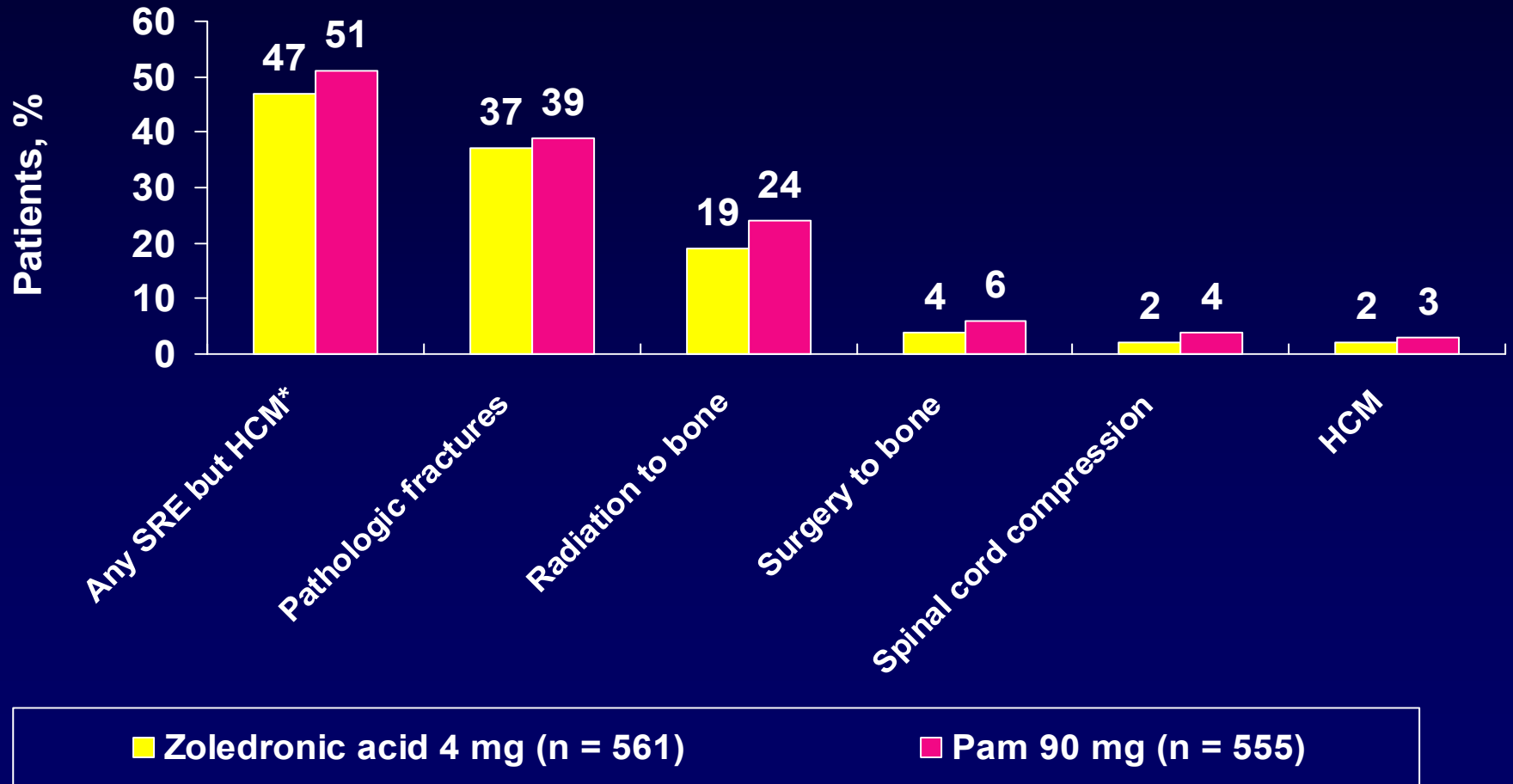
Zoledronic Acid Significantly Delayed Time to First Palliative Radiotherapy Versus Pamidronate



	0	120	240	360	480	600	720	840
Zol 4 mg	561	455	392	313	158	130	75	6
Pam 90 mg	555	448	347	276	150	124	67	6

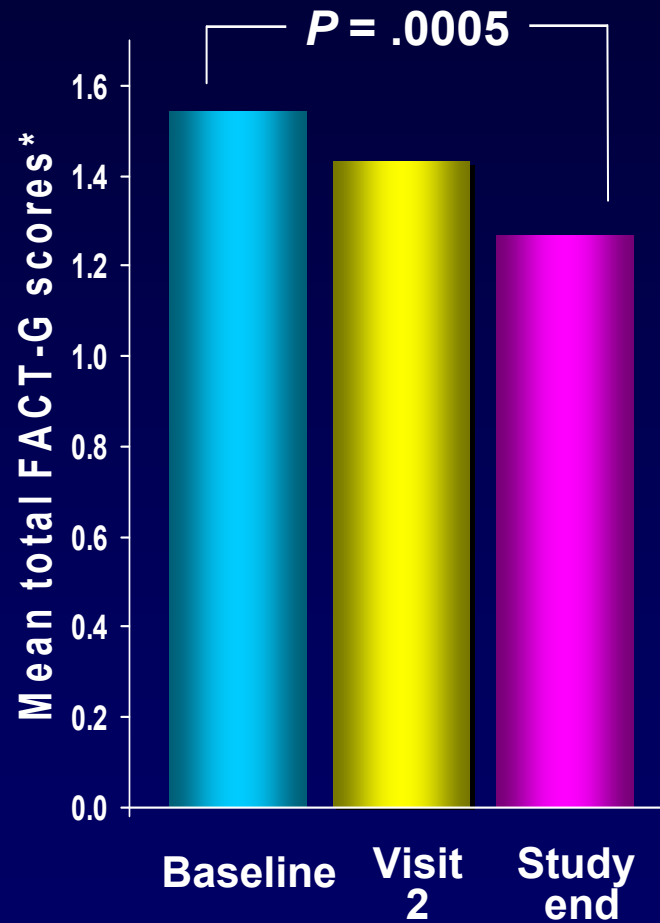
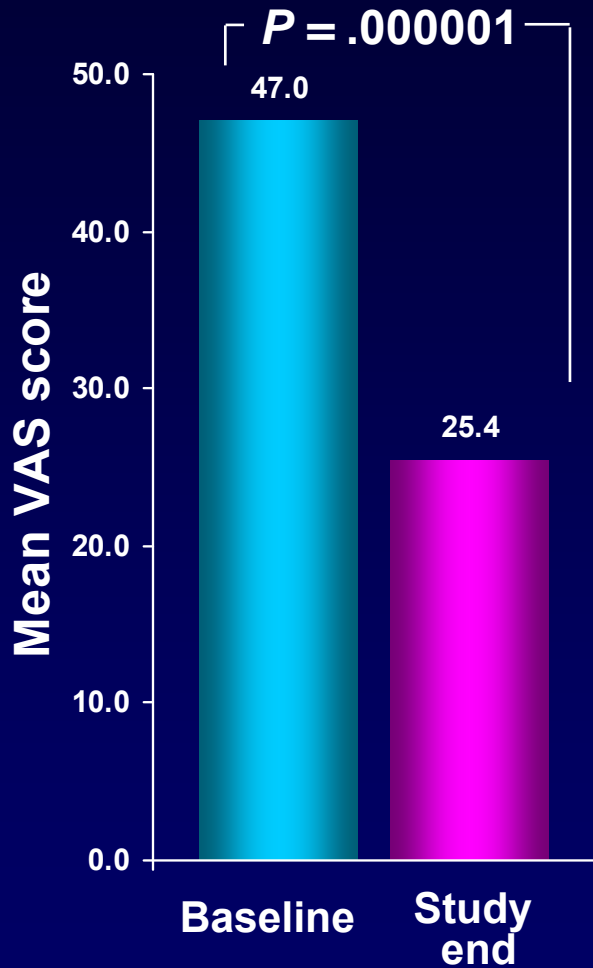
*After start of study drug.

Zoledronic Acid Consistently Reduced the Incidence of All Types of SREs



*Primary endpoint of trial.

Zoledronic Acid Significantly Improved Bone Pain and QOL in Patients With Multiple Myeloma

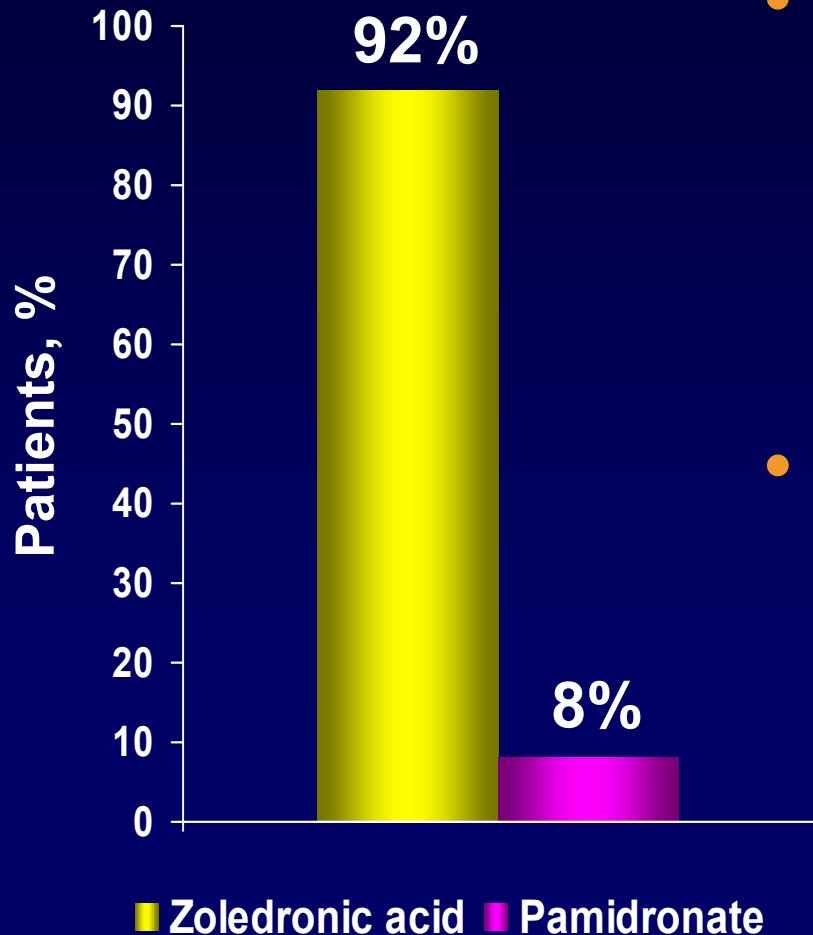


- ZOL significantly improved well-being

- Physical ($P < .001$)
- Emotional ($P < .002$)

*Lower FACT-G scores indicate improved quality of life.

92% of Patients Preferred Shorter Infusion Time of Zoledronic Acid Over That of PAM

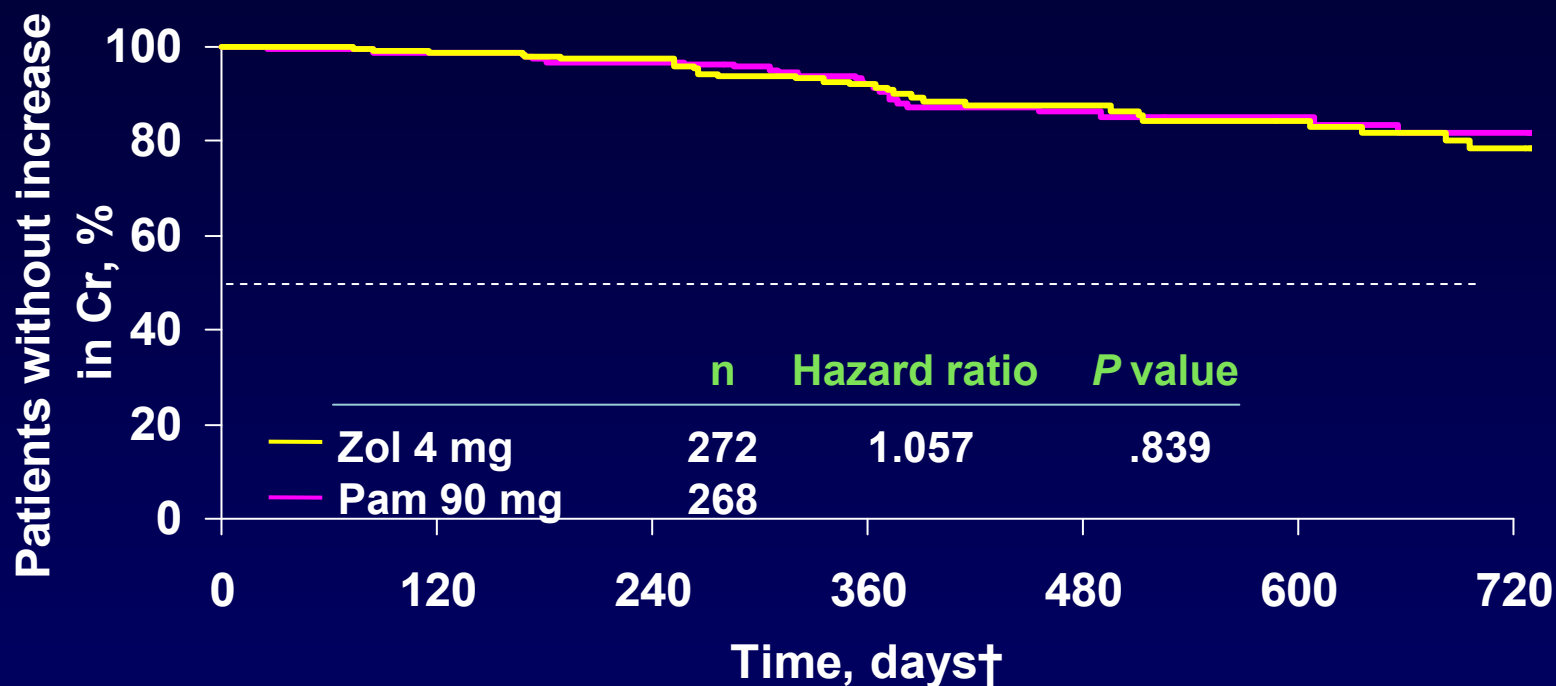


- Crossover study assessing patient preference of bisphosphonates (N = 184)
- Zoledronic acid was preferred because shorter infusions caused less disruptions in patients' daily activities

Bisphosphonates and Renal Insufficiency

- **IV bisphosphonates are cleared almost entirely by the kidneys**
- **2007 ASCO Multiple Myeloma Guidelines**
 - **In patients with pre-existing renal impairment (serum creatinine clearance 30-60 mL/min) should receive reduced dosage of zoledronic acid**
 - **No change in infusion time or interval of zoledronic acid is required**
- **Use of these bisphosphonates in patients with more severe renal dysfunction has been minimally assessed**

ZOL Infused over 15 min Compared to PAM Given over 2 hrs: Similar Time to First Serum Creatinine Increase in BC and MM



Zol 4 mg	272	226	197	152	81	68	30
Pam 90 mg	268	213	182	138	73	59	27

†After start of study drug.

Use of ZOL: Renal Considerations

- Monitor renal function prior to each dose
- Maintain hydration status
- If serum creatinine increases, resume therapy only after it returns to within 10% of baseline
- Dose adjustment in patients with mild to moderate renal dysfunction at baseline
- Infuse over no less than 15 minutes

Baseline CrCl, mL/min	Recommended ZOL dose, mg
>60	4.0 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3.0 mg

Osteonecrosis of the Jaw (ONJ) Clinical Presentation and Working Diagnosis

Clinical Features of Suspected ONJ*

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing

Working Diagnosis of ONJ

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

*Refer for appropriate dental evaluation and care as soon as possible.

Signs and Symptoms of Suspected ONJ

- **Signs**

- Rough area on the jawbone
- Soft tissue swelling, drainage, or infection
- Exposed bone in the oral cavity
- Sudden change in the health of periodontal tissue
- Failure of oral mucosa to heal
- Loosening of teeth

- **Symptoms**

- “Heavy jaw,” a dull aching sensation
- Numbness/Tingling of the jaw
- Oral pain

Frequency of ONJ in Malignant Bone Disease: Prior to Implementation of Prevention Strategies

STUDY	Study type	Pts treated w BP, n	Pts w Suspect or Proven ONJ, n	Frequency, %
Hoff et al MDACC JBMR 2008	Chart review	4,019	34	0.8%
Durie et al	Web-based survey	1,203	152	12.6%
Pozzi et al Italian Multicenter study	Chart review	888	16	1.8%
Badros et al	Chart review/observational	340	11	3.2%
Tosi et al Analysis of Bologna 2002 trial	Retrospective review of trial database	259	9	3.5%
Zervas et al	Observational	254	28	11%
Dimopoulos et al	Chart review	202	15	7.4%
Cafro et al	Chart review	118	14	11.9%
Berenson et al.	Chart review	100	10	10.0%

Managing patients with ONJ

- **Diagnosis — get someone who knows the entity to evaluate pt**
- **Assess its severity — it takes on a wide spectrum!**
- **Maintain excellent dental hygiene & regular exams**
- **Avoid surgical intervention**
- **No standard treatment**
 - **Antibacterial & antifungal rinses (chlorhexidine gluconate & Nystatin)**
 - **Systemic oral antibacterial, antiviral & antifungal treatments have been used**
- **Hyperbaric oxygen has not proven useful**
- **Discontinuing IV BPs: no evidence that it is necessary or changes the course of ONJ**

AAOMS Recommendations: ONJ Is Treatable in the Majority of Patients

Stage	Symptoms	Recommended treatment
1	Exposed/Necrotic bone in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none">• Antibacterial mouth rinse• Quarterly clinical follow-up• Patient education
2	Exposed/Necrotic bone associated with infection (ie, pain and erythema in the region of exposed bone)	<ul style="list-style-type: none">• Symptomatic treatment w broad-spectrum antibiotics• Antibacterial mouth rinse• Pain control• Superficial debridements to relieve soft-tissue irritation
3	Stage 2 symptoms + 1 or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending into the inferior border	<ul style="list-style-type: none">• Antibacterial mouth rinse• Antibiotic therapy• Pain control• Surgical debridement/resection for longer-term palliation

Minimizing the Risk of ONJ : Preventive Measures

- **Excellent oral hygiene — the best prophylaxis**
- **Limit alcohol & tobacco use**
- **Pts should have a dental assessment before starting BPs**
 - **Any necessary dental procedures should be completed prior to starting IV BPs if possible**
- **Avoid dental surgery after BP therapy has started**

Retrospective Analyses: Preventive Measures Can Reduce Incidence of ONJ in Multiple Myeloma

- ONJ incidence was compared between patients before and after the implementation of preventive measures before zoledronic acid therapy (N = 128)¹

	ONJ Incidence	P value
Preventive measures	2%	< .001
No preventive measures	23%	

Incidence rate ratio = 4.758 P=0.0293

- Antibiotic prophylaxis before dental procedures reduced the incidence of ONJ ($P = .007$)²

IV BPs Benefit: Risk Summary

- ZOL has demonstrated meaningful clinical benefits in pts with myeloma bone disease
 - Treatment benefits outweigh risk
 - Improvements in survival and disease progression are being investigated in clinical trials
- Proactive monitoring of renal and oral health recommended to ensure patient safety and comfort
- Ongoing clinical trials are evaluating dosing schedules for BPs to further optimize their benefit/risk ratios