

# **Treatment of Myeloma Bone Disease**

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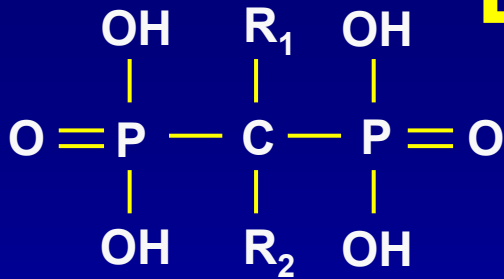
**Los Angeles, CA**

# Clinical Consequences of Myeloma Bone Disease

- **Pathological fractures**
  - Non-vertebral
  - Vertebral compression
- **Spinal cord compression/collapse**
- **Radiation therapy**
- **Surgery to bone**
- **Hypercalcemia**
- **Bone pain**
- **Use of analgesics**
- **Quality-of-life effects**
- **Survival**






# Bisphosphonates



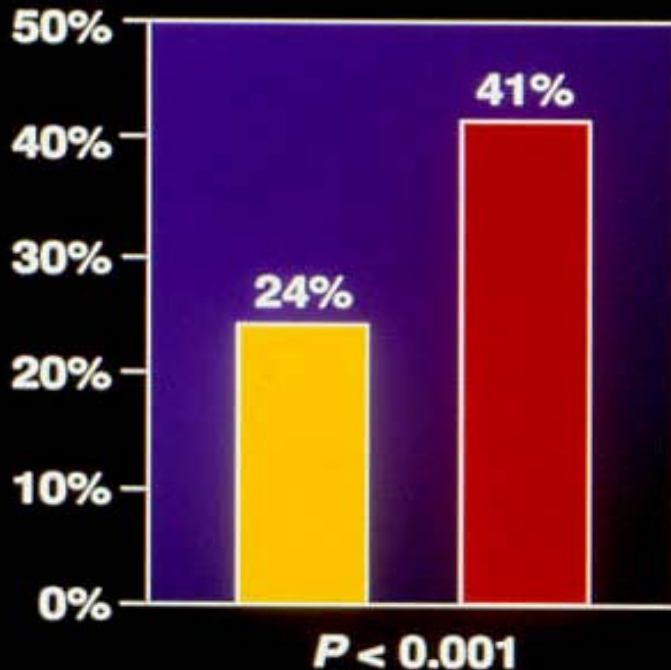
- inhibitors of bone loss

- potency varies greatly depending upon R1 & R2 side chains

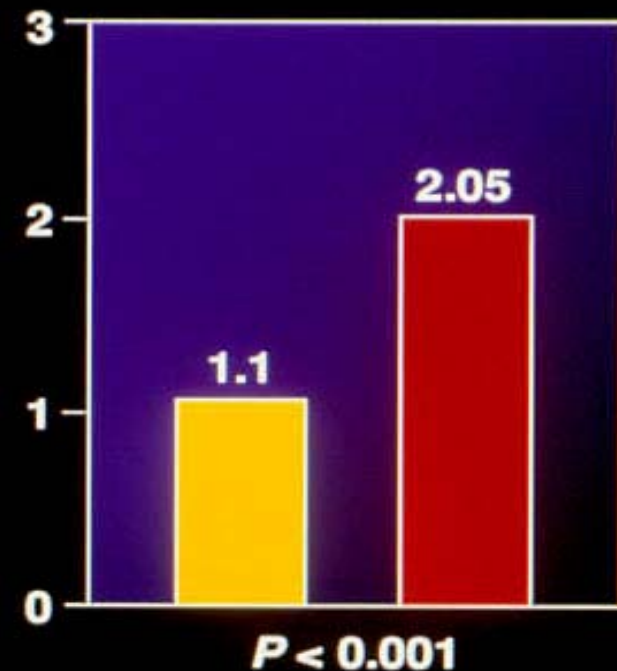
	R <sub>1</sub>	R <sub>2</sub>	Relative potency	
Etidronate	OH	-CH <sub>3</sub>	} <b>no N</b>	1
Clodronate	Cl	-Cl		10
Tiludronate	H	-S-  -Cl		10
Pamidronate	OH	-(CH <sub>2</sub> ) <sub>2</sub> -NH <sub>2</sub>	} <b>N</b>	100
Alendronate	OH	-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>		1,000
Risedronate	H	-CH <sub>2</sub> -  <sup>N</sup>		5,000
Ibandronate	OH	(CH <sub>2</sub> ) <sub>2</sub> -N-(CH <sub>2</sub> ) <sub>4</sub> -CH <sub>3</sub>   CH <sub>3</sub>		10,000
Zoledronic acid	OH	-N  <sup>N</sup>		100,000

# Effect of Monthly Intravenous Pamidronate (90 mg) in Reducing Skeletal Events in Patients with Advanced Multiple Myeloma: A Phase III Trial

Proportion of patients with skeletal events at 9 months



Skeletal morbidity rate (events/year) at 9 months



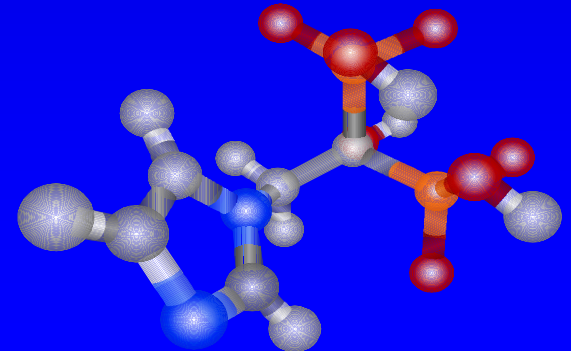
■ Pamidronate     ■ Placebo

# Zoledronic Acid



- Zoledronic acid belongs to a new class of highly potent bisphosphonates<sup>1,2</sup>
- Heterocyclic, nitrogen-containing bisphosphonate composed of:
  - A core bisphosphonate moiety
  - An imidazole-ring side chain containing 2 critically positioned nitrogen atoms

1. Green J, et al. *J Bone Miner Res.* 1994.
2. Green J, et al. *Pharmacol Toxicol.* 1997.



# **Zoledronic Acid in Multiple Myeloma and Breast Cancer Patients: Protocol 010 Trial Design**

- **24-mo dosing regimen**
  - Pamidronate 90 mg every 3 to 4 wk/  
120-min infusion
  - ZOMETA<sup>®</sup> 4 mg and 8/4 mg every 3 to 4 wk/  
5-min amended to 15-min infusion
  - Double-blind, double-dummy
- **Study duration: 25 mo**
- **Patients received oral vitamin D 400 IU  
and calcium 500 mg**

# Breast Cancer and Multiple Myeloma

## Efficacy Summary

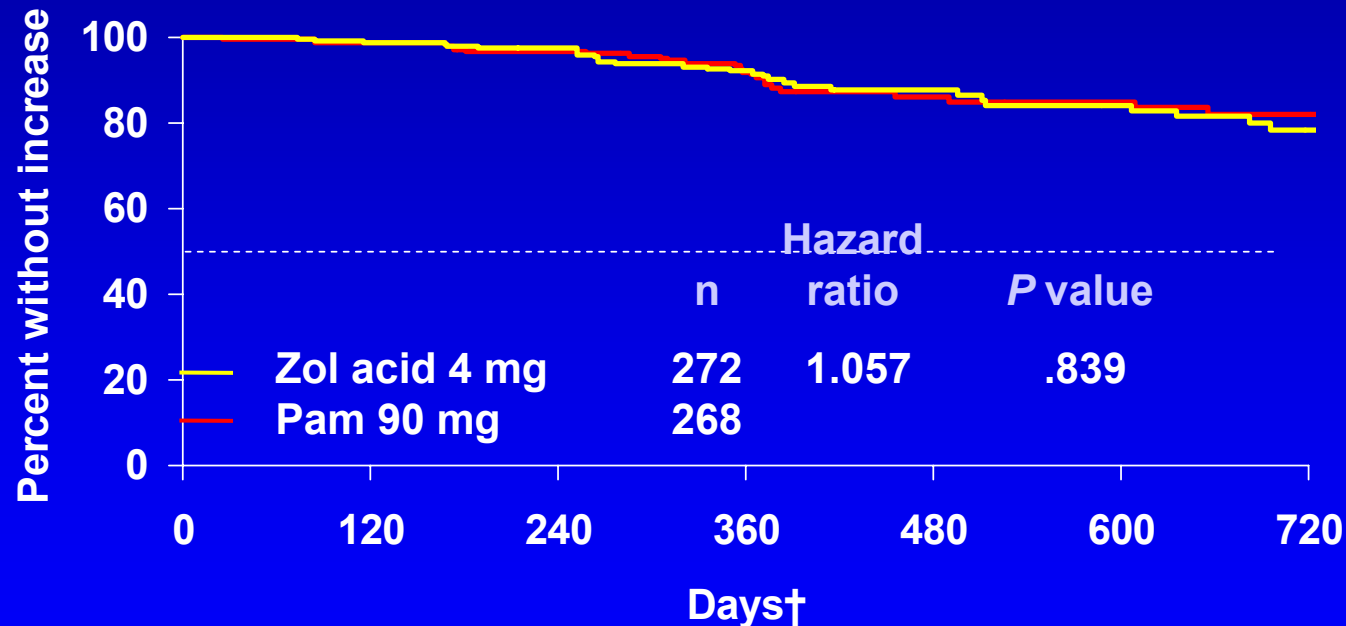
	Proportion with SRE, %	Time to first SRE (median)*	Mean skeletal morbidity rate*	Multiple-event analysis hazard ratio*
Zol acid 4 mg	47	376	1.04	0.841
Pam 90 mg	51	356	1.39	—
<i>P</i> value	.243	.151	.084	.030

\*Hypercalcemia of malignancy is included as a skeletal-related event.

# Breast Cancer and Multiple Myeloma

## Estimates of First Serum Creatinine Increase\*

Zoledronic acid 4 mg infused over 15 min has a renal safety profile comparable to pamidronate 90 mg infused over 120 min



\*Post 15-minute infusion amendment.

†After start of study drug.

# **Bisphosphonates: Anti-Tumor Effects in MM**

- **Pre-clinical**

- **Direct**

- **Indirect**

- **Immune effects**

- **Reduce myeloma tumor burden in murine models**

- **Clinical data**

- **Subsets in trials (w/ other anti-myeloma therapy)**

- **Anecdotal clinical reports w/ BPs alone**

# Predictive Value of Bone-Specific Alkaline Phosphatase (BALP)

- BALP is a bone formation marker that has been significantly correlated with bone pain, bone lesions, and fractures in untreated patients with multiple myeloma<sup>1</sup>
- Recent trials have shown that patients with elevated BALP levels during treatment are at significantly higher risk for negative clinical outcomes relative to patients with normal BALP levels<sup>2</sup>

1. Fonseca R, et al. *Br J Haematol*. 2000;109:24-29.

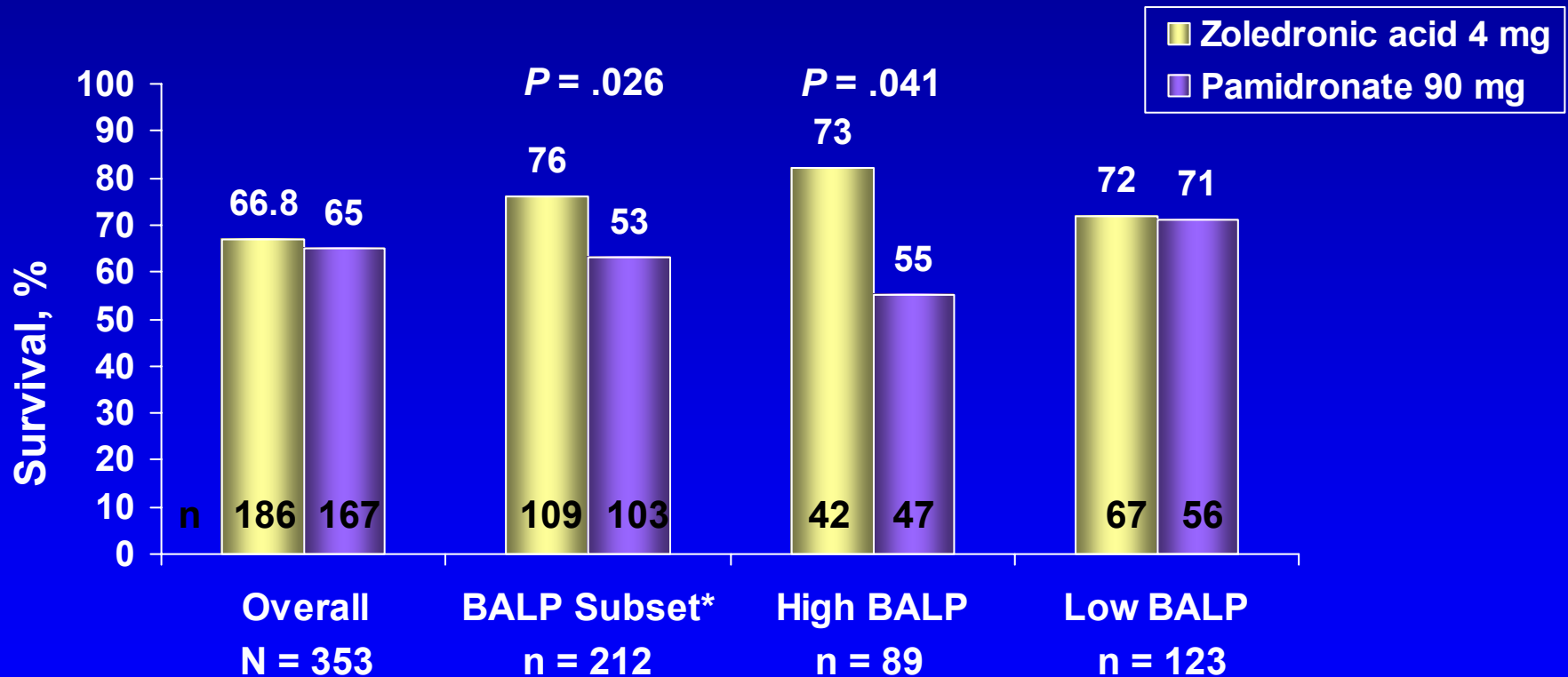
2. Coleman RE, et al. *J Clin Oncol*. 2005;23:4925-4935.

# **Survival in Patients with Multiple Myeloma Receiving Zoledronic Acid Compared to Pamidronate: Stratification by Baseline Bone Alkaline Phosphatase (BALP) Levels**

- **In a retrospective analysis of MM pts enrolled on Protocol 010, myeloma patients were stratified by BALP levels at baseline**
  - **High (BALP  $\geq$  146 IU/L**
  - **Low BALP  $<$  146 IU/L**
- **Survival analysis assessed using Cox regression model**

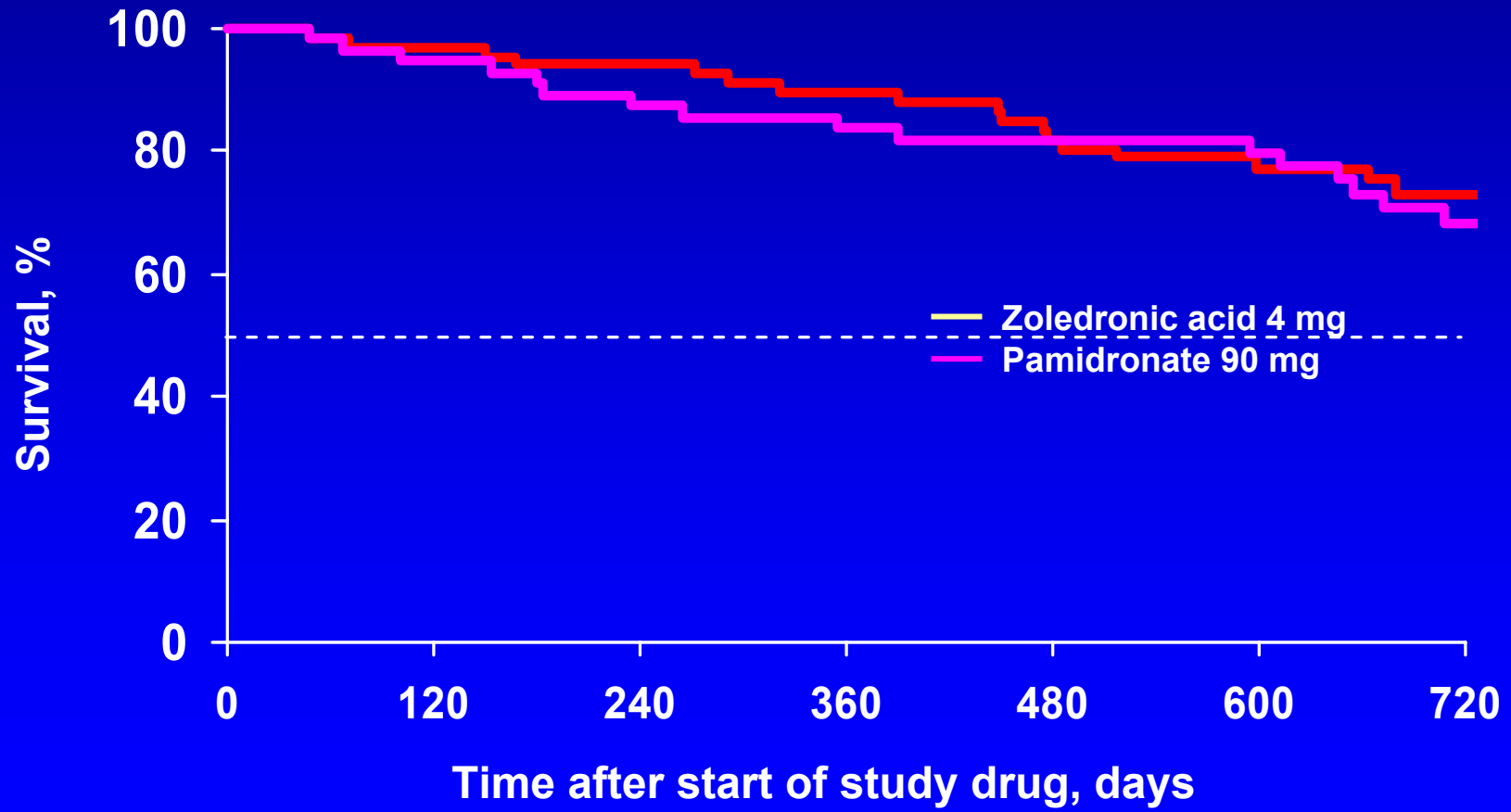
# Zoledronic Acid May Improve Survival Compared with Pamidronate in MM Patients with High BALP

Survival rate at 25 months



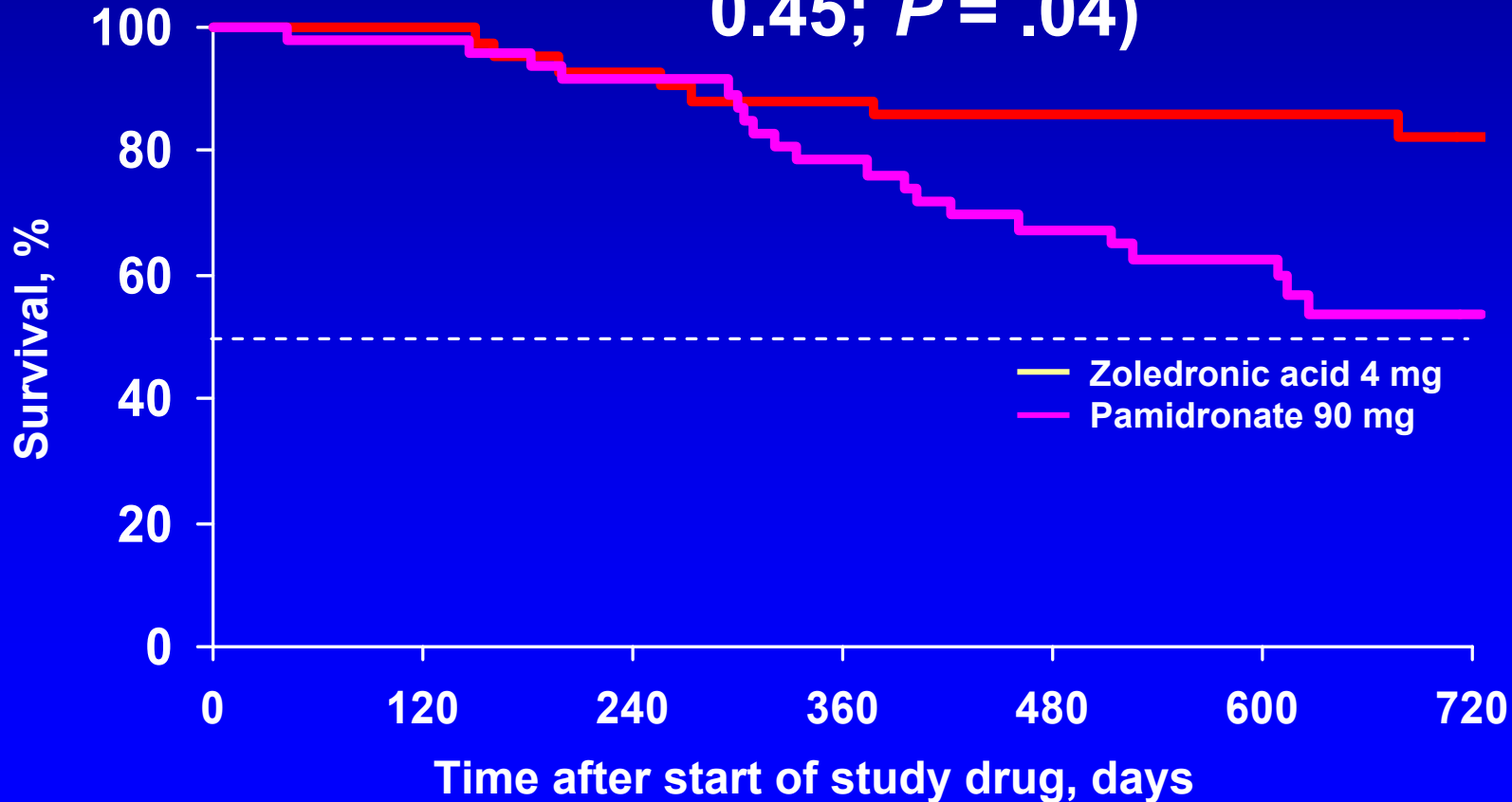
\*Multiple myeloma patients with information on baseline BALP levels and at least 1 postbaseline safety evaluation.

# Kaplan-Meier Estimates of Time to Death by Treatment Group Stratum: Low BALP



# Kaplan-Meier Estimates of Time to Death by Treatment Group Stratum: High BALP

Zoledronic acid reduced risk of death by 55% (HR = 0.45;  $P = .04$ )



# Multivariate Analysis Shows Significant Reductions in Risk of Death Among Patients Treated with Zoledronic Acid Compared to Pamidronate

	Univariate analysis		Multivariate analysis*	
	Hazard Ratio	<i>P</i> value	Hazard Ratio	<i>P</i> value
Evaluable patients† (n = 212)	0.58	.03	0.57	.03
High BALP (n = 89)	0.45	.04	0.43	.03
Low BALP (n = 123)	0.69	.25	0.72	.32

\*Additional risk factors included in multivariate model include previous SRE and baseline ECOG status.

†Multiple myeloma patients with information on baseline BALP levels and at least 1 postbaseline safety evaluation.

# Survival in patients with multiple myeloma receiving zoledronic acid: stratification by baseline bone alkaline phosphatase levels

## Conclusions

- High baseline BALP levels are significantly correlated with increased risk of SREs in multiple myeloma patients
- Zoledronic acid significantly improved survival compared with pamidronate in the subset of multiple myeloma patients with high BALP
  - Reduced risk of death by 55% ( $P = .04$ )
  - Increased survival rate at 25 months (82% vs 53%;  $P = .041$ )

# Bisphosphonates: Side Effects

- Oral: GI intolerance (in up to 1/3<sup>rd</sup> of pts) especially esophagitis & esophageal ulcers
- Intravenous (pamidronate or zoledronic acid)
  - Flu-like symptoms (fever, myalgias, arthralgias)
    - Occurs usually 12-48 hrs following the infusion
    - Lasts 6-24 hrs
    - Occurs in a minority of pts (10-20%)
    - Not observed w/ continued dosing
    - Similar frequency w/ different drugs
    - Steroids may help reduce risk & intensity
- Ocular effects
- Anemia
- Renal dysfunction
- Osteonecrosis of the jaw (ONJ)

# Kidney Function and the Use of Bisphosphonates (BPs)

- Changes in kidney function are related to Cmax
  - i.e. the highest level of BP is in the blood
    - As a result, rate of infusion is the key factor in prevention of kidney problems
      - Rates faster than 0.3-0.7 mg/min are associated w/ problems
- Importantly, rate of infusion has no impact on its ability to prevent skeletal complications
  - Efficacy related to AUC (how much remains in patient)
- Zoledronic acid and pamidronate affect different parts of the kidney
  - Zoledronic acid- tubular
  - Pamidronate- glomerular

***Thus, if a renal issue occurs w/ zoledronic acid or pamidronate, you can try the other BP***

# Kidney Function and the Use of Bisphosphonates (BPs)

- *Since kidney deleterious effects occur at similar rates of infusion (mg/min) among different BPs, more potent BPs such as zoledronic acid (4 mg) can be given safely much more rapidly (over 15 min) than weaker BPs such as pamidronate (90 mg) ( $\geq 2$  hrs)*
- *Small changes in dose (as recommended for zoledronic acid based on creatinine clearance) make little sense when infusion time is the factor that determines renal risk*

# Use of BPs for Patients w/ Renal Dysfunction

- If serum creatinine < 3 mg/dL, no reason to change dose, infusion time or schedule is required
- Use among patients with worse function minimally assessed
  - Pamidronate (Berenson et al. J Clin Pharmacol 1997)
  - Zoledronic acid (ongoing studies)
- However, if on dialysis (irreversibly), may use either zoledronic acid at same dose, infusion time & interval
- If renal dysfunction reverses w/ anti-MM Rx, IV BPs may be initiated
- If hypercalcemia, use zoledronic acid even w/ renal dysfunction

# Osteonecrosis of the Jaw Is an Emerging Issue in Patients Taking Long Term Bisphosphonates



# **What factors may contribute to ONJ in cancer pts receiving IV BPs?**

- **Inhibition of osteoclast function and remodeling of bone (poor repair of bone)**
- **High level of bacteria in the oral cavity (increases risk of infection & inflammation)**
- **Embryologic origin of jaw- different type of bone**
- **Constant trauma on jaw (chewing)**
- **Anti-angiogenesis effects of BPs**
  - **Poor vascularization of areas treated w/ BPs**

# Incidence of ONJ\*

- **Preliminary MSKCC study w/ IV BPs**
  - 0.6% of breast CA pts
- **Second larger MSKCC study**
  - 1.2% of breast CA pts
  - 4.5% of MM pts
- **Web-based survey (no confirmation of ONJ)**
  - 4.3% (13/299) of breast CA pts
  - 6.9% (62/904) of MM pts
- **Prospective Greek study**
  - 2.9% of breast CA pts
  - 9.9% of MM pts
  - 6.5% of prostate CA pts
- **Single institutional Greek study of 202 MM pts**
  - 7.4%

\*among pts who have received IV BPs

# Relative Risk Factors for ONJ

- **Cancer**
- **Radiation Therapy**
- **Corticosteroids**
- **Poor dental hygiene**
- **Poor diet**
- **Dental work**
- **Trauma**
- **EtOH or tobacco use**
- **Coagulopathy**
- **Chemotherapy**
- **Infection**
- **Bisphosphonates**

# Minimizing the Risk of ONJ

- **Excellent oral hygiene is the best prophylaxis**
- **Limit EtOH & tobacco use**
- **Pts who are starting IV BPs should have a dental assessment first**
- **Dental procedures (extensive)**
  - **should be done prior to starting IV BPs**
  - **avoid once start IV BPs**
  - **If necessary, hold IV BPs Rx before (2 mo) and following (2 mo) surgery**

# Managing ONJ

- **Make a diagnosis**
  - i.e.- get someone to evaluate who knows the entity
- **Assess its severity**
  - it takes on a wide spectrum!
- **Maintain excellent dental hygiene**
- **Keep surgical intervention to a minimum**
- **There is no standard treatment**
  - Antibacterial & antifungal rinses (chlorhexidine gluconate & nystatin)
  - Systemic oral antibacterial, antiviral & antifungal treatments have been used
- **Hyperbaric oxygen has not generally proven useful**
  - However, anecdotal reports of benefit
- **No evidence that discontinuing IV BPs is necessary or changes the course of ONJ**

# Mayo Clinic Consensus Statement for the use of Bisphosphonates in Multiple Myeloma<sup>1</sup>

- **IV bisphosphonates are**
  - indicated for pts w/ lytic disease
  - reasonable to use for pts w/ osteopenia or osteoporosis but w/o lytic disease
  - not to be used for pts w/ smoldering disease

**These recommendations are consistent  
w/ the ASCO guidelines<sup>2</sup>**

<sup>1</sup>Lacy et al. Mayo Clin Proc 2006

<sup>2</sup>Berenson et al. J Clin Oncol 2002

# Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma<sup>1</sup>

- **Recommend**
  - IV BPs monthly for only 2 yrs among pts in plateau phase
  - only continue for pts that require active treatment but change the frequency to every 3 months
- **Basis for recommendation**
  - Duration of randomized trials completed w/ zoledronic acid and pamidronate were only 2 y
  - Long elimination half-life of BP in bone (> 300 d)
  - Risk of ONJ

**These recommendations are not consistent w/ the ASCO guidelines<sup>2</sup>**

<sup>1</sup>Lacy et al. Mayo Clin Proc 2006

<sup>2</sup>Berenson et al. J Clin Oncol 2002

# Discontinuing IV BPs after 2 years of Treatment for MM Patients is Likely to Put Patients at High Risk

- Benefits of IV BPs demonstrated among MM pts regardless of clinical status
- Discontinuation of oral BPs after several years of chronic use for osteoporosis leads to ongoing bone loss & fracture risk compared to pts that continue the drugs
- Rate of bone loss much more rapid in patients with MM than among pts w/ osteoporosis

***Thus, one would expect to see clinical deleterious effects of discontinuing IV BPs much more rapidly than in osteoporotic pts***

# Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma<sup>1</sup>

- **Recommend**

- **Pamidronate over zoledronic acid based on**
  - **No difference in reducing skeletal complications**
  - **Higher risk of ONJ w/ zoledronic acid compared to pamidronate**

**These recommendations are not consistent w/ the ASCO guidelines<sup>2</sup>**

<sup>1</sup>Lacy et al. Mayo Clin Proc 2006

<sup>2</sup>Berenson et al. J Clin Oncol 2002

# Limitations of the Data on ONJ Risk in MM Patients Treated with IV BP

- **Mostly retrospective**
- **Web-based surveys**
- **Diagnosis not confirmed**
- **Time to event biased by time ZOL vs PAM has been available**
- **Recognition of ONJ in BP-treated pts made in post-ZOL era (little use of PAM)**
  - **Heightened sense of awareness of dental issues**
  - **New drugs used in MM pts**

# IV Bisphosphonates for Patients With Myeloma Bone Disease— Benefits vs Risks

## Benefits

- ↓ Fractures
- ↓ Radiotherapy
- ↓ Bone pain



Humeral fracture in  
a myeloma patient

## Risks

- ONJ ?
- Renal  
(infrequent)