

Multiple Myeloma: Use of Bisphosphonates

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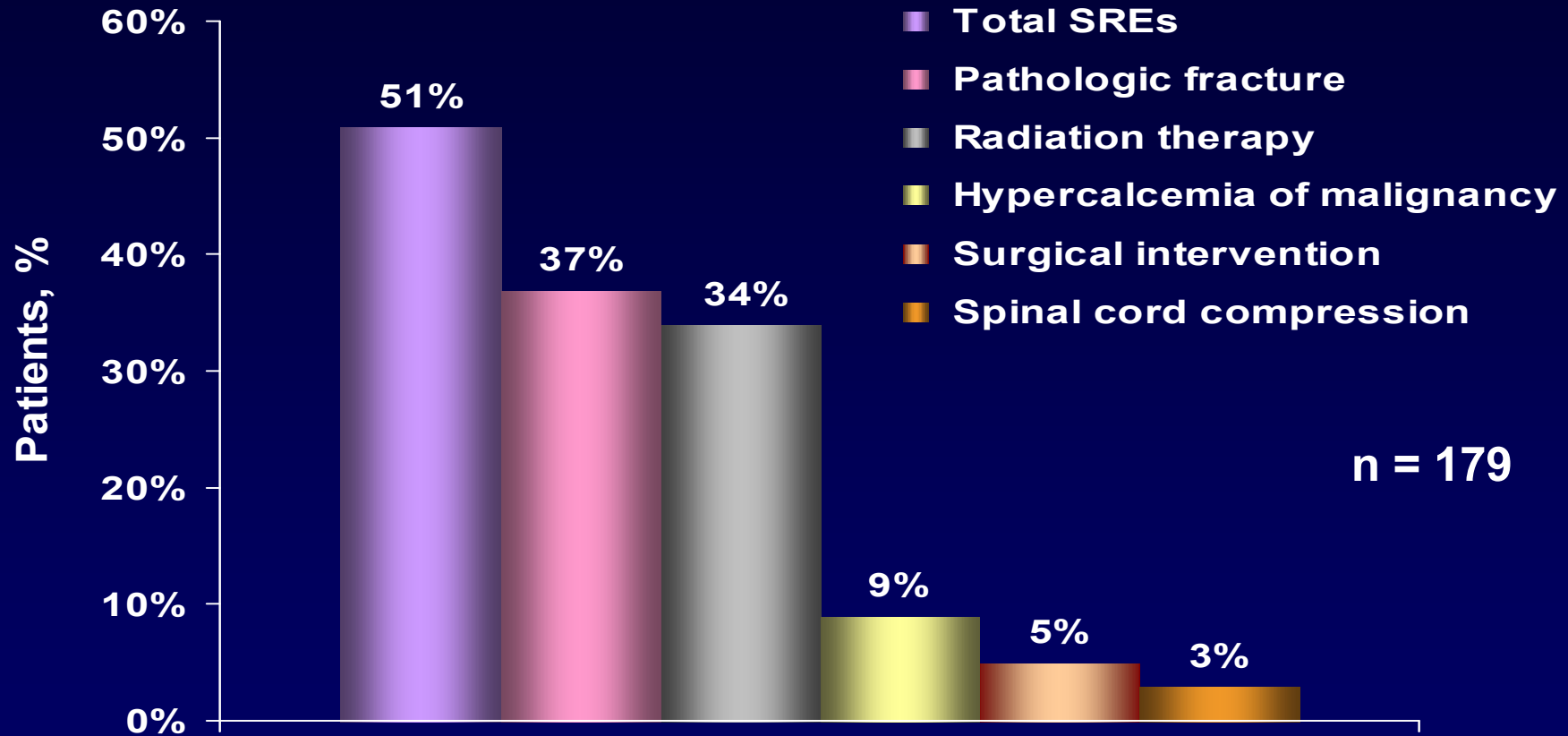
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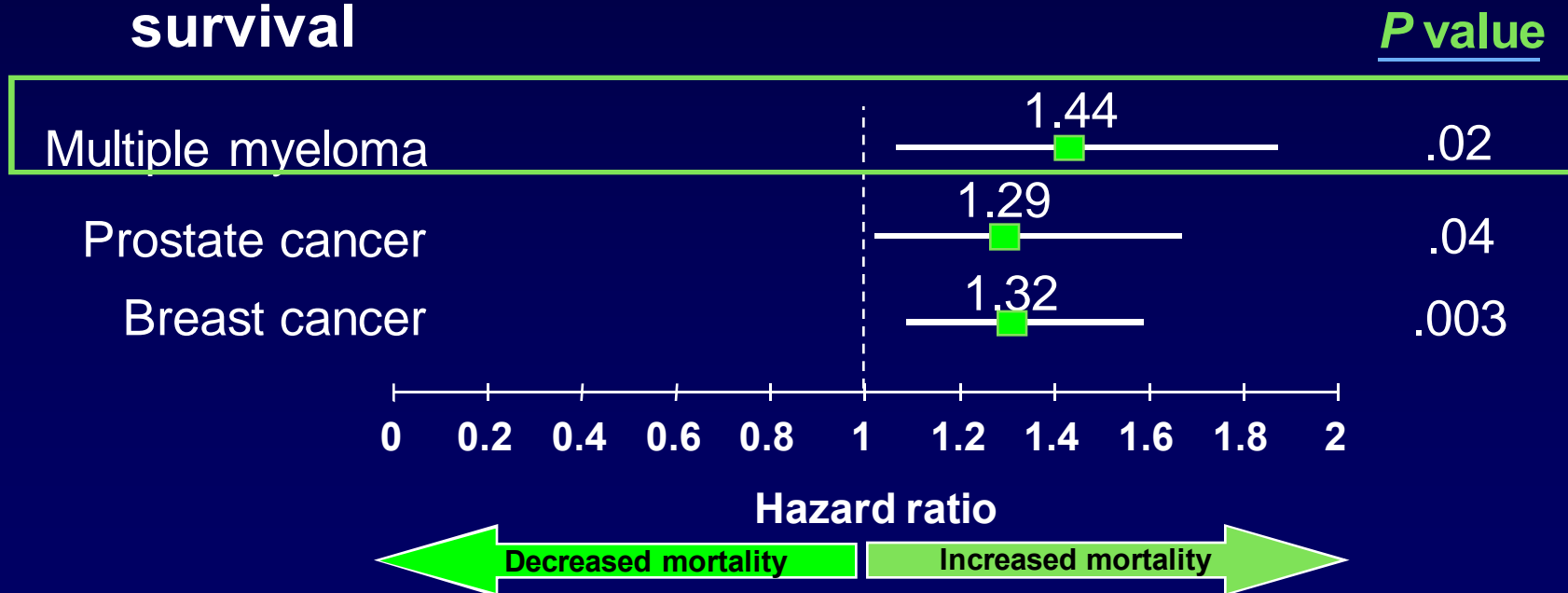
Skeletal-Related Events (SREs) In Myeloma Patients*



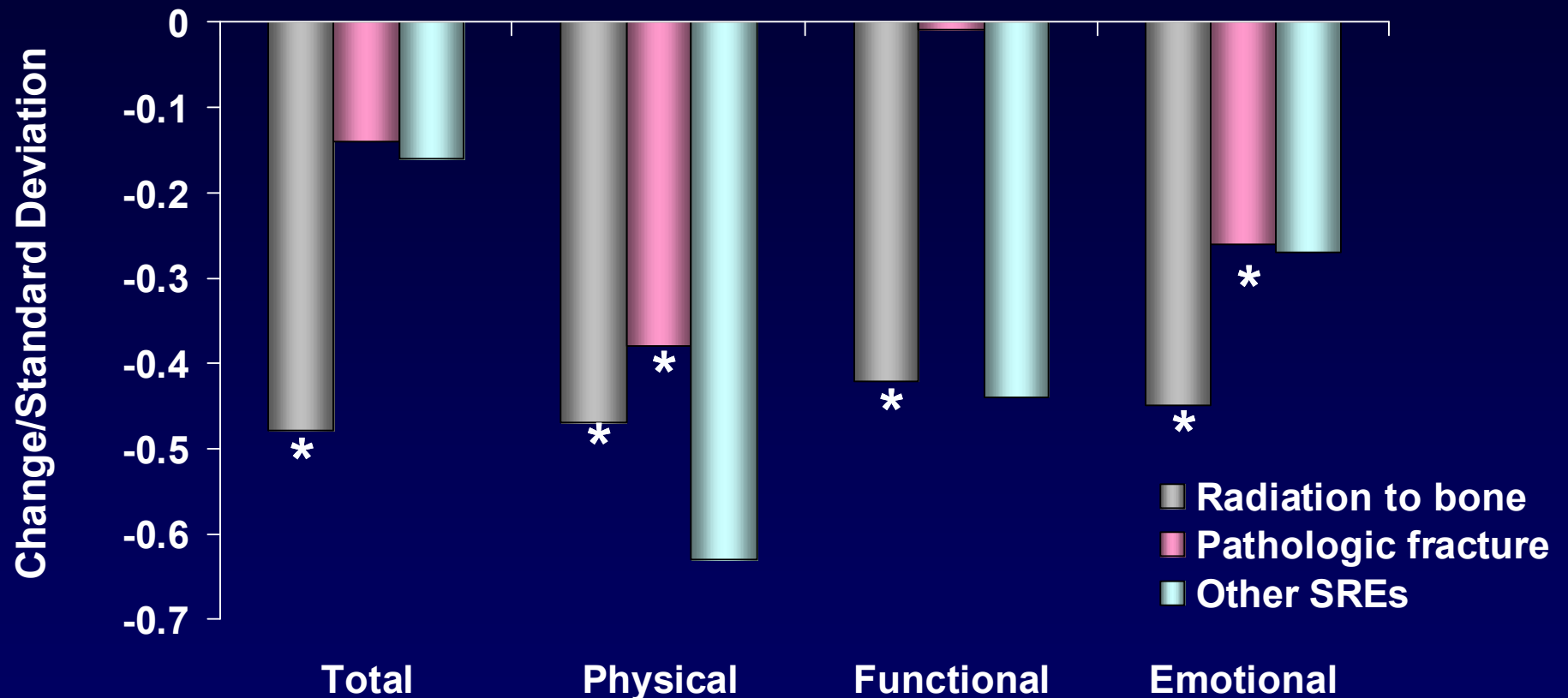
*21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.

Early Treatment to Prevent SREs Is Important Because...

- Patients who experience a first SRE are 2-fold more likely to experience subsequent SREs
- Pathologic fractures are associated with reduced survival



Skeletal Complications Reduce Quality of Life

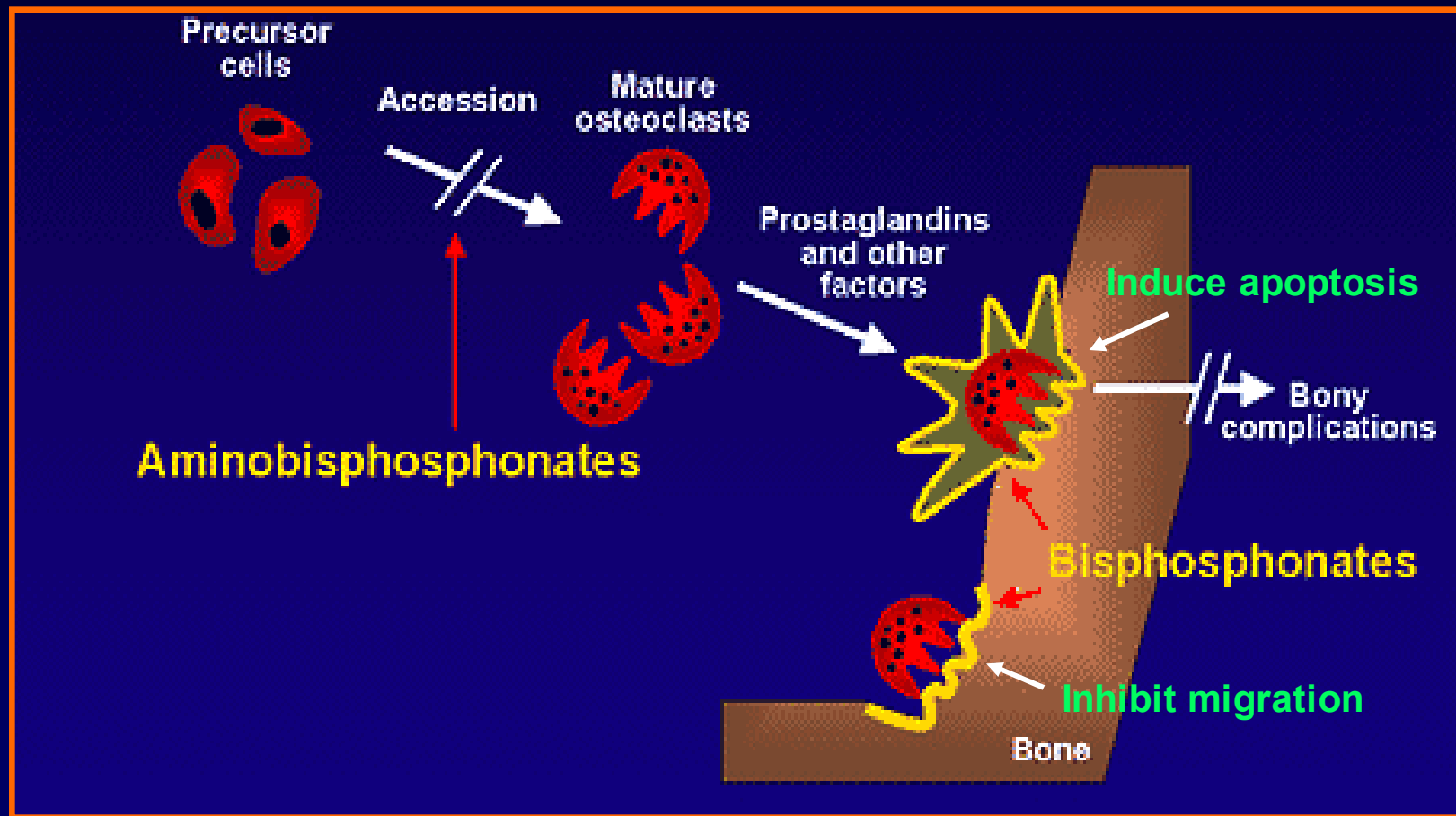


Change in FACT-G score for prostate cancer patients with an event compared with patients without an event (* $P < .05$)

The Goal of Therapy for Myeloma Bone Disease

- Preserve patient's functional independence and QOL by
 - Preventing 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

Bisphosphonates

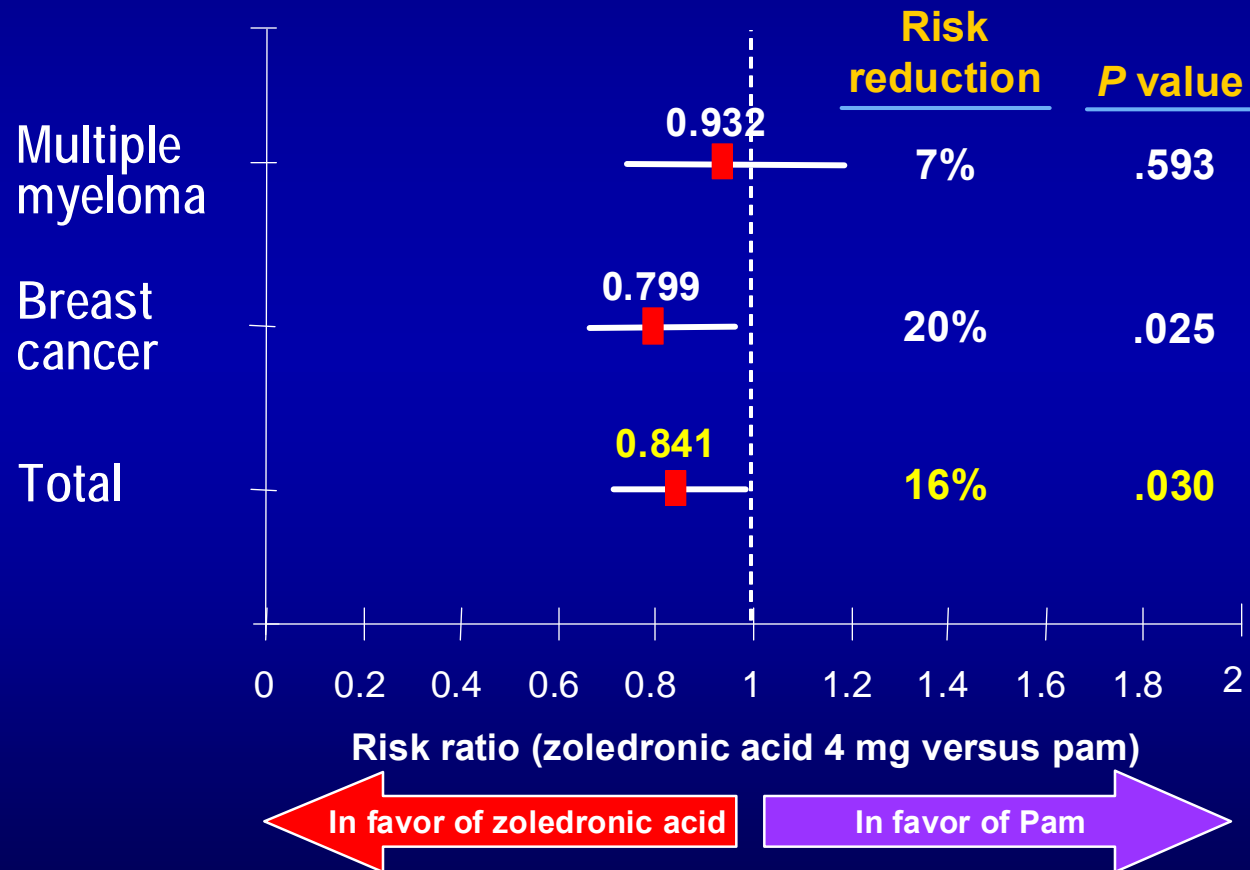


Major Double-Blind, Placebo-Controlled, Trials On Bisphosphonates In MM

Authors/Year	Type of BP	No. Pts	↓ of Pain	↓ of SREs	Survival Benefit
Belch et al, 1991 ¹	Etidronate	173	No	No	No
Daragon et al, 1993 ²	Etidronate	94	No	No	No
Lahtinen et al, 1992 ³	Clodronate	350	Yes	Yes	NE
McCloskey et al 1998 ⁴ & 2001 ⁵	Clodronate	530	Yes	Yes	+/-
Brincker et al, 1998 ⁶	Pamidronate	300	Yes	No	No
Berenson et al, 1996 ⁷	Pamidronate	392	Yes	Yes	+/-
Menssen et al, 2002 ⁸	Ibandronate	198	No	No	No
Berenson et al, 2001 ⁹	Zoledronic acid	108	Yes	Yes	NE
Rosen et al, 2001 ¹⁰ & 2003 ¹¹	Zoledronic acid	513	Yes	Yes	+?

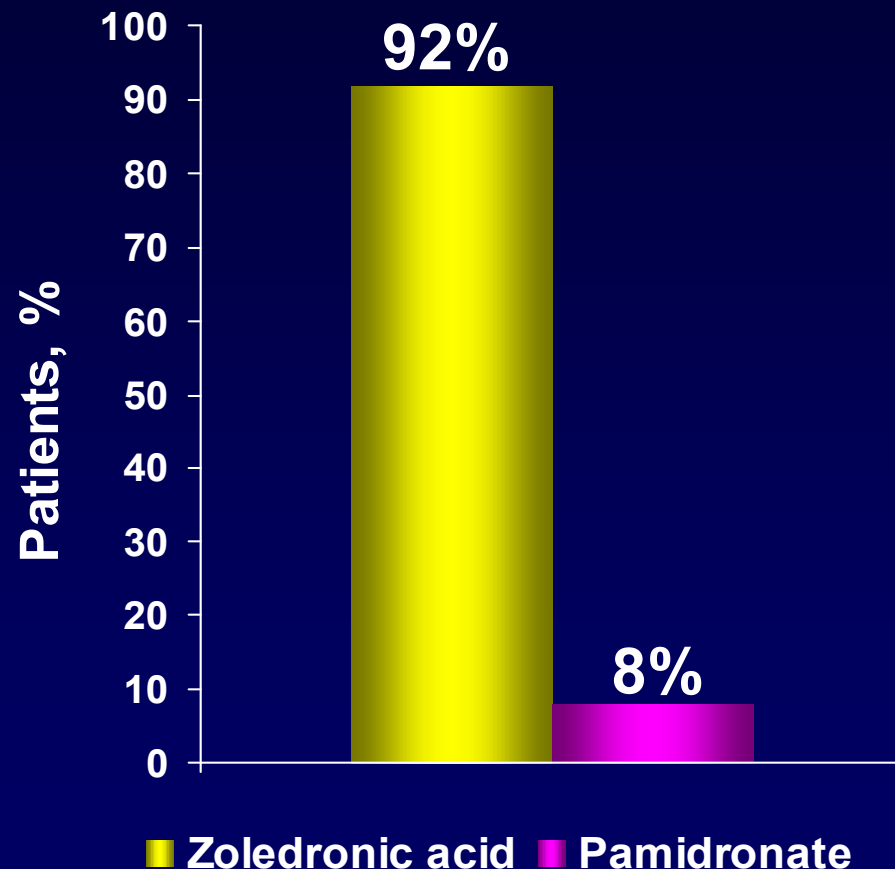
Belcher AR, et al. *J Clin Oncol*. 1991;9(8):1397-1402. 2. Daragon A, et al. *Eur J Med*. 1993;2(8):449-452. 3. Lahtinen R, et al. *Lancet*. 1992;340(8827):1049-1052. 4. McCloskey EV, et al. *Br J Haematol*. 1998;100(2):317-325. 5. McCloskey EV, et al. *Br J Haematol*. 2001;113(4):1035-1043. 6. Brincker H, et al. *Br J Haematol*. 1998;101(2):280-266. 7. Berenson JR, et al. *N Engl J Med*. 1996;334(8):488-493. 8. Menssen HD, et al. *J Clin Oncol*. 2002;20(9):2353-2359. 9. Berenson JR, et al. *Cancer*. 2001;91(7):1191-1200. 10. Rosen LS, et al. *Cancer J*. 2001;7(5):377-387. 11. Rosen LS, et al. *Cancer*. 2003;98(8):1735-1744.

Zoledronic Acid Was at Least as Efficacious as Pamidronate in the MM Stratum in a Noninferiority Trial



*Hypercalcemia of malignancy is included as an SRE.

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



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

Bisphosphonates: Adverse Events

- **Oral**
 - **GI intolerance (in up to 33% of patients)**
 - Especially esophagitis & esophageal ulcers
- **Intravenous (pamidronate or zoledronic acid)**
 - **Common adverse events**
 - Flu-like symptoms
 - Fever/myalgias/arthralgias
 - **Uncommon adverse events**
 - Renal function effects
 - Osteonecrosis of the jaw

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**

ONJ: Novel Complication of Bisphosphonates

- Avascular osteonecrosis of the jaw (ONJ) is a recent complication that has been described in multiple myeloma and other patients with cancer who receive potent bisphosphonates
- ONJ presents as an exposure of the mandible or maxilla that can be either painless or painful



Clinical Presentation and Working Diagnosis of ONJ



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



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

Study	Study Type	Pts treated with BP, n	Pts with suspect or proven ONJ, n	Frequency, %
Hoff et al. MDACC (<i>JBMR</i> 2008) ¹	Chart review	3994	29	0.7%
Durie et al (<i>NEJM</i> 2005) ²	Web-based survey	1203	152	12.6%
Badros et al (<i>JCO</i> 2006) ³	Chart review/ observational	340	11	3.2%
Zervas et al (<i>BJH</i> 2006) ⁴	Chart review/ prospective after 2001	254	28	11.0%
Dimopoulos et al (<i>Haematologica</i> 2006) ⁵	Chart review/ prospective after 2003	202	15	7.4%

1. Hoff AO, et al. *J Bone Miner Res.* 2008;23(6):826-836. 2. Durie BG, et al. *N Engl J Med.* 2005;353(1):99-102. 3. Badros A, et al. *J Clin Oncol.* 2006;24(6):945-952. 4. Zervas K, et al. *Br J Haematol.* 2006;134(6):620-623. 5. Dimopoulos MA, et al. *Haematologica.* 2006;91(7):968-971.

Relative Risk for ONJ Development

15/202 Developed ONJ (7.4%)	Relative Risk							
	12 Months		24 Months		36 Months		48 Months	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI
All (n = 202)	1	0-2	3	1-4	6	2-10	13	5-21
Zoledronic acid (n = 93)	1	0-3	5	0-11	15	3-27	15	3-27
Pamidronate (n = 33)	0	0	1	0-3	1	0-3	5	0-11

ONJ	Yes	No	P value
Thalidomide			
Yes	8 (7.5%)	99 (92.5%)	0.977
No	7 (7.4%)	88 (92.6%)	

ASCO Guidelines

- **The Update Committee suggests that bisphosphonate treatment continues for a period of 2 years**
- **At 2 years, physicians should seriously consider discontinuing bisphosphonates in patients with responsive or stable disease, but further use is at the discretion of the treating physician**
- **Re-initiation at relapse**

Update for ONJ and Bisphosphonates in Myeloma (1)

- ONJ incidence was compared between patients who did or did not receive preventive measures before zoledronic acid therapy (N = 128)¹

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

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

1. Dimopoulos MA, et al. *Ann Oncol.* 2008; 20(1):117-120.

2. Montefusco V, et al. *Blood.* 2007;110: Abstract 3613.

Update for ONJ and Bisphosphonates in Myeloma (2)

- ONJ resolved and did not recur in 60/97 cases (62%)
- Resolved and then recurred in 12 patients (12%)
- Did not resolve over a follow-up period of at least 9 months in 25 patients (26%)
- ONJ recurrence followed re-initiation of bisphosphonate in 6 of 12 patients
- Patients in whom ONJ was precipitated by dental procedures were less likely to have recurrence or nonhealing lesions after BP re-initiation following ONJ healing, as compared to those who develop spontaneous ONJ lesions ($P = .007$)

Recommendations by An Expert Panel on Behalf of the EMN (1)

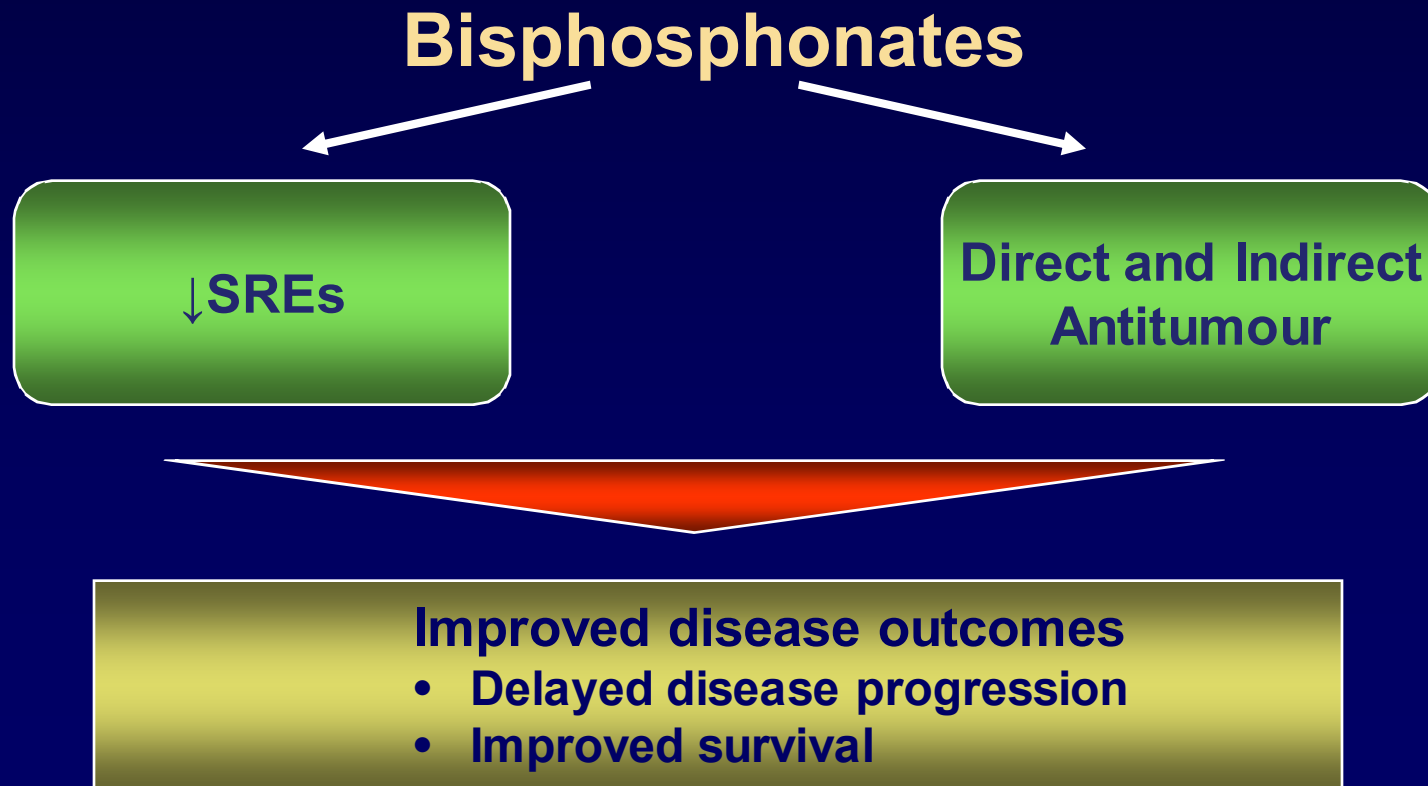
- Bisphosphonates should be given for 2 years; then at the physician's discretion
- In patients in CR after 12 months the benefit of an additional 12 months of treatment is debatable
- Bisphosphonate therapy should be resumed upon relapse
- **Comprehensive dental examination & education on dental hygiene. Existing dental conditions should be treated before initiating BPs**
- **After therapy initiation, unnecessary invasive dental procedures should be avoided and dental status should be monitored annually**

Recommendations by An Expert Panel on Behalf of the EMN (2)

- Temporary bisphosphonate suspension if invasive dental procedures needed
- Initial ONJ therapy should include discontinuation of bisphosphonate until healing
- The decision to restart bisphosphonates should be individualized, until prospective long-term studies are available
- The physician has to take into consideration the advantages and disadvantages of bisphosphonates mainly in the relapsed/refractory setting

Emerging Data on the Antitumor Activity of Bisphosphonates

- There is a growing body of evidence that N-BPs improve disease outcomes in metastatic disease
- Two potential mechanisms for improved outcomes



Osteoclast: Key Cell for Myeloma Cell Growth



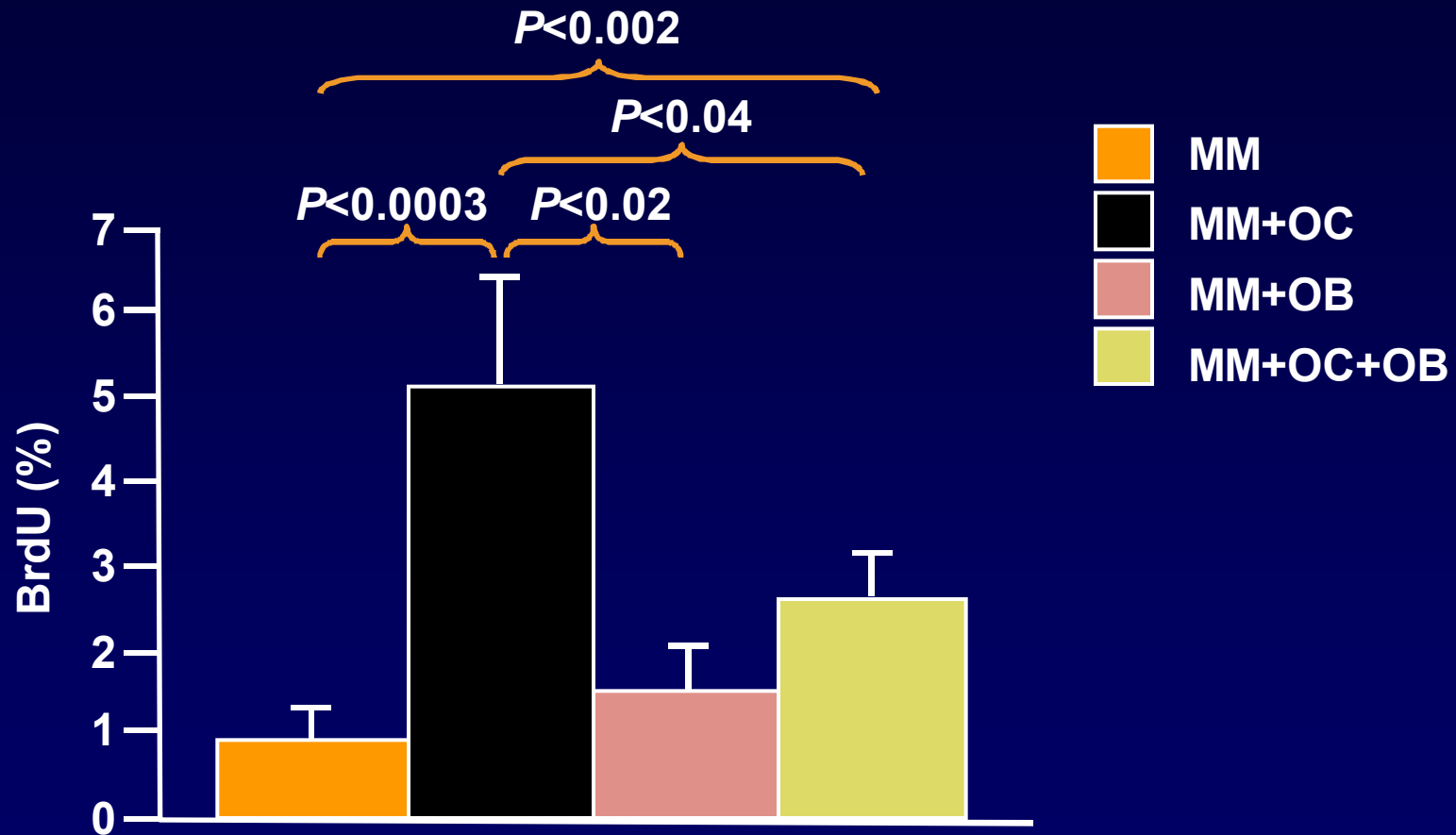
without OC



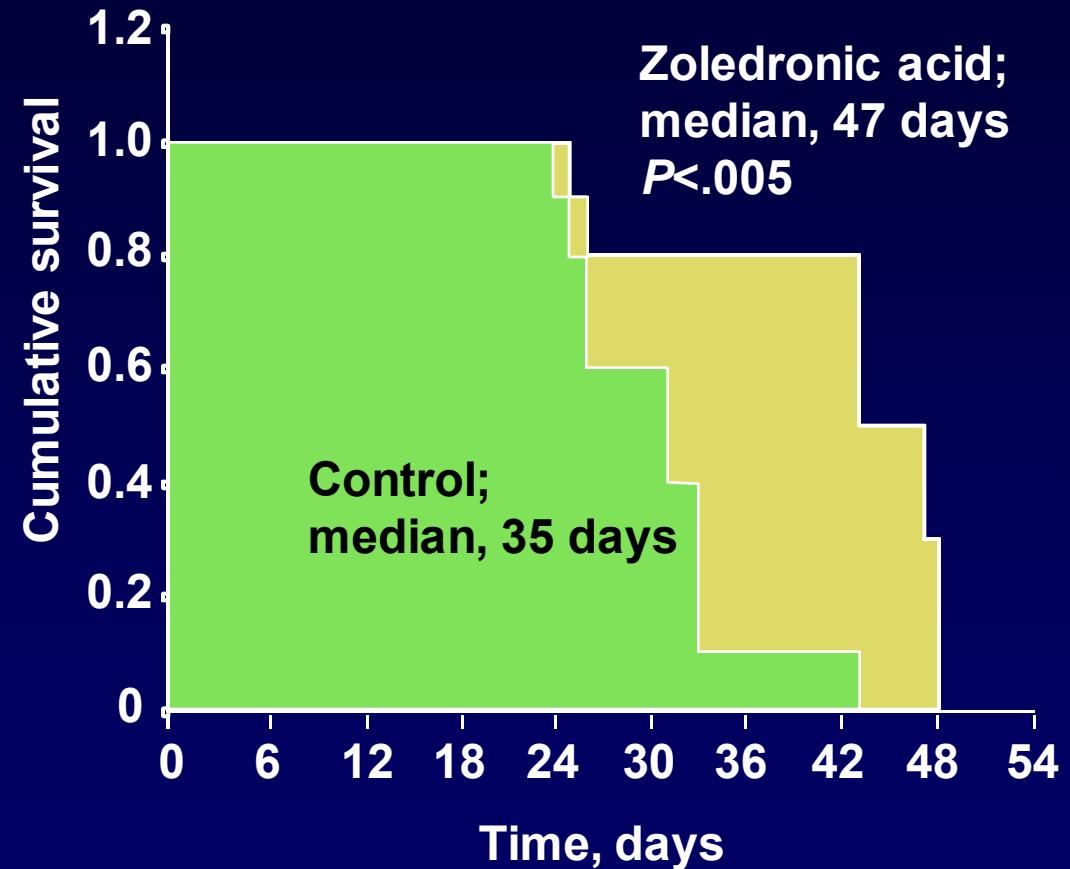
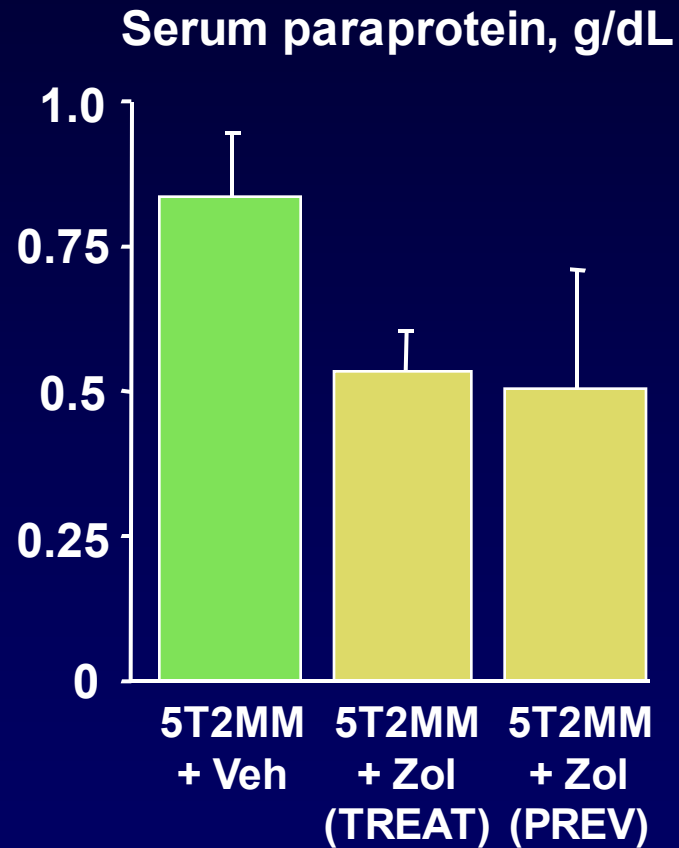
myeloma cell culture after 14 days

with OC

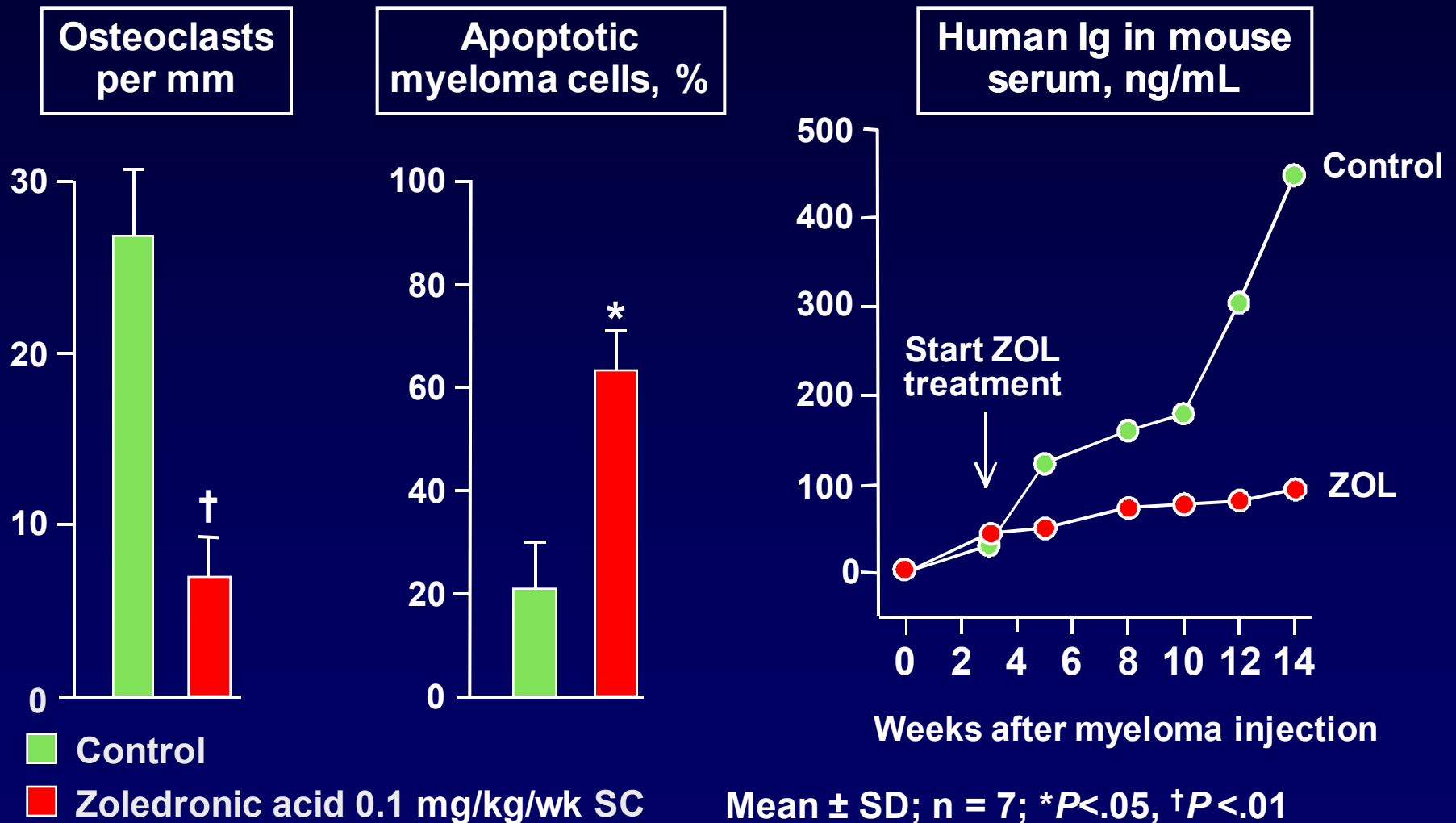
Osteoclasts–Osteoblasts: Antagonists of Myeloma Cell Growth?



Zoledronic Acid Decreases Tumor Burden and Improves Survival in the 5T2MM Model



Zoledronic Acid Inhibits Myeloma Growth in the SCID/Hu Bone Implant Model

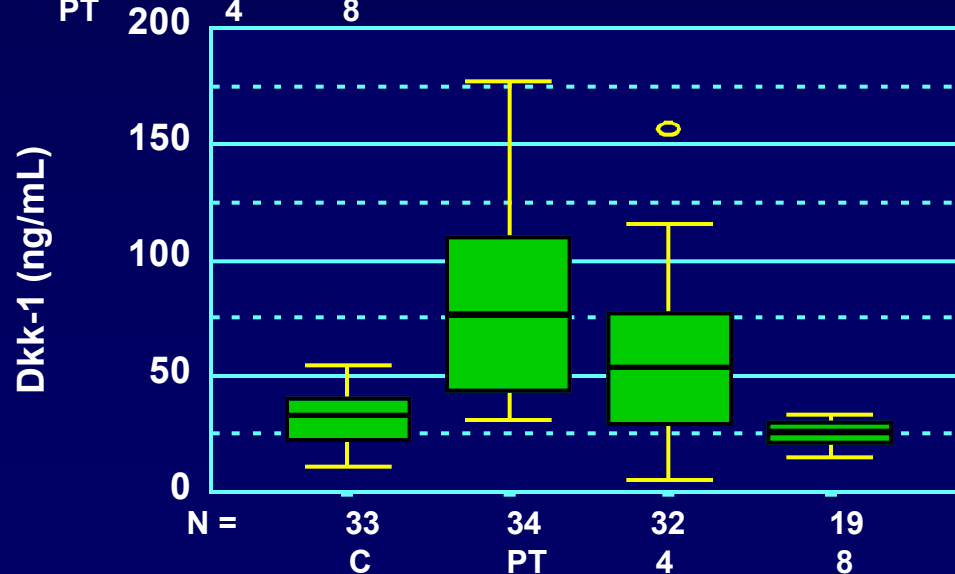
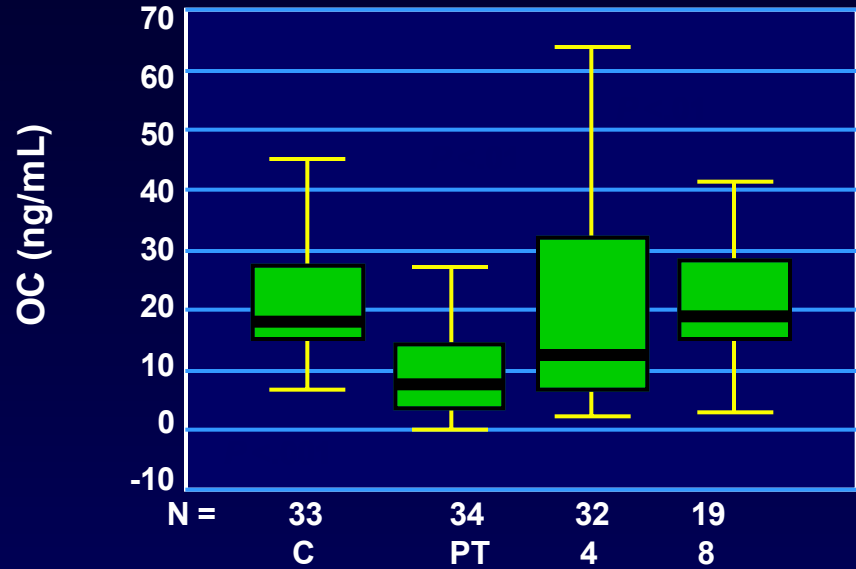
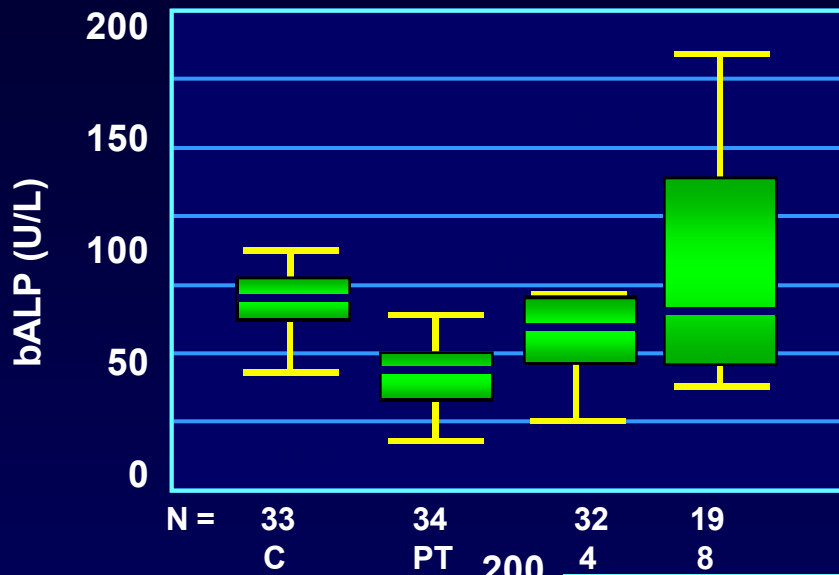


Antitumor Effect of Zoledronic Acid Being Explored in Clinical Studies in Multiple Myeloma

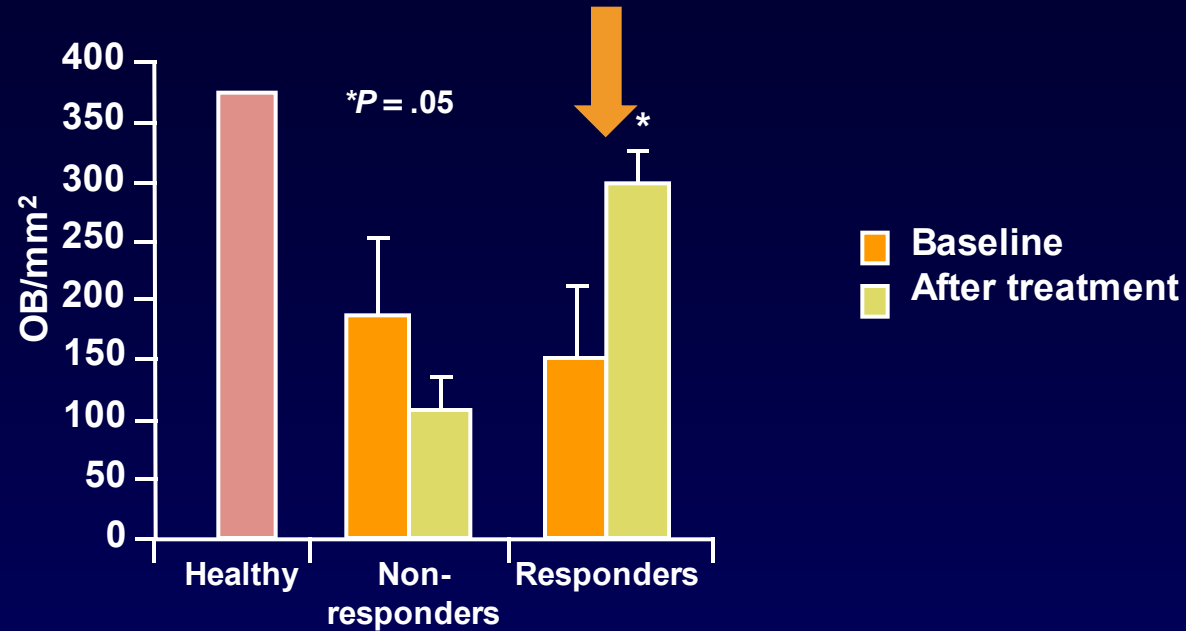
Study	Patients	Treatments	Primary endpoint	Status
DAZZLE	50 / 53	Dexamethasone, thalidomide, ZOL, single arm	Disease progression at month 6	Accrual complete
CZOL446EU S52 USA	120 / 66	Thalidomide + ZOL vs ZOL	Time to disease progression, response rate, PFS	Active
CZOL446EF R05 France	310 / 53 (MM stage 1)	ZOL vs no ZOL	Disease progression, symptomatic myeloma	Active
CZOL446EU S33 USA	176 / 89	Thalidomide/ Dexamethasone vs VAD ± prior ZOL	Response rate of chemo; PFS, OS; antitumor effect of ZOL	Active

ZOL = Zoledronic acid; OS = Overall Survival; PFS = Progression-free survival;

Bortezomib in Combination with ZA Affects Markers of Bone Formation and Osteoblast Stimulators

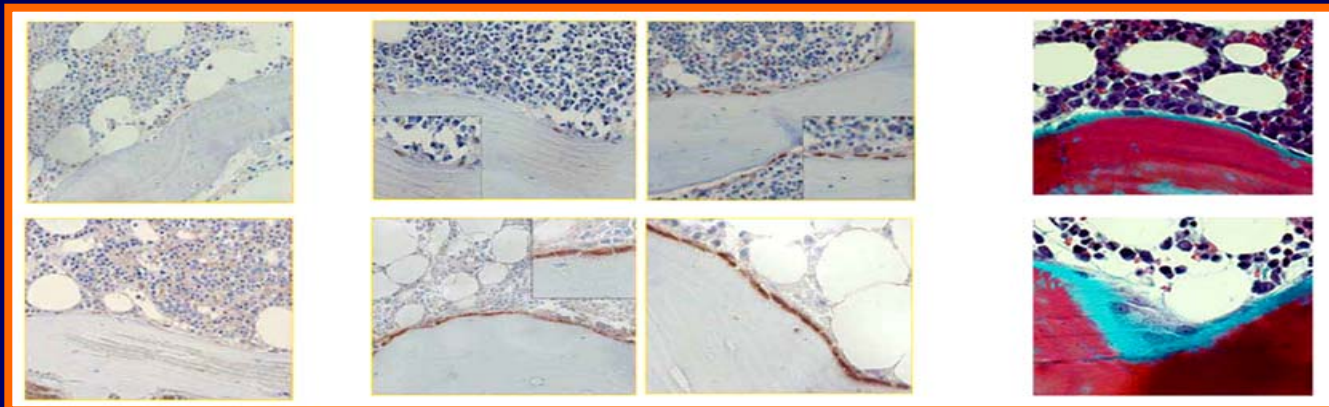


Bortezomib Increases Osteoblast Counts in Responding Patients



Baseline

After Treatment



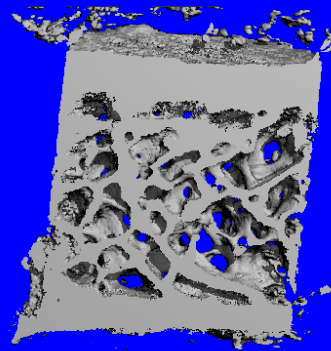
MM "Non-responder"

MM "Responder"

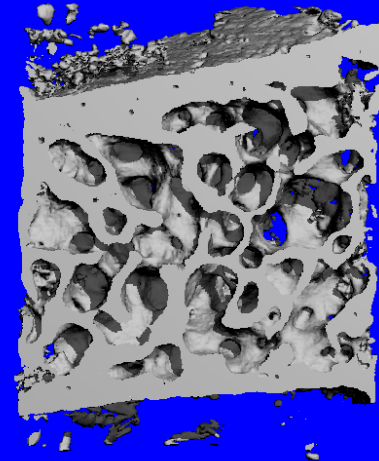
MM "Responder"

Pre-Bortezomib

Post-Bortezomib



1.0 mm



1.0 mm

BV/TV = 12.85%

Tb.Th = 0.1

Tb.Sp. = 0.7

Tb.N. = 1.5

BV/TV = 90%

Tb.Th = 0.7

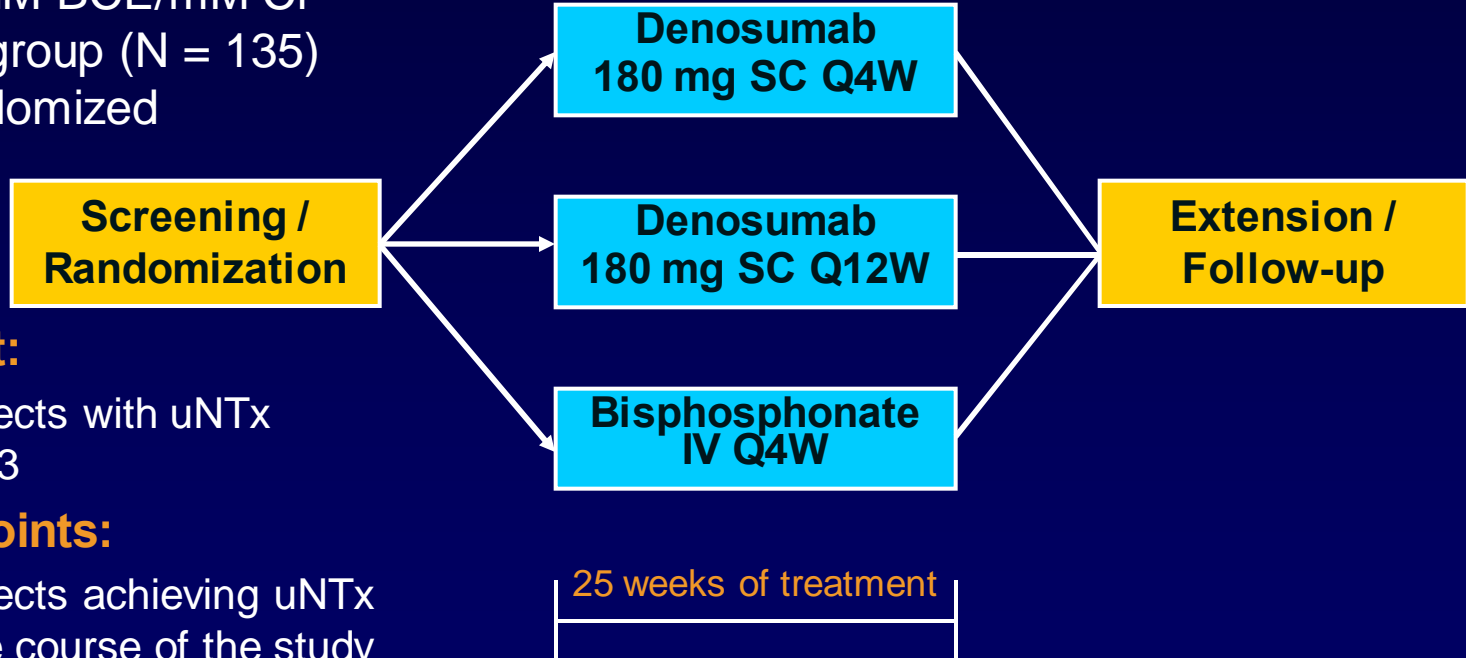
Tb.Sp. = 0.2

Tb.N. = 2.8

Denosumab (anti-RANKL) in MM & Advanced Cancer Patients with Bone Metastases

Study Features:

- Bone metastases from solid tumors (except lung) or MM bone disease
- Patients receiving bisphosphonates and uNTX >50 nM BCE/mM Cr
- 45 patients per group (N = 135)
- Open label, randomized
- ECOG = 0,1,2



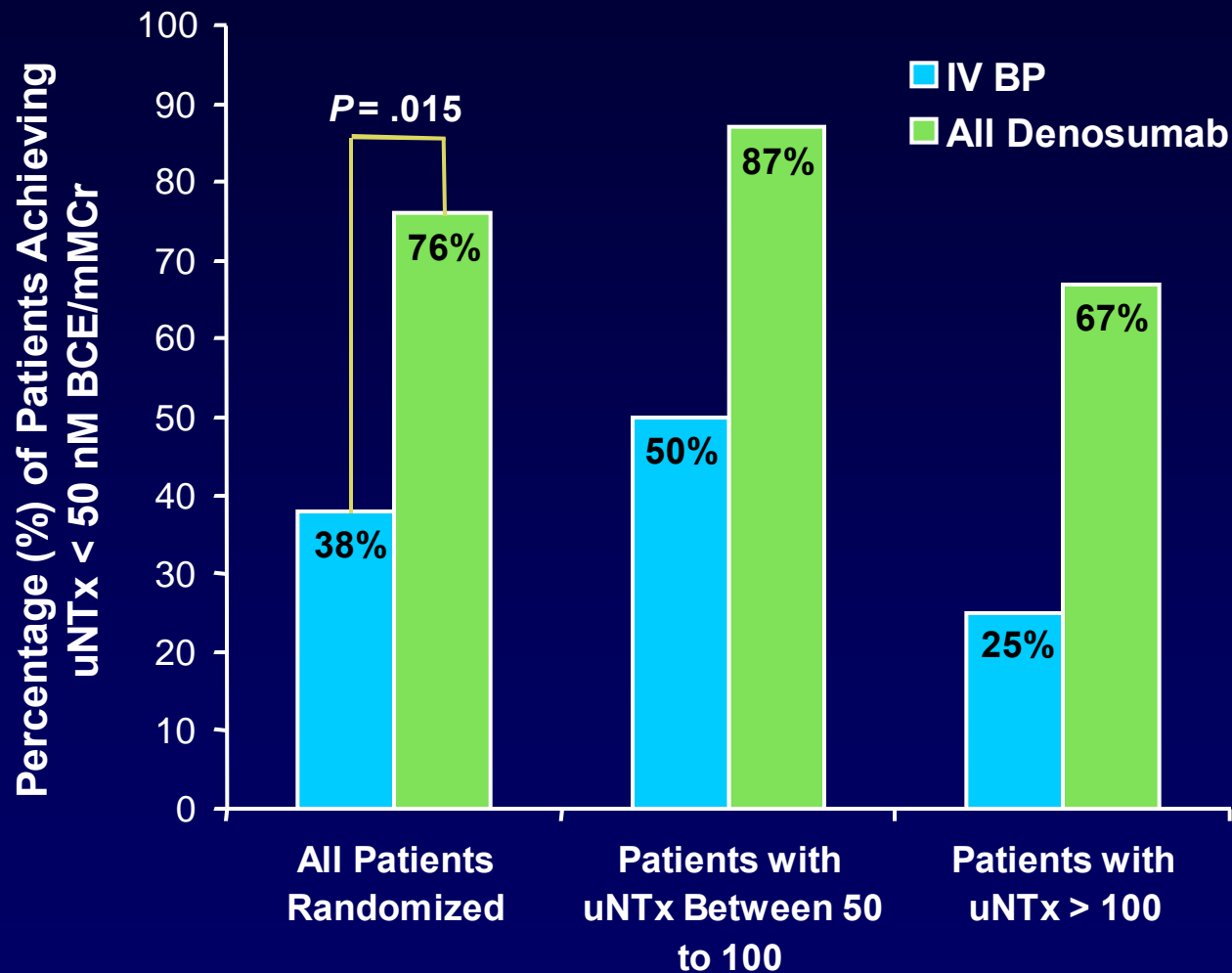
Primary Endpoint:

- Proportion of subjects with uNTx <50 nM at week 13

Secondary Endpoints:

- Proportion of subjects achieving uNTx <50 nM during the course of the study
- Time to reduction of uNTx < 50 nM

Primary Endpoint: Proportion of Subjects with uNTx < 50 nM. All Subjects



Optimizing Therapy in MM: Conclusions

- **Introduction of IV BPs has transformed management of myeloma bone disease**
- **Opportunity to achieve benefit with earlier use?**
 - Prevention of bone loss
 - Possible effects on the disease course
- **Benefit/risk ratio could be further optimized**
 - Proactive monitoring of oral and renal health
 - Optimal duration of therapy requires further study
- **Emerging goal for zoledronic acid: extending survival**
- **Novel agents in combination with or without BPs may have an affect on bone metabolism of MM patients**
- **Clinical trials are underway in MM**