Case 8—Current Approaches to Newly Diagnosed MM: Bone-Targeted Therapy

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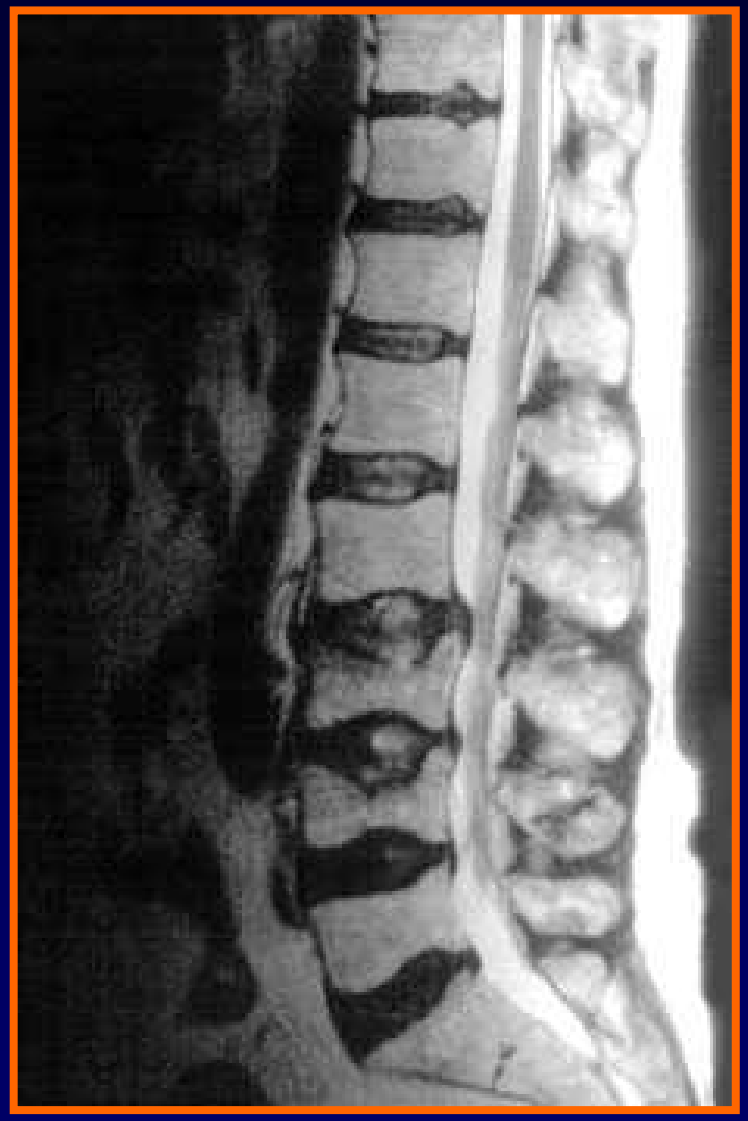
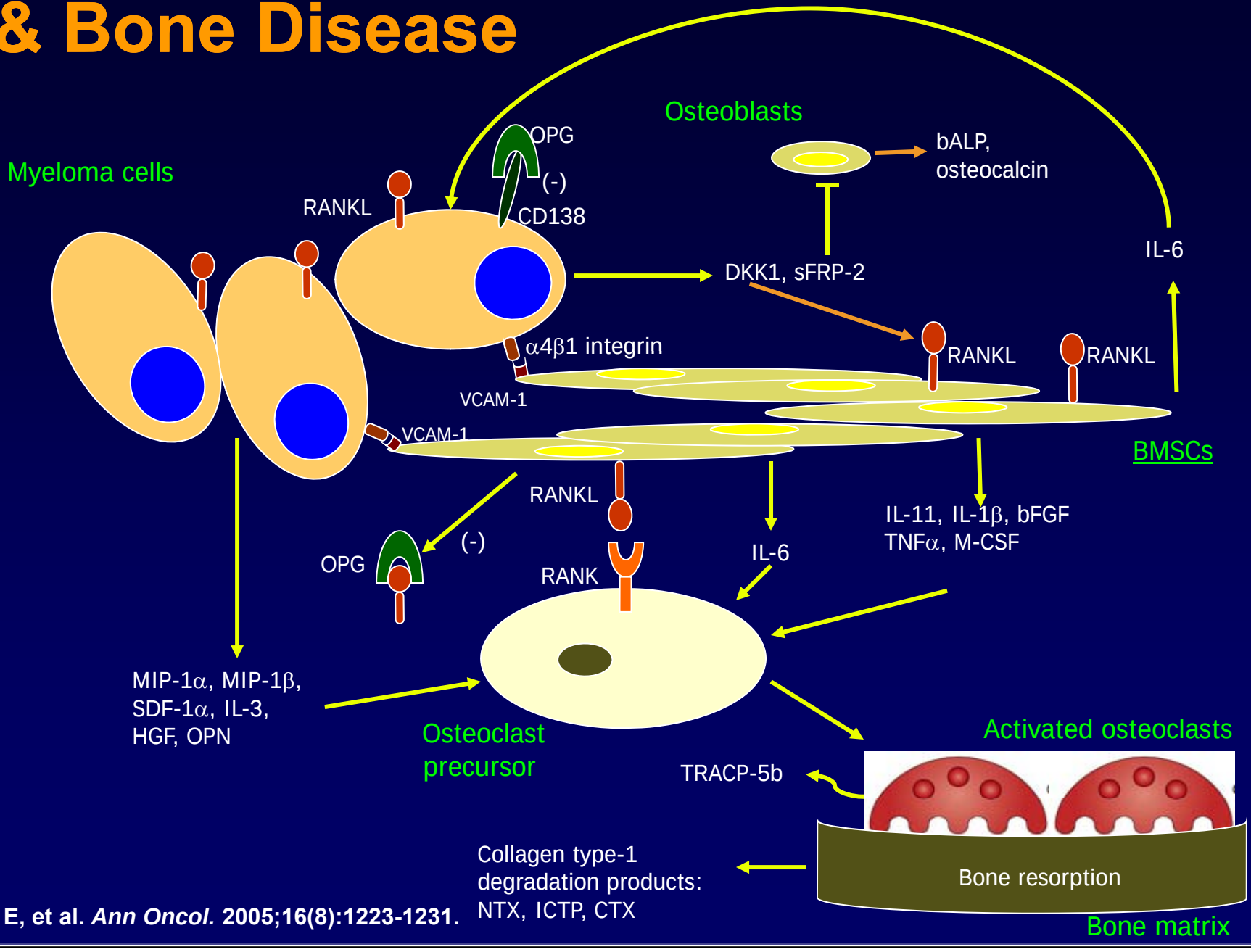
Bone Disease in Multiple Myeloma



Kyle RA. *Mayo Clin Proc.* 1975;50(1):29-40.

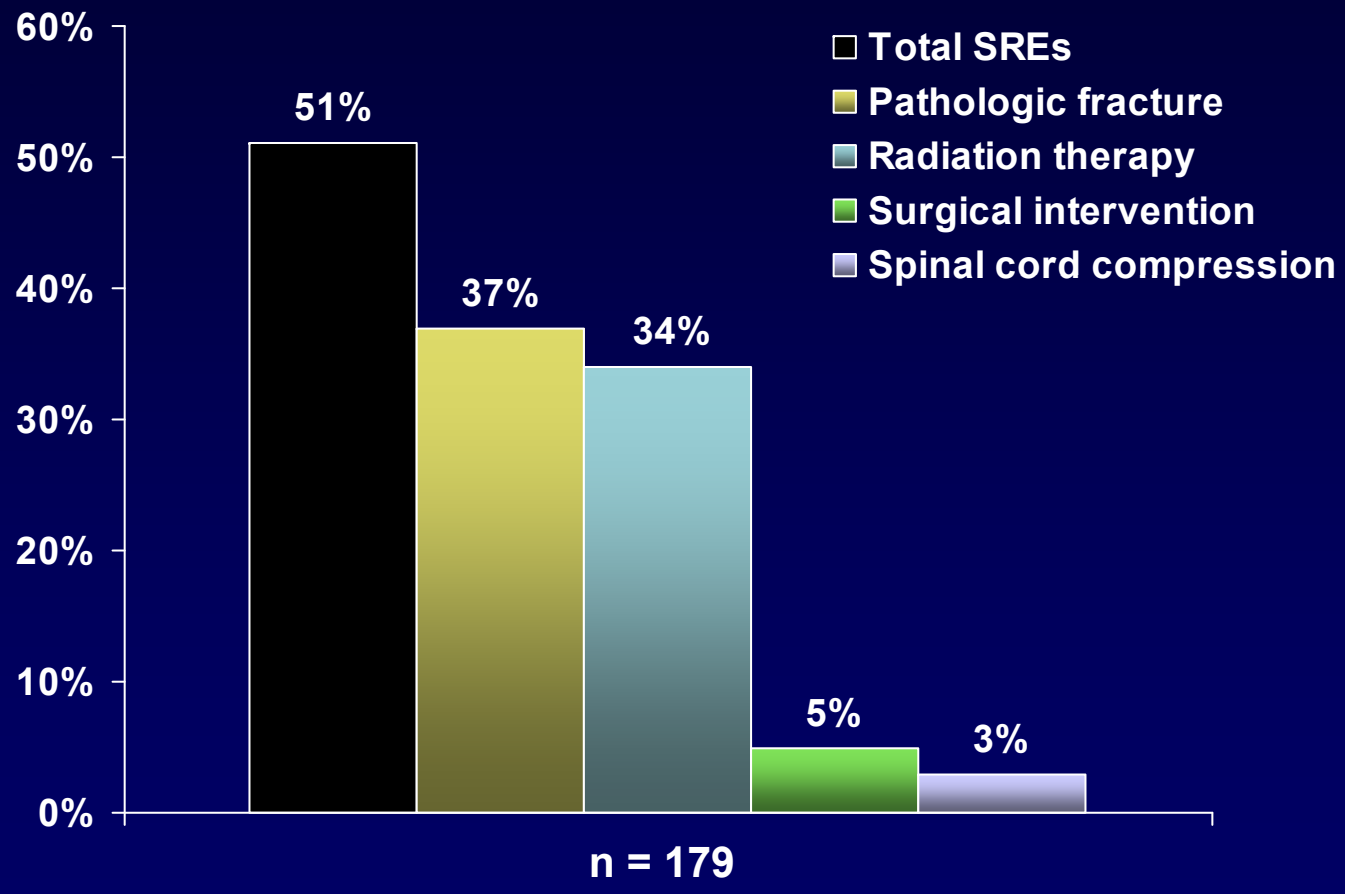
- A burdensome and frequent complication in MM
  - Present in up to 80% of patients at diagnosis
- Characterized by osteolytic bone lesions secondary to increased bone resorption and impaired bone formation
- Sequelae
  - Pathologic fractures
  - Osteoporosis
  - Hypercalcemia
  - Bone pain
  - Spinal cord compression

Myeloma Microenvironment & Bone Disease



Terpos E, et al. *Ann Oncol.* 2005;16(8):1223-1231.

SREs Are a Serious Problem for Patients With Multiple Myeloma



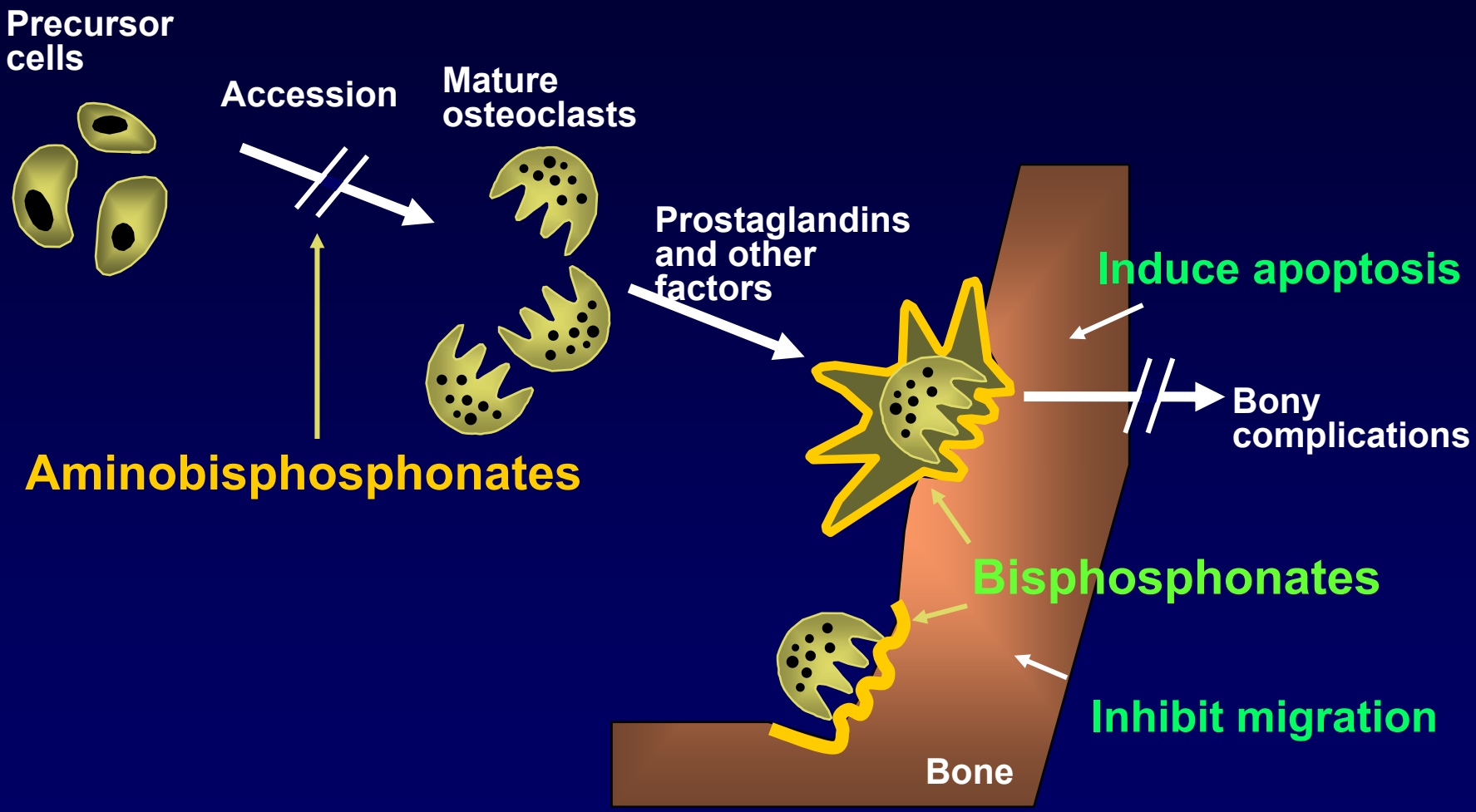
SRE, skeletal-related event.
21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.

Berenson R, et al. *J Clin Oncol*. 1998;16(2):593-602.

The Goal of Therapy for Bone Lesions in Myeloma

- Preserve patient's functional independence and quality of life by
  - Preventing SREs
    - Prevent the first SRE
    - Delay the onset of the first SRE
    - Prevent the recurrence of SREs
  - Palliating and controlling bone pain
    - Reduce the need for analgesics and palliative radiotherapy

Bisphosphonates



Saad F, et al. *Eur Urol.* 2004;45(1):26-34.

Major Double-Blind Clinical Trials of Bisphosphonates in Multiple Myeloma

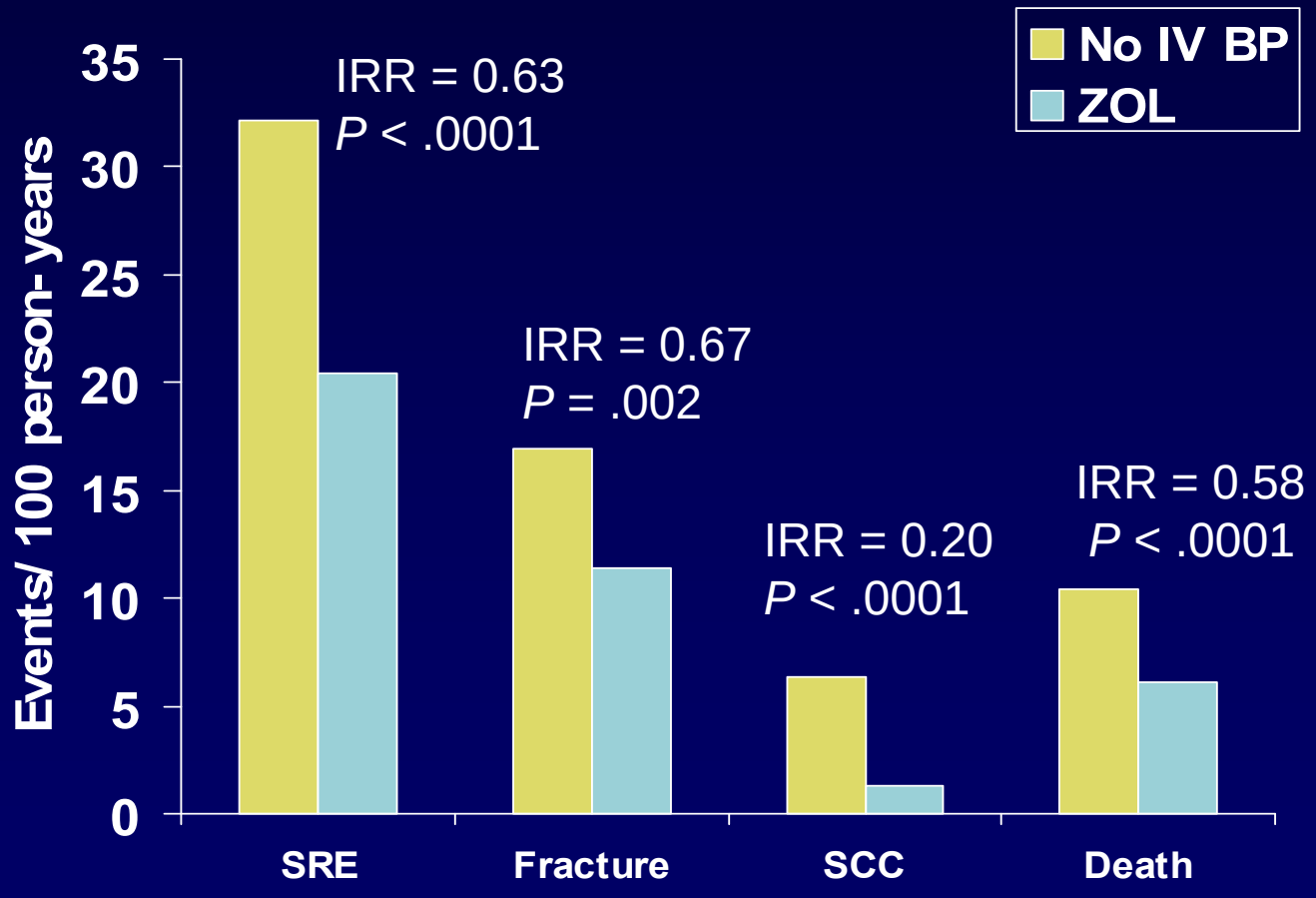
Authors and year	BP	Dosage	N[a]	Reduction of pain	Reduction of SREs	Survival benefit
Placebo-controlled trials[b]						
Lahtinen et al. (1992) and Laakso et al. (1998)	CLO	2.4 g/day, po, for 2 years	350	Yes	Yes	NE
McCloskey et al. (1998) and (2001)	CLO	1.6 g/day, po	530	Yes	Yes	subset[c]
Brincker et al. (1998)	PAM	300 mg/day, po	300	Yes	No	No
Berenson et al. (1996) and (1998)	PAM	90 mg, IV, every 4 weeks for 21 cycles	392	Yes	Yes	subset[d]
Menssen et al. (2002)	IBN	2mg, IV, monthly	198	No	No	No
PAM-controlled trials						
Berenson et al. (2001)	ZOL	2 or 4 mg, IV, monthly	108	Yes	Yes	NE
Rosen et al. (2001) and (2003)	ZOL	2 or 8 mg, IV, monthly	513	Yes	Yes	subset[e]

[a] Number of patients with MM.
[b] SREs include new lytic lesions, vertebral and nonvertebral fractures, and need for radiation or surgery to the bone.
[c] In post hoc analysis, patients without vertebral facture at study entry survived significantly longer on CLO (23 months) compared with placebo.
[d] Survival in patients with more advanced disease was significantly increased in the PAM group (median survival 21 vs 14 months; $P = .041$ adjusted for baseline serum β_2-microglobulin and Eastern Cooperative Oncology Group performance status).
[e] Survival benefit with ZOL over PAM in a subgroup of patients who had elevated baseline bone-specific alkaline phosphatase levels.

Terpos E, et al. *Ann Oncol.* 2009;20:1303-1317.

Use of ZOL Corresponded With ↑ Outcomes vs No IV BP in a Database Study in Patients With Myeloma Bone Disease

1,655 patients: 1,060 (64%) received ZOL & 595 (36%) received no IV BP (control group)



Henk HJ, et al. *Blood.* 2009;114: Abstract 3881.

Zoledronic Acid and Pamidronate Are Generally Well-Tolerated

- Most frequently reported AEs include[1]
  - Bone pain, nausea, fatigue, pyrexia, and emesis (regardless of relationship to study drug)
  - Infections, arthralgia/myalgias, cytopenias, pyrexia, eye disorders, electrolyte abnormalities, and injection site reactions (study drug-related)
- No significant differences in renal safety profile between 4 mg ZOL group and 90 mg PAM group[1]
  - Effects on renal function are dose- and infusion rate-dependent
  - Cases are transient and manageable
- Osteonecrosis of the jaw (ONJ) is an uncommon adverse event during bisphosphonate therapy (<2% in prospective series)[2]
  - Risk can be significantly reduced by proactive dental care
  - Most cases are manageable, and complete healing of ONJ is possible

1. Rosen LS, et al. *Cancer.* 2003;98(8):1735-44.
2. Terpos E, et al. *Ann Oncol.* 2009;20(8):1303-1317.

EMN Recommendations For Renal Impairment

Creatinine Clearance rate (mL/min)	Recommended dosage of CLO (1600 mg)
>80	100%
50-80	75%
12-50	50-75%
<12	50% or discontinue

Creatinine Clearance rate (mL/min)	Recommended dosage of ZOL (mg)
> 60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

Creatinine Clearance rate (mL/min)	Recommended infusion time for PAM (90 mg)
>30	2-4 hours
<30	Not recommended

Terpos E, et al. *Ann Oncol.* 2009;20(8):1303-1317.

ONJ: Characteristics

ONJ presents as an exposure of the mandible or maxilla that may or may not be associated with pain.

Symptoms

- "Heavy jaw"; a dull, aching sensation
- Numbness/tingling of the jaw
- Tooth pain
- Undiagnosed oral pain

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

Data from Weitzman R, et al. *Crit Rev Oncol Hematol*. 2007;62(2):148-152.

Incidence of ONJ in a Study of Denosumab vs Zoledronic Acid

Event	Zoledronic Acid (N = 878) n (%)	Denosumab (N = 878) n (%)
Infectious AEs	349 (39.7)	358 (40.8)
Infectious serious AEs	118 (13.4)	128 (14.6)
Acute phase reaction (first 3 days)	127 (14.5)	61 (6.9)
Potential renal toxicity AEs*	96 (10.9)	73 (8.3)
Renal failure	25 (2.8)	20 (2.3)
Acute renal failure	16 (1.8)	11 (1.3)
Cumulative rates of ONJ†	11 (1.3)	10 (1.1)
Year 1	5 (0.6)	4 (0.5)
Year 2	8 (0.9)	10 (1.1)
New primary malignancy	3 (0.3)	5 (0.6)

* Includes blood creatinine increased, renal failure, renal failure acute, proteinuria, blood urea increased, renal impairment, urine output decreased, anuria, oliguria, azotaemia, hypercreatininemia, creatinine renal clearance decreased, renal failure chronic, blood creatinine abnormal

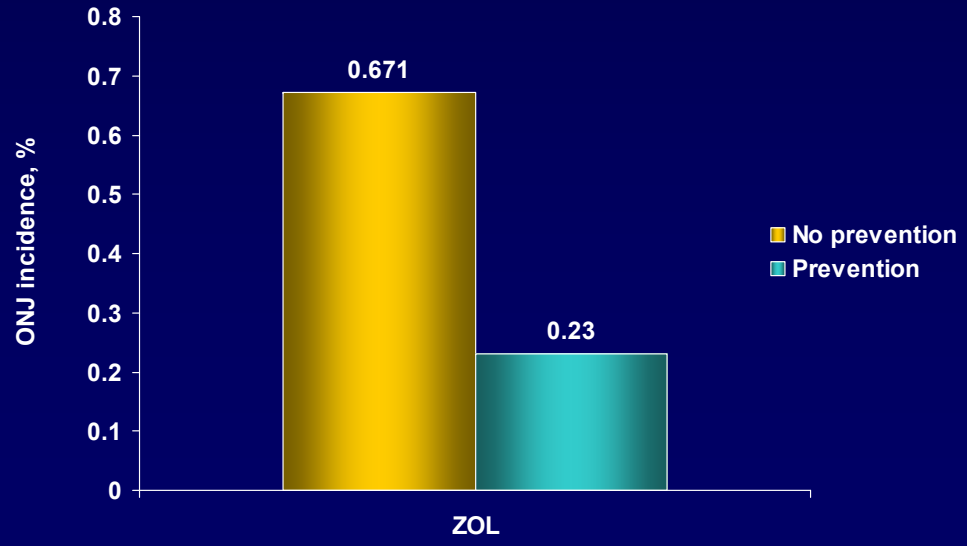
† $P = 1.0$

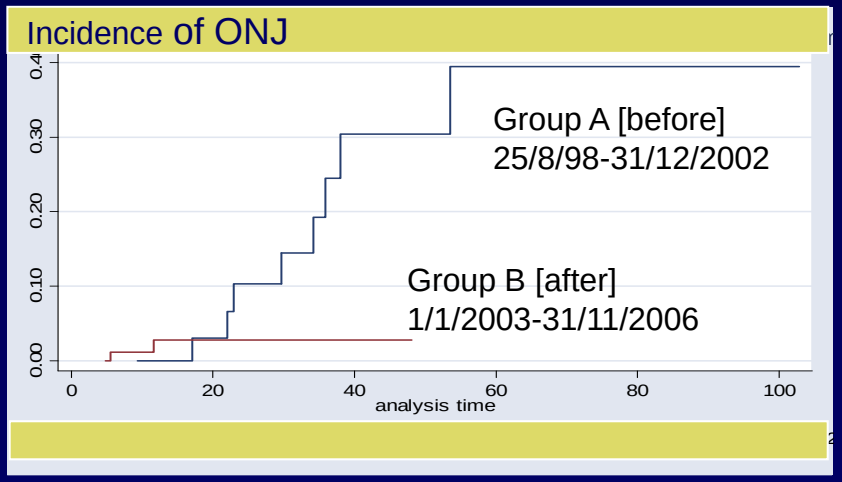
No neutralizing anti-denosumab antibodies were detected

Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

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

- ONJ incidence was compared between patients who did or did not receive preventive measures before zoledronic acid therapy (N = 128)[1]
- Antibiotic prophylaxis before dental procedures reduced the incidence of ONJ in 178 patients (*P* = .007)[2]
- 9 ONJ cases (7.7%) – 8 after dental procedures/all in those who did not receive antibiotic prophylaxis





1. Dimopoulos MA, et al. *Ann Oncol* 2009;20(1):117-120. 2. Montefusco V, et al. *Leuk Lymphoma* 2008;49(11):2156-2162

Natural History of ONJ in Myeloma (1)

- 97 patients with myeloma and ONJ from the US (n = 37) and Greece (n = 60) were observed prospectively for a minimum 3.2 years
- Dental procedures preceded ONJ in 46 patients (47%) and were more common in those with single episodes (35 of 60, 58%) than those with recurrent or nonhealing ONJ (11 of 37, 30%; *P* = .007)

Badros A, et al. *J Clin Oncol.* 2008;26(36):5904-5909.

Natural History of ONJ in Myeloma (2)

- ONJ resolved and did not recur in 60/97 (62%)
- ONJ resolved and then recurred in 12 patients (12%)

ONJ healed in ~75%

- **Patients in whom ONJ was precipitated by dental procedures were less likely to have recurrence or non-healing lesions** after BP re-initiation following ONJ healing, compared to those who developed spontaneous ONJ lesions (*P* = 0.007)

Badros A, et al. *J Clin Oncol.* 2008;26(36):5904-5909.

Recommendations for Prevention of ONJ

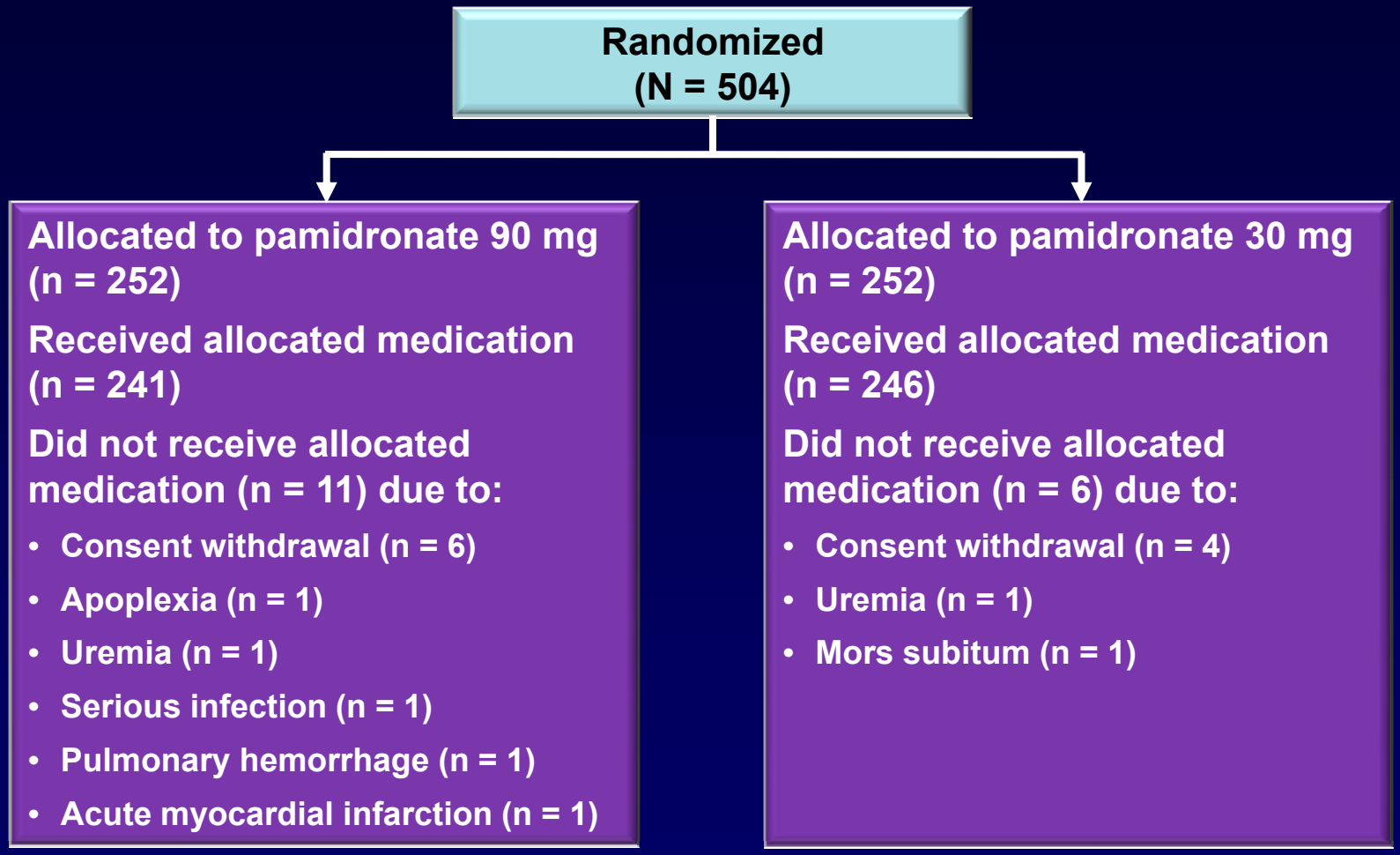
- Prior to treatment with bisphosphonates:
  - Dental exam with appropriate preventive dentistry
  - Remove abscessed teeth and teeth with poor long-term prognosis
  - Record tooth mobility, periodontal condition, and concomitant treatments
  - Educate patients on oral hygiene and sign & symptoms of ONJ
- During bisphosphonate treatment:
  - Daily calcium supplements
  - Dental exam every 6 months
  - In case of dental procedure, administer wide-spectrum antibiotics given 7 days prior and until healing

Ripamonti CI, et al. *Ann Oncol.* 2009;20(1):137-145.

Bone-Targeted Therapy

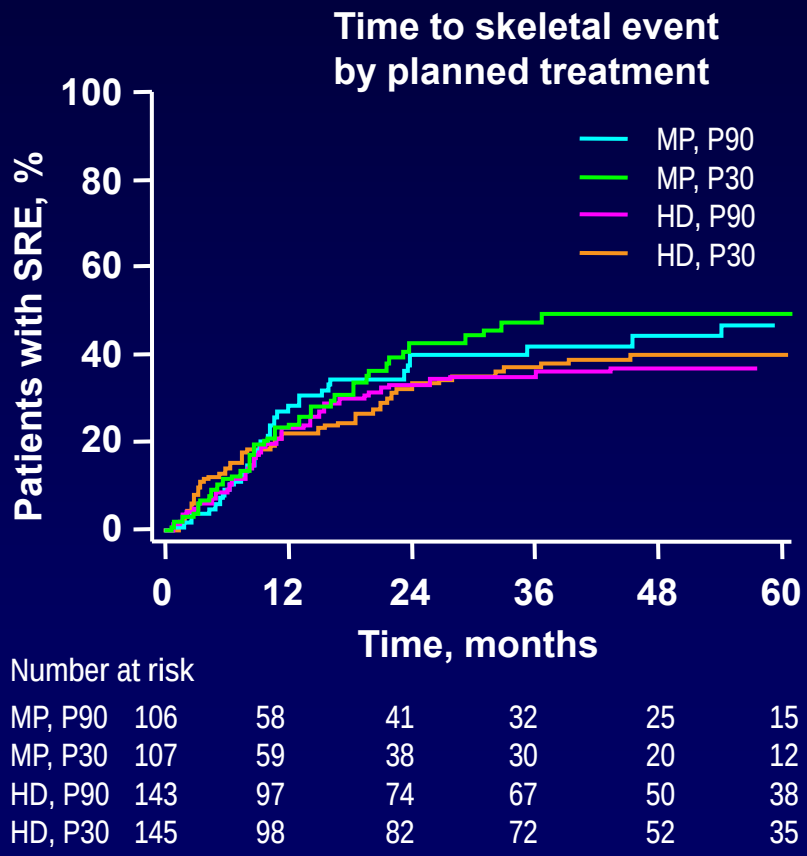
Recent Reports

Pamidronate: 30 mg versus 90 mg



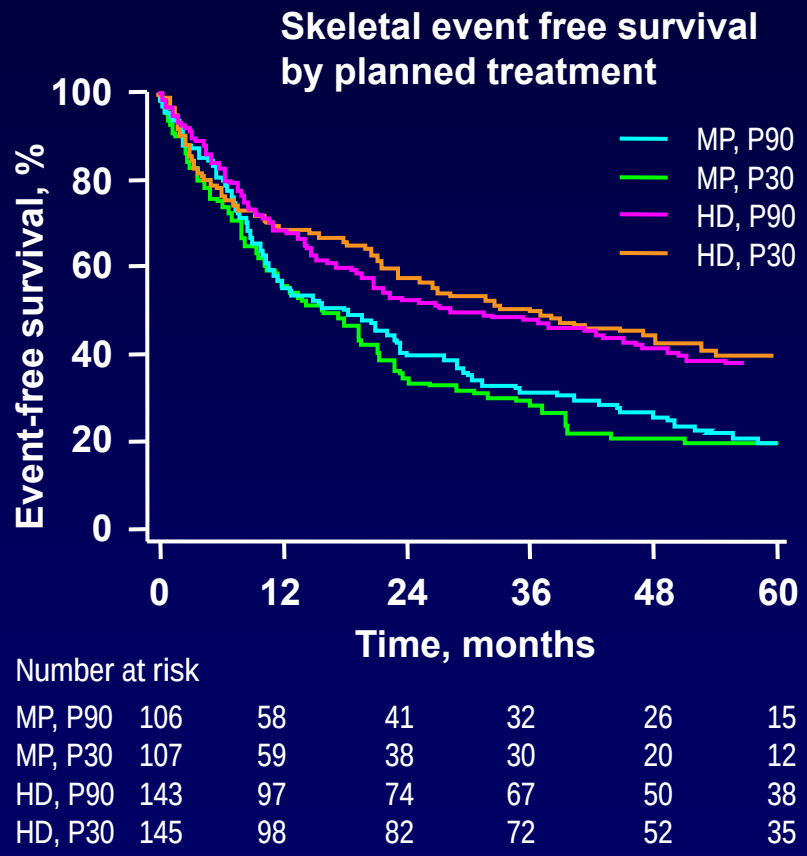
Gimsing P, et al. *Lancet Oncol.* 2010;11(10):973-982.

Pamidronate: 30 mg versus 90 mg (2)



Number at risk

MP, P90	106	58	41	32	25	15
MP, P30	107	59	38	30	20	12
HD, P90	143	97	74	67	50	38
HD, P30	145	98	82	72	52	35



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HD, P30	145	98	82	72	52	35

Gimsing P, et al. *Lancet Oncol.* 2010; In press.

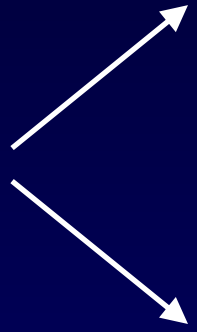
A Double-Blind, Randomised Study of Denosumab vs Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

Ph III Denosumab vs Zoledronic Acid for Advanced Cancer: Study Schema

Pts ≥ 18 yrs with advanced solid tumors (excluding breast and prostate) or myeloma who had no current or previous IV bisphosphonates

(N = 1776)



Denosumab 120 mg SC + placebo IV* Q4W (n = 886)

Supplemental calcium and vitamin D

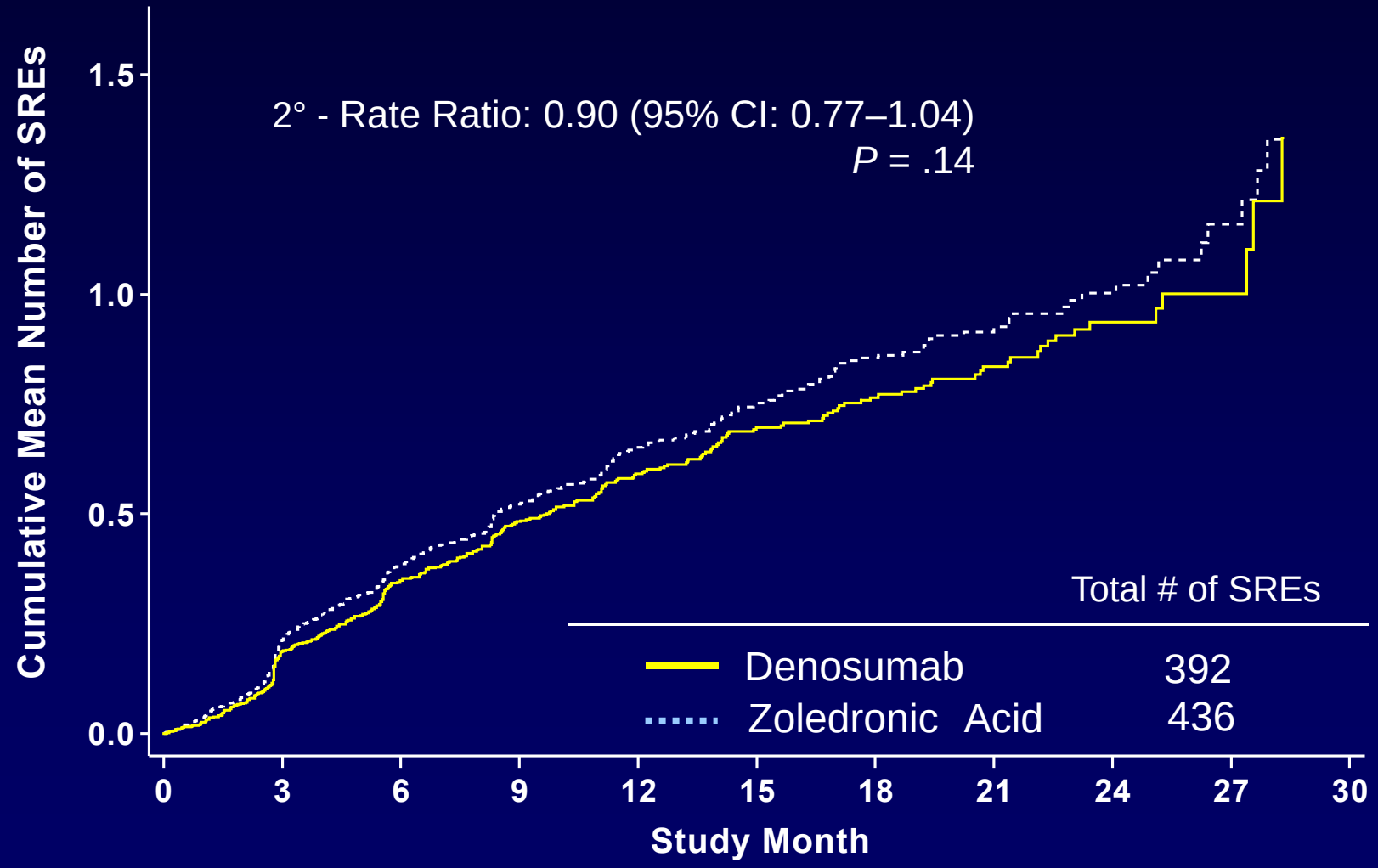
Zoledronic acid 4 mg IV* + placebo SC Q4W (n = 890)

- 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 (superiority)

* IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine per product label.

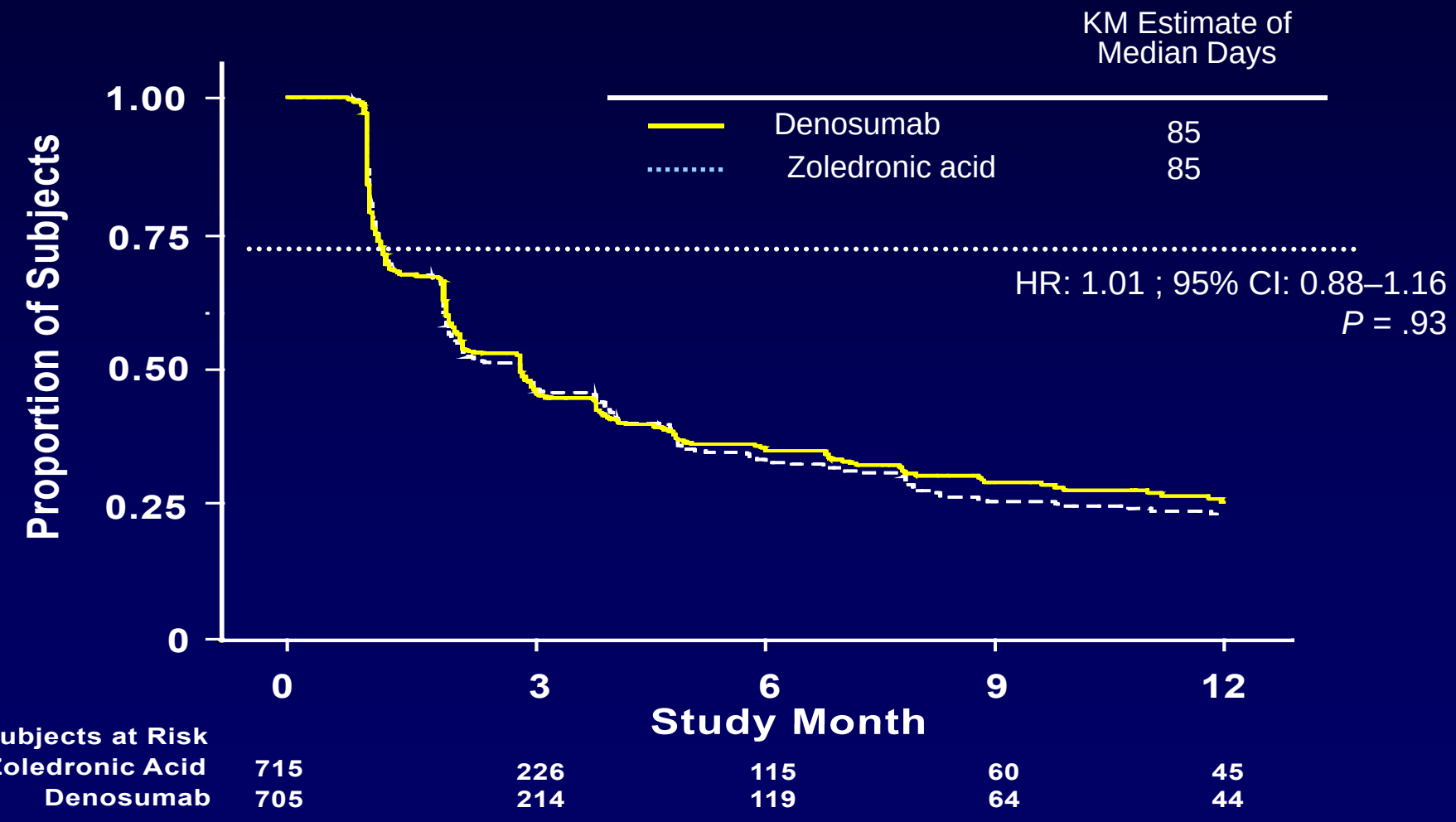
Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

Time to First-and-Subsequent On-Study SRE (Multiple Event Analysis)



Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

Time to Experiencing Pain Improvement (≥ 2-Point Decrease in Worst Pain Score of Brief Pain Inventory)



Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

Adverse Events of Interest

Event	Zoledronic acid (N = 878) n (%)	Denosumab (N = 878) n (%)
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* Includes blood creatinine increased, renal failure, renal failure acute, proteinuria, blood urea increased, renal impairment, urine output decreased, anuria, oliguria, azotaemia, hypercreatininemia, creatinine renal clearance decreased, renal failure chronic, blood creatinine abnormal

† $P = 1.0$

No neutralizing antidenosumab antibodies were detected

Henry D, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 20LBA.

Denosumab vs Zoledronic Acid in Patients With Solid Tumors or Multiple Myeloma

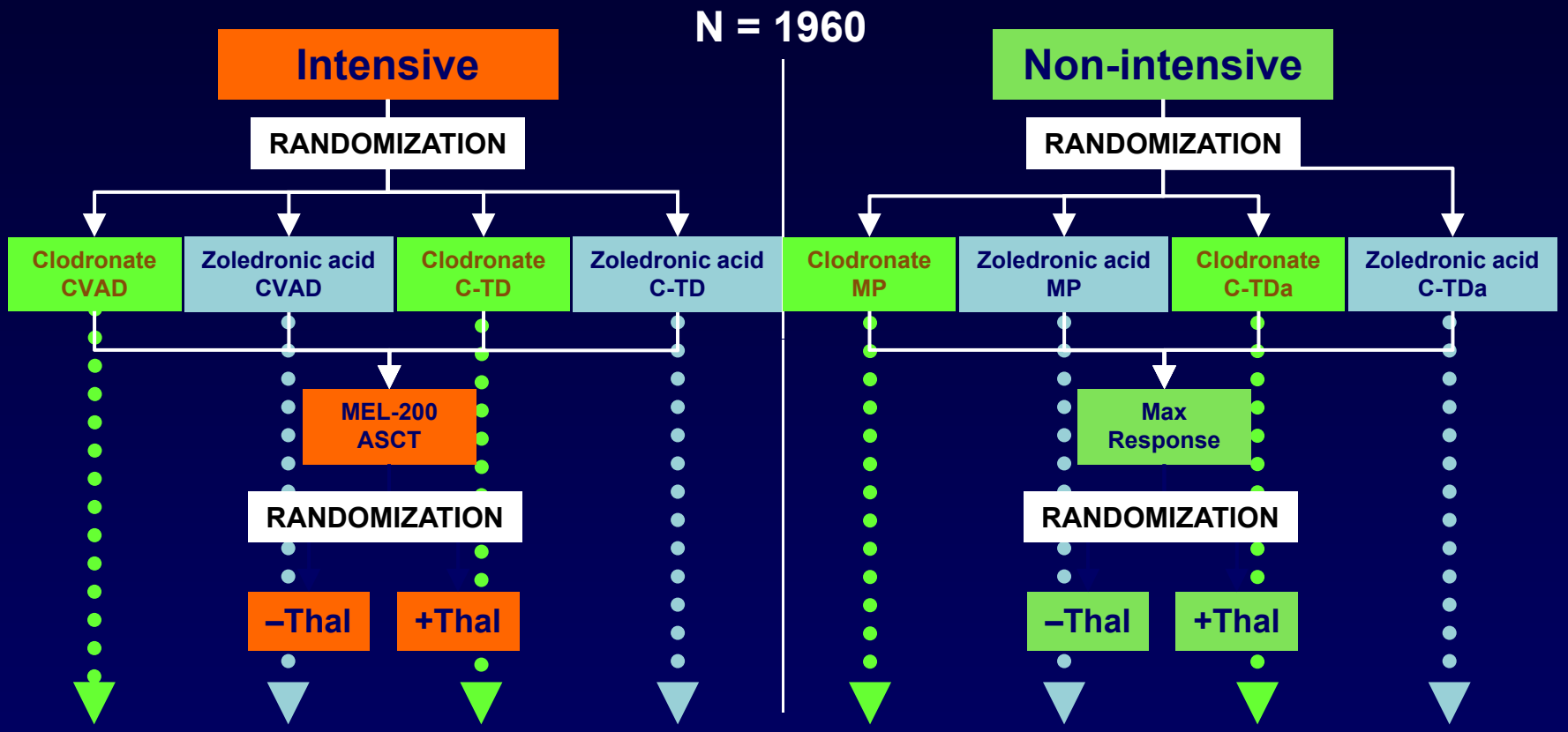
- Dmab is a fully-humanized monoclonal antibody against RANKL that can inhibit osteolysis
- Double-blind, active-controlled study evaluated efficacy and safety of Dmab (n = 886; 120 mg) vs ZOL (n = 890; 4 mg) every 4 weeks in patients with solid tumors (excluding breast and prostate) or MM
  - Only the primary endpoint of non-inferiority for time to first SRE was met
- In the overall population of patients with solid tumors or MM, time to disease progression was similar for Dmab vs ZOL (HR = 1.00, 95% CI: 0.89-1.12; *P* = 1.0)
- In post hoc analyses of the MM subset (n = 180), ZOL significantly improved OS vs Dmab (*P* < .05)

Abbreviations: Dmab, denosumab; MM, multiple myeloma; OS, overall survival; RANKL, receptor activator of nuclear factor kappa B ligand; ZOL, zoledronic acid.

Henry D, et al. *Eur J Cancer Suppl*. 2009;7(3):11. Abstract 20LBA.

Shifting Paradigms—Potential Anticancer Effects of Bone-Targeted Therapies in Multiple Myeloma

MRC Myeloma IX: Trial Design

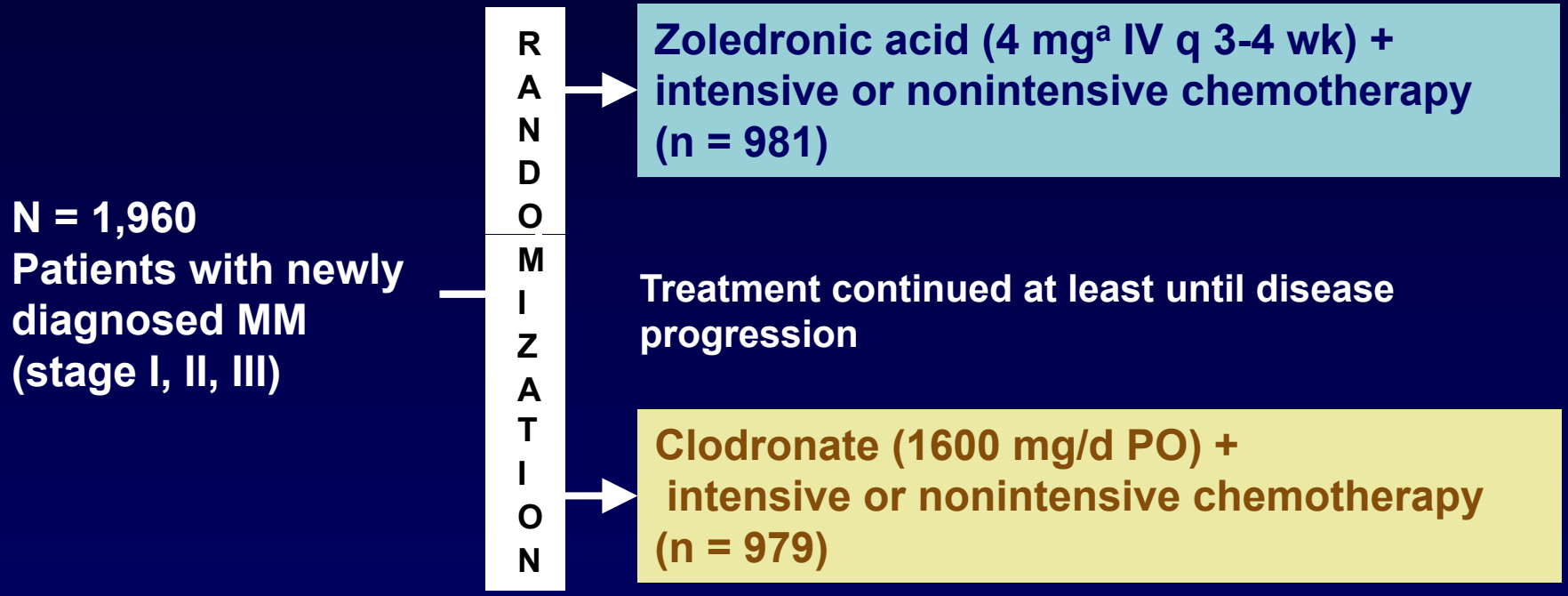


ISRCTN68454111

CVAD, cyclophosphamide (500 mg PO days 1, 5, and 15), vincristine (0.4 mg/d IV days 1-4), doxorubicin (9 mg/m^2/d days 1-4), dexamethasone (40 mg/d PO days 1-4, 13-15 q 3 wk); C-TD, cyclophosphamide (500 mg PO days 1, 9, and 15), thalidomide (100-200 mg/d), dexamethasone (40 mg/d PO days 1-4, 12-15 q 3 wk); C-TDa is C-TD except thalidomide 50-200 mg/d, dexamethasone 20 mg/d days 1-4, 15-18 q 4 wk; MP, melphalan (7 mg/m^2), prednisolone (40 mg) PO for 4 days; Thal, thalidomide (50 mg/d); PFS, progression-free survival; ORR, overall response rate; OS, overall survival, SRE, skeletal-related event; QoL, quality of life.

Morgan G, et al. *J Clin Oncol.* 201028(15S); Abstract 8021. Morgan G, et al. *Haematologica.* 2010;95(suppl 2): Abstract 0562.

MRC Myeloma IX: Analysis Schematic for ZOL vs CLO



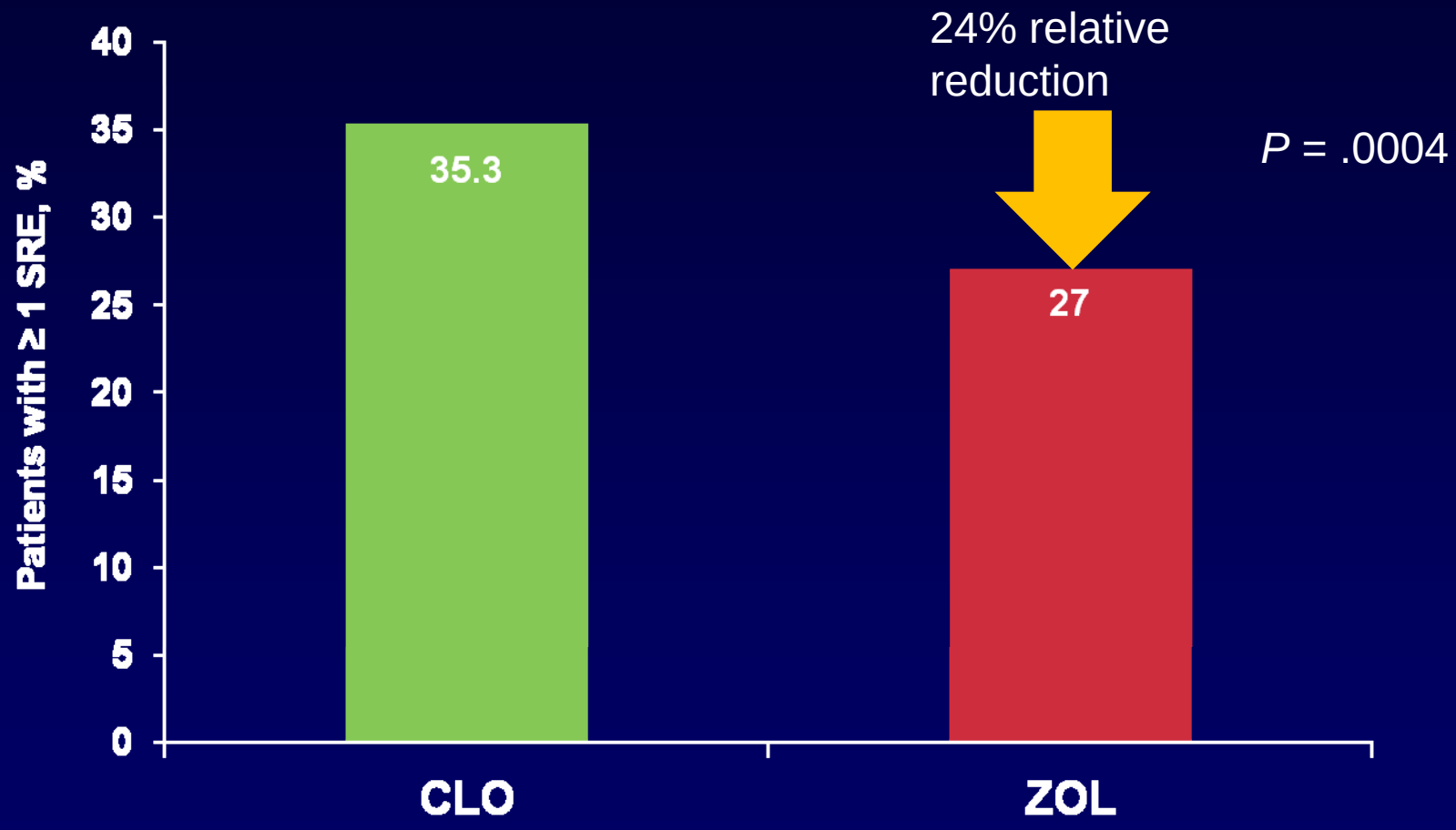
- Endpoints (ZOL vs CLO)
  - Primary: PFS, OS, and ORR
  - Secondary: Time to first SRE, SRE incidence, and safety

Abbreviations: CLO, clodronate; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; PO, oral; SRE, skeletal-related event; ZOL, zoledronic acid.

[a] Dose-adjusted for patients with impaired renal function, per the prescribing information.

Morgan G, et al. *J Clin Oncol*. 2010;28(7s): Abstract 8021.

MRC Myeloma IX: ZOL Significantly Reduced SREs vs. CLO[a] (1)



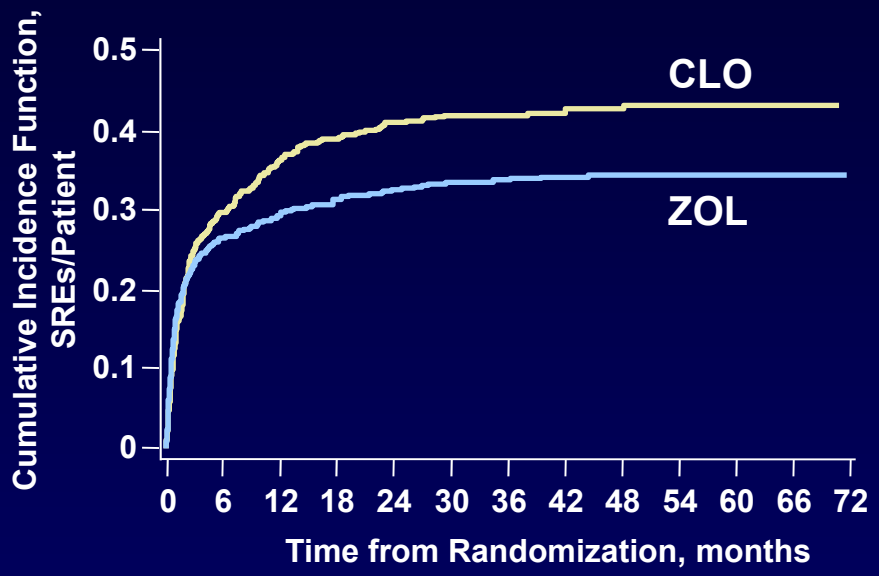
Abbreviations: CLO, clodronate; SRE, skeletal-related event; ZOL, zoledronic acid.

[a] SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.

Morgan G, et al. *J Clin Oncol.* 201028(15S); Abstract 8021. Morgan G, et al. *Haematologica.* 2010;95(suppl 2): Abstract 0562.

MRC Myeloma IX—
ZOL ↓ SREs vs CLO Regardless of Bone Lesions at Baseline

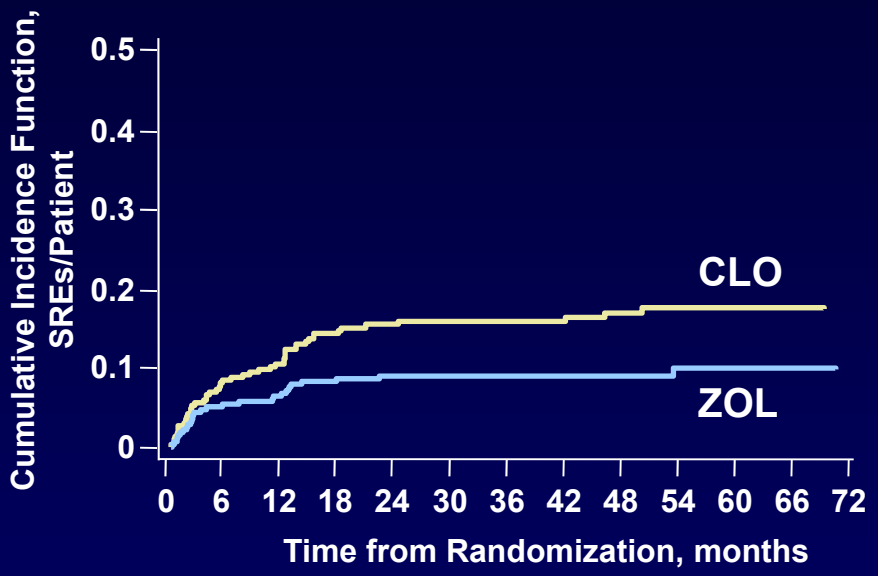
Bone Lesions at Baseline



Patients, n

ZOL	668	415	325	250	189	136	100	69	50	35	18	6	0
CLO	682	402	297	212	164	117	75	50	37	24	12	4	0

No Lesions at Baseline



Patients, n

ZOL	302	241	185	135	92	63	38	28	18	11	8	5	0
CLO	276	212	159	118	91	56	37	24	18	12	7	4	0

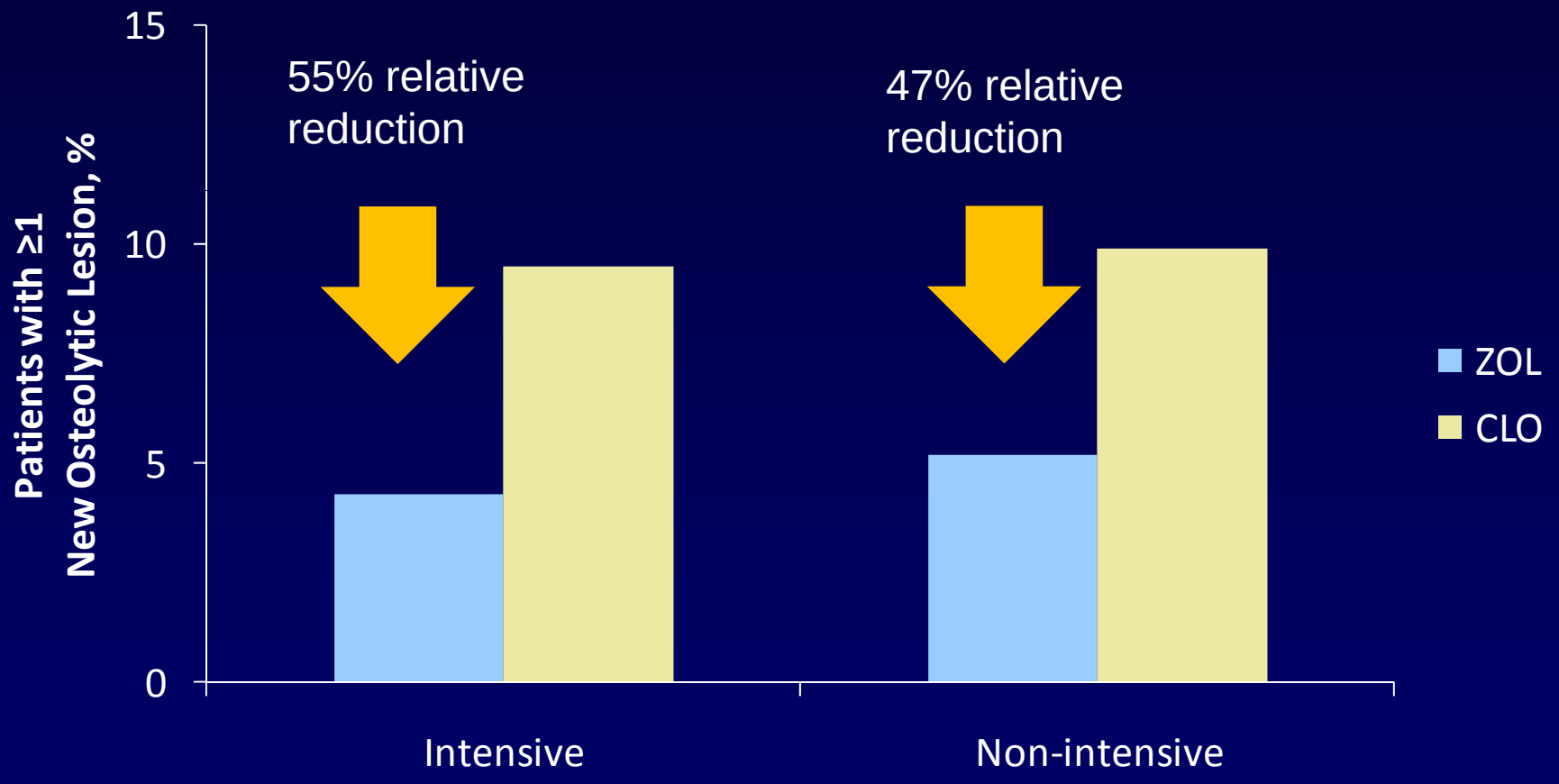
Highlights the importance of treating all patients regardless of skeletal morbidity at presentation

Abbreviations: CLO, clodronate; SRE, skeletal-related event; ZOL, zoledronic acid.

[a] SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.

Morgan G, et al. Presented at: 15th European Hematology Association Congress—Presidential Symposium; June 12, 2010: Barcelona, Spain. Abstract 0562.

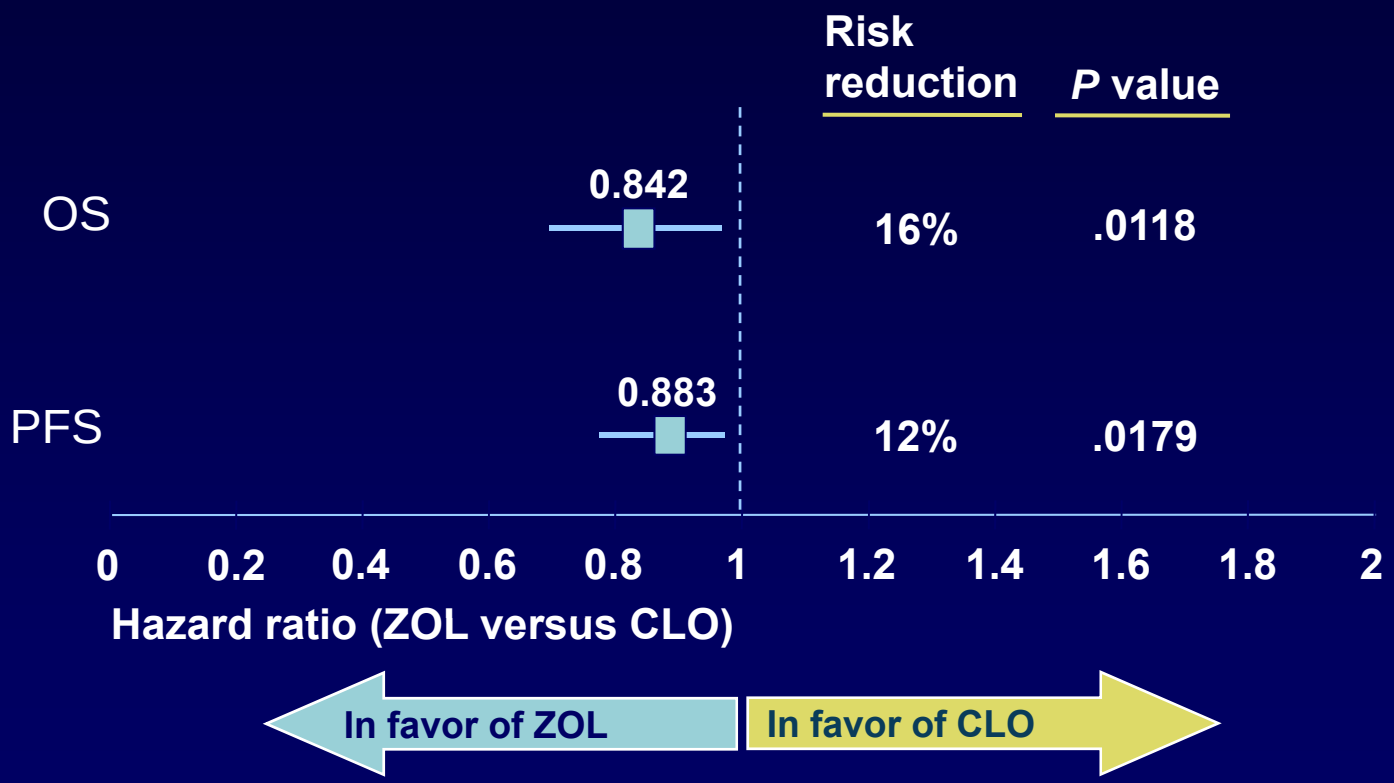
MRC Myeloma IX—
ZOL Significantly ↓ Development of New Osteolytic Lesions vs CLO



Morgan G, et al. Presented at: 15th European Hematology Association Congress—Presidential Symposium; June 12, 2010: Barcelona, Spain. Abstract 0562.

MRC Myeloma IX: ZOL Improved OS and PFS vs. CLO[a]

- ZOL significantly reduced the relative risk of death by 16% vs CLO (HR = 0.842; 95% CI = 0.736, 0.963; *P* = .0118)

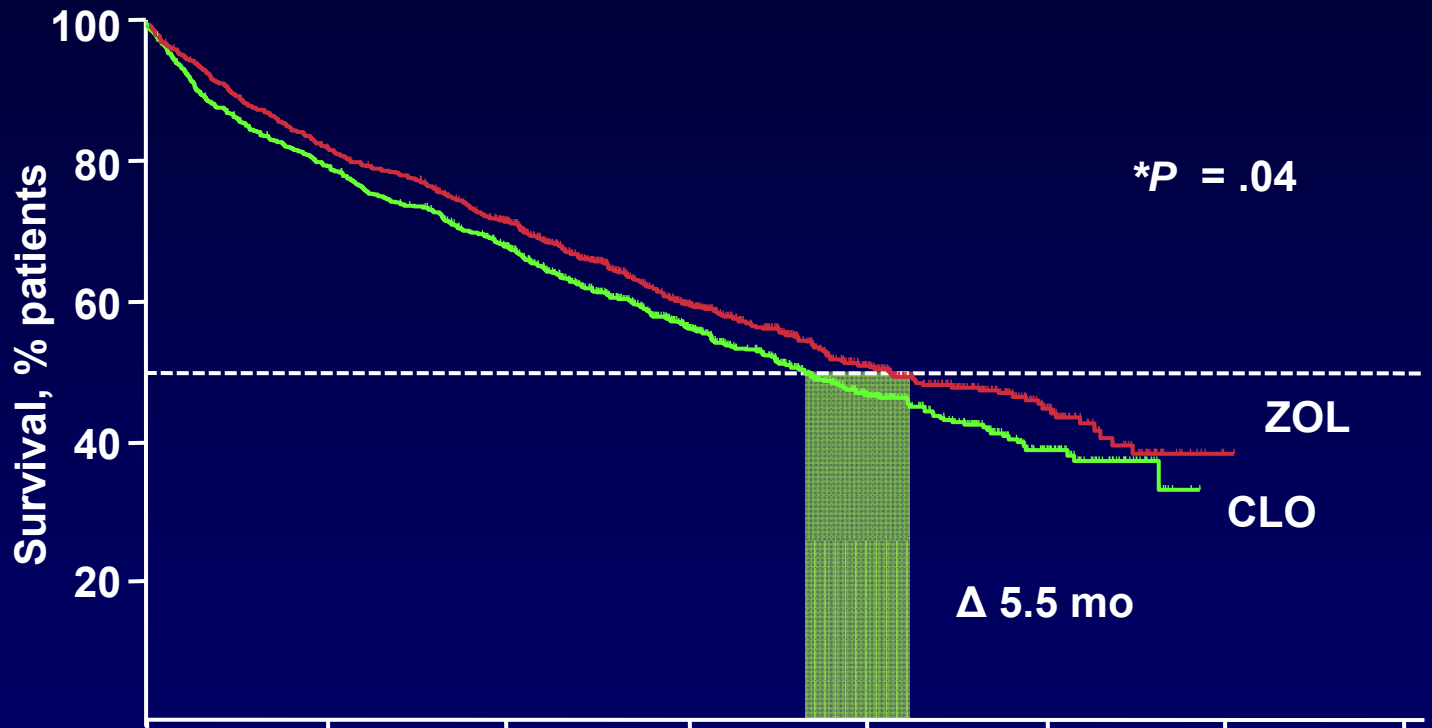


Abbreviations: CI, confidence interval; CLO, clodronate; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; ZOL, zoledronic acid.

[a] Cox model adjusted for chemotherapy, and minimization factors.

Morgan G, et al. *J Clin Oncol.* 201028(15S); Abstract 8021. Morgan G, et al. *Haematologica.* 2010;95(suppl 2): Abstract 0562.

MRC Myeloma IX – ZOL Significantly Improved OS vs CLO[a]



Number at risk:

ZOL	981	806	675	418	222	79	3
CLO	979	776	642	399	208	69	0

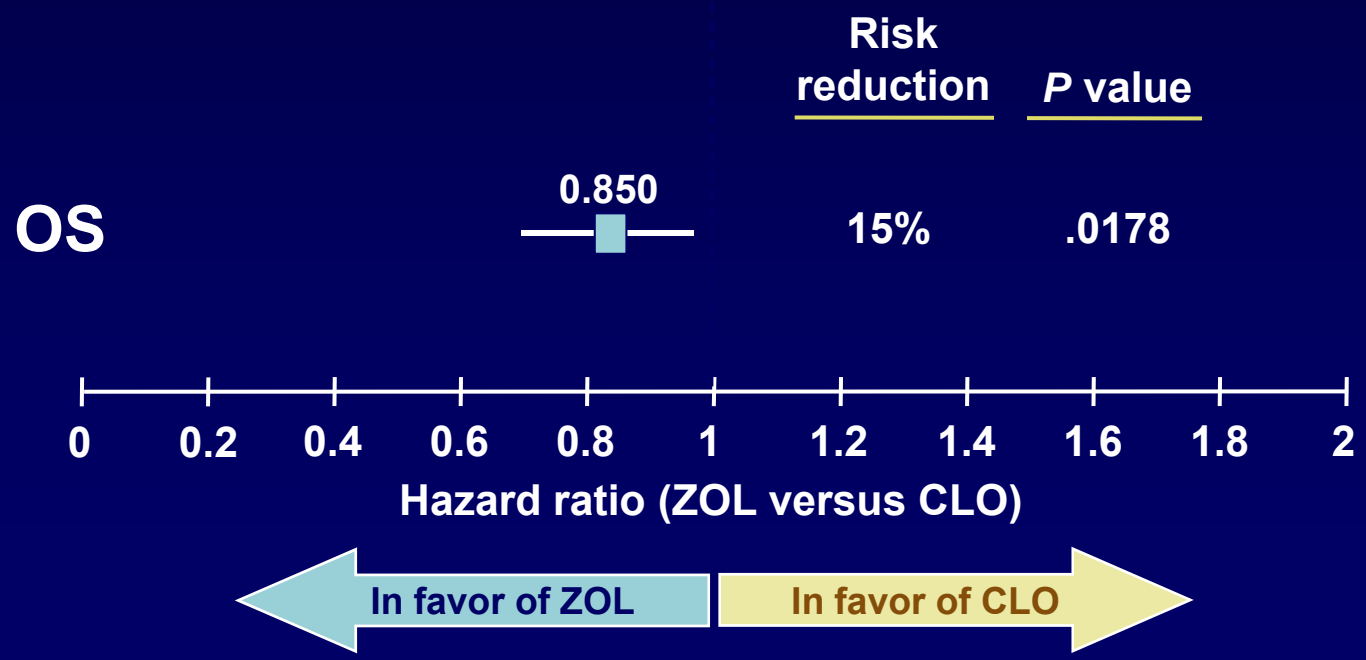
Abbreviations: CLO, clodronate; ZOL, zoledronic acid.
*Log-rank, stratified by treatment pathway.

Morgan G, et al. *J Clin Oncol*. 2010;28(7s): Abstract 8021.

[a] Kaplan-Meier analysis adjusted for treatment pathway (intensive vs not).

ZOL Improved OS vs CLO After Adjustment for SREs[a]

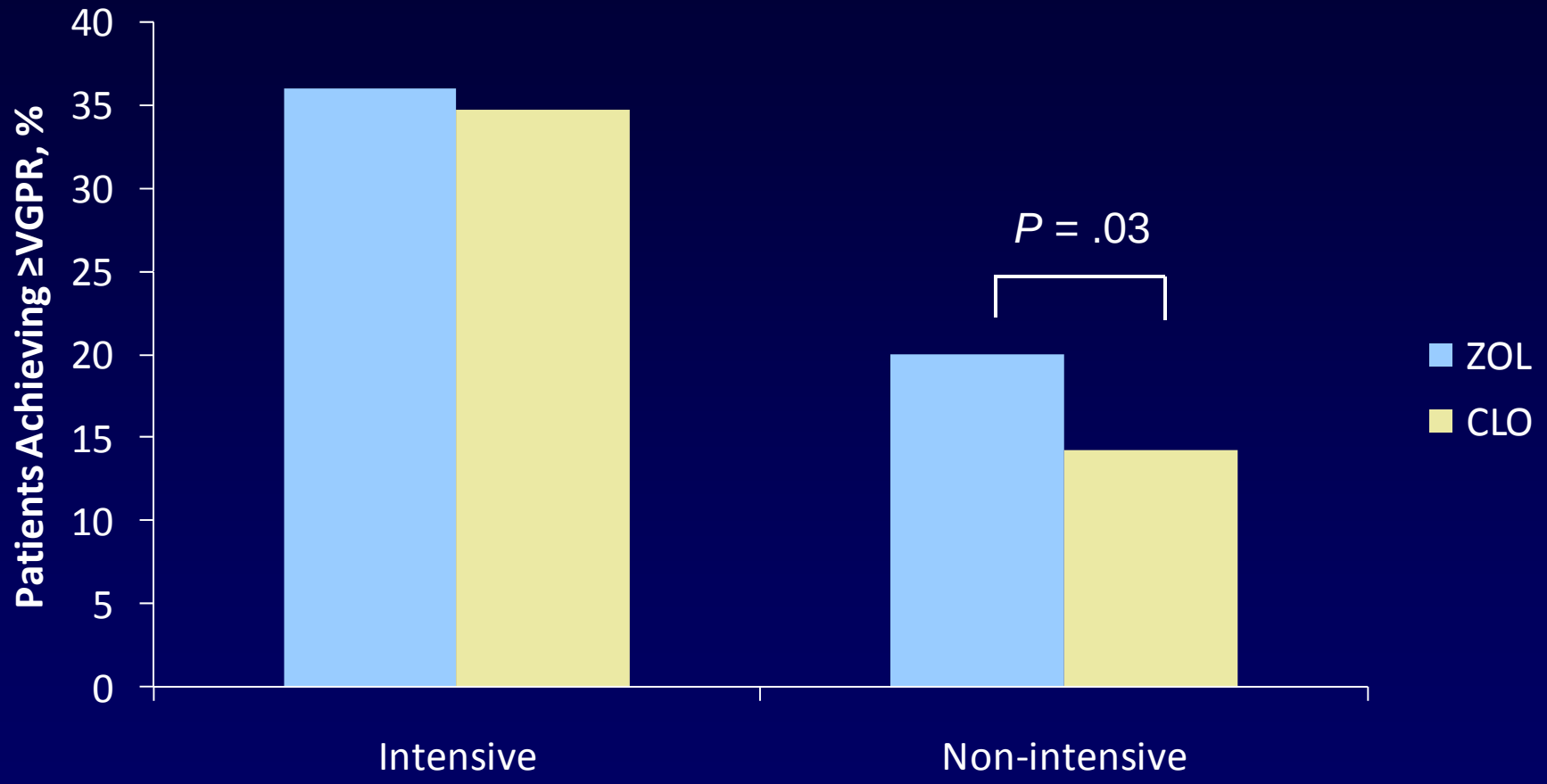
- **Is the observed OS ↑ with ZOL because of SRE prevention, or does it represent an anti-myeloma effect?**
- **Exploratory analysis that adjusted for SREs**
- **ZOL reduced the risk of death by 15% vs CLO (HR = 0.850; *P* = .0178)**



[a] Time to first SRE was included as a time-dependent covariate in an exploratory Cox model examining OS.

Morgan G, et al. *J Clin Oncol*. 2010;28(7s): Abstract 8021.

MRC Myeloma IX—ZOL ↑ Rates of CR/VGPR vs CLO in Non-intensive Pathway



Abbreviations: CLO, clodronate; VGPR, very good partial response (defined as ≥90% but <100% reduction in serum M-protein, with positive immunofixation); ZOL, zoledronic acid

Morgan G, et al. Presented at: 15th European Hematology Association Congress—Presidential Symposium; June 12, 2010: Barcelona, Spain. Abstract 0562.

MRC Myeloma IX: Summary

- After a median follow-up of 3.7 years
  - ZOL significantly prolonged OS vs CLO (*P* = .0118)
  - ZOL significantly prolonged PFS vs CLO (*P* = .0179)
  - ZOL significantly reduced the proportion of patients with SREs vs CLO (*P* = .0004)
  - ZOL and CLO were generally well tolerated, and safety profiles were as expected
    - ONJ was low overall, but higher for ZOL vs CLO (3.6% vs 0.3%, respectively)

Morgan G, et al. *J Clin Oncol.* 201028(15S); Abstract 8021. Morgan G, et al. *Haematologica.* 2010;95(suppl 2): Abstract 0562.

Conclusions

- Bisphosphonates remain the cornerstone of the management of myeloma bone disease
- Optimal dose and more effective BP needs to be defined
- The results of MRC IX study confirm the anti-myeloma effect of zoledronic acid
- Denosumab needs to be further tested in MM
- Anti-Dkk1 drugs (BHQ-880) are underway
- Bortezomib has an anabolic bone effect but larger studies with bone specific end-points are needed