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Updated Recommendation of Bisphosphonate Treatment Including Prevention and Management of Osteonecrosis of the Jaw

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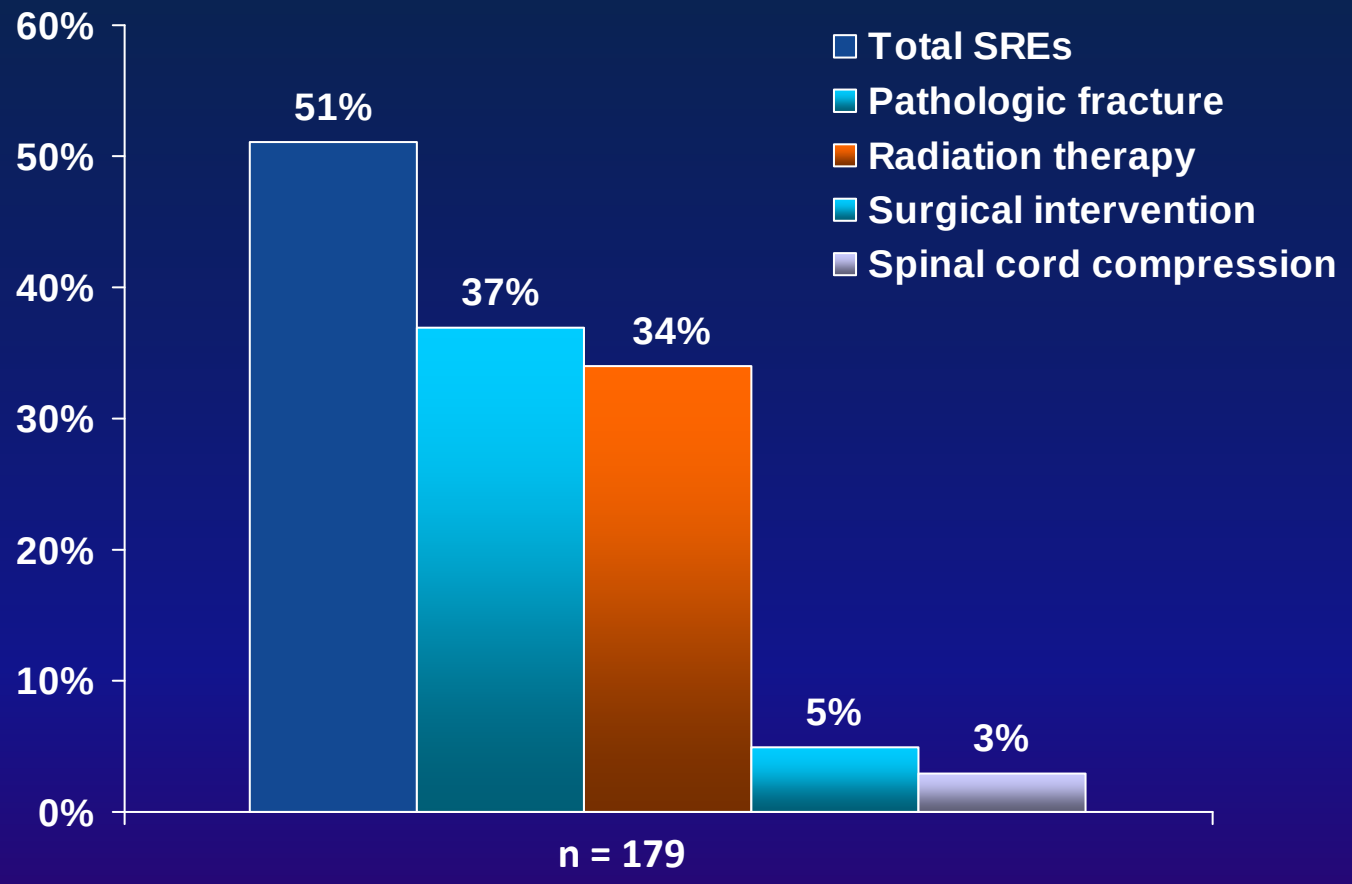
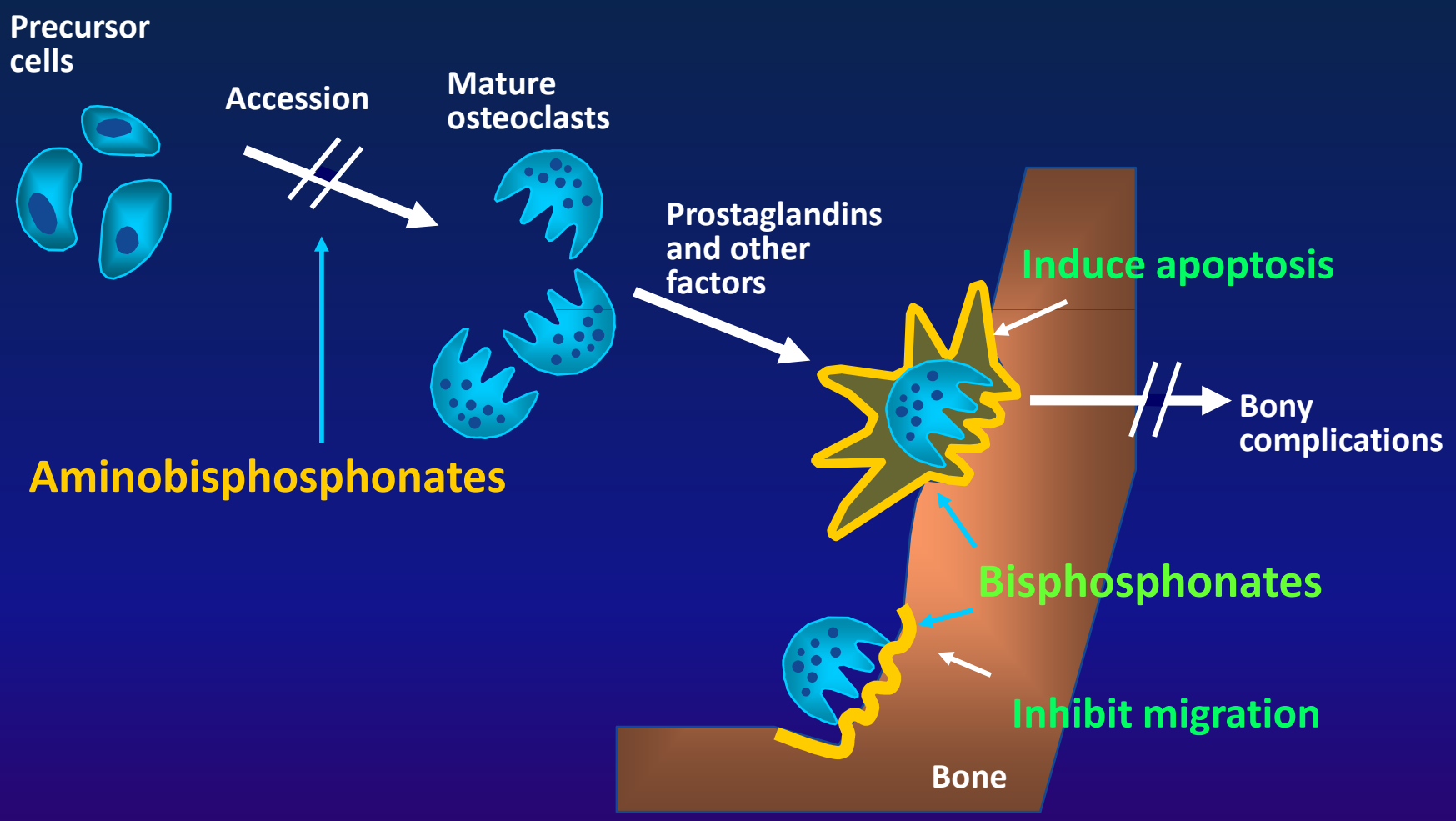
SREs Are a Serious Problem for Patients With Multiple Myeloma



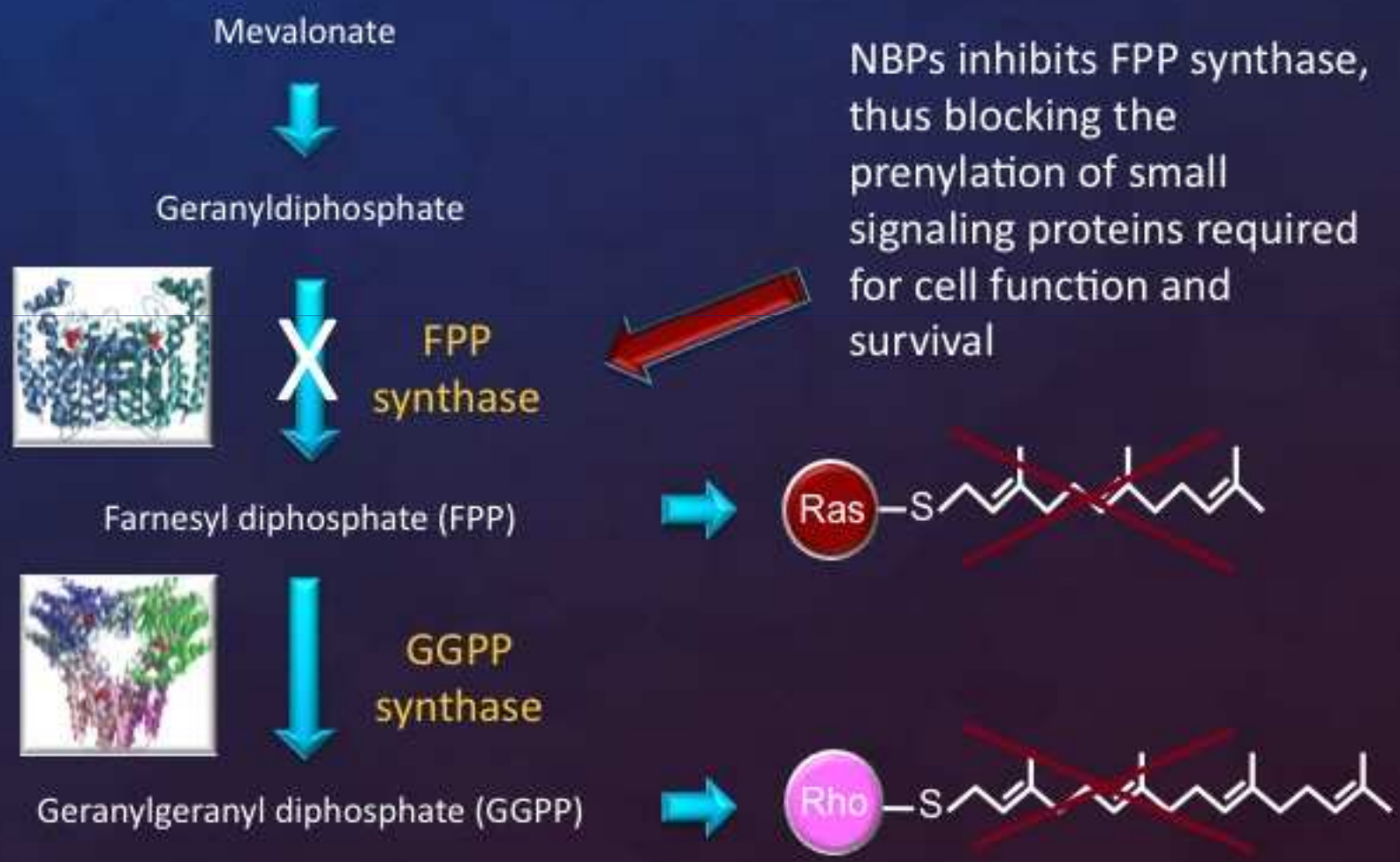
SRE, skeletal-related event.
a. 21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.
Berenson JR, et al. J Clin Oncol. 1998;16:593-602.

Bisphosphonates (BPs)



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

Molecular Mechanisms of Action of Nitrogen-containing Bisphosphonates



Kavanagh *et al.*, PNAS, 2006; Rondeau *et al.*, Chem Med Chem, 2006; Kavanagh *et al.*, JBC, 2006

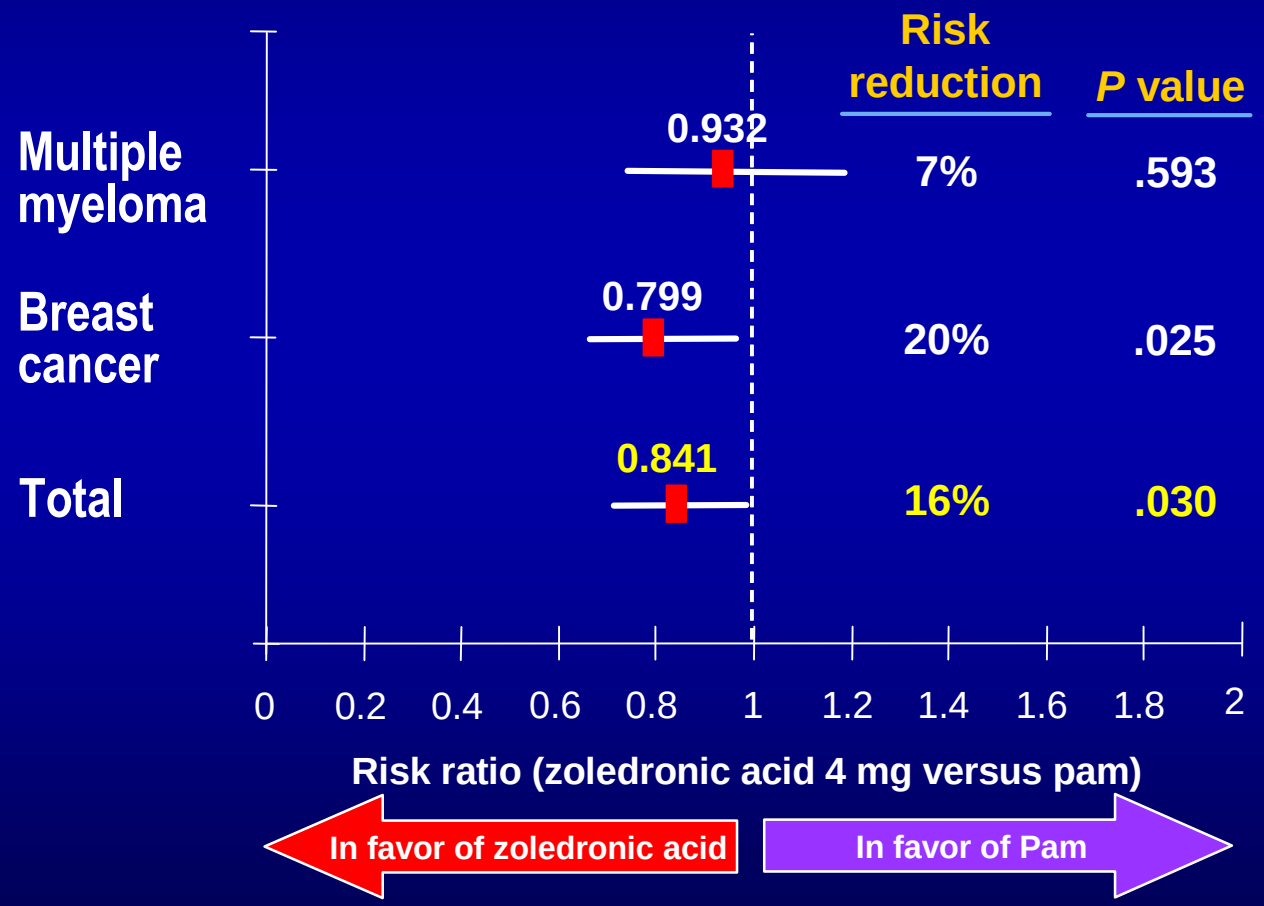
Double-Blind Clinical Trials of BPs in Patients With MM

First Author (year)	BP	Dosage	N[a]	Reduction of Pain	Reduction of SREs[b]	Survival Benefit
Placebo-controlled trials[b]						
Lahtinen (1992) and Laakso (1998)	CLO	2.4 g/day, PO, for 2 yr	350	Yes	Yes	NE
McCloskey (1998; 2001)	CLO	1.6 g/day, PO	530	Yes	Yes	Subset[c]
Brincker (1998)	PAM	300 mg/day, PO	300	Yes	No	No
Berenson (1996; 1998)	PAM	90 mg, IV, q 4 wks for 21 cycles	392	Yes	Yes	Subset[c]
Menssen (2002)	IBN	2 mg, IV, mo	198	No	No	No
Aviles (2007)	ZOL	4 mg IV q 28 d	94	Yes	Yes	Yes
PAM-controlled trials						
Berenson (2001)	ZOL	2 or 4 mg, IV, mo	108	Yes	Yes	NE
Rosen (2001; 2003)	ZOL	2 or 8 mg, IV, mo	513	Yes	Yes	Subset[c]

[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] Subsets were, patients without vertebral facture (McCloskey), patients with relapsed/refractory MM (Berenson), patients with elevated baseline bone-specific alkaline phosphatase levels (Rosen).
Abbreviations: BP, bisphosphonate; CLO, clodronate; IBN, ibandronate; IV, intravenous; MM, multiple myeloma; NE, not evaluated; PAM, pamidronate; PO, by mouth; SREs, skeletal-related events; ZOL, zoledronic acid.

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

ZOL Was as Efficacious as PAM Regarding Reduction of SREs in the MM Stratum

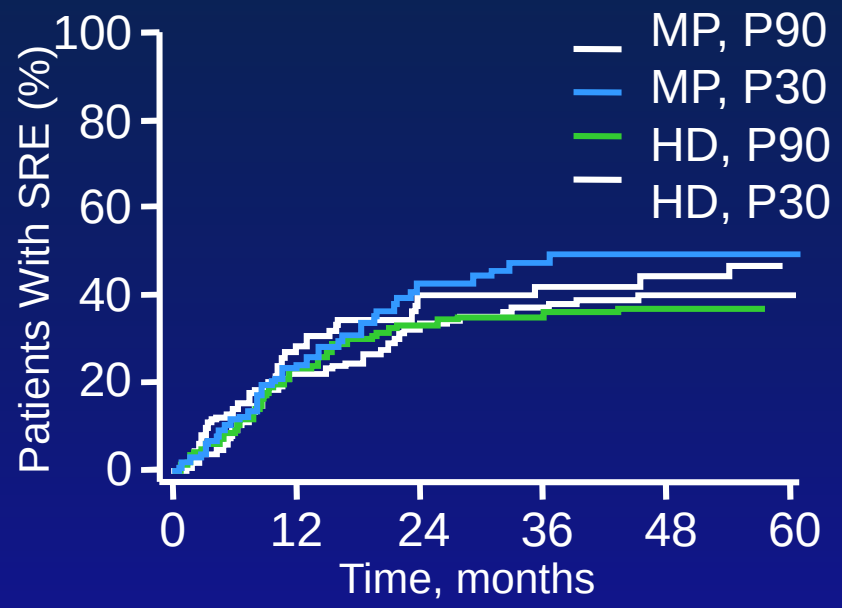


*Hypercalcemia of malignancy is included as an SRE.

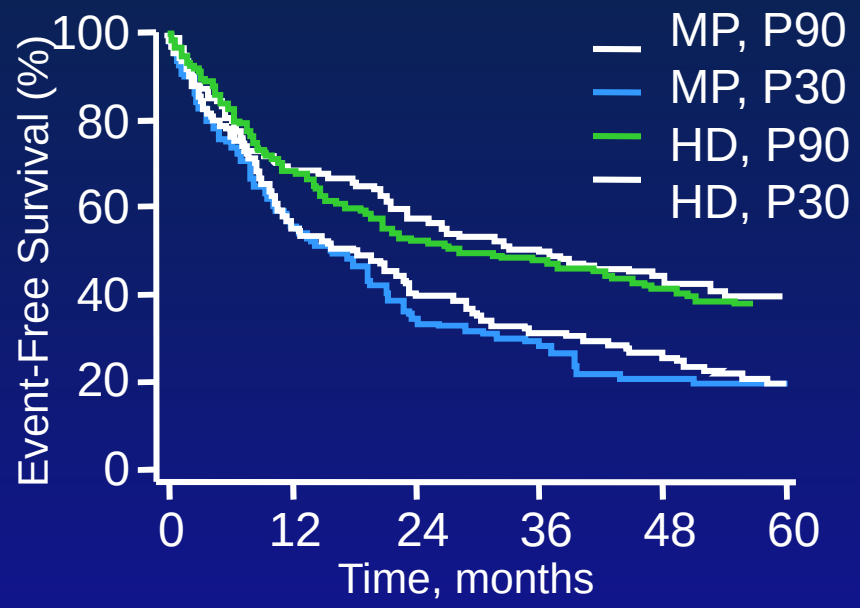
Rosen et al. Cancer 2003;98:1735-1744.

Pamidronate: 30 mg *versus* 90 mg

Time to skeletal event
by planned treatment



Skeletal event free survival
by planned treatment



Number at risk

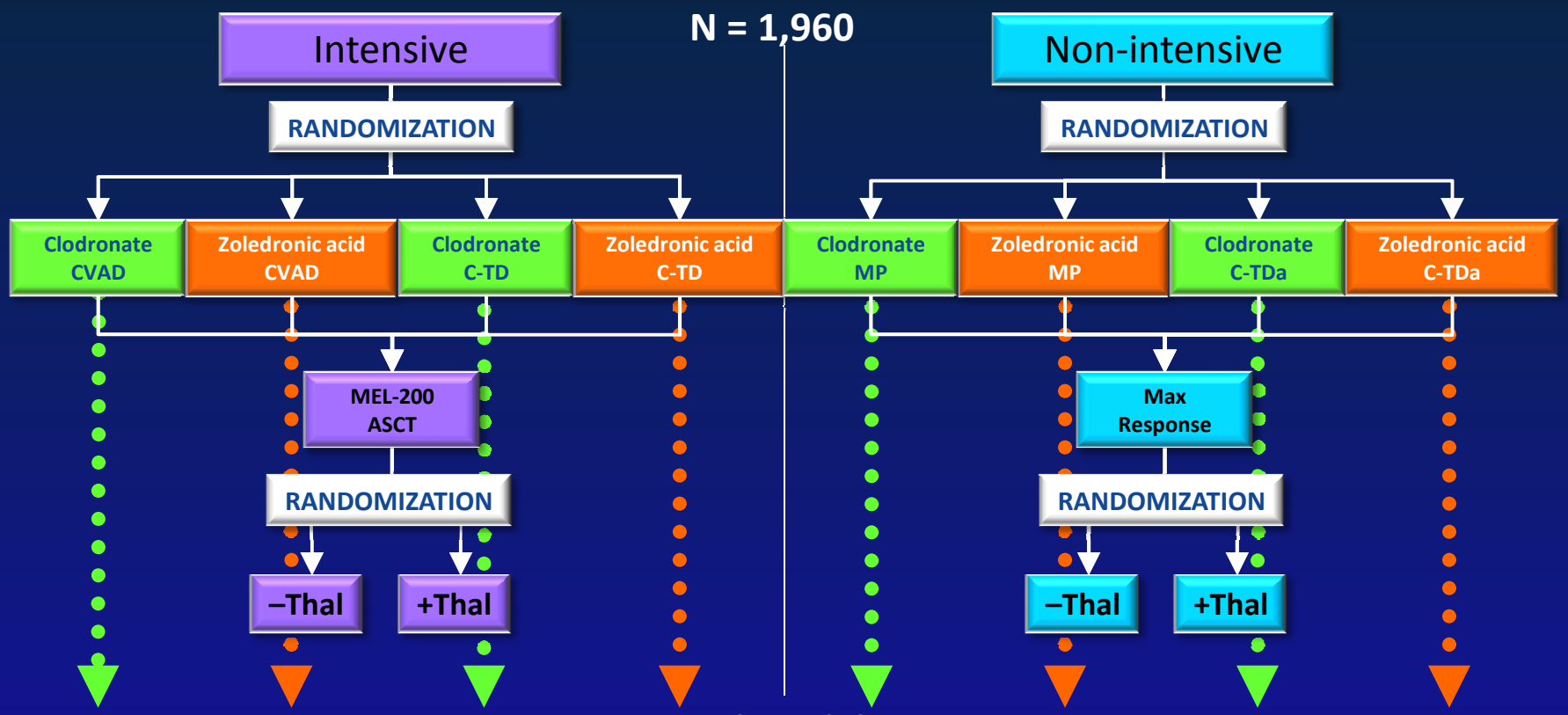
MP, P90	106	58	41	32	25	15
MP, P30	107	59	38	30	20	12
HD, P90	143	97	74	67	50	38
HD, P30	145	98	82	72	52	35

Number at risk

MP, P90	106	58	41	32	26	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

Gimsing P, et al. Lancet Oncol. 2010;11:973.

MRC Myeloma IX: Trial Design



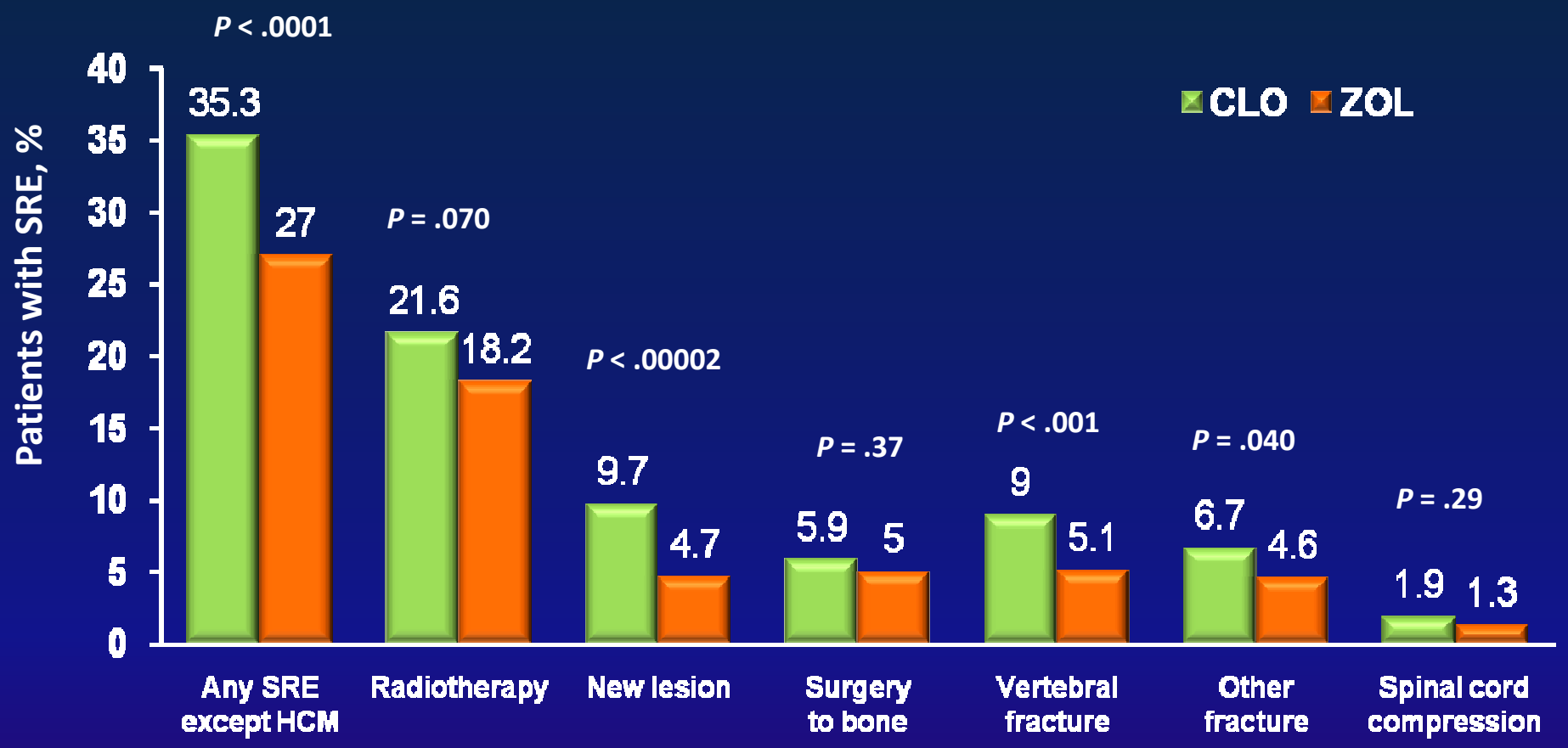
Treatment continued until disease progression

Primary endpoints: PFS, OS, ORR
Secondary endpoints: Time to first SRE, SRE incidence, Safety, and QoL
Zoledronic acid (4 mg IV q 3-4 wk); Clodronate (1,600 mg/d PO)

Abbreviations: C-TD, cyclophosphamide (500 mg PO d1, 9, 15), thalidomide (100-200 mg/d), dexamethasone (40 mg/d PO d1-4, 12-15 q3wk); C-Tda, C-TD except thalidomide 50-200 mg/d, dexamethasone 20 mg/d d1-4, 15-18 q4wk; CVAD, cyclophosphamide (500 mg PO d1, 5, 15), vincristine (0.4 mg/d IV d1-4), doxorubicin (9 mg/m^2/d d1-4), dexamethasone (40 mg/d PO d1-4, 13-15 q3wk); MP, melphalan (7 mg/m^2), prednisolone (40 mg) PO for 4 days; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; PO, oral; QoL, quality of life; SRE, skeletal-related event; Thal, thalidomide (50 mg/d).

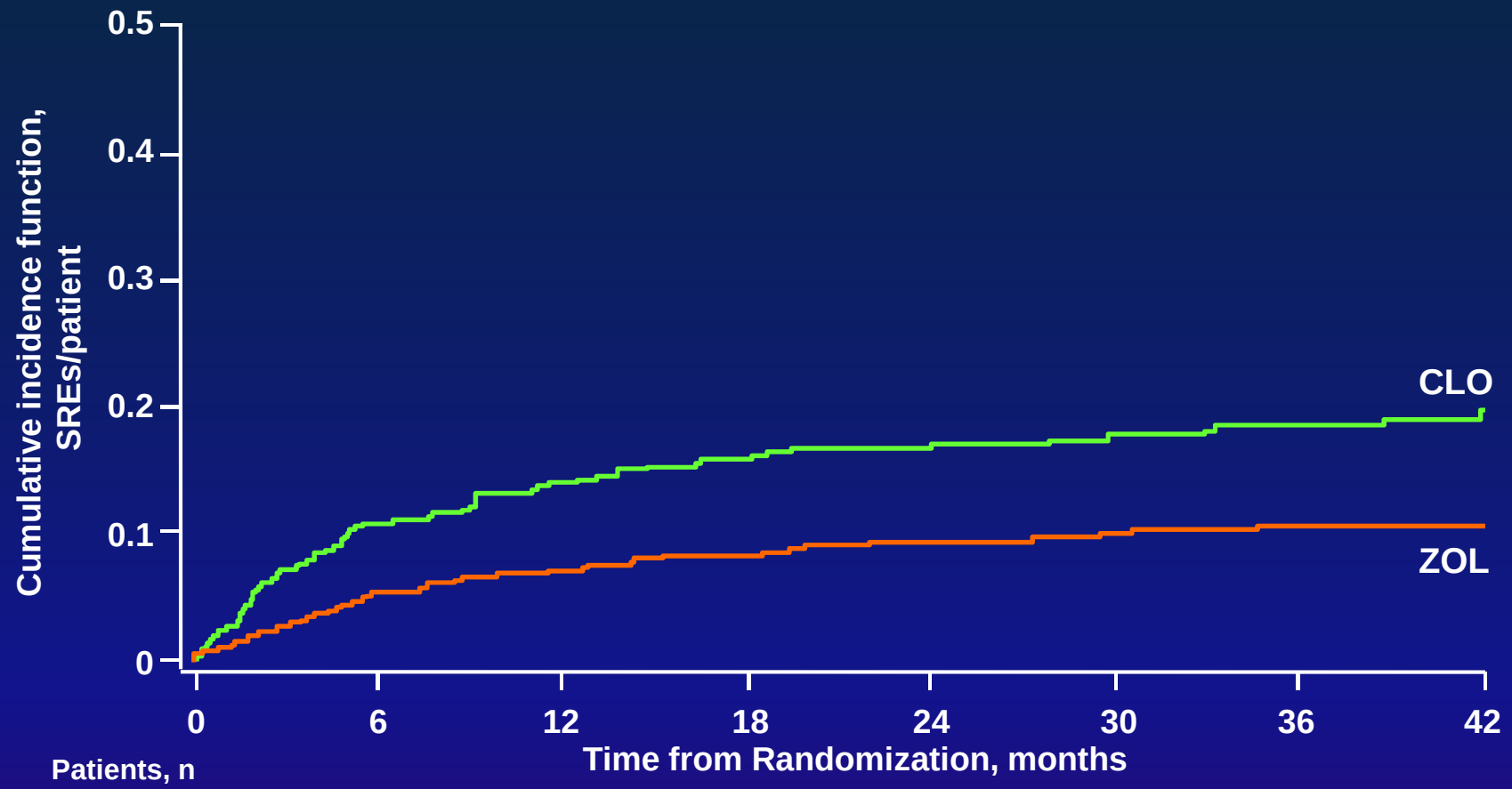
Morgan G, et al. Lancet. 2010;376(9757):1989-1999.

MRC Myeloma IX:
ZOL ↓ SREs *vs.* CLO in Overall Population



Morgan G, et al. Lancet Oncol. 2011;12(8):743-52.

MRC Myeloma IX—ZOL Reduced SREs vs CLO During Maintenance Therapy

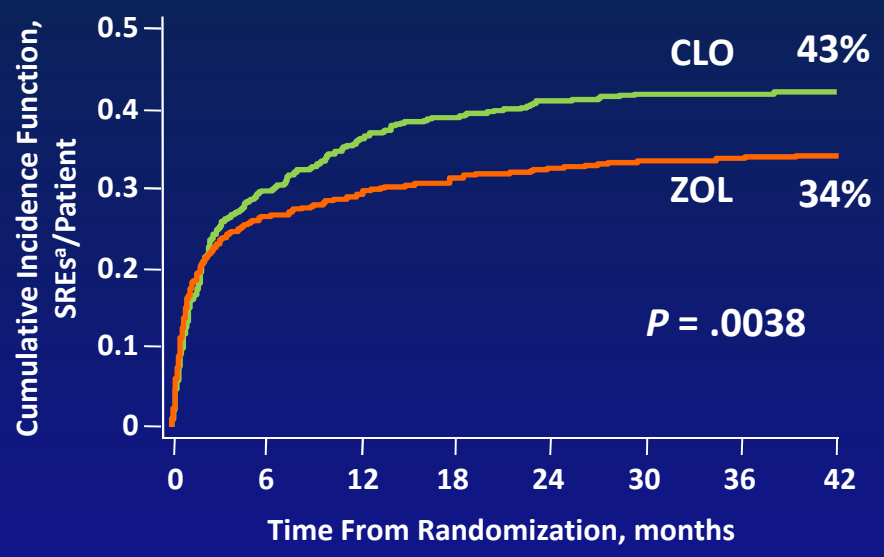


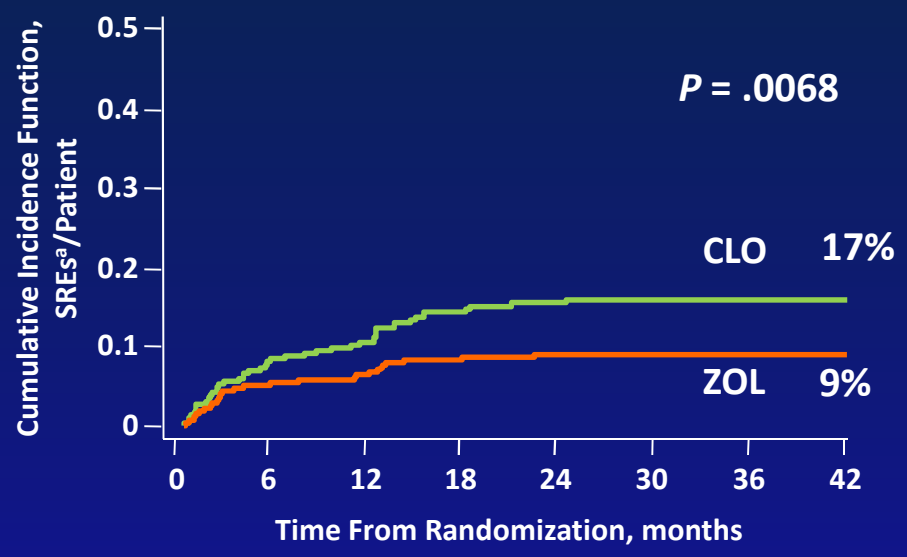
Patients, n								
ZOL	428	324	251	190	143	102	75	54
CLO	390	281	210	150	114	67	53	31

Morgan GJ, et al. Blood 2012;119:5374-83.

GM

MRC Myeloma IX: ZOL ⬇ SREs vs CLO Regardless of Bone Lesions at Baseline





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

[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.
Abbreviations: CLO, clodronate; MRC, Medical Research Council; SRE, skeletal-related event; ZOL, zoledronic acid.

Morgan G, et al. Lancet Oncol. 2011;12(8):743-52.

Cochrane Meta-analysis

- Use of bisphosphonates in patients with MM reduces pathological vertebral fractures, SREs and pain. Assuming a baseline risk of 20% to 50% for vertebral fracture without treatment, between 8 and 20 MM patients should be treated to prevent vertebral fracture(s) in one patient.
- Assuming a baseline risk of 31% to 76% for pain amelioration without treatment, between 5 and 13 MM patients should be treated to reduce pain in one patient.
- With a baseline risk of 35% to 86% for SREs without treatment, between 6 and 15 MM patients should be treated to prevent SRE(s) in one patient.
- No evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) for any outcome.
- However, zoledronate appears to be superior to placebo and etidronate in improving OS.

Mhaskar R, et al. Cochrane Database Syst Rev. 2012;5:CD003188.

IMWG Guidelines 2013: When Should BPs Be Started?

- Bisphosphonates should be initiated in MM patients, with (grade A) or without (grade B) detectable osteolytic bone lesions in conventional radiography, who are receiving anti-myeloma therapy as well as patients with osteoporosis (grade A) or osteopenia (grade C) due to myeloma.
- ***The beneficial effect of zoledronic acid (ZOL) in patients without detectable bone disease by MRI or PET/CT is not known.***
- Intravenous (IV) ZOL and pamidronate (PAM) exhibit comparable efficacy in reducing SREs in patients with MM, and are recommended for preventing SREs in patients with active MM (grade A).
- Intravenous ZOL is recommended over oral clodronate (CLO) because it is more efficacious at preventing SREs (grade A).

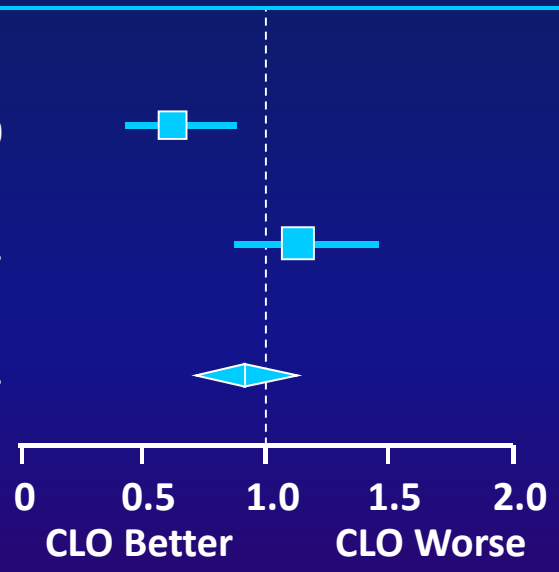
Terpos E, et al. J Clin Oncol. 2013;in press.

Clinical Evidence for Anti-Myeloma Effect of Bisphosphonates

CLO ⬆ OS vs Placebo in Subgroup of Patients With MM

- Prospective study of CLO (1,600 mg/day) vs PLA in MM
  - Similar median OS between treatment arms (34 vs 36 months; *P* = .38)
  - Patients (n = 153) with no vertebral fractures at presentation had significant ⬆ OS with CLO vs PLA (59 vs 37 months; *P* = .004)

	Patients, %		CLO Events		Ratio of Annual Event Rates	
Category	CLO	PLA	Logrank O-E	Variance of O-E	Ratio (95% CI) CLO:PLA	Reduction %
Baseline vertebral						
No fractures	74.0	92.5	–15.3	31.0		39
Fractures	96.6	93.1	6.4	54.1		–13
Total	87.9	92.9	–8.9	85.1		9.9

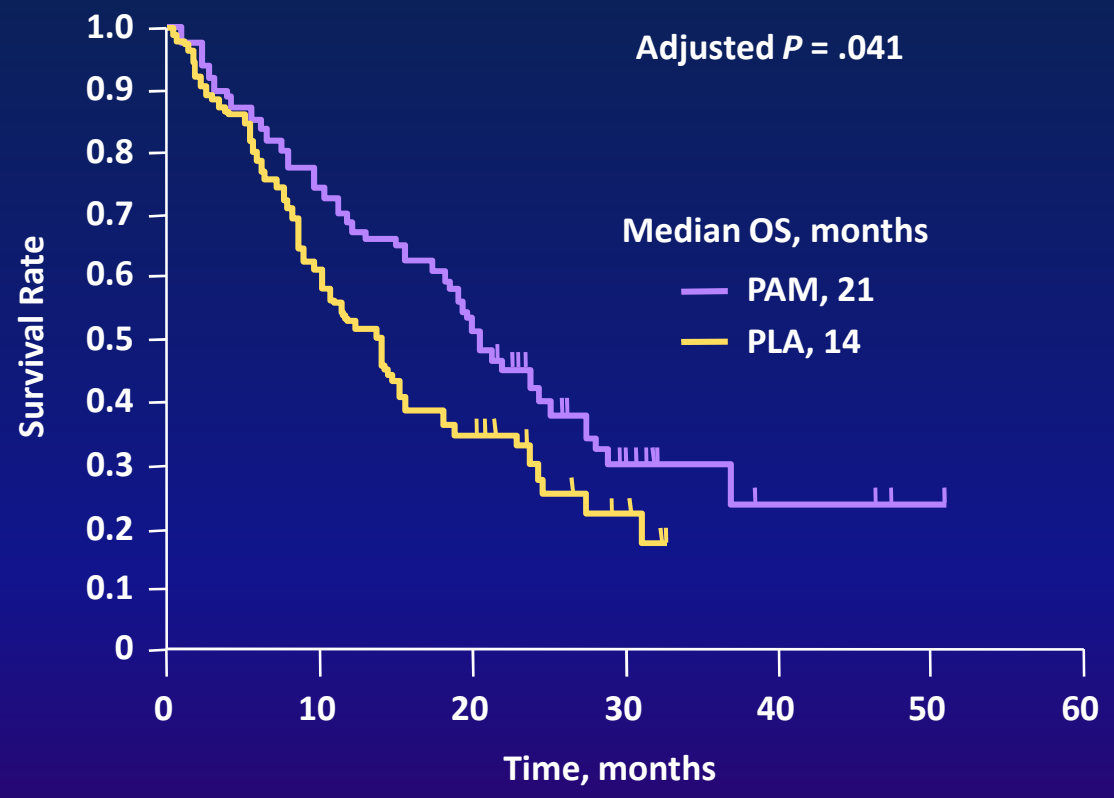


Abbreviations: CLO, clodronate; E, expected; MM, multiple myeloma; O, observed; PLA, placebo.

McCloskey EV, et al. Br J Haematol. 2001;113(4):1035-1043.

PAM ⬆ OS vs Placebo in MM Patients

- PAM (n = 205; 90 mg q4w) vs PLA (n = 187) in MM stage III patients

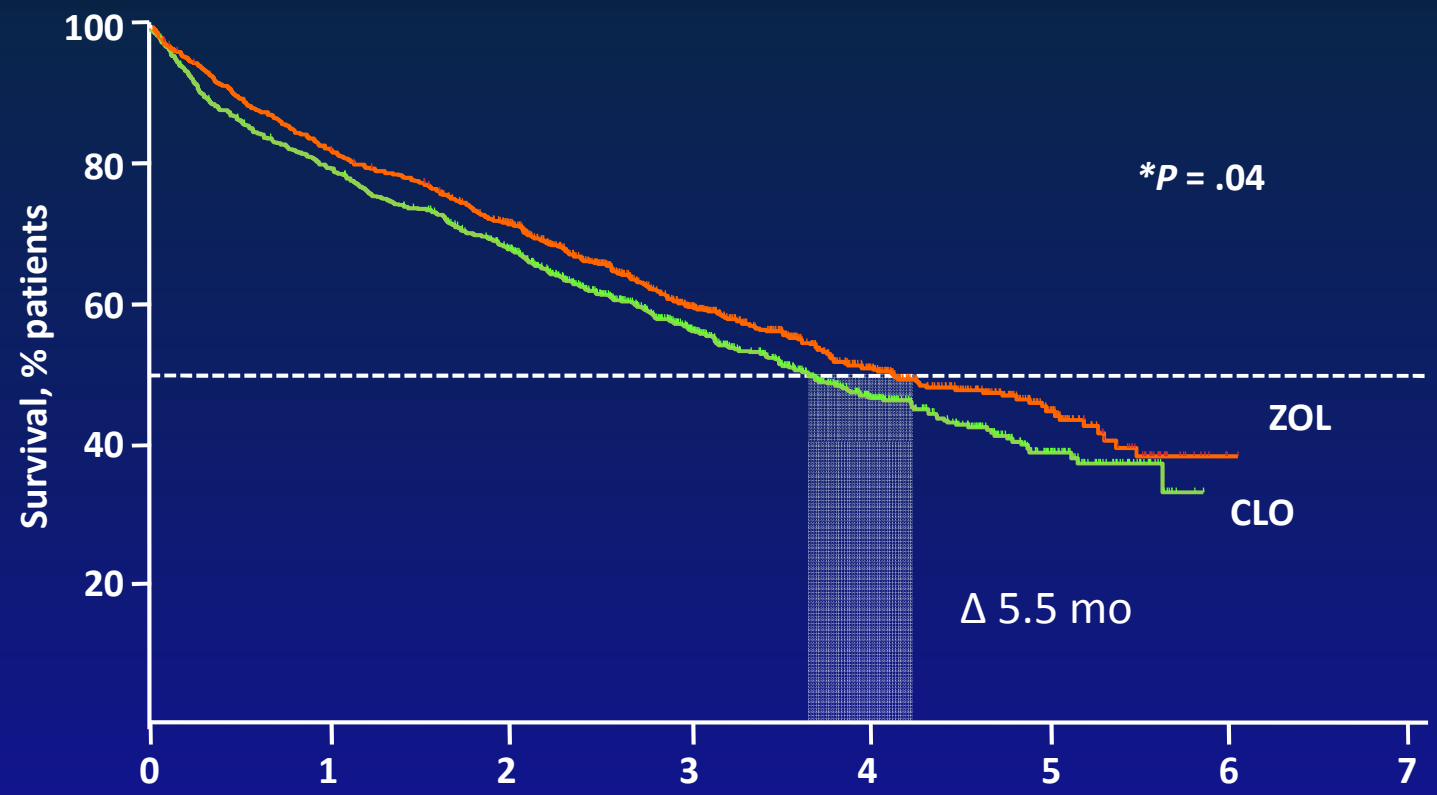


- Similar OS for PAM vs PLA (26 vs 24 mo; *P* = .377)
- PAM ⬆ OS vs PLA in pts receiving 2nd-line chemotherapy (n = 131; 21 vs 14 mo; *P* = .081)

Abbreviations: MM, multiple myeloma; OS, overall survival; PAM, pamidronate; PLA, placebo; q4wk, every 4 weeks.

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

MRC Myeloma IX: ZOL Significantly ⬆ OS vs CLO



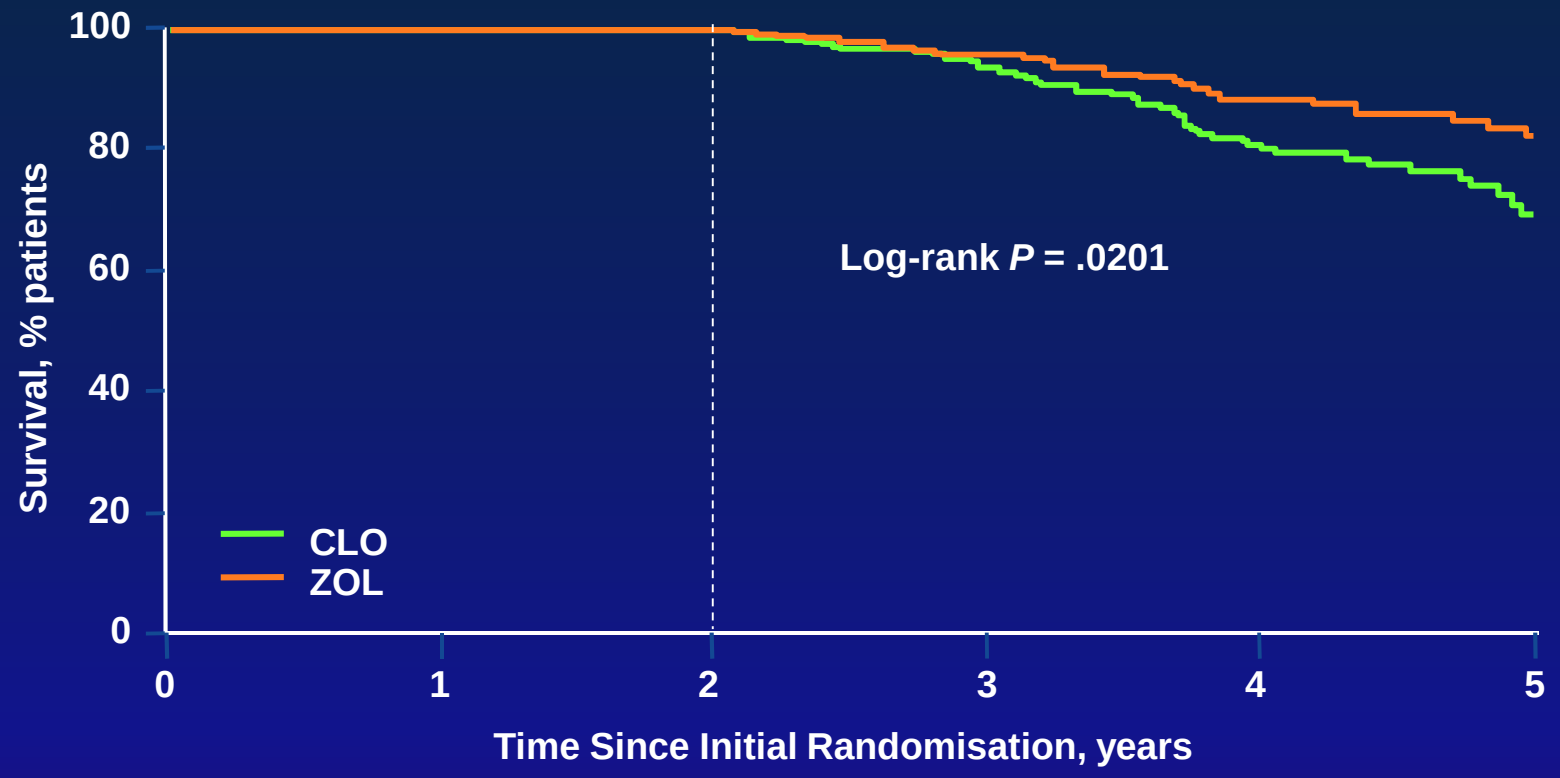
Number at risk:

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

Kaplan-Meier analysis adjusted for treatment pathway (intensive vs non-intensive).
*Log-rank, stratified by treatment pathway.
Abbreviations: CLO, clodronate; OS, overall survival; ZOL, zoledronic acid.

Morgan G, et al. Lancet. 2010;376(9757):1989-1999.

Among Patients Treated ≥ 2 Years, ZOL ⬆ OS vs CLO

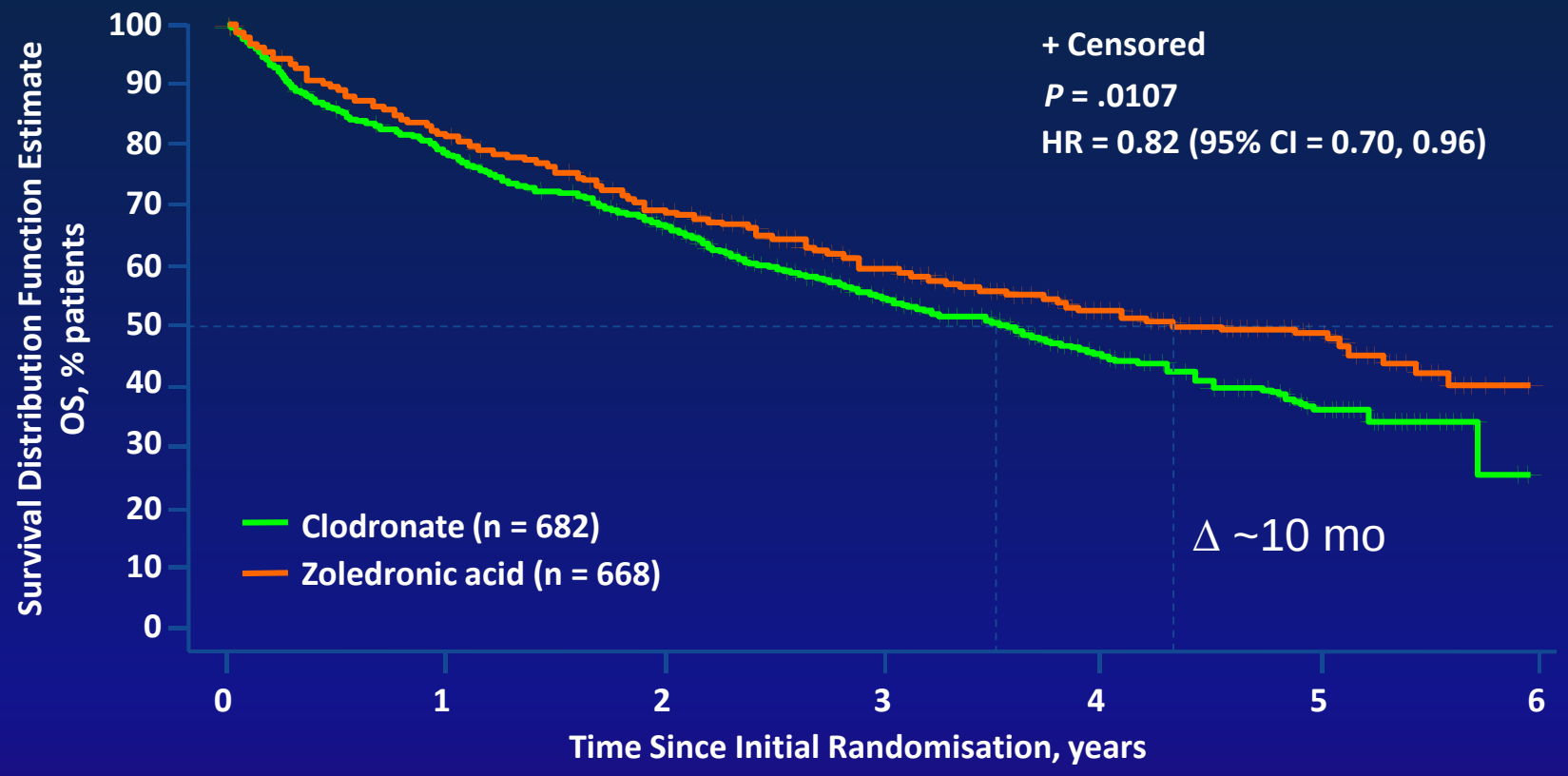


Patients, n						
CLO	292	286	280	202	123	41
ZOL	290	286	279	215	133	58

Abbreviations: CLO, clodronate; OS, overall survival; ZOL, zoledronic acid.

Morgan G, et al . Blood 2012;119:5374-83.

ZOL Significantly ⬆ OS vs CLO in Patients With Bone Disease at Baseline (n = 1,350)

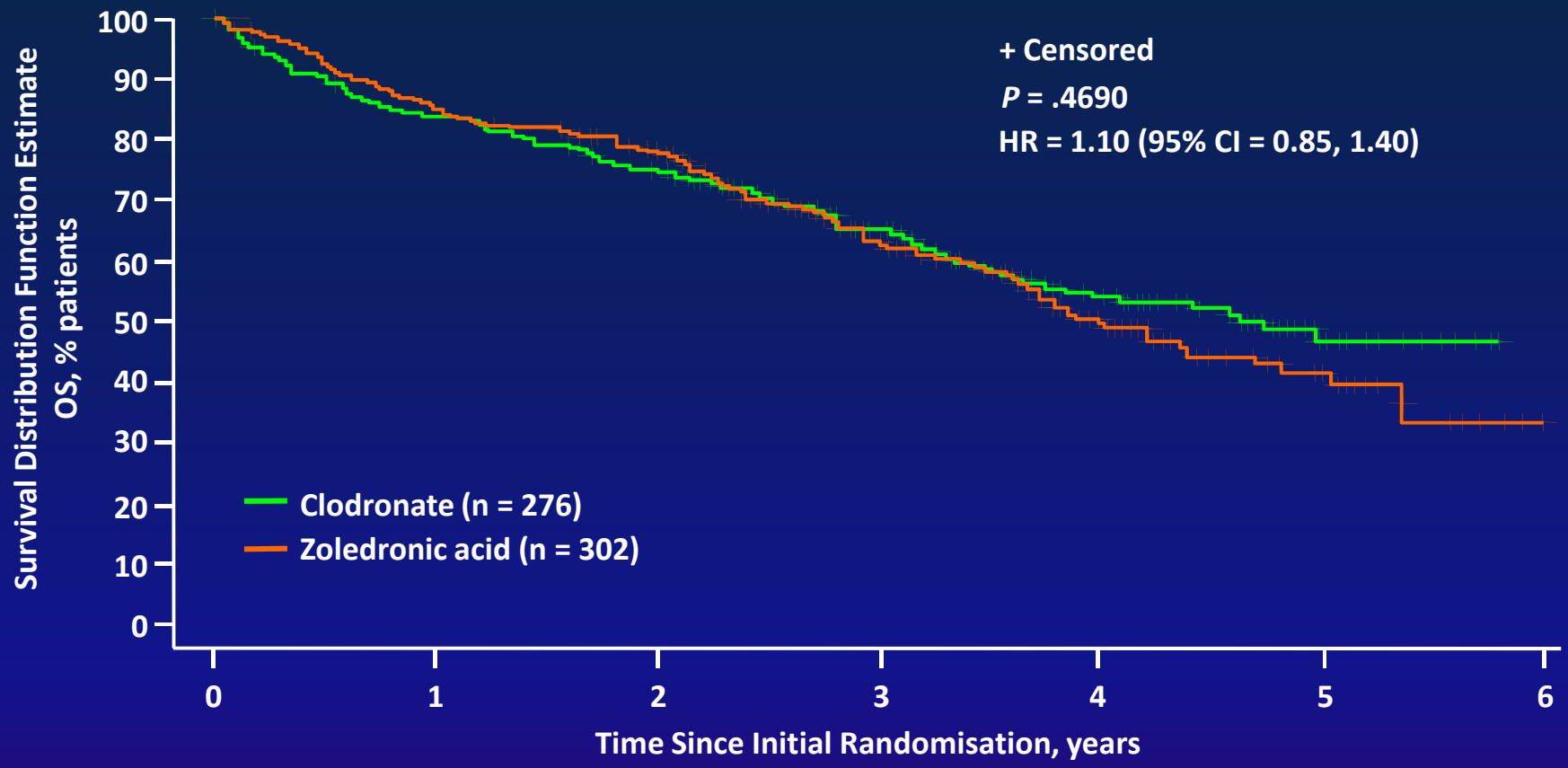


ZOL	668	544	447	292	165	64	3
CLO	682	534	437	271	143	53	0

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

Morgan G, et al . Blood 2012;119:5374-83.

OS Was Similar for ZOL and CLO in Patients with No Bone Disease at Baseline (n = 578)



ZOL	302	254	225	135	56	25	1
CLO	276	228	200	136	79	23	0

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

Morgan G, et al . Blood 2012;119:5374-83.

IMWG guidelines 2013: Treatment Duration

- Intravenous bisphosphonates should be administered at 3- to 4-week intervals to all patients with active MM (grade A).
- ZOL improves OS and reduces SREs over CLO in patients who received treatment for more than two years; thus it should be given until disease progression in patients not in CR or a vgPR and further continued at relapse (grade B).
- There is not similar evidence for PAM. PAM may be continued in patients with active disease at the physician's discretion (grade D), and PAM therapy should be resumed after disease relapse (grade D).
- For patients in CR/vgPR, the optimal treatment duration of BPs is not clear; the panel agrees that BPs should be given for at least 12 months and up to 24 months and then at the physician's discretion (grade D; panel consensus).

Terpos E, et al. J Clin Oncol. 2013;in press.

IMWG Guidelines 2013: Asymptomatic Myeloma & MGUS

- Bisphosphonates are recommended for low and intermediate risk asymptomatic MM (AMM) if osteoporosis is identified by DXA scan in doses used in patients with osteoporosis (grade C). For high-risk AMM or if one cannot differentiate between MM-related versus age-related bone loss, the treating physician should consider using dosing and schedule of bisphosphonates as with symptomatic MM, especially in patients with abnormal MRIs (grade D; panel consensus).
- Bisphosphonates are recommended for the treatment of osteoporosis in MGUS in doses used for patients with osteoporosis (grade C). DXA scan should be considered for patients with MGUS because of their reported increase in skeletal-related events compared to age-matched controls (grade B).

Terpos E, et al. J Clin Oncol. 2013;in press.

Zoledronic Acid and Pamidronate Are Generally Well Tolerated

- Most frequently reported AEs include
  - 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
  - Effects on renal function are dose- and infusion rate-dependent
  - Cases are transient and manageable

Abbreviations: AEs, adverse events; PAM, pamidronate; ZOL, zoledronic acid.

Rosen LS, et al. *Cancer*. 2003;98(8):1735-1744.

Adverse Events of Bisphosphonates: MRC-IX Study

	Non-Intensive Pathway (n = 851)				Intensive Pathway (n = 1,111)			
	MP (n = 424)		C-TDa (n = 427)		CVAD (n = 556)		C-TD (n = 555)	
	ZOL (n = 213)	CLO (n = 211)	ZOL (n = 215)	CLO (n = 212)	ZOL (n = 278)	CLO (n = 278)	ZOL (n = 277)	CLO (n = 278)
Acute renal failure	15 (7)	13 (6)	13 (6)	14 (7)	14 (5)	17 (6)	15 (5)	16 (6)
ONJ[b]	10 (5)	0 (0)[a]	4 (2)	1 (< 1)	13 (5)	2 (1)[a]	8 (3)	0 (0)[a]
Thromboembolic	10 (5)	10 (5)	43 (20)	25 (12)[a]	59 (21)	41 (15)	45 (16)	41 (15)
Infection TESAE	4 (2)	4 (2)	12 (6)	14 (7)	28 (10)	37 (13)	24 (9)	25 (9)
All SAEs	97 (46)	81 (38)	115 (53)	117 (55)	167 (60)	155 (56)	160 (58)	125 (45)[a]
TESAEs	27 (13)	18 (9)	63 (29)	67 (32)	74 (27)	69 (25)	84 (30)	72 (26)

CLO = clodronate; C-TD = cyclophosphamide, thalidomide, dexamethasone; C-TDa = attenuated C-TD; CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone; MP = melphalan, prednisolone; ONJ = osteonecrosis of the jaw; SAE = serious adverse event; TESAE = treatment-emergent SAE; ZOL = zoledronic acid.

[a] $P \leq .05$; statistical significance determined by Fisher's exact test.

[b] ONJ cases were confirmed by an independent adjudication committee.

Boyd K, et al. J Clin Oncol. 2011;29(suppl). Abstract 8010.

Adverse Events: Zoledronic Acid vs. Denosumab

Event, n (%)	Zoledronic acid (N = 878)	Denosumab (N = 878)
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. J Clin Oncol 2011;29(9):1125-32

IMWG Guidelines 2013: Patients with Renal Failure

- Patients with mild to moderate renal impairment (CrCl: 30-60 mL/min) should receive reduced doses of zoledronic acid and clodronate. No change to zoledronic acid infusion time is recommended.
- Pamidronate should be administered via 4 hours infusion in patients with mild to moderate renal impairment.
- Pamidronate and zoledronic acid are not recommended for patients with CrCl <30 mL/min.
- Bisphosphonate therapy should be discontinued in patients experiencing renal problems until CrCl returns to within 10% of baseline values.

Terpos E, et al. J Clin Oncol. 2013;in press.

Dosage of BPs according to CrCl

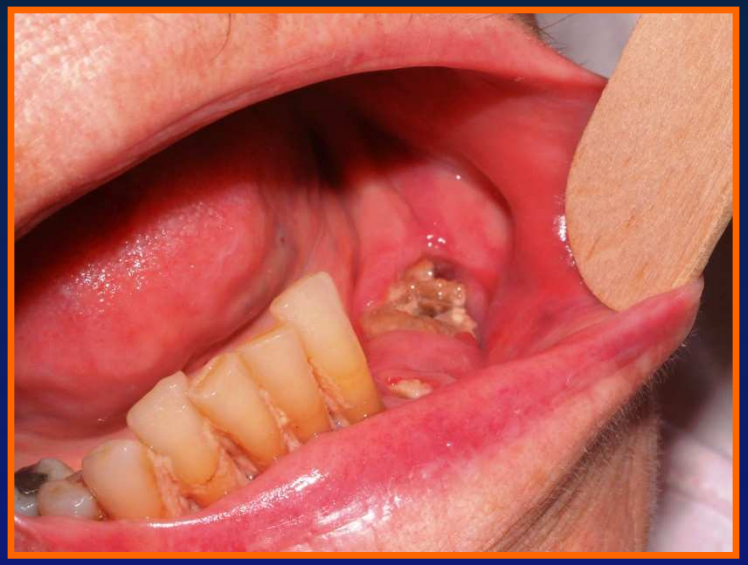
Creatinine Clearance rate (mL/min)	Recommended dosage of CLO (1600 mg)
>80	100%
50-80	75%
12-50	50-75%
<12	50% or discontinue

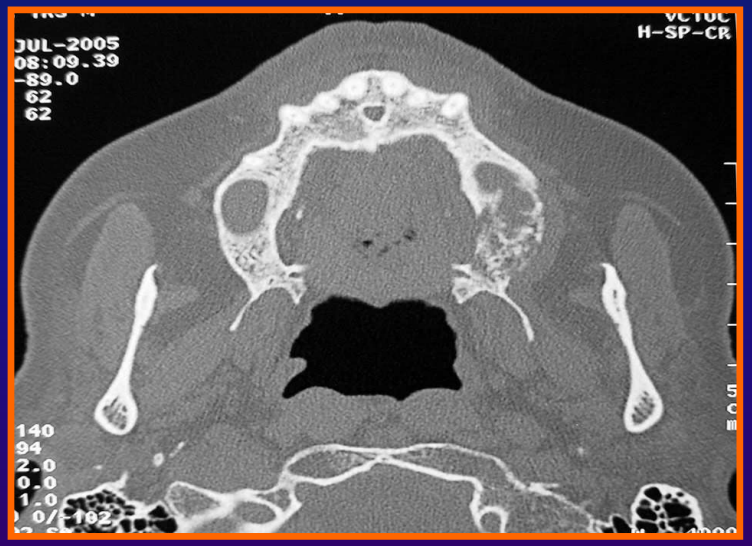
Creatinine Clearance rate (mL/min)	Recommended dosage of ZOL (mg)
> 60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

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

Terpos et al. Ann Oncol 2009;20:1303-17

Clinical Presentation and Working Diagnosis of ONJ





Clinical features of suspected ONJ

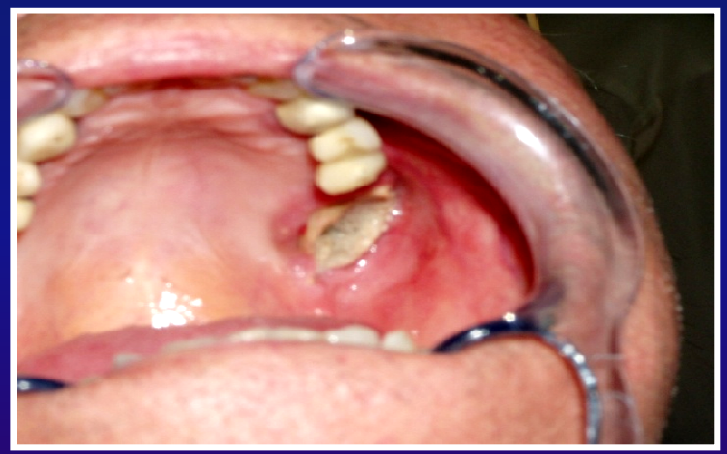
- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing

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

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

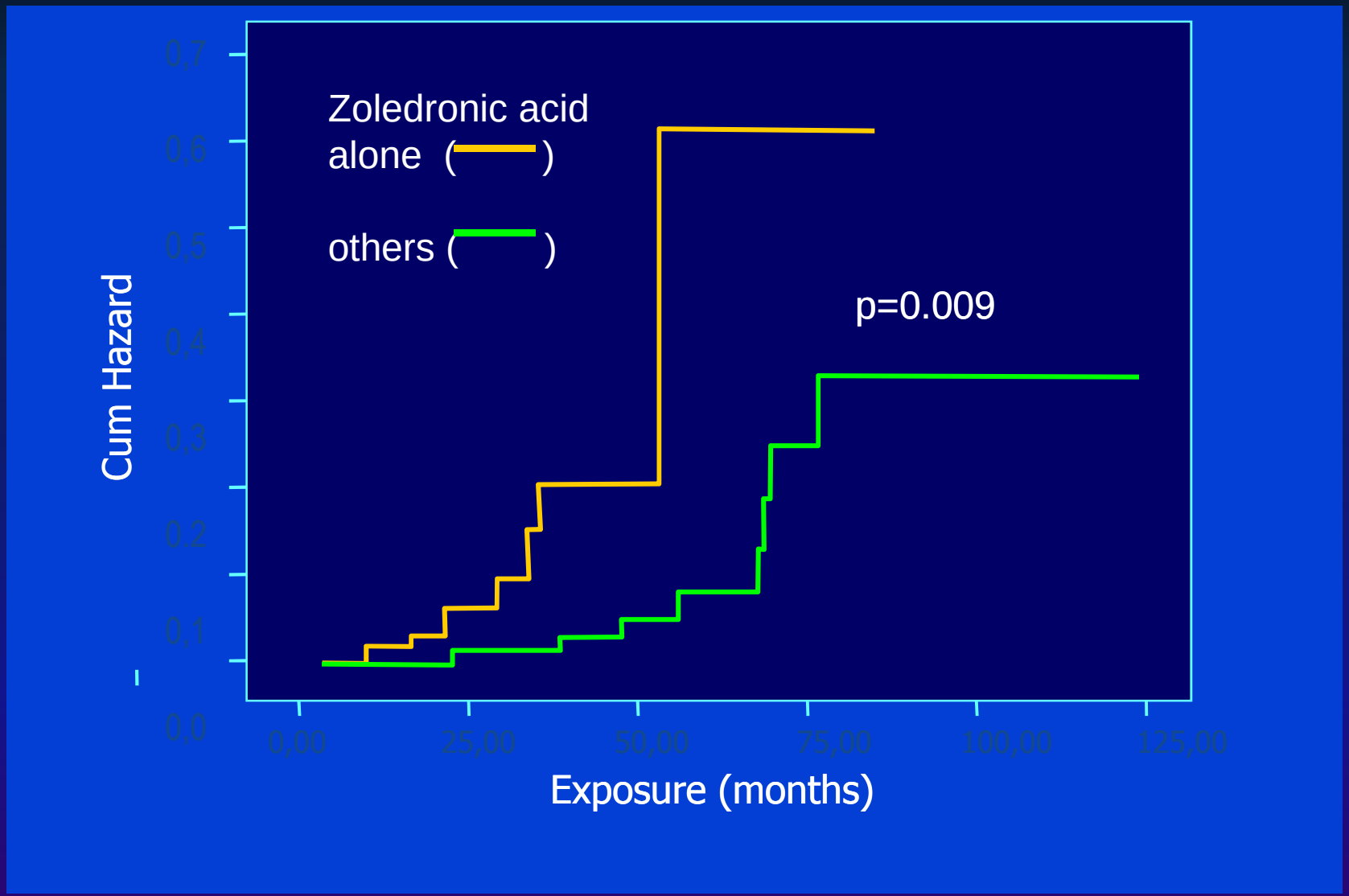
ONJ: Characteristics



- 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

Weitzman R et al. *Crit Rev Oncol Hematol*. 2007;62:148.
Zervas K et al. *Br J Haematol*. 2006;134:620.

Relative Risk for ONJ Development



Dimopoulos et al, Haematologica 2006;91:968

Antibiotic Prophylaxis Can Reduce the Incidence of ONJ

	Patients with MM N = 178		
	Low risk (n = 112)	**High risk (n = 29)**	**High risk (n = 37)**
Antibiotic Prophylaxis	No	No	Yes
Median Time of exposure, months (range)	13.2 (3–69)	12 (4–67)	43 (11–70)
Dental Procedures Performed, n			
Cleanings (professional)	NA	6	16
Extractions	NA	14	10
Implants	NA	1	1
Prosthesis surgery	NA	8	10
ONJ, n (%)	1 (0.9%)	8 (15%)	None

- Antibiotic prophylaxis significantly ⬇ ONJ incidence in patients who had high-risk dental procedures during BP therapy vs no prophylaxis (0% vs 15%; *P* =.012)

Montefusco V, et al . *Leuk Lymphoma*. 2008;49(11):2156-2162.

Update of our Center Experience

- N= 238 patients who
  - received at least one dose of zolendronic acid (ZA)
  - received ***only*** zolendronic acid (ZA)
  - survived at least 6 months after 1st infusion of ZA
- Implementation of preventive measures since 2003
- All patients were assessed for ONJ by an experienced maxillofacial surgeon and a dental surgeon
- Median follow up for all patients is 3 years (range 0.5-11)
- Median number of infusions was 17 (range 1-107)

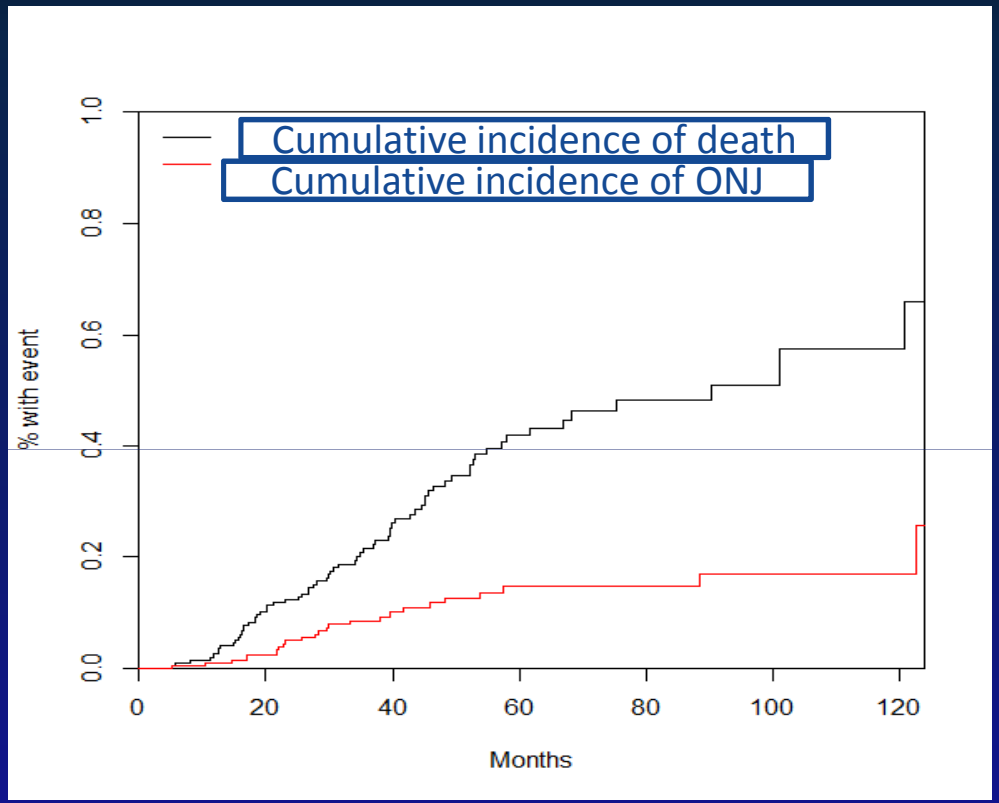
N= 25 (10.5%) patients developed ONJ

Update of our Center Experience (2)

- Median number of ZOL infusions for patients who developed ONJ was 25 (range 6-79) vs. 15 for those who did not ($P<0.001$)
- Median relative dose intensity (RDI) for patients who developed ONJ was 1 infusion per 5 weeks while for patients who have not developed ONJ is 1 infusion per 8 weeks ($p<0.001$)
- Median time from first ZA infusion to development of ONJ was 30 months (range 6-122)

Cumulative incidence of ONJ

(accounting for death due to MM as a competing event)



	1-year	2-years	3-years	4-years
% OS	97%	88%	79%	67%
% ONJ (95%CI)	1% (0.2%-5%)	4.9% (2.5%-8.5%)	8.5% (5%-13%)	11.6% (7.2%-17.1%)

Natural History of ONJ in Myeloma

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

ONJ healed in ~75%

- ONJ 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 non-healing lesions, after BP re-initiation following ONJ healing, as compared to those who develop spontaneous ONJ lesions (p=0.007)

Badros et al. J Clin Oncol 2008;26:5904-9

Management of ONJ

Stage and Recommended treatment
Stage 1: Patients who are asymptomatic and have no evidence of infection ▪Antibacterial mouth rinse ▪Clinical follow-up on a quarterly basis ▪Patient education and review of indications for continued bisphosphonate therapy
Stage 2: Associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent discharge ▪Broad-spectrum oral antibiotic ▪Antibacterial mouth rinse ▪Pain control ▪Superficial debridement to relieve soft tissue irritation
Stage 3: Pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border ▪Antibacterial mouth rinse ▪Antibiotic therapy and pain control ▪Surgical debridement/resection for longer term palliation of infection and pain

American Association of Oral and Maxillofacial Surgeons. *J Oral Maxillofac Surg*. 2007;65:369-376.

IMWG Guidelines 2013: BPs and ONJ (1)

- Preventive strategies should be adopted to avoid ONJ. Patients should receive a comprehensive dental examination and be educated regarding optimal dental hygiene (grade C; panel consensus). Existing dental conditions should be treated before initiating bisphosphonate therapy (grade C; panel consensus).

- After bisphosphonate treatment initiation, unnecessary invasive dental procedures should be avoided and dental health status should be monitored on at least an annual basis (grade C). Patients' ongoing dental health status should be monitored by a physician and a dentist (grade D; panel consensus). Dental problems should be managed conservatively if possible (grade C).

IMWG Guidelines 2013: BPs and ONJ (2)

- Temporary suspension of bisphosphonate treatment should be considered if invasive dental procedures are necessary (grade D). The panel consensus is to stop bisphosphonates for 90 days before and after invasive dental procedures (tooth extraction, dental implants and surgery to the jaw). Bisphosphonates do not need to be discontinued for routine dental procedures including root canal.

- Initial treatment of ONJ should include discontinuation of bisphosphonates until healing occurs (grade C). The decision to restart bisphosphonates should be individualized, until the results of prospective long-term studies are available (grade D). The physician should consider the advantages and disadvantages of continued treatment with bisphosphonates, especially in the relapsed/refractory MM setting (grade D).

Conclusions

- ZOL and PAM are recommended for symptomatic patients with MM
- ZOL is more effective than clodronate regarding reduction of SREs
- BPs have shown antimyeloma activity; ZOL ⬆ OS versus clodronate in MM patients, mainly in those with bone disease at baseline. It is recommended for use in active myeloma till disease progression (for CR/vgPR patients for 12-24 months)
- Caution is needed for patients with renal impairment.
- Preventive measures can reduce the incidence of ONJ.
- The majority of patients with ONJ manage to heal their lesions.

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