Zoledronic Acid in the Management of Multiple Myeloma:

Results From the MRC Myeloma IX Study

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Disclosures

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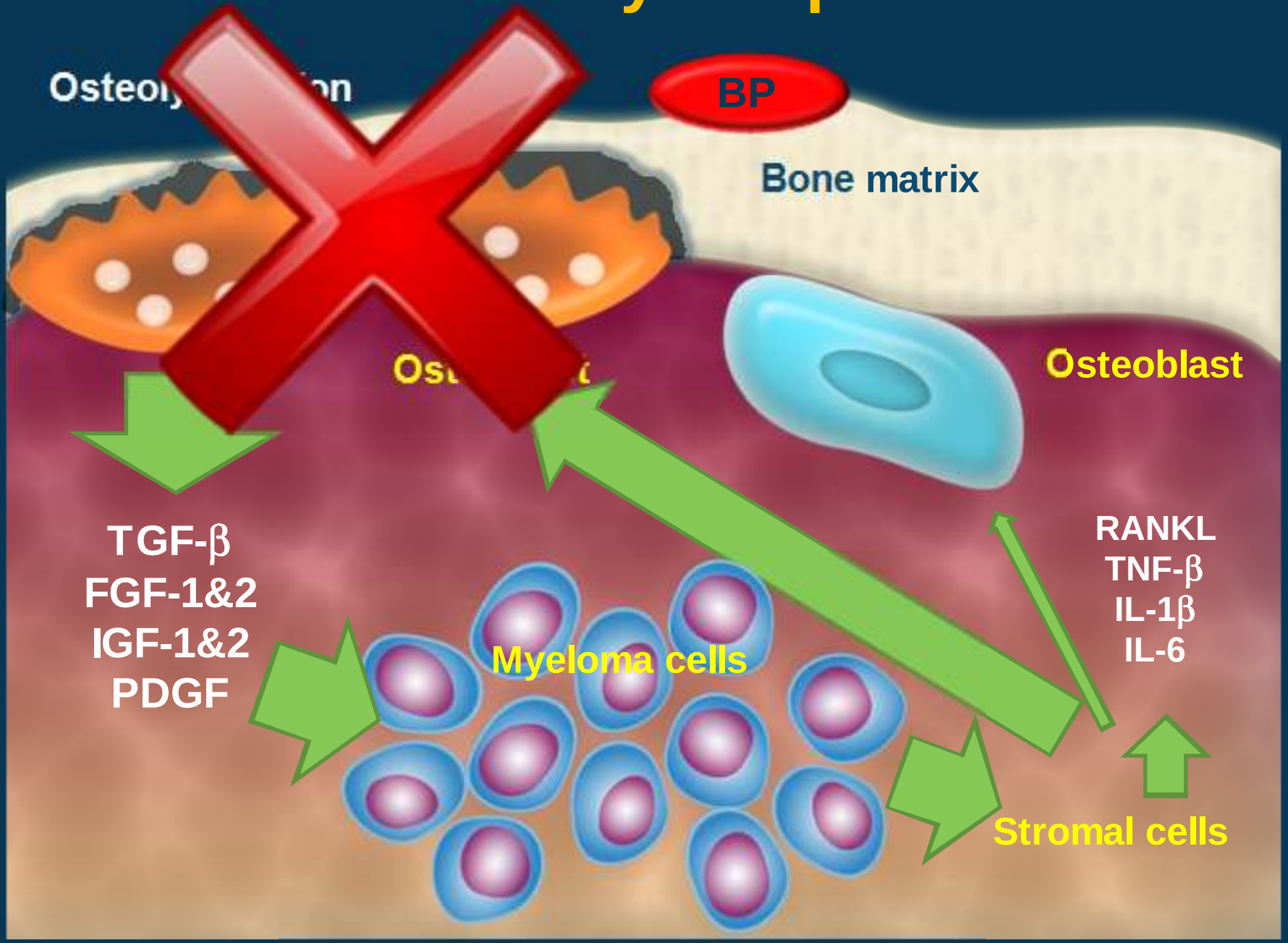
- Professor J. A. Child was the principal grant holder of these on behalf of the Myeloma IX Chief Investigators and the University of Leeds, the sponsor of the trial

Bone Destruction and Myeloma Growth—a Stimulatory Loop



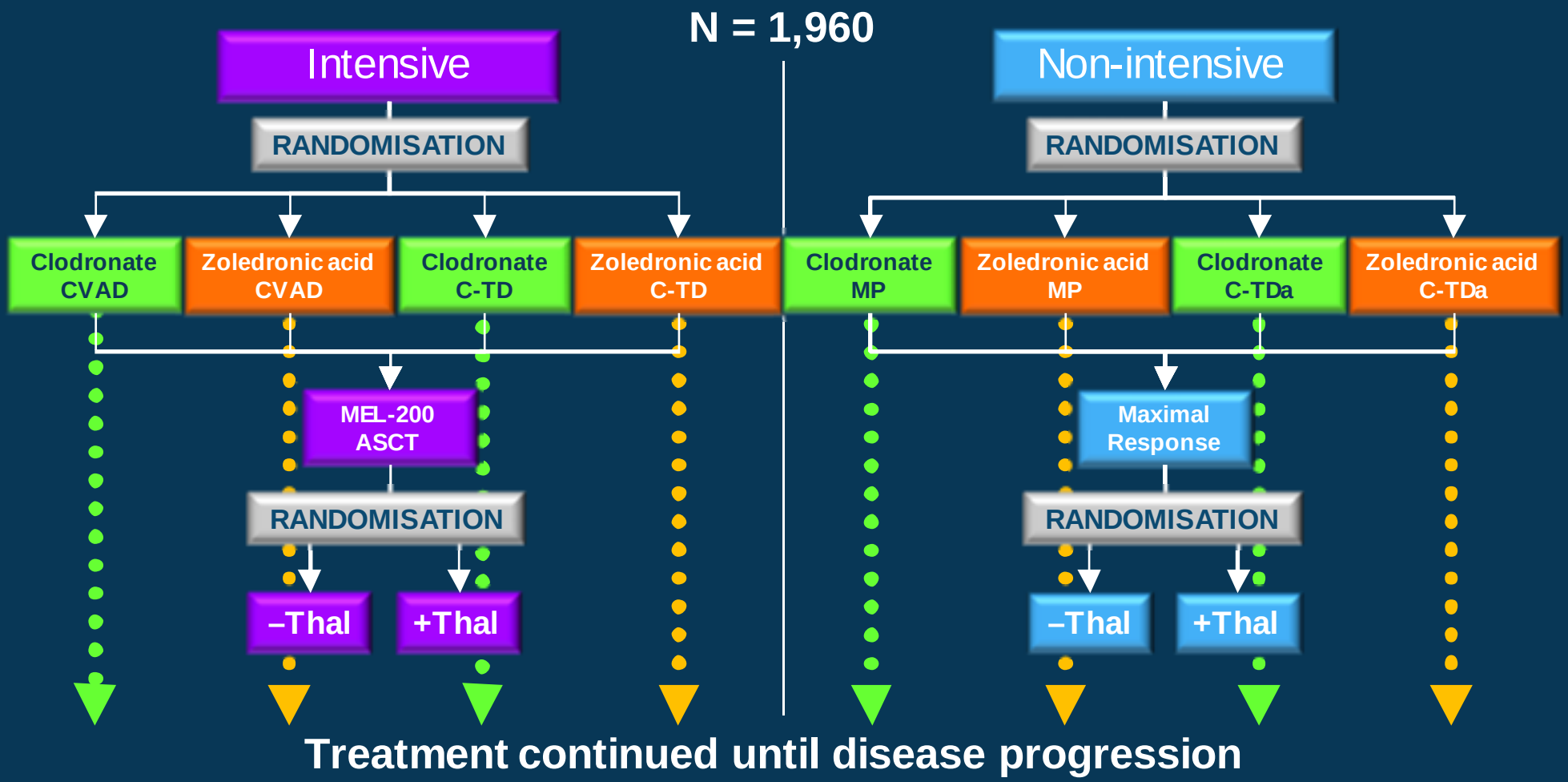
Bisphosphonates Have Demonstrated Significant Palliative Benefits in MM[1]

First Author (year)	BP	Dosage	N[a]	Reduction of Pain	Reduction of SREs[b]	Survival Benefit
Placebo-controlled trials[b]						
Lahtinen (1992) and Laakso (1994)	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 monthly	198	No	No	No
Aviles (2007)[2]	ZOL	4 mg IV q 28 days	94	Yes	Yes	Yes
PAM-controlled trials						
Berenson (2001)	ZOL	2 or 4 mg IV monthly	108	Yes	Yes	NE
Rosen (2001; 2003)	ZOL	2 or 8 mg IV monthly	513	Yes	Yes	Subset[c]

[a] Number of patients with MM.
[b] SREs include newly tic 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.

1. Adapted from Terpos E, et al. *Ann Oncol.* 2009;20(8):1303-1317; 2. Aviles A, et al. *Med Oncol.* 2007;24(2):227-230.

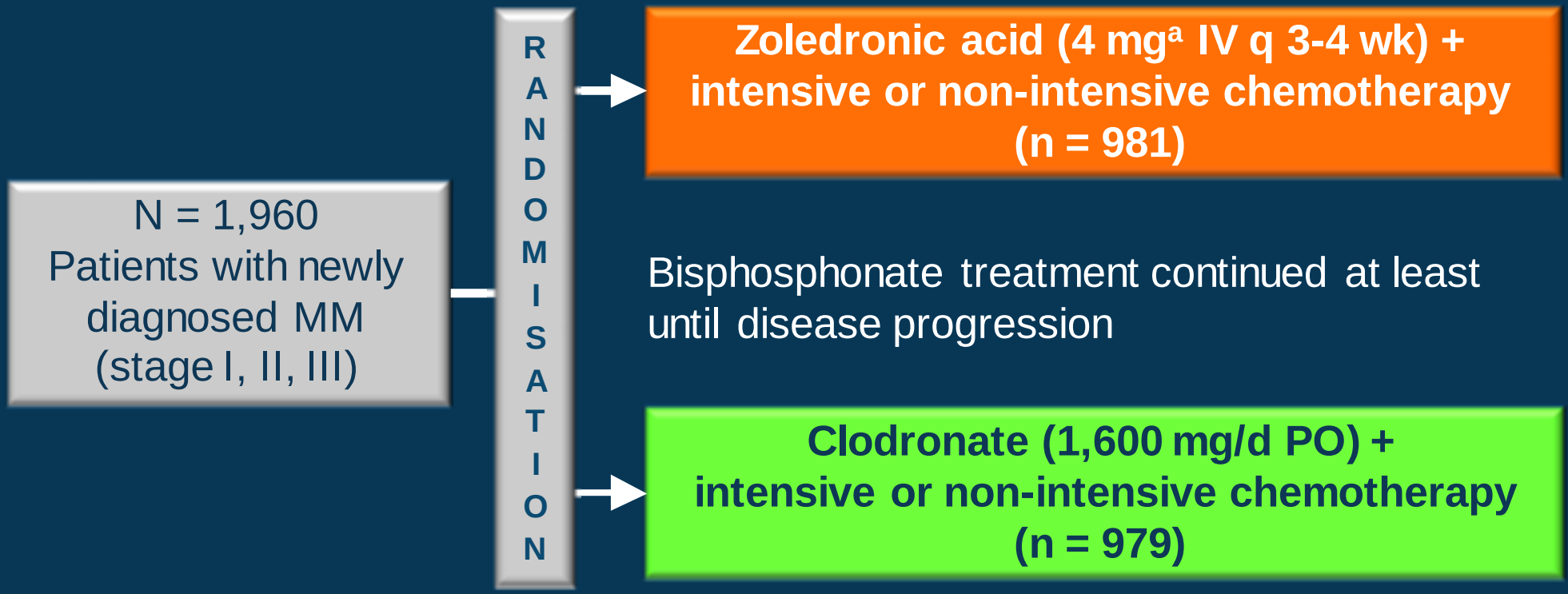
MRC Myeloma IX—Trial Design



Primary endpoints: PFS, OS, Response
Secondary endpoints: SREs (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: ASCT, autologous stem-cell transplantation; CVAD, cyclophosphamide (500 mg PO days 1, 8, 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, 12-15 q 3 wk); C-TD, cyclophosphamide (500 mg PO days 1, 8, and 15), thalidomide (100-200 mg/d), dexamethasone (40 mg/d PO days 1-4, 12-15 q 3 wk); C-TDa, attenuated C-TD (except thalidomide 50-200 mg/d, dexamethasone 20 mg/d days 1-4, 15-18 q 4 wk); MEL, melphalan; MP, melphalan (7 mg/m^2), prednisolone (40 mg) PO for 4 days; Thal, thalidomide (50-100 mg/d); PFS, progression-free survival; OS, overall survival, SRE, skeletal-related event; QoL, quality of life.

MRC Myeloma IX—Analysis Schematic for ZOL vs CLO



Endpoints (ZOL vs CLO)

Primary: PFS, OS, and Response

Secondary: SREs (time to first SRE, SRE incidence), and Safety

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

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

MRC Myeloma IX—Study Endpoints

- Primary endpoints
  - Overall survival (OS)
  - Progression-free survival (PFS), defined as time from randomisation to disease progression or death
  - Response
- Secondary endpoints
  - Skeletal-related events (SREs): proportion of patients with an SRE
  - Safety
- Statistical methods
  - PFS and OS were assessed by Kaplan-Meier and Cox proportional hazards models
  - Statistical significance was assigned for $P < .05$ with no correction for multiplicity of comparisons

Morgan GJ, et al. *Lancet. 2010;376:1989-1999.*

MRC Myeloma IX—Trial Status

- 1,960 evaluable patients
- 121 centres

	ZOL (n = 981)	CLO (n = 979)
Median follow-up, years (cutoff date 5 Oct 2009)	**3.7**	**3.8**
Still receiving BP, n (%)	**111 (11.3)**	**132 (13.5)**
Administration of BP not confirmed, n (%)	**54 (5.5)**	**36 (3.7)**
Stopped before progression, n (%)	**235 (24)**	**185 (18.9)**
Progressed or died, n (%)	**581 (59.2)**	**626 (63.9)**
Median time on treatment, days		
Intensive	**396**	**409**
Non-intensive	**320**	**306**

Abbreviations: BP, bisphosphonate; CLO, clodronate; ZOL, zoledronic acid.

Morgan GJ, et al. *Lancet. 2010;376:1989-1999.*

MRC Myeloma IX—Trial Status

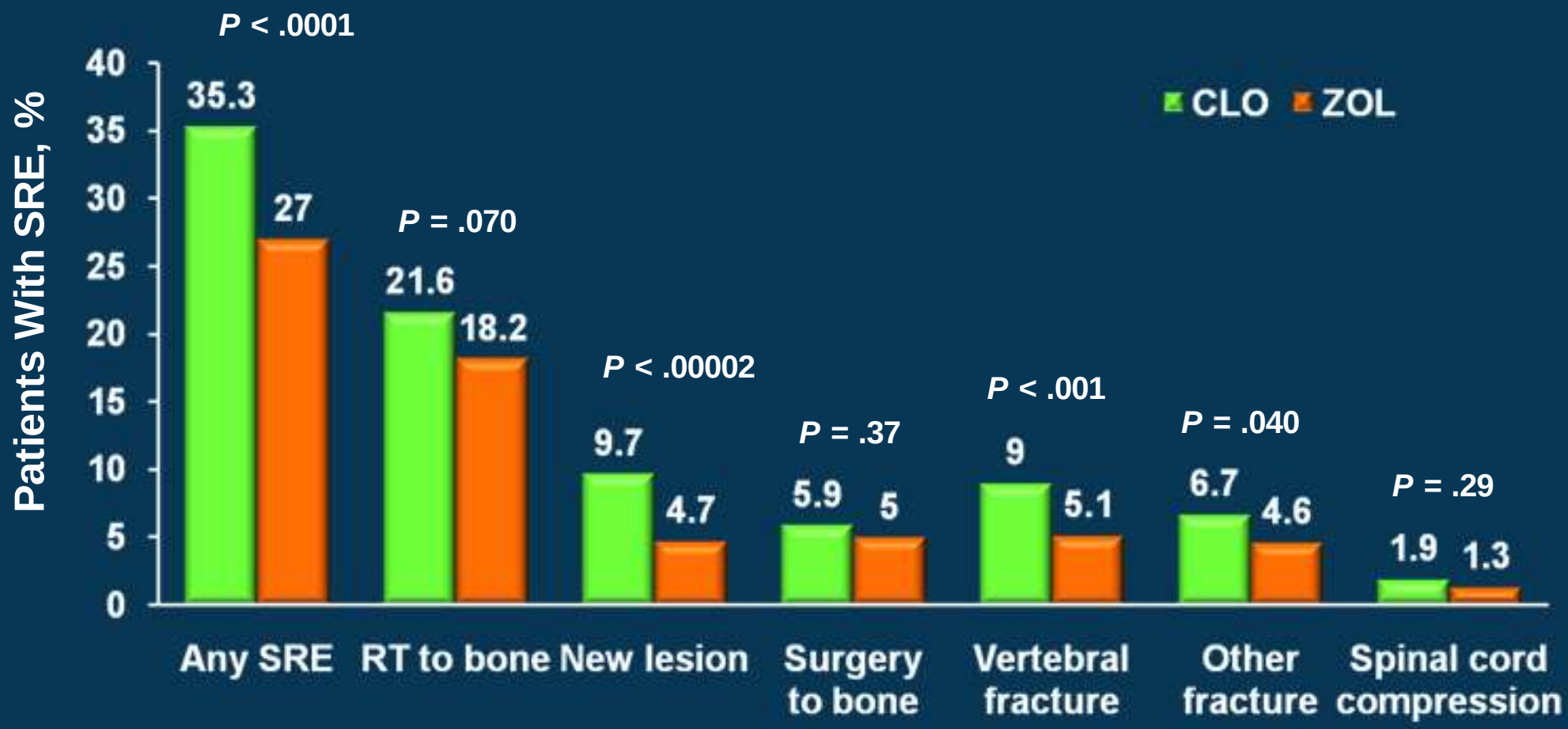
- 1,960 evaluable patients
- 121 centres

>70% remained on study until progression or death or had ongoing treatment

	[illegible] (n = 960)	[illegible] (n = 979)
Median follow-up, years (cut-off date 3 Oct 2010)	3.7	3.9
Still receiving BP, n (%)	**111 (11)**	**132 (14)**
Administration of BP not confirmed, n (%)	34 (3.5)	38 (3.7)
Stopped before progression, n (%)	235 (24)	368 (38)
Progressed or died, n (%)	**581 (59)**	**626 (64)**
Median time on treatment, days		
Intensive	168	196
Non-intensive	120	126

Abbreviations: BP, bisphosphonate; CLO, clodronate; ZOL, zoledronic acid.

MRC Myeloma IX Trial—SRE Profile With CLO and Improvement With ZOL

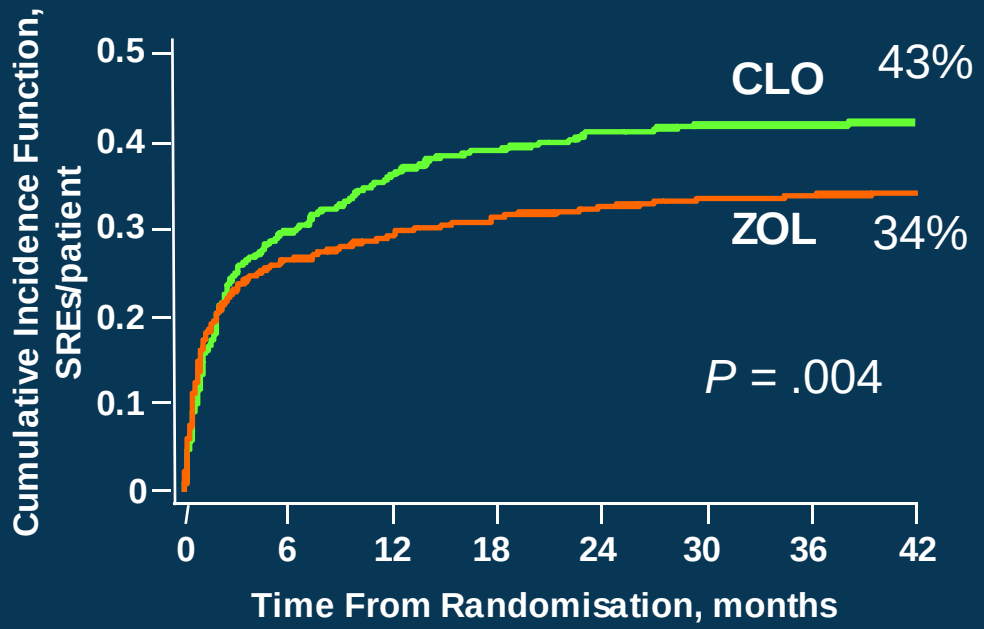


Abbrev iations: CLO, clodronate; RT, radiotherapy; SRE, skeletal-related event; ZOL, zoledronic acid.
SREs were def ined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.

Does the Presence of Bone Lesions at Baseline Make a Difference for SRE Benefits?

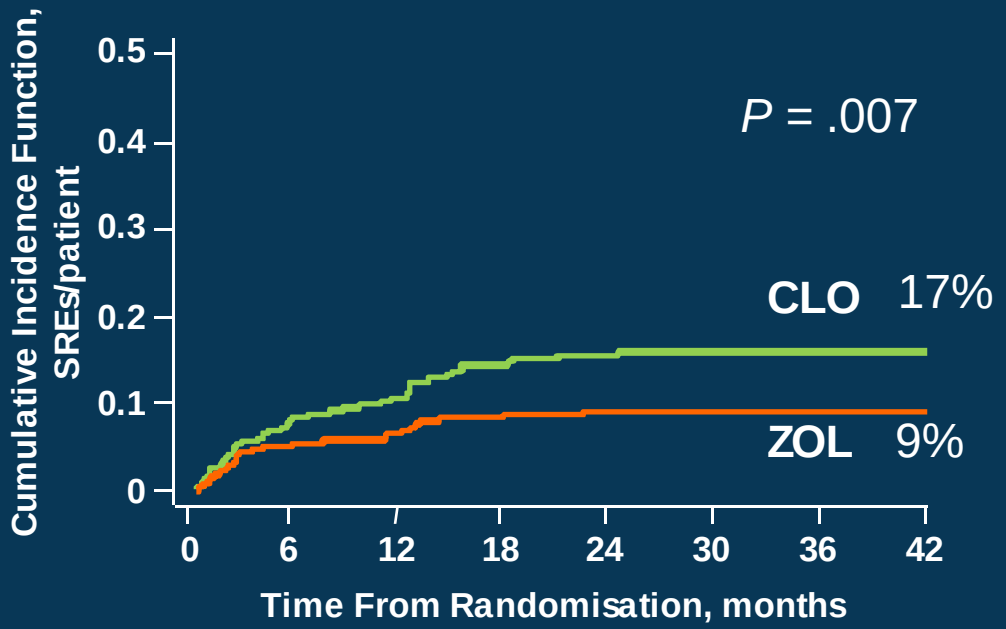
MRC Myeloma IX—ZOL Œ SREs vs CLO Regardless of Bone Lesions at Baseline

Bone Lesions at Baseline



Patients, n								
ZOL	668	415	325	250	189	136	100	69
CLO	682	402	297	212	164	117	75	50

No Lesions at Baseline



Patients, n								
ZOL	302	241	185	135	92	63	38	28
CLO	276	212	159	118	91	56	37	24

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

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; SRE, skeletal-related event; ZOL, zoledronic acid.

Are There Any Differences in SRE Effects Between Antimyeloma Regimens?

MRC Myeloma IX—Baseline Characteristics Were Similar Across Non-Intensive Regimens

	Non-Intensive Pathway (ITT; n = 849)			
	MP (n = 423)		C-TDa (n = 426)	
	ZOL (n = 212)	CLO (n = 211)	ZOL (n = 214)	CLO (n = 212)
Age, years				
Median (range)	73 (59 - 89)	74 (57 - 88)	74 (61 - 87)	73 (58 - 85)
Sex, n (%)				
Female	95 (44.8)	97 (46.0)	96 (44.9)	88 (41.5)
Male	117 (55.2)	114 (54.0)	118 (55.1)	124 (58.5)
ISS stage, n (%)				
I	37 (17.5)	27 (12.8)	26 (12.1)	20 (9.4)
II	63 (29.7)	93 (44.1)	76 (35.5)	80 (37.7)
III	92 (43.4)	73 (34.6)	81 (37.9)	87 (41.0)
Data unavailable	20 (9.4)	18 (8.5)	31 (14.5)	25 (11.8)
Bone disease[a], n (%)				
Yes	145 (68.4)	153 (72.5)	146 (68.2)	142 (67.0)
No	65 (30.7)	55 (26.1)	65 (30.4)	68 (32.1)
Data unavailable	2 (0.9)	3 (1.4)	3 (1.4)	2 (0.9)

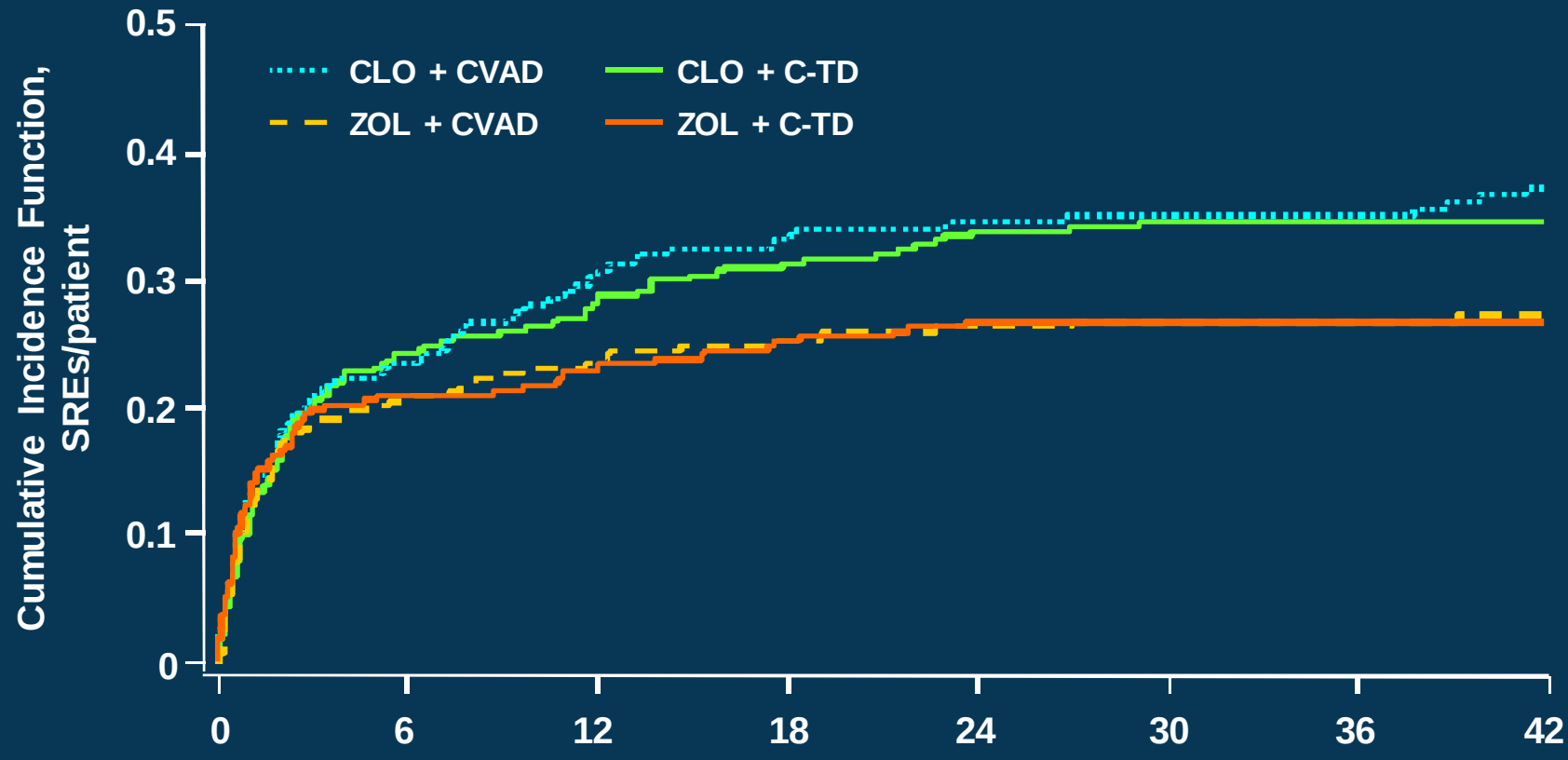
[a] Bone disease was defined as vertebral fractures, other fractures, or osteolytic lesions.
Abbreviations: CLO, clodronate; C-TDa, cyclophosphamide (500 mg PO days 1, 8, and 15), thalidomide (50-200 mg/d), dexamethasone (20 mg/d days 1-4, 15-18 q 4 wk); MP, melphalan (7 mg/m^2, prednisolone (40 mg) PO for 4 days; ISS, International Staging System; ITT, intent to treat; ZOL, zoledronic acid.

MRC Myeloma IX—Baseline Characteristics Were Similar Across Intensive Regimens

	Intensive Pathway (ITT; n = 1,111)			
	CVAD (n = 556)		C-TD (n = 555)	
	ZOL (n = 278)	CLO (n = 278)	ZOL (n = 277)	CLO (n = 278)
Age, years				
Median (range)	59 (31 - 74)	58 (39 - 72)	58 (33 - 71)	59 (33 - 78)
Sex, n (%)				
Female	100 (36.0)	108 (38.8)	101 (36.5)	110 (39.6)
Male	178 (64.0)	170 (61.2)	176 (63.5)	168 (60.4)
ISS stage, n (%)				
I	59 (21.2)	65 (23.4)	70 (25.3)	81 (29.1)
II	93 (33.5)	98 (25.3)	105 (37.9)	84 (30.2)
III	98 (35.3)	85 (30.6)	76 (27.4)	84 (30.2)
Data unavailable	28 (10.1)	30 (10.8)	26 (9.4)	29 (10.4)
Bone disease[a], n (%)				
Yes	202 (72.7)	212 (76.3)	202 (72.9)	199 (71.6)
No	75 (27.0)	63 (22.7)	74 (26.7)	75 (27.0)
Data unavailable	1 (1.4)	3 (1.1)	1 (0.4)	4 (1.4)

[a] Bone disease was defined as vertebral fractures, other fractures, or osteolytic lesions.
Abbreviations: CLO, clodronate; C-TD, cyclophosphamide (500 mg PO days 1, 8, and 15), thalidomide (100-200 mg/d), dexamethasone (40 mg/d PO days 1-4, 12-15 q 3 wk); CVAD, cyclophosphamide (500 mg PO days 1, 8, 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, 12-15 q 3 wk); ISS, International Staging System; ITT, intent to treat; ZOL, zoledronic acid.

MRC Myeloma IX—ZOL Œ SREs vs CLO[a] in Both Treatment Arms of the Intensive Pathway

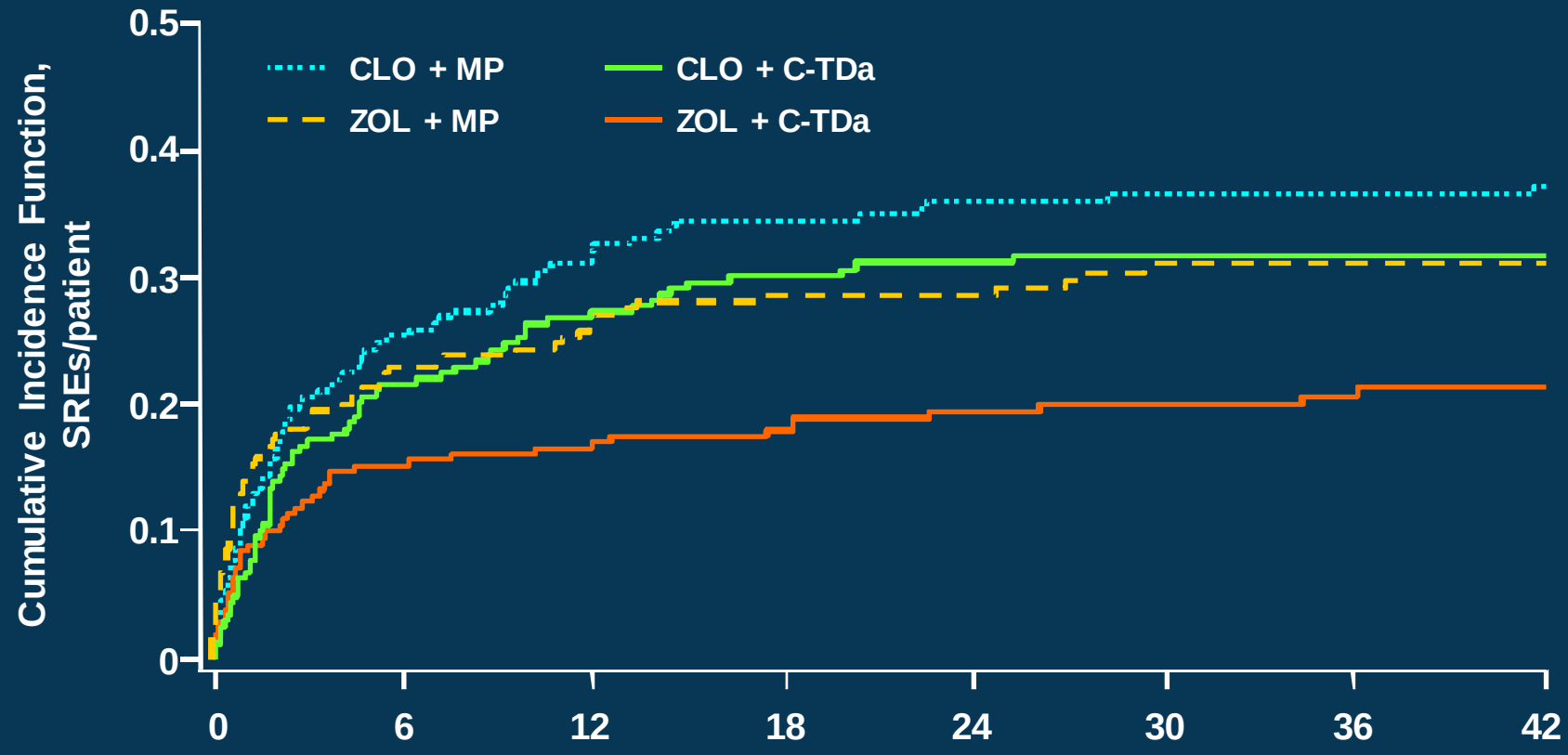


Patients, n								
ZOL + C-TD	277	191	165	136	107	80	58	41
ZOL + CVAD	278	195	165	139	105	79	53	39
CLO + C-TD	278	186	159	131	106	69	47	29
CLO + CVAD	278	192	151	115	97	68	43	29

[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; C-TD, cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; SRE, skeletal-related event; ZOL, zoledronic acid.

MRC Myeloma IX—ZOL Œ SREs vs CLO[a] in Both Treatment Arms of the Non-Intensive Pathway

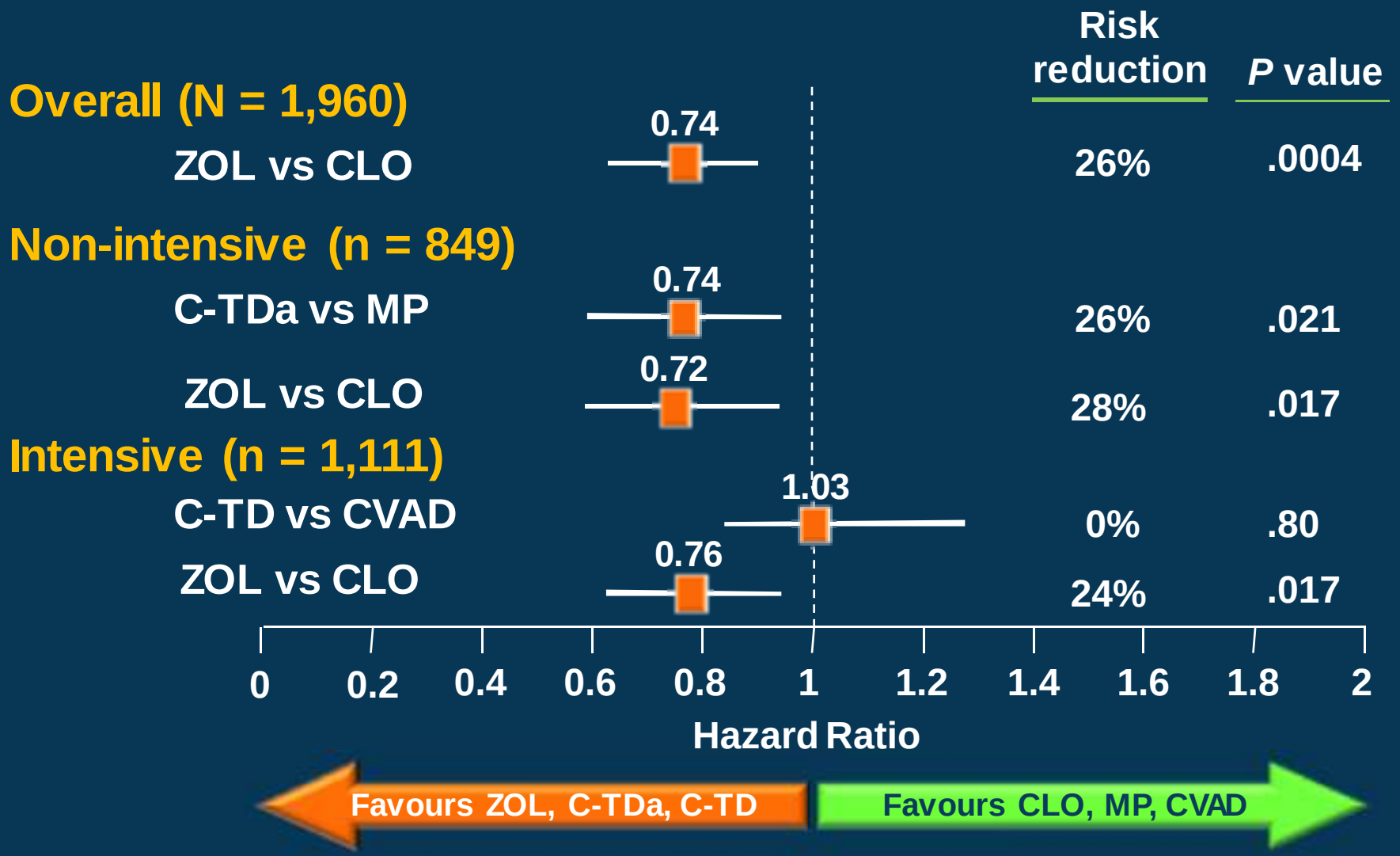


Patients, n								
ZOL + C-TDa	214	143	89	62	41	26	18	12
ZOL + MP	212	134	87	53	31	16	9	5
CLO + C-TDa	212	132	84	52	28	21	12	9
CLO + MP	211	119	71	39	25	15	10	7

[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; C-TDa, attenuated cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; MP, melphalan, prednisolone; SRE, skeletal-related event; ZOL, zoledronic acid.

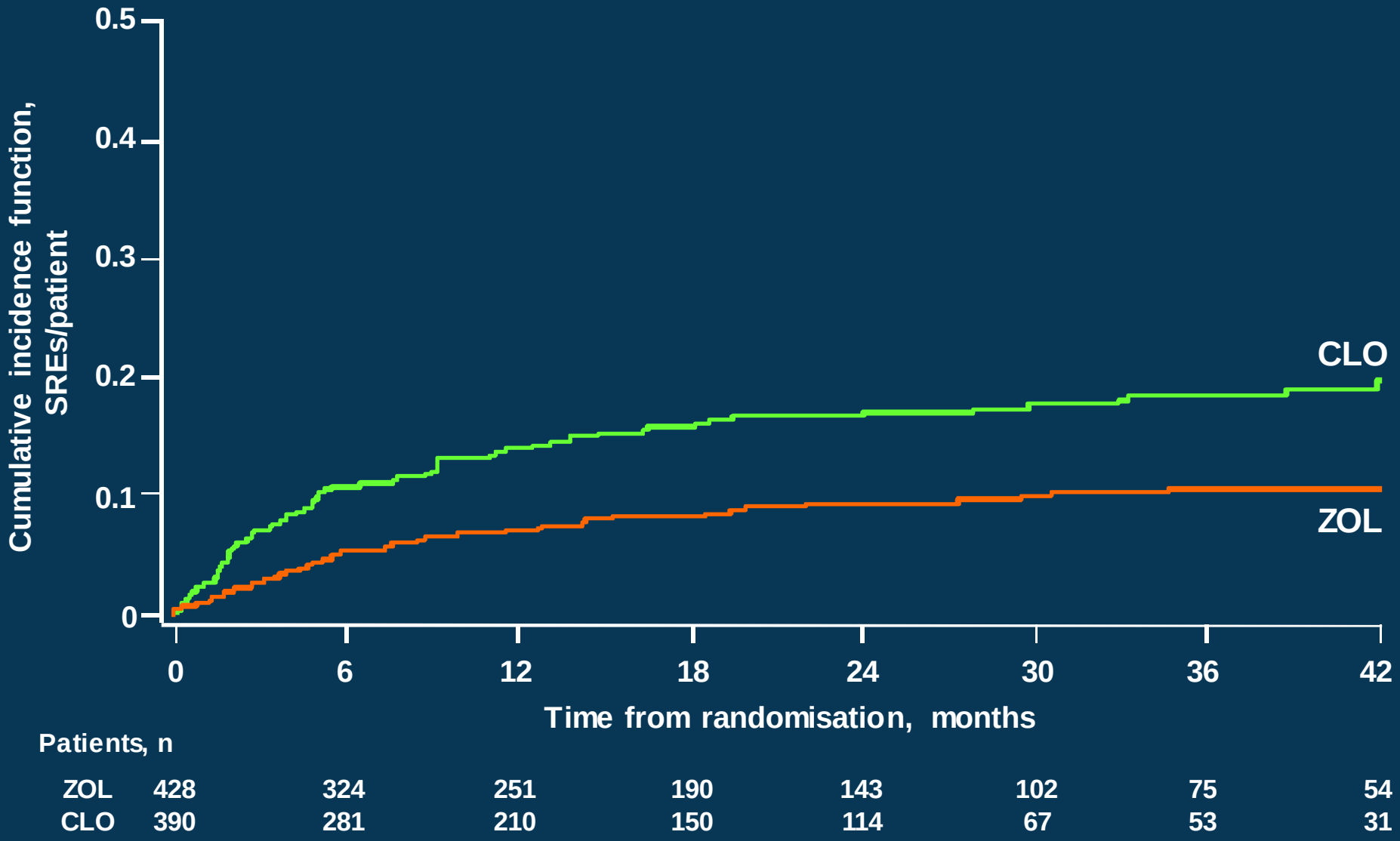
MRC Myeloma IX— Relative Risk of SREs by Treatment[a]



[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; C-TD, cyclophosphamide, thalidomide, dexamethasone; C-TDa, attenuated CTD; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; MP, melphalan, prednisolone; SRE, skeletal-related event; ZOL, zoledronic acid.

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



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

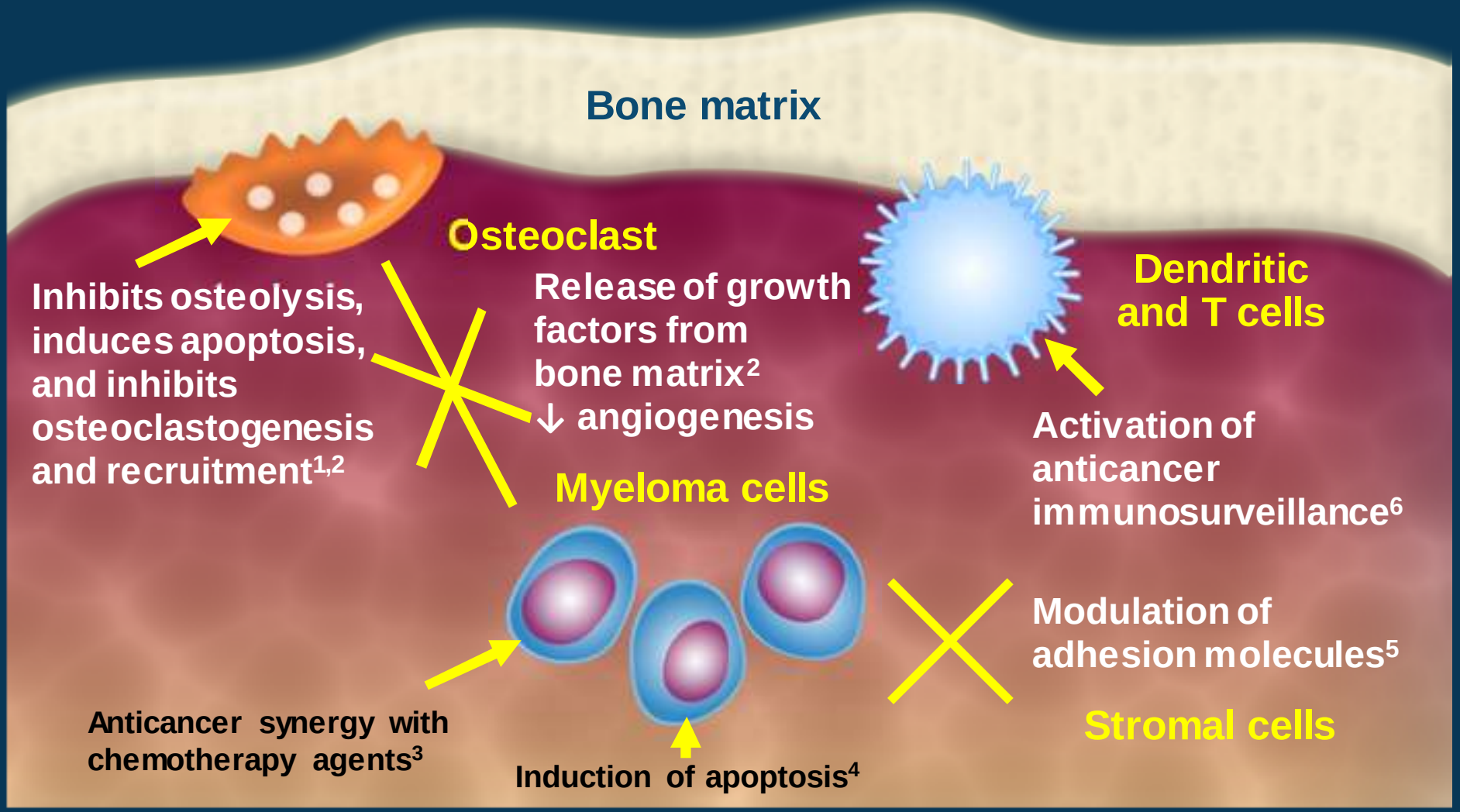
Abbreviations: CLO, clodronate; SRE, skeletal-related event; ZOL, zoledronic acid.

[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 ASH 2010. Abstract 311.

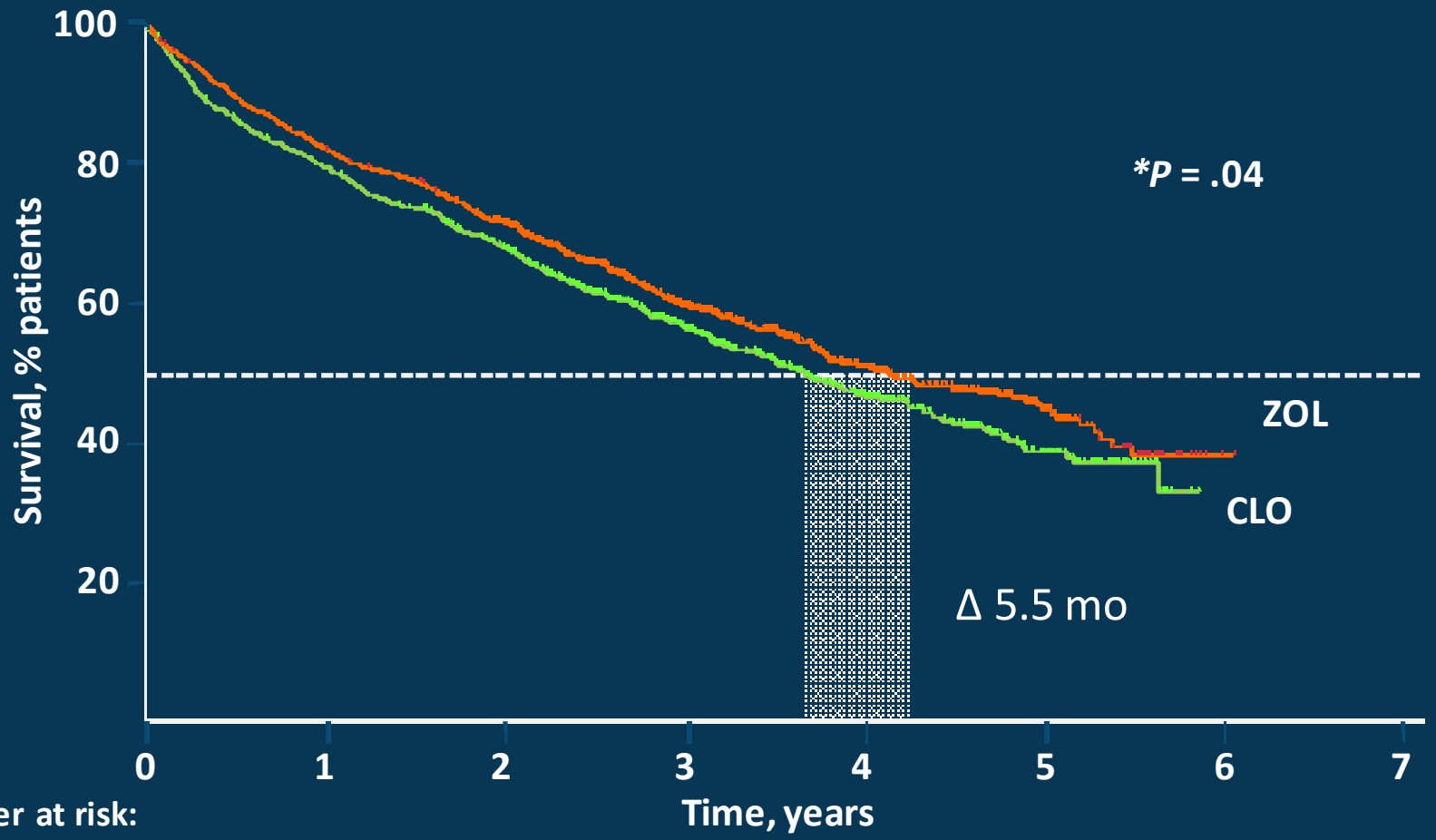
What About Antimyeloma Effects?

Zoledronic Acid Exerts Both Direct and Indirect Antimyeloma Effects Beyond SRE Prevention



1. Rosen LS, et al. *Cancer J*. 2001;7(5):377-387; 2. Mundy GR. *Nat Rev Cancer*. 2002;2(8):584-593; 3. Winter MC, et al. *Cancer Treat Rev*. 2008;34(5):453-475;
4. Shipman CM, et al. *Br J Haematol*. 1997;98(3):665-672; 5. Corso A, et al. *Cancer*. 2005;104(1):118-125; 6. Uchida R, et al. *Biochem Biophys Res Commun*. 2007;354(2):613-618.

MRC Myeloma IX: ZOL Significantly ō OS vs CLO



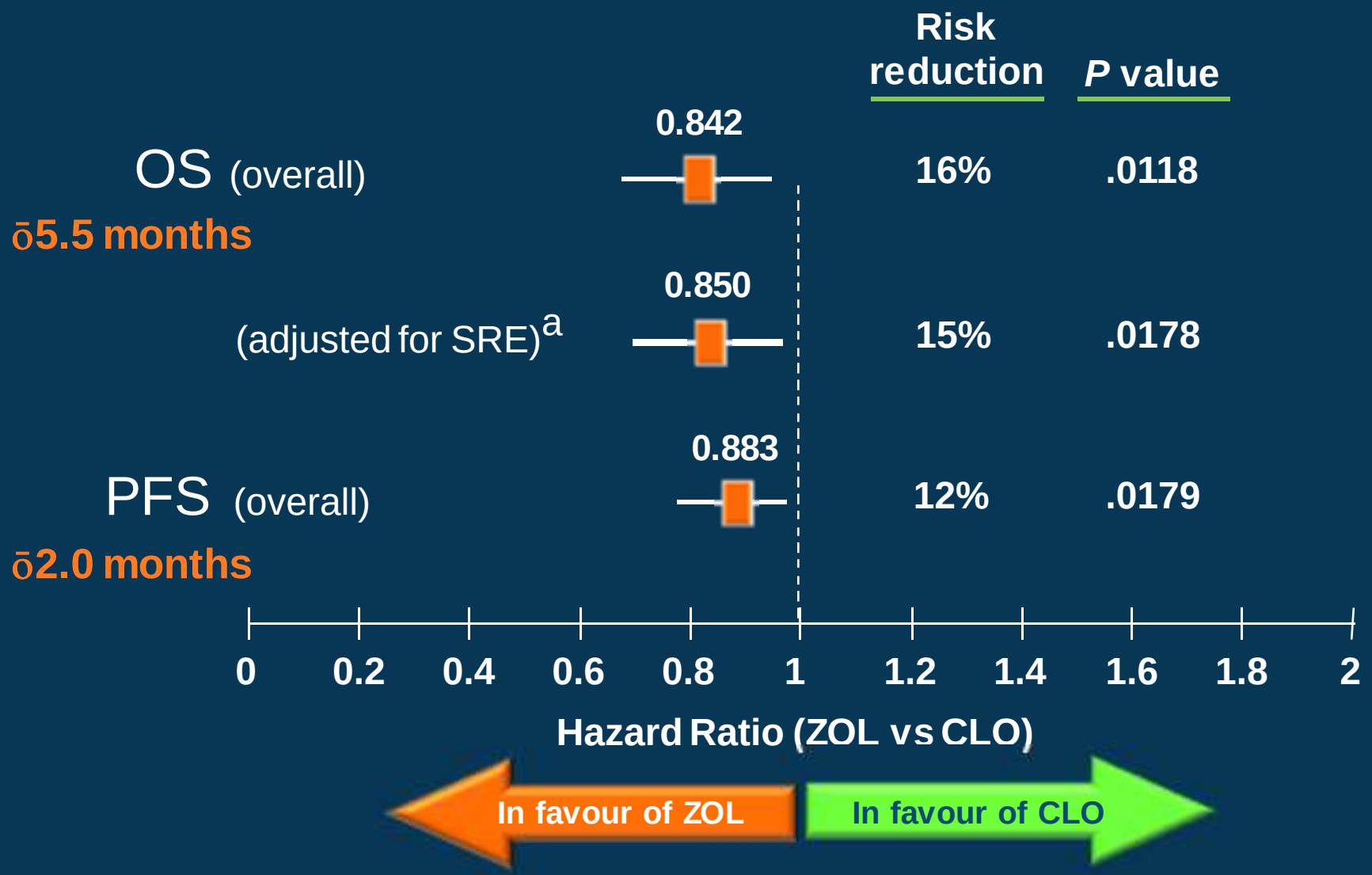
Number at risk:

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

Abbreviations: CLO, clodronate; OS, overall survival; ZOL, zoledronic acid.
* Kaplan-Meier analysis adjusted for treatment pathway (intensive vs not).

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

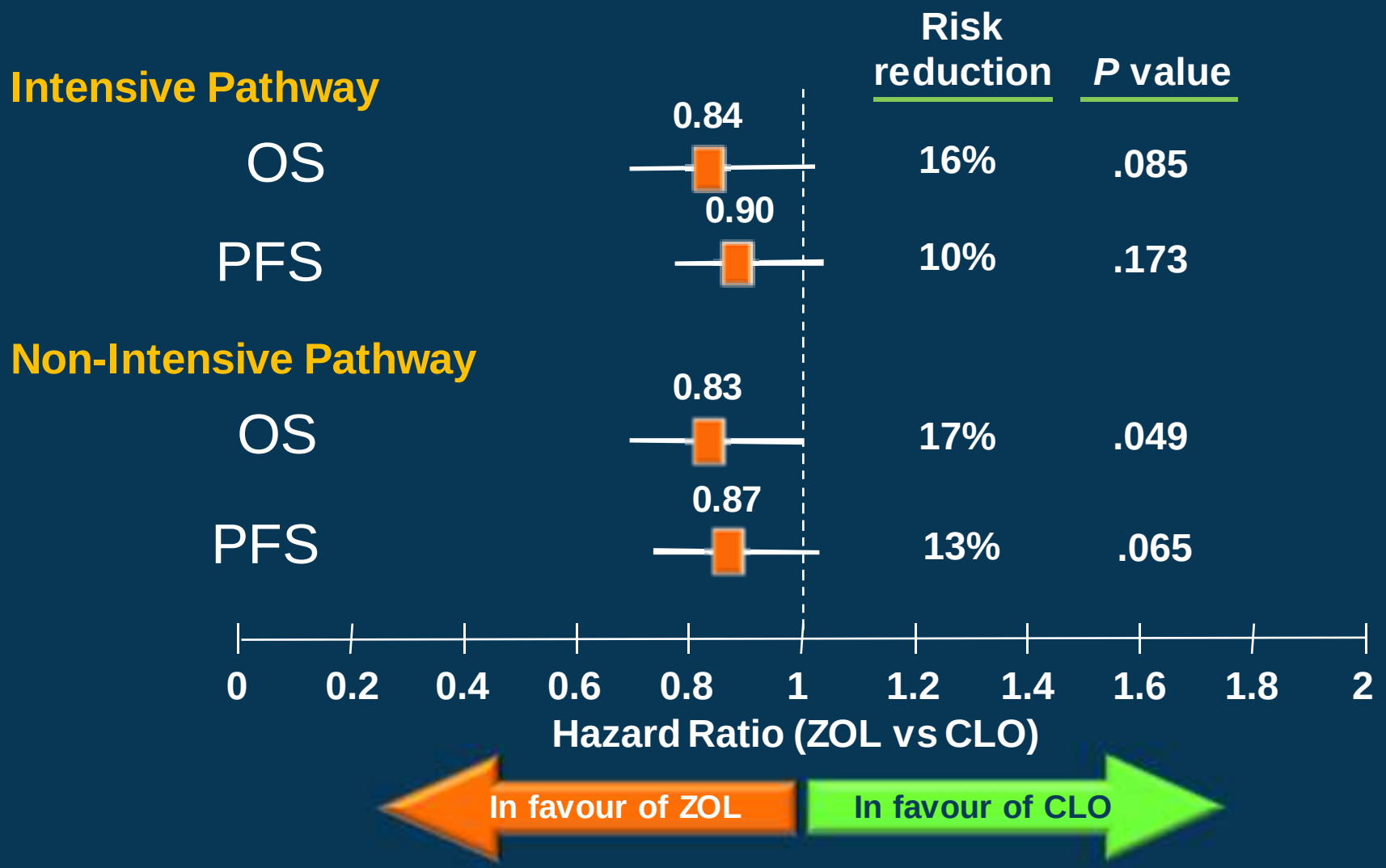
MRC Myeloma IX—ZOL ō OS and PFS vs CLO OS Benefit Was Independent of SRE Effect



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

Abbrev iations: CLO, clodronate; OS, overall survival; PFS, progression-free survival; SRE, skeletal-related event; ZOL, zoledronic acid.

MRC Myeloma IX—ZOL Affects OS and PFS vs CLO in Both Intensive and Non-Intensive Pathways*



* Cox model adjusted for chemotherapy and minimisation factors (including study centre).

Abbreviations: CLO, clodronate; OS, overall survival; PFS, progression-free survival; ZOL, zoledronic acid.

MRC Myeloma IX—Intensive Pathway Adverse Events

	Intensive Pathway (n = 1,111)					
	CVAD (n = 556)			C-TD (n = 555)		
	ZOL (n = 278)	CLO (n = 278)	*P*[a]	ZOL (n = 277)	CLO (n = 278)	*P*[a]
Acute renal failure	14 (5.0)	17 (6.1)	.71	15 (5.4)	16 (5.8)	1.0
ONJ[b]	13 (4.7)	2 (0.7)	.0067	8 (2.9)	0	.0037
Thromboembolic	59 (21.2)	41 (14.7)	.060	45 (16.2)	41 (14.7)	.64
Catheter-related	25 (9.0)	11 (4.0)	.024	3 (1.1)	2 (0.7)	.69
Infection TESAE	28 (10.1)	37 (13.3)	.29	24 (8.7)	25 (9.0)	1.0
All SAEs	167 (60.1)	155 (55.8)	.34	160 (57.8)	125 (45.0)	.0029
TESAEs	74 (26.6)	69 (24.8)	.70	84 (30.3)	72 (25.9)	.26

[a] Statistical significance determined by Fisher's exact test.
[b] ONJ cases were confirmed by an independent adjudication committee.
Abbreviations: CLO, clodronate; C-TD, cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; ONJ, osteonecrosis of the jaw; SAE, serious adverse event; TESAE, treatment-emergent SAE; ZOL, zoledronic acid.

MRC Myeloma IX—Non-Intensive Pathway Adverse Events

	Non-Intensive Pathway (n = 851)					
	MP (n = 424)			C-TDa (n = 427)		
	ZOL (n = 213)	CLO (n = 211)	*P*[a]	ZOL (n = 215)	CLO (n = 212)	*P*[a]
Acute renal failure	15 (7.0)	13 (6.2)	.85	13 (6.0)	14 (6.6)	.84
ONJ[b]	10 (4.7)	0	.0018	4 (1.9)	1 (0.5)	.37
Thromboembolic	10 (4.7)	10 (4.7)	1.0	43 (20.0)	25 (11.8)	.024
Infection TESAE	4 (1.9)	4 (1.9)	1.0	12 (5.6)	14 (6.6)	.69
All SAEs	97 (45.5)	81 (38.4)	.14	115 (53.5)	117 (55.2)	.77
TESAEs	27 (12.7)	18 (8.5)	.21	63 (29.3)	67 (31.6)	.67

[a] Statistical significance determined by Fisher's exact test.
[b] ONJ cases were confirmed by an independent adjudication committee.
Abbreviations: CLO, clodronate; C-TDa, attenuated cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisolone; N/A, not applicable; ONJ, osteonecrosis of the jaw; SAE, serious adverse event; TESAE, treatment-emergent SAE; ZOL, zoledronic acid.

Osteonecrosis of the Jaw (ONJ)—Risk and Prevention

ONJ is an uncommon adverse event

- ONJ is an uncommon adverse event reported in cancer patients receiving complex treatment regimens including bisphosphonates (BPs)
- ONJ is relatively a more frequent event in multiple myeloma

Preventive measures before BP treatment[1,2]

- Dental examination and appropriate preventive dentistry reduces relative incidence of ONJ by up to 70%[3,4]
- Remove abscessed non-restorable teeth, teeth with severe periodontal disease, and teeth with poor long-term prognosis
- Functionally rehabilitate salvageable dentitions
- Educate patients on oral hygiene and signs and symptoms of ONJ

Preventive measures during BP treatment

- Seek dental maintenance care at least every 6 months
- Avoid invasive dental procedures if possible
- Maintain good dental hygiene

1. Weitzman R, et al. *Crit Rev Oncol Hematol*. 2007;62(2):148-152; 2. Mehrotra B, et al. *Hematology Am Soc Hematol Educ Program*. 2006;356-360, 515; 3. Ripamonti CI, et al. *Ann Oncol*. 2009;20(1):137-145; 4. Dimopoulos MA, et al. *Ann Oncol*. 2009;20(1):117-120.

MRC Myeloma IX—Conclusions

- ZOL significantly Œ the relative risk of SREs vs CLO (*P* = .0004)
  - ZOL Œ relative risk of SREs vs CLO regardless of treatment pathway
  - ZOL Œ relative risk of all types of SREs vs CLO regardless of bone disease status at presentation
- ZOL significantly ō survival outcomes vs CLO
  - ZOL ōOS vs CLO (*P* = .012)
  - ZOL ōPFS vs CLO (*P* = .018)
  - ZOL ō in OS vs CLO was independent of SRE Œ (*P* = .018)

MRC Myeloma IX—Conclusions

- ZOL and CLO were generally well tolerated, with AEs consistent with established safety profiles
  - ONJ incidence was low, but ō for ZOL vs CLO (3.6% vs 0.3%)
  - Low incidence of renal failure; similar for ZOL vs CLO
- Patients who received thalidomide had the best outcomes (ō CR/VGPR, ō OS, Œ SREs)
  - ZOL benefits were seen across all treatment groups (ie, CVAD, C-TD, MP, C-TDa)
  - In the non-intensive pathway, C-TDa + ZOL was strikingly superior
- These data suggest inhibiting progression of myeloma improves bone status
  - In addition, improving bone integrity may beneficially affect the course of disease (vicious circle becomes virtuous cycle)

MRC Myeloma IX—Remaining Questions

- What is the optimal timing of BP therapy?
  - Data already support early treatment of newly diagnosed MM
- Evidence of maintenance benefit
  - What is the optimal duration and dose?
- Do benefits correlate with any risk factors?
- Is there synergy of ZOL's antimyeloma effects with other novel agents?

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MRC Leukaemia Trial Steering Committee

MRC Leukaemia Data Monitoring and Ethics Committee

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Backups

MRC Myeloma IX—Trial Status

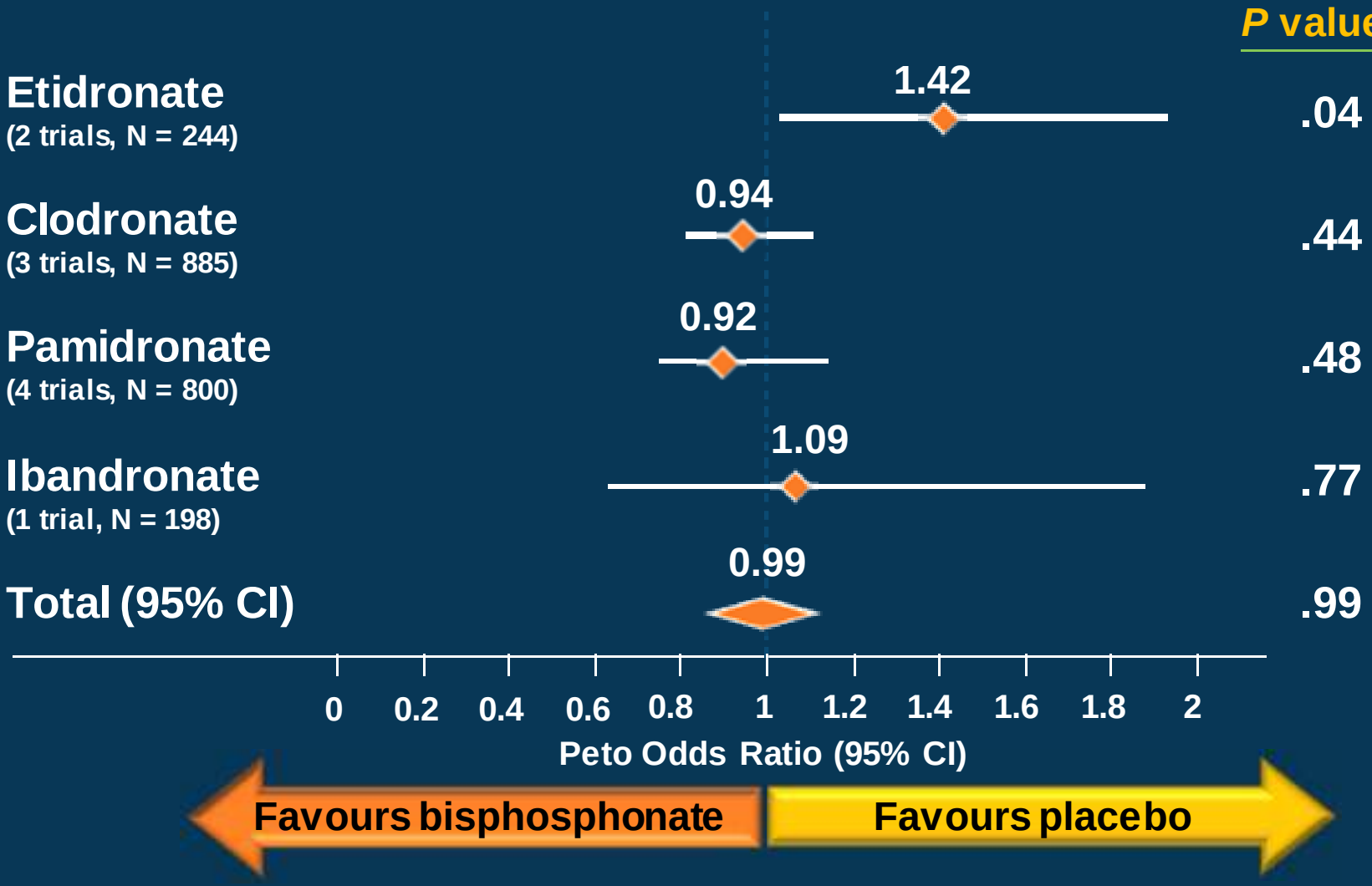
- 1,960 evaluable patients
- 121 centres

>70% remained on study until progression or death or had ongoing treatment

	ZOL (n = 981)	CLO (n = 979)
Median follow-up, years (cutoff date 5 Oct 2009)	3.7	3.8
Still receiving BP, n (%)	**111 (11)**	**132 (14)**
Administration of BP not confirmed, n (%)	54 (5.5)	36 (3.7)
Stopped before progression, n (%)	235 (24)	185 (18.9)
Progressed or died, n (%)	**581 (59)**	**626 (64)**
Median time on treatment, days		
Intensive	395	409
Non-intensive	320	305

Abbreviations: BP, bisphosphonate; CLO, clodronate; ZOL, zoledronic acid.

Bisphosphonate Use in Multiple Myeloma—Systematic Review of Survival Outcomes

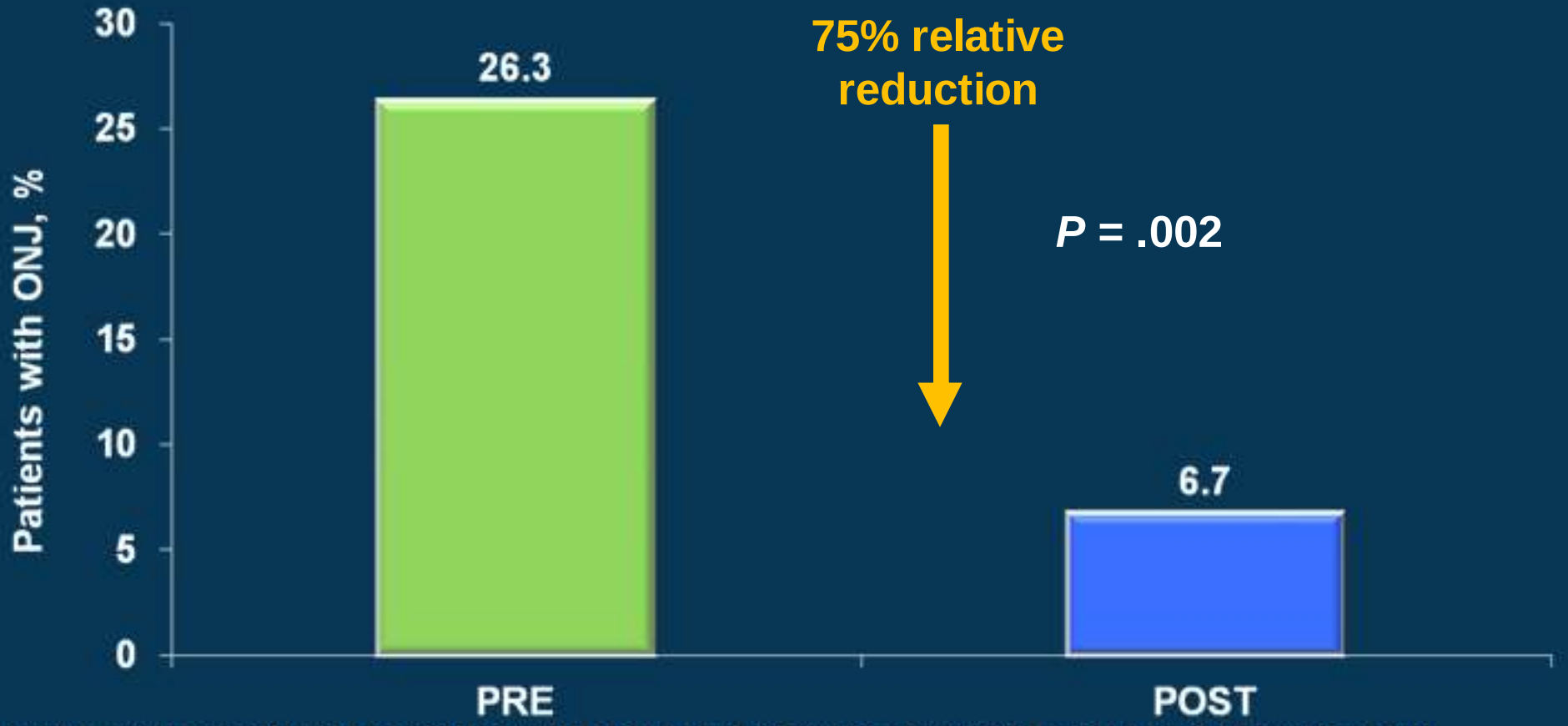


[a] Trials of bisphosphonates compared with placebo.
Note: Zoledronic acid was not included in this review.
Abbreviation: CI, confidence interval.

Adapted from Djulbegovic B, et al. *Cochrane Database Syst Rev.* 2002;(4):CD003188.

Preventive Measures Reduce the Risk of ONJ by 75% in Patients With Multiple Myeloma

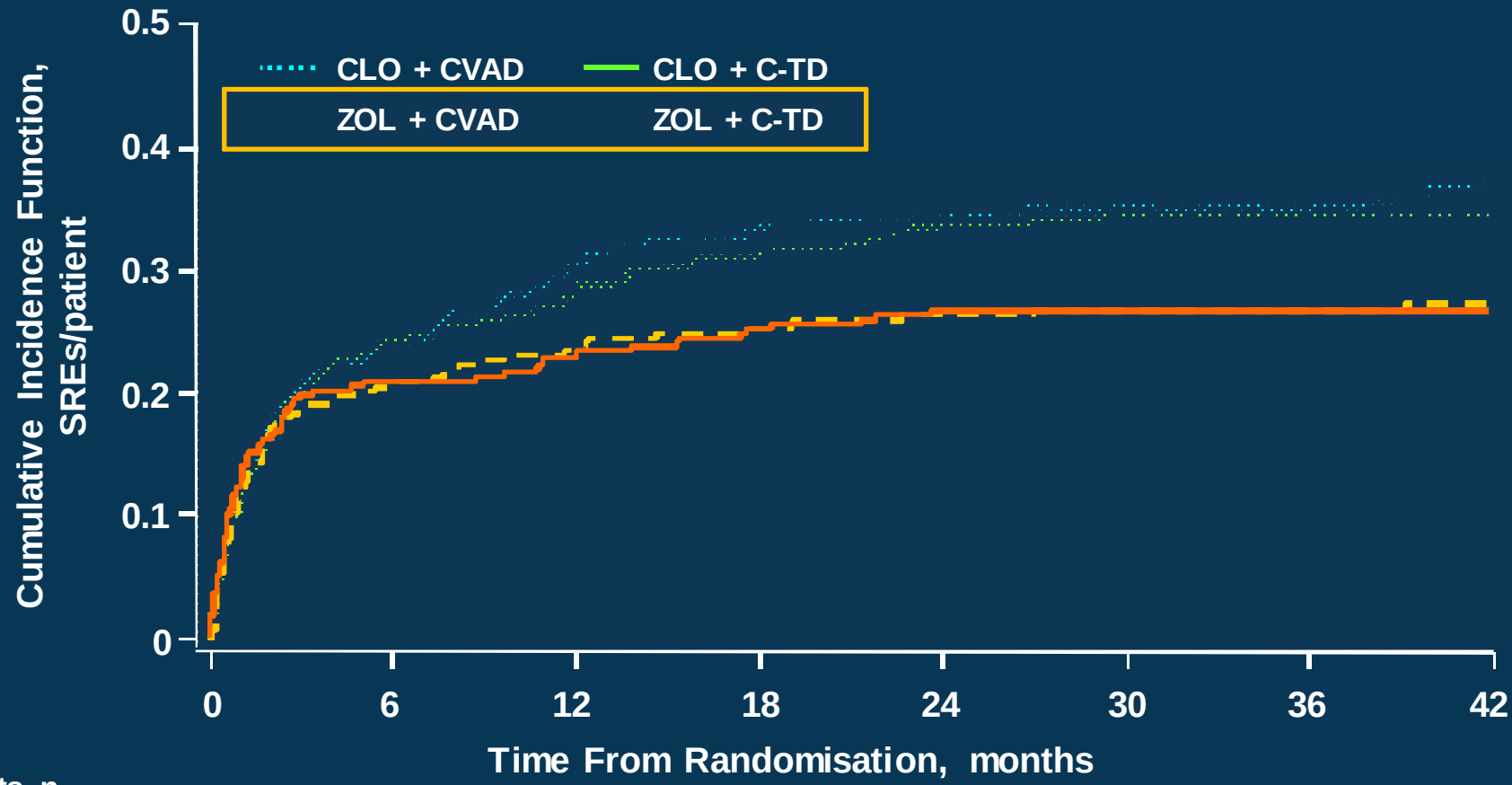
- Retrospective analysis of patients with MM who received ZOL (N = 128)
  - PRE group (n = 38) received ZOL before implementation of preventive measures
  - POST group (n = 90) started ZOL after implementation of preventive measures



Abbreviations: MM, multiple myeloma; ONJ, osteonecrosis of the jaw; PRE, pre-implementation of preventive measures; POST, post-implementation of preventive measures; ZOL, zoledronic acid.

Dimopoulos MA, et al. *Ann Oncol.* 2009;20(1):117-120.

MRC Myeloma IX—ZOL Œ SREs vs CLO[a] in Both Treatment Arms of the Intensive Pathway

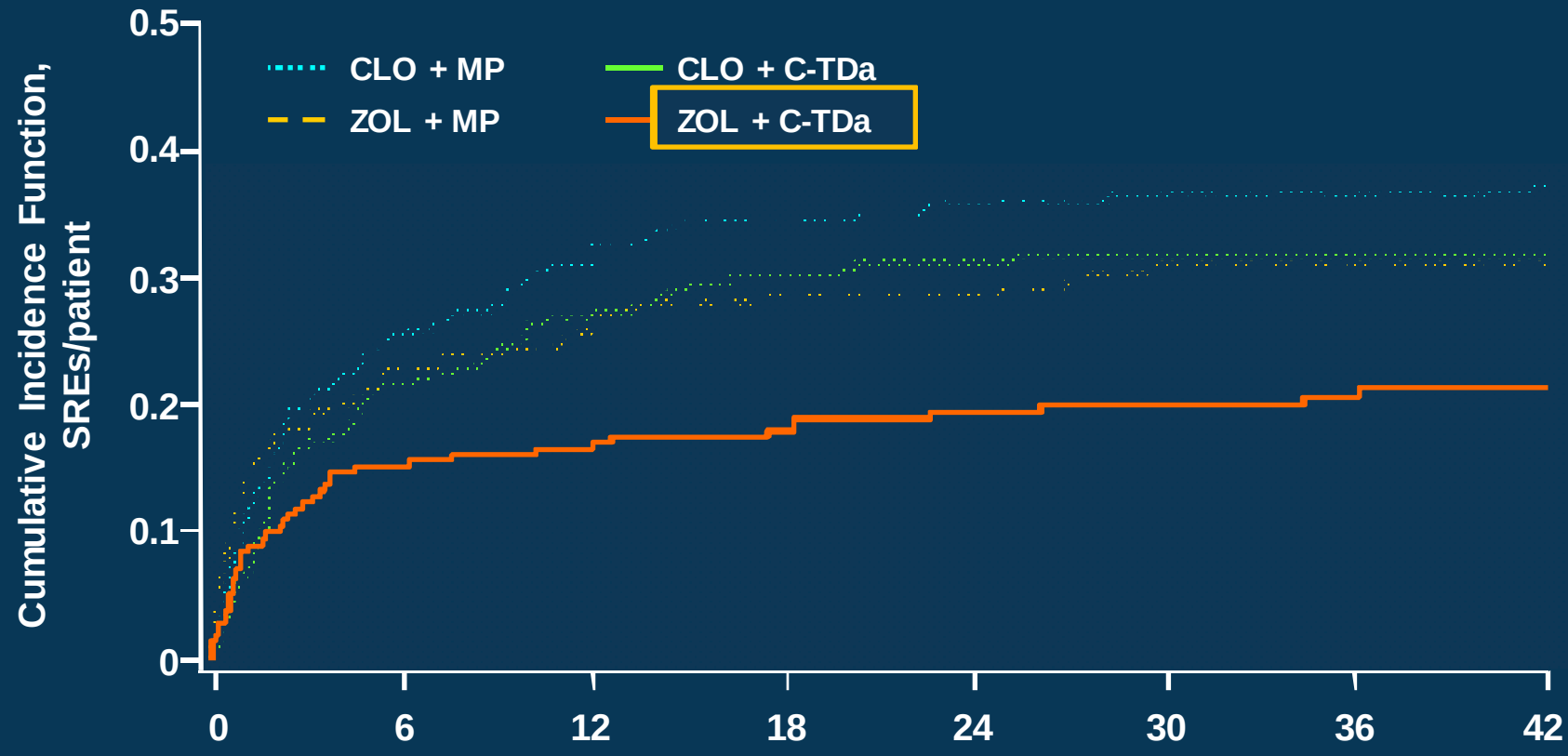


Patients, n								
ZOL + C-TD	277	191	165	136	107	80	58	41
ZOL + CVAD	278	195	165	139	105	79	53	39
CLO + C-TD	278	186	159	131	106	69	47	29
CLO + CVAD	278	192	151	115	97	68	43	29

[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; C-TD, cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; SRE, skeletal-related event; ZOL, zoledronic acid.

MRC Myeloma IX—ZOL Œ SREs vs CLO[a] in Both Treatment Arms of the Non-Intensive Pathway

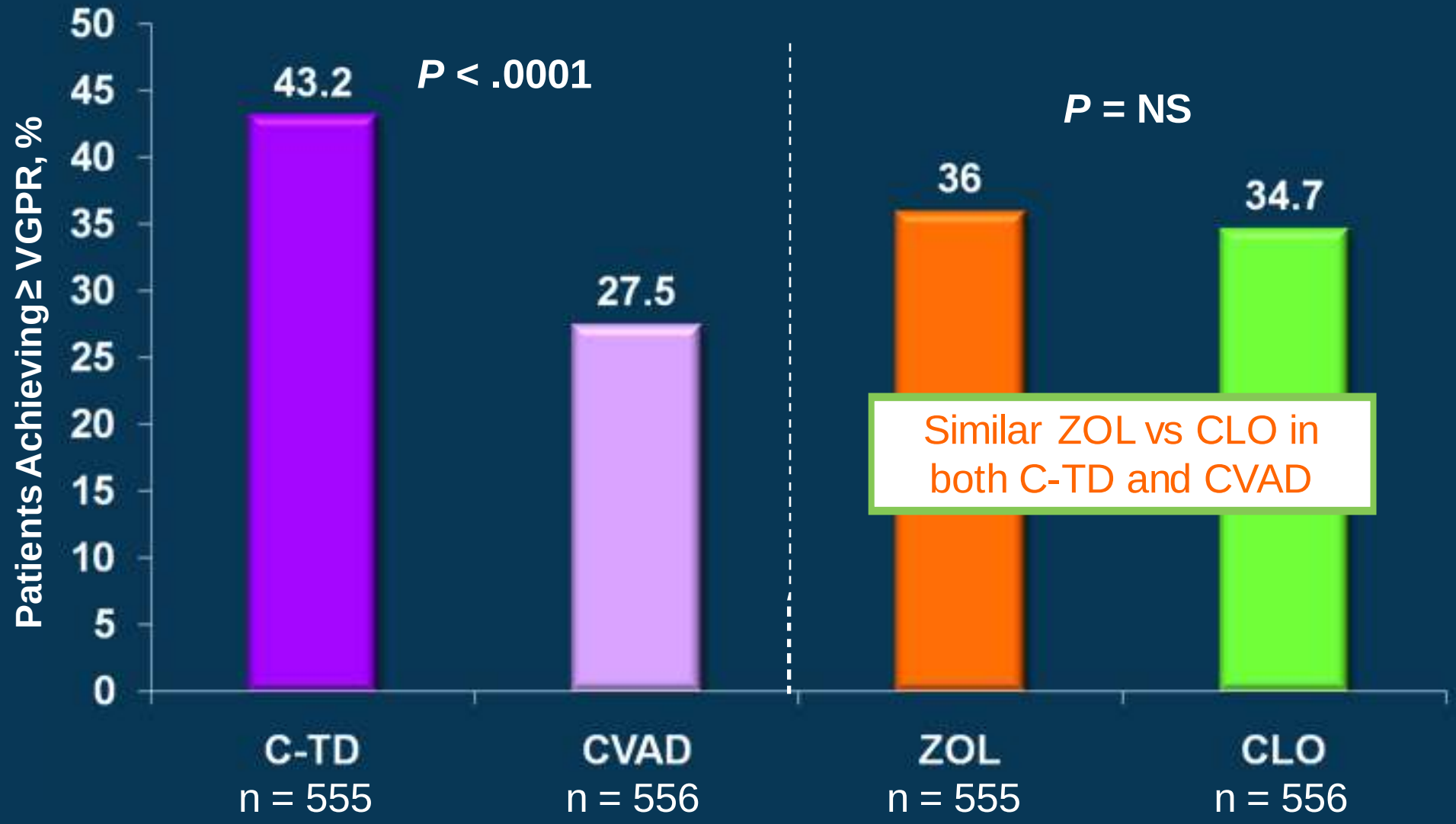


Patients, n								
ZOL + C-TDa	214	143	89	62	41	26	18	12
ZOL + MP	212	134	87	53	31	16	9	5
CLO + C-TDa	212	132	84	52	28	21	12	9
CLO + MP	211	119	71	39	25	15	10	7

[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.

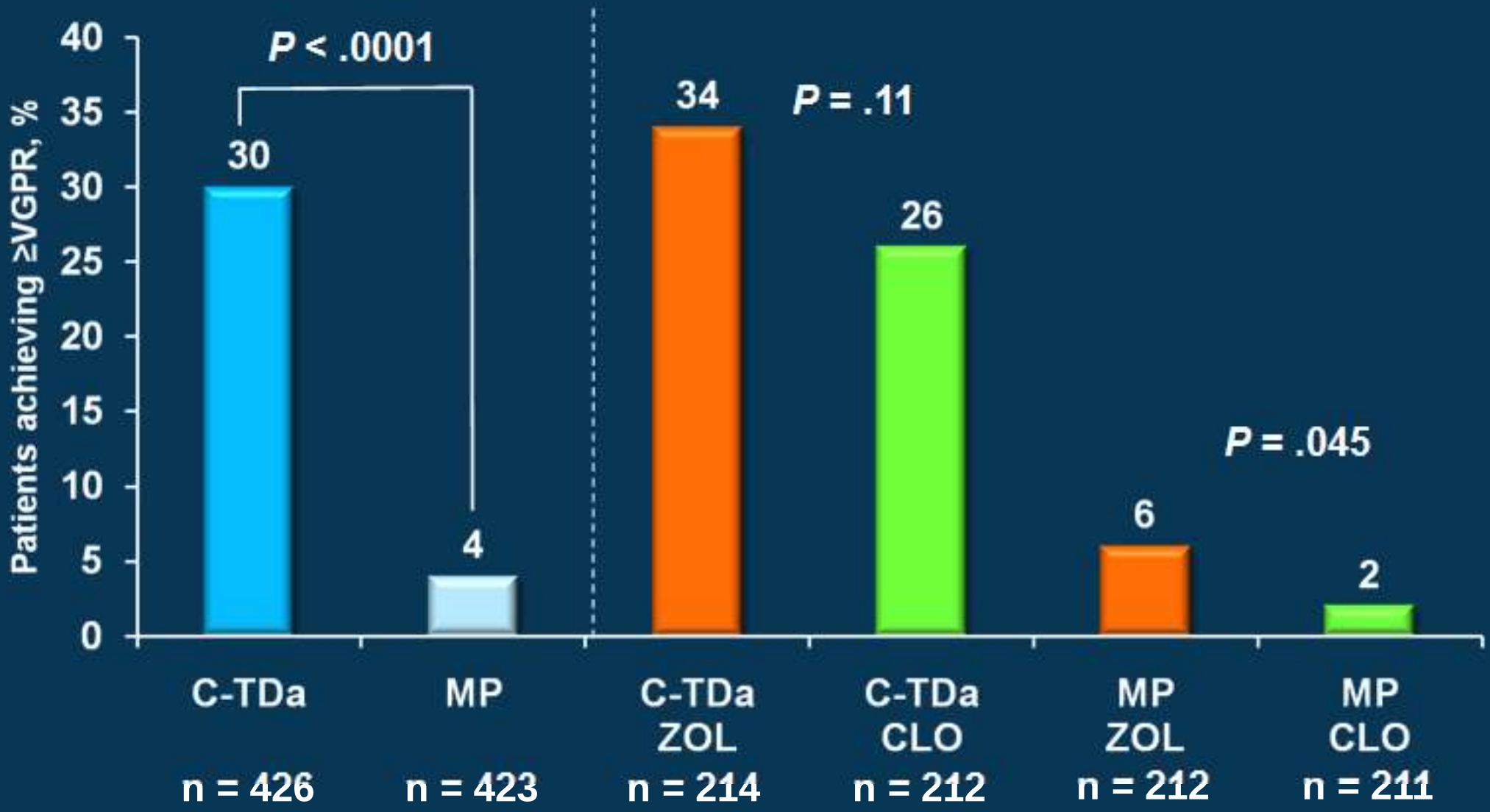
Abbreviations: CLO, clodronate; C-TDa, attenuated cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; MP, melphalan, prednisolone; SRE, skeletal-related event; ZOL, zoledronic acid.

MRC Myeloma IX—Higher CR/VGPR[a] Rate With C-TD vs CVAD in the Intensive Pathway



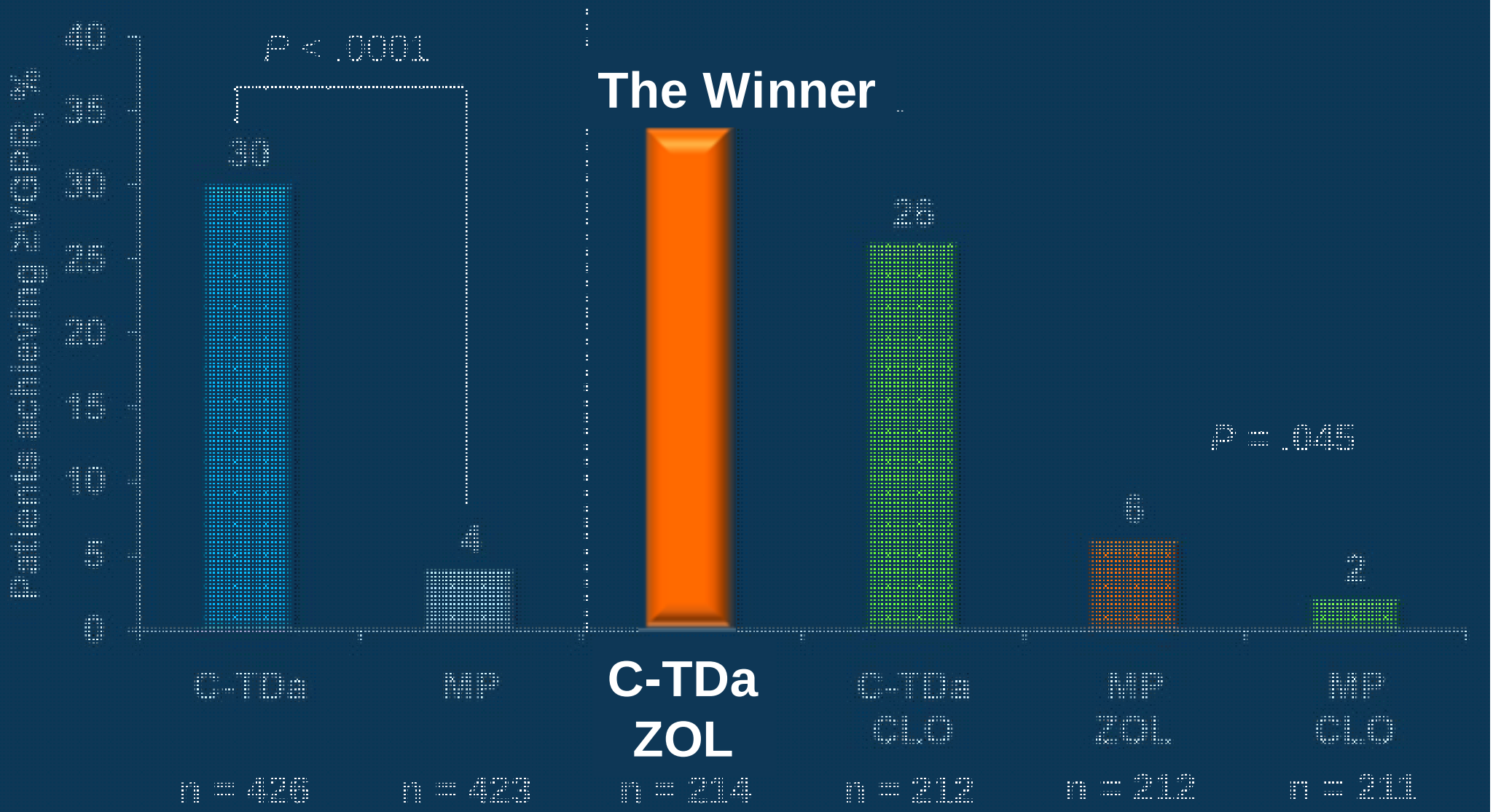
[a] After induction therapy.
Abbreviations: CLO, clodronate; CR, complete response; C-TD, cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; NS, not significant; VGPR, very good partial response (defined as ≥ 90% but < 100% reduction in serum M-protein, with positive immunofixation); ZOL, zoledronic acid.

MRC Myeloma IX—Higher CR/VGPR Rates for C-TDa and ZOL in the Non-Intensive Pathway



Abbrev iations: CLO, clodronate; C-TDa, attenuated cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisolone; VGPR, very good partial response (defined as ≥ 90% but < 100% reduction in serum M-protein, with positive immunofixation); ZOL, zoledronic acid.

MRC Myeloma IX—Higher CR/VGPR Rates for C-TDa and ZOL in the Non-Intensive Pathway



European Myeloma Network Guidelines

Treat all patients with

- Osteolytic bone disease on plain radiographs
- Osteopenia or osteoporosis based on bone mineral density
- Patients on chemotherapy

Bisphosphonate therapy for 2 years

- After 1 year continue at physician's discretion
- Restart after disease relapse
- ZOL, PAM, or oral CLO (where indicated)

Do not treat patients with MGUS or asymptomatic MM

Monitor patients for

- Compromised renal function (creatinine clearance)
- Osteonecrosis of the jaw[a]

[a] Monitoring for ONJ includes: comprehensive dental examination prior to starting BP; avoid unnecessary invasive dental procedures; temporary suspension of BP for invasive dental procedures; discontinue BP until completely healed.

Abbreviations: BP, bisphosphonate; CLO, clodronate; MM multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; ONJ, osteonecrosis of the jaw; PAM, pamidronate; ZOL, zoledronic acid.

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

Zoledronic Acid Improves Disease Outcomes in Advanced Disease

ZOL activates γδ T cells in patients with MM

- ZOL-activated γδ T-LAK cells increased the level of circulating γδ T cells in the peripheral blood and bone marrow in all patients after 4 treatments (N = 6)[1]
- ZOL-activated γδ T cells from the peripheral blood of MM patients showed cytotoxic activity against myeloma/lymphoma cell lines[2]

ZOL in combination with standard antimyeloma therapy is active and generally well tolerated

- ZOL (4 mg q 4 wk) + thalidomide (100 mg/d) + dexamethasone produced a 68% overall response rate in patients with newly diagnosed MM (N = 26)[3]
- ZOL (4 mg q 4 wk) + thalidomide was well tolerated in patients who had received autologous stem cell transplants[4]

Abbreviations: MM, multiple myeloma; T-LAK, lymphocyte-activated T killer; ZOL, zoledronic acid.

1. Abe Y, et al. *Exp Hematol.* 2009;37(8):956-958; 2. Saitoh A, et al. *Med Oncol.* 2008;25(2):137-147; 3. Klueppelberg U, et al. *J Clin Oncol.* 2004;22(14 suppl):606 . Abstract 6702; 4. Spencer A, et al. *J Clin Oncol.* 2004;22(14 suppl):594. Abstract 6655.

Adverse Events Associated With Intravenous Bisphosphonates

Flu-like symptoms[a]

- Observed in ~20% of patients after initial infusion[1]
- Characteristics: fever, muscle and joint aches, fatigue
- Manageable with over-the-counter analgesics

Hypocalcemia

- Assess baseline serum calcium levels
- Ensure adequate calcium and vitamin D supplements

Increased serum creatinine (Cr) levels

- If elevated, thorough evaluation required
- Treatment should be withheld for renal impairment, defined as[2]
  - An increase of 0.5 mg/dL in patients with normal baseline Cr
  - An increase of 1.0 mg/dL in patients with abnormal baseline Cr
- Treatment can be resumed when Cr levels return to within 10% of baseline
- Alternative dosing is recommended based on renal function

[a] Commonly observed with the administration of all intravenous bisphosphonates.

1. Berenson JR. *Oncologist.* 2005;10(1):52-62; 2. ZOMETA® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2009.

Renal Safety in Patients With Multiple Myeloma

Renal impairment occurs in up to 30% of patients at presentation and in up to 50% of patients at some disease stage[1]

Other factors affecting renal function in patients with myeloma include dehydration, hypercalcemia, hyperuricemia, infection, and use of nephrotoxic drugs[1]

Failure to follow ZOL safety instructions can adversely affect renal function in patients with renal impairment. Serum creatinine must be monitored before each dose of ZOL[2]

- Dose should not exceed 4 mg
- Infusion time should not be less than 15 minutes

Abbrev iation: ZOL, zoledronic acid.

1. Smith A, et al. *Br J Haematology*. 2005; 132:410-451; 2. ZOMETA® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2009.

MRC Myeloma IX Trial—Caveats

Multi-comparator trial design

Newer agents are now available

Not all patients had bone lesions at study entry

- All patients had symptomatic MM
- Bone lesions develop in virtually all patients during the disease course

Potential effect of SREs on survival

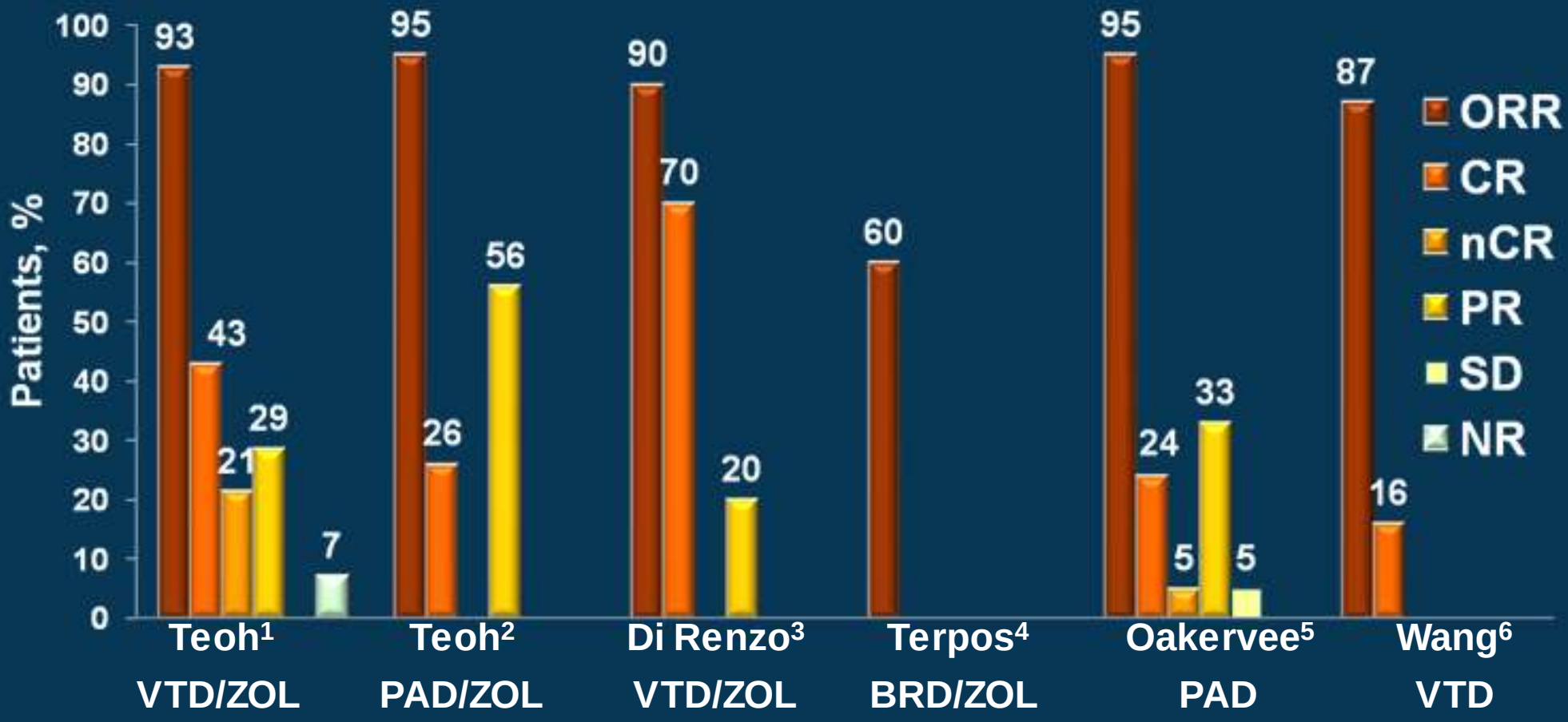
- OS benefit with ZOL was maintained after adjustment for potential effects of SREs on survival

All patients received bisphosphonate (ie, no control group)

- CLO and ZOL were used because both are approved in the UK for preventing SREs in patients with myeloma bone disease
- SRE patterns are consistent with previously reported placebo-controlled studies in the MM setting

Abbreviations: CLO, clodronate; MM, multiple myeloma; OS, overall survival; SRE, skeletal-related event; UK, United Kingdom; ZOL, zoledronic acid.

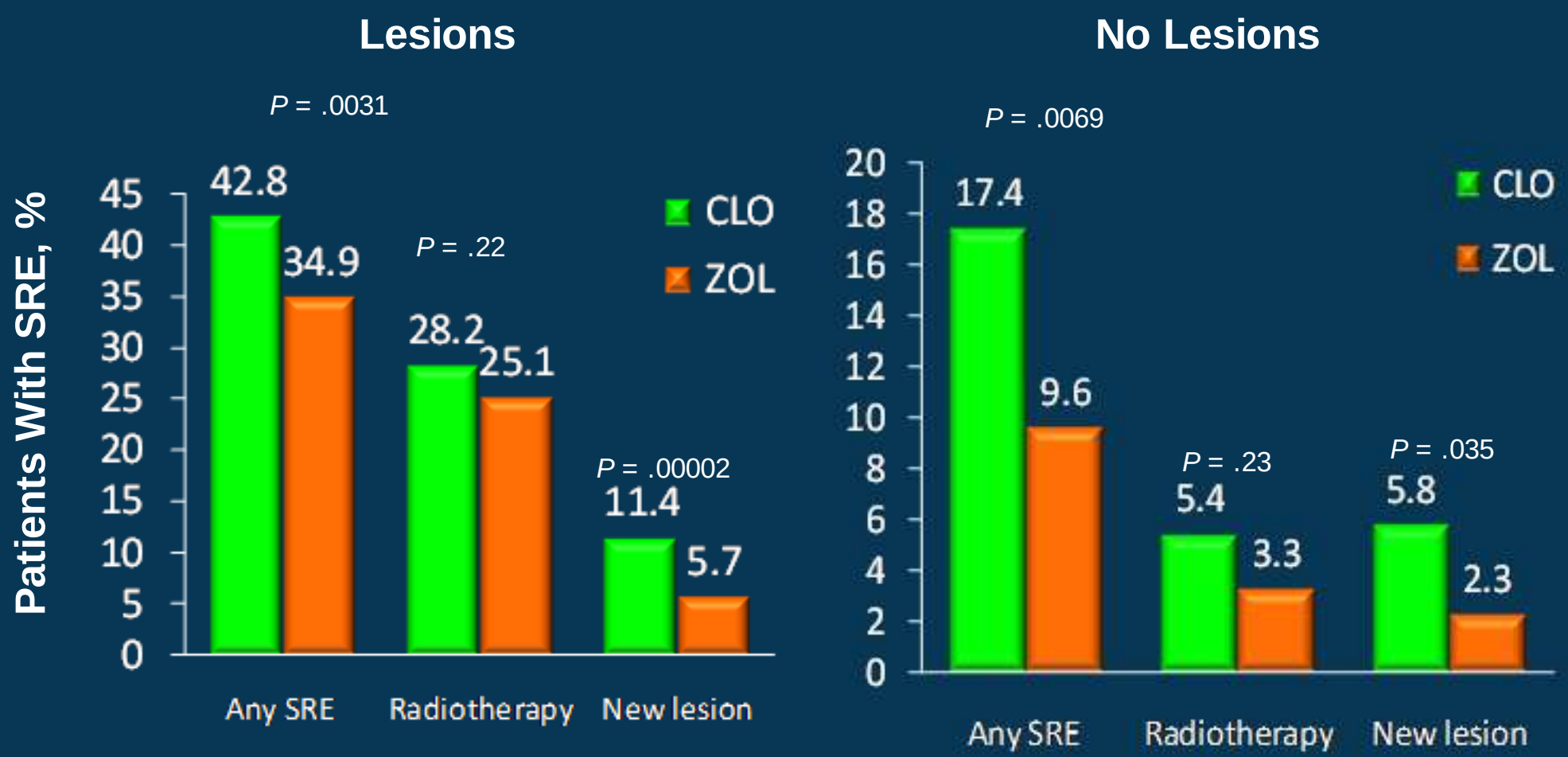
ZOL Can Be Administered With Bortezomib—Promising Results in Initial Trials



Abbreviations: BRD, V+Len+Dex; CR, complete response; Dex, dexamethasone; Dox, doxorubicin; Len, lenalidomide; nCR, near-complete response; NR, no response; PAD, V+Dex+Dox; PR, partial response; SD, stable disease; Thal, thalidomide; V, Velcade (bortezomib); VTD, V+Thal+Dox; ZOL, zoledronic acid.

1. Teoh G, et al. *J Clin Oncol*. 2006;24:683s. Abstract 17537; 2. Terpos E, et al. *Blood* . 2007;110. Abstract 3596; 3. Di Renzo N, et al. *Blood*. 2008;112. Abstract 5203;
4. Terpos E, et al. *Blood*. 2009;114. Abstract 1815; 5. Oakervee HE, et al. *Br J Haematol*. 2005;129(6):755-762; 6. Wang M, et al. *Hematology*. 2007;12(3):235-239.

MRC Myeloma IX Trial—ZOL Œ Each Type of SRE vs CLO Regardless of Baseline Bone Status



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; SRE, skeletal-related event; ZOL, zoledronic acid.