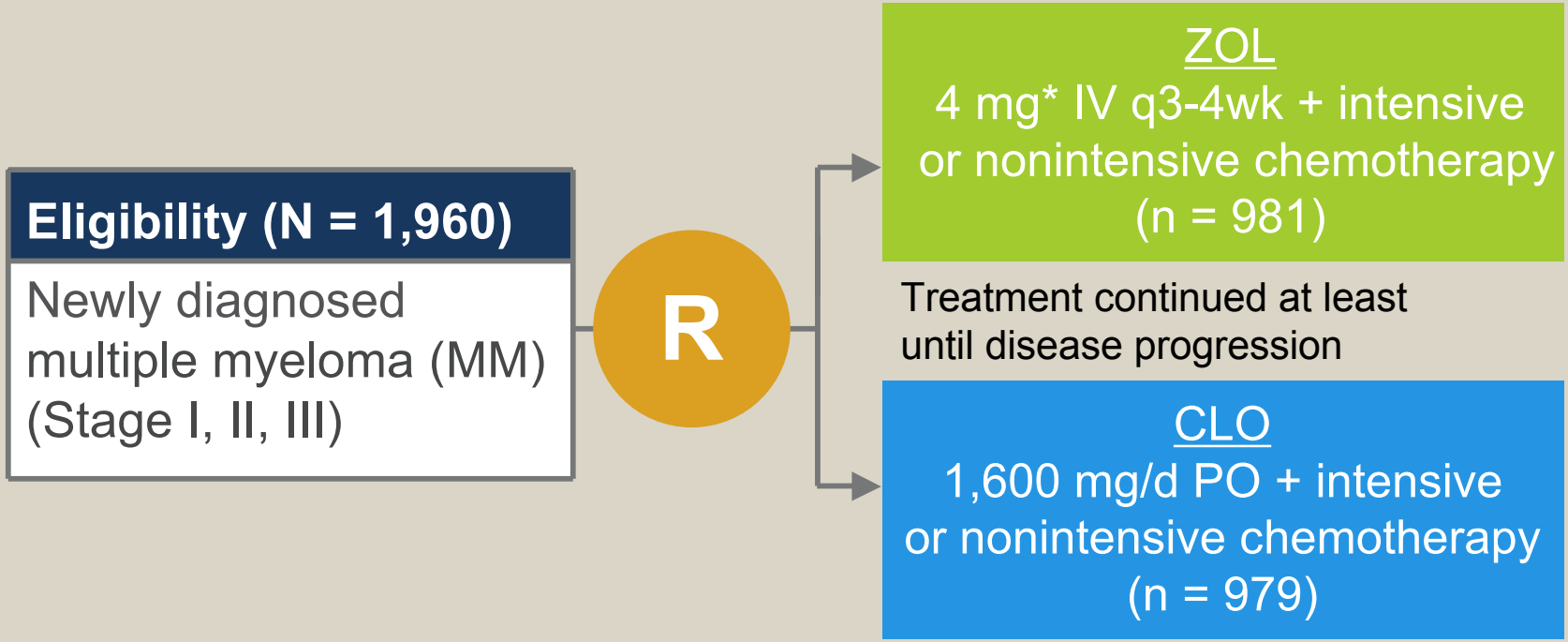
First-Line Treatment with Zoledronic Acid as Compared with Clodronic Acid in Multiple Myeloma (MRC Myeloma IX): A Randomized Controlled Trial

Morgan GJ et al.
Lancet 2010;376(9757):1989-99.

MRC Myeloma IX: A Phase III Trial of Zoledronic Acid (ZOL) versus Clodronic Acid (CLO)



* Dose-adjusted for patients with impaired renal function, per the prescribing information

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Treatment Status

	ZOL (n = 981)	CLO (n = 979)
Follow-up (median)	3.7 years	3.8 years
Still receiving bisphosphonate (BP)	11%	13%
BP administration not confirmed	6%	4%
Discontinued study before disease progression	24%	19%
Disease progression or death	59%	64%
Time on treatment		
Intensive pathway	396 days	409 days
Nonintensive pathway	320 days	306 days

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Primary Endpoints

Clinical variable	ZOL (n = 981)	CLO (n = 979)	Hazard ratio	*p*-value
Median overall survival	50.0 mo	44.5 mo	0.87	0.04
Median progression-free survival	19.5 mo	17.5 mo	0.91	0.07

Overall response rates did not differ significantly between ZOL and CLO groups

- Patients receiving intensive induction chemotherapy (78% vs 76%; $p = 0.43$)
- Patients receiving nonintensive induction chemotherapy (50% vs 46%; $p = 0.18$)

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Relative Risk Reduction

	Risk reduction	Hazard ratio	*p*-value
Overall survival	16%	0.84	0.0118
Progression-free survival	12%	0.88	0.0179

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Select Adverse Events (AEs)

	Intensive pathway		Nonintensive pathway		
AE	**ZOL (n = 555)**	**CLO (n = 556)**	**ZOL (n = 428)**	**CLO (n = 423)**	**Overall *p*-value**
Osteonecrosis of the jaw (ONJ)	4%	<1%	3%	<1%	<0.0001
Thromboembolic events	19%	15%	12%	8%	0.01
Any serious AE	59%	50%	50%	47%	<0.0001
Infection	9%	11%	4%	7%	0.07
Musculoskeletal, connective tissue, bone disorders	1%	<1%	3%	0%	0.0007

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Author Conclusions

- ZOL is superior to CLO for the prevention of skeletal-related events (SREs) in patients with newly diagnosed MM.
- Adding ZOL to standard antimyeloma therapy is generally well tolerated and prolongs overall survival vs CLO.
  - Survival benefit is independent of SRE reduction.
- These data further support the anticancer activity of ZOL and provide evidence that ZOL should be considered for early integration into treatment regimens for patients with newly diagnosed MM.

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Faculty Comments

DR BENSINGER: This is a landmark study by the Medical Research Council in the United Kingdom that included all patients with myeloma enrolled in the United Kingdom over a 4-year period between 2003 and 2007. Compared to clodronate (CLO), zoledronic acid (ZOL) extended survival by 5 1/2 months. The absolute time of progression-free interval was about 2 months, but it provided compelling evidence of a direct antimyeloma effect of ZOL. This result underscores that ZOL is one of the most potent of the bisphosphonates. With regard to adverse events, a difference was observed between the 2 groups in the incidence of ONJ — it was 3% to 4% for ZOL versus <1% for CLO. Although ONJ is something you need to be aware of and counsel your patients about, I believe the benefits of using continuous ZOL markedly outweigh the risks.

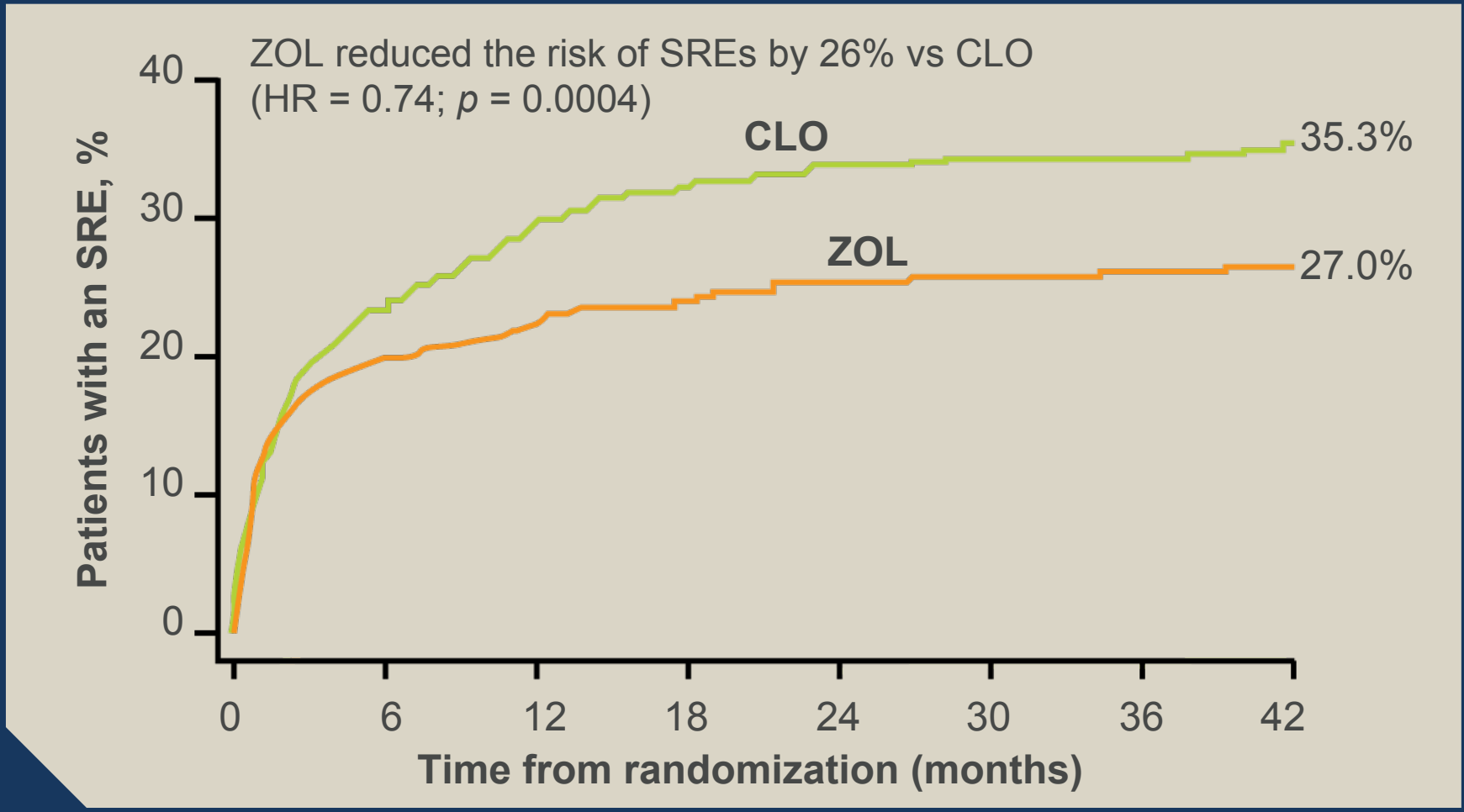
Does Zoledronic Acid Reduce Skeletal-Related Events and Improve Progression-Free Survival in Patients with Multiple Myeloma with or without Bone Disease? MRC Myeloma IX Study Results[1]

Bisphosphonate Treatment in Multiple Myeloma: Should They Be Used Until Progression?[2]

[1] Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

[2] Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

Skeletal-Related Events (SREs) — Overall Population



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SREs by Baseline Bone Lesion Status

	Patients with an SRE			
Baseline status	**ZOL**	**CLO**	**Hazard ratio**	***p*-value**
Bone lesions at baseline	34%	43%	0.774	0.004
No bone lesions at baseline	9%	17%	0.526	0.007

Highlights the importance of administering treatment to all patients regardless of skeletal morbidity at presentation

Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Author Conclusions

- ZOL significantly reduced the relative risk of SREs vs CLO ($p = 0.0004$).
  - Reductions were documented regardless of bone disease status at presentation.
- SRE rates were higher among patients with preexisting versus no bone disease at presentation.
- SRE reduction with ZOL was apparent within the first year regardless of bone disease status at presentation (data not shown).

Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Overall Survival (OS) — Patients with Bone Disease at Baseline

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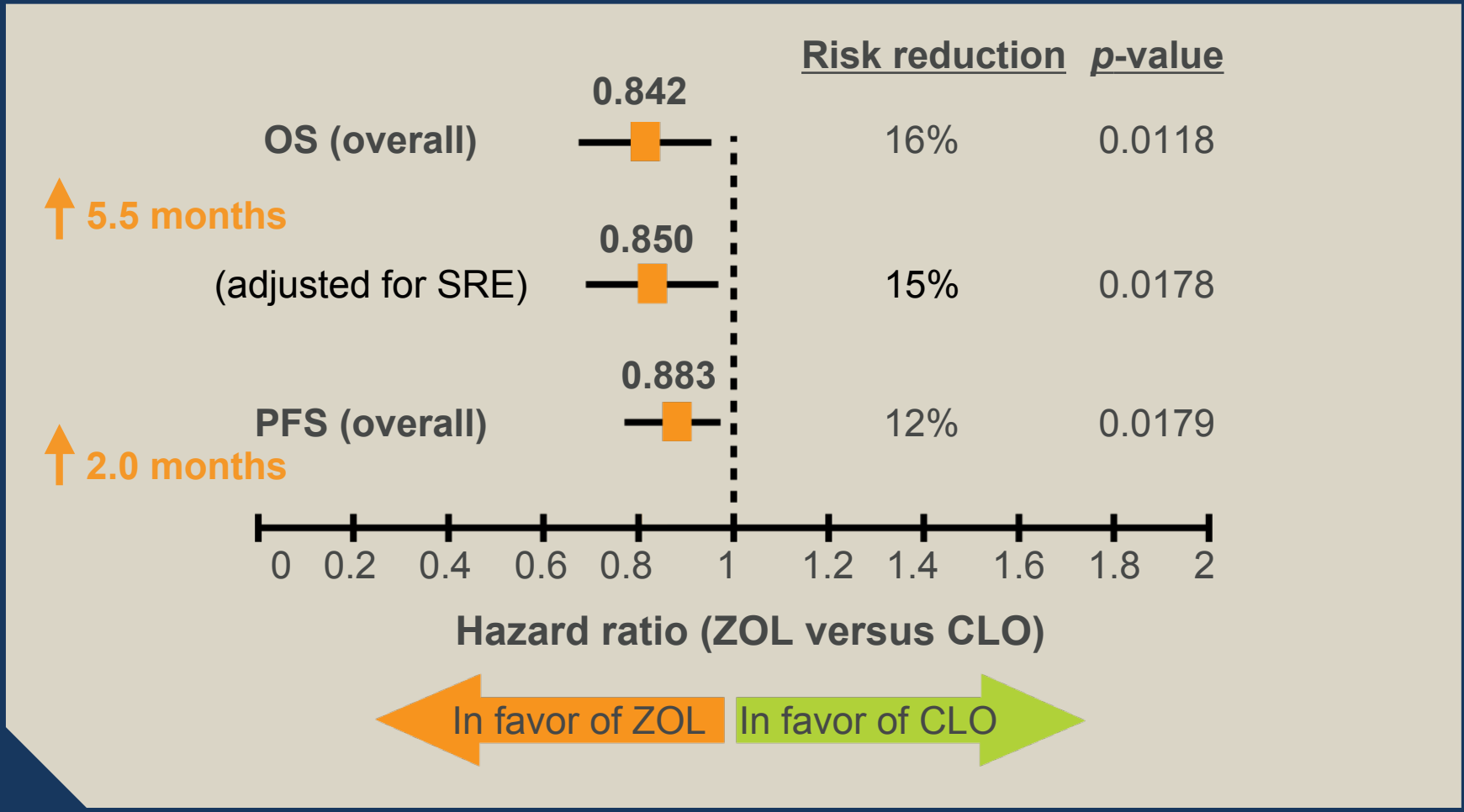
Survival — Overall Population



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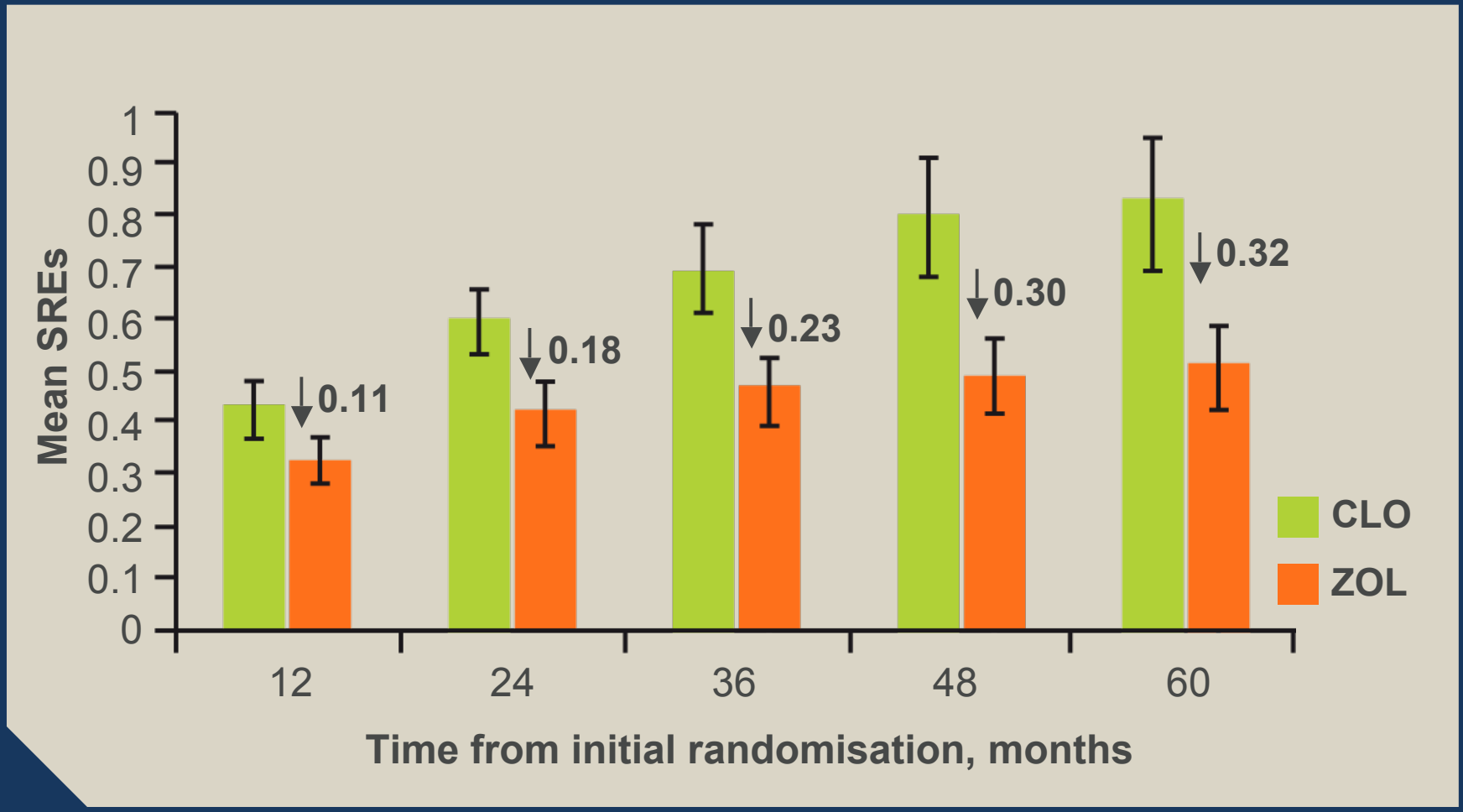
Author Conclusions — Disease Outcomes

- ZOL significantly increased OS and PFS in the overall patient population compared to CLO.
  - OS and PFS benefits appeared limited to the patients with bone disease at presentation (data not shown).
  - The Myeloma IX study was not powered to compare the effects of the treatments on survival in different patient subsets.
- Adverse events were consistent with established safety profiles of the agents (data not shown).

Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Multiple Event Analyses — SREs by Year



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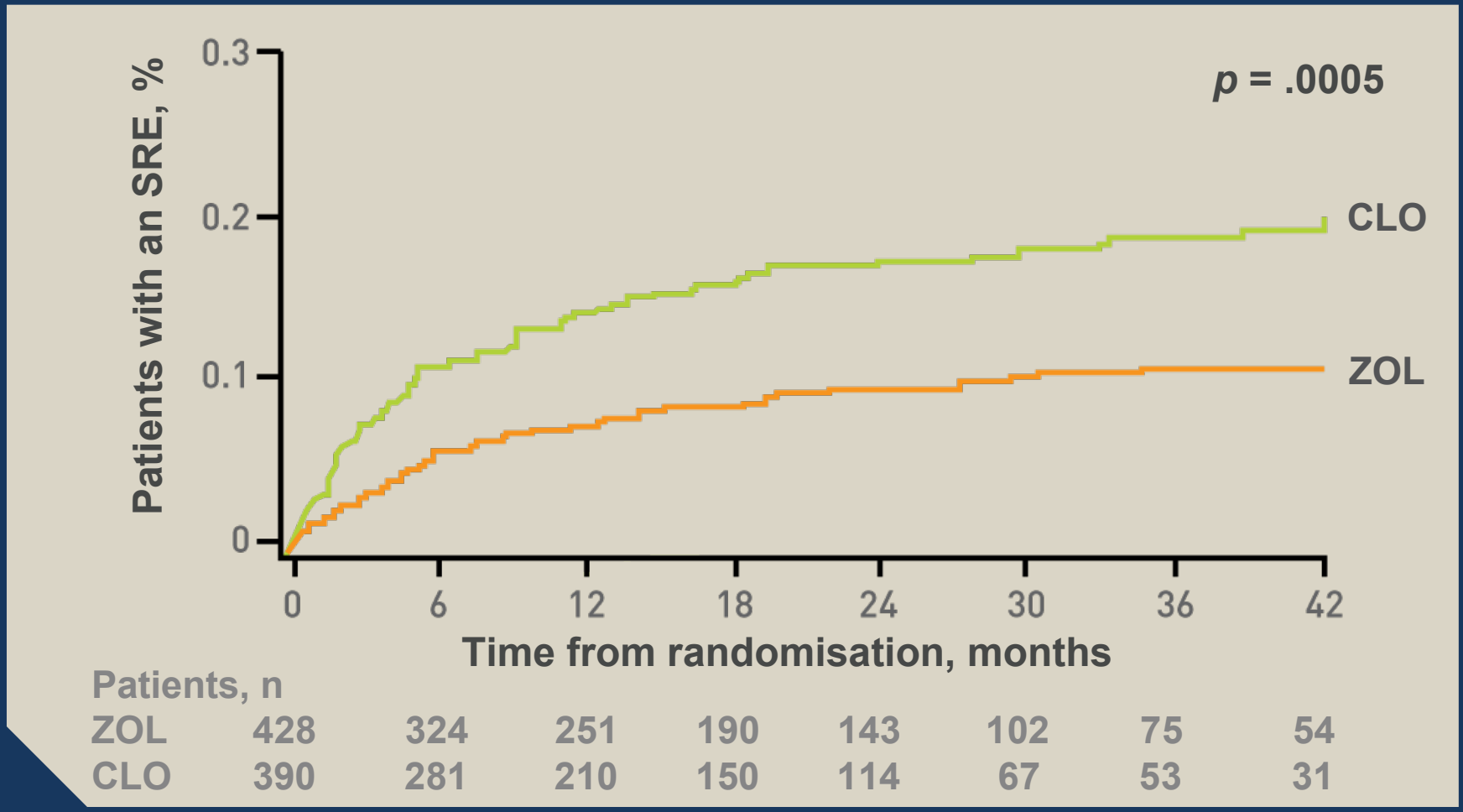
ZOL Reduced SREs versus CLO During Maintenance Therapy



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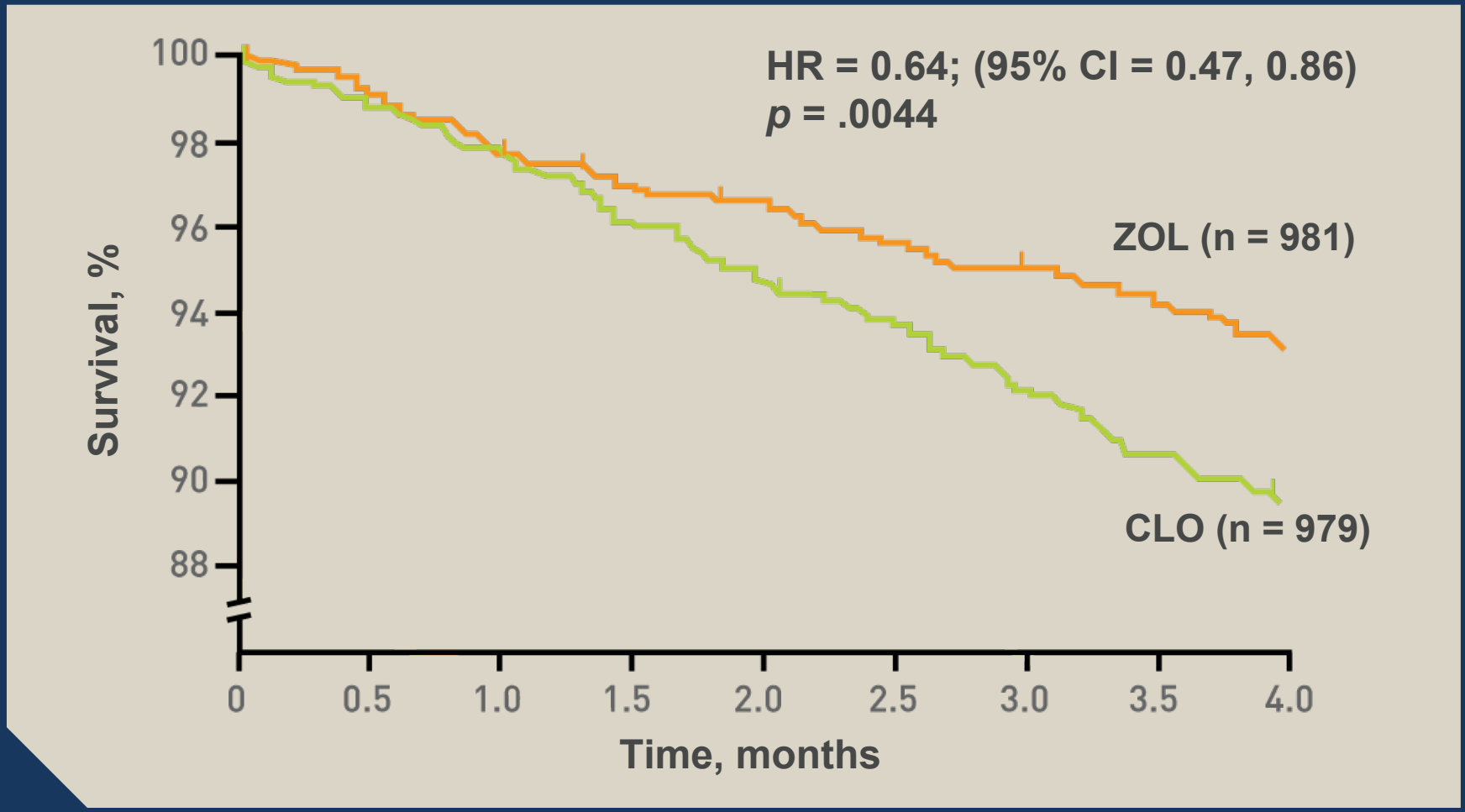
OS Benefit with ZOL Becomes Significant Early in the Course of Treatment



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Author Conclusions — Benefit of Bisphosphonates Over Time

- ZOL increases overall survival versus CLO with benefits becoming significant within the first 4 months of treatment.
- ZOL significantly decreased the risk of SREs versus CLO during each of the first 3 years on study, though additional follow-up is needed (data not shown).
- ZOL significantly decreased the risk of SREs versus CLO during the maintenance portion of the study.
- SRE benefits with ZOL were seen within the first year.
- These analyses support the early initiation of ZOL to prevent SREs and prolong survival, and they support treatment at least until disease progression to provide long-term reduction in SREs.

Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

Faculty Comments

DR BENSINGER: The use of ZOL resulted in fewer SREs for the entire population. Not only did ZOL reduce bone lesions in patients with preexisting disease, but patients with no bone disease at baseline who received ZOL had fewer SREs. The fact that bisphosphonates can prevent SREs in patients who do not have them at presentation has been reported previously, but the fact that ZOL was superior to CLO is useful to know.

The study by Davies examined the benefit of ZOL over time, focusing on a remarkable aspect of this trial, that patients received bisphosphonates continuously until disease progression. Previously we used a 2-year treatment term based on initial studies. This changed my practice, and I now recommend ZOL throughout the course of the patient's disease.