Bisphosphonates, can the dose be lowered

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Disclosures for Peter Gimsing, M.D.

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Scientific Advisory Board	Novartis

- For the last 2-3 decades prophylactic treatment with bisphosphonates (BPs) has been ’standard of care’ in multiple myelom

- Evidence is based on placebo controlled trials and comparative studies of new BPs and a ’gold’ standard

- The development of nitrogen containing BPs has increased the potency and shown significant antimyeloma effect in the laboratory and to some extend in clinical trials

Bisphosphonates and myeloma bone disease

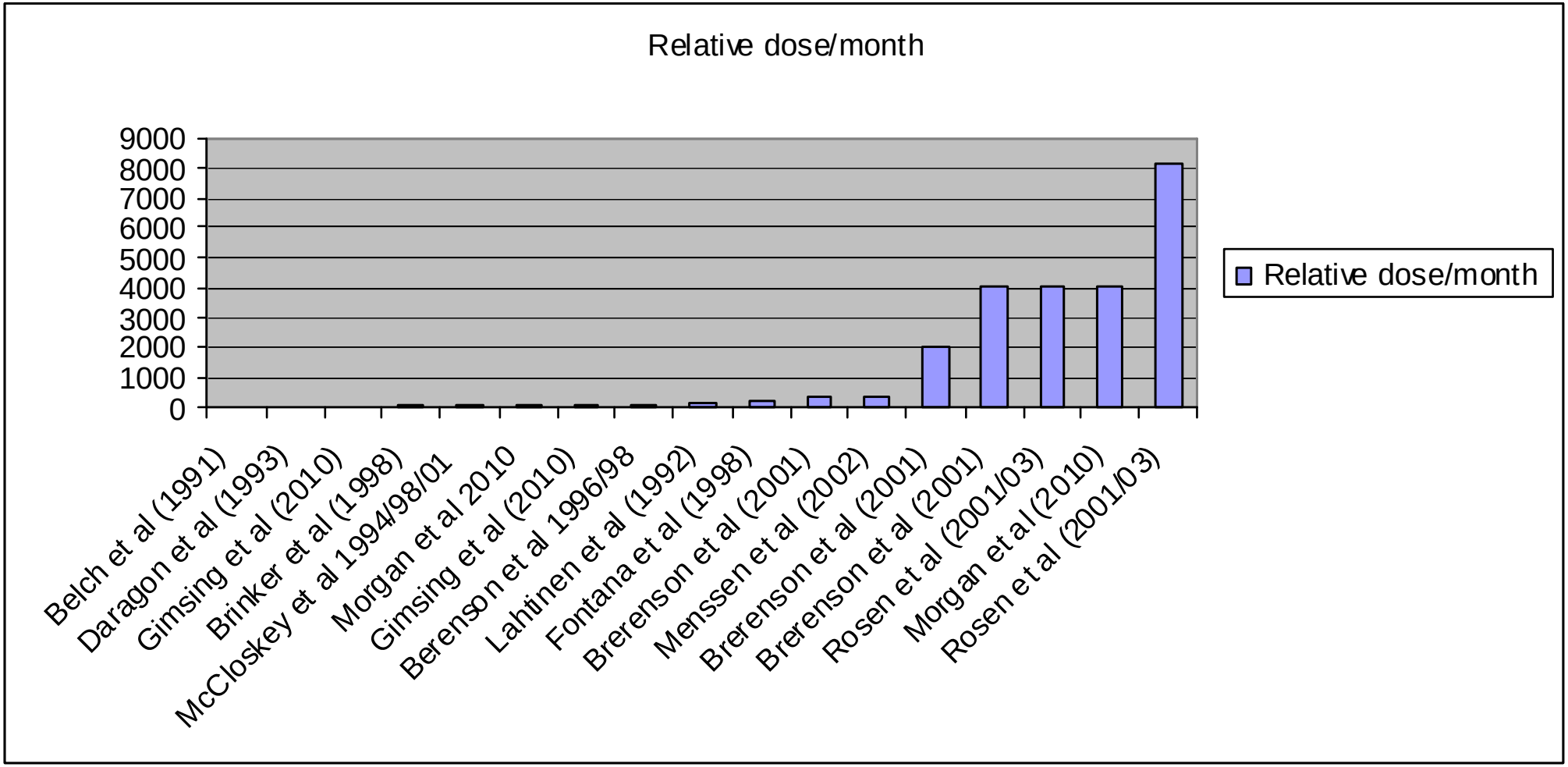
Relative potency

• Etidronate	(non-N-containing bisphosphonate)	1
• Clodronate	(non-N-containing bisphosphonate)	10
• Tiludronate	(non-N-containing bisphosphonate)	10
• Pamidronate	(N-containing bisphosphonate)	100
• Alendronate	(N-containing bisphosphonate)	1000
• Ibandronate	(N-containing bisphosphonate)	10000
• Zoledronic acid	(N-containing bisphosphonate)	100000

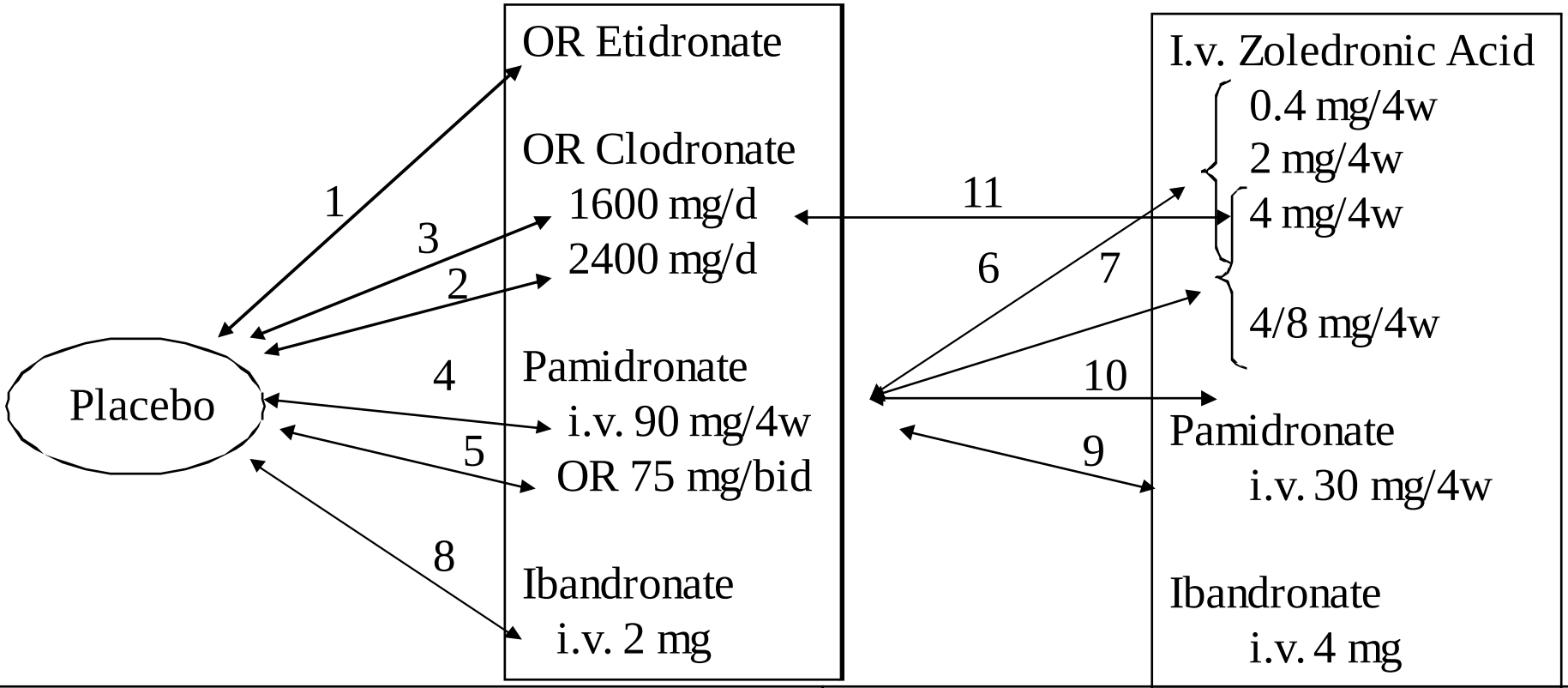
ASCO Guidelines JCO 2002

Bisphosphonates and myeloma bone disease

Relative potency for clinical controlled studies



Cinical trials of bisphosphonates in multiple myeloma or partly in multiple myeloma



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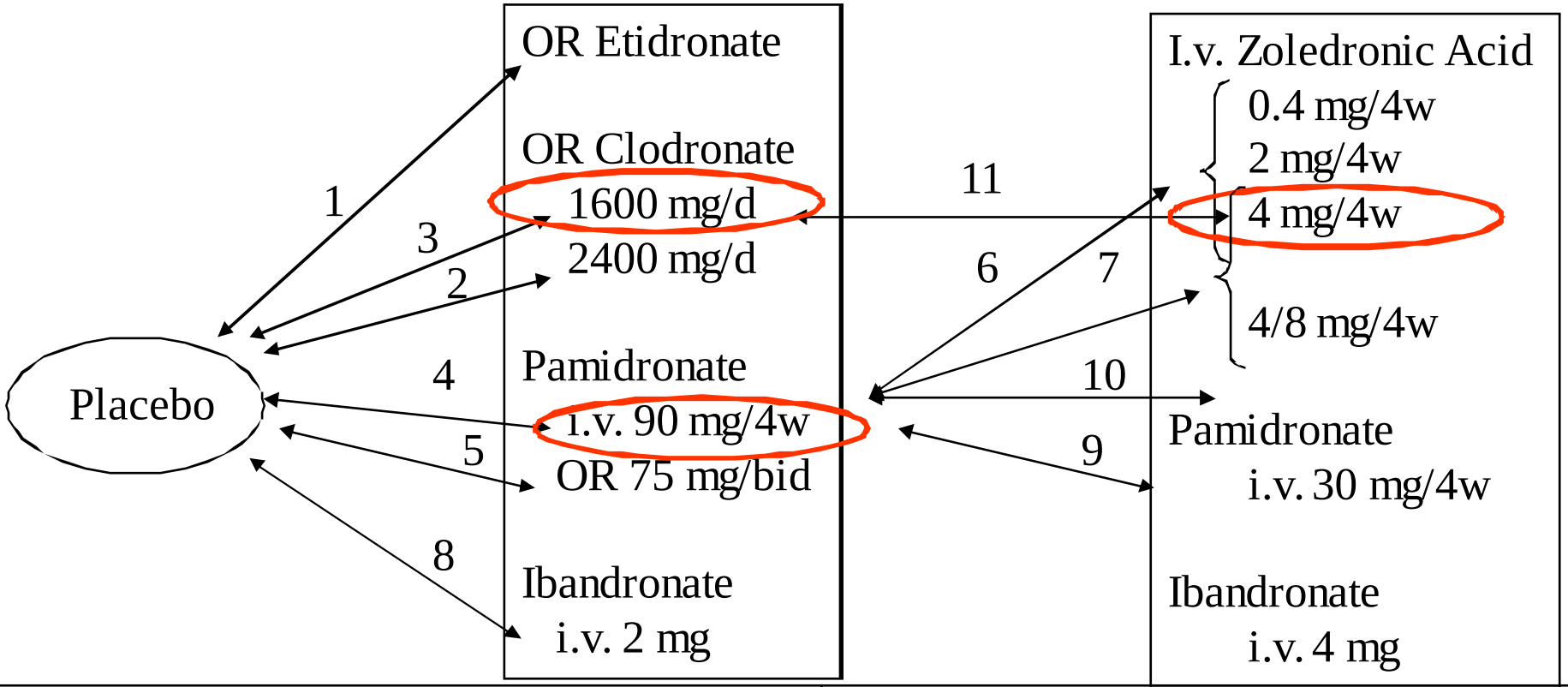

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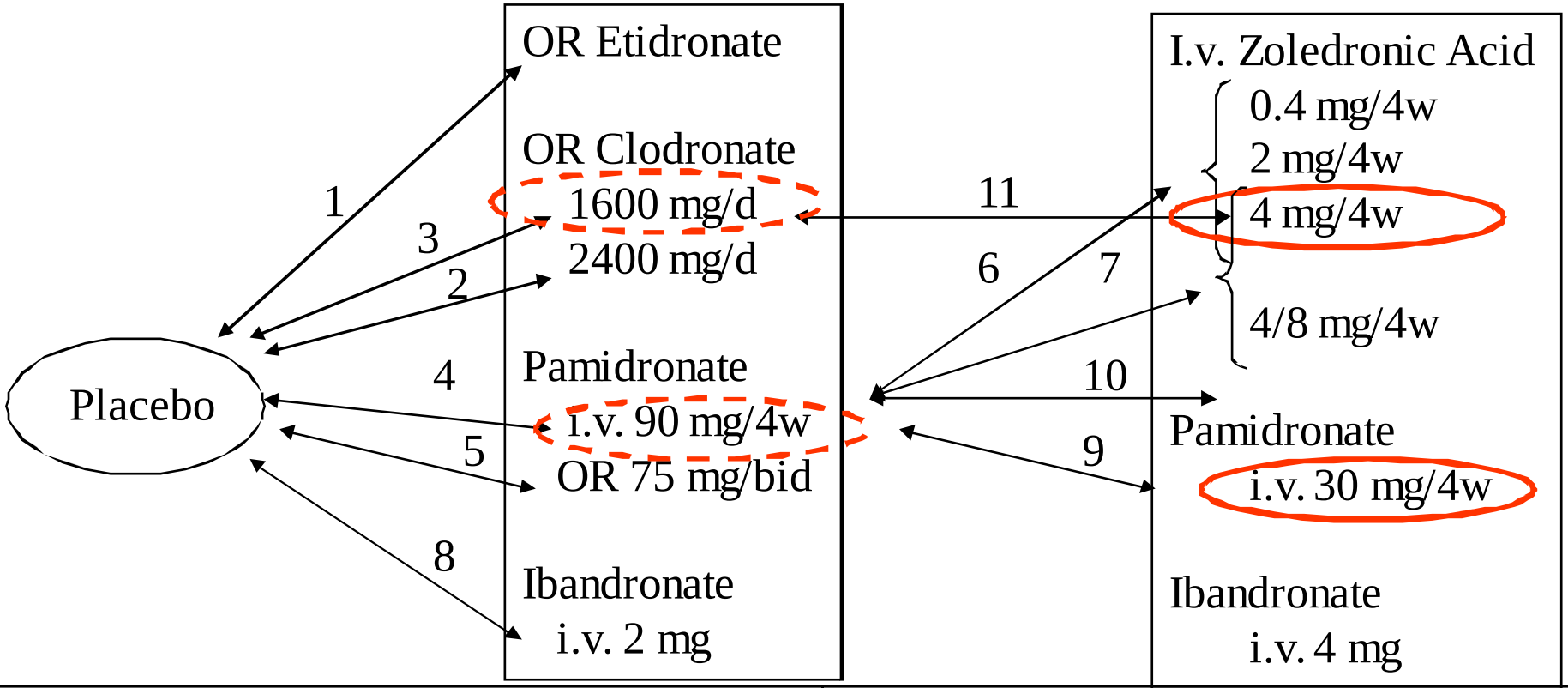

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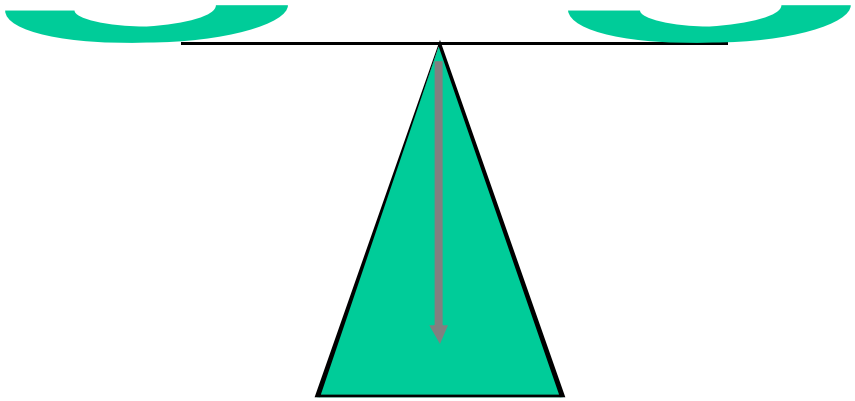
The optimal bisphosphonate dose

Efficacy:
- bone disease
  - Bone markers
  - Bone density
  - SRE
  - Skeletal event free survival
- QoL
- OS

Cost:
- Toxicity
  - Renal toxicity
  - ONJ
- Drug-cost
- Related cost (i.v. vs. OR)
- Compliance
- Logsistics



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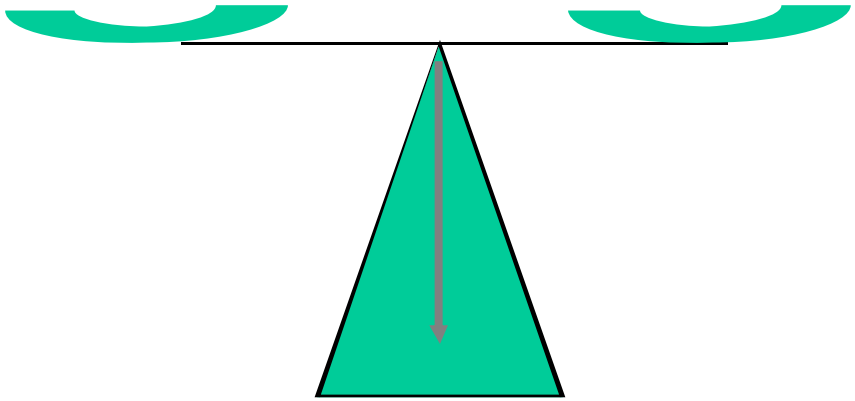
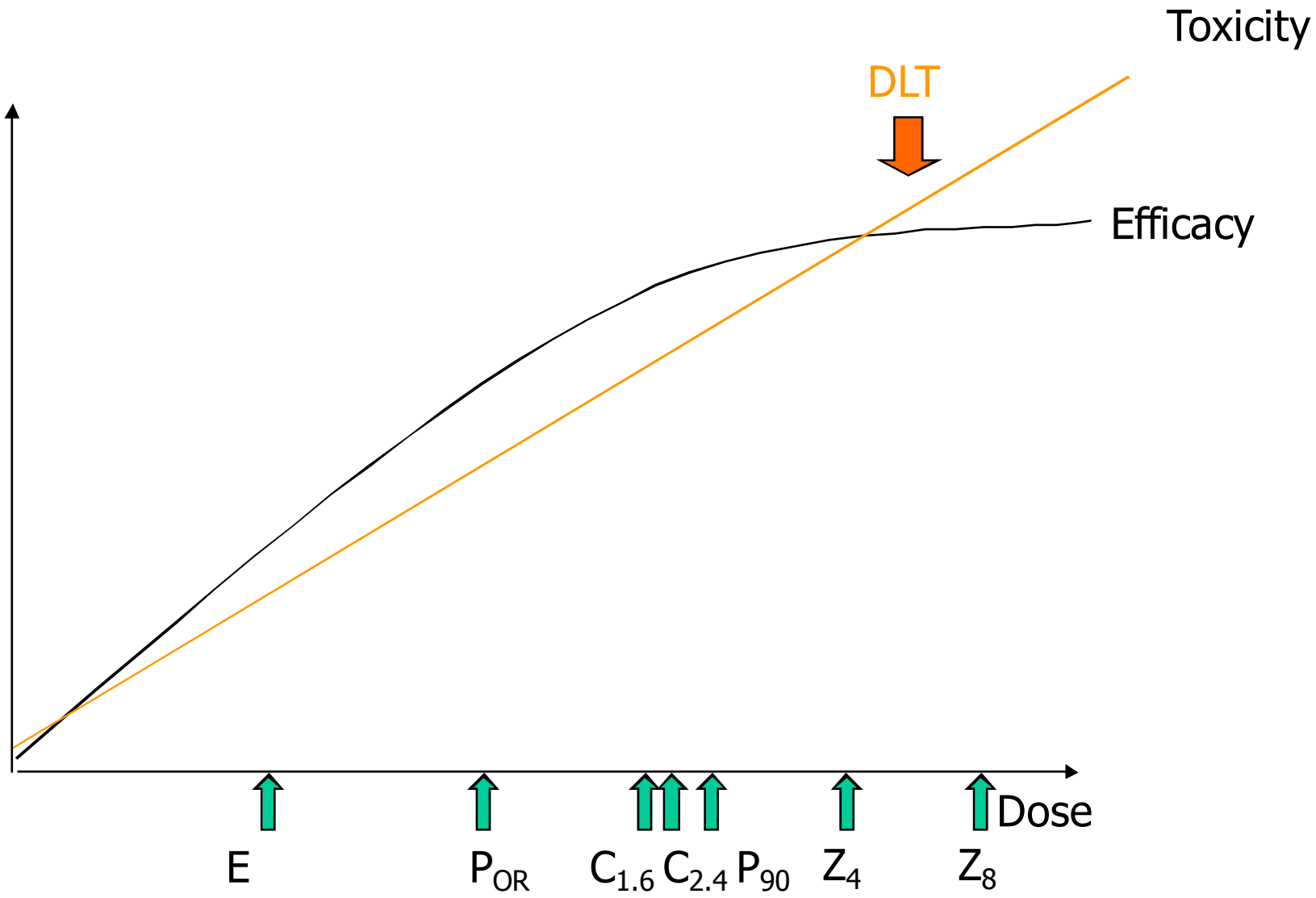


Bisphsphonates and myeloma bone disease

Theoretical relation between toxicity and efficay



Bisphsphonates and myeloma bone disease

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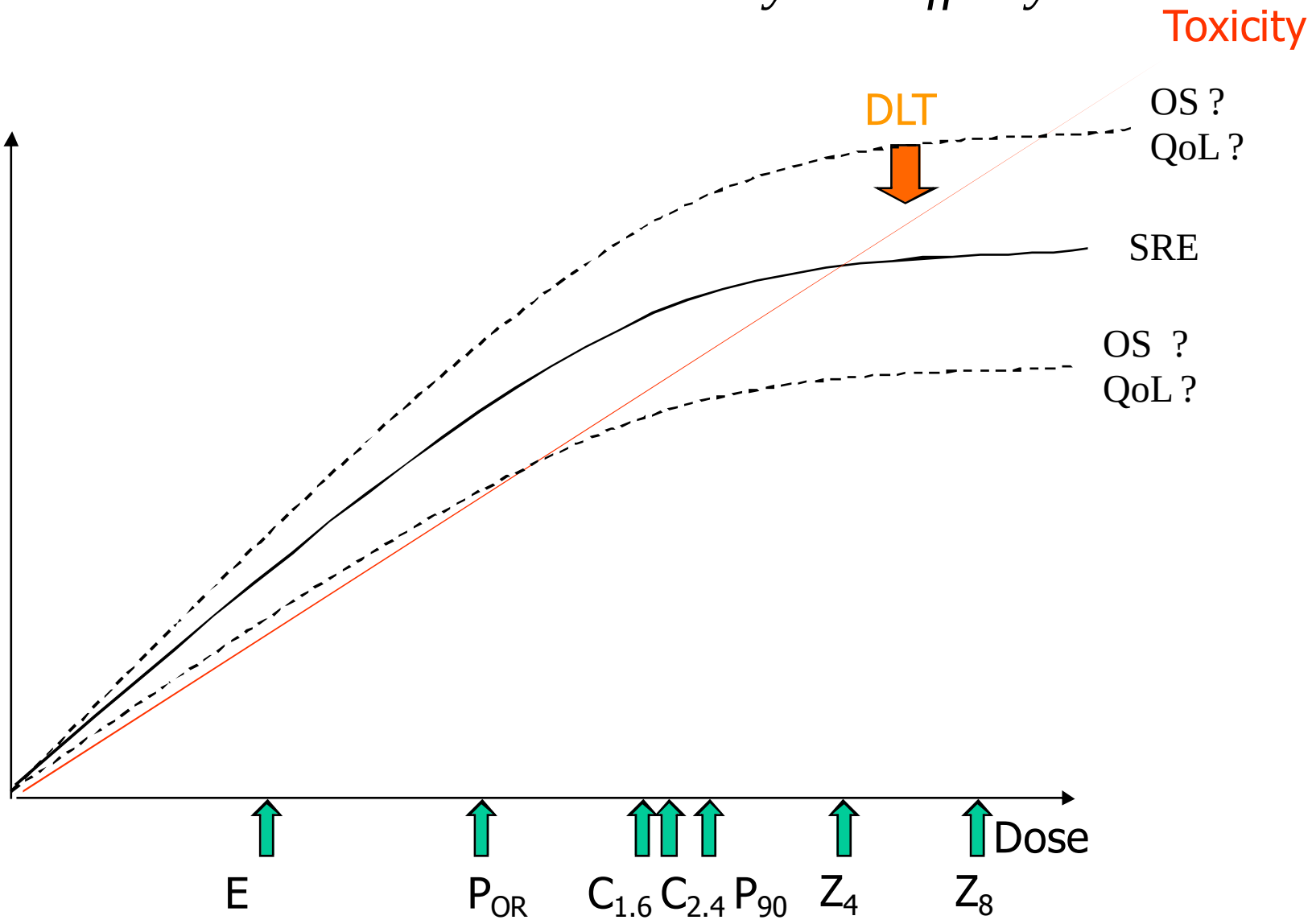

Zoledronic Acid Reduces Skeletal-Related Events in Patients with Osteolytic Metastases

A Double-Blind, Randomized Dose–Response Study

Berenson et al. Cancer 2001

MM 39% BC 61%	Patients irradiated against bone (primary end-point)	Any skeletal event	U-NTX/creatinine (change from baseline)
PAM 90 (N=73)	18% ($p<0.05$)	30% ($p<0.05$)	-57.5% ($p<0.05$)
ZOL 0.4 (N=68)	24%	46%	-37.1%
ZOL 2.0 (N=72)	19% ($p<0.05$)	35%	-58.6% ($p<0.05$)
ZOL 4.0 (N=67)	21% ($p<0.05$)	33%	-60.8% ($p<0.05$)

Conclusion:

Zoledronic acid 2 mg and 4 mg/month is as effective as pamidronate 90 mg/month, while zoledronic acid 0.4 mg/month was less effective

Long-Term Efficacy and Safety of Zoledronic Acid Compared with Pamidronate Disodium in the Treatment of Skeletal Complications in Patients with Advanced Multiple Myeloma or Breast Carcinoma

A Randomized, Double-Blind, Multicenter, Comparative Trial

Rosen et Cancer 2003

Cancer J 2001

MM 31% BC 69%	Patients with any SRE (primary end-point) 13 months	 25 months	Time to 1. SRE	OS	ECOG PS
PAM 90 (N=555)	46% (MM: 49%)	51% (MM: 54%)	356 days (MM: 286 days)	n.s.	n.s
ZOL 4.0 (N=561)	44% (MM: 47%)	47% (MM: 50%)	376 days (MM: 380 days)	n.s.	n.s
ZOL 4.0/8.0 (N=524)	46% (MM: 49%)	49% (MM: 50%)	351 days	n.s.	n.s

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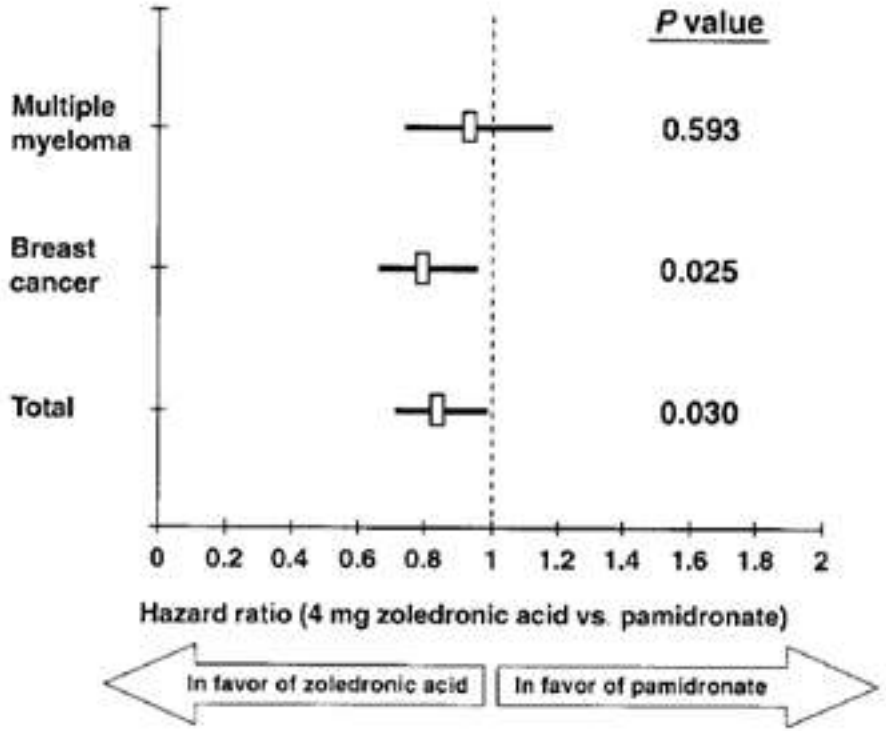


FIGURE 3. Relative risk ratios for skeletal-related events (including hypercalcemia of malignancy) in patients treated with 4 mg zoledronic acid versus those treated with 90 mg pamidronate.

Conclusion:

Zoledronic acid 4 mg/month is as effective as pamidronate 90 mg/month in patients with advanced multiple myeloma.

No difference in overall survival or performance status

Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial

Peter Gimsing, Birgitta Carlson, Ingemar Turesson, Peter Fayers, Anders Waage, Annette Vangsted, Anne Wisløff, Christian Glad, Gunnar Juliusson, Henrik Gregersen, Henrik Hjorth-Hansen, Ingrid Kvam Tjønneland, Inger Marie S Dahl, Jan Westin, Johan Lorenz Nielsen, Lene Meldgaard Knudsen, Lucia Ahlberg, Martin Gimsing, Niels Abildgaard, Niels Frost Andersen, Ola Landgren, Finn Wisløff

Lancet Oncol 2010; 11: 973–82

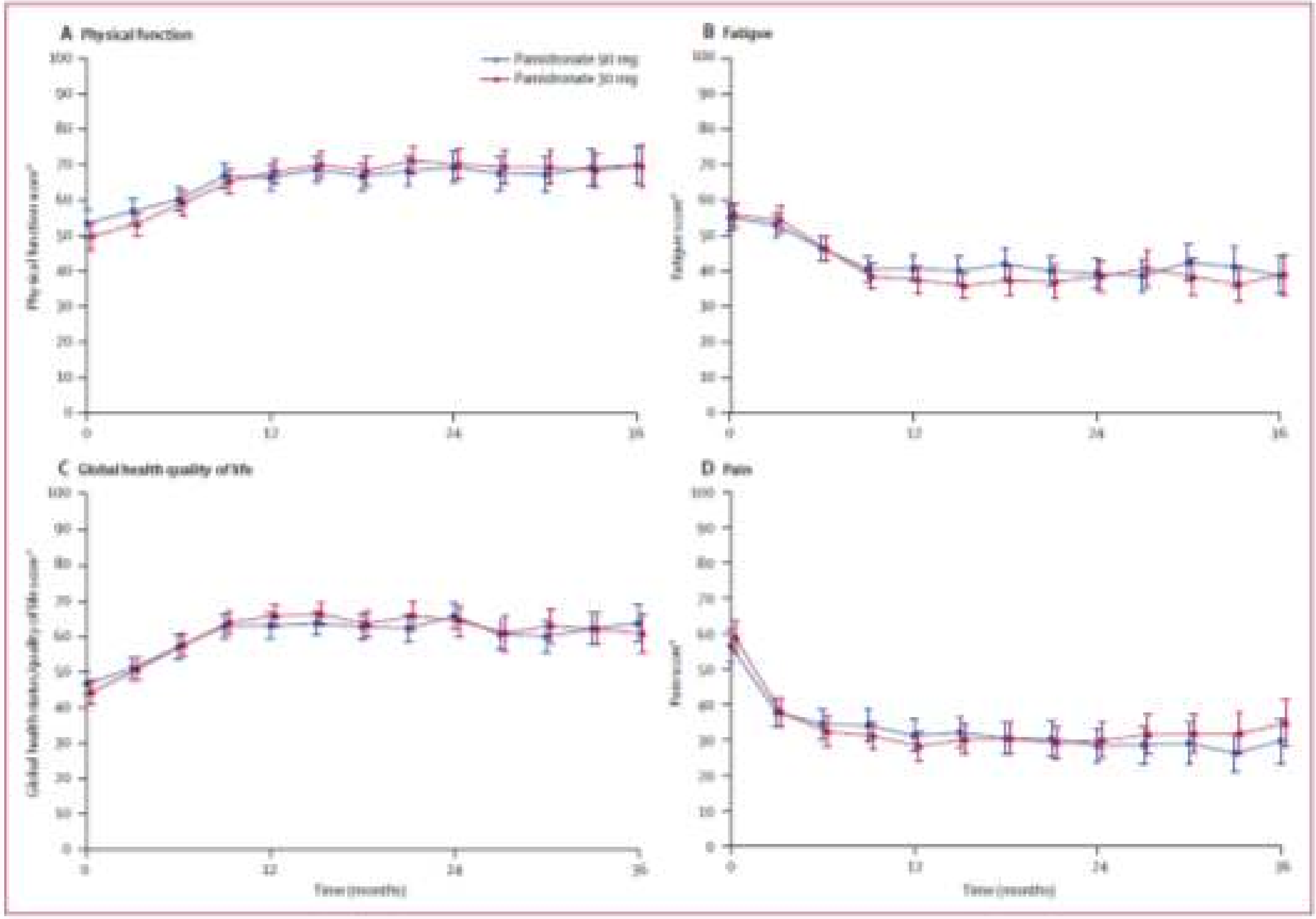
	EORTC QLQ C30 Physical function score at 12 months (primary endpoint)	Time to first SRE (median)	Skeletal event free suvival (median)	Overall survival (median)	PFS (median)
PAM 90 (N=252)	65	NR	21.4 months	42 months	21 months
PAM 30 (N=252)	68 (p=0.56)	NR (p=0.63)	22.1 months (p=0.98)	48 months (p=0.54)	22 months (p=0.51)

Conclusion:

No significant difference in QoL, SRE, OS or PFS between pamidronate 90 mg/month and 30 mg/month

Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial

Quality of Life (EORTC QLQ C30)



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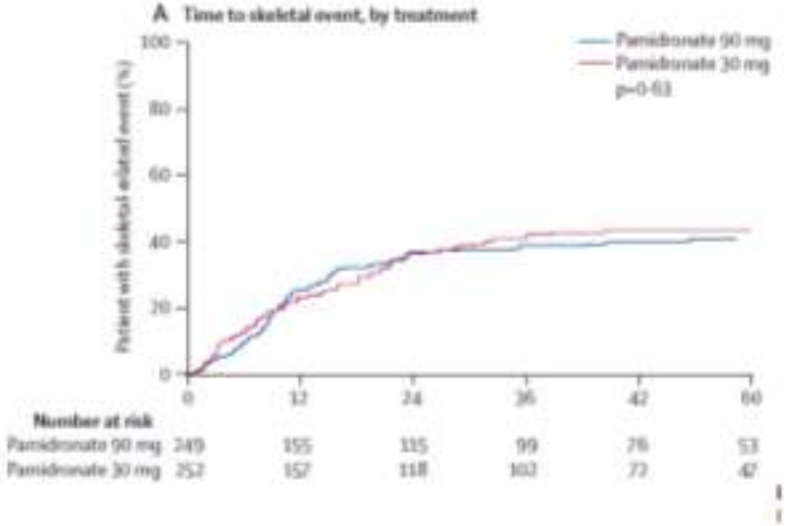
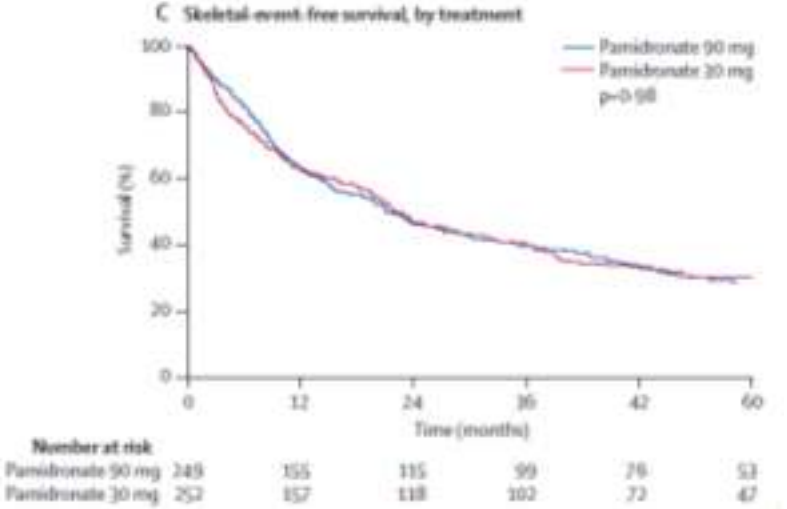
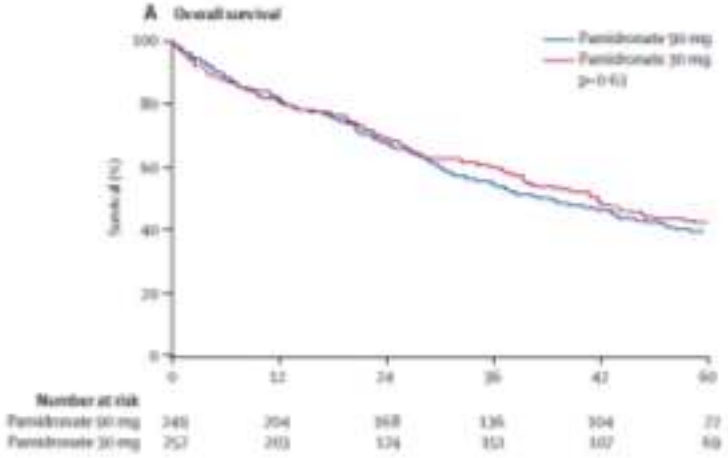
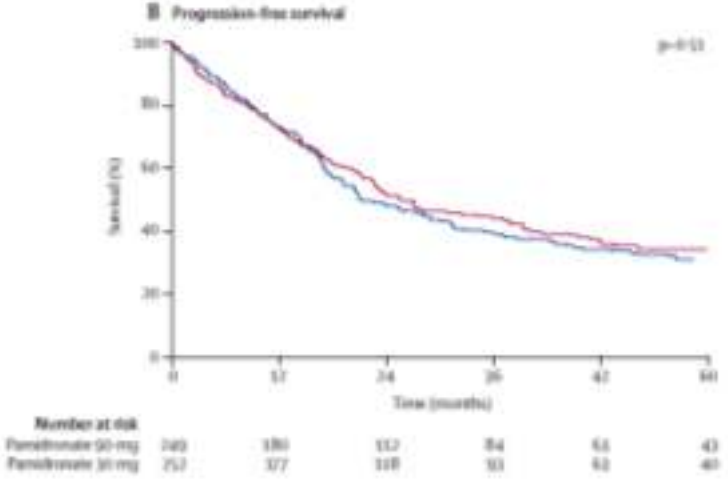




- Time to first SRE
- Skeletal event free surival
- Overall survival
- Profressions free survival





First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial

Gareth J Morgan, Faith E Davies, Walter M Gregory, Kim Cocks, Sue E Bell, Alex J Szubert, Nuria Navarro-Coy, Mark T Drayson, Roger G Owen, Sylvia Feyler, A John Ashcroft, Fiona Ross, Jennifer Byrne, Huw Roddie, Claudius Rudin, Gordon Cook, Graham H Jackson, J Anthony Child, on behalf of the National Cancer Research Institute Haematological Oncology Clinical Study Group

Lancet 2010; 376: 1989–99

	Overall survival (primary end-point)	PFS	Patients with any SRE
CLO 1600 (N=979)	44.5 months (p=0.04)	17.5 months (p=0.07)	35.3% (p=0.0004)
ZOL 4.0 (N=981)	50.0 months	19.5 months	27.0%

Conclusion:

Zoledronic 4 mg/month is more effective than clodronate 1600 mg/day with survival benefit and reduced number of patients with skeletal events.

Dose toxicity

- Nephropathy
- Osteonecrosis of the jaw

Zoledronic Acid Reduces Skeletal-Related Events in Patients with Osteolytic Metastases

A Double-Blind, Randomized Dose–Response Study

Berenson et al. Cancer 2001

MM 39% BC 61%	Increase in S-creatinine > 0.5 mg/L	Grade 3 creatinine elevation	ONJ
PAM 90 (N=73)	7 (9.6 %)	2	Unknown
ZOL 0.4 (N=68)	? (?%)	1	Unknown
ZOL 2.0 (N=72)	? (?%)	1	Unknown
ZOL 4.0 (N=67)	11 (16.4 %)	1	Unknown

19 (13.6%)

Conclusion:

No significant difference on creatinine between Zoledronic acid 4 mg/month and pamidronate 90 mg/month. OJN was not an issue at the time of the study.

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A Randomized, Double-Blind, Multicenter, Comparative Trial

Rosen et Cancer 2003

Cancer J 2001

MM 31% BC 69%	Discontinuation of study medicine due to AE 13 months	 25 months	Creatinine increase ZOL infusion rate 5 min	 15 min	Grade 3-4 creatinine increase (25 m)
PAM 90 (N=555)	1.4%	9.6 %	6.3%	9.3%	1.9%
ZOL 4.0 (N=561)	1.8%	9.0%	14.3%	10.7%	0.4%
ZOL 4.0/8.0 (N=524)	4.3%	10.6%	21.3%	19.4%	2.7%

Conclusion:

No significant difference on creatinine between Zoledronic acid 4 mg/month given as 15 min infusion and pamidronate 90 mg/month. Zoledronic acid 8 mg/month gave higer incidence of creatinine increase. OJN was not an issue at the time of the study.

Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial

Peter Gimsing, Kristina Carlson, Ingemar Turesson, Peter Fayers, Anders Waage, Annette Vangsted, Anne Klyvi, Christian Gimsing, Gunnar Juliusson, Henrik Gregersen, Henrik Hjorth-Hansen, Ingrid Kvam Tjønneland, Inger Marie S Dahl, Jan Westin, Johan Lorenz Nielsen, Lene Meldgaard Knudsen, Lucia Ahlberg, Martin Gimsen, Niels Abildgaard, Niels Frost Andersen, Ole Linder, Finn Wisløff

Lancet Oncol 2010; 11: 973–82

	Discontinuation of study medicine due to increased creatinine	Time to more than 15% increase of creatinine (median)	ONJ (%)
PAM 90 (N=252)	15	10.7 months	8 (4.2%)
PAM 30 (N=252)	7 (p=0.072)	14.8 months (p=0.48)	2 (1.0%) (p=0.087)

Conclusion:

There was a trend of increased incidence of nephrotoxicity and ONJ with pamidronate 90 mg/month compared to 30 mg/months

Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial

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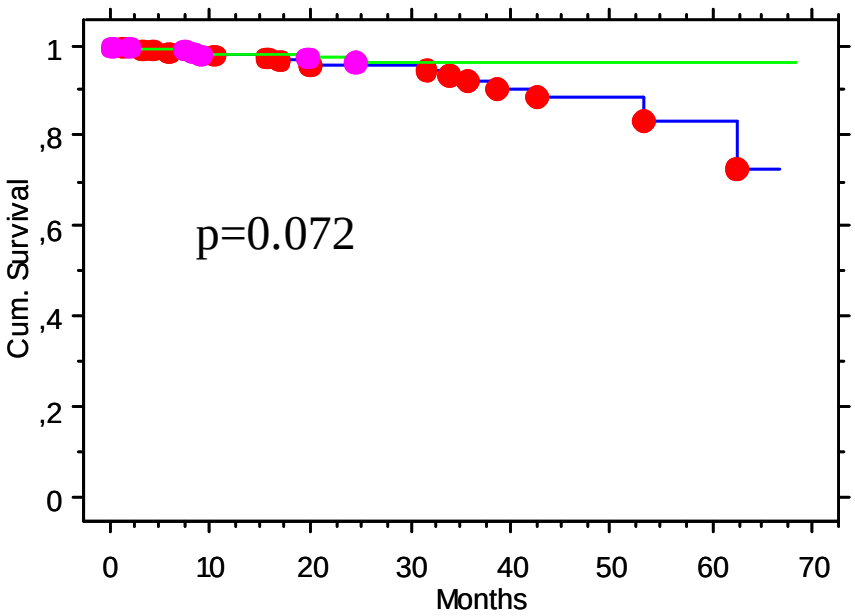
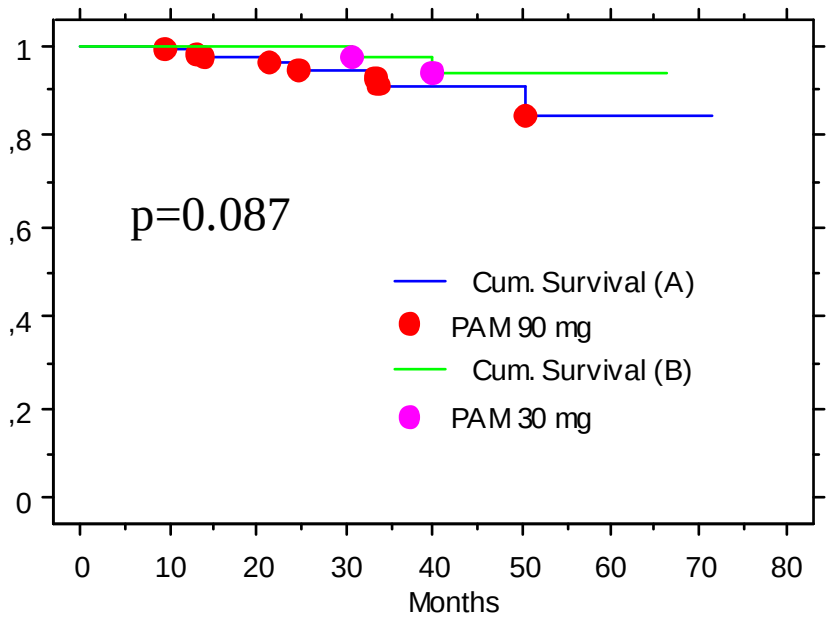
Time to exit due to nephrotoxicity - Kapplan Meier Plot



Kaplan-Meier Cum. Survival Plot for Time to ONJ



Conclusion:

Trend toward cumulative dose dependent risk of nephrotoxicity and ONJ by pamidronate treatment.

Time-related AE should be presented to determined cumulative dose related AE.

First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial

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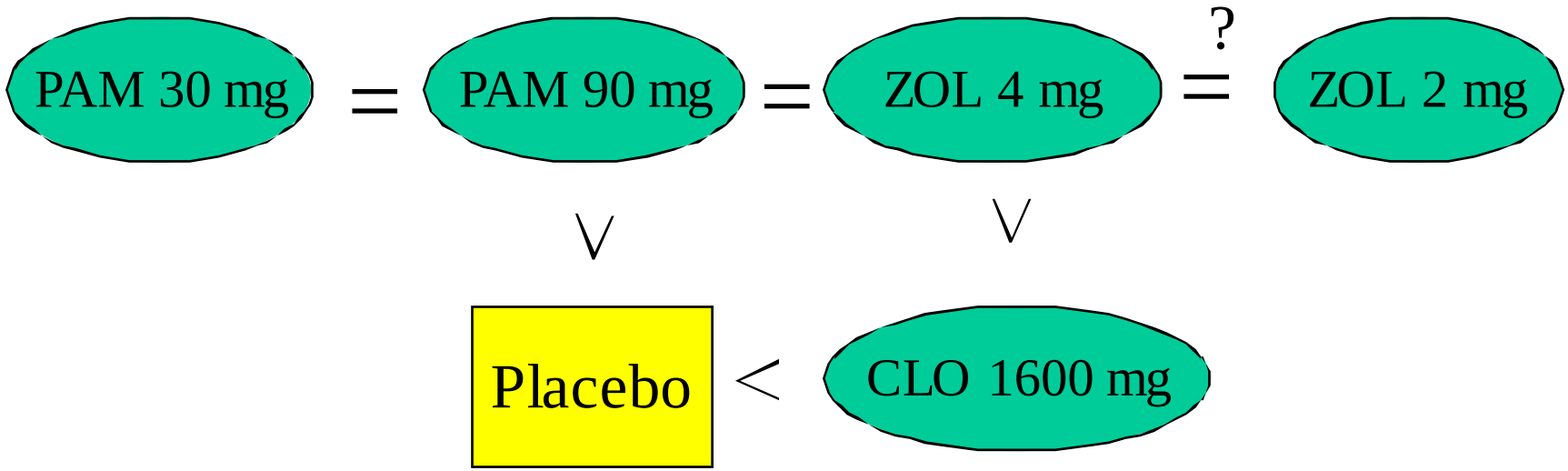
Lancet 2010; 376: 1989–99

	Acute renal failure	ONJ (crude incidence)
CLO 1600 (N=979)	60 (6%)(p=0.75)	3 (0.003%) (p<0.0001)
ZOL 4.0 (N=981)	57 (6%)	35 (0.036%)

Conclusion:

Zoledronic 4 mg/month increased the risk of ONJ significantly compared to clodronate 1600 mg/day while there was no significant difference of the incidence of acute renal failure.

Summary and conclusion



Conclusions:

1. ***Pamidronate 30 mg/month is the recommended pamidronate dose***
2. ***Zoledronic acid 4 mg/months is more effective than clodronate 1600 mg/day but with 10 fold increased risk of ONJ***
3. ***Future studies are needed to determine***
   - ***If pamidronate 30 mg /month is as effective as zoledronic acid 4 mg/month with less side effects***
   - ***If another dose schedule of zoledronic acid (e.g. 2 mg/month or 4 mg/3 month) is as effective as zoledronic acid 4 mg/month with less side effects***