Osteonecrosis of the Jaw

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Disclosures

- Consultant: Amgen, Celgene, Novartis
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Clinical Diagnosis of ONJ

Exposed bone in MF area that

Occurred spontaneously

Or

Was induced by dental surgery

With e/o delayed healing for > 6 weeks after appropriate care.

May be associated with: pain, infection

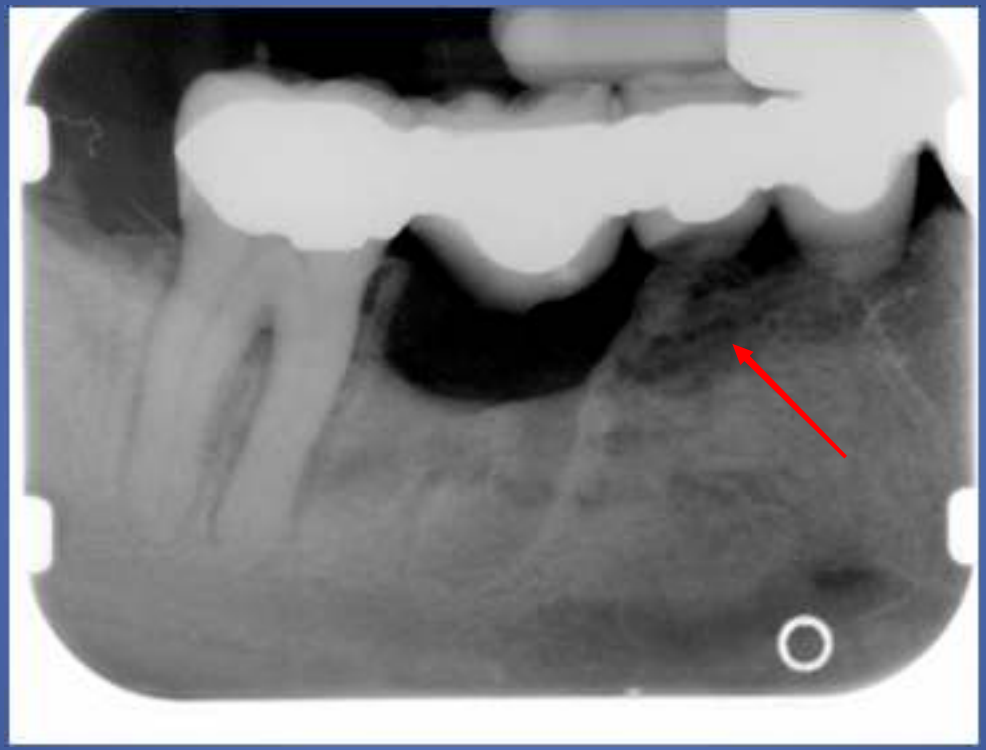
No previous XRT

Clinical features: Pt #2

Patient #2: p/w roughness and irritation
h/o dex 4 mths, CTX, EDAP 3/3 mths, PBSCT and Pamidronate 61 mths and Zometa 20 mths
h/o dental extraction

Raje et al. Clin Can Res 2008

Radiology: Pt #2



Loss of cortical bone and mixed radiolucency @ site of exposed bone

Raje et al. Clin Can Res 2008

Box 3 | Staging system for BON*

At risk category

No apparent necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates

Stage 0

No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms

Stage 1

Exposed and necrotic bone in asymptomatic patients without evidence of infection

Stage 2

Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone without purulent drainage

Stage 3

Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (such as inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture; extra-oral fistula; oral antral and/or oral nasal communication; or osteolysis extending to the inferior border of the mandible or the sinus floor

*Staging system proposed by the American Association of Oral and Maxillofacial Surgeons.[12] Abbreviation: BON, bisphosphonate-associated osteonecrosis.

Staging System

Migliorati CA et al . Nat Rev Endocrinology 2011

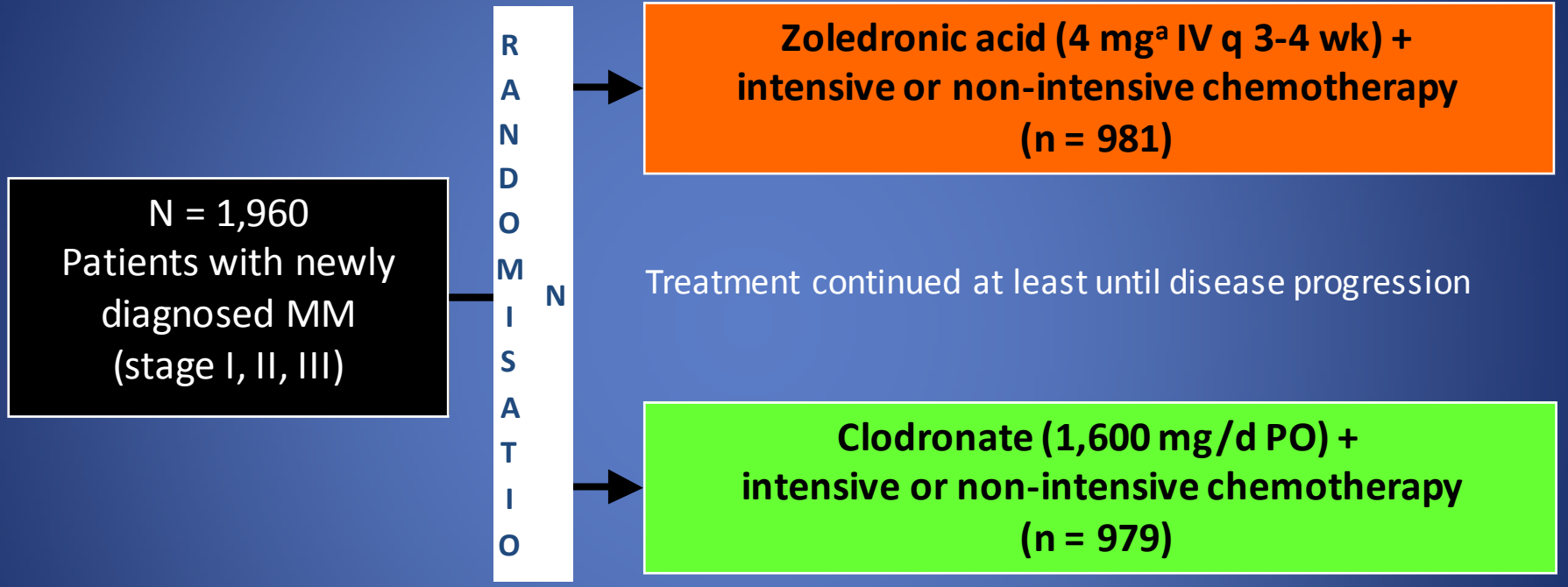
ONJ Incidence

Table 1. Incidence of ONJ from selected reported studies

Author/year	Number of patients investigated (*n*)	Incidence of ONJ (%)
Bamias *et al.*[6]	252	Multiple myeloma 11/111 (9.9%)
		Breast cancer 2/70 (2.9%)
		Prostate cancer 3/46 (6.5%)
Dimopoulos *et al.*[14]	202	Multiple myeloma 15/202 (7.4%)
Zervas *et al.*[13]	254	Multiple myeloma 28/254 (11%)
Tosi *et al.*[9]	259	Multiple myeloma 9/259 (3.5%)
Sanna *et al.*[11]	81	Breast cancer 5/81 (6.2%)
Badros *et al.*[7]	340	Multiple myeloma 11/340 (3%)
Kraj *et al.*[10]	113	Multiple myeloma 2/113 (1.7%)
Pozzi *et al.*[12]	1402	Multiple myeloma 28/1402 (1.9%)
Jadu *et al.*[15]	655	Multiple myeloma 21/655 (3%)
Walter *et al.*[18]	43	Prostate cancer 8/43 (18,6%)
Hoff *et al.*[16]	3994	Multiple myeloma 13/548 (2.4%)
		Breast cancer 16/1338 (1.2%)
		Prostate cancer 0/185 (0%)
		Other cancers 0/1782
Ibrahim *et al.*[17]	539	Multiple myeloma 2/59 (3.4%)
		Breast cancer 5/220 (2.3%)
Walter *et al.*[20]	75	Breast cancer 4/75 (5.3%)
Cetiner *et al.*[19]	32	Multiple myeloma 5/32 (15%)
Fehm *et al.*[21]	233	Breast cancer 10/233 (4.3%)
Aragon-Ching *et al.*[31]	60	Prostate cancer 11/60 (18.3%)

Hoff AO et al Ann. N.Y. Acad.Sci 2118 (2010)

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.

MRC Myeloma IX—Adverse Events (Safety Population)

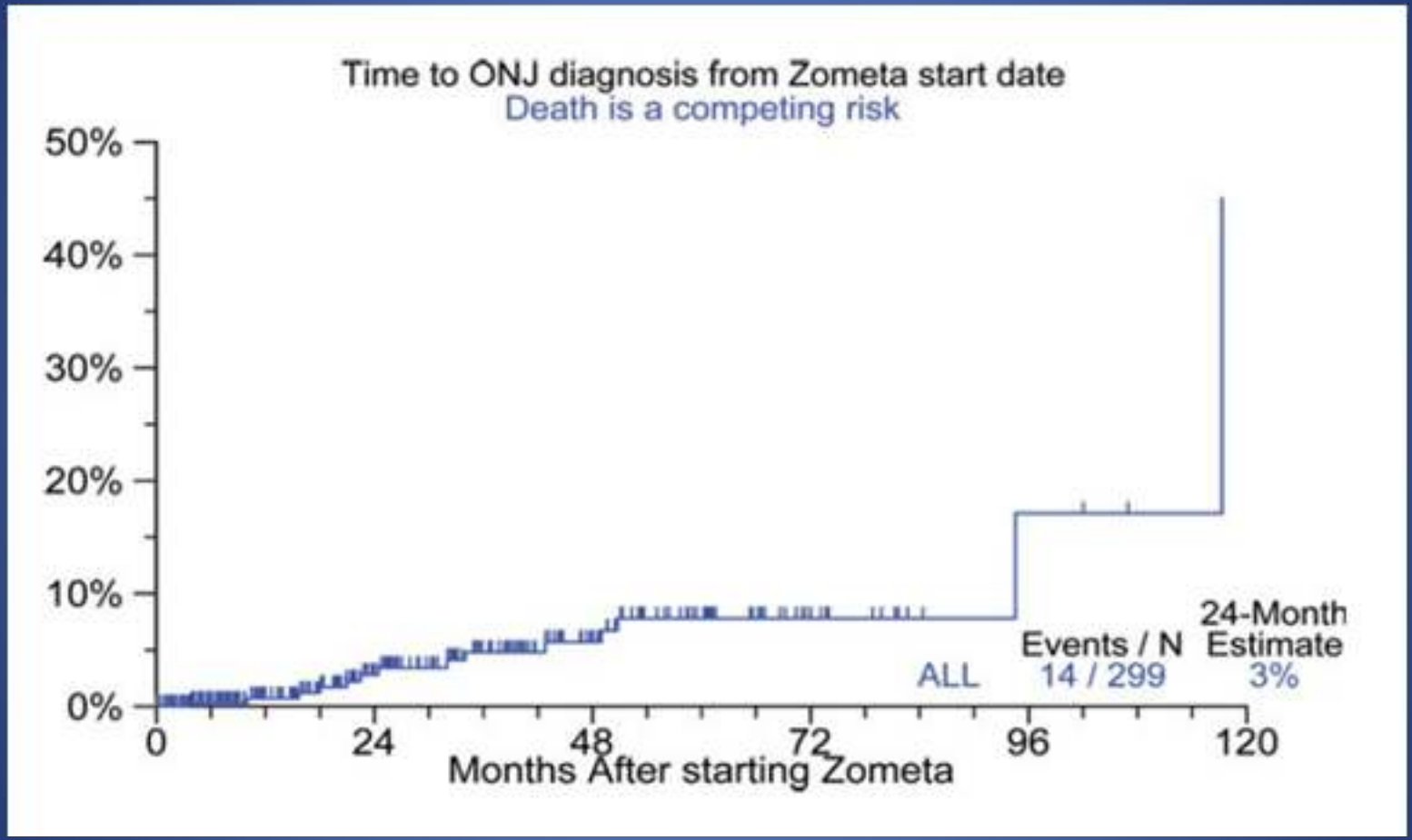
	Patients, n (%)					
	Intensive pathway			Non-intensive pathway		
	ZOL (n = 555)	CLO (n = 556)	*P*[a]	ZOL (n = 428)	CLO (n = 423)	*P*[a]
Acute renal failure	29 (5.2)	33 (5.9)	.70	28 (6.5)	27 (6.4)	1.0
ONJ[b]	21 (3.8)	2 (0.4)	< .0001	14 (3.3)	1 (0.2)	.0009
Thromboembolic	104 (18.7)	82 (14.7)	.08	53 (12.4)	35 (8.3)	.06
Infection SAE	52 (9.4)	62 (11.2)	.37	16 (3.7)	28 (6.6)	.06

Abbreviations: CLO, clodronate; ONJ, osteonecrosis of the jaw; SAE, serious adverse event; ZOL, zoledronic acid.

[a] Statistical significance determined by Fisher's exact test.

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

Time to ONJ



Berenson JR et al. Am J Hematol 2011

Risk Factors

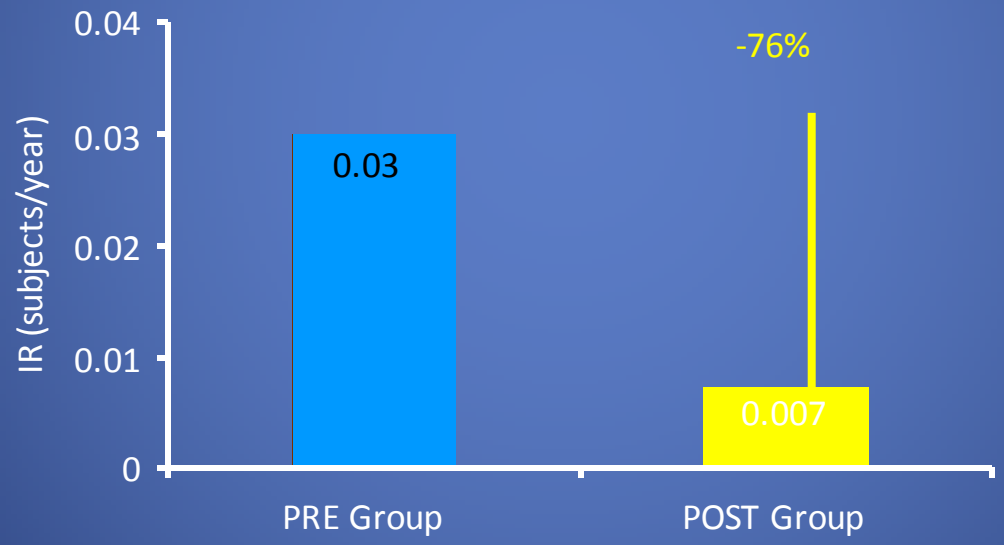
- Poor dental hygiene
- Trauma
- Corticosteroid use
- Anti-angiogenic Agents
- Polymorphisms of p450 of CYP 2C8

Managing ONJ

- Make a diagnosis
- Assess its severity
  - It takes on a wide spectrum!
- Maintain excellent dental hygiene and regular exams
- Keep surgical intervention to a minimum
- There is no standard treatment
  - Antibacterial and antifungal rinses (chlorhexidine gluconate and nystatin)
  - Systemic oral antibacterial, antiviral, and antifungal treatment

Preventive Dental Measures Reduce Incidence of ONJ

- A retrospective study in cancer pts receiving BPs



IR = Incidence rate; PRE = Pre-implementation of preventive measures; POST = Post-implementation of preventive measures.

1. Ripamonti C, et al. Presented at: 30th Annual SABCS; December 13-16, 2007 San Antonio, Texas; Abstract 2056. In press Annals of Oncology, 2008

ASCO Clinical Practice Guidelines: Update

- Bisphosphonates
  - Indicated for MM pts w/ lytic bone disease
  - osteopenia
- Useful as an adjunct for pts w/ bone pain
- The bisphosphonates recommended are either
  - Zoledronic acid: 4 mg over 15 mins, IV q 3-4 wks
  - Palmidronate: 90 mg over ≥ 2 hrs, IV q 3-4 wks
- Monitoring w/ serum creatinine (both BPs) and/or urine albumin (for palmidronate only)
- PAM preferred in setting of renal dysfunction
- **Re-evaluate after 2 years and consider stopping if stable disease**

Kyle R, et al. *JCO.* 200725: 2464-2472

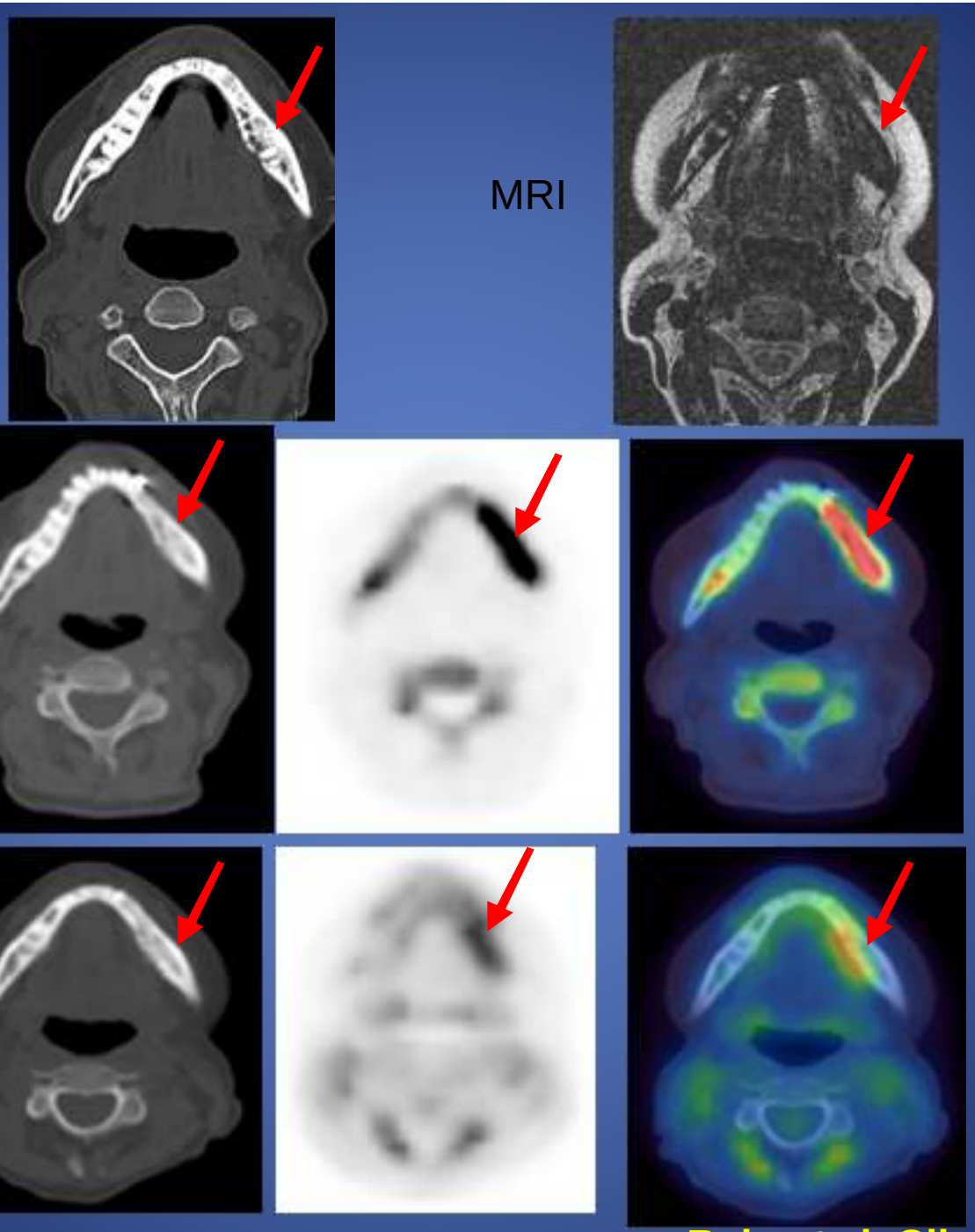
Patient 2

CT

MRI

F18

FDG



Raje et al. Clin Can Res 2008

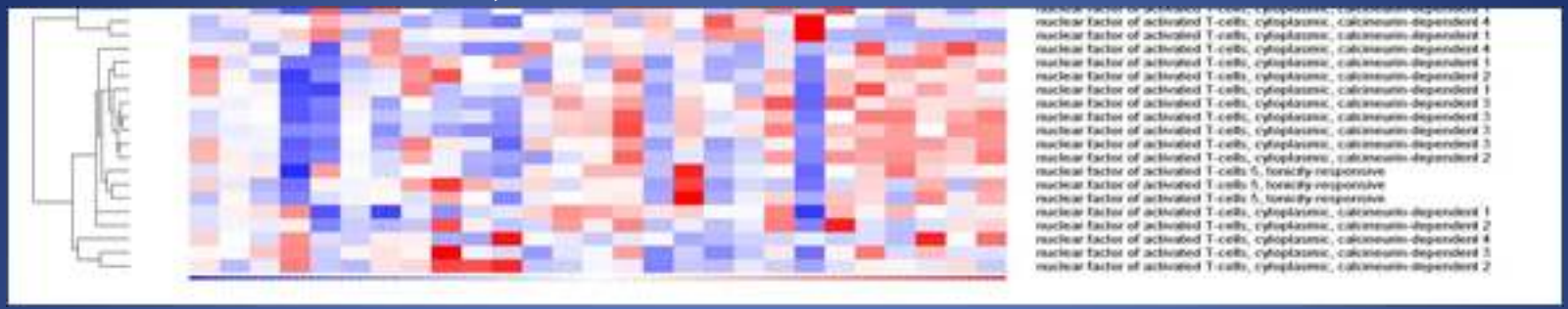
Biochemical Markers

Pt #	Urinary NTX M:11-103nmol F:4-64nmol	Calcium 8.4-10.2 mg/dL	Vitamin D (25-OH) 20-100 Ung/ml	I-PTH 16-62 pg/ml
1	17	8.5	25	111
2	29	9.4	29	56.25
3	67	10.7	25	138.56
4	21	11.2	28	73.51
5	18	8.3	22	42.67
6	15	9.2	18	64.73
7	16	9.0	10	116.85
8	39	8.3	nd	121.87
9	12	10	31	11.83
10	21	9.4	24	56.96
11	11	9.3	38	85.76
Average	24.18	9.39	25	79.99
Median	18	9.3	25	73.51
Std Dev	16.3	0.9	7.6	38.7

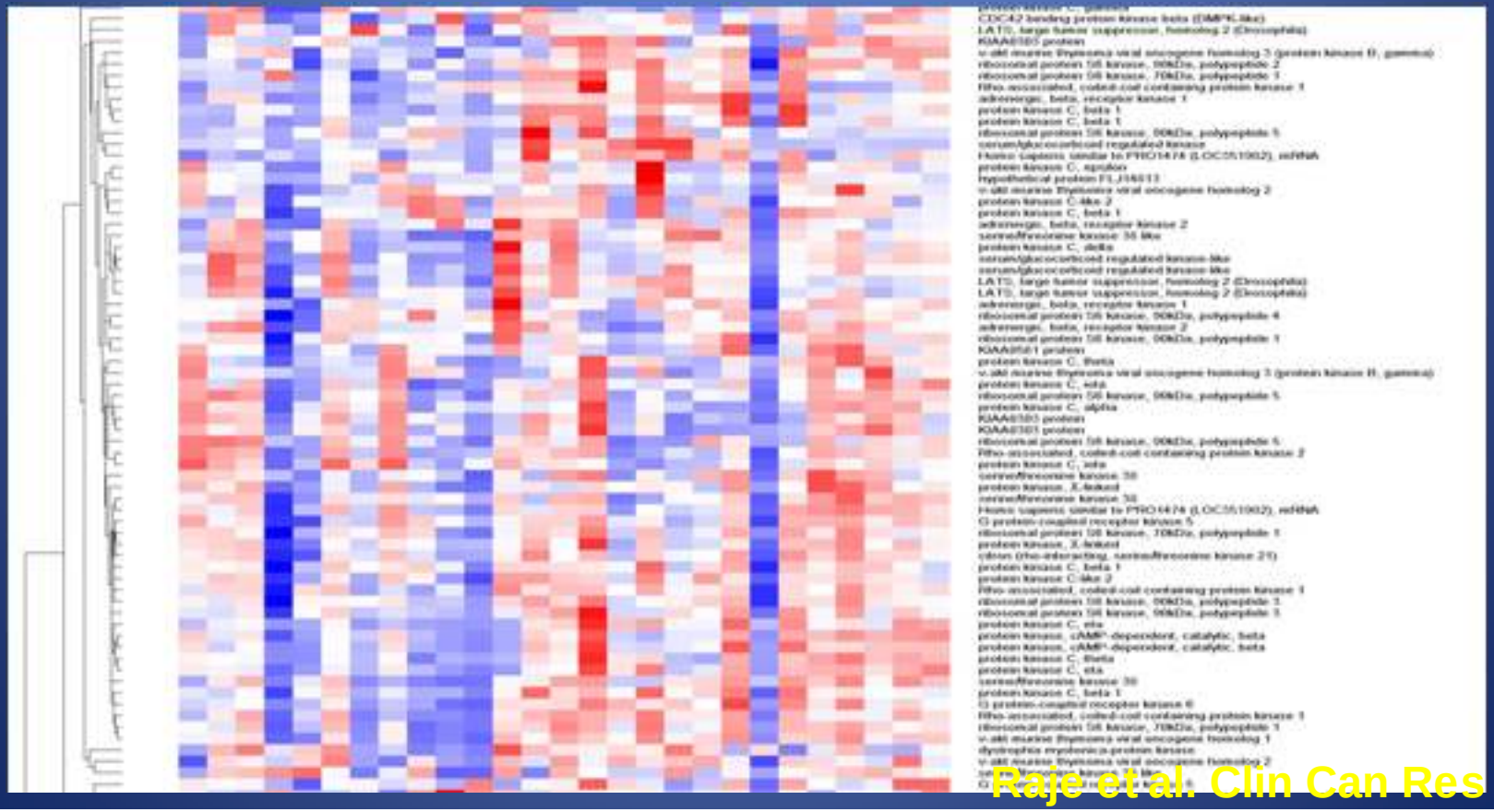
Raje et al. Clin Can Res 2008

NFAT TRANSCRIPTION FACTORS

ONJ MM Normals

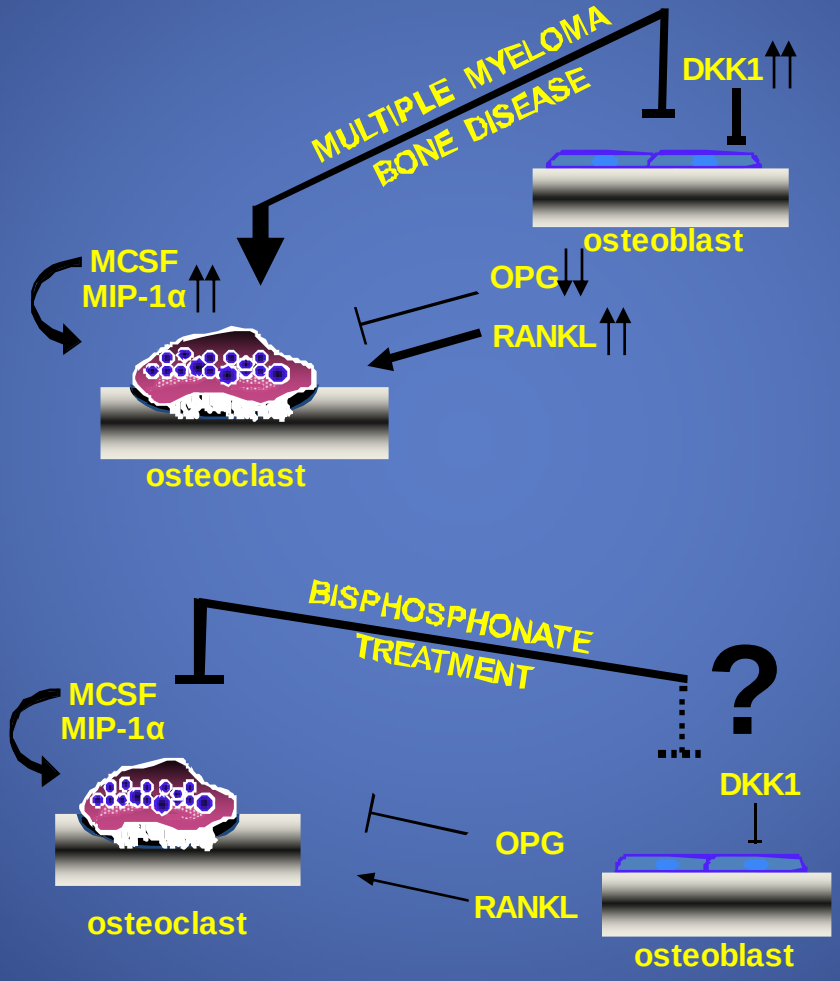


PROTEIN KINASE C FAMILY

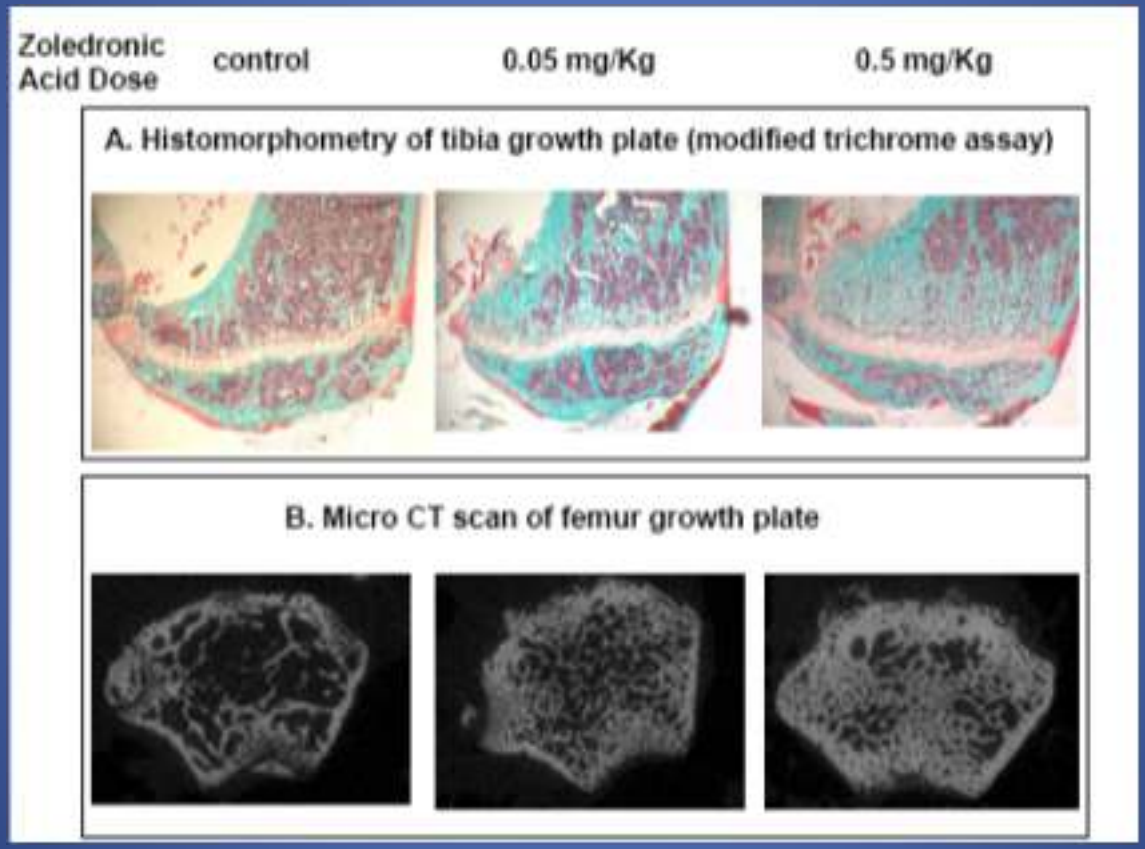


Raje et al. Clin Can Res 2008

? Bone Remodeling with Bisphosphonates

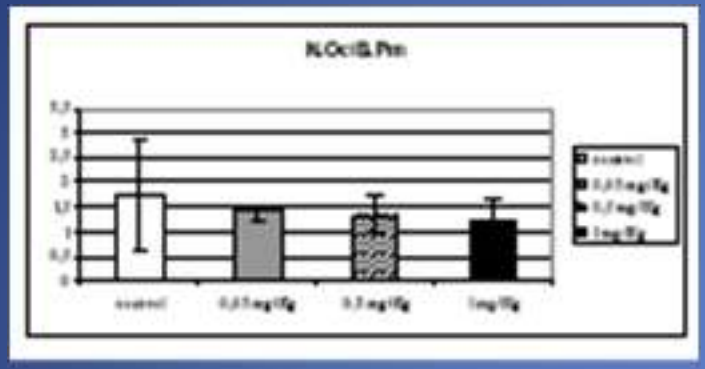


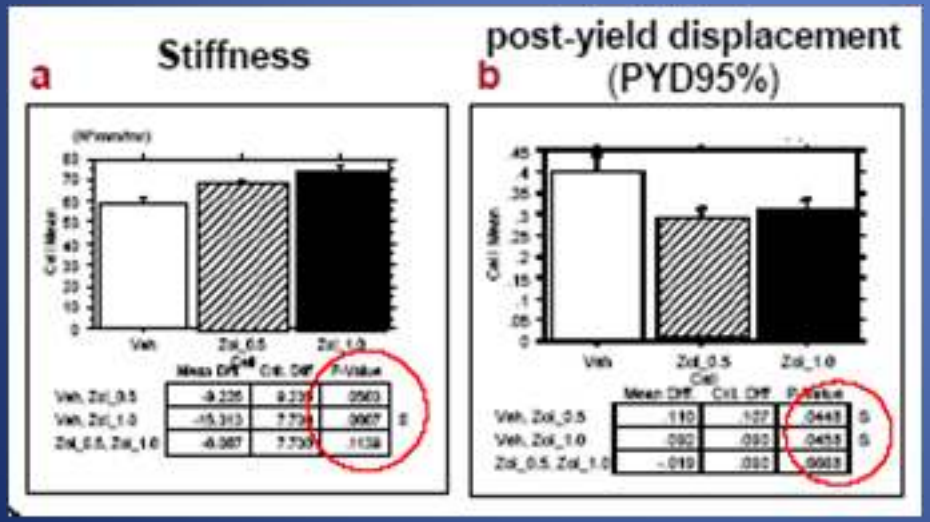
High Dose Zoledronic Acid increases Trabecular Bone



Pozzi et al, Clin Can Res 2009

High Dose Zoledronic Acid Decreases Bone Formation





Zoledronic Acid decreased osteoblast numbers associated with increased tendency to fracture

Pozzi et al, Clin Can Res 2009

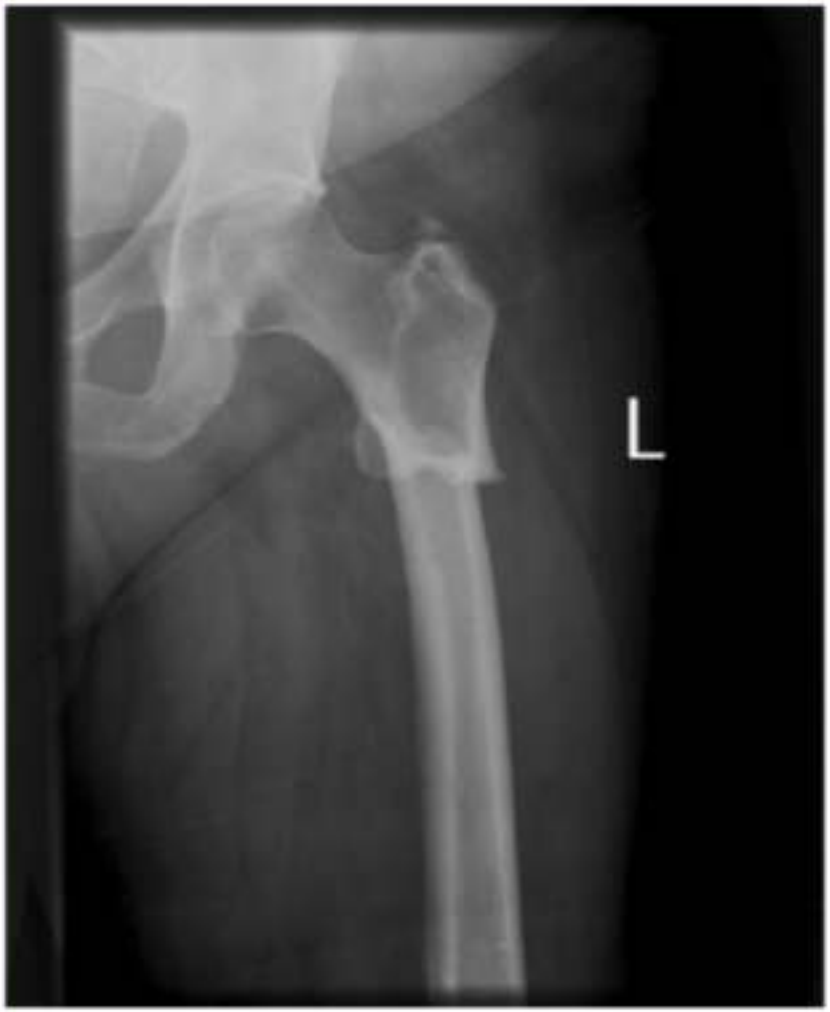


FIGURE 1. X-ray of subtrochanteric fracture of femoral shaft.

Grasko, Herrmann, and Vasilkaran. Bisphosphonate, Low-Energy Femoral Shaft Fractures, and ONJ. J Oral Maxillofac Surg 2009.

? Stress Fractures

Grasko, J Oral Maxillofacial Surg 2009

Urine NTx to tailor Therapy

30 MM patients in CR and or PR with h/o 8-12 months of IV bisphosphonate therapy

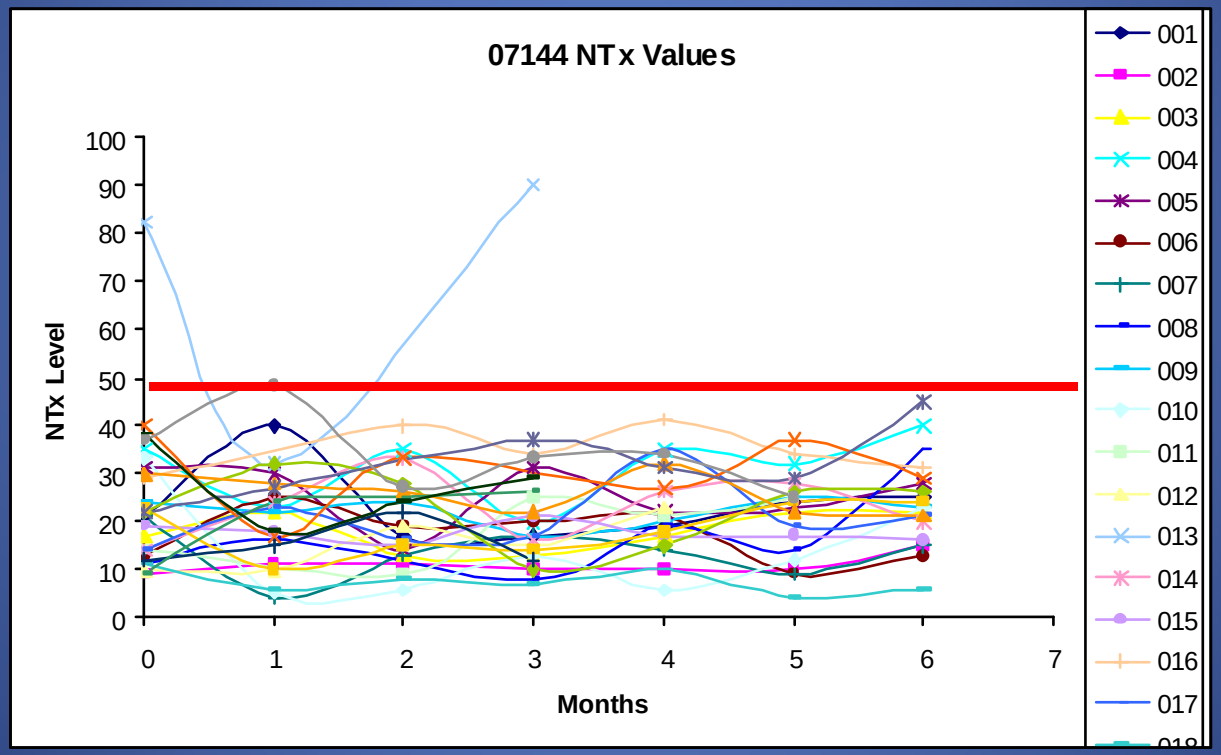
6 m end of study with BM aspirate and biopsy and Skeletal Survey

Baseline NTX followed by monthly x 6
- Serum Markers followed by monthly x 6
- BM aspirate and core

Skeletal Survey
- Zoledronic acid single dose

Raje et al. J Clin Oncol 2010 ASCO Ab

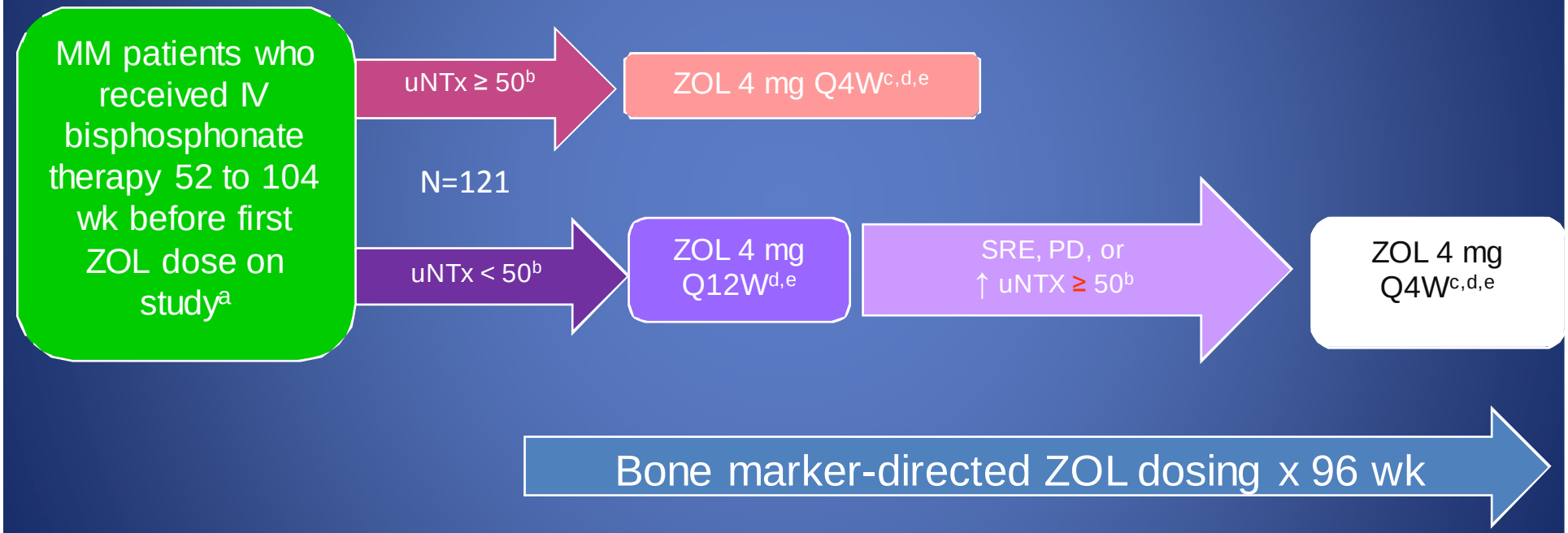
Results
NTx levels (n=28patients)



Raje et al. J Clin Oncol 2010 ASCO Ab

Z-MARK Study Design

Prospective, single-arm, open-label, multicenter study



Abbreviations: MM, multiple myeloma; Q4W, every 4 weeks; Q12W, every 12 weeks; PD, progressive disease; uNTX, urinary N-telopeptide; SRE, skeletal-related event; ZOL, zoledronic acid.

[a]Patient had to receive ≥ 4 doses of IV bisphosphonate; last prior IV bisphosphonate dose must have been administered ≥ 3 weeks before initial zoledronic acid dose on study.

[b]nmol/mmol creatinine.

[c]Patients will remain on zoledronic acid q 4 weeks for remainder of the study.

[d]All patients were reminded to take supplemental oral calcium (≥ 500 mg) and vitamin D (≥ 400 IU) daily.

[e]Dose adjusted for patients with mild–moderate renal impairment at study entry.

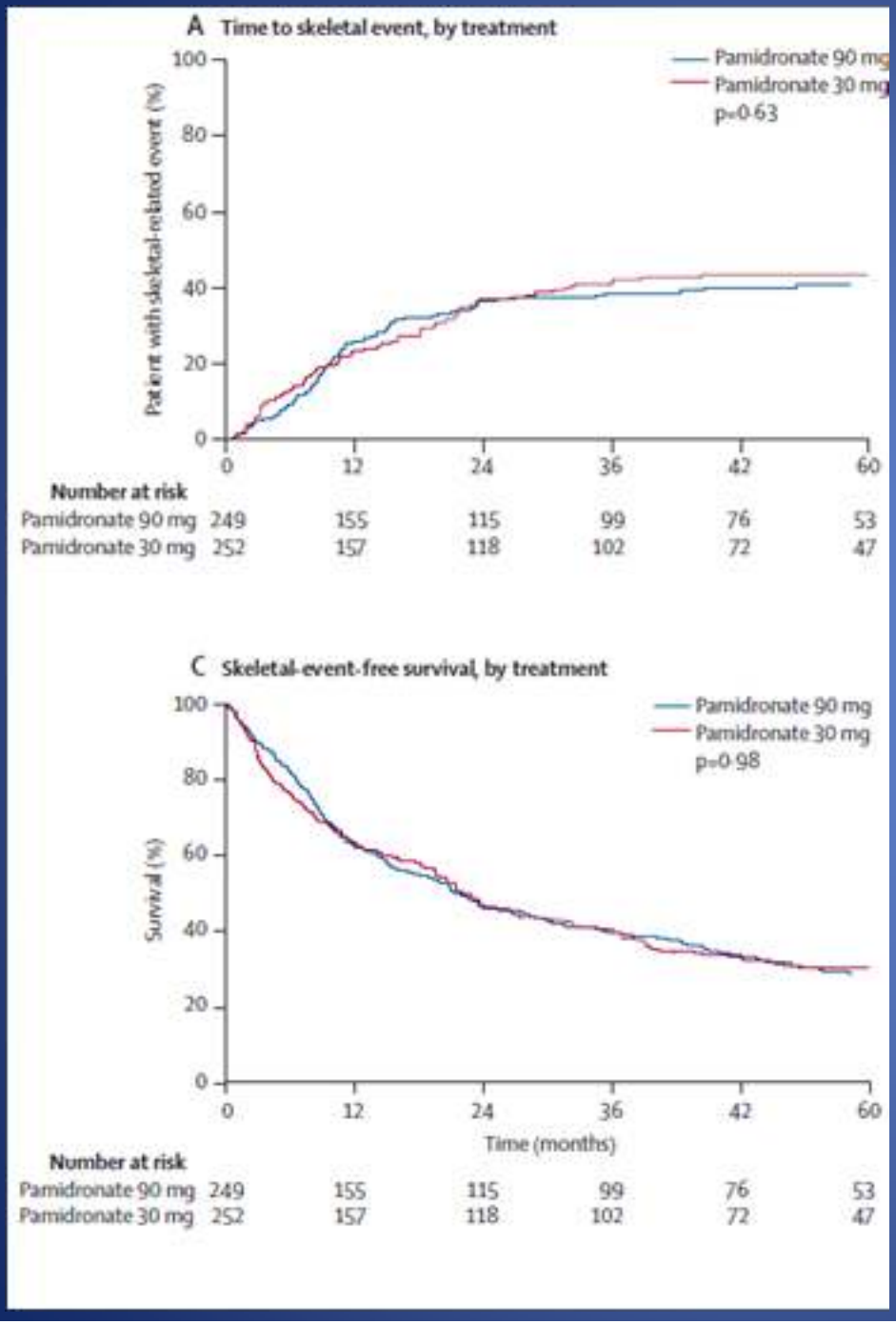
Raje et al, ASH 2010

Results

- SREs by end of year 1
  - 2 Patients receiving ZOL every 12 wk (Q12W)
    - Spinal cord compression (1 patient)
    - Radiation therapy to bone x 4 (1 patient)
  - 0 Patients receiving ZOL every 4 wk (Q4W)

- uNTX
  - Baseline uNTX
    - Median: 17 nmol/mmol Cr
    - Range: 7–71 nmol/mmol Cr
  - Median % change from baseline in uNTX
    - Wk 12–36: range, 0%–11.7%
    - Wk 48: 0%, range, -67.5%–188.9%

Raje et al, ASH 2010



Nordic Myeloma Study Group

PAM 90 vs 30

ONJ 8 vs 2 cases

Gimsing P et al, Lancet Oncol 2010

Novel Drug Approaches

Teriparatide

Cheung A et al. N Engl J Med 2010