Should We Use Markers of Bone Remodeling in Myeloma? Which One and When?

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Disclosures (Evangelos Terpos)

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Research Support/P.I.	N/A
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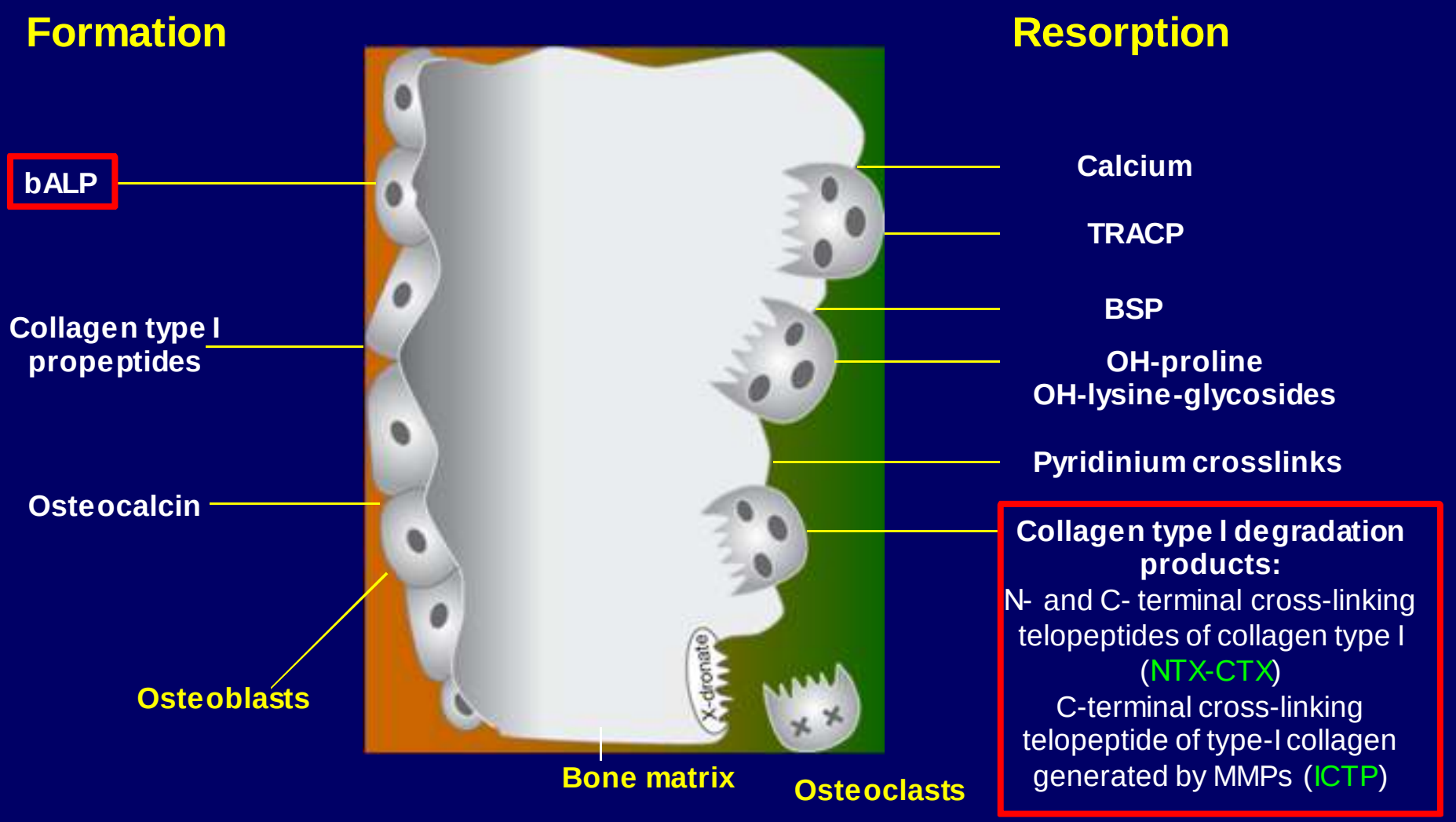
Why do we use bone markers for the assessment and monitoring MM bone disease?

- Bone lesions do not normally heal even if MM goes into remission (osteoblast dysfunction).
- Radiographs frequently do not indicate increased bone resorption in MM progression.
- BMD measurements are often not informative for bone disease status in MM.

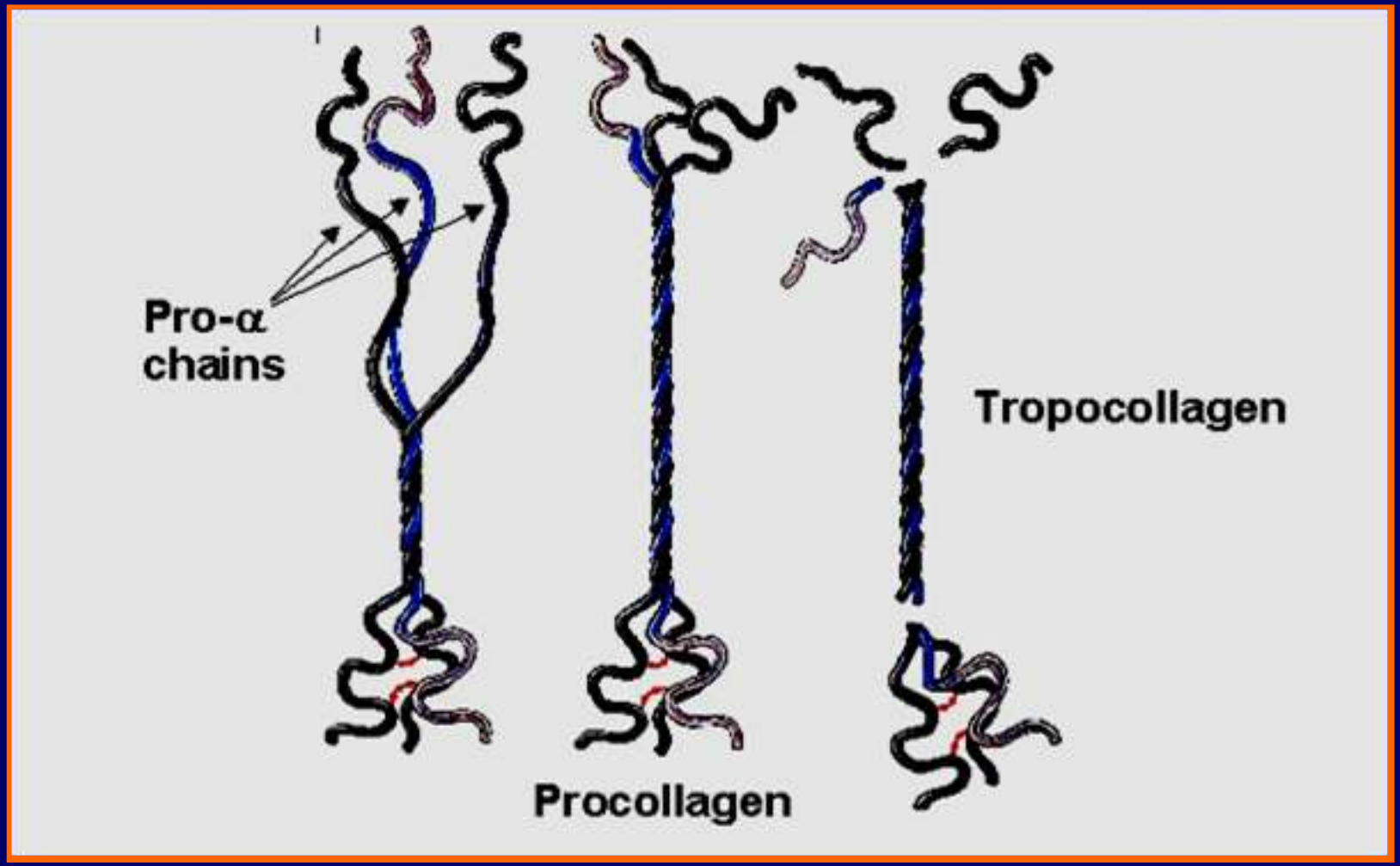
- Biochemical markers of bone metabolism have been used in an effort to better monitor the myeloma bone disease and improve assessment of disease progression.

Biochemical markers of bone remodeling

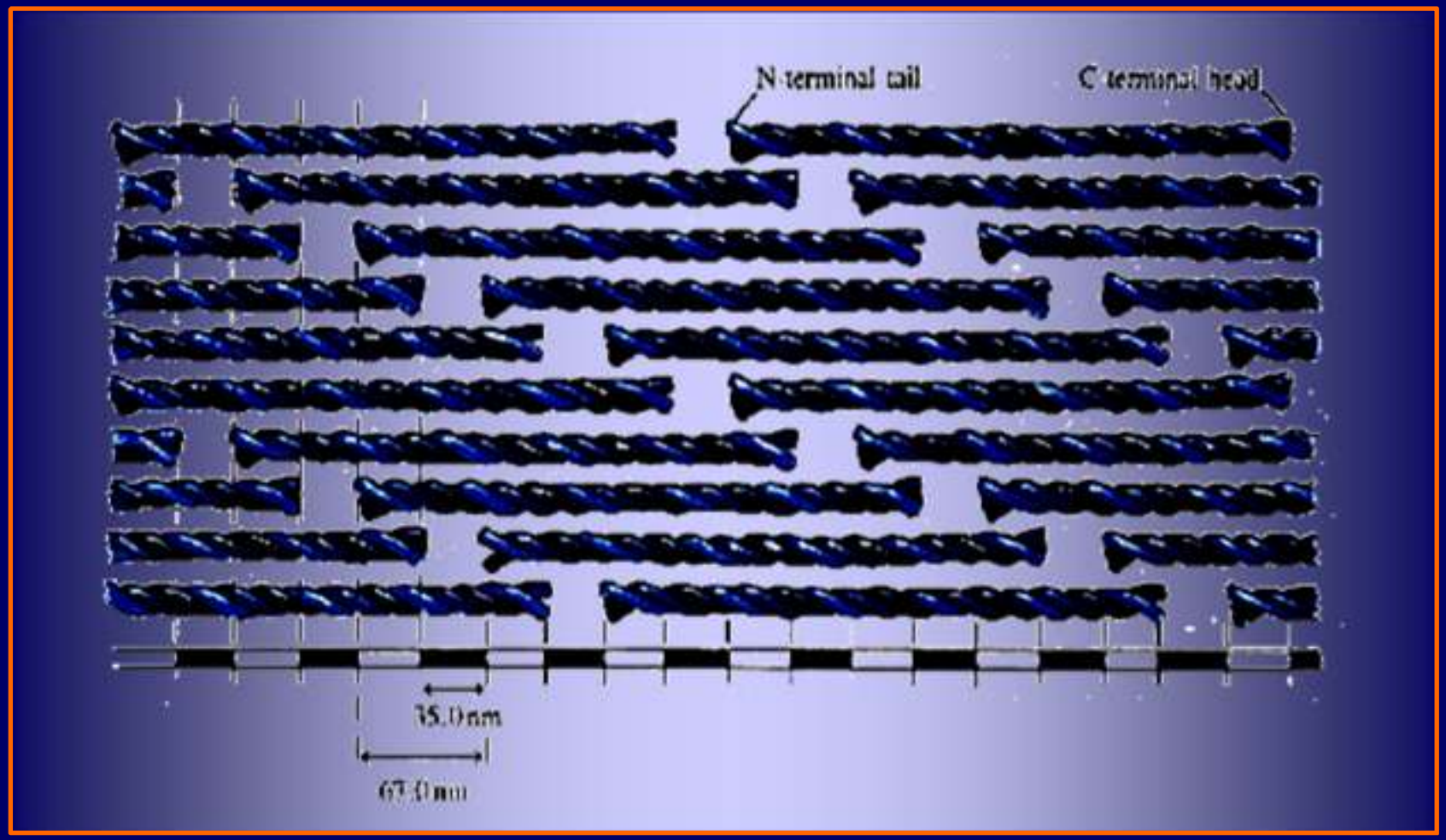


Lipton et al. Clin Lymphoma Myeloma 2007;7:346-53

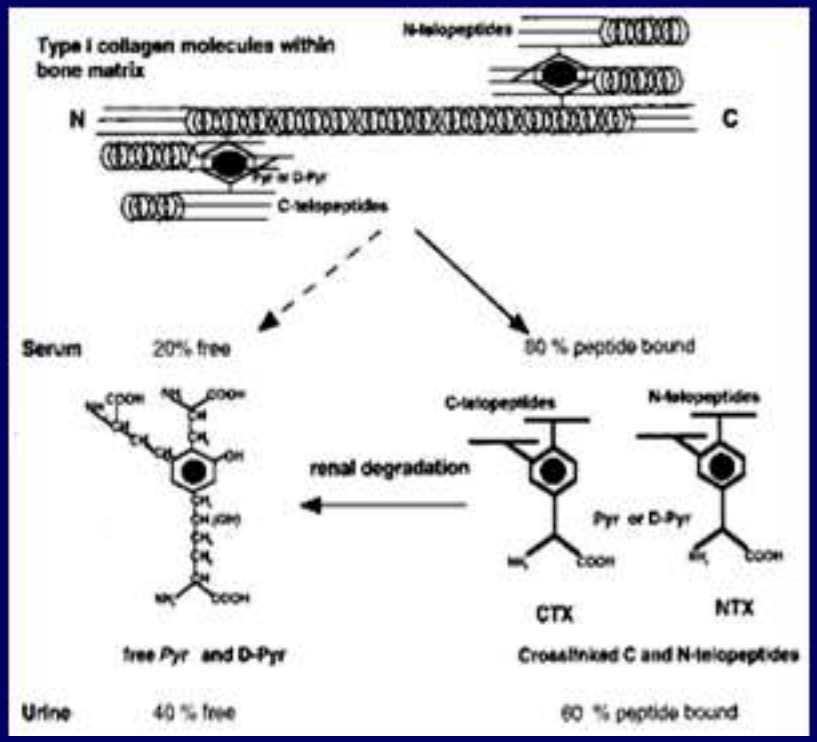
Assembly of pro-a collagen and processing into tropocollagen

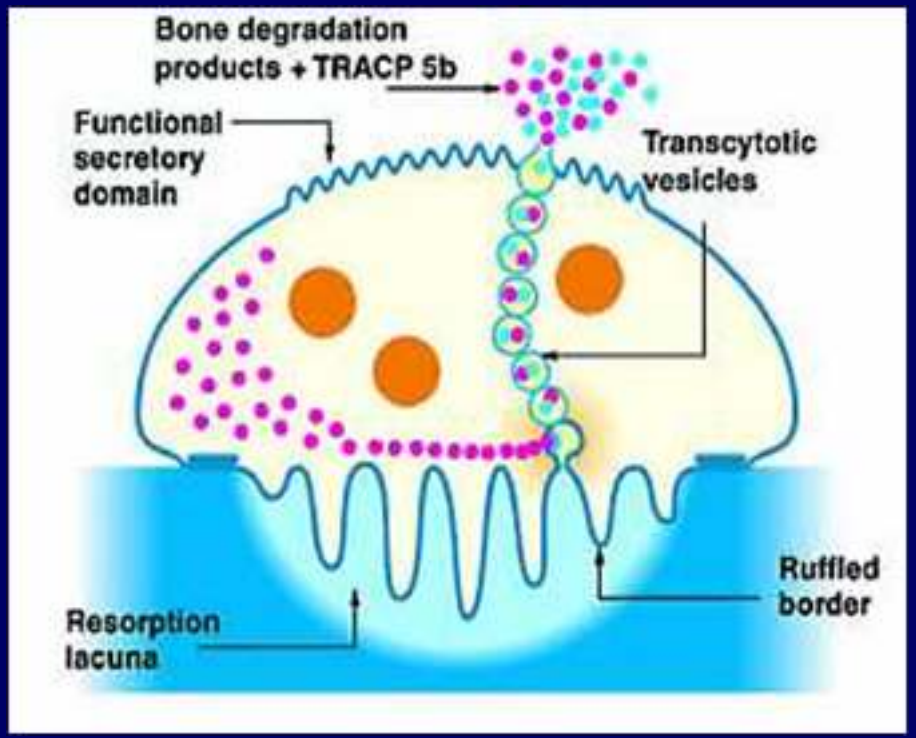


Assembly of tropocollagen into fibers



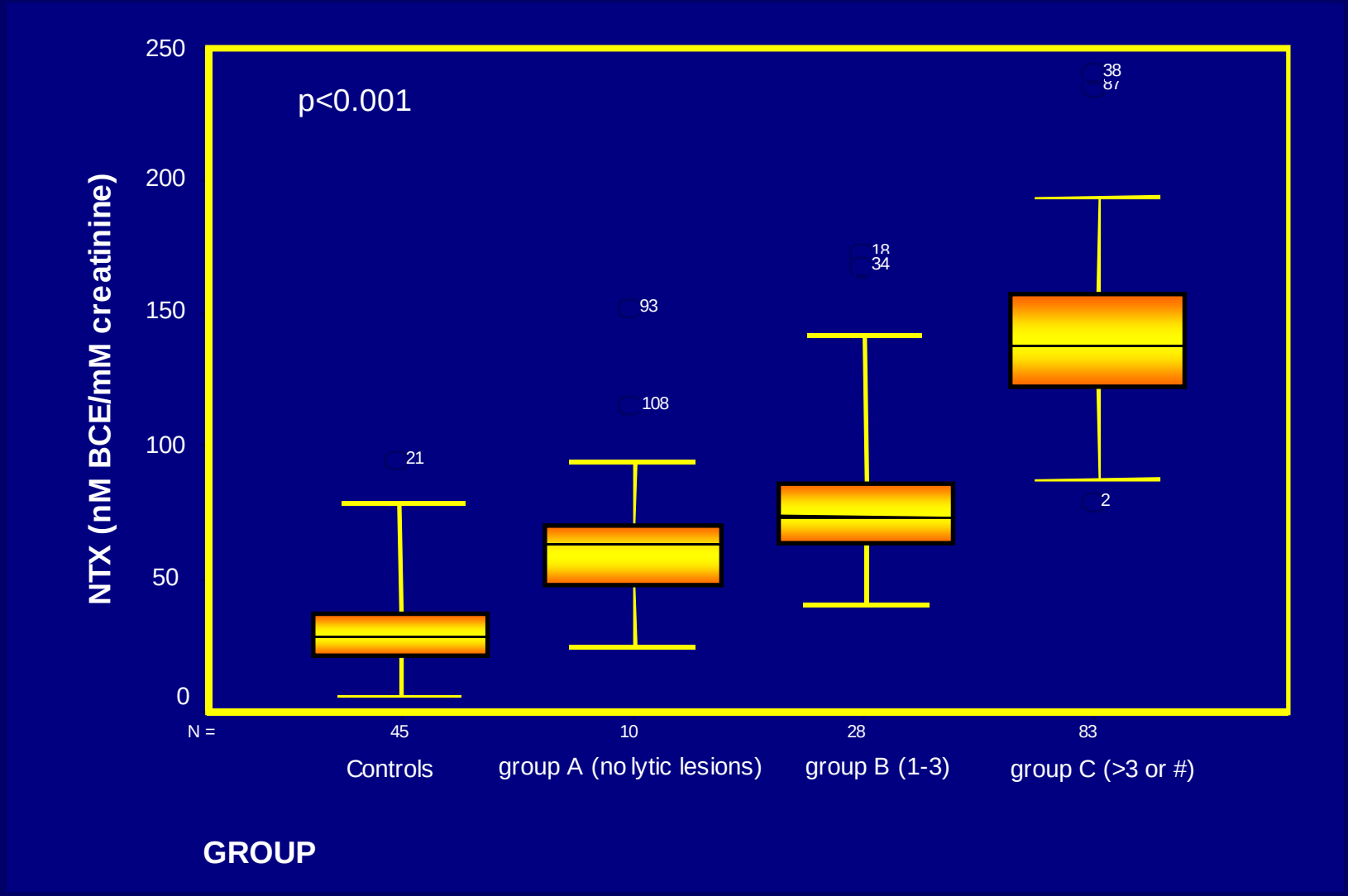
Bone collagen degradation products





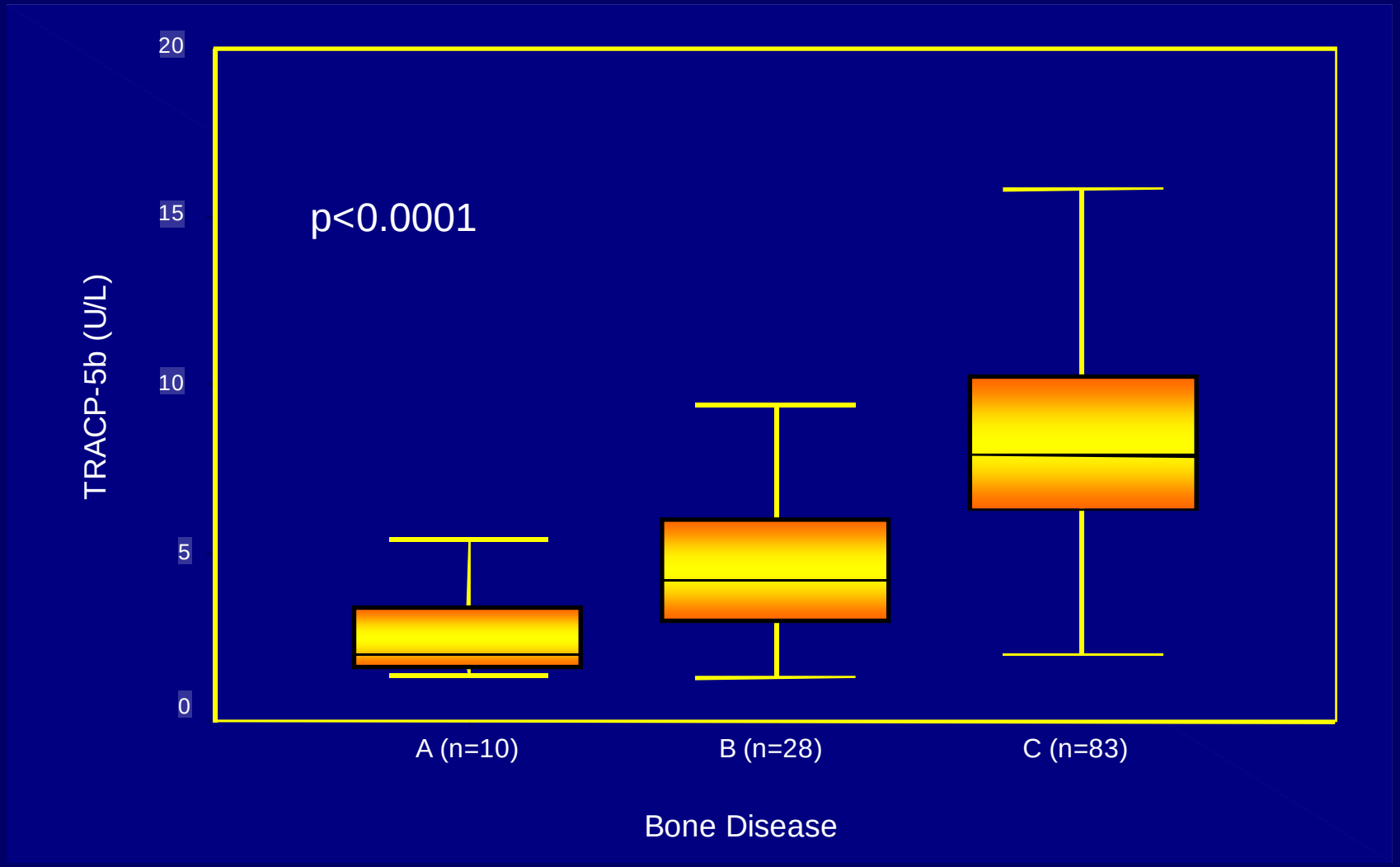
Due to bone specificity and their unique characteristics NTX, ICTP, and CTX have almost totally replaced the use of older resorption indices in the diagnostic assessment of bone diseases.

Urinary NTX in myeloma bone disease



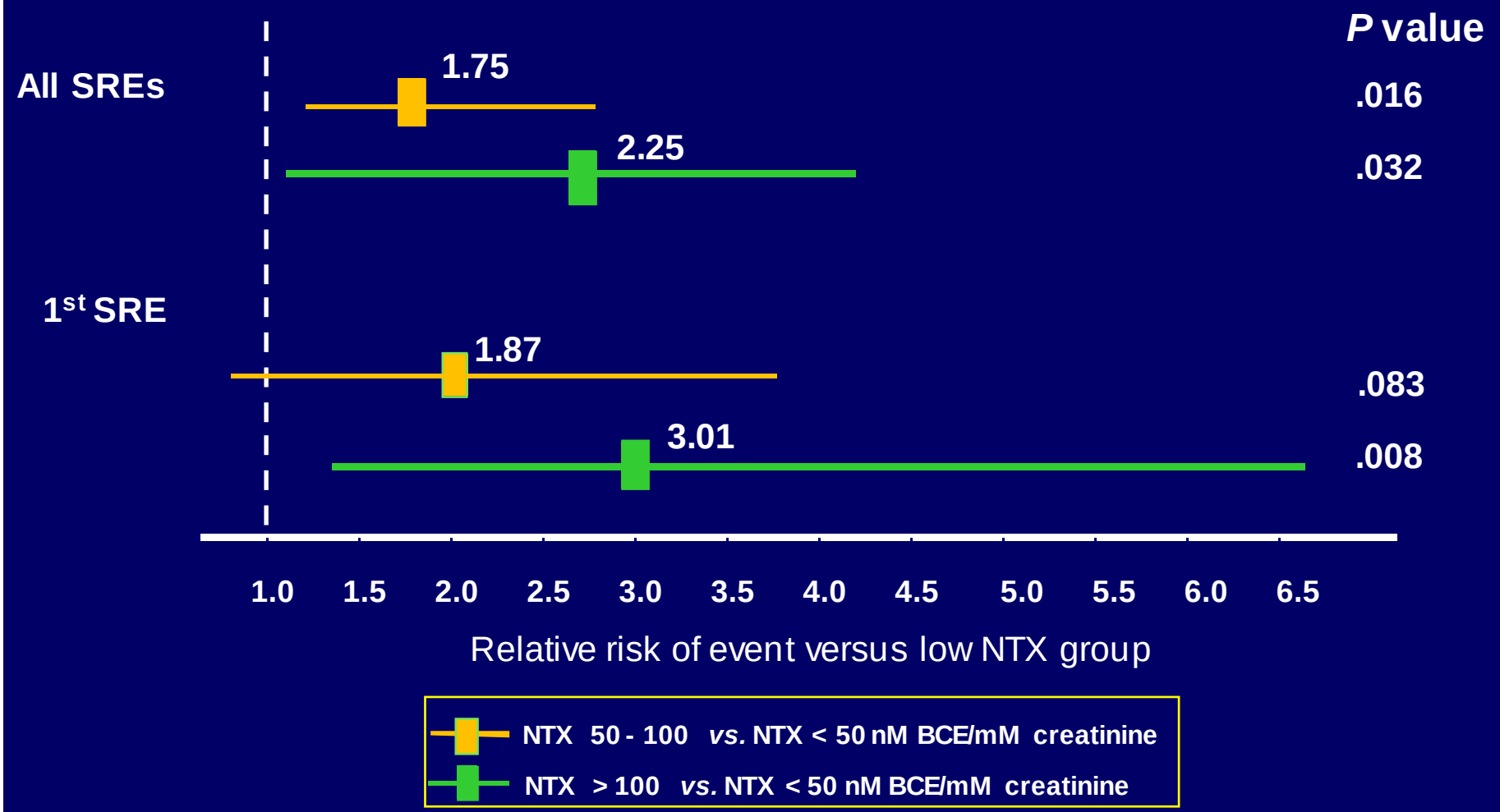
Terpos et al. Blood 2003;102:1064-9

Serum TRACP-5b and myeloma bone disease



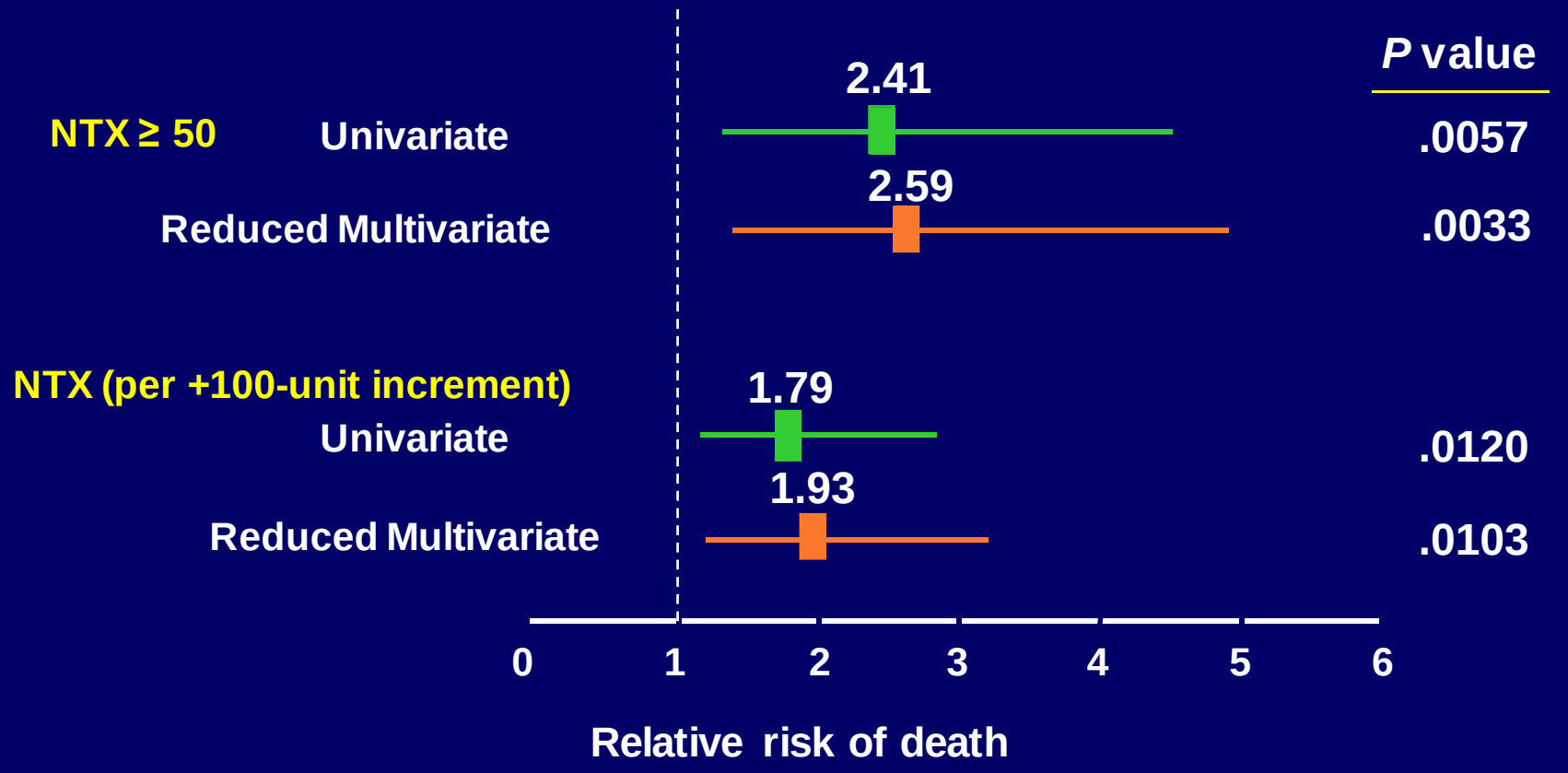
Terpos et al. Int J Cancer 2003;106:455-7

MM patients with moderate or high urinary NTX levels are at Higher Risk of SREs



Coleman et al. J Clin Oncol 2005;23:4925-35;
Lipton et al. Clin Lymphoma Myeloma 2007;7:346-53.

Baseline NTX is an Independent Prognostic Indicator of Death in 510 patients with MM (Dichotomous and Continuous Variable)

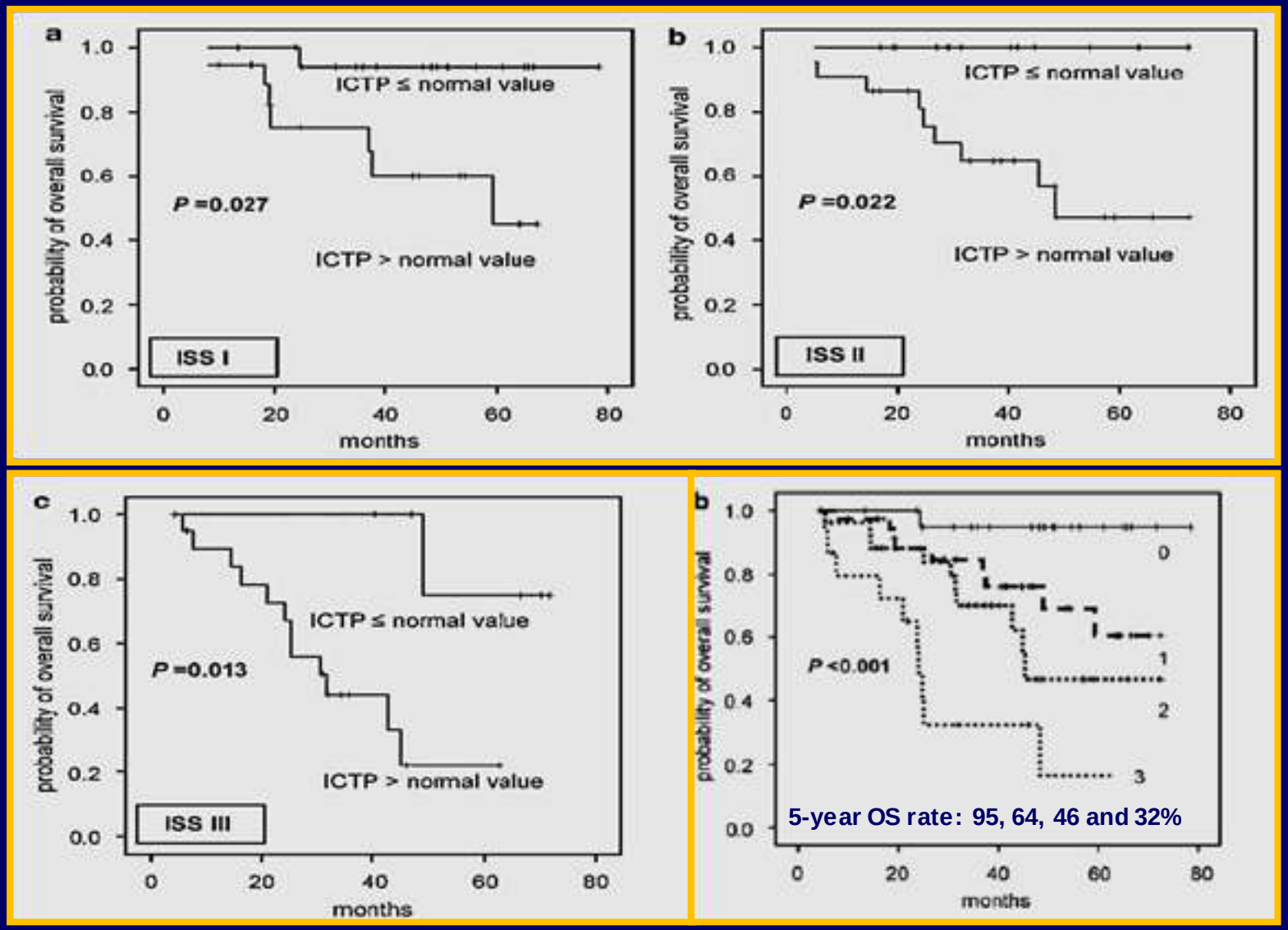


Pts had to have a complete set of data for all variables assessed; NTX in nmol/mmol creatinine.
Reduced multivariate model included age, myeloma Ig type, NTX level, hemoglobin level, and SGOT level.

Terpos et al. Leukemia 2010;24:1043-9

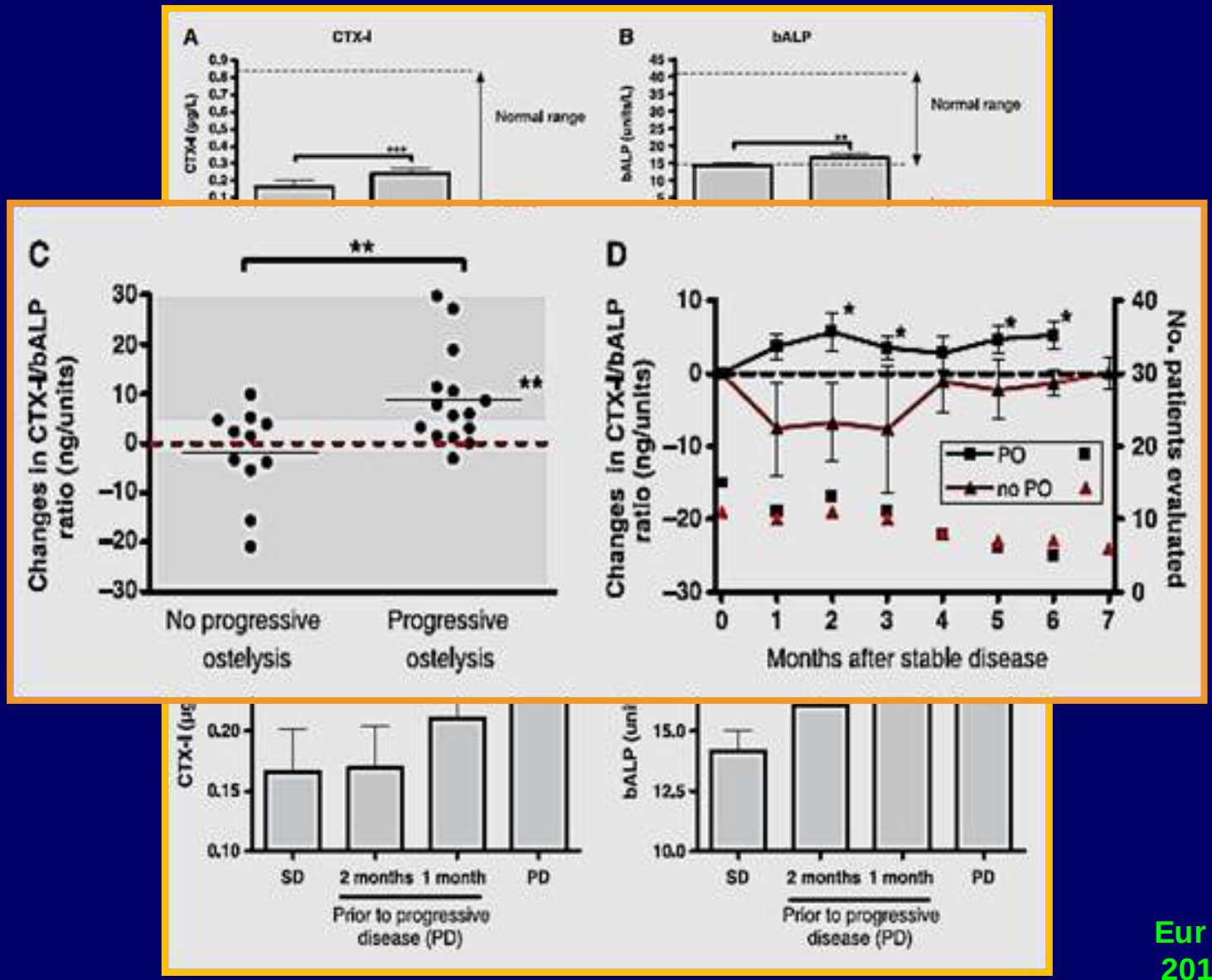
ICTP & OS in Myeloma

N=100 patients with newly diagnosed MM



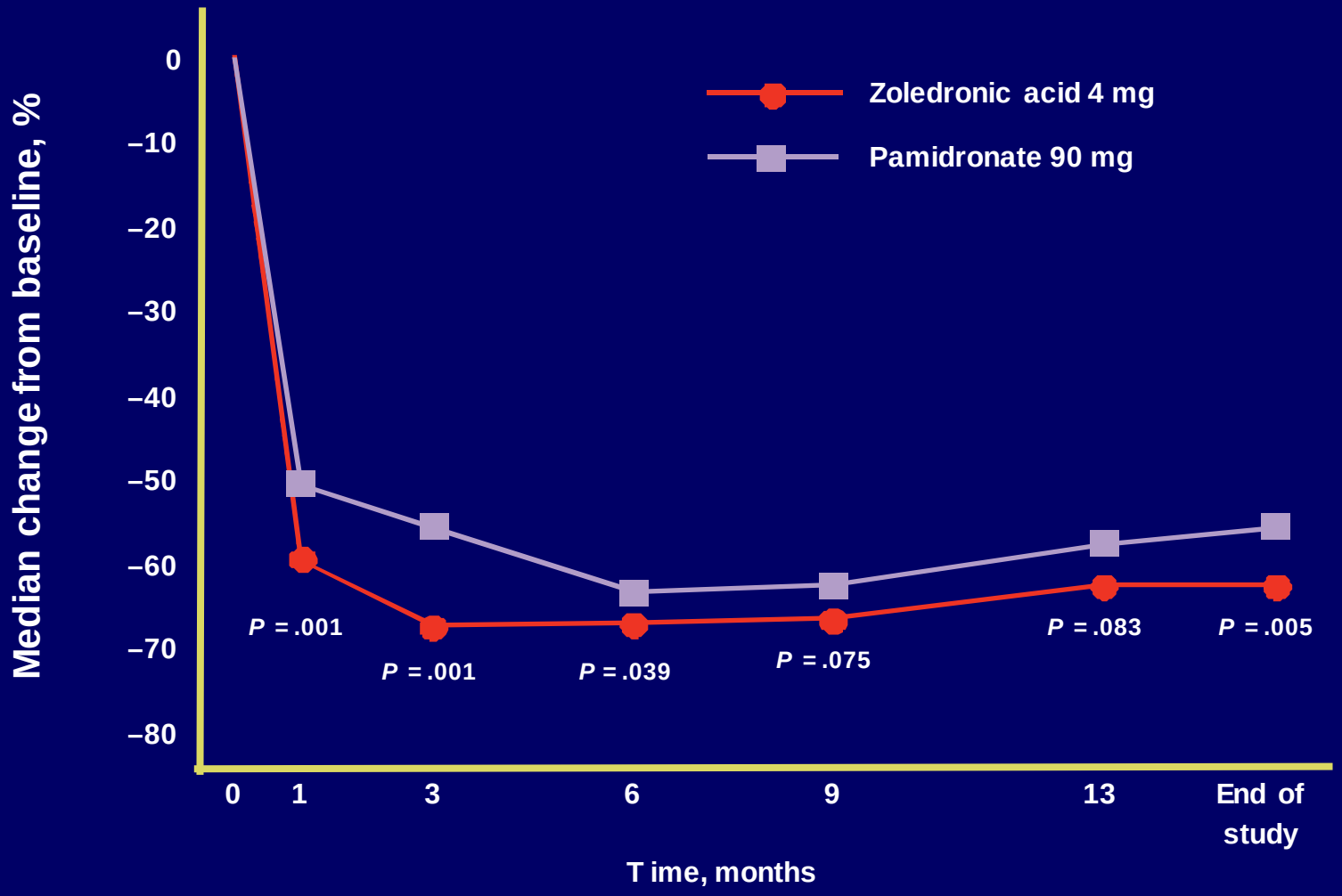
Jacob et al. Leukemia 2008;22:1767-72

Serum CTX and bALP are elevated prior to MM progression



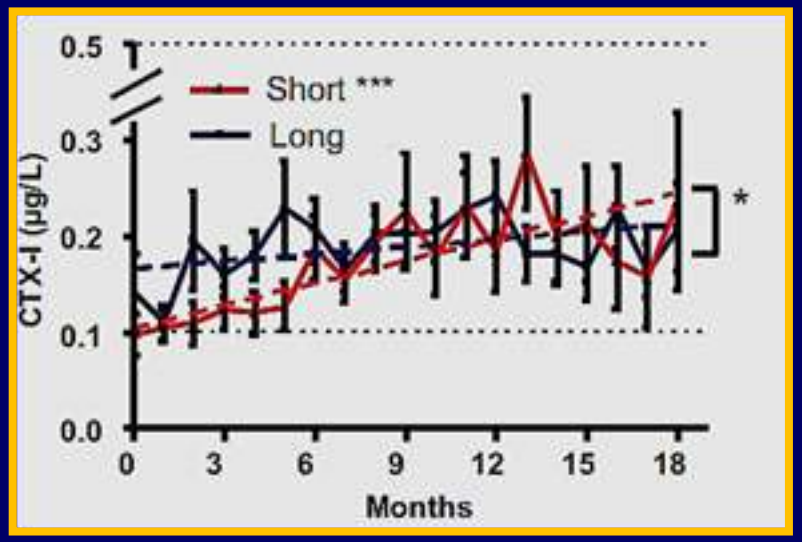
Lund et al.
Eur J Haematol
2010;84:412-20

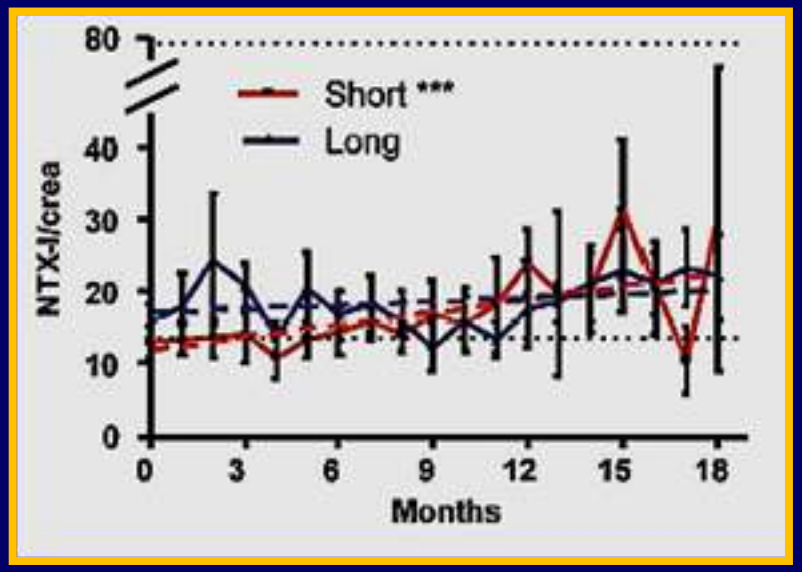
ZOL significantly reduces NTX levels *vs.* PAM in patients with bone lesions



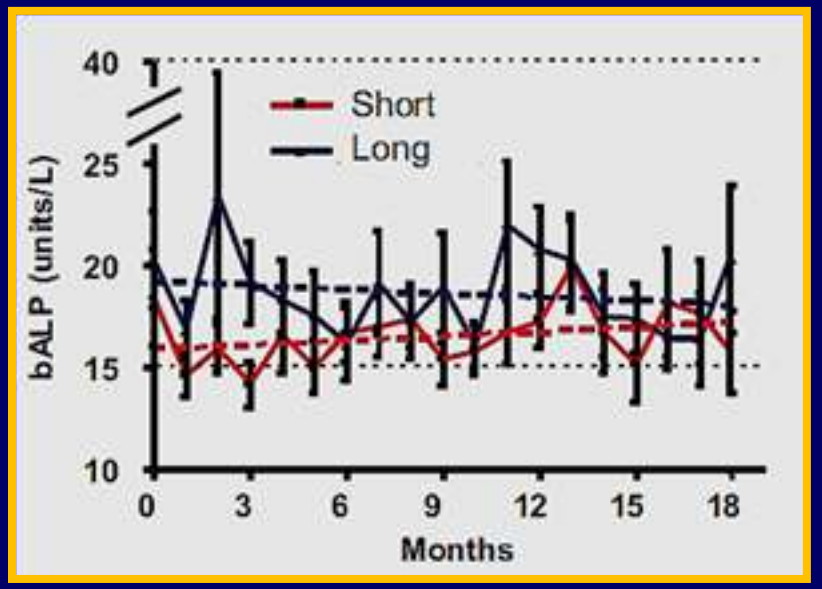
Lipton et al. Clin Lymphoma Myeloma 2007;7:346-53.

Bone Markers After Discontinuation of Zoledronic Acid



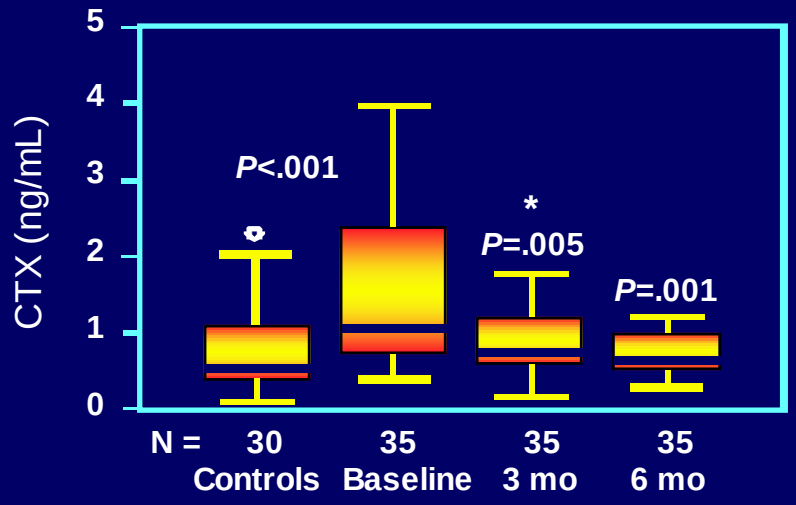


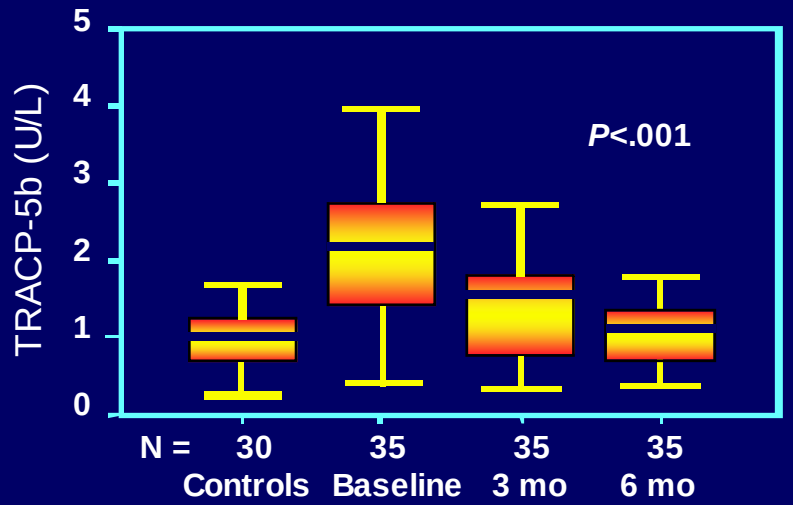
29 patients were treated with ZOL for a period of 12 months
and
34 for a period of 24 months

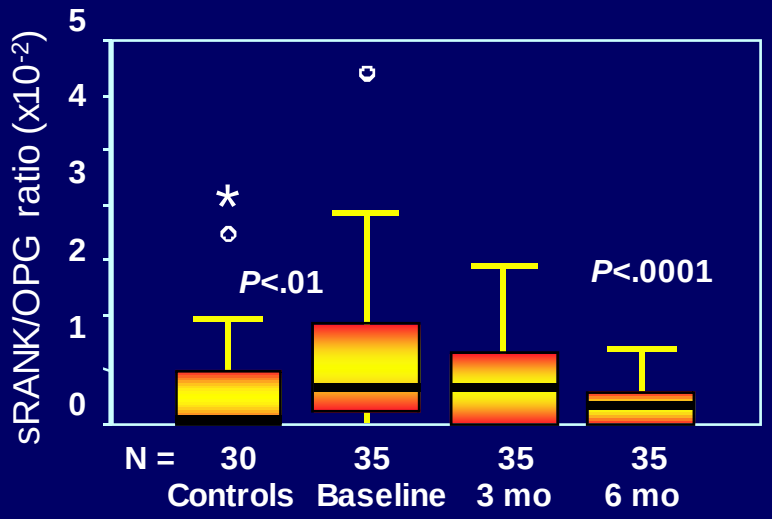


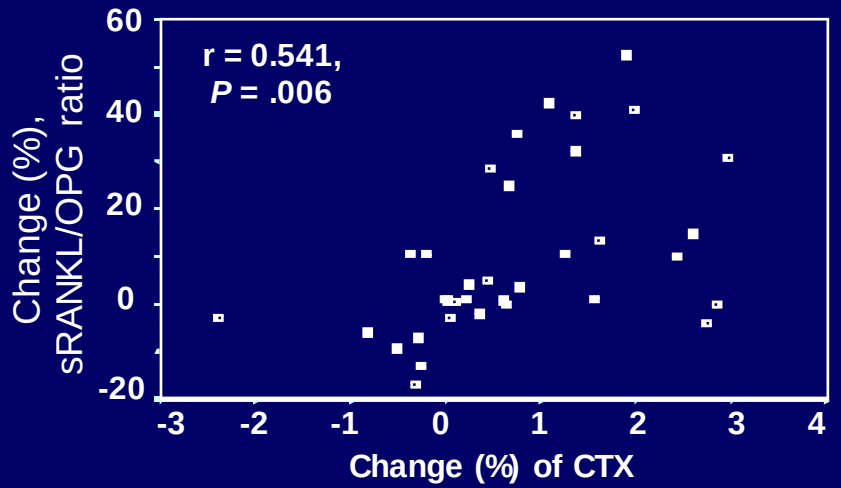
Lund et al. Br J Haematol 2010;151:92-3

Thal/Dex effect on bone markers of relapsed/refractory MM





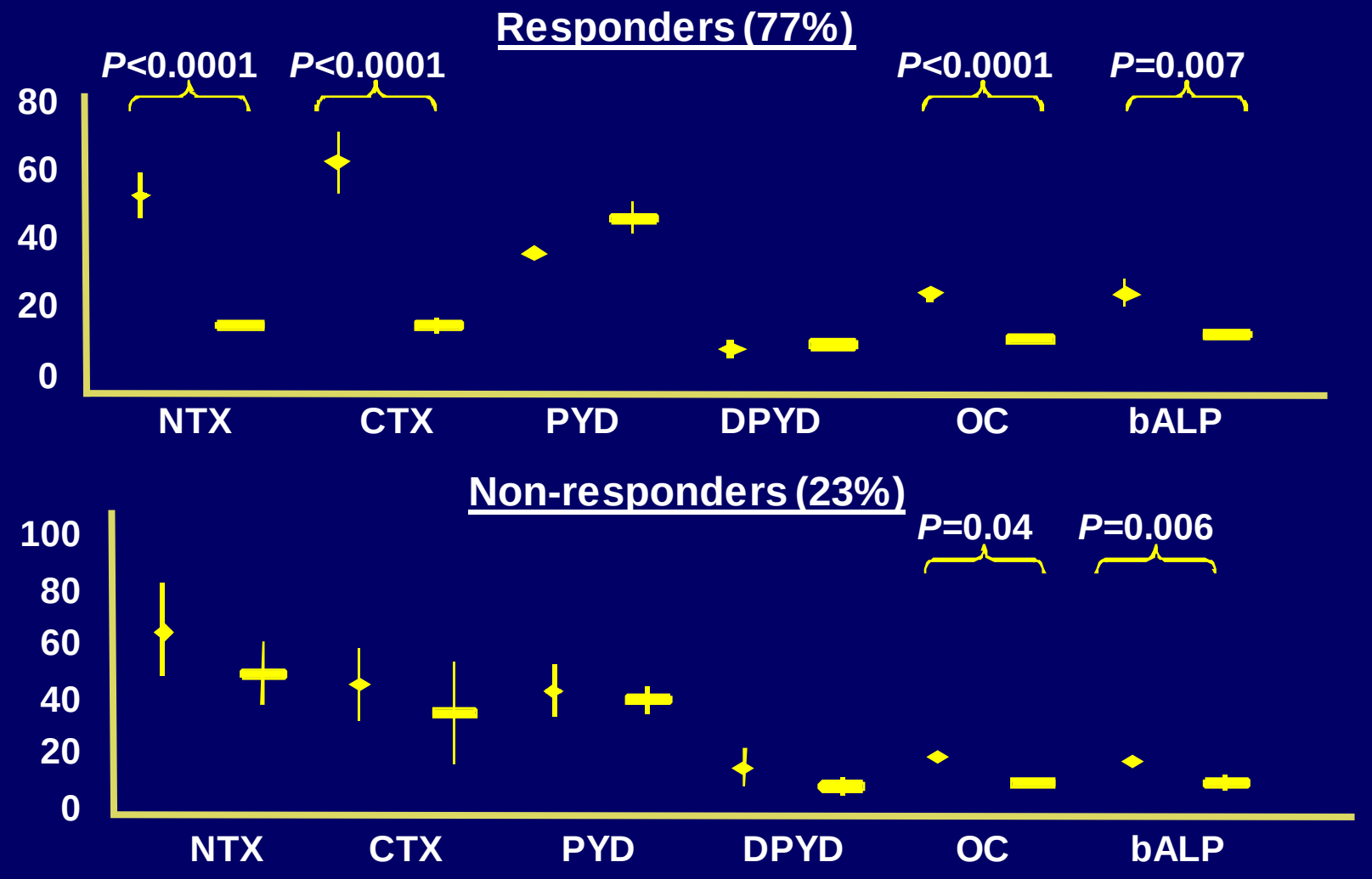




All patients were received zoledronic acid.

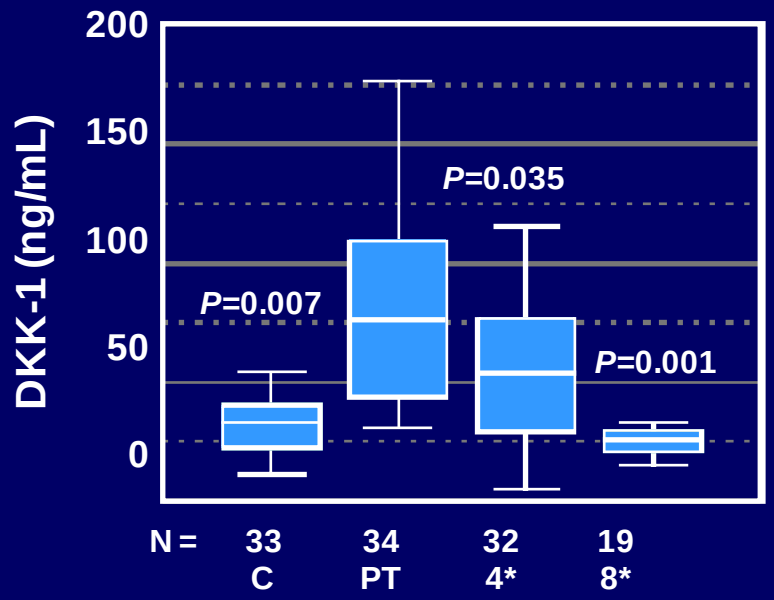
Terpos et al. Leukemia 2005;19:1969-76

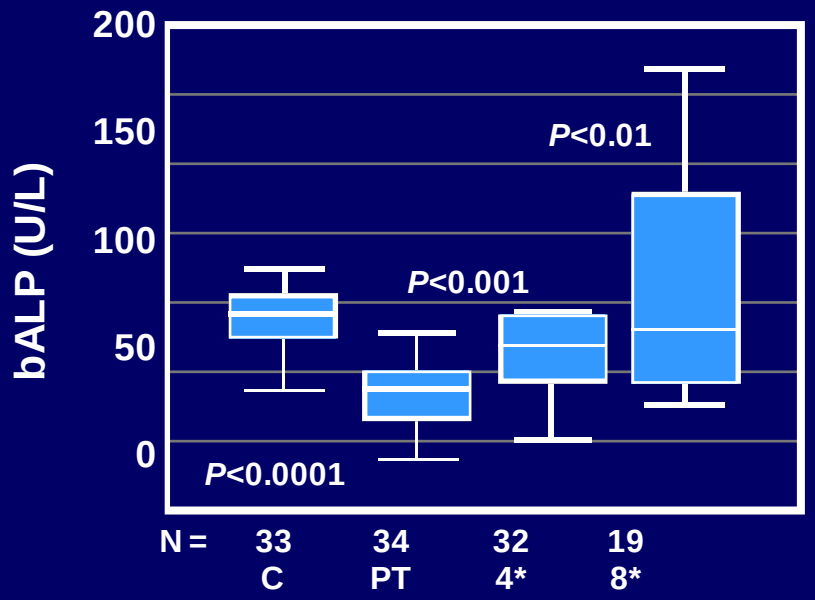
Thal/dex effect on bone metabolism of newly diagnosed MM patients

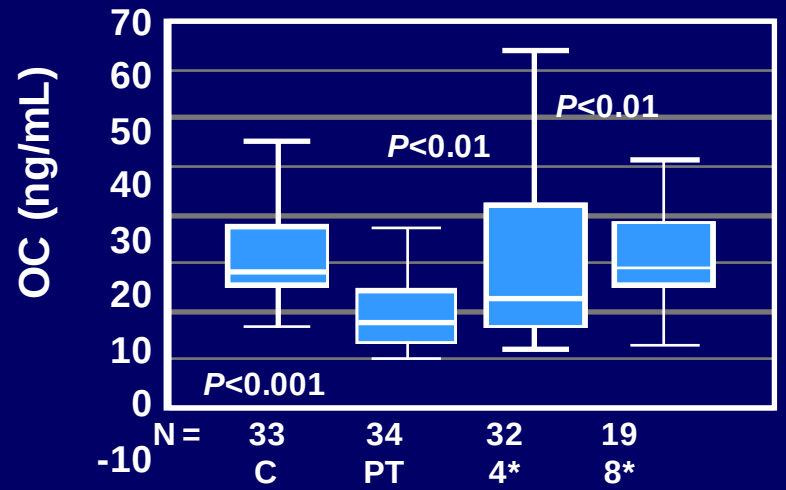


Tosi *et al.* Eur J Haematol 2006;76:399-404

Bortezomib Affects Markers of Bone Formation and Osteoblast Stimulators



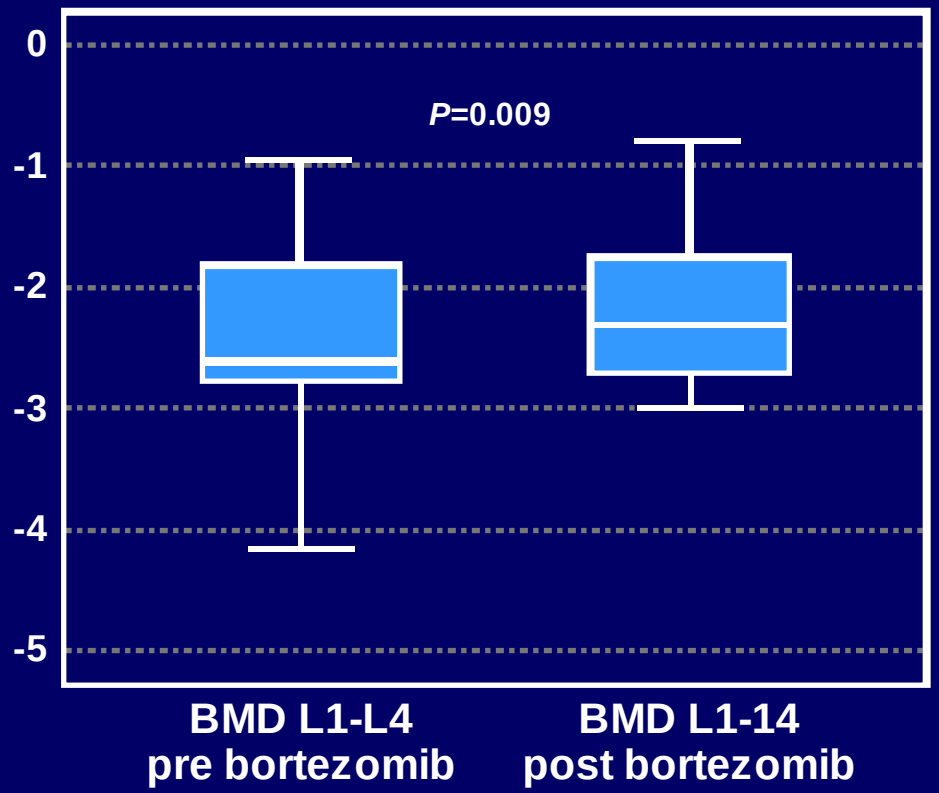




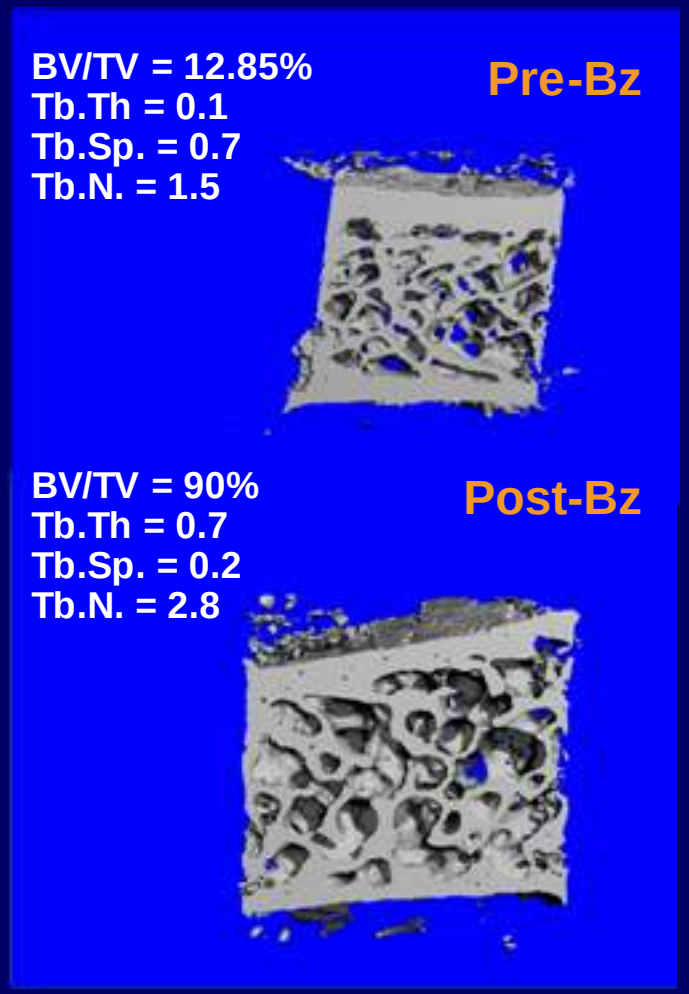
*After cycle number.

Terpos et al. Br J Haematol 2006;135:688-92

BMD: Pre- and Post-Bortezomib

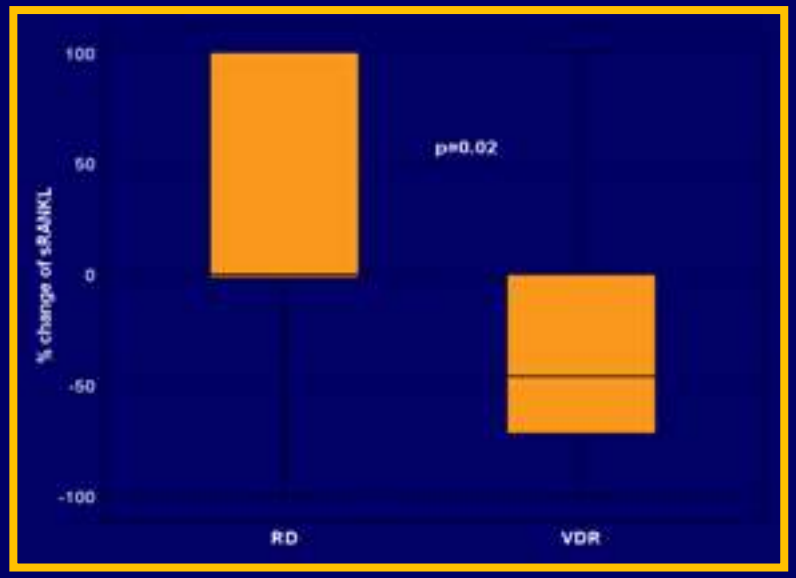


4/27 patients (14%) showed at least 10% of increase in L1-L4 BMD; all these patients had osteoporosis according to DXA, had responded to VD therapy (3 PR and one CR), and had received VD as 2nd-line treatment

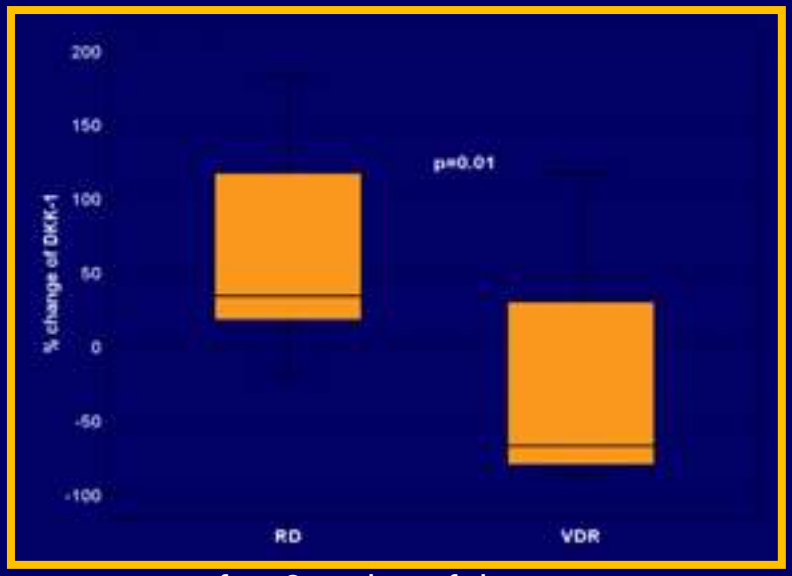


Terpos E et al. Ann Oncol. 2010;21:1561.
Zangari et al. Haematologica. 2011;96:333.

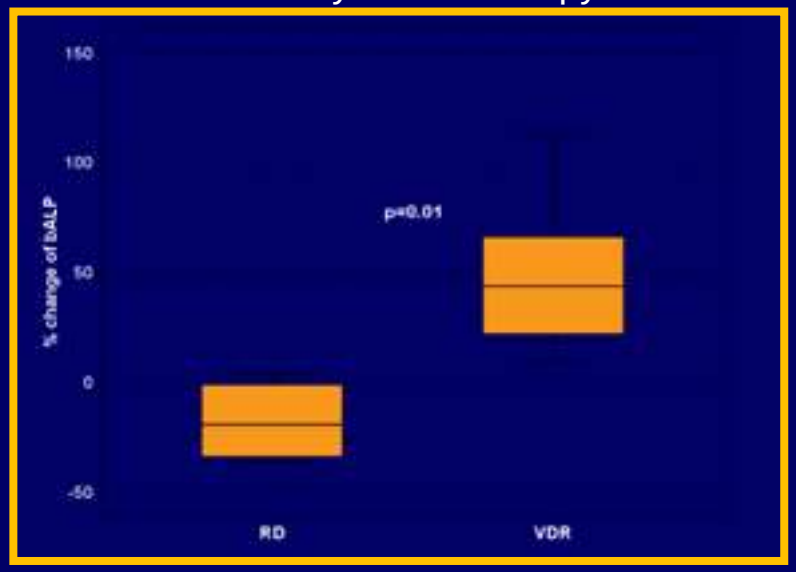
Effect of RD and VRD on RANKL in Patients with Relapsed/Refractory MM

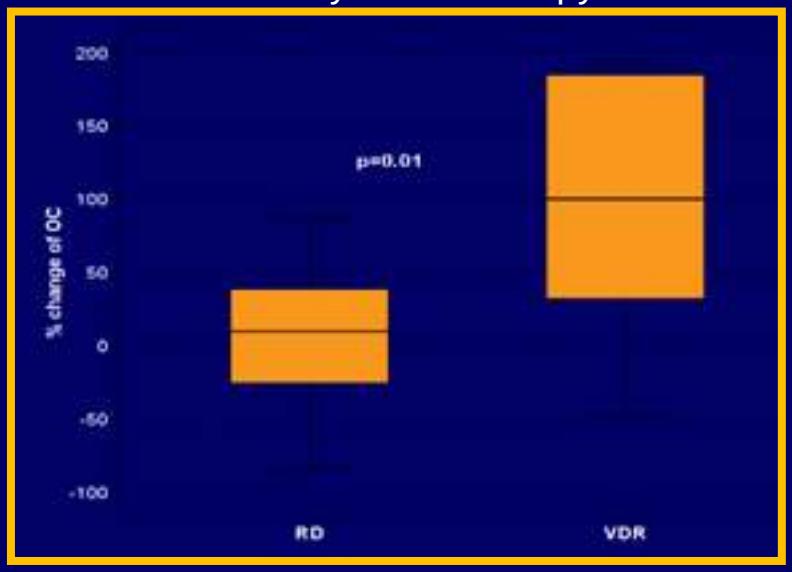


after 6 cycles of therapy



after 6 cycles of therapy





Terpos et al. IMW 2011; abstract No 1267

Conclusions for Bone Markers in MM

Parameter	Reflection of the extend of myeloma bone disease	Prediction for SRE	Prediction for OS	Future possible use
Bone Resorption Markers				1. Symptomatic patients to drive initial therapy (NTX)
Urinary NTX	+++	+++	+++	
Serum ICTP	+++	++	++	2. Asymptomatic patients to drive decision for antiresorptive therapy (NTX, ICTP, CTX)
Serum CTX	++	-	-	
Serum TRACP-5b	+	-	-	3. Symptomatic patients under bisphosphonates to decide the duration and intervals of therapy (NTX, ICTP, CTX)
Bone Formation Markers				
Serum bALP	+/-	-	-	1.Use for the evaluation of bone anabolic agents, such as bortezomib, anti-Dkk1, anti-SOST antibodies (bALP only)
Serum OC	+/-	-	-	
Serum PINP or PICP	-	-	-	2.No future use is seen for other bone formation markers
Osteoclast/osteoblast regulators				1.Use for the follow-up of novel therapies (denosumb-antiRANKL, anti-Dkk1 etc)
Serum sRANKL or tRANKL	+/-	-	+/-	
Serum OPG	+/-	-	-	
Serum Dkk-1	+	-	-	

•(-): no evidence
(+/-): conflicting evidence
(+): low evidence
(++): intermediate evidence
(+++): strong evidence

IMWG paper for the use of bone markers in MM
Terpos et al. Leukemia 2010;24:1700-12

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