Novel Bone Targeting Agents in Myeloma

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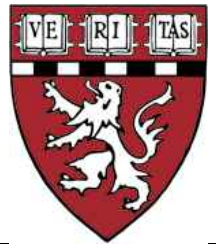
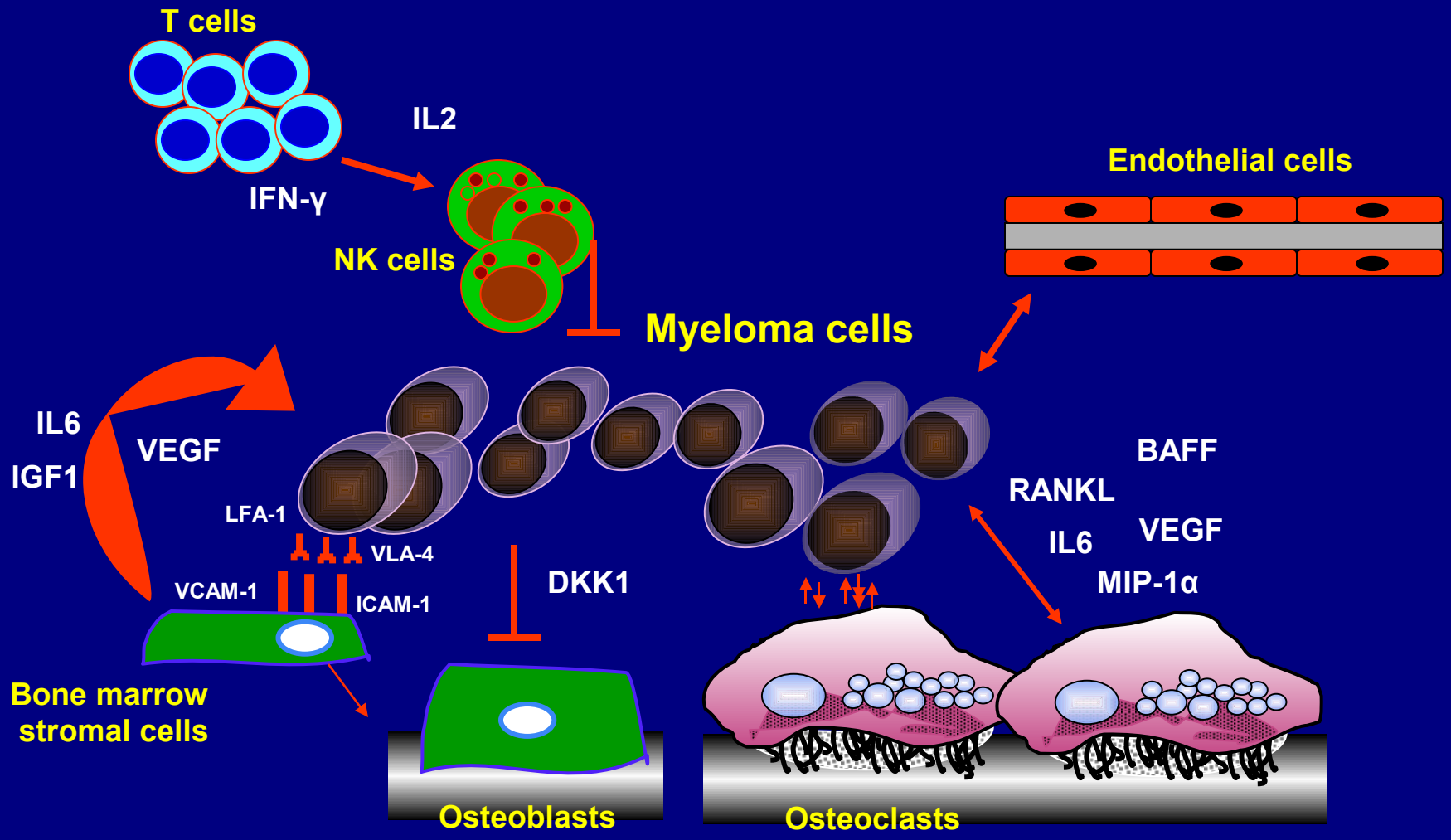
MGH Cancer Center



MASSACHUSETTS GENERAL HOSPITAL

CANCER CENTER

Clonal plasma cell proliferation:
microenvironment-dependent



Bisphosphonates in MM

- Inhibit bone resorption
- Pamidronate better than placebo
- Pamidronate and Zoledronic Acid equivalent

ONJ :Clinical features:

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

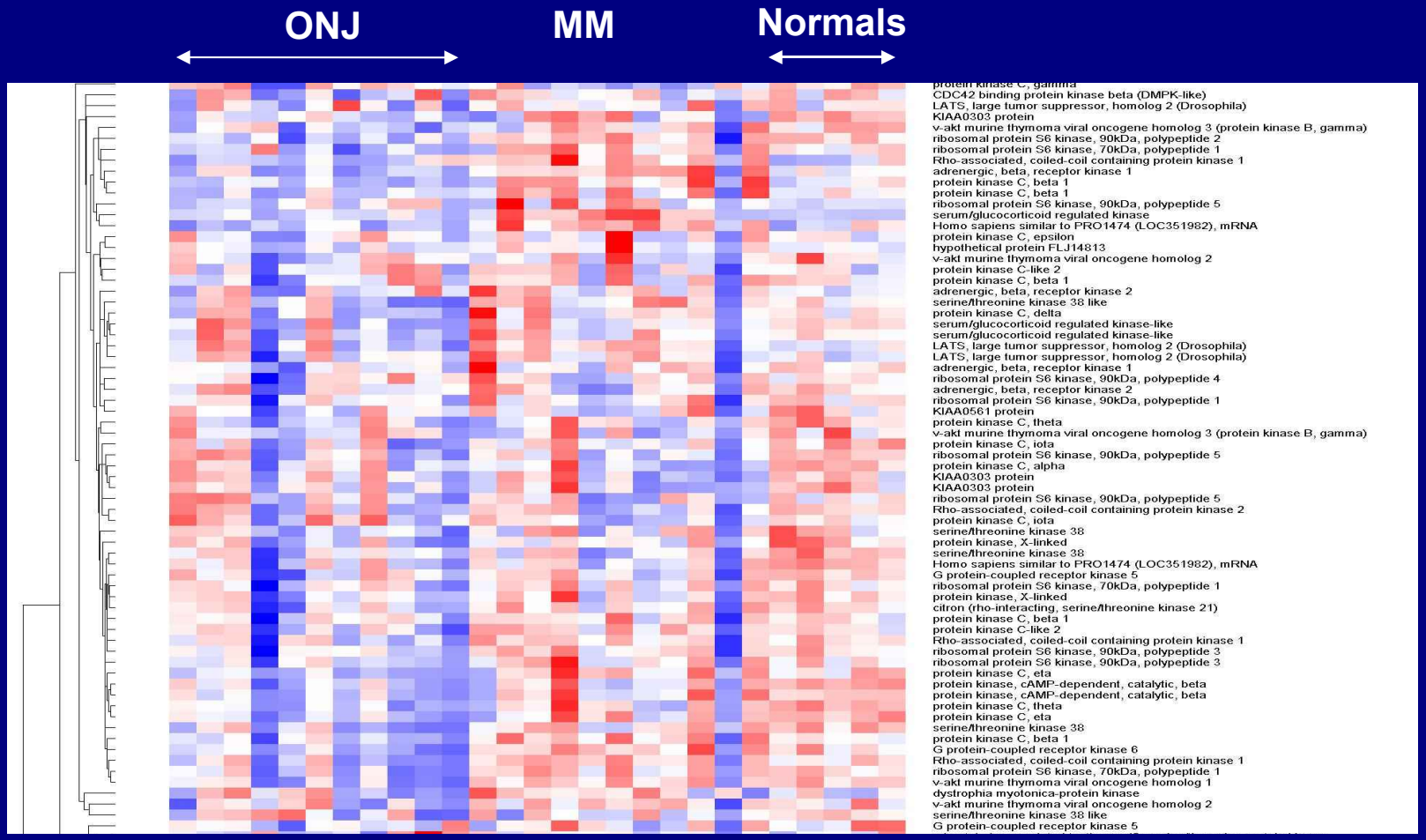
ASCO Clinical Practice Guidelines: Update

- 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

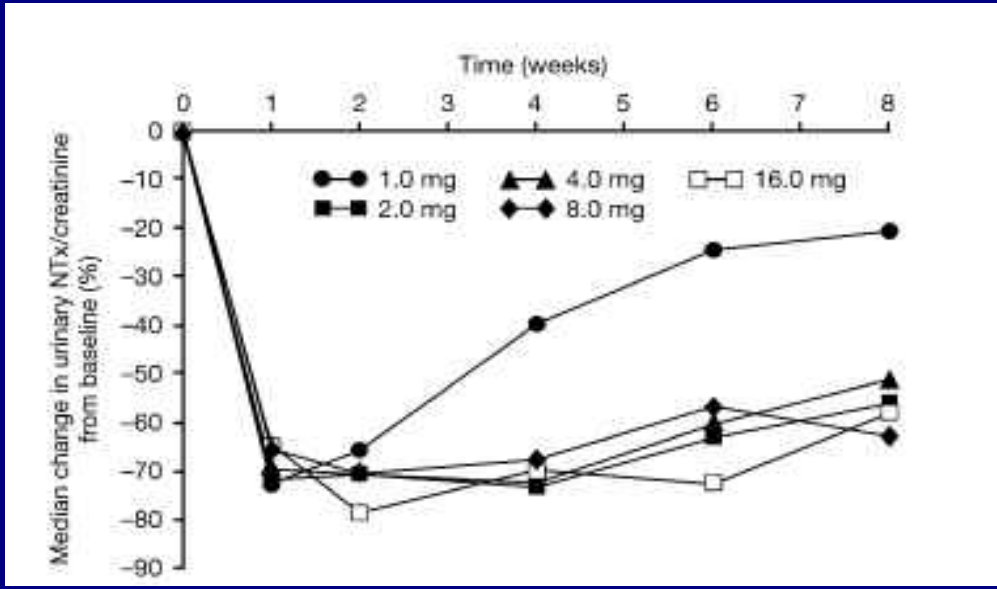
Biochemical and GEP studies suggest inhibition of bone formation

PROTEIN KINASE C FAMILY



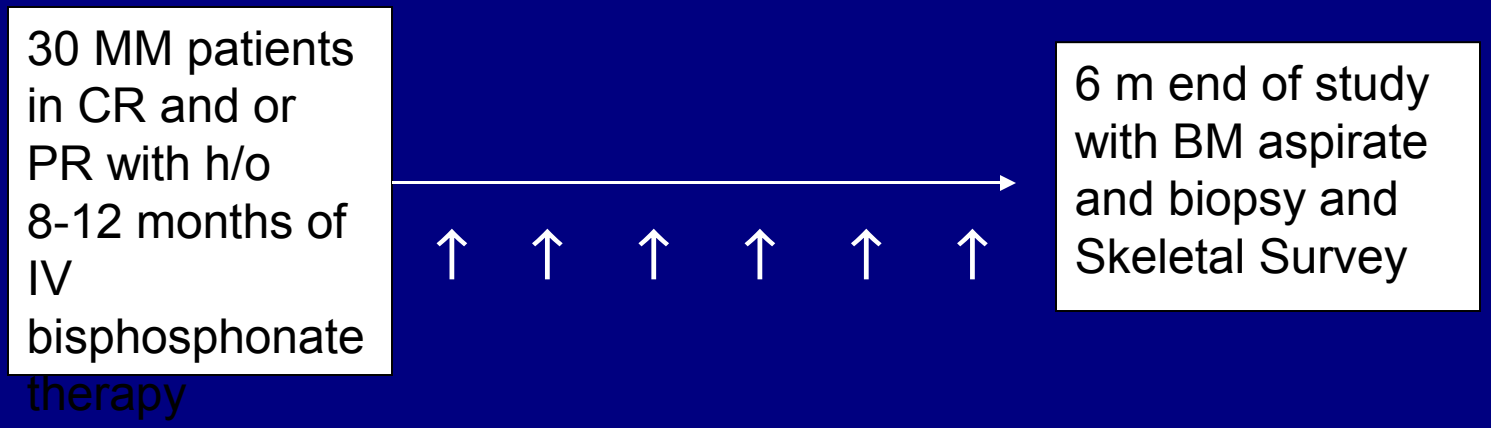
Raje et al. Clin Can Res 2008

Ntx levels stay suppressed for upto 8 weeks following a single dose of zoledronic acid.



Berenson et al, 2001; Chen et al, 2002

Pharmacodynamic Study of Zometa in MM

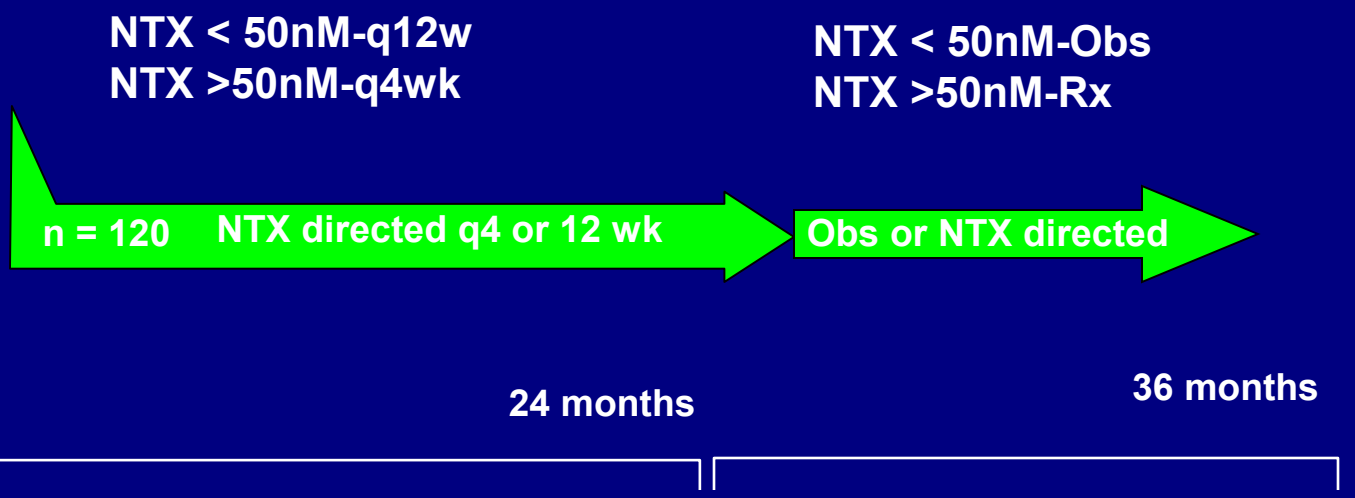


Baseline NTX followed by monthly x 6
Serum Markers followed by monthly x 6
BM aspirate and core
Skeletal Survey
Zoledronic acid single dose

Phase IV ZMARK Trial

Multiple Myeloma
BP treated:
Upto 6 -24mo

N = 120



* Primary efficacy endpoint: Time to first SRE

Denosumab in MM

- Phase I study completed
- Phase II: Treatment of Relapsed/Plateau phase MM

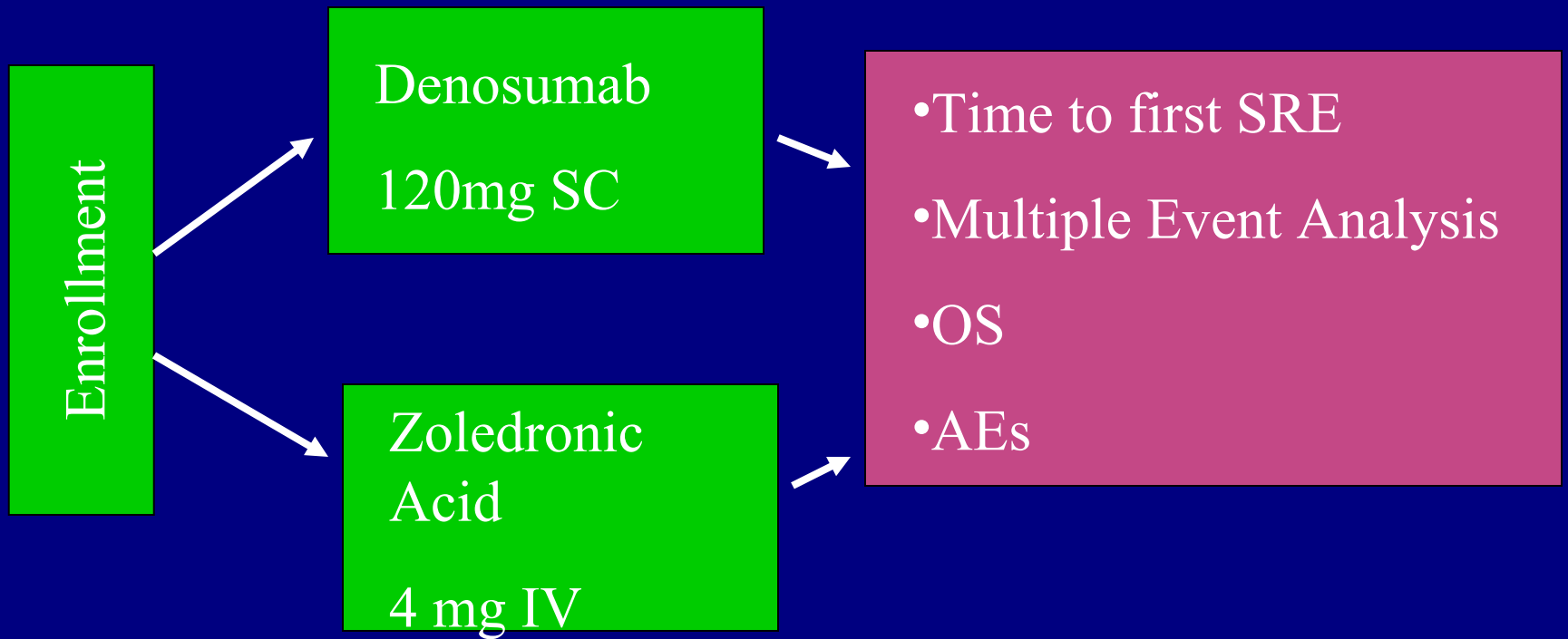
96 patients 53 R and 43 P-no effect on paraprotein

Decrease in sCTX levels by 50-70% for upto 7 months

Vij R et al, Blood 2007;110:1054A

Denosumab in MM

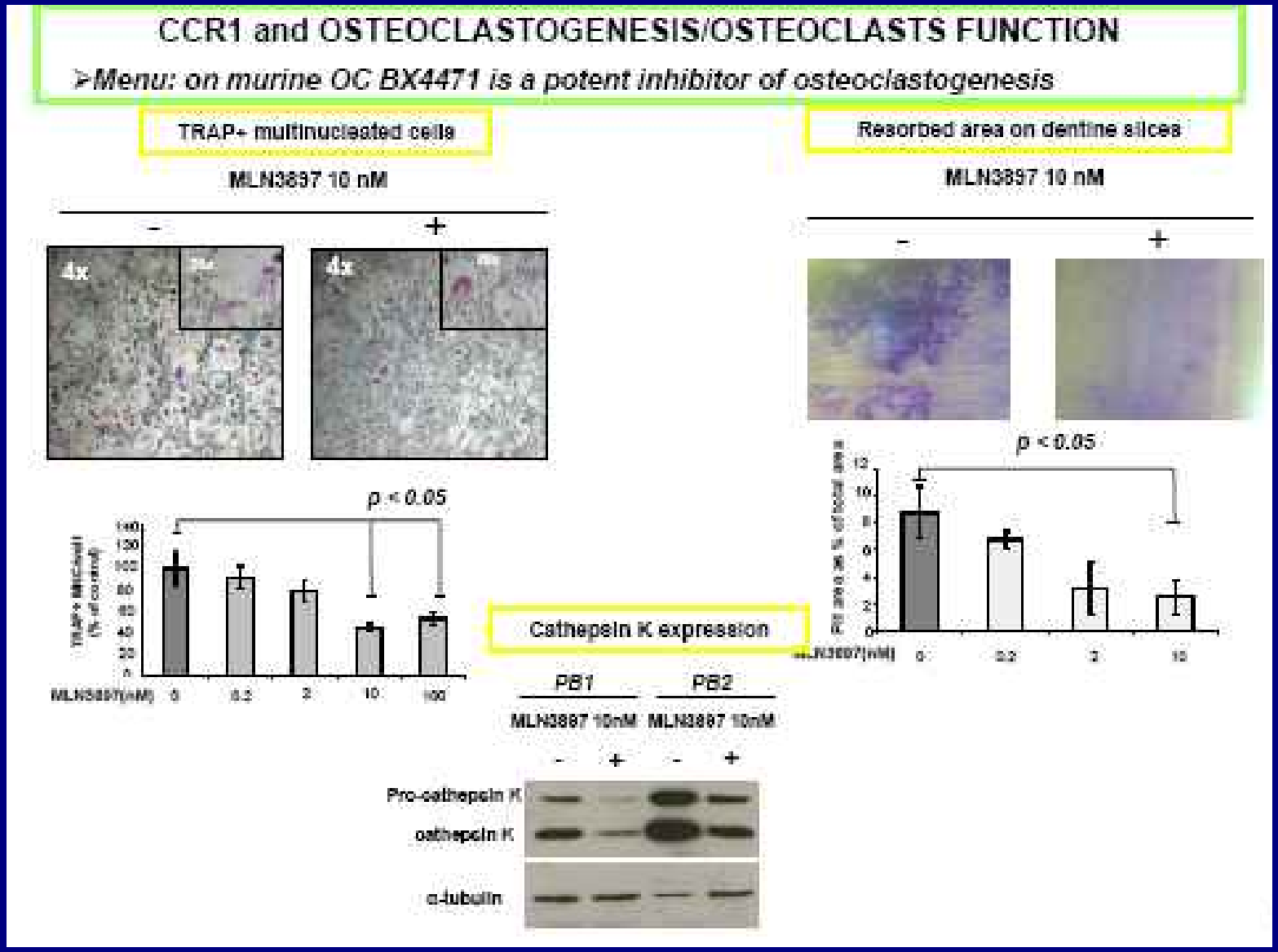
- Ongoing phase III trial in patients with advanced cancer with bone metastasis



MLN 3897, A NOVEL CCR1 INHIBITOR

- Small molecule, CCR1 antagonist
- Highly specific for human CCR1, IC50= 0.8 nM; CCR5, IC50 = 4μM.
- No inhibition of RAF, AKT or receptor tyrosine kinase up to 10μM
- Long half-life= 2-3 days
- Oral available

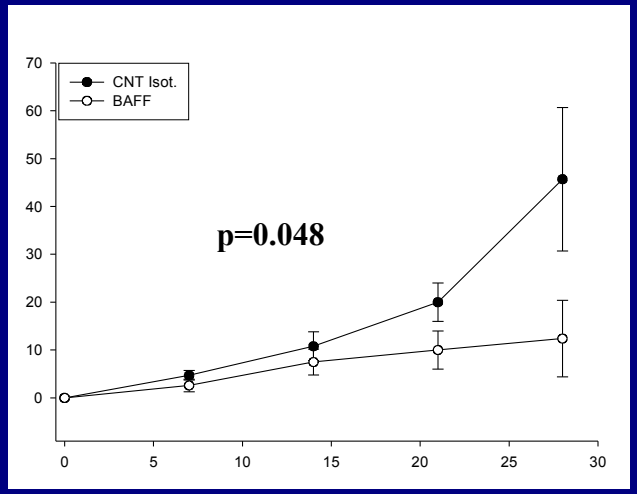
MLN3897 inhibits Osteoclastogenesis



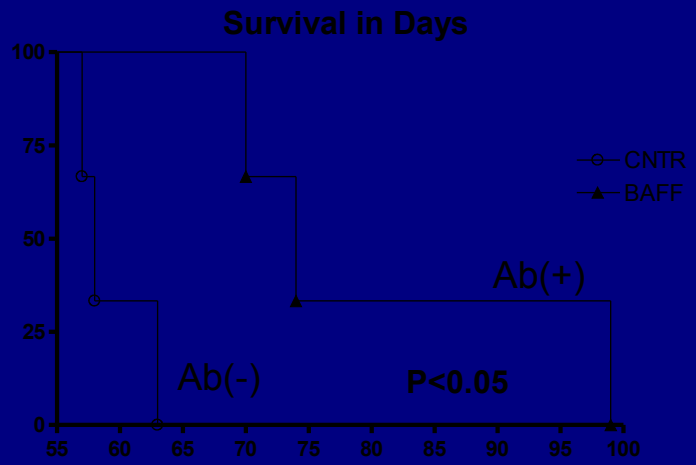
Vallet et al, Blood 2007

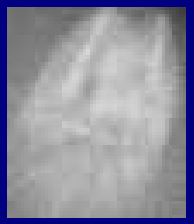
Anti-BAFF Neutralizing Ab Prolongs Survival and Inhibits Osteoclasts in SCID-Hu Model of MM

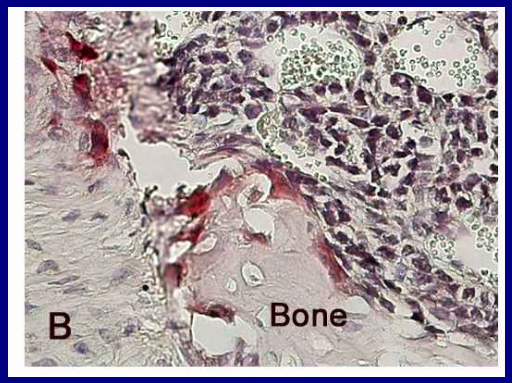
Control Animal



Anti-BAFF Ab-Treated

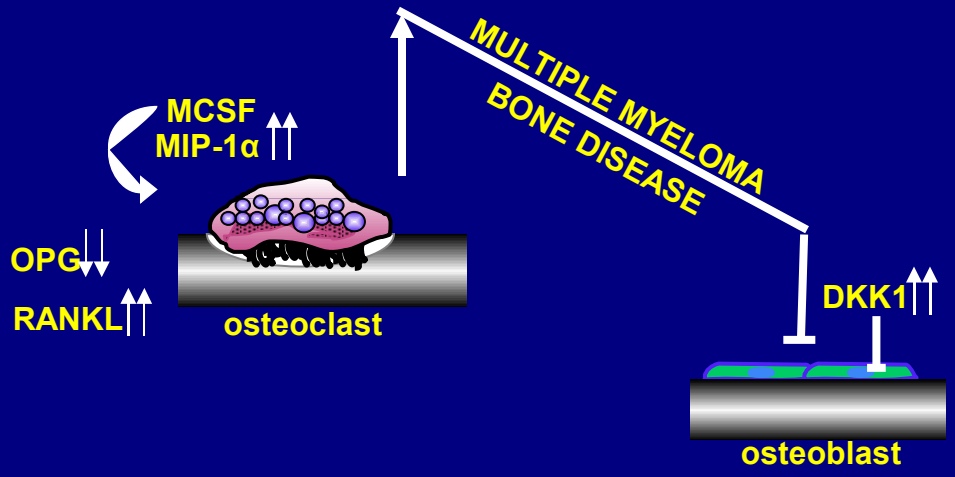






Neri et al. Clin Can Res 2007

Myeloma Bone Remodeling



Bortezomib and Bone Disease

A Clinical Insight

Velcade (Bortezumib is a proteasome Inhibitor known to be active in MM

Velcade responsive patients show Activation of B-alk-Phos

Alk-Phos responsiveness is a predictor of MM response

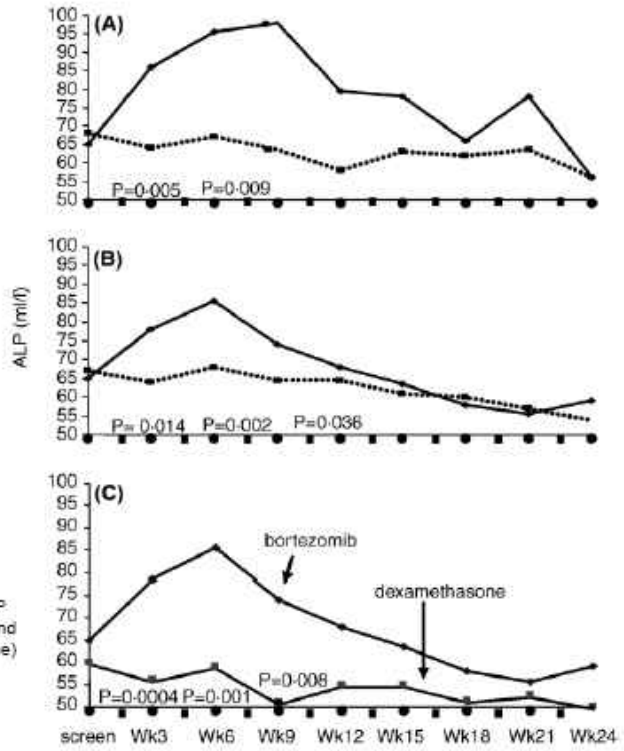
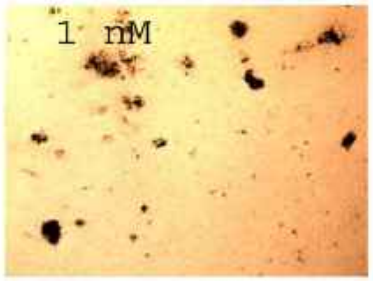


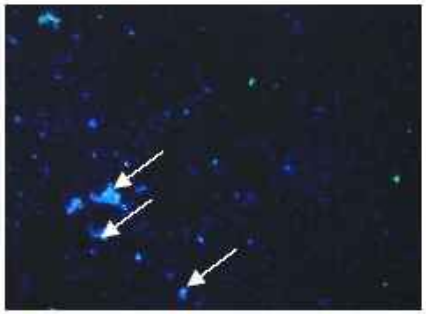
Fig 1. Median levels of ALP in responders (solid line) and non-responders (broken line) patients enrolled in the M34100-025 [summit trial (A), within the bortezomib arm of the M34101-039 (APEX) trial (B), and within responder patients of bortezomib and dexamethasone arms of the APEX trial (C)].

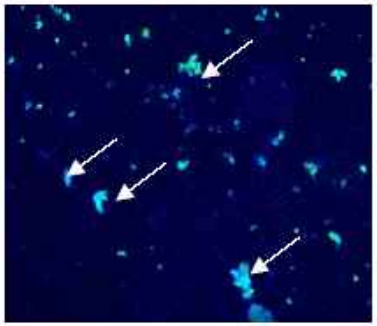
Bortezomib induces OBL Differentiation

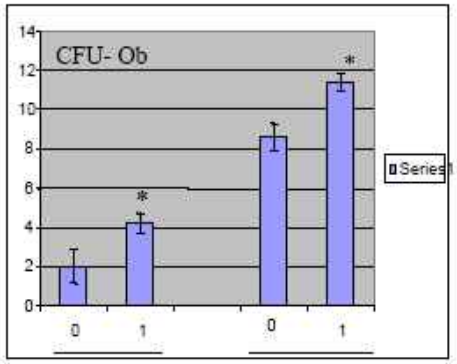
Bortezomib affects VanKossa+ colonies, CFU-Ob and Collagen+ colonies

VanKossa stain





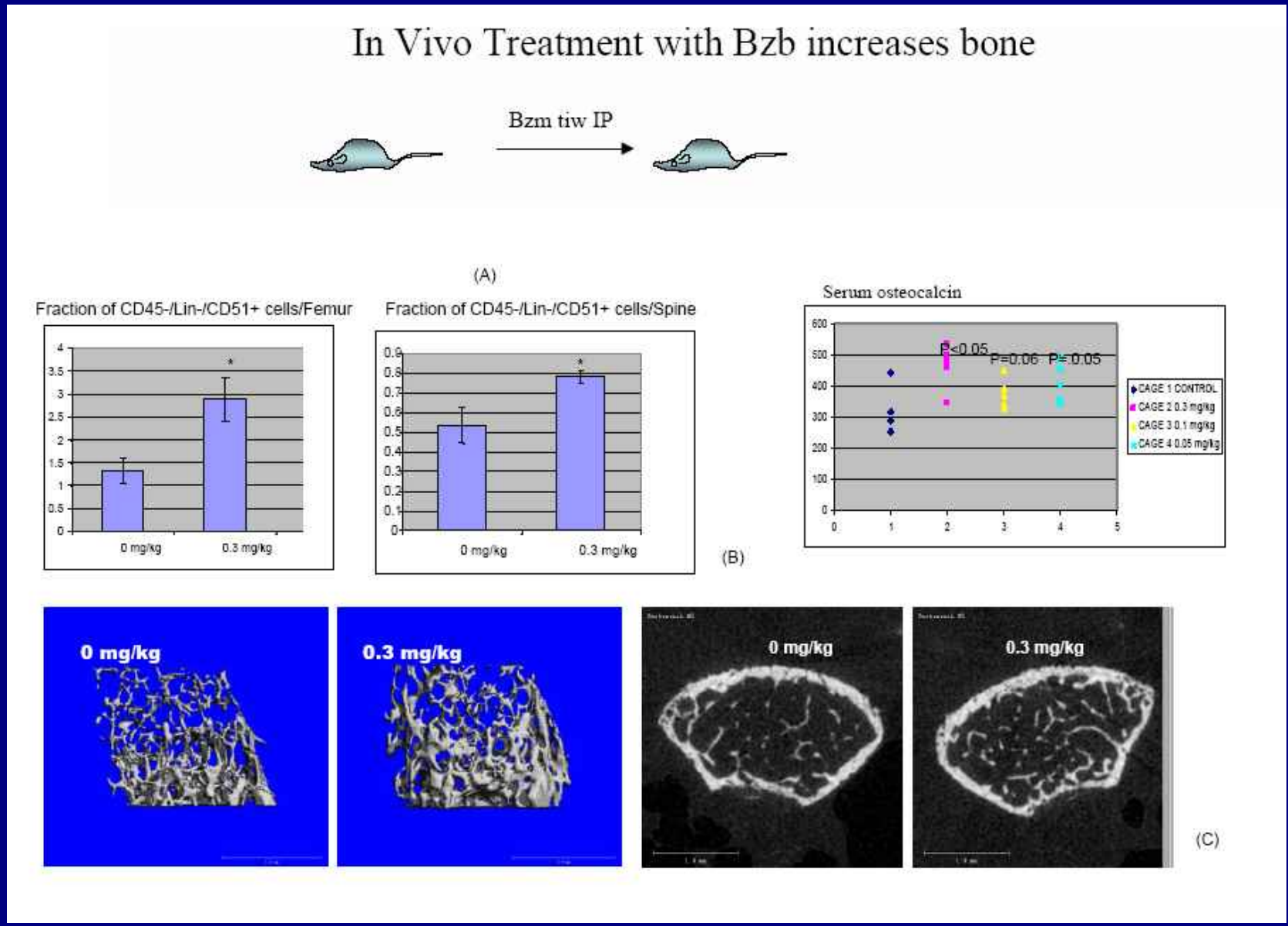




Collagen 1 stain

Mukherjee et al. J Clin Inv 2008

Bortezomib induces OBL Differentiation

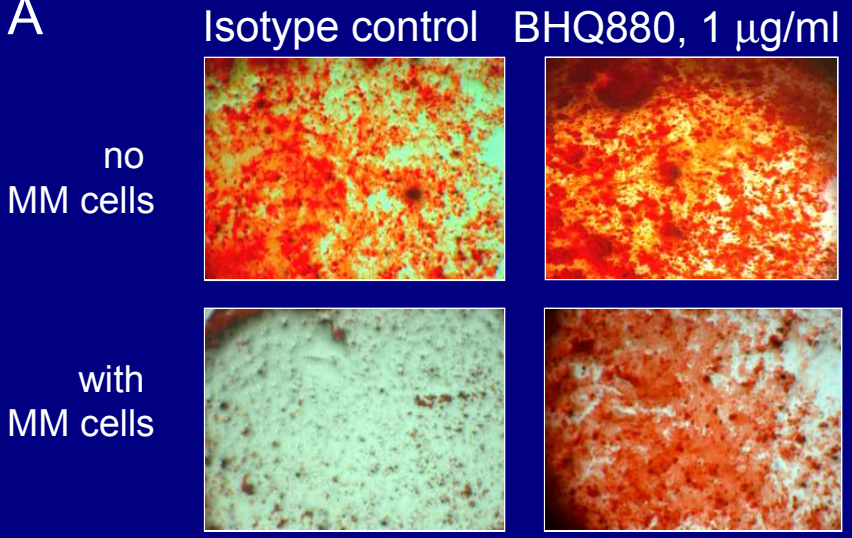


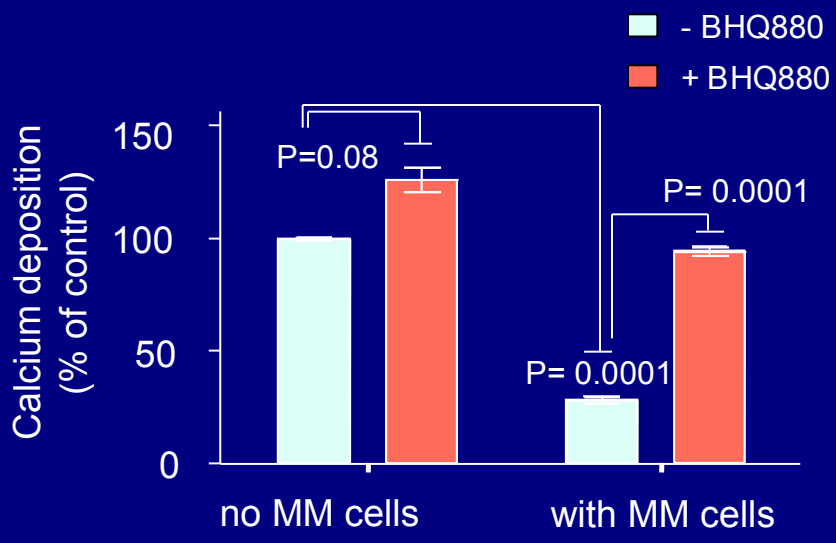
Mukherjee et al. J Clin Inv 2008

Phase I Study of LY2127399(Anti-BAFF Ab) antibody in combination with Velcade in the treatment of relapsed/ refractory Multiple Myeloma

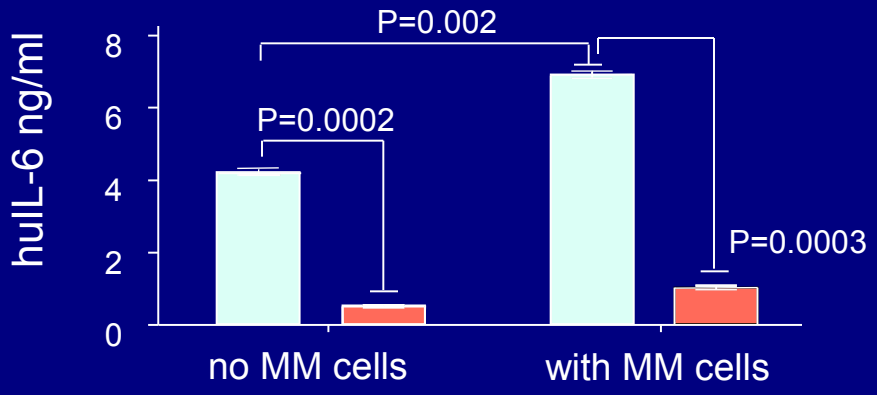
Anti-DKK-1 BHQ880 Reverses the Inhibitory Effect of MM Cells on Osteoblastogenesis

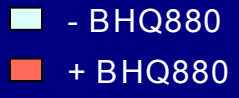
A





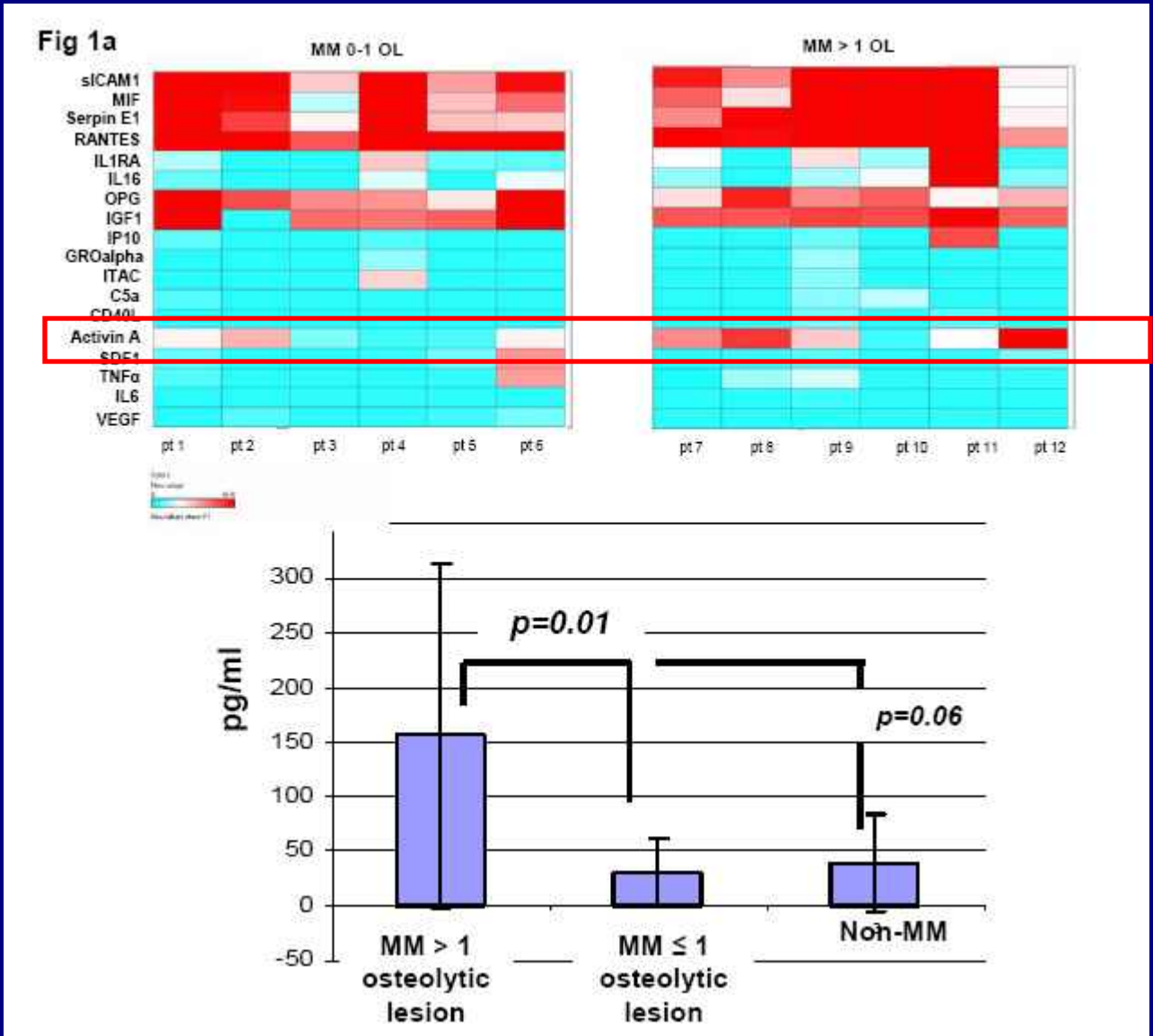
B



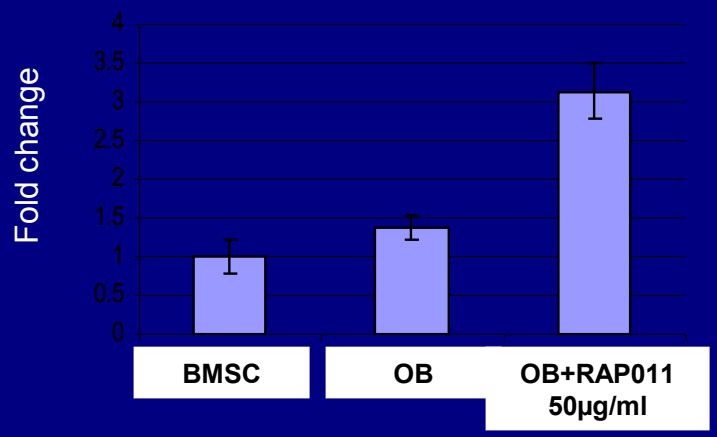


Fulciniti et al Blood 2009

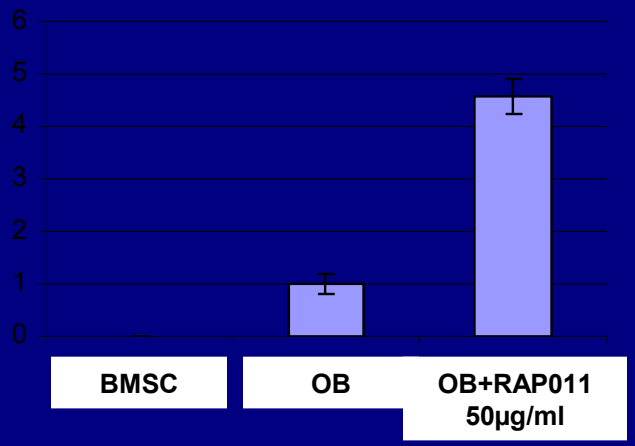
Activin A levels are increased in osteolytic disease



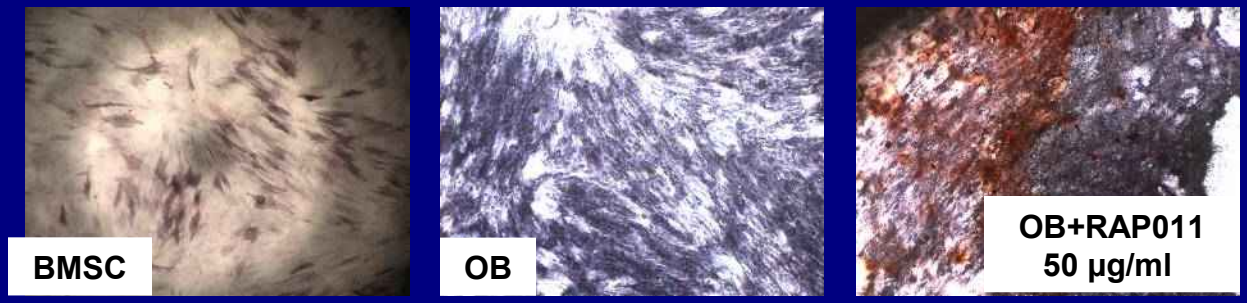
Induction of alkaline phosphatase mRNA expression, day 7



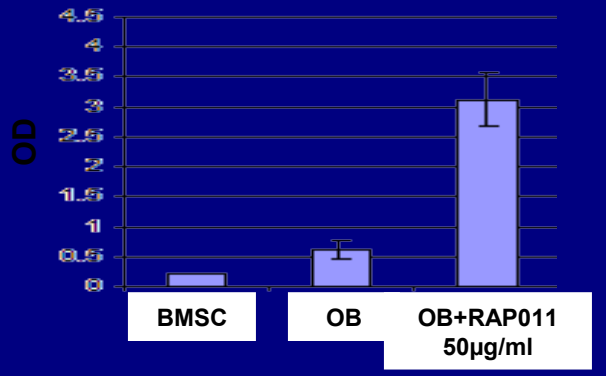
Induction of osteocalcin mRNA expression, day 14



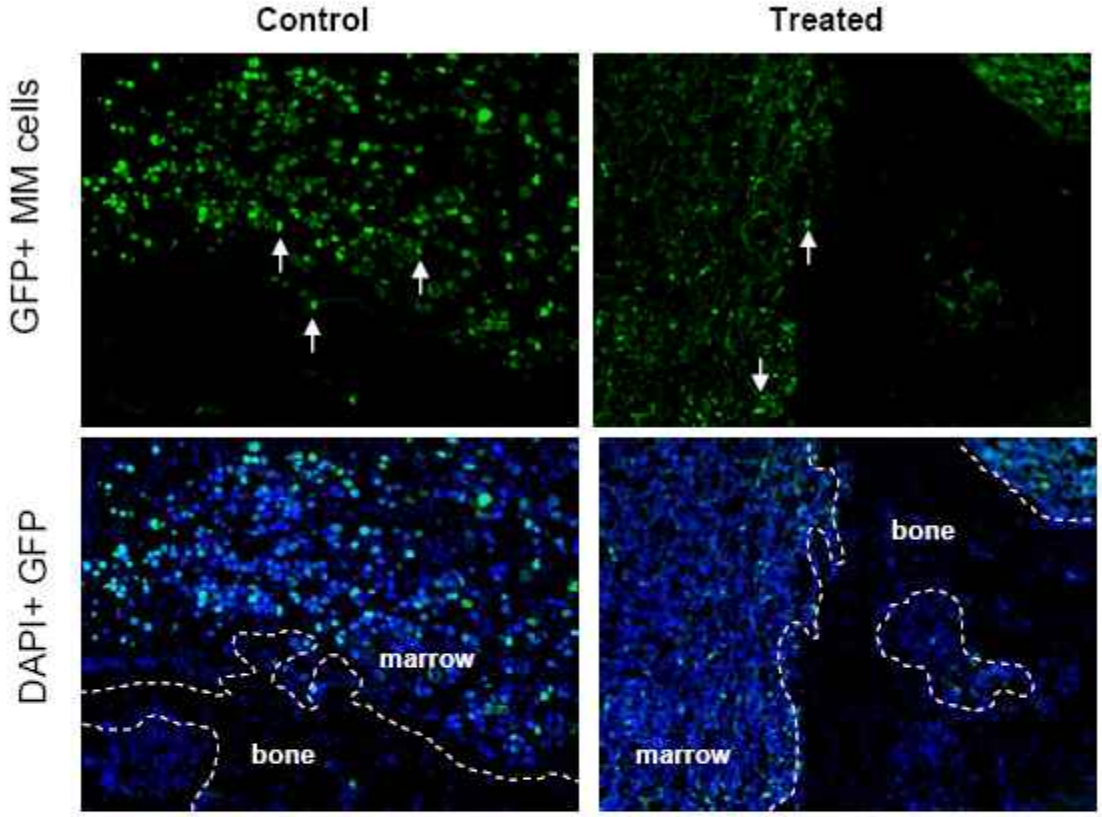
Dual staining for ALP and calcium at day21

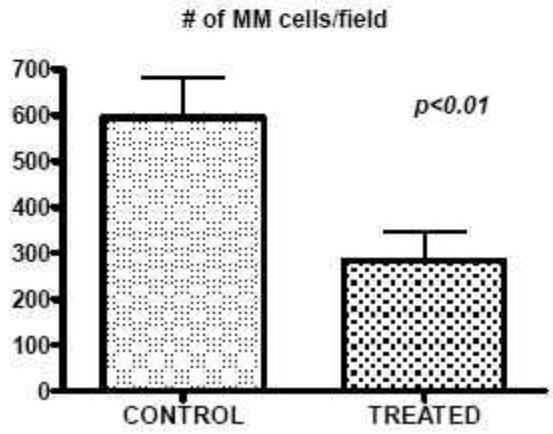


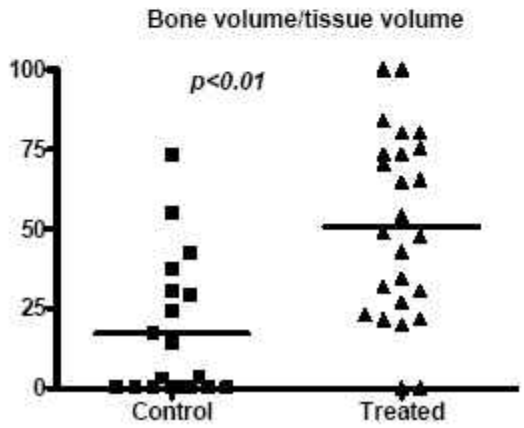
Enhanced calcium deposition, day 14



RAP-011 STIMULATES OB FUNCTION



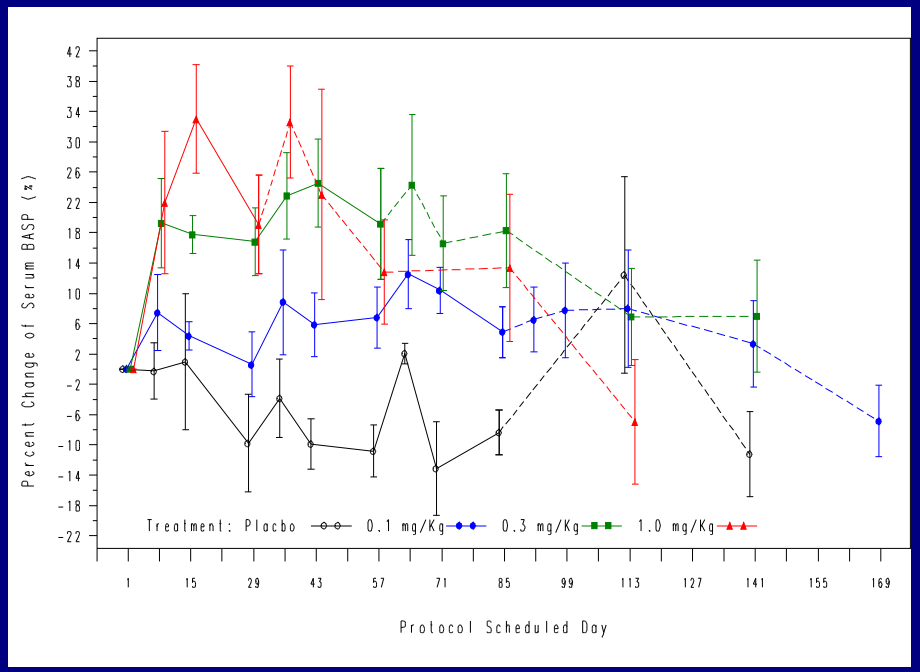




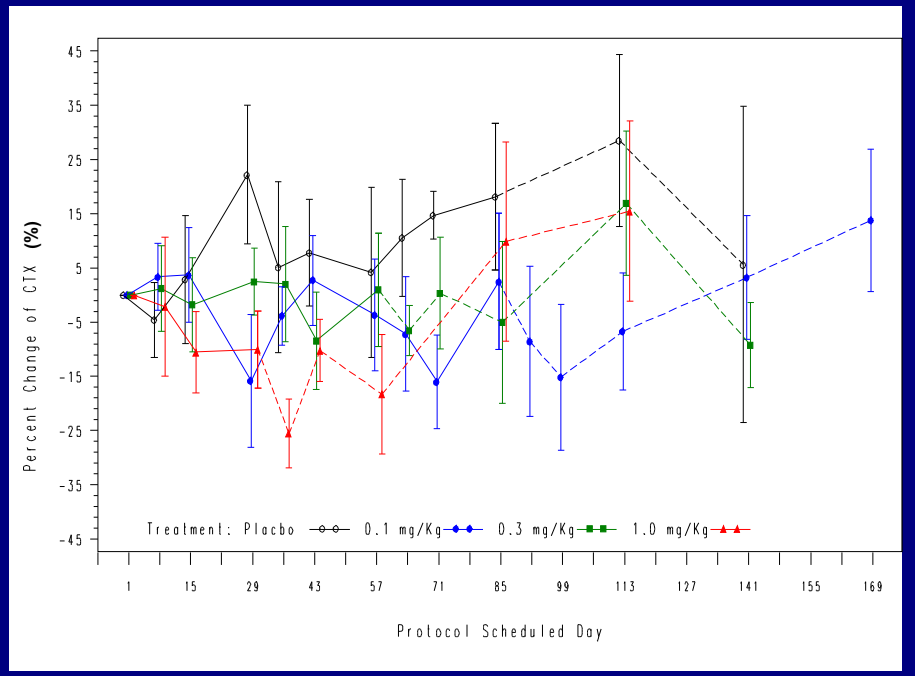
RAP-011 STIMULATES BONE FORMATION AND HAS INDIRECT ANTI-TUMOR ACTIVITY IN AN INVIVO MM MODEL.

ACE-011 Effect on Bone in Healthy Volunteers

ACE-011 Increases Markers of Bone



ACE-011 Decreases Markers of Bone

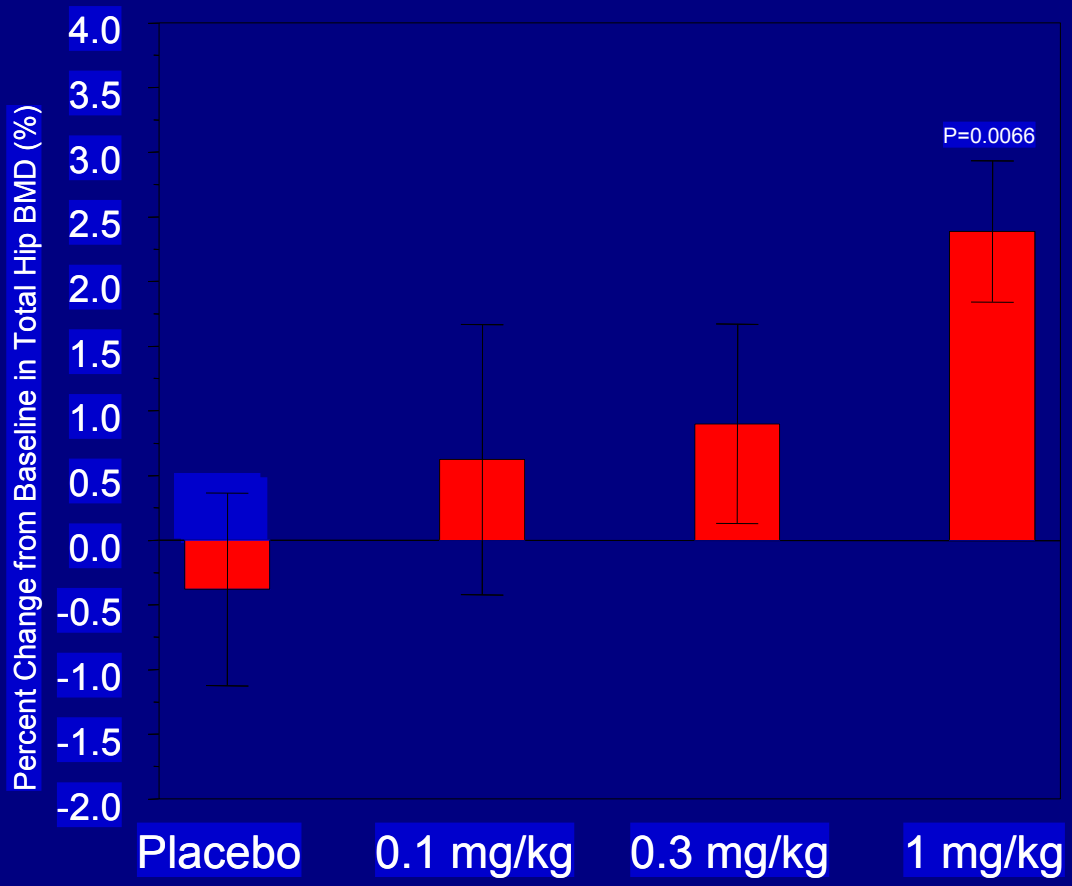


ACE-011 SC 4 doses every 4 weeks

Data Presented at 2008 San Antonio Breast Cancer Symposium # 1160 Courtesy;Acceleron and Celgene

ACE-011 generates Rapid and Significant Increases in BMD

ACE-011 Generates Significant Increases Total Hip BMD



Data Presented at 2008 San Antonio Breast Cancer Symposium # 1160
Courtesy;Acceleron and Celgene

A Phase 2 Study in Multiple Myeloma is Currently Underway

Study Title

A Phase 2, Multi-Center, Randomized, Multiple-Dose Study to Evaluate the Safety, Tolerability and Efficacy of ACE-011 (hActRIIA-IgG1) in Patients With Osteolytic Lesions of Multiple Myeloma

Study Objectives

- To evaluate the safety and tolerability of multiple doses of ACE-011 in patients with multiple myeloma and determine the effect of ACE-011 on biochemical markers of bone formation and resorption
- To determine the pharmacokinetics (PK) of multiple doses of ACE-011 in patients with multiple myeloma, assess skeletal-related events and evaluate bone pain

Study Design

- Randomized, Double-Blind, Placebo Controlled
- Dose-Ranging, Multiple Dose, Parallel-Assignment
- N=30

www.clinicaltrials.gov (ID: NCT00747123)

Future Directions

- Optimize duration of BP therapy
- Incorporate Novel Imaging

- Use of novel agents---
  - RANK Ligand inhibitors
  - Bortezomib
  - MIP1alpha inhibitors
  - DKK1 inhibitors
  - RAP011

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Nikhil Munshi

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Teru Hideshima

Dharminder Chauhan

Our Patients

Clinical Team