

## PTH and PTH Combination therapy for osteoporosis

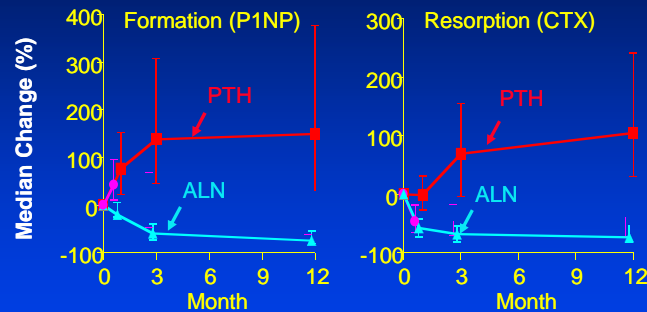
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## Disclosures D. Black

Research Funding: Novartis, Roche

Consulting: Nycomed

## Anabolic therapy *increases* bone remodeling rates



\* PaTH study, Black, et. al, NEJM, 2002

## Background: Types of PTH

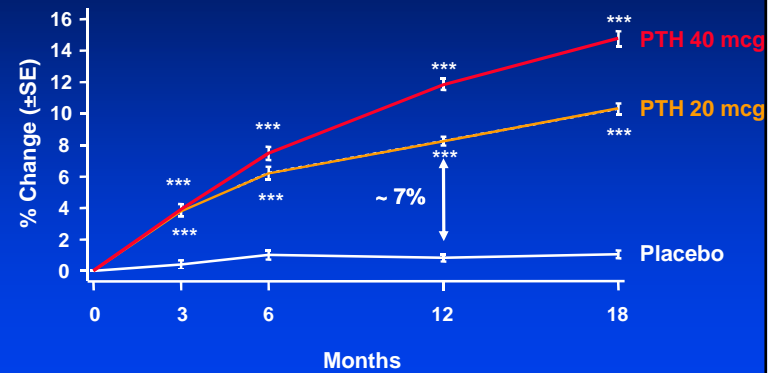
- 84 amino acid sequence
- Most of bone activity in first 34 amino acids
  - PTH 1-34 (teriparatide) approved @ 20 mcg/day
  - PTH 1-84 studied @ 100 mcg/day (not available in US)
  - Other fragments in development
- Response is very dose-dependent
- All require (currently) daily injection

## PTH (1-34) (Teriparatide) Fracture Prevention Trial

- 1637 PM women
- Randomized to PBO, rPTH(1-34) 20 ug or 40 ug
- Fractures primary endpoints
- 3 year study, halted after 21 mos (median)
  - Safety problem with high doses in rodents
- Teriparatide, only anabolic in US

Neer RM, et al. NEJM, 5/2001

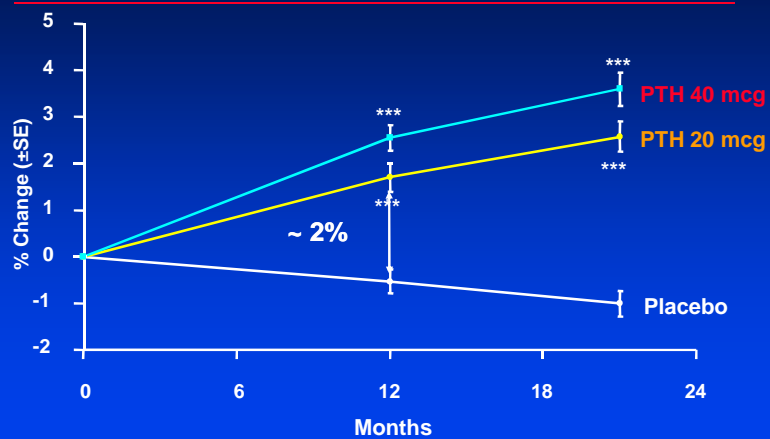
## Effect of PTH 1-34 on Lumbar Spine BMD



Neers, NEJM

\*\*\* p < 0.001 vs. Placebo

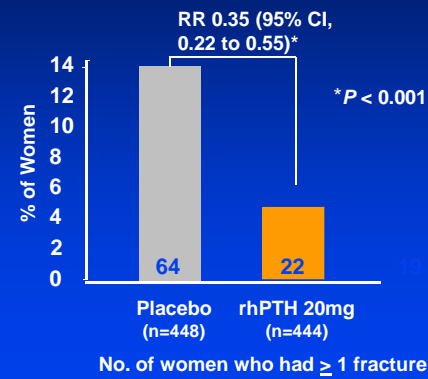
## Effect of PTH 1-34 on Total Hip BMD



Neer, NEJM

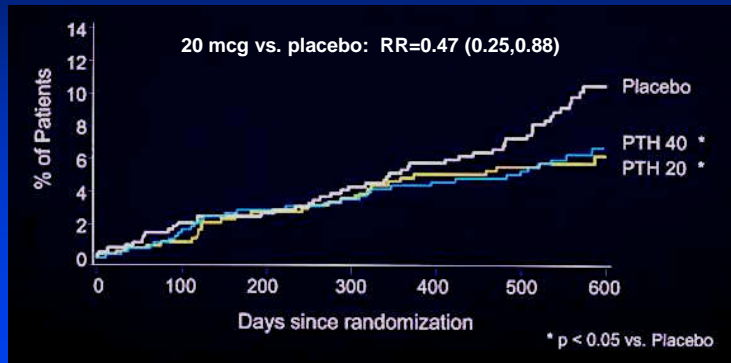
\*\*\* p < 0.001 vs. Placebo

## Effect of rhPTH(1-34) On The Risk of New Vertebral Fractures



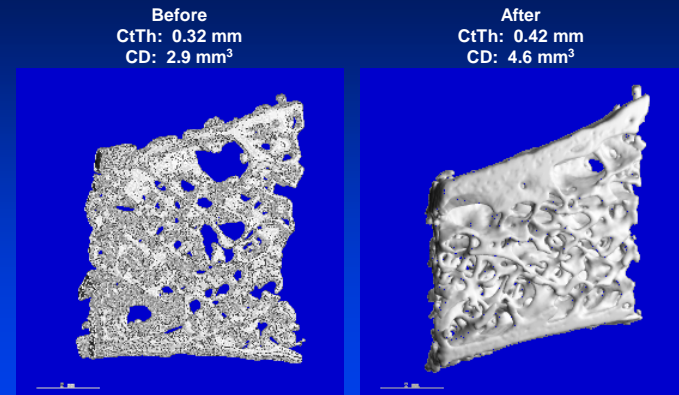
Neer et al. N Engl J Med. 2001;344:1434-1441.

## PTH 1-34 and reduction in Non-vertebral Fragility Fracture



Adapted from Neer et al. *N Engl J Med.* 2001;344:1434-1441.

## Histomorphometry-- Effect of PTH 1-34 in a 64-Year-Old Woman



Dempster DW et al. *J Bone Miner Res.* 2001;16:1846-1853.

## Dose of PTH (1-34) (teriparatide)

- 40 mcg more effective on BMD
- 20 and 40 mcg similar fracture reduction
- More side effects (e.g. nausea, dizziness) with 40 mcg dose
- 20 mcg approved

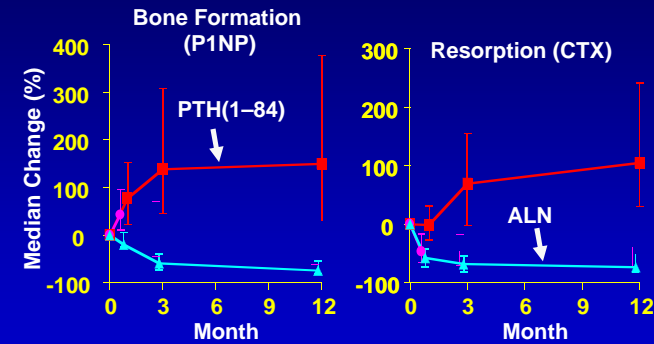
## PTH as clinical treatment for osteoporosis

- PTH very effective in increasing BMD and decreasing bone strength
- Approved for up to 2 years duration
- Limited adoption in clinical practice
  - Cost (~\$7000/year)
  - Need for daily injections
- New molecules (different fragments), delivery modes under development
- May become more widely used
  - Shorter courses of therapy
  - In combination with antiresorptive

## Clinical question: Combination of PTH with antiresorptives?

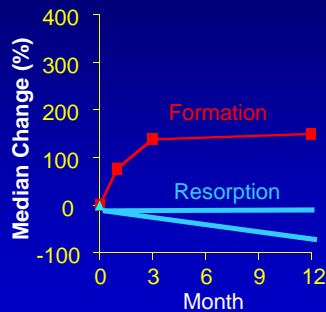
- PTH increases formation, then resorption
- Antiresorptives decrease resorption, then formation
  - Combine PTH with antiresorptives to increase formation with smaller increase in resorption
- Could be synergistic:  $1 + 1 = 3\dots$
- Or cancel each other:  $1 + 1 = 0$

## Impact of PTH vs. bisphosphonates on bone formation (PaTH) study\*

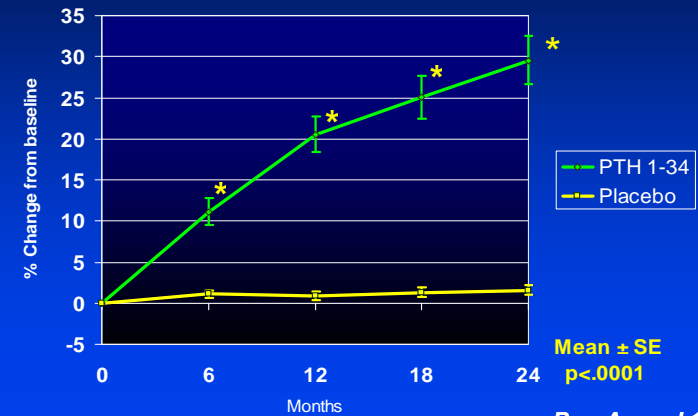


\*Black, et al. *New Engl J Med* 2003;349:1207-15

## The Holy Grail for Combination therapy



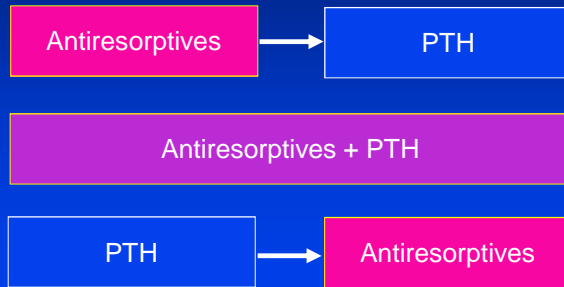
## Effect of PTH 1-34 (40mcg) on spine BMD by DXA in women taking estrogen + progestin



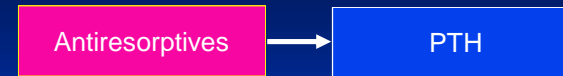
Roe, Arnaud 1999

## Clinical question: combination of PTH (1-84) with antiresorptives?

- 3 distinct possibilities

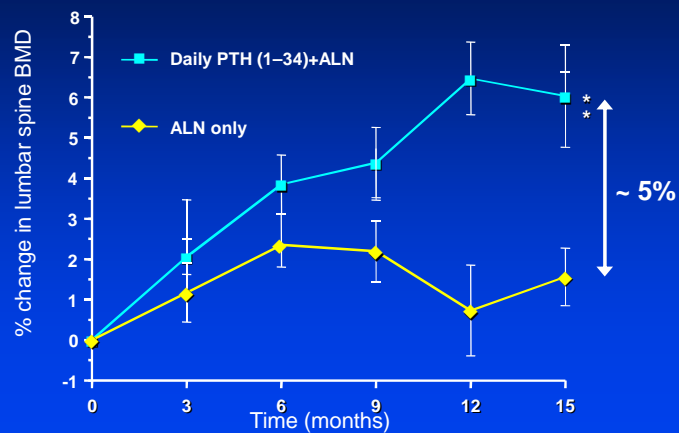


## PTH Combination #1



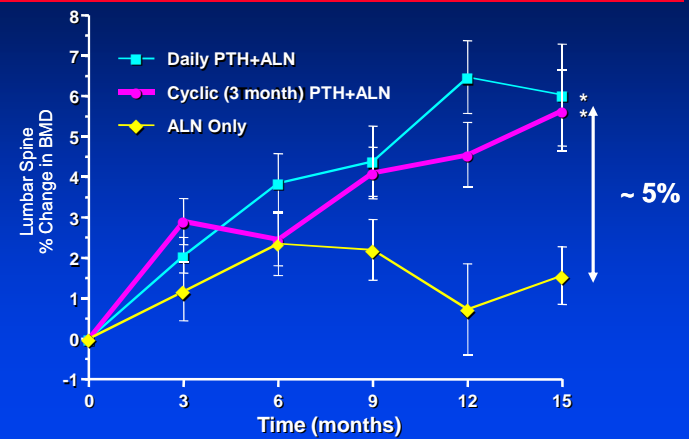
- Pre-treatment with antiresorptives followed by PTH
  - Key clinical question
  - Many patients on bisphosphonates and other antiresorptives

## PTH (1-34) added to ongoing alendronate: lumbar spine BMD (% change)



\*Cosman F et al. *N Engl J Med* 2005;353:566-75.

## 3 month on-off cycles of PTH(1-34): Lumbar Spine BMD



\* p<0.05 Change from Baseline ALN Only vs both PTH groups

## PTH following bisphosphonates

Several additional studies in 2006-07

Similar conclusions:

### - Anabolic effect still evident and strong

Magnitude somewhat blunted compared to treatment naïve patients

May be similar whether or not antiresorptive is continued

## PTH combination # 2

Antiresorptives + PTH

- Concurrent initiation of PTH and antiresorptives (treatment-naïve women)
- PaTH year 1\*:
  - PTH vs PTH & ALN

\*Black DM et al. *N Engl J Med* 2003;349:1207–15.

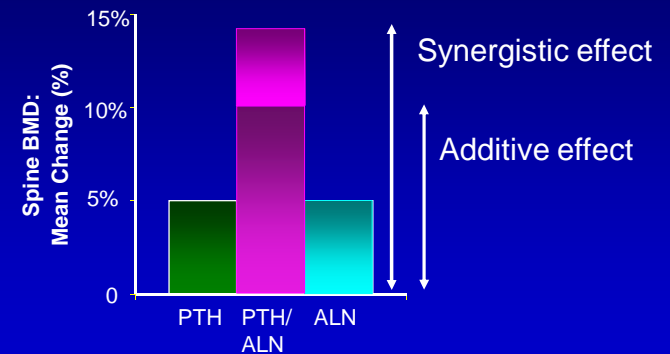
## PTH and Alendronate (PaTH) study:

- 238 post-menopausal women with osteoporosis
  - Treatment naïve
- Randomized to four treatment groups for 2 years
- Combination of PTH 1-84 and daily alendronate

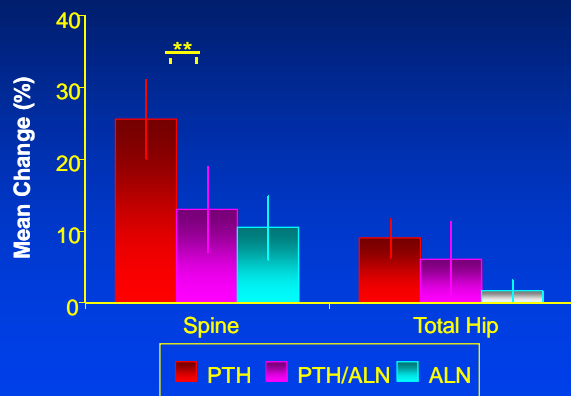
N	Year 1	Year 2
59	PTH(1–84)	PLB
60	PTH(1–84)	ALN
59	PTH(1–84) + ALN	ALN
60	ALN	ALN

\*Black, et al. *New Engl J Med* 2003;349:1207–15

Hypothesis: PTH + Alendronate will increase BMD much more than either alone



## Changes in Trabecular Volumetric BMD by QCT (g/cm<sup>3</sup>)



\*\* p<.01

NEJM 2003

## Concurrent initiation of PTH with antiresorptives from PaTH: summary

- No advantage to concurrent use of PTH with (daily) alendronate compared to monotherapy with PTH alone
- Anabolic effect of PTH, particularly on trabecular bone, is blunted by concurrent use with alendronate
- To be studied:
  - Does less frequent or less potent antiresorptive work better with PTH?

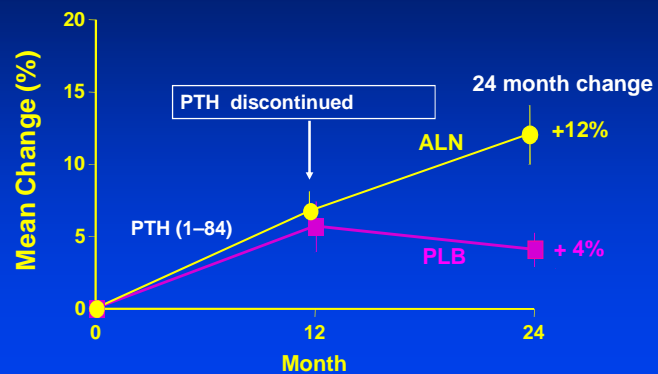
## Combination studies #3



- Use of antiresorptives following PTH
- PaTH: 1 year of PTH followed by 1 year of ALN or placebo

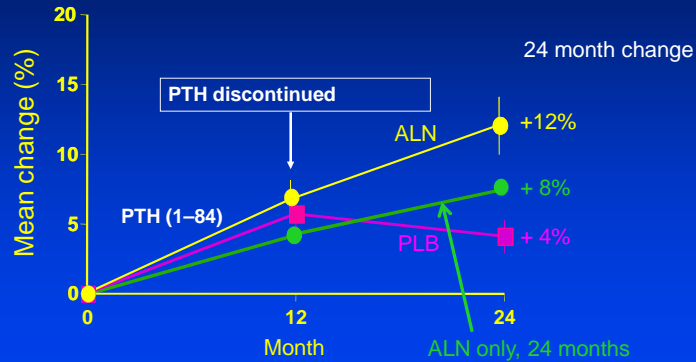
Black DM et al. *N Engl J Med* 2005;353:555–65.

## Change in DXA spine BMD over 24 months



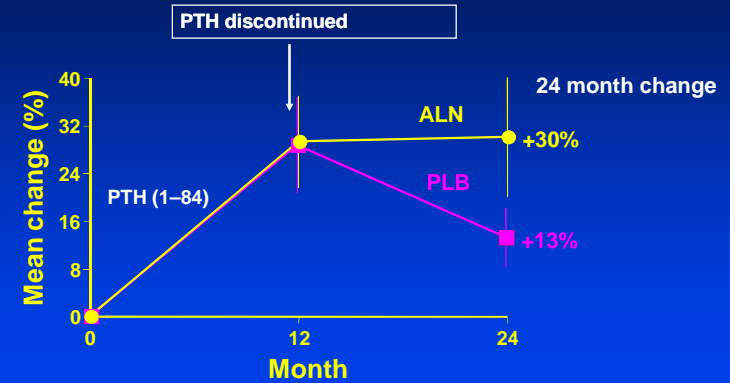
Black DM et al. *N Engl J Med* 2005;353:555–65.

## Change in DXA spine BMD over 24 months of treatment



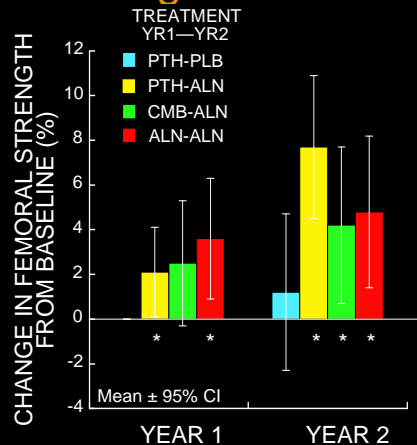
Black DM et al. *N Engl J Med* 2005;353:555-65

## Change in QCT trabecular spine BMD over 24 months



Black DM et al. *N Engl J Med* 2005;353:555-65

## Finite element modeling of femoral strength in PaTH new



Keaveny et al. *JBMR*, 2008

\* P<0.05 within group from baseline

## What to do following PTH treatment?

- PTH followed by nothing will result in the loss of most, if not all, gains
- Bisphosphonates seem to add to BMD gains
- Clinical conclusion: Follow PTH with some form of antiresorptive therapy
- Many interesting future BMD studies



## Some Limitations on what we know about PTH combination

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- BMD/Marker studies only: no fracture data
- Most of studies with alendronate
  - Other bisphosphonates and other a/r's may differ
- Most studies with daily bisphosphonates
  - Weekly, monthly, yearly may be different
  - New study with once per year ZOL was similar

## Combination of PTH Therapy with Antiresorptives: Conclusions

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- Rapidly growing literature of BMD (not fracture) trials
- In patients on antiresorptive therapy, increases in bone formation and BMD with PTH after A-R's
  - Some blunting of response to PTH depending on type of previous A-R
- PTH therapy followed by anti-resorptives seems to maximize BMD gains
- When PTH initiated, probably best alone
- More studies (particularly of other A-R's) needed (some in progress)

## Future of Anabolic Therapy

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- Teriparatide (PTH(1-34)) will soon be off patent
  - Might be more widely used at lower cost
- Other forms and delivery methods being developed (oral, nasal, patch) but not clear that any will succeed
- Other anabolic therapies being studied (not PTH or analogues)...Steve Cummings to discuss