Anabolics: First Line Osteoporosis Treatment for Patients at High Risk of Fracture

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Amgen: *Advising, Speaking, Research Grants and Medication*

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Radius: *Consulting, Advising, Speaking*

Tarsa/RPharm: *Consulting*

Objectives

- Who are the Highest Risk Patients?
- Rationale for First Line Anabolic Therapy in Highest Risk Patients
  - Review Pivotal Trial Data for Antiresorptives
  - Review Pivotal Trial Data for Anabolics
  - Overview Fracture Trials Comparing Anabolic and Antiresorptive Treatments
- Optimal Treatment Sequences in a Goal Directed Treatment Strategy

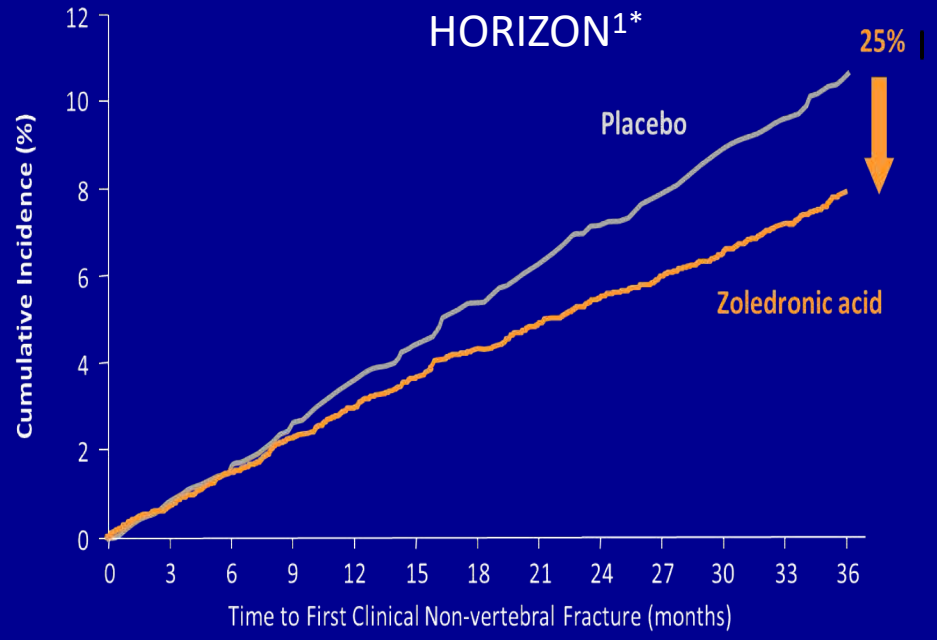
Who are the Highest Risk Patients?

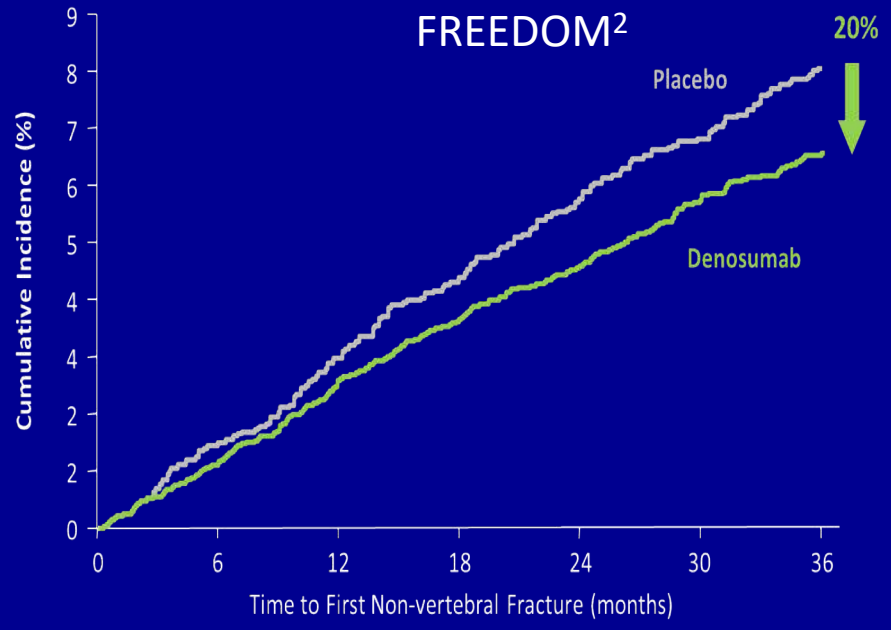
- Prior fracture is most important risk factor for another fracture[1]
  - Recent Fx suggest very high risk (Osteoporosis Emergency)
    - In over 377,000 women with first fx, absolute risk of another fracture:
    - 10% first year , 18% first 2 years, 31% first 5 years[2]
  - Multiple Fractures also very high risk[3]
  - Proactive Spine Imaging Required to find Vertebral Fractures
    - In NHANES VFA Study 2017, vertebral Fx prevalence:
    - 5% in the 60s, 10% in the 70s, 20% in the 80s[4]
- People with very low BMD: high long-term risk for fracture
  - not necessarily high imminent risk

1. Kanis J Bone 2004
2. Balasubramanian A OI 2018
3. Gehlbach et al OI 20007
4. Cosman F et al OI 2017

Treatment of High Risk Patients: Limitations of Most Potent Antiresorptives

- For zoledronic acid[1] and denosumab[2]: nonvertebral fracture risk reductions at best 20%-25%
- No significant fracture risk reduction seen before 3 years





*STRATA I and II

1. Black DM et al. *N Eng J Med*. 2007;356:1809.

2. Cummings SR et al. *N Engl J Med*. 2009;361(8):756-65.

Treatment of High Risk Patients: Limitations of Antiresorptives

- Longterm bisphosphonates
  - Effect on fractures beyond 3-4 years inconsistent
  - BMD plateaus after 3-4 years and if $\leq$-2.5, patients still at risk [1-2]
- Longterm Efficacy with denosumab
  - low fracture rates after 3 years and continued increase in BMD after 3 yrs[3]
    - higher hip BMD predicts lower risk of future fx[4,] but may require very longterm therapy
- Longterm safety risks (AFF, ONJ) with both Dmab and BPs

[1] Cosman F et al JCEM 2014

[2] Black DM JAMA 2006

[3] Bone H et al. *Lancet Diab Endo*.2017.

[4]Ferrari S et al. ASBMR 2016

Anabolic Agents Produce Rapid Fracture Reduction

- From respective pivotal clinical trials:
  - Over median 19 months, Teriparatide[1]
    - Reduced vertebral fracture by 65%
    - Reduced nonvertebral fragility fx by 53%
  - Over 18 months, Abaloparatide [2]
    - Reduced vertebral fracture by 86%
    - Reduced nonvertebral fracture by 43%
  - Over 12 months, Romosozumab[3]
    - Reduced vertebral fracture by 73%
    - Reduced nonvertebral fracture by 25% (*P*=0.096)
      - 42% for ROW, excluding LA (p<0.05)

[1] Neer R et al NEJM 2001 [2] Miller P et al JAMA 2016[3] Cosman F et al. *NEJM*. 2016

Comparing Anabolic and Antiresorptive Agents

- Comparing across different studies with different populations, varying baseline characteristics and baseline risk problematic.
- What about data comparing anabolic with antiresorptive agents in head to head trials?

Fracture Outcome Studies
Anabolic vs Antiresorptive Agents

- Two Studies (Fracture Outcomes Not Primary Endpoints):
  - In Glucocorticoid Induced Osteoporosis:
    - Teriparatide reduced vertebral fractures by 90% compared to Alendronate over 18 months[1]
  - In Patients with acute painful vertebral fractures:
    - Teriparatide reduced vertebral fractures by 50% compared to Risedronate over 1 year[2]
- Two New Studies Where Fracture Outcomes Were Primary Endpoints:
  - VERO: Compared Teriparatide with Risedonrate [3]
  - ARCH: Compared Romosozumab with Alendronate[4]

[1] Saag et al NEJM 2007
[2] Hadji et al OI 2012
[3] Kendler et al Lancet 2017
[4] Saag et al ASBMR 2017, NEJM 2017

VERO: Teriparatide vs Risedronate in Severe Osteoporosis

Patients: Key Inclusion Criteria

- Ambulatory postmenopausal women aged ≥45 years
- Radiographic evidence for at least 2 moderate (i.e. a reduction in vertebral body height of 26% to 40%) or 1 severe (more than 40% reduction) prevalent vertebral fragility fractures
- BMD T-score ≤-1.5 standard deviations at the lumbar spine, total hip, or femoral neck

Protocol

- Women randomized to receive:
  - Teriparatide 20 mcg/day plus blinded oral Risedronate placebo or
  - Risedronate 35 mg orally once weekly plus blinded Teriparatide placebo

Trial Sponsor:
Lilly

Kendler DL et al. Lancet. 391:230, 2018

VERO: Teriparatide vs Risedronate in Severe Osteoporosis

Primary Endpoint

- Percentage of patients with at least 1 new vertebral fracture during the 24-month study

Key Secondary Endpoints

- Pooled new and worsened vertebral fractures.
- Clinical fractures (composite of clinical vertebral and non-vertebral fragility fractures).
- Non-vertebral fragility fractures*.
- Major non-vertebral fragility fractures**

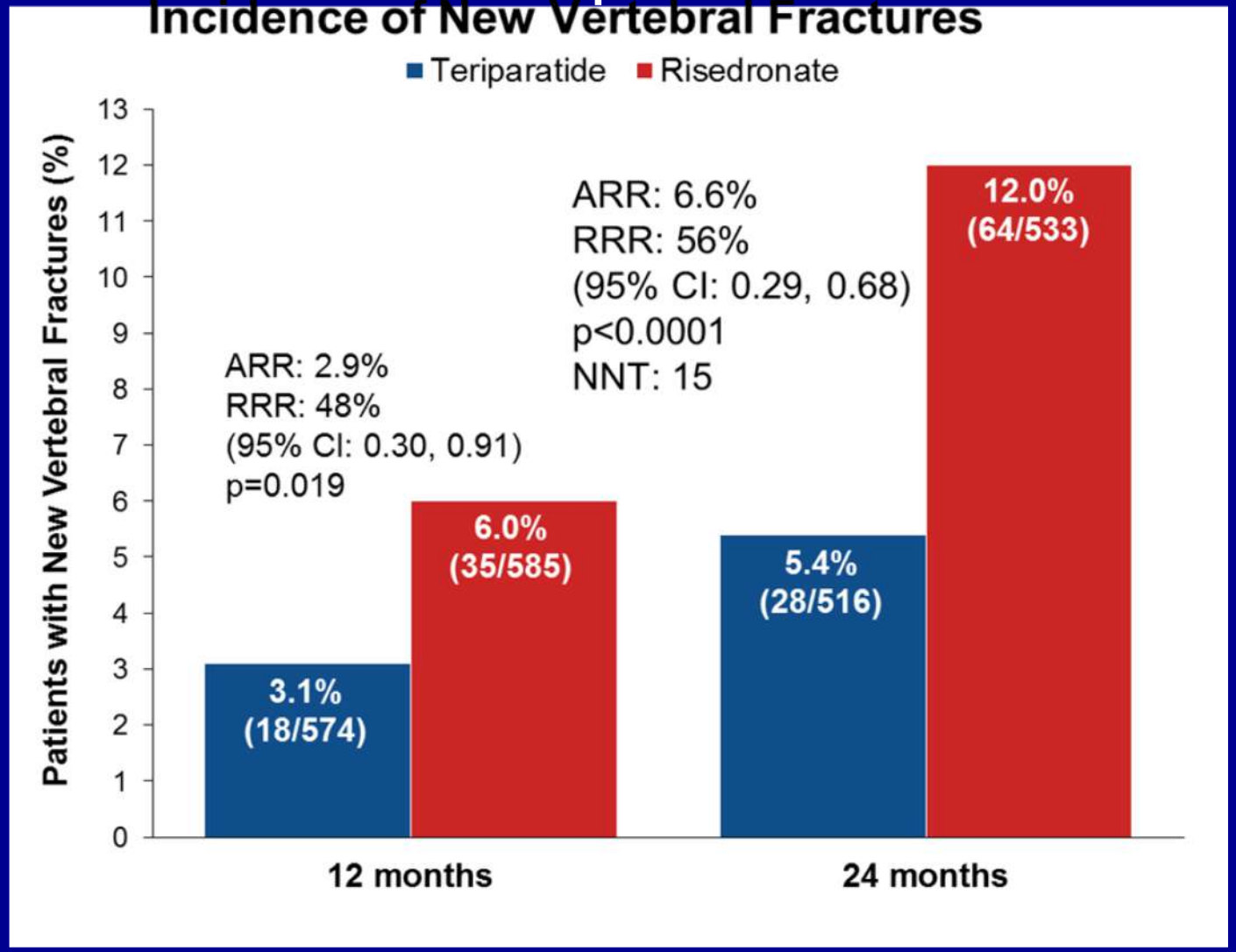
* excluding pathologic fractures and fractures of the skull, face, fingers, metacarpals, or toes.

** hip, radius, humerus, ribs, pelvis, tibia, or femur

Trial Sponsor: Lilly

Kendler DL et al. Lancet. 391:230, 2018

VERO: Teriparatide vs Risedronate in Severe Osteoporosis



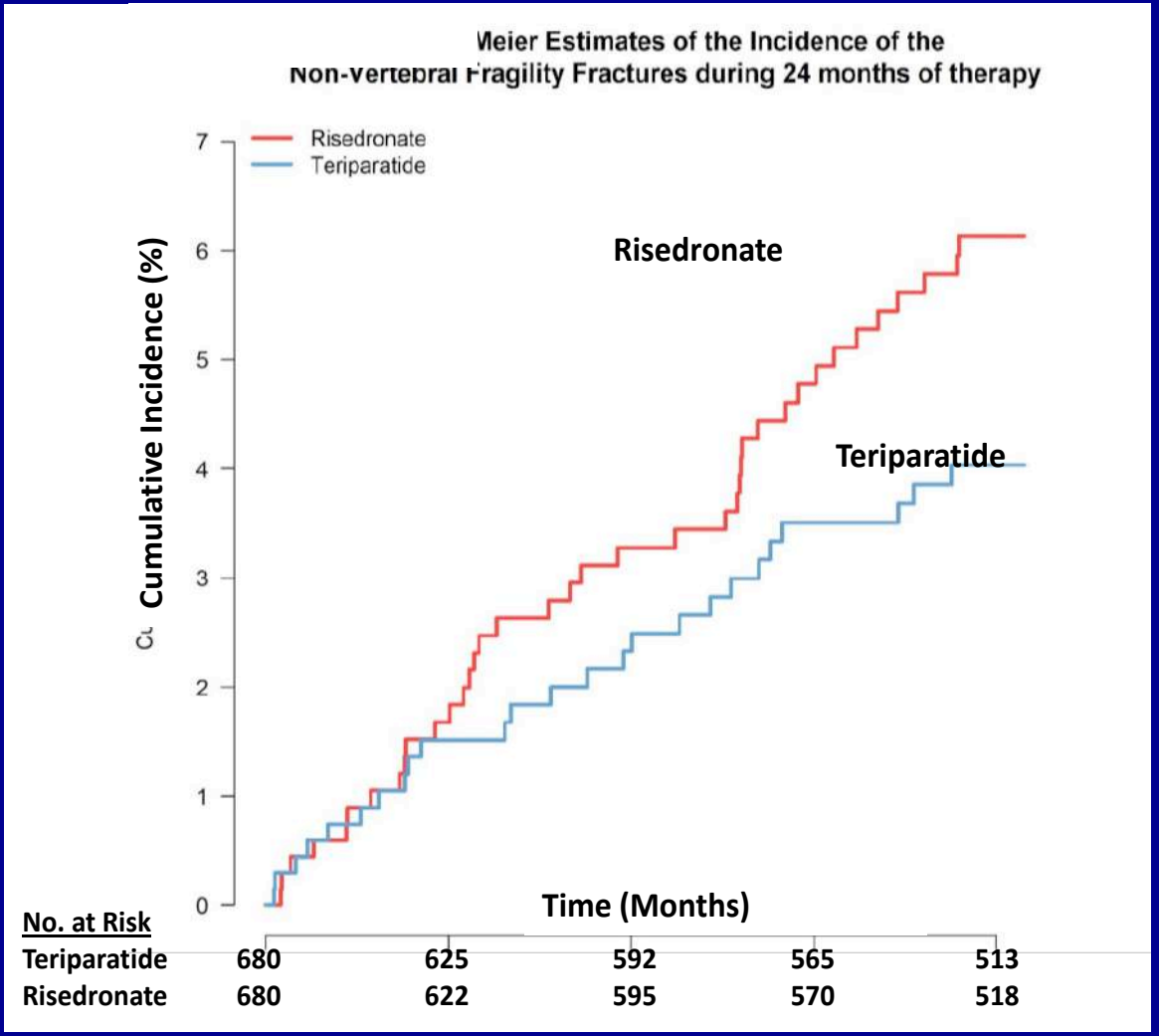
Analysis at 12 months was a pre-specified exploratory endpoint.
ARR = Absolute Risk Reduction; RRR = Relative Risk Reduction CI = confidence interval NNT = number needed to treat

Trial Sponsor: Lilly

Kendler DL et al. Lancet. 391:230, 2018

VERO: Teriparatide vs Risedronate in Severe Osteoporosis

Incidence of Nonvertebral Fx



CI = confidence interval.

* Fractures of the clavicle, scapula, ribs, sternum, sacrum, coccyx, humerus, radius, ulna, carpus, pelvis, hip, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, or metatarsus (excluding pathologic fractures and fractures of skull, face, fingers, metacarpals, and toes).

Trial Sponsor: Lilly

Kendler DL et al. Lancet. 391:230, 2018

VERO: Teriparatide vs Risedronate in Severe Osteoporosis

Number of Incident Nonvertebral Fractures

	Teriparatide (N=680)	Risedronate (N=680)
Patients with at least 1 non-vertebral fragility fracture, n (%)	**25 (3.7)**	**38 (5.6)**
with 1 non-vertebral fragility fracture	23 (3.4)	28 (4.1)
with 2 non-vertebral fragility fractures	2 (0.3)	10 (1.5)
Total number of non-vertebral fragility fractures	**27**	**48**

N = total number of patients; n = number of patients in the specified category

Adjusted rate ratio for teriparatide vs risedronate: 0.56 (0.35; 0.90) p=0.017*

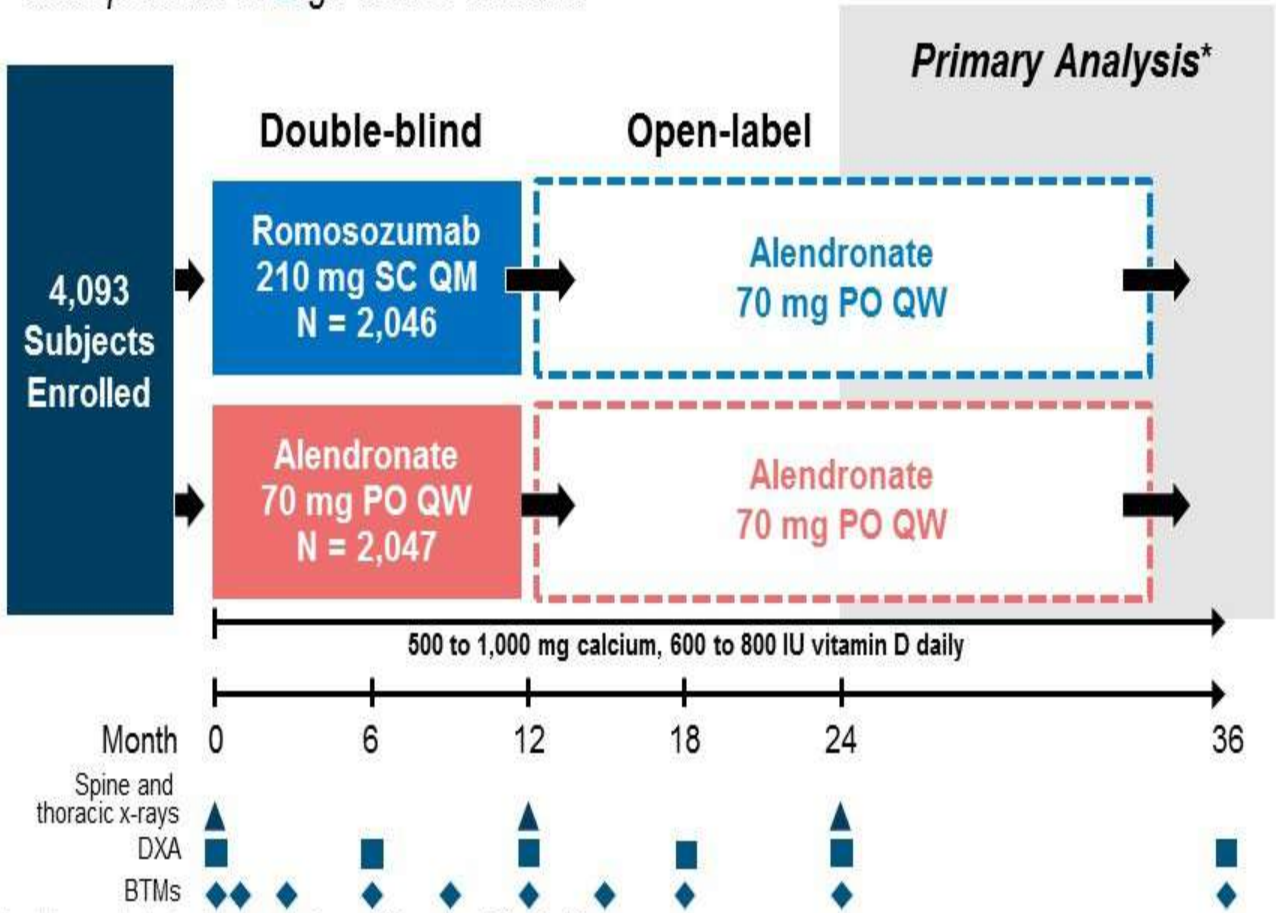
*Non-longitudinal analysis of fracture occurrence was carried out using a **Poisson regression model** (Poisson distribution and log link) including the following variables: treatment, antecedent of recent clinical vertebral fractures, and recent use of bisphosphonate.

Trial Sponsor: Lilly

Kendler DL et al. Lancet. 391:230, 2018

ARCH Phase 3 Study Design

Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk of fracture



*Median time on study at primary analysis was 33 months (IQR: 27–40).
BTM = bone turnover marker; DXA = dual-energy x-ray absorptiometry; IQR = interquartile range; IU = international units; PO = orally; QM = once monthly; QW = once weekly; SC = subcutaneously

Adapted from: Saag KG, et al. *N Engl J Med.* 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.

Key Eligibility Criteria

Inclusion Criteria[1]	• Postmenopausal women aged 55 to 90 years • BMD T-score and fracture history – BMD T-score ≤ –2.5 at the total hip or femoral neck, and ▪ ≥ 1 moderate or severe vertebral fractures or ▪ ≥ 2 mild vertebral fractures OR – BMD T-score ≤ –2.0 at the total hip or femoral neck, and ▪ ≥ 2 moderate or severe vertebral fractures or ▪ a hip fracture sustained 3–24 months prior to randomization
Exclusion Criteria[1,2]	• Contraindications or signs of intolerance to alendronate • Recent use of agents affecting bone metabolism

BMD = bone mineral density

1. Saag KG, et al. *N Engl J Med*. 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.
2. Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.

Primary and Key Secondary Endpoints

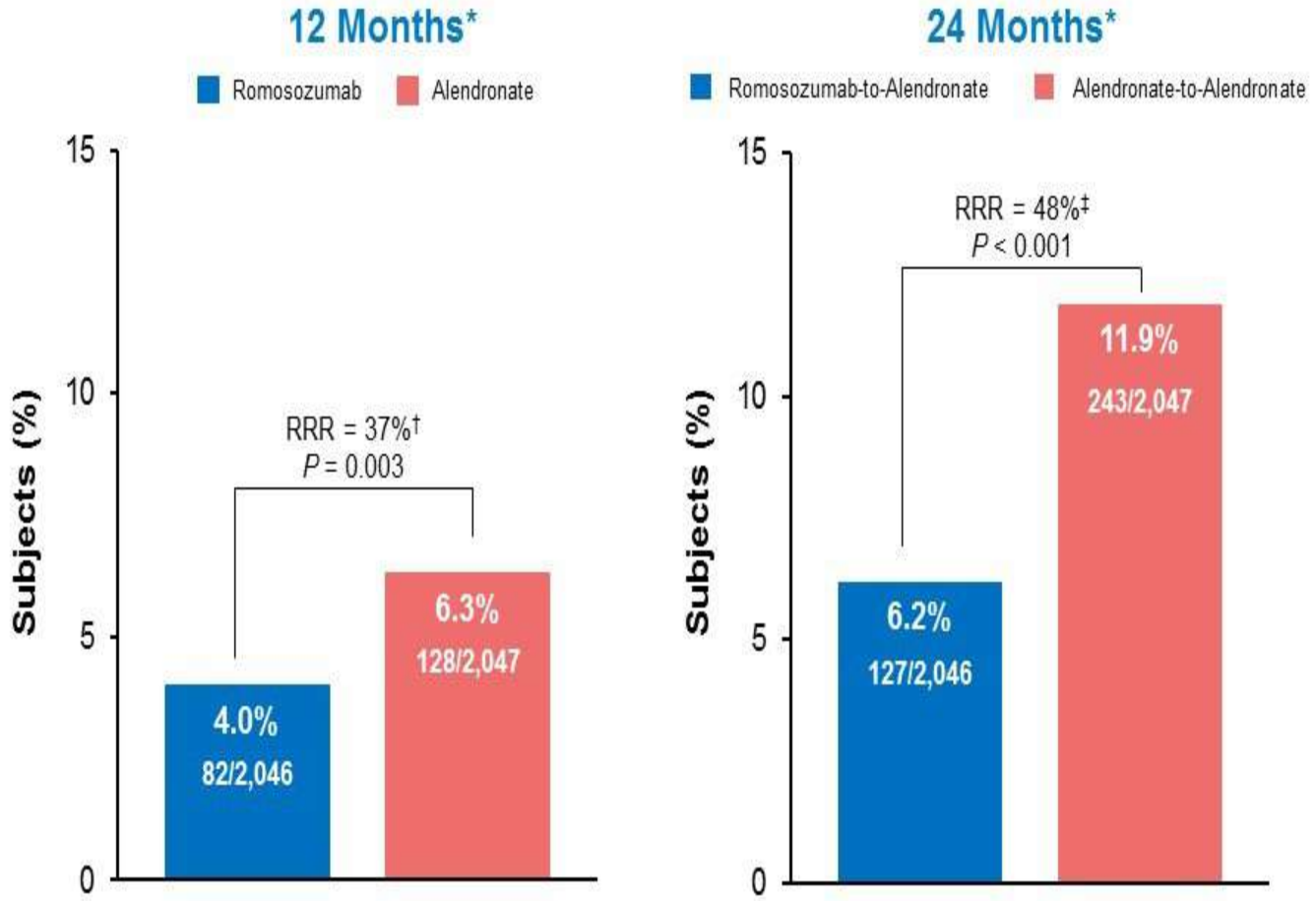
Primary Endpoints	• Subject incidence of new vertebral fracture through 24 months • Subject incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at primary analysis
Key Secondary Endpoints	• Subject incidence of nonvertebral fracture at primary analysis • BMD at the lumbar spine, total hip and femoral neck at 12 and 24 months
Other Secondary/ Exploratory Endpoints	• Hip fracture, major osteoporotic fracture and other fracture categories at primary analysis

BMD = bone mineral density

Saag KG, et al. *N Engl J Med.* 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.

Primary Endpoint

Incidence of New Vertebral Fracture Through Month 24

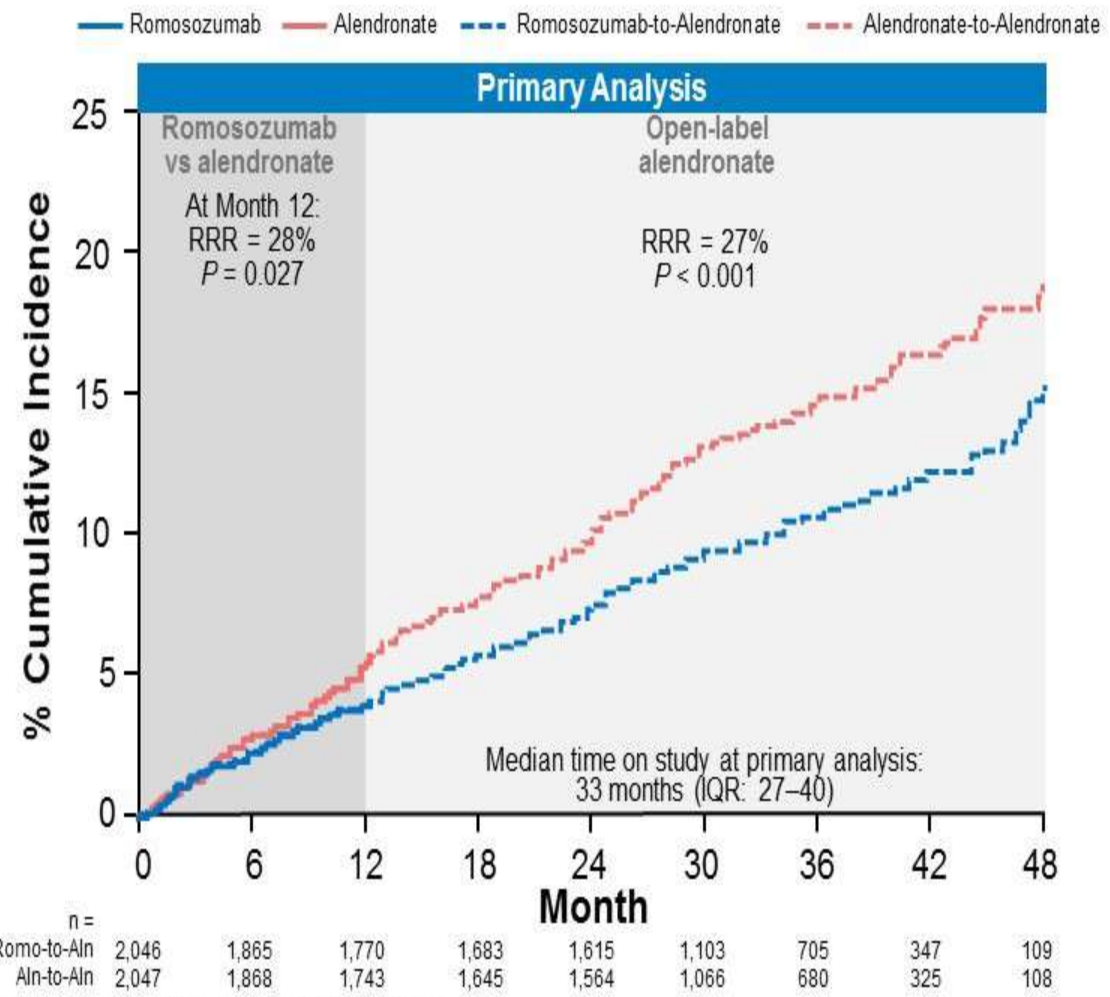


n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.
*Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier time point. n and % are based on the average across 5 imputed datasets.
†RRR at 12 months by LOCF: 36% (nominal $P = 0.008$): Romosozumab: 3.2% (55/1,696) vs Alendronate: 5.0% (85/1,703).
‡RRR at 24 months by LOCF: 50% (nominal $P < 0.001$): Romo-to-Aln: 4.1% (74/1,825) vs Aln-to-Aln: 8.0% (147/1,843).
Aln = alendronate; LOCF = last-observation-carried-forward; Romo = romosozumab; RRR = relative risk reduction

Adapted from: Saag KG, et al. *N Engl J Med.* 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.

Primary Endpoint

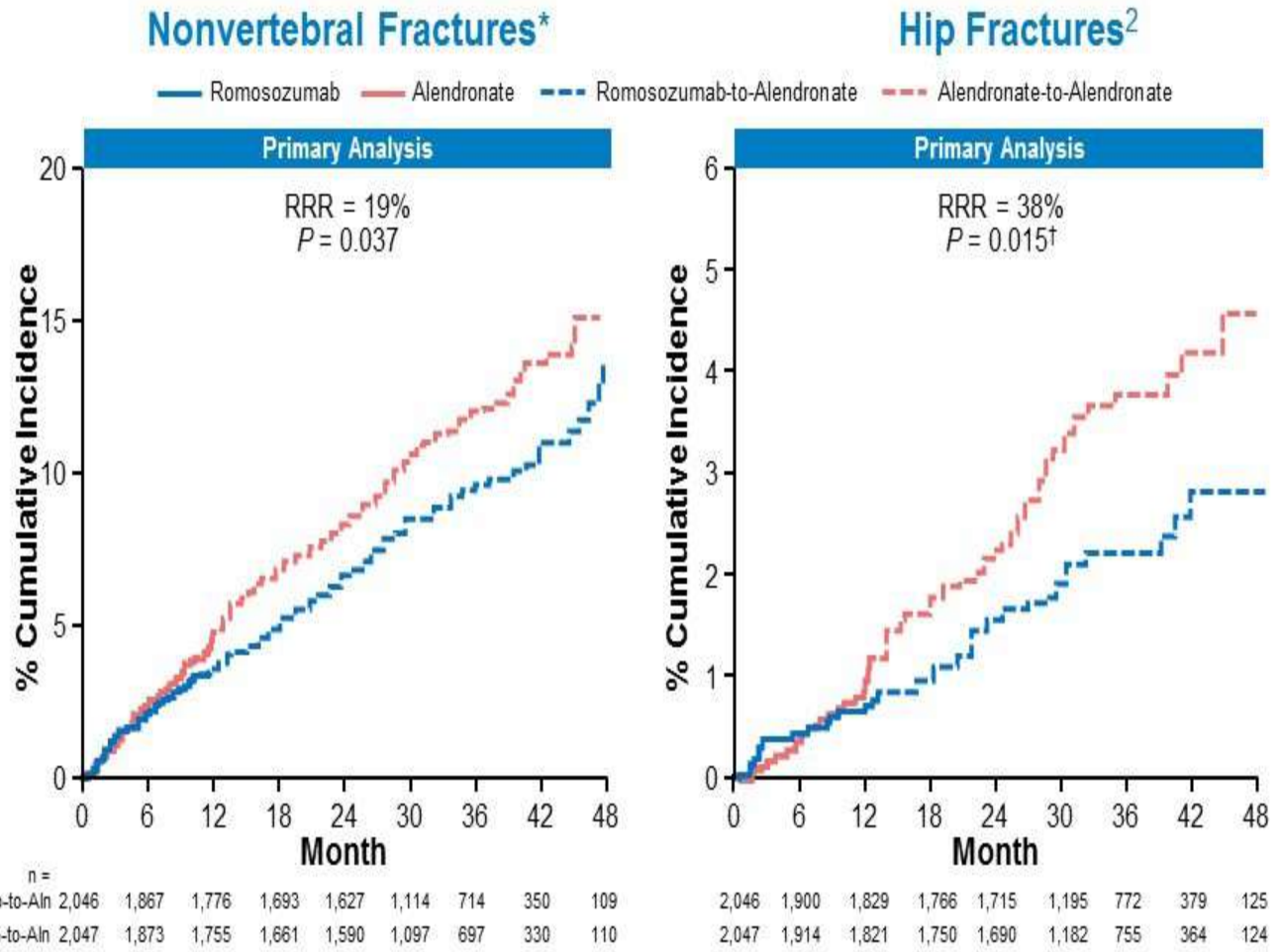
Incidence of Clinical Fracture at Primary Analysis



n = number of subjects at risk for event at time point of interest.
Aln = alendronate; IQR = interquartile range; Romo = romosozumab; RRR = relative risk reduction

Adapted from: Saag KG, et al. *N Engl J Med.* 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.

Incidence of Nonvertebral and Hip Fractures at Primary Analysis



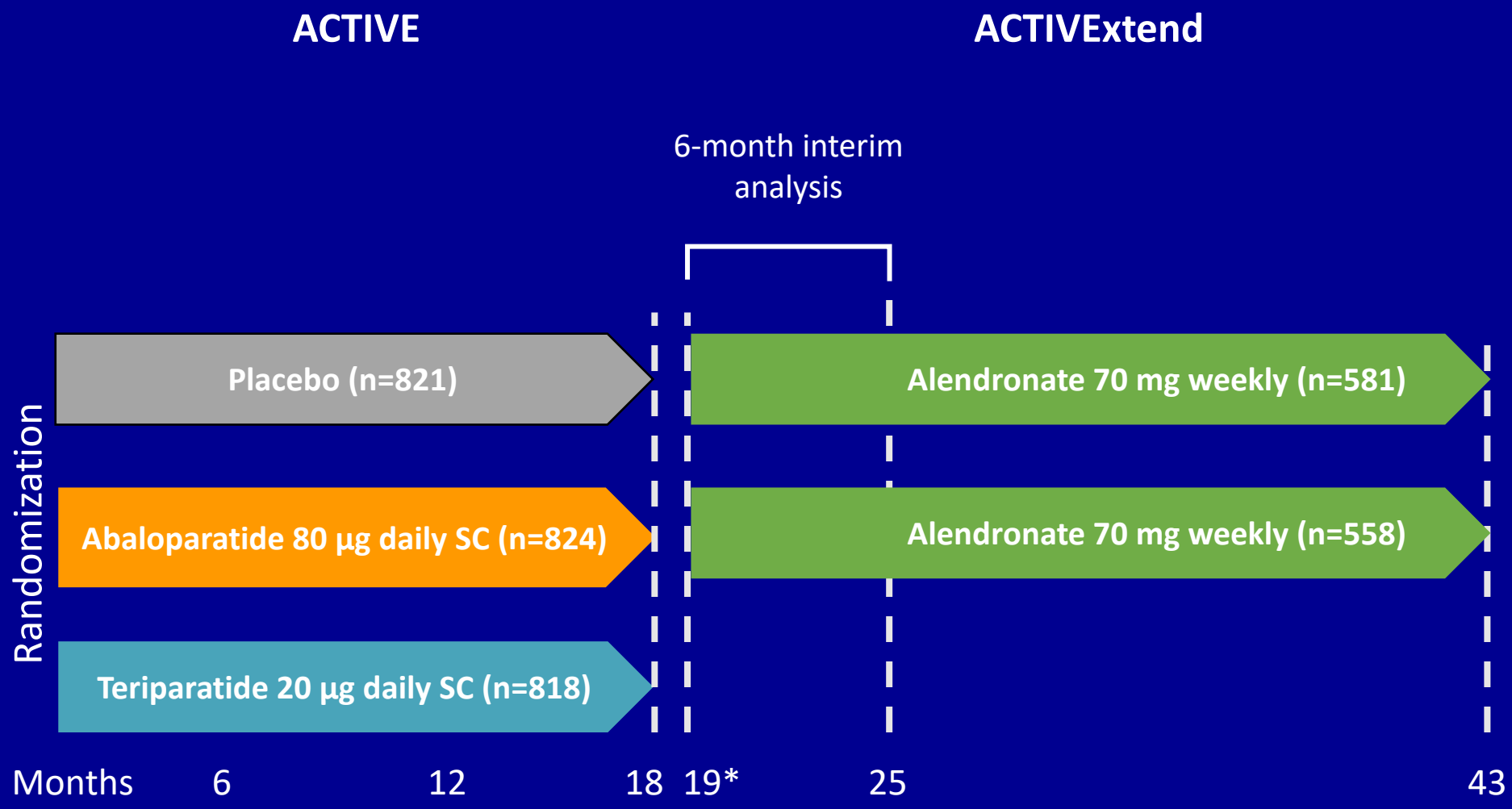
*Secondary endpoint. †Not adjusted for multiplicity. n = number of subjects at risk for event at time point of interest.
Aln = alendronate; Romo = romosozumab; RRR = relative risk reduction

1. Adapted from: Saag KG, et al. *N Engl J Med.* 2017; [Published only ahead of print September 11, 2017]. 10.1056/NEJMoa1708322.
2. Data on file, Amgen.

Rationale for Early Proactive Use of Anabolic Agents in Patients at High Imminent Risk of Fracture

- Anabolic Agents reduce fractures more than antiresorptive agents
- Anabolic agents reduce fractures faster than even the best antiresorptive agents
- Antifracture effects are sustained after transition to antiresorptives therapy

ACTIVE and ACTIVExtend Trial Design



*A 1-month gap in treatment was allowed for rollover from ACTIVE to ACTIVExtend.

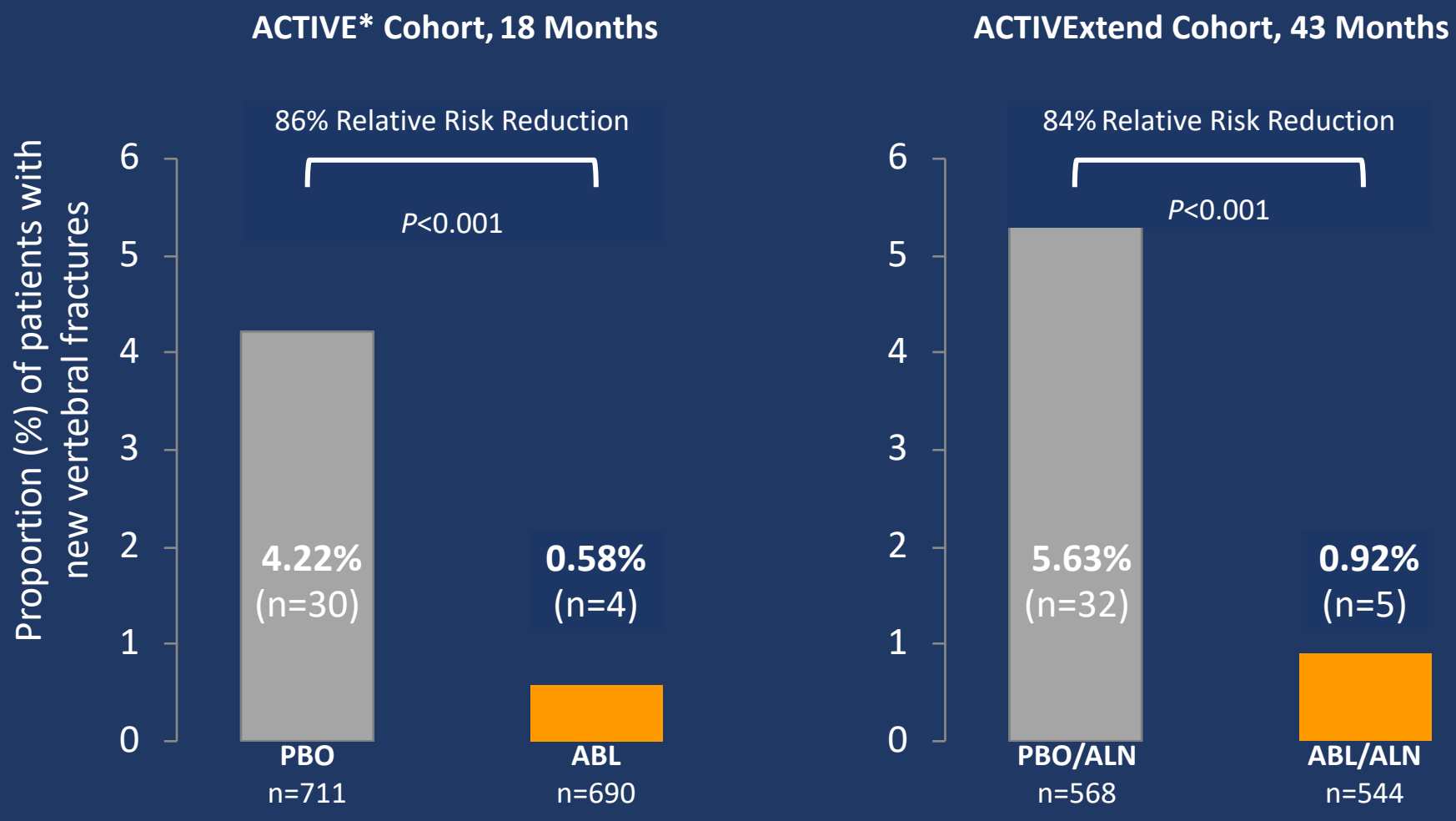
Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F, Miller PD, et al. JCEM 2018

ACTIVExtend Baseline Characteristics

- 92% of eligible patients who completed ACTIVE were enrolled in ACTIVExtend
  - No clinically meaningful differences between ACTIVExtend cohort and full ACTIVE cohorts
- Abaloparatide/alendronate and placebo/alendronate groups well matched
  - Mean age was 68.6 years
  - 22% had prevalent vertebral fracture
  - Mean BMD at baseline of ACTIVE Study
    - Lumbar spine T-Score −2.9
    - Total hip T-Score −1.9
- 88% of enrolled patients completed the ACTIVExtend study

Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F. JCEM 2018

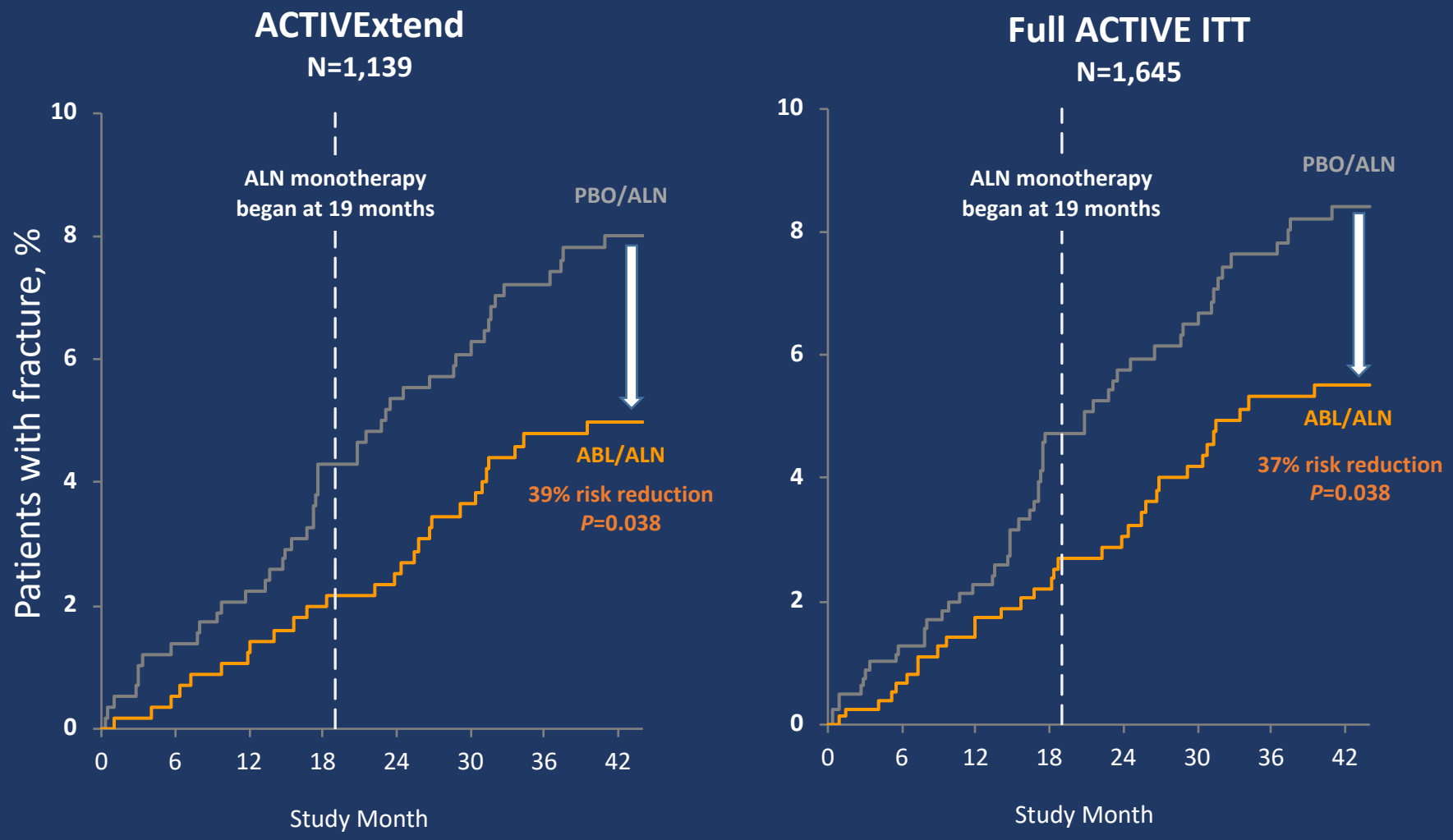
Sustained Vertebral Fracture Risk Reduction



Modified intent to treat population was used for new vertebral fracture rate.
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F et al. JCEM 2018

Sustained Nonvertebral Fracture Risk Reduction



ABL, abaloparatide; **ALN**, alendronate; **ITT**, intent to treat; **PBO**, placebo.

Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F et al. JCEM 2018

Fracture Endpoints: ACTIVExtend and ACTIVE ITT

	ACTIVExtend		Full ACTIVE ITT	
Fracture type	**PBO/ALN, n=581**	**ABL/ALN, n=558**	**PBO + PBO/ALN, n=821**	**ABL + ABL/ALN, n=824**
Nonvertebral, number of patients KM rate, % *HR (95% CI)* *P-value*	**45** 8.0	**27** 5.0 0.61 (0.38, 0.98) 0.038	**53** 8.4	**33** 5.5 0.63 (0.41, 0.98) 0.038
Clinical, number of patients KM rate, % *HR (95% CI)* *P-value*	**58** 10.4	**38** 7.0 0.66 (0.44, 0.99) 0.045	**72** 11.3	**49** 8.1 0.69 (0.48, 0.99) 0.045
Major osteoporotic, number of patients KM rate, % *HR (95% CI)* *P-value*	**40** 7.2	**20** 3.7 0.50 (0.30, 0.86) 0.011	**51** 8.2	**21** 3.5 0.42 (0.25, 0.70) 0.001
Hip, number of patients KM rate, % *HR (95% CI)* *P*-value	**3** 0.6	**0** 0 NE* 0.085	**5** 0.8	**0** 0 NE* 0.027

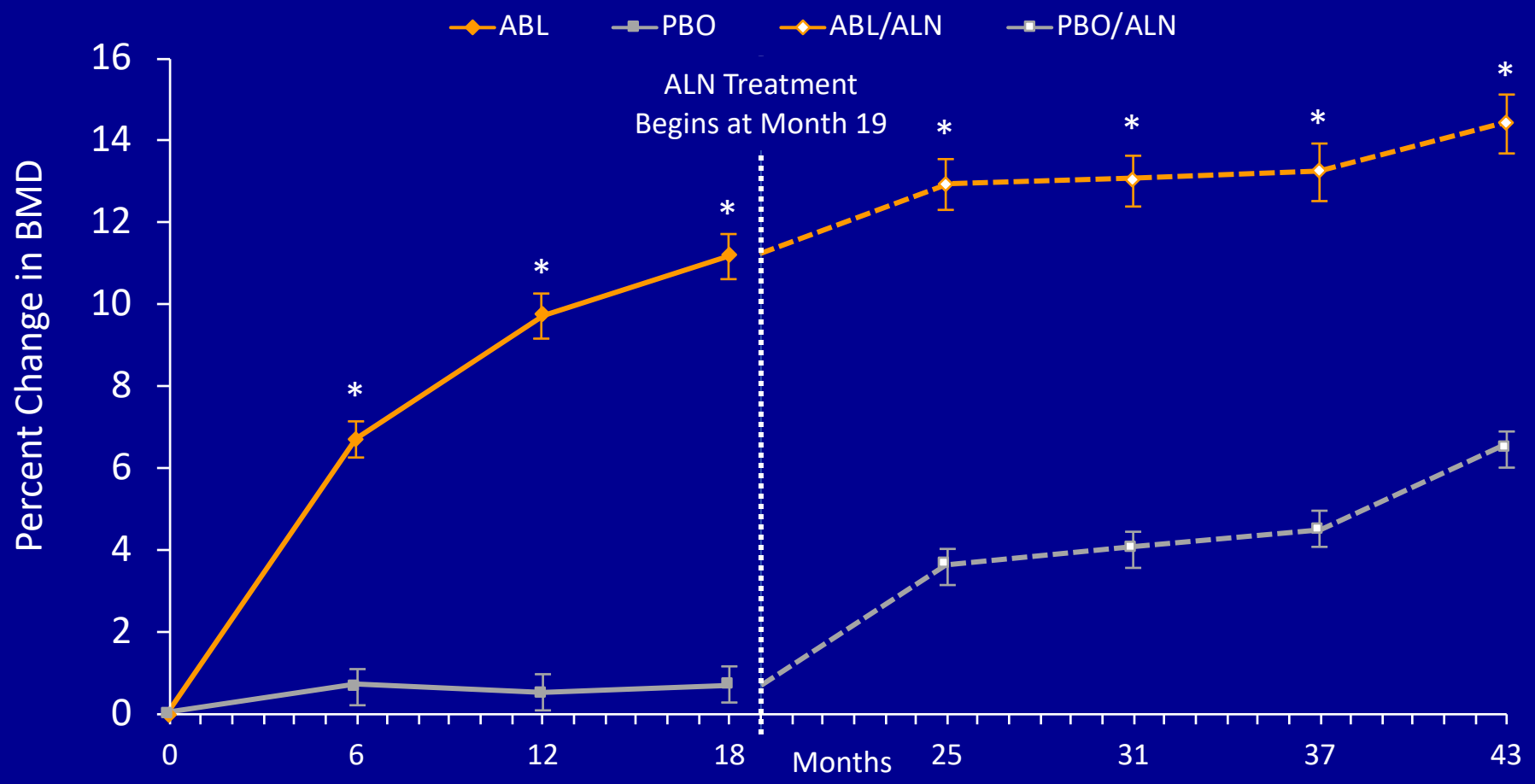
bo.

Bone HG, Cosman F, Miller PD, et al. JCEM 2018

Rationale for Early Use of Anabolic Agents in Patients with Very Low BMD

- Treatment Sequence Matters
- Greatest BMD gains when used first line followed by a potent antiresorptive agent

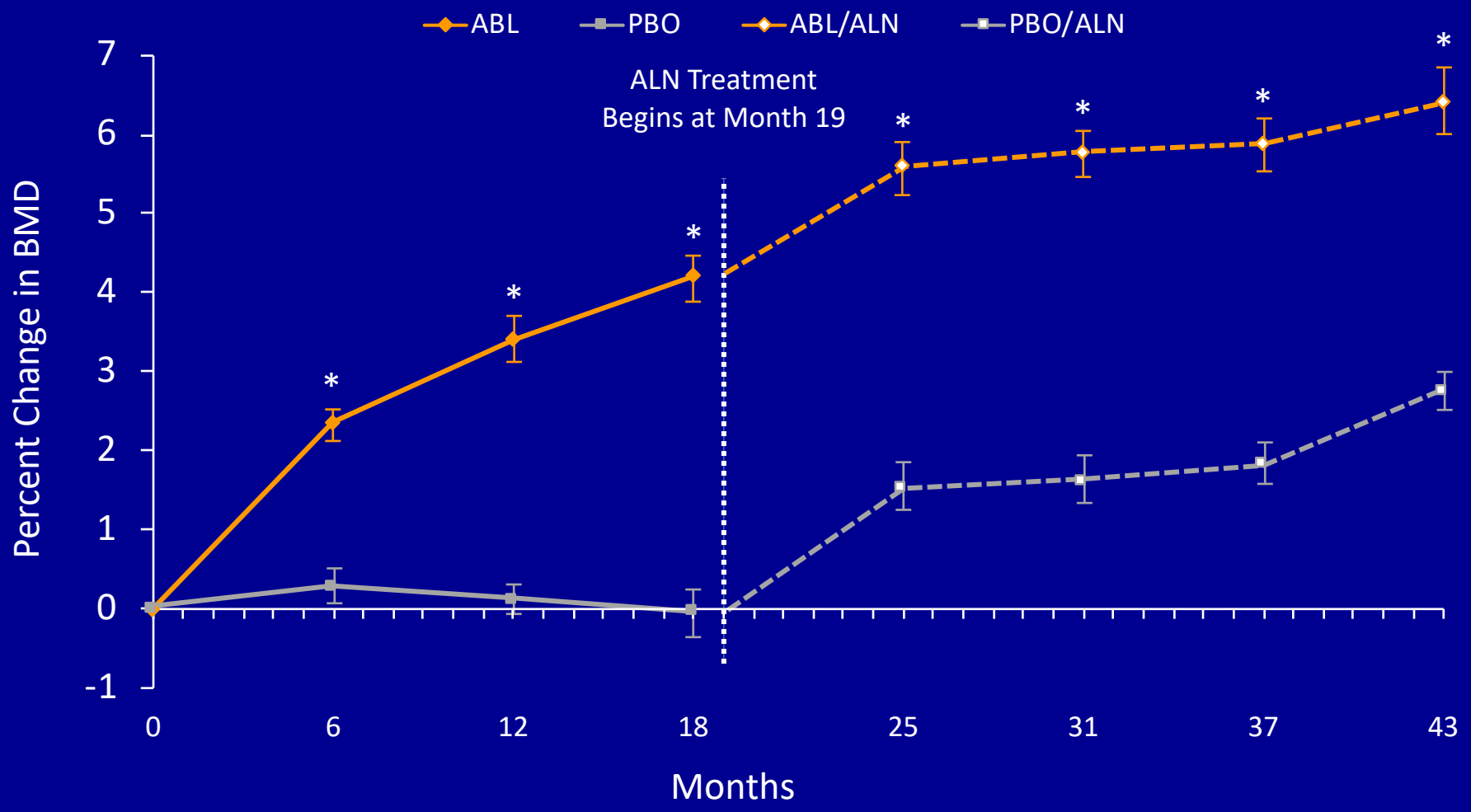
Spine BMD: Mean Change from ACTIVE Baseline to End of ACTIVExtend



*P<0.001 for ABL vs PBO and for ABL/ALN vs PBO/ALN. A gap in treatment of up to 1 month (from months 18 to 19) was allowed for rollover and re-consenting from ACTIVE to ACTIVExtend. Error bars represent 95% confidence intervals. **ABL**, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F, et al. JCEM 2018

Total Hip BMD: Mean Change from ACTIVE Baseline to End of ACTIVExtend



*P<0.001 for ABL vs PBO and for ABL/ALN vs PBO/ALN. A gap in treatment of up to 1 month (from months 18 to 19) was allowed for rollover and re-consenting from ACTIVE to ACTIVExtend. Error bars represent 95% confidence intervals. **ABL**, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

Miller PD et al. *JAMA*. 2016. Cosman F et al. Mayo Clin Proc. 2017. Bone HG, Cosman F, et al. JCEM 2018

Rationale for Early Use of Anabolic Agents in Patients with Very Low BMD

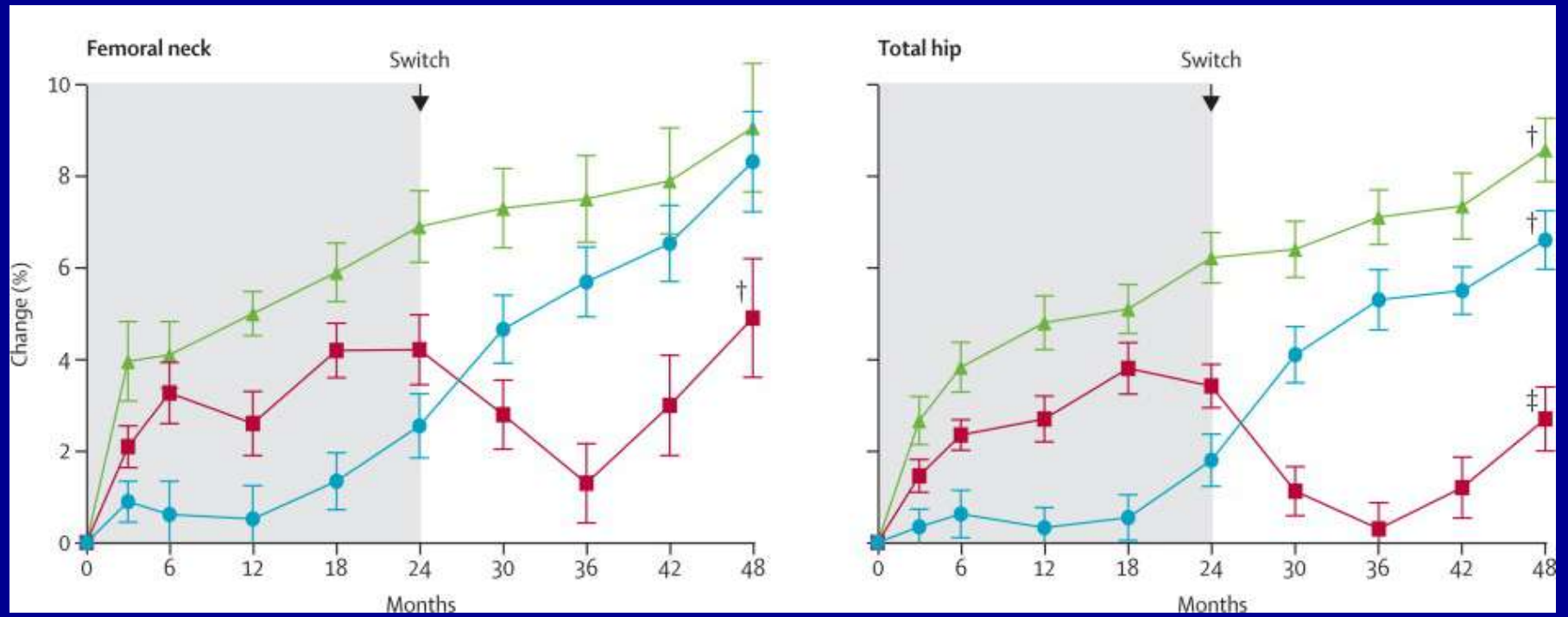
- Treatment Sequence Matters
- Greatest BMD gains when used first line followed by a potent antiresorptive agent
- When Teriparatide Used Second Line after prior therapy with bisphosphonates[1-3] or denosumab[4]
  - Increments in Spine BMD very similar with either sequence
  - Lesser increments in Hip BMD and strength Improvement

[1] Cosman F et al JBMR 2017
[2] Cosman F et al JCEM 2009
[3] Langdahl B et al Lancet 2017
[4] Leder BZ et al Lancet 2015

Hip BMD Effect Upon Switching From Potent Antiresorptive Therapy to Teriparatide

Study	Sample Size	Relevant Treatment Paradigm	Change in Total Hip During TPTD			
			6 mo	12 mo	18 mo	24 mo
Ettinger, et al. (JBMR 2004)	33	Aln (mean 29 mo) → TPTD	-1.8%	-1.0%	+0.3%	-
Boonen, et al. (JCEM 2008)	107	Aln (median 29 mo) → TPTD	-1.2%	-0.6%	+0.6%	+2.1%
Boonen, et al. (JCEM 2008)	59	Ris (mean 23 mo) → TPTD	-1.6%	-0.4%	+0.9%	+2.9%
Miller, et al. (JCEM 2008)	158	Ris (mean 37 mo) → TPTD	-1.2%	-0.3%		-
Miller, et al. (JCEM 2008)	166	Aln (mean 38 mo) → TPTD	-1.9%	-1.7%		-
Cosman, et al. (JCEM 2009)	50	Aln (mean 46 mo) → TPTD	-0.8%	-	+0.9%	-
Leder, et al. (Lancet 2015)	27	Dmab (24 mo) → TPTD	-1.7%	-2.7%	-1.7%	-0.7%
Langdahl, et al (Lancet2017)	209	Aln (mean 66 mos) → TPTD	-0.8%	-0.5	-	-
Adapted from Cosman et al JBMR 2017[17]						

4 Year Sequential Treatment with Teriparatide and Denosumab

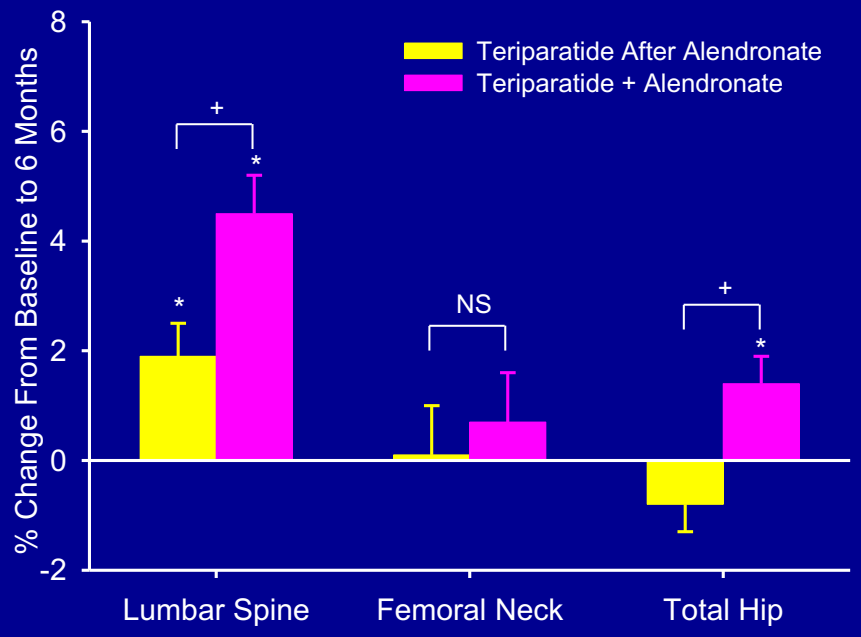


Green: Combination Teriparatide +Denosumab for 2 years followed by Denosumab for 2 years
Red: Denosumab for 2years followed by Teriparatide for 2 years
Blue: Teriparatide for 2 years followed by Denosumab for 2 years

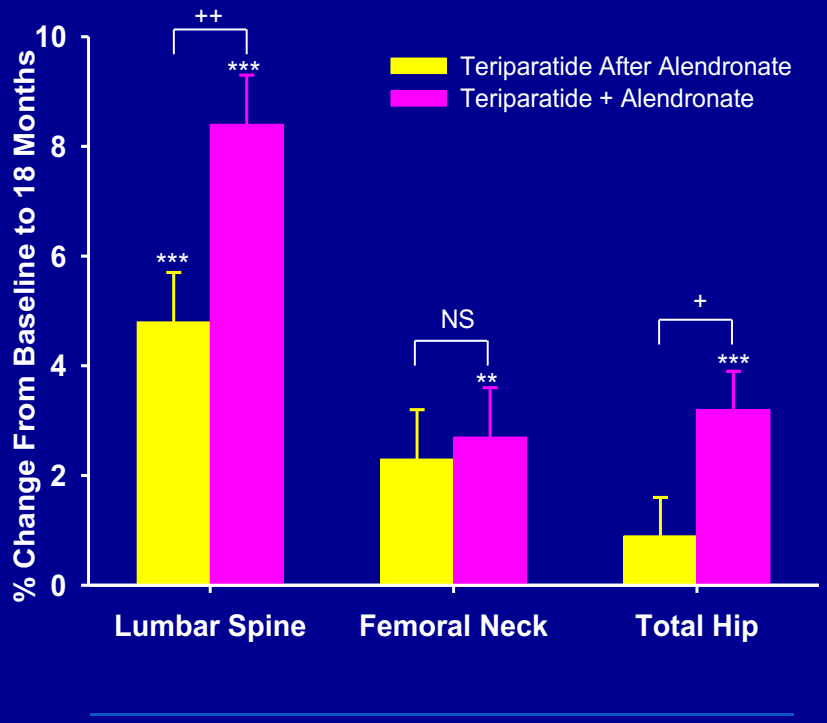
Leder BZ et al. Lancet 2015, 386:1147–55

Teriparatide in Alendronate Treated Switch vs Add At 6 and 18 Months

6 Months



18 Months

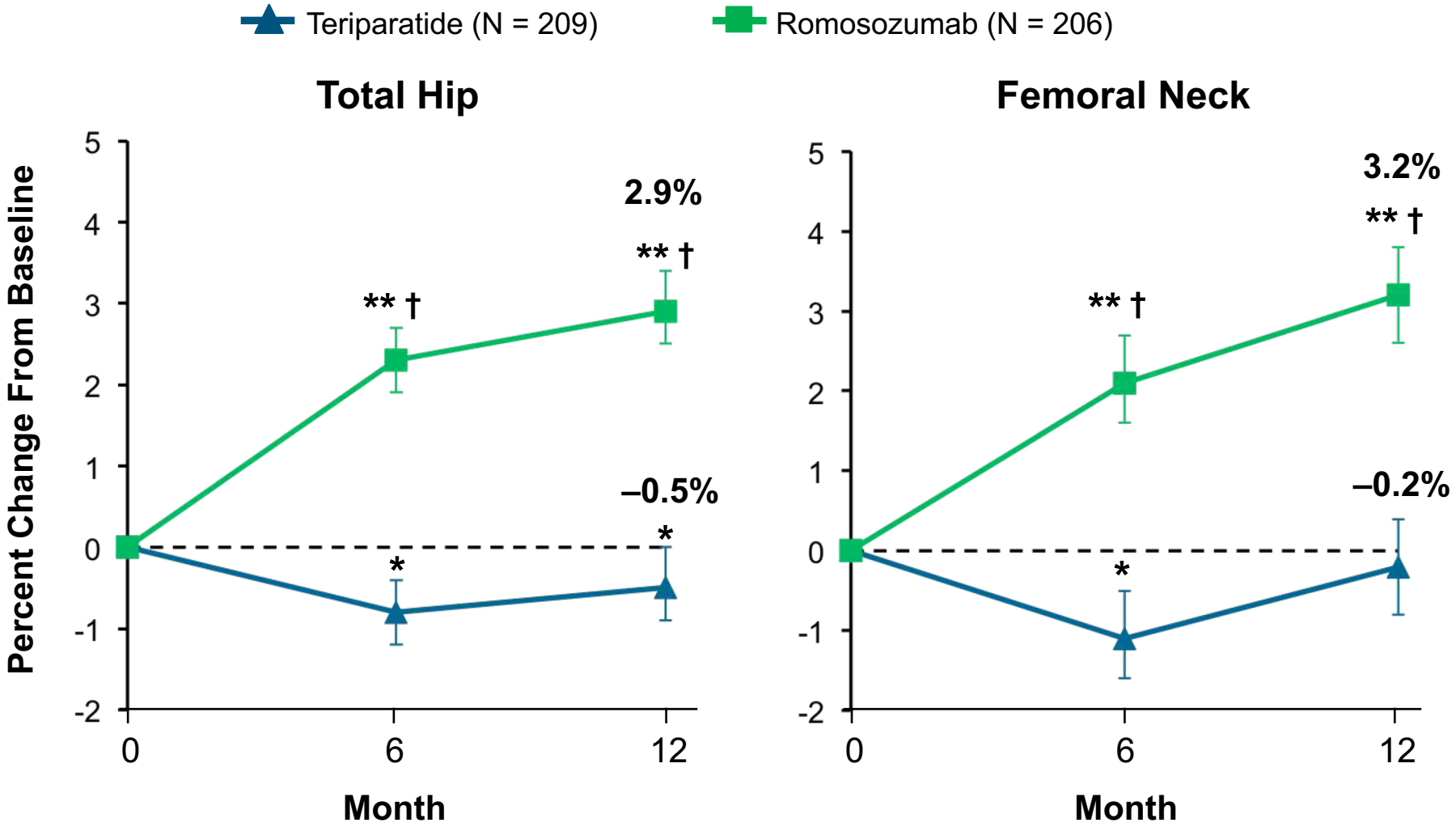


Cosman F et al, JCEM 2009; 94:3772–3780

Strategy for Patients On Potent BPs Who Need Anabolic Treatment

- Caveat: No Data on Abaloparatide in these patients
- In Patients on Bisphosphonates
  - With incident spine fracture and hip BMD not that low, *switch to Abaloparatide/Teriparatide*
  - With incident hip fracture or very low hip BMD, *Add Abaloparatide/Teriparatide and continue AR* (possibly switch to denosumab)
  - Patients with more remote exposure to BPs probably not an issue
    - Unknown when recent becomes remote
  - In future, romosozumab might be ideal for these patients

Total Hip and Femoral Neck BMD by DXA



N = number of subjects in the primary efficacy analysis set for DXA endpoints. Data are shown as least squares means and 95% confidence intervals. *P < 0.05 compared with baseline; **P < 0.0001 compared with baseline; †P < 0.0001 compared with teriparatide.

B Langdahl et al Lancet Sept 2017

Strategy for Patients On Denosumab Who Need Anabolic Treatment

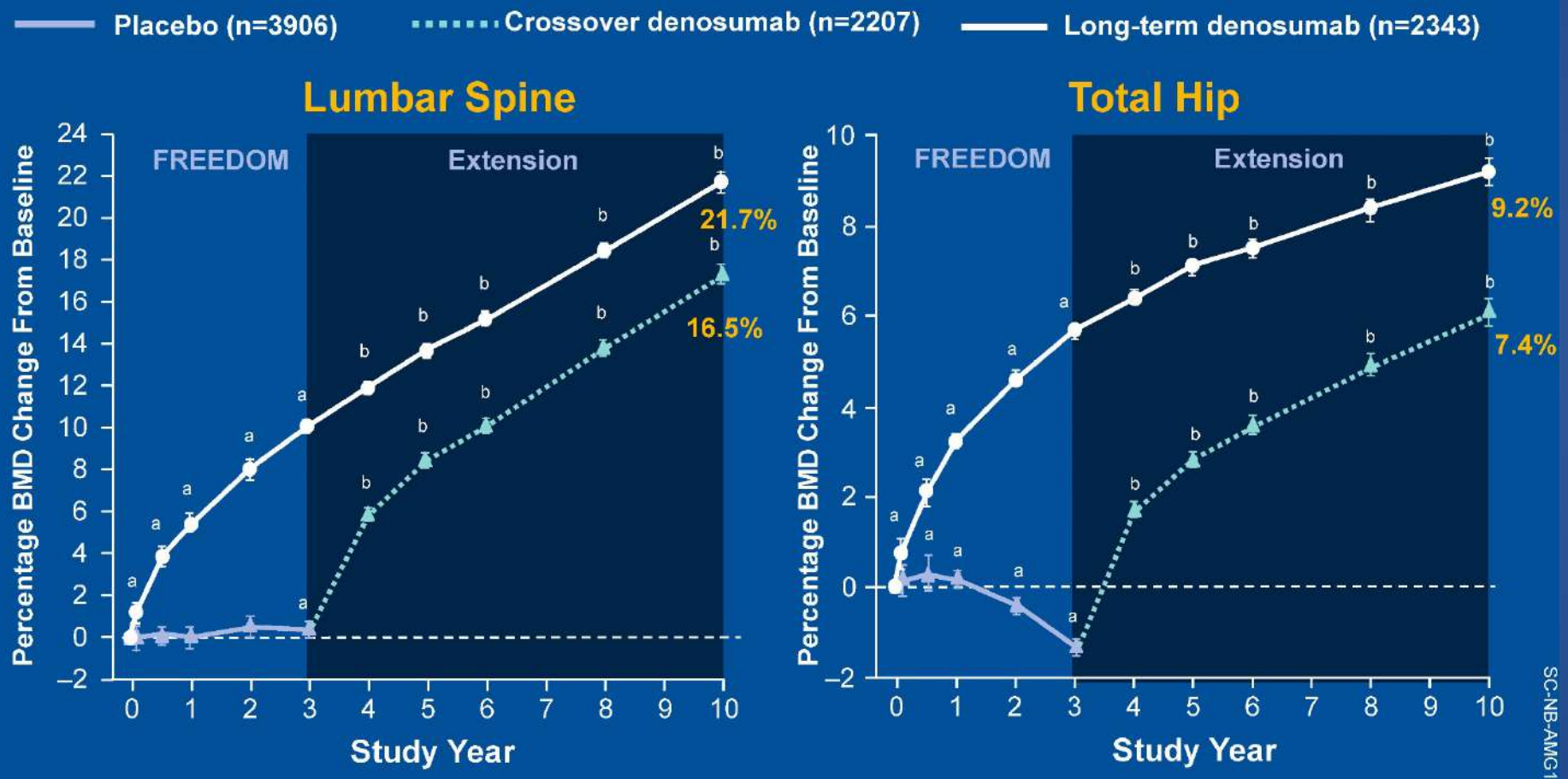
- In Patients on Denosumab
  - Add *Abaloparatide/Teriparatide* and continue Denosumab
    - Have no specific data evaluating this patient population
  - Recommendation based on analogy with
    - observations in patients on bisphosphonates who add Teriparatide
    - observations in patients from the DATA trial (de novo combination Teriparatide plus Denosumab)

Sequential Monotherapy

- After Abaloparatide or Teriparatide, Denosumab vs Bisphosphonates?
  - Reassess severity of disease and magnitude of response to anabolic treatment
  - For patients who are close to treatment goals
    - Probably go straight to bisphosphonate
    - For most severe patients, use denosumab
      - To help achieve fracture free interval of 3-5 years
      - To help achieve BMD goals (T-Scores above -2.5)

Change in Lumbar Spine and Total Hip BMD Through 10 Years With Denosumab Treatment

FREEDOM and the Open-Label FREEDOM Extension



Data represent least-squares means and 95% CI.
[a]p<0.05 compared with FREEDOM baseline. [b]p<0.05 compared with FREEDOM and extension baselines.
BMD = bone mineral density. Adapted from: Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017; 5: 513-523.

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Sequential Monotherapy

- What should be done if treatment goals are met while on denosumab?
  - If denosumab treatment is stopped, BMD is lost rapidly and fracture risk increases rapidly
    - Especially multiple vertebral fractures
  - Either continue indefinitely or switch to Bisphosphonates
    - *Optimal timing* of switch from dmab unknown
    - *Optimal regimen* (Intravenous and/or oral, dose and frequency) unknown

Sequential Monotherapy: Maintenance

- Maintenance Therapy
  - Low dose intermittent bisphosphonates
  - For younger women, after anabolic and AR sequence (including bisphosphonate at end)
    - Consider raloxifene
    - Other low potency antiresorptives needed
- During Maintenance Period
  - Monitor Fracture History and Height (to diagnose vertebral Fracture), BMD and BTMs
  - Repeat sequential monotherapy as needed

Safety Considerations Anabolic Agents

- Teriparatide and Abaloparatide
  - Rodent Osteosarcoma- not likely human issue
  - Hypercalcemia and Hypercalciuria
  - Orthostatic Hypotension- Dizziness, tachycardia, nausea
  - Erythema at injection site
  - Leg cramps/Musculoskeletal Pains/Fatigue
- Romosozumab
  - Injection Site Reactions
  - Hypersensitivity
  - Imbalance in Cardiovascular and Cerebrovascular Events in ARCH but not FRAME

Summary

- For highest risk previously untreated patients
  - Treatment Sequencing beginning with anabolic treatment followed by denosumab and ultimately switching to an intermittent bisphosphonate is optimal
- For patients currently on denosumab or bisphosphonates who require anabolic therapy
  - Consider Adding rather than switching to Abaloparatide or Teriparatide especially if incident hip fracture or very low hip BMD
    - More data are needed to confirm the validity of this approach, particularly in patients on denosumab

Conclusion

Optimal Proactive Initial Use of Anabolic Agents and Sequential monotherapy for highest risk patients can minimize duration of exposure to pharmacology while maximizing benefits on strength and BMD.