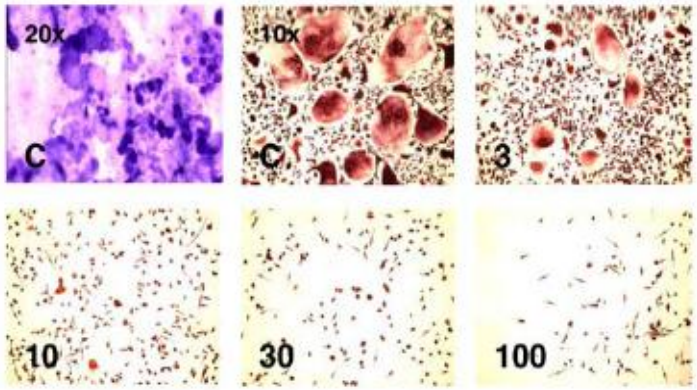
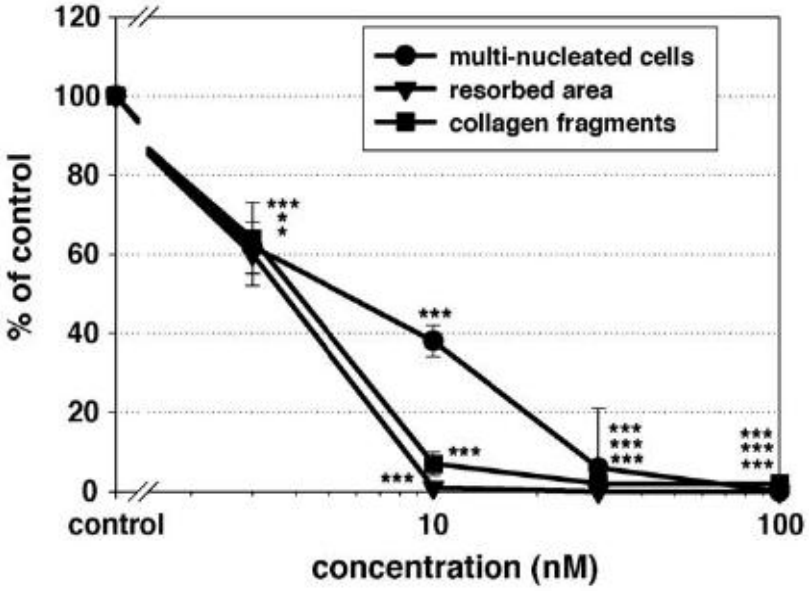
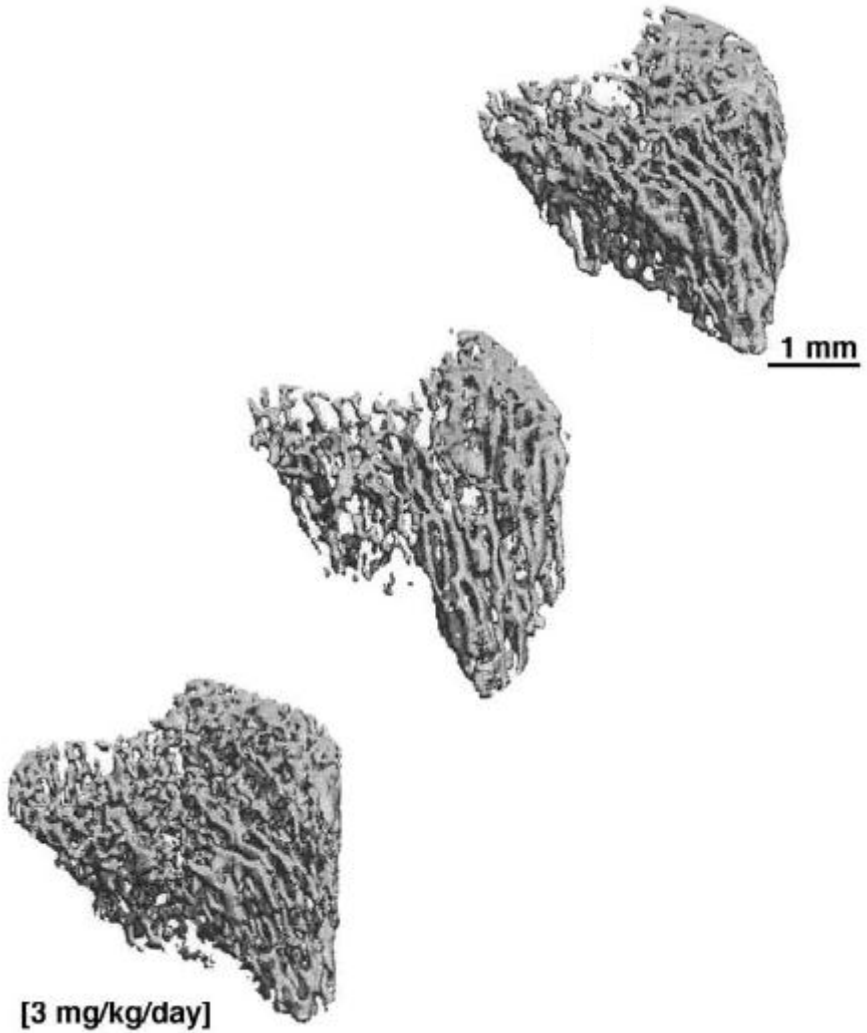
Everolimus nelle pazienti con metastasi ossee ER+

Alessia Levaggi

Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts







Kneissel, Bone 2004

Bolero 2: study design and endpoints

- BOLERO-2 (NCT00863655) is a phase III study comparing EVE vs placebo (PBO) in postmenopausal women with metastatic or locally advanced ER+ BC refractory to NSAIs2
- Patients (N = 724) receiving EXE 25 mg/day were randomized (2:1) to EVE 10 mg/day (n = 485) or PBO (n = 239)
- Primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival, overall response rate, quality of life, safety, and pharmacokinetics

- Exploratory analyses presented here include
  – Percentage change from baseline in bone turnover marker levels
  – Cumulative incidence of disease progression in bone between the 2 treatment arms

Bone Marker Assessment

Bone turnover marker levels were analyzed to assess:

– Osteoclast metabolism (bone-specific alkaline phosphatase, BSAP)

– Bone resorption (C-terminal cross-linking telopeptide of type I collagen, CTX)

– Bone formation (amino-terminal propeptide of type I collagen, P1NP)

Blood samples (8.5 mL, fasting preferred) were collected at baseline and at 6 and 12 weeks after treatment initiation

- – Protocol required specimen collection to be consistent across study visits

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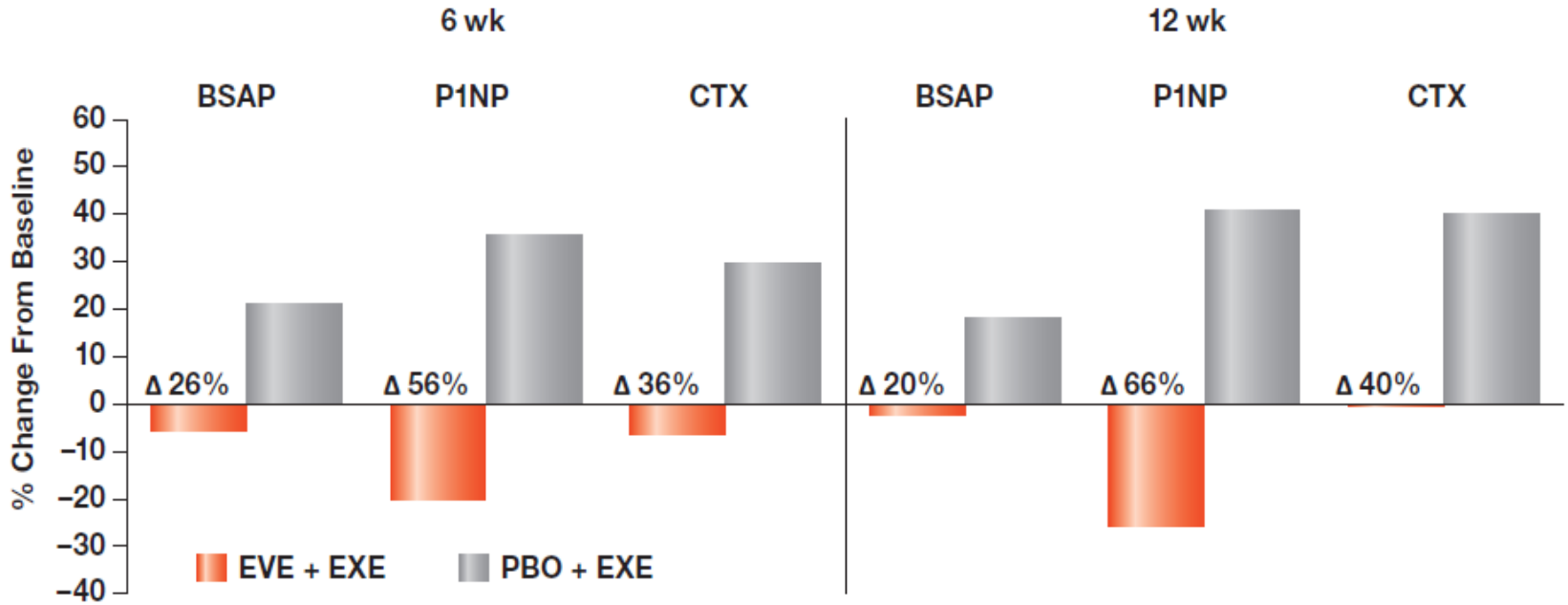
Baseline bone metastases and bisphosphonate use
- BOLERO 2 -

	Everolimus + Exemestane	Exemestane + Placebo
Overall population, No. (%)	n = 485	n = 239
Baseline bone metastases	371 (76.5)	185 (77.4)
Baseline bisphosphonate use	213 (43.9)	129 (54.0)
Presence of bone metastases at baseline in patients, No. (%)	n = 371	n = 185
With baseline bisphosphonate use	199 (53.6)	121 (65.4)
Without baseline bisphosphonate use	172 (46.4)	64 (34.6)
Rates of bisphosphonate use at baseline in patients, No. (%)	n = 213	n = 129
With baseline bone metastases	199 (93.4)	121 (93.8)
Without baseline bone metastases	14 (6.6)	8 (6.2)

Changes in bone turnover marker levels at 6 and 12 weeks vs baseline in the overall population
- BOLERO 2 -



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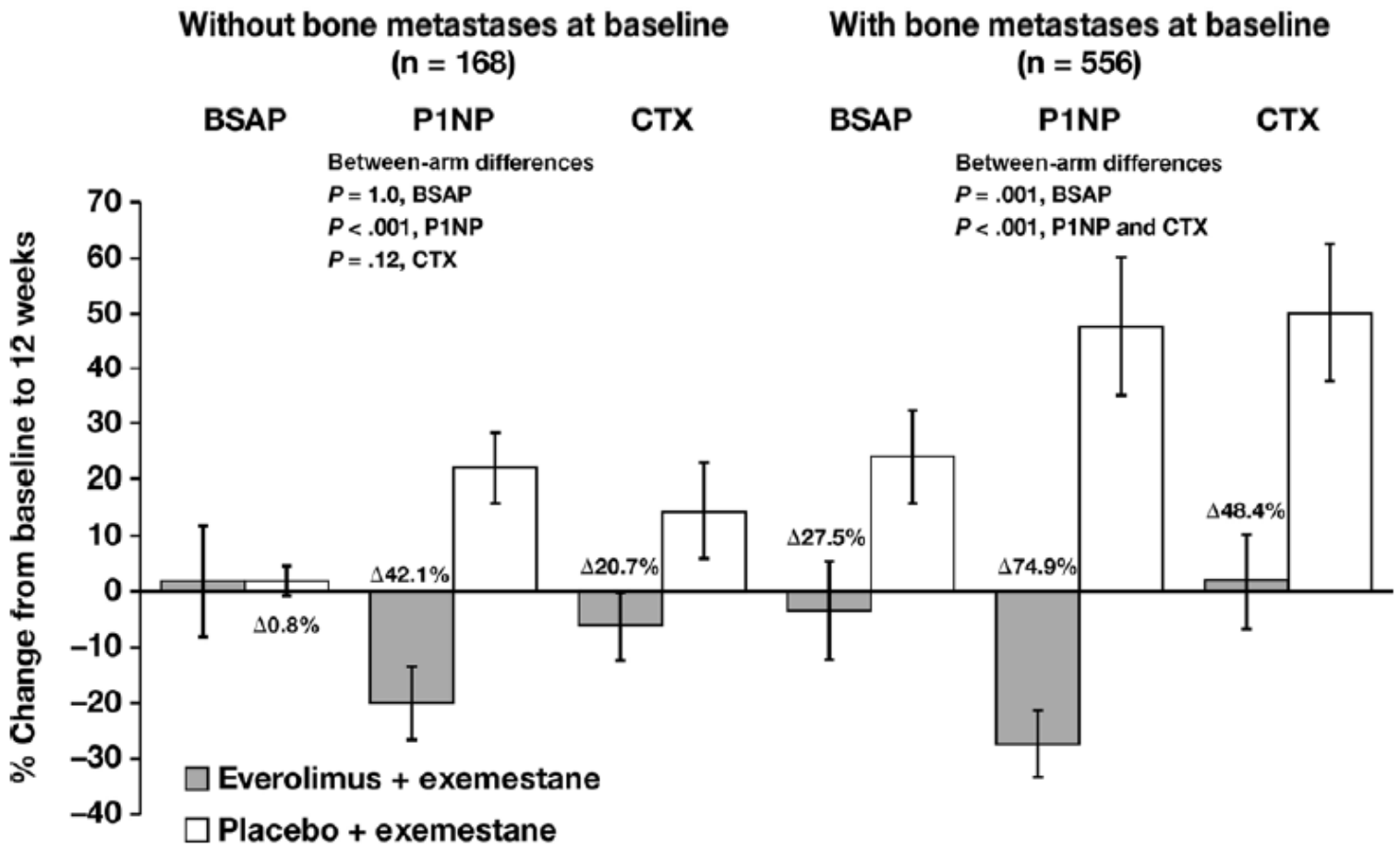
Changes in bone turnover marker levels at 12 weeks vs baseline in patients with or without bone metastases at baseline. - BOLERO 2 -



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Summary of progression-free survival
- BOLERO 2 -

	Everolimus + Exemestane	Exemestane + Placebo
Overall population, No. (%)	n = 485	n = 239
Total number of PFS events	310 (63.9)	200 (83.7)
Deaths before progression	n 16 (3.3)	2 (0.8)
Progressive disease	294 (60.6)	198 (82.8)
Progressive disease in bone	63 (13.0)	45 (18.8)
Patients with baseline bone metastases, No. (%)	n = 371	n = 185
Progressive disease	239 (64.4)	151 (81.6)
Progressive disease in bone	60 (16.2)	43 (23.2)

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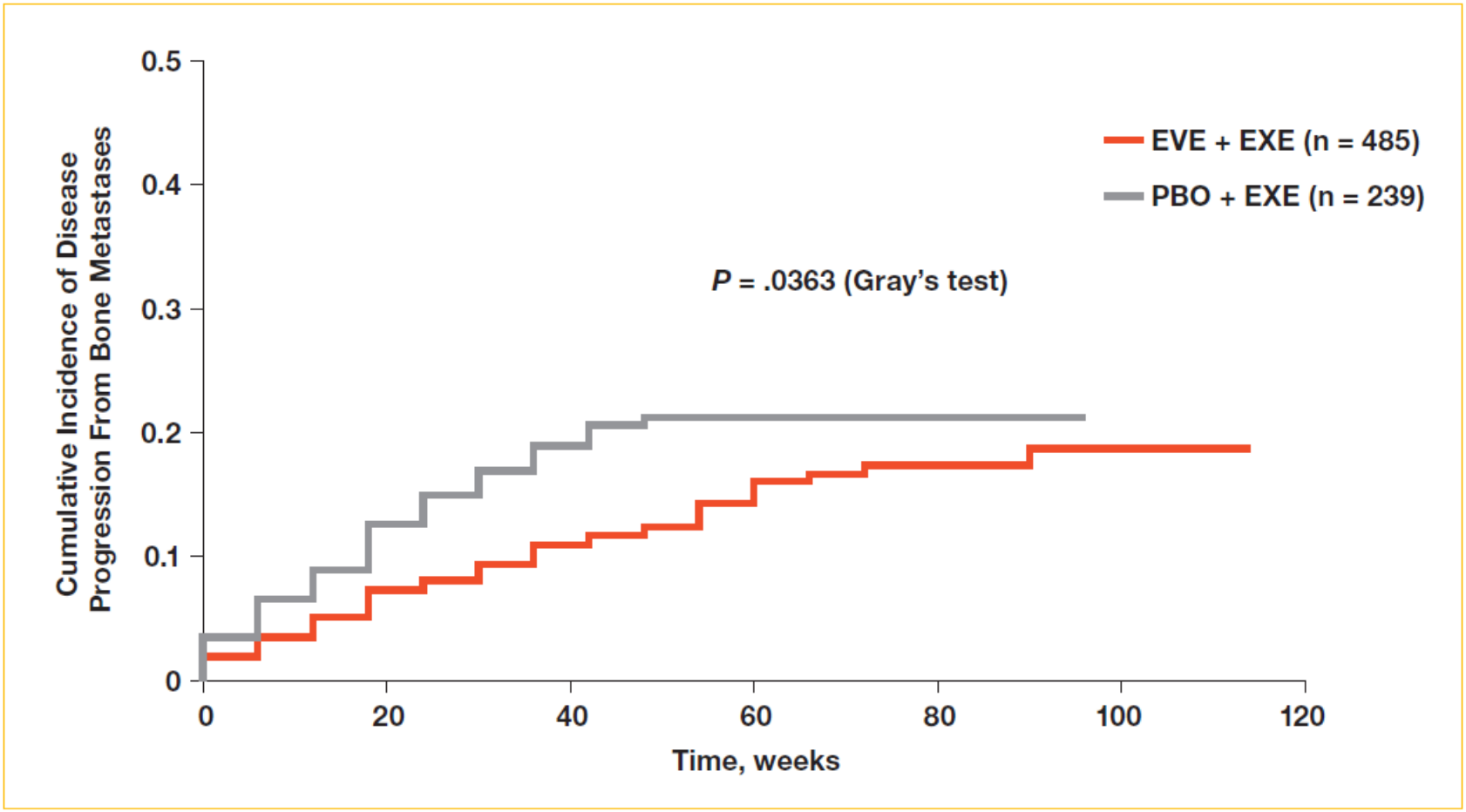
Progressive disease in bone in the overall population



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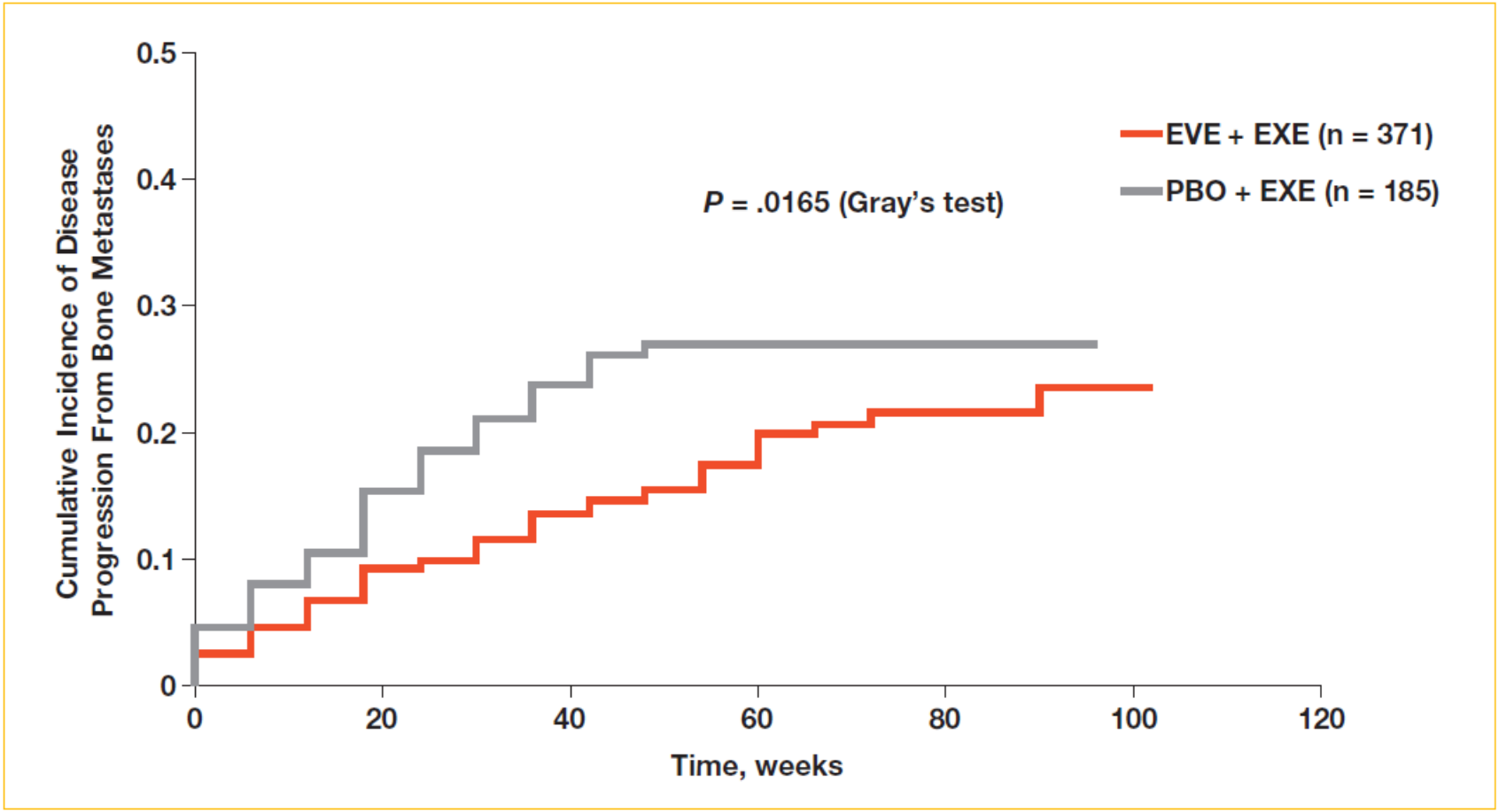
Progressive disease in bone in patients with bone metastases at baseline



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Bone related adverse events

	Everolimus + Exemestane, % (n = 482)		Placebo + Exemestane, % (n = 238)	
Adverse Event	**All Grades**	**Grade 3[b]**	**All Grades**	**Grade 3[b]**
Any	3.3	0	4.2	1.7
All fractures[a]	2.3	0	3.8	1.7
Femur	0	0	0.8	0.8
Hip	0	0	0.4	0.4
Rib	1.5	0	0.4	0
Spinal	0.2	0	0	0
Spinal compression	0.4	0	0	0
Wrist	0.2	0	0	0
Pubis	0	0	0.4	0
Pathological fracture	0	0	1.3	0.4
Osteonecrosis of the jaw	0.4	0	0.4	0
Osteonecrosis (other)	0.4	0	0	0
Osteoporosis	0.4	0	0	0

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Conclusions

Bone marker data suggest that EVE ↓ bone turnover and reverses the increase in bone resorption associated with endocrine therapy (ie, EXE) regardless of the presence of bone metastases or BP use at baseline

– Bone-protective effect with EVE suggests the potential for using EVE in the adjuvant BC setting for this purpose

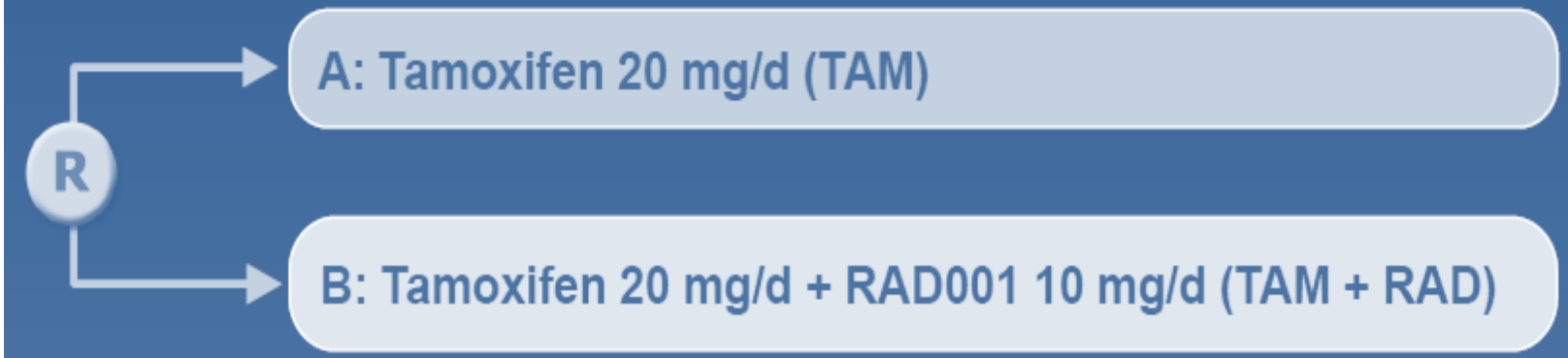
EVE + EXE ↓ disease progression in bone vs PBO + EXE

– Potential mTOR signaling in osteoclast survival might account for the ↓ bone turnover and ↓ disease progression in bone with EVE

TAMRAD Protocol

Randomized phase II

Metastatic patients with previous exposure to AIs



- **Stratification: Primary or secondary hormone resistance**
  - **Primary: Relapse during adjuvant AI treatment; progression within 6 months of starting AI treatment in metastatic setting**
  - **Secondary: Late relapse (≥6 months) or previous response and subsequent progression to metastatic AI treatment**

Bachelot, JCO 2012

Patient Characteristics

	TAM n = 57	TAM + RAD n = 54
Median age, years (range)	66 (42-86)	62.5 (41-81)
Median duration of metastatic disease, months (range)	14.4 (0.7-102)	13.2 (1.2-94.8)
Disease stage, n (%)		
Bone	45 (78.9)	41 (75.9)
Bone only	14 (24.6)	16 (29.6)
Visceral	28 (49.1)	31 (57.4)
3 or more	16 (28.1)	13 (24.1)
Previous anti-aromatase treatment, n (%)		
Adjuvant only	20 (35.1)	17 (31.5)
Metastatic only	33 (57.9)	33 (61.1)
Adjuvant + metastatic	4 (7)	4 (7.4)
Previous adjuvant TAM treatment, n (%)	24 (42.1)	18 (33.3)
Previous chemotherapy, n (%)		
Adjuvant	32 (56.1)	25 (46.3)
Metastatic	15 (26.3)	13 (24.1)

Bachelot, JCO 2012

Clinical Benefit in Selected Subgroup

CBR, n (%)	TAM n = 57	TAM + RAD n = 54
ALL	24/57 (42.1)	33/54 (61.1)
Visceral metastases	11/28 (39.3)	19/31 (61.3)
No visceral metastases	13/29 (44.8)	14/23 (60.9)
Previous adjuvant tamoxifen	9/24 (37.5)	12/18 (66.7)
No previous adjuvant tamoxifen	15/33 (45.5)	21/36 (58.3)
Previous metastatic chemotherapy	4/15 (26.7)	6/13 (46.2)
No previous metastatic chemotherapy	20/42 (47.6)	27/41 (65.9)
Primary hormone resistance	10/28 (35.7)	12/26 (46.2)
Secondary hormone resistance	14/29 (48.3)	20/27 (74.1)

Bachelot, JCO 2012