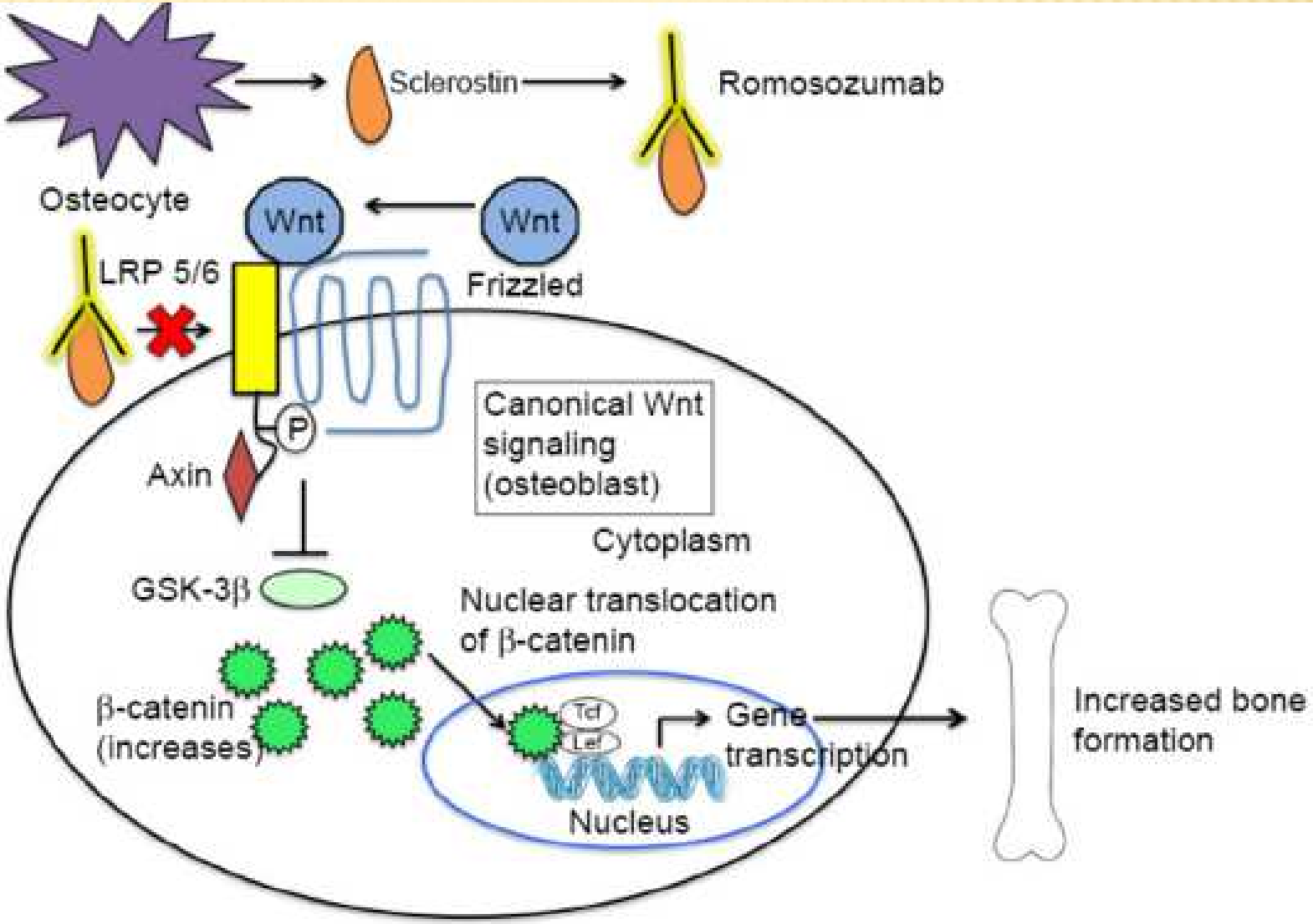
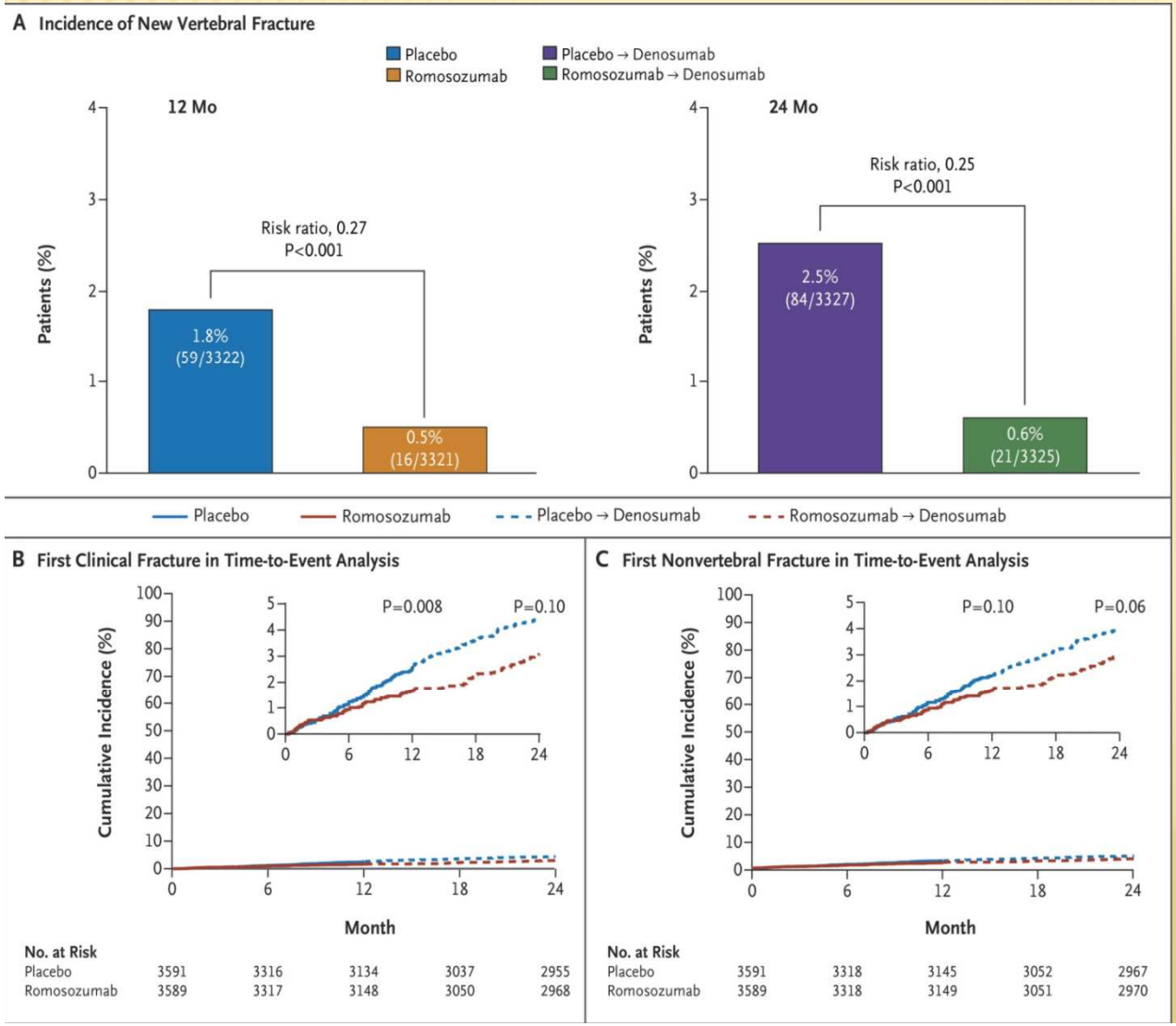
ACTUALITÉS 2018
SUR LES TRAITEMENTS DE L'OSTÉOPOROSE
LE CŒUR FENDU?

Yves Maugars

ROMOSOZUMAB



ROMOSOZUMAB: ÉTUDE PIVOT

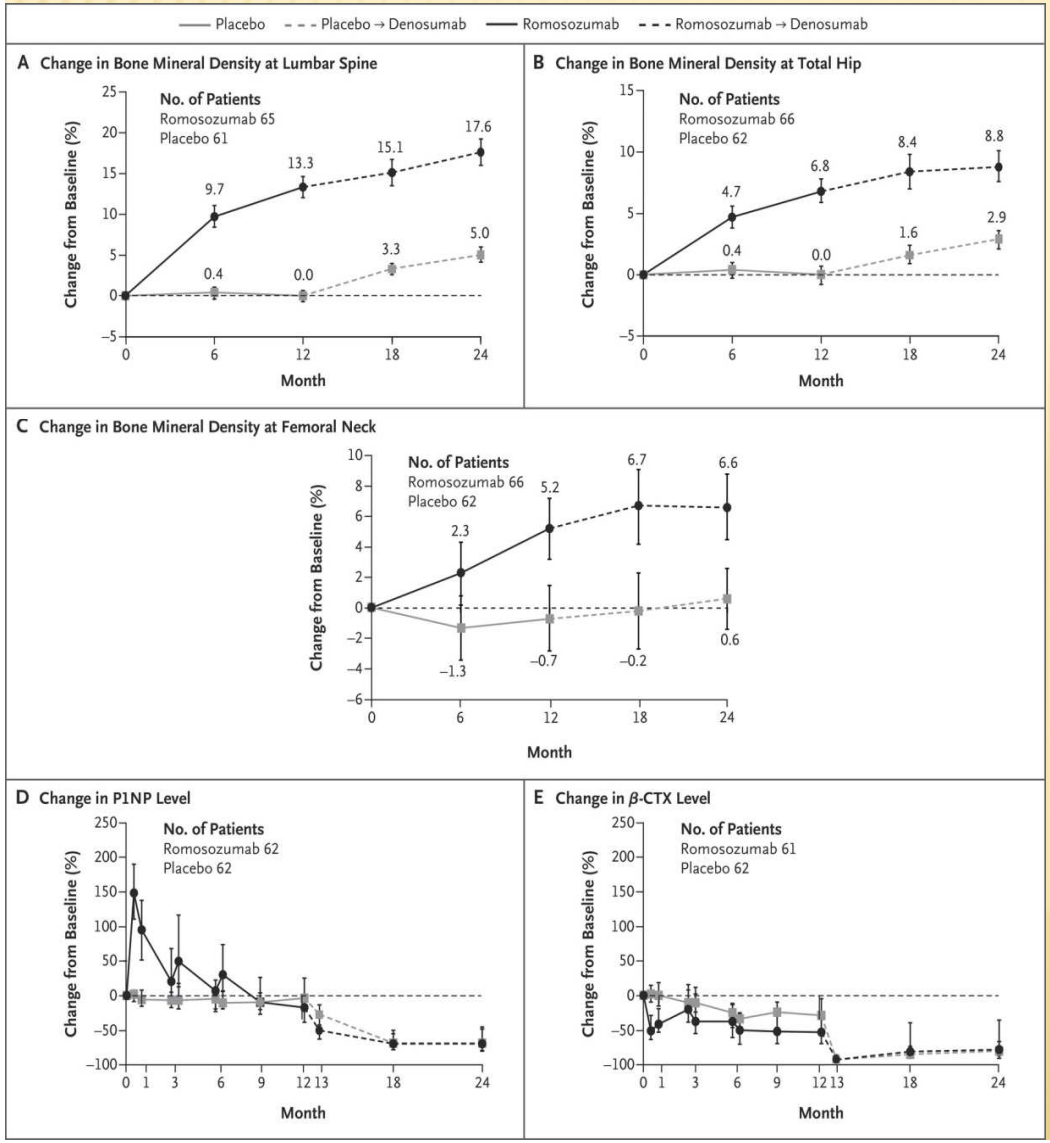


Efficacité sur les fractures vertébrales (-75%)

mais chiffres limites sur les fractures périphériques (-25%)

Cosman et al.
Romosozumab Treatment in Postmenopausal Women with Osteoporosis.
N Engl J Med. 2016 ;375:1532-1543

ROMOSOZUMAB: ÉTUDE PIVOT



DMO +17,6% en 2 ans en lombaire et +8,8% à la hanche

Marqueurs de la formation: +150% rapidement épuisable,

encore plus inhibés par le Déno

Marqueurs de la résorption: -50% non épuisable,

encore plus inhibés par le Déno

Quasiment plus de remodelage

Cosman et al.
Romosozumab Treatment in Postmenopausal Women with Osteoporosis.
N Engl J Med. 2016 ;375:1532-1543

ROMOSOZUMAB: ÉTUDE PIVOT

Table 2. Adverse Events.*

Event	12 Months		24 Months	
	Placebo (N=3576)	Romosozumab (N=3581)	Placebo to Denosumab (N=3576)	Romosozumab to Denosumab (N=3581)
	number of patients (percent)			
Adverse event during treatment†	2850 (79.7)	2806 (78.4)	3069 (85.8)	3053 (85.3)
Arthralgia	429 (12.0)	467 (13.0)	565 (15.8)	585 (16.3)
Nasopharyngitis	438 (12.2)	459 (12.8)	546 (15.3)	557 (15.6)
Back pain	378 (10.6)	375 (10.5)	516 (14.4)	463 (12.9)
Serious adverse event	312 (8.7)	344 (9.6)	540 (15.1)	565 (15.8)
Adjudicated serious cardiovascular event‡	41 (1.1)	44 (1.2)	79 (2.2)	82 (2.3)
Death	23 (0.6)	29 (0.8)	47 (1.3)	52 (1.5)
Adjudicated cardiovascular death‡	15 (0.4)	17 (0.5)	29 (0.8)	31 (0.9)
Event leading to discontinuation of trial regimen	94 (2.6)	103 (2.9)	110 (3.1)	122 (3.4)
Event leading to discontinuation of trial participation	50 (1.4)	44 (1.2)	56 (1.6)	52 (1.5)
Event of interest§				
Hypocalcemia	0	1 (<0.1)	3 (0.1)	6 (0.2)
Hypersensitivity¶	245 (6.9)	242 (6.8)	331 (9.3)	314 (8.8)
Injection-site reaction‖	104 (2.9)	187 (5.2)	106 (3.0)	188 (5.2)
Hyperostosis	27 (0.8)	19 (0.5)	40 (1.1)	35 (1.0)
Cancer	69 (1.9)	59 (1.6)	100 (2.8)	105 (2.9)
Osteoarthritis	315 (8.8)	281 (7.8)	431 (12.1)	396 (11.1)
Osteonecrosis of the jaw‡	0	1 (<0.1)	0	2 (<0.1)
Atypical femoral fracture‡	0	1 (<0.1)	0	1 (<0.1)

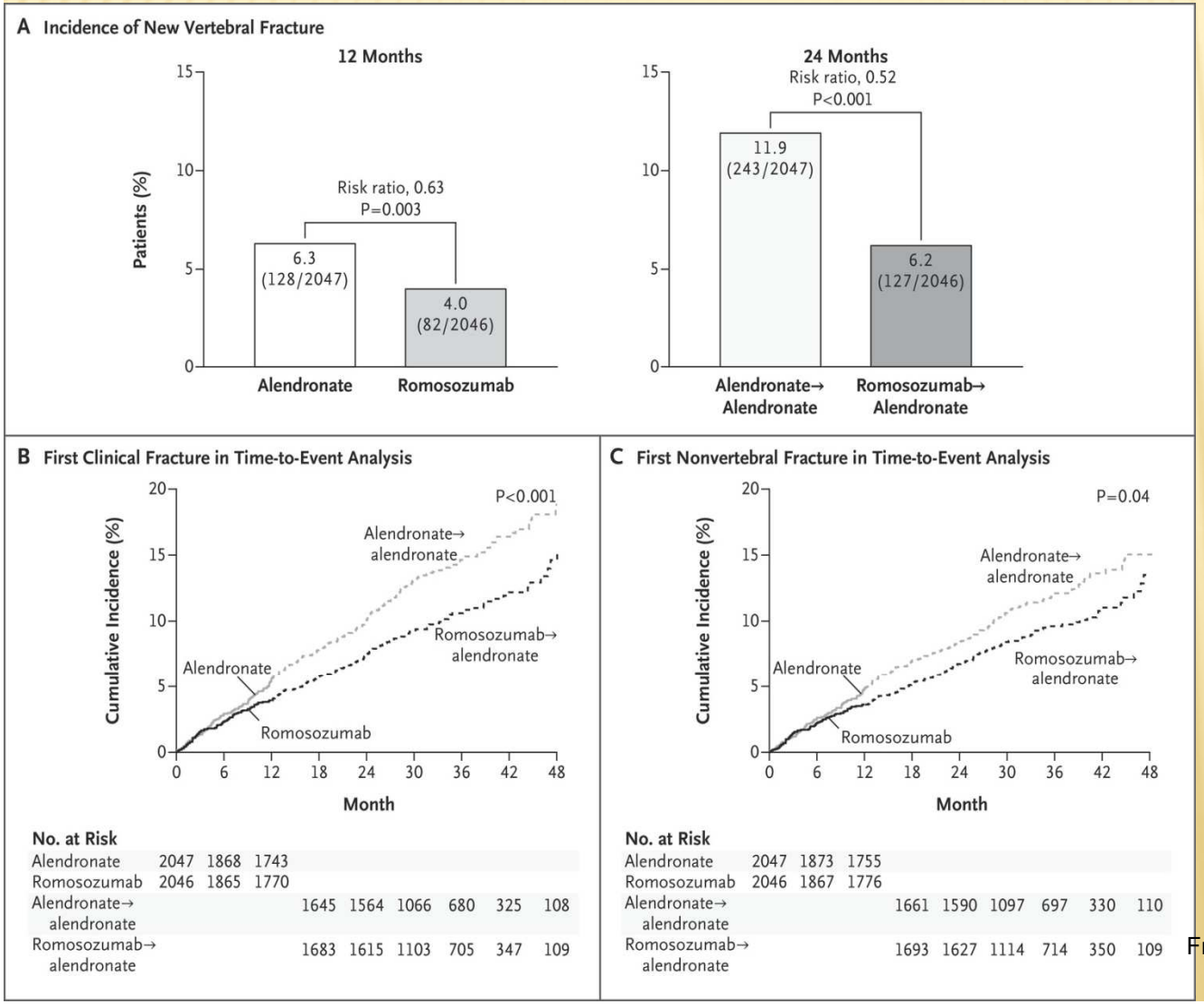
* The population for this analysis included all the patients who underwent randomization and received at least one dose of placebo or romosozumab in the 12-month double-blind period. At month 12, patients made the transition to denosumab for the second year of the trial.
† The events listed are the most frequent adverse events in the double-blind period that occurred in 10% or more of the patients in either group.
‡ The events listed include adverse events that were adjudicated as positive by an independent adjudication committee. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (presumed to be cardiac-related).
§ Events of interest were those that were identified by prespecified *Medical Dictionary for Regulatory Activities* search strategies.
¶ Seven patients in the romosozumab group had serious adverse events during the 12-month double-blind period. Events that were reported by the investigator as being related to romosozumab included dermatitis, allergic dermatitis, and macular rash, all of which resolved; the drug was withdrawn or withheld in these cases.
‖ The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the 12-month double-blind period included injection-site pain (in 1.7% of the patients), erythema (1.5%), bruising (0.8%), pruritus (0.7%), swelling (0.4%), hemorrhage (0.4%), rash (0.3%), and hematoma (0.2%).

Effets secondaires

Pas de différence entre les groupes

Cosman et al.
Romosozumab Treatment in Postmenopausal Women with Osteoporosis.
N Engl J Med. 2016 ;375:1532-1543

ROMOSO VS ALENDRONATE

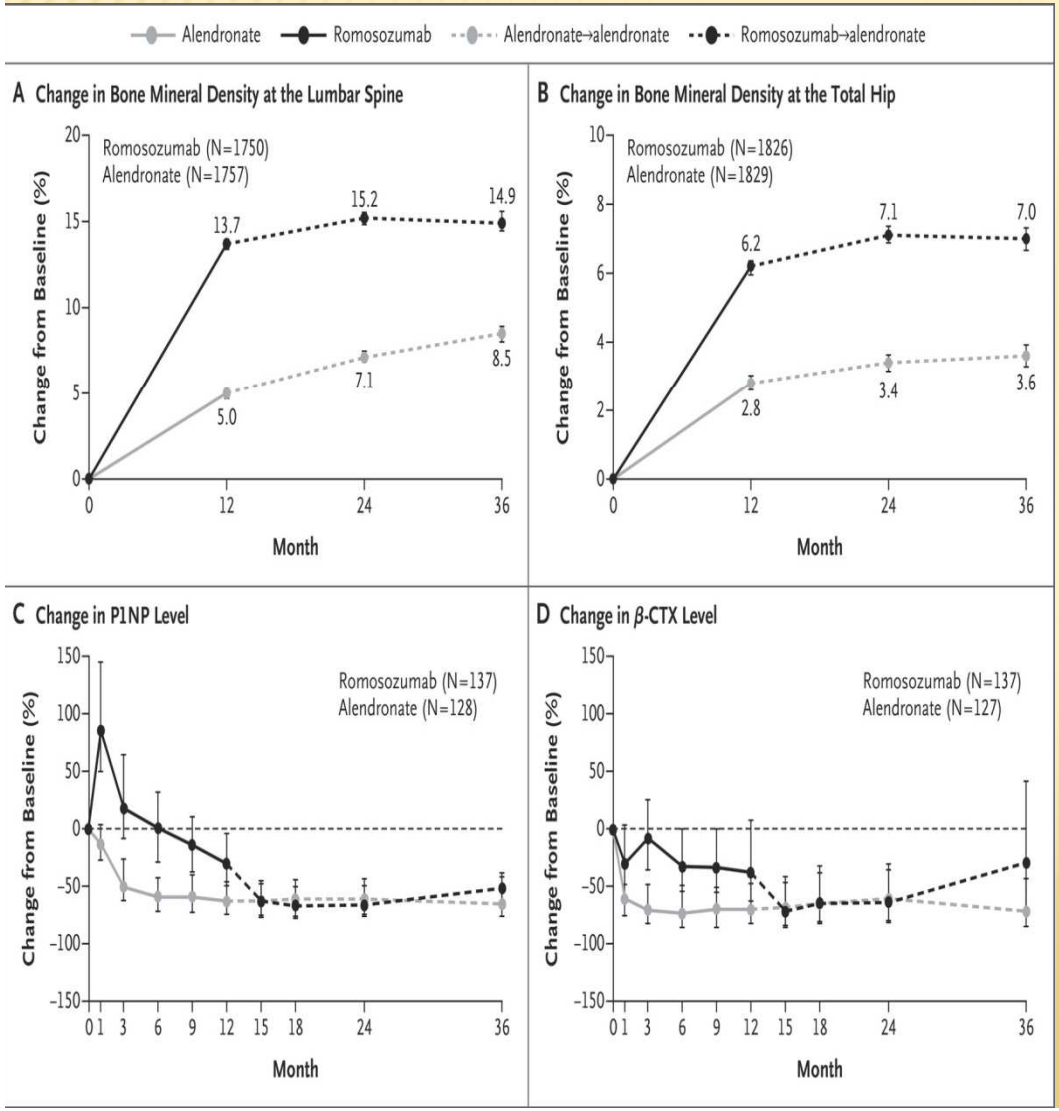


Supériorité à 2 ans significative tant en vertébral qu'en périphérique:

Gain de -48% FV et de -19% Fp

Saag et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med. 2017;377:1417-1427

ROMOSO VS ALENDRONATE



- DMO quasiment doublée, tant en axial qu'en périphérique
- Marqueurs de la formation: +100% rapidement épuisable, encore plus inhibés par l'Alendro
- Marqueur de la résorption: -50% non épuisable, encore plus inhibés par l'Alendro

Saag et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med. 2017;377:1417-1427

ROMOSO VS ALENDRONATE

Table 2. Adverse Events.

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Event of interest¶				
Osteoarthritis‖	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Hypersensitivity	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Injection-site reaction**	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Cancer	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Hyperostosis††	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Hypocalcemia	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Atypical femoral fracture‡	0	0	4 (0.2)	2 (<0.1)
Osteonecrosis of the jaw‡	0	0	1 (<0.1)	1 (<0.1)

* Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27, 2017) in patients who received at least one dose of open-label alendronate.
† Shown are events that occurred in 10% or more of the patients in either group during the double-blind period.
‡ Serious cardiovascular adverse events were adjudicated by the Duke Clinical Research Institute, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were adjudicated by independent committees. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (and, therefore, possibly cardiovascular-related).
§ One patient had a non–treatment-related serious adverse event of pneumonia that was incorrectly flagged as death in the primary analysis snapshot and was not included in the analysis of fatal events.
¶ Events of interest were those that were identified by prespecified *Medical Dictionary for Regulatory Activities* search strategies.
‖ Prespecified events that were reported under osteoarthritis were osteoarthritis, spinal osteoarthritis, exostosis, arthritis, polyarthritis, arthropathy, monoarthritis, and interspinous osteoarthritis.
** The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the double-blind period included injection-site pain (in 1.6% of the patients), erythema (1.3%), pruritus (0.8%), hemorrhage (0.5%), rash (0.4%), and swelling (0.3%).
†† Prespecified events reported under hyperostosis were exostosis (mostly reported as heel spurs), lumbar spinal stenosis, spinal column stenosis, cervical spinal stenosis, enostosis, extraskeletal ossification, and vertebral foraminal stenosis.

Effets secondaires

+0,6% de complications cardio-vasculaires

Ro 2,5% vs Al 1,9%

Décès: 1,5% vs 1%

(CV: 0,8% vs 0,6%)

IDM: 0,8% vs 0,3%

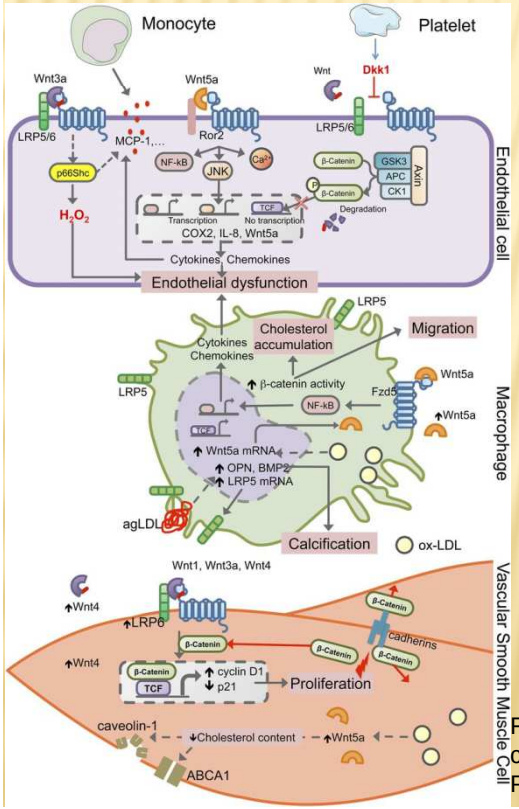
AVC: 0,8% vs 0,3%

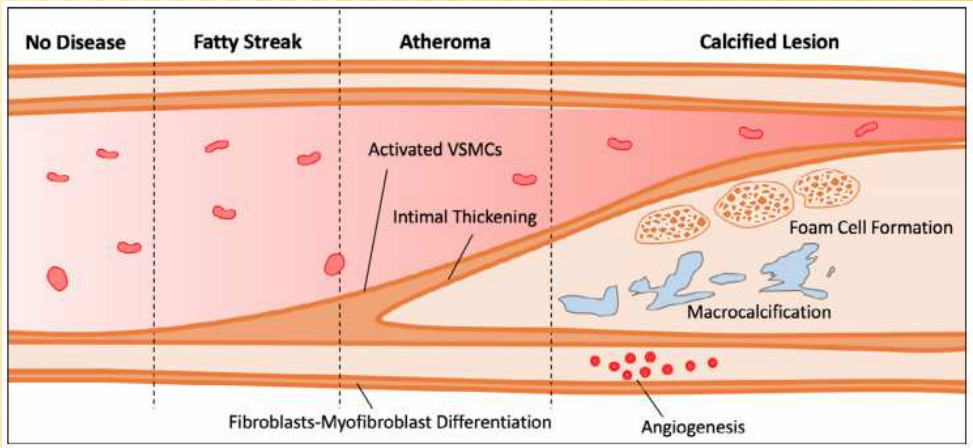
Saag et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med. 2017;377:1417-1427

PHYSIOPATHOGENIE DE LA CALCIFICATION ATHEROMATEUSE

La voie Wnt (inhibée par la sclérostine), par ses 2 voies, canonique et non canonique, permet l'adhésion du monocyte, la prolifération cellulaire, la différenciation de cellules spumeuses, et la genèse de calcifications, favorisant la sténose artérielle.

La Sclérostine est un inhibiteur de l'athérosclérose chez la souris.

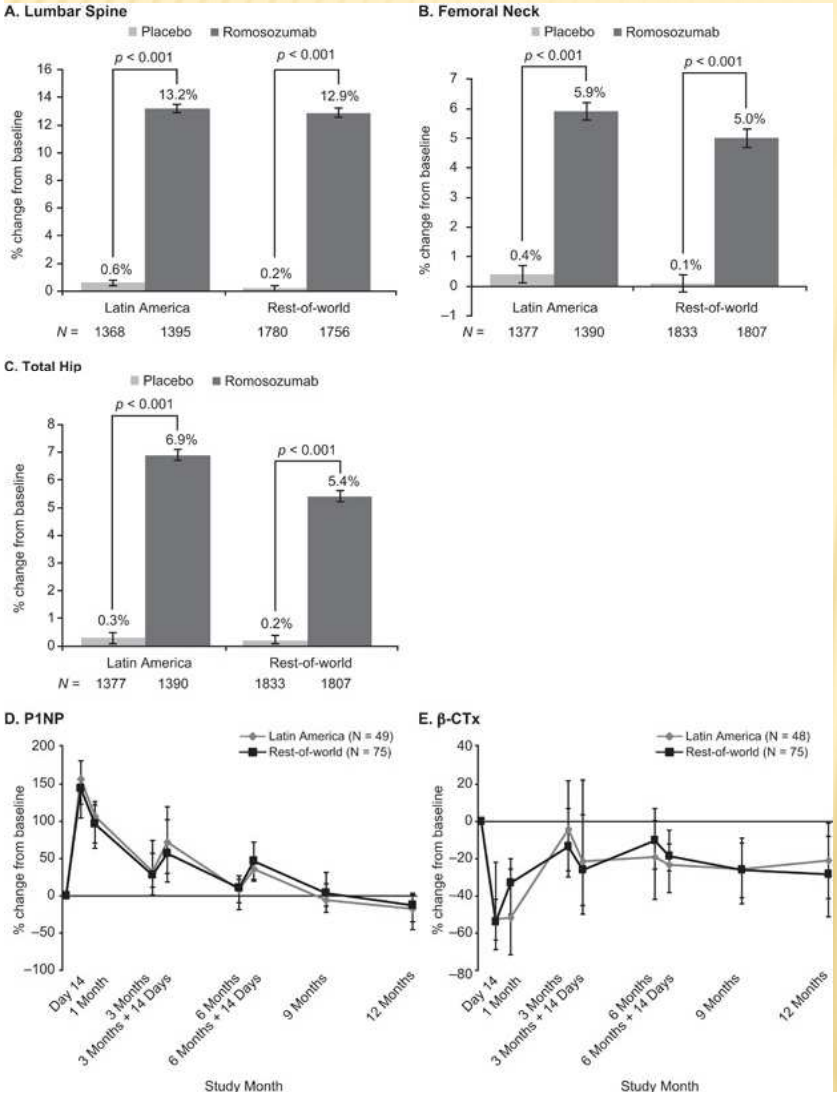




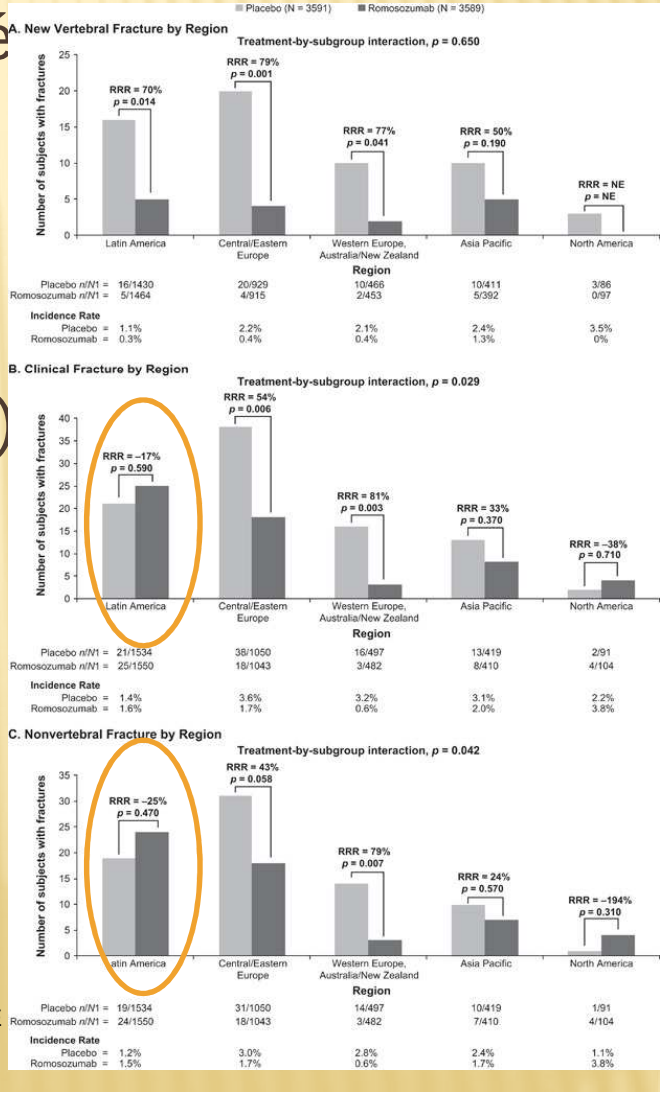
Foulquier et al. Wnt signaling in cardiac and vascular disease. Pharmacol Rev 2018;70:68-141

Albanese et al. Atherosclerostic calcification: Wnt is the hint. J Am Heart Assoc 2018;7:e007356

ROMOSOZUMAB CHEZ LES LATINS

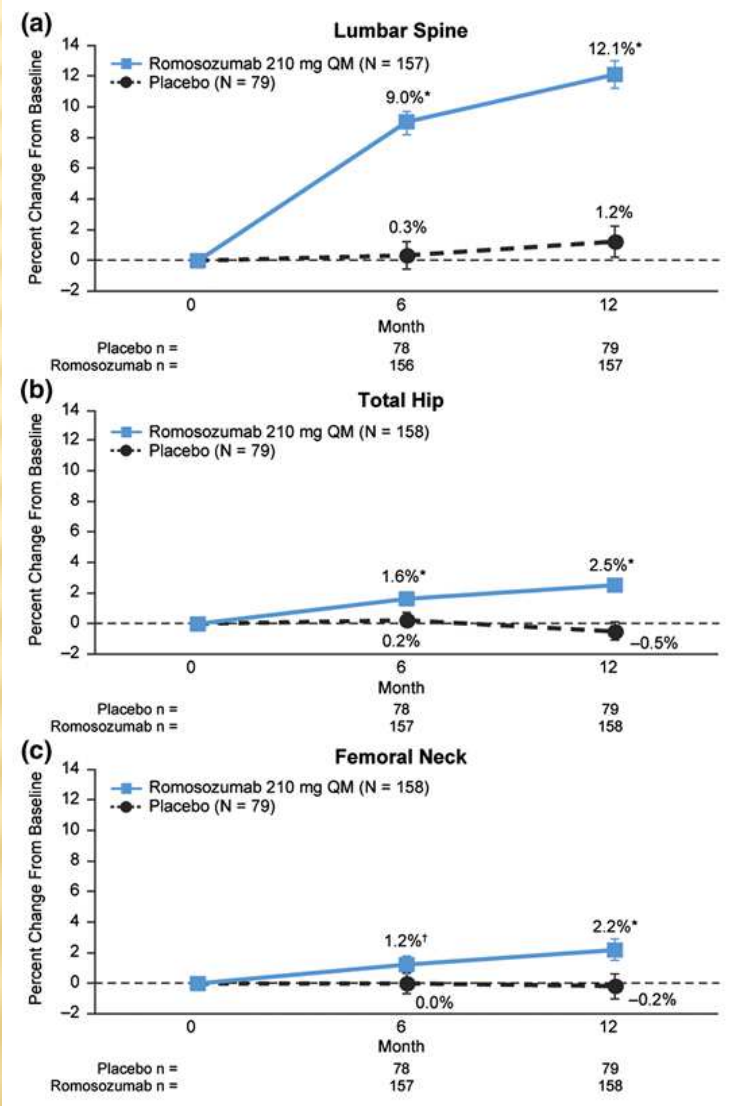


Pas d'efficacité sur les fractures périphériques des « latins » (43% patients)



Cosman F et al. Romosozumab FRAME Study.
J Bone Miner Res. 2018;33:1407-1416

ROMOSO HOMMES

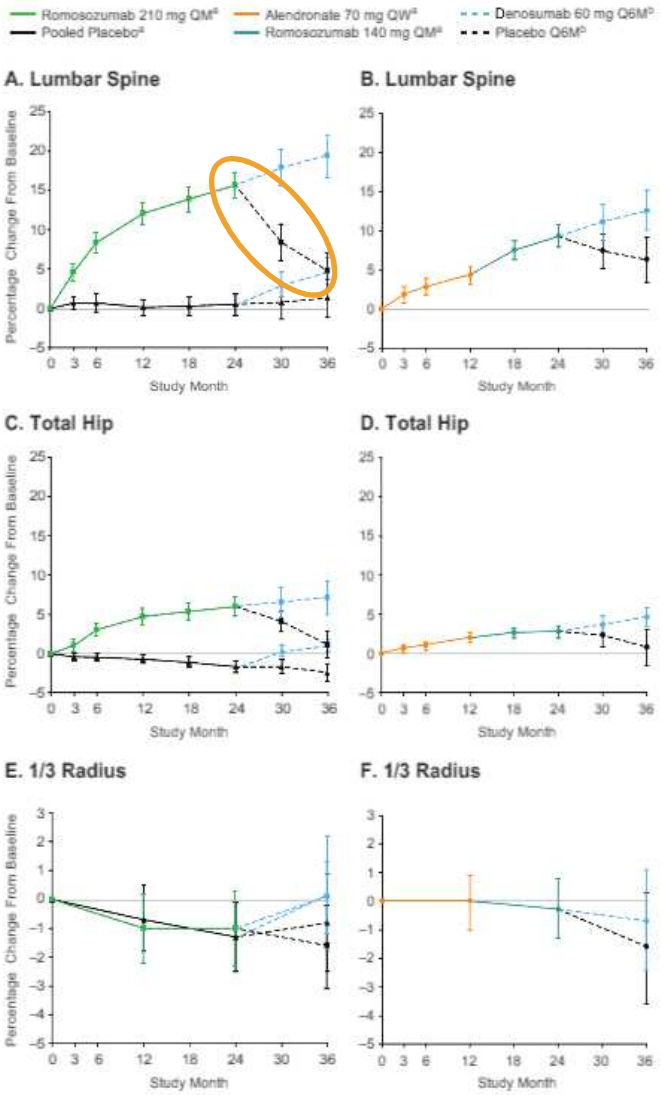


Effet similaire à la femme en terme de DMO mais aussi avec une augmentation du risque cardio-vasculaire mais pas de surmortalité

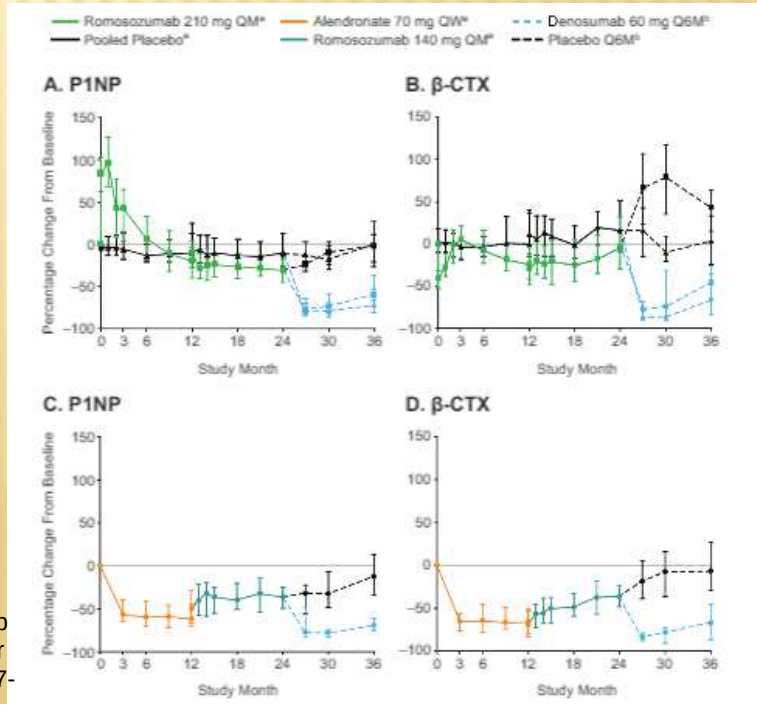
Lewiecki et al. A Phase 3 Randomized Placebo-controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis. J Clin Endocrinol Metab. 2018 Jun 2018

Adverse event, n (%)	Romosozumab 210 mg QM (N = 163)	Placebo (N = 81)
Any adverse event	123 (75.5)	65 (80.2)
Serious adverse event	21 (12.9)	10 (12.3)
Adjudicated cardiovascular serious adverse event[a]	8[b] (4.9)	2 (2.5)
Cardiac ischemic event	3 (1.8)	0 (0.0)
Cerebrovascular event	3 (1.8)	1 (1.2)
Death[c,d]	2[e] (1.2)	1 (1.2)
Heart failure	1 (0.6)	0 (0.0)
Death	1 (0.6)	1 (1.2)
Leading to discontinuation of investigational product	5 (3.1)	1 (1.2)
Events of interest		
Hypocalcemia	0 (0.0)	0 (0.0)
Hypersensitivity	8 (4.9)	4 (4.9)
Injection-site reaction[f]	9 (5.5)	3 (3.7)
Malignancy	3 (1.8)	2 (2.5)
Hyperostosis	0 (0.0)	0 (0.0)
Osteoarthritis	8 (4.9)	4 (4.9)
Atypical femoral fracture[a]	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw[a]	0 (0.0)	0 (0.0)
Incident fracture[g]	3 (1.8)	2 (2.5)
Subject incidence of anti-romosozumab antibody formation		
Binding antibodies	28 (17.2)	NA
Neutralizing antibodies	1 (0.6)	NA

SUIVI À 3 ANS DE LA PHASE 2
ROMOSO VS PBO, PUIS DÉNO VS PBO



Effet rebond majeur après arrêt du Romoso
Perte osseuse au 1/3 distal du radius
Pas d'effet inhibiteur d'un ttt BP préalable
Le Dénosumab garde son efficacité en appui
(mais effet rebond après arrêt du Romoso)



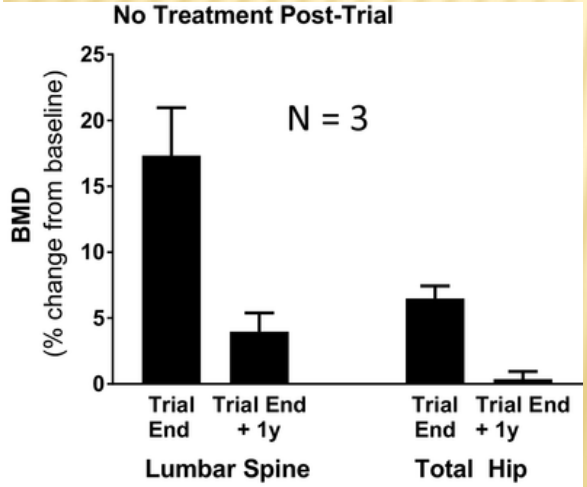
McClung et al. Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo. J Bone Miner Res. 2018;33:1397-

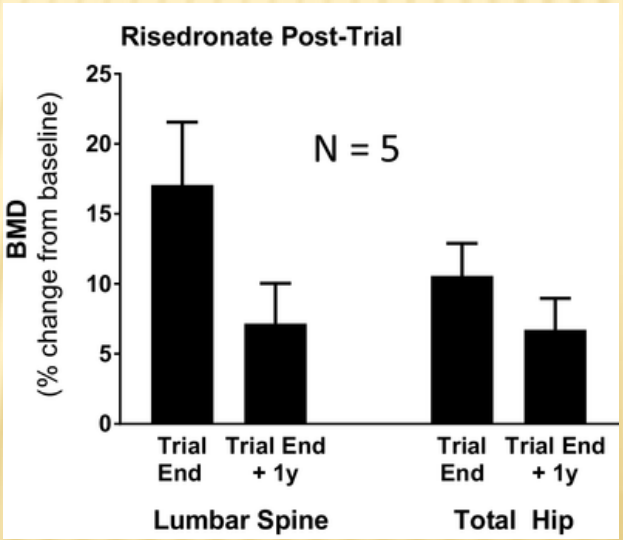
EFFET REBOND APRES ARRET DU DENOSUMAB

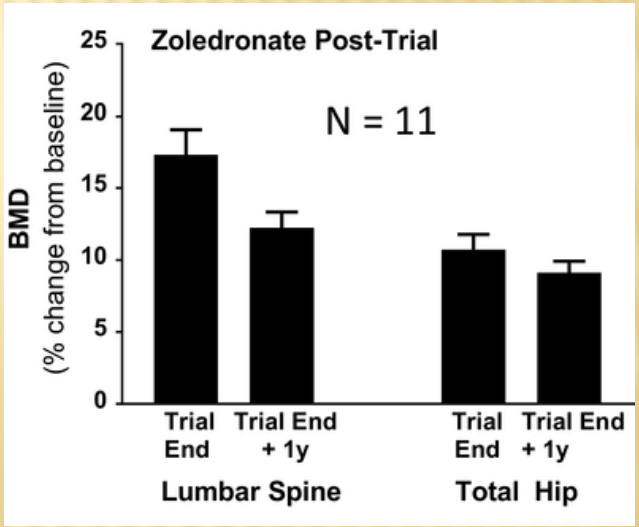
Etude FRAME: ROMO 1 an vs Pbo, puis 1 an de Denosumab

- 11 patientes traitées par Zolédronate
- 5 traitées par Risédronate
- 3 sans traitement

Résultats à 1 an

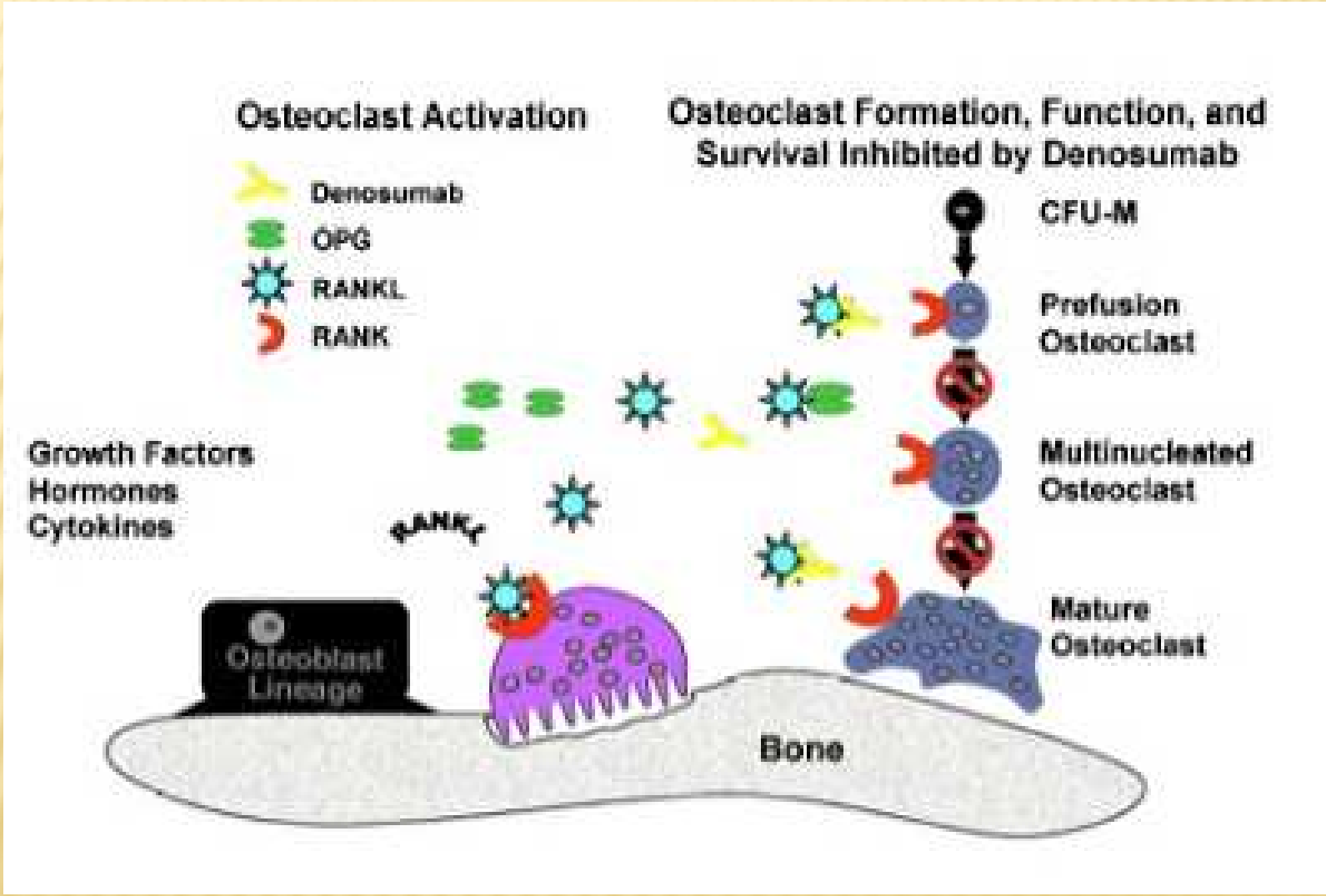




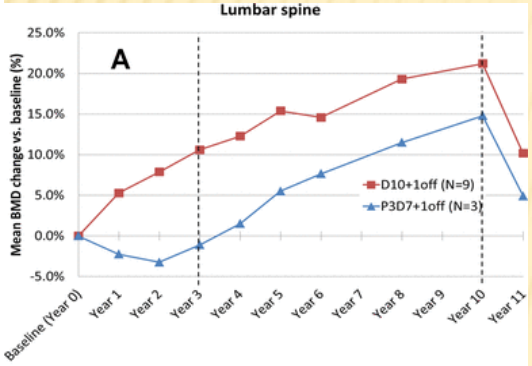


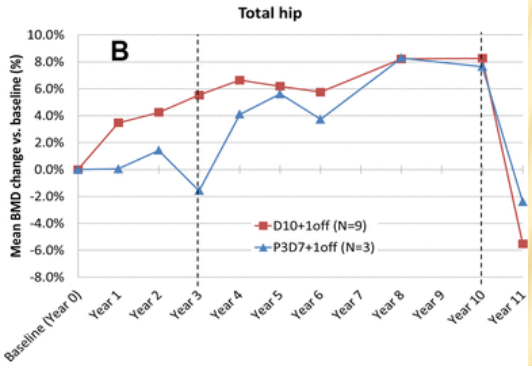
Horne et al. Bone Loss After Romosozumab/Denosumab: Effects of

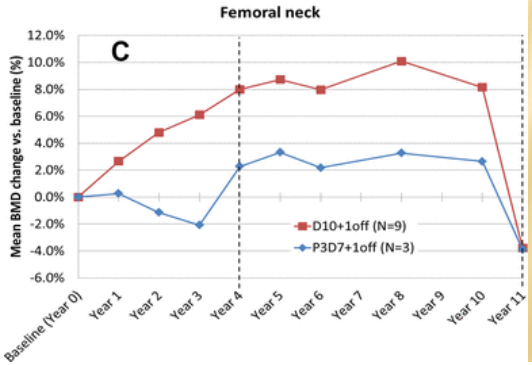
DENOSUMAB


Osteoclast Activation
Denosumab
OPG
RANKL
RANK
Growth Factors
Hormones
Cytokines
RANKL
Osteoblast Lineage
Bone
Osteoclast Formation, Function, and Survival Inhibited by Denosumab
CFU-M
Prefusion Osteoclast
Multinucleated Osteoclast
Mature Osteoclast

DENOSUMAB ET EFFET REBOND







Perte osseuse des gains préalables:

complète en 1 an !

Sur-risque de fracture vertébrale établi (-> 10%)

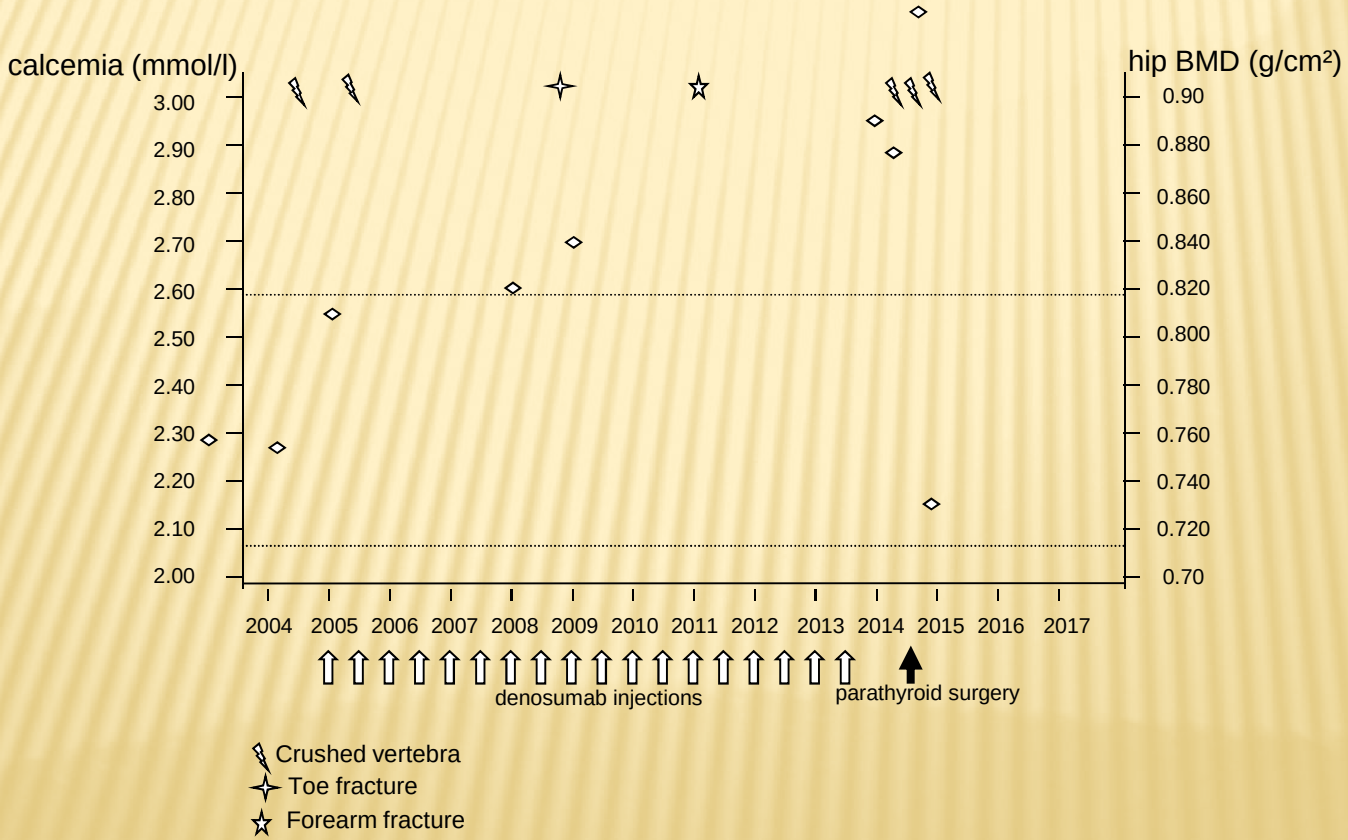
Parfois hypercalcémie

CTX très élevés

Popp et al. Bone Mineral Density Changes After 1 Year of Denosumab Discontinuation in Postmenopausal Women with Long-Term Denosumab Treatment for Osteoporosis. Calcif Tissue Int. 2018;103:50-54

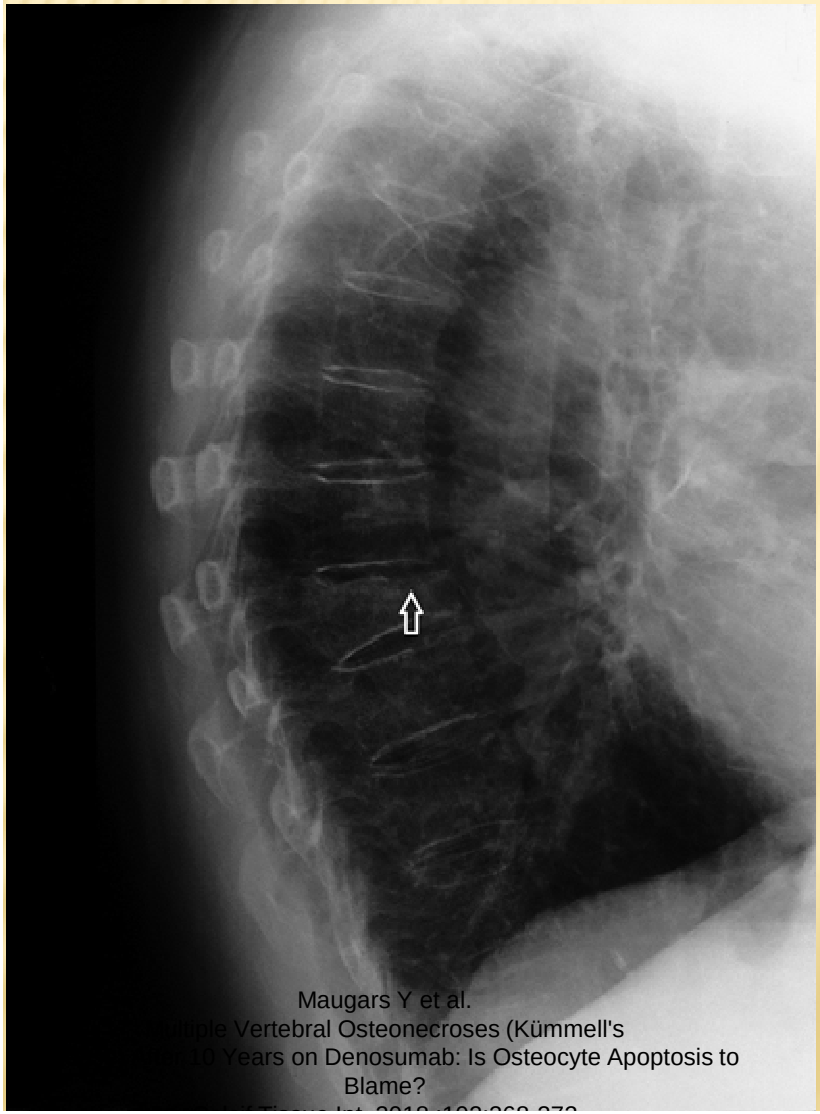
DENOSUMAB ET EFFET REBOND
OBSERVATION DU SERVICE

Calcemia, bone mineral density and fracture events for a patient treated with denosumab for 9 years who experienced a rebound effect when treatment was stopped
with combination of hypercalcemia related to hyperparathyroidism, multiple fractures, and rapid bone loss



soumis pour publication

DENOSUMAB ET EFFET REBOND OBSERVATION DU SERVICE



Maugars Y et al.
...ultiple Vertebral Osteonecroses (Kümmell's
...10 Years on Denosumab: Is Osteocyte Apoptosis to Blame?

10 ans de Dénosumab: pas de fracture avant / pendant traitement

DXA lombaire + 24% (T= -0,8)

DXA hanche + 13,4% (T= -1,6)

12 mois après arrêt Déno:

dorsalgie aigue puis rachialgies diffuses chronicisées

Rx: 4 fractures vertébrales successives

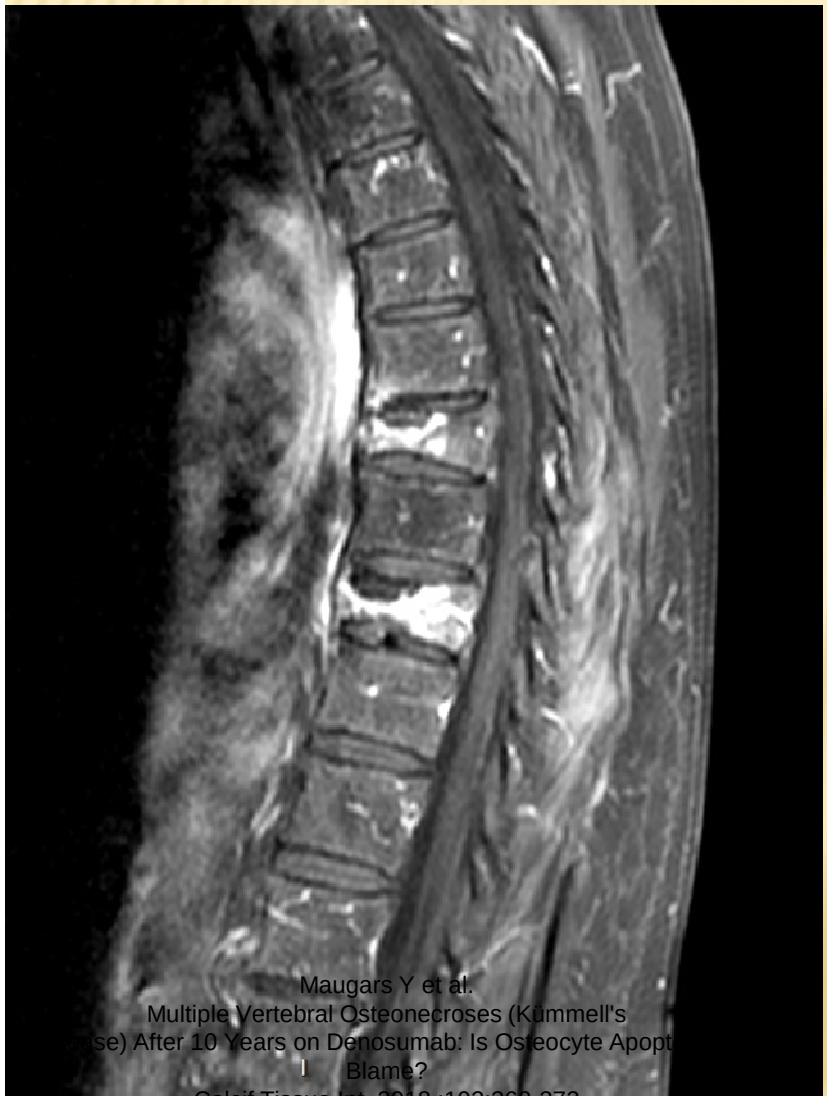
CTX 0,98 PBO: hyperremodelage

DXA (arrêt Déno = 18 mois)

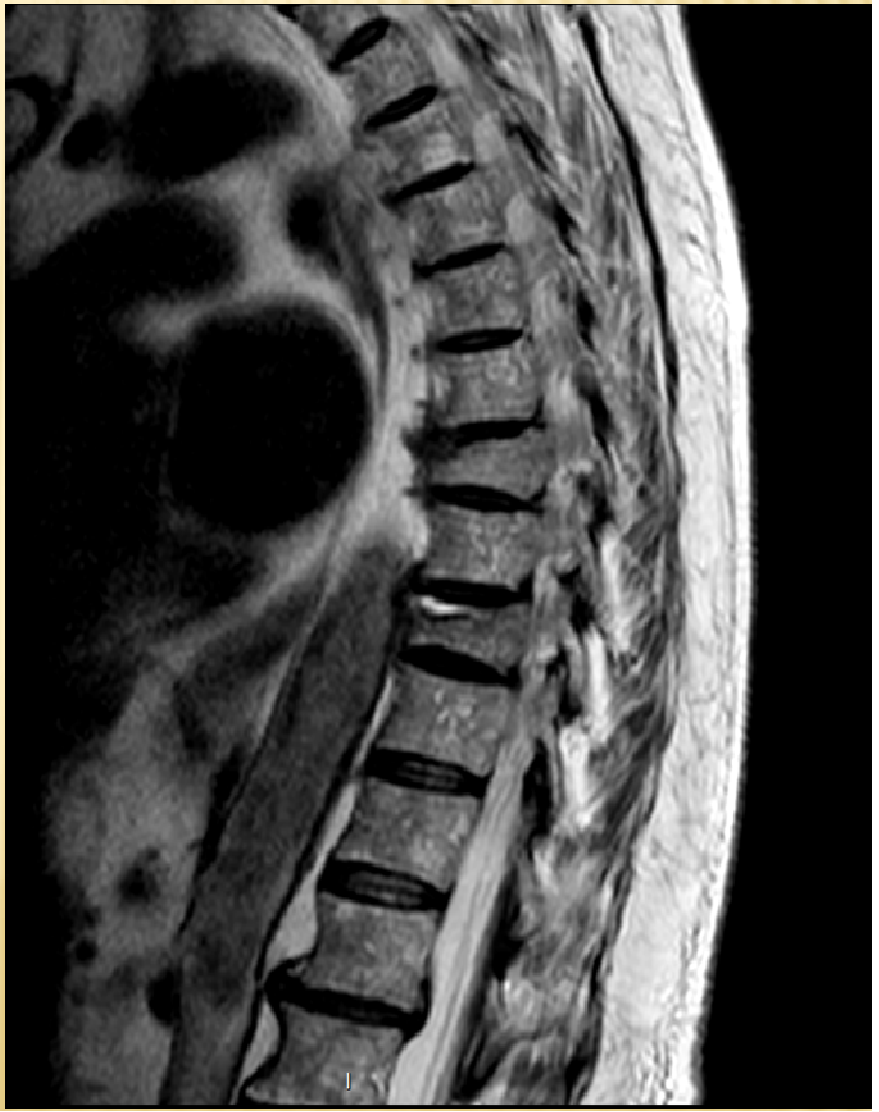
DMOl : -10,4%

DMOh: -13,8%

DENOSUMAB ET EFFET REBOND OBSERVATION DU SERVICE



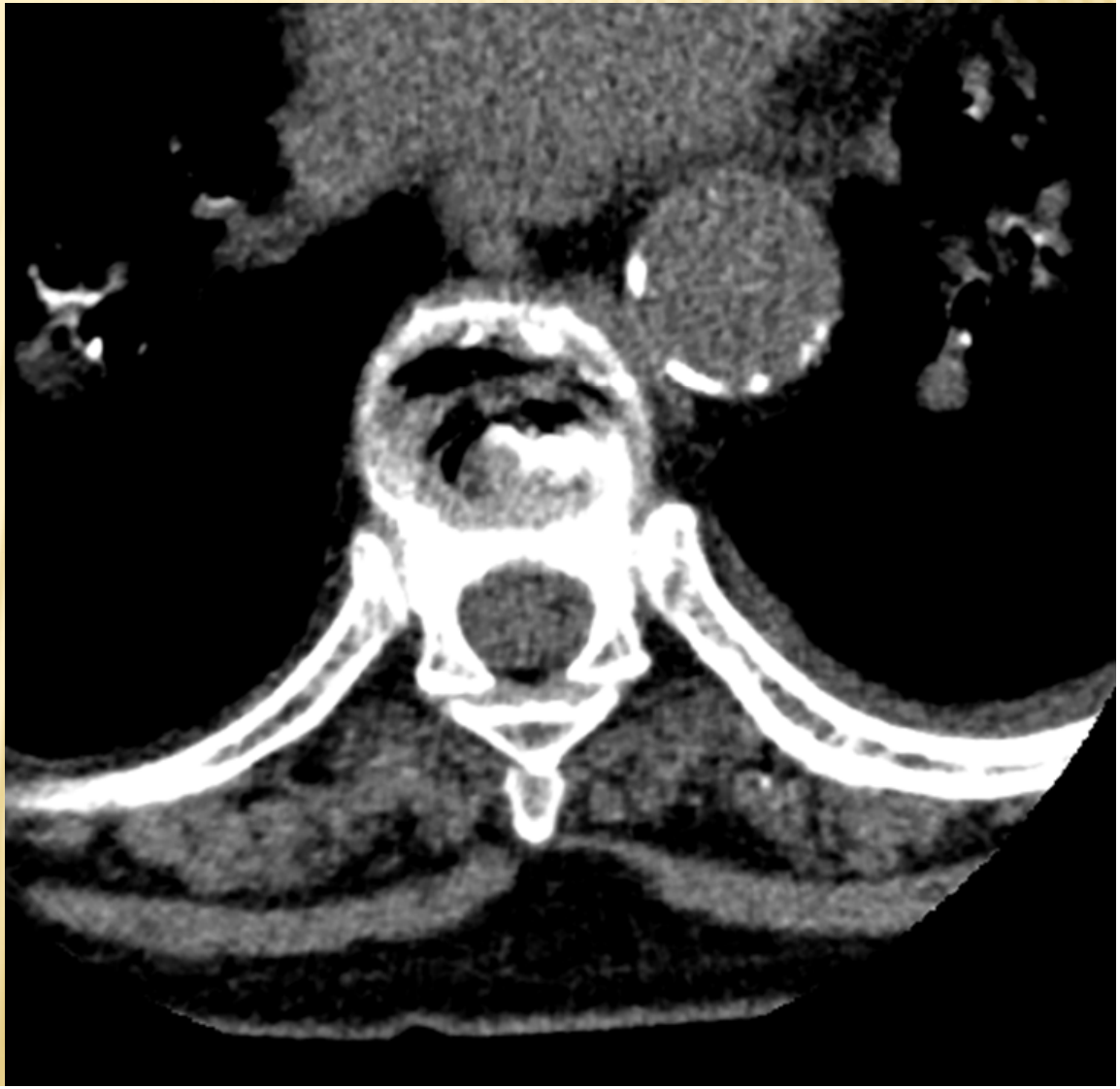
Maugars Y et al.
Multiple Vertebral Osteonecroses (Kümmell's
se) After 10 Years on Denosumab: Is Osteocyte Apopt
l Blame?



DENOSUMAB ET EFFET REBOND OBSERVATION DU SERVICE

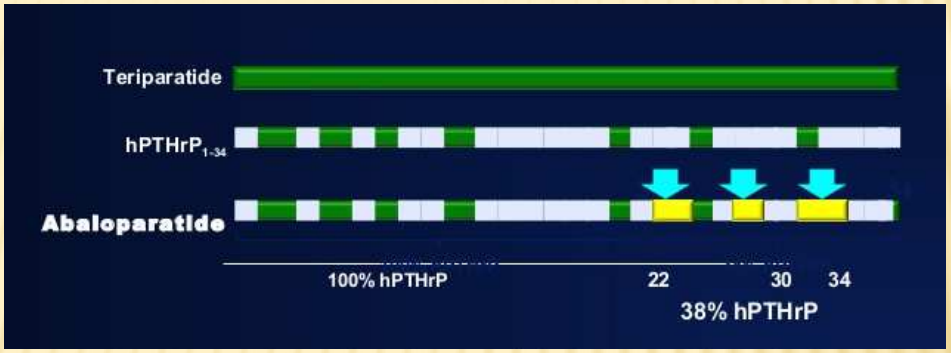
Ostéonécrose vertébrale

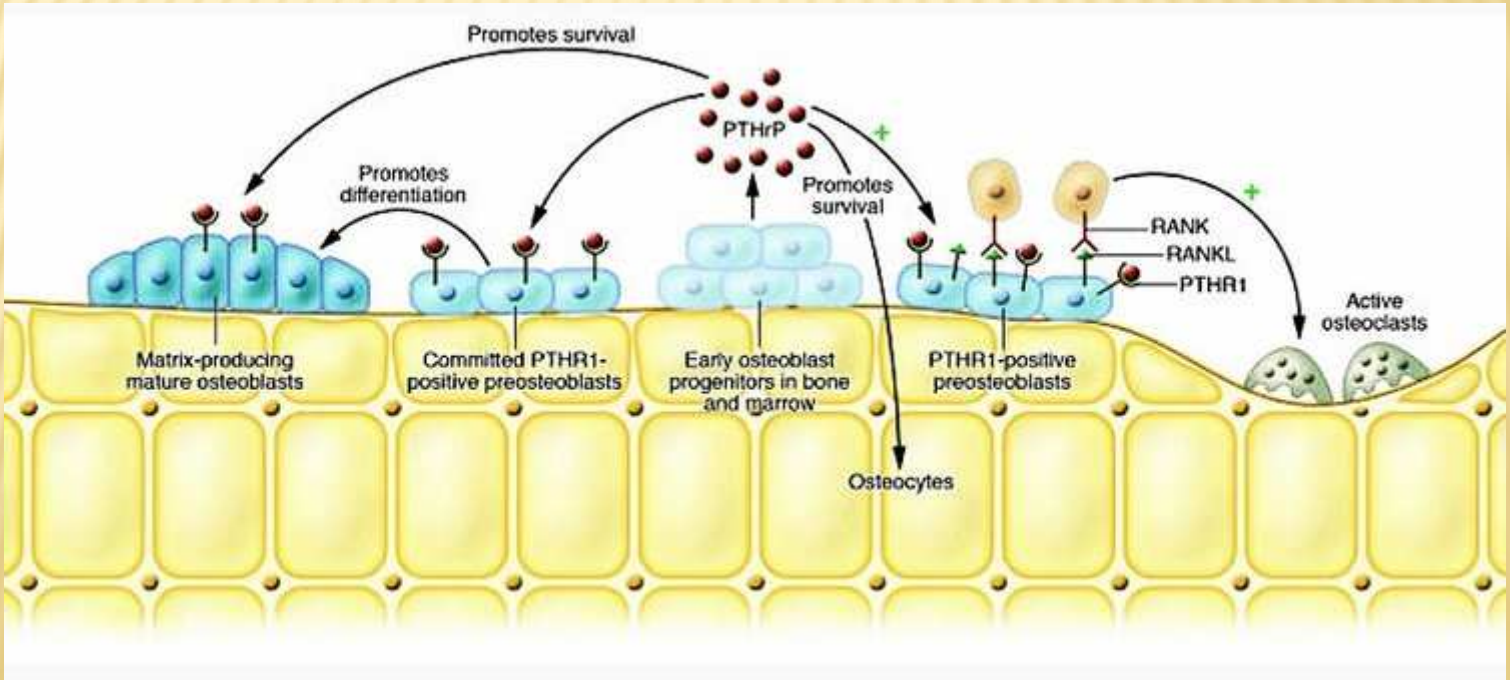
Id ostéonécrose aseptique: apoptose des ostéocytes?



Maugars Y et al.
Multiple Vertebral Osteonecroses (Kümmell's Disease) After 10 Years on Denosumab: Is Osteocyte Apoptosis to Blame?
Calcif Tissue Int. 2013;193:269-273

ABALOPARATIDE

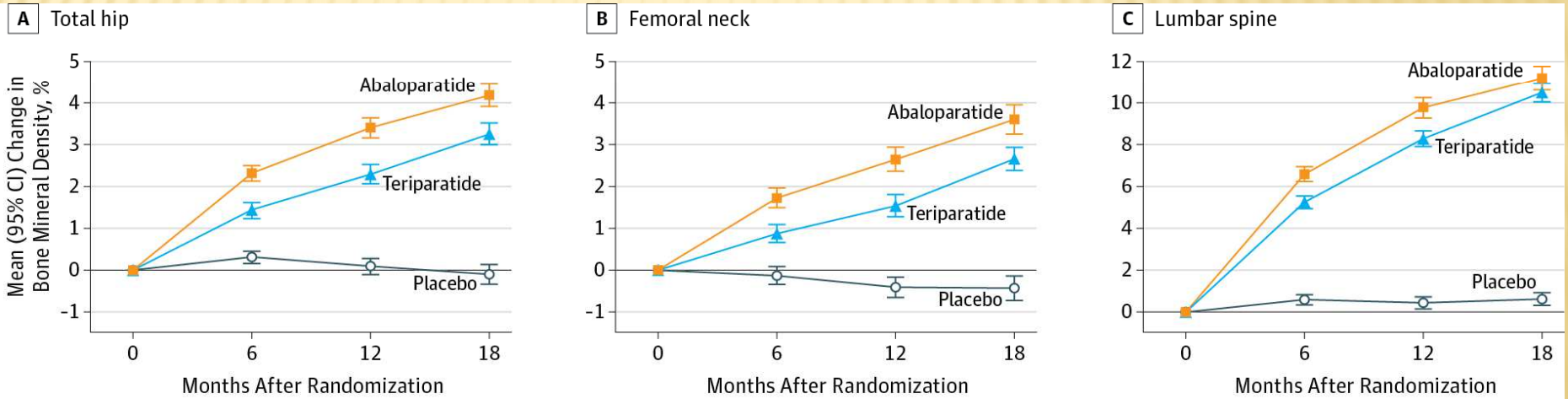




ABALOPARATIDE: ÉTUDE PIVOT

DMO: Pas de différence significative Abalo vs Téri

Pas de rôle prédictif du FRAX, ni de l'âge

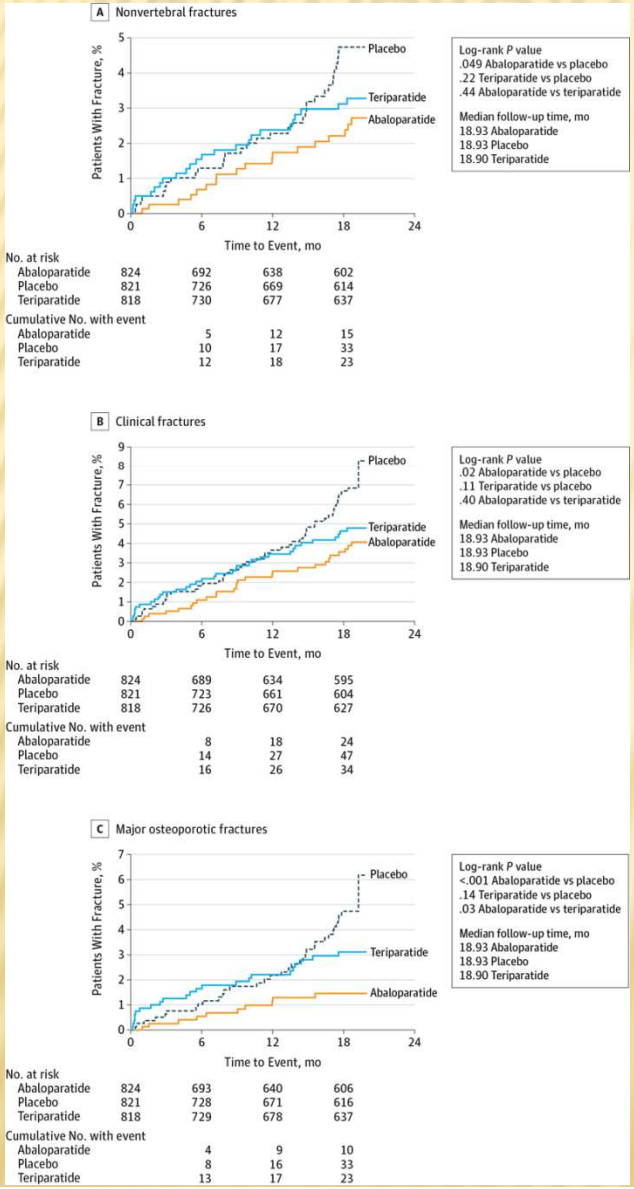


No. of participants evaluated

Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

Miller et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA. 2016 ;316:722-33

ABALOPARATIDE: ÉTUDE PIVOT



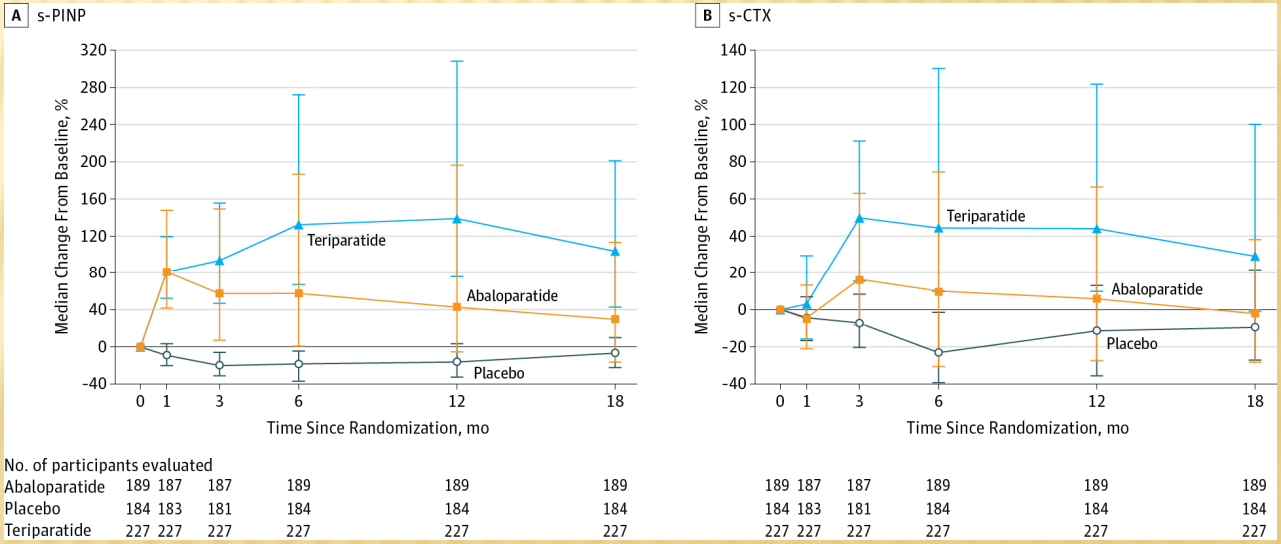
FRACTURES:

Pas de différence Abalo – Téri

Fractures vertébrales:

Abalo 0,58%* (-86%) Téri 0,84%* (-80%)

Pbo 4,22%



Miller et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA. 2016 ;316:722-33

ABALOPARATIDE: ÉTUDE PIVOT

Table 3. Safety and Adverse Events[a]

	Abaloparatide (n = 822)	Placebo (n = 820	Teriparatide (n = 818)
All treatment-emergent adverse events	735 (89.4)	718 (87.6)	727 (88.9)
Serious treatment-emergent adverse events	80 (9.7)	90 (11.0)	82 (10.0)
Deaths[b]	3 (0.4)	5 (0.6)	3 (0.4)
Adverse events leading to discontinuation	81 (9.9)	50 (6.1)	56 (6.8)
Discontinuation due to >7.0% BMD decrease[c]	1/218 (0.5)	12/184 (6.5)	1/160 (0.6)
Most frequently observed adverse events[d]			
Hypercalciuria	93 (11.3)	74 (9.0)	102 (12.5)
Dizziness	82 (10.0)	50 (6.1)	60 (7.3)
Arthralgia	71 (8.6)	80 (9.8)	70 (8.6)
Back pain	70 (8.5)	82 (10.0)	59 (7.2)
Nausea	68 (8.3)	25 (3.0)	42 (5.1)
Upper respiratory tract infection	68 (8.3)	63 (7.7)	73 (8.9)
Headache	62 (7.5)	49 (6.0)	51 (6.2)
Hypertension	59 (7.2)	54 (6.6)	41 (5.0)
Influenza	52 (6.3)	39 (4.8)	34 (4.2)
Nasopharyngitis	48 (5.8)	66 (8.0)	53 (6.5)
Urinary tract infection	43 (5.2)	38 (4.6)	41 (5.0)
Palpitations	42 (5.1)	3 (0.4)	13 (1.6)
Pain in extremity	40 (4.9)	49 (6.0)	42 (5.1)
Constipation	37 (4.5)	42 (5.1)	34 (4.2)
Hypercalcemia (prespecified safety end point)[e]	28/820 (3.4)[f]	3/817 (0.4)	52/816 (6.4)
Adverse events of special interest[g]			
Orthostatic hypotension[h]	140 (17.1)	134 (16.4)	127 (15.5)
Neoplasms, benign, malignant, and unspecified[i]	20 (2.4)	29 (3.5)	31 (3.8)
Fall[j]	4 (0.5)	2 (0.2)	4 (0.5)
Drug hypersensitivity[j,k]	2 (0.2)	2 (0.2)	0
Renal impairment[j]	2 (0.2)	4 (0.5)	3 (0.4)
Myocardial infarction[j]	1 (0.1)	2 (0.2)	2 (0.2)

[a] Values are reported as No. (%) unless otherwise indicated. Statistical testing of adverse events was not prespecified in the statistical analysis plan (Supplement 2), with the exception of hypercalcemia.

[b] Causes of death in the placebo group: bowel cancer. intestinal obstruction. myocardial infarction, dissecting aneurysm of the aorta, sudden death. Causes of death in the abaloparatide group: sepsis, bronchiectasis, ischemic heart disease. Causes of death in the teriparatide group: pancreatic cancer, general health deterioration, cardiorespiratory arrest.

[c] The denominator indicates the total number of patients who discontinued study participation.

[d] Indicates adverse events that occurred in at least 5% of patients in any single study group.

[e] Hypercalcemia defined as albumin-corrected serum calcium of at least 10.7 mg/dL (≥2.67 mmol/L) at any time point, which was a prespecified safety end point and was analyzed using the χ^2 test. Values are reported as No. with hypercalcemia/No. in study group (%).

[f] For abaloparatide and teriparatide vs placebo, $P < .001$; for abaloparatide vs teriparatide. $P = .006$.

[g] Adverse events of special interest were selected based on those related to mechanism of action, drug class effects and/or ongoing review of the study.

[h] Derived from vital sign data as a decrease in systolic blood pressure of at least 20 mm Hg from a supine position to standing or of at least 10 mm Hg in diastolic blood pressure from a supine position to standing in a postdose measurement.

[i] Summarized by system organ class.

[j] Based on patient self-report and assessed by the investigator.

[k] None of the events of drug hypersensitivity were associated with the study drug but were allergic reactions to other drugs provided to the participant.

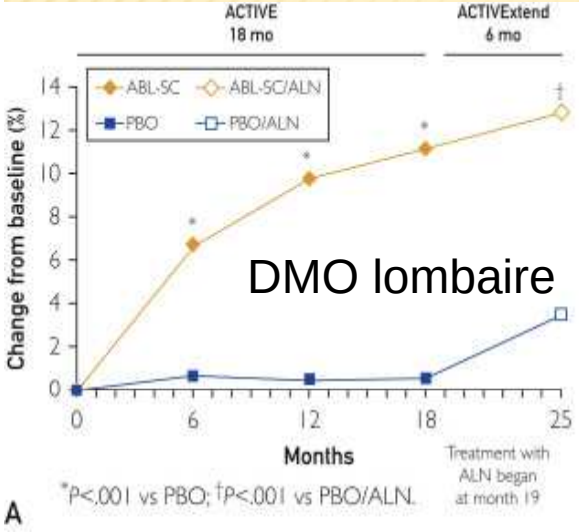
Effets secondaires

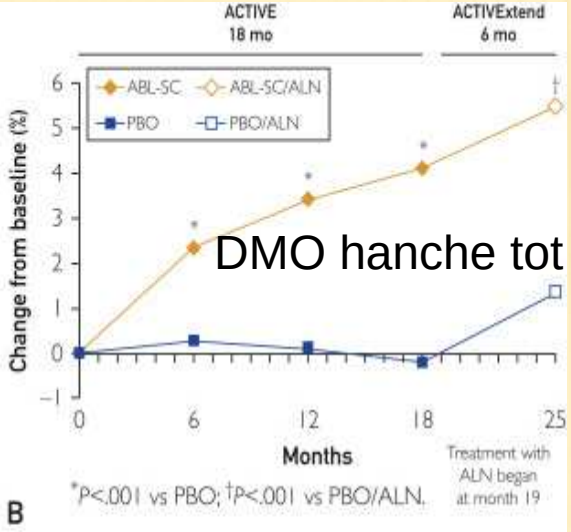
Palpitations – céphalées en rapport avec une **tachycardie** après l'injection d'Abaloparatide: 0,9% d'arrêt

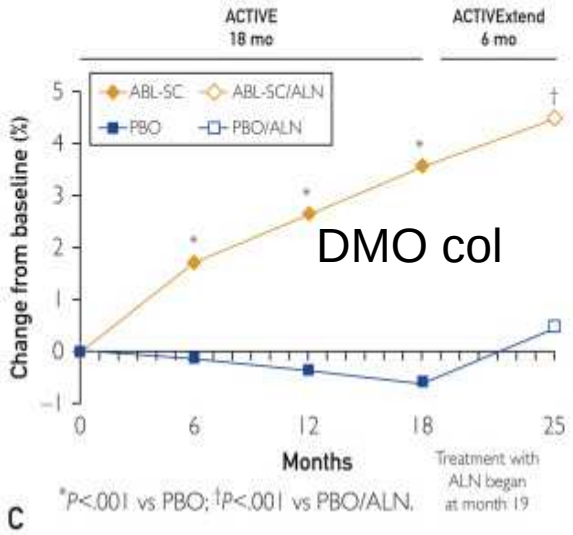
Moins d'hypercalcémie avec Abaloparatide

Miller et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial.

ABALOPARATIDE 18 MOIS
SUIVI DE 6 MOIS D'ALENDRONATE







<u>DMO</u>

Efficacité spectaculaire en lombaire
et très significative à la hanche

Maintenue voire augmentée après relais par un bisphosphonate

Cosman et al. Eighteen Months of Treatment With Subcutaneous Abaloparatide Followed by 6 Months of Treatment With Alendronate in Postmenopausal Women With Osteoporosis: Results of the ACTIVExtend Trial. Mayo Clin Proc. 2017;92:200-210

SYNTHESE

DENOSUMAB: 2ème ligne, avec la problématique de cet effet rebond qui doit être prévenu (Zolédronate), mais très longue durée d'inhibition de la résorption (BP avant et après Déno): quelle durée totale pour quel risque de fracture atypique?

En pratique: réseau ostéoporose d'Amgen supprimé

nouvelle perte de confiance des patients

Le Dénosumab touché au cœur de l'info

SYNTHESE

Le très prometteur ROMOSOZUMAB pourra-il se sortir de ce tout petit % mais très important en valeur absolue sur risque cardiovasculaire?

En pratique: il faudrait pouvoir définir un sous-groupe à risque et l'exclure, mais les facteurs de risque cardiovasculaires sont tellement nombreux et communs…

Le dossier est présenté actuellement à nouveau aux autorités (FDA, EMA)

Le Romosozumab touche au cœur d'un effet collatéral

SYNTHESE

Le très prometteur ABALOPARATIDE peut-il se sortir d'une efficacité proche du Tériparatide avec comme effet secondaire une tachycardie?

De plus, ostéosarcome chez la souris à fortes doses rapportés

En pratique: Le dossier a été présenté à 2 reprises et refusé par l' EMA

Le Tymlos* est labellisé FDA depuis mars 2017

L'abaloparatide touché au cœur qui bat trop fort

CONCLUSIONS

Les traitements de l'ostéoporose font l'objet d'une désinformation, et d'effets secondaires « improbables », qui plombent la prise en charge de l'ostéoporose depuis plusieurs années avec une persistance qui fait mal au cœur …