

乳癌引致之骨骼問題 及治理方法

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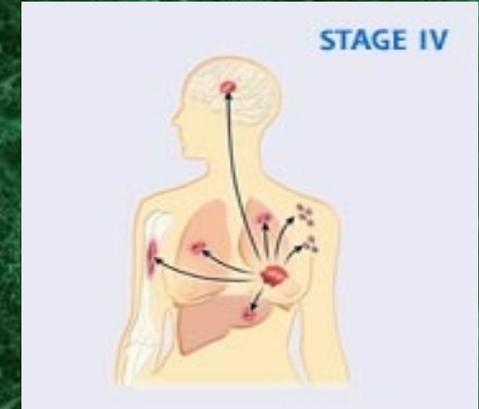
19-6-2010, HKBCF

乳癌和骨骼的關係

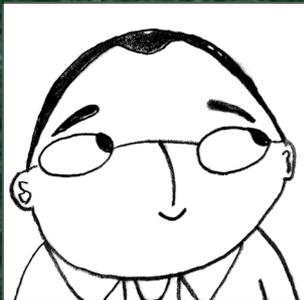
- 為何乳癌會引致骨骼問題
- 乳癌引致之各類骨骼問題及症狀
- 其預防及治療方法
- 何謂癌症骨轉移
- 於更年期階段罹患乳癌的女士需特別注意的骨骼問題
- 乳癌引致之骨骼問題治療方法之最新趨勢

講座內容

• 乳癌擴散至骨骼

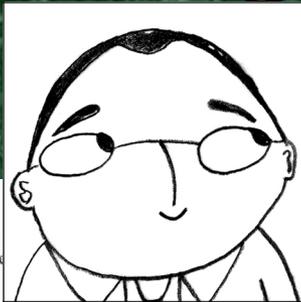


• 乳癌治療對骨骼的影響



講座內容

- 乳癌擴散至骨骼的治理方法
- 乳癌治療對骨骼的影響
- “骨質流失”影響著 **>50%** 在 **55** 歲以上的婦女



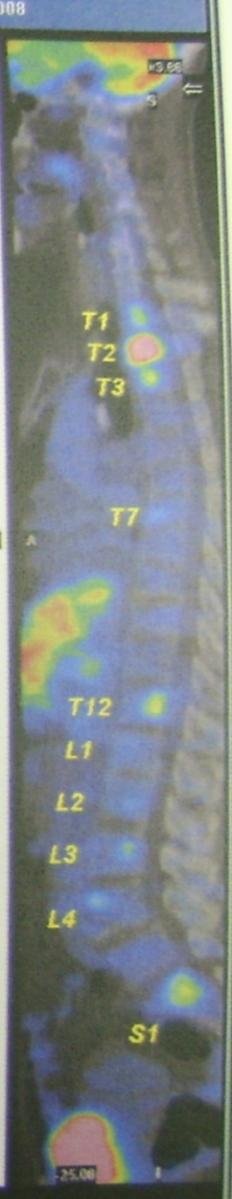
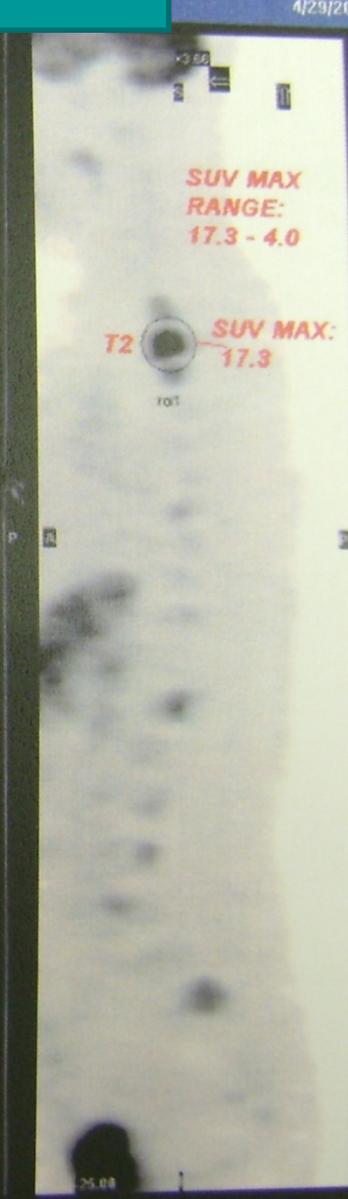
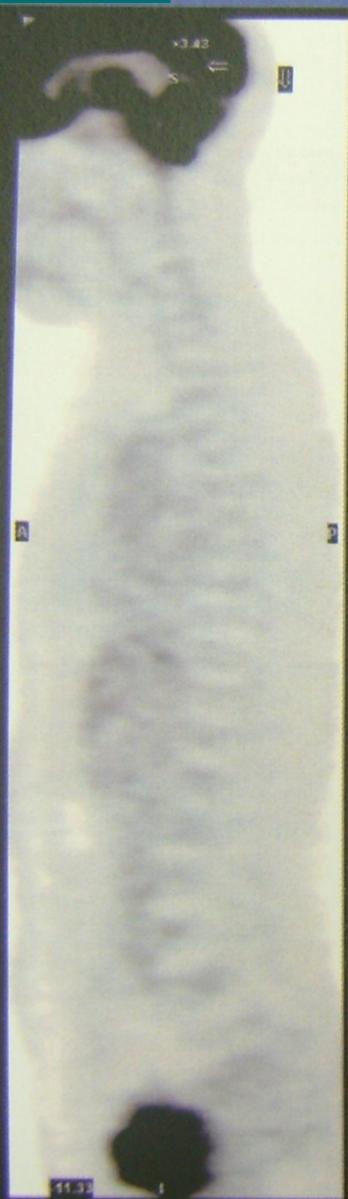
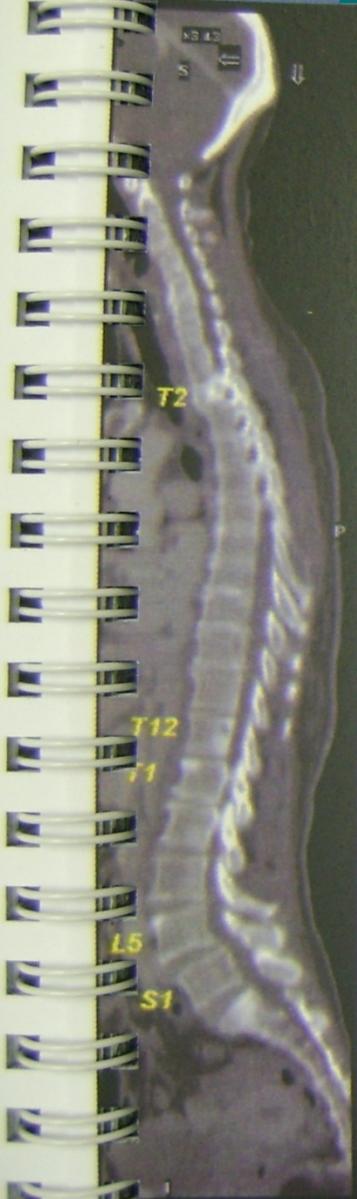
誰最大機會發生癌症骨轉移？

原發性癌症	發生癌症骨轉移比率
多發性骨髓瘤	95-100%
乳腺癌	65-75 %
前列腺癌	65-75 %
甲狀腺癌	60%
膀胱癌	40%
肺癌	30-40 %
腎癌	20-25 %
黑素瘤	14-25 %

WB
9/8/2008

metrix

WB
4/29/2008



CT Sagittals

PET Sagittals

Fused Sagittals

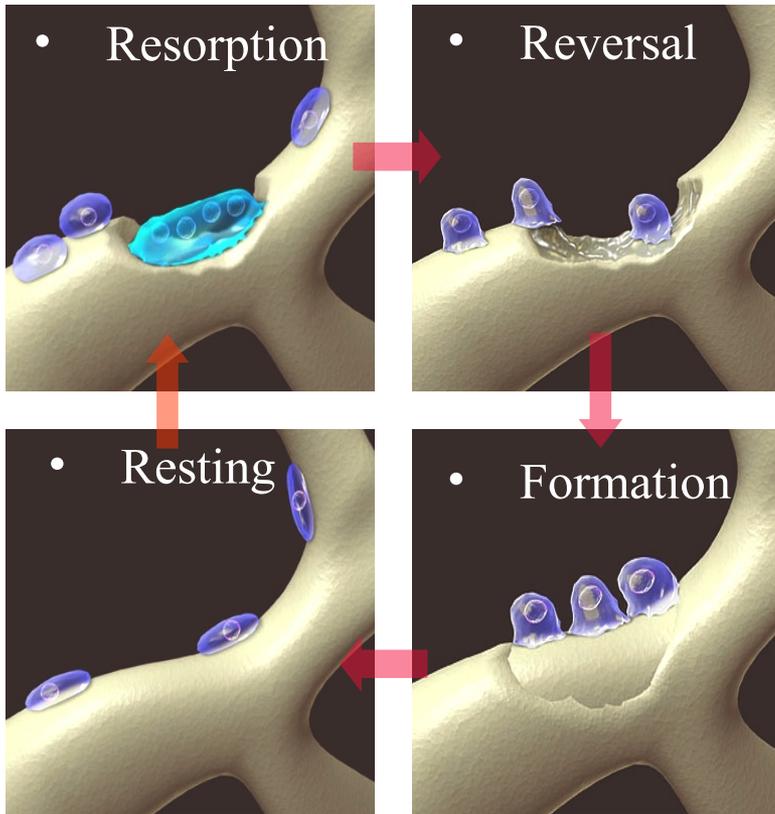
CT Sagittals

PET Sagittals

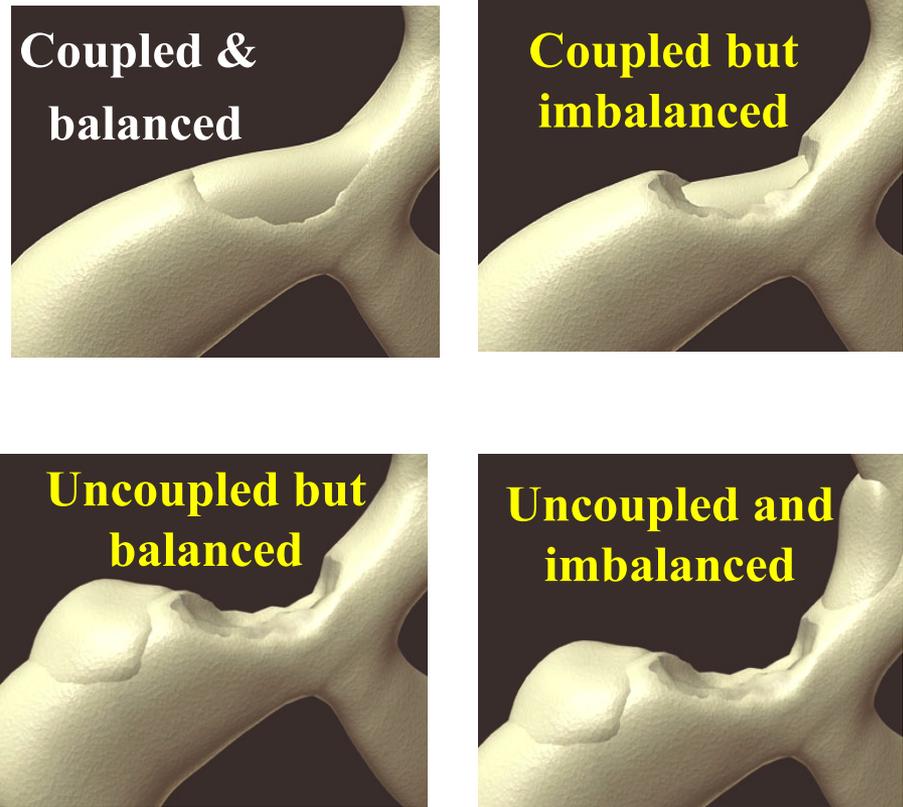
Fused Sagitt

BM Disease Background

Normal bone remodelling



Bone remodelling in metastasis cancer



OB Osteoblasts = bone forming cells

OC Osteoclasts = bone destroying cells

Mechanisms of Action of Bisphosphonates

Inhibit osteoclast formation and migration, and osteolytic activity; promote apoptosis

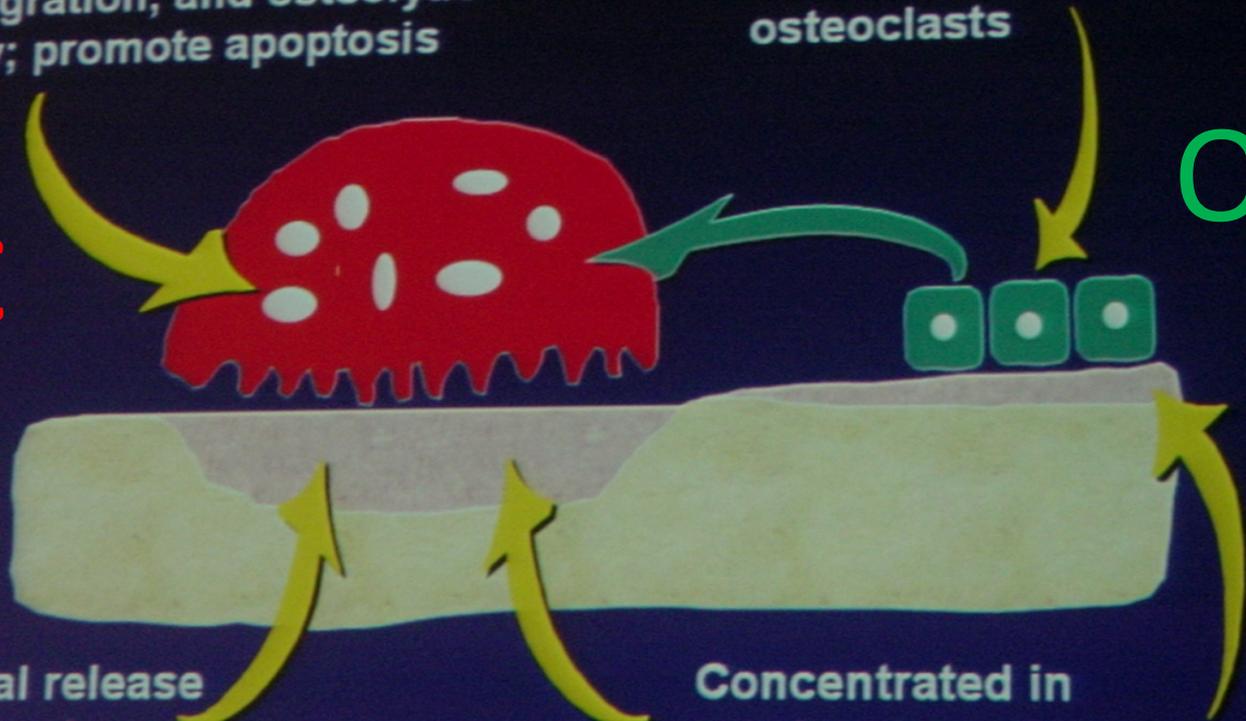
Modulate signaling from osteoblasts to osteoclasts

OC

OB

Local release during bone resorption

Concentrated in newly mineralizing bone and under osteoclasts



與骨骼有關的併發症 (SRE)

1. 骨折

2. 脊髓阻塞

3. 癌症引致的血鈣過高 (HCM)

4. 需要予放射治療





10/2004

10/2004

Patented 11/11/04
2" pen nib

© 2004



乳癌骨骼轉移的治療

• 抗癌治療： 荷爾蒙療法，化療，標靶治療

• OC 治療法： 如雙磷酸鹽 (BP)

• 止痛藥

• 放射治療

• (局部放射, 全身放射 e.g. P-32, Sr-89)

• 外科手術

Mechanisms of Action of Bisphosphonates

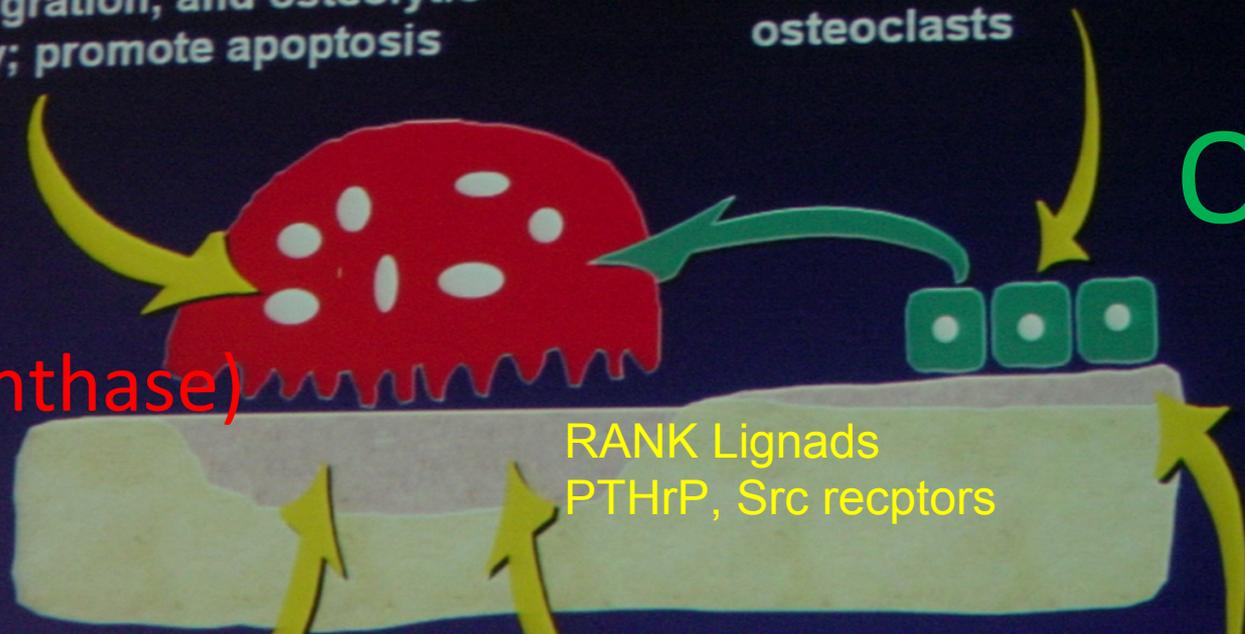
Inhibit osteoclast formation and migration, and osteolytic activity; promote apoptosis

Modulate signaling from osteoblasts to osteoclasts

OC

(FPP Synthase)

OB



Local release during bone resorption

Concentrated in newly mineralizing bone and under osteoclasts

OC 治療法

- 如雙磷酸鹽 (Biphosphonates - BP)*

- FPP Synthase

- 口服, 靜脈

- Denosumab (D'Mab)*

- RANK Ligands

- 皮下注射

- 正在研究中 : PTHrP , Src receptors

- *FDA 驗證了其在收經後骨質疏鬆的效果

- 有 30-60% 減低骨折的作用

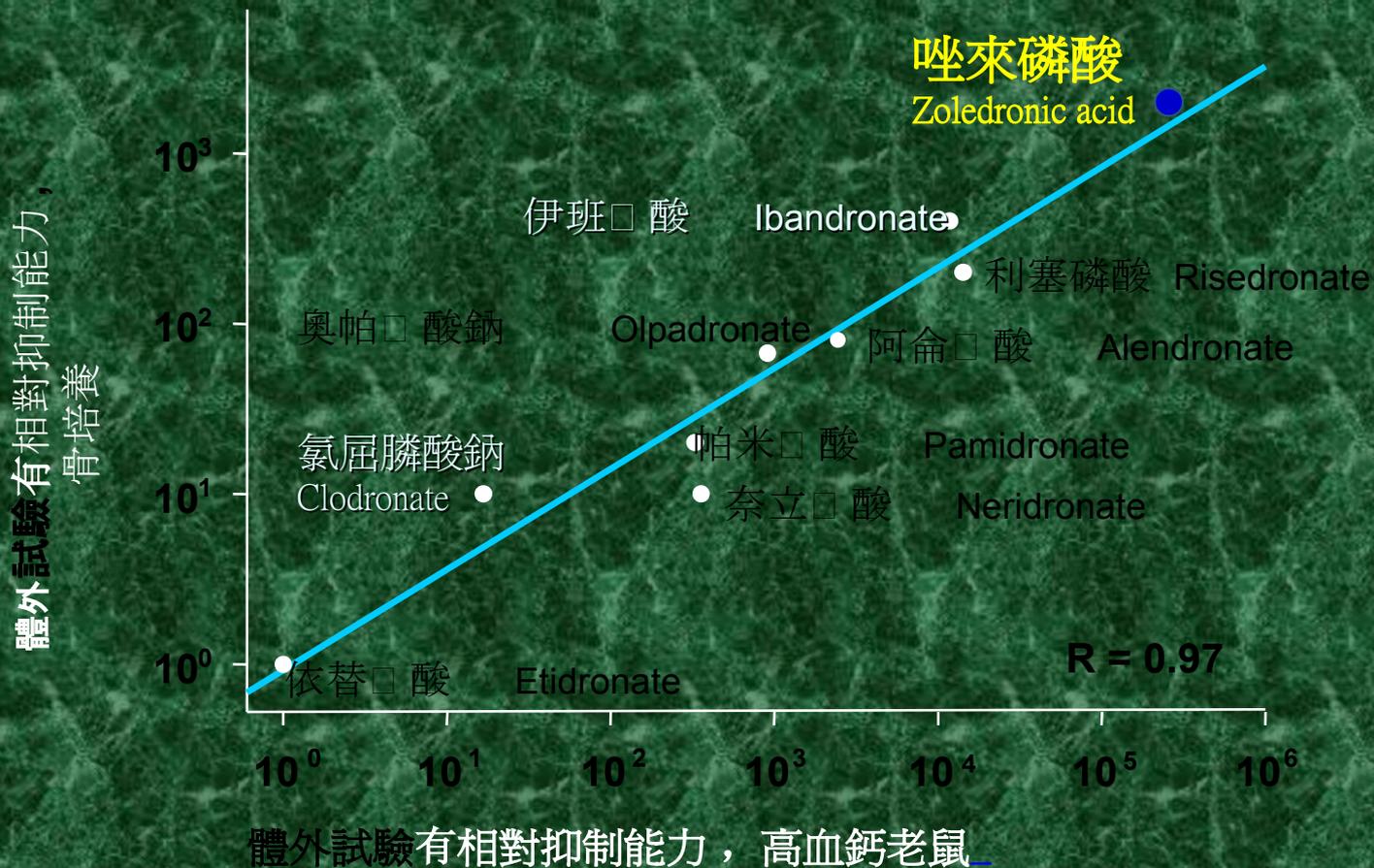
雙磷酸鹽 (BP) 治療對 癌症骨骼轉移的作用

- 減少 **SRE** (如 **Zoledronic Acid** - 減 45%)

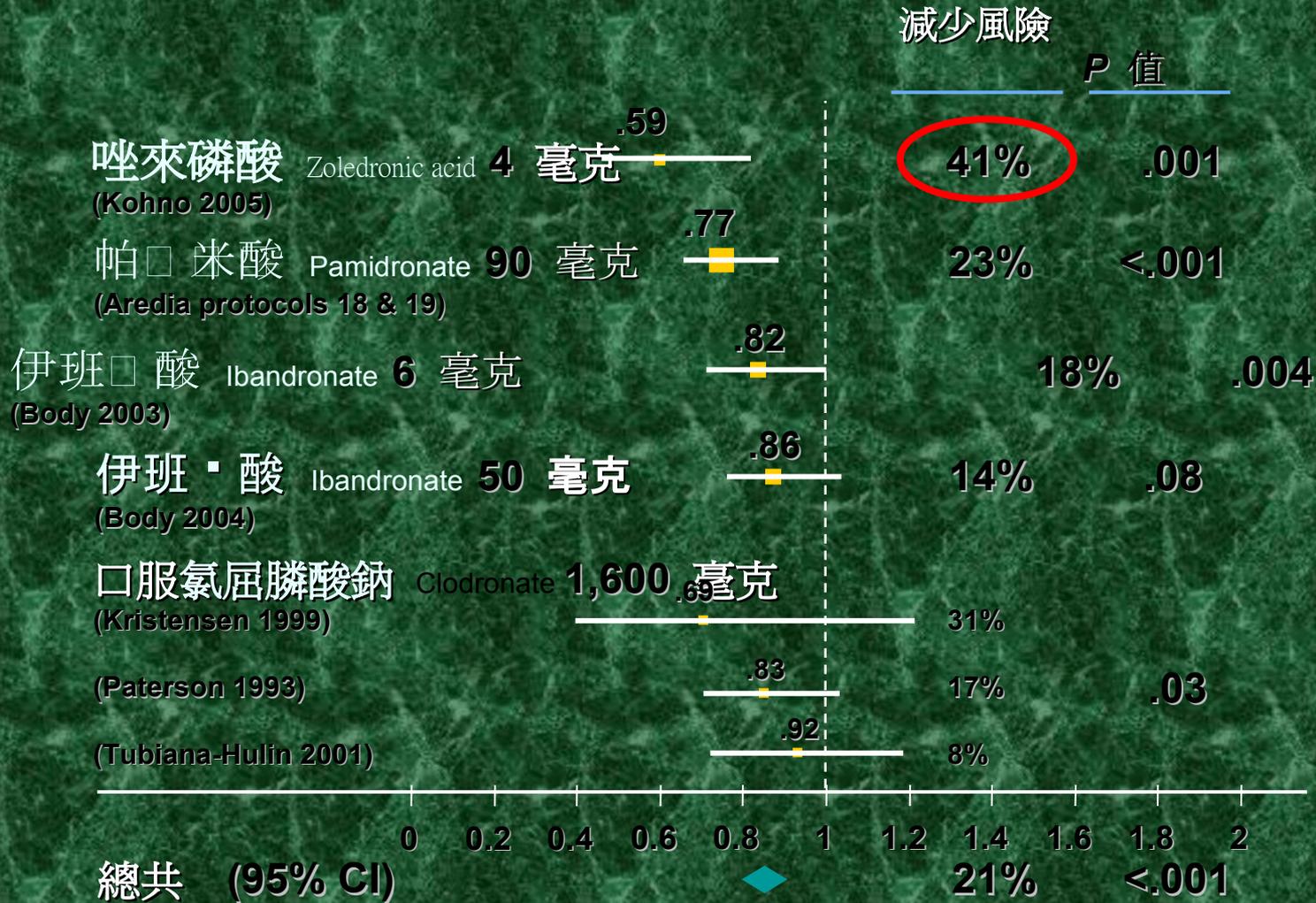
- 減慢 **SRE** 的發生

- 減低腫瘤生長，活躍程度，新血管增生

雙磷酸鹽類 (Bisphosphonate) 的壓抑效果



以雙磷酸鹽類 (Bisphosphonate) 治療乳癌： 減少骨骼併發症 (SRE) 風險



CI = 可信區間

不同的雙磷酸鹽 (BP) 治療對 減低 SRE 的成效

• 在不同的 BP 對比安慰劑臨床研究結果：

• **Zoledronic Acid – HR 0.59**

• **Pamidronate – HR 0.77**

• **Ibandronic Acid – HR 0.82**

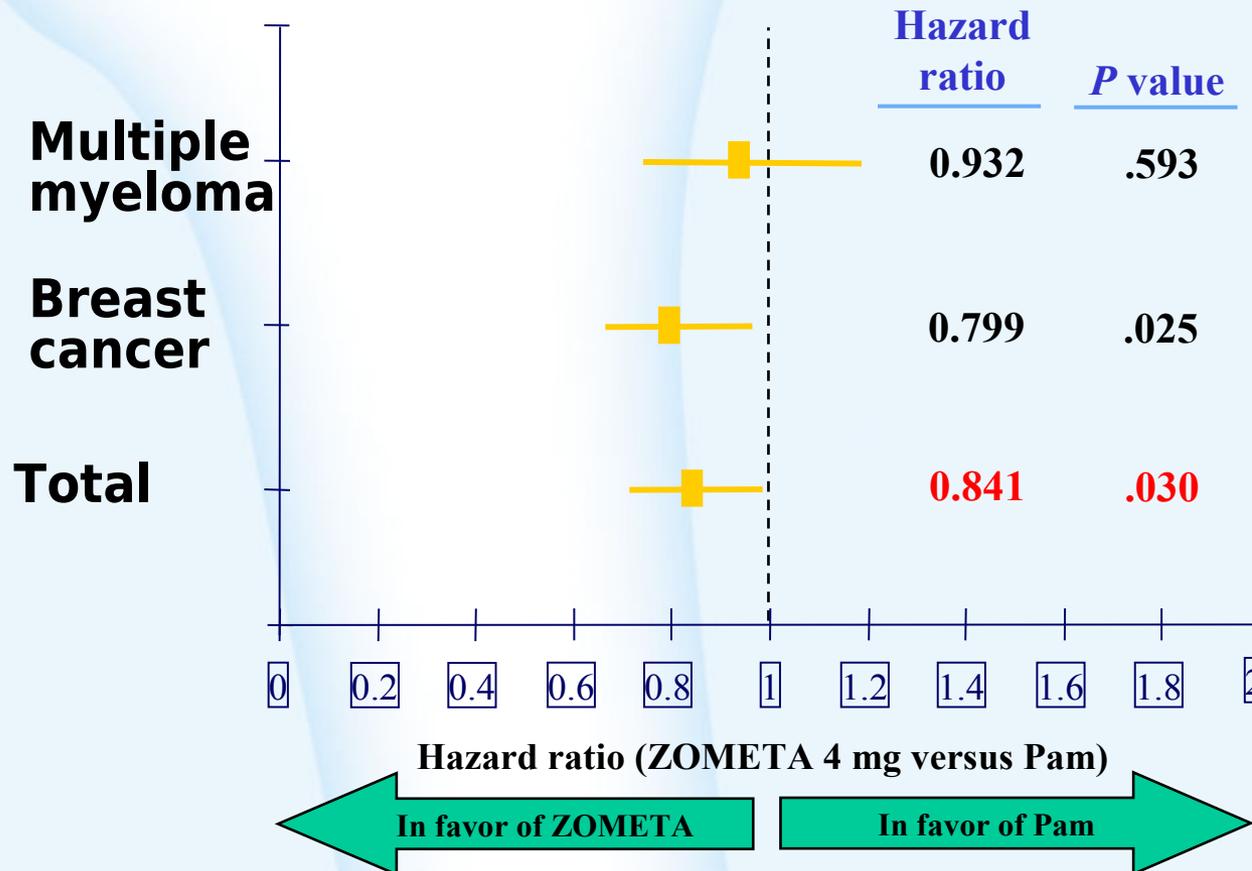
• **Oral Clodronate / Ibandronic Acid**

• - 無統計學上成立的效果

Breast Cancer and Multiple Myeloma

Andersen-Gill Multiple Event Analysis*

- ZOMETA® significantly decreases the risk of developing a skeletal complication (16% reduction)



*Hypercalcemia of malignancy is included as an SRE. 25-month time point.

雙磷酸鹽 (BP) 治療的副作用

- 口服 BP: 腸胃不適
- 靜脈注射 BP: 發燒, 骨痛 (首次注射), 腎衰竭
- 特別但少見 (1-2%) 之副作用: 牙骨壞死

治療乳癌引起 對骨骼系統的副作用

- 化療： 減弱卵巢功能，提早收經現象
(? 直接影響骨骼新陳代謝，類固醇副作用)
- 荷爾蒙治療： 卵巢壓抑治療（收經術），
A.I.

提高乳癌病患者 對骨骼系統健康的注意

- 背景： 婦女在收經後骨質會流失
- 閣下若是乳癌病患者，受診治時醫生有無主動替妳檢查骨質密度 (BMD)?
 - 西歐情況：
 - 英 (06) - >70% 接受 A.I. 荷爾蒙治療病人沒有作 BMD 檢查
 - 美 (09) - <20% 乳癌患者沒有 BMD 檢查

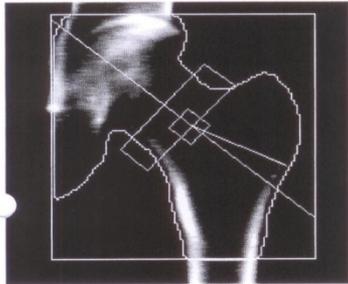
BMD 骨質密度檢查

Alpha Medical Diagnostic &

Dr. Ho Wing To, Iris

Sex: Female
Ethnicity: Asian

Referring Physician: DR. MICHAEL CHEUNG M. C.



k = 1.133, d0 = 51.9
98 x 105

Scan Information:

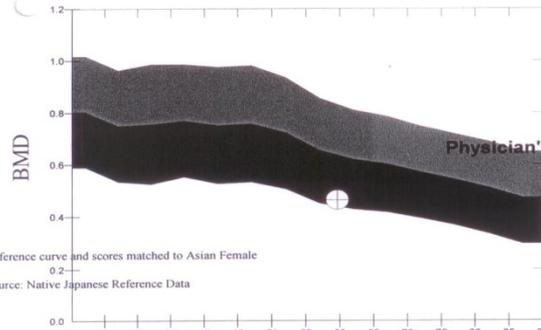
Scan Date: 03 July 2008 ID: A07030809
Scan Type: e Left Hip
Analysis: 03 July 2008 11:42 Version 12.3:3
Left Hip
Operator:
Model: Explorer (S/N 90219)
Comment:

DXA Results Summary:

Region	Area (cm ²)	BMD (g/cm ³)	T - Score	Z - Score
Neck	5.11	0.464	-3.2	-1.8
Troch	9.60	0.436	-2.1	-1.3
Inter	17.23	0.765	-1.7	-1.0
Total	31.94	0.618	-2.0	-1.2
Ward's	1.25	0.293	-3.5	-1.6

Total BMD CV 1.0%, ACF = 0.993, BCF = 0.977, TH = 4.668
WHO Classification: Osteopenia
Fracture Risk: Increased

Neck



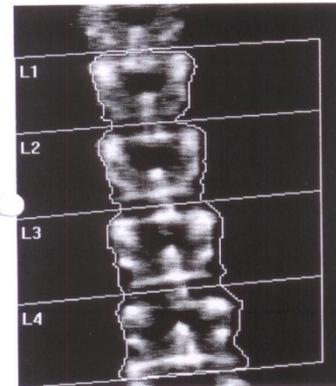
Reference curve and scores matched to Asian Female
Source: Native Japanese Reference Data

Alpha Medical Diagnostic &
Laboratory Center

Dr. Ho Wing To, Iris

Sex: Female
Ethnicity: Asian

Referring Physician: DR. MICHAEL CHEUNG M. C.



k = 1.127, d0 = 47.0
116 x 147

Scan Information:

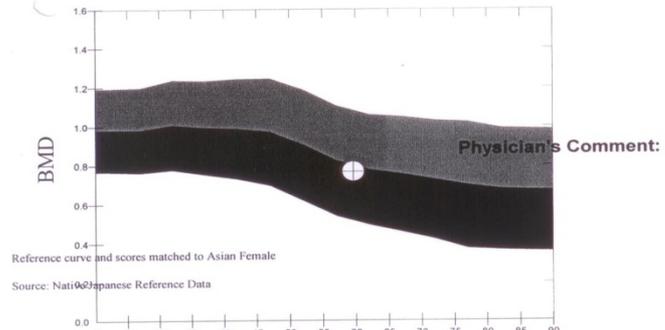
Scan Date: 03 July 2008 ID: A07030808
Scan Type: e Lumbar Spine
Analysis: 03 July 2008 11:42 Version 12.3:3
Lumbar Spine
Operator:
Model: Explorer (S/N 90219)
Comment:

DXA Results Summary:

Region	Area (cm ²)	BMD (g/cm ³)	T - Score	Z - Score
L1	10.85	0.637	-2.3	-0.6
L2	13.14	0.669	-2.7	-0.8
L3	14.85	0.835	-1.7	0.1
L4	16.09	0.874	-1.8	0.1
Total	54.94	0.768	-2.1	-0.2

Total BMD CV 1.0%, ACF = 0.993, BCF = 0.977, TH = 6.224
WHO Classification: Osteopenia
Fracture Risk: Increased

Total



Reference curve and scores matched to Asian Female
Source: Native Japanese Reference Data

ZEBRA: Trial Design

Surgery ± radiotherapy

Pre-/perimenopausal patients with node-positive early breast cancer, aged ≤ 50 years

Randomised 1:1 (open, multicentre)

**'Zoladex' 3.6mg
every 28 days
for 2 years**

Follow-up

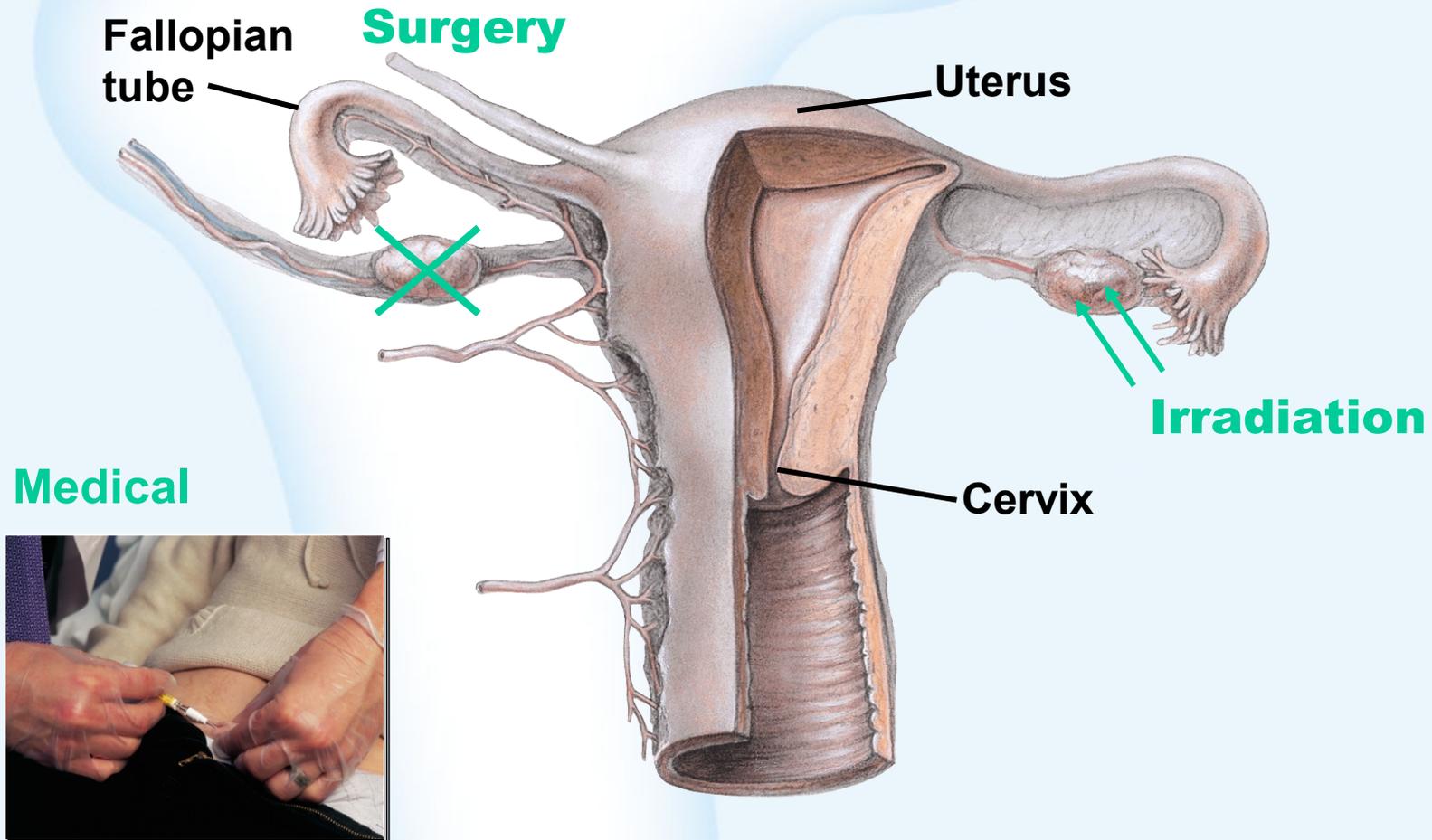
**CMF 6 × 28-day
cycles**

Tumour recurrence

Death

Death

Methods for Achieving Ovarian Ablation



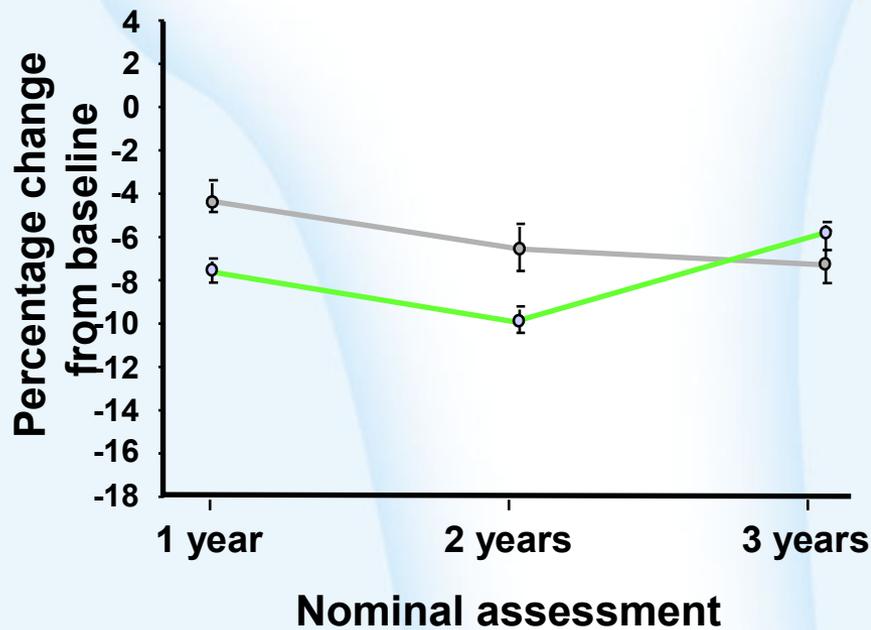
LHRH antagonists provide a medical 'ovarian ablation' by suppressing ovarian function

ZEBRA: Bone Mineral Density (1)

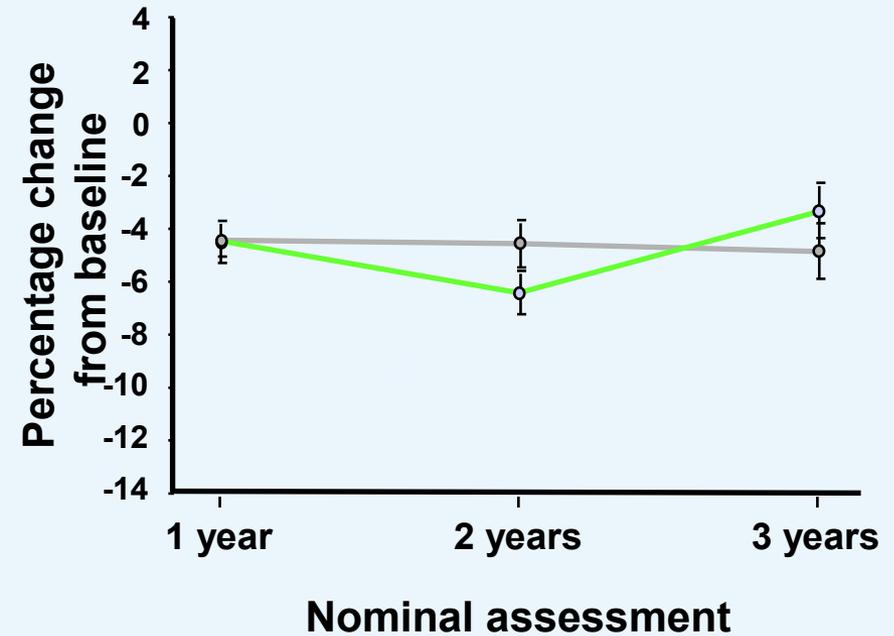
- 96 patients included in the analysis ('Zoladex' 3.6mg, $n=53$; CMF, $n=43$)
- BMD: lumbar spine and neck of femur
- BMD levels decreased in both treatment groups during the first 2 years, with greater BMD loss seen in the 'Zoladex' 3.6mg group
- At 3-year assessment:
 - partial recovery of BMD in the 'Zoladex' 3.6mg group
 - BMD losses persisted in the CMF group
 - no difference in BMD between treatment groups

ZEBRA: Bone Mineral Density (2)

Total spine
% change from baseline



Neck of femur
% change from baseline



Treatment received
● 'Zoladex' 3.6mg QMF

有關芳香酵素抑制劑 (A.I.) 的第 3 期雙盲研究

1. 5 年輔助治療

三苯氧胺 (5 年)

AI (5 年)

2. 按序治療法：中途更換藥物

三苯氧胺 (5 年)

三苯氧胺 (2 年)

AI (3 年)

3. 5 年後延續輔助治療

三苯氧胺 (5 年)

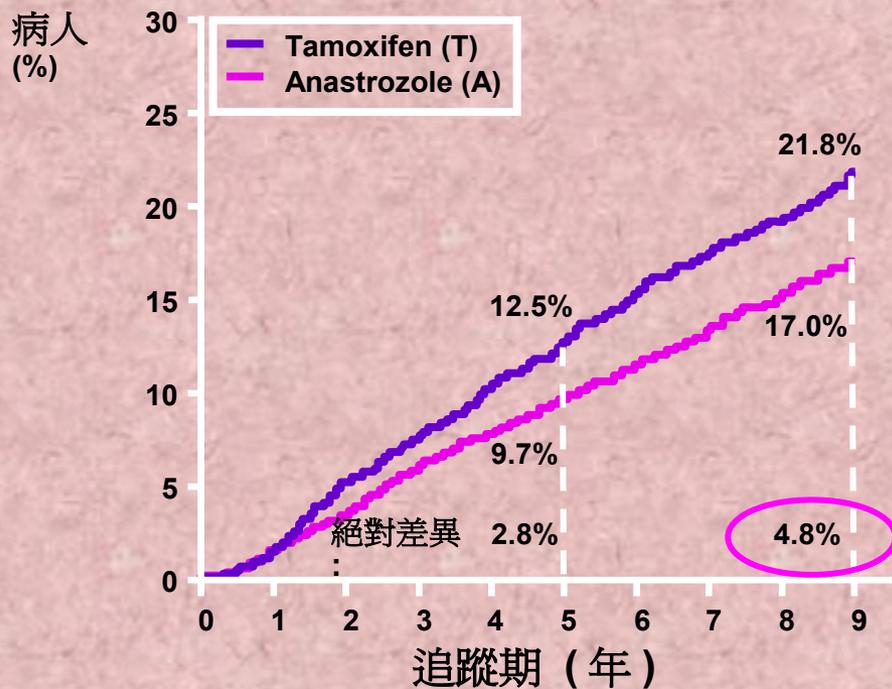
AI (5 年)

三苯氧胺 (5 年)

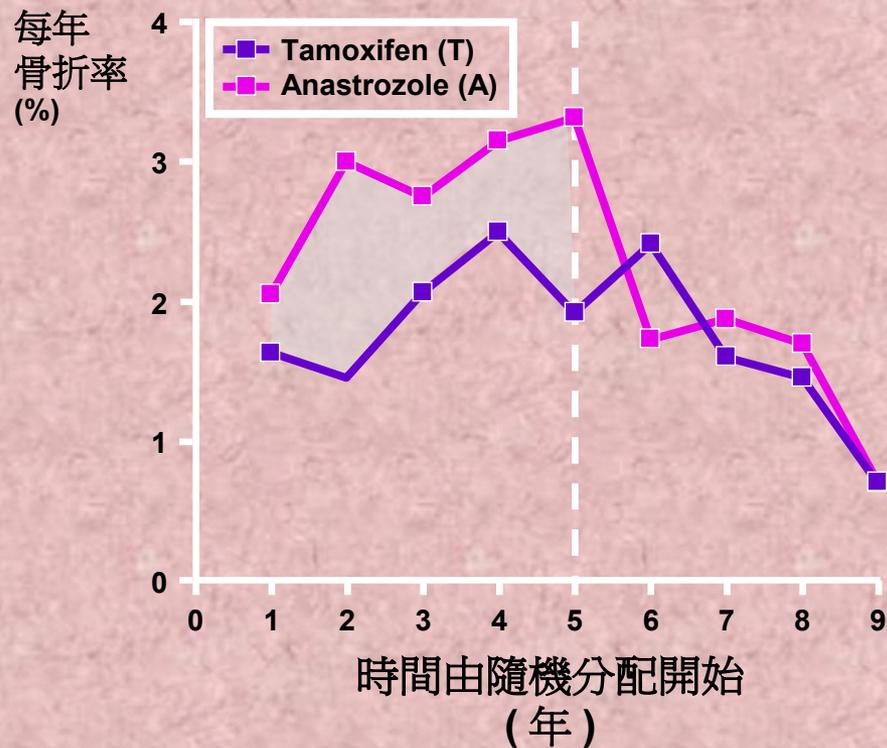
安慰劑 (5 年)

荷爾蒙治療 - Arimidex

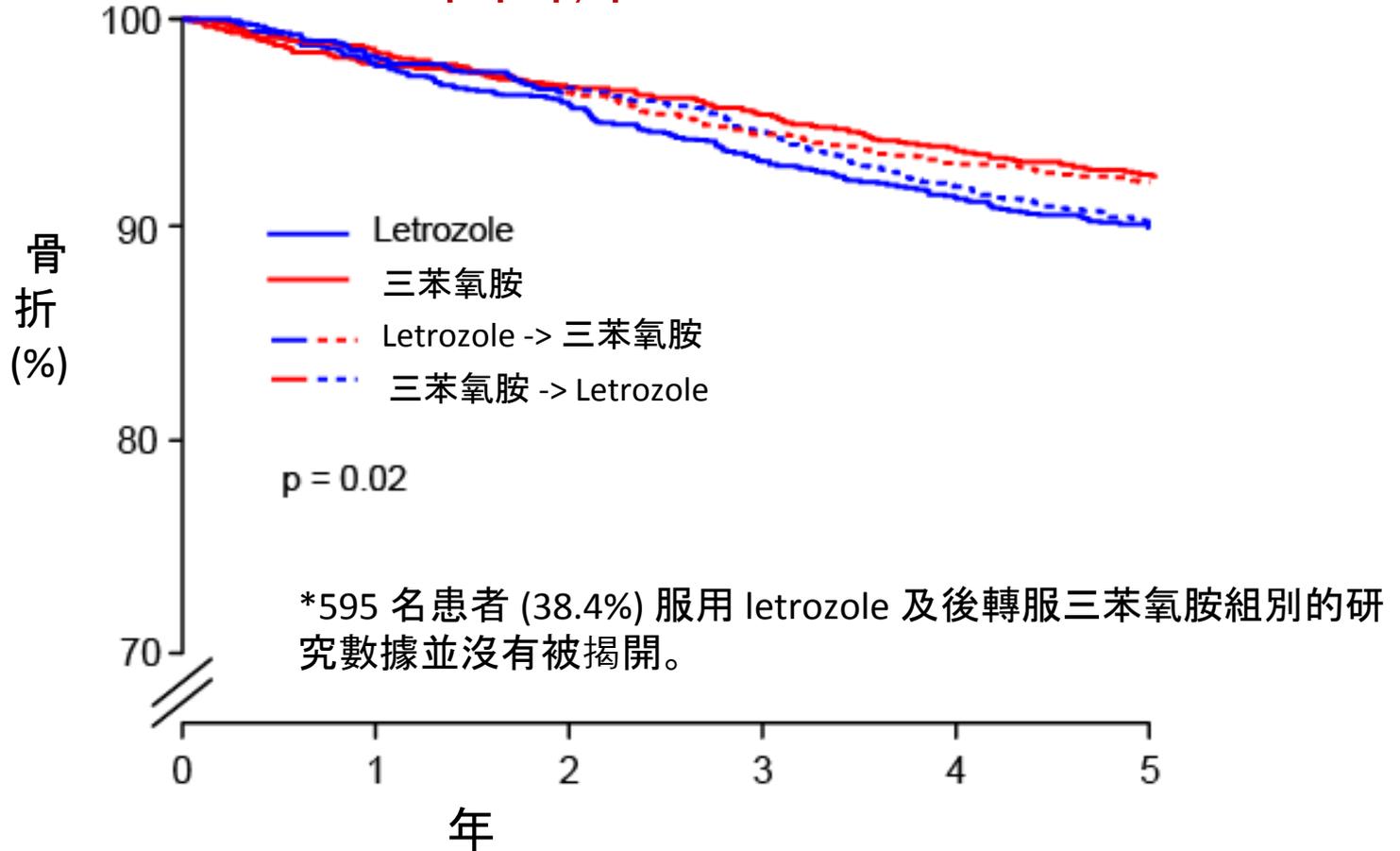
復發時間率



骨折比率



骨折



三苯氧胺 *	Letrozole	三苯氧胺 □ Letrozole	Letrozole → 三苯氧胺
N=1541	N=1535	N=1541	N=1527
113 (7.3%)	150 (9.8%)	146 (9.5%)	115 (7.5%)

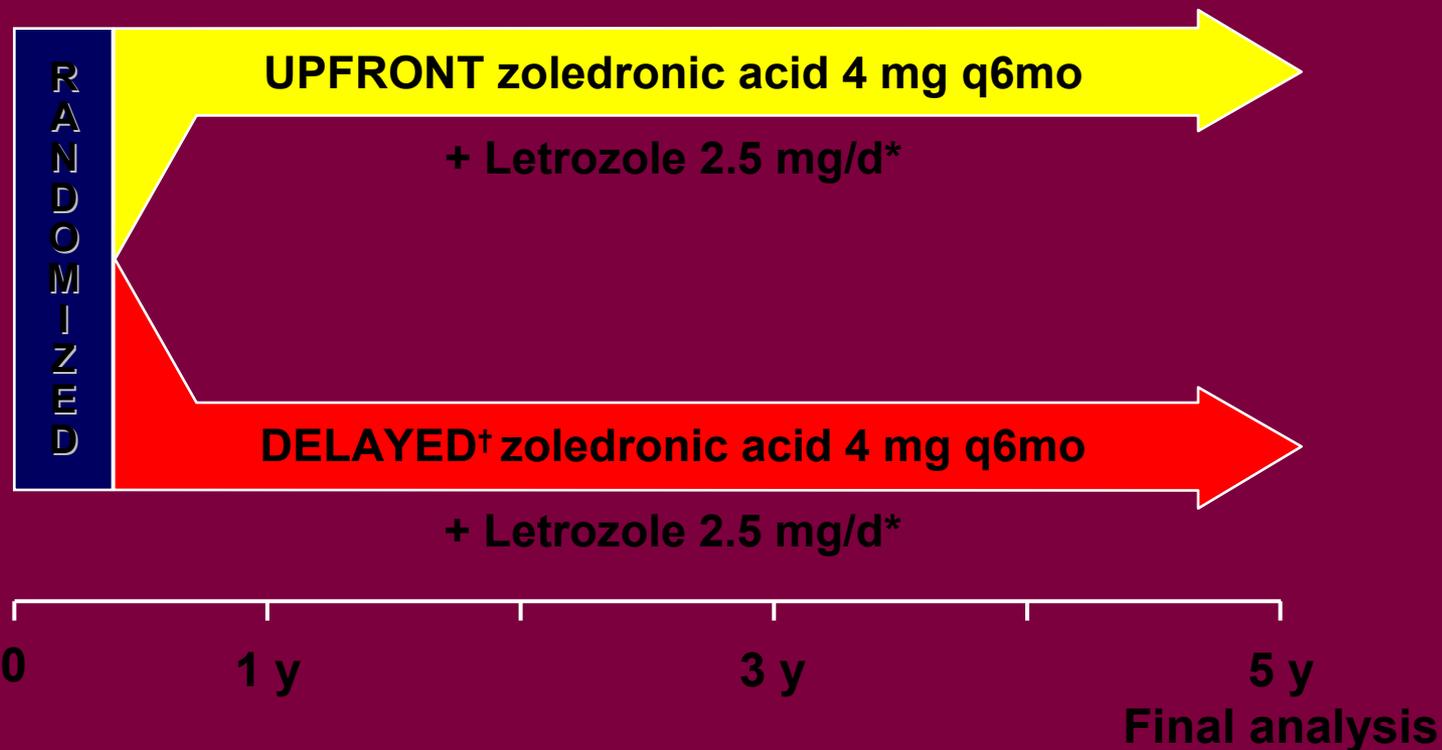
Z/ZO-FAST Trial Design: Zometa®-Femara® Adjuvant Synergy Trial

Eligibility:

ER+/PgR+ BCa
PMW with
T score ≥ -2

Stratification:

- Adjuvant CT (yes or no)
- T score (> -1 or between -1 and -2)



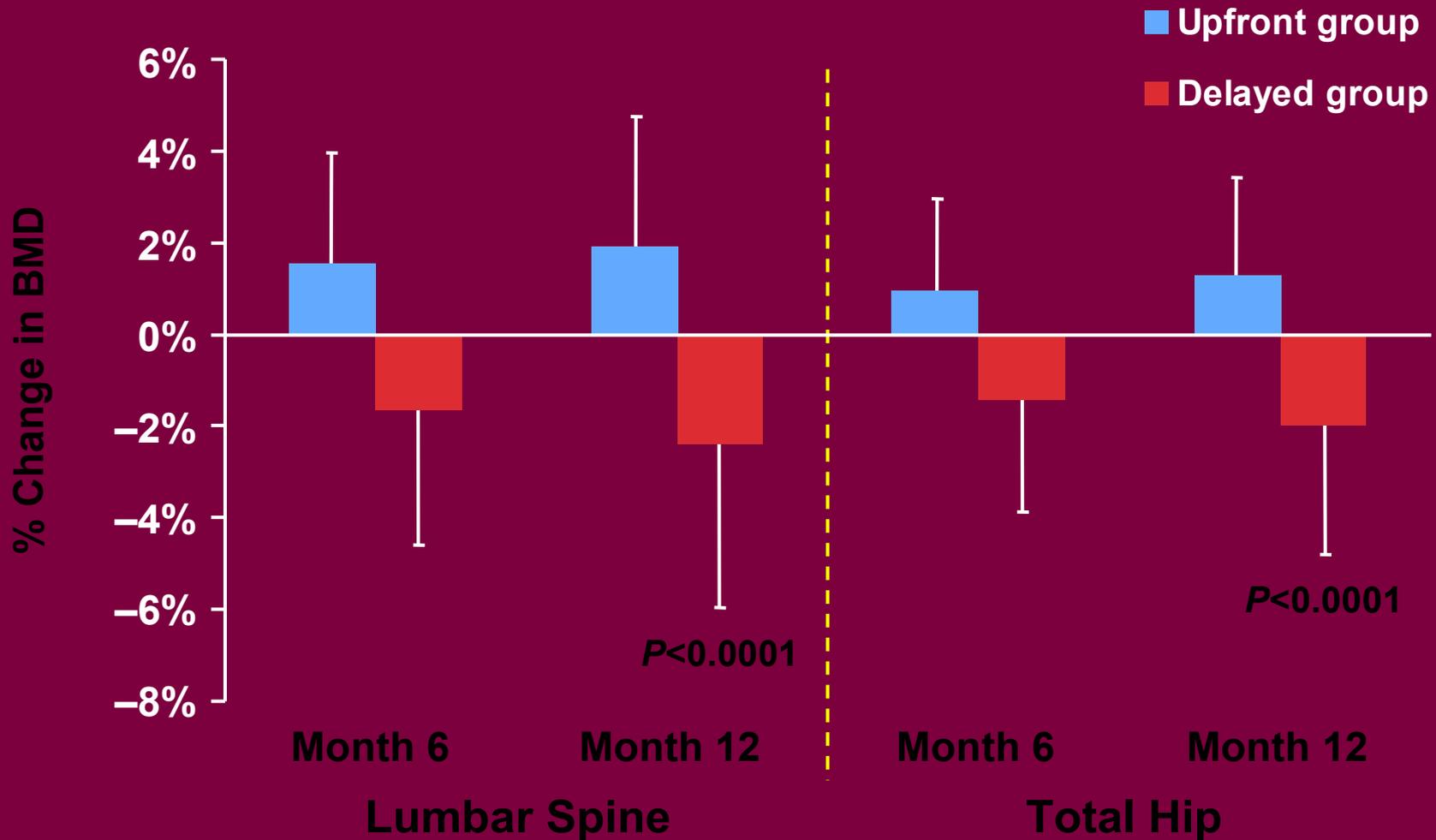
Accrual complete: ZO-FAST: N=1066; Z-FAST: N=602.

ER = estrogen receptor; PgR = progesterone receptor; BCa = breast cancer; PMW = postmenopausal women; CT = chemotherapy.

*Plus daily calcium (1000-1200 mg) and vitamin D (400-800 IU).

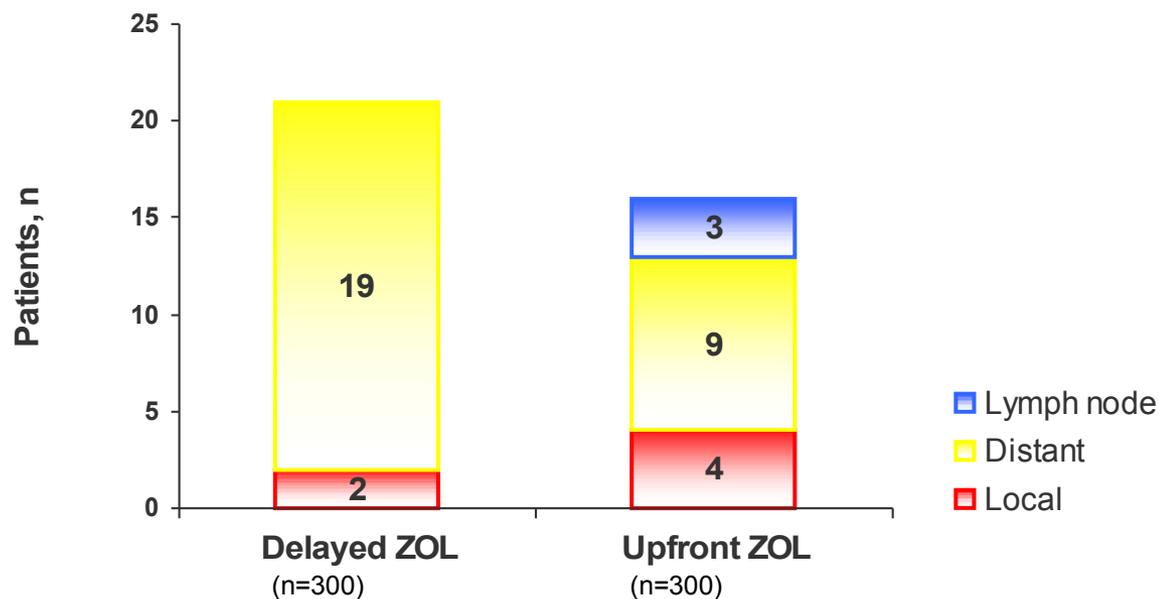
†Initiation determined by a postbaseline T score < -2 , any clinical fracture, or an asymptomatic fracture at 36 months.

Z-FAST: Mean (SD) Percentage Change in BMD (g/cm²)



Z-FAST (61 mo): fewer HR+ early-stage BC patients receiving upfront ZOL experienced disease recurrence

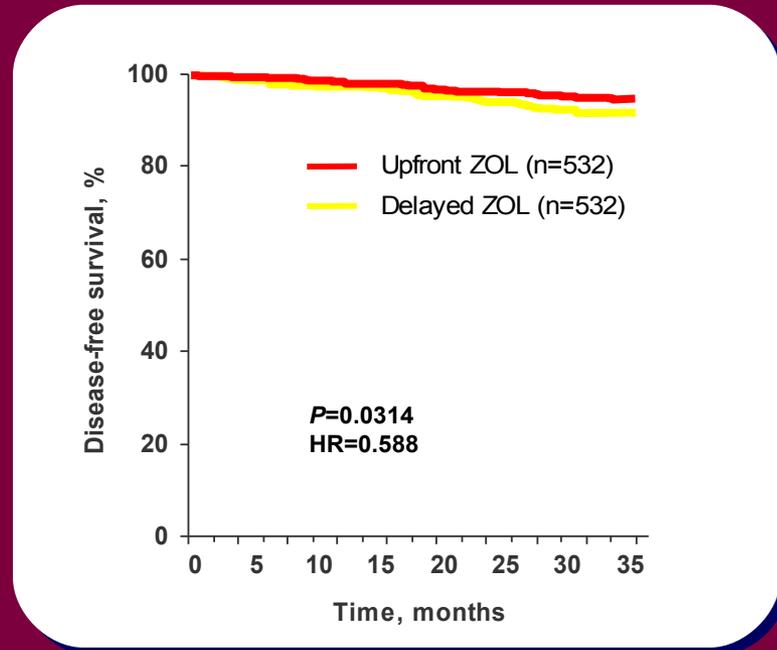
Disease recurrence at 61 months



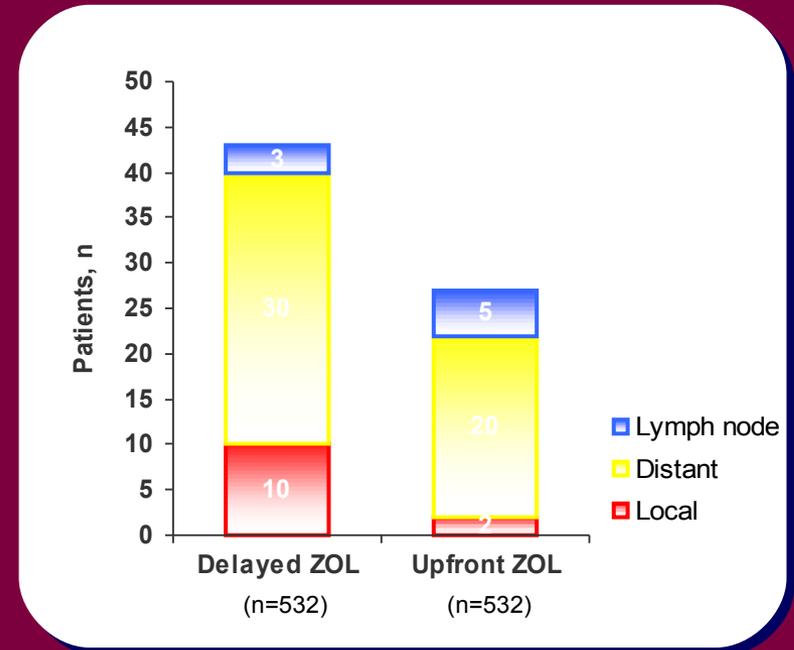
- N=602
- Primary endpoint: % change in BMD at 12 months
- Secondary endpoints: DFS, TDR, bone markers, fractures

ZO-FAST (36 mo): upfront ZOL reduced the risk of DFS events and recurrence in early-stage postmenopausal BC

Disease-free survival



Disease recurrence*



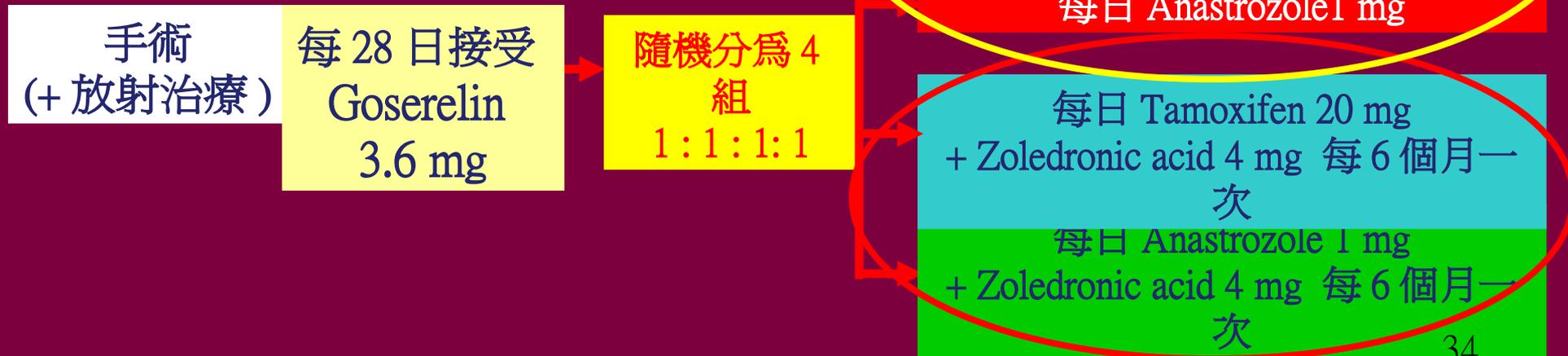
- N=1065
- Primary endpoint: % change in BMD at 12 months
- Secondary endpoints: DFS, TDR, bone markers, fractures

HR=hazard ratio (Cox regression); BMD=bone mineral density; DFS=disease-free survival; TDR=time-to-disease recurrence; BC=breast cancer.

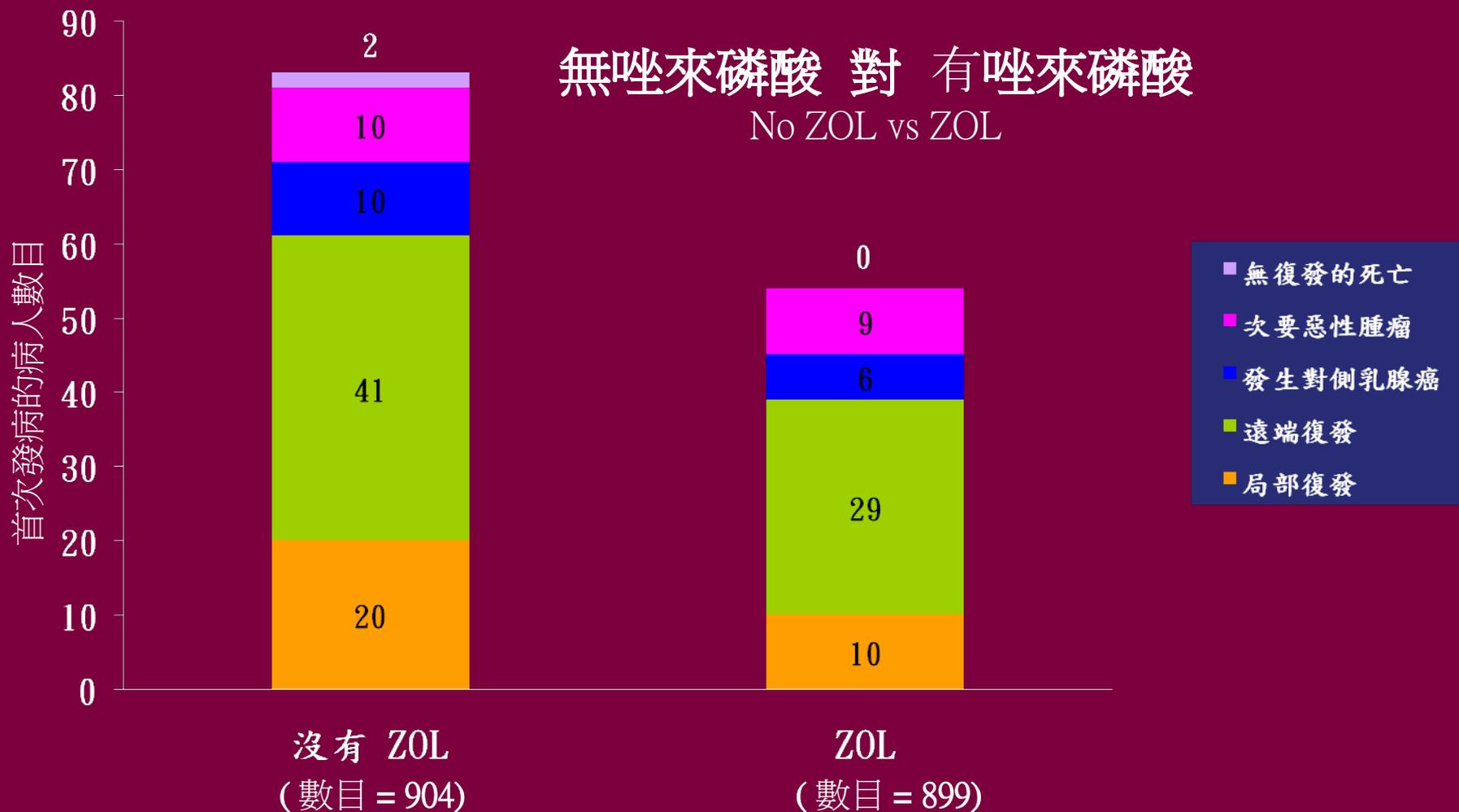
*Multiple sites of metastases may be reported for the same patient.
Sites of distant metastases include bone, brain, liver, lung, skin, lymph node, and other.

ABCSSG-12: 研究背景

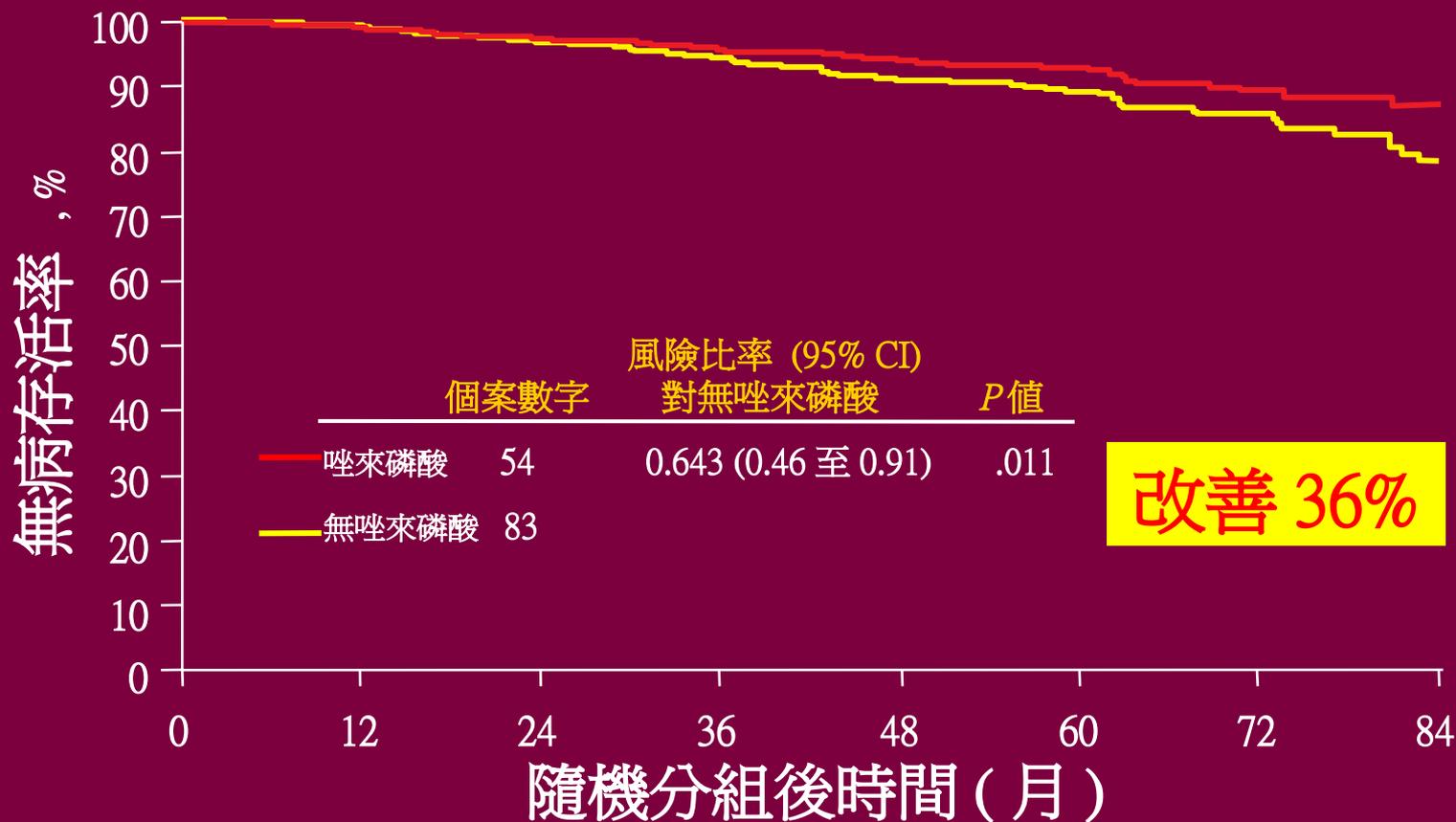
- 1999-2006 病案
- 1,803 名更年期前乳腺癌病人 (接受年齡 19 - 59 歲)
- 對內分泌治療有反應 (雌激素受體 及 / 或 孕激素受體呈陽性)
- 第一 / 二期, <10 陽性淋巴結轉移
- 除新輔助化療外, 無接受其他的化療
- 跟進期的中位數: 60 個月
- 治療期: 3 年



單一內分泌治療 VS 唑來磷酸混合療法 首次發病的人數



使用唑來磷酸混合療法比單一使用內分泌治療 可改善無病存活率 (Disease-free survival)

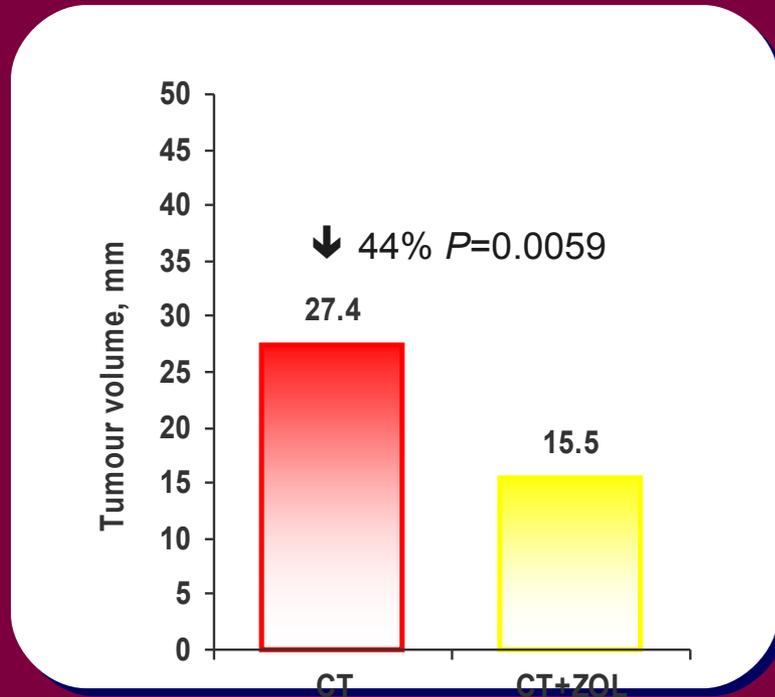


跟進期中位數 = 60 months.

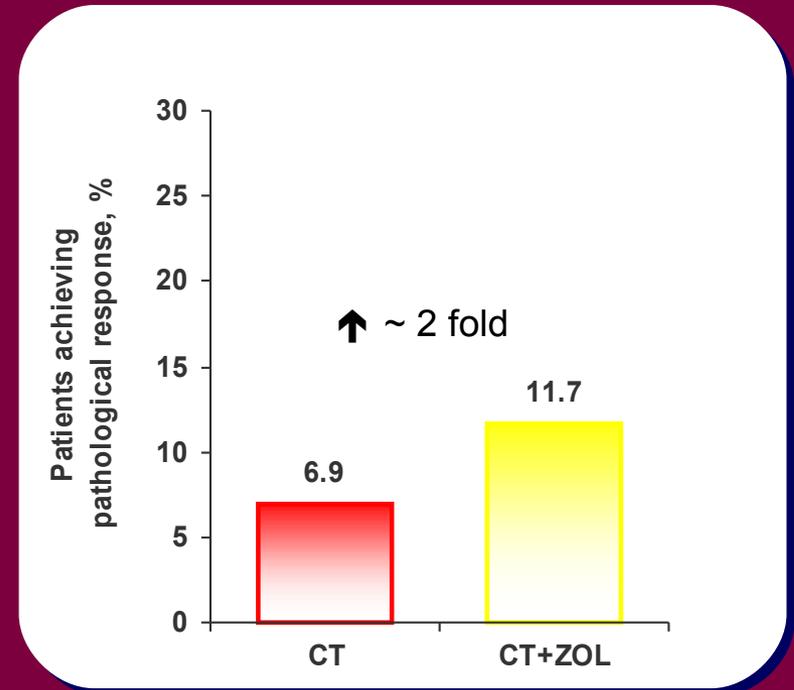
Gnant M, 主編: 2008 年, ASCO 會, 芝加哥, IL. LBA4 節錄彙報

AZURE (neoadjuvant): ZOL reduced tumour volume and increased pathological response in BC patients*

Tumour volume
Tumour volume



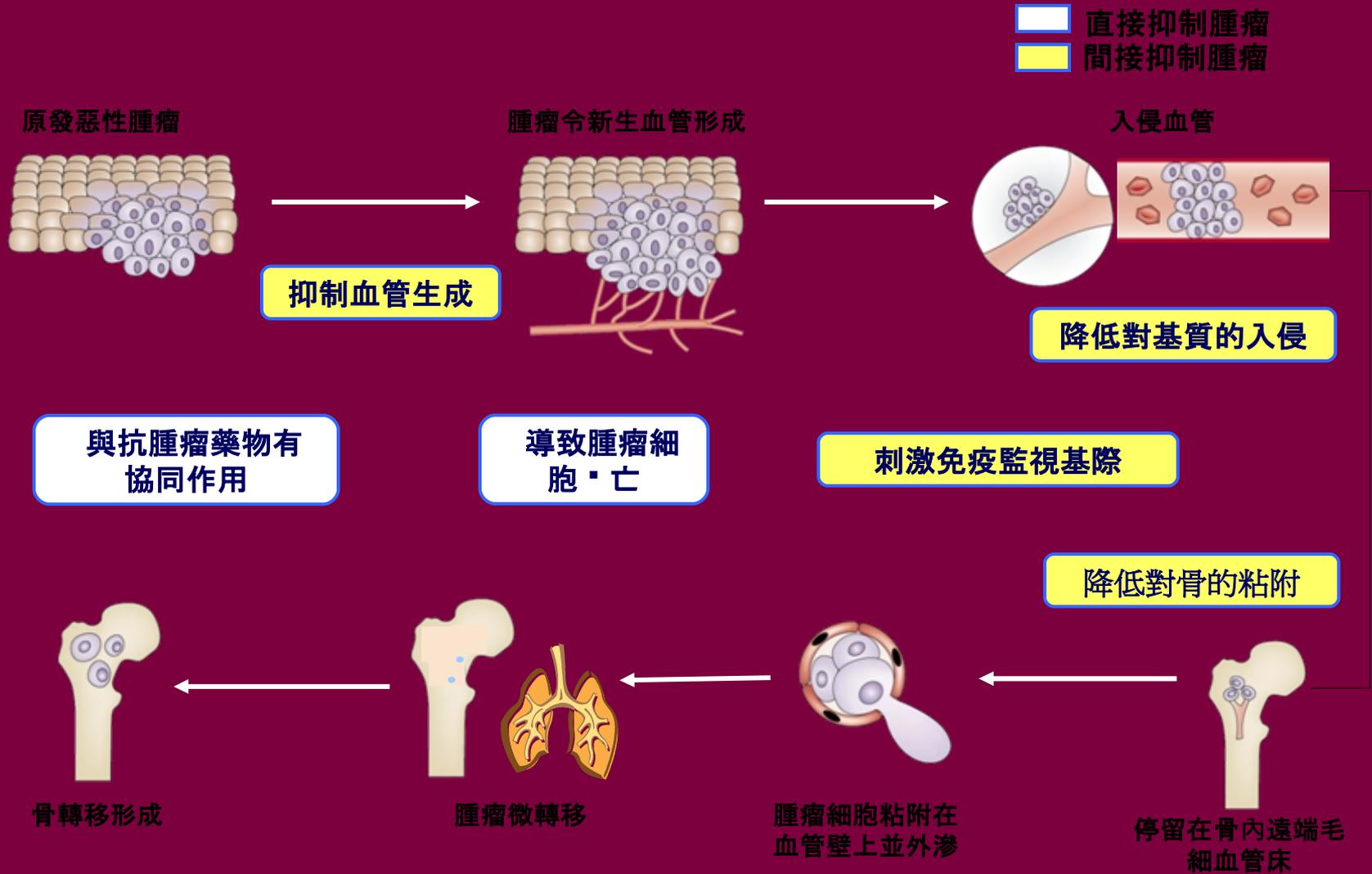
Pathological response



- N=205
- Primary endpoint: Tumour volume
- Secondary endpoint: Pathological response, number of axillary nodes

* Exploratory analysis CT=chemotherapy.

唑來磷酸 (Zoledronic Acid) 能在多個步驟 抑制骨轉移



結論

- 癌症（特別是乳癌）與骨骼健康已成為一個專門的學問！骨骼可直接因癌細胞轉移，或間接受乳癌治療受損
- 科學家在進一步了解癌細胞如何透過骨骼細胞 OB, OC 對骨質的影響，提供了（防預及）治療骨轉移和治癌引致骨質流失的問題
- BP 仍然是”保骨藥”中的主角，新藥則留意 D'Mab, 及將來用於 PTHrP, Src 受體的藥物

對收經後（+/- 接受乳癌治療）婦女的忠告

- 飲食習慣： 注意鈣質和維生素 D 的攝取
- 注意運動： 幫助骨骼系統作健康正常的新陳代謝
- 生活習慣： 不煙少酒

謝謝來臨

!

