

乳癌的復發及治療

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Case Sharing

- 44 yr.; Premenopausal;
- 12/1998 - Incidental finding of Rt breast lump
FNA - +ve for malignant cells.
- 12/1998 - Rt Total mastectomy with axillary dissection
- Metastasis workup – CXR; CT abd & pelvis;
bone scan; LFT; RFT – No metastasis

Case Sharing II

- Pathology
 - Primary tumour: Infiltrative ductal carcinoma;
 - (浸潤性導管癌)
 - Bloom's and Richardson's Grade III
 - 3.5 cm largest diameter
 - Extensive Lymphovascular invasionLVI
 - All resection margins clear

Case Sharing II

- Pathology II
 - Lymph nodes:
 - 21/30 LN's
 - 2 cm largest
 - Extensive extracapsular extension.(廣泛囊外擴展)
- Biological Markers
 - ER 200; PR 200 ; c-erbB2 +++

Case Presentation

Adjuvant Therapy

- Chemotherapy (1/99 – 7/99)
 - Adriamycin 50 mg/M2
 - Taxol 175 mg/M2
 - Cyclophosphamide 600mg/M2

Sequentially at 2 weekly intervals with GCSF support.
- Radiotherapy
 - Chest wall and SCF 50 Gy in 25 frs
- Hormonal therapy
 - Tamoxifen 20 mg qd since July 1999

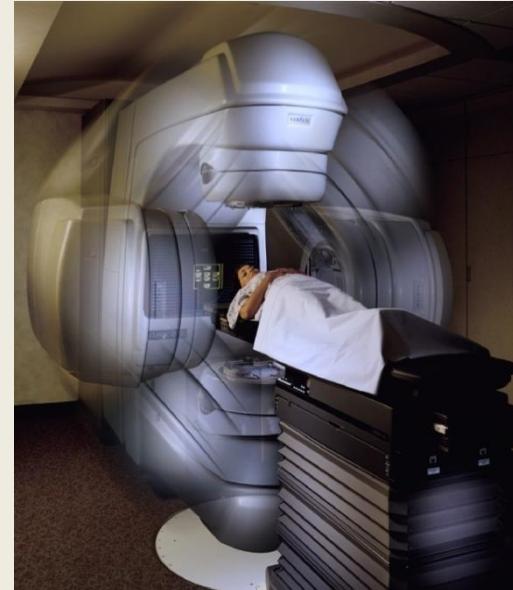
乳癌復發分類

1. 腫瘤在同一邊乳房
2. 轉移至另一邊乳房生長
3. 腫瘤擴散至其他器官

Risk of local-regional recurrence

乳房及淋巴結復發的風險因數

- Risk of recurrence after lumpectomy
- 乳房保留手術後復發的風險
 - No RT 26% in 5 yrs.
 - WBRT (+ Boost) 7% (~4%)
- Risk factors
 - Margins
 - Age
 - Lymph nodes status 0; 1-3; > 4
 - Estrogen receptor status + ve/- ve
 - Tumour nuclear grading I/II/III
 - C-erbB2 (HER2) Status +/-
 - Tumour size



Risk of Distant Metastasis

遠距擴散的高危因數

- Age
- Histology subtype
- Tumour Grade
- Tumour size
- Chest wall and skin involvement
- LN status (0/1-3/4-9/>10)
- ER/PR status
- Multigene array expression profile
- BRCA status

Pathology of breast cancer 1

Ductal carcinomas

Three histopathologic classes

1. Ductal carcinomas (> 90%)
2. Lobular carcinomas (~ 3%)
3. Special forms of breast cancer (~ 6%)

Ductal carcinomas

Histologic type of adenocarcinoma	Breast cancer cases (%)
Infiltrating ductal	70–80
Medullary	5–8
Mucinous colloid	2–4
Tubular	1–2
Papillary	1–2
Intraductal	2–3

Molecular/Intrinsic Subtyping

- Microarray identified gene expression profiles or gene signatures
 - Consistent with the heterogeneous collection of biologically distinct diseases
- “Molecular portrait” first pioneered by the Stanford and UNC groups (Sørlie and Perou)
- Divides breast cancer into 2 main types, using 5 subtypes:

ER-positive

Luminal A

Luminal B

ER-negative

HER2 (cerbB2) +

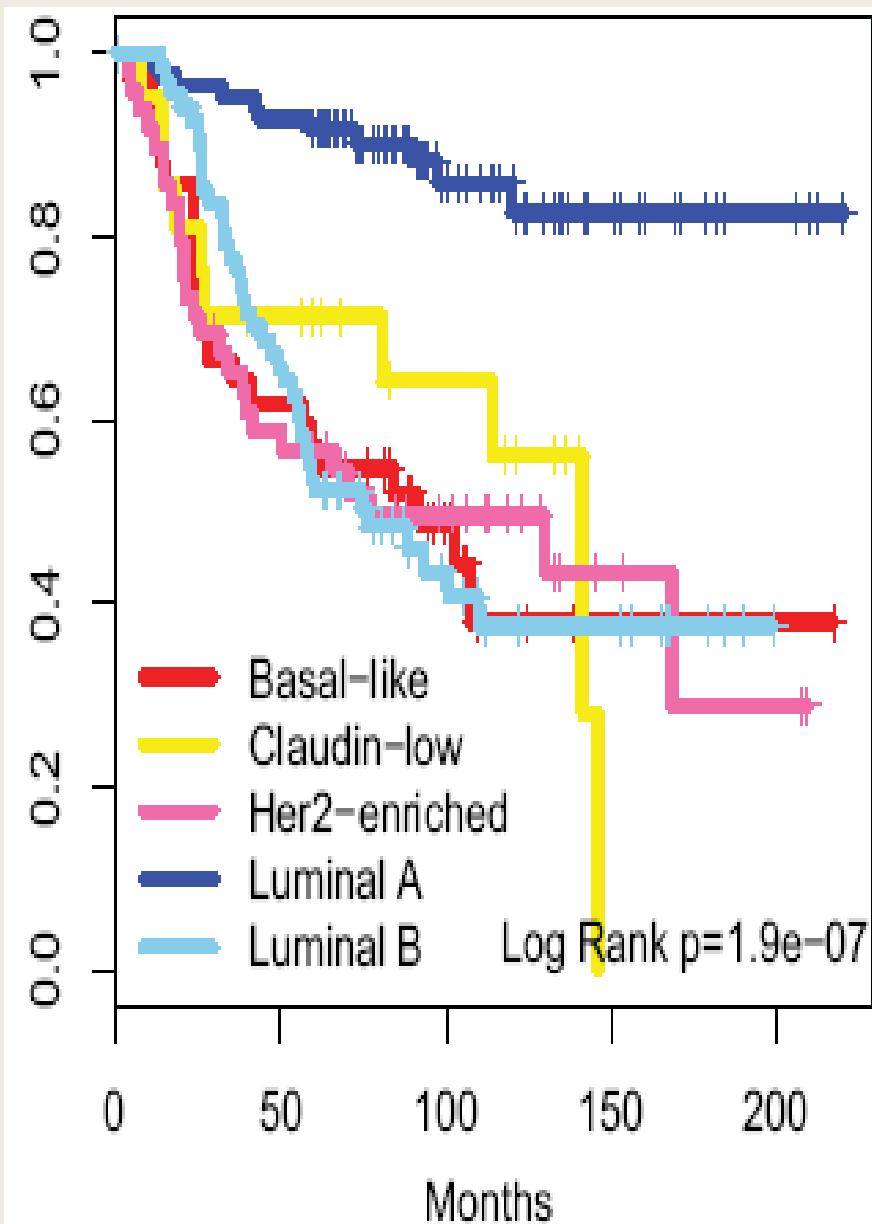
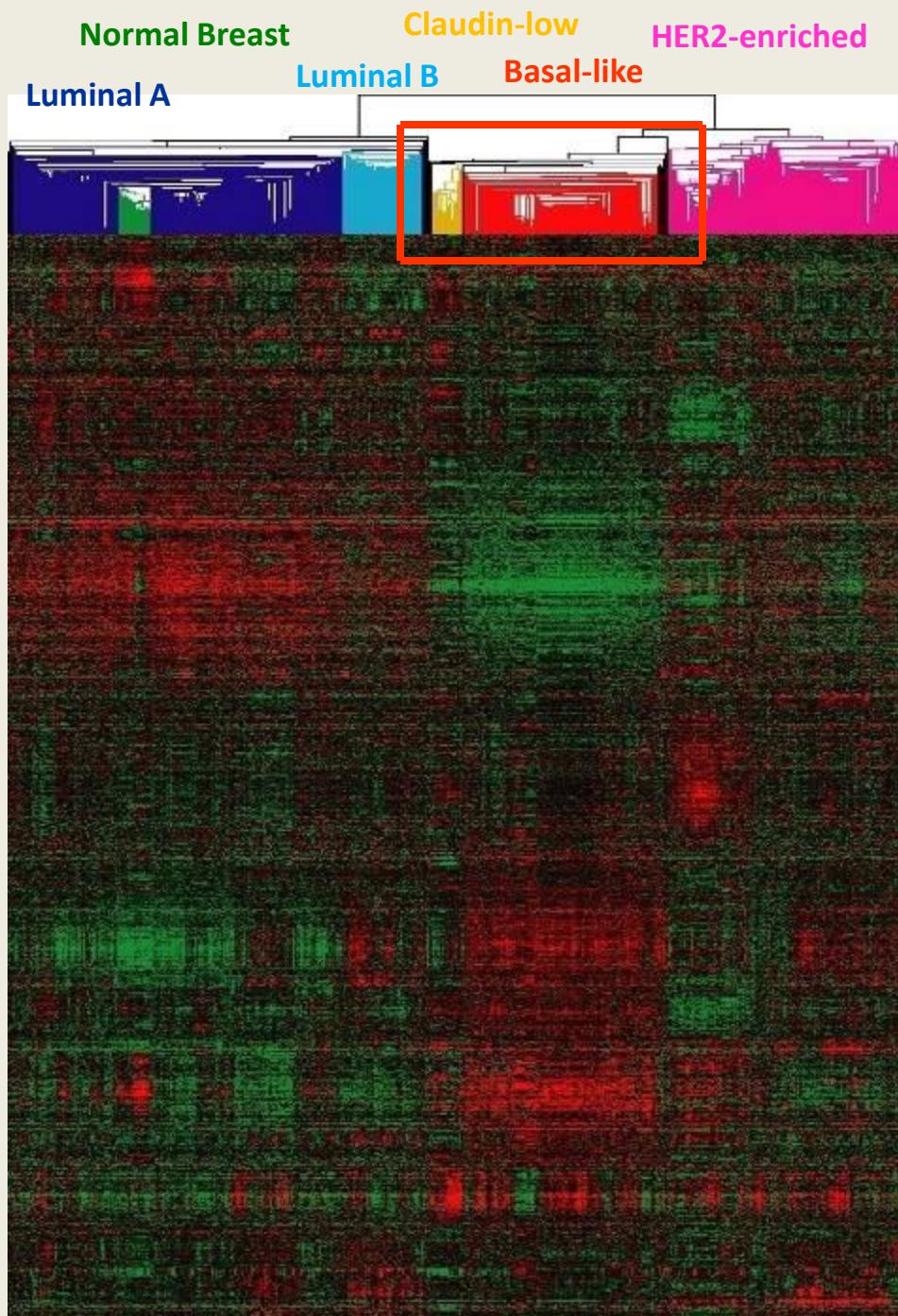
Basal-like

Normal-like

Breast Cancer Molecular Subtypes: Clinical Course and Treatment

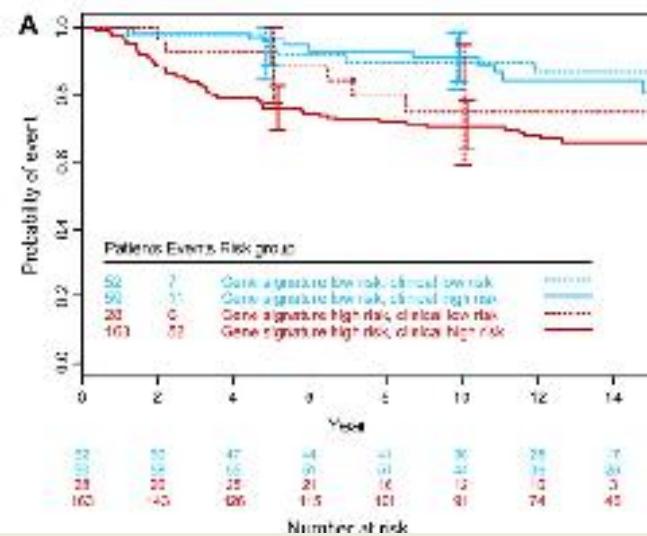
Subtype	%	Clinical course	Prevailing treatment
HR+/ HER2- (luminal A)	30–38	indolent (bone,soft tissue)	endocrine agents
HR+/HER2+ or high Ki-67 (luminal B)	15–24	aggressive (viscera)	antiHER2 agents endocrine agents chemotherapy
HER2+/HR- (HER2+)	8–10	very aggressive (viscera & CNS)	antiHER2 agents chemotherapy
Triple Negative* (basal-like)	15–25	very aggressive (viscera & CNS)	chemotherapy PARPi promising
BRCA 1/2 mutation	< 5	moderately aggressive	chemo (Pt-salts) PARPi promising

*Apocrine, adenoid-cystic and low-grade metaplastic tumours are also included in the TNBC group; these rare subtypes have a very good prognosis

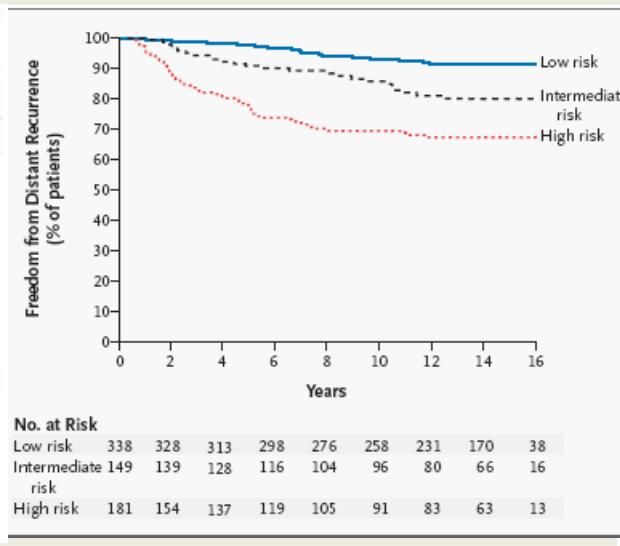


Genomic Assays for Breast Cancer Prognosis

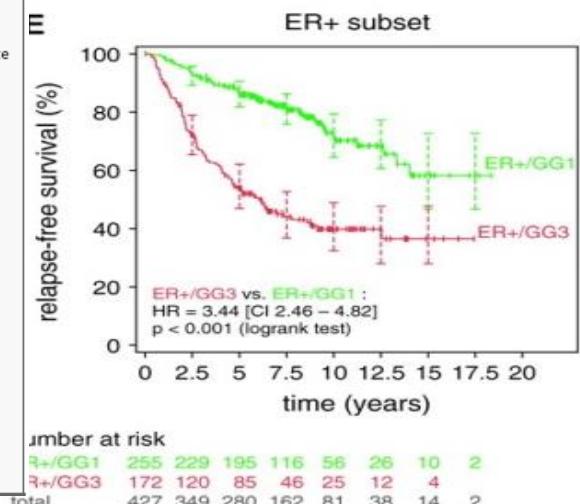
Mammaprint



Oncotype DX



Genomic Grade



Buyse,
JNCI, 2006

Paik, et al. NEJM
2004

Sotiriou, JNCI, 2006

復診和追蹤檢查：

局部復發：檢查原開刀部位附近之胸壁。

遠處轉移：檢查肺、骨骼及肝臟。

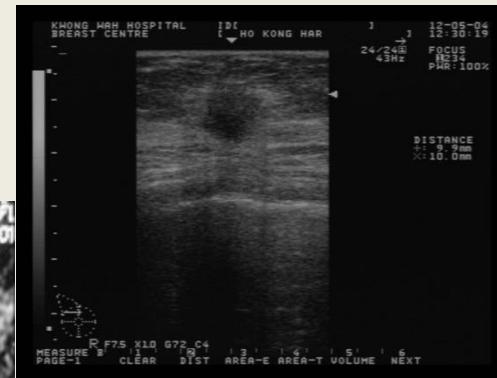
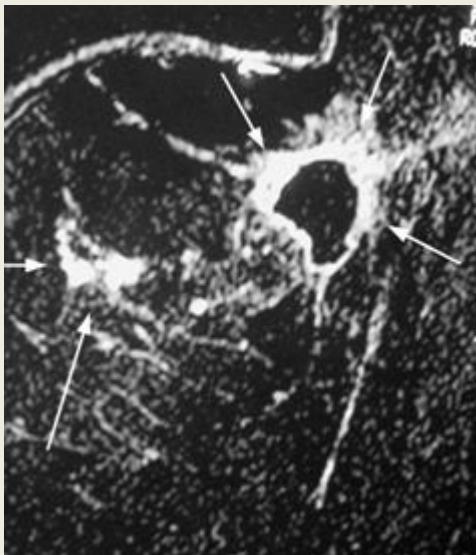
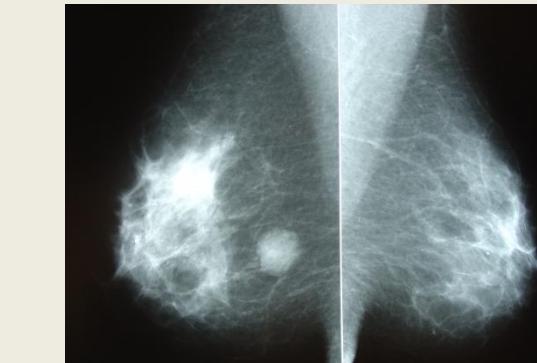
定期復診及檢查：肺部X光、骨骼攝影、超聲波、電腦掃描或正電子掃描。

乳房造影術（以X光檢查乳房）超聲波（利用聲波製造腫塊的影像）

磁力共振——利用磁場掃描，製造出病人身體橫切面的圖像

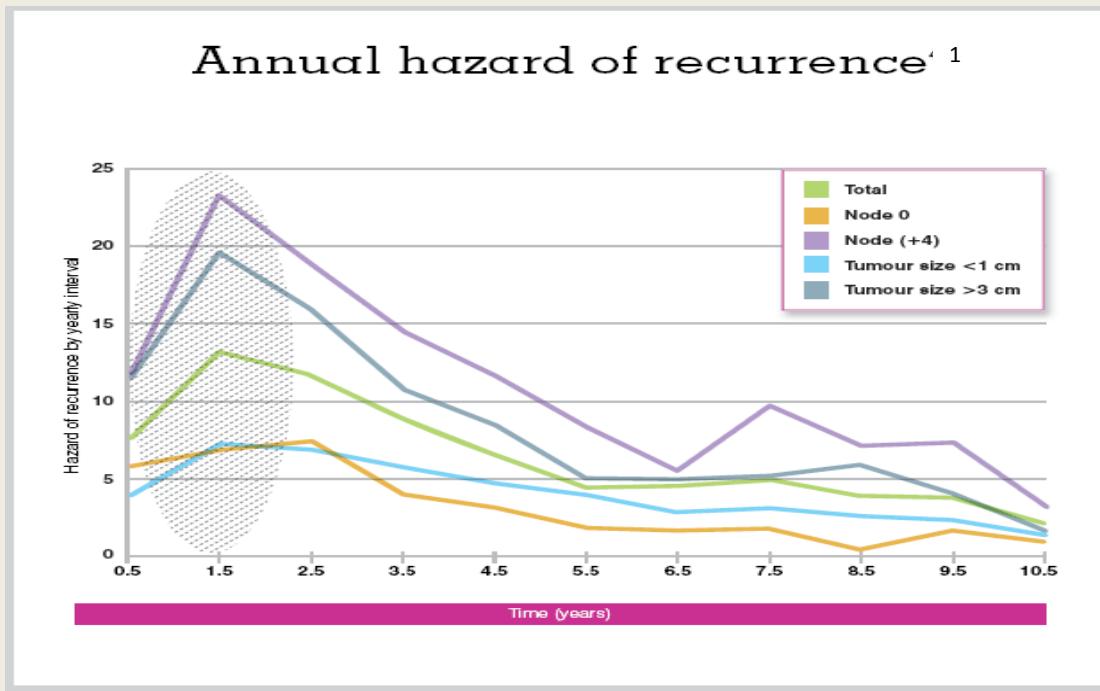
癌症指數: CA 15.3 ; CEA; CA125

肝功能：ALP及 AST



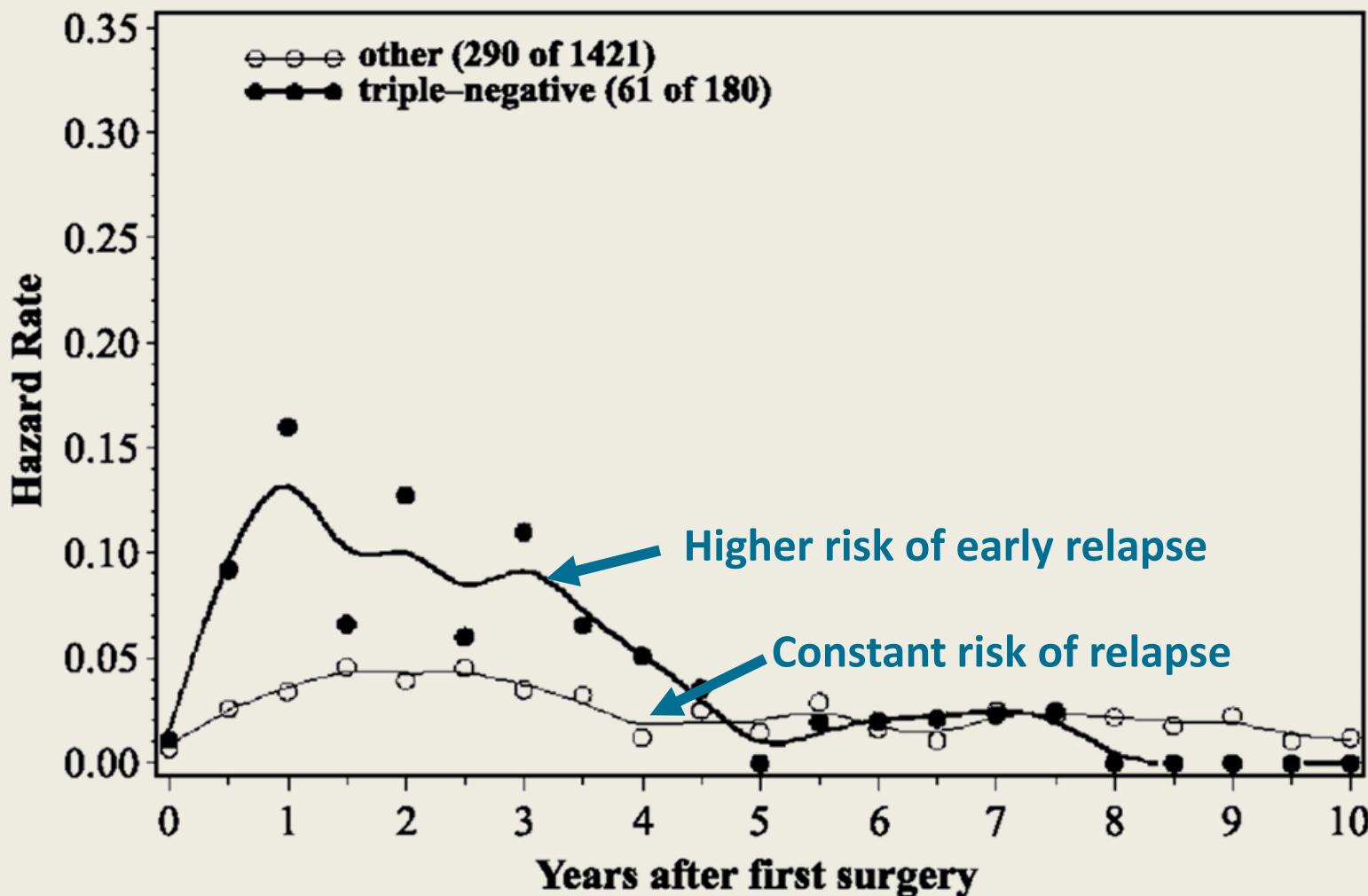
乳癌復發

- 手術後首一至兩年是復發高風險期
- 手術後的五至六年期間，復發風險會逐漸減低



1. Saphner T et al. J Clin Oncol 1996; 14: 2738-2746

Basal-like Breast Cancer: Frequent and Early Relapse



如何減少乳癌復發的風險

- 減少雌激素
- 減少高脂肪，高碳水化合物的食物
- 健康飲食
 - 少吃: 紅肉, 含高飽和脂肪及高膽固醇的食物
 - 多吃: 蔬果
- 多做運動
 - 每日三十分鐘
- 遠離煙酒

Case Sharing -Treatment I

- 5/2001 CA 153 42 – 131
- Ix : CT thorax; PET/CT scan; MRI brain
 - MRI brain – Multiple secondaries

Common Sites of Metastasis

乳癌擴散

- Most common
 - Bone (~40%)
- Others
 - Brain (triple negative; HER2 +)
 - Leptomingeal
 - Lymph Nodes (Contralateral axilla, SCF, IMC
Medinstinal etc)
 - Liver
 - Lung
 - Soft tissue

Workup for recurrence

- Physical examination
- Blood Tests: LFT, Tumour markers (CA15.3, CEA, CA125)
- Local and contralateral breast: MMG, U/S breast (MRI breast)
- Metastatic workup: CXR, U/S liver and abdomen (CT, PET/CT, Whole body MRI, NM/MR Bone scan)
- Biopsy of metastasis : histological confirmation/ Change of biological marker status

Individualized Therapy and Personalized Medicine

Individualized Therapy

- Adjusting treatment to the tumor characteristics
- 針對癌細胞的治療

Personalized Medicine (個人化的治理)

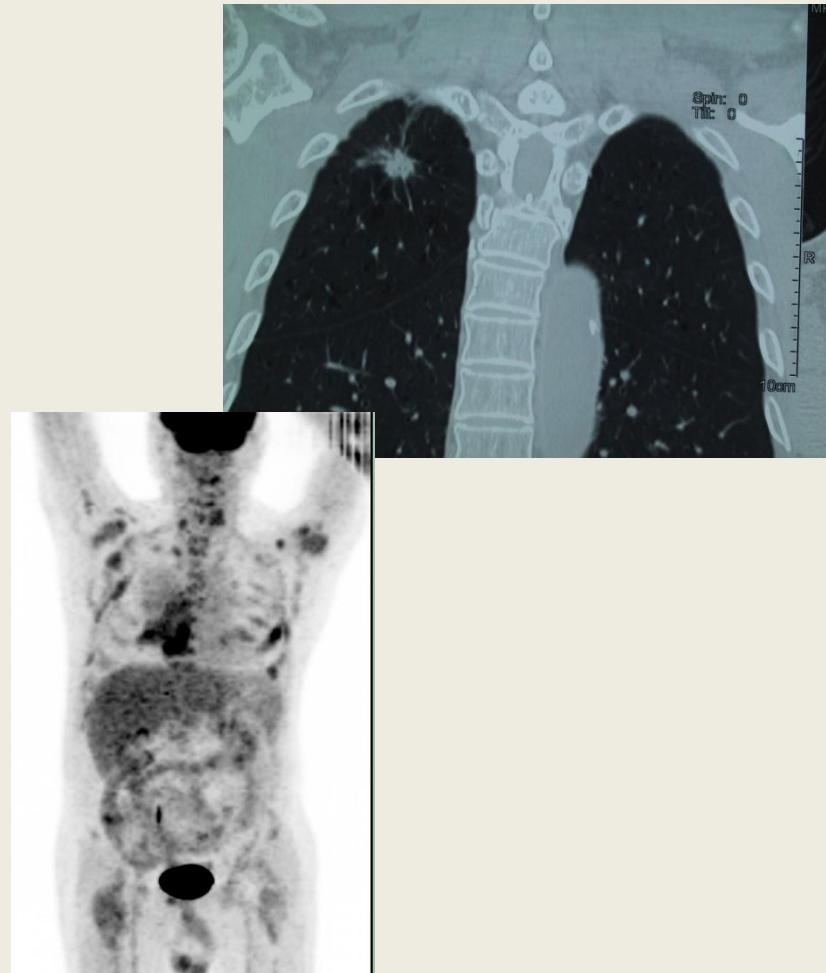
- Adjusting treatment to the patient characteristics
 - The right treatment
 - For the right patient
 - At the right time

因應患的情况作出治療的方向

治療方法

因人而異，考慮因素：

1. 年齡（是否停經）
2. 腫瘤的生長速率
3. 淋巴擴散及轉移其它部位
4. 雌激素受體 (ER)/黃體酮受體 (PR)
7. **HER2**過度表達
8. 病人的意願及其健康狀況



Treatment of Metastasis

Aim of Treatment : 對擴散病者的治療目的

Control disease 控制腫瘤

Prolong life (curative intent for a selected group) 延長生命

Relieve symptoms 舒解症狀

Maintain quality of life 保持生活質素

如何選擇治療方法？

1. 外科手術切除
2. 電療
3. 化學藥物治療
4. 內分泌(賀爾蒙)治療
5. 標靶治療
6. 其他藥物

單一或合併起來??
來提高治愈率

Treatment II

- 7/01 – Whole brain RT
- Stopped Tamoxifen
- 9/01 – Herceptin 2mg/Kg weekly
 - CA 153 --- >1444
 - Vinorelbine 20 mg/M2 weekly added
 - CA 153 -----50
- Cont. weekly VBL + Herceptin with GCSF till
- 10 /2002 MRI brain -1 cm lesion in left cerebellum. Other lesions regressed
- Stereotactic Radiosurgery to cerebellar lesion (16 Gy X 1)

Treatment III

- after 52 courses of VBL + Herceptin, stopped VBL and continue with Herceptin every 3 weekly and started Femara 2.5 mg q.d.
- 11/03 CA 153 243
 - PET scan /MRI – multiple liver mets; no other systemic disease
 - Restarted on VBL and Herceptin every 2 weekly
 - Continue Femara 2.5 mg daily
- 11/03 – 12/04 CA 153 243 --- 50
 - 07/04 MRI PR of liver mets

Treatment IV

- VBL 1/05 - 9/05
 - Cont + Herceptin
 - 02/05 MRI liver SD
 - 02/05 MRI brain - 3 new mets – SRS (16 – 18 Gy)
- 2/2006 CA 153 131
- 5/2006 MBI brain & liver – new lesions

Treatment V

- 9/2006 – pending Lapatinib; cont VBL + Herceptin (pt. reluctant to change chemo in fear of side effects)
- 6/2007 Rapid progression of liver mets – AST/ALT - > 500
- 8/2007 Switched to Xeloda & Laprtinib

Treatment for Local-Regional Recurrence

乳房局部復發後的治療

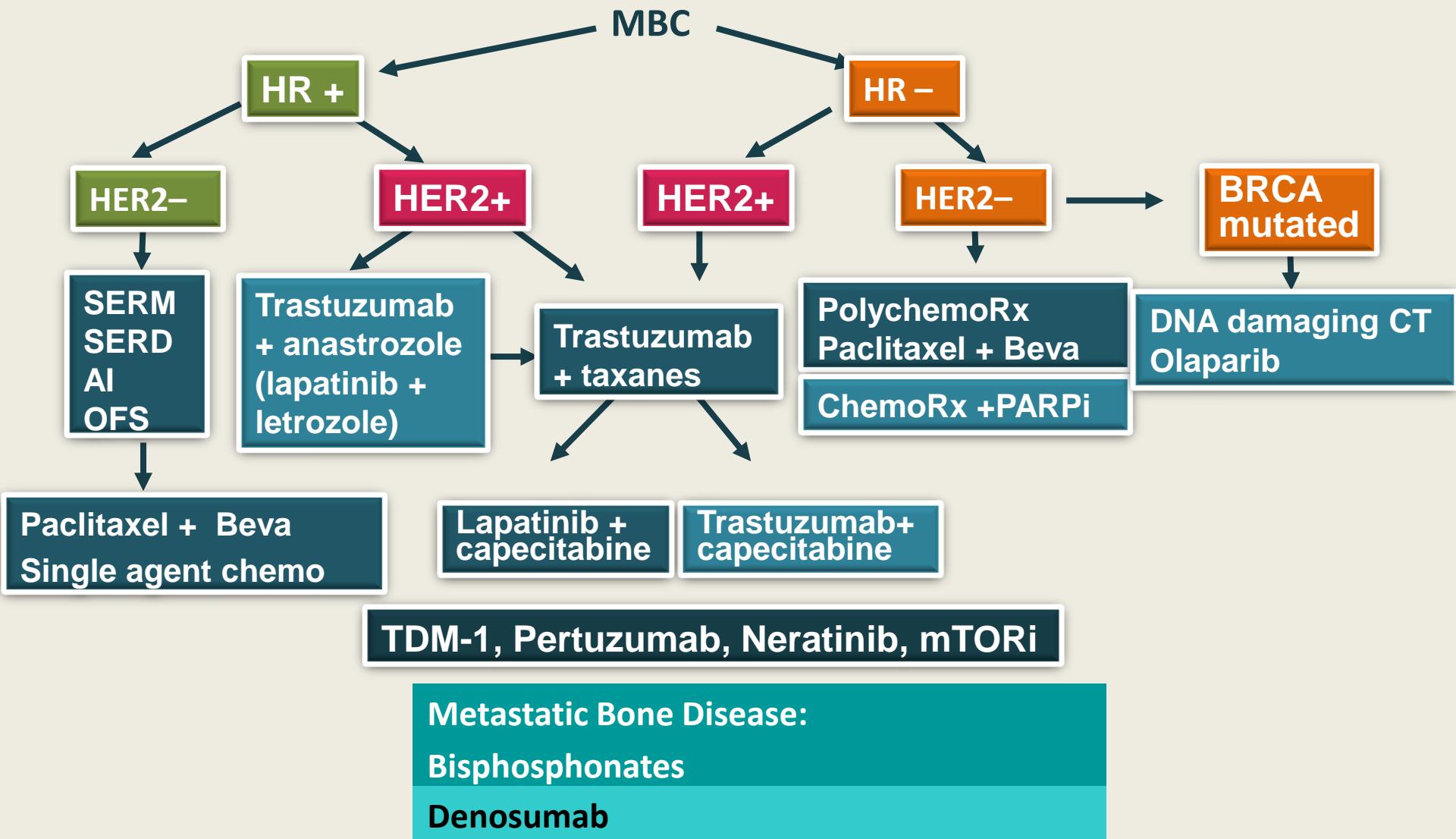
- Surgery (手術)
 - Mastectomy(全乳房切除) operability rate 75 – 100%
 - 5 yrs relapse free survival (無復發存活率) 55 – 73%
 - 10 yrs survival rate (存活率) 60 - 70 %
 - Chest wall recurrence (胸壁復發率) < 10%
- Important prognostic factors
 - Disease free interval <2yrs. Vs. > 2 yrs.
 - Skin involvement
 - Lymph node status
 - ER /PR status
 - CerbB2 Status
 - BRCA1/BRCA2 mutation

Treatment for Local-Regional Recurrence

乳房局部復發後的治療

- Breast conservative surgery (局部切除)
 - 20% to 30% with residual disease (遺留)
 - Local recurrence (復發率) 14 % - 48%
- Re-irradiation (電療)
 - External beam RT (外放射)
 - Brachytherapy (近距放射)
 - Selected patients; high complication rate
 - 高度選擇性；後遺症較嚴重

Treatment Algorithm for MBC



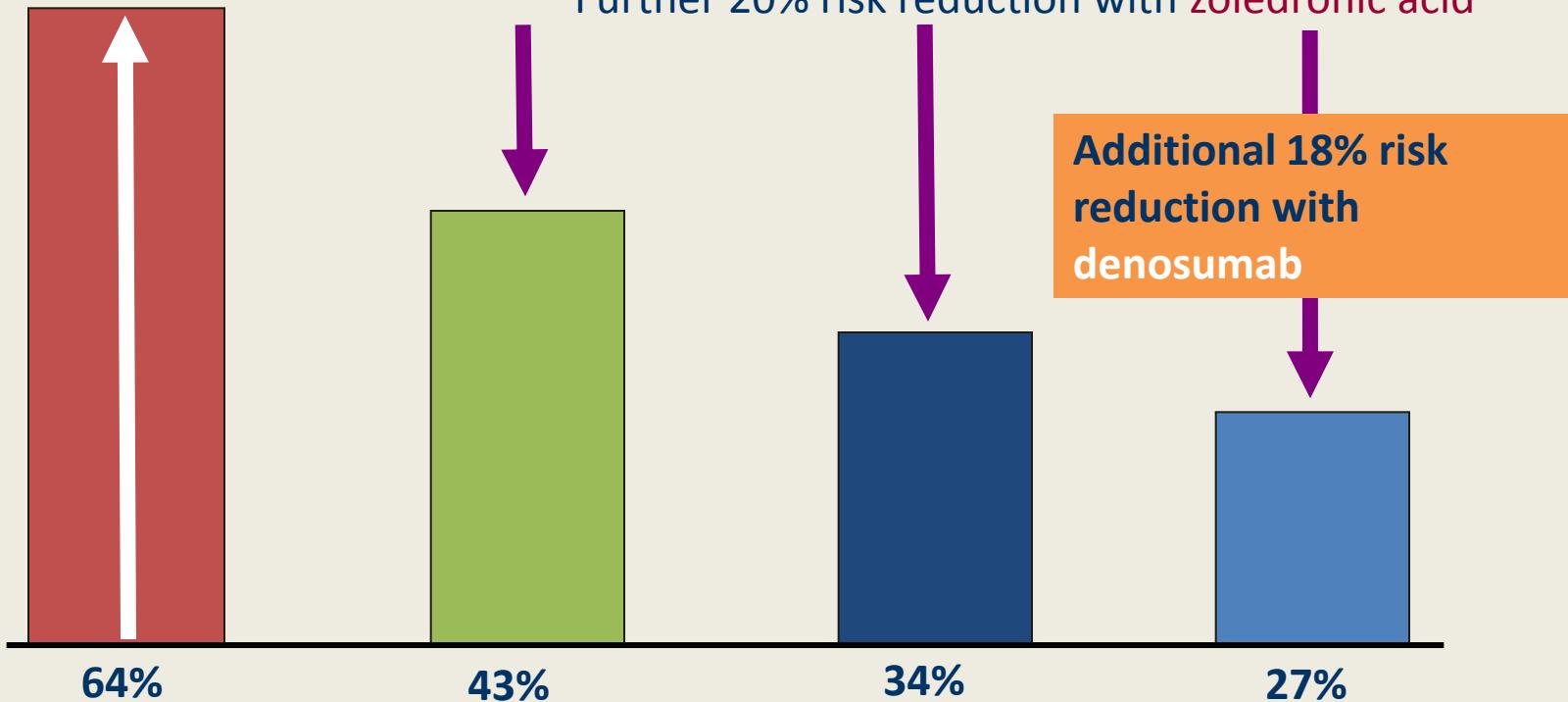
Metastatic Bone Disease - Bisphosphonates in Breast Cancer

64% risk of skeletal complication with **no bisphosphonate** at 2 yrs

Approx 33% risk reduction with **pamidronate**

Further 20% risk reduction with **zoledronic acid**

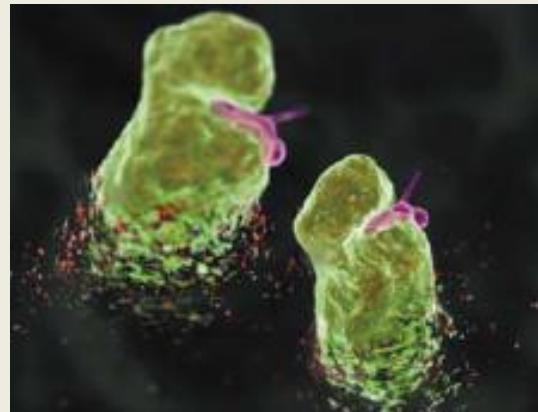
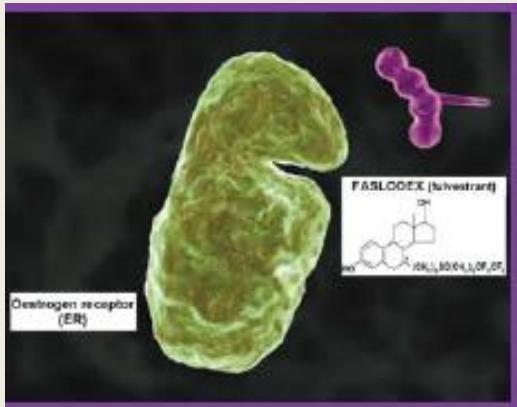
Additional 18% risk reduction with **denosumab**



What's New ?

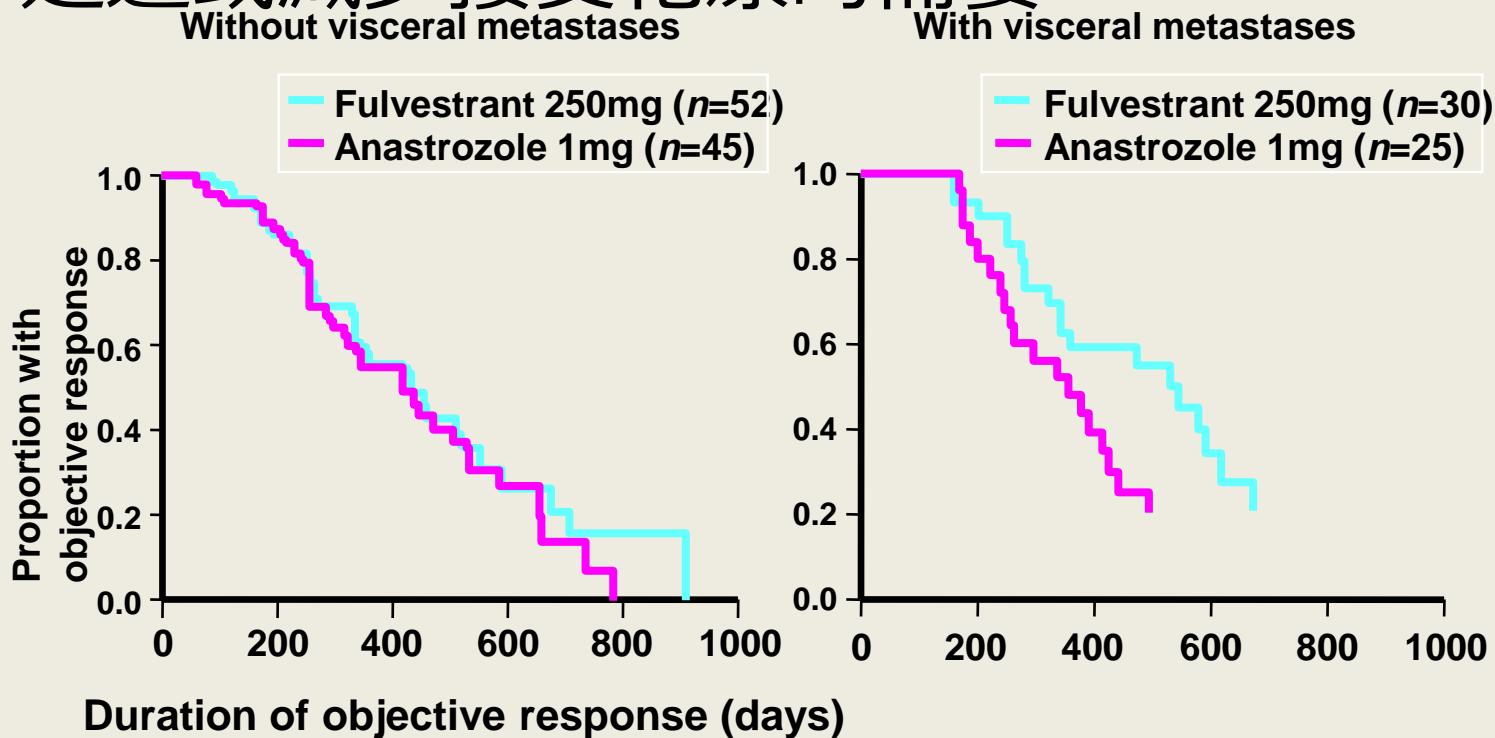
Fulvestrant- 針對雌激素受體

- 能與雌激素受體結合，阻礙其運作，再將其分解；作用是阻止癌細胞的生長及擴散。
- 其運作模式有別於他莫昔芬及芳香化酶抑制劑(AI)



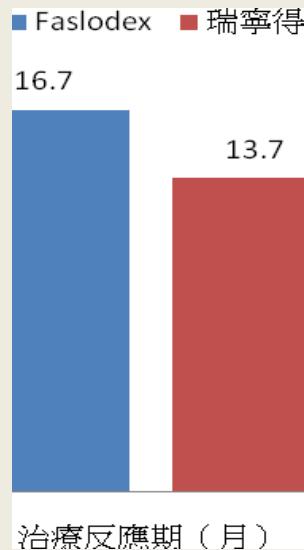
Faslodex 的功效

- 功效與Arimidex大致相同；包括癌症有轉移到其他內臟的病人
- 延遲或減少接受化療的需要



Faslodex 的功效

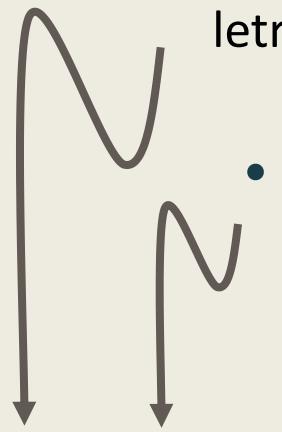
- Faslodex 能延長對治療有反應的患者的癌症受控制時間
(治療反應期)
- 重新及持續控制病情



BOLERO-2: ER⁺ Adv Breast Cancer, Exemestane + Everolimus After Recurrence or Progression on Anastrozole or Letrozole

- Postmenopausal women with ER+ locally advanced or metastatic breast cancer with prior recurrence or progression on letrozole or anastrozole

- Stratification by sensitivity to prior hormonal therapy and visceral metastases



S
C
R →
E
E
N

Randomize
2:1
N = 705

**Everolimus 10 mg PO daily
Exemestane 25 mg PO daily**

**Placebo 10 mg PO daily
Exemestane 25 mg PO daily**

< 21 days
prior to day 1

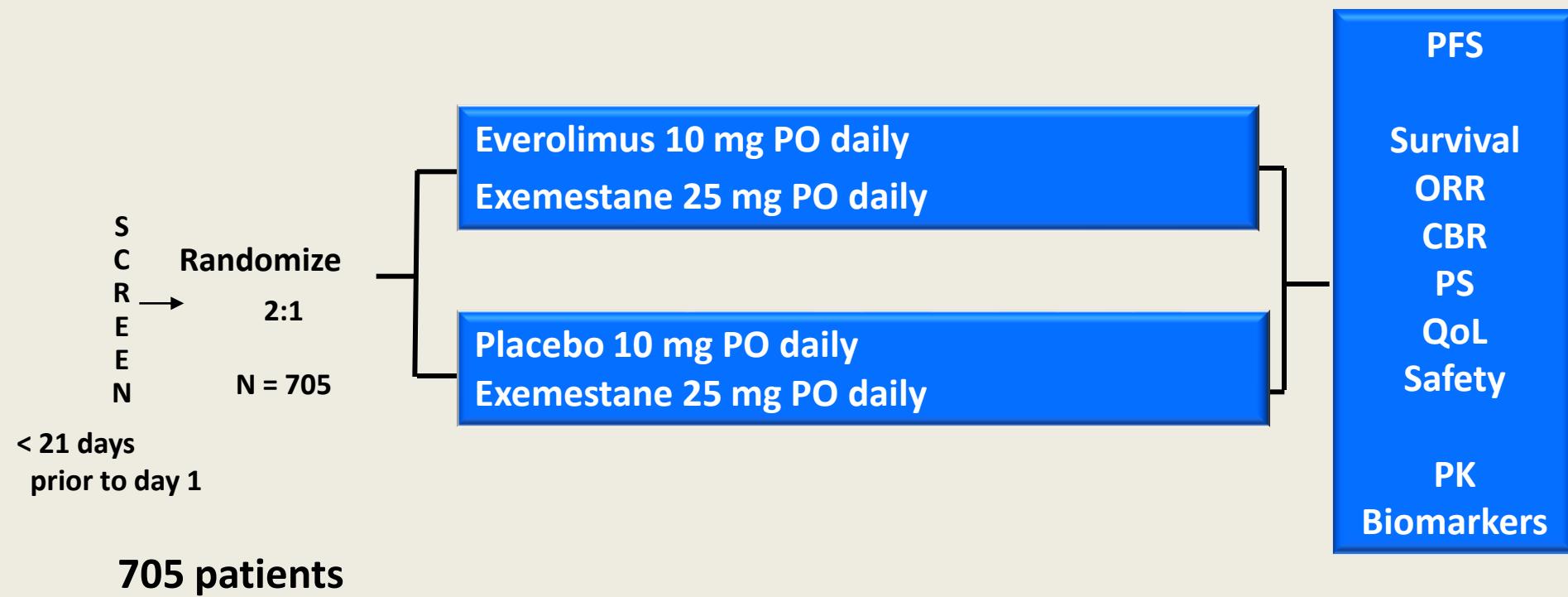
705 patients

PFS
Survival
ORR
CBR
PS
QoL
Safety

PK
Biomarkers

BOLERO-2: ER⁺ Adv Breast Cancer, Exemestane + Everolimus After Recurrence or Progression on Anastrozole or Letrozole

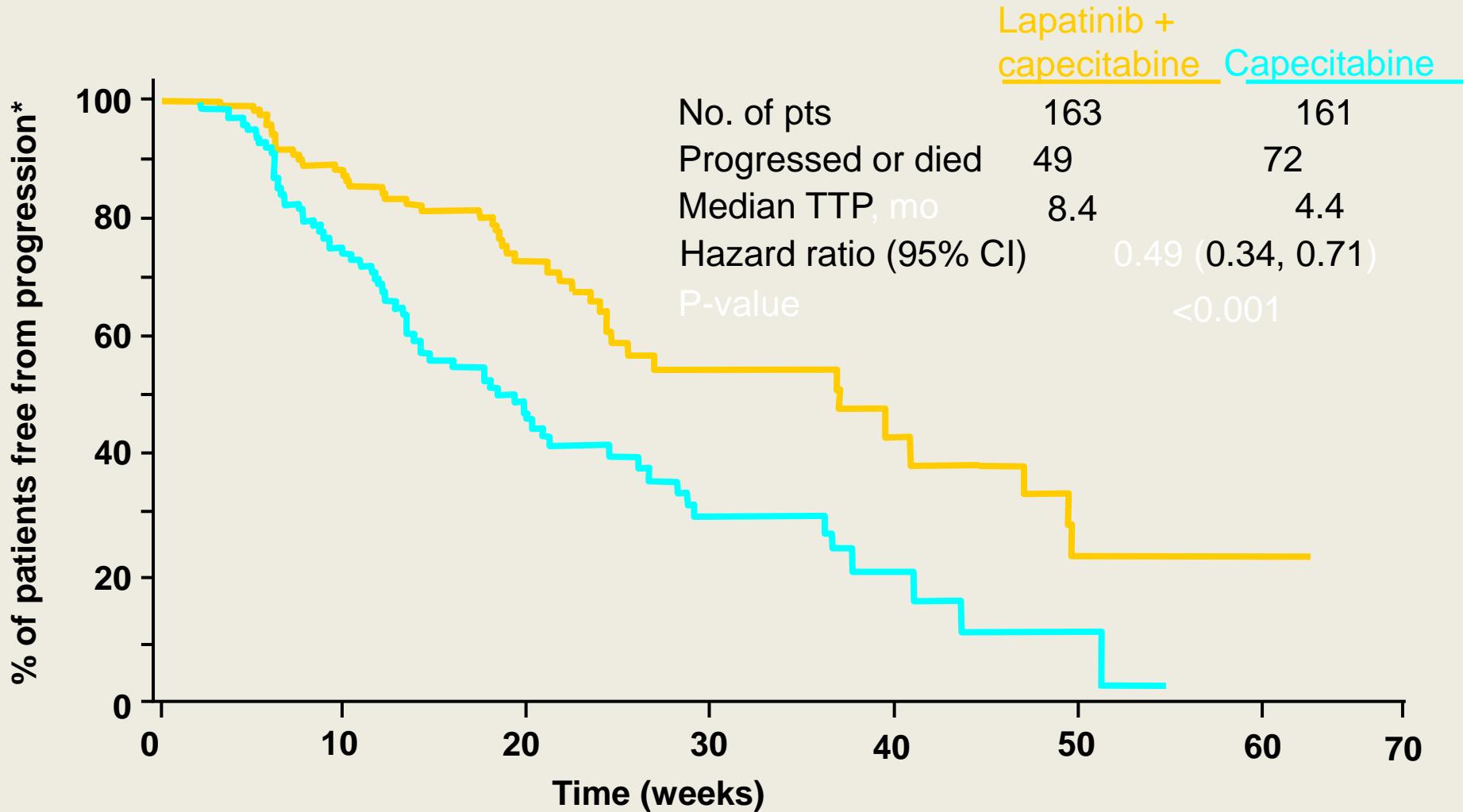
median progression-free survival was **6.9** months with **everolimus plus exemestane** Vs. **2.8** months with **placebo plus exemestane**, (hazard ratio for progression or death, 0.43; 95% confidence interval [CI], 0.35 to 0.54; P<0.001).



Does Lapatinib Work in Trastuzumab Resistant HER2 Positive Cells?

Time to progression - ITT population

Independent assessment

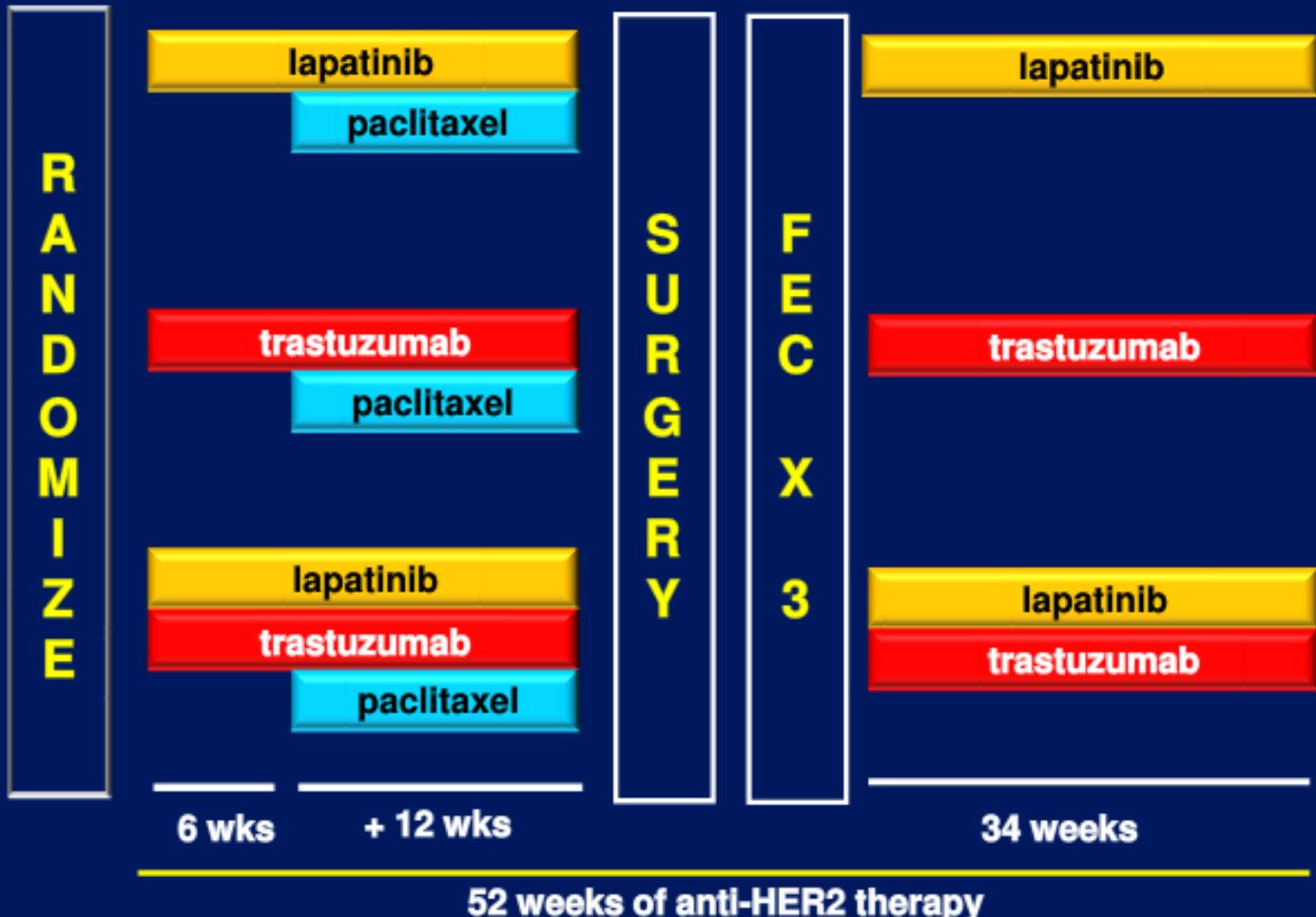


Study Design

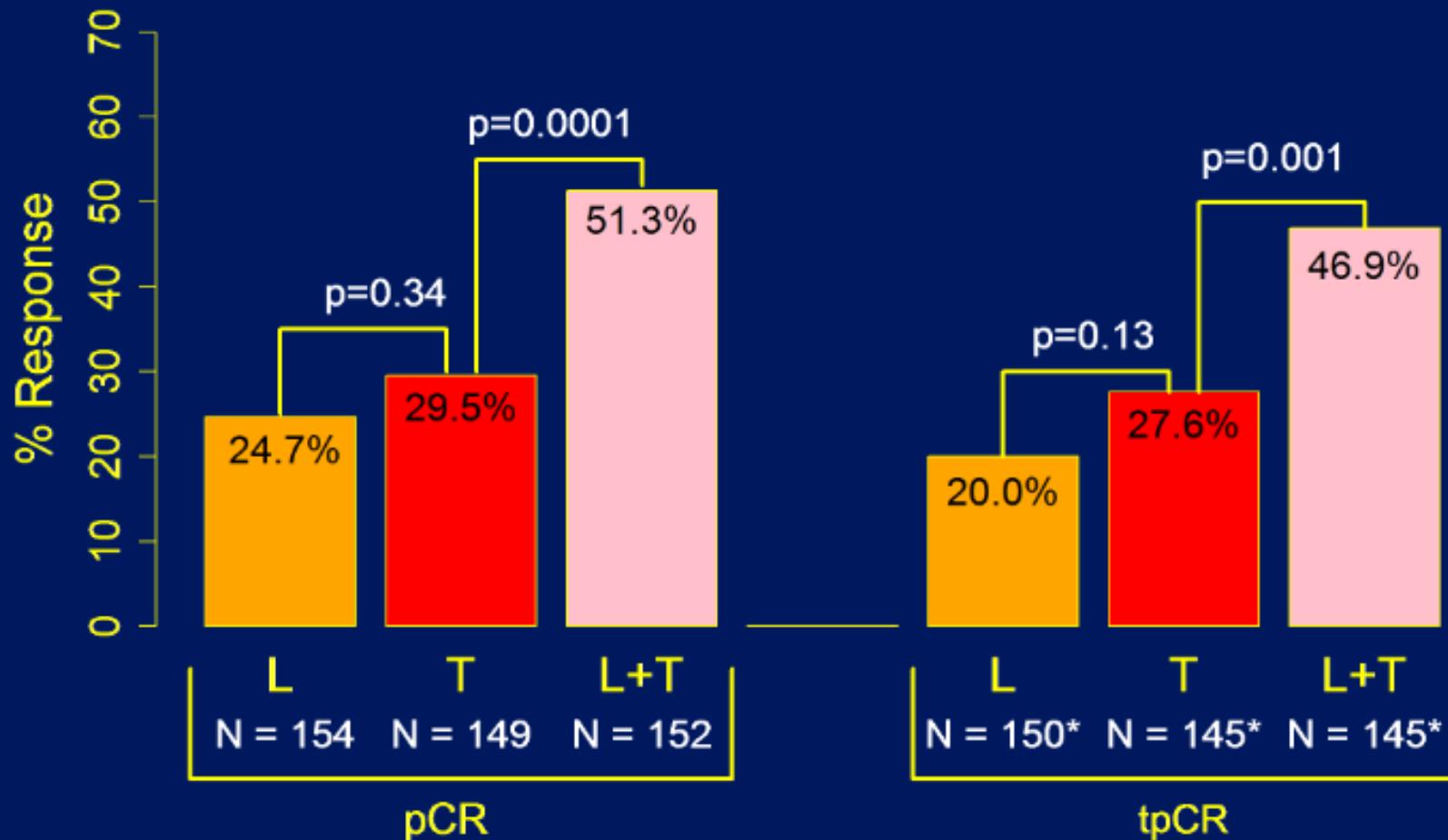
Invasive operable
HER2+ BC
 $T > 2 \text{ cm}$
(inflammatory BC
excluded)
 $\text{LVEF} \geq 50\%$
N=450

Stratification:

- $T \leq 5 \text{ cm}$ vs. $T > 5 \text{ cm}$
- ER or PgR + vs.
ER & PgR –
- N 0-1 vs. N ≥ 2
- Conservative surgery
or not



Efficacy – pCR and tpCR



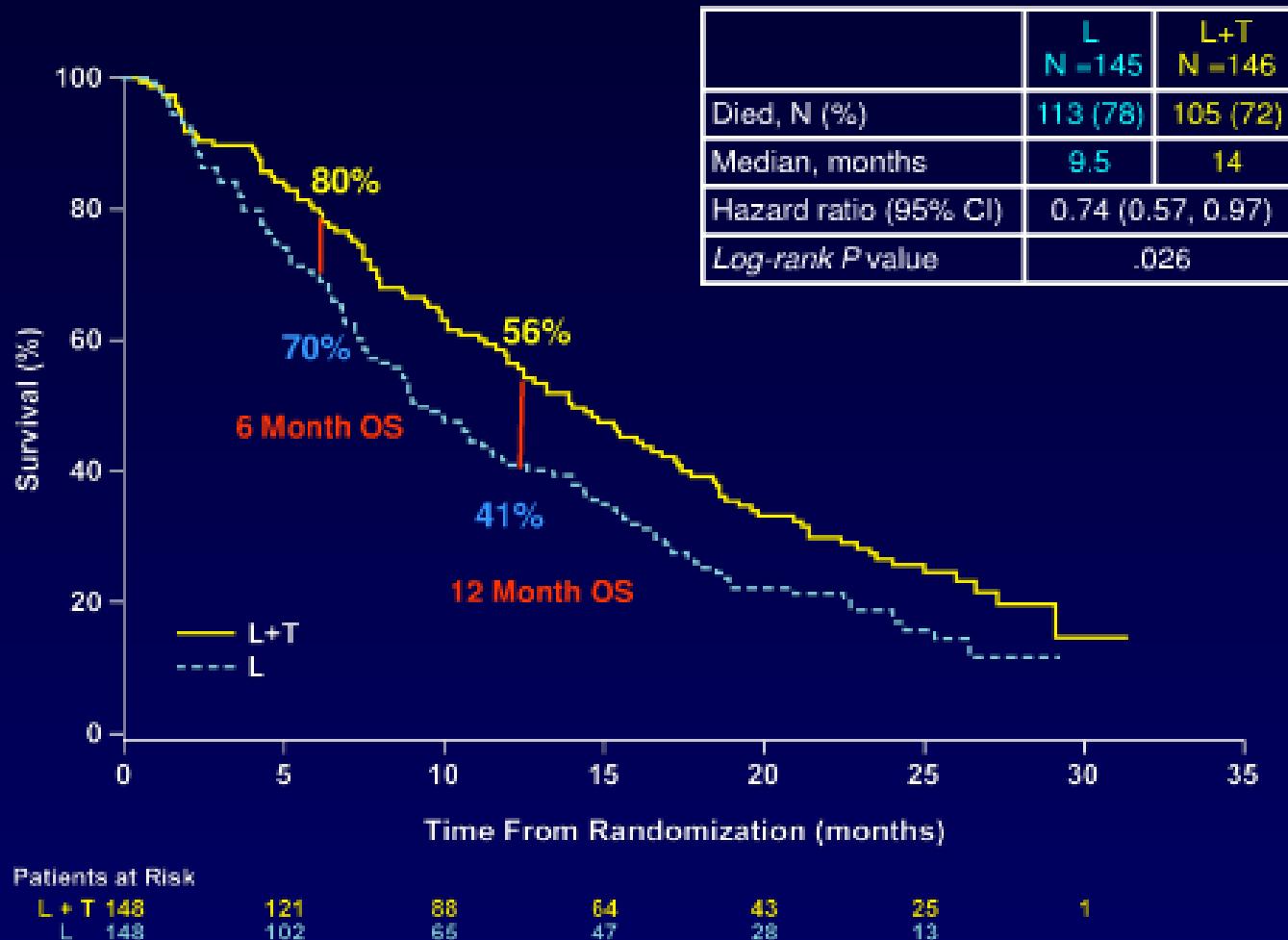
Pathological Complete Response

L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response

Locoregional (total) pCR

* Excludes 15 patients with non-evaluable nodal status

Updated Overall Survival in ITT



MBC – RCTs After A/T failure in Unselected Patients

Trial	Study population	Pts #	ORR %	PFS/TTP months	OS months
Ixabepilone+capecitabine Vs capecitabine ¹	A/T resistant	752	35 vs 14 P <0.0001	5.8 vs 4.2 P 0.0003	12.9 vs 11.1
Ixabepilone+capecitabine Vs capecitabine ²	A/T pretreated	1121	43 vs 29 p<0.0001	6.2 vs 4.2 P 0.0005	16.4 vs 15.6
Gemcitabine+vinorelbine Vs vinorelbine ³	A/T pretreated	252	36 vs 26 P 0.09	6 vs 4 P 0.0028	15.9 vs 16.4
Bevacizumab+capecitabine Vs capecitabine ⁴	A/T pretreated	462	20 vs 9 P 0.001	4.9 vs 4.2	15.1 vs 14.5

¹Thomas et al, J Clin Oncol 2007, 25:5210-17; ²Sparano et al, J Clin Oncol 2010, 28:3256-63;

³Martin et al, Lancet Oncology 2007, 8: 219-25; ⁴Miller et al, J Clin Oncol 2005,23:792-9;

EMBRACE Phase III Trial of Eribulin in Heavily-Pretreated MBC

Patients (N = 762)

- Locally recurrent or MBC
- 2-5 prior chemotherapies
 - ≥2 for advanced disease
 - Prior anthracycline and taxane
- Progression ≤6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG ≤2

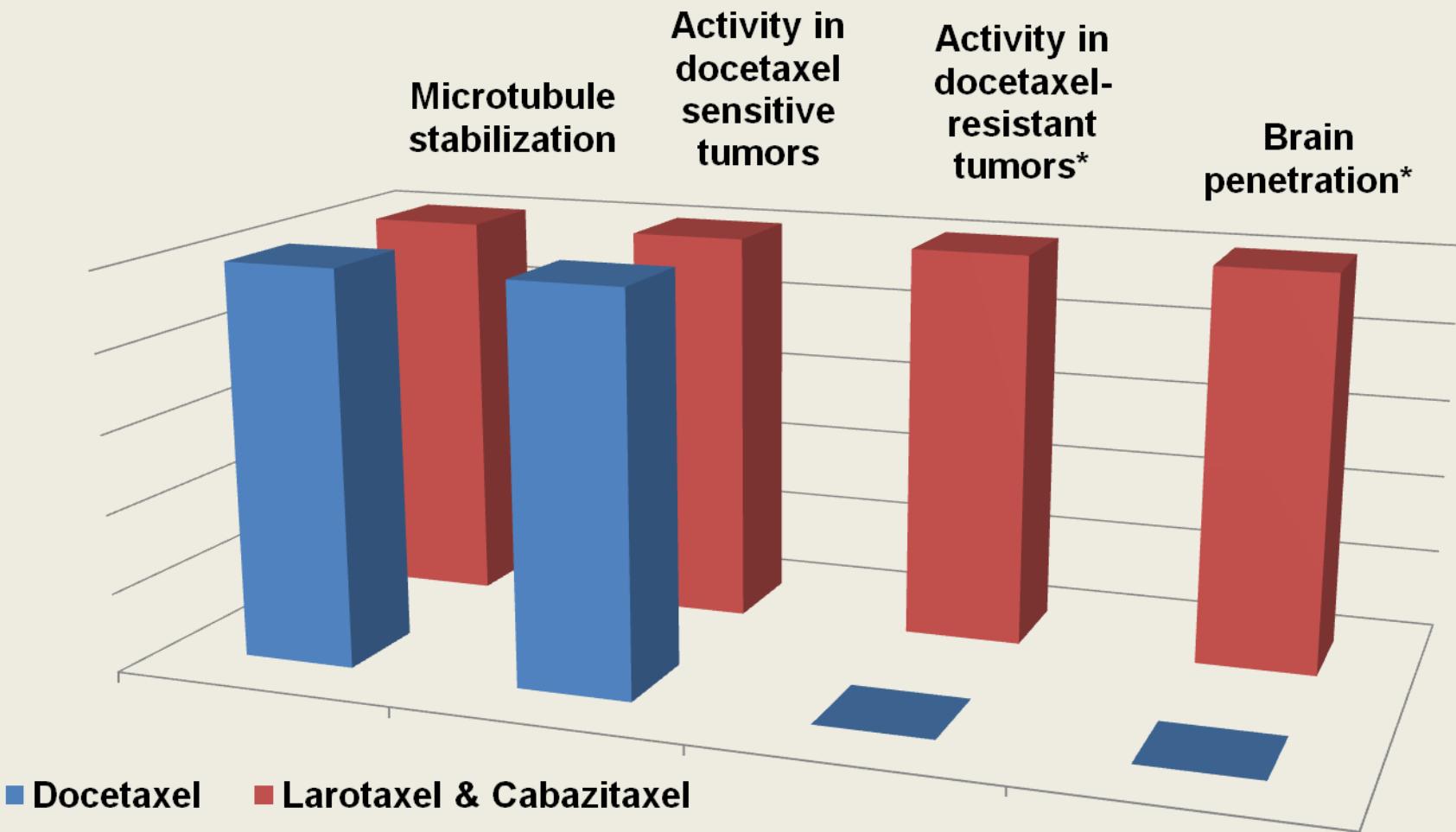


Eribulin mesylate
1.4 mg/m², 2-5 min IV
Day 1, 8 q21 days

Treatment of Physician's Choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological) or supportive care only

- Global, randomized, open-label
- Primary endpoint: OS
- Final analysis after 422 deaths
 - Median age 55.2 yrs, 16% HER2+, 19% TNBC, median 4 prior agents

Novel Taxoids: Improved Tubulin Targeting Profile



*Minimally recognized by P-gp (MDR-1).

PARP inhibition and tumor-selective synthetic lethality



Normal
BRCA1/BRCA2



HR-based repair

DNA replication fork
arrest and collapse

BRCA1/BRCA2
failure

Impaired HR repair

Alternative error prone repair

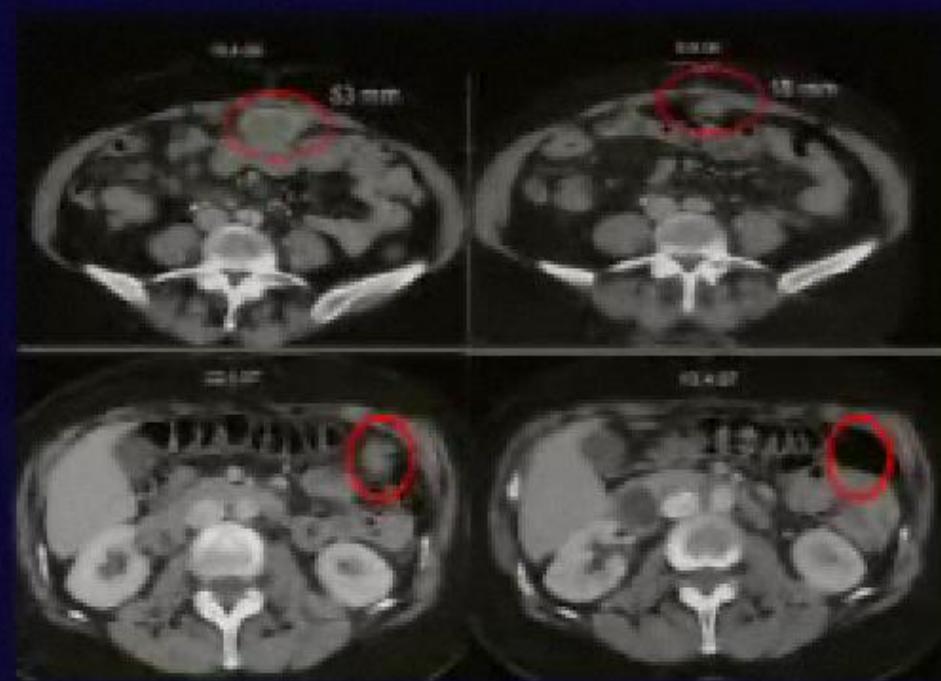
Chromosome Stability
Cell Survival

Chromosomal Instability
Cell Death

Olaparib

A novel, orally active PARP inhibitor

- A phase I trial identified olaparib (AZD2281; KU-0059436) 400 mg bid as the maximum tolerated dose¹ with a signal of efficacy in BRCA-mutated ovarian cancer²
 - Most common toxicities: CTCAE grade 1 and 2 nausea and fatigue
 - Significant PARP inhibition and tumor response at olaparib doses 100–400 mg bid



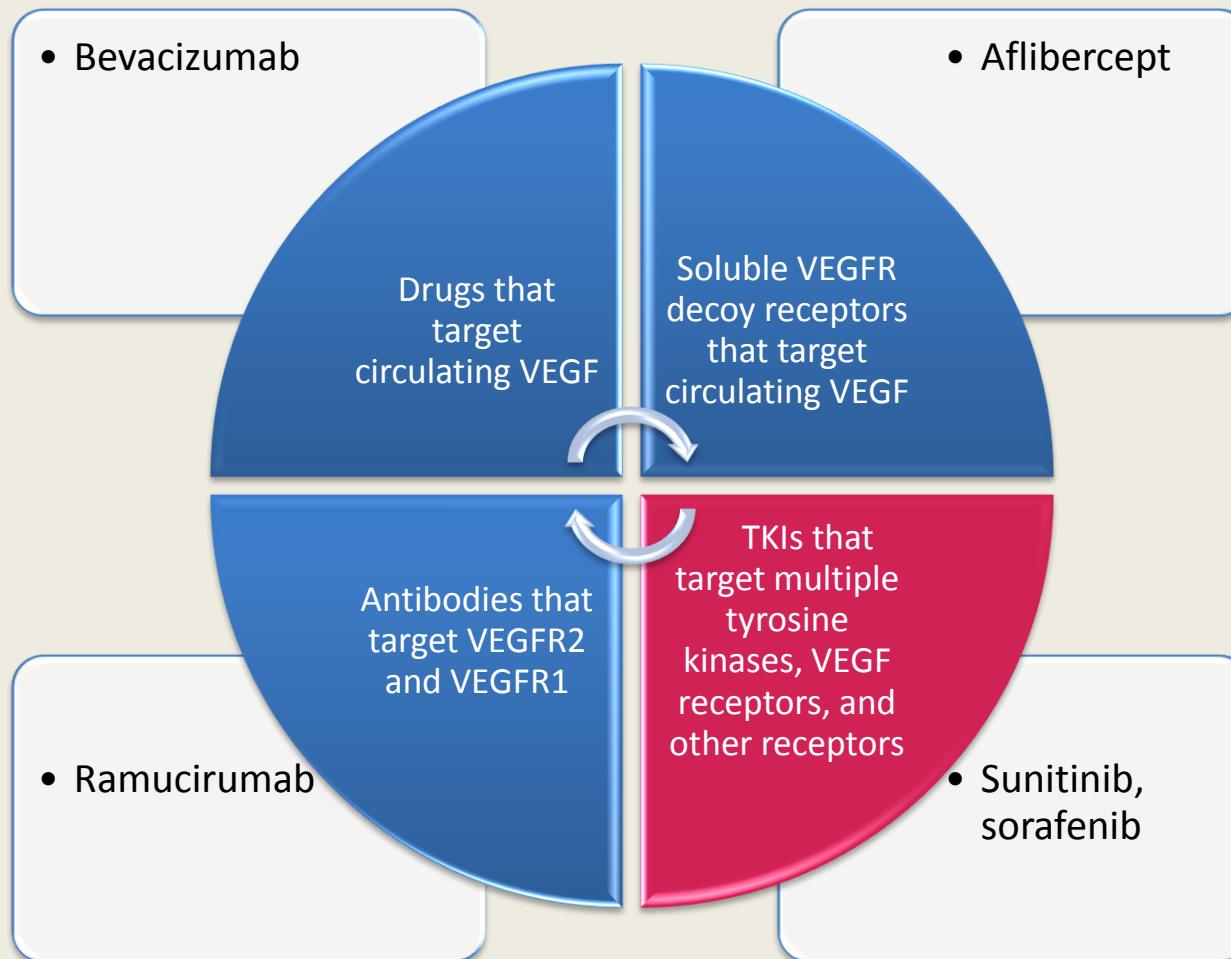
1. Yeo T et al. J Clin Oncol 2007;25(18S):abst 3529. 2. Fong P et al. J Clin Oncol 2008;26(15S):abst 5510.

Pooled Efficacy Analysis of Bevacizumab + Chemotherapy vs Chemotherapy Alone

Outcome	Chemotherapy + Bevacizumab (n = 1439)	Chemotherapy Alone (n = 1008)
Median PFS, mos	9.2	6.7
▪ HR (95% CI)	0.64 (0.57-0.71)	
ORR, * %	49	32
Median OS, mos	26.7	26.4
▪ HR (95% CI)	0.97 (0.86-1.08)	
1-yr OS, %	82	77

*Assessed in patients with measurable disease at baseline: n = 1105 for chemotherapy plus bevacizumab; n = 788 for chemotherapy alone.

Types of Drugs for Inhibiting VEGF-Pathway



Tailored Management of MBC

Tumor Biology

- Hormone receptor status
- HER2 status

Tumor Aggressiveness

- Duration of RFI since primary diagnosis
- Location of mets (visceral vs non-visceral)
- Extent of metastatic spread (oligo vs polymets)

Prior Adjuvant Treatments

- Endocrine, biologic or chemotherapy
- Combined treatments

Feasibility of multidisciplinary treatments

- Oligometastatic disease
- Surgery, radiofrequency ablation, stereotactic radiotherapy

Patient

- Preferences
- Symptoms
- Comorbidities