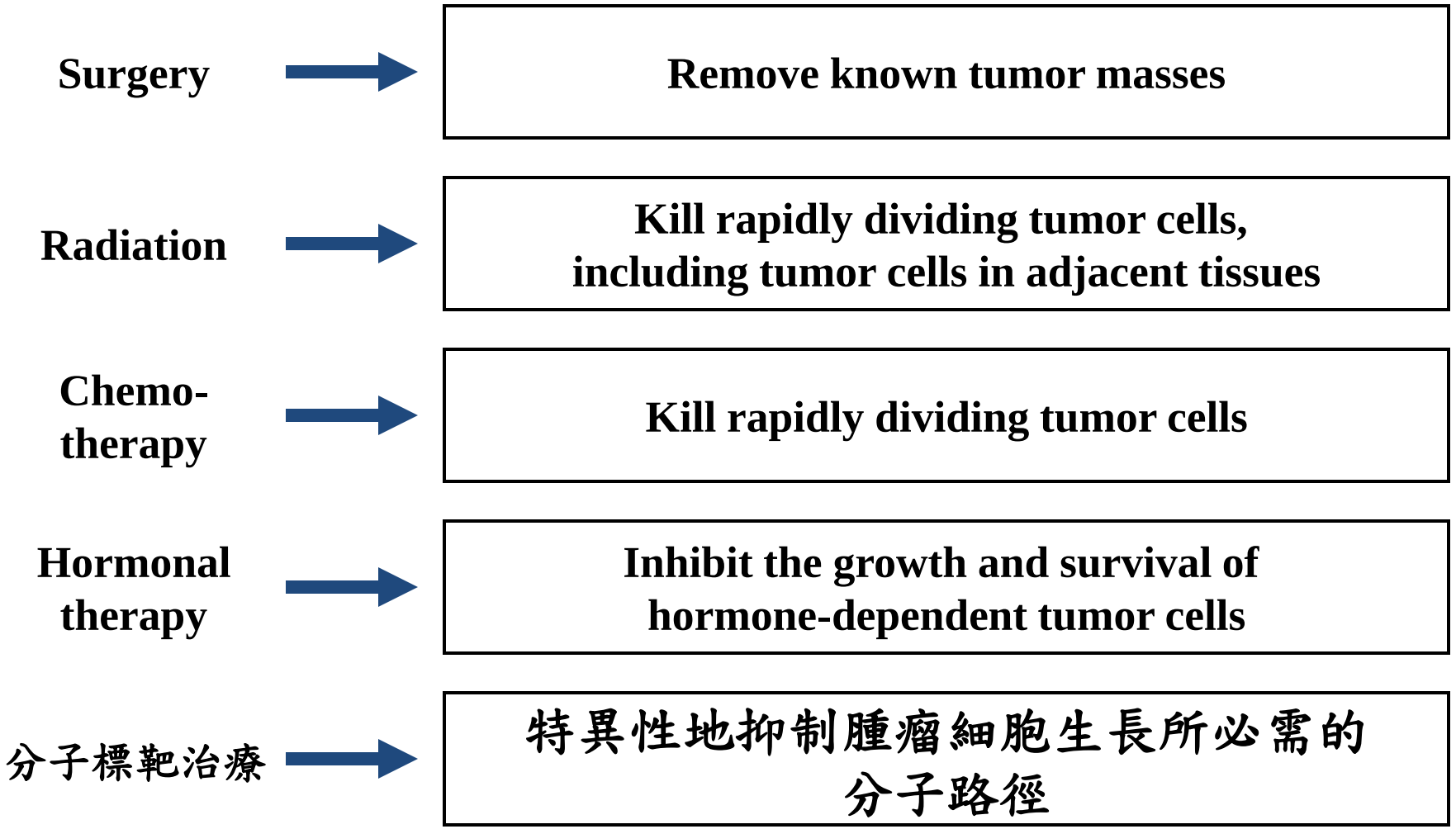
現代醫學控制癌症的方法



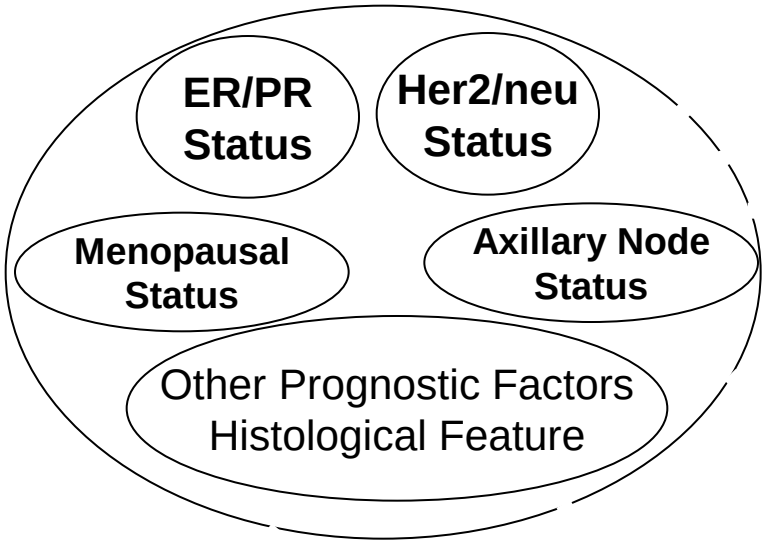
化學治療 Chemotherapy

- 全身性的治療
- 相對藥物作用特異性不高
- 可使用劑量被可能毒性反應限制
- 療效也為潛在的或後天得來的抗藥性所限

化學治療可以

- 延長轉移患者的存活期
  - @ Primary chemotherapy
- 減輕癌症引起的不適
  - @ Palliative chemotherapy
- 增加手術或放射治療的療效
  - @ Neoadjuvant & adjuvant
  - @ Concommitent radiosensitizer
- 改善臨床的治療方式

多變相的乳癌



Mastectomy /Lumpectomy **Sentinal Node Biopsy**
+/-Axillary Dissection

Radiation Therapy

Adjuvant Therapy

Chemotherapy…regimen ?
Hormonal therapy
Tamoxifen ? AI ?

Neoadjuvant Therapy

Chemotherapy…regimen ?
Hormonal therapy ?

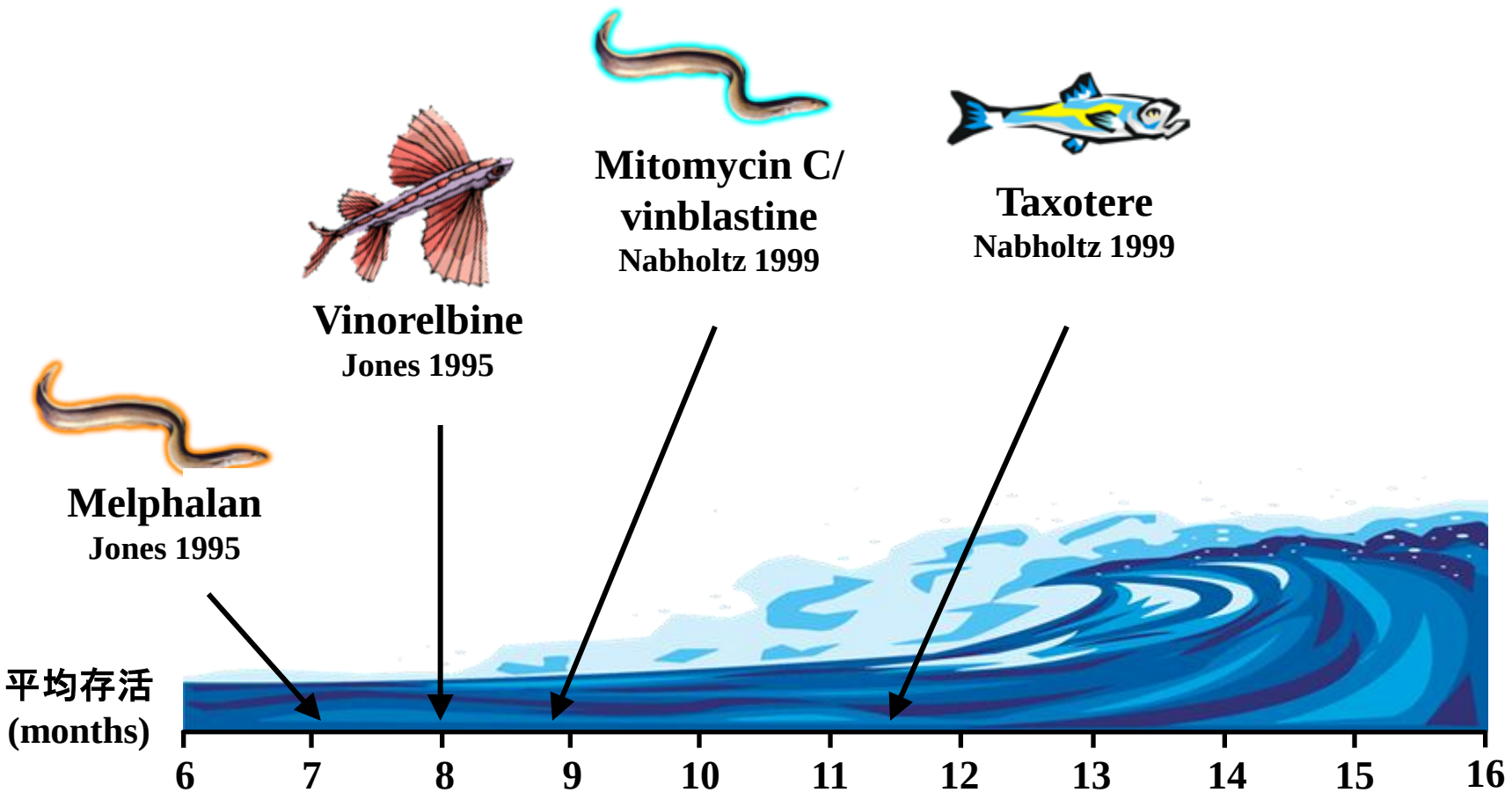
Biological Therapy

HER2 IHC -FISH
Herceptin
Single/Chemo Combination
Hormonal Therapy

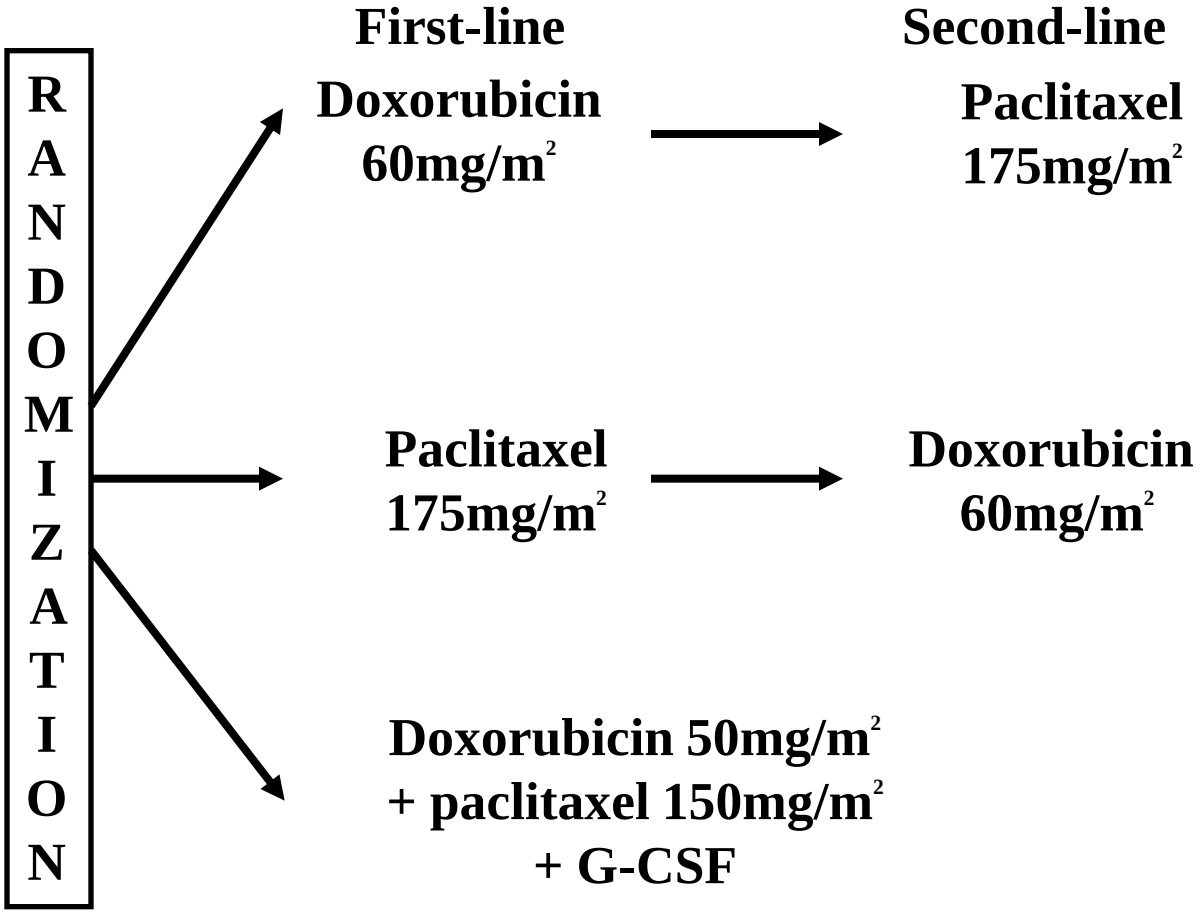
Palliative Therapy

Chemotherapy…regimen ? Combo/sequence ?
Hormonal therapy
Tamoxifen ? AI ? Sequence ?

晚期乳癌化學治療的演進



E1193: Combination therapy more effective than sequential therapy?

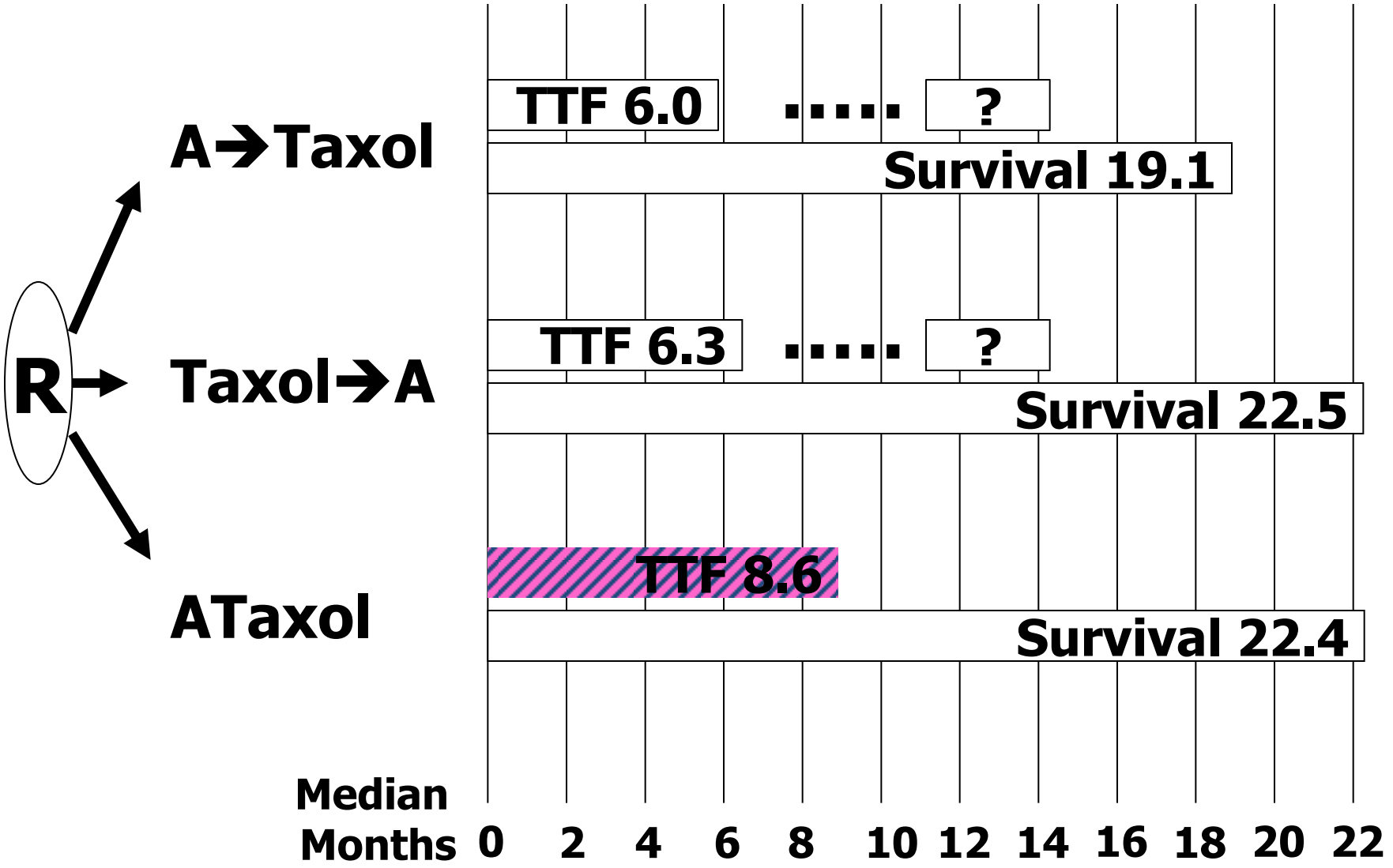


Sledge G et al. J Clin Oncol 2003;21:588–92

晚期乳癌的化學治療 E1193

	RR%	CR%	TTF(mo.)	存活期(mo.)
A	36	6	6	19.1
T	34	3	6.3	22.5
AT	47	9	8.2	22.4
P=	A 0.017 T 0.006		A 0.002 T 0.057	

Intergroup/ECOG 1193
Delay of disease progression but no impact on survival



Combinations . . . For ***Whom***?

- **Younger Patients?**
- **Visceral Dominant Disease?**
- **"Aggressive" Molecular Phenotype?**
- **Tempo of Disease Progression?**
  - **Short *relapse-free interval* after adjuvant therapy?**
  - **Lack of durable (or any) response to prior mono-chemotherapy for MBC?**
  - **Rapid "Volumetric" tempo of progression?**

Combination Chemotherapy

Chemo-naïve:

- Anthracyclines containing regimens
- ➢ FAC, FEC
- Cardiac risk → CMF

Prior anthracyclines(s/p Adjuvant)

- XT (capecitabine/doxetaxel)
- GT (gemcitabine/paclitaxel)

>>2nd line Chemotherapy

Prior anthracyclines(2nd line)

- XT
- GT

After Anthracyclines/taxanes

- Single agent preferred
- Capecitabine
- Navelbine

Chemotherapy for MBC
Fragile patient, poor performance

- Usually single agent
- Consider liver and renal function
- Closed monitoring

- May worth trying due to good chance of response

Her-2(+) MBC

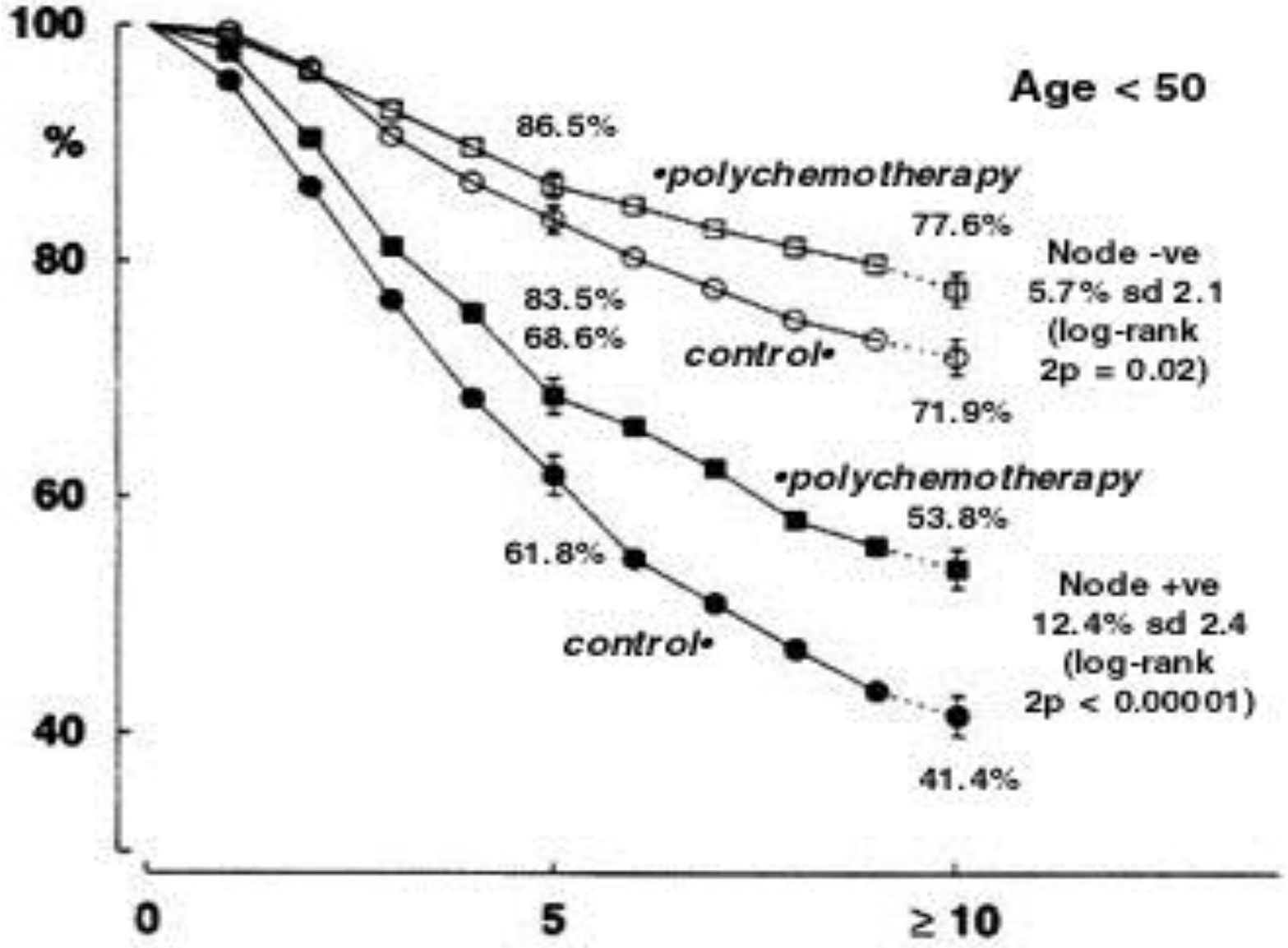
- Taxol (weekly) +/- Carboplatin
- Taxotere
- Navelbine

- In combination with Herceptin

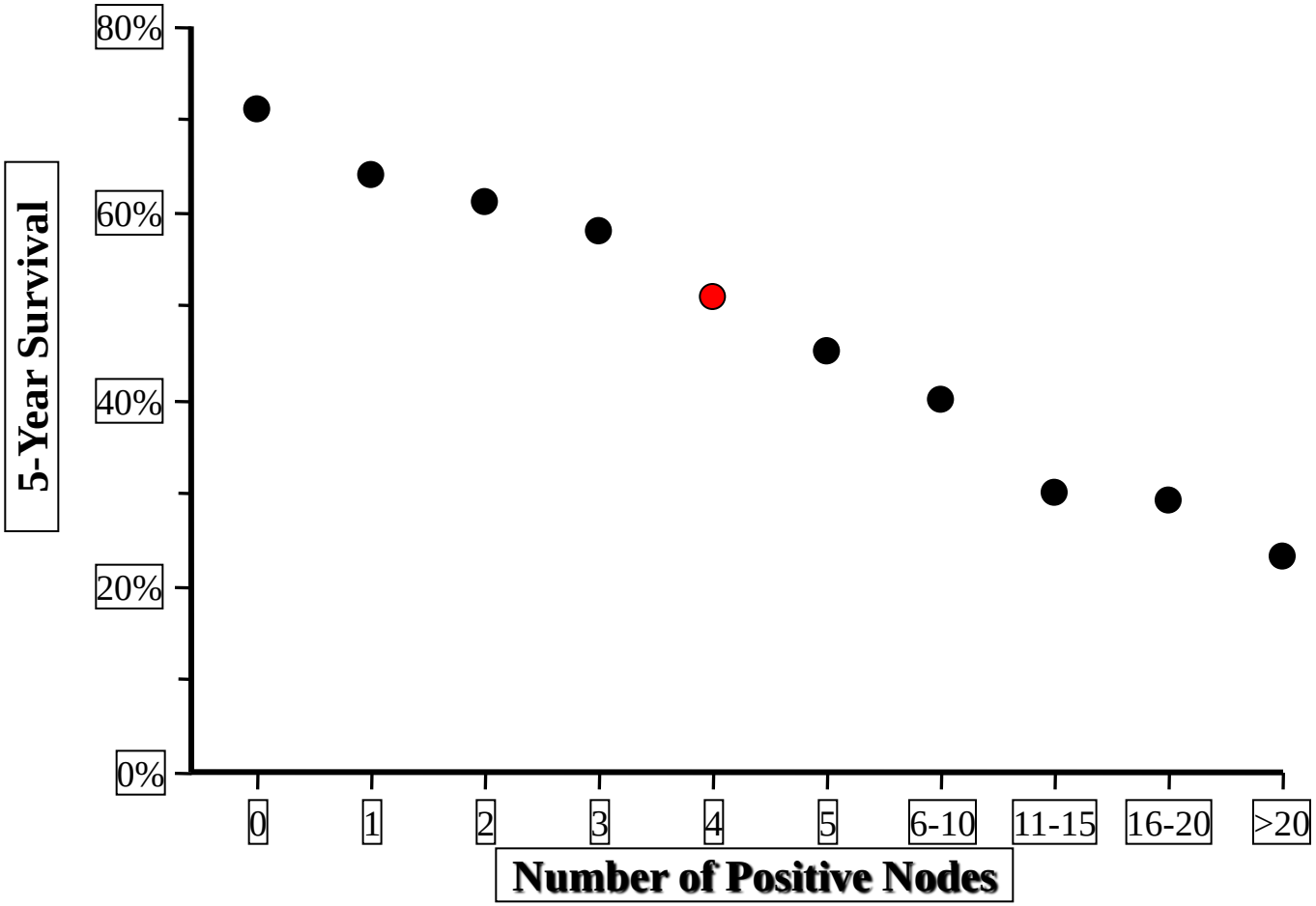
乳癌輔助性化學治療可以

減少術後復發

增加治癒的機會


100
%
80
60
40
0
5
≥ 10
Age < 50
86.5%
•polychemotherapy
77.6%
Node -ve
5.7% sd 2.1
(log-rank
2p = 0.02)
83.5%
68.6%
control•
71.9%
•polychemotherapy
53.8%
61.8%
Node +ve
12.4% sd 2.4
(log-rank
2p < 0.00001)
control•
41.4%

乳癌：五年存活期
相對於陽性淋巴結的數目



Harris J, et al. *Cancer: Principles & Practice of Oncology.* 5th ed. 1997;1557-1616.

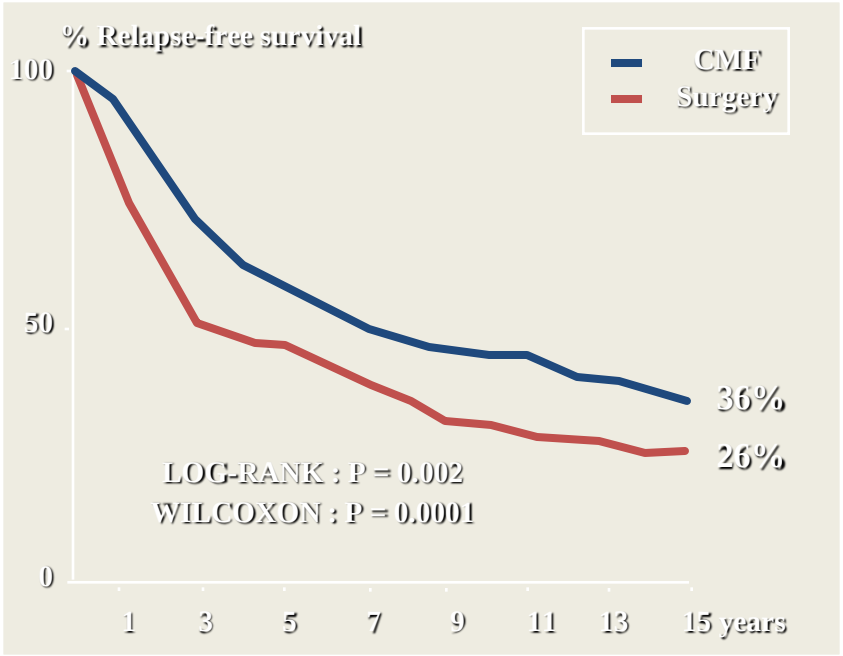
10年無病存活比率與淋巴結的數目
4 MDACC FAC Studies (N=982)

Groups	1	2	3	4
	第二期			
1-3	64%	73%	86%	65%
4-10	55%	49%	56%	51%
10+	36%	28%	22%	36%
第三期	32%	31%	37%	41%

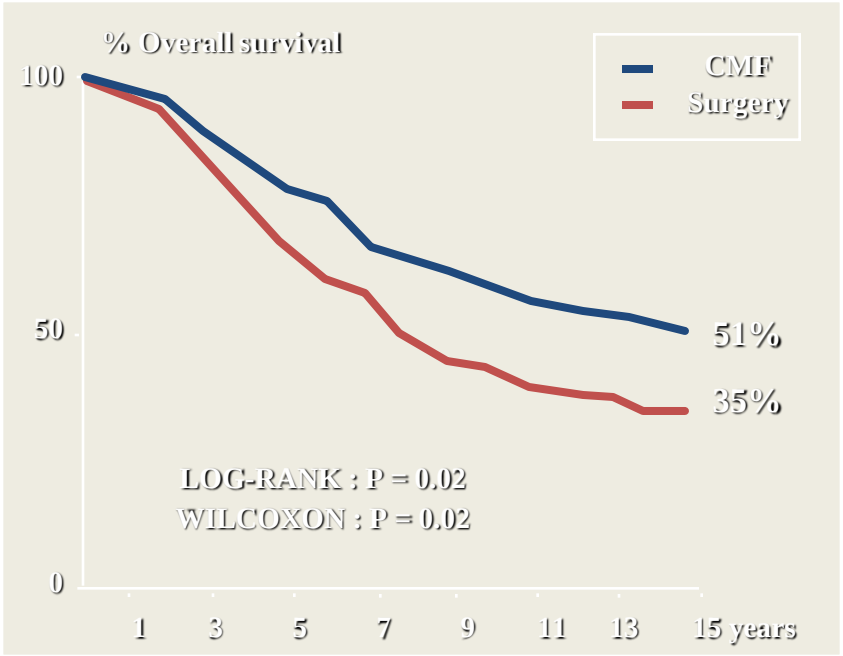
Buzdar A, et al, Adjuvant Therapy of Cancer VIII, 1997

Breast Cancer: Adjuvant CMF (12 months) or Surgery Alone

All Patients



Premenopausal



Adapted from Bonadonna G. *Cancer Res.* 1992.

BREAST CANCER

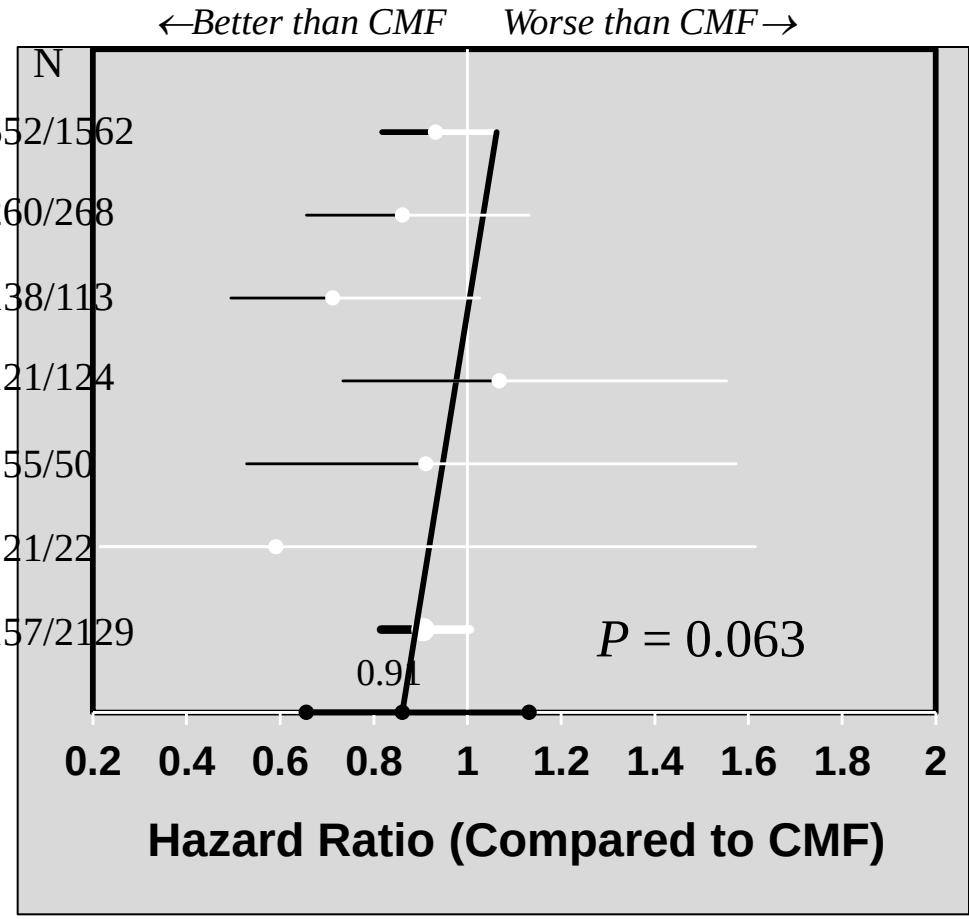
Commonly assessed prognostic factors

- Number of positive axillary nodes
- Tumor size
- Lymphatic and vascular invasion
- Histologic tumor type
- Histologic grade
- Nuclear grade
- Estrogen/progesterone receptors
- HER2/*neu* overexpression

Slamon DJ. *Chemotherapy Foundation*. 1999;46.
Harris J, et al. *Cancer: Principles & Practice of Oncology.* 1997;1557-1616.

Disease-Free Survival: 1998 EBCTCG Meta-Analysis of Doxorubicin Polychemotherapy vs CMF

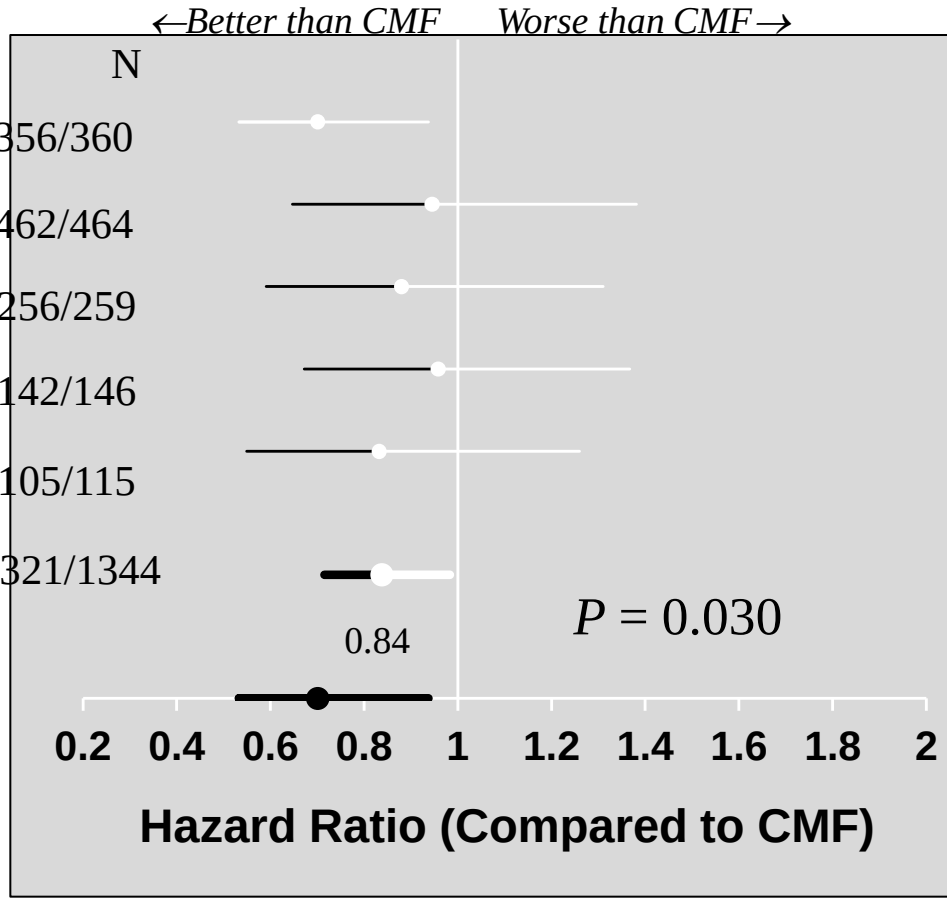
Study	Therapy	N
NASBP B-15	4AC±3CMF vs 6CMF (+R)	1552/1562
SECSG2	6FAC vs 6CMF	260/268
ONCOFRANCE	12FACV vs 12CMF	138/113
Austrian BCSG 3	6CMFVA vs 6CMF	121/124
NSABC Israel	2CMF+4AVbCMF vs 6CMF	55/50
SE Swedenl	8AC vs 7CMF (+R)	21/22
Meta Analysis (6 studies)		2157/2129



Analysis derived from EBCTCG *Lancet*. 1998; Data on file, Pharmacia

Disease-Free Survival: 1998 EBCTCG Meta-Analysis of Epirubicin Polychemotherapy vs CMF

Study	Therapy	N
NCI-C MA-5	6CEF vs 6CMF	356/360
Brussels, Belgium	8EC vs 6CMF	462/464
ICCG CharingCross	8/6FEC vs 6CMF	256/259
GABG Germany	6FEC vs 6CMF (±Tam)	142/146
GUN-3 Naples, Italy)	6CMFEV vs 6CMF	105/115
Meta Analysis (5 studies)		1321/1344



Analysis derived from EBCTCG *Lancet*. 1998; Data on file, Pharmacia

NCIC CTG MA.5 Trial: CEF-120 vs CMF in Node-Positive Breast Cancer

N = 710

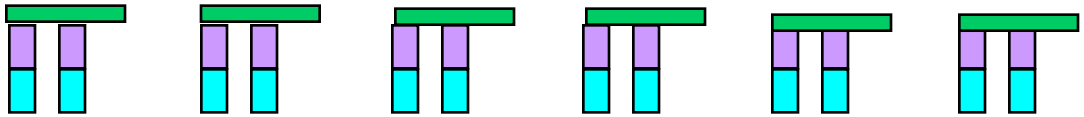
Patient Population

- Pre- or perimenopausal
- Node-positive

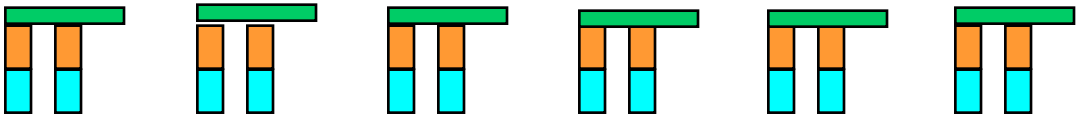
Stratification

- Total vs partial mastectomy
- HR status
- No. + nodes

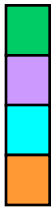
RANDOMIZATION



C 75 mg/m^2 po q d days 1–14
E 60 mg/m^2 IV days 1 and 8 q 4 wk x 6
F 500 mg/m^2 IV days 1 and 8
+ Prophylactic antibiotics*



C 100 mg/m^2 po q d days 1–14
M 40 mg/m^2 IV days 1 and 8 q 4 wk x 6
F 600 mg/m^2 IV days 1 and 8



= Cyclophosphamide
= Epirubicin
= Fluorouracil
= Methotrexate

* No prophylactic G-CSF administered.

Levine et al. *J Clin Oncol*. 1998;16:2651-2658.

Adjuvant E→CMF vs CMF in Early Breast Cancer: NEAT/BR9601 Trial

N = 2,391

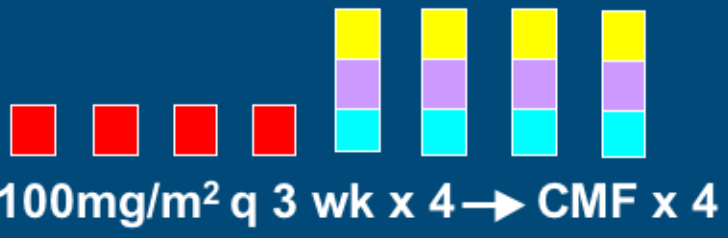
Patient Population

- Early stage breast cancer
- Definitive surgery completed

Stratification

- Study site
- Age (≤ 50, > 50 years)
- Nodal status
  - NEAT (negative, 1-3, 4+)
  - BR9601 (negative, 1-3, 4-9, 10+)

RANDOMIZATION



CMF

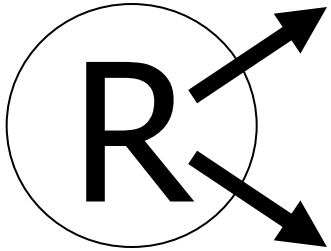
- NEAT: Classical d 1, d 8 CMF q 4 wk x 6
- BR9601: CMF IV q 3 wk x 8

= Epirubicin
= Cyclophosphamide
= Methotrexate
=5-Fluoro-uracil

Poole CJ. *Proc Am Soc Clin Oncol. 2003*;22:48. Abstract 13.

Design

F	5-FU	500 mg/m^2
A	Doxorubicin	50 mg/m^2
C	Cyclophosphamide	500 mg/m^2



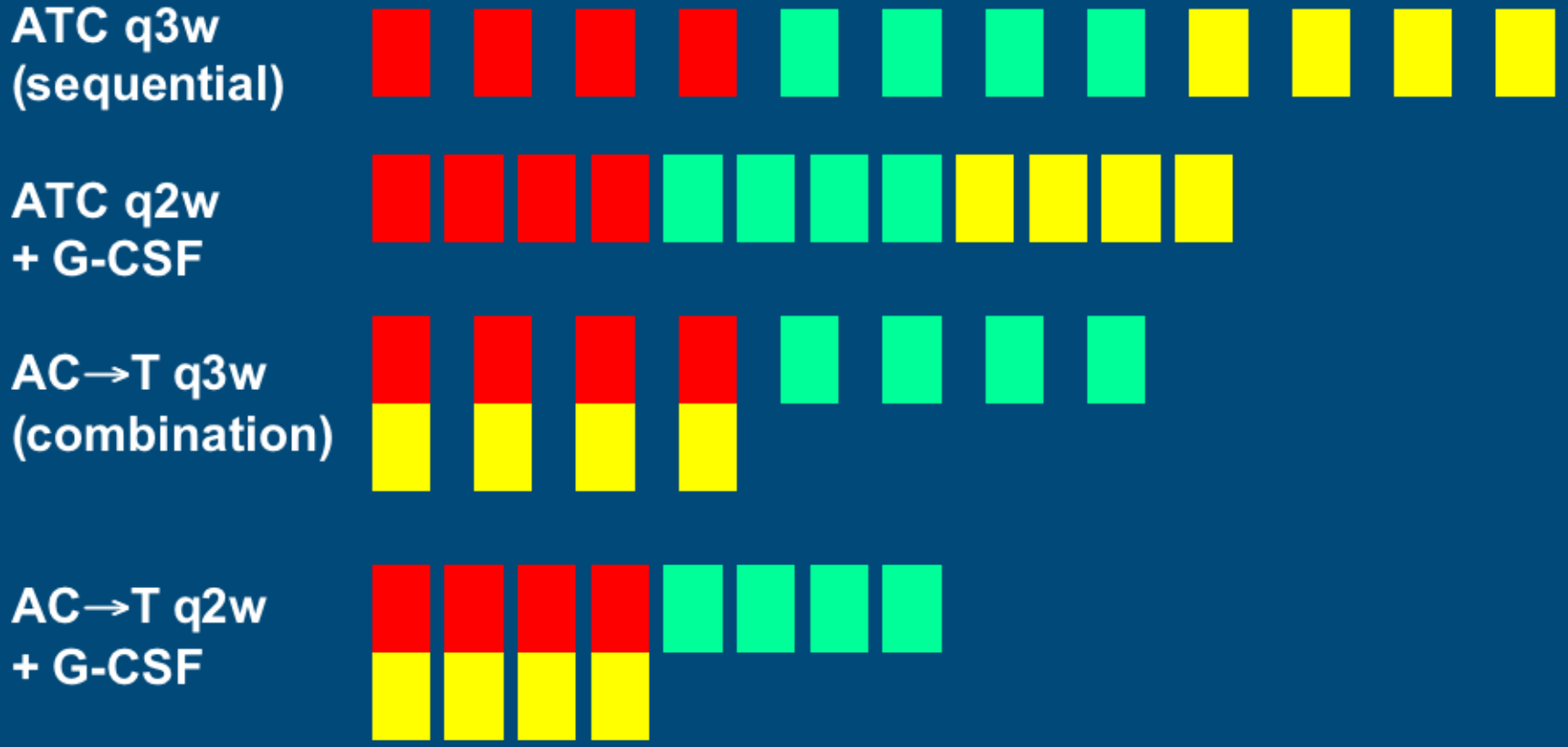
Every 3 weeks x 6 cycles

Stratification:
- Nodes:
  - 1-3
  - 4+
- Center

T	Docetaxel	75 mg/m^2
A	Doxorubicin	50 mg/m^2
C	Cyclophosphamide	500 mg/m^2

Dexamethasone premedication, 8 mg bid, 3 days
Prophylactic ciprofloxacin 500 mg bid, day 5-14

CALGB C9741



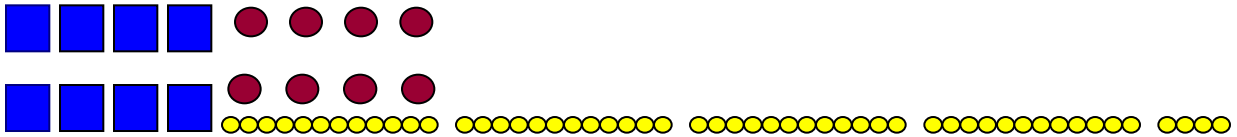
Citron et al. *J Clin Oncol*. 2003;21:1431-1439.

NSABP B-31

Control: AC→T

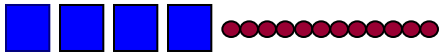
Arm 1

Arm 2



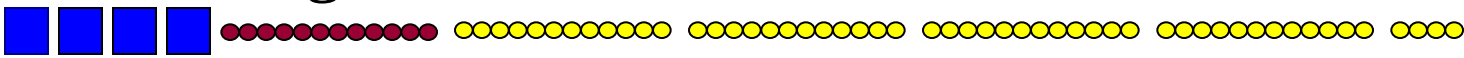
NCCTG N9831

Arm A

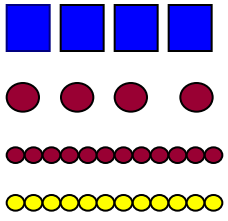


Investigational: AC→T+H

Arm B



Arm C



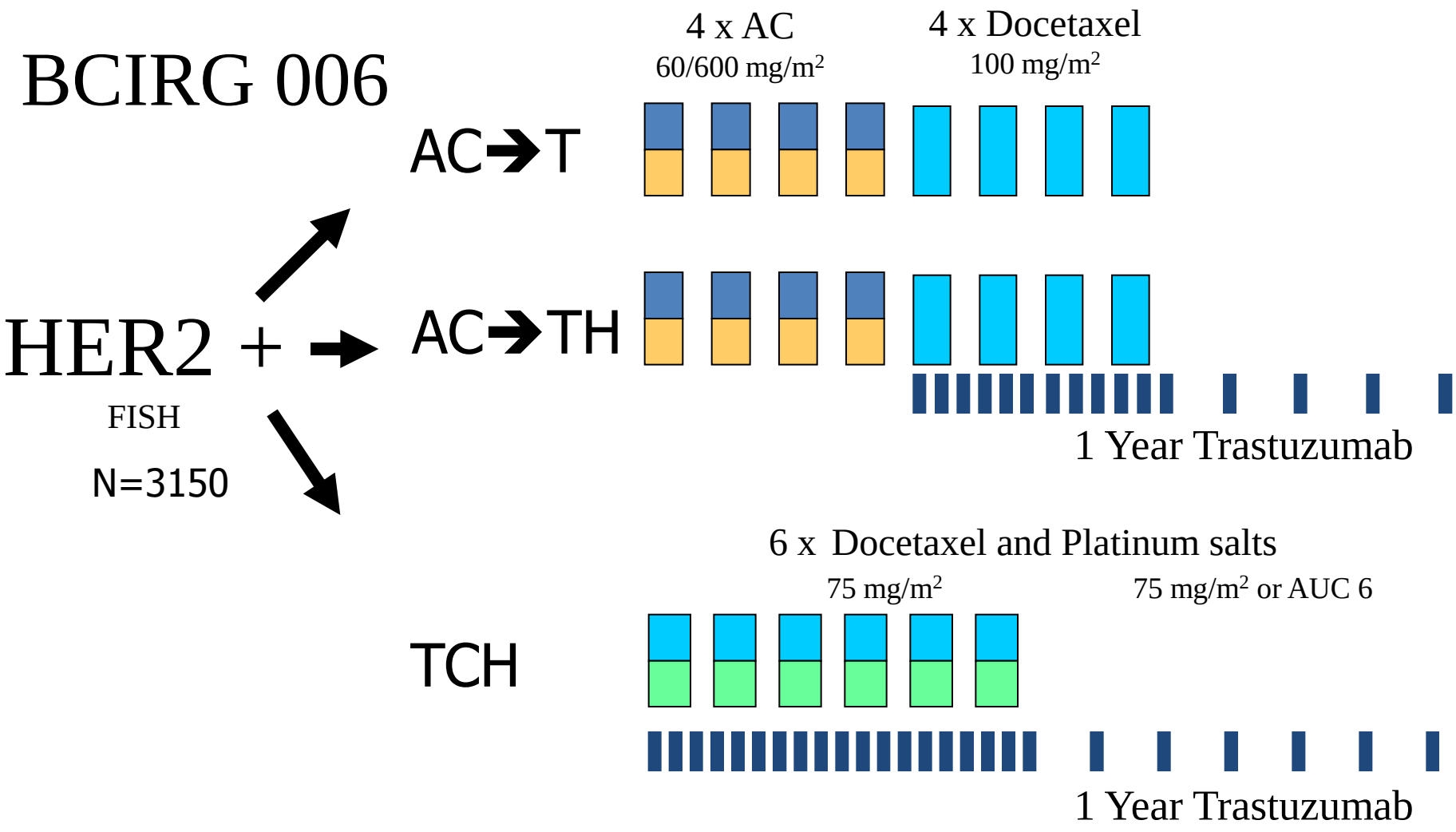
= doxorubicin/cyclophosphamide (AC) 60/600 mg/m2 q 3 wk x 4

= paclitaxel (T) 175 mg/m2 q 3 wk x 4

= paclitaxel (T) 80 mg/m2/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

Can Doxorubicin Be Eliminated?



傳統化學治療藥物

- 非特異性及細胞毒殺

- 對正常組織也有作用
- 療效與腫瘤特性有關
- “腫瘤縮小” 視為療效
- “有療效” 不見得存活上有助益

標靶治療

- 選擇性的同時也是 Cytostatic

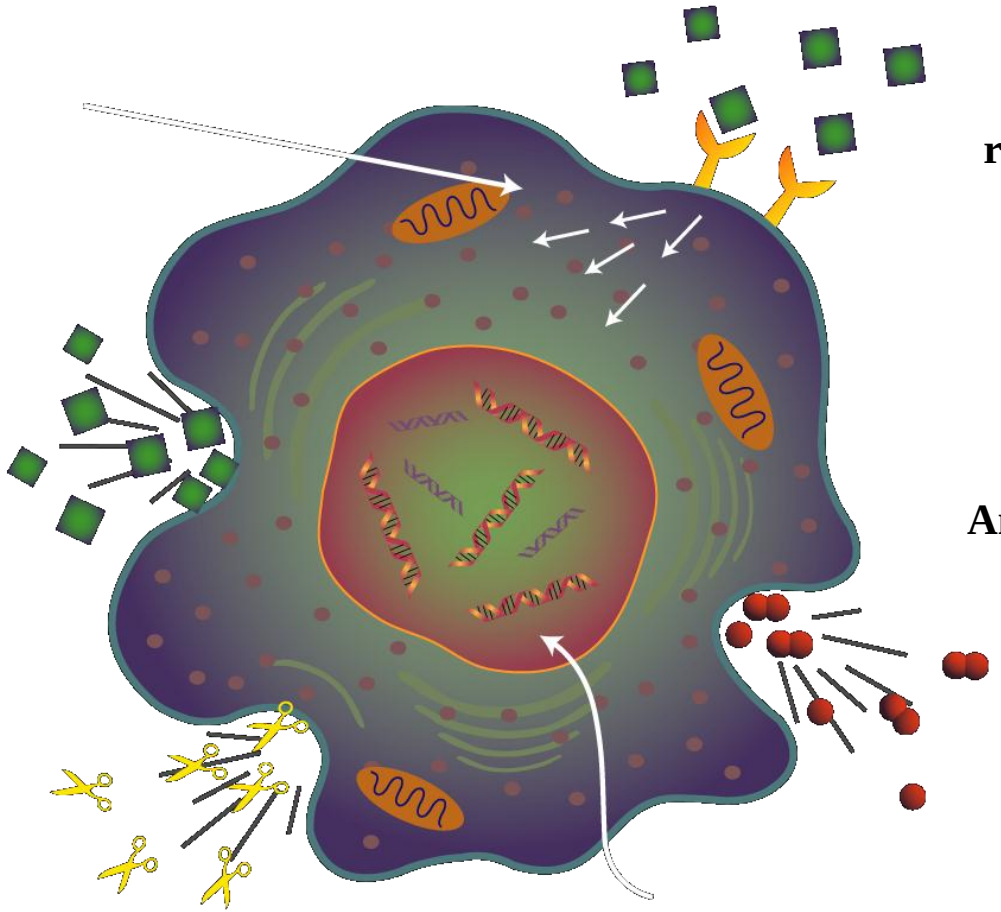
- ✓ 毒性低
- ✓ 有標靶才有活性
- ✓ “ 療效 ” 不一定須見到腫瘤縮小

化學治療的演進

- 目前在使用的藥物
  - **Biosynthetic Enzymes**
  - **DNA**
  - **Topoisomerase**
  - **Tubulin**
  - **Hormonal Manipulation**

- **發展中的藥物**
  - **Signal Transduction (Her2, EGFR)**
  - **Angiogenesis (MMPI'S, VEGF)**
  - **Cell Cycle (cdk's)**
  - **Apoptosis (bcl2)**
  - **Immunotherapy /Vaccines**
  - **Gene Therapy/Antisense**
  - **Monoclonal Antibodies**

癌細胞相關重要分子路徑



Aberant signal transduction

Growth factor and receptor deregulation

Autocrine growth factor secretion

Angiogenic factors secretion

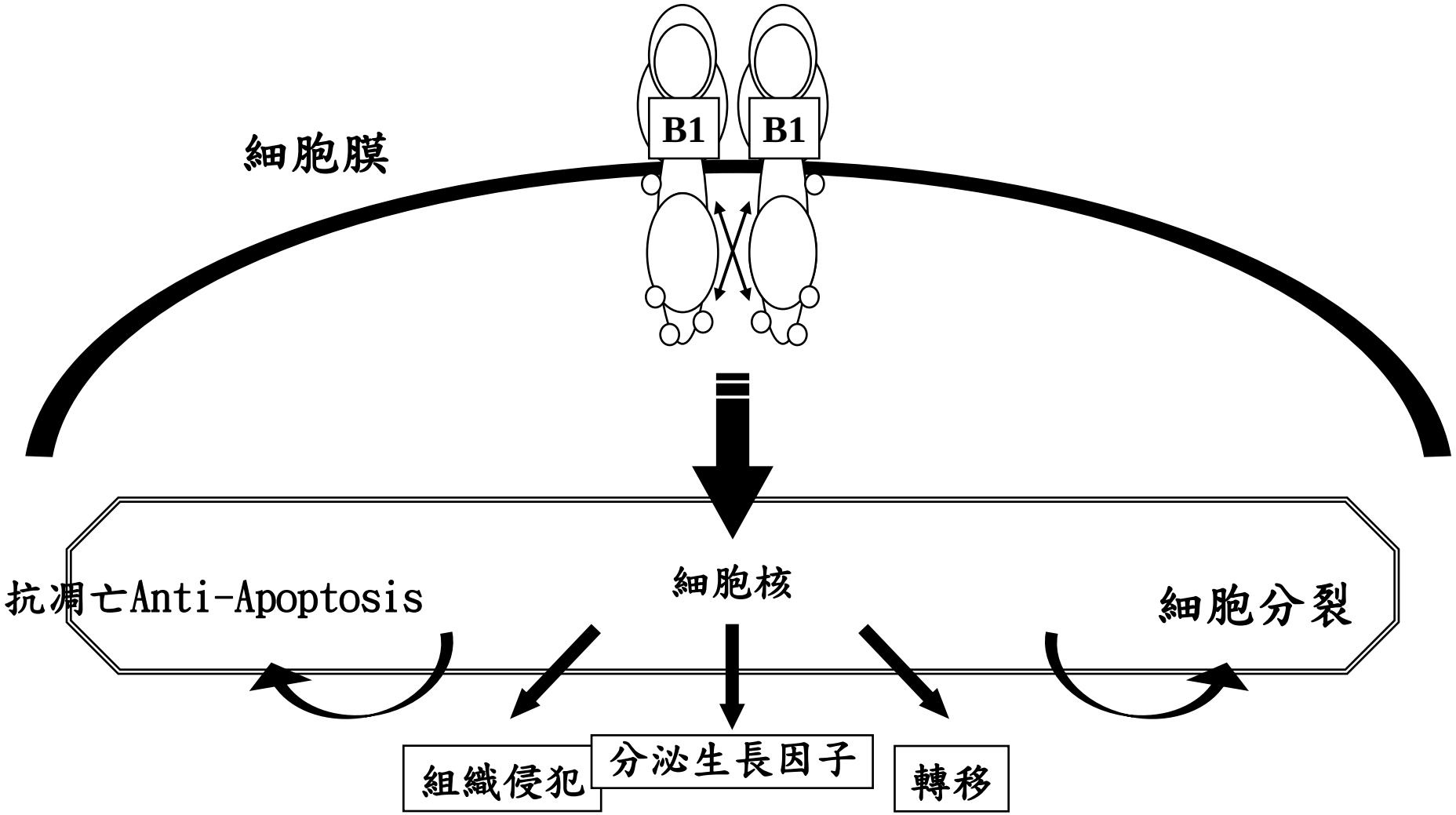
Matrix Metaloproteinase secretion

Oncogene expression
Loss of tumor supressor genes

理想的標靶藥物

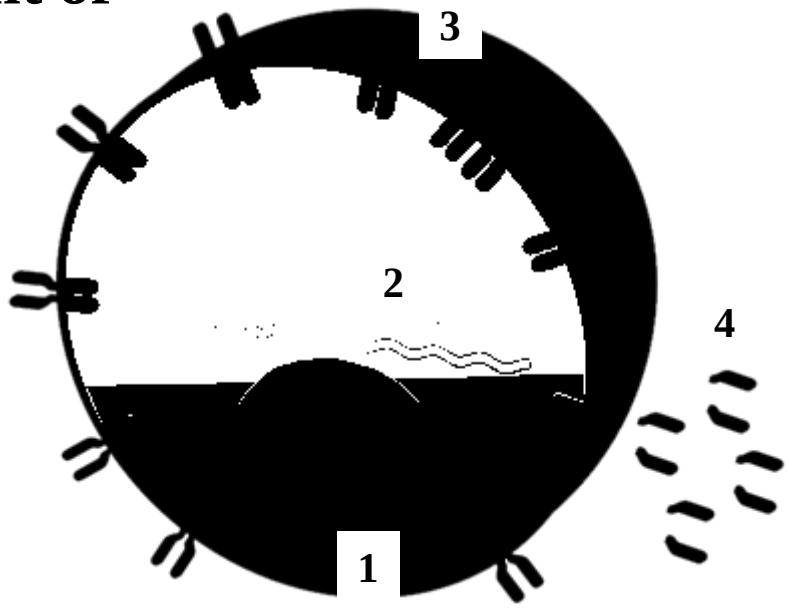
- 大部分有該癌症的患者均有存在
- 標靶與腫瘤發生或形成相關
- 對腫瘤細胞而言是必須的
- 正常細胞不須此標靶相關的功能

表皮生長因子藉接受器將訊號傳入細胞而引起反應



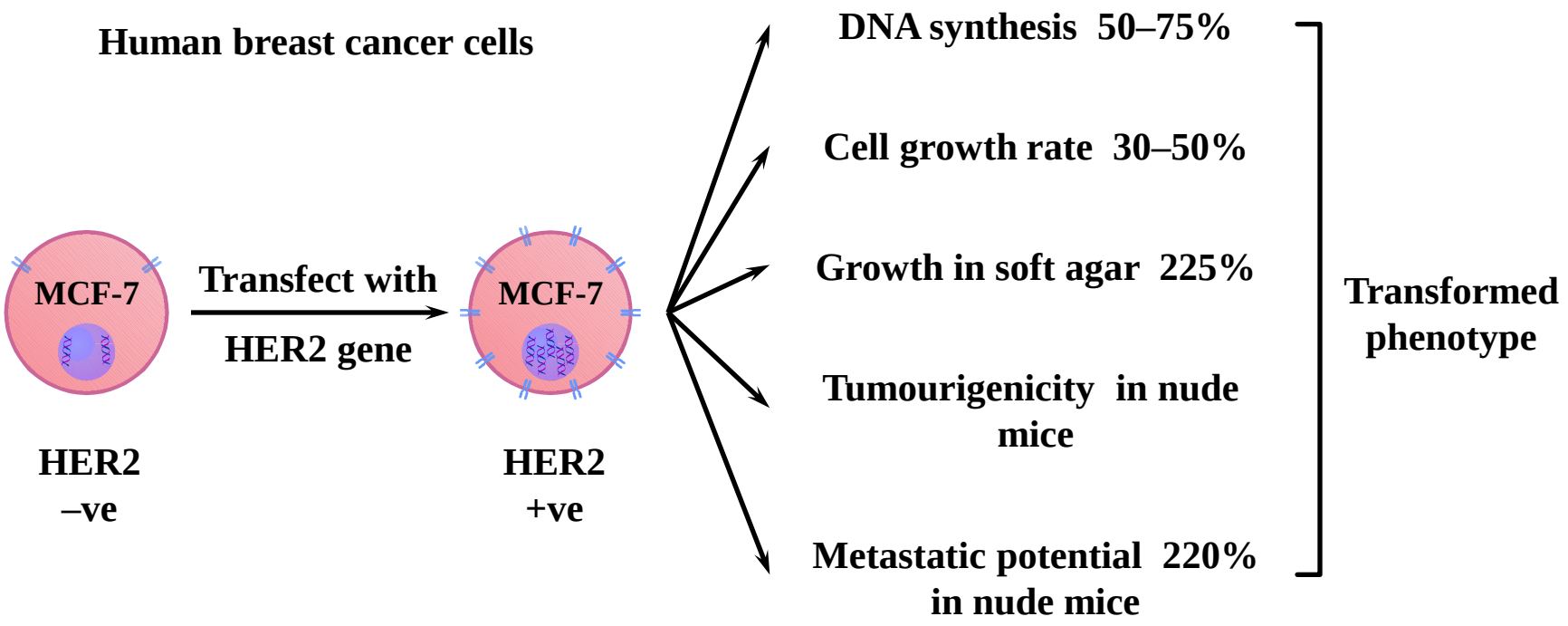
乳癌的Her-2表現增加會引起

HER2 overexpression is the result of HER2 gene amplification

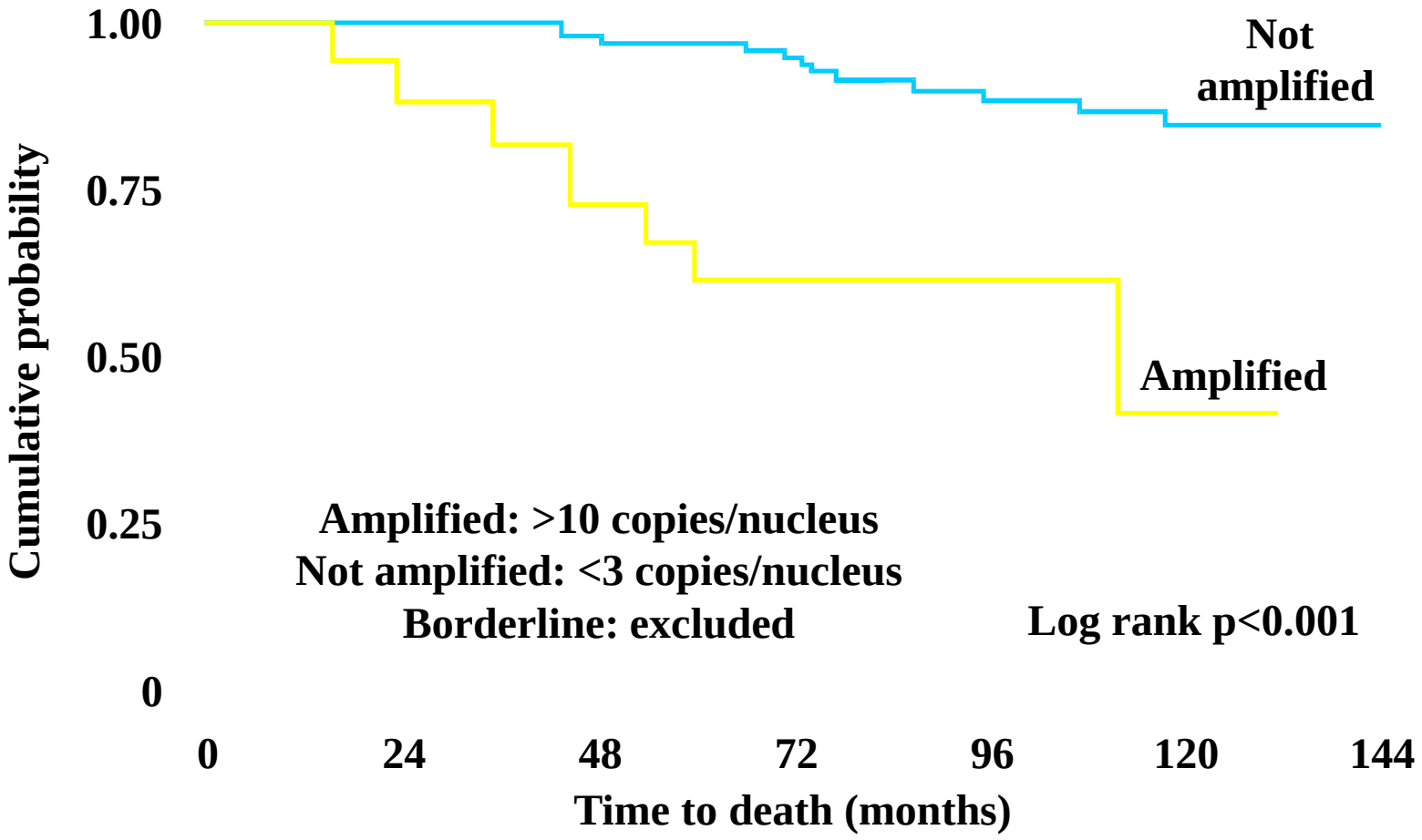


1. **Gene amplification**
   ➔ increased gene copies
2. **增加 mRNA transcription**
3. **增加 HER2 受體的數目**
   ➔ protein overexpression
4. **Released extracellular domain (ECD, sHER2)**

Effect of HER2 amplification on human breast cancer cells

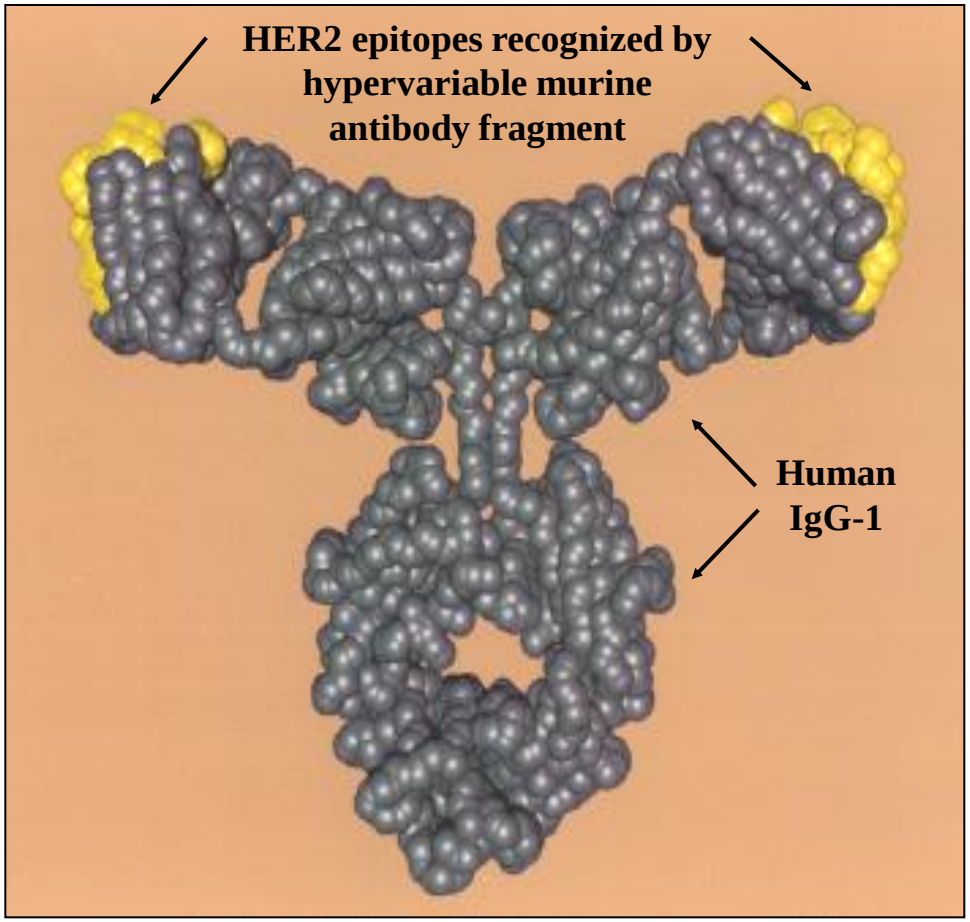


Her-2表現程度與早期乳癌手術後的預後有關



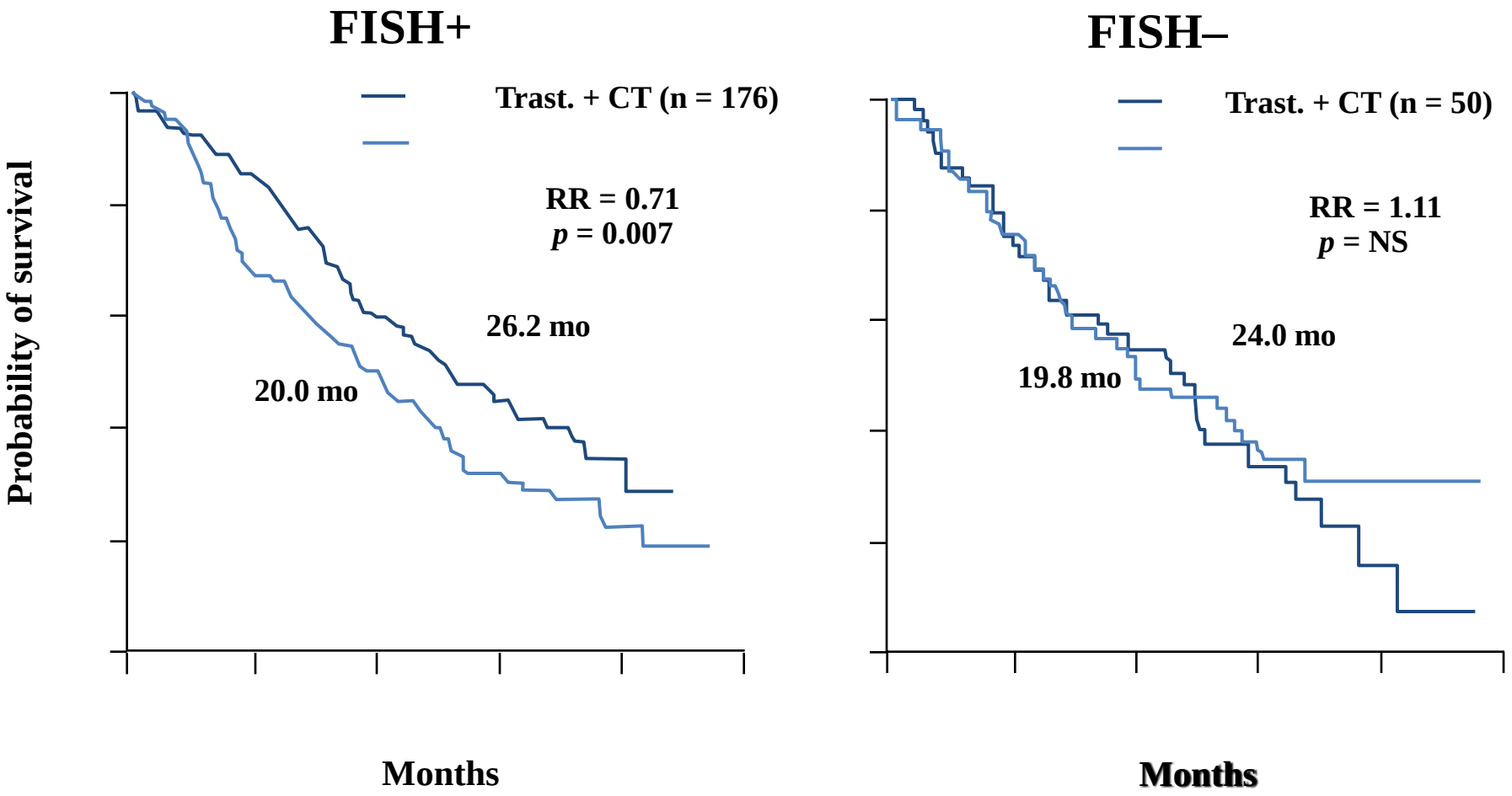
Ross JS, Fletcher JA. Stem Cells 1998; 16: 413–428

Trastuzumab: Humanized Anti-HER2 Antibody



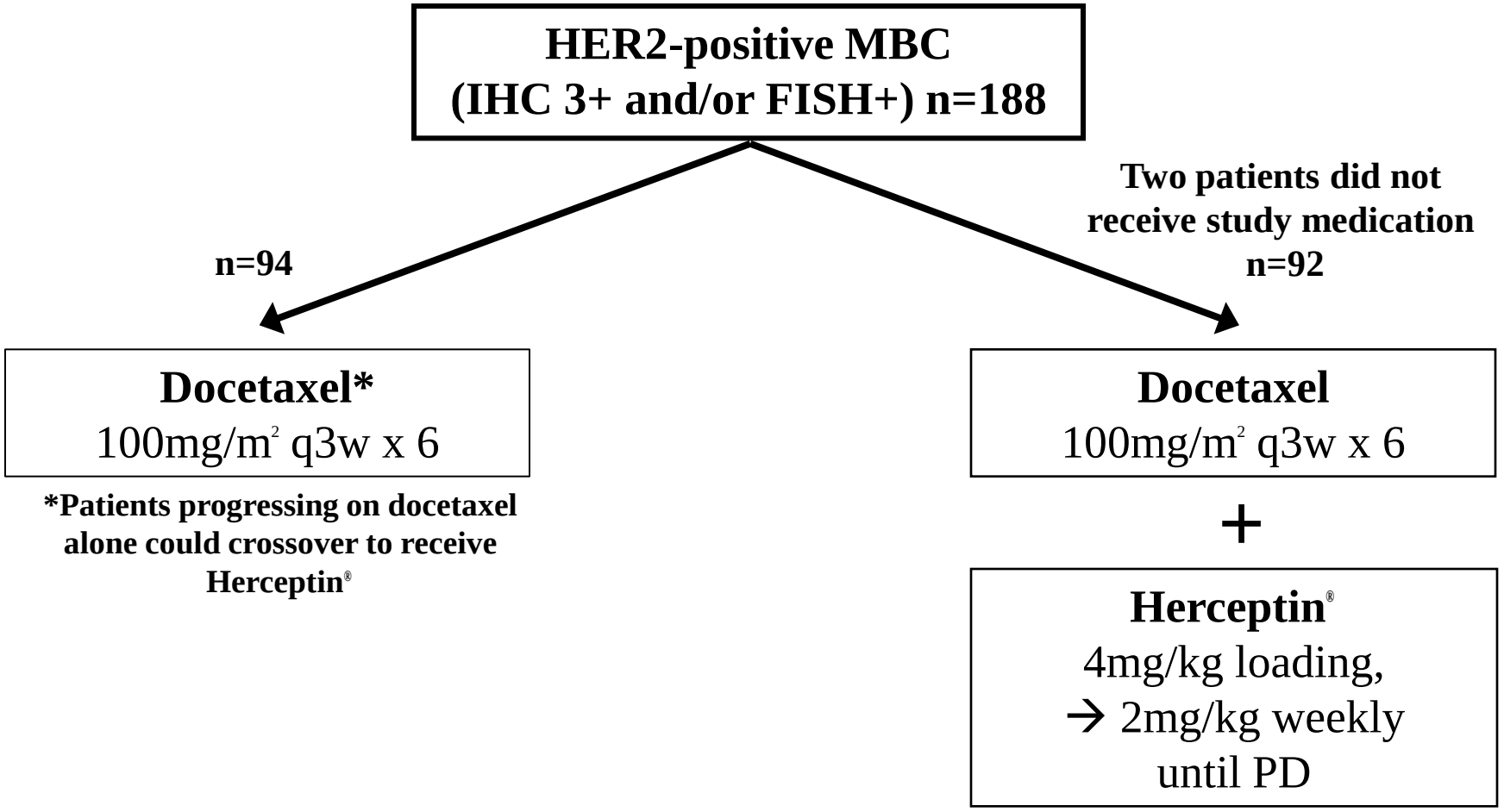
- Targets HER2 protein
- High affinity (K_d = 0.1 nM) and specificity
- 95% human, 5% murine
  - Decreases potential for immunogenicity
  - Increases potential for recruiting immune effector mechanisms

Herceptin 在晚期乳癌合併使用化學治療的療效

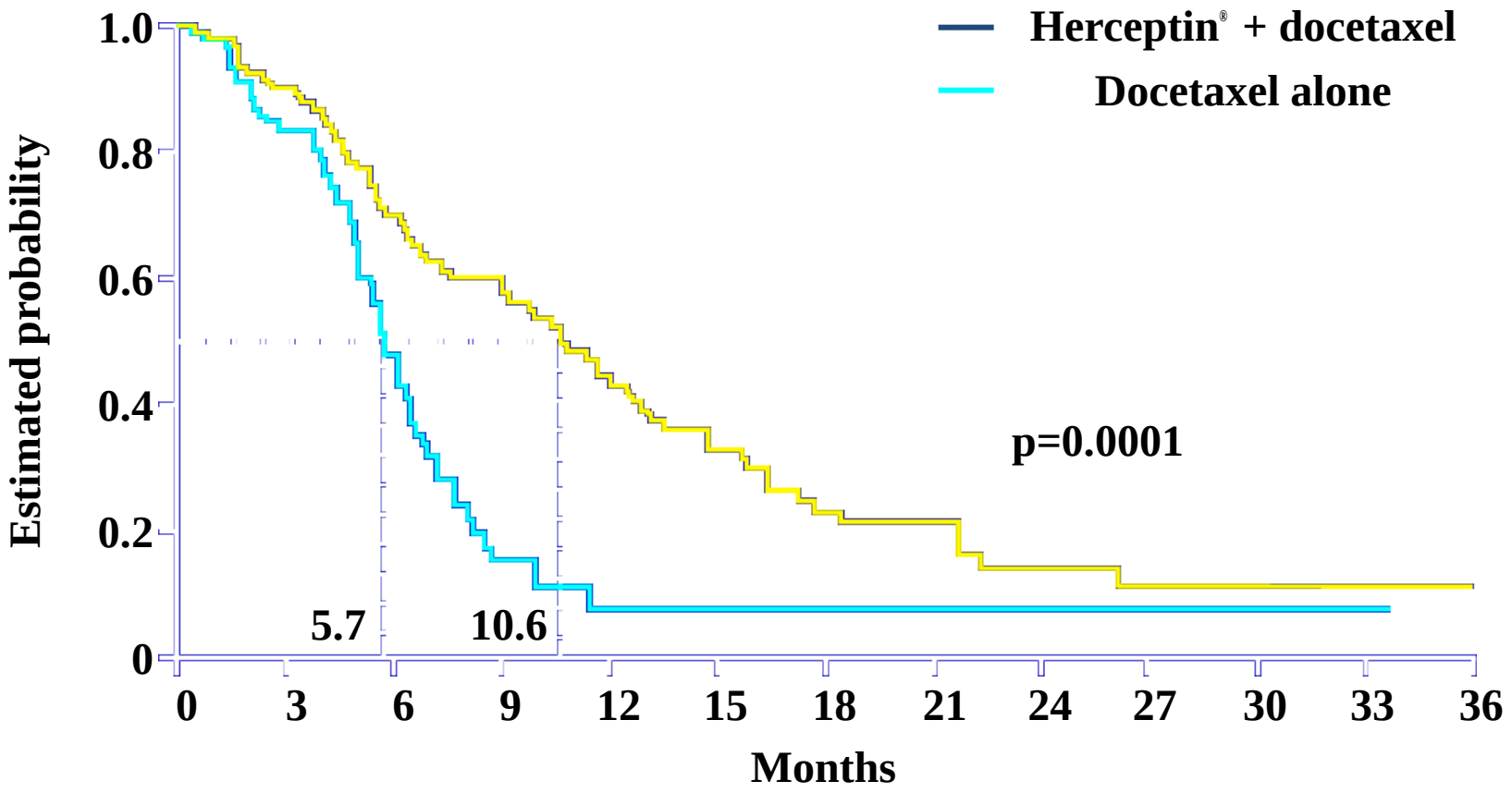


Update of Mass. *Proc Am Soc Clin Oncol*. 2001;20:22a. Abstract 85.

晚期乳癌的化學治療 M77001

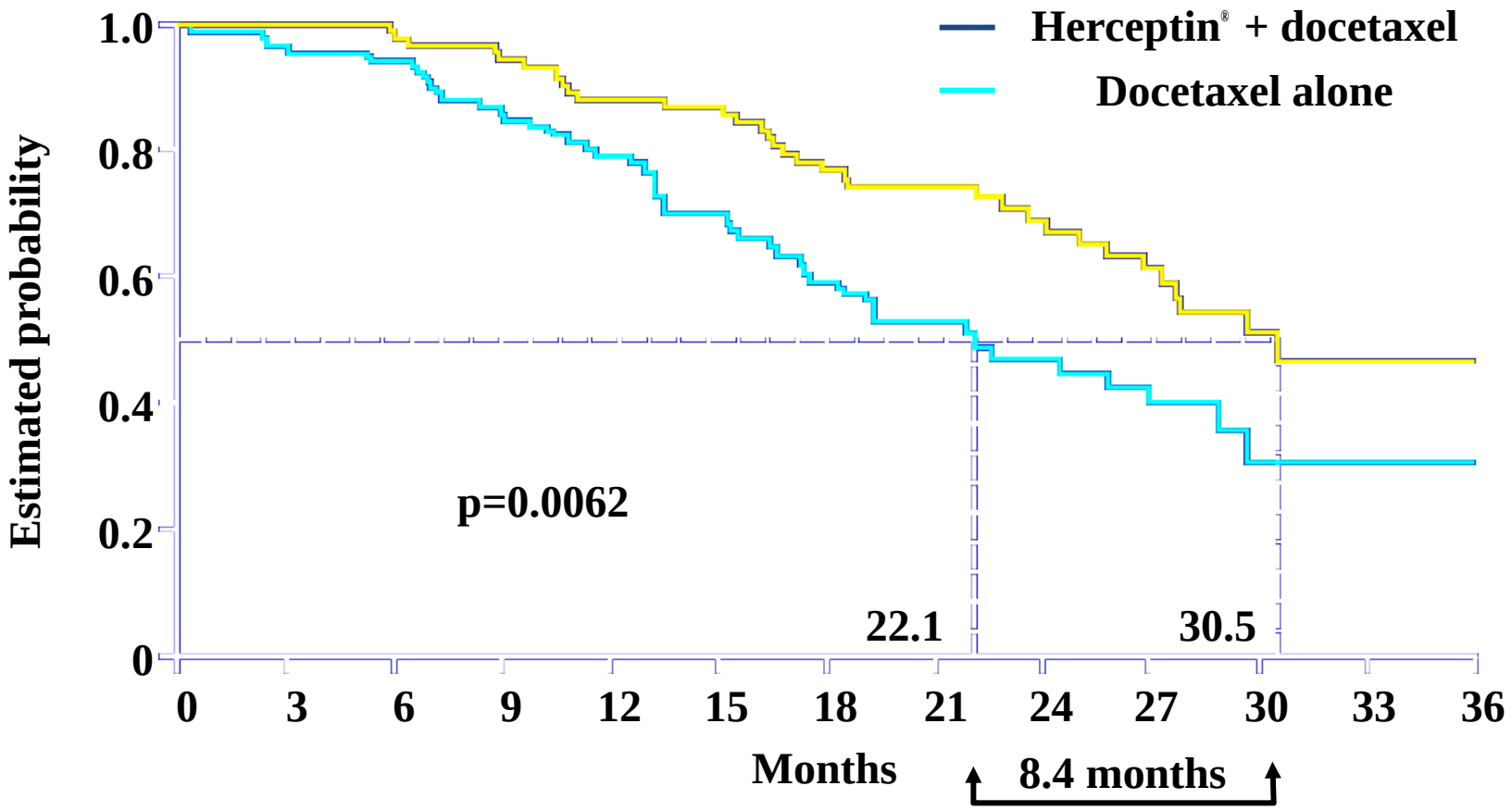


M77001: 疾病平均恶化期



Intent-to-treat population, 12-month cut-off

M77001: 存活期比較



Intent-to-treat population, 12-month cut-off
Documented crossover = 48%

M77001: 治療效果總結

Outcome	Herceptin® + docetaxel (n=92)	Docetaxel alone (n=94)	p-value
緩解比率	61.0	34.0	0.0002
DR (median, months)	11.4	5.1	0.0011
TTP (median, months)	10.6	5.7	0.0001
平均存活期	30.5	22.1	0.0062

***Kaplan-Meier estimate**

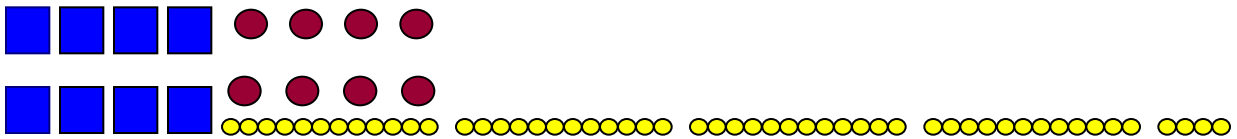
Intent-to-treat population, 12-month cut-off

NSABP B-31

Control: AC T

Arm 1

Arm 2



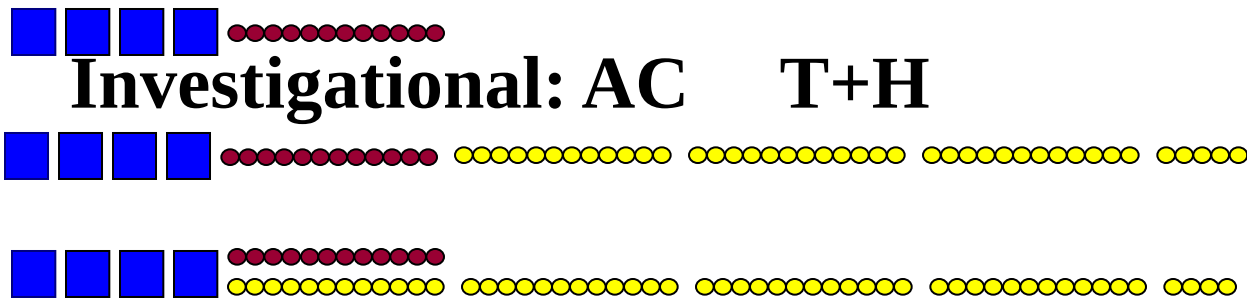
NCCTG N9831

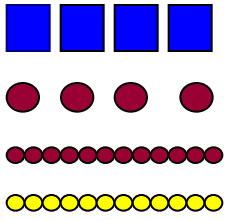
Arm A

Investigational: AC T+H

Arm B

Arm C





= doxorubicin/cyclophosphamide (AC) 60/600 mg/m2 q 3 wk x 4

= paclitaxel (T) 175 mg/m2 q 3 wk x 4

= paclitaxel (T) 80 mg/m2/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

THE HERA TRIAL

Women with HER2 POSITIVE invasive breast cancer IHC3+ or FISH+ centrally confirmed

↓

Surgery + (neo)adjuvant chemotherapy (CT) ± radiotherapy

↓

Stratification

Nodal status, adjuvant CT regimen, hormone receptor status and endocrine therapy, age, region

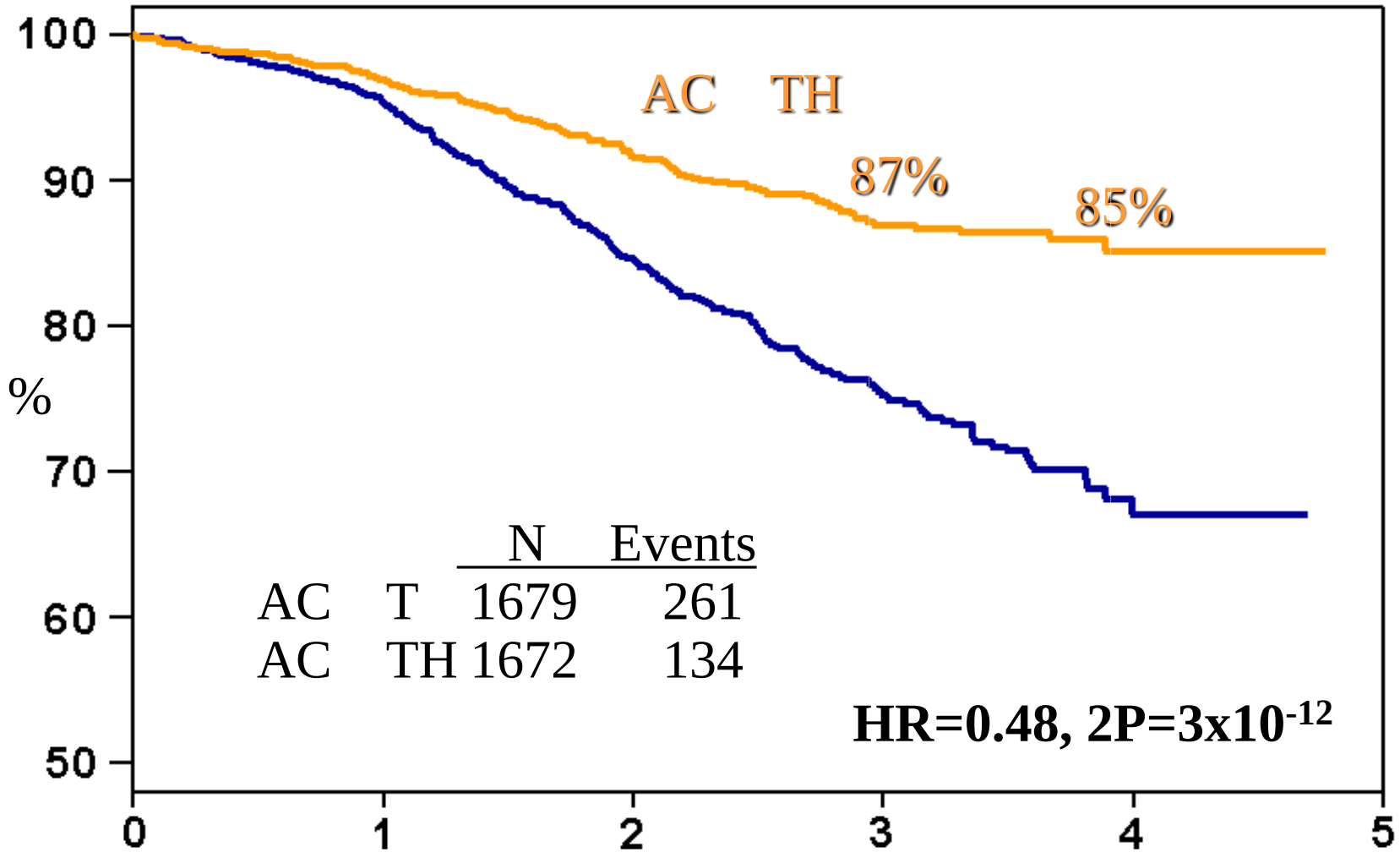
Randomization

Trastuzumab 8 mg/kg → 6 mg/kg 3 weekly x 2 years	Trastuzumab 8 mg/kg → 6 mg/kg 3 weekly x 1 year	Observation

Does adjuvant trastuzumab improve disease-free survival?

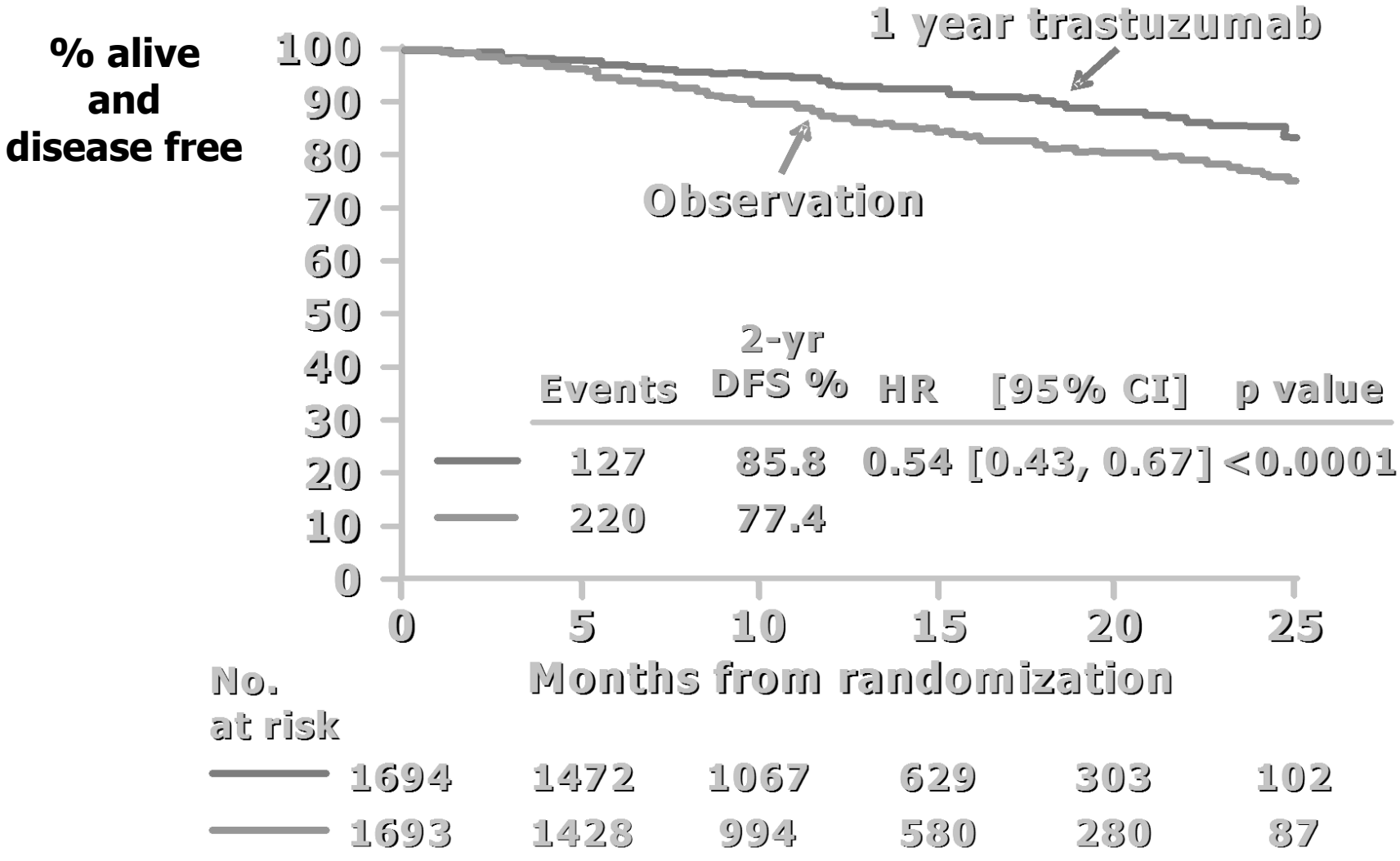
- 輔助性的治療可否延長無病存活期 ？
- 使用Herceptin可否減少復發甚至避免復發 ？

Disease-Free Survival



B31/N9831

乳癌的術後輔助化學治療
無病存活期



Ethnic Difference

	Japanese Study[1]	Carolina Breast Cancer Study[2]	
	Japanese	Non-AA	AA
No. of Pts.	793	300	196
Luminal A	63.3%	54.0%	47.4%
Luminal B	19.5%	17.3%	12.8%
HER2+/ER-	6.9%	5.7%	8.2%
Basal-like	8.4%	16.0%	26.5%
Unclassified	1.8%	7.0%	5.1%
Prognosis	Good		Poor