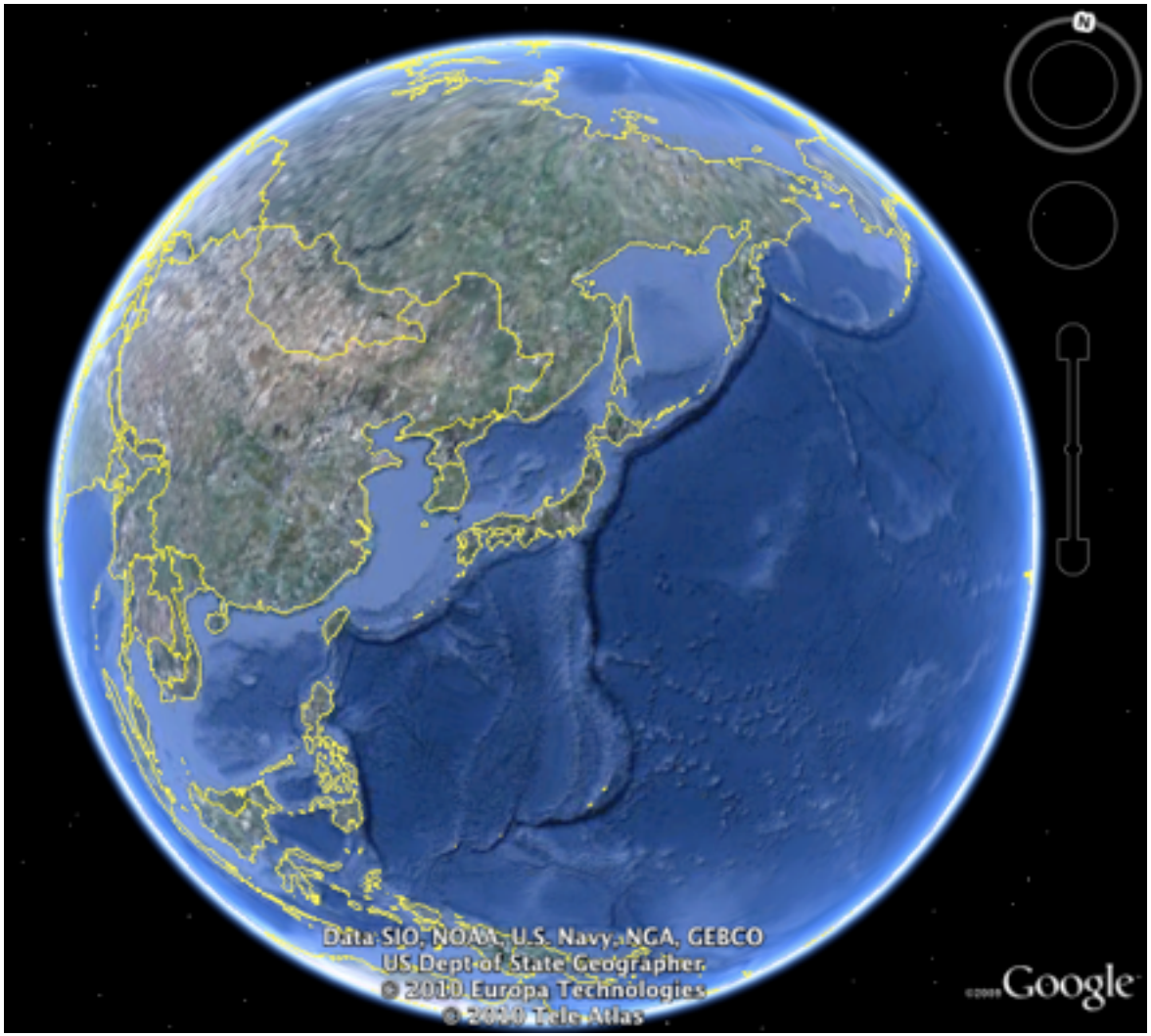
2010/03/06

第6回　中部乳癌会議

「乳癌診療のマクロとミクロ」

岩手医科大学外科学講座
柏葉　匡寛

乳癌診療のマクロ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Data SIO, NOAA, U.S. Navy, NGA, GEBCO
US Dept of State Geographer
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Clinical Trials against Specific Target?

EBCTCG

ATAC

BIG1-98

TEAM

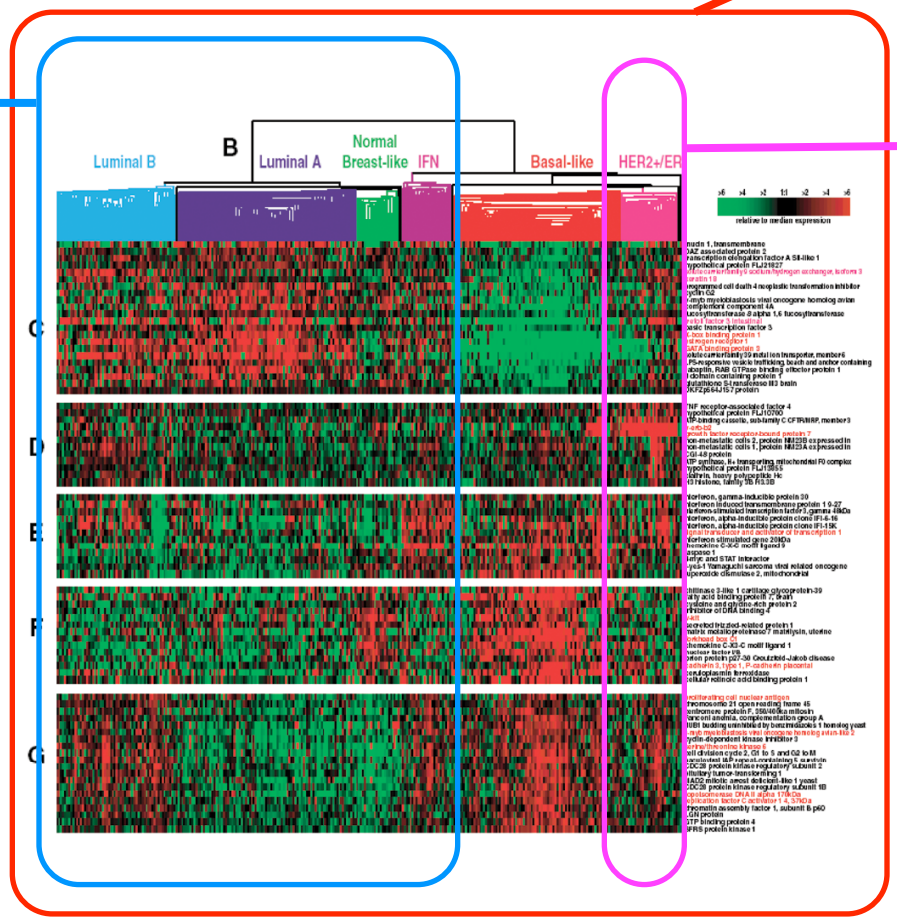
NSABP-B14

HERA

NSABP-B31/

N9831

BCIRG006



乳癌治療の実際？

私のがんはどんながんなの？性格の良いもの？それとも…？

私も実は解らないんです…

先生は抗がん剤が必要だと
ど、私には本当に効果があ

治療による乳癌死亡抑制効果
（リンパ節転移陽性乳癌を想定して）

人

1000

760

669

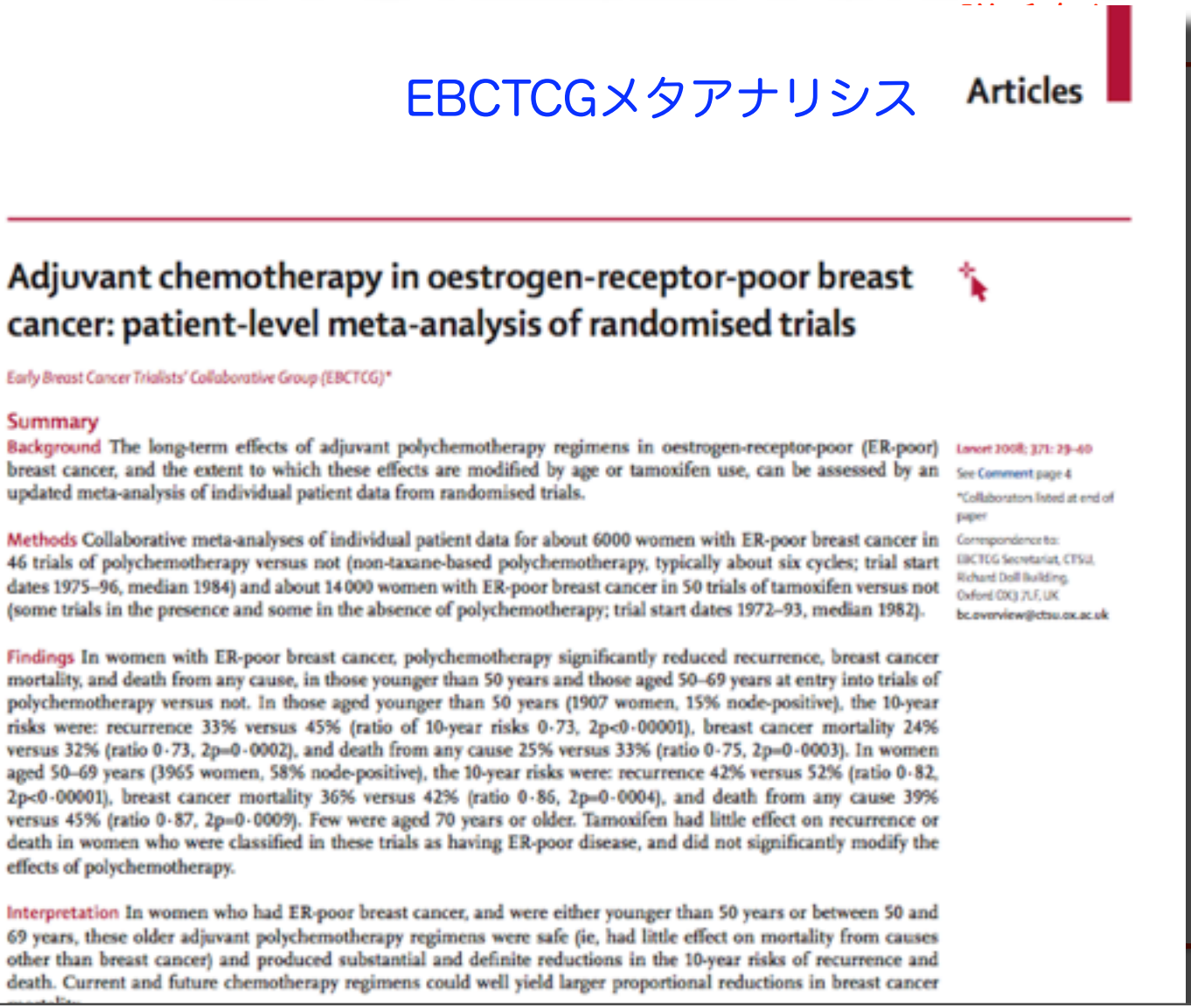
555

410

0

ホ

EBCTCGメタアナリシス



Articles

Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Summary

Background The long-term effects of adjuvant polychemotherapy regimens in oestrogen-receptor-poor (ER-poor) breast cancer, and the extent to which these effects are modified by age or tamoxifen use, can be assessed by an updated meta-analysis of individual patient data from randomised trials.

Methods Collaborative meta-analyses of individual patient data for about 6000 women with ER-poor breast cancer in 46 trials of polychemotherapy versus not (non-taxane-based polychemotherapy, typically about six cycles; trial start dates 1975–96, median 1984) and about 14 000 women with ER-poor breast cancer in 50 trials of tamoxifen versus not (some trials in the presence and some in the absence of polychemotherapy; trial start dates 1972–93, median 1982).

Findings In women with ER-poor breast cancer, polychemotherapy significantly reduced recurrence, breast cancer mortality, and death from any cause, in those younger than 50 years and those aged 50–69 years at entry into trials of polychemotherapy versus not. In those aged younger than 50 years (1907 women, 15% node-positive), the 10-year risks were: recurrence 33% versus 45% (ratio of 10-year risks 0·73, 2p<0·00001), breast cancer mortality 24% versus 32% (ratio 0·73, 2p=0·0002), and death from any cause 25% versus 33% (ratio 0·75, 2p=0·0003). In women aged 50–69 years (3965 women, 58% node-positive), the 10-year risks were: recurrence 42% versus 52% (ratio 0·82, 2p<0·00001), breast cancer mortality 36% versus 42% (ratio 0·86, 2p=0·0004), and death from any cause 39% versus 45% (ratio 0·87, 2p=0·0009). Few were aged 70 years or older. Tamoxifen had little effect on recurrence or death in women who were classified in these trials as having ER-poor disease, and did not significantly modify the effects of polychemotherapy.

Interpretation In women who had ER-poor breast cancer, and were either younger than 50 years or between 50 and 69 years, these older adjuvant polychemotherapy regimens were safe (ie, had little effect on mortality from causes other than breast cancer) and produced substantial and definite reductions in the 10-year risks of recurrence and death. Current and future chemotherapy regimens could well yield larger proportional reductions in breast cancer

Lancet 2008; 371: 29–40

See Comment page 4

*Collaborators listed at end of paper

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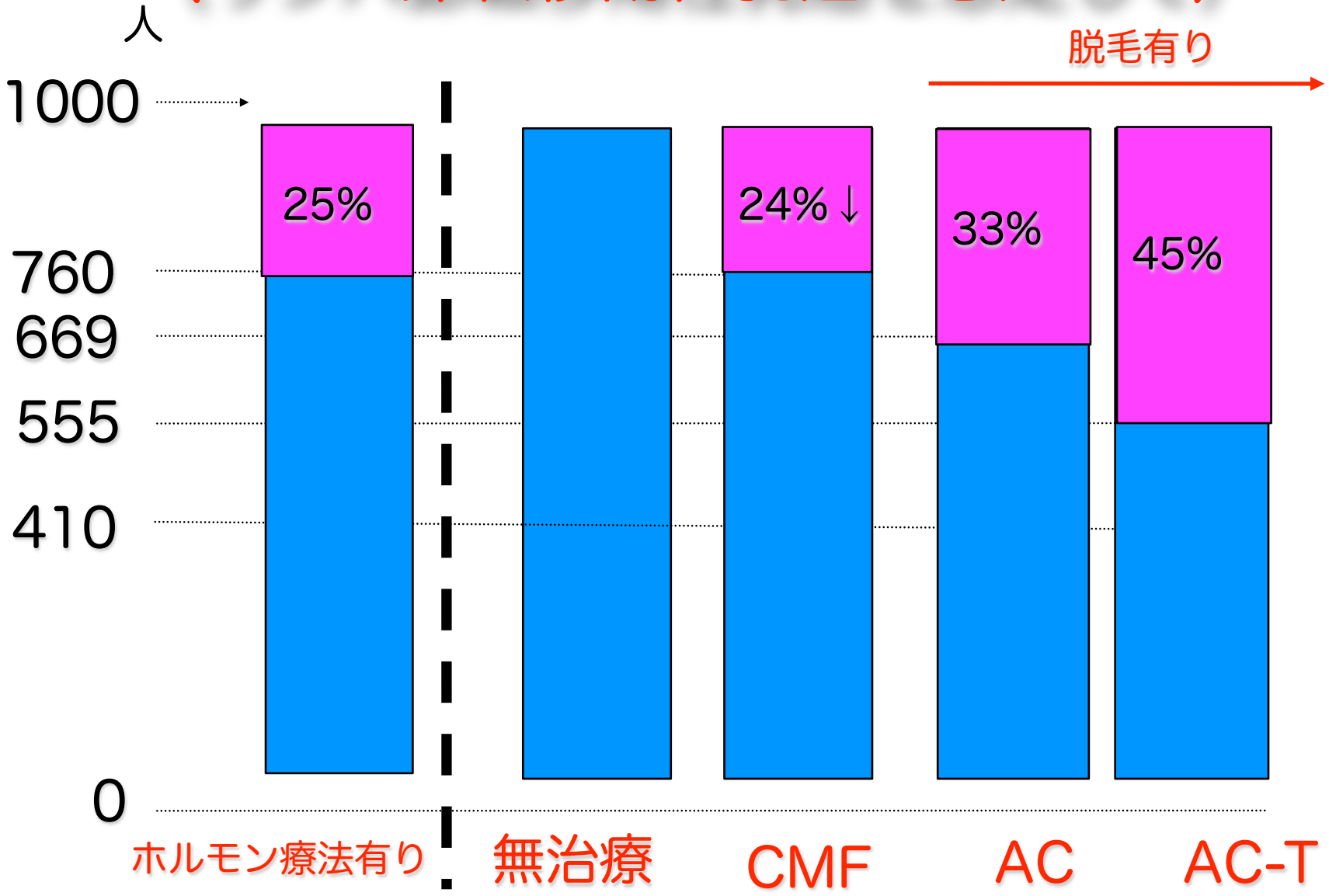
Richard Doll Building,
Oxford OX3 7LF, UK
bc.overview@ctsu.ox.ac.uk

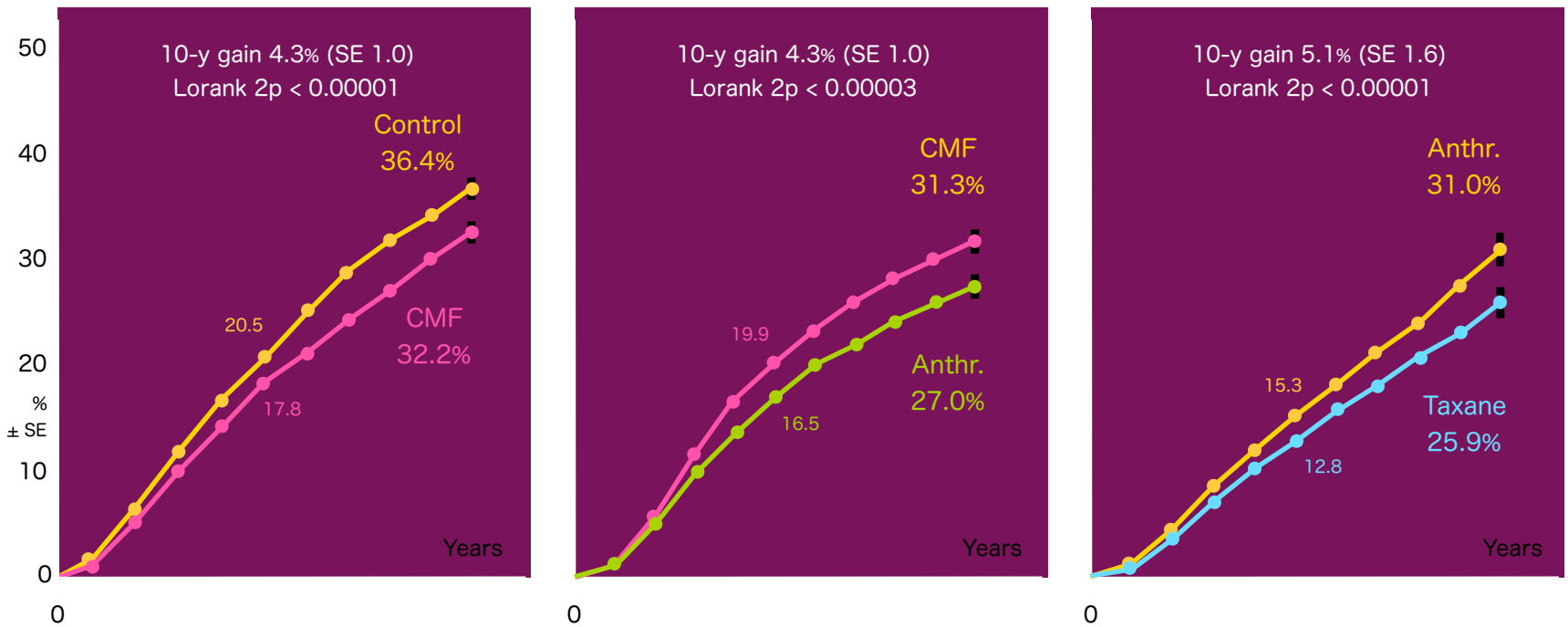
-T

治療による乳癌死亡抑制効果
（リンパ節転移陽性乳癌を想定して）



EBCTCG Meta-analysis 2005-06
Breast cancer mortality

Taxanes > Anthra. > CMF > No Chemo.



Death rates (% / year: total – rate in women without recurrence) & logrank analyses

Peto R on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Presented at SABCS 2007, December 13, 2007. San Antonio, TX.

有効性？
優先性？

分子標的療法

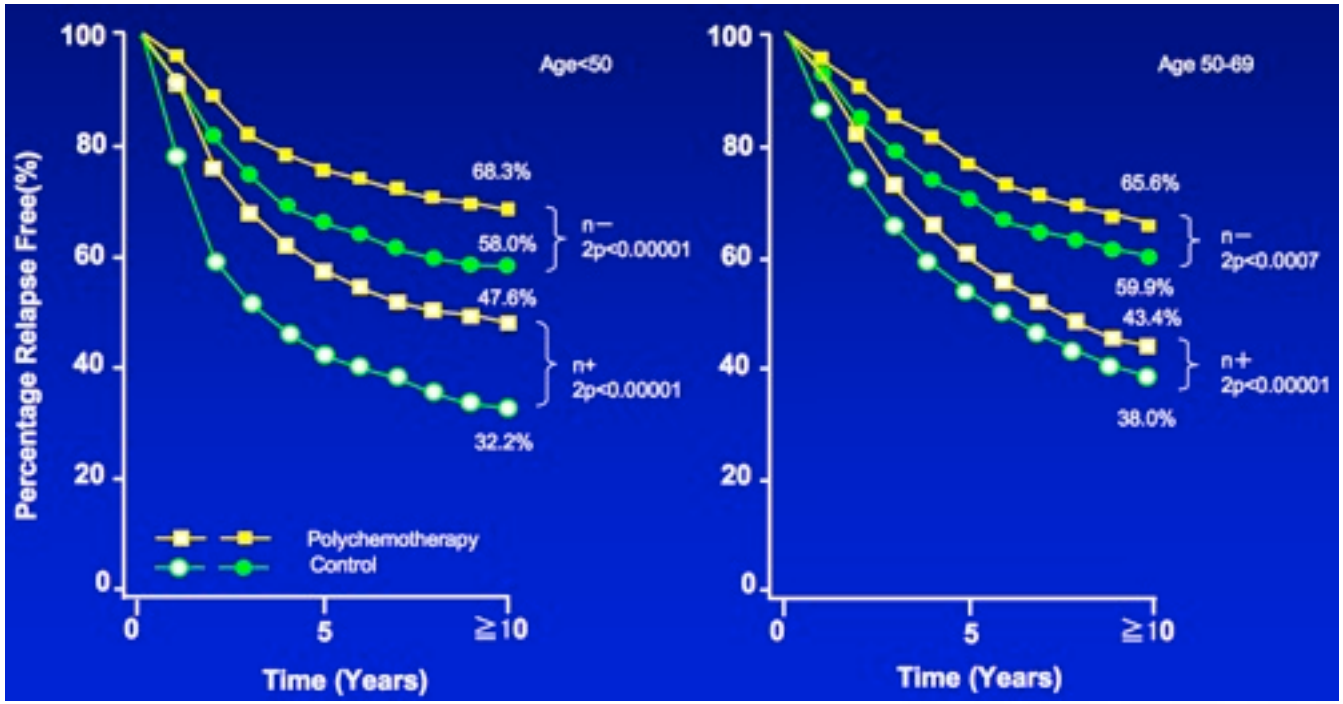
化学療法（タキサン）

化学療法（アンスラサイクリン系薬剤）

化学療法（CMF）

ホルモン療法

メタアナリシスの恩恵⇔個別化治療



Lancet 2005; 365: 1687–1717

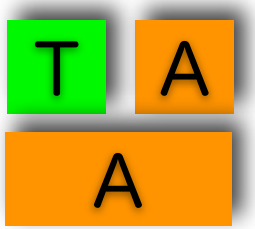
Pros:

・不確定な生物学的因子によらない絶対的傾向
・直接比較しにくい背景因子、バイアスの制御

Cons:

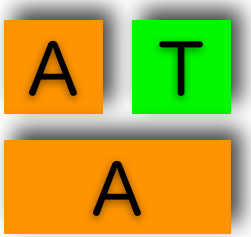
・←年代毎のER/HER2/Triple Negative等の分布の解析不可
・化学療法不応性癌（ER++）への抗癌剤投与
・更新が遅く、個別化に相反

1st generationの21のタキサントライアル



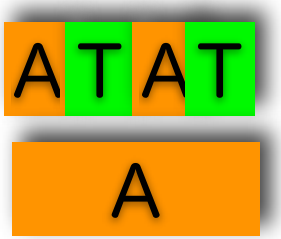
N=3 Trials

FinHER(n=1010)
HORG (n=750)
MDACC (n=524)



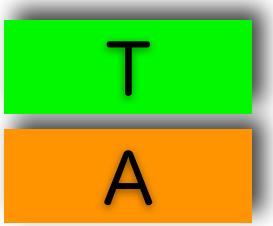
N=10.5 Trials

TACT(n=4162)
CALGB9344 (n=3121)
NSABP-B28 (n=3060)
BIG2-98 (n=2887/2)
NSABP-B27 (n=2411)
NCICMA-21 (n=2104)
WGSG/AGO (n=2011)
GEICAM9906 (n=1999)
PACS-01 (n=999)
TAXIT216 (n=972)
HeCOG10/97 (n=595)



N=6.5 Trials

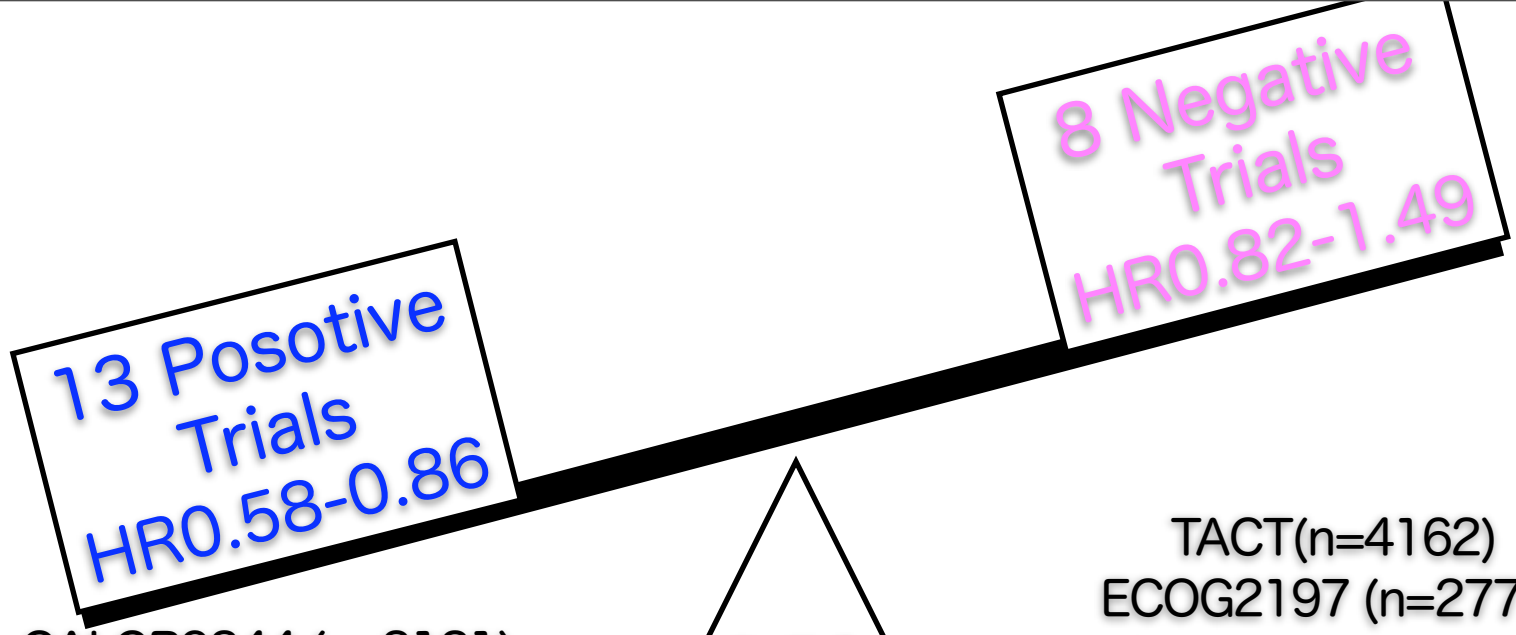
BIG2-98
(n=2887/2)
ECOG2197
(n=2778)
BCIRG001(n=1491)
ECTO (n=1355)
GONO-
MIG-5(n=1055)
Anglo-Celtic
(n=363)



N=1Trial

USO9735 (n=1016)

Piccart ASCO2009



CALGB9344 (n=3121)
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BIG2-98 (n=2887/2)
WGSG/AGO (n=2011)
PACS-01 (n=999)
BCIRG001(n=1491)
ECTO (n=1355)
GEICAM9906 (n=1999)
GEICAM9805 (n=1059)
USO9735 (n=1016)
FinHER(n=1010)
HORG(n=756)
MDACC (n=524)

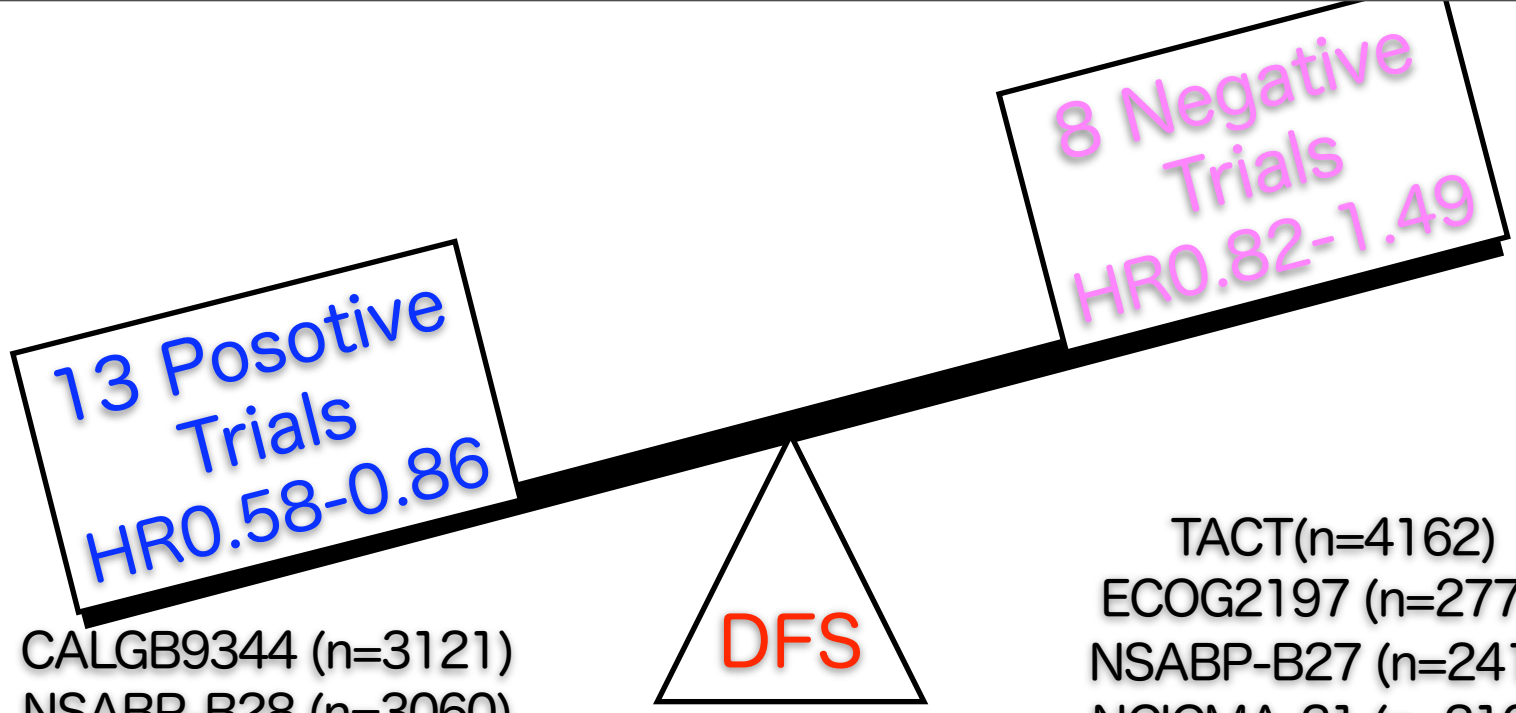
TACT(n=4162)
ECOG2197 (n=2778)
NSABP-B27 (n=2411)
NCICMA-21 (n=2104)
GONO-MIG-5(n=1055)
TAXIT216 (n=972)
HeCOG10/97 (n=595)
Anglo-Celtic (n=363)

Piccart ASCO2009

８つのTrialがnegativeとなった理由

- 統計学的 under-power（症例数の少なさ）
- Anthracyclineを含む強力な標準アーム
- Tの至適投与のタイミング、量、スケジュール
- 対象内の低増殖群/Luminal Aの混在

Piccart ASCO2009



CALGB9344 (n=3121)
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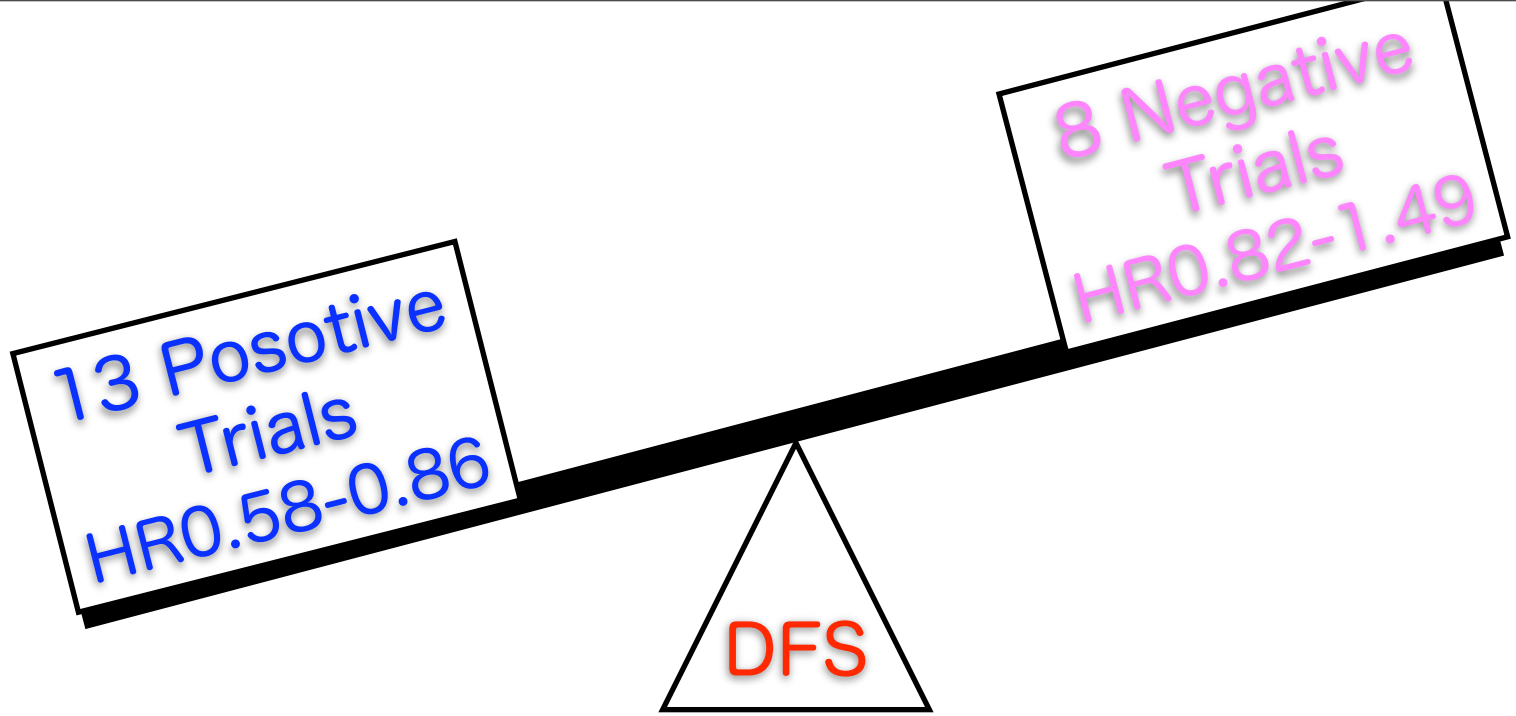
Anglo-Celtic (n=363)

統計的Under-power

Piccart ASCO2009



SEQ.(9)

CALGB9344 (n=3121)
NSABP-B28 (n=3060)
BIG2-98 (n=2887/2)
WGSG/AGO (n=2011)
PACS-01 (n=999)
GEICAM9906 (n=1999)
FinHER(n=1010)
HORG(n=756)
MDACC (n=524)

Conc.(4)

BCIRG001(n=1491)
ECTO (n=1355)
GEICAM9805 (n=1059)
USO9735 (n=1016)

SEQ.(5)

TACT(n=4162)
NSABP-B27 (n=2411)
NCICMA-21 (n=2104)
TAXIT216 (n=972)
HeCOG10/97 (n=595)

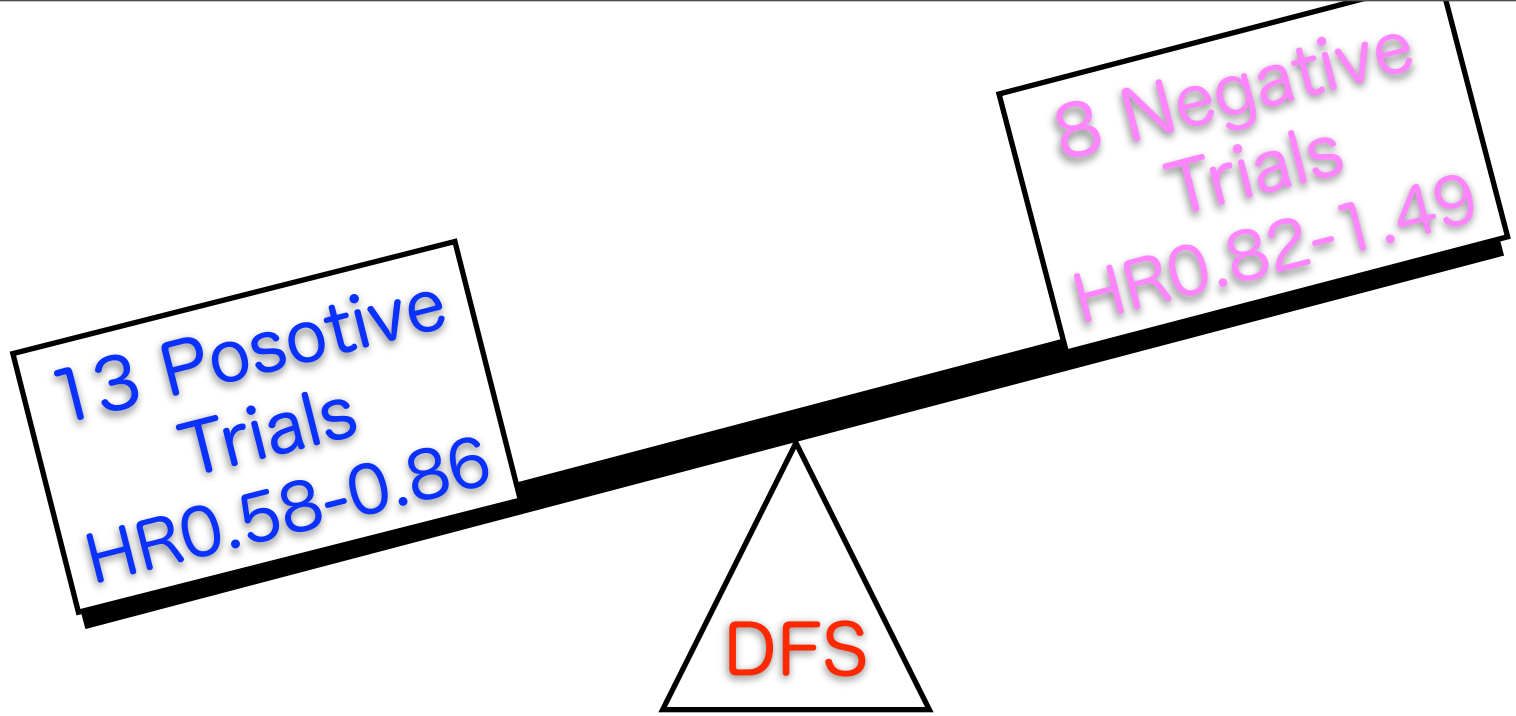
Conc.(3)

ECOG2197 (n=2
GONO-MIG-5(n=1
Anglo-Celtic (n=3

Taxane Up-front

Timinig&Scedule

Piccart ASCO2009



SEQ.(9)

CALGB9344 (n=3121)
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Conc.(4)

BCIRG001(n=1491)
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SEQ.(5)

TACT(n=4162)
NSABP-B27 (n=2411)
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HeCOG10/97 (n=595)

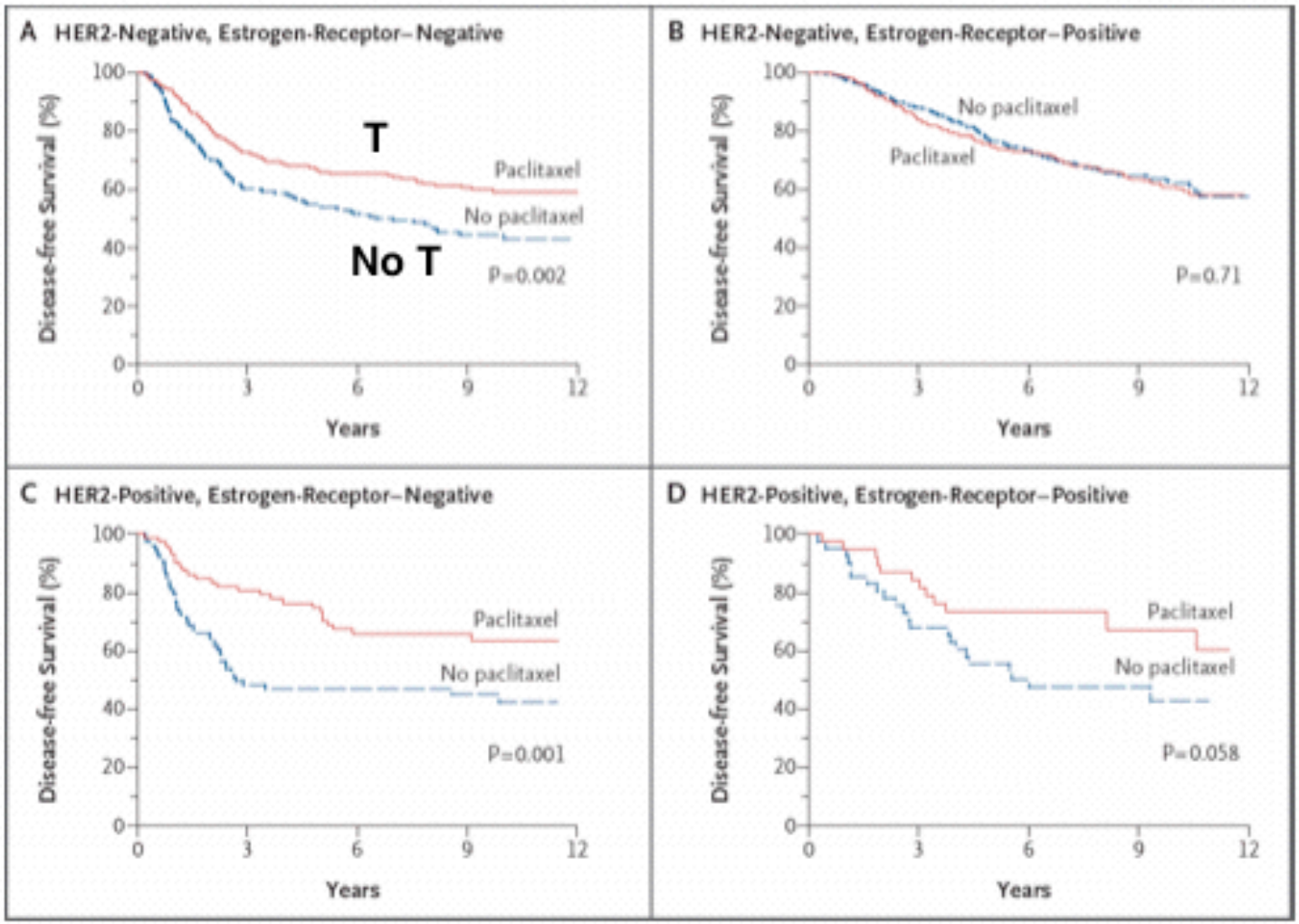
Conc.(3)

ECOG2197 (n=2
GONO-MIG-5(n=1
Anglo-Celtic (n=3

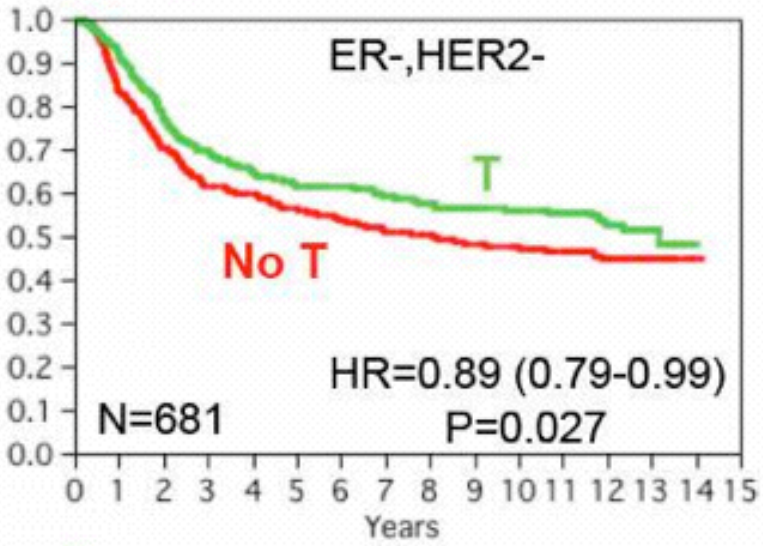
qW Pacli&q3W Doc.

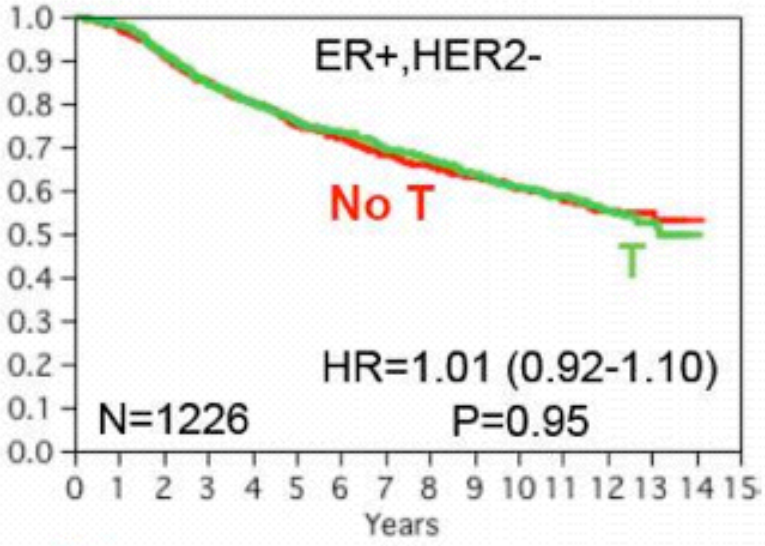
Piccart ASCO2009

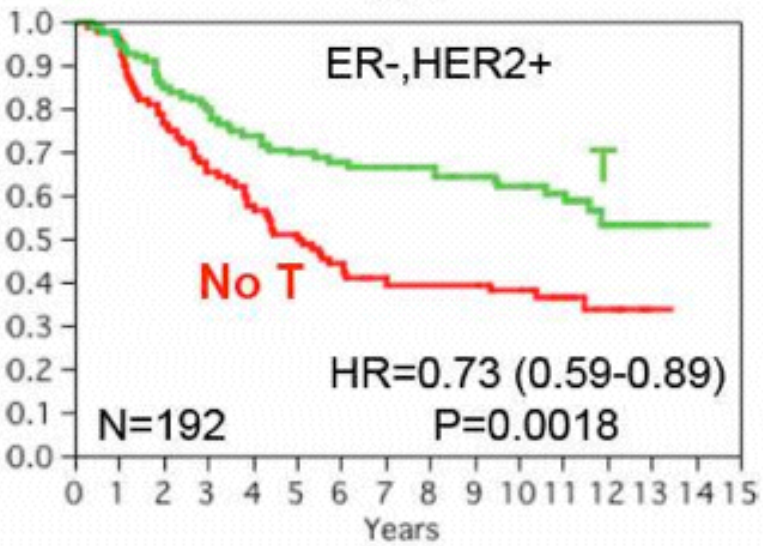
SABCS2009 #606 Benefits of Adding Paclitaxel to Adjuvant Doxorubicin/Cyclophosphamide in Node-Positive Breast Cancer Depending on HER2 & ER Status:Analysis of Tumor Tissue Microarrays & IHC in CALGB9344. Berry D et al.

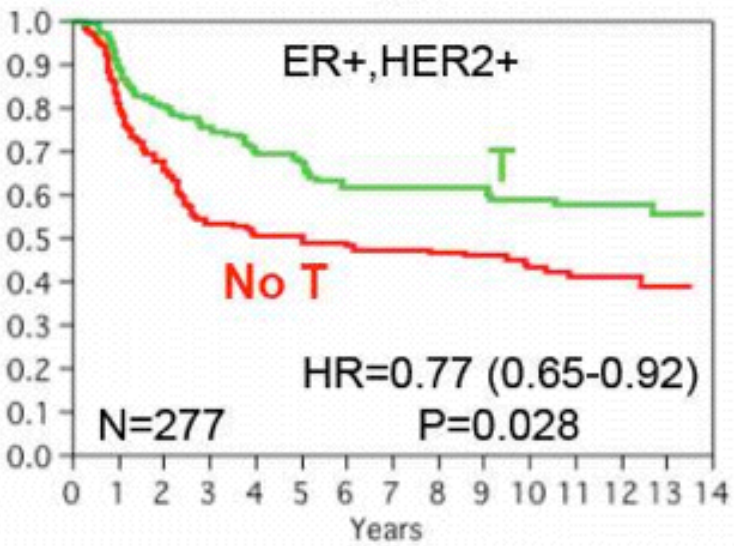


Relapse-free survival in CALGB 9344; n = 2376

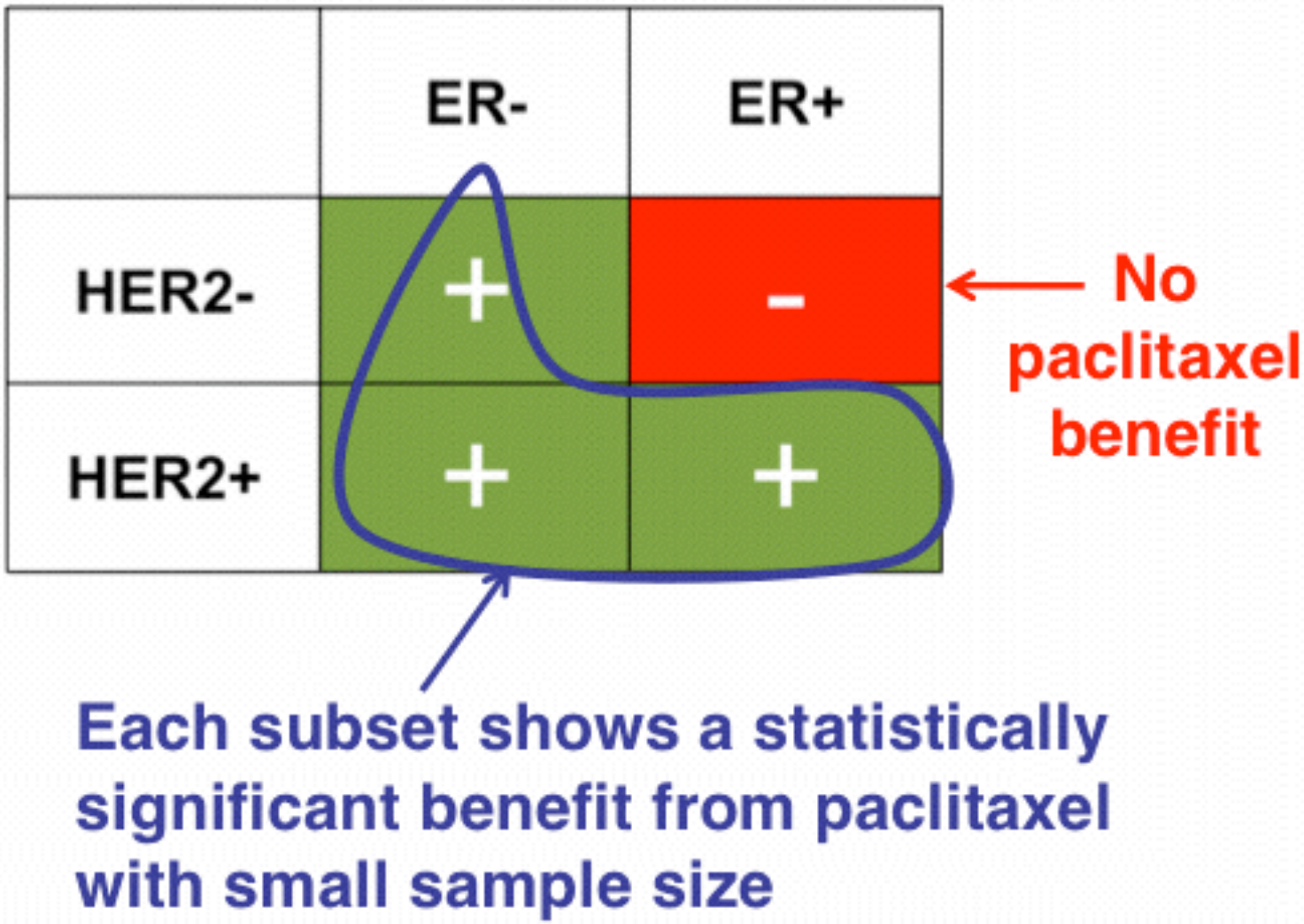








Role of CTx/Paclitaxel?



Conclusions / Caveats

- TMA-based marker studies are concordant with whole section analyses
- Assessing ER/HER2 is helpful in predicting the benefit of paclitaxel
- Results for overall survival are similar to that of RFS
- Whether signatures such as Oncotype DX™ and MammaPrint® provide predictive value of the benefit of paclitaxel over that of ER/HER2 is not clear
- CALGB 9344 provides 3 distinct subsets, each of which shows a statistically significant benefit from paclitaxel
- Small sample sizes are feasible in phase III clinical trials of adjuvant therapy in node-positive breast cancer by excluding nonresponding patients
- ER+/HER2- tumors, representing more than 50% of breast cancer, receive little of no benefit from taxane-based chemotherapy, and perhaps not from standard anthracycline-based therapy
- No clinical trial of a taxane has shown a statistical benefit in ER+/HER2- breast cancer
- The incremental benefit of paclitaxel for HER2+ by ER status may be different in the context of trastuzumab

・LA以外での有用性を証明
・(１–LA)はminorityなので今までより少ないサンプルサイズでの試験が可能

・ER+/HER2-ではPaclitaxelの有用性は乏しい≒化学療法自体も？？

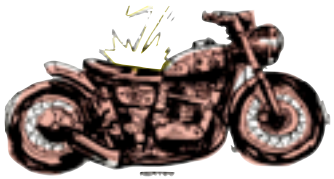
Limitations...

	ER-	ER+
HER2-	+	-
HER2+	+	+

Highly proliferative

Luminal B

Ki67 high etc...



Lower proliferative

Luminal A

→現行の治療効果予測因子であるバイオマーカーでは
化学療法一般までの効果予測は困難であろう…

乳癌治療の？

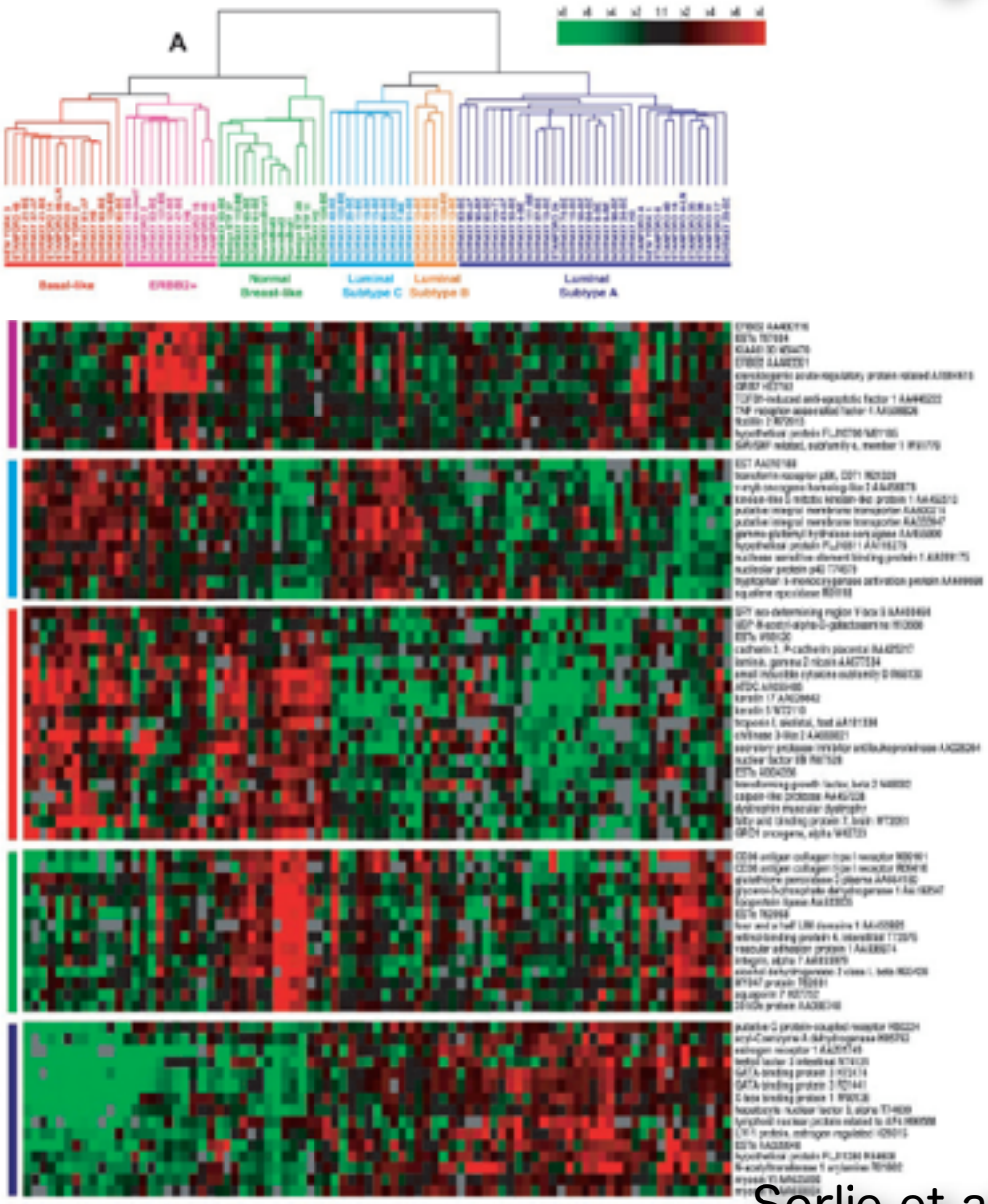
私のがんはどんながんなの？性格の良いもの？それとも…？

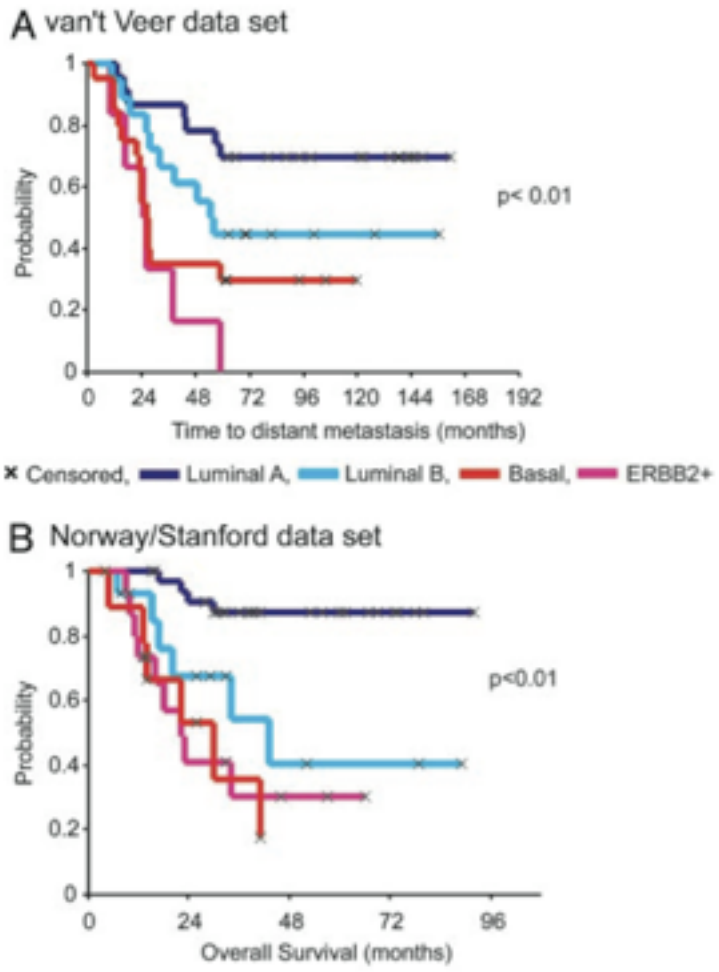
私も実は解らないんです…

先生は抗がん剤が必要だと
ど、私には本当に効果があ

乳癌診療のミクロ

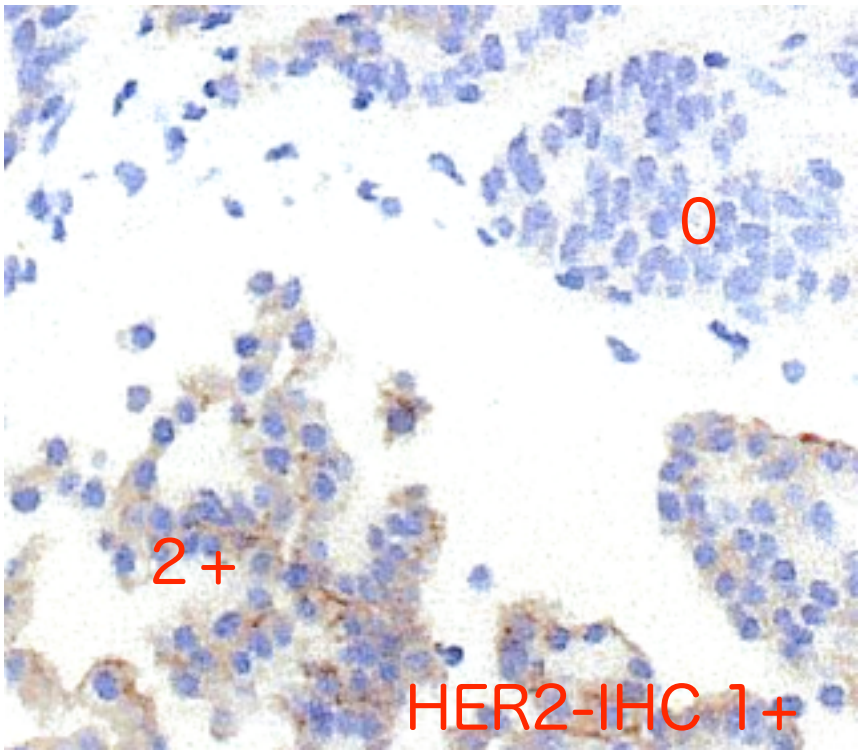
Intrinsic subtypes of BC





Sorlie et al. PNAS 98(19),10869-10874,2001

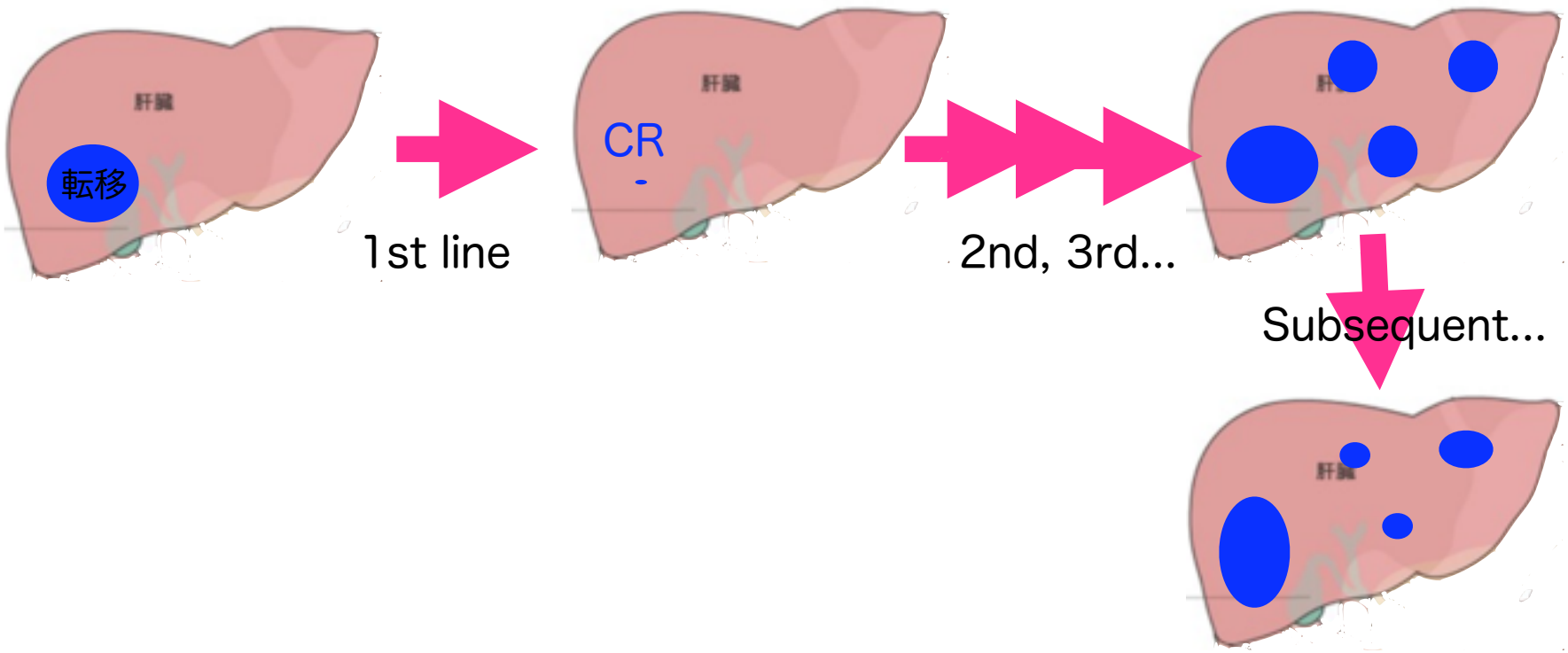
乳癌のHeterogeneity-1



heterogeneity
＜普遍性・代表的

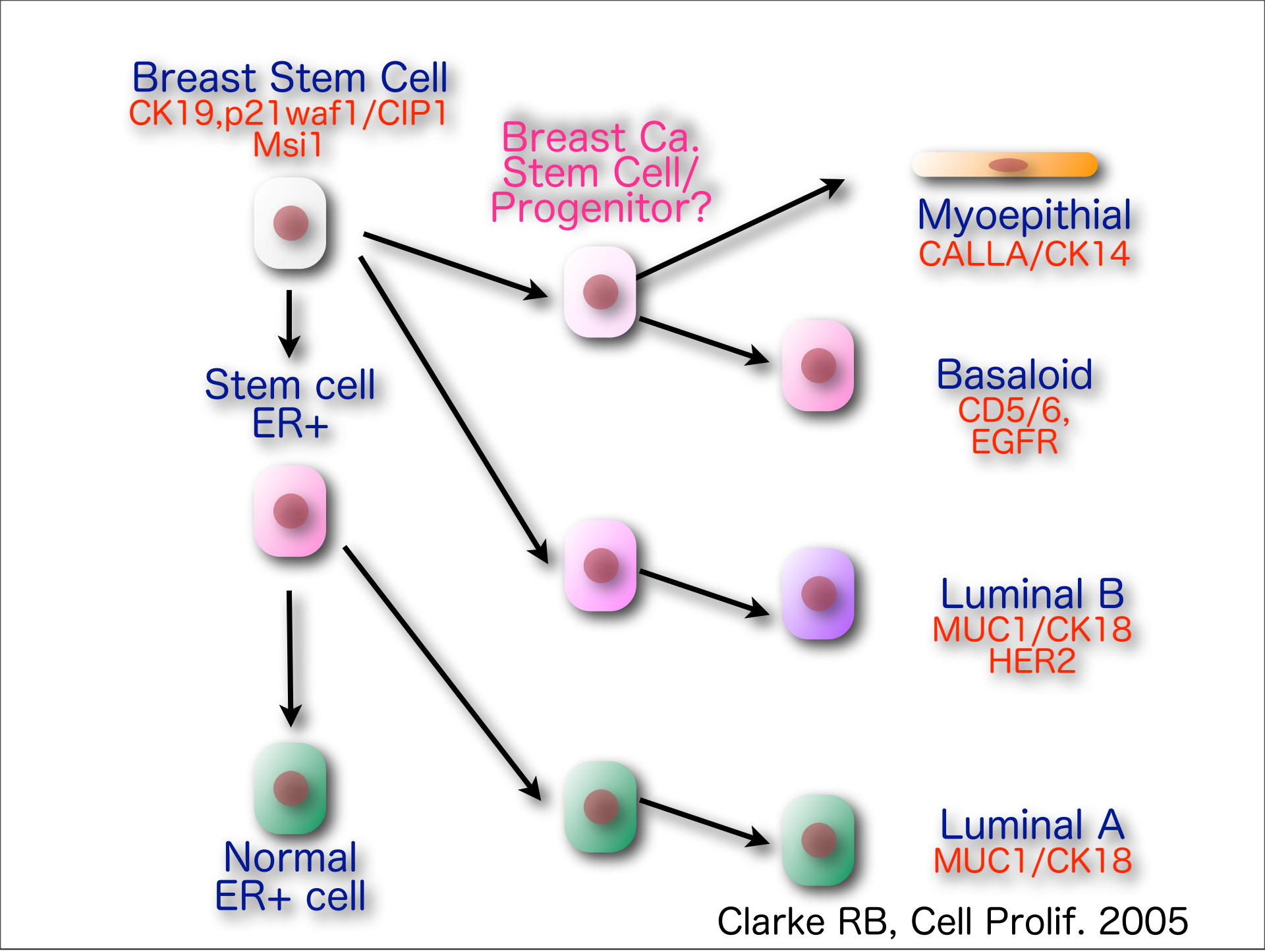
１腫瘍内のheterogeneityも事実…

乳癌のHeterogeneity-2



→進行する1個人の腫瘍内のheterogeneity？

≒Differentiation?


Breast Stem Cell
CK19,p21waf1/CIP1
Msi1
Breast Ca.
Stem Cell/
Progenitor?
Myoepithial
CALLA/CK14
Basaloid
CD5/6,
EGFR
Stem cell
ER+
Luminal B
MUC1/CK18
HER2
Normal
ER+ cell
Luminal A
MUC1/CK18
Clarke RB, Cell Prolif. 2005

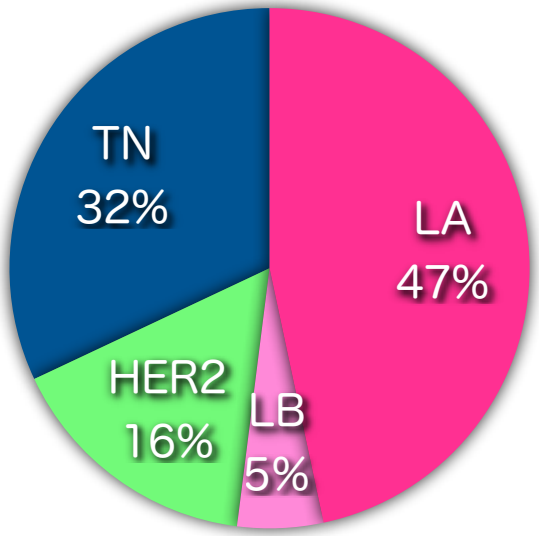
→これらの現象への私の研究…
2008年癌治より

腫瘍マーカーの変動からみた再発Triple Negative乳癌のclonalityの検討

岩手医科大学　外科学講座
柏葉匡寛、稲葉　亨、武田雄一郎、小松英明、
滝山郁雄、若林　剛

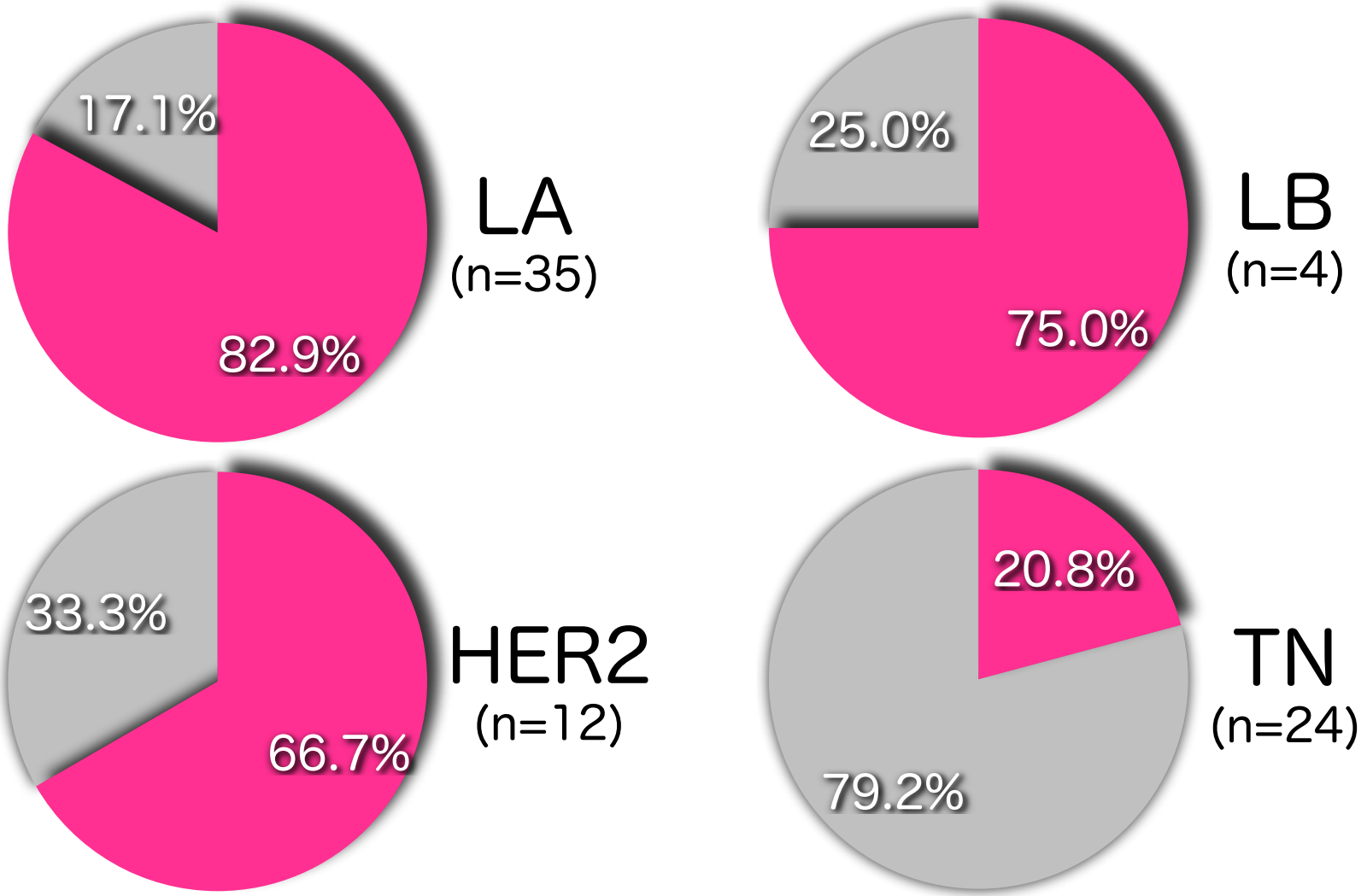
対象と方法

- 2001.11月から2007.9月
  連続した進行・再発乳癌 75名
- 診断時年齢：27-78（中央値：53）
- 転移臓器数：１－４　（平均1.7）
- 転移臓器　胸壁24　リンパ節17
  肺・胸膜26　CNS2
  肝　18　骨32
- 再発・診断時の腫瘍マーカー４種類を測定(CEA,CA15-3,BCA225, NCC-ST439: 25%> 上限を陽性)

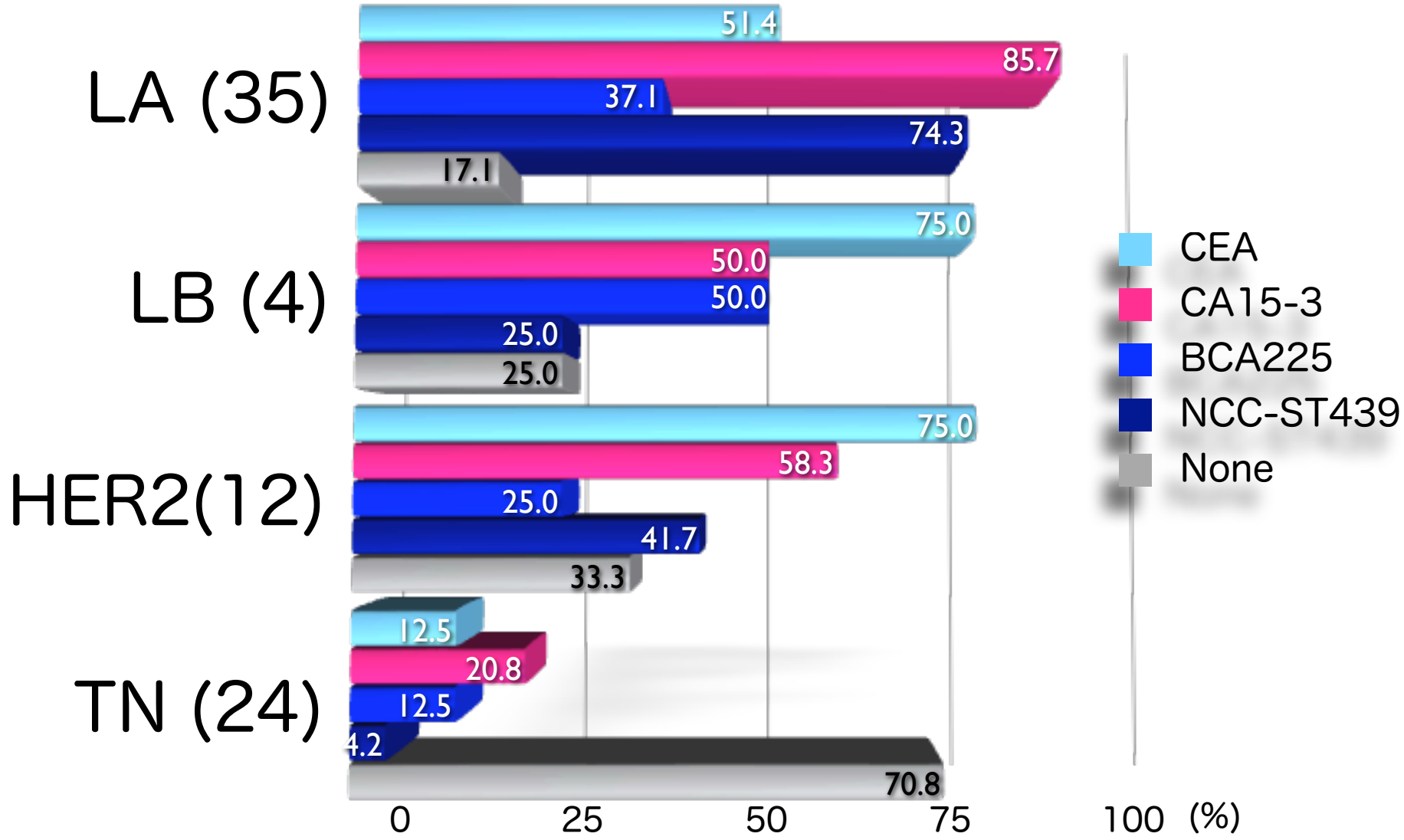


	ER	PgR	HER2
LA	+	+/-	-
LB	+	+/-	+
HER2	-	-	+
TN	-	-	-

結果-1
-Subtypeと腫瘍マーカー陽性率（ANY）-



結果-2
-Subtypeと腫瘍マーカー陽性率（EACH）-



結果-3
-Luminal/非LuminalでのCA15-3陽性率-

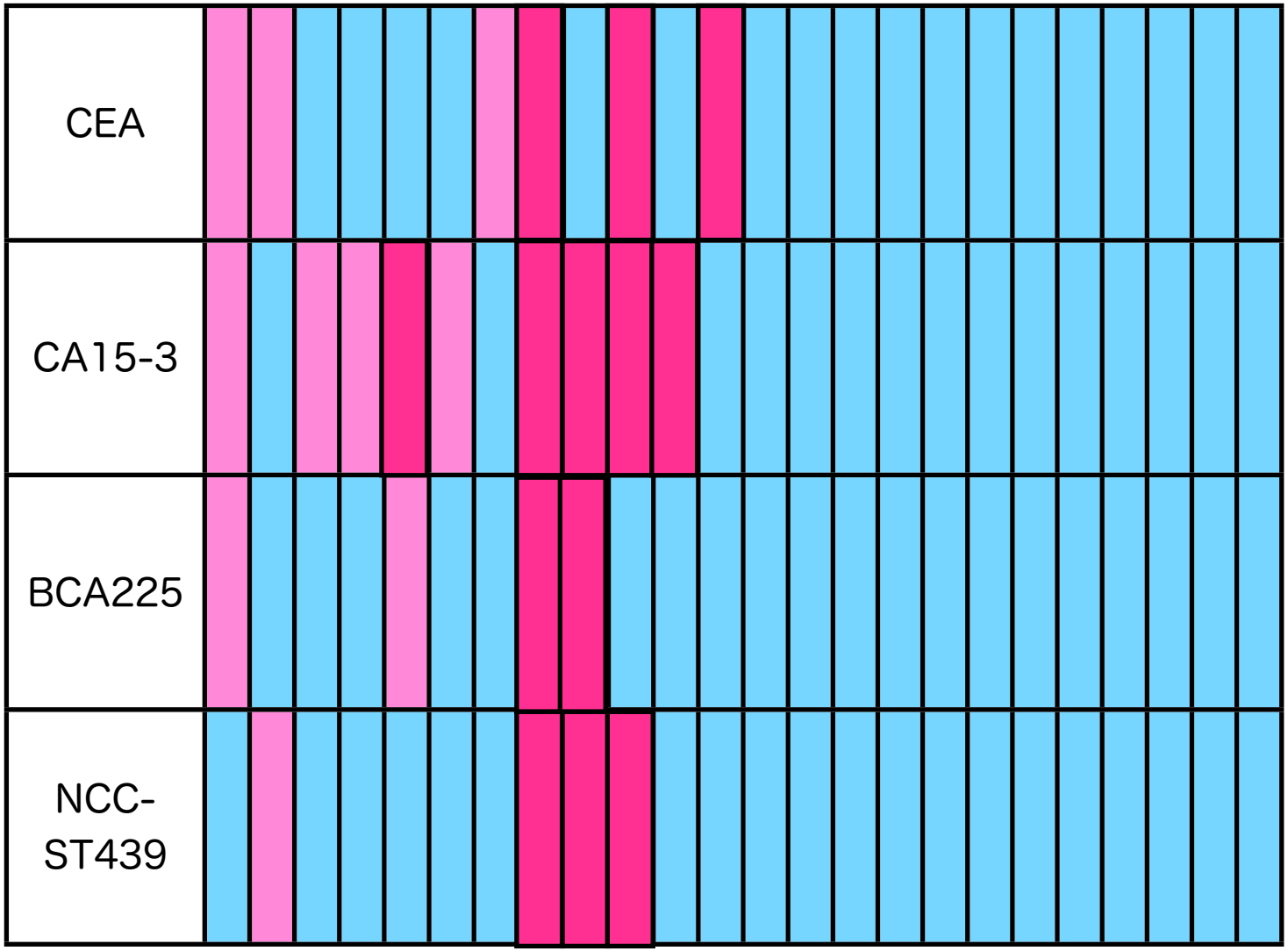
		Luminal LA+LB(39)	Non-L HER2+TN(36)
CA15-3	+	25	12
	-	14	24

P=0.011

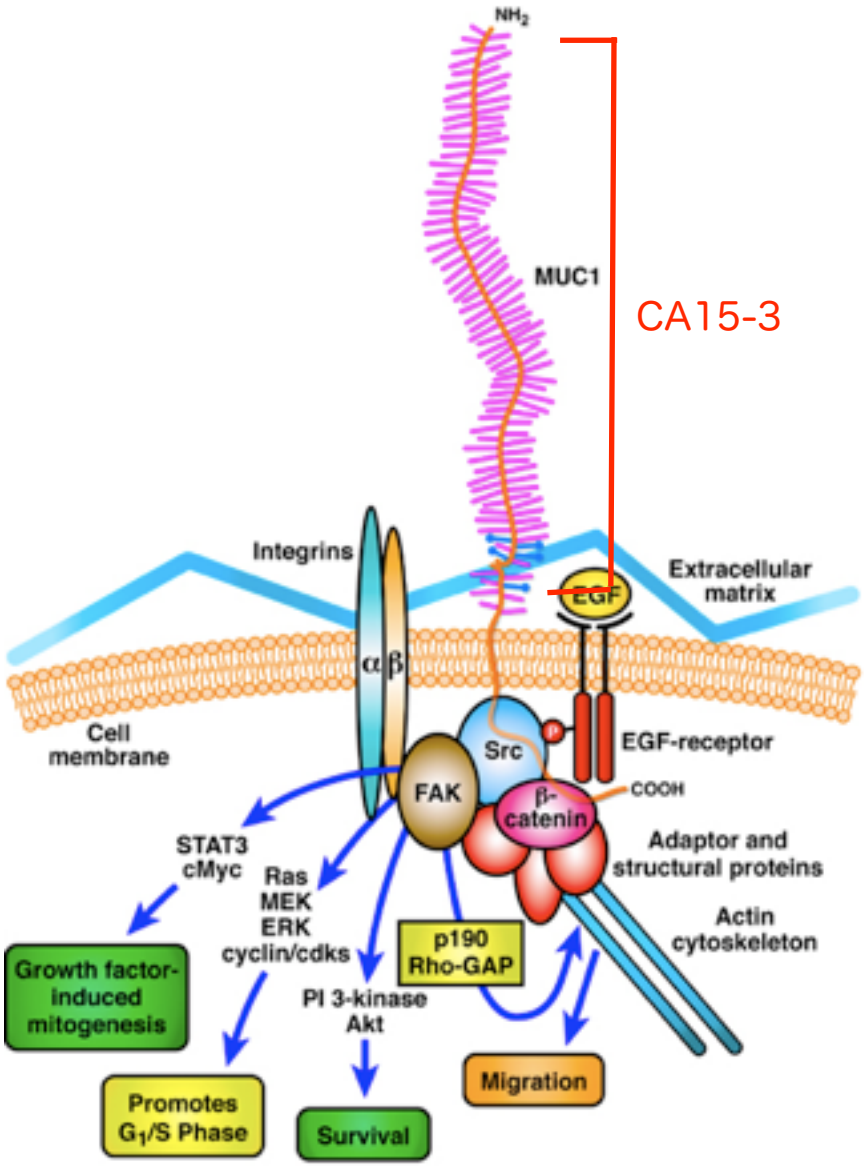
結果-4
-トリプルネガティブ乳癌治療経過中の腫瘍マーカーの変動-

		Onset	After Tx
Any Marker	+	7	12
	-	17	12
CA15-3	+	5	9

結果-5
-TN治療経過中の腫瘍マーカーの変動-



考察



MUC1

1. 腫瘍マーカーはsubtype 毎に陽性率が異なる→もし用いるなら再発surveillanceではLuminal typeで有用、Luminal type特異的に選択・汎用された可能性

2. CA15-3の陽転化は乳腺幹細胞の分化に伴う表面マーカーMUC1の過剰発現を表し、ER陰性細胞からLuminal typeへの分化lineageと合致

Serendipity for WHAT?

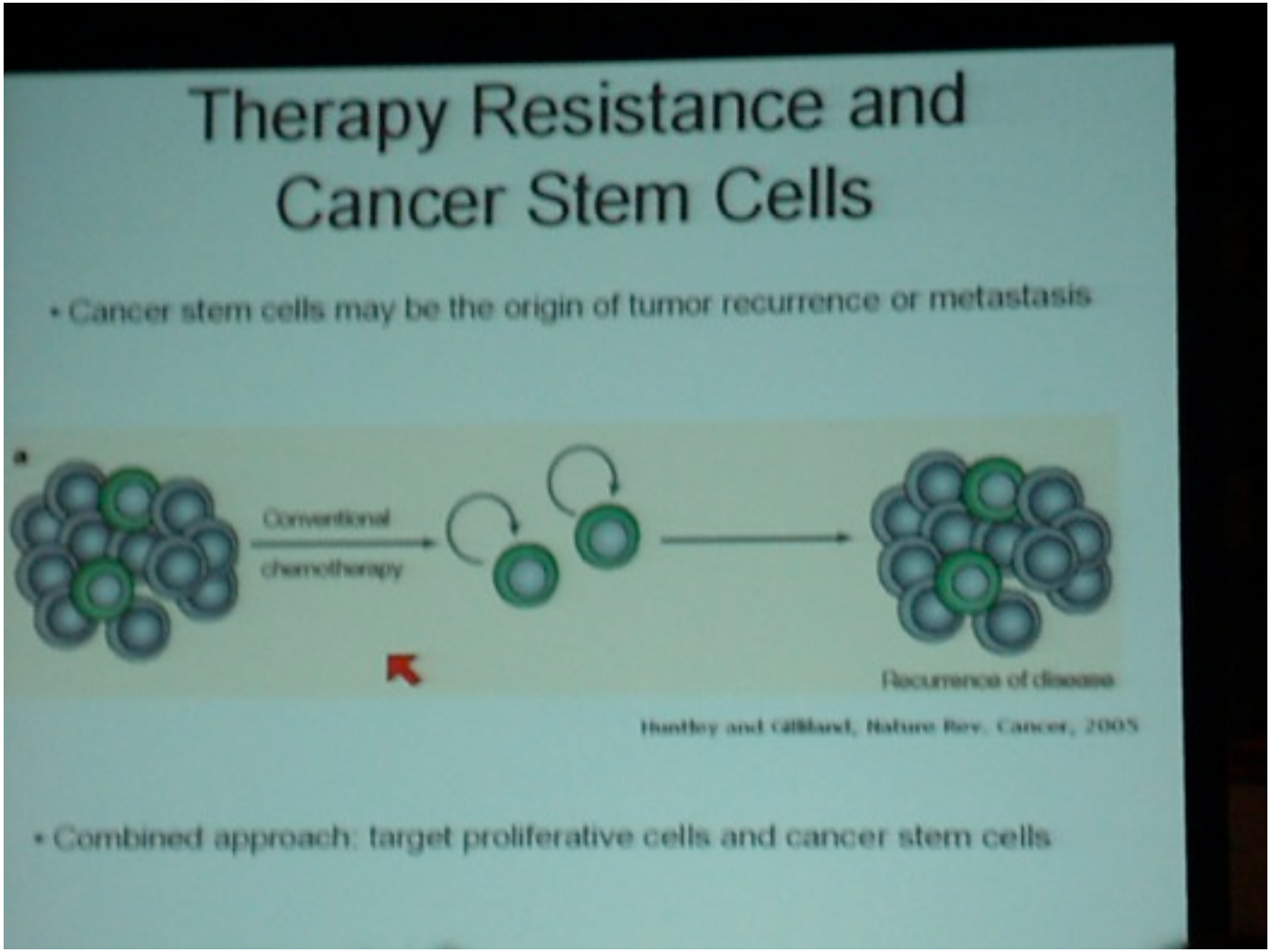
-ものをうまく見つけ出す能力、不思議な発見力-

何のため？

- 論文を書いて偉くなるため？
- 個人としての業績を残すため？
- 基礎研究をしたいから…
- SABCSで発表するため…

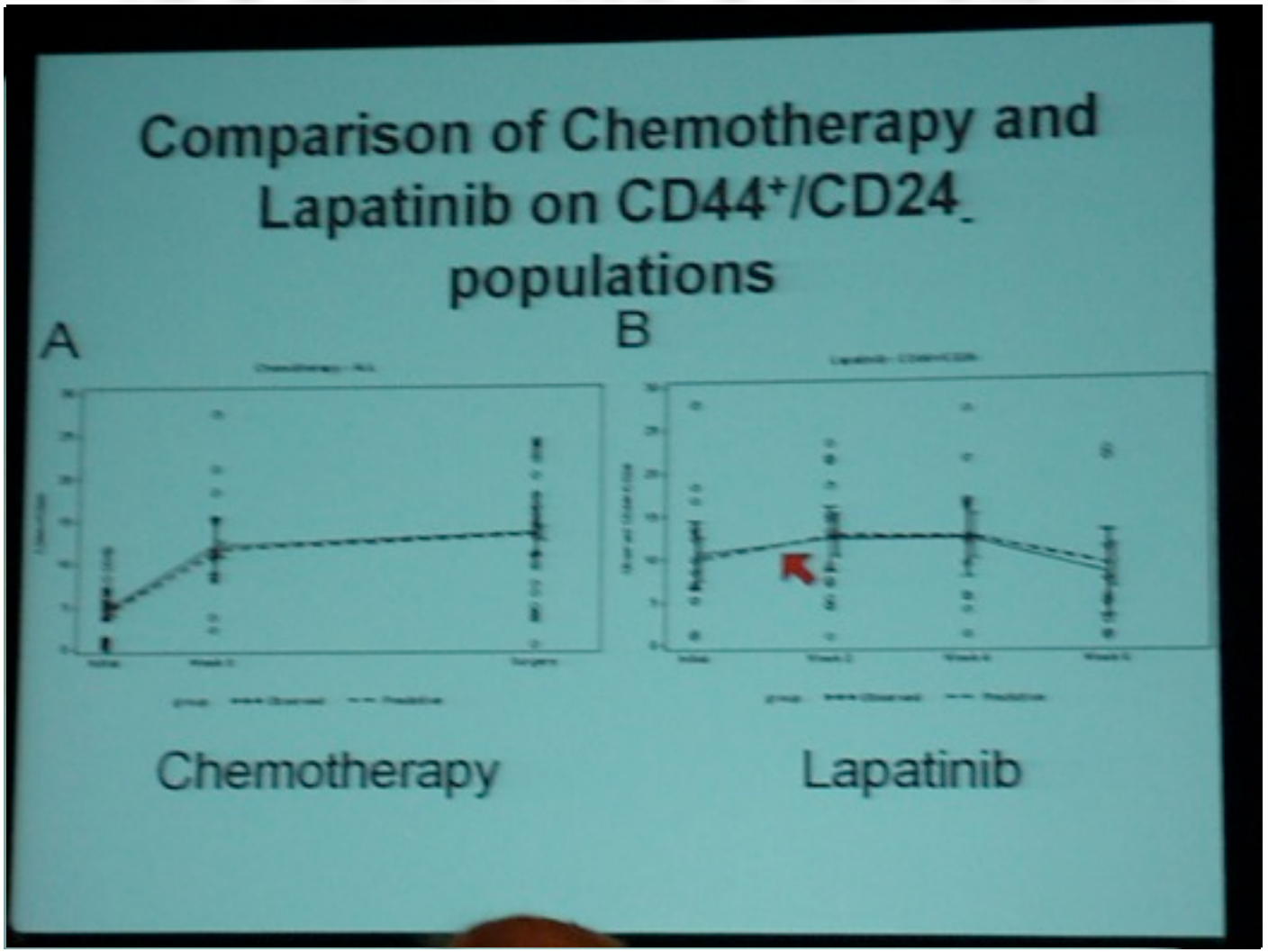
→乳癌患者さんの治療に役立つことを優先したい、役立つものに洗練したい…

化学療法vs分子標的療法



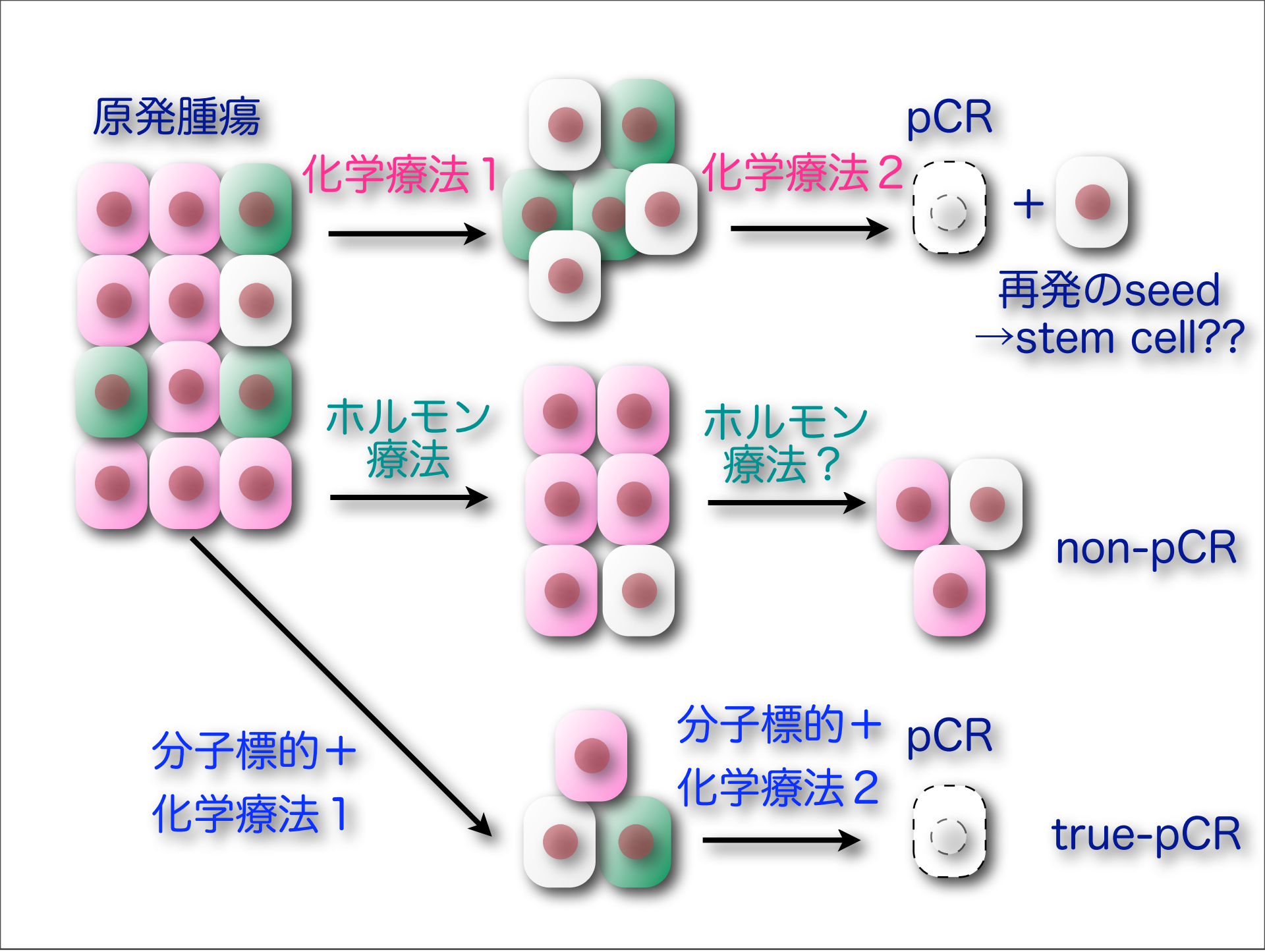
Chang J. Baylor, presented at St.Antonio 2007

化学療法vs分子標的療法

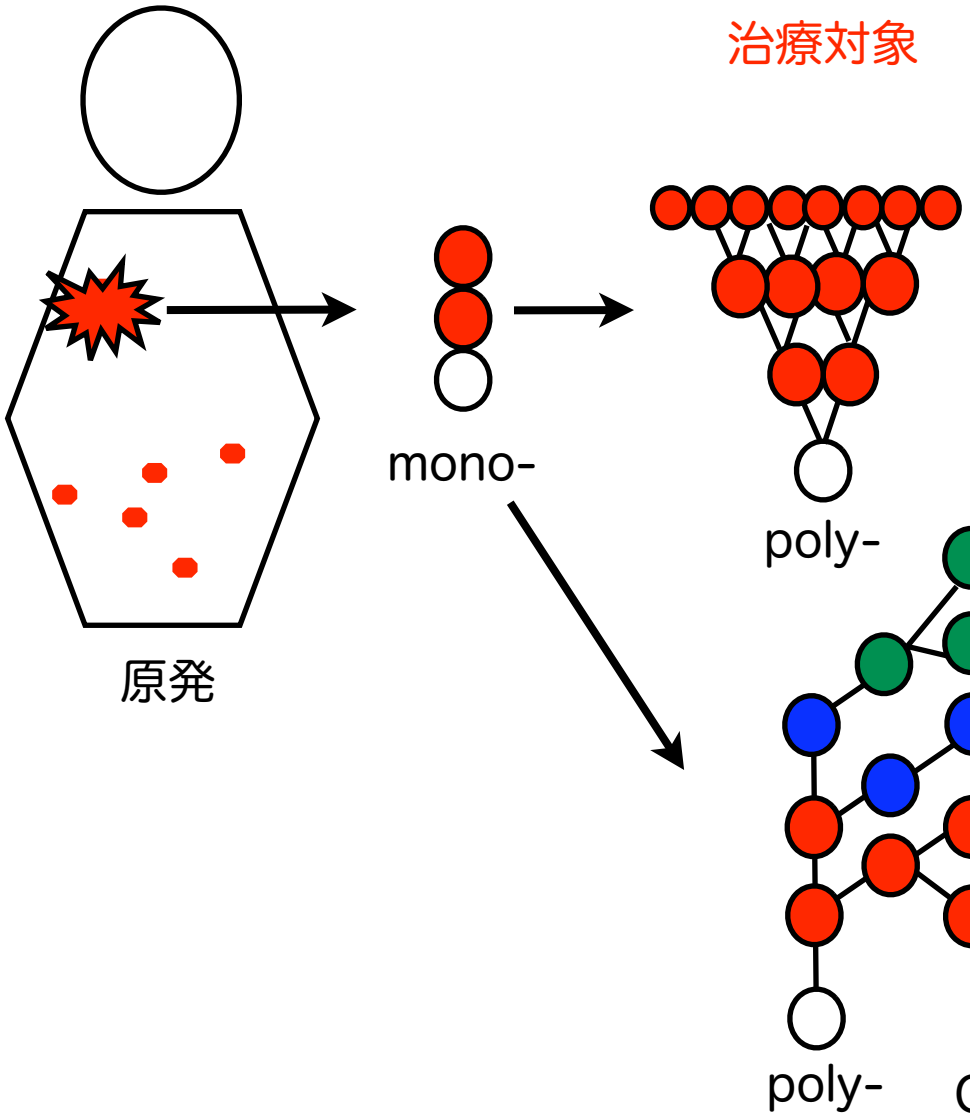


Chang J. Baylor, presented at St.Antonio 2007

→化学療法は主に分化した癌のみを減少させるが、Stem/Progenitorを攻撃することは出来ない？


原発腫瘍
化学療法１
化学療法２
pCR
＋
再発のseed
→stem cell??
ホルモン
療法
ホルモン
療法？
non-pCR
分子標的＋
化学療法１
分子標的＋
化学療法２
pCR
true-pCR

乳癌のclonality



対称性分化

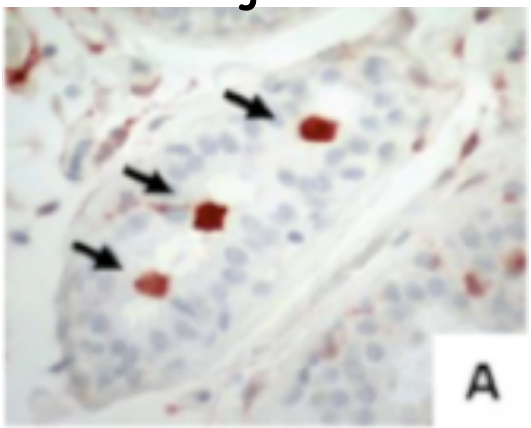
Potentials of
metastasis?
invasion?
Drug-resistance?

非対称性分化

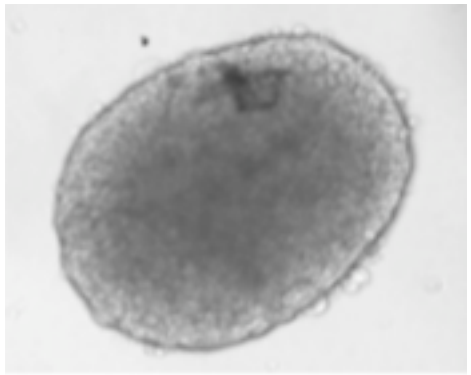
Clarke RB, Cell Prolif. 2005

乳癌幹細胞の同定

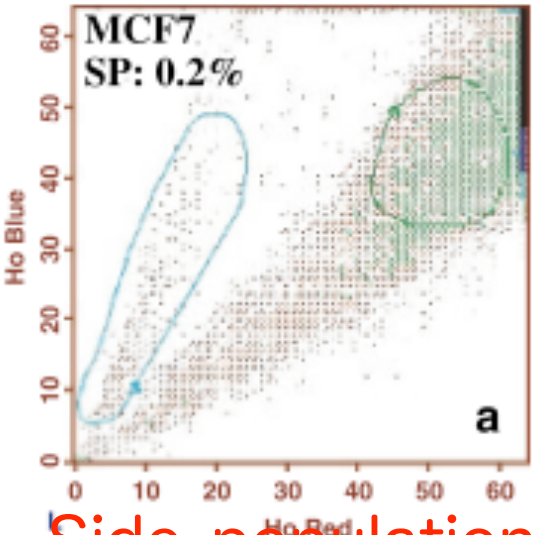
Al-Haji 2003



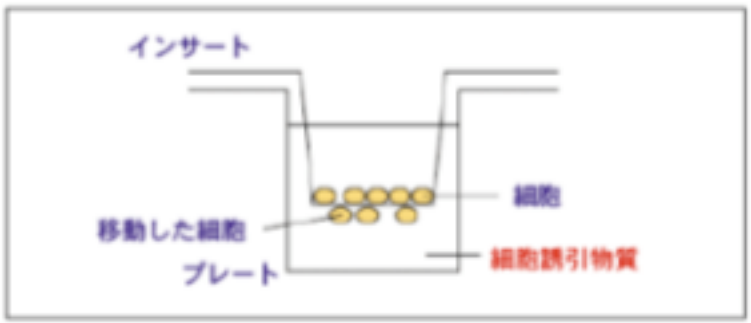
IHC(CD44high/
24low、ALDH1)

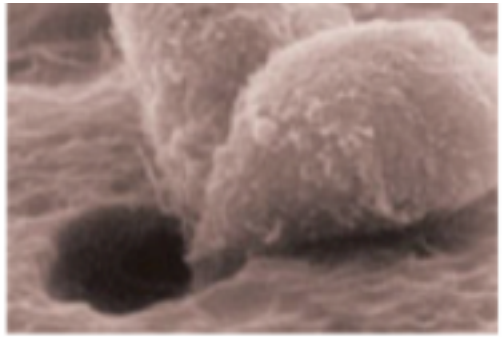


Mammoshpere



Side-population

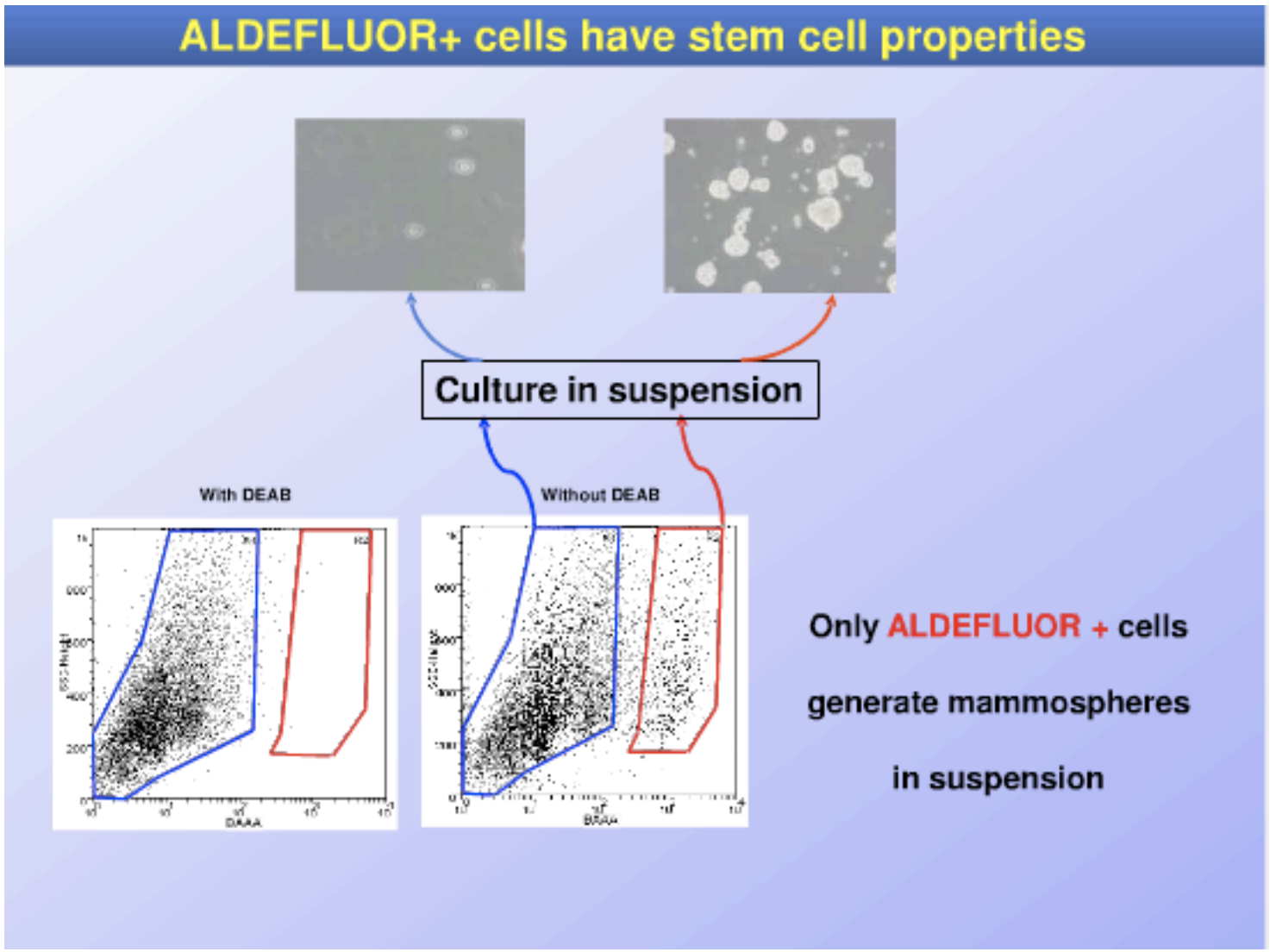




Cell chamberによるMigration

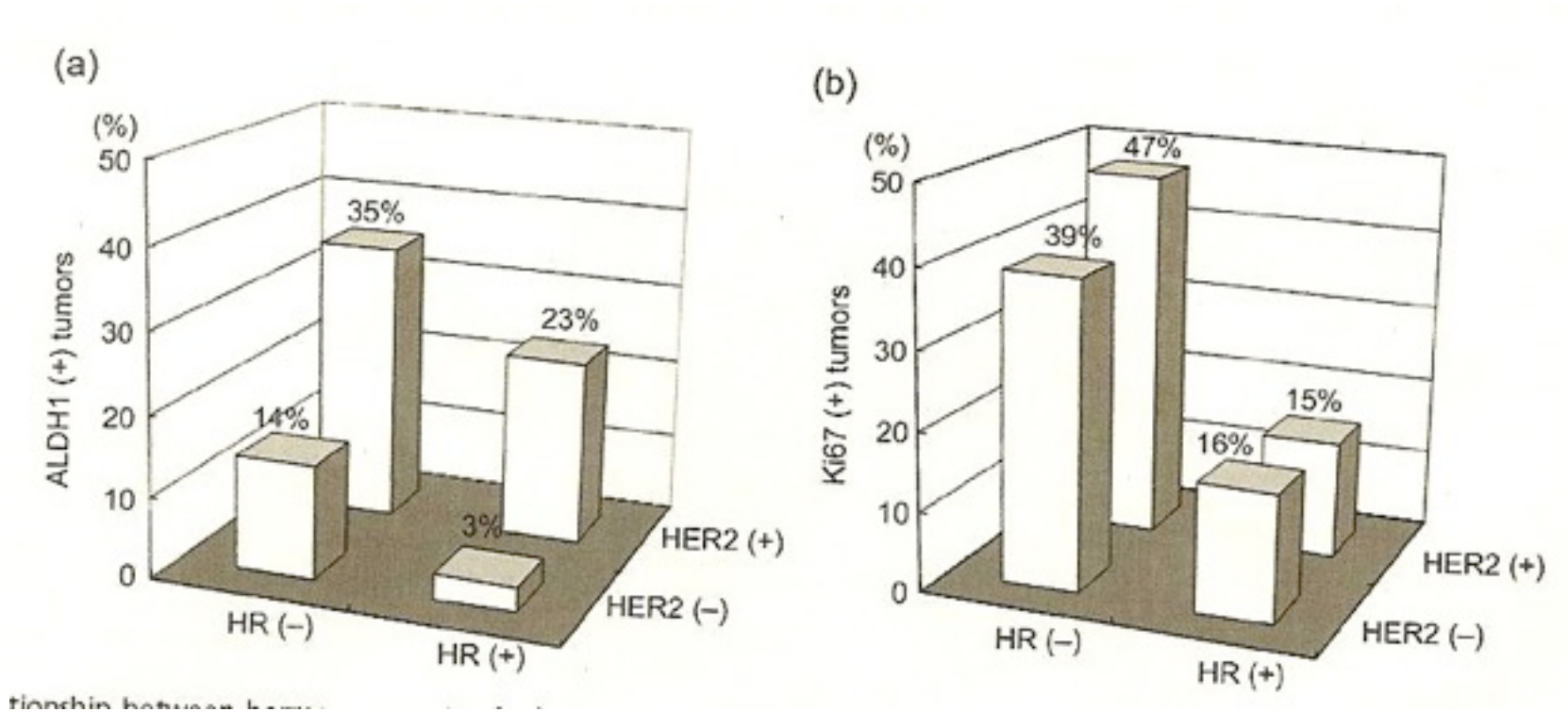
乳癌幹細胞の同定

- Aldehyde Dehydroganase 1(ALDH1) -



分化のheterogeneity

-ALDH1とER/HER2/Ki67-

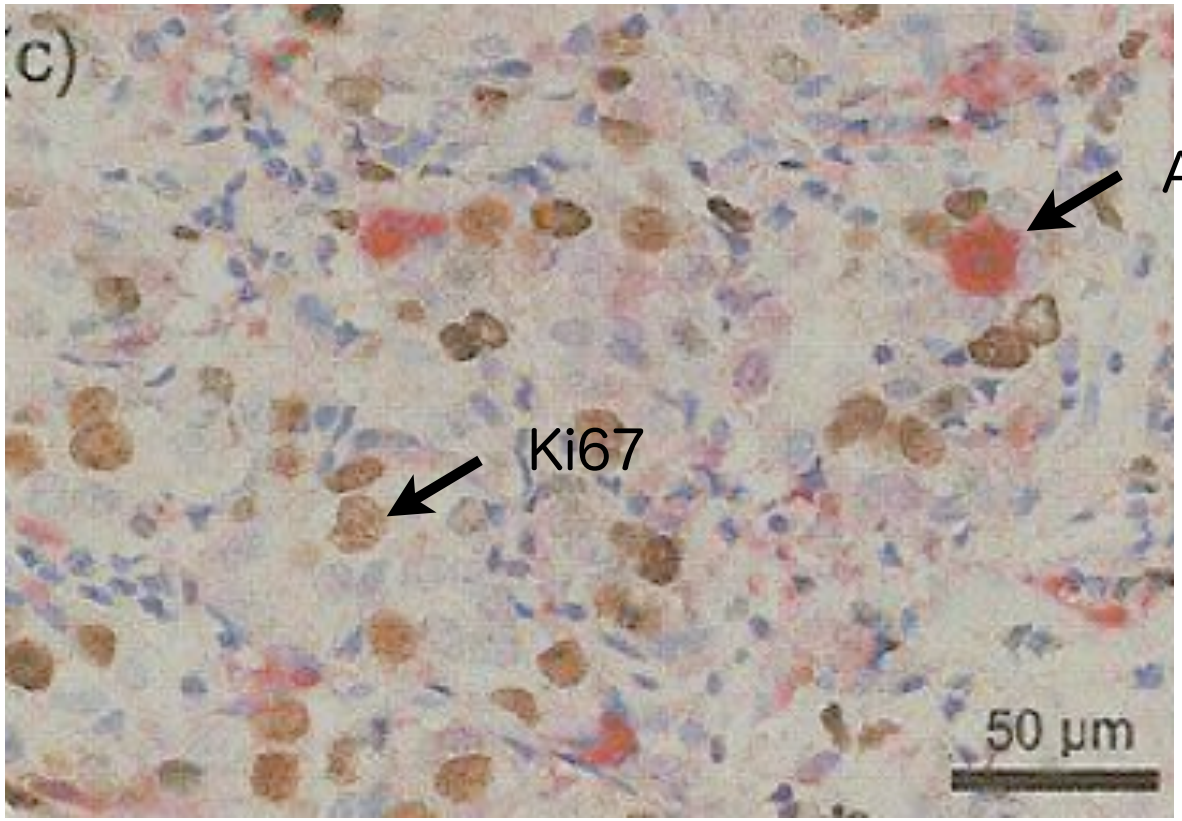


乳癌幹細胞はトリプルネガティブ→HER2陽性→ホルモン感受性へと変化する？

Morimoto N et al. Cancer Sci. 100(6) 1062-68,2009

分化のheterogeneity

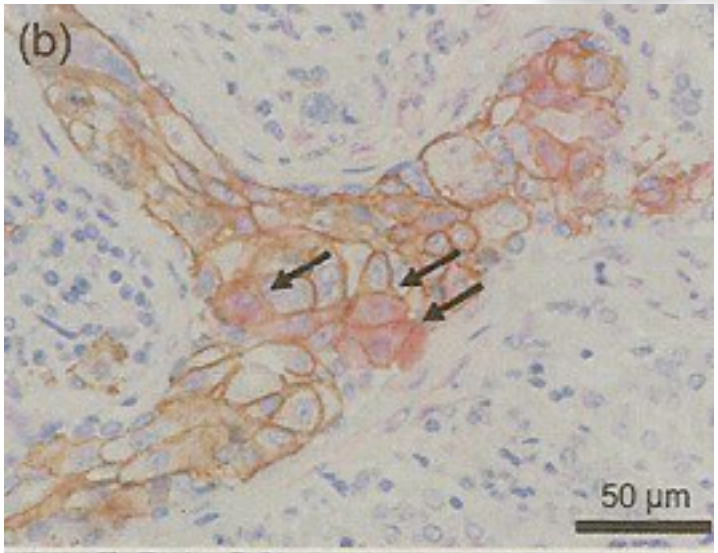
- ALDH1とKi67 -

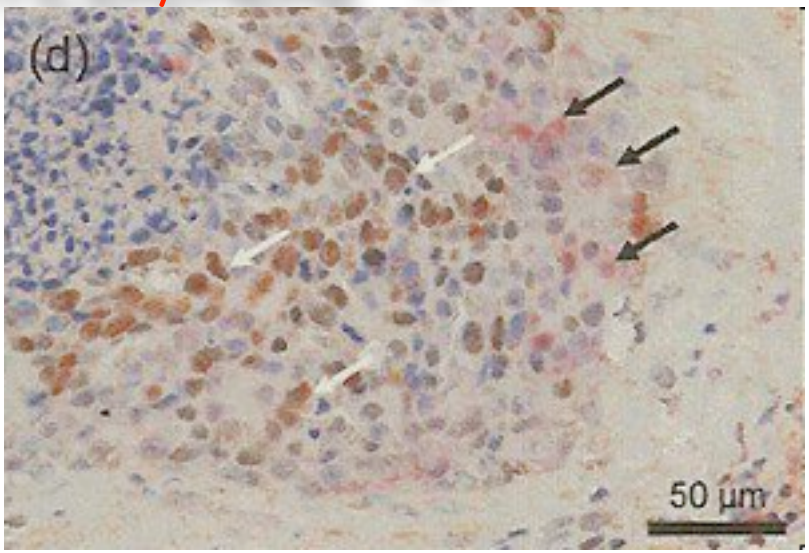


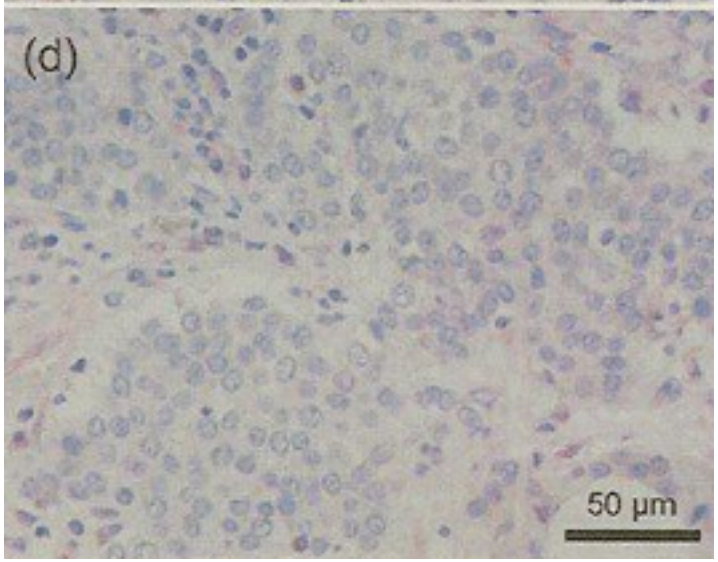
Morimoto N et al. Cancer Sci. 100(6) 1062-68,2009

分化のheterogeneity

- ALDH1とER/HER2 -







HER2+/ALDH1 | ER+/ALDH1

HER2-/ALDH1

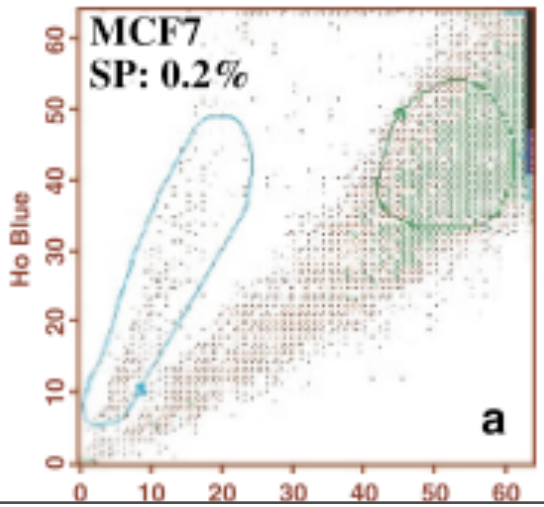
Morimoto N et al. Cancer Sci. 100(6) 1062-68,2009

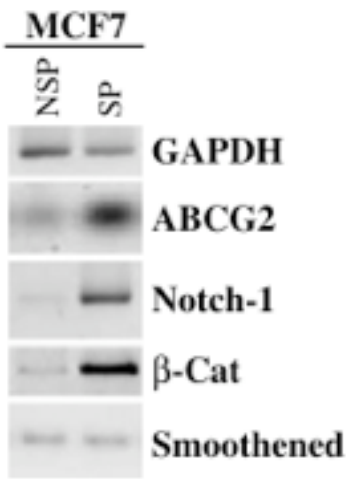
Stem cell research

-検出法による違い-

Cell line	Gene cluster	SP (%)	CD44$^+$/CD24$^-$ (%)	ALDH$^+$ (%)
MCF-7	Lu	0.39 ± 0.15	4.80 ± 0.49	0.33 ± 0.19
MCF-7/HER2-18	Lu	3.38 ± 0.27**	7.36 ± 3.03*	1.17 ± 0.27*
MCF-7/TAM1	Lu	0.87 ± 0.27	20.25 ± 0.23**	0.82 ± 0.26*
Ac1/ANAR	Lu	6.00 ± 0.39**	0.875 ± 0.8	0.45 ± 0.07
MDA-MBA-468	Ba	0.00 ± 0.00	0.29 ± 0.17	7.56 ± 1.26
MDA-MB-231	Bb	0.00 ± 0.00	80.3 ± 3.86	4.42 ± 0.34
GCC-BC4	Lu-like	2.02 ± 0.95	1.68 ± 0.94	1.02 ± 0.36

Nakanishi T et al Br. J of Cancer 102(5), 815 – 826, 2010

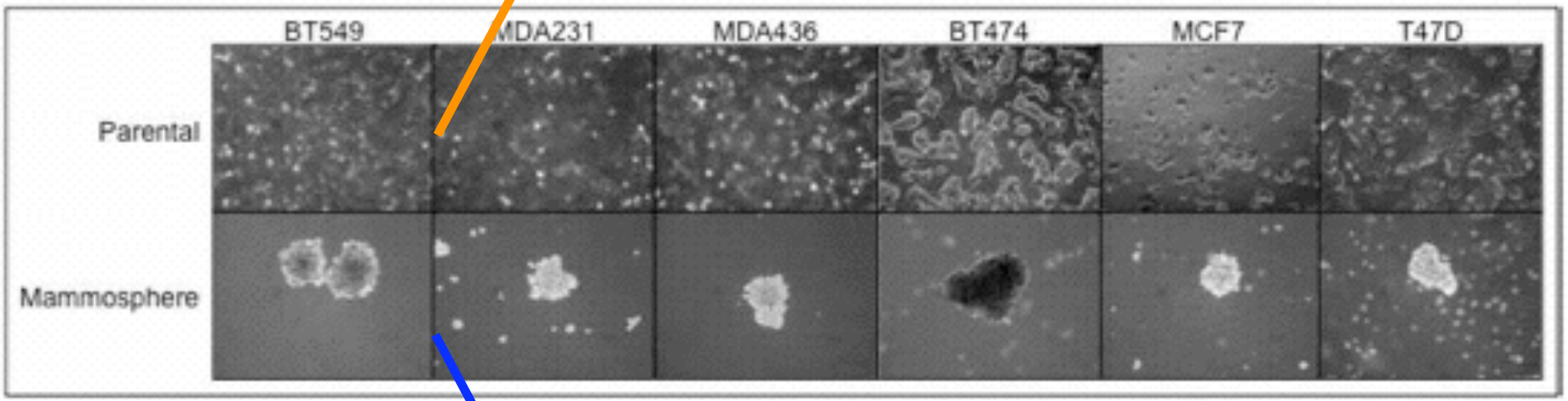




Patrawala et al. Cancer Res 2005; 65: (14), 2005

Stem cell research
- Breast Cancer Stem in Cell Lines -

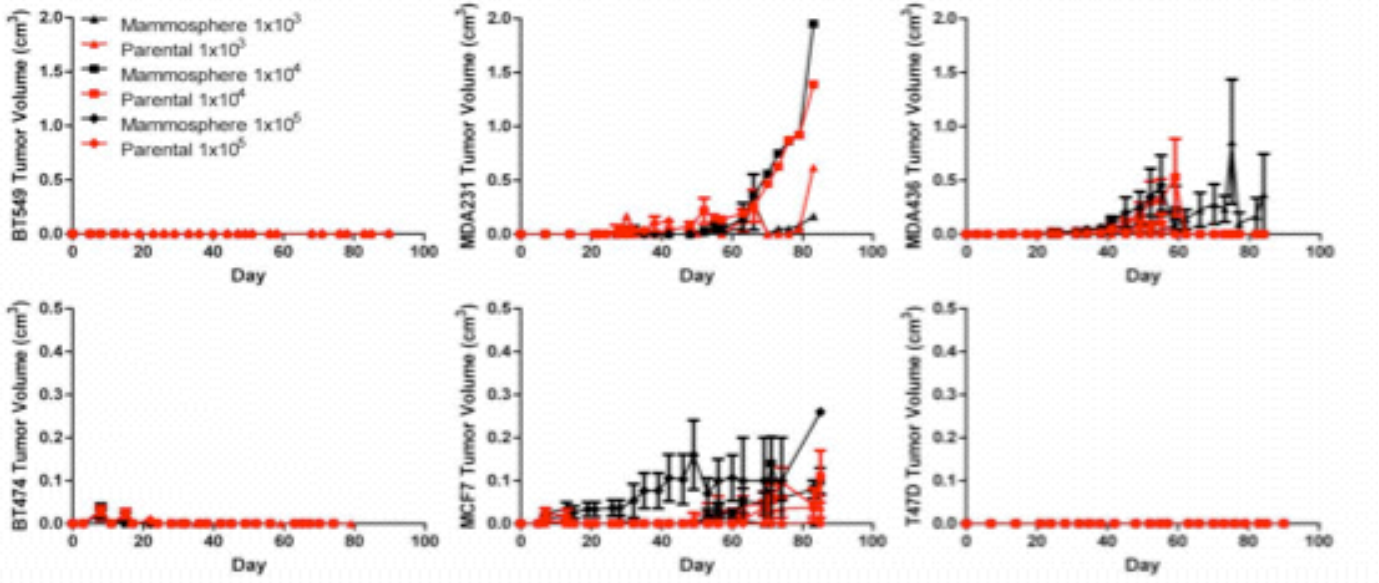
Differentiated cells, Lower self renewal→Tumorigenesity↓



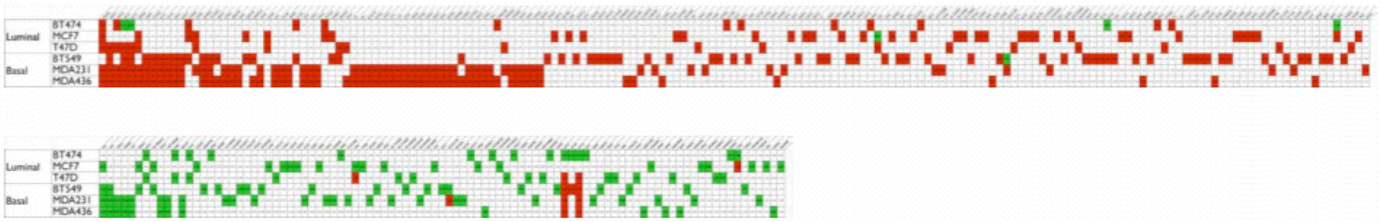
Basal (BT549, MDA231, MDA436) and luminal (BT474, MCF7, T47D) breast cancer cell lines were cultured as monolayers (top panel) in standard media or as mammospheres (bottom panel) in non-adherent sphere forming media. Cultures were maintained for seven days and imaged using a bright field microscope equipped with an Olympus digital camera.

Multipotent cells,Higher self renewal→Tumorigenesity↑

SABCS2009 #502



SCIDマウスでの腫瘍増殖能は親株とMMS細胞で変わらない



遺伝子プロファイルでも変わらない

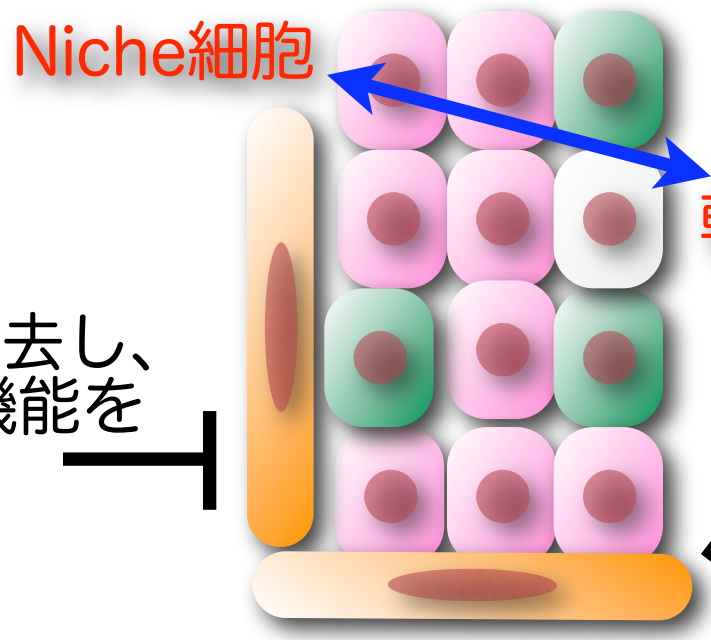
“Mammosphere Culture of Established Cell Lines does not enrich for a more Tumorigenic Breast Cancer Stem Cell Population.”

SABCS2009 #502

幹細胞への治療戦略

-造血幹細胞をモデルとして-

幹細胞Niche細胞の相互作用により
細胞周期を静止期にして治療抵抗性



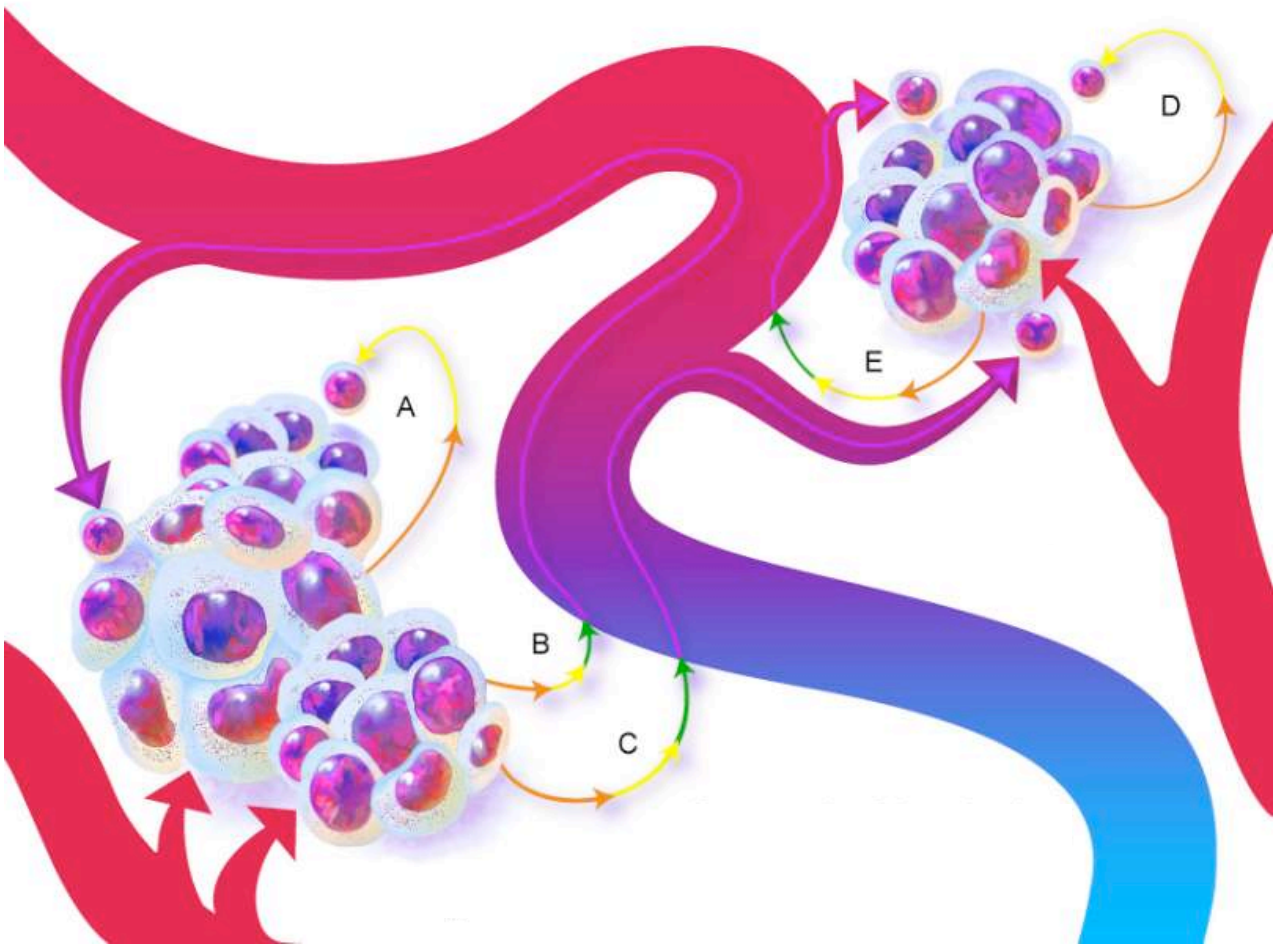
幹細胞の細胞内シグナルを阻害、自己複製を制御

Nicheを除去し、幹細胞の機能を制御

静止期の維持等の薬剤耐性機構を破壊、感受性の変化を誘導

腫瘍増殖・転移のダイナミクス

-Self-seeding?-



Norton, Massagué: Nature Med 2006

DTC(Disseminated-tumor cell)
-予後因子-

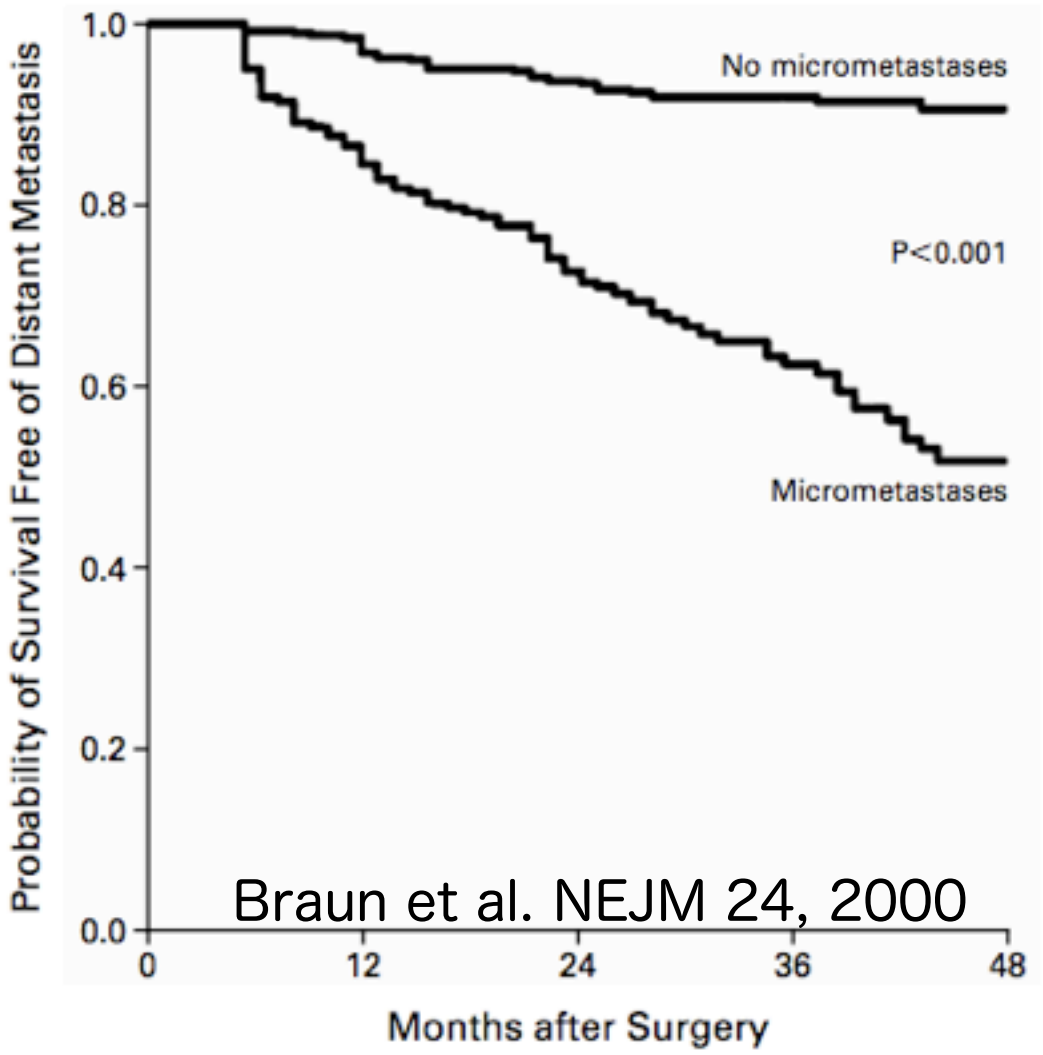
- 228例の術後無再発患者（術後21.3ヶ月後：中央値）の骨髄中癌細胞をretrospectiveに検討
  - 陽性率12.7%
  - 無再発生存（149.7M vs 86.5M p=0.0003）、全生存（162.1M vs 98.7M, p=0.0008）で有意にDTC陽性が不良

Janni W et al. Cancer 103(5):884-91, 2005

- 817例の原発患者の骨髄中癌細胞をprospectiveに検討
  - 陽性率13.2%
  - 再発（13.7% vs 31.7%, p<0.001）、乳癌死亡（10.9% vs 26.9%, p<0.001）で有意にDTC陽性が不良

Wiedswang G et al. J Clin Oncol 15;21(18): 3469-78, 2003

DTC(Disseminated-tumor cell)
-予後因子-



値)

良

2005

に検

vs

1(18):

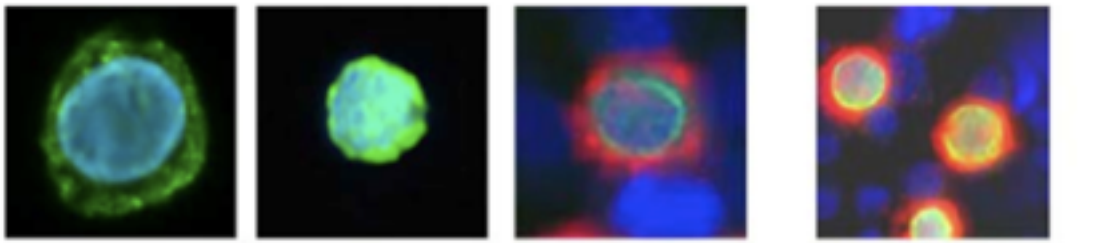
乳癌全身病説の現実
-原発以外の腫瘍の存在-

- 137例の原発乳癌患者の骨髄中癌細胞(DTC)を検討
  - 陽性率34%
  - 内20例でHER2陽性が検出
  - 12/20(60%)は原発陰性でDTCがHER2陽転

Erich F et al. Breast Cancer Research and Treatment 98: 179–184, 2006

- 24例の再発患者の血液循環腫瘍(CTC)を検討
  - 9/24（37.5%）が原発HER2陰性でCTC陽転
  - 4人がTrastuzumab治療、3/4(CR1, PR2) 奏効率75%

Meng S et al. PNAS 9393-9398, 2004



Only CK-positive cells

CK / HER positive and CK-positive / HER2 negative

Only CK / HER2 positive cells

原発と転移巣でのHER2発現の変化
-転移巣からの生検-

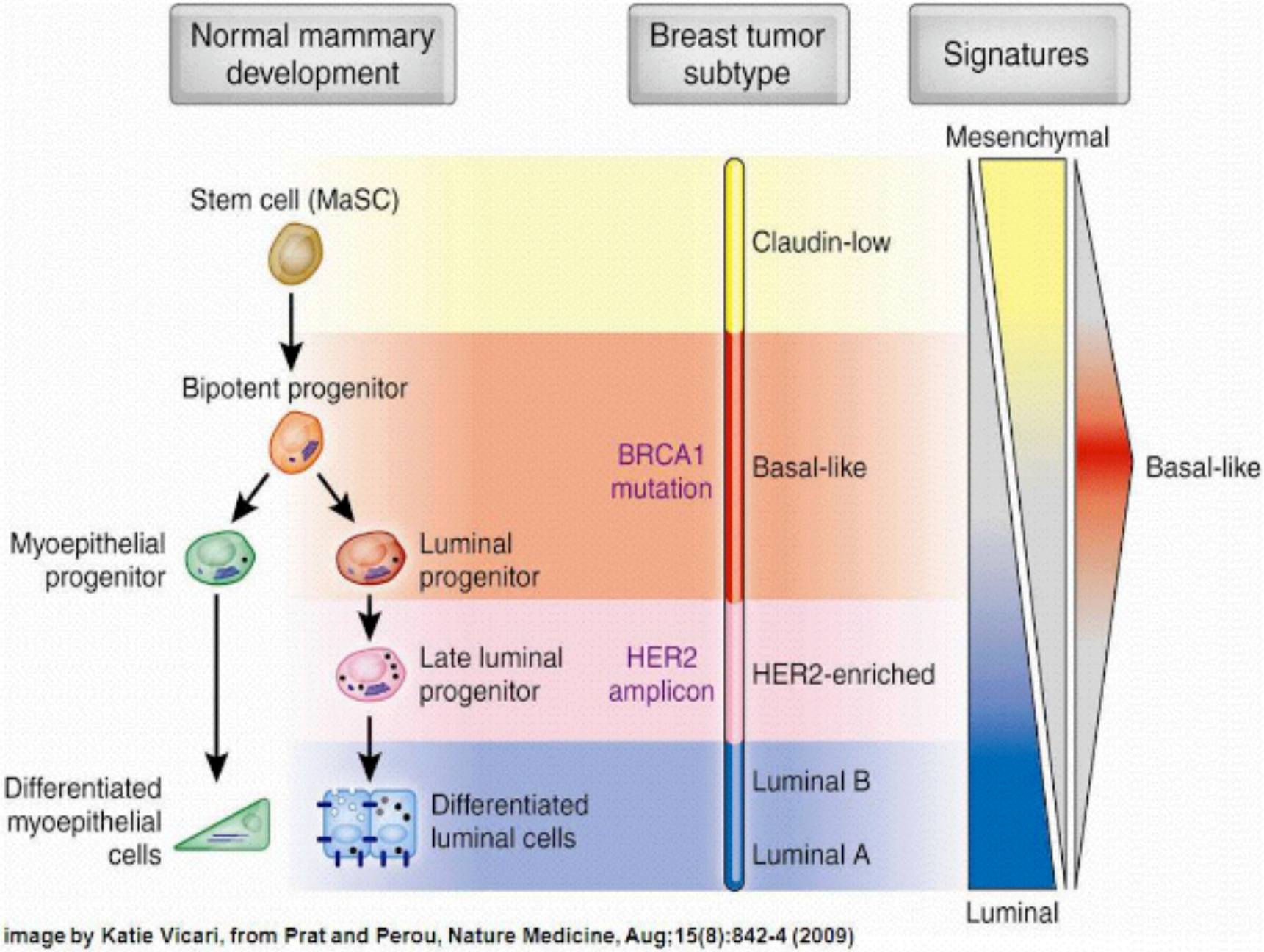
- n=69
- 採取可能であった転移・再発症例のHER2の発現を検討
- 12%が原発-転移巣間でHER2発現の変化

75%: 陰性→陽性

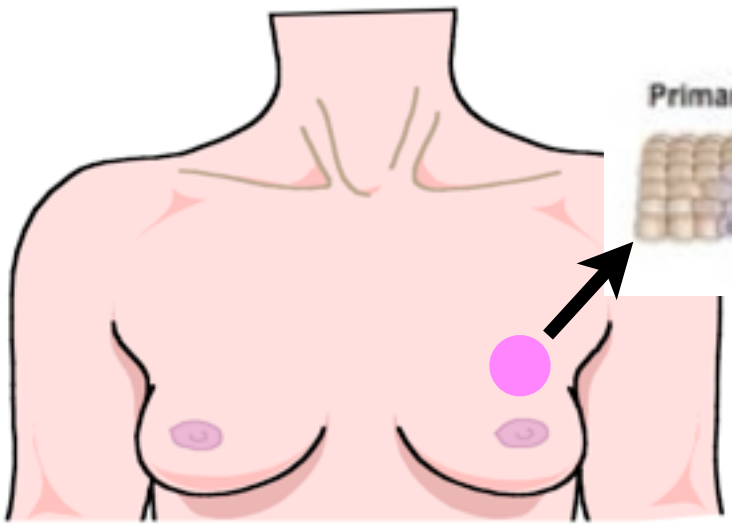
25%: 陽性→陰性

		転移巣	
		HER2＋	HER2−
原発	HER2＋	7	2
	HER2−	6	54

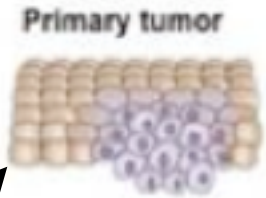
Thery et al. ASCO 2008


Normal mammary development
Breast tumor subtype
Signatures
Mesenchymal
Stem cell (MaSC)
Claudin-low
Bipotent progenitor
BRCA1 mutation
Basal-like
Basal-like
Myoepithelial progenitor
Luminal progenitor
Late luminal progenitor
HER2 amplicon
HER2-enriched
Differentiated myoepithelial cells
Differentiated luminal cells
Luminal B
Luminal A
Luminal
image by Katie Vicari, from Prat and Perou, Nature Medicine, Aug;15(8):842-4 (2009)

腫瘍の局在と標的



CD44+24+



Self-seeding

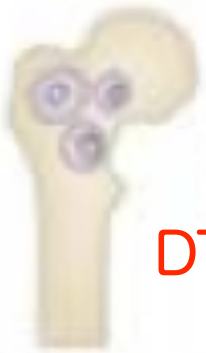
TGF β
Hh
Wnt
Oct-4

Homing?

EMT(Epithelial-mesenchymal transition)

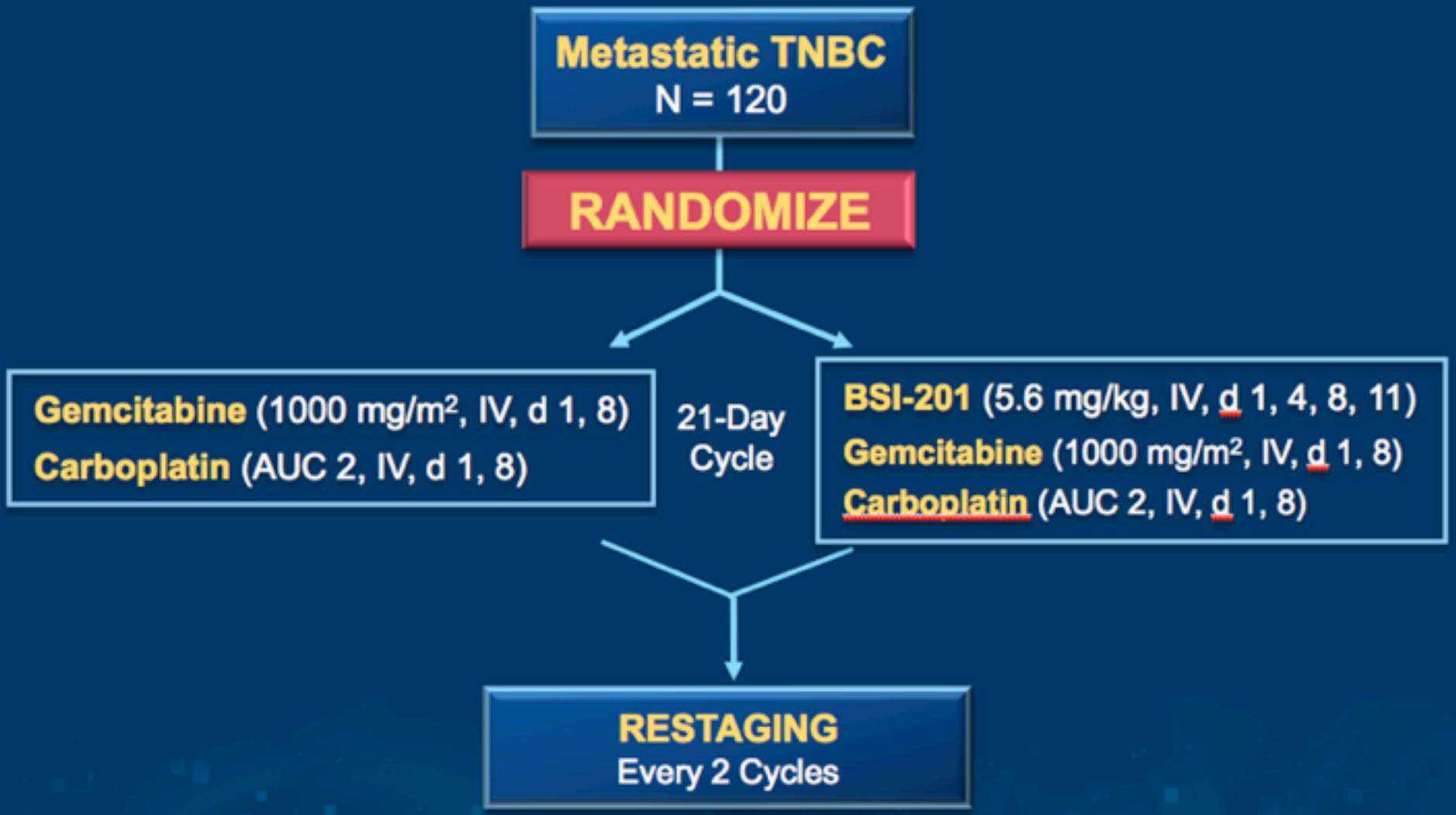
CTC

CD44+24-
ADLH1
ABCG/MRD
Sphere



DTC(niche?)

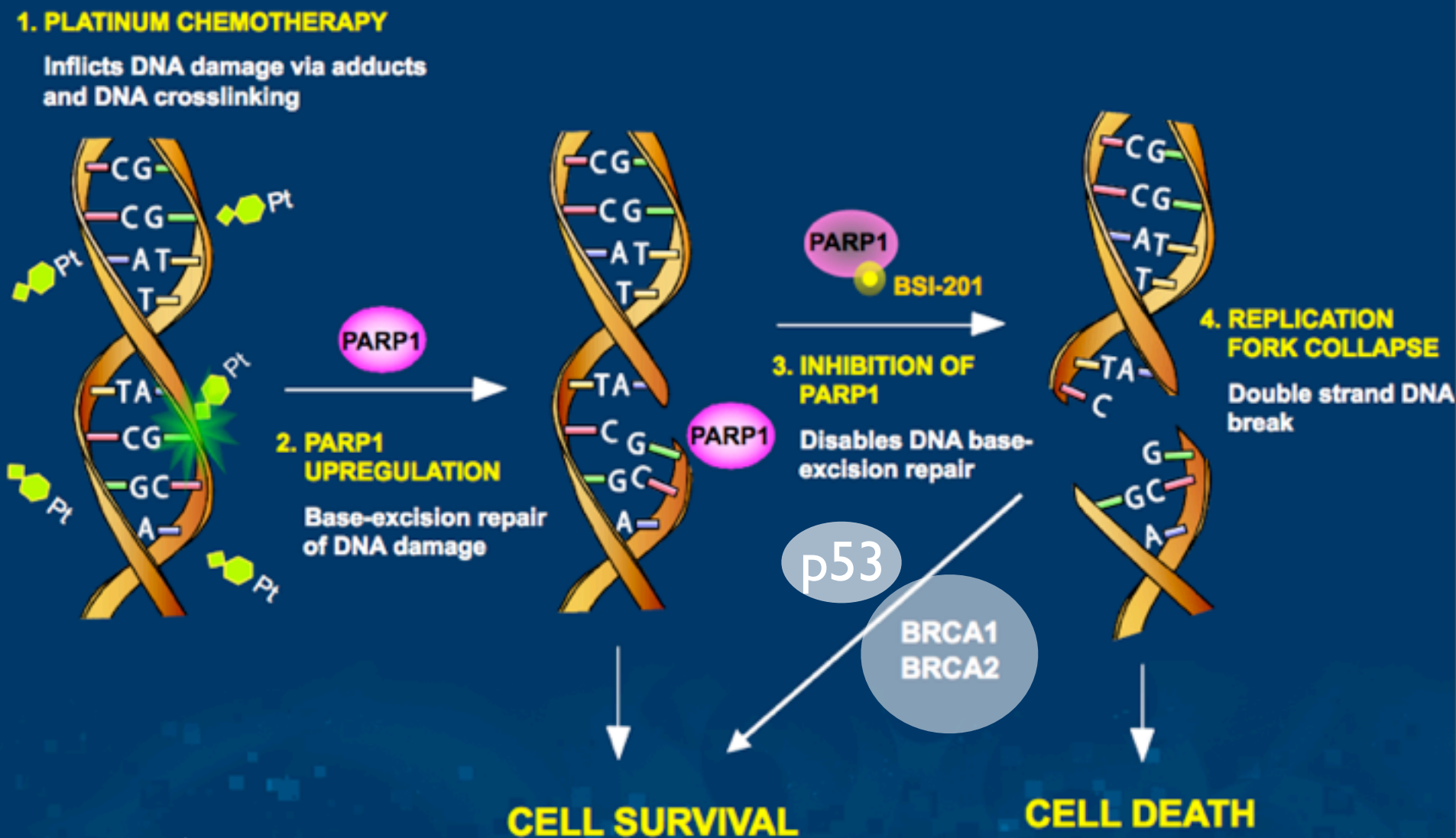
Phase II TNBC Study: Treatment Schema



ASCO Annual '09 Meeting

* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

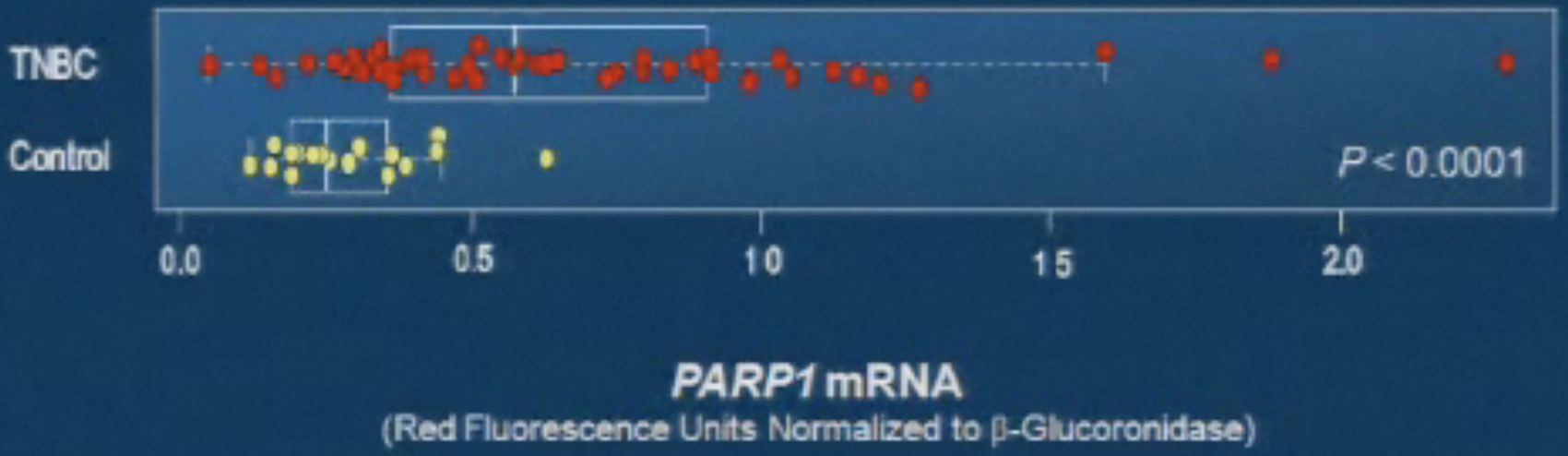
PARP Inhibitor Mechanism of Action



ASCO | Annual '09 Meeting

PARP1 is Upregulated in TNBC

Gene expression profiling showed that *PARP1* was significantly upregulated in the majority of triple negative breast cancers (n = 50)



Phase II TNBC trial

	n	ORR(%)	CBR(%)	PFS(M)	OS(M)
BSI-201/ Gem/ Carbo	42	48	62	6.9	9.2
Gem/ Carbo	44	16	21	3.3	5.7

1.癌の基礎研究から弱点を発見し、標的にした

2.治療によるコンディショニングにより誘導可？

Yes... We are about to witness a revolution!

... 2012!

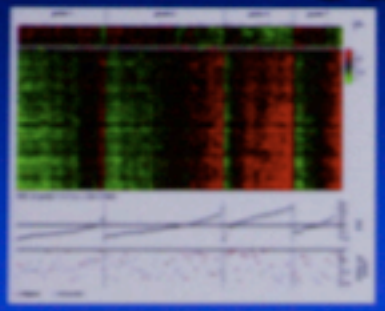
Courtesy of Cordon-Cardo C. ECCO 13

Requires huge “NASA type ” Collaborative effort!

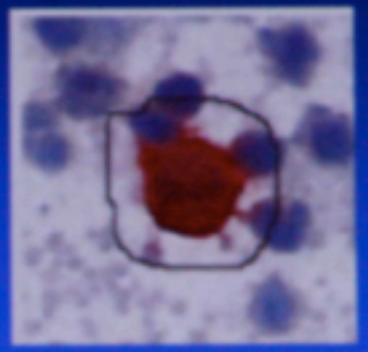
Piccart SABCS2009

THE NEO-BIG PROGRAM 2009-2010

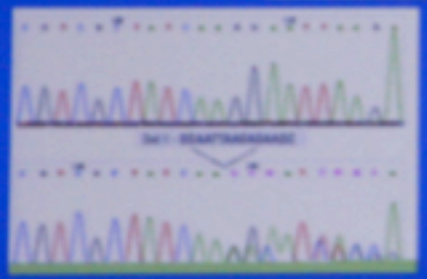
Cutting-edge technologies



Genomics

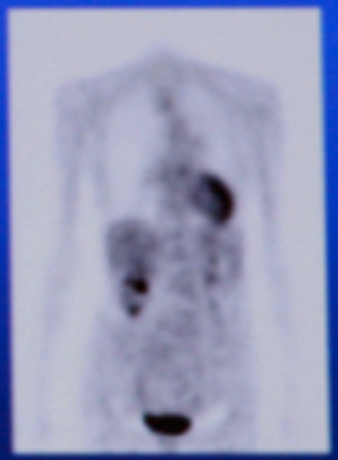


Circulating Tumor Cells

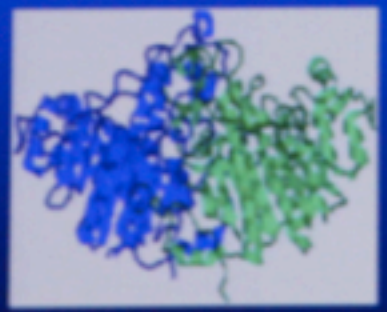


Genetics

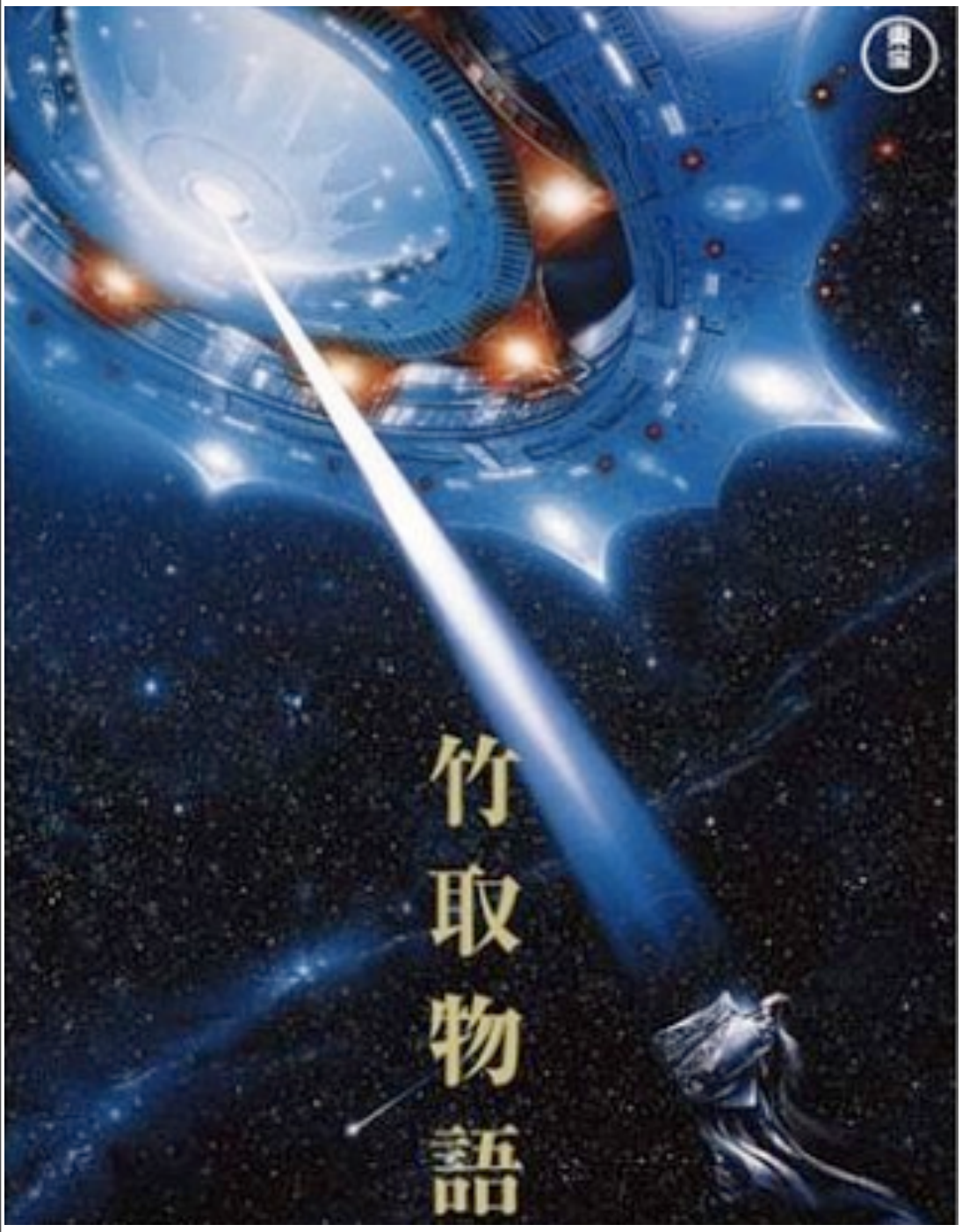
The NEOBIG platform



Modern imaging



Proteomics/metabolomics



夢と基礎体力を
持ったプラット
フォームでの臨床
試験の推進…

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ございました