Touch-Ten *Medical Conference* –

**2018年 9月 20日(木)**

# これからのTriple-Negative Breast Cancer (TNBC) 治療

圭友会　浜松オンコロジーセンター
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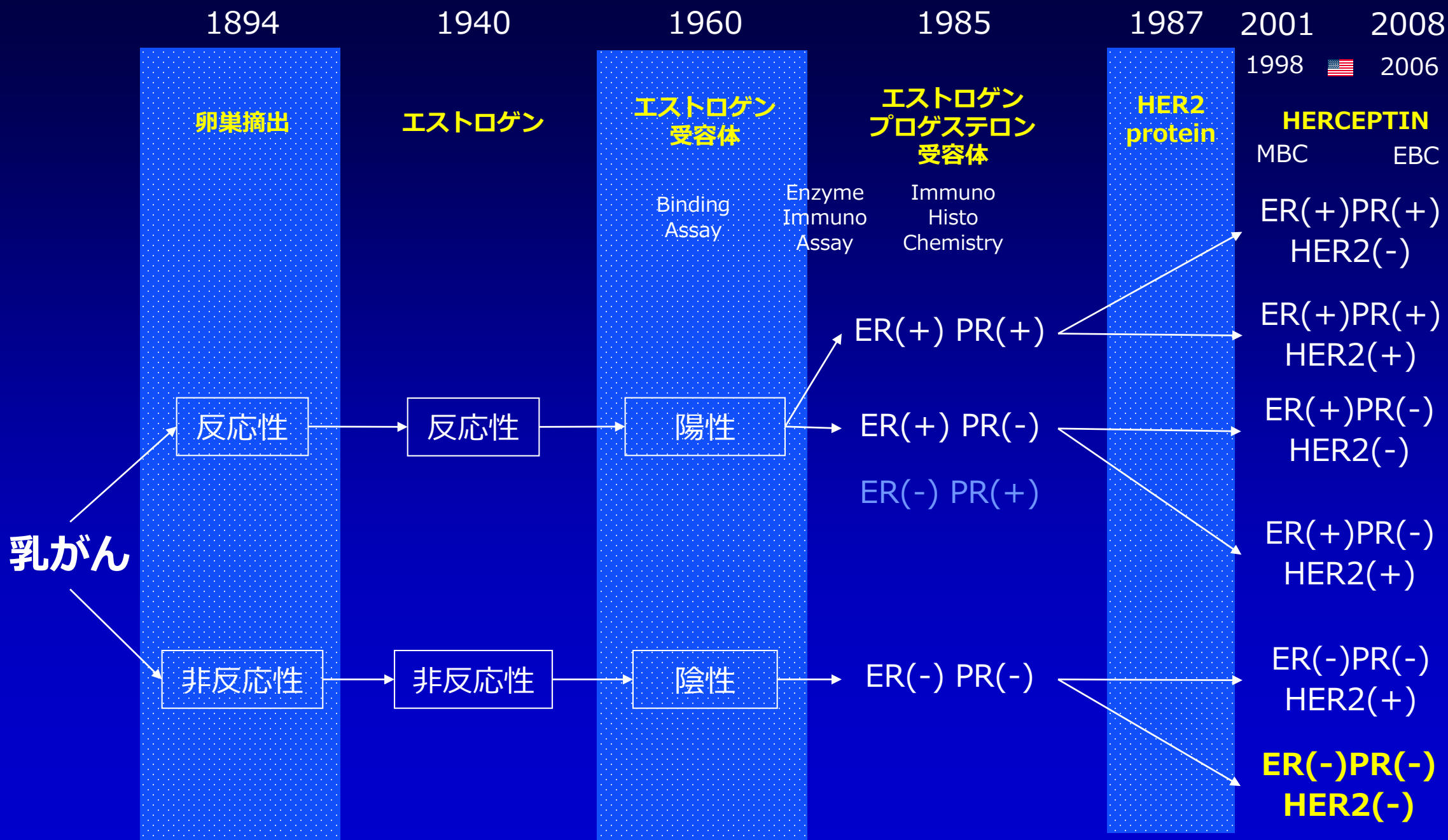
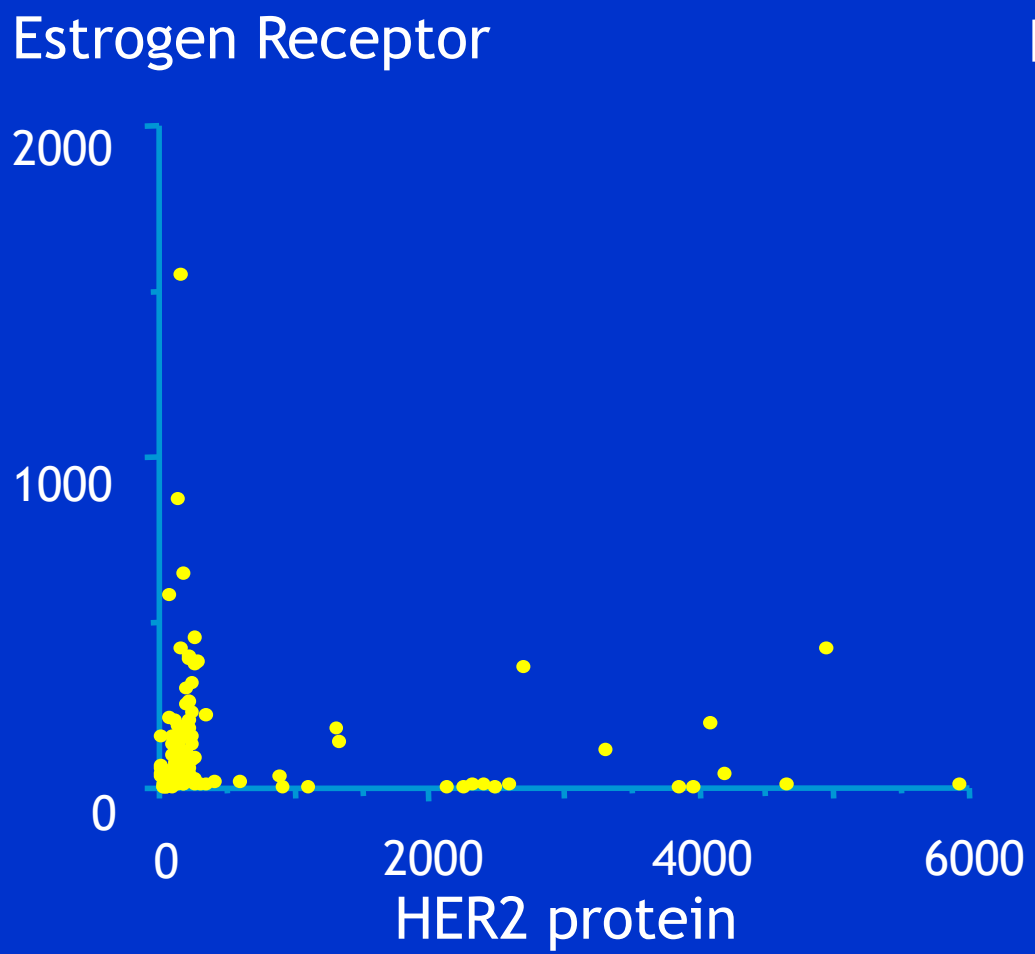
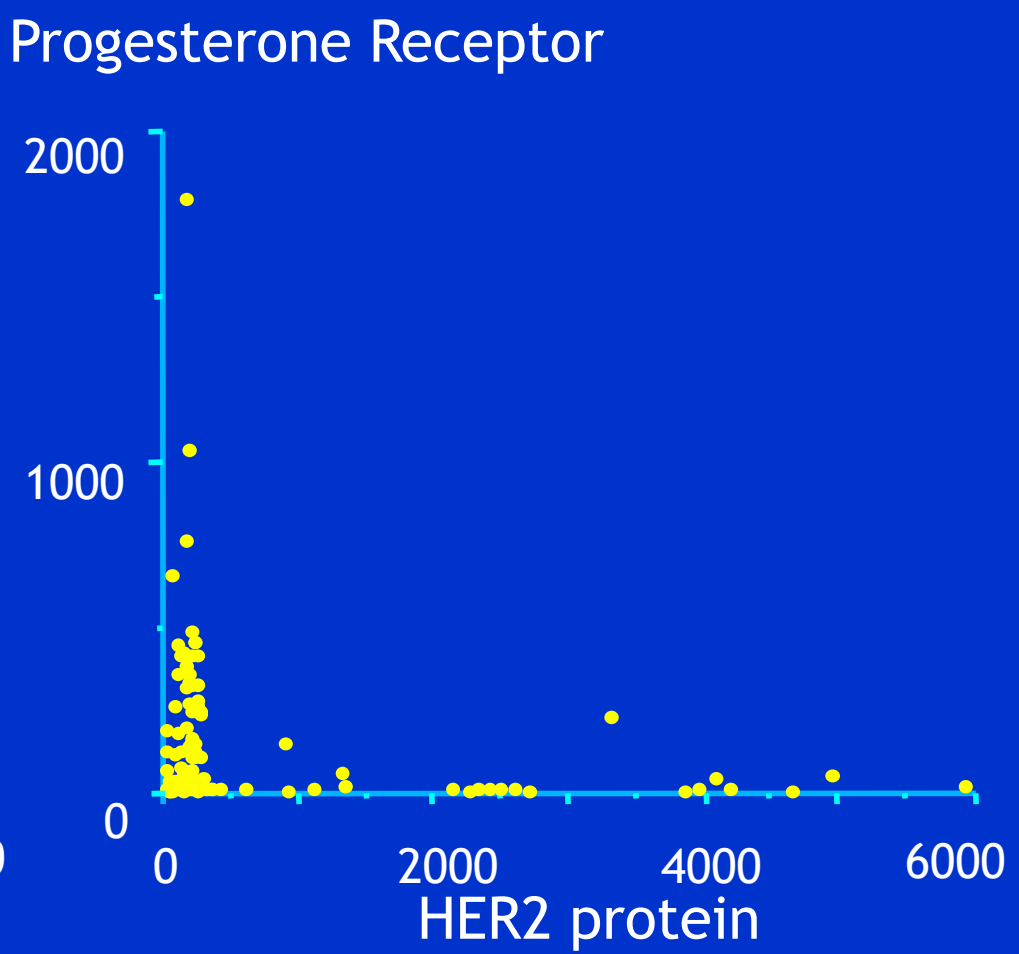
# Triple Negative Breast Cancerという言葉（概念）はいつごろできたのか？



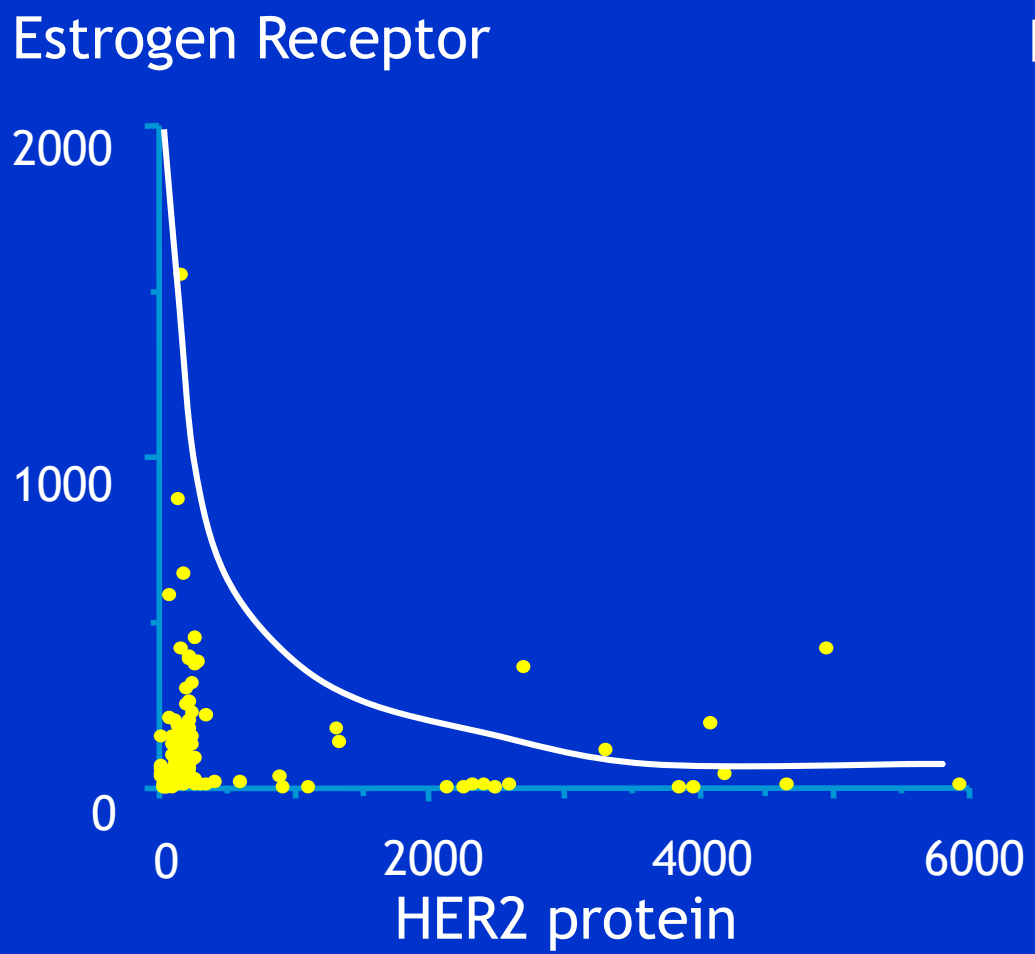
# Relationship between Hormone Receptors and HER2 Protein Content in Breast Cancer Tissues

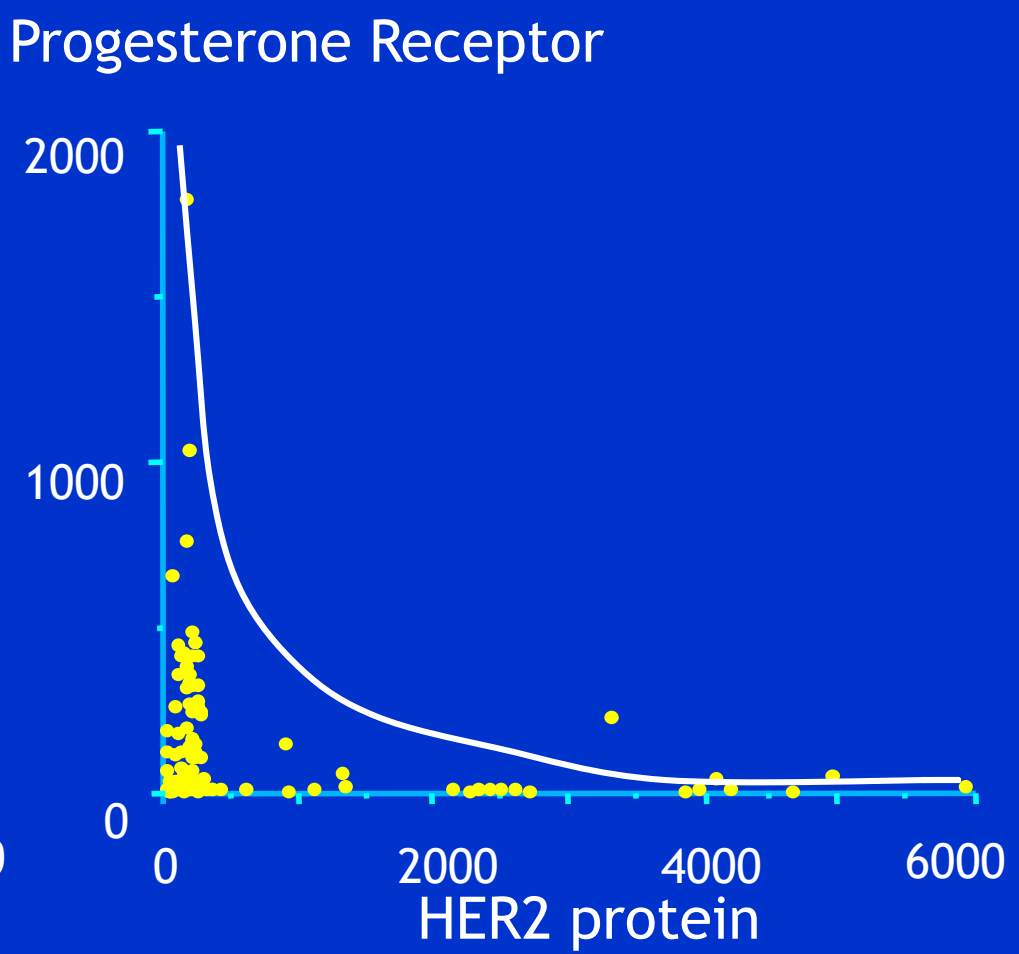



Watanabe T et al. Japanese Journal of Cancer Research 1993;84:1279-86.

# Relationship between Hormone Receptors and HER2 Protein Content in Breast Cancer Tissues




Watanabe T et al. Japanese Journal of Cancer Research 1993;84:1279-86.

# Breast Cancer Patient Subsets

352 female Operated Patients at NCCH in 1999

| | HER2 (IHC) | | | | | |
|---|---|---|---|---|---|---|
| | 3+ | 2+ | 1+ | 0 | total | |
| ER(+) PgR(+) | 11 | 28 | 12 | 64 | 115 | |
| ER(-) PgR(+) | 4 | 3 | 1 | 9 | 17 | 146 |
| ER(+) PgR(-) | 2 | 3 | 2 | 7 | 14 | |
| ER(-) PgR(-) | 22 | 5 | 2 | 16 | 45 | |
| | 39 | 39 | 17 | 96 | 191 | |

# ER(-) PgR(-) HER2 (-)

我々はこのような乳がんを「つるつる乳がん」と呼んだ。

そして無理矢理、英語に訳し「 slippery Breast Cancer」として発表したが、
まったく反響がなかった。

どうもこのネーミングがいけなかったらしい。

# Triple Negative Breast Cancerという言葉（概念）はいつごろできたのか？

Triple Negative Breast Cancer

という言葉は2006-2007年頃から

論文で使われはじめました~

VOLUME 24 · NUMBER 36 · DECEMBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Locoregional Relapse and Distant Metastasis in Conservatively Managed Triple Negative Early-Stage Breast Cancer

*Bruce G. Haffty, Qifeng Yang, Michael Reiss, Thomas Kearney, Susan A. Higgins, Joanne Weidhaas, Lyndsay Harris, Willam Hait, and Deborah Toppmeyer*

**Table 2.** Five-Year Outcomes As a Function of Tumor Subtype

| Outcome | Tumor Subtype (%) | | *P* |
|---|---|---|---|
| | Triple Negative | Others | |
| Breast relapse-free rate | 83 | 83 | NS |
| Nodal relapse-free rate | 94 | 99 | .05 |
| Distant metastasis-free rate | 68 | 83 | .002 |
| Cause-specific survival rate | 72 | 85 | .047 |
| Overall survival rate | 80 | 89 | NS |

Abbreviation: NS, not significant.

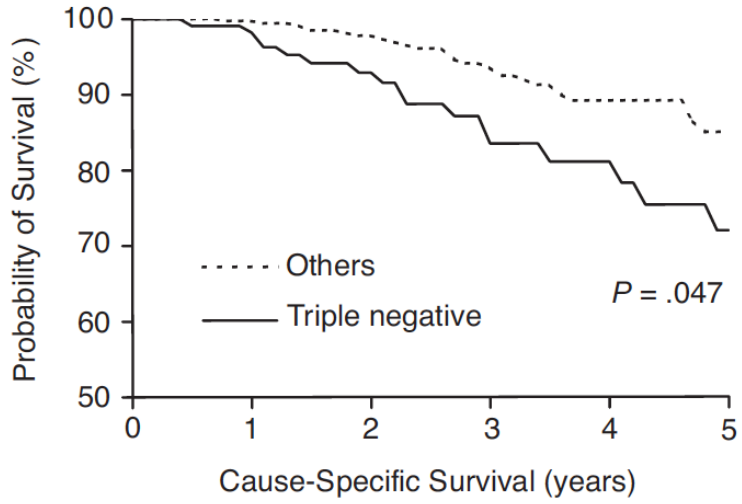



**Fig 2.** Cause-specific survival as a function of subtype.

# Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence

Rebecca Dent,[1] Maureen Trudeau,[1] Kathleen I. Pritchard,[1] Wedad M. Hanna,[1] Harriet K. Kahn,[1] Carol A. Sawka,[1] Lavina A. Lickley,[1] Ellen Rawlinson,[2] Ping Sun,[2] and Steven A. Narod[2]

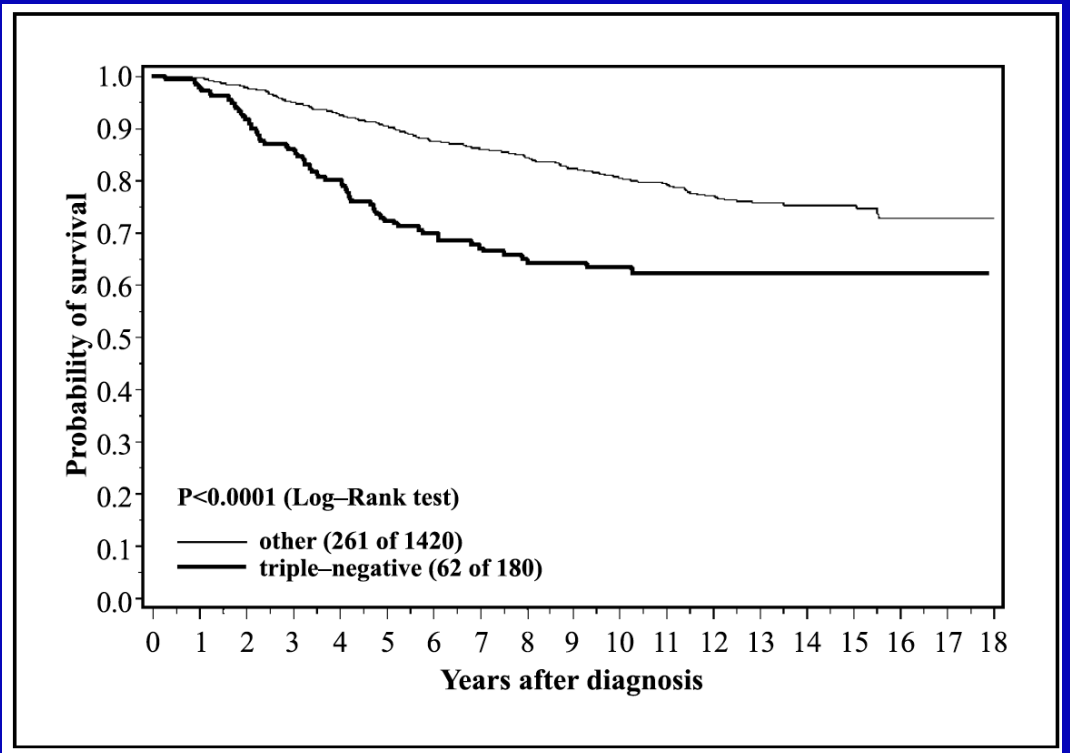



**Fig. 2.** Rates of breast-specific survival in triple-negative and other breast cancers.

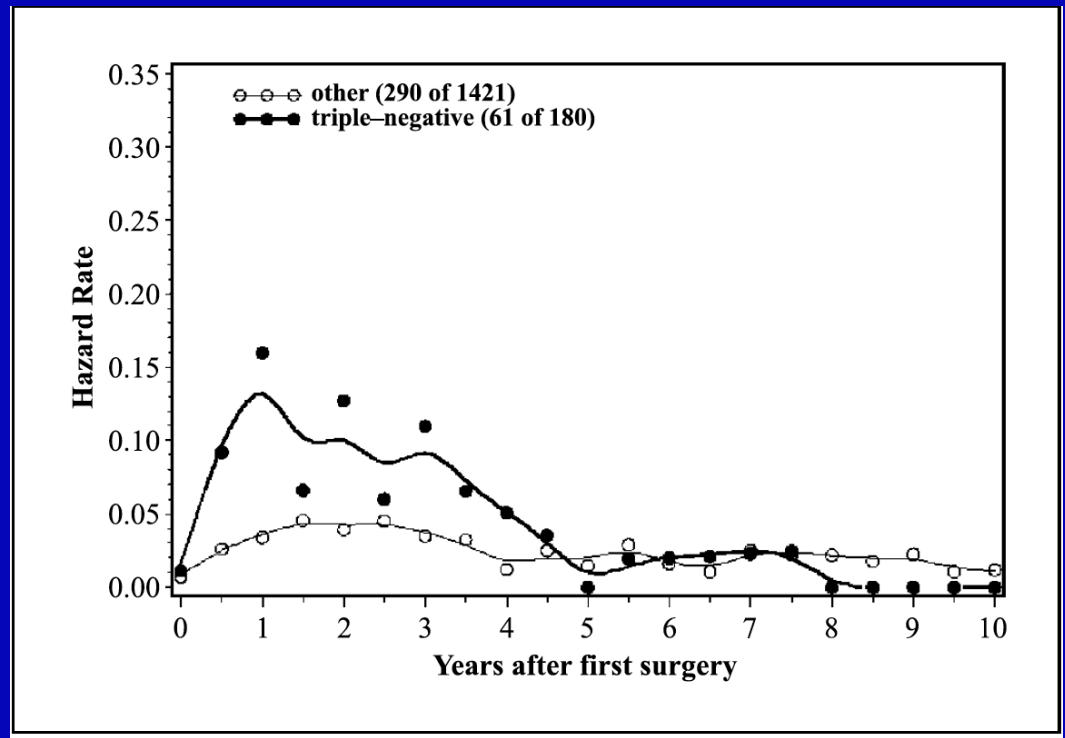



**Fig. 3.** Rates of distant recurrences following surgery in triple-negative and other breast cancers.

Clinical Cancer Research 2007;13:4429-34.

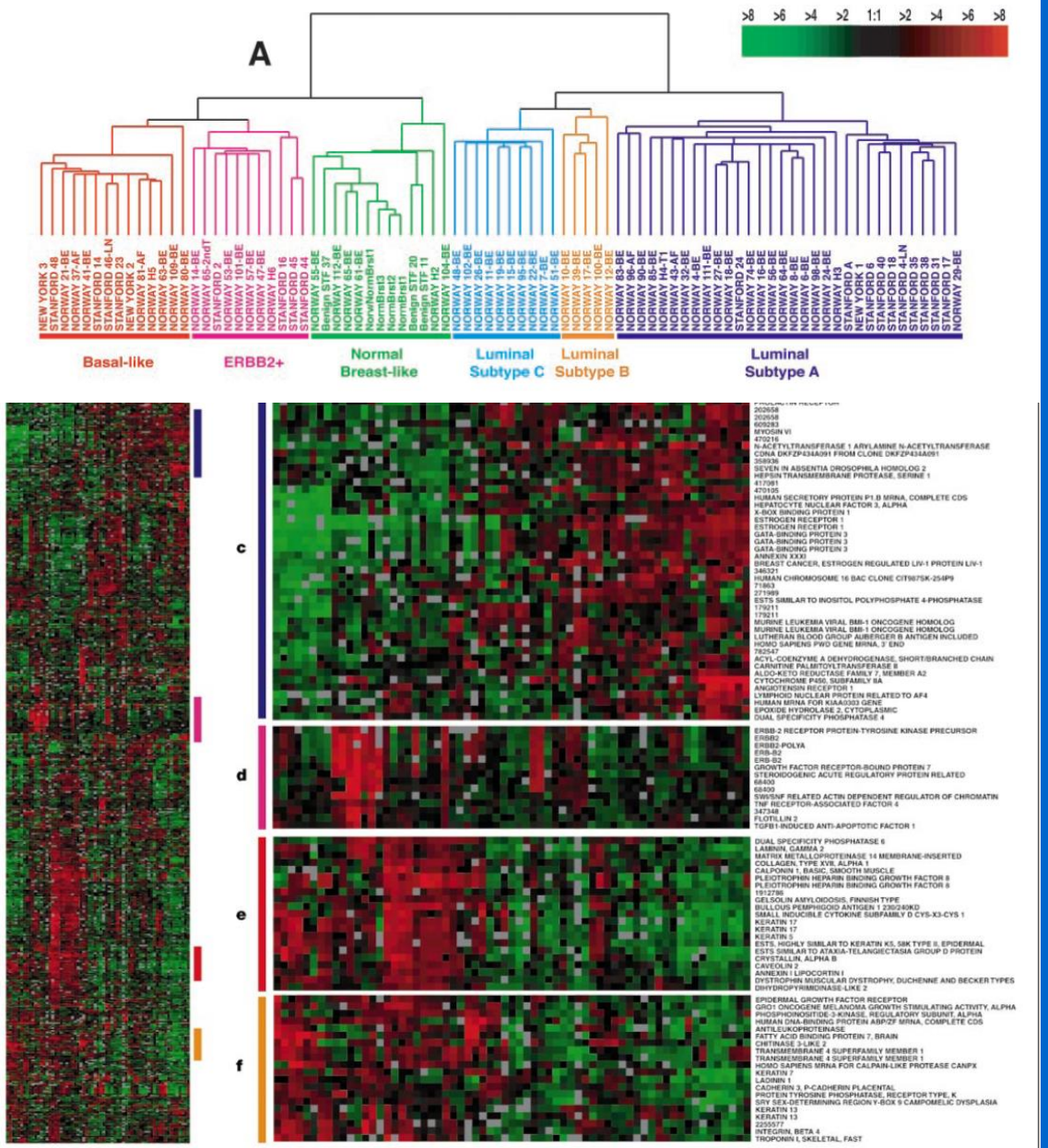



**Figure 3** Cluster analysis using the 'intrinsic' gene subset. Two large branches were apparent in the dendrogram, and within these large branches were smaller branches for which common biological themes could be inferred. Branches are coloured accordingly: basal-like, orange; *Erb-B2*+, pink; normal-breast-like, light green; and luminal epithelial/ER+, dark blue. **a**, Experimental sample associated cluster dendrogram. Small black bars beneath the dendrogram identify the 17 pairs that were matched by this hierarchical clustering; larger green bars identify the positions of the three pairs that were not matched by the clustering. **b**, Scaled-down representation of the intrinsic cluster diagram (see Supplementary Information Fig. 6). **c**, Luminal epithelial/ER gene cluster. **d**, *Erb-B2* overexpression cluster. **e**, Basal epithelial cell associated cluster containing keratins 5 and 17. **f**, A second basal epithelial-cell-enriched gene cluster.

Perou, C. M., et al. (2000). "Molecular portraits of human breast tumours." *Nature* 406(6797): 747-752.

65個の乳がん組織について、8102のヒト遺伝子から構成されるcDNA microarraysを用いて遺伝子発現解析とclaster解析をおこなった。

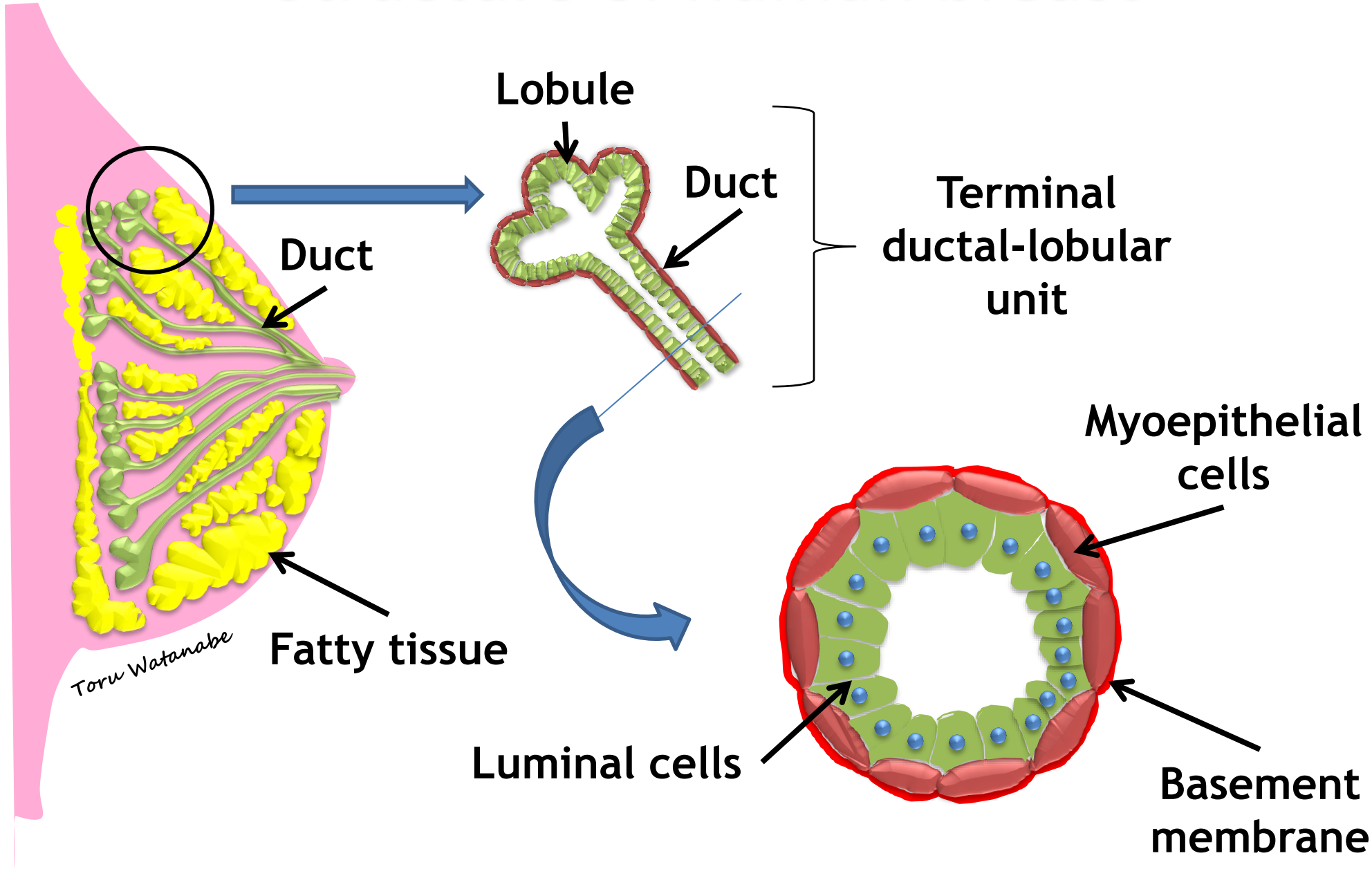
その結果　Luminal subtype A
Luminal subtype B
Luminal subtype C
Normal Breast-like
ERBB2+
Basal-like　　の6つのサブタイプに分類できた。

このような遺伝子発現状況（genotype）の多様性は、メッセンジャーRNAを経てタンパク（酵素、刺激伝達経路など）発現を制御し、がんの様々な生物学的多様性（薬剤感受性、転移・増殖形態など= phenotype ）をもたらすと考えられる。

Phenotypic diversity <<< Diversity of gene expression pattern

# 乳がん治療の選択　1995

# Structure of human breast



# 初期治療選択のための乳がんのサブタイプ分類 St.Gallen 2011

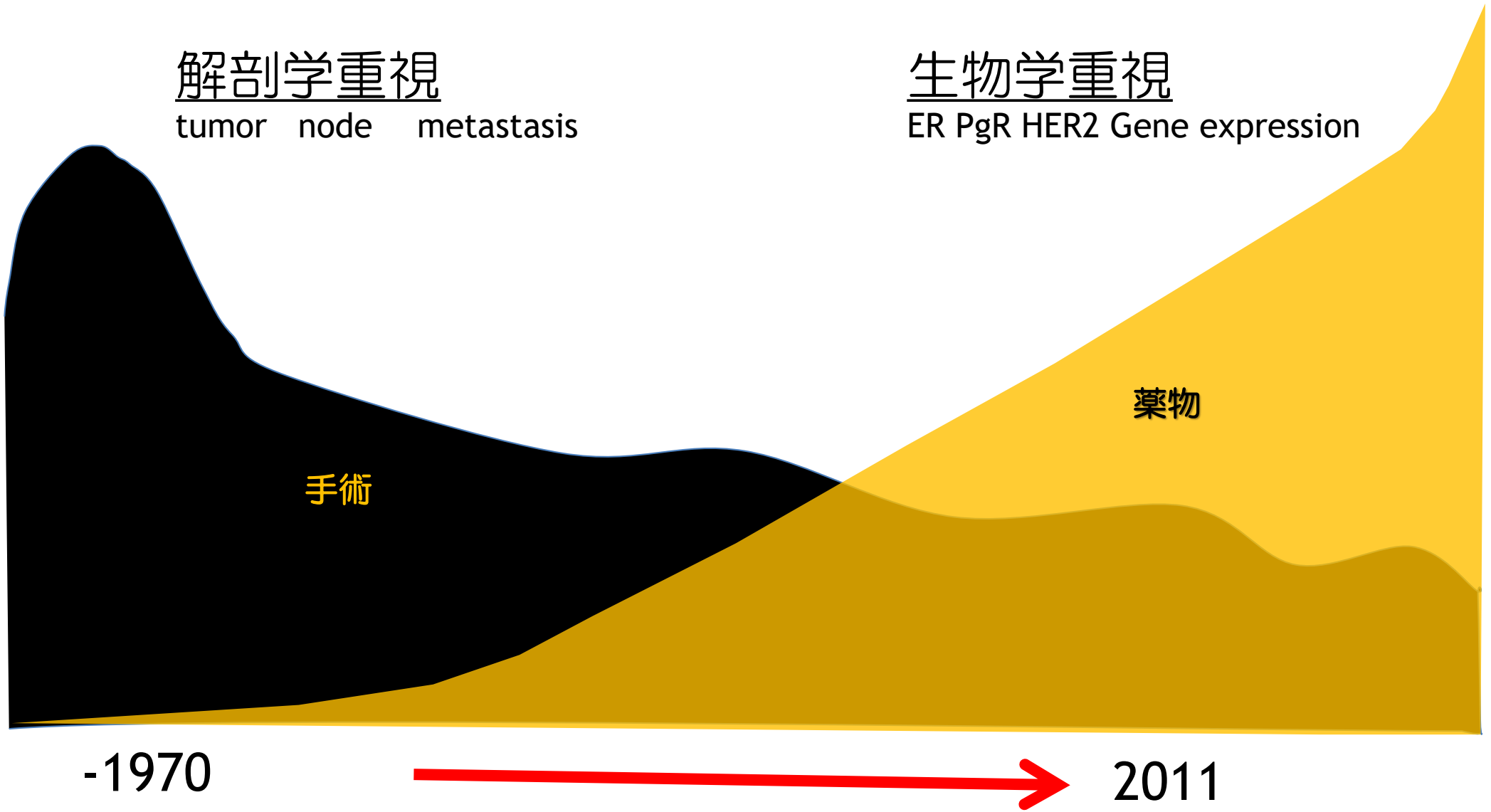
- Luminal A
- Luminal B
  - HER2 negative
  - HER2 positive
- HER2-rich
- Basal-like
- 特殊型


乳がん治療の選択　2011
Basal like
HER2 Rich
Luminal B
Luminal A
入り口が変わりました


乳がん治療の選択　2011
Basal like
HER2 Rich
Luminal B
Luminal A

# Luminal B 劇場にようこそ

# 時代的変遷


解剖学重視
tumor node metastasis
生物学重視
ER PgR HER2 Gene expression
手術
薬物
-1970
2011

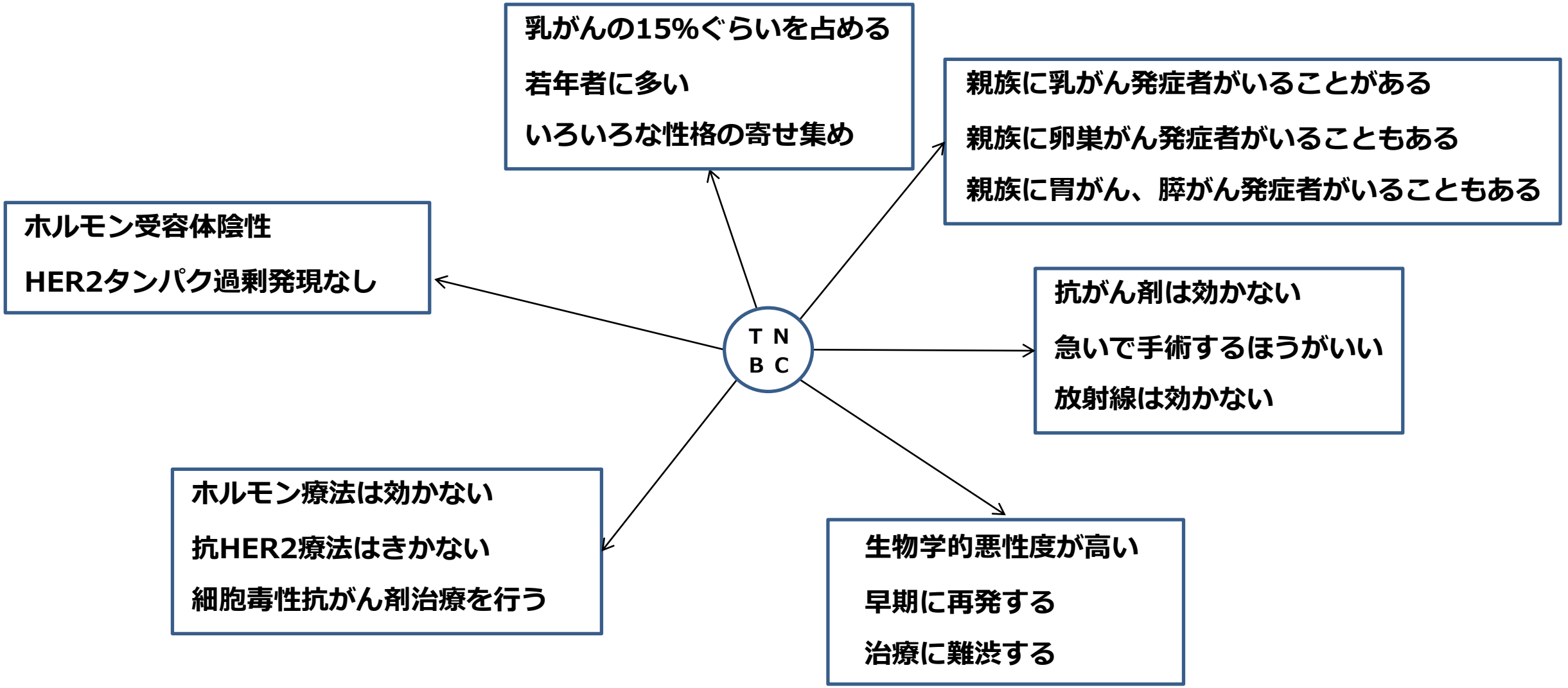
# 乳がん薬物療法の選択

病理検査

組織診断・グレード
腫瘍浸潤径・脈管浸潤
腋窩リンパ節転移
ER陽性細胞割合
HER2過剰発現・Ki-67

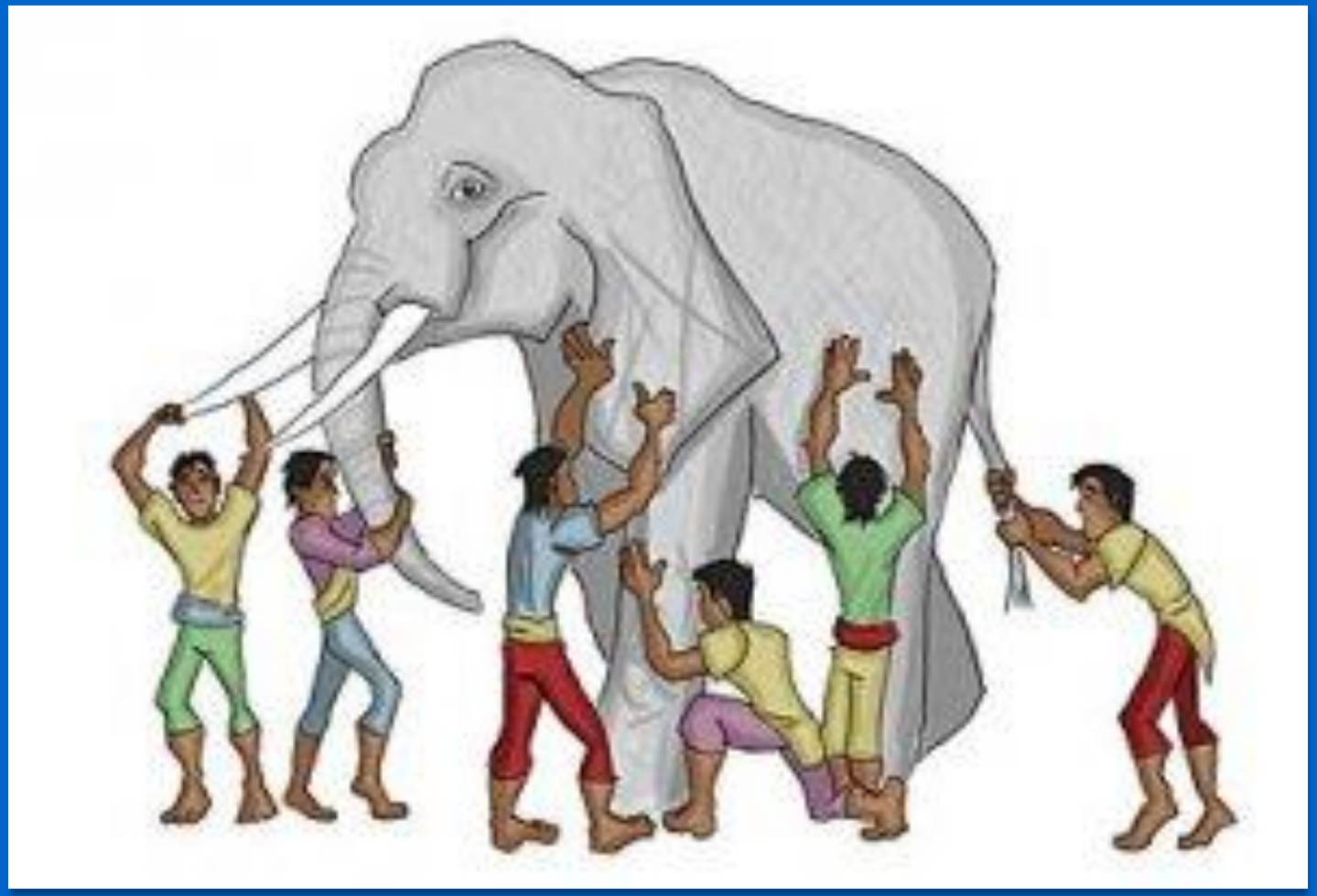
- Luminal A → ホルモン療法
- Luminal B-HER2 陰性 → ホルモン療法 / 細胞毒性抗がん剤
- Luminal B-HER2陽性 → ホルモン療法 / 細胞毒性抗がん剤 / 抗HER2療法
- HER2 Enriched → 抗HER2療法 / 細胞毒性抗がん剤
- Basal-like ≒ Triple Negative → 細胞毒性抗がん剤

# TNBCに関する正解と誤解　2018



# 誤解の原因

blind men and an elephant　「群盲象をなでる」



# Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies

Brian D. Lehmann,[1] Joshua A. Bauer,[1] Xi Chen,[2] Melinda E. Sanders,[3] A. Bapsi Chakravarthy,[4] Yu Shyr,[2] and Jennifer A. Pietenpol[1]

[1]Department of Biochemistry, [2]Department of Biostatistics, [3]Department of Pathology, and [4]Department of Radiation Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Journal of Clinical Investigation. 2011;121(7):2750-67

**TNBCを遺伝子プロファイルにより6種類のサブタイプに分類**

Basal-Like（BL1、BL2）subtype：細胞増殖能が極めて高く，細胞周期関連遺伝子やDNA傷害応答性遺伝子が高発現

Immunomodulatory（IM）subtype：髄様癌で見られるように，免疫反応に関連した遺伝子が高発現

Mesenchymal 、Mesenchymal-Stem Like（M,MSL）subtype：（TGF]-β，EMT，増殖因子，Wnt/β-cateninシグナルに関連した遺伝子が高発現，後者では幹細胞関連遺伝子も高発現

Luminal Androgen Receptor（LAR）サブタイプ（アポクリン癌が代表，ARやluminal関連遺伝子の高発現）が同定されている。

# 明日からのTriple-Negative Breast Cancer (TNBC) 治療(1)

- Basal-likeに対して：
  見分け方：充実型で圧排性に増殖　Ki67高値
  治療のコツ

（１）効果の見える「術前化学療法」がお薦め
（２）AC（ADM+CPA) 4サイクル、タキサン4サイクル
（３）Dose Dense でもよい
（４）ジプレキサ、ジーラスタ、アバスチンなどを効果的に併用
（５）頭部、手指冷却などできれば併用
（６）中心静脈ポート装着を強く推奨する

# 明日からのTriple-Negative Breast Cancer (TNBC) 治療(2)

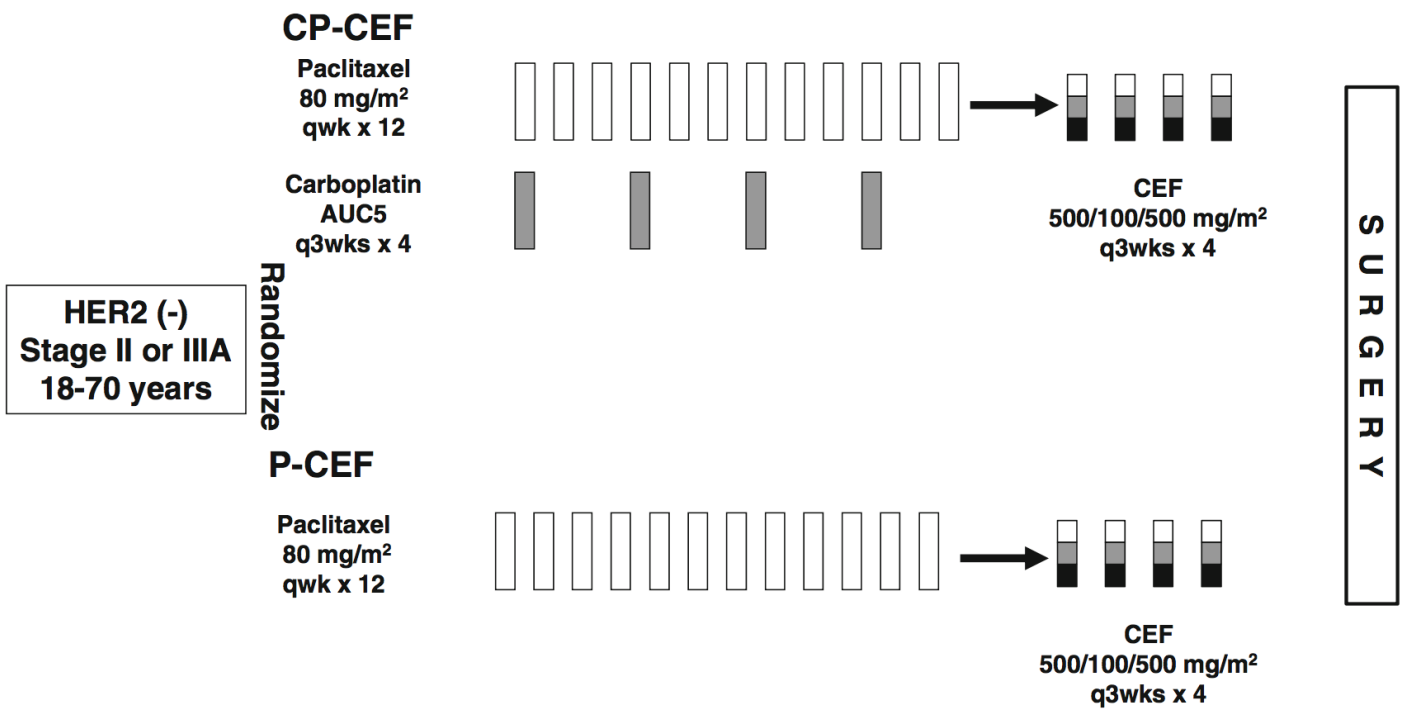
## Carboplatinを使いこなす

**Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/ epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression**

**Masashi Ando · Hideko Yamauchi · Kenjiro Aogi · Satoru Shimizu · Hiroji Iwata · Norikazu Masuda · Naohito Yamamoto · Kenichi Inoue · Shinji Ohono · Katsumasa Kuroi · Tetsutaro Hamano · Tamie Sukigara · Yasuhiro Fujiwara**

Breast Cancer Res Treat. 2014;145(2):401-9.

# 明日からのTriple-Negative Breast Cancer (TNBC) 治療




| | 全症例 | | | TNBC症例 | | |
|---|---|---|---|---|---|---|
| | n | pCR | *p* | n | pCR | *p* |
| CP-CEF | 88 | 31.8% | *0.01* | 37 | 61.2% | *0.003* |
| P-CEF | 91 | 17.6% | | 38 | 26.3% | |

Breast Cancer Res Treat. 2014;145(2):401-9.

# これからのTriple-Negative Breast Cancer (TNBC) 治療

1. PARP阻害薬　「Olaparib」「Talazoparib」
2. Anti-androgens「bicartamide」「 Enzaltamide」
3. 抗EGFR抗体「cetuximab」
4. Src阻害薬
5. Sunitinib，Imatinib
6. PI3K/AKT/mTOR阻害薬

# これからのTriple-Negative Breast Cancer (TNBC) 治療

1. PARP阻害薬　「Olaparib」「Talazoparib」

進行・再発乳がんを対象にした検討結果

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

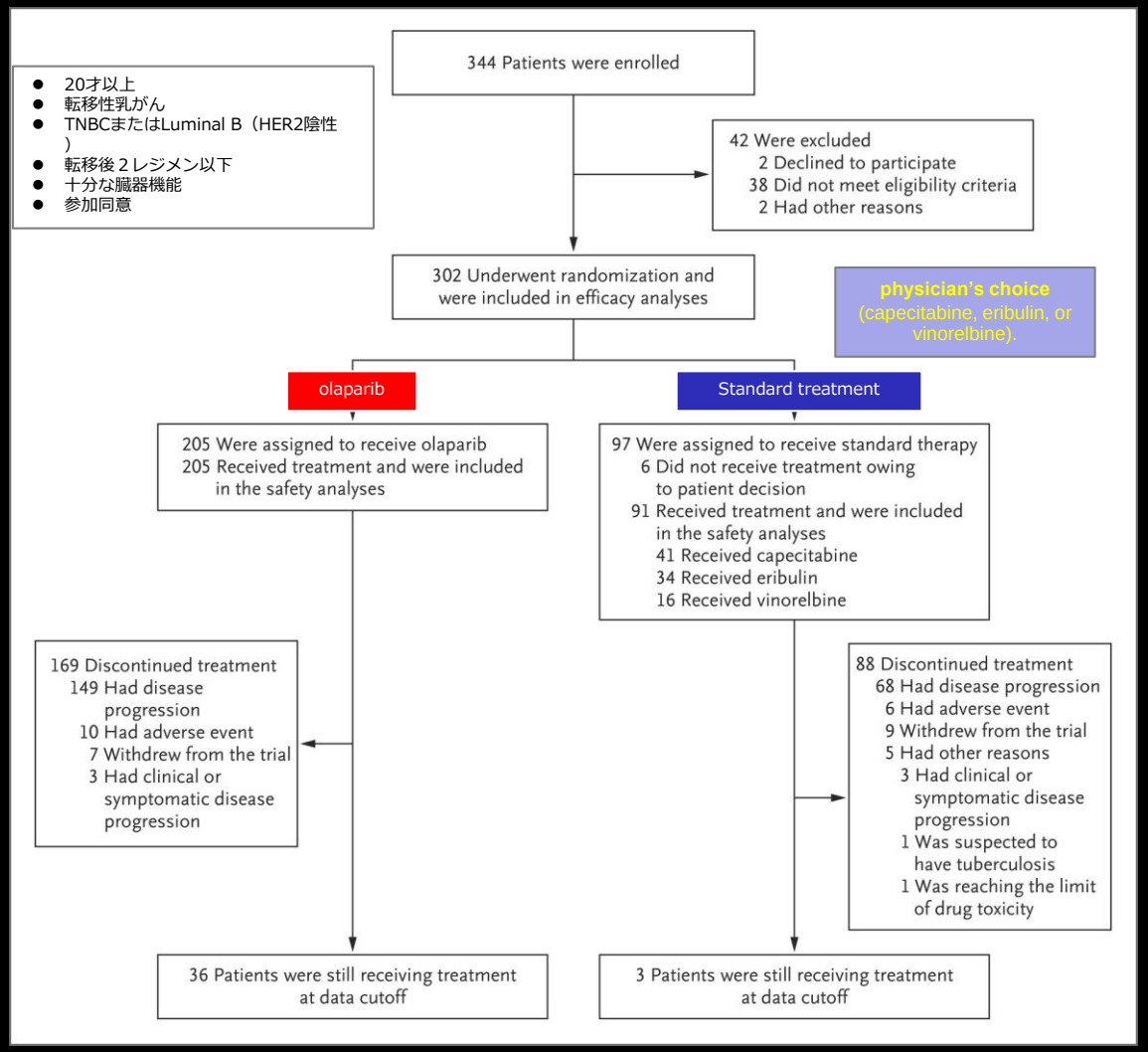
# Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

# 試験概略

BRCA遺伝子の胚細胞変異のある転移性乳がん患者で、PARP阻害剤であるオラパリブ（商品名：リムパーザ）の内服治療は標準的単剤治療に比べて長い無増悪生存期間が得られた。

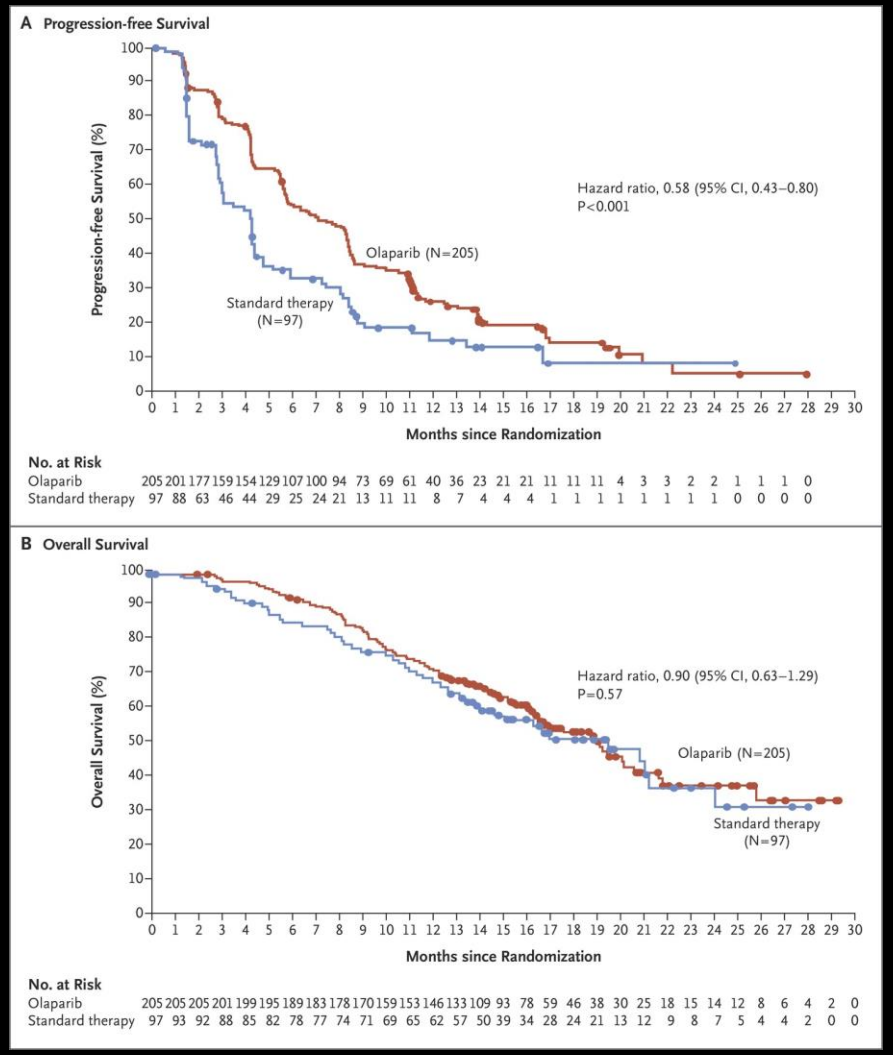
# Enrollment, Randomization, and Treatment.




Robson M et al. N Engl J Med ;377:523-533

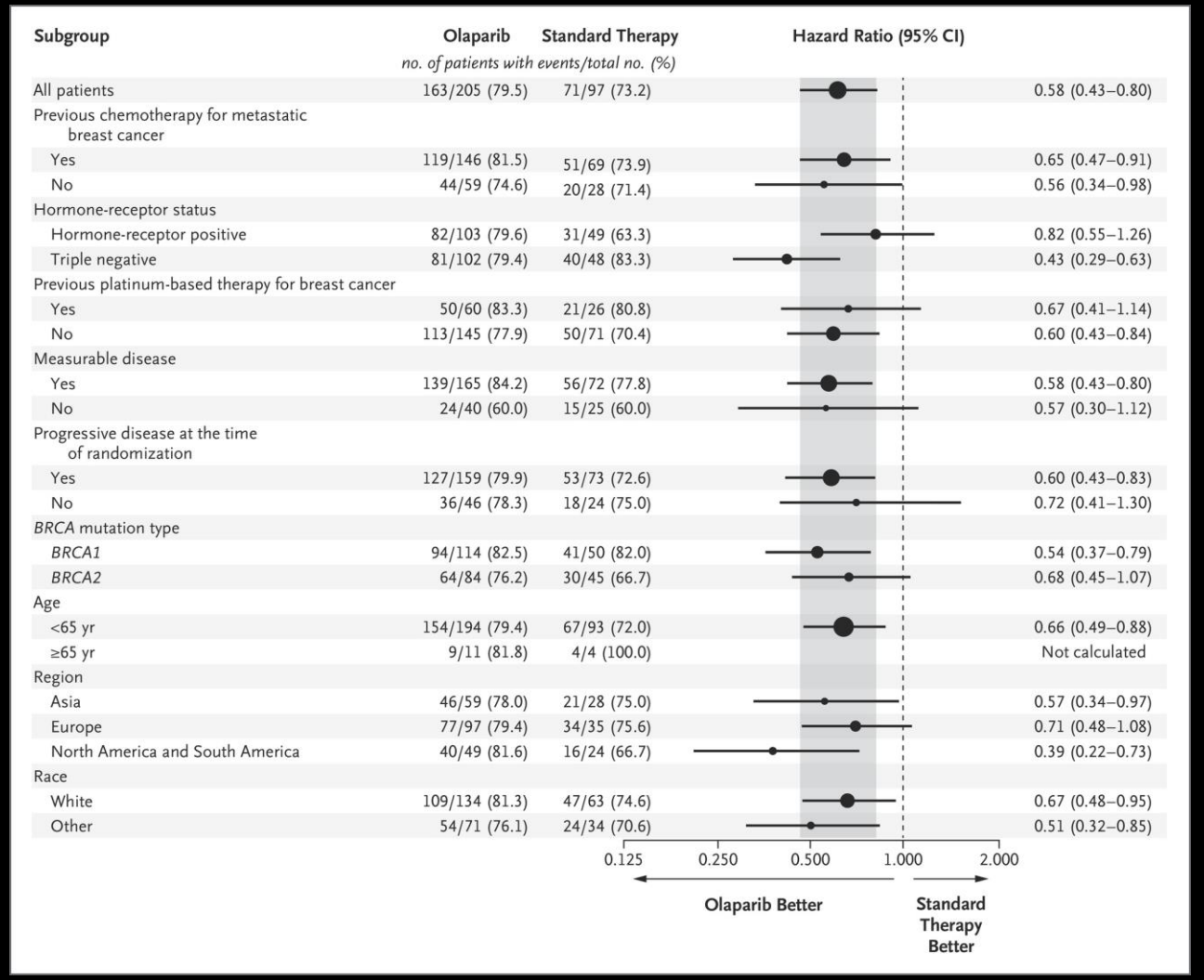
The NEW ENGLAND JOURNAL of MEDICINE

# Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.




Robson M et al. N Engl J Med ;377:523-533

# Subgroup Analysis of Progression-free Survival.




Robson M et al. N Engl J Med ;377:523-533

# Baseline Characteristics of the Patients.

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Olaparib Group (N=205) | Standard-Therapy Group (N=97) |
|---|---|---|
| Age — yr | | |
| Median | 44 | 45 |
| Range | 22–76 | 24–68 |
| Male sex — no. (%) | 5 (2.4) | 2 (2.1) |
| Race or ethnic group — no. (%)† | | |
| White | 134 (65.4) | 63 (64.9) |
| Asian | 66 (32.2) | 28 (28.9) |
| Other | 5 (2.4) | 6 (6.2) |
| ECOG performance status — no. (%)‡ | | |
| 0 | 148 (72.2) | 62 (63.9) |
| 1 | 57 (27.8) | 35 (36.1) |
| *BRCA* mutation type — no. (%)§ | | |
| *BRCA1* | 117 (57.1) | 51 (52.6) |
| *BRCA2* | 84 (41.0) | 46 (47.4) |
| *BRCA1* and *BRCA2* | 4 (2.0) | 0 |
| Hormone-receptor status — no. (%)¶ | | |
| Hormone-receptor positive | 103 (50.2) | 49 (50.5) |
| Triple negative | 102 (49.8) | 48 (49.5) |
| New metastatic breast cancer — no. (%) | 26 (12.7) | 12 (12.4) |
| Previous chemotherapy for metastatic breast cancer — no. (%) | 146 (71.2) | 69 (71.1) |
| Previous platinum-based therapy for breast cancer — no. (%) | 60 (29.3) | 26 (26.8) |
| ≥2 Metastatic sites — no. (%) | 159 (77.6) | 72 (74.2) |
| Location of the metastasis — no. (%) | | |
| Bone only | 16 (7.8) | 6 (6.2) |
| Other‖ | 189 (92.2) | 91 (93.8) |
| Measurable disease — no. (%) | 167 (81.5) | 66 (68.0) |

* Standard therapy was a single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine).
† Race or ethnic group was self-reported. The other category includes black (5 patients), American Indian or Alaska Native (4), unknown (1), and declined to specify (1).
‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
§ In the majority of patients, *BRCA* mutation type was confirmed by central testing with BRACAnalysis (Myriad Genetics); in 3 patients in the olaparib group and 2 patients in the standard-therapy group, mutation type was confirmed by local testing only. Percentages may not sum to 100 because of rounding.
¶ Hormone-receptor positive disease is estrogen-receptor positive, progesterone-receptor positive, or both. Triple-negative disease is human epidermal growth factor receptor type 2 (HER2) negative, estrogen-receptor negative, and progesterone-receptor negative.
‖ Data for the other category include patients who did not have metastases in the bone, as well as patients who may have had metastases in the bone along with metastases in other locations.

Robson M et al. N Engl J Med ;377:523-533

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# Summary of Adverse Events.

**Table 2. Summary of Adverse Events.***

| Variable | Olaparib Group (N=205) | | Standard-Therapy Group (N=91) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number (percent)* | | | |
| Adverse event | | | | |
| Any | 199 (97.1) | 75 (36.6) | 88 (96.7) | 46 (50.5) |
| Anemia† | 82 (40.0) | 33 (16.1) | 24 (26.4) | 4 (4.4) |
| Neutropenia‡ | 56 (27.3) | 19 (9.3) | 45 (49.5) | 24 (26.4) |
| Decreased white-cell count | 33 (16.1) | 7 (3.4) | 19 (20.9) | 9 (9.9) |
| Nausea | 119 (58.0) | 0 | 32 (35.2) | 1 (1.1) |
| Vomiting | 61 (29.8) | 0 | 14 (15.4) | 1 (1.1) |
| Diarrhea | 42 (20.5) | 1 (0.5) | 20 (22.0) | 0 |
| Decreased appetite | 33 (16.1) | 0 | 11 (12.1) | 0 |
| Fatigue | 59 (28.8) | 6 (2.9) | 21 (23.1) | 1 (1.1) |
| Headache | 41 (20.0) | 2 (1.0) | 14 (15.4) | 2 (2.2) |
| Pyrexia | 29 (14.1) | 0 | 16 (17.6) | 0 |
| Cough | 35 (17.1) | 0 | 6 (6.6) | 0 |
| Increased alanine aminotransferase level | 23 (11.2) | 3 (1.5) | 16 (17.6) | 1 (1.1) |
| Increased aspartate aminotransferase level | 19 (9.3) | 5 (2.4) | 15 (16.5) | 0 |
| Palmar–plantar erythrodysesthesia | 1 (0.5) | 0 | 19 (20.9) | 2 (2.2) |
| Dose reduction owing to adverse event | 52 (25.4) | NA | 28 (30.8) | NA |
| Treatment interruption or delay owing to adverse event | 72 (35.1) | NA | 25 (27.5) | NA |
| Treatment discontinuation owing to adverse event | 10 (4.9) | NA | 7 (7.7) | NA |

* The table includes adverse events of any grade that occurred in at least 15% of patients in either treatment group and corresponding grade 3 or higher adverse events, which were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA denotes not applicable.
† The anemia category includes anemia, decreased hemoglobin level, decreased hematocrit, decreased red-cell count, and erythropenia.
‡ The neutropenia category includes febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count, and neutropenic infection.

Robson M et al. N Engl J Med ;377:523-533

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# 結論

BRCA遺伝子の胚細胞変異のある転移性乳がん患者でオラパリブ単剤の内服治療は、標準的治療と比べて無増悪生存期間を2.8か月延長し、病状増悪または死亡のリスクを42%減弱させた。

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

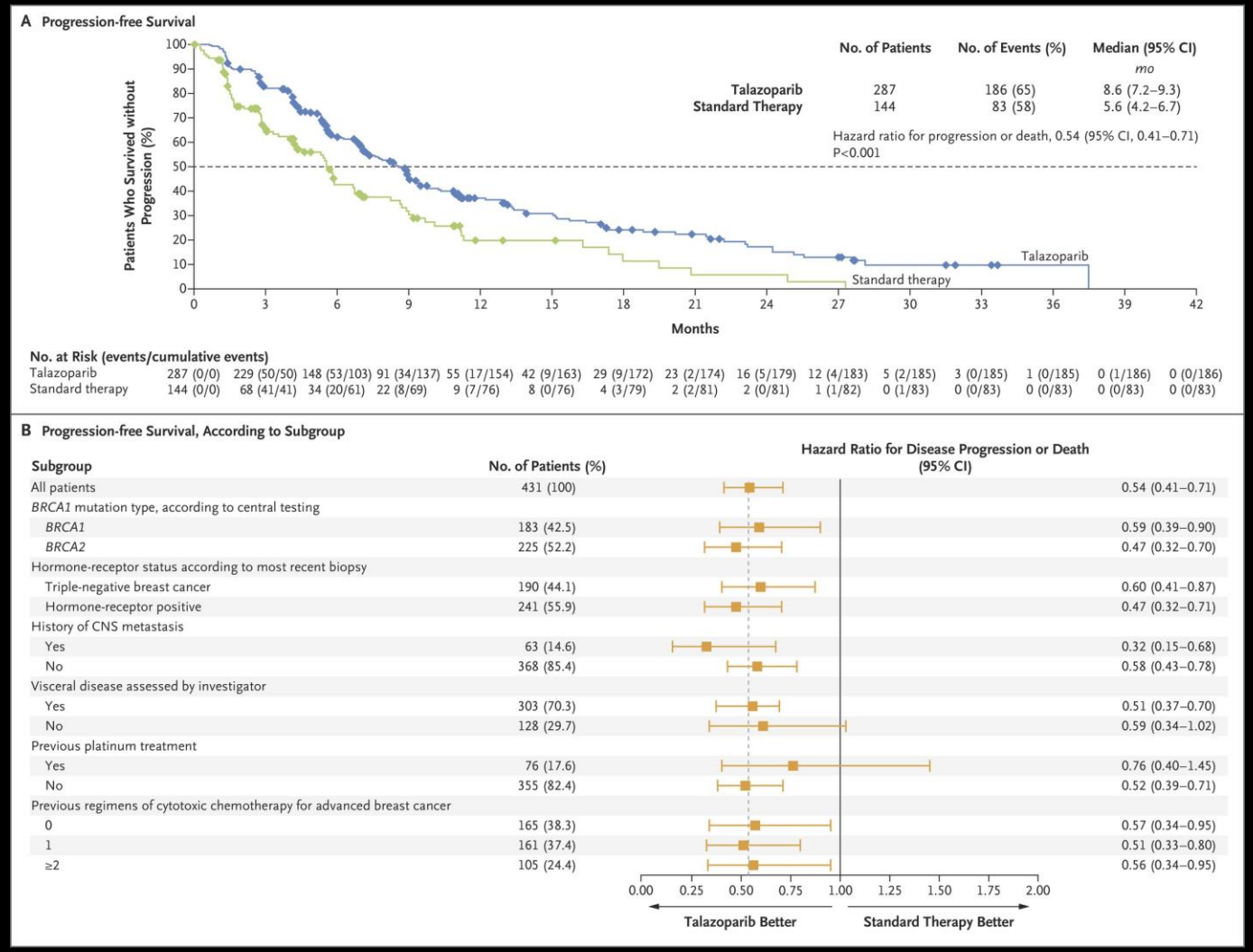
Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.

# 試験概略

## EMBRACA trial

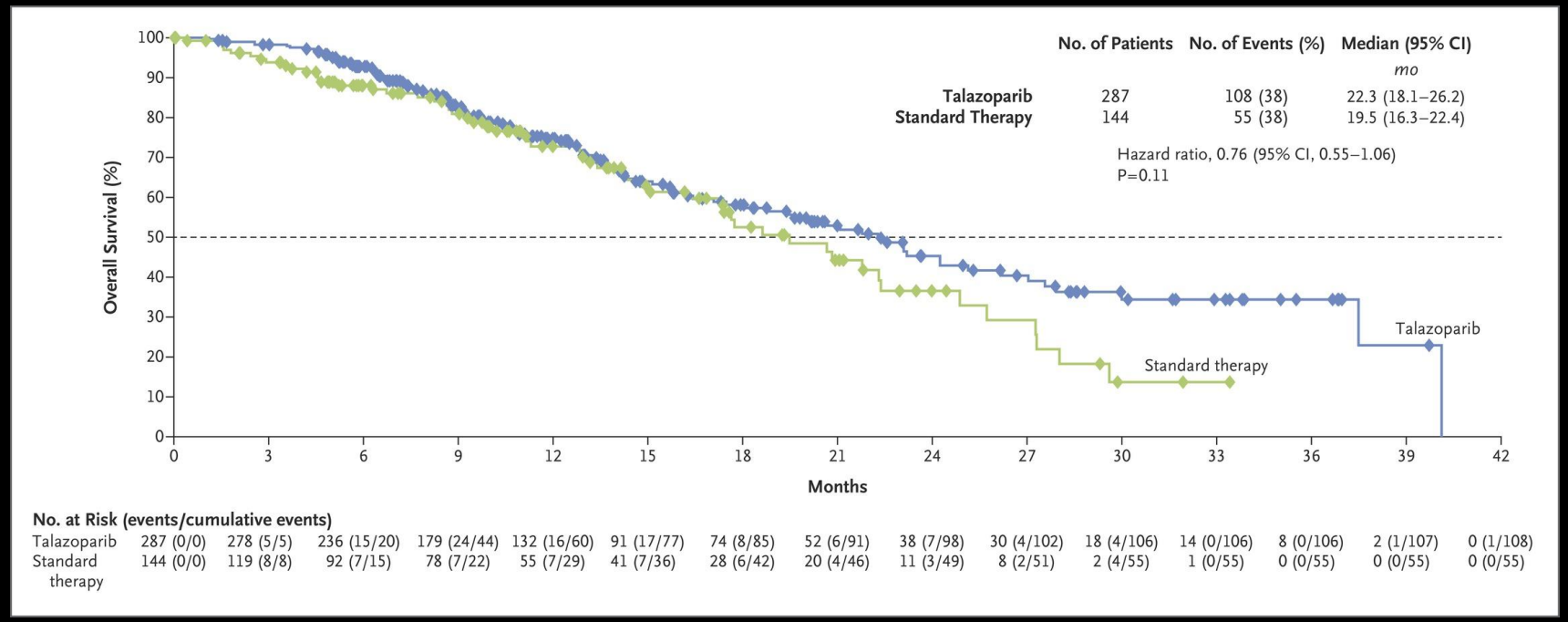
BRCA （DNA修復経路の遺伝子）に胚細胞変異のある乳がん患者で、PARP阻害剤であるタラゾパリブは標準的化学療法 (capecitabine, eribulin, gemcitabine, vinorelbine)に比べ、無増悪生存期間において優位なベネフィットをもたらした。

# Progression-free Survival among All Patients and According to Subgroup.




Litton JK et al. N Engl J Med 2018;379:753-763

# Interim Analysis of Overall Survival.

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# Baseline Characteristics of the Patients (Intention-to-Treat Population).

**Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).***

| Characteristic | Talazoparib Group (N = 287) | Standard-Therapy Group (N = 144) |
|---|---|---|
| Age — yr | | |
| Median | 45 | 50 |
| Range | 27.0–84.0 | 24.0–88.0 |
| Age <50 yr — no. (%) | 182 (63.4) | 67 (46.5) |
| Female sex — % | 98.6 | 97.9 |
| ECOG performance status score — %† | | |
| 0 | 53.3 | 58.3 |
| 1 | 44.3 | 39.6 |
| 2 | 2.1 | 1.4 |
| Breast cancer stage — no. (%)‡ | | |
| Locally advanced | 15 (5.2) | 9 (6.2) |
| Metastatic | 271 (94.4) | 135 (93.8) |
| Measurable disease assessed by investigator — no. (%) | 219 (76.3) | 114 (79.2) |
| History of CNS metastases — no. (%) | 43 (15.0) | 20 (13.9) |
| Visceral disease — no. (%) | 200 (69.7) | 103 (71.5) |
| Hormone-receptor status — no. (%) | | |
| Triple-negative | 130 (45.3) | 60 (41.7) |
| Hormone-receptor–positive | 157 (54.7) | 84 (58.3) |
| *BRCA* status — no. (%)§ | | |
| *BRCA1*-positive | 133 (46.3) | 63 (43.8) |
| *BRCA2*-positive | 154 (53.7) | 81 (56.2) |
| <12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%) | 108 (37.6) | 42 (29.2) |
| Previous adjuvant or neoadjuvant therapy — no. (%) | 238 (82.9) | 121 (84.0) |
| No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients) | | |
| Median | 2.0 | 2.0 |
| Range | 0–6 | 0–6 |
| Previous platinum therapy — no. (%) | 46 (16.0) | 30 (20.8) |
| Previous cytotoxic regimens for advanced breast cancer — no. (%) | | |
| 0 | 111 (38.7) | 54 (37.5) |
| 1 | 107 (37.3) | 54 (37.5) |
| 2 | 57 (19.9) | 28 (19.4) |
| 3 | 12 (4.2) | 8 (5.6) |

* Standard therapy was a single-agent chemotherapy of the physician's choice. Percentages may not total 100 because of rounding. *BRCA* denotes breast cancer susceptibility gene, and CNS central nervous system.
† Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
‡ Data were missing for one patient in the talazoparib group.
§ Only 10 patients (6 patients in the talazoparib group and 4 patients in the standard-therapy group) were identified as having a suspected deleterious mutation. The remainder who underwent central testing with BRACAnalysis had a known pathogenic variation.

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# Secondary and Exploratory Efficacy End Points.

**Table 2. Secondary and Exploratory Efficacy End Points.**

| Variable | Talazoparib Group (N = 219) | Standard-Therapy Group (N = 114) | Odds Ratio (95% CI) | P Value* |
|---|---|---|---|---|
| | *number (percent)* | | | |
| Best overall response among patients with measurable disease — no. (%)† | | | | |
| Complete response | 12 (5.5) | 0 | — | — |
| Partial response | 125 (57.1) | 31 (27.2) | — | — |
| Stable disease | 46 (21.0) | 36 (31.6) | — | — |
| Could not be evaluated | 4 (1.8) | 19 (16.7) | — | — |
| Investigator-assessed overall objective response among patients with measurable disease — % of patients (95% CI)† | 62.6 (55.8–69.0) | 27.2 (19.3–36.3) | 5.0 (2.9–8.8) | <0.001 |
| Clinical benefit rate at 24 wk in intention-to-treat population | | | | |
| Patients with clinical benefit — no./total no. | 197/287 | 52/144 | — | — |
| Percent of patients (95% CI) | 68.6 (62.9–74.0) | 36.1 (28.3–44.5) | 4.3 (2.7–6.8) | <0.001 |
| Investigator-assessed response in subgroup of patients with objective response | | | | |
| No. with response | 137 | 31 | — | — |
| Median duration of response — mo | 5.4 | 3.1 | — | — |
| Interquartile range | 2.8–11.2 | 2.4–6.7 | — | — |

* The P value was calculated with the use of the stratified Cochran–Mantel–Haenszel method. Stratification factors were the number of previous cytotoxic chemotherapy regimens, triple-negative status, and history of central nervous system metastases.
† According to Response Evaluation Criteria in Solid Tumors, version 1.1, confirmation of complete response or partial response was not required.

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# Summary of Adverse Events.

**Table 3. Summary of Adverse Events.***

| Adverse Event | Talazoparib Group (N = 286) | Standard-Therapy Group (N = 126) |
|---|---|---|
| | *number of patients (percent)* | |
| Any adverse event | 282 (98.6) | 123 (97.6) |
| Serious adverse event† | 91 (31.8) | 37 (29.4) |
| Serious and drug-related adverse event | 26 (9.1) | 11 (8.7) |
| Grade 3 or 4 serious adverse event | 73 (25.5) | 32 (25.4) |
| Adverse event resulting in permanent drug discontinuation | 17 (5.9) | 11 (8.7) |

* Adverse-event grades were evaluated with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patients with multiple adverse events were counted once for each preferred term, system organ class, and overall. Data on adverse events leading to permanent discontinuation of a trial drug were obtained from the adverse-event electronic case report form.

† A serious adverse event was defined as any adverse event that resulted in death, was considered to be life-threatening or medically important, resulted in hospitalization or prolongation of existing hospitalization, or resulted in persistent or clinically significant disability or incapacity or a congenital anomaly or birth defect.

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# 結論

BRCA½遺伝子に胚細胞変異のある進行乳がん患者で、タラゾパリブ単剤は標準的化学療法 (capecitabine, eribulin,　gemcitabine, vinorelbine)に比べ、無増悪生存期間において優位なベネフィットをもたらした。

また、患者申告顛末（Patient Reported Outcome）も、タラゾパリブ群で優れていた。

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# これからのTriple-Negative Breast Cancer (TNBC) 治療

2. Anti-androgens「bicartamide」「 Enzaltamide」

# Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies

Brian D. Lehmann,[1] Joshua A. Bauer,[1] Xi Chen,[2] Melinda E. Sanders,[3] A. Bapsi Chakravarthy,[4] Yu Shyr,[2] and Jennifer A. Pietenpol[1]

[1]Department of Biochemistry, [2]Department of Biostatistics, [3]Department of Pathology, and [4]Department of Radiation Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Journal of Clinical Investigation. 2011;121(7):2750-67

**TNBCを遺伝子プロファイルにより6種類のサブタイプに分類**

Basal-Like（**BL1**、**BL2**）subtype ：細胞増殖能が極めて高く，細胞周期関連遺伝子やDNA傷害応答性遺伝子が高発現

Immunomodulatory（**IM**）subtype ： 髄様癌で見られるように，免疫反応に関連した遺伝子が高発現

Mesenchymal 、Mesenchymal-Stem Like（**M**,**MSL**）subtype ：（TGF]-β，EMT，増殖因子，Wnt/β-cateninシグナルに関連した遺伝子が高発現，後者では幹細胞関連遺伝子も高発現

Luminal Androgen Receptor（**LAR**）サブタイプ（アポクリン癌が代表，ARやluminal関連遺伝子の高発現）が同定されている。

# 78才　女性　左炎症性乳がん

右乳癌術後　左乳癌疑い

2011/12/5 浜松医療センター乳腺外科初診 右乳癌T2N1M0
ER0% PgR0% HER2/3+ Ki67/37%の診断。
VNR+HER→nabPTX+HER→HER

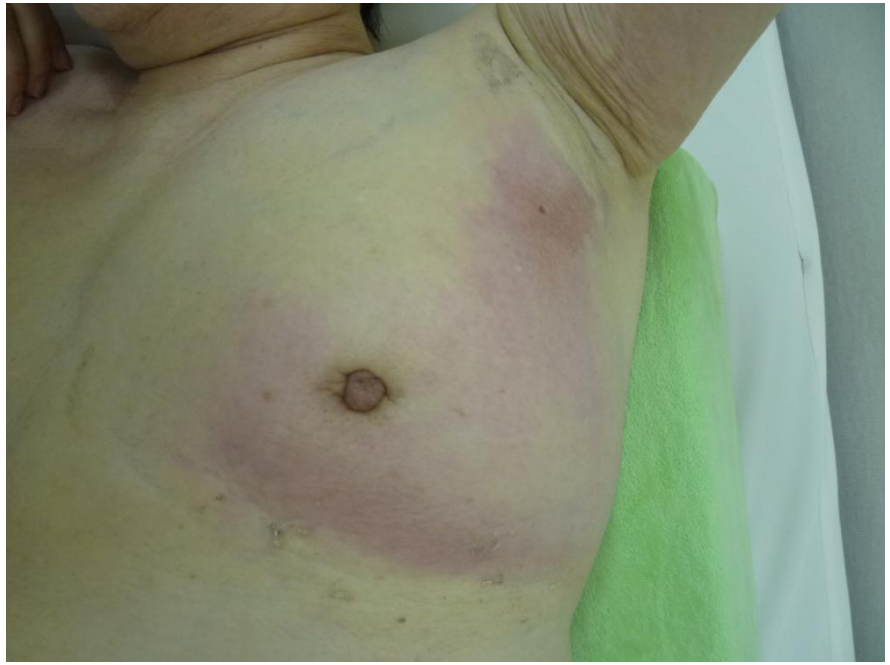
2012/9/19 右Bp+Ax　効果判定 grade3

HERCEPTIN 施行後、神田クリニックでフォローされていた。

2016/10 左乳房腫瘤自覚

2016/11/21 神田クリニック受診　左乳房全体に浮腫性変化あり　腋窩リンパ節腫大あり
2016/11/24 浜松医療センター紹介

20代の頃両側乳房にオイル注入
視触診 左乳房皮膚肥厚 乳頭陥凹あり E領域中心に5*4cm大硬結触知　腋窩腫大リンパ節触知 皮膚も肥厚
US　左Eに低エコー腫瘤あり　全体に浮腫あり



# 病理診断報告書

乳腺、左、針生検：検体適性；悪性、浸潤性乳管癌・硬癌

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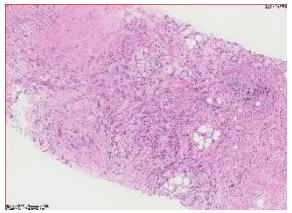
標本個数：3本
標本大きさ： 20mm 15mm 7mm
所見：索状配列から小胞巣状構造、孤細胞性に浸潤する腫瘍組織が見られる。周囲脂肪織への浸潤も見られる。小葉内病変が見られており、浸潤性小葉癌の可能性も考えられる。
E-cadherinにてわずかに膜が染色されている細胞も含まれるので浸潤性乳管癌・硬癌に分類する。

Nuclear grade【1】： nuclear atypia【2】 mitotic counts【1】
ER：【0%】
PgR：【0%】
HER2：【0】
Ki67 index：【16%】

AR【100%】

# 78才女性　左炎症性乳がん



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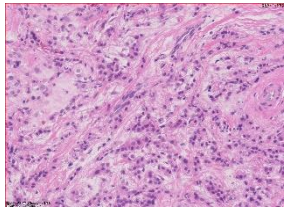

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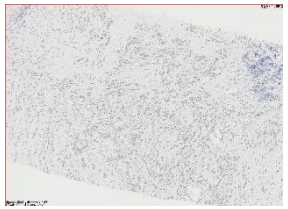

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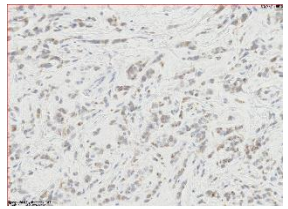
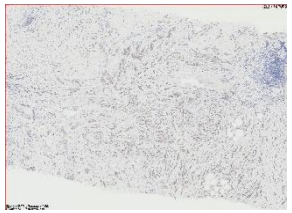


ER 20x



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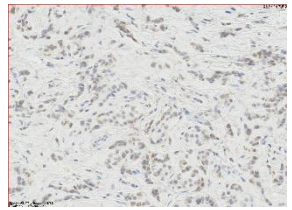

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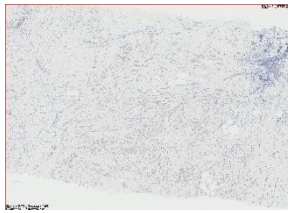
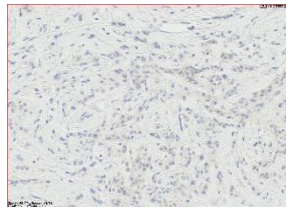
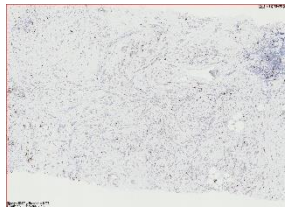


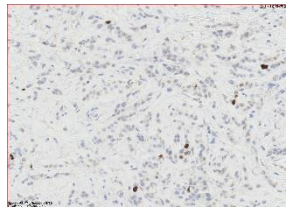
HER2 4x



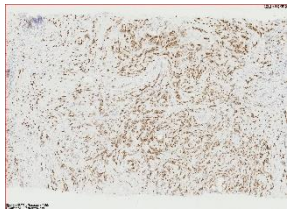
HER2 20x



Ki67 4x



Ki67 20x



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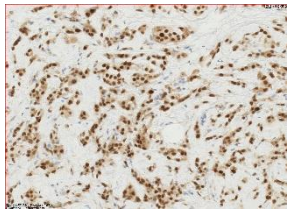
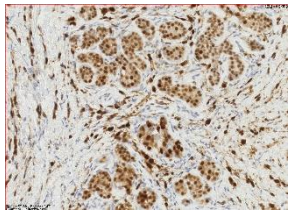


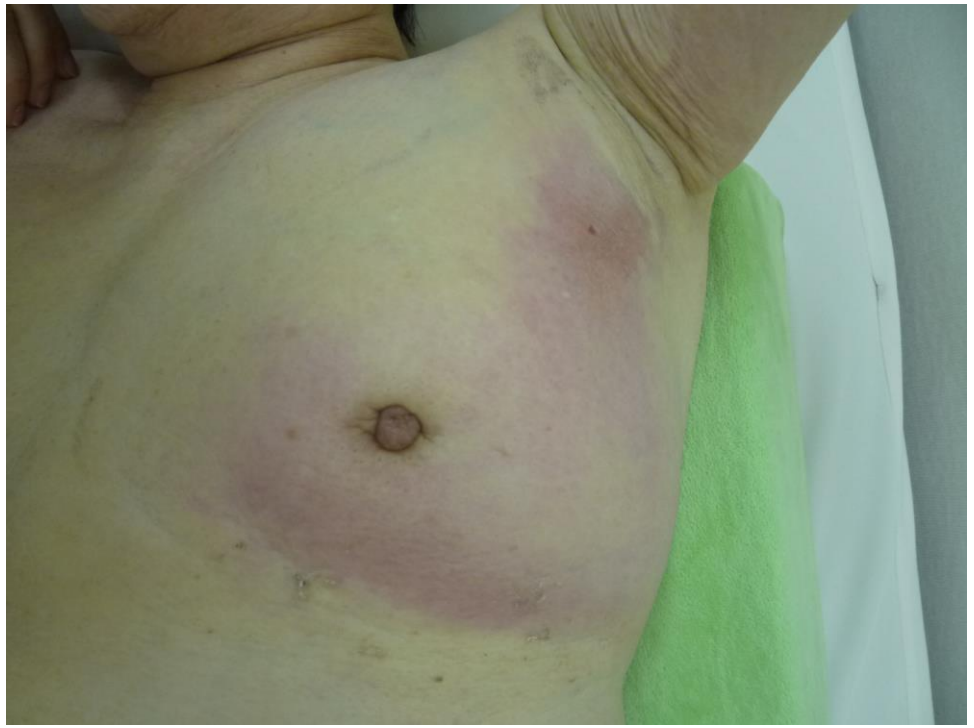
AR 20x



AR 20x

# 78才女性　炎症性乳がん

2017年1月18日　浜松医療センターから
治療を依頼されて当院受診
　　抗アンドロゲン剤「ビカルタミド」開始



2017年2月15日　NC　本人も変わらないと

2017年3月22日　NC　本人も変わらないと

2017年4月19日　NC　本人も変わらないと

2017年5月17日　NC　本人も変わらないと

2017年6月14日　NC　本人も変わらないと

2017年7月12日　NC　本人も変わらないと

2017年8月10日　腫瘍の大きさ、皮膚病変とも変化なかったが疼痛増強してきたのでビカルタミド中止

効果があったのか、なかったのか、わからない

VOLUME 36 · NUMBER 9 · MARCH 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Enzalutamide for the Treatment of Androgen Receptor–Expressing Triple-Negative Breast Cancer

*Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Janice Eakle, Lee S. Schwartzberg, Joyce O'Shaughnessy, William Gradishar, Peter Schmid, Eric Winer, Catherine Kelly, Rita Nanda, Ayca Gucalp, Ahmad Awada, Laura Garcia-Estevez, Maureen E. Trudeau, Joyce Steinberg, Hirdesh Uppal, Iulia Cristina Tudor, Amy Peterson, and Javier Cortes*

Of 118 patients enrolled, 78 were evaluable. Clinical Benefit Rate(CBR) at 16 weeks was 25% (95% CI, 17% to 33%) in the ITT population and 33% (95% CI, 23% to 45%) in the evaluable subgroup.

J Clin Oncol. 2018;36(9):884-90.

# Is the Clinical Benefit Rate at Sixteen Weeks a Reliable End Point?

TO THE EDITOR: The number of clinical trials on advanced breast cancer with clinical benefit rate (CBR) at 16 weeks is increasing.[1,2] We asked these questions: Is this end point appropriate and reliable? Could the conclusions based on this end point be misleading? CBR includes complete response (CR), partial response (PR), and stable disease. The study by Traina et al[1] reports on patients with androgen receptor (AR)–positive triple-negative breast cancer (TNBC) treated with enzalutamide. The CBR was 33% at 16 weeks, but the rate for CR and PR was only 8% (Table 2). This suggests that CBR at 16 weeks is not a true marker of efficacy. This is also shown by the low progression-free survival and overall survival (OS; Fig 2). Traina et al studied TNBC with more than 0% AR as their inclusion criteria. They report that 80% of patients had more than 0% AR positivity and 55% had 10% AR positivity. They do not report on those with a different outcome. Other reports use 10% as a criterion for positivity.[2-4] Although the study met its primary end point, we think 4-month CBR is unreliable evidence of efficacy in such a setting. It is noteworthy that two small phase II trials evaluating other antiandrogens, namely bicalutamide and abiraterone acetate, in the same setting used CBR at 24 weeks as their primary end point.[3,4] Only one patient in those two studies achieved CR.

There are three major reasons behind our concern. First, previous experience with those agents showed that AR-positive TNBC seems to be a more indolent subtype with peculiar clinical characteristics.[3] One meta-analysis of 19 studies (including 7,693 patients with early-stage breast cancer) showed that AR-positive breast cancer (regardless of estrogen receptor status), had superior disease-free survival and OS compared with AR-negative patients.[5] On the basis of historical data focusing mainly on responses to endocrine agents in metastatic breast cancer, the CBR was defined by adding CR, PR, and stable disease of 6 or more months. Shortening this period to 16 weeks might give false-positive results in indolent subgroups such as those with AR-positive disease. One pooled analysis[6] of 13 phase III trials of metastatic breast cancer failed to show an association between OS hazard ratio and the odds ratio of CBR. In that analysis, CBR included patients with stable disease for 6 or more months. Historically, the CBR was an accepted end point provided that the patients with stable disease achieved overall time to progression and survival similar to patients with objective response.[7] Stable disease might reflect the natural history of the disease or a continued benefit from a prior line of treatment.

This leads to our second reason: we are concerned about the wide range of metastatic disease burden in this study population and the corresponding prior lines of treatment (range, 0 to 7 prior lines). A considerable number of patients (37%) with nonvisceral metastatic disease were allowed into the study. However, we still believe that enzalutamide has antitumor activity in such a setting and did achieve objective responses with two CRs. It would be of value if the authors reported the baseline characteristics of the patients who had objective responses. It seems that metastatic sites vary in their AR expression and thus in their response to antiandrogen. One reverse-phase protein array study[8] showed that AR expression and its phosphorylated form, p-AR were increased in the chest wall metastases compared with primary breast cancer, especially in TNBC. In addition, estrogen receptor–positive liver metastases hold a unique profile of activation of AR along with overexpression of mTOR and human epidermal growth factor receptor 1 and 3 (HER1/3). This indicates inadequacy of antiandrogen monotherapy in those with liver metastases and the need to be combined with either mTOR inhibitor or anti-HER agent.

Our third reason is the lack of an approved companion diagnostic test. The recent withdrawal of the randomized phase III ENDEAR (NCT02929576; Efficacy and Safety Study of Enzalutamide in Combination With Paclitaxel Chemotherapy or as Monotherapy Versus Placebo With Paclitaxel in Patients With Advanced, Diagnostic-Positive, Triple-Negative Breast Cancer) trial confirms our concern. ENDEAR was supposed to compare enzalutamide and paclitaxel to placebo and paclitaxel in diagnostic-positive (Dx-positive) advanced TNBC. Dx+ is a genomic signature associated with androgen biology that was shown to predict response to enzalutamide in TNBC.[9] Developing predictive biomarkers will be crucial in selecting patients in the future trials to overcome the molecular heterogeneity of breast cancer that leads to variable responses to the same agent and compromising the survival end points in an unselected population.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at jco.org.

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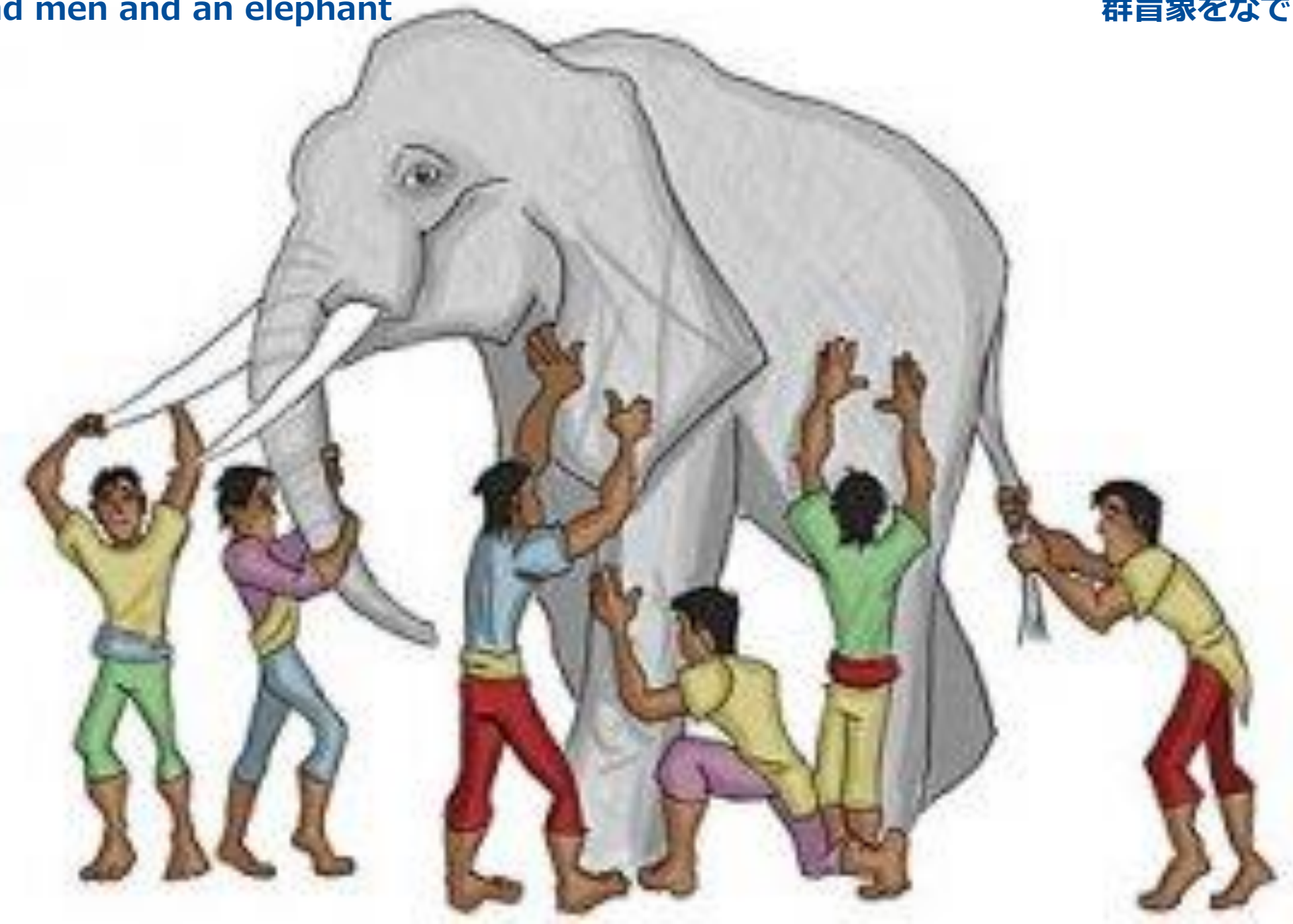
# おわりに

TNBCは，luminalやHER2サブタイプ乳癌と異なり，明確な「治療の標的」が存在しないことが最大の問題である。また，最近の基礎研究により，遺伝子発現プロファイルを用いればTNBCは，複数のサブタイプに分類することが可能であり，サブタイプ毎に治療効果の期待できる薬剤を選別できることが示唆されている。今後は，TNBCの明確かつ簡便なサブタイプ分類の検査法を確立し，そのサブタイプ分類で選別されたTNBC患者を対象に，最も有効性が期待される薬剤を用いた臨床試験が行われるべきである。そのようなアプローチにより，治療に難渋するTNBCの「個別化治療」が実現するかも知れない。さらに，各々のサブタイプ毎にTNBCの進展を牽引する“driver”遺伝子が判明すれば，その“driver”因子を標的とした新たな治療戦略の開発が可能である。

# blind men and an elephant

# 群盲象をなでる



blind men and an elephant

群盲象をなでる

# Open Your Eyes