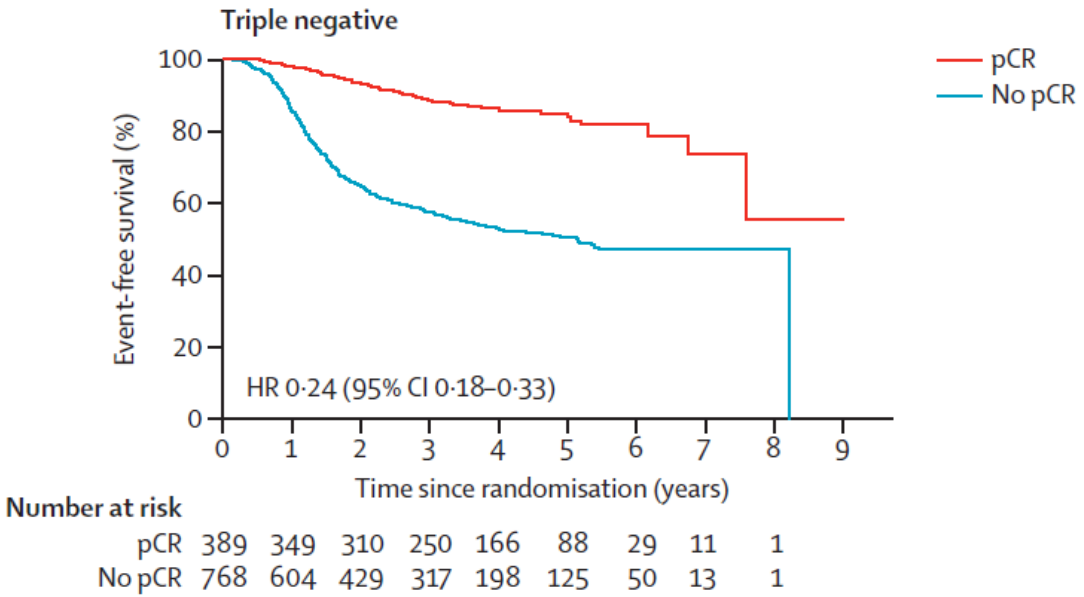
# Case Study

Chikako Shimizu, MD
Breast and Medical Oncology Division
National Cancer Center Hospital

# Triple-negative paradox




Cortazar P et al. Lancet 2014

# Case 1
# 34 y0 T1cN3bM0, Stage IIIc

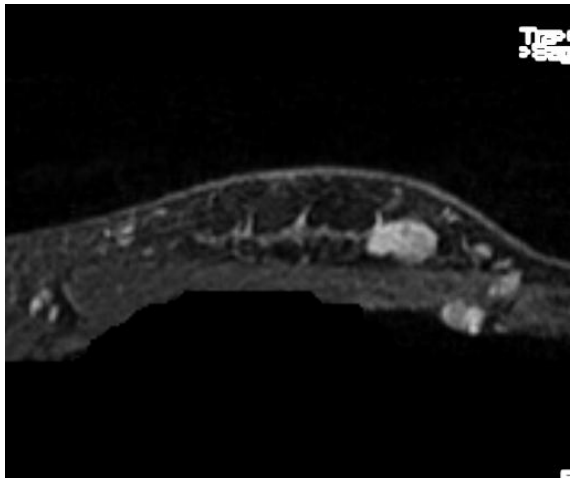
- Chief Complaints
  - A lump in the right breast
  - Fertility preservation
- Past History
  - Bipolar disorder
  - oGoP
- Family History
  - Mother: breast cancer (43yr)
  - Mother's sister: cancer
  - Mother's grandfather: cancer
  - Father: pancreatic cancer, renal cancer, gastric cancer

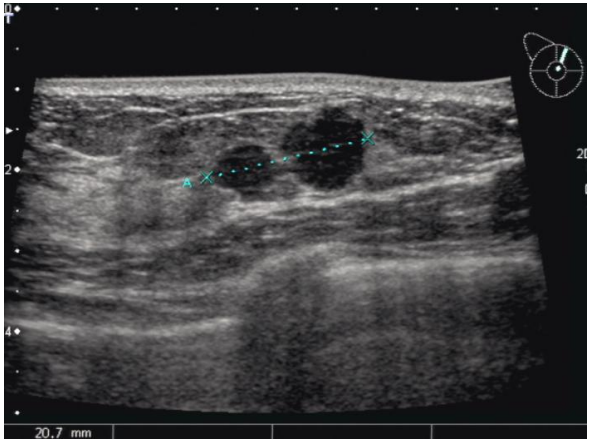
# Case 1
# 34 y0 T1cN3bM0, Stage IIIc

- Present History
  - Jul 2008 Consultation to NCCH
    - Clinical diagnosis: right breast cancer, T1cN3b(parasternal LN swelling) M0, Stage III B
    - CNB: Invasive carcinoma, Grade 3, ER<1%, PgR0, HER2 0.
  - Sep 2008 – Mar 2009
    - $FE_{100}C$ x4 f/b weekly paclitaxel x12⇒clinical CR
  - Apr 2009 rt. Bp+Ax
    - Residual intraductal carcinoma component of invasive ductal carcinoma (0.07x0.05 cm) with clear margin, n=0/5
  - Jun –Jul 2009 adjuvant radiotherapy
    - 66Gy, chest wall

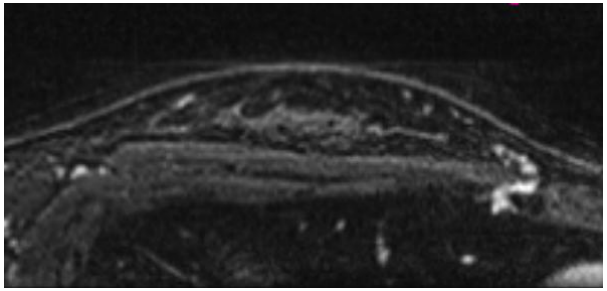
# Case 1 Clinical Images

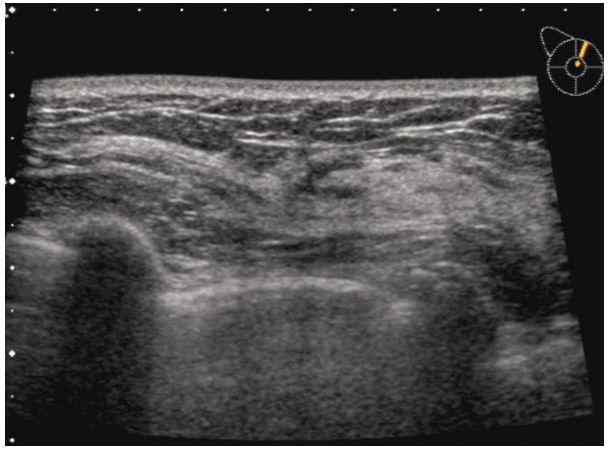
Pre NAC



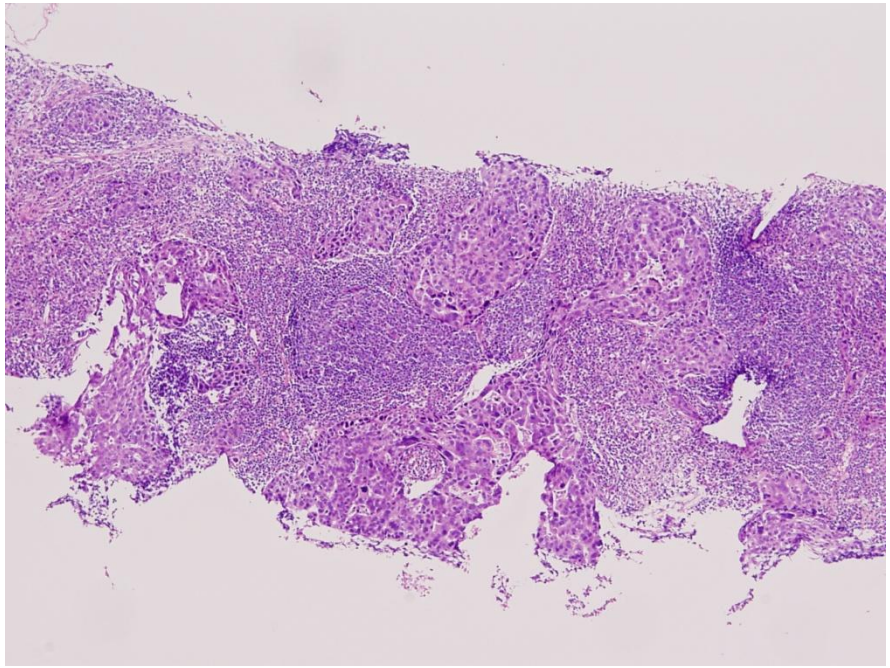



Post NAC

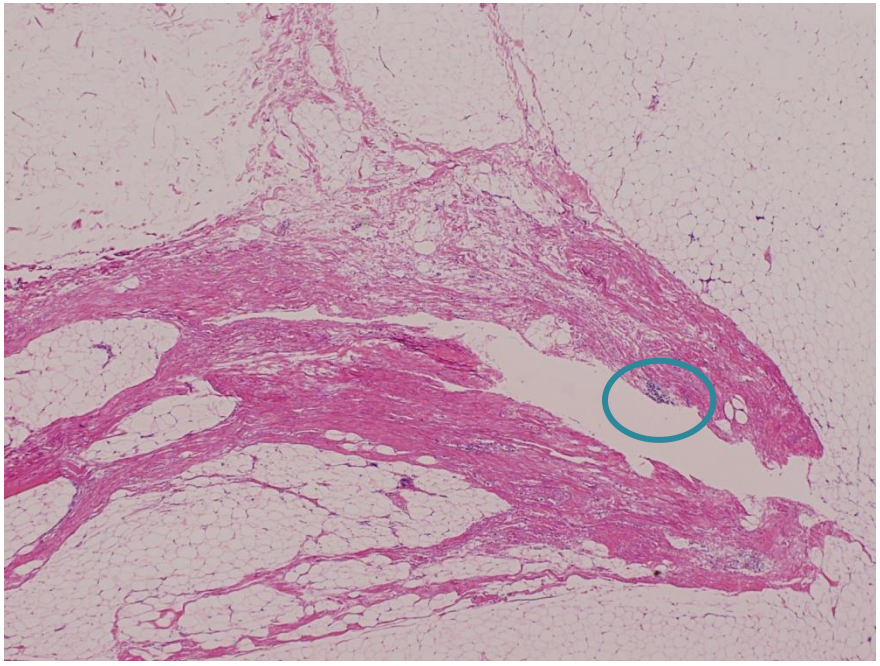


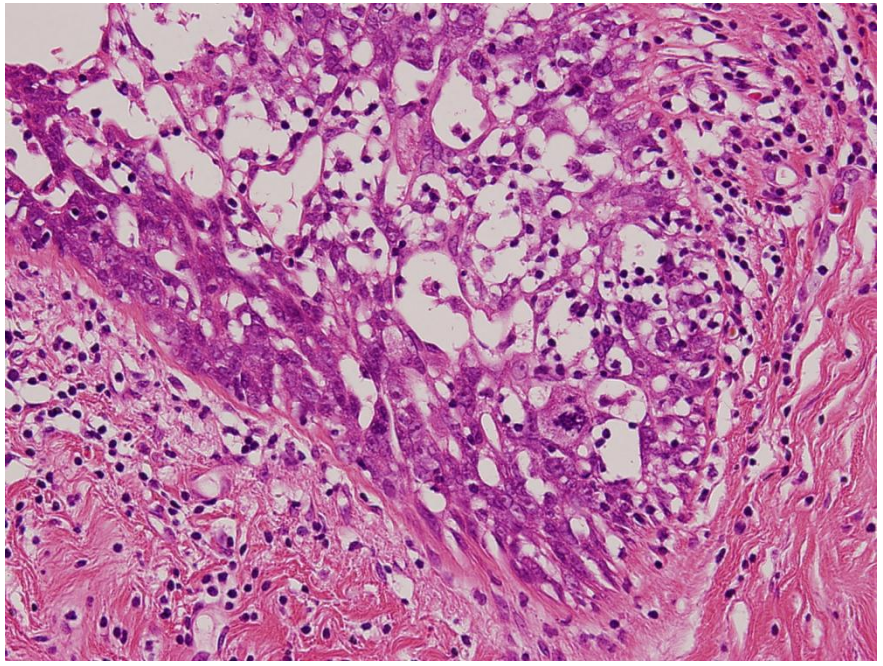


Pre NAC



Post NAC





# Case 1
# 34 yo T1cN3bM0, Stage IIIc

- Present History
  - Jul 2008 First visit to NCCH
  - Aug 2008 Consultation to a reproductive specialist
  - Sep 2009 Egg collection, embryo Cryopreservation (1 embryo)
  - Sep 2008 – Mar 2009
    - $FE_{100}C$ x4 f/b weekly paclitaxel x12⇒clinical CR
    - Oct 2008 Egg collection, embryo cryoprervation (3 embryos)
  - Apr 2009 rt. Bp+Ax
  - Oct 2009 Restoration of menstrual cycle
  - Jun –Jul 2009 adjuvant radiotherapy
    - 66Gy, chest wall
  - Oct 2010 Embryo transfer (successful pregnancy in the 3rd attempt)
  - Aug 2011 Delivery
  - No evidence of recurrence as of Apr 2014

# Case 2
# 37 yo T2N1M0, Stage IIB

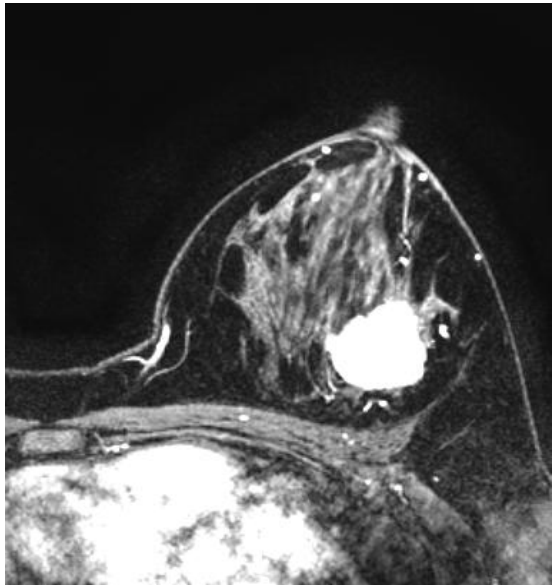
- Chief Complaints
  - A lump in the left breast
- Past History
  - oGoP
- Family History
  - No family history of cancer

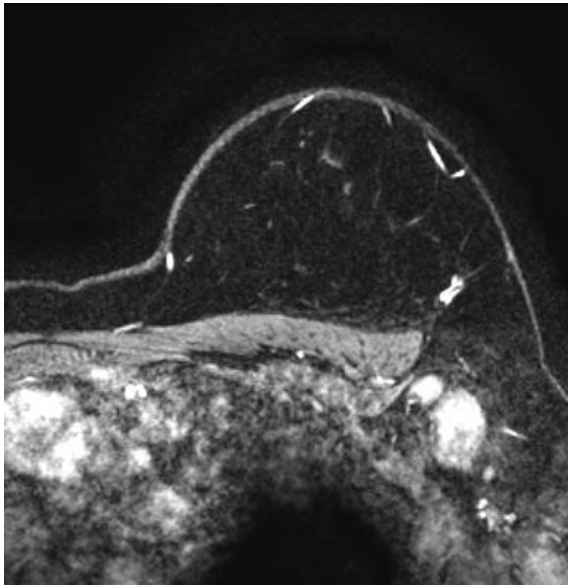
# Case 2
# 37 yo T2N1M0, Stage IIB

- Present History
  - Jun 2011 Consultation to NCCH
    - Clinical diagnosis: left breast cancer, T2N1M0, Stage II B
    - CNB: Invasive ductal carcinoma, Grade 3, ER 0, PgR<1%, HER2 0.
    - Did not give consent to participate in a randomized neoadjuvant study of carboplatin
  - Jul 2011 – Jan 2012
    - $FE_{100}C$ x4 f/b weekly paclitaxel x12⇒clinical PR
  - Feb 2012 lt. Bp+Ax
    - Residual invasive ductal carcinoma (2.3x1.4cm) with positive margin, n=3/13
  - Mar 2012 additional resection with clear margin
    May –Jun 2012 adjuvant radiotherapy
    - 50Gy+10Gy boost, left breast
  - Jun 2013 recurrence to ipsilateral breast and supraclavicular LNs

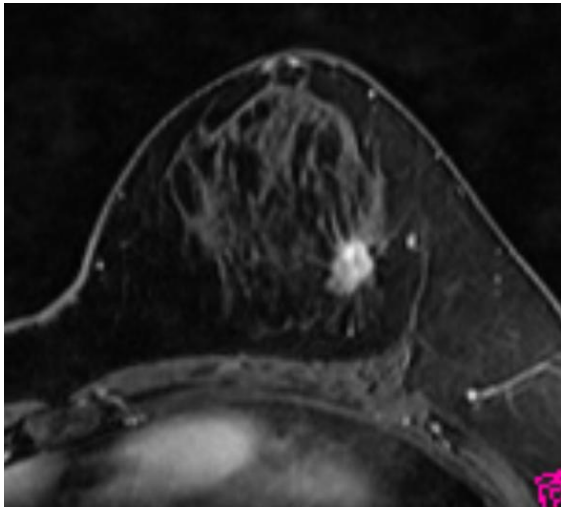
# Case 2 Clinical images

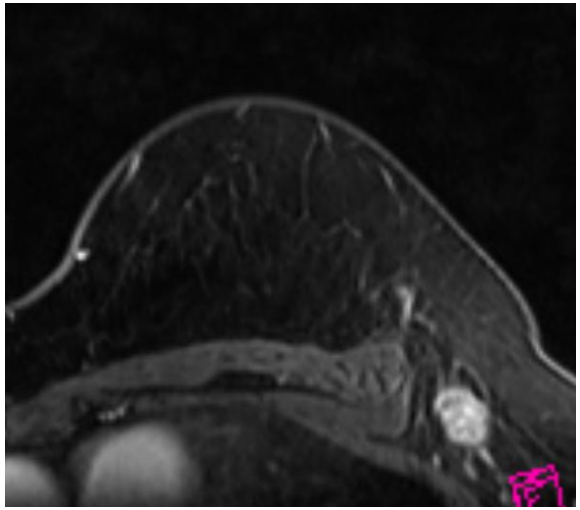
Pre NAC



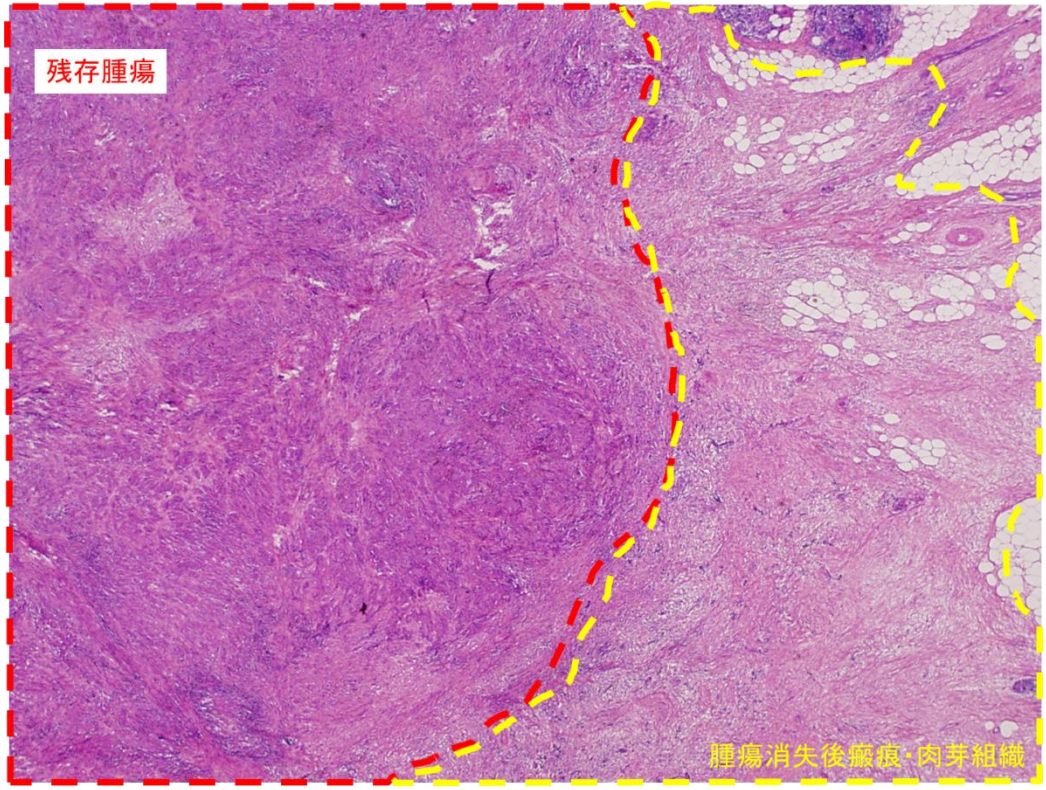


Post NAC

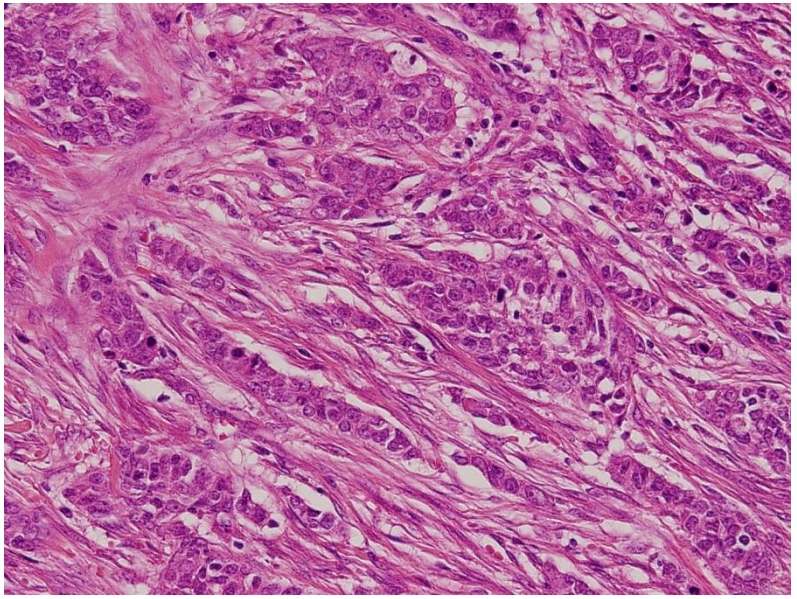


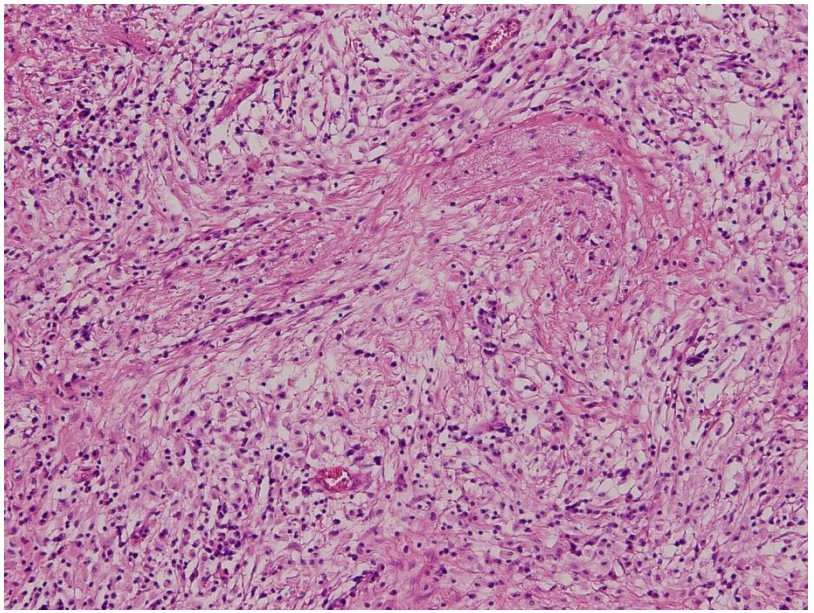


Residual tumor

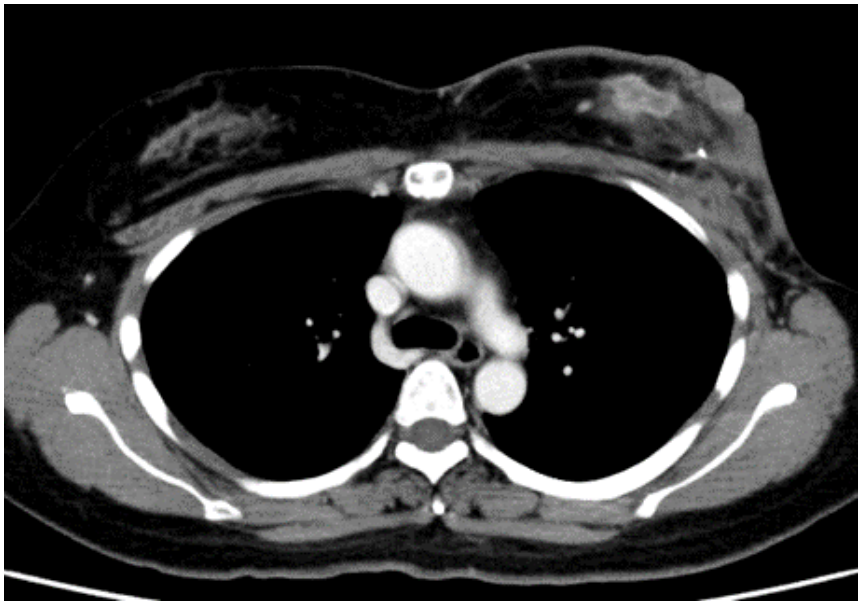


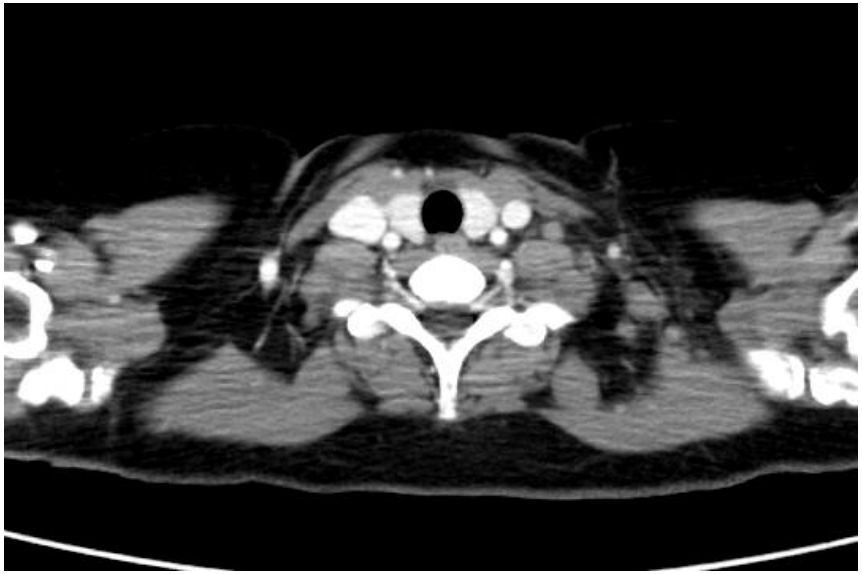

Granulation tissue





recurrence to ipsilateral breast and supraclavicular LNs
(a year after adjuvant radiotherapy)



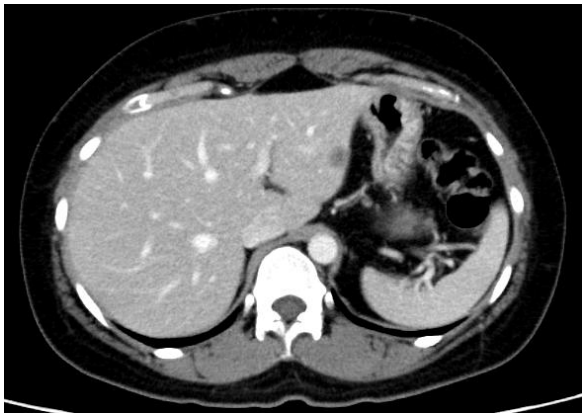


# What kind of treatment would you offer to her?

1. Eriburin
2. Oral FU
3. Platinum agents
4. Taxane-rechallenge + bevacizumab
5. Others
6. Clinical trials

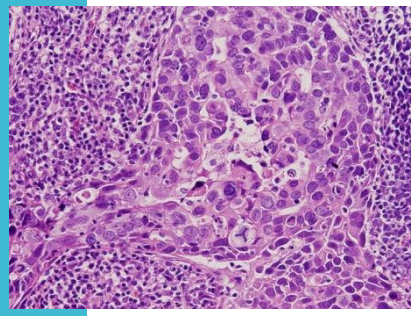
# Case 2
# 37 yo T2N1M0, Stage IIB

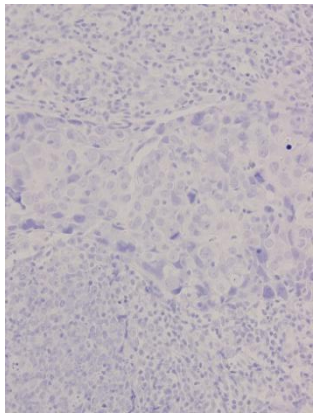
- Jun - Aug2013 Phase I/II study of eriburin/oraparib for patients with TNBC pretreated with an anthracycline and a taxane
- Aug 2013 PD
- Consent to TOPICS/TOP-GEAR
- Sep 2013-Mar 2014 Phase II study of carboplatin/S1 for metastatic TNBC (best response: SD)
- Mar 2013 PD (local progression and solitary liver metastasis)
- Apr 2014- gemcitabine

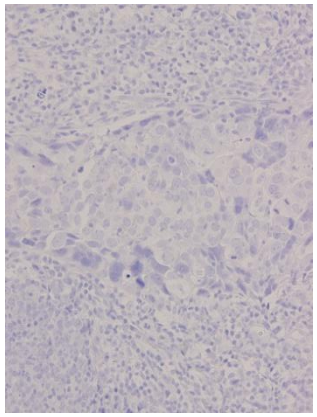


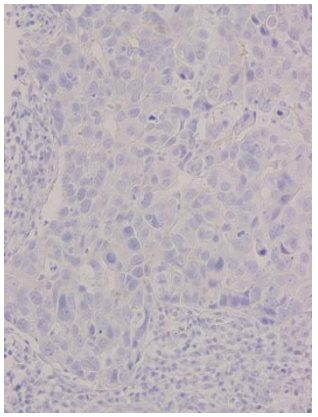
# What makes this difference?

**Case 1**



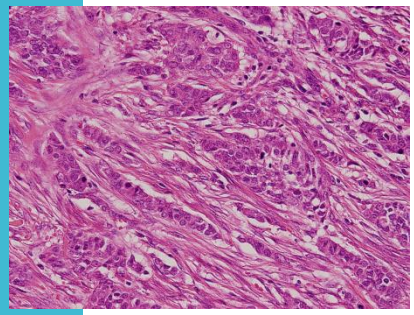


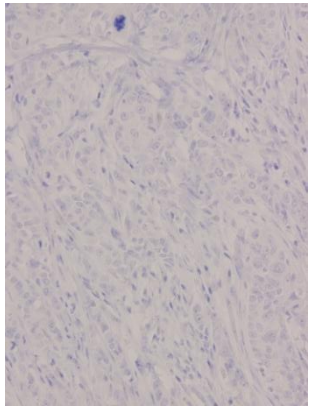


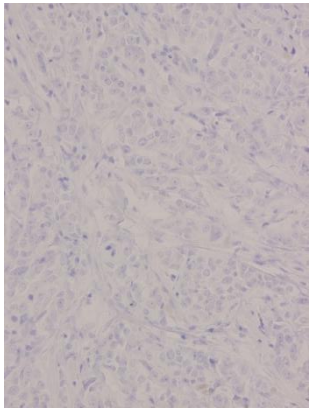


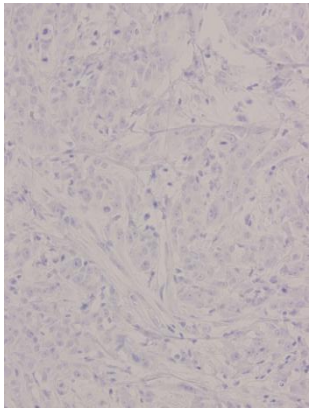
ER PgR HER2

**Case 2**





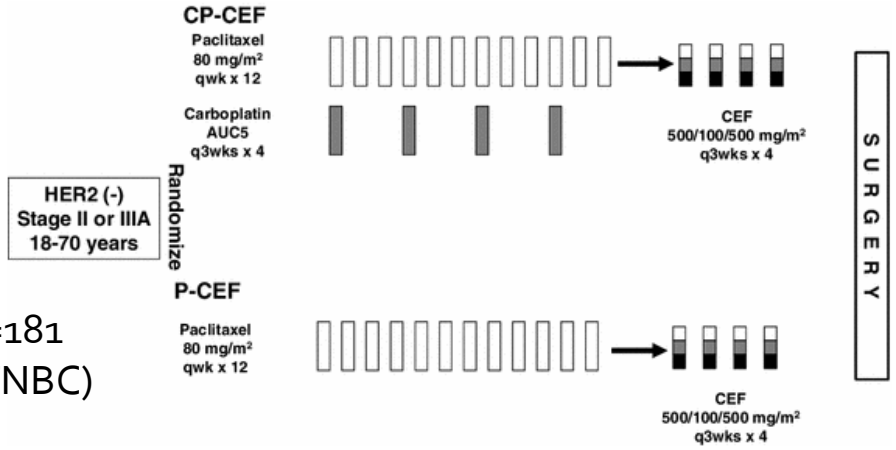




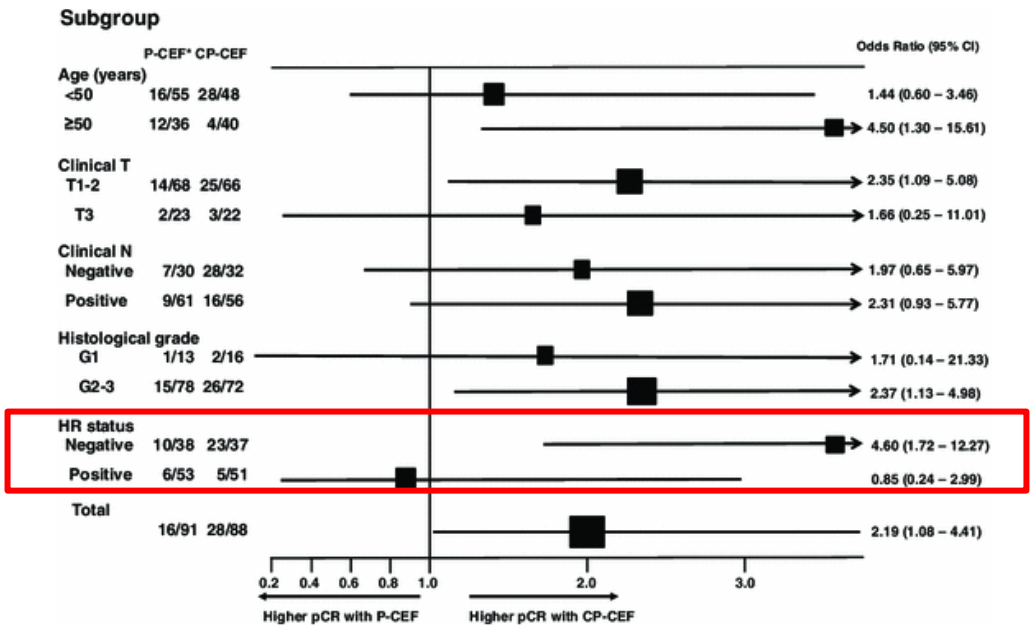
- Treatment
- Biology

# carboplatin

Randomized phase II study of weekly paclitaxel with or without carboplatin followed by FEC as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression

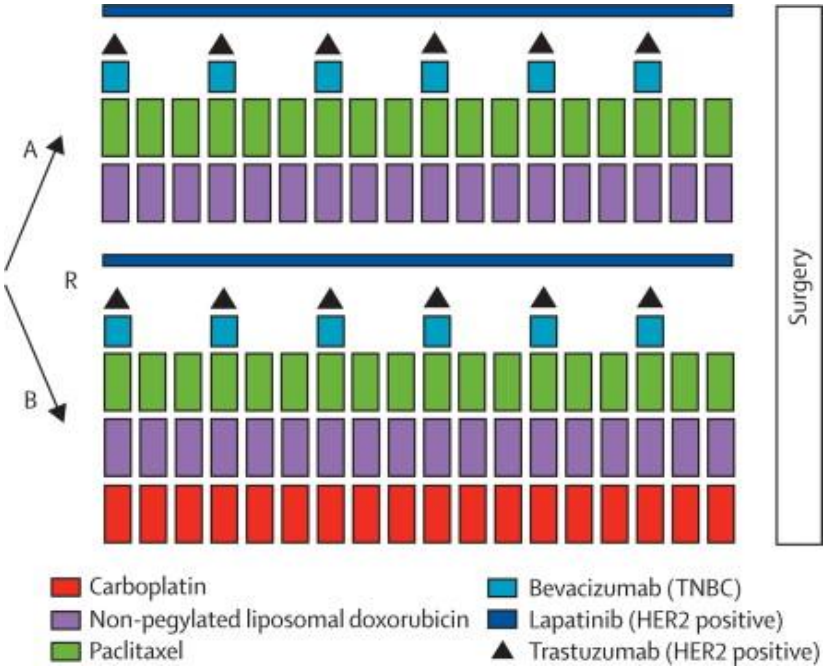



N=181
(75 TNBC)

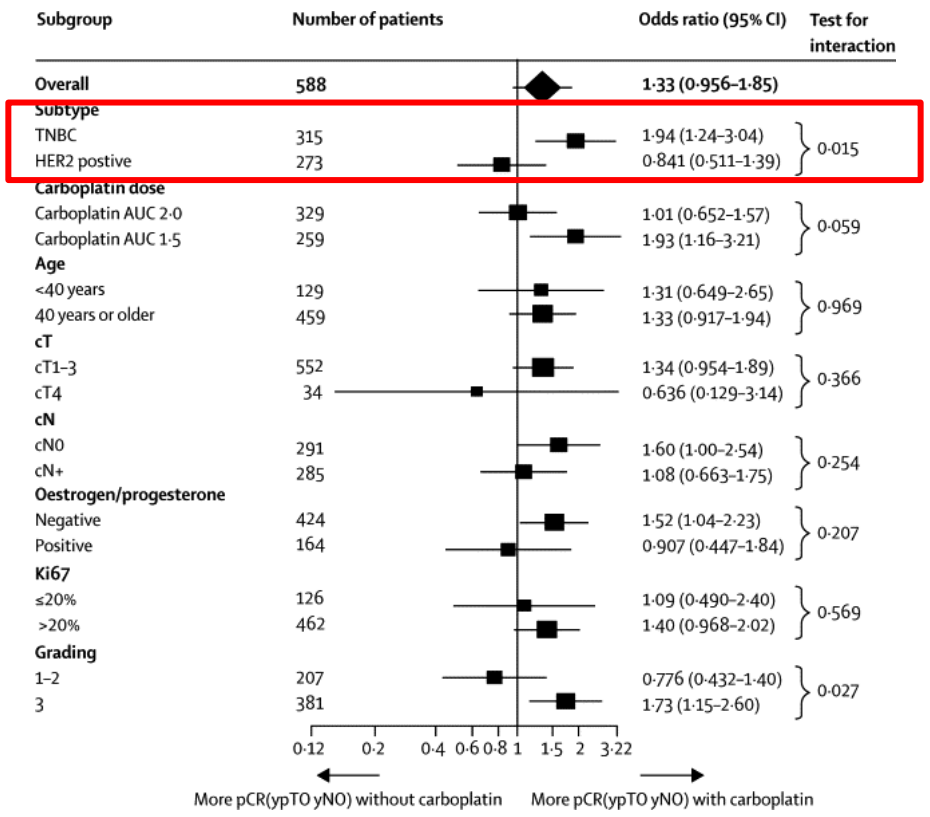



Ando et al. Breast Cancer Res Treat 2014

# GeparSixto

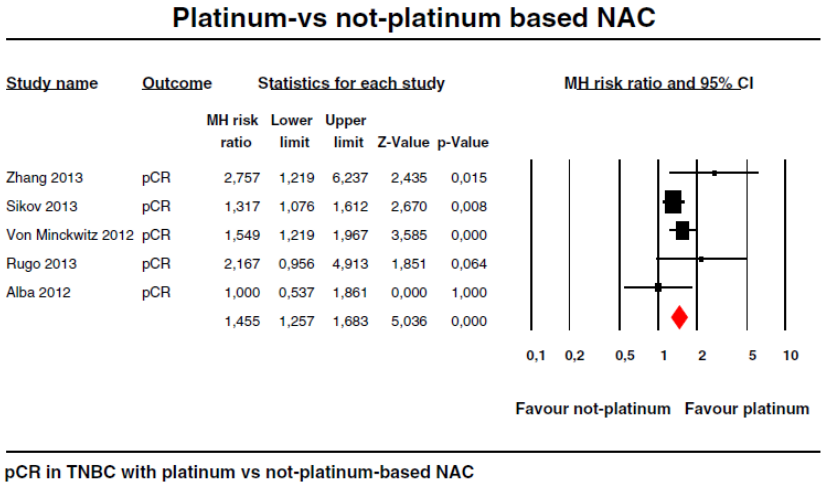



carboplatin: AUC 1.5-2.0 q1wks



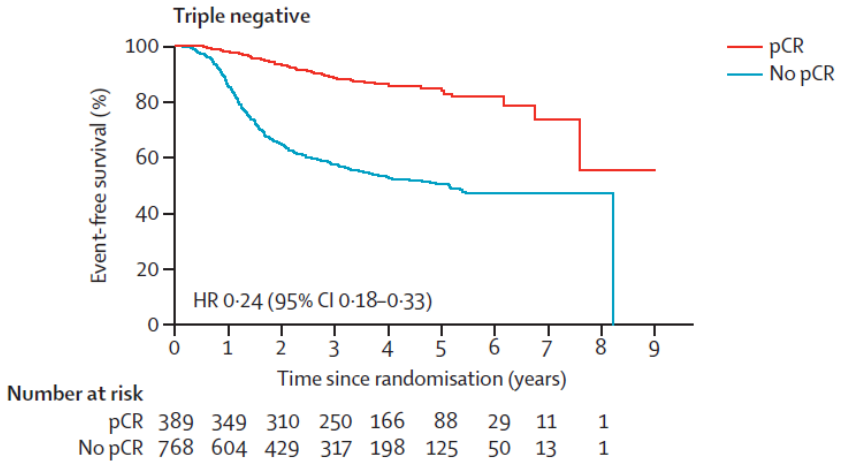

von Minckwitz, Lancet Oncol 2014

# Platinum agents in TNBC: meta-analysis of published data




pCR in TNBC with platinum vs not-platinum-based NAC

Petrelli, Breast Cancer Res Treat 2014

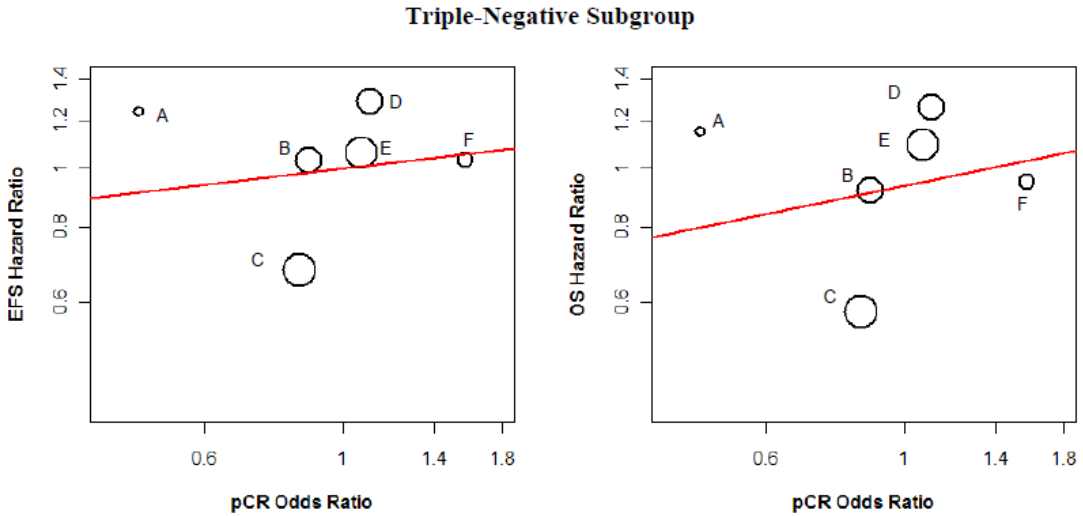



Cortazar P et al. Lancet 2014

# VOTING 1

Do you think that pCR an appropriate endpoint for new drug approval for TNBC ?

1. Yes
2. No



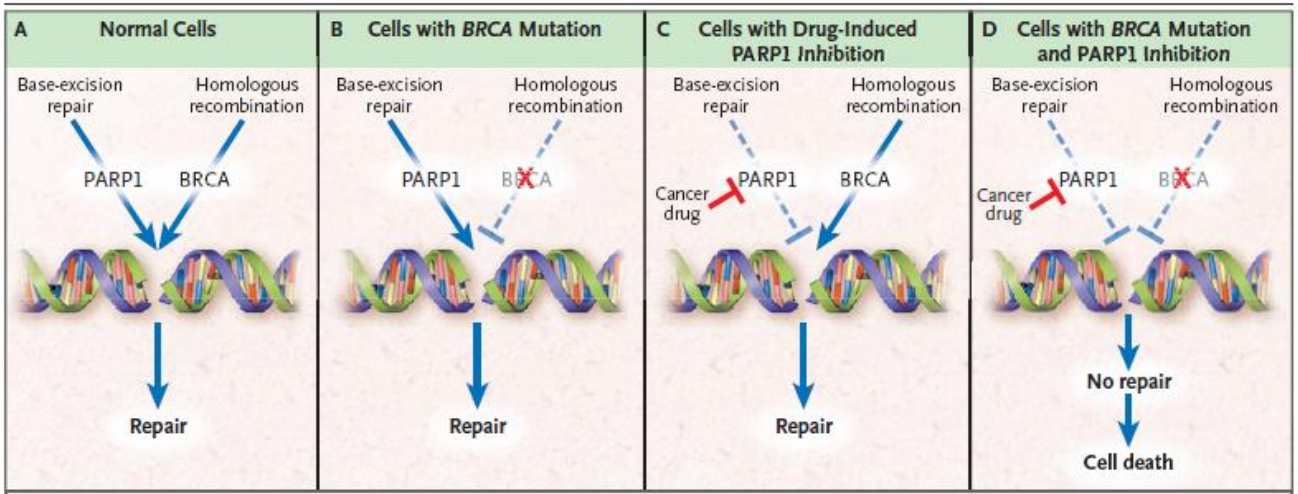
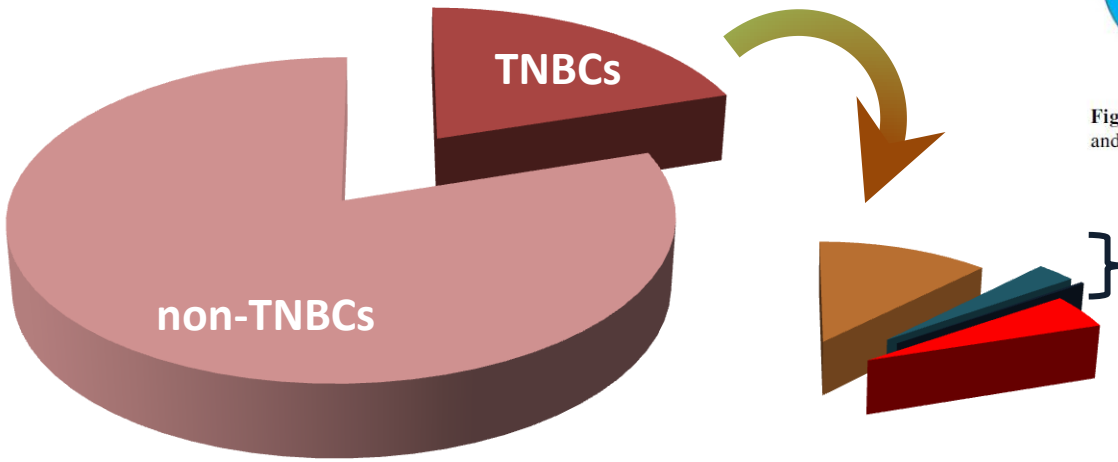



Figure 1. Mechanism of Cell Death from Synthetic Lethality, as Induced by Inhibition of Poly(Adenosine Diphosphate [ADP]–Ribose) Polymerase 1 (PARP1).

# All breast cancers



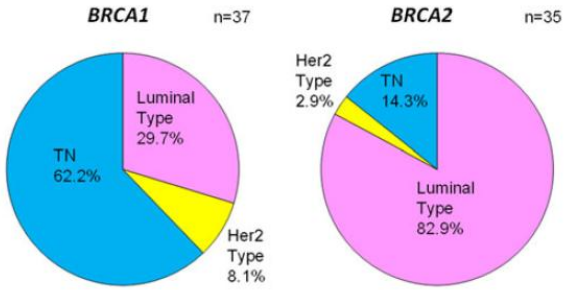




**Fig. 2** Type of breast cancer with *BRCA1/2* mutation in probands and family members

Nakamura, Breast Cancer, e-pub ahead of print 2013

*BRCA1* mutation

germline (14% of TNBCs)

sporadic ( 1% of TNBCs)

[Gonzalez-Angulo, *Clin. Cancer Res.*,(2011)]

# PARP inhibitor

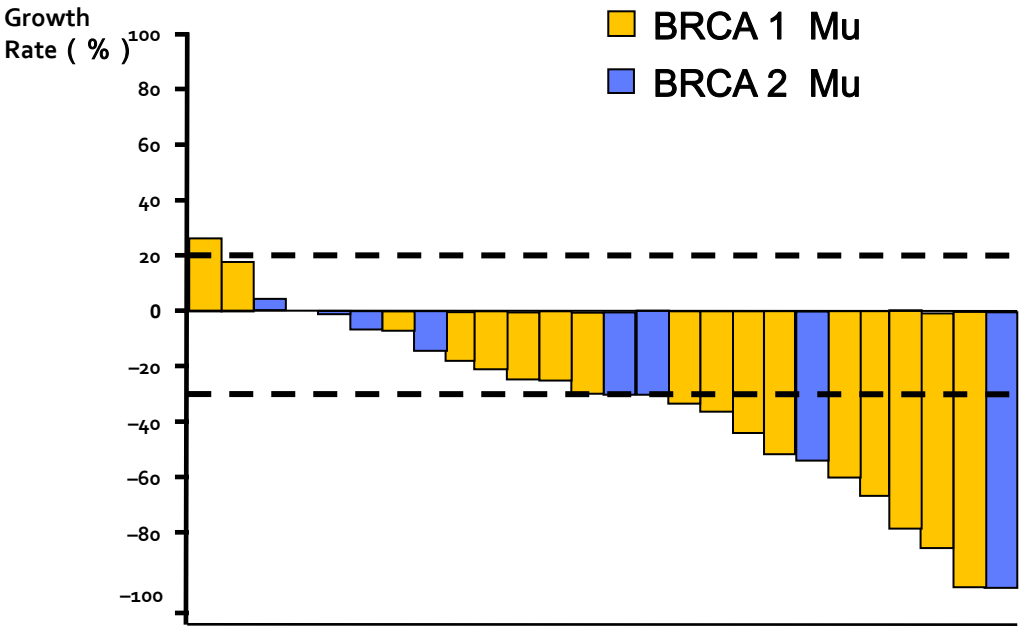
## Patient's characteristics of phase I AZD-2281 (Olaparib)

| Phase IA | | Phase IB | |
|---|---|---|---|
| Tumor Type-no. (%) | N=60 | Tumor Type-no. (%) | N=50 |
| Ovarian | 21 (35) | Ovarian | 47 (94) |
| Breast | 9 (15) | Primary peritoneal | 2 ( 4) |
| Colorectal | 8 (13) | Fallopian tube | 1 ( 2) |
| Melanoma | 4 ( 7) | Histology | |
| Sarcoma | 4 ( 7) | Serous papillary | 34 (68) |
| Prostate | 3 ( 5) | Endometrioid | 2 ( 4) |
| Other | 11( 18) | Others | 14 ( 2) |
| BRCA mutation status all patients | | BRCA mutation status all patients | |
| BRCA1 Mutation | 17(28) | BRCA1 Mutation | 41(82) |
| BRCA2 Mutation | 5( 8) | BRCA2 Mutation | 9(18) |

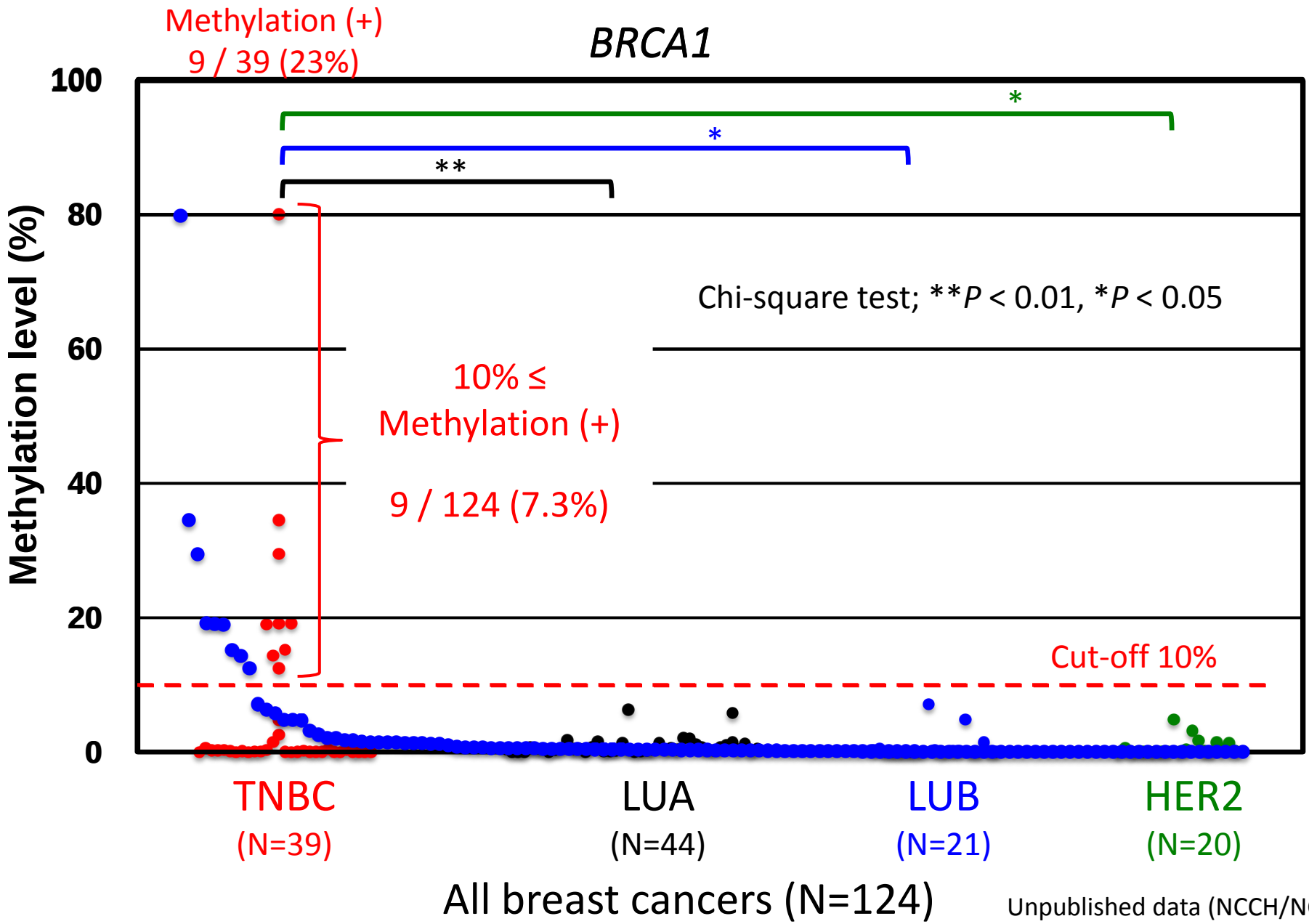
Fong PC et al.
N Engl J Med 361:123-134, 2009

Fong PC et al.
J Clin Oncol 28:2512-2519 2010

## Phase II Trial of Olaparib in BRCA Mu Breast Ca



# BRCA1 methylation in breast cancer




Unpublished data (NCCH/NCC-RI)

# Phase I/II trial of Eribulin plus Olaparib in Pts with Advanced Triple Negative BC

- Locally advanced or Metastatic BC.
- Triple negative BC
- Prior chemotherapy with an anthracycline & a taxane
- Adequate Organ Function
- ECOG PS 0 -1
- Age > 18 years
- Recovery of AE to Gr1
- Written IC

▶ Olaparib (25-100mg/continuous Or intermitted)
+
Eribulin (1.1-1.4mg/$m^2$,Day1, 8)

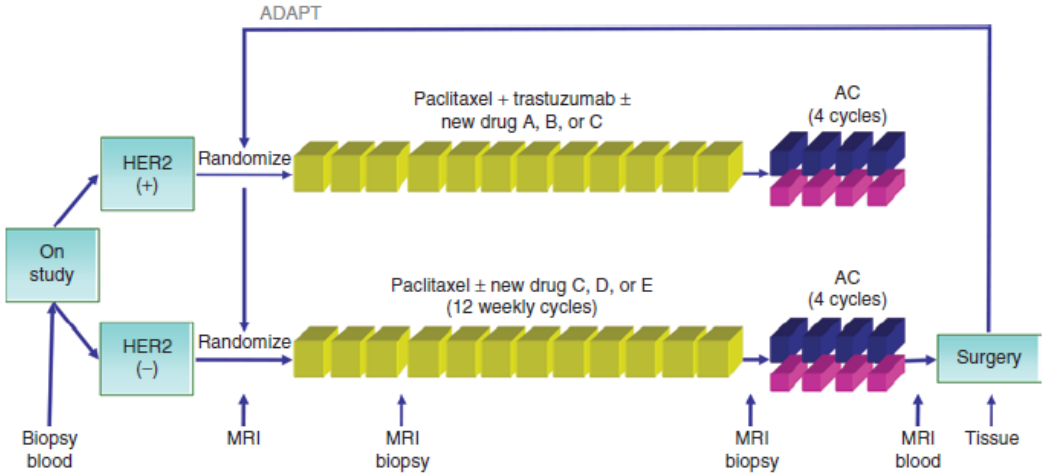
▶ Until PD

N=12-66

国内でPARP阻害剤が使用できる唯一の試験

- Primary Endpoint: MTD, DLT, RD (Phase I); Response rate (Phase II)
- Secondary Endpoint: PK/PD, POC, PGx (Phase I); Biomarker (Phase II)

# Assessment of IND using neoadjuvant platform with novel trial design **(I-SPY2)**




Veraparib (ABT888): a PARPi

| Signature | Estimated pCR Rate (%) | | Probability Veriparib/ CBDCA is superior to control (%) | Predictive probability of success in Phase 3 (%) |
|---|---|---|---|---|
| | Veriparib/ CBDCA (n=72) | Concurrent control (n=44) | | |
| All HER2- | 33 (23-43) | 22 (10-35) | 92 | 55 |
| HR+/HER2- | 14 (4-27) | 19 (6-35) | 28 | 9 |
| HR-/HER2- | 52 (35-69) | 26 (11-40) | 99 | 90 |

Rugo et al. SABCS 2013

# VOTING 2

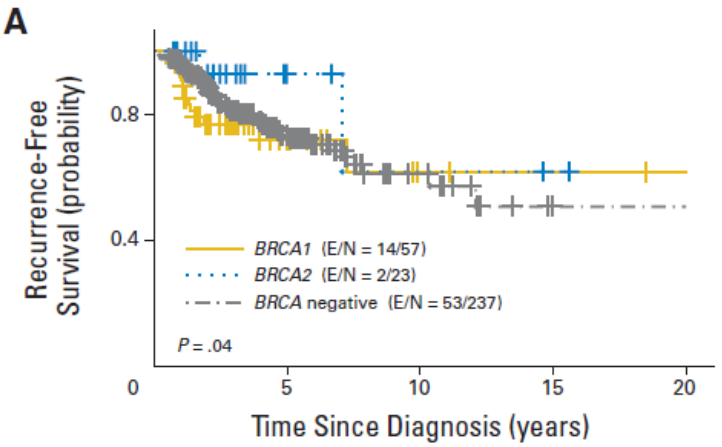
Should germline BRCA status be factored into systemic therapy decisions?

1. Yes
2. No

**Table 3.** Multivariate Logistic Regression Model for Pathologic Complete Response

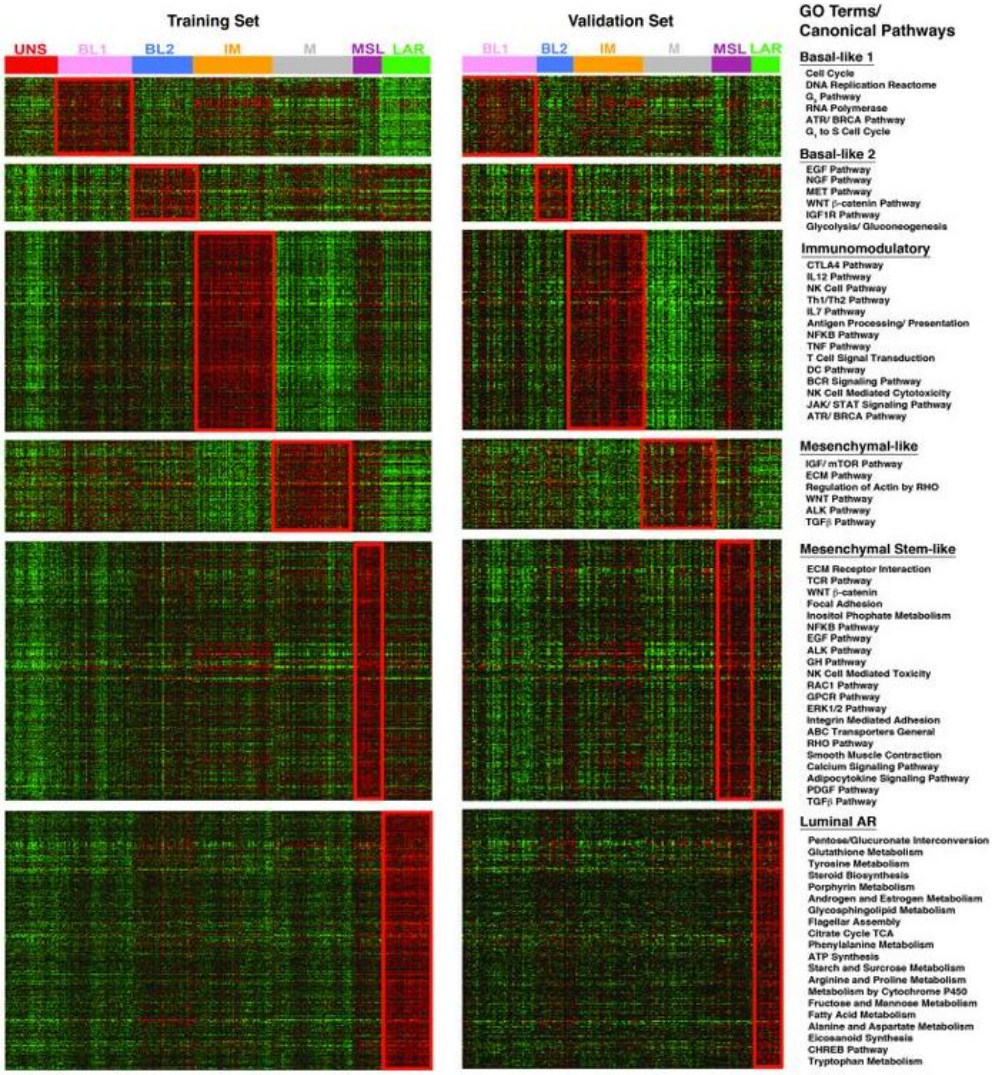
| Variable | OR | 95% CI | *P* |
|---|---|---|---|
| Age (n = 304) | 1.01 | 0.98 to 1.05 | .47 |
| Clinical tumor stage | | | |
| T2 (n = 166) *v* T1 (n = 38) | 0.63 | 0.27 to 1.47 | .28 |
| T3 (n = 56) *v* T1 (n = 38) | 0.88 | 0.32 to 2.38 | .80 |
| T4 (n = 29) *v* T1 (n = 38) | 0.42 | 0.12 to 1.49 | .18 |
| T4d (n = 15) *v* T1(n = 38) | 1.87 | 0.49 to 7.15 | .36 |
| ER status, negative (n = 112) *v* positive (n = 192) | 1.98 | 1.06 to 3.69 | .03 |
| Nuclear grade, 3 (n = 180) *v* 1/2 (n = 124) | 1.56 | 0.82 to 2.99 | .18 |
| Trastuzumab use, yes (n = 45) *v* no (n = 259) | 4.16 | 2.03 to 8.52 | < .001 |
| *BRCA* mutation, *BRCA1* (n = 54) *v* noncarriers (n = 227) | 3.10 | 1.52 to 6.32 | .002 |
| *BRCA2* (n = 23) *v* noncarriers (n = 227) | 0.91 | 0.24 to 3.47 | .89 |

Abbreviations: ER, estrogen receptor; OR, odds ratio.



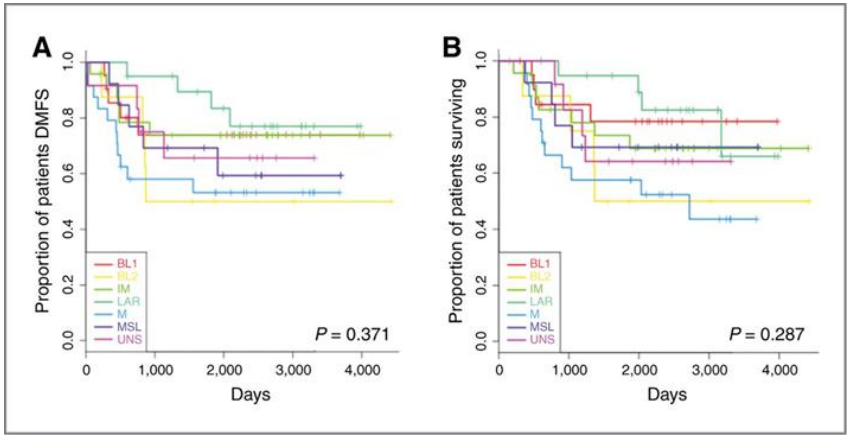

Arun. J Clin Oncol 2011

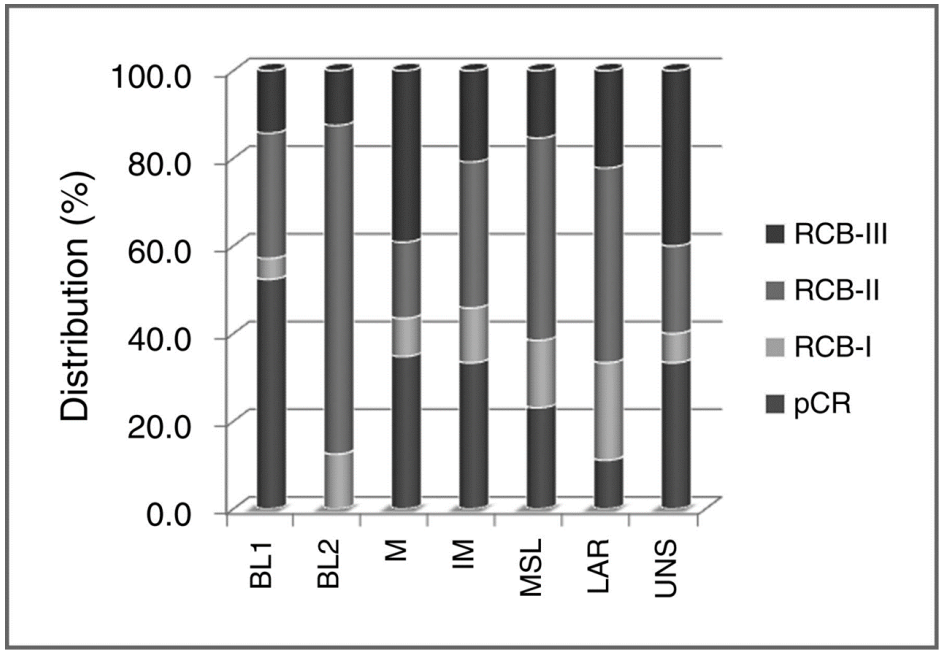
# Biology: TNBC subtypes




Lehmann et al. JCI 2011

# TNBC subtype and response to NAC




Masuda H et al. Clin Cancer Res 2013

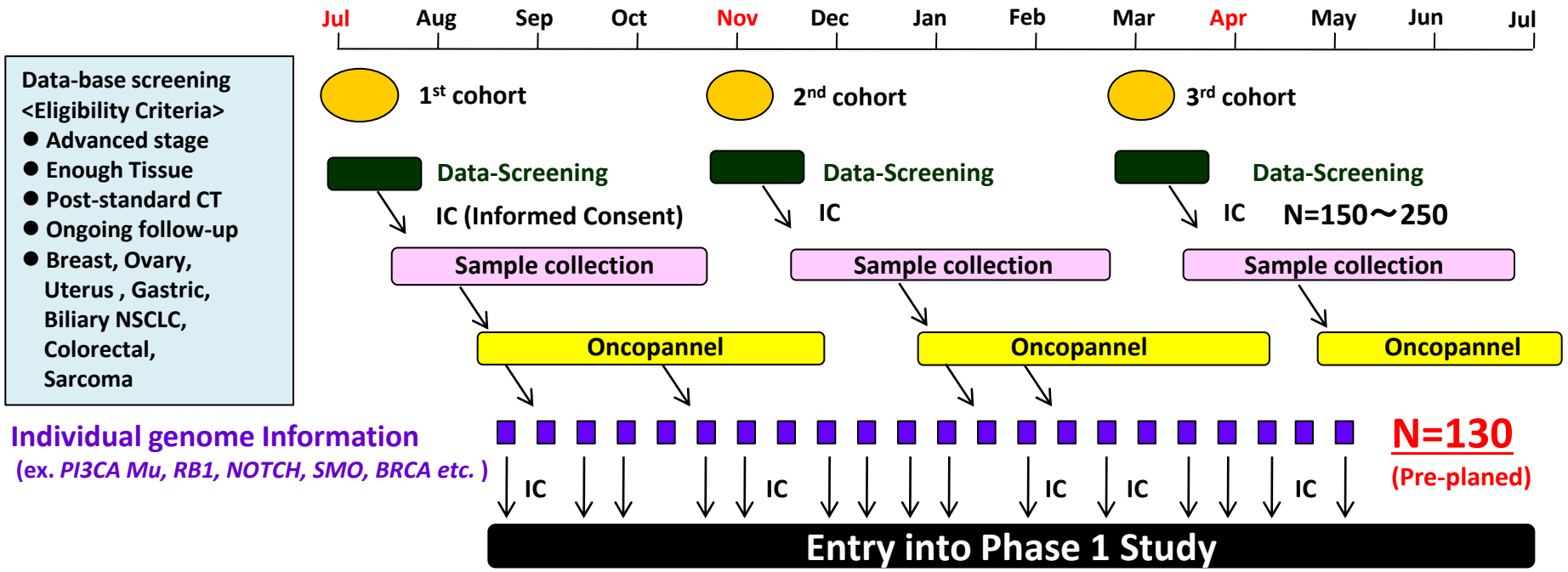
# Multiplex gene test

## NCC Oncopanel (Original)

| 90 mutation/amplicication genes (whole exon) | | | | | | 10 fusion genes |
|---|---|---|---|---|---|---|
| ABL1 | BRCA2 | EZH2 | JAK3 | NOTCH1 | RAC2 | ALK |
| AKT1 | CCND1 | FBXW7 | KEAP1 | NOTCH2 | RAD51C | RET |
| AKT2 | CDK4 | FGFR1 | KIT | NOTCH3 | RAF1 | ROS1 |
| AKT3 | CDKN2A | FGFR2 | KRAS | NRAS | RB1 | FGFR2 |
| ALK | CHEK2 | FGFR3 | MAP2K1 | NRG1 | RET | FGFR3 |
| APC | CREBBP | FGFR4 | MAP2K4 | NT5C2 | ROS1 | AKT3 |
| ARID1A | CTNNB1 | FLT3 | MAP3K1 | PALB2 | SETD2 | BRAF |
| ARID2 | CUL3 | HRAS | MAP3K4 | PBRM1 | SMAD4 | RAF1 |
| ATM | DDR2 | IDH1 | MDM2 | PDGFRA | SMARCA4 | NOTCH1 |
| AXIN1 | EGFR | IDH2 | MET | PDGFRB | SMO | NRG1 |
| BAP1 | ENO1 | IGF1R | MTOR | PIK3CA | STAT3 | . |
| BARD1 | EP300 | IGF2 | MYC | PIK3R1 | STK11 | . |
| BIM | ERBB2 | IL7R | MYCN | PTCH1 | TP53 | . |
| BRAF | ERBB3 | JAK1 | NF1 | PTEN | TSC1 | . |
| BRCA1 | ERBB4 | JAK2 | NFE2L2 | RAC1 | VHL | . |

- Formalin-fixed paraffin embedded tissue
- Customization of gene selection according to scientific and/or clinical interest
- Removal of Japanese polymorphism
- Accumulation of precise genomic datan

# Trial of Onco-Panel for Introduction into Clinical Study -Phase 1 (TOPICS-1)




◆ Primary Endpoint; **N=32 (25%)**

Percentage of No. Pt. entries Phase 1

◆ Secondary Endpoints; **N=26 (20%)**

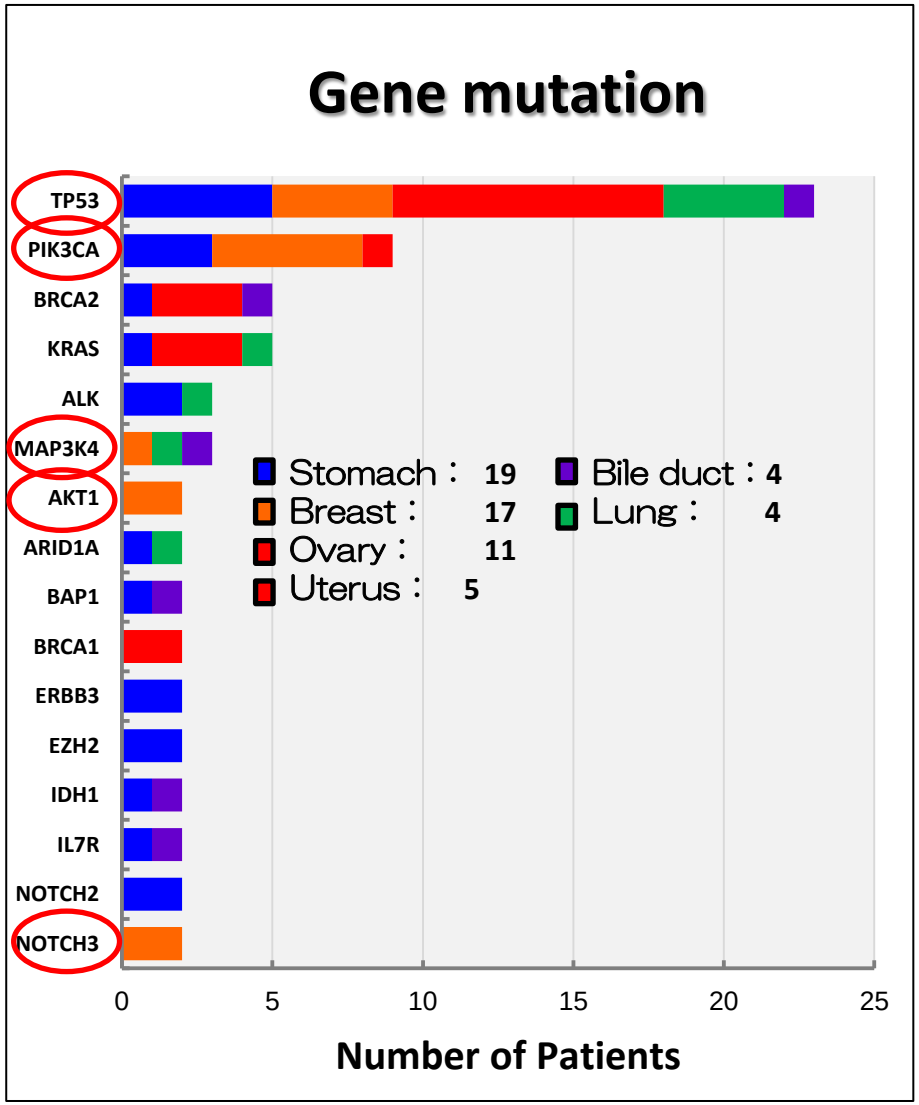
Percentage of No. Pt. entries Phase 1 with matched molecular target

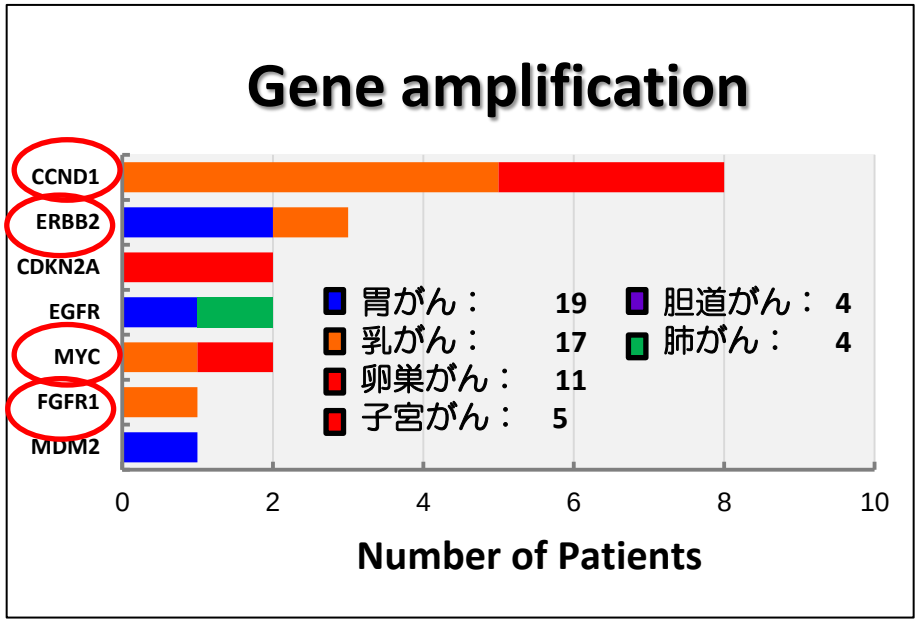
Feasibility of the assay.
Feasibility of the procedure.
Cost.

Candidate Of Phase 1

- PI3K inhibitor
- AKT inhibitor
- CDK4/6 inhibitor
- Hedgehog inhibitor
- PIM inhibitor
- PARP inhibitor
- PDL1 Antibody
- FGFR inhibitor
- PRL inhibitor
- PD1 Antibody
- Vintafolide
- Hsp90 inhibitor

# Detected mutation and amplification（n=60）



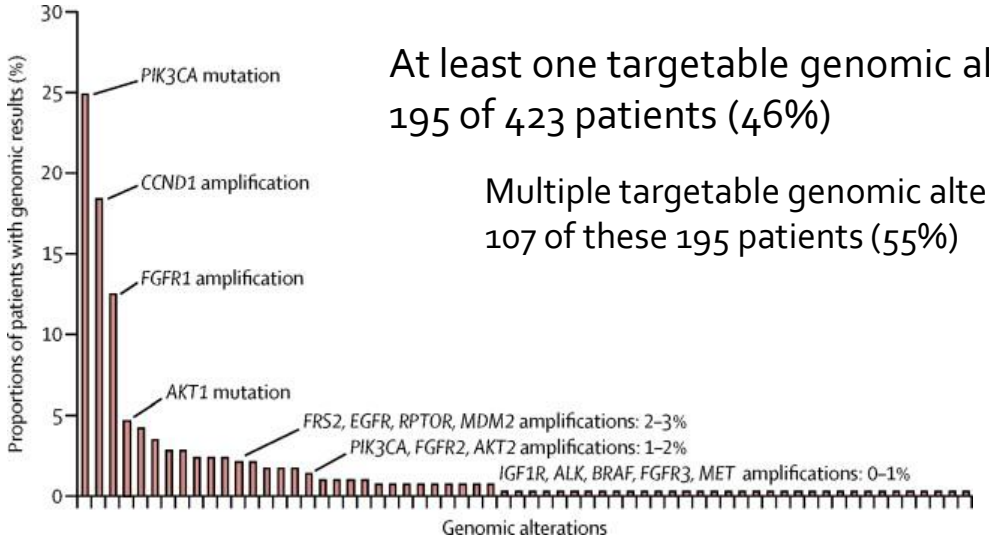

**Actionable mutations/amplifications**
**（治療方針の決定に関連しうる変異・増幅）**

COSMIC mutation:
PIK3CA (9), AKT1 (2), DDR2 (1), ERBB2 (1), ERBB3 (1), FGFR2 (1), MAP2K1 (1), PDGFRB (1)
3’-truncation mutation:
BRCA2 (2), BRCA1 (1)
Gene amplification:
CCND1 (8), ERBB2 (3), EGFR (2), FGFR2 (1)

**Patients with more than one actionable mutations： 28 of 60 patients (46%)**

Enrollment in phase I trial (breast cancer: n=3)

| | Genomic target | Matched drug | Anti-tumor activity |
|---|---|---|---|
| Breast ca. | AKT1 | AKT1 inhibitor | **PR** |
| Breast ca. | PIK3CA | PI3K inhibitor | PD |
| Breast ca. | - | Eribulin/Oraparib | PD |

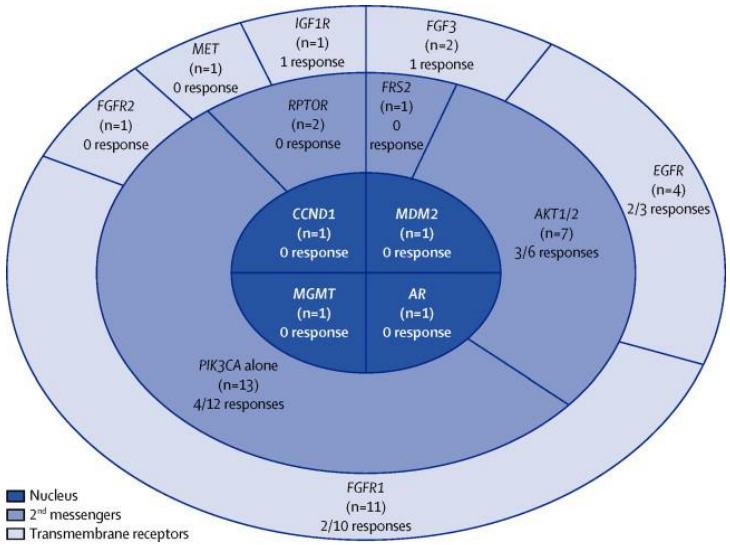



At least one targetable genomic alteration
195 of 423 patients (46%)

Multiple targetable genomic alterations
107 of these 195 patients (55%)

Figure 2 Distribution of targetable genomic alterations among screened patients

55 (13% of the biopsied patients, 28% of those with targetable alterations) received targeted treatment based on a genomic alteration




Andre F. Lancet Oncology 2014

# VOTING 3

Do you think that "oncopanel(s)" would be useful tools in drug development for TNBC?

1. Yes, it will become a necessary tool.
2. No, there's a room for innovation.

# Summary

Points to consider in developing treatment strategies for TNBC

1. Actionable biomarker / Drug development
2. Clinical trials using neoadjuvant platform / validation of surrogate endpoint
3. Patient enrichment by host genotyping/ TNBC subtyping
4. Innovative trial design
5. Integrative translational research