TNBC: (Neo) Adjuvant systemic therapy

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“Triple Negative” Breast Cancer

Immunohistochemistry

- ER and PR <1% nuclear
- HER2 “negative”: IHC 0 or 1+ staining or 2+ IHC staining with negative FISH

Histology

- High grade ductal
Triple-negative breast cancer (TNBC)

- No expression of ER, PR, HER2
- TNBC are biologically aggressive, with higher rates of relapse in the early stage and decreased overall survival in the metastatic setting.
- 15-20% of all breast cancers\(^1\), higher in African American
- 60% of BRCA1 mut and 20% of BRCA2 mut
- There is a major need to better understand the molecular basis of TNBC as well as to develop effective therapeutic strategies against it.
- Disease heterogeneity and the absence of well-defined molecular targets have made treatment of TNBC challenging.
- Current SOC: chemotherapy…

TNBC is histologically heterogeneous

- Invasive Ductal Carcinoma high grade
- Invasive Lobular Carcinoma high grade, pleomorphic
- High grade neuroendocrine
- Metaplastic, high grade
- Myoepithelial carcinoma
- Medullary
- Apocrine
- Adenoid-cystic
- Metaplastic, low grade

Poor prognosis

Good prognosis
Deconstructing the molecular portraits of breast cancer

Basal-like Claudin-low  HER2-enriched  Normal-like Luminal A and B

Claudin-low (CL)  Basal-like (BL)  Normal Breast-like (NBL)  Luminal A and B (LA and LB)  HER2-enriched (H2)
Molecular Characterization of Basal-Like and Non-Basal-Like Triple-Negative Breast Cancer

ALEIX PRAT, BARBARA ADAMO, MAGGIE C.U. CHEANG, CAREY K. ANDERS, LISA A. CAREY, CHARLES M. PEROU

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The Oncologist 2013;18:123–133
What do TNBCs that are nonBasal-like look like?

- Hierarchical clustering of 1,005 tumors from a combined data set using the available PAM50 genes.

- TN tumors that are HER2-enriched have similar gene expression patterns as nonTN that are HER2-enriched.

- TN tumors that are Luminal A/B have similar gene expression patterns as nonTN that are Luminal A/B.
What do TNBCs that are nonBasal-like look like?

A. ESR1

B. PGR

C. ERBB2

D. EGFR

E. AR

F. FOXA1

Basal-like  HER2-enriched  Luminal A/B

The Oncologist 2013;18:123–133
Identification of Human TNBC Subtypes

Basal-like 1: Cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: Immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

TNBC encompasses multiple subtypes identified by gene expression

- Cell cycle, proliferation genes and DNA repair
- Growth factor signaling genes
- Immune cell processes (medullary breast cancer)
- Cell motility and differentiation
- MET processes
- Similar to mesenchymal but growth factor signalling (medulary)
- AR downstream genes; luminal features

**Subtypes:***
- **UNS** Unclassified
- **BL1** Basal-like 1
- **BL2** Basal-like 2
- **IM** Immunomodulatory
- **M** Mesenchymal
- **MSL** Mesenchymal/Stem-like
- **LAR** Luminal/Androgen receptor

**Pathways:**
- Cell cycle/DNA replication
- p63/cell communication
- Immune Signaling
- Focal Adhesion/growth factors stem cell
- Androgen Signaling

**GO Terms/Canonical Pathways:**
- Basal-like 1 Cell Cycle/ERBB/Notch/IL-6/PI3K/AKT/MAPK/MTOR/Notch Pathway/DEB Pathway
- Basal-like 2 Cell Cycle/ERBB/Notch/IL-6/PI3K/AKT/MAPK/MTOR/Notch Pathway/DEB Pathway
- Immunomodulatory: Chronic Inflammation/Carcinogenesis Pathway
- Growth factor signaling: Medullary Breast Cancer

Lehmann/ Pietenpol, JCI 2011
PAM50 versus 7-TN subtype Classifications

Masuda et al. CCR 2013
How can Triple Negative Breast Cancers be stratified

TNBC

20-30%
Luminal/AR

Luminal A+B
HER2-Enriched

70-80%
Basal

Claudin-low / Mesenchymal
Basal-like

AR Expression

Low – Immune – High
Gene Expression or TILs

Low – Immune – High
Gene Expression or TILs

Lapatinib-Sensitivity

Proliferation

Chemo-Sensitivity

Prat et al., JAMA Oncology 2016 (PMID:27281556).
Prat et al., The Oncologist, 2013 (PMID:23404817)
Rationale for neoadjuvant therapy

- Down-staging allows breast-conservative surgery (BCS) in selected cases (absolute increase of 10% in conservation with same local control rates)
- *In vivo* assessment of tumor sensitivity to CT
- Less chance of emerging resistant tumor clones
- Intact vasculature
- Residual disease burden has prognostic value
- Tissue collection for research
- Triple negative disease:

Liedtke, JCO 2008
von Minckwitz, JCO 2012
Role of platinum agents
The concomitant use of platinum agents with chemo in GeparSixto was associated with markedly higher toxicity, which resulted in less than 60% patients completing all their chemo cycles, compared to the control group. 49 vs 36% patients discontinued due to toxicity.
CALGB40603: phase II trial neoadjuvant chemo +/- carbo +/- bev. pCR rate in TNBC

The concomitant use of platinum agents with chemo in CALGB 40603 was associated with markedly higher toxicity, which resulted in significantly fewer patients receiving 11-12 doses of paclitaxel when carboplatin was added, compared to the control group (<65% in PCarbo → AC vs. >85% in P → AC).

Sikov, JCO 2015
GeparSixto: phase II trial neoadjuvant chemo/bev +/- carbo – DFS in TNBC

3 yr DFS 85.8%
3 yr DFS 76.1%

HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), p=0.0350
PM 36/157 events
PMCb 21/158 events

von Minckwitz, SABCS 2015
CALGB40603: phase II trial neoadjuvant chemo +/- carbo +/- bev. EFS in TNBC

Sikov, SABCS 2015
CALGB40603: phase II trial neoadjuvant chemo +/- carbo +/- bev. OS in TNBC

HR=1.15 (0.74-1.79), p=0.53

Sikov, SABCS 2015
pCR improvements with carboplatin and survival benefit in TNBC

- Existing clinical trials have **not shown statistically valid** improvement of DFS or OS with the incorporation of platinum (current trials are not powered for that)

- The CALGB 40603 investigators, the Alliance Breast Committee, and NCCN **have not endorsed** the use of neoadjuvant platinum agents as a **new standard of care** for patients with TNBC

- **Previous studies** (BEATRICE, E5103, GeparQuinto, NSABP B-40) have failed to demonstrate improvements in long-term outcomes (EFS, RFS or OS) in stage I-III TNBC with the addition of **bevacizumab** to a control (neo)adjuvant chemotherapy regimen

  We don’t know how much of a pCR delta is needed to translate into DFS or OS advantage…
Platinum sensitivity biomarkers

- BRCA
- HRD
- Intrinsic subtype
- TILs
GeparSixto and BRCA status: pCR

ypT0 ypN0

<table>
<thead>
<tr>
<th>gBRCA wt</th>
<th>gBRCA mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 2.09 (1.24-3.53)</td>
<td>OR 1.60 (0.52-4.93)</td>
</tr>
<tr>
<td>P=0.005</td>
<td>P=0.413</td>
</tr>
</tbody>
</table>

- PM
  - gBRCA wt: 33.1%
  - gBRCA mut: 50.0%
  - N=121

- PM+Cb
  - gBRCA wt: 50.8%
  - gBRCA mut: 61.5%
  - N=120

Von Minckwitz G, SABCS 2015
GeparSixto and BRCA status: DFS

- Favorable prognosis after pCR was confirmed and is independent of gBRCA status.

Von Minckwitz G, SABCS 2015
HR score

\(\text{(nº LOH regions of intermediate size} > 1\text{Mb and} < \text{whole chromosome in the tumor genome)}\)

- HR deficiency characterizes breast cancers in BRCA 1/2 mutation carriers
  - Due to loss of heterozygosity at BRCA1 or BRCA2

- HR deficiency implicated in sporadic TNBC
  - Methylation
  - Somatic mutation
  - Other epigenetic mechanisms

- Identifies non-BRCA 1/2 carriers with “BRCA-like” cancers who may benefit from DNA repair-targeted strategies

GeparSixto and HR score

**PM**
- OR 2.05 (0.73-5.78)
- P=0.162

**PMCb**
- OR 4.13 (1.60 – 10.71)
- P=0.002

<table>
<thead>
<tr>
<th></th>
<th>HR non-deficient</th>
<th>HR deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM</strong></td>
<td>N=30</td>
<td>N=62</td>
</tr>
<tr>
<td>non-deficient</td>
<td>20.0%</td>
<td>33.9%</td>
</tr>
<tr>
<td>deficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PMCb</strong></td>
<td>N=27</td>
<td>N=74</td>
</tr>
<tr>
<td>non-deficient</td>
<td>29.6%</td>
<td></td>
</tr>
<tr>
<td>deficient</td>
<td>63.5%</td>
<td></td>
</tr>
</tbody>
</table>
Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers.

Denkert et al., J Clin Oncol. 2015 (PMID: 25534375)

GeparSixto Trial (n=580 tumors)
Role of nab-paclitaxel
GeparSepto

TN 275 pts (23%)

Untch, SABCS 2014

cT2 - cT4a-d

TN 275 pts (23%)

Untch, SABCS 2014
GeparSepto

TN 275 pts (23%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subgroup</th>
<th>pCR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPARC</td>
<td>SPARC negative</td>
<td>28.8 vs 37.7</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>SPARC positive</td>
<td>29.8 vs 48.3</td>
<td>.074</td>
</tr>
<tr>
<td>Ki67</td>
<td>Ki67&lt;=20%</td>
<td>19.6 vs 26.1</td>
<td>.137</td>
</tr>
<tr>
<td></td>
<td>Ki67&gt;20%</td>
<td>33.1 vs 44.0</td>
<td>.001</td>
</tr>
<tr>
<td>Biological subtype</td>
<td>HER2-, HR+</td>
<td>12.0 vs 16.0</td>
<td>.183</td>
</tr>
<tr>
<td></td>
<td>HER2-, HR-</td>
<td>25.7 vs 48.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HER2+ , HR+</td>
<td>50.0 vs 56.4</td>
<td>.275</td>
</tr>
<tr>
<td></td>
<td>HER2+ , HR-</td>
<td>66.7 vs 74.6</td>
<td>.371</td>
</tr>
<tr>
<td>HER2</td>
<td>HER2-</td>
<td>17.7 vs 27.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HER2+</td>
<td>54.1 vs 61.8</td>
<td>.120</td>
</tr>
<tr>
<td>HR-status</td>
<td>HR-</td>
<td>36.1 vs 56.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HR+</td>
<td>25.6 vs 29.9</td>
<td>.169</td>
</tr>
</tbody>
</table>

OR 2.69

Jntch, SABCS 2014
Adapt

cT1c-cT4c
RE<1%
cN0/+ 

N 336
N0: 81 y 72%
Grade 3: 93%

pCR (ypT0N0): 25 vs 49,2%

Gluz O, Harbeck N, ASCO 2015
ETNA (Evaluating Treatment With Neoadjuvant Abraxane) Randomized Phase III Study Comparing Neoadjuvant nab®-Paclitaxel (nab-P) Versus Paclitaxel (P) Both Followed by Anthracycline Regimens in Women With HER2-Negative High-Risk Breast Cancer: a MICHELANGELO Study


nab® is a registered trademark of Celgene Corporation.
ETNA: Phase III Study of Neoadjuvant nab-Paclitaxel vs Paclitaxel Both Followed by Anthracycline in HER2− High-Risk Breast Cancer

**Study Design**

- HER2 negative\(^a\)
- Operable/locally advanced unilateral breast cancer
- Triple-negative or luminal B-like

\[N = 695^b\]

**STRATIFICATION VARIABLES**
- Cooperative Research Group
- Disease stage (operable vs locally advanced)
- Centrally assessed tumor subtype (triple-negative\(^c\) vs luminal B-like high\(^d\) vs luminal B-like intermediate\(^e\))

- Tumor and blood banked for correlative studies
- Endocrine therapy after surgery if HR+ tumors

\(^a\) ER, PgR, HER2, and Ki67 were centrally tested before randomization. \(^b\) N = 814 registered. \(^c\) Defined as ER and PgR ≤ 1%, HER2 0/1+, or HER2 2+ and ISH negative. \(^d\) Defined as ER and/or PgR > 1%, Ki67 > 20%, HER2 0/1+, or HER2 2+ and ISH negative. \(^e\) Defined as Ki67 from 14% to 20%.

ETNA: Phase III Study of Neoadjuvant *nab*-Paclitaxel vs Paclitaxel Both Followed by Anthracycline in HER2− High-Risk Breast Cancer

**Efficacy: pCR Rate**

<table>
<thead>
<tr>
<th></th>
<th>P n = 349</th>
<th>nab-P n = 346</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR rate, %</strong></td>
<td>18.6</td>
<td>22.5</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>14.7 - 23.1</td>
<td>18.2 - 27.3</td>
</tr>
<tr>
<td><strong>Difference: P - nab-P (95% CI)</strong></td>
<td>-3.9 (-9.9 - 2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong>&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>0.77 (0.52 - 1.13)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1858</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Cochran-Mantel-Haenszel test, controlling for tumor subtype and disease stage and quantified by OR and rate difference.

ETNA: Phase III Study of Neoadjuvant *nab*-Paclitaxel vs Paclitaxel Both Followed by Anthracycline in HER2− High-Risk Breast Cancer

**Efficacy: Subgroup Analysis of pCR Rate**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>nab-P, %</th>
<th>P, %</th>
<th>nab-P</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor subtype</strong></td>
<td>All</td>
<td>22.5</td>
<td>18.6</td>
<td></td>
<td></td>
<td>0.77 (0.52 - 1.13)</td>
</tr>
<tr>
<td></td>
<td>Luminal B-like</td>
<td>13.9</td>
<td>10.0</td>
<td></td>
<td></td>
<td>0.69 (0.39 - 1.21)</td>
</tr>
<tr>
<td></td>
<td>Triple negative</td>
<td>41.3</td>
<td>37.3</td>
<td></td>
<td></td>
<td>0.85 (0.49 - 1.45)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>Non–locally advanced</td>
<td>23.1</td>
<td>20.7</td>
<td></td>
<td></td>
<td>0.87 (0.57 - 1.31)</td>
</tr>
<tr>
<td></td>
<td>Locally advanced</td>
<td>20.7</td>
<td>12.5</td>
<td></td>
<td></td>
<td>0.55 (0.24 - 1.25)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>≤ 50</td>
<td>22.0</td>
<td>20.7</td>
<td></td>
<td></td>
<td>0.90 (0.53 - 1.51)</td>
</tr>
<tr>
<td></td>
<td>&gt; 50</td>
<td>23.1</td>
<td>16.1</td>
<td></td>
<td></td>
<td>0.63 (0.35 - 1.14)</td>
</tr>
</tbody>
</table>

Ongoing trials: Before surgery
**NeoTRIPaPDL1** (Fondazione Michelangelo)  
(Neoadjuvant therapy in TRIPle negative breast cancer with antiPDL1)

“Neo-Adjuvant Ph III study with the PDL1-directed antibody in Triple Negative Locally Advanced Breast Cancer undergoing treatment with nab-paclitaxel and carboplatin”

**TNBC (N = 272)**

- Carboplatin day 1, 8  
  Nab-Paclitaxel day 1, 8  
  q3weeks x 8 cycles

- Carboplatin day 1, 8  
  Nab-Paclitaxel day 1, 8  
  MPDL3280A  
  q3weeks x 8 cycles

**SURGERY**

**Primary endpoint:**  
5-year EFS

**AC / EC / FEC**  
q3weeks x 4 cycles
AKT inhibitors: FAIRLANE

Stratify by:
- PTEN status (null/low vs. moderate vs. normal)
- Node involvement (positive vs. no known involvement)
- T size (T1-T2 vs. T3)

TNBC
- T ≥ 1.5 cm, N 0-2
- R 1:1
- N = 150

Pretreatment | Day 1 | Day 8 | Week 10 | Pre-Surgery | Surgery
---|---|---|---|---|---
Tumor Tissue | | | | | |
ctDNA | | | | | |
Breast MRI | | | | | |
Mammogram | | | | | |
PK | | | | | |

Paclitaxel 80 mg/m² IV once weekly + Placebo 400 mg PO daily on Days 1-21, every 28 days x 3 cycles
Paclitaxel 80 mg/m² IV once weekly + Ipatasertib 400 mg PO daily on days 1-21, every 28 days x 3 cycles

pCR
SURGERY
Investigator's choice of additional adjuvant chemotherapy and/or radiotherapy

Oliveira M, ASCO 2015
Post-neoadjuvant treatment trials

- Convenient for non-pCR patients in high-risk subgroups

- The unbiased identification of targetable molecular alterations in (residual) breast cancers after neoadjuvant therapy may identify somatic alterations causally associated with drug resistance.

- These alterations could be therapeutically targeted as adjuvant treatment

- No prior “success stories”
CREATE-X: Trial Design

HER2-
NAC  Surgery  Pathology Non-pCR or node + (n=900)
Control: Standard therapy
Standard therapy + Capecitabine

Stratification factors:
ER, Age, NAC, ypN, 5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

Capecitabine (X): 2,500 mg/m²/day, po, day 1-14
Repeat every 3 weeks for 8 cycles

298 pts (33%) TN

Lee SJ, SABCS 2015
Molecular discovery in drug-resistant residual TNBC (after neoadjuvant chemo): Basal-like tumors have the worse prognosis

Clinical outcomes of 89 patients with stage II-III basal-like and non-basal-like TNBC with residual disease after treatment with neoadjuvant chemotherapy

Of the multiple TNBC subtypes identified by gene expression, the basal-like ones are sensitive to platinum agents

Balko/ Arteaga, Cancer Discovery, 2013
Lehmann/ Pietenpol, JCI 2011
Ongoing trials: after surgery
Hypothesis:
In patients that have the highest risk of recurrence - basal-like TNBC with >1cm residual disease post neoadjuvant chemo - the addition of adjuvant platinum-based chemo will improve DFS
SWOG1418 Phase III Trial of Adjuvant Pembrolizumab for patients with non-pCR TNBC

Patients with TNBC, ≥1cm residual invasive breast cancer, or any + LN after neoadjuvant chemotherapy, followed by surgery

Step 1 Registration
Submit slides to central laboratory for PD-L1 evaluation. SWOG Statistical Center will notify sites when PD-L1 testing is completed.

Step 2 Registration
Randomization
Randomization stratification factors will include:
- Nodal Stage: ypN0 vs. ypN+
- Residual tumor size: ≤20 mm vs. >20 mm
- PD-L1: positive vs. negative (blinded to sites)
- Prior post-operative (adjuvant) chemotherapy: yes vs. no

Arm 1
Observation

Arm 2
MK-3475 (pembrolizumab) IV q 3 weeks for 52 weeks

NOTE: Radiation therapy may be given concurrently on Arm 1 or Arm 2.

Primary Endpoint: Invasive Disease Free Survival (IDFS)
OlympiA: Updated Design Chart

Post Neoadjuvant gBRCA
TNBC patients
Non pCR
ER/PgR positive /HER2 negative patients
Non pCR AND CPS&EG score ≥3

Post Adjuvant gBRCA
TNBC patients
axillary node-positive (any tumour size) or axillary node-negative tumour > 2cm (pathological size)
ER/PgR positive/HER2 negative patients
≥ 4 pathologically confirmed positive lymph nodes

Randomisation 1:1
Double blind
N=1500

Follow-up
IDFS, distant IDFS, OS

Olaparib 300 mg twice daily (bid) for 12 months
Placebo twice daily (bid) for 12 months
• Adition of platinum agents in neoadjuvant tx TN BC
  - individualize
  - need for a good clinical response (inflammatory, inoperability)
  - very high risk of relapse (young pts, stage III)
  - BRCA mut stage II

• Consider nabPaclitaxel

• Capecitabine as adjuvant tx in residual disease?
  - CREATE not published
  - consider in young / high risk patients, high residual burden

• Clinical trials
  - **Before surgery**: improve pCR and select homogeneous population (intrinsic subtype, HRD / BRCA, etc)
  - **After surgery**: based on molecular characteristics of residual disease (inmunotherapy)