(Neo-) Adjuvant systemic therapy in Triple Negative Early Breast Carcinoma

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Disclosures

- Board Member: Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my Institute: MSD, AstraZeneca
- Speakers bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None
Outline

- Triple negative breast cancer
- Neo-Adjuvant treatment in triple negative disease
- Adjuvant treatment in triple negative disease
- Conclusions
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

- Basal-like: 23.3%
- HER2-enriched: 7.5%
- Luminal A: 59.7%
- Luminal B: 2.9%
- Normal-like: 4.4%
- Claudin-low: 4.4%

TNBC: An heterogeneous disease

- 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
TNBC: An heterogeneous disease

- 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
Triple negative disease

• PST should be used to reduce the extent of surgery in locally advanced and large operable cancers, in particular when mastectomy is required due to tumour size [I, A]. It should also be considered in all patients with tumours > 2 cm for which ChT is deemed necessary, in particular with triple-negative subtypes [I, B].

• Drugs and drug regimens used in preoperative setting should be selected according to rules identical to those in postoperative setting [I, A]. A sequential regimen of anthracyclines and taxanes is recommended for the vast majority of patients [I, B].
The addition of a platinum compound may be considered in triple-negative tumours and/or in patients with deleterious BRCA1/2 mutations [I, C].

In high-risk, triple-negative patients not achieving pCR after standard neoadjuvant ChT, the addition of 6-8 cycles of capecitabine post-operatively may be considered [I, C].
Neoadjuvant approach

**Triple negative**

- pCR
- No pCR

**Event-free survival (%)**

**Time since randomisation (years)**

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
<th>No pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>389</td>
<td>349</td>
<td>768</td>
</tr>
<tr>
<td>310</td>
<td>310</td>
<td>604</td>
</tr>
<tr>
<td>250</td>
<td>250</td>
<td>429</td>
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<tr>
<td>166</td>
<td>166</td>
<td>317</td>
</tr>
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<td>88</td>
<td>88</td>
<td>198</td>
</tr>
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<td>29</td>
<td>29</td>
<td>125</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

HR 0.24 (95% CI 0.18–0.33)

Neoadjuvant approach

Symmans et al. J Clin Oncol 2017

| RCB   | (
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (pCR)</td>
<td>35%</td>
</tr>
<tr>
<td>1</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>33%</td>
</tr>
<tr>
<td>3</td>
<td>17%</td>
</tr>
</tbody>
</table>

RCB: Response Criteria for Breast Cancer
Immune-infiltration and response

Denkert, et al. Lancet Oncol 2018
Immune-infiltration and residual disease


Carboplatin in TN

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Drugs</th>
<th>Population</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM</td>
<td>94</td>
<td>EC-D</td>
<td>Basal-like</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EC-D+carbo</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>GeparSixto</td>
<td>165</td>
<td>PM/bev</td>
<td>TNBC (subset)</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMCb/bev</td>
<td></td>
<td>59%*</td>
</tr>
<tr>
<td>CALGB 40603</td>
<td>455</td>
<td>T-AC(bev)</td>
<td>TNBC</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T/carbo-AC(bev)</td>
<td></td>
<td>60%*</td>
</tr>
<tr>
<td>ADAPT-TN</td>
<td>336</td>
<td>Nab-P/wkly Gem</td>
<td>TNBC</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nab-P/wkly Carbo</td>
<td></td>
<td>46%*</td>
</tr>
</tbody>
</table>

Alba, BCRT’12; von Minckwitz, Lancet Oncol’14; Sikov, JCO’14; Gluz, AACR-SABCS’15

Carboplatin augments pCR in TNBC
Carboplatin in TN

Study Objectives

Primary objectives:
• Pathologic complete response (pCR) in breast and ipsilateral axillary lymph nodes

Secondary objectives:
• EFS, OS, and rate of eligibility for breast conservation after therapy

S. Loibl et al. The Lancet Oncology 2018
Carboplatin in TN

Pathologic Complete Response
ypT0/Tis ypN0

Intent to Perform a Breast Conserving Surgery

Minimal Residual Disease
Residual Cancer Burden Class 0 or I

Error bars are 95% confidence intervals based on normal approximation. *p-values were calculated from Cochran-Mantel-Haenszel test versus Arm A (V+Cb+P).

*Clinical response rate after paclitaxel based treatment on serial MRI assessment
PARP inhibitors in TN

- PARP inhibitors and « synthetic lethality »
- Current available evidence that this concept is clinically actionable
PARP inhibitors in TN

- N = 17 BRCA1 mut
- N = 3 BRCA2 mut
- 17 TNBC/3HR+
- Clin st I - III

Talazoparib 1 mg PO x 6 months

Side effects
Mostly hema-toxicity resulting in
- RBC transfusions (8/19)
- dose delays/reductions (9/10)

Interim biopsy to predict « resistance » (not done)

pCR 53%
95% CI: 32%-73%

Systemic therapy of physician’s choice

Is any further therapy needed?
If yes, can it be given « full dose »?

Validated « surrogate endpoint » in TNBC
In the range of pCR rates seen w/chemo + PARPi in neoadj trials mixing TNBC/BRCA mut (I-SPY, Brightness, ...)
UNIQUE to Talazoparib given its higher trapping potency?

Litton JK, Breast NJP, 2018
HRD in TNBC

Homologous Recombination Deficiency (HRD) Testing

• HRD or “BRCA-pathway or BRCAness” deficient cancers are quite prevalent:
  • ~25% of breast cancer, 40-50% of TNBC, ~45% of ovarian cancer and approximately 10-15% of all cancer

• Myriad HRD test = large structural alterations (LST, nTAI, LOH-HRD)

• HR gene mutations:
  • Deleterious vs VUS (variant of unknown significance)
  • LOH for HR gene not always equal
  • False positive rate is the concern
HRD in TNBC

GeparOla Study Design

Core Biopsies
- Screening
- Chemotherapy
- After PO/PCb
- Chemotherapy
- Surgery

Blood Collection

N=102
Homologous Recombination Deficiency (HRD)*
HER2-

12x Paclitaxel weekly 80mg/m² + Olaparib 100mg twice daily (PO)

65 PO : 37 PCB

12x Paclitaxel weekly 80mg/m² + Carboplatin AUC 2 (PCb)

Epirubicin/Cyclophosphamide 90/600 mg/m² q2w or q3w

SURGERY + pCR Rate

Stratification Factors:
- Age (<40 years vs >= 40 years)
- Hormone Receptor Status (HR+ vs HR-)

* Patients with either a known somatic or germline BRCA1/2 mutation or HRD score high

1 Timms et al. Breast Cancer Res 2014
# HRD in TNBC

## Pathologic CR Rates Observed

<table>
<thead>
<tr>
<th>Comparison Group</th>
<th>PO-EC (%)</th>
<th>PCB-EC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>55.1</td>
<td>48.6</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>76.2</td>
<td>45.5</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>45.8</td>
<td>50.0</td>
</tr>
<tr>
<td>Hormone R-positive</td>
<td>52.6</td>
<td>20.0</td>
</tr>
<tr>
<td>Hormone R-negative</td>
<td>56.0</td>
<td>59.3</td>
</tr>
</tbody>
</table>
TBCRC 030: A randomized phase II study of preoperative cisplatin vs paclitaxel in TNBC: evaluating the HRD assay

Eligibility:
- ER/PR negative (≤ 5%), HER2 negative invasive breast cancer
- Clinical Stage I (T1 > 1.5 cm), or Stage II-III
- Known clinical LN status
- No known BRCA1/2 germline mutation

Stratification Factors:
- Positive vs Negative lymph node status
- Pre-treatment tumor size, T1-2 vs T3-4

Randomize

Cisplatin 75 mg/m² q 3 weeks x 4

1:1

Paclitaxel 80 mg/m² x 12 weeks

Biopsy

SURGERY

Further chemotherapy per provider

Biopsy

If residual disease after 12 wks, patient may crossover to alternative preoperative chemotherapy

Primary Objective: To determine the association of HRD score with pathologic response to neoadjuvant platinum or taxane-based chemotherapy in TNBC

Primary Endpoint: Response determined by Residual Cancer Burden: RCB 0/1 = response, RCB 2/3 or crossover = non-response

Secondary Endpoint: Pathologic complete response (pCR)

Presented By Erica Mayer at 2019 ASCO Annual Meeting
HRD Assay Methodology

- The HRD assay developed by Myriad Genetics is a next generation sequencing test targeting ~27,000 SNPs and the coding regions of BRCA1/2. The HRD score is based on three methods to measure DNA repair deficiency.\(^1\)\(^-\)\(^3\)

- BRCA1/2 deficient tumors almost always test HRD positive

- HRD assay was performed on baseline clinical diagnostic tissue, i.e. initial tumor biopsy.

- The threshold for HRD positivity used in this analysis was \(\geq 33\).\(^4\)

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Co-author A. Richardson is a co-inventor of the HRD assay and DFCI is an owner of the interest.
Baseline Patient Characteristics

- 147 patients registered for protocol therapy.
  - 4 withdrew before starting therapy
  - 1 found to be ineligible before starting therapy
  - 2 stopped protocol therapy within first cycle due to hypersensitivity reactions

- 140 patients were evaluable for response at 12 weeks.

- Post-enrollment genetic panel and tumor testing later identified 7 patients with BRCA1/2 mutations
  - 4 germline: BRCA1 (2), BRCA2 (2)
  - 3 somatic BRCA1

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Cisplatin (N=75)</th>
<th>Paclitaxel (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>53 (28-82)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>60 80%</td>
<td>51 71%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>8 11%</td>
<td>11 15%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7 9%</td>
<td>4 6%</td>
</tr>
<tr>
<td>Asian</td>
<td>0 0%</td>
<td>2 3%</td>
</tr>
<tr>
<td>Other</td>
<td>0 0%</td>
<td>4 6%</td>
</tr>
<tr>
<td><strong>Tumor Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 7%</td>
<td>9 13%</td>
</tr>
<tr>
<td>III</td>
<td>70 93%</td>
<td>62 86%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 0%</td>
<td>1 1%</td>
</tr>
<tr>
<td>Clinical lymph node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>29 39%</td>
<td>26 36%</td>
</tr>
<tr>
<td>Negative</td>
<td>46 61%</td>
<td>46 64%</td>
</tr>
<tr>
<td>Tumor Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>59 79%</td>
<td>61 85%</td>
</tr>
<tr>
<td>T3-4</td>
<td>15 20%</td>
<td>11 15%</td>
</tr>
<tr>
<td>Unknown/pending</td>
<td>1 1%</td>
<td>0 0%</td>
</tr>
</tbody>
</table>

Presented By Erica Mayer at 2019 ASCO Annual Meeting
TBCRC 030: Pathologic Outcomes After Preoperative Chemotherapy

- Of the 140 response-evaluable patients:
  - 87 patients (62.1%) had surgery at 12 weeks
  - 51 patients (36.4%) crossed over to alternative preoperative chemotherapy and are considered non-responders
  - Crossover regimens included: AC (n=33), AC + T (n=8), cisplatin (n=5), paclitaxel (N=5)

<table>
<thead>
<tr>
<th>Response</th>
<th>Cisplatin (N=72)</th>
<th>Paclitaxel (N=68*)</th>
<th>Total (N=140*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Responder (RCB 0/1)</td>
<td>19</td>
<td>26.4%</td>
<td>15</td>
</tr>
<tr>
<td>Non-responder (RCB 2/3 or crossover)</td>
<td>53</td>
<td>73.6%</td>
<td>52</td>
</tr>
<tr>
<td>pCR</td>
<td>11</td>
<td>15.3%</td>
<td>8</td>
</tr>
<tr>
<td>non-pCR</td>
<td>61</td>
<td>84.7%</td>
<td>60</td>
</tr>
</tbody>
</table>

* One patient completed paclitaxel treatment but was lost to f/u before surgery and does not have an RCB score.
**TBCRC 030: Results of HRD Testing on Baseline Clinical Samples**

- Of the 140 evaluable patients, HRD results were available for 105 patients (75.0%)
- 35 patients (25.0%) had inadequate tissue or inconclusive results for HRD analysis:
  - 16 from Cisplatin arm, 19 from Paclitaxel arm
- Of the 105 patients with HRD results, using the HRD threshold of ≥ 33:
  - 75 (71.4%) had HRD positive tumors, 30 (28.6%) had HRD negative tumors

<table>
<thead>
<tr>
<th>HRD Result</th>
<th>Cisplatin (N=56)</th>
<th>Paclitaxel (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Median score</td>
<td>51 (10-86)</td>
<td>47 (18-89)</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRD positive</td>
<td>39 69.6%</td>
<td>36 73.5%</td>
</tr>
<tr>
<td>(≥ 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRD negative</td>
<td>17 30.4%</td>
<td>13 26.5%</td>
</tr>
<tr>
<td>(&lt; 33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TBCRC 030: Primary Objective: Clinical Outcomes by HRD Score

- No association was observed between HRD score and pCR to either cisplatin or paclitaxel.
- There was no evidence of an interaction between response by HRD and chemotherapy arm.

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=56</td>
<td>pCR</td>
<td>No pCR</td>
</tr>
<tr>
<td>HRD+</td>
<td>5 (13%)</td>
<td>34 (87%)</td>
<td></td>
</tr>
<tr>
<td>HRD-</td>
<td>1 (6%)</td>
<td>16 (94%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=49</td>
<td>pCR</td>
<td>No pCR</td>
</tr>
<tr>
<td>HRD+</td>
<td>5 (14%)</td>
<td>30 (86%)</td>
<td></td>
</tr>
<tr>
<td>HRD-</td>
<td>3 (23%)</td>
<td>10 (77%)</td>
<td></td>
</tr>
</tbody>
</table>
TBCRC 030: Clinical Outcomes by HRD Score

*One BRCA1/2 carrier in Arm T had RCB 0 with paclitaxel, but tissue inadequate for HRD testing*
TBCRC 030: Conclusions

- In this mostly BRCA1/2-proficient TNBC cohort, HRD positivity by this HRD assay was not predictive of response to preoperative cisplatin or paclitaxel chemotherapy. Results mirror a similar experience in the metastatic TNBC setting. At this time, this HRD assay cannot be used to select a preoperative chemotherapy regimen.

- 12 weeks of either preoperative cisplatin or paclitaxel monotherapy had similar activity and predictable toxicity, with a response rate (RCB 0/1) of about 25%.

- The small population of BRCA1/2 deficient tumors had high HRD scores, but did not uniformly achieve a response to preoperative chemotherapy.

- Overall power of these analyses was limited by study size, and inconclusive HRD in 25% of samples.

- Correlative analyses of research tissues for markers predictive of response to specific chemotherapy in TNBC is ongoing.

1. Tutt et al, Nat Med 2018
Conclusions for TBCRC 030 for HRD Breast Cancer?

- HRD needs to be accurately diagnosed
- Cisplatin versus Paclitaxel – no winner overall for TNBC
- Sub-group analysis:
  - Cisplatin response do better for HRD tumors (23% vs 12%)
  - Taxanes show NO DIFFERENCE for HRD vs HRP (29% vs 31%)
  - Platinum alone not that good even in HRD tumors
  - Platinum is 85% intra-strand crosslinks – repaired by NER
  - Only 15% of cisplatinum DNA damage are inter-strand crosslinks (where HR repair is needed)
### PARP Inhibitors or Cisplatin?

<table>
<thead>
<tr>
<th></th>
<th>Talazoparib</th>
<th>Cisplatin ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>107</td>
</tr>
<tr>
<td>BRCA 1</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>BRCA 2</td>
<td>15%</td>
<td>N/A</td>
</tr>
<tr>
<td>Neoadjuvant treatment duration</td>
<td>6 months</td>
<td>75 mg/m2 q21 days, 4 cycles = 3 months</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>According to physician’s choice</td>
<td>Doxorubicin + Cyclophosphamyde</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Hematological</td>
<td>Emesis, neuropathy, nephrotoxicity</td>
</tr>
<tr>
<td>pCR rates</td>
<td>53%</td>
<td>61%</td>
</tr>
<tr>
<td>Estimated costs of the neoadjuvant treatment</td>
<td>$ 28,000*</td>
<td>$ 240**</td>
</tr>
</tbody>
</table>

Immunotherapy in neoadjuvant setting

GepardoNuevo Trial

Chemotherapy + anti-PDL1
Pathological CR = ypT0 ypN0

OP

44.2%
Control (no immunotherapy)

53.4%
Immunotherapy

with window treatment

Chemotherapy + anti-PDL1

OP

41.4%
Control (no immunotherapy)

61%
Immunotherapy

Paclitaxel + carboplatin Q1W x12 + durvalumab Q2W x 6 → AC Q2W x4 + durvalumab Q2W x4

Loibl S, et al. ASCO 2018
Immunotherapy in neoadjuvant setting

**Pembrolizumab**
- **KEYNOTE-522**
- NCT03036488

- Pembrolizumab + chemo (taxanes – anthracyclines)
- Placebo + chemo (taxanes – anthracyclines)
- Surgery
- Pembrolizumab 9 cycles
- Placebo 9 cycles
- Primary endpoints: pCR & EFS

**Atezolizumab**
- **GeparDouze**
- NCT03281954

- Atezolizumab 1200 mg Q3W
- Paclitaxel 80 mg/m wkly
- Carboplatin AUC 5 Q3W x4

- N=1520
  - Previously untreated, locally advanced, nonmetastatic TNBC

- Placebo
  - Paclitaxel 80 3/1
  - Carboplatin AUC5 Q3W x4

- AC/EC X 4

- Surgery
  - Atezo 1200 mg
  - Every 3 weeks
  - 1 year

  - Placebo
  - Every 3 weeks
  - 1 year

**Co-Primary Endpoints:** pCR rate and EFS

Sponsor: NSABP and GBG with support from Genentech/Roche
NCT: NCT03281954
Post-Neoadjuvant setting TN

C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281
Post-Neoadjuvant setting TN

- Preplanned interim analysis of a randomized, open-label phase III study[1]
  
  **Stratified by ER status, age, neoadjuvant chemotherapy, use of 5-FU, institution, node status**

  - Pts 20-74 yrs of age with stage I-IIIB HER2- BC and residual disease (non-pCR, N+) after neoadjuvant chemotherapy* and surgery; ECOG PS 0 or 1; no previous oral fluoropyrimidines (N = 910)†
  - Primary endpoint: DFS
  - Secondary endpoints: OS, time from first day of preoperative chemotherapy to recurrence or death, safety, cost-effectiveness

  - Capecitabine 2500 mg/m²/day PO Days 1-14 Q3W for 8 cycles‡
  - Hormonal therapy if ER/PgR+ (n = 455)†
  - Hormonal therapy if ER/PgR-
  - No further therapy if ER/PgR- (n = 455)†

*Anthracycline/taxane, anthracycline containing, or docetaxel/cyclophosphamide.
†25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.
‡IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.[2]

Post-Neoadjuvant setting TN
Triple negative BRCA mutated

Figure 1. OlympiA study design

- **Screening**
- **Randomization (1:1)**
  - Olaparib 300 mg bid (12 months’ duration)
  - Matched placebo (12 months’ duration)
- **Invasive disease-free survival assessment**
  (mammogram/breast MRI 6 months from randomization)
- **Follow-up for local and distant recurrence and survival status**
**Triple negative IO**

**BRAVE Protocol**

- TNBC
- Neoadj Chemo
- Surgery
- pCR: 40%
- No pCR: 60%
- Placebo
- Radiotherapy
- Avelumab

Principle Investigator: Pierfranco Conte
Adjuvant therapy in TN

• Sequential anthracycline, cyclophosphamide and taxane-based therapy
• An option ddAC → paclitaxel in high risk
• Alternative regimens
• Preferred regimen without anthracyclines: TC
• Preferred regimen without taxanes: AC or CMF
• Neoadjuvant regimens = adjuvant regimens
Adjuvant therapy in TN: When to start

- 24,843 patients diagnosed with BC stages I to III.
- TTC 91 or more days after surgery experienced worse overall survival and worse breast cancer–specific survival.

Subgroup analysis according to subtype
- Longer TTC caused patients with triple-negative breast cancer to have worse overall survival (HR, 1.53; 95% CI, 1.17-2.00) and worse breast cancer–specific survival (HR, 1.53; 95% CI 1.17-2.07).

Adjuvant therapy in TN: When to start

N=687 pts

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<thead>
<tr>
<th>TTC (days)</th>
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<th>60mo</th>
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Morante Z, et al. SABCS 2018
Adjuvant therapy in TN: When to start

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Morante Z, et al. SABCS 2018
Adjuvant therapy in triple negative disease

Early Breast Cancer

ER-negative

HER2-positive

ChT$^a$ + anti-HER2$^b$
[I, A]

ER-positive

HER2-negative

ET
ChT only in selected cases with high-disease burden
[I, A]

HER2-positive

Luminal B

ET + ChT$^b$
[I, A]

ChT$^p$ + anti-HER2$^b$ + ET [I, A]

Luminal A

ET

Luminal B

Observation or ChT
[II, B]

TNBC

Special histological types, N$, no other risk factors

Ductal

ChT
[I, A]

ESMO EBC Guidelines, Cardoso F et al, Annals of Oncology 2019
<table>
<thead>
<tr>
<th>Subtype</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Chemo-Case by case</td>
</tr>
<tr>
<td>T1b</td>
<td>TC chemo or AC/T</td>
</tr>
<tr>
<td>T1c</td>
<td>AC/T chemo</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>Neoadjuvant Preferred</td>
</tr>
<tr>
<td>IIB (N+)</td>
<td>AC/T chemo +/- platinum</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
</tr>
<tr>
<td>Residual invasive cancer after NST</td>
<td>Capecitabine</td>
</tr>
</tbody>
</table>

**Adjuvant therapy in triple negative disease**
### Considerations in triple negative breast cancer

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum routine in neo-adjuvant Rx</td>
<td>No according to St Gallen 2019 (justifiable but no known EFS advantage)</td>
</tr>
<tr>
<td>Capecitabine in residual disease</td>
<td>An option - Stage II+ who has received anthracycline/taxane-based Rx</td>
</tr>
<tr>
<td></td>
<td>Uncertain in non adequately treated</td>
</tr>
<tr>
<td>Biological subsets to tailor escalating Rx</td>
<td>No</td>
</tr>
<tr>
<td>Immunotherapy/PARPi/anti androgens or other novel strategies</td>
<td>Not off-trial</td>
</tr>
</tbody>
</table>
## Considerations in triple negative breast cancer

<table>
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<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical low risk subsets can omit chemotherapy</td>
<td>Only in very small, node-negative (T1a pN0)</td>
</tr>
<tr>
<td>Biologic low risk subsets can omit / limit chemotherapy</td>
<td>No</td>
</tr>
<tr>
<td>Neoadjuvant Rx to reduce surgery</td>
<td>No stage I</td>
</tr>
<tr>
<td></td>
<td>Yes stage II+</td>
</tr>
<tr>
<td>Treating to pCR to de-escalate systemic therapy</td>
<td>No</td>
</tr>
<tr>
<td>Anthracyclines may be omitted</td>
<td>No (may consider in low risk)</td>
</tr>
</tbody>
</table>
Conclusions

• Existing clinical trials with carboplatin have not shown statistically valid improvement of EFS or OS

• PARPi role is unknown when platinum compounds are used
  – De-escalation strategy in gBRCA mutations?

• We don’t know how much of a pCR delta is needed to translate into DFS or OS advantage...
Conclusions

• Delayed adjuvant chemotherapy has a big negative impact in eTNBC

• Adjuvant capecitabine for high-risk patients (residual disease after neoadjuvant chemotherapy) should be considered
  – No data after platinum compounds

• Biology-driven clinical trials in residual tumors will be key to optimize new strategies in TNBC
Thank You

Giuseppe Curigliano MD, PhD
ESMO BREAST CANCER
Annual Congress

BERLIN GERMANY
7-9 MAY 2020

Save the date!