Triple Negative Breast Cancer: (Neo-) Adjuvant systemic therapy

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Disclosures

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

• Neoadjuvant treatment in triple negative BC
• Adjuvant treatment in triple negative BC
• The post-neoadjuvant setting
• The adjuvant setting: de-escalating and escalating
The Panel strongly endorsed the use of neoadjuvant therapy for stage II or III, HER2 positive or triple-negative breast cancer as the preferred initial treatment approach, particularly when there is any suggestion that treatment response might enable de-escalation of surgery or radiotherapy.
Neoadjuvant therapy in TNBC

In TN and HER2 positive EBC should be the preferred approach

• Pro:
  – Conservative surgery
  – Pathologic complete response
  – New drug development

• Contras:
  – Safety issues for unknown agents
  – Enrich by subtypes
  – Implication for surgeon and radiation therapist
Pathological complete response

- Absence of invasive tumor in breast and nodes
- Absence of invasive tumor in breast and nodes with residual carcinoma *in situ*.
pCR and outcome

(N=11,955)
Should all TNBC receive PST?

• **Neoadjuvant approach**

  • Advantages
    – **Minimize surgery = no controversy**
    – **Minimize chemotherapy?**

  • Disadvantages
    – Clinical staging - less accurate
    – Locoregional management less clear
(Neo)Adjuvant therapy in TN EBC

• Who needs more treatment?
• Addition of carboplatin
• Tumor infiltrating lymphocytes
• Post-neoadjuvant setting if residual disease
Clinical Heterogeneity of TNBC Subtype

- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal
- Mesenchymal stem-like
- Luminal androgen receptor

Gene expression profile

- High Ki-67; DNA damage response
- GF pathways
- Immune genes
- Cell motility
- Cell motility; claudin-low
- Steroid pathways

Clinical

- BRCA-associated
- Higher pCR
- Lower DDFS
- Apocrine features, higher LRF; PI3Kmut

## 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>ADAPT-TN</td>
<td>336</td>
<td>T/carbo-AC(bev)</td>
<td>TNBC</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nab-P/wkly Gem</td>
<td></td>
<td>46%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nab-P/wkly Carbo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data from 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

AC, doxorubicin plus cyclophosphamide; Cb, carboplatin; EFS, event free survival; OS, overall survival; P, paclitaxel; V, veliparib
Carboplatin in TN

<table>
<thead>
<tr>
<th>Characteristic, n%</th>
<th>V+Cb+P (n=316)</th>
<th>Cb+P (n=160)</th>
<th>P (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median [range], years</strong></td>
<td>51 [26–79]</td>
<td>49 [23–76]</td>
<td>50 [22–75]</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>140 (44.3)</td>
<td>73 (45.6)</td>
<td>79 (50.0)</td>
</tr>
<tr>
<td>Europe</td>
<td>119 (37.7)</td>
<td>65 (40.6)</td>
<td>58 (36.7)</td>
</tr>
<tr>
<td>Asian Pacific</td>
<td>57 (18.0)</td>
<td>22 (13.8)</td>
<td>21 (13.3)</td>
</tr>
<tr>
<td><strong>gBRCA status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleterious mutation</td>
<td>45 (14.2)</td>
<td>25 (15.6)</td>
<td>23 (14.6)</td>
</tr>
<tr>
<td>No deleterious mutation</td>
<td>271 (85.8)</td>
<td>135 (84.4)</td>
<td>135 (85.4)</td>
</tr>
<tr>
<td><strong>Tumor Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>37 (11.7)</td>
<td>20 (12.5)</td>
<td>15 (9.5)</td>
</tr>
<tr>
<td>T2</td>
<td>229 (72.5)</td>
<td>107 (66.9)</td>
<td>117 (74.1)</td>
</tr>
<tr>
<td>T3-4ä</td>
<td>50 (15.8)</td>
<td>33 (20.6)</td>
<td>26 (16.5)</td>
</tr>
<tr>
<td><strong>Lymph Node Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>180 (57.0)</td>
<td>92 (57.5)</td>
<td>94 (59.5)</td>
</tr>
<tr>
<td>N1-N2</td>
<td>136 (43.0)</td>
<td>68 (42.5)</td>
<td>64 (40.5)</td>
</tr>
<tr>
<td><strong>Planned Schedule of AC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 weeks</td>
<td>173 (54.7)</td>
<td>88 (55.0)</td>
<td>89 (56.3)</td>
</tr>
<tr>
<td>Q3 weeks</td>
<td>140 (44.3)</td>
<td>70 (43.8)</td>
<td>69 (43.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (1.0)</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Longest Tumor Diameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30 mm</td>
<td>145 (45.9)</td>
<td>71 (44.4)</td>
<td>79 (50.0)</td>
</tr>
<tr>
<td>&gt; 30 mm</td>
<td>171 (54.1)</td>
<td>89 (55.6)</td>
<td>79 (50.0)</td>
</tr>
</tbody>
</table>

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

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

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

- Addition of V and Cb to P followed by AC demonstrated a significant improvement in pCR compared with P followed by AC (53.2% vs 31.0%, p<0.001) confirming results of I-SPY-2.
- However, addition of V to Cb and P followed by AC did not show improvement in pCR compared to Cb+P followed by AC (53.2% vs 57.5%, p=0.36).
- Increase in pCR with addition of carboplatin was independent of gBRCA mutation status.
TILs

INFORM: Cisplatin vs AC for BRCA 1/2 carriers

- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

Stage II/III BC with BRCA1 or 2 mutation

AC x 4
CDDP x 4

N = 170; approximately 60 enrolled

Additional Chemo

Principal Investigators:
Nadine Tung and Judy Garber
TBCRRC and other sites
Hitting tumor "targets" with the hope to de-escalate therapy

- PARP inhibitors and « synthetic lethality »
- Current available evidence that this concept is clinically actionable
Hitting tumor “targets” with the hope to de-escalate therapy

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

Talazoparib 1 mg PO x 6 months

Surgery

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

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

Interim biopsy to predict « resistance »
(not done)

- 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?

Systemic therapy of physician’s choice

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

Litton JK, Breast NJP, 2018
## 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

N = 272
Primary endpoint: Event-free survival (EFS)
Secondary endpoint: pCR (ypT0-ypTis ypN0)

+/- ATEZOLIZUMAB 1200 mg

nab-Paclitaxel 125 mg/m² + CBDCA AUC2
Immunotherapy in neoadjuvant

N = 174  Primary endpoint: pCR (ypT0 ypN0)

nab-Paclitaxel

EC

MEDI 4736/Durvalumab

Placebo

Window of opportunity 2 weeks

nab-P 125 mg/m²

Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m²

MEDI 4736/durvalumab 2g total q4w

Surgery
KEYNOTE-173 Phase I/II Trial

Cohort A (no platinum)
Chemotherapy + anti‒PD-1
OP
pCR = ypT0 ypN0
Paclitaxel Q1W x 12 ± carboplatin Q1W x 12 + pembrolizumab Q3W x 4 → AC Q3W x 4 + pembrolizumab Q3W x 4
60%

Cohort B (platinum)
Chemotherapy + anti‒PD-1
OP
pCR = ypT0 ypN0
Paclitaxel Q1W x 12 + pembrolizumab Q3W x 4 → AC Q3W x 4
80%

I-SPY-2 Trial

Control (no immunotherapy)
Chemotherapy ± anti‒PD-1
OP
pCR = ypT0/is ypN0
Paclitaxel Q1W x 12 + pembrolizumab Q3W x 4 → AC Q3W x 4
20%

Immunotherapy (no platinum)
Chemotherapy ± anti‒PD-1
OP
pCR = ypT0/is ypN0
Paclitaxel Q1W x 12 + pembrolizumab Q3W x 4 → AC Q3W x 4
60%

Post-Neoadjuvant setting TN

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

• Theory:
  • pCR = no further therapy needed
  • Residual disease = give more treatment
Post-Neoadjuvant setting

- 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

  *Anthracline/taxane, anthracline 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.\[2\]

  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)†
## Post-Neoadjuvant setting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yrs (range)</td>
<td>48 (25-74)</td>
<td>48 (25-74)</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pre</td>
<td>59.3</td>
<td>56.0</td>
</tr>
<tr>
<td>▪ Post</td>
<td>40.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ I, IIA, IB</td>
<td>58.9</td>
<td>62.0</td>
</tr>
<tr>
<td>▪ IIIA, IIB</td>
<td>40.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Hormonal receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ ER+ or PgR+</td>
<td>63.9</td>
<td>62.9</td>
</tr>
<tr>
<td>▪ ER- and PgR-</td>
<td>33.4</td>
<td>33.5</td>
</tr>
<tr>
<td>Lymph nodes with metastatic disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ 0</td>
<td>39.3</td>
<td>38.7</td>
</tr>
<tr>
<td>▪ 1-3</td>
<td>37.5</td>
<td>39.1</td>
</tr>
<tr>
<td>▪ ≥ 4</td>
<td>22.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Histologic effect grading by NAC, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ 0, 1a, 1b</td>
<td>56.4</td>
<td>52.6</td>
</tr>
<tr>
<td>▪ 2, 3</td>
<td>41.6</td>
<td>45.4</td>
</tr>
</tbody>
</table>
Post-Neoadjuvant setting

- Capecitabine achieved significantly higher 5-yr DFS and OS in HER2- BC pts with residual disease

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS</td>
<td>74.1</td>
<td>67.7</td>
<td>0.70</td>
<td>.00524</td>
</tr>
<tr>
<td></td>
<td>(0.53-0.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-yr OS</td>
<td>89.2</td>
<td>83.9</td>
<td>0.60</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>(0.40-0.92)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Masuda N, NEJM 2017
Post-Neoadjuvant setting

Masuda N, NEJM 2017
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% → pCR: 60% → No pCR

R → 1 → Placebo

R → 2 → Avelumab

Radiotherapy

Principle Investigator: Pierfranco Conte
Options for Stage I Disease

- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Enthusiasm for Chemotherapy</th>
<th>Possible Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microinvasion only</td>
<td>Virtually none</td>
<td>---</td>
</tr>
<tr>
<td>T1a</td>
<td>Low to moderate</td>
<td>None</td>
</tr>
<tr>
<td>T1b</td>
<td>Moderate to high</td>
<td>Simple</td>
</tr>
<tr>
<td>T1c</td>
<td>High</td>
<td>Simple or selectively sequential approach</td>
</tr>
<tr>
<td>Strategy</td>
<td>Opinion</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Clinical low risk subsets can omit chemotherapy</td>
<td>Only in very small, node-negative (T1a pN0)</td>
<td></td>
</tr>
<tr>
<td>Biologic low risk subsets can omit / limit chemotherapy</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant Rx to reduce surgery</td>
<td>No stage I</td>
<td></td>
</tr>
<tr>
<td>Treating to pCR to de-escalate systemic therapy</td>
<td>Yes stage II+</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines may be omitted</td>
<td>No (may consider in low risk)</td>
<td></td>
</tr>
</tbody>
</table>
## Escalating in TN EBC

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum routine in neo-adjuvant Rx</td>
<td>Yes (questionable) (justifiable but not 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 Consider EFS and not pCR to approve I-O in neoadjuvant</td>
</tr>
</tbody>
</table>
Adjuvant therapy in TN

• Based on direct comparisons, subset analyses and considerations of toxicity/tolerability
• 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

Treatment decision

Who needs more?
Prognostic Factors

Which is the Best therapy?
Predictive factors
Escalation

More Patients Treated

Longer Drug Exposure

More Drugs

Therapeutic Escalation
De-Escalation: Surgery

- Mastectomy and axillary dissection
- QUAD and axillary dissection only if SN+
- Sentinel node up to 2 SN+
- No surgery on the axilla
De-Escalation: Radiotherapy

Bar chart showing the duration in days for different types of radiotherapy:
- Standard RT
- AWBI
- APBI
- IORT
- No RT

The chart indicates that Standard RT has the longest duration, while No RT has the shortest.
Clinical research in the future

Drug treatment de-escalation
- Governments
- EU
- [Charities]

Drug treatment escalation
- Pharma
Thank you