Triple Negative Breast Cancer - neoadjuvant and adjuvant systemic therapy

Sung-Bae Kim, MD, PhD
Department of Oncology, Asan Medical Center
University of Ulsan College of Medicine
Seoul, Korea
Disclosure Information

Dr. SB Kim has received research funding from Novartis, Sanofi-Aventis, Kyowa-Kirin Inc, and DongKook Pharm Co. and has participated as a consultant in advisory boards for Novartis, AstraZeneca, Lilly, Enzychem, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, and Daiichi-Sankyo.
Outline

- Triple negative breast cancer as an heterogeneous disease
- How to improve pCR
  - Platinum
  - PARP inhibitor
  - Post neoadjuvant treatment (Capecitabine in non-pCR)
  - Immune check point inhibitor
- Practical issues
  - impact of delaying adjuvant CT in TNBC
  - small tumor
  - TIL
- Conclusions
Triple negative breast cancer

- TNBC = ER (0), PgR (0) and HER2 (IHC 0-1+ or FISH -)
- TNBC comprises approximately 15-20% of incident breast cancers
- Generally exhibit poor clinical outcomes
- BRCA mutations in nearly 20% of TNBC patients (vs 5% in non-TNBC)
  - 16% BRCA1
  - 4% BRCA2
- No targeted treatment available for non-BRCA mutated TNBC
- Main treatment remains chemotherapy
Triple Negative – A clinically convenient term but is biological nonsense that puts patients in a singular basket of hopelessness. In fact, the basket contains +ve subtypes with targetable biology.
TNBCs are heterogeneous disease

- IDC NOS, high-grade
- ILC high-grade, pleomorphic
- Metaplastic, high-grade
- Myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
  - Medullary
  - Adenoid-cystic
  - Metaplastic, low-grade
  - low grade adenosquamous
- Firbromatosis -like
Molecular characterization of basal-like and non-basal like TNBC

Clinical Characteristics of TNBC

- Relapse pattern\(^1\):
  - Short disease-free interval
  - Increase in visceral mets
  - Differs from luminal:
    - CNS mets in 46% of cases

<table>
<thead>
<tr>
<th>Rate of Recurrence(^2)</th>
<th>n</th>
<th>Bone, %</th>
<th>Soft Tissue, %</th>
<th>Viscera, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>79</td>
<td>13</td>
<td>13</td>
<td>74</td>
</tr>
<tr>
<td>ER+</td>
<td>123</td>
<td>39</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>HER2+</td>
<td>78</td>
<td>7</td>
<td>12</td>
<td>81</td>
</tr>
</tbody>
</table>

Prognostic implication of pCR: neoadjuvant therapy for TNBC

- Highest pCR rates are seen in TNBC
- pCR associated with excellent outcomes

pCR and EFS and OS by Breast Cancer Subtype

Patient level Meta-analysis: 27,000 Patients

TNBC

- common theme for neoadjuvant studies, which are typically powered for primary endpoint of pCR and not secondary long-term survival outcomes

5-year EFS pCR vs RD: 90% vs 57%

Spring Let al. SABCS2018
Outline

• Triple negative breast cancer as an heterogeneous disease
• **How to improve pCR**
  - Platinum
  - PARP inhibitor
  - Post neoadjuvant treatment (Capecitabine in non-pCR)
  - Immune check point inhibitor
• **Practical issues**
  - impact of delaying adjuvant CT in TNBC
  - small tumor
  - TIL
• Conclusions
GeparSixto: Phase 2 trial neoadjuvant chemotherapy/Bev ± Carbo (pCR in TNBC)

Germline (g)BRCA status

Significant predictor of pCR; results were nonconclusive for predicting the effect of carboplatin.


CAUTION: The concomitant use of platinum agents with chemo in GeparSixto was associated with markedly higher toxicity, which resulted in <60% patients completing all their chemo cycles, compared with the control group.
CALGB 40603: Phase 2 neoadjuvant chemotherapy/± Bev ± Carbo in TNBC

**CAUTION**: The concomitant use of platinum agents with chemotherapy 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 vs >85% in P → AC).


OR 1.71 (p=0.0029)
pCR rates by gBRCA status following chemotherapy/Bev ± Carboplatin (GeparSixto)

- Increase overall CTX response with gBRCA1 mutations
- No carboplatin difference with gBRCA1 mutations
- Positive carboplatin effect in BRCA wild type

Hahnen E et al. JAMA Oncol3:1378, 2017
**GeparSixto**
CARBO AUC 1.5-2 weekly

- **No Carbo**: N=157, 37%
- **Carbo**: N=158, 53%

P = 0.005

Adapted from Dent. ESMO2019

**CALGB 40603**
CARBO AUC 6 q3 weeks

- **No Carbo**: N=212, 41%
- **Carbo**: N=221, 54%

1-sided P = 0.0029

EFS
- HR = 0.84
- p = 0.38

EFS
- HR = 0.56
- p = 0.0350

9.7% increase
4.9% increase

Adapted from Dent. ESMO2019
BrighTNESS Trial: Paclitaxel Alone or with Carboplatin or Carboplatin/Veliparib followed by AC
### Platinum in TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>TNBC, #</th>
<th>pCR</th>
<th>DFS/EFS</th>
<th>OS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparSixto Carbo vs no</td>
<td>315</td>
<td>53.2 vs 36.9, P=0.005</td>
<td>HR0.56, P=0.22</td>
<td>NS</td>
<td>Wkly carbo Wkly lipo dox</td>
</tr>
<tr>
<td>CALGB40603 Carbo vs no</td>
<td>433</td>
<td>54 vs 41%, P=0.0029</td>
<td>NS</td>
<td>NR</td>
<td>Carbo q3wks</td>
</tr>
<tr>
<td>Brightness Carbo vs no</td>
<td>474</td>
<td>51 vs 31%, P&lt;0.0001</td>
<td>NR</td>
<td>NR</td>
<td>Carbo wkly</td>
</tr>
</tbody>
</table>

- Despite differences in study design, similar results with paclitaxel, or addition of carboplatin
- No differences in OS at 3-4 years of FU
- Long-term outcome of Brightness study still pending

GeparSepto: Untch JCO 2019
Benefit of platinum regardless of germline BRCA status

Loibl S et al, Lancet Oncol 2018

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>22.2 (13.1 to 31.2)</td>
</tr>
<tr>
<td>BRCA1 or BRCA2 mutation, or both</td>
<td>15.6 (-9.4 to 40.7)</td>
</tr>
<tr>
<td>No mutation in BRCA1 or BRCA2</td>
<td>23.2 (13.5 to 32.9)</td>
</tr>
<tr>
<td>Lymph node stage N0</td>
<td>28.0 (15.8 to 40.2)</td>
</tr>
<tr>
<td>Lymph node stage N1-2</td>
<td>15.1 (1.7 to 28.5)</td>
</tr>
<tr>
<td>AC dose every 2 weeks</td>
<td>25.0 (12.9 to 37.1)</td>
</tr>
<tr>
<td>AC dose every 3 weeks</td>
<td>18.6 (4.9 to 32.2)</td>
</tr>
</tbody>
</table>
Differential benefit in gBRCA carriers?


<table>
<thead>
<tr>
<th>pCR</th>
<th>gBRCA mutation (15%)</th>
<th>Wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>41% (9/22)</td>
<td>29% (40/136)</td>
</tr>
<tr>
<td>VCbP</td>
<td>57% (26/46)</td>
<td>53% (142/270)</td>
</tr>
<tr>
<td>CbP</td>
<td>50% (12/24)</td>
<td>59% (80/136)</td>
</tr>
</tbody>
</table>
## Meta-analysis of Neoadjuvant Platinum in TNBC

### Carboplatin neoadjuvant studies powered for pCR and not long-term survival outcomes

Poggio F et al, Ann Oncol 2018

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>Platinum</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM/2006-03</td>
<td>2012</td>
<td>0.97 (0.40, 2.35)</td>
<td>14/47</td>
<td>14/46</td>
</tr>
<tr>
<td>GeparSixto GBG66</td>
<td>2014</td>
<td>1.78 (1.14, 2.78)</td>
<td>90/158</td>
<td>67/157</td>
</tr>
<tr>
<td>CALGB 40603 Alliance</td>
<td>2014</td>
<td>1.68 (1.15, 2.45)</td>
<td>119/221</td>
<td>87/212</td>
</tr>
<tr>
<td>UMIN000003355</td>
<td>2014</td>
<td>4.60 (1.72, 12.27)</td>
<td>23/37</td>
<td>10/38</td>
</tr>
<tr>
<td>Aguilar Martinez et al.</td>
<td>2015</td>
<td>2.38 (0.85, 6.64)</td>
<td>18/30</td>
<td>12/31</td>
</tr>
<tr>
<td>NCT01276769</td>
<td>2016</td>
<td>3.88 (1.35, 11.15)</td>
<td>17/44</td>
<td>6/43</td>
</tr>
<tr>
<td>GeparOcto GBG84</td>
<td>2017</td>
<td>1.14 (0.77, 1.68)</td>
<td>105/203</td>
<td>97/200</td>
</tr>
<tr>
<td>WSG-ADAPT</td>
<td>2018</td>
<td>2.11 (1.33, 3.35)</td>
<td>67/146</td>
<td>51/178</td>
</tr>
<tr>
<td>BrightTness</td>
<td>2018</td>
<td>3.01 (1.90, 4.77)</td>
<td>92/160</td>
<td>49/158</td>
</tr>
<tr>
<td>Random effect (I-squared = 56.3%, (P = 0.019))</td>
<td></td>
<td>1.96 (1.46, 2.62)</td>
<td>545/1046</td>
<td>393/1063</td>
</tr>
</tbody>
</table>

Platinum-based NACT increased pCR rate from 37.0% to 52.1% (OR 1.96, 95% CI 1.46–2.62, \(P < 0.001\))
I-SPY 2 trial

- Adaptive randomization of veliparib-carboplatin treatment in breast cancer
- Treatment: paclitaxel then AC vs paclitaxel/veliparib/carboplatin then AC

## ISPY-2: Pembrolizumab & Carboplatin Improve pCR

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% probability interval)</th>
<th>Probability pembrolizumab is superior to control</th>
<th>Predictive probability of success in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All HER2-</td>
<td>0.44 (0.33 – 0.55)</td>
<td>0.17 (0.11 – 0.23)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>TNBC</td>
<td>0.60 (0.44 – 0.75)</td>
<td>0.22 (0.13 – 0.30)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>0.30 (0.17 – 0.43)</td>
<td>0.13 (0.07 – 0.19)</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

### Estimated pCR Rate (95% probability interval)

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>Veliparib + Carbo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HER2-</td>
<td>33% (22% to 43%)</td>
<td>22% (10% to 35%)</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14% (4% to 27%)</td>
<td>19% (6% to 35%)</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>52% (35% to 69%)</td>
<td>26% (11% to 40%)</td>
</tr>
</tbody>
</table>

ADAPT-TN

- Neoadjuvant chemotherapy for TNBC
  - Capitalizes on GeparSepto finding of higher pCR with weekly nab-paclitaxel vs paclitaxel
- Randomized to chemotherapy, 2 weeks on, one week off x 4 cycles (12wks)
  - nab-paclitaxel 125 mg/m²/gemcitabine 1000 mg/m² (A)
  - nab-paclitaxel 125 mg/m²/Carbo AUC2 (B)
- 336 randomized, 298 completed therapy
  - Gemcitabine arm associated with greater toxicity
- Excellent outcome in those achieving pCR

Gluz et al JNCI 2017
ADAPT- TN: superiority of Nab-P+ Carbo for pCR and survival impact of pCR

Event-free survival by pCR status

ADPAT -TN: no survival impact of additional 4 EC in pts with pCR after 12 weeks of NACT

What is the role of carboplatin”

- All trials show increased toxicity with the addition of carboplatin
- Different results?
  - CALGB added carboplatin an established adjuvant chemotherapy including an anthracycline, an alkylating agent, and a taxane
- What does BrighTNess tell us?
  - For sporadic TNBC, the addition of a weak PAPR inhibitor does not appear to increase pCR
- From GeparSixto and BrighTNess
  - BRCA mutation associated TNBC had a higher pCR, which was not improved with carboplatin
- Not everyone with TNBC needs a platinum.
Even though the results of randomized trials show improvement in pCR rates when carboplatin is added to anthracycline- and taxane-based chemotherapy, the long-term outcomes such as OS or DFS associated with the incorporation of carboplatin are not yet known. Therefore, at this time, the NCCN Panel does not recommend addition of carboplatin to neoadjuvant standard chemotherapy for patients with TNBC outside a clinical trial setting.
Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

F. Cardoso¹, S. Kyriakides², S. Ohno³, F. Penault-Llorca⁴,⁵, P. Poortmans⁶,⁷, I. T. Rubio⁸, S. Zackrisson⁹ & E. Senkus¹⁰, on behalf of the ESMO Guidelines Committee*

The addition of a platinum compound may be considered in triple-negative tumours and/or in patients with deleterious BRCA1/2 mutations [I, C].
Proposed Algorithm and Ongoing Trial

- **TNBC > 2 cm or positive nodes**
  - Anthracycline/Cyclophosphamide x 4 cycles
  - Weekly taxane x 12 weeks
    - Little or no response by week 4
    - Responding disease
    - Responding
    - Poor or little response

- **Responding disease**
  - Taxane x 12 weeks or 4 cycles
  - Taxane plus carboplatin
  - Add carboplatin
  - Anthracycline/Cyclophosphamide x 4 cycles
  - Surgery

- **Responding**
  - Capecitabine (or platinum: E1131)

- **Add carboplatin**
  - Surgery

Incorporation of immunotherapy, biomarkers to drive treatment choice

Adapted from Rugo. ESMO2019
PAPR inhibition as neoadjuvant therapy

Talazoparib: 1 mg daily × 6 months

![Bar chart showing number of patients and pathologic results for different subtypes.]

- **BRCA1**: 17 patients
- **BRCA2**: 3 patients
- **TNBC**: 15 patients
- **HR positive**: 5 patients

**Pathologic Results**
- **RCB-0**: 10 patients, 95% CI 32%, 73%
- **RCB-I**: 2 patients
- **RCB-II**: 5 patients
- **RCB-III**: 3 patients

**RCB-0 + I: 12/19 = 63%, 95% CI = 41%, 81%**

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy
Norikazu Masuda, M.D., Ph.D., Soo-Jung Lee, M.D., Ph.D., Shoichiro Ohtani, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Eun-Sook Lee, M.D., Ph.D., Isao Yokota, Ph.D., Katsumasa Kuroi, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Byeong-Woo Park, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Yasuhiro Yanagida, M.D., Ph.D., Shinji Ohno, M.D., Ph.D., Shintaro Takao, M.D., Ph.D., Kenjiro Aogi, M.D., Ph.D., Hiroji Iwata, M.D., Ph.D., Jooh Jeong, M.D., Ph.D., Kyong-Hwa Park, M.D., Ph.D., Hironobu Sasano, M.D., Ph.D., Yasuo Ohashi, Ph.D., and Masakazu Toi, M.D., Ph.D.

Capecitabine in non-pCR HER2-

Control: Standard
Standard therapy

(n=900)

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

Disease Free Survival

Overall Survival

Toi et al. NEJM 2017

Adjuvant/neoadjuvant cohort: All TNBC patients, no preselection

- TNBC: ER-, PR-, HER2- (centrally confirmed)
- T1c-T3, N0-N3a*, M0
- Prior standard neo/adjuvant CT with anthras +/- taxanes
- Surgery with free-margins

Stratification Factors:
- Institution
- Basal Phenotype according to CK 5/6 and/or EGFR staining (yes vs no)
- ALN (0 vs 1-3 vs ≥4)
- Prior CT (anthras vs anthras + taxanes)

Capecitabine 1000 mg/m² p.o., b.i.d. x 14 days every 3 weeks x 8 cycles

Radiation therapy according to institution standards

Martin m, et al, SABCS 2018
No statistically significant increase in DFS by adding capecitabine to standard neo/adjuvant chemotherapy in early TNBC
TILs as a Predictive and Prognostic Biomarker for pCR and Outcome: Meta-Analysis of 3771 Pts

- High TILS are more frequent in TNBC (30%) > HER2 (19%) > luminal (13%)
- TILS linked to increased pCR rates in all subtypes
- High TILS associated with OS for TNBC and HER2; low TILS a/w OS for luminal

Denkert et al, Lancet Oncol 2018
Neoadjuvant Chemo + anti-PDL1/anti-PD1 in TNBC

KEYNOTE-173 phase 1/2 trial

Chemotherapy + anti-PD1

OP

Pathological CR = ypT0 ypN0

60%

Cohort A (no platinum)

80%

Cohort B (platinum)

Paclitaxel Q1W x12 ± carboplatin Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4 + pembrolizumab Q3W x4

I-SPY 2 trial

Chemotherapy+/-anti-PD1

OP

Pathological CR = ypT0/is ypN0

20%

Control (no immunotherapy)

60%

Immunotherapy (no platinum)

Paclitaxel Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4

AC, doxorubicin + cyclophosphamide; CR, complete response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Q1W, every week; Q3W, every 3 weeks; ypT0/Tis ypN0, no invasive residual in breast or nodes - noninvasive breast residuals allowed; ypT0 ypN0, no invasive or noninvasive residual in breast or nodes

Strategies for Immunotherapy in TNBC

Early Breast Cancer

Neoadjuvant Trial

Adjuvant Trial post neoadjuvant treatment

Metastatic Breast Cancer

1st line MBC

≥2nd line MBC

Keynote 522, IMpassion031

A-Brave

Adapted from Schmid
Neoadjuvant Chemo + anti-PD1 in early TNBC

KEYNOTE-522 trial

Primary Endpoints:
1. Path CR = ypT0/Tis ypN0
2. EFS

pCR (ypT0/Tis; ypN0): 64.8% with pembrolizumab vs 51.2% with placebo ($P = .00055$) improved 18-Mo EFS with addition of pembrolizumab (HR: 0.63)

*Prespecified $P$ value boundary of .000051 not reached at this analysis (the first interim analysis of EFS).
Impact of delaying adjuvant CT in TNBC

Gagliato et al. JCO 2014

Farolfi et al. EJC 2015

Breast cancer subtype
Hormone receptor–positive 1
ERBB2+ 1.04 (0.95-1.15)
TNBC 0.72 (0.63-0.81)
Unknown 1.02 (0.88-1.19)

Chavez-MacGregor et al. JAMA Oncol 2016
Survival outcomes in patients with sTILs $\geq$30%

- iDFS: 81% (75-87)
- D-DFS: 88% (83-93)
- OS: 88% (83-93)

Intrinsic prognostic value of tumor infiltrating lymphocytes (TILs) in early-stage triple negative breast cancer (TNBC) not treated with adjuvant chemotherapy

A pooled analysis of 4 individual cohorts

Park et al. Ann Oncol 2019
Further Excellent Outcomes In pStage I Tumors

- 5Y: 91% 3Y: 93%
  - 84-96 89-96

- 5Y: 97% 3Y: 97%
  - 95-100 95-99

- 5Y: 98% 3Y: 99%
  - 95-100 97-100
Neoadjuvant systemic therapy (NST)
- NST is the preferred initial approach in women with stage 2 or 3 HER+ or TNBC
- NST increasingly enables tailored approaches to therapy in TNBC and HER2 + BC that can improve long-term outcomes for women with breast cancer

TNBC adjuvant therapy
- Women with TNBC and residual tumor after NST should consider capecitabine in the adjuvant setting
Conclusion

• Neoadjuvant therapy is preferred for most early stage TNBC
  - Allow assessment of response with modification of treatment
  - Post neoadjuvant treatment (CREATE-X)
  - pCR and minimal residual disease correlates with excellent outcome

• New therapies are improving response
  - the key is knowing when to use them and in which patients
    - carboplatin, PARPi, immune checkpoint inhibitor
  - De-escalation of therapy in excellent responders

• Future studies in patients with TNBC will need to individualize therapies according to the different molecular subgroups