Triple negative breast cancer
-neoadjuvant and adjuvant systemic therapy

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DISCLOSURE SLIDE

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Outline

• Overview
• Current guideline
• How can we improve more?
  - Dose dense
  - Nab-paclitaxel?
  - Platinum+/-PARP inhibitor
  - Capecitabine in non-pCR
• Practical issues
  - impact of delaying adjuvant CT in TNBC
  - small tumor
  - TIL
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.
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>

TNBCs are heterogeneous

- 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
- Fibromatosis -like

Poor Prognosis

Good Prognosis
### Table 5. Adjuvant systemic treatment recommendations for triple negative and HER2 positive early breast cancer

<table>
<thead>
<tr>
<th>Subtypes according to clinical-pathologic and genomic risk assessment</th>
<th>Treatment recommendation</th>
<th>De-escalation</th>
<th>Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal triple negative pT1a node negative</td>
<td>Neoadjuvant therapy for stage II or III is suggested as initial treatment approach. Chemotherapy should include anthracycline and taxanes</td>
<td>No routine adjuvant chemotherapy for stage pT1a pN0. Dose-dense adjuvant chemotherapy preferred by only a minority of the consensus panel</td>
<td>No consensus on post-neoadjuvant treatment in case of residual disease. In BRCA1/2 associated cancers, the Panel was evenly split on whether to recommend (neo)adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.</td>
</tr>
</tbody>
</table>
NCCN Guidelines Version 3.2018
Invasive Breast Cancer
NCCN Evidence Blocks™

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Negative

• Preferred regimens:
  ▶ Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
  ▶ Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
  ▶ TC (docetaxel and cyclophosphamide)

• Useful in certain circumstances:
  ▶ Dose-dense AC (doxorubicin/cyclophosphamide)
  ▶ AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
  ▶ CMF (cyclophosphamide/methotrexate/fluorouracil)
  ▶ AC followed by weekly paclitaxel

• Other recommended regimens:
  ▶ AC followed by docetaxel every 3 weeks
  ▶ EC (epirubicin/cyclophosphamide)
  ▶ TAC (docetaxel/doxorubicin/cyclophosphamide)

See Evidence Blocks on BINV-K (EB-1)

HER2-Positive

• Preferred regimens:
  ▶ AC followed by T + trastuzumab
    (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
  ▶ AC followed by T + trastuzumab + pertuzumab
    (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab)
  ▶ Paclitaxel + trastuzumab
  ▶ TCH (docetaxel/carboplatin/trastuzumab)
  ▶ TCH (docetaxel/carboplatin/trastuzumab) + pertuzumab

• Useful in certain circumstances:
  ▶ Docetaxel + cyclophosphamide + trastuzumab

• Other recommended regimens:
  ▶ AC followed by docetaxel + trastuzumab
    (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
  ▶ AC followed by docetaxel + trastuzumab + pertuzumab
    (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)
Neoadjuvant treatment

ESMO  The addition of a platinum compound (carboplatin) to neoadjuvant chemotherapy allows for an increase in the pCR rate in triple-negative tumours, particular those carrying deleterious BRCA1/2 or RAD51 mutations or those occurring in patients with a family history of breast or ovarian cancer. But the effect of those compounds on long-term outcomes is unknown.

NCCN  The NCCN panel does not recommend the addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative BCa outside a clinical trial setting.

Adjuvant treatment

ESMO  Triple-negative tumours benefit from adjuvant chemotherapy with the possible exception of low-risk “special histologic subtypes” such as secretory juvenile, apocrine, or adenoid cystic carcinomas.

ASCO/CCO  When considering lymph node–negative tumours with T > 5 mm, these features should be considered high-risk (and thus the patient should be considered a candidate or chemotherapy):

- Grade 3
- Triple-negative
- Lymphovascular invasion–positive
- An Oncotype DX recurrence score that is associated with an estimated relapse risk of 15% or more at 10 years
- HER2 positivity
Anthracycline-Taxane in EBC

- A-T in EBC: Reduces recurrence, breast cancer mortality & overall mortality compared to anthracycline alone

How can we improve more?

*EBCTCG, Lancet 2012
Three ways to increase dose intensity (ie, the drug dose in mg/m$^2$ per week)

1. Use higher doses of drugs in each cycle
2. Reduce the interval between treatment cycles
3. Give drugs sequentially rather than concurrently

* Norton L. Sem Oncol 1997
Anthracyclines: no apparent benefit from escalation beyond standard dose

2-weekly (dose dense) vs the same chemotherapy given 3-weekly

Any Recurrence

10004 women

RR 0.83 (0.76–0.91)
Logrank 2p = 0.00004
10-y gain 4.3% (CI 2.2 – 6.5)

Stnd
28.3%

Dose dense
19.5%

Breast Cancer Mortality

10004 women

RR 0.86 (0.77–0.95)
Logrank 2p = 0.004
10-y gain 2.8% (CI 0.8 – 4.8)

Stnd
19.6%

Dose dense
16.8%
Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

**Any Recurrence**

- 11028 women
- RR 0.87 (0.80–0.94)
- Logrank 2p = 0.0006
- 10–y gain 3.2% (CI 0.8 – 5.6)

**Breast Cancer Mortality**

- 11028 women
- RR 0.89 (0.80–0.99)
- Logrank 2p = 0.03
- 10–y gain 2.1% (CI 0.1 – 4.1)
Sequential (2-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence

Breast Cancer Mortality

EBCTCG SABCS 2017
Pooled Analysis: recurrence by ER status

ER- Negative

9209 women
RR 0.82 (0.76–0.88)
Logrank 2p < 0.00001
10–y gain 4.7% (CI 2.3 – 7.1)

Stnd 38.3%
Dose dense 33.6%

ER - Positive

23495 women
RR 0.86 (0.81–0.91)
Logrank 2p < 0.00001
10–y gain 3.1% (CI 1.5 – 4.7)

Stnd 29.4%
Dose dense 26.3%
New standard adjuvant regimen?
EC x 4 q 2wks → Paclitaxel x 4 q 2wks

Del Mastro et al. Lancet 2015

TNBC patients
Gold standard adjuvant regimen:
EC q2wks x 4 → weekly paclitaxel x 12
pCR and EFS

- FDA Meta Analysis (Cortazar et al, Lancet 2014)
  - >11K patients from 12 neoadjuvant trials
  - Median follow-up for EFS: 5.4 years
GeparSepto Study Design

N = 1200

Arm A
Arm B

R

1:1

12 weeks

12 weeks

Core biopsy (before study entry)

CT2-cT4a-d, cT1c + high risk
- HER2+/HR- vs. HER2+/HR+ vs. HER2-/HR- vs. HER2-/HR+
- Ki67 (≤20% vs. >20%)
- SPARC (positive vs. negative)

Paclitaxel 80 mg/m² weekly
Nab-paclitaxel 150 mg/m² weekly
The dose was reduced to 125 mg/m² after recruitment of 464 patients

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Trastuzumab 8 mg/kg (loading dose) → 6 mg/kg
Pertuzumab 840 mg (loading dose) → 420 mg

HER2 positive patients

G3 PPN: 15% -> 8%
Primary Endpoint: pCR (ypT0 ypN0)

TNBC: 26% vs 48%, p=0.00027
HR+/HER2-: 12% vs 16%, p=0.23
HR+/HER2+: 50% vs 56%, P=0.30
HR-/HER2+: 67% vs 75%, P=0.49

Untch et al. Lancet Oncol 2016
Disease-Free Survival

- Median FU of 49 months (IQR 44.6 - 52.9)
- HR (nP-EC vs. P-EC) = 0.69 (95% CI 0.54-0.89)
- Number needed to treat (NNT; 3yrs) = 16 pts

DFS rates (estimated):

<table>
<thead>
<tr>
<th>Time</th>
<th>P-EC</th>
<th>95% CI, P-EC</th>
<th>nP-EC</th>
<th>95% CI, nP-EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yrs</td>
<td>80.7%</td>
<td>(77.2-83.7)</td>
<td>87.1%</td>
<td>(84.1-89.6)</td>
</tr>
<tr>
<td>4 yrs</td>
<td>76.2%</td>
<td>(72.3-79.5)</td>
<td>83.5%</td>
<td>(80.2-86.4)</td>
</tr>
</tbody>
</table>
Disease-Free Survival per Subtype

**TNBC**

<table>
<thead>
<tr>
<th>P-EC</th>
<th>nP-EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>44/137 events</td>
<td>33/139 events</td>
</tr>
</tbody>
</table>

**HR+HER2-**

<table>
<thead>
<tr>
<th>P-EC</th>
<th>nP-EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/266 events</td>
<td>50/268 events</td>
</tr>
</tbody>
</table>
Forest Plot: Disease-Free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
<th>Test for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>1206</td>
<td>.693 (.537, .893)</td>
<td>.005</td>
<td>.913</td>
</tr>
<tr>
<td><strong>Biological subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-/HR+</td>
<td>534</td>
<td>.712 (.495, 1.02)</td>
<td>.067</td>
<td></td>
</tr>
<tr>
<td>HER2-/HR-</td>
<td>276</td>
<td>.660 (.420, 1.04)</td>
<td>.072</td>
<td></td>
</tr>
<tr>
<td>HER2+/HR+</td>
<td>289</td>
<td>.753 (.377, 1.50)</td>
<td>.420</td>
<td></td>
</tr>
<tr>
<td>HER2+/HR-</td>
<td>107</td>
<td>.500 (.178, 1.41)</td>
<td>.189</td>
<td></td>
</tr>
<tr>
<td><strong>Ki67</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=20%</td>
<td>373</td>
<td>.431 (.256, .724)</td>
<td>.001</td>
<td>.046</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>633</td>
<td>.813 (.506, 1.09)</td>
<td>.188</td>
<td></td>
</tr>
<tr>
<td><strong>SPARC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative (IRS 0-5)</td>
<td>1015</td>
<td>.681 (.516, .898)</td>
<td>.007</td>
<td>.705</td>
</tr>
<tr>
<td>positive (IRS 6-12)</td>
<td>191</td>
<td>.744 (.392, 1.41)</td>
<td>.365</td>
<td></td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>610</td>
<td>.698 (.526, .927)</td>
<td>.013</td>
<td>.927</td>
</tr>
<tr>
<td>positive</td>
<td>396</td>
<td>.675 (.380, 1.20)</td>
<td>.180</td>
<td></td>
</tr>
<tr>
<td><strong>ER/PgR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>383</td>
<td>.618 (.409, .935)</td>
<td>.023</td>
<td>.530</td>
</tr>
<tr>
<td>positive</td>
<td>623</td>
<td>.727 (.527, 1.00)</td>
<td>.052</td>
<td></td>
</tr>
<tr>
<td><strong>pCR ypT0 ypN0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no pCR</td>
<td>772</td>
<td>.693 (.520, .922)</td>
<td>.012</td>
<td>.350</td>
</tr>
<tr>
<td>pCR</td>
<td>404</td>
<td>.975 (.502, 1.89)</td>
<td>.941</td>
<td></td>
</tr>
</tbody>
</table>

HR: nP-EC better, P-EC better
**Overall Survival: Overall**

- Log rank p=0.2968

- HR (nP-EC vs. P-EC) = 0.83 (95% CI 0.59-1.17)

**OS rates (estimated):**

<table>
<thead>
<tr>
<th>Time</th>
<th>P-EC</th>
<th>95% CI, P-EC</th>
<th>nP-EC</th>
<th>95% CI, nP-EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yrs</td>
<td>91.1%</td>
<td>(88.4-93.1)</td>
<td>92.3%</td>
<td>(89.8-94.2)</td>
</tr>
<tr>
<td>4 yrs</td>
<td>87.0%</td>
<td>(83.8-89.6)</td>
<td>89.6%</td>
<td>(86.8-91.9)</td>
</tr>
</tbody>
</table>

*P-EC: 72/600 deaths, nP-EC: 61/606 deaths*
Surrogate Value of pCR (exploratory analysis)

Disease-Free Survival

Overall Survival

Disease-Free Survival

Overall Survival

<table>
<thead>
<tr>
<th>Pac no pCR</th>
<th>416</th>
<th>398</th>
<th>348</th>
<th>305</th>
<th>194</th>
<th>9</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>nPac no pCR</td>
<td>356</td>
<td>346</td>
<td>312</td>
<td>286</td>
<td>163</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Pac pCR</td>
<td>172</td>
<td>167</td>
<td>157</td>
<td>144</td>
<td>79</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>nPac pCR</td>
<td>232</td>
<td>227</td>
<td>217</td>
<td>208</td>
<td>123</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

DFS, months

<table>
<thead>
<tr>
<th>Pac no pCR</th>
<th>417</th>
<th>410</th>
<th>383</th>
<th>352</th>
<th>229</th>
<th>11</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>nPac no pCR</td>
<td>357</td>
<td>353</td>
<td>327</td>
<td>308</td>
<td>180</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Pac pCR</td>
<td>172</td>
<td>167</td>
<td>163</td>
<td>152</td>
<td>85</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>nPac pCR</td>
<td>232</td>
<td>228</td>
<td>224</td>
<td>214</td>
<td>126</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

OS, months
Questions/Concerns raised

• Toxicity: G3-4 peripheral neuropathy of 8% in nab-paclitaxel arm
• There were inconsistent findings for the use of nab-paclitaxel instead of paclitaxel as neoadjuvant chemotherapy.
Outline

• Overview
• Current guideline
• How can we improve more?
  - Dose dense
  - Nab-paclitaxel?
  - Platinum+/-PARP inhibitor
  - Capecitabine in non-pCR
• Practical issues
  - impact of delaying adjuvant CT in TNBC
  - small tumor
  - TIL
GeparSixto

CAUTION: 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.

von Minckwitz, Lancet Oncol. 2014
GBG GeparSixto had randomised design but showed High HRD group responds better to both chemotherapy regimens than Low HRD.
CALGB 40603 – randomised phase II trial

Clinical stage II-III TN

Primary EP – pCR in breast (trial did not mandate surgery of axilla)

*Gcsf primary prophylaxis for ddAC cycles

Sikov et al, SABCS 2013
pCR (carboplatin)

pCR breast

OR 1.76 (p=0.0018)

Sikov et al, SABCS 2013

pCR breast/axilla

OR 1.71 (p=0.0029)
The Role of Platinum in TNBC

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>pCR in Carbo arm</th>
<th>pCR in Control arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 40603</td>
<td>443</td>
<td>54%</td>
<td>41%</td>
<td>P=0.003</td>
</tr>
<tr>
<td>GeparSixto</td>
<td>315</td>
<td>59%</td>
<td>38%</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>I-SPY 2</td>
<td>116</td>
<td>52%</td>
<td>26%</td>
<td>90% probability</td>
</tr>
</tbody>
</table>

Pusztai L. SABCS 2013
Disease Free Survival
GeparSixto (Med FU 35Mo) vs CALGB 40603 (Med FU 39Mo)
Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial

Sibylla Loibl, Joyce O'Shaughnessy, Michael Untch, William M Sikov, Hope S Rugo, Mark D McKee, Jens Hueber, Mehra Golshan, Gunter von Minckwitz, David Maqs, Danielle Sullivan, Norman Wolmark, Kristi McIntyre, Jose Ponce Lorenzo, Otto Metzger Filho, Priya Rastogi, W Fraser Symmans, Xuan Liu, Charles E Geyer Jr

1) paclitaxel (80 mg/m² IV weekly) + carboplatin (AUC 6 mg/mL/min, IV q 3wks) + veliparib (50 mg po bid)
2) paclitaxel plus carboplatin
3) paclitaxel alone.
→ AC q 2-3 wks for four cycles.

Loibl S et al Lancet Oncol 2018
Gr 3/4 toxicities and Severe AE were more common in those receiving carboplatin. Most common Gr 3/4 in the first 12 weeks were neutropenia (56%), anemia (29%), and thrombocytopenia (12%). Febrile neutropenia (15%) was most common during the second segment.

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel + carboplatin + veliparib</th>
<th>Paclitaxel + carboplatin + veliparib placebo</th>
<th>Paclitaxel + carboplatin placebo + veliparib placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>168/316 (53%)</td>
<td>92/160 (58%)</td>
<td>49/158 (31%)</td>
</tr>
<tr>
<td>Germline BRCA status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation in BRCA1 or BRCA2, or both</td>
<td>26/46 (57%)</td>
<td>12/24 (50%)</td>
<td>9/22 (41%)</td>
</tr>
<tr>
<td>No mutation in BRCA1 or BRCA2, or both</td>
<td>142/270 (53%)</td>
<td>80/136 (59%)</td>
<td>40/136 (29%)</td>
</tr>
<tr>
<td>Lymph node stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>108/174 (61%)</td>
<td>54/87 (62%)</td>
<td>29/88 (33%)</td>
</tr>
<tr>
<td>N1–N2</td>
<td>62/142 (44%)</td>
<td>38/73 (52%)</td>
<td>20/70 (29%)</td>
</tr>
<tr>
<td>Dose density of doxorubicin–cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 2 weeks</td>
<td>98/176 (56%)</td>
<td>50/89 (56%)</td>
<td>27/88 (31%)</td>
</tr>
<tr>
<td>Every 3 weeks</td>
<td>70/140 (50%)</td>
<td>42/71 (59%)</td>
<td>22/70 (31%)</td>
</tr>
<tr>
<td>High grade</td>
<td>166/185 (85%)</td>
<td>81/87 (85%)</td>
<td>53/62 (85%)</td>
</tr>
<tr>
<td>Other grades</td>
<td>62/126 (49%)</td>
<td>31/63 (49%)</td>
<td>13/66 (20%)</td>
</tr>
</tbody>
</table>

Loibl S et al Lancet Oncol 2018
When to consider for platinum in daily practice?

• Need for rapid loco-regional control
  - increased resectability
• Highest risk of relapse-stage III, very young patient
• Benefit to BRCA mutation carriers
• Careful patient selection due to added risks of short term and long term toxicity

DeMichele et al. SABCS 2015
**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 Yagaita, M.D., Ph.D., Shinji Ohno, M.D., Ph.D., Shintaro Takeda, M.D., Ph.D., Kenjiro Aogi, M.D., Ph.D., Hiroshi Iwata, M.D., Ph.D., Joon Jeong, M.D., Ph.D., Aeree Kim, M.D., Ph.D., Kyong-Hwa Park, M.D., Ph.D., Hironobu Sasanou, M.D., Ph.D., Yasuo Ohashi, Ph.D., and Masakazu Toi, M.D., Ph.D.

*N Engl J Med 2017; 376:2147-2159 | June 1, 2017 | DOI: 10.1056/NEJMoa1612645*

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**Capecitabine in non-pCR HER2-**

**Capecitabine Therapy**

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

**Pathology**
- Pathology Non-pCR or node +

**Control:**
- Standard therapy

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

**HER2-**
- NAC
- Surgery

**Disease Free Survival**

- HR (95%E) 0.70 (0.53-0.93)
- One-sided p=0.00524 < 0.00671

- 82.8% Capecitabine
- 74.0% Control

- 74.1% Capecitabine
- 67.7% Control

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**Overall Survival**

- HR (95%E) 0.60 (0.40-0.92)
- One-sided p<0.01

- 89.2% Capecitabine
- 83.9% Control

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Toi et al. *NEJM* 2017
ECOG-ACRIN 1131 (Ingrid Mayer, Chair)

TNBC stage II/III, received anthracycline-based NACT ≥ 1 cm residual disease at surgery Basal subtype on PAM-50

Randomized

Capecitabine

Cisplatin or Carboplatin x 4 (Physician’s discretion)

EFS and OS

Powered to detect a 33% improvement in EFS
Sample size: 558
Neo/Adjuvant ongoing trials in BRCA+

**Randomized Neoadjuvant Trial: INFORM Trial**

- BRCA1/BRCA2 + TNBC or HiGrade ER+ (HER2 negative) T1-T3

- Cisplatin 75/m^2 q21d x 4
- Cytoxan 600/m^2 + Doxorubicin 60/m^2 q21d x 4

- Surgery
- Additional ChemoRx

**BIDMC, DFCI, MGH, MSKCC, UMDNJ, UPENN, UTMDACC, WIH, Yale, TBCRC sites**

**OlympiaA**

- Randomisation 1:1
  - Double blind N=1500
  - Olaparib 300 mg twice daily (bid)
  - Placebo twice daily (bid)
  - 1 yr*
  - 9 yr+

**IDFS**
- distant IDFS, Q5

* HR*/Her2 subset may continue on aromatase inhibitors or tamoxifen.
Classification of TNBC into 6 different subtypes

- **Basal-like 1 (BL1):** Cell-cycle, proliferation and DNA damage response genes
- **Basal-like 2 (BL2):** Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)
- **Immunomodulatory (IM):** Immune cell and cytokine signaling (overlap with medullary breast cancer gene signature)
- **Mesenchymal (M):** Cell motility and differentiation (Wnt, ALK, TGF-β)
- **Mesenchymal stem-like (MSL):** Similar to M, but increased growth factors signaling, low proliferation, enrichment of genes associated with stem cells
- **Luminal androgen receptor (LAR):** Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

Lehmann et al, J Clin Invest 2011
TRIPLE-NEGATIVE BREAST CANCER SUBTYPES

BLIA: basal-like /immune activated
MES: mesenchymal
LAR: Luminal/Androgen receptor
BLIS: basal-like/immune-suppressed
Outline

• Overview
• Current guideline
• How can we improve more?
  - Dose dense
  - Nab-paclitaxel?
  - Platinum+/-PARP inhibitor
  - Capecitabine in non-pCR
• **Practical issues**
  - Impact of delaying adjuvant CT in TNBC
  - Small tumor
  - TIL
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**
Triple negative breast cancer – adjuvant chemotherapy use and survival outcomes in Stage IA Disease

Ami Patel¹, Runhua Shi¹, Prakash Peddi¹ and Gary V. Burton¹
¹LSU Health Shreveport, Shreveport, LA

- Patients with National Cancer Database (2004-2012)
- 13065 breast cancer patients btwn the ages of 18-90 YO, Stage IA

### Baseline characteristics

<table>
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<tr>
<th>Factor</th>
<th>Level</th>
<th>n</th>
<th>%</th>
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<td>Age (years)</td>
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<td></td>
<td>18-49</td>
<td>2942</td>
<td>22.5</td>
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<td>50-64</td>
<td>5634</td>
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<tr>
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<td>65-74</td>
<td>2960</td>
<td>22.7</td>
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<td></td>
<td>75+</td>
<td>1529</td>
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<tr>
<td>Race</td>
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<td>White</td>
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<td>2</td>
<td>325</td>
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<td>0-11</td>
<td>1929</td>
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<td>Treatment Started from Diagnosis (days)</td>
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<td></td>
<td>12-23</td>
<td>3735</td>
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<td>24-39</td>
<td>4100</td>
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<tr>
<td></td>
<td>40+</td>
<td>3081</td>
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<tr>
<td>Tumor Size (mm)</td>
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<tr>
<td></td>
<td>1-5</td>
<td>1275</td>
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<td>6-10</td>
<td>3197</td>
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<td>11-20</td>
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<td>Radiation</td>
<td>None Radiation</td>
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<td></td>
<td>Radiation Only</td>
<td>869</td>
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<td>Radiation+Boost</td>
<td>4868</td>
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### 4YR OS for TNBC with/without adjuvant CTx. use

<table>
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<tr>
<th>Tumor size</th>
<th>No Chemotherapy</th>
<th>Chemotherapy</th>
<th>P value</th>
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<tbody>
<tr>
<td>T1a</td>
<td>93.78%</td>
<td>98.36%</td>
<td>0.146</td>
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<tr>
<td>T1b</td>
<td>91.91%</td>
<td>97.10%</td>
<td>&lt; 0.0001</td>
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<tr>
<td>T1c</td>
<td>80.62%</td>
<td>94.41%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Prognostic value of TIL. DFS for all patients (A) and in ER+/HER2 (B) ER−/HER2− (C) HER2+ (D).

M. V. Dieci et al. Ann Oncol 2015;annonc.mdv239
Prognostic value of stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative breast cancer.

Sylvia Adams et al. JCO 2014;32:2959-2966

©2014 by American Society of Clinical Oncology
Co-primary endpoints: PFS and OS in ITT and PD-L1+ populations

Eligibility criteria:
- Metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC, > 12 m since (neo)adj

Stratification factors:
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status

Atezo + nab-P arm:
- Atezolizumab 840 mg IV
  - On days 1 and 15 of 28-day cycle
- Nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

Plac + nab-P arm:
- Placebo IV
  - On days 1 and 15 of 28-day cycle
- Nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

RECIST v1.1 PD or toxicity

Schmid P et al, NEJM 2018
<table>
<thead>
<tr>
<th>Phases</th>
<th>NCT ID &amp; number</th>
<th>Defined condition of breast Cancer subtype</th>
<th>setting</th>
<th>stage</th>
<th>Experimental Drugs</th>
<th>Control</th>
<th>Primary endpoint</th>
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<td><strong>IO monotherapy</strong></td>
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<tr>
<td>III</td>
<td>SWOG1418 (NCT02954874)</td>
<td>Residual TNBC (ypT&gt; 1cm or ypN+)</td>
<td>Adjuvant after NAC</td>
<td>Pembrolizumab for 1 year</td>
<td>Observation as per guideline</td>
<td>Invasive DFS (IDFS)</td>
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<tr>
<td>III</td>
<td>NCT02926196</td>
<td>High risk TNBC</td>
<td>Adjuvant or post-NAC</td>
<td>Avelumab for 1 year</td>
<td>Observation as per guideline</td>
<td>- Overall DFS - DFS in PD-L1(+) patients</td>
<td></td>
</tr>
<tr>
<td><strong>IO-based combination</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>II</td>
<td>I-SPY 2 (NCT01042379)</td>
<td>Locally advanced breast cancer including TNBC and HR+HER2- BC</td>
<td>Neoadjuvant</td>
<td>Pembrolizumab + paclitaxel - Followed by doxorubicin + cyclophosphamide</td>
<td>Standard NAC</td>
<td>pCR : 62.4% vs 22.3%</td>
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<tr>
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<td>* Neoadjuvant, personalized adaptive trial with novel agents</td>
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<tr>
<td>II/II</td>
<td>KEYNOTE-173 (NCT02622074)</td>
<td>Locally advanced TNBC</td>
<td>Neoadjuvant</td>
<td>Pembrolizumab → Pembrolizumab + nabPaclitaxel (Arm A) : Carboplatin Followed by ddAC (Arm B) : Arm A+ Carboplatin Followed by ddAC</td>
<td>NA</td>
<td>pCR (Arm A vs B) : 60% vs 90%</td>
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</tr>
<tr>
<td>III</td>
<td>KEYNOTE-522 (NCT03036488)</td>
<td>TNBC</td>
<td>Neo/adjuvant</td>
<td>Pembrolizumab + wPaclitaxel + Carboplatin (4C) → Pembrolizumab + AC (4C) - Adjuvant : Pembrolizumab (9C)</td>
<td>placebo rather than pembrolizumab</td>
<td>pCR, EFS</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02489448</td>
<td>TNBC</td>
<td>Neoadjuvant</td>
<td>Pembrolizumab + nab-paclitaxel for 12 weeks</td>
<td>NA</td>
<td>pCR</td>
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</tbody>
</table>
Take home message

• Current standard treatment for early TNBC remains the chemotherapeutic approaches
  - Anthracycline+ taxane-based chemotherapy backbone for all patients.
  - Neoadjuvant therapy for stage II or III is suggested as initial treatment
  - Sequential strategy, dose-dense → preferred but balanced with toxicity
• Consider platinum drugs if patient has known BRCA1/BRCA2 germline mutation.
• Consider neoadjuvant approach to tailor use of adjuvant therapy with capecitabine on the basis of residual disease burden at surgical excision.
• Future studies in patients with TNBC will need to individualize therapies according to the different molecular subgroups