Systemic Therapy for Locally Advanced Breast Cancer

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Neoadjuvant Systemic Therapy in Locally Advanced Breast Cancer

INDICATIONS

Operable but unable to conserve breast (need mastectomy)

Convert inoperable to operable

Convert non-conservable to conservable

Test biology of tumor

Possibility to add agent(s) to conventional chemotherapy to improve pCR

Non-\( pCR \)

Identifies poor risk patients who may benefit from additional adjuvant therapy
Neoadjuvant Chemotherapy Schema

Neoadjuvant Chemotherapy 3-6 months

Definitive Breast Cancer Surgery

+/- Adjuvant chemotherapy

+/- Other Adjuvant Therapies

Clinical response monitored at every cycle

Pathological Response
Outcomes from Neoadjuvant Chemotherapy

Clinical response rates 60-90%
Breast conservation rates 40-70%
Pathological complete response rates (pCR) 10-50% *(has prognostic relevance)*

Risk of clinical progression in <5%
- Operable → Non-operable
- Locally advanced → Metastatic

*Failure to achieve clinical response (CR/PR) after 6-12 weeks of neoadjuvant chemotherapy is associated with low probability of pCR*

Smith et al. JCO 2002, 20: 1456-66
pCR is Prognostic in most Breast Cancer Subtypes except for Luminal A

**Prognostic** in Luminal B, HER2+, and TNBC

**Not prognostic** in Luminal A

N=6377
7 randomized trials

*pCR is the parameter to improve (surrogate for long-term survival)*

**Improving pCR rate**

*Adding Taxanes to Anthracyclines; 6 months vs 3 months*

### 3 months neoadjuvant chemotherapy (All subtypes) (anthracyclines)

<table>
<thead>
<tr>
<th>Study</th>
<th>pCR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B18</td>
<td>13%</td>
</tr>
<tr>
<td>n=2309</td>
<td></td>
</tr>
<tr>
<td>AC x 4 (60/600)</td>
<td>Surgery upfront</td>
</tr>
</tbody>
</table>

### 6 months neoadjuvant chemotherapy (All subtypes) (sequential anthracyclines and taxanes)

<table>
<thead>
<tr>
<th>Study</th>
<th>pCR Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B27</td>
<td>14%</td>
</tr>
<tr>
<td>n=1609</td>
<td></td>
</tr>
<tr>
<td>AC x 4 (60/600)</td>
<td>AC x 4 (60/600)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>Docetaxel (100) x 4</td>
</tr>
</tbody>
</table>

*NSABP B18; JCO 2004, 24: 2019-27*

*NSABP B27; Bear et al. JCO 2006; 24: 2019-27*
Improving pCR rate in special subtypes

HER2+ breast cancers
Improving pCR rate in HER2 Positive Breast Cancers

Adding Trastuzumab to Chemotherapy

Noah
N=235

- ATx3 → Tx4 → CMFx3
- ATx3 → Tx4 → CMFx3
- Trastuzumab

pCR
19%
38%

Geparquattro
N=445

- ECx4 → docetaxel+/− capecitabine x4
- ECx4 → docetaxel+/− capecitabine x4
- Trastuzumab

16%
32%

Gianni et al. Lancet 2010; 375: 377-84
Pierga et al. Breast Cancer Research and Treatment 2010, 122(2P 429-37
**Improving pCR rate in HER2 Positive Breast Cancers**

**Dual Anti-HER2 Blockade + Chemotherapy**

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**NeoSPHERE (neoadjuvant)**

N=417 (HER2+)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + Docetaxel</td>
<td>29%</td>
</tr>
<tr>
<td>Pertuzumab + Docetaxel</td>
<td>24%</td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab</td>
<td>46%</td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab</td>
<td>17%</td>
</tr>
</tbody>
</table>

*P=0.01*

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Pertuzumab is synergistic with trastuzumab and is a first-in-class dimerization inhibitor.


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Improving pCR rate in special subtypes

TNBC (adding agents to anthracyclines/taxanes)

- chemotherapy (carboplatin)
- biological agents (PARP inhibitors, Immune checkpoint inhibitors)
Adding Platinums to Neoadjuvant Anthracyclines/Taxanes to improve pCR in TNBC

**GEPARSIXTO; n=315 TNBC (Phase II randomized)**

- Paclitaxel/Liposomal dox x 18 weeks
- Carboplatin x 18 weeks (AUC 1.5-2)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Liposomal dox x 18 weeks</td>
<td>37%</td>
</tr>
<tr>
<td>Carboplatin x 18 weeks (AUC 1.5-2)</td>
<td>53%</td>
</tr>
</tbody>
</table>

\[ \Delta 17\% \]

\[ \Delta 17\% \]

\[ P=0.005 \]

**CALGB 40603; n=443 TNBC (Phase II randomized; 2x2 factorial)**

- Paclitaxel x 12 weeks
- Carboplatin 3-weekly x 4 (AUC 6)
- ddAC x 4 (60/600)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel x 12 weeks</td>
<td>41%</td>
</tr>
<tr>
<td>Carboplatin 3-weekly x 4 (AUC 6)</td>
<td>54%</td>
</tr>
</tbody>
</table>

\[ \Delta 13\% \]

\[ \Delta 13\% \]

\[ P=0.029 \]

Carboplatin added to Neoadjuvant Chemotherapy in TNBC

Meta-analysis of TNBC neoadjuvant trials
5 studies, n=988 TNBCs
Carboplatin vs no carboplatin

**Odds Ratio** of improving pCR

- **OR 1.80**
- **CI 1.39-2.32**
- **p<0.001**

More toxicities
G3,4 thrombocytopenia
G3,4 anemia

More dose discontinuations

May be considered in *selected patients* (higher risk, younger, fitter), platinum sensitive

_Cao et al. PLOS One 2015; 10(12): e0145442_
BRCA mutant breast cancers are exquisitely sensitive to platinums

Neoadjuvant **single agent cisplatin** 75mg/m², 3 weekly x 4

<table>
<thead>
<tr>
<th>Tumor types (BRCA1+ mutants)</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumors (n=107)</td>
<td>61%</td>
</tr>
<tr>
<td>TNBC (n=80)</td>
<td>61%</td>
</tr>
<tr>
<td>ER+ (n=16)</td>
<td>56%</td>
</tr>
</tbody>
</table>

Neoadjuvant **single agent cisplatin x 4** in unselected TNBC (n=28): **pCR 22%**

Neoadjuvant **dose dense AC x 4 followed by taxanes** in **BRCA1/2+ TNBC** (n=37): **pCR 67%**

Ongoing neoadjuvant study

BRCA1/2+ tumors (n=166)


Silver et al. JCO 2010; 28(7): 1145-53; Clinical Trials.gov: NCT01670500
# Addition of Bevacizumab to Neoadjuvant Chemotherapy in TNBC

## Anthracyclines + Taxanes backbone

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>TNBC pCR rates</th>
</tr>
</thead>
</table>
| **GEPARQUINTO**        | EC x 4 (90/600)             | Docetaxel (100) x 4         | 28%  
|                        |                             |                             | $\Delta 11\%$   |
|                        | EC x 4 (90/600)             | Docetaxel (100) x 4         | 39%  
|                        |                             |                             | $p=0.003$       |
|                        | Bevacizumab 3 weekly x 8    |                             |                 |
| **ARTemis**            | Docetaxel (100) x 3         | FEC x 3 (500/50/500)        | 31%  
| (800 HER2-)            |                             |                             | $\Delta 14\%$  |
|                        | Docetaxel (100) x 3         | FEC x 3 (500/50/500)        | 45%  
|                        |                             |                             | P: not reported |
|                        | Bevacizumab 3 weekly x 4    |                             |                 |

## Anthracyclines + Taxanes + additional chemotherapy backbone

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>TNBC pCR rates</th>
</tr>
</thead>
</table>
| **NSABP-B40**          | Docetaxel x 4 +/- gem or cape| AC x 4 (60/600)             | 47%  
| (2x3 factorial)        |                             |                             | $\Delta 5\%$   |
|                        |                             |                             | $P=0.34$        |
|                        | Docetaxel x 4 +/- gem or cape| AC x 4 (60/600)             | 52%  
|                        |                             |                             |                 |
|                        | Bevacizumab 3 weekly x 6    |                             |                 |
| **CALGB 40603**        | Paclitaxel x 12W +/- carbo   | ddAC x 4                    | 44%  
| (2x2 factorial)        |                             |                             | $\Delta 8\%$   |
|                        | Paclitaxel x 12W +/- carbo   | ddAC x 4                    | 52%  
|                        |                             |                             | $P=0.057$       |
|                        | Bevacizumab 2 weekly x 9    |                             |                 |

Bevacizumab added to Chemotherapy in TNBC

Neoadjuvant and Adjuvant

Meta-analysis of neoadjuvant therapy in TNBC
3 studies, n=1586 TNBCs (exclude ARTemis)

Bevacizumab vs no bevacizumab

Meta-analysis of carboplatin vs no carboplatin: OR 1.80 (5 trials, 988 patients)

BEATRICE (Adjuvant bevacizumab; Phase III randomized)
N=2591 TNBC; Node negative 63%, Asian ~24%

Bevacizumab x 1 year

Cao et al. PLOS One 2015; 10(12): e0145442; Cameron et al. Lancet Oncol 2013, 14: 933-42
Biological Agent + Neoadjuvant Chemotherapy in TNBC

**PARP Inhibitor; Immune Checkpoint Inhibitor**

**I-SPY2; phase II adaptive randomized**

**N=44 HER2- (n=21 TNBC)**
- Paclitaxel x 12 weeks
- AC x 4 (60/600)

**pCR in TNBC**
- 26% (19% for HER2-)

**N=72 HER2- (n=39 TNBC)**
- Paclitaxel x 12 weeks
- AC x 4 (60/600)
- Veliparib + carboplatin

**51% (14% for HER2-)**

**88% predicted probability of phase III success in TNBC**

**N=180 HER2-**
- Paclitaxel x 12 weeks
- AC x 4 (60/600)

**pCR in TNBC**
- 20% (13% for HER2-)

**N=69 HER2- (n=29 TNBC)**
- Paclitaxel x 12 weeks
- AC x 4 (60/600)
- Pembrolizumab

**60% (34% for HER2-)**

**>99% predicted probability of phase III success in TNBC**

*Promising preliminary data but small sample size*

Rugo et al. NEJM 2016, 375(1): 23-34; Rugo et al. NEJM June 2017
# Probability of achieving pCR from Neoadjuvant Chemotherapy in different Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Treatment Regimen</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subtypes</td>
<td>Anthracyclines combination (3 months)</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td><strong>Sequential anthracyclines and taxanes (6 months)</strong></td>
<td>26%</td>
</tr>
<tr>
<td>HER2+</td>
<td>Single agent taxanes + Trastuzumab</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Single agent taxanes + <strong>Trastuzumab + Pertuzumab</strong></td>
<td>50%</td>
</tr>
<tr>
<td>TNBC</td>
<td>Sequential anthracyclines and taxanes (6 months)</td>
<td>30-35%</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines and taxanes + <strong>carboplatin</strong></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines + taxanes + <strong>bevacizumab</strong></td>
<td>45-50%</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines + taxanes + <strong>carboplatin + veliparib</strong></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines + taxanes + <strong>pembrolizumab</strong></td>
<td>60%</td>
</tr>
<tr>
<td>BRCA1/2+</td>
<td>Sequential anthracyclines and taxanes (6 months)</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td><strong>Single agent cisplatin</strong></td>
<td>60%</td>
</tr>
</tbody>
</table>

* Fewer than 50 patients in the experimental arm
CREATE-X; Phase III randomized
N=910 HER2- stage I-III breast cancer (n=286 TNBC)
Non-pCR after neoadjuvant chemotherapy (chest wall/skin infiltration ~15%)
- 81% sequential anthracyclines-taxanes; - 14% concurrent anthracyclines-taxanes

Capecitabine 1250mg/m² days 1-14, every 21 days, x 6 or 8 cycles

Masuda et al. NEJM 2017; 376: 2147-59
Systemic Therapy in Locally Advanced Breast Cancer

Effectively *downstages* tumor to facilitate surgery

Provides *prognostic information* (pCR) and *tests* tumor biology

Tumor characteristics influence drug choice:
- **Anti-HER2 agents** (trastuzumab +/- pertuzumab) in **HER2+** cancers
- **Platinums**: some **TNBCs, BRCA+** tumors
- Some **biological agents promising in TNBC** (*bevacizumab, PARP inhibitors, immune checkpoint inhibitors*)

**Adjuvant capecitabine** may be considered in **HER2-** (particularly **TNBC**) non-pCR patients