Predictive Immunohistochemical Biomarkers in the Context of Neoadjuvant Therapy

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CTNeoBC Selected Trials

- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBG/AGO: 7</td>
<td>6377</td>
</tr>
<tr>
<td>NSABP: 2</td>
<td>3171</td>
</tr>
<tr>
<td>EORTC/BIG: 1</td>
<td>1856</td>
</tr>
<tr>
<td>ITA: 2</td>
<td>1589</td>
</tr>
<tr>
<td>Total # patients</td>
<td>12993</td>
</tr>
</tbody>
</table>
pCR Rates by Tumor Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>No Tras</th>
<th>Yes Tras</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+</td>
<td></td>
<td></td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>HER2+ HR+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+ HR-</td>
<td></td>
<td></td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>TRIPLE NEG</td>
<td></td>
<td></td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>
Association of pCR with EFS in Triple Negative Subtype

HR=0.24, P* < 0.001

pCR=ypT0/is ypN0

* Nominal p-value
Association of pCR with EFS in Her2+ Subtype

**HER2+**

- Event-Free Survival Probability
- Months since Randomization
- HR=0.39, P* < 0.001
- pCR (n=586) vs no pCR (n=1403)

**HER2+ HR+**

- Event-Free Survival Probability
- Months since Randomization
- HR=0.58, P* = 0.001
- pCR (n=247) vs no pCR (n=839)

**HER2+ HR-**

- Event-Free Survival Probability
- Months since Randomization
- HR=0.25, P* < 0.001
- pCR (n=325) vs no pCR (n=510)

pCR= ypT0/is ypN0

* Nominal p-value
Association of pCR with EFS with/ without Trastuzumab

**HER2+ HR+ No Trastuzumab**
- **HER2+ HR+ With Trastuzumab**

**HER2+ HR- No Trastuzumab**
- **HER2+ HR- With Trastuzumab**

- **HR=0.63, \(P^* = 0.023\)**
- **HR=0.53, \(P^* = 0.028\)**
- **HR=0.35, \(P^* < 0.001\)**
- **HR=0.15, \(P^* < 0.001\)**

* Nominal p-value
Association of pCR with EFS in HR+ HER2- Subtype

pCR=ypT0/is ypN0

* Nominal p-value

HR=0.49, P* < 0.001

HR=0.63, P* = 0.07

HR=0.27, P* < 0.001

CTNeoBC
Ki67 levels in pretherapeutic core biopsies as predictive and prognostic parameters in the neoadjuvant GeparTrio trial

Carsten Denkert, Jens Uwe Blohmer, Berit Maria Müller, Holger Eidtmann, Wolfgang Eiermann, Bernd Gerber, Hans Tesch, Jörn Hilfrich, Jens Huober, Tanja Fehm, Jana Barinoff, Christian Jackisch, Judith Prinzler, Thomas Rüdiger, Jan Budczies, Erhard Erbstößer, Sibylle Loibl, Gunter von Minckwitz
Systematic cutpoint analysis for Ki67

- pCR: 93 out of 94 cutpoints are significant
- DFS: 48 out of 94 cutpoints are significant
- OS: 58 out of 94 cutpoints are significant

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Ki67

≤15% vs. 15.1-35% vs. >35%

pCR – all cases
p<0.0005

DFS – all cases
p<0.0005

OS – all cases
p<0.0005
Proliferation Rate in the Residual Invasive Carcinoma After Neoadjuvant Chemotherapy

102 patients
All received weekly paclitaxel x 12 followed by FEC x 4
IHC for Ki67 in whole tissue sections, image analysis quantitation

Before
After
Changed

A

B

C

Relapse-free survival (%)

Relapse-free survival (%)

Relapse-free survival (%)

Years since operation

Years since operation

Years since operation

Ki67<16.9% (n=51)
Ki67≥16.9% (n=51)
pCR (n=30)
Ki67<3.9% (n=36)
Ki67≥3.9% (n=36)
decrease (n=36)
increase, unchanged (n=36)

P = 0.570

P = 0.041

P = 0.384
Value of Ki67 Measured at Day 14 After Endocrine Treatment (Aromatase Inhibitor) is Prognostic (IMPACT Trial)

Relapse Free Survival

Day 15 Ki67

- <2.7%
- 2-7-7.3%
- >7.3%

Dowsett et al. JNCI 2007
Value of Ki67 Measured at Surgery After 3-4 Months of Endocrine Therapy is Prognostic

Pre-Operative Endocrine Prognostic Index (PEPI)

Developed from the P024 Trial

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
<th>BCSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>KI67 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%-2.7% (0-1†)</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.7%-7.3% (1-2†)</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;7.3%-19.7% (2-3†)</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>&gt;19.7%-53.1% (3-4†)</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4†)</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>ER status, Allred score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>3-8</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>

Ellis et al. JNCI 2008
Role of Tau (MAPT): Highest Rank in 30-Gene Predictor of pCR vs. Residual Disease

High Tau Expression is Associated With Residual Disease After Chemotherapy

Rouzier et al. PNAS 2005;11:5678-85
Years After Randomization

% Disease-free

0 20 40 60 80 100

Years After Randomization

NSABP B-28 (DFS)

Tau-by-Tx Interaction p=0.92

Tau high

P<0.0001

ER+

Tau high 57%

ER-

Tau high 15%

AC 525 248
ACT 583 254 RR=0.88 p=0.16481

AC 425 160
ACT 408 138 RR=0.86 p=0.20417

Conclusions

Pathologic response rates differ according to tumor phenotype (HR & HER2 status)

- Excellent response imparts better prognosis, no matter what phenotype or treatment

Proliferation is generally associated with likelihood of pathologic complete response from chemotherapy

But predicted response is paradoxically associated with worse survival survival

- Generally applies to tests that rely on proliferation markers

Identification of pharmacodynamic suppression will probably be more successful than measuring the baseline proliferation rate

Sometimes a highly plausible biological rationale will fail

- Tau protein inhibits paclitaxel, but is also associated with HR+ status and endocrine sensitivity