Targeting EGFR in Inflammatory Breast Cancer

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Naoto Ueno
Why EGFR as a target in IBC?

- Hyperactivation of interferon-α & hypoactivation of EGFR and TGF-β were markedly associated with pCR in IBC.
- In a preclinical IBC model, treatment with an EGFR inhibitor reversed the mesenchymal phenotype of IBC cells to an epithelial phenotype and inhibited tumor growth and metastatic progression.
- In a HR+ IBC preclinical model, bisphenol A activated EGFR and elicited ERK signaling, leading to tumor spheroid formation and resistance to EGFR inhibition.

Bertucc F et al. Ann Oncol 2014;25358-365
Sauer et al. Carcinogenesis 38, 2017;252
EGFR as a therapeutic target in IBC

- EGFR overexpression was detected in 30% of IBC.
- Expression of EGFR is associated with poor outcome and high risk of recurrence.

EGFR targeting therapy

EGFR-targeted therapy reversed EMT

### Graphical Data

#### Tumor Volume

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Mice</th>
<th>Incidence of lung metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>control (vehicle)</td>
<td>3 of 7</td>
<td>(43%)</td>
</tr>
<tr>
<td>25 mg/kg erlotinib</td>
<td>0 of 7</td>
<td>(0%)</td>
</tr>
<tr>
<td>50 mg/kg erlotinib</td>
<td>0 of 7</td>
<td>(0%)</td>
</tr>
<tr>
<td>100 mg/kg erlotinib</td>
<td>0 of 7</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

Cancer stem cells mediate metastasis and poor clinical outcome in IBC

Development of novel therapies targeting IBC CSCs will improve outcomes of patients with this disease.

Charafe-Jauffret E, et. al., Clin Cancer Res. 2009; 16(1):45-55
Inactivation of EGFR signaling reduces the IBC CSC markers

Inactivation of EGFR signaling

**SUM149**

Mammosphere formation

ALDH activity

CD44^+ / CD24^- subpopulation
The COX-2 inflammatory pathway is functionally linked to EGFR signaling in IBC.

COX-2 mediates the EGFR-regulated CSC phenotype in IBC cells

Nodal is a potential downstream molecule that mediates EGFR/COX-2-regulated IBC CSC

EGFR regulates Nodal signaling in IBC

Phase II Study of Neoadjuvant Panitumumab + Chemotherapy with low HER2 IBC

Primary Objective: pCR
Secondary Objective: EGFR Expression
Exploratory Objective: Monitoring Dynamic Change of Genomic under Panitumumab monotherapy

Tissue Biopsy
- IHC staining
- RNA sequencing

PaCT
- Panitumumab
- Nab-paclitaxel
- Carboplatin

FEC* 4 cycles

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Recruitment n=47

Screen failure n=7

Operation complete n=37

Discontinued chemotherapy with adverse events 2
Due to distant metastasis 1

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<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Weekly (n=17), number (%)</th>
<th>3 weeks on 1 week off (n=23), number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>0</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nonhematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>5 (29)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Skin peeling</td>
<td>3 (18)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Hand-foot reaction</td>
<td>3 (18)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (24)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (12)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (41)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (18)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (35)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (12)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (53)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (35)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3 (18)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2 (12)</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

CTCAE, Common Terminology Criteria for Adverse Events.

A Adverse events possibly, probably, or definitely related to treatment with PNC regimen (panitumumab, nab-paclitaxel, and carboplatin) or FEC regimen (5-fluorouracil, epirubicin, and cyclophosphamide).
### Treatment Response to PaCT/FEC

<table>
<thead>
<tr>
<th>Pathological response</th>
<th>N=37 (%)</th>
<th>Non-pCR (n=26)</th>
<th>pCR (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TNBC</td>
<td>HR+</td>
</tr>
<tr>
<td>RCB-0 (pCR)</td>
<td>11 (30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RCB-I</td>
<td>3 (8)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>RCB-II</td>
<td>10 (27)</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>RCB-III</td>
<td>13 (35)</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>TNBC (n=17)</th>
<th>ER+/HER2- (n=20)</th>
<th>ER+/HER2+</th>
<th>ER-/HER2+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>47% (8/17)</td>
<td>15% (3/20)</td>
<td>Not Eligible</td>
<td>Not Eligible</td>
<td>30% (11/37)</td>
</tr>
<tr>
<td>pCR/RCB-I rate</td>
<td>65% (11/17)</td>
<td>15% (3/20)</td>
<td>Not Eligible</td>
<td>Not Eligible</td>
<td>38% (14/37)</td>
</tr>
</tbody>
</table>

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### Comparison to Historical Data

<table>
<thead>
<tr>
<th></th>
<th>TNBC</th>
<th>ER+/HER2-</th>
<th>ER+/HER2+</th>
<th>ER-/HER2+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IBC Historic pCR</td>
<td>30-40%</td>
<td>7-16%</td>
<td>35%</td>
<td>40-60%</td>
<td></td>
</tr>
<tr>
<td>IBC pCR with standard chemo</td>
<td>12%</td>
<td>7%</td>
<td>30%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>pCR with PaCT</td>
<td>44% (60%)</td>
<td>17%</td>
<td>Not Eligible</td>
<td>Not Eligible</td>
<td>36%</td>
</tr>
</tbody>
</table>

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**Primary HER2-negative IBC**

- **Weeks 1-13**
  - **Weeks 1-4:** Panitumumab, Nab-paclitaxel, Carboplatin
  - **Weeks 5-12:** Standard of care: FEC* (Fluorouracil, Epirubicin, Cyclophosphamide) every 3 weeks
  - **Week 13:** Biopsy

*FEC: Fluorouracil (500 mg/m²), Epirubicin (100 mg/m²), Cyclophosphamide (500 mg/m²), every 3 weeks

**Biomarker Study**

- Biopsy: EGFR, pEGFR, pAKT, pMAPK, p27, EMT markers
- RNA-seq
- Multiplex imaging

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### Expression of Candidate Proteins at Baseline and Week 2 and Change in Expression of Candidate Proteins between Baseline and Week 2 by Patient pCR Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No pCR (N=26)</th>
<th>pCR (N=11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>18 0 (0-300)</td>
<td>5 120 (0-300)</td>
<td>.14</td>
</tr>
<tr>
<td>Week 2</td>
<td>3 285 (20-300)</td>
<td>4 105 (10-285)</td>
<td>.48</td>
</tr>
<tr>
<td>Change</td>
<td>3 0 (0-265)</td>
<td>2 7.5 (-15-30)</td>
<td>.77</td>
</tr>
<tr>
<td>pEGFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7 60 (20-300)</td>
<td>4 160 (160-300)</td>
<td>.05</td>
</tr>
<tr>
<td>Week 2</td>
<td>6 225 (30-300)</td>
<td>4 110 (0-240)</td>
<td>.28</td>
</tr>
<tr>
<td>Change</td>
<td>6 185 (-30-280)</td>
<td>4 -50 (-300-80)</td>
<td>.09</td>
</tr>
<tr>
<td>E-cadherin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12 170 (0-300)</td>
<td>7 5 (0-300)</td>
<td>.49</td>
</tr>
<tr>
<td>Week 2</td>
<td>6 300 (300-300)</td>
<td>4 300 (180-300)</td>
<td>.31</td>
</tr>
<tr>
<td>Change</td>
<td>6 90 (0-300)</td>
<td>4 89.5 (0-300)</td>
<td>1.00</td>
</tr>
<tr>
<td>Vimentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9 0 (0-210)</td>
<td>7 30 (0-60)</td>
<td>.31</td>
</tr>
<tr>
<td>Week 2</td>
<td>5 15 (0-270)</td>
<td>4 40 (5-270)</td>
<td>.38</td>
</tr>
<tr>
<td>Change</td>
<td>4 9.5 (0-110)</td>
<td>4 25 (-25-210)</td>
<td>.66</td>
</tr>
<tr>
<td>COX-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12 115 (0-300)</td>
<td>7 240 (150-300)</td>
<td>.05</td>
</tr>
<tr>
<td>Week 2</td>
<td>6 200 (80-300)</td>
<td>4 160 (80-300)</td>
<td>.66</td>
</tr>
<tr>
<td>Change</td>
<td>6 15 (-140-240)</td>
<td>4 -85 (-160-140)</td>
<td>.59</td>
</tr>
<tr>
<td>Nodal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11 240 (70-300)</td>
<td>7 285 (80-300)</td>
<td>.58</td>
</tr>
<tr>
<td>Week 2</td>
<td>6 250 (0-300)</td>
<td>4 180 (160-300)</td>
<td>.91</td>
</tr>
<tr>
<td>Change</td>
<td>5 0 (-100-120)</td>
<td>4 0 (-100-80)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Gene expression in patient samples was measured by immunohistochemical staining before (baseline) and after (week 2) the first dose of PmAb.*
Genes differentially expressed after PmAb treatment by RNA-Seq analysis

Candidates of PmAb-regulated genes in IBC patients with TN-IBC

Molecular and cellular function of PmAb-regulated genes in IBC patients with HR+/HER2- subtype

Genes whose change in expression after PmAb treatment predicting pCR status have not been identified yet.
Conclusions and Future Directions

**Inflammation and cancer stem cells**

**Predictive biomarker**

**Tumor microenvironment**

**Panitumumab clinical trials**
- Single-arm trial in patients with HER2-negative IBC
- Randomized trial in patients with TN-IBC

**Preclinical study of targeting EGFR in IBC**

**Enhance the therapeutic efficacy of EGFR-targeted therapy in IBC**
Randomized Phase II study of panitumumab and neoadjuvant chemotherapy (PmAb/NAC) in patients with triple negative receptor (TN)-IBC.

COX2/Nodal/CSC, microenvironment changes, chemokine, cytokine N=36, 72 samples

Arginine methylation, N=72, 72 samples

RNA seq Baseline, N=72, Post PmAb N=36, Residual = 60
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### Other Collaborators
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- Kazuo Shirakawa

*and many, many others*

Patients with IBC who participated in the Study
Any Questions?

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