Phased Multicenter II PACS-09/Bevery1 Trial: First Efficacy And Safety Results Of Neoadjuvant Chemotherapy Combined With Bevacizumab in HER2-Negative Patients With Non-Metastatic Inflammatory Breast Cancer.

VIENS P1, PETIT T1, DALENC T1, PIEGAR1, DELOZIER1, ROLEUL1, GONTERRE1, FERRERO JM2, KERBATP3, MOURET REYNARD1, BACHELOT1, SOUILL2, LEBEUBR1, EYMARDIC1, DEBLONDE3, LOTHOLARY1, HARDY BASSAL1, BOHER J1, ASELSAN1, CHARAF-JAIFRIP2, LEONARDON1, MARTIN AL1, ANDRE1.


# P4-20-01

INTRODUCTION
Inflammatory breast cancer (IBC) is relatively rare but is the most aggressive form of locally advanced breast cancer with significantly lower overall survival than non-IBC.

IBCs tend to be highly angiogenic.

Compared with non-inflammatory breast cancer (IBC) breast tumors, IBC is more frequently estrogen receptor negative (ER-negative) and progesterone receptor negative (PR-negative).

Primary chemotherapy is used to render these patients operable. Standard local control is achieved with mastectomy followed by radiotherapy.

Several angiogenesis-related genes are upregulated in IBC.

Vascular endothelial growth factor (VEGF) is a secreted molecule that promotes endothelial cell growth and viability among other properties.

Because this disease exhibits angiogenic properties, inhibiting VEGF may block endothelial cell proliferation, decrease vascular permeability and vasoconstriction.

Bevacizumab (BEV), a humanized monoclonal antibody targeting all isoforms of VEGF, significantly decreases serous fluid and tumor necrosis in advanced breast cancer, as demonstrated in three randomised, phase III trials in the first-line setting.

In the BIBE3-01 trial, the combination of bev with anthracycline-based combination therapy was found to be tolerable, with no substantial increase in risk of cardiac effects.

A safety profile study has shown that in inflammation and locally advanced breast cancer, IBC BEV has inhibitory effects on VEGF receptor activation and vascular permeability, and induces apoptosis in tumor cells. Moreover, BEV induces significant modifications in angiogenic/angiopoietin gene expression.

BEV may improve the efficacy of neoadjuvant chemotherapy (CT)-in-IBC.

The BEVERLY study was designed to evaluate bevacizumab in combination with chemotherapy in patients with HER2-negative IBC.

STUDY DESIGN & OBJECTIVES
BEVERLY is a multicenter single-arm phase II study evaluating bevacizumab in combination with sequential neoadjuvant chemotherapy in HER2-negative IBC.

Primary objective: To assess the rate of pathologic complete response (pCR) according to Sataloff classification.

Secondary objectives: Disease-free survival (DFS) at 3 and 5 years; Overall survival (OS) at 5 years; Safety (CTCAE version 3.0); Translational research studies.

METHODS
Eligible patients included those with locally advanced breast cancer (T4b or T4a), with or without inflammatory component, who had good performance status (ECOG 0 or 1).

Between December 2006 and September 2010, 161 patients were included in the study. Baseline characteristics are summarized in Table 1.

Methods of treatment: Treatment consists of 4 cycles of S-Famustine, epirubicin, and cyclophosphamide (FEC) followed by 4 cycles of docetaxel plus trastuzumab, with bevacizumab 15 mg/kg administered twice every 3 weeks prior to neoadjuvant therapy.

At baseline, patients underwent computed tomography scan of the thorax, abdomen, and pelvis, bone scintigraphy, and bilateral ultrasonography to confirm the absence of metastasis.

Patients participating in the translational research study were required to provide a written informed consent.

Mucitis defined as:

- Histologically confirmed breast cancer and confirmed IBC (T4a any N; Institute Gustave Roussy PEV or FEC in lieu with tumor embed in the lymph vessels of the superficial dermis).

- HER2-negative disease; no metastasis.

- Normal hematologic, hepatic, renal, coagulation, and cardiac function.

- No prior chemotherapy or hormonal treatment for breast cancer.

- Female, aged ≤18 years; ECOG performance status ≤2.

- The number of evaluable patients was calculated based on a two-stage T. Fleming method with the following assumptions:

  - 20% pCR rate considered as point of efficiency.

  - 

Table 2: pCR rate according to Sataloff classification, investigator assessment (n=100)

<table>
<thead>
<tr>
<th>pCR (%)</th>
<th>N3S</th>
<th>N3D</th>
<th>N2S</th>
<th>N2D</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>8</td>
<td>19</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: pCR rate is increased in HR-positive group according to Sataloff classification investigator assessment (n=100)

<table>
<thead>
<tr>
<th>pCR (%)</th>
<th>N3S</th>
<th>N3D</th>
<th>N2S</th>
<th>N2D</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>8</td>
<td>19</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: pCR rate is increased in HR-positive group according to Sataloff classification investigator assessment (n=100)

<table>
<thead>
<tr>
<th>pCR (%)</th>
<th>N3S</th>
<th>N3D</th>
<th>N2S</th>
<th>N2D</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>8</td>
<td>19</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CONCLUSION
These data suggest that:

- The combination of neoadjuvant chemotherapy and bevacizumab has a good safety profile in IBC.

The 27% pCR is one of the highest described in IBC.

However, the place of this combined treatment remains to be precisely specified, in IBC, long-term survival data are needed to confirm these results.

REFERENCES

ACKNOWLEDGMENTS
Funders:
BenGa, Centre of Excellence in Breast Cancer Research, France.

Institutional Support From:
- Groupe赞成
- .
- .

Sponsorship by):
Institut Gustave Roussy, Villejuif, France.
Centre Paul Pailler, Angers, France.
Institut Claudius, Paoli, France.
Institut Claudius, Rambouillet, France.
Institut Claire, Paris, France.
Centre Françoise-Béclere, Cervans, France.
Centre Luc Emile, Marquilly, France.
Centre Oscar Lambret, Lille, France.
Centre Oscar Lambret, Lille, France.
Centre Urgences, Rouen, France.
Centre Eric Vonk, Romee, France.
Centre Emanuele Gattinara, Milan, Italy.
Centre Marie Curie, Marseille, France.
Centre Clinic Paoli-Calmettes, Moncalieri, Italy.

Figure 2bis. Grade 3 adverse events occurring in >1 patient during neoadjuvant therapy.

Cycles 1 – 8

Figure 2. Grade 3 adverse events occurring in >1 patient during neoadjuvant therapy.

Cycles 1 – 8

Media, inflammation and necrosis.

Patients were followed up 5 years after enrolment of the trial without evidence of disease recurrence.

Figure 1: Treatment Scheduled in Beverley1.

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Surgical Incision

Institutional Support From:
- Groupe赞成
- .
- .

Sponsorship by):
Institut Gustave Roussy, Villejuif, France.
Centre Paul Pailler, Angers, France.
Institut Claudius, Rambouillet, France.
Institut Claire, Paris, France.
Centre Françoise-Béclere, Cervans, France.
Centre Oscar Lambret, Lille, France.
Centre Oscar Lambret, Lille, France.
Centre Urgences, Rouen, France.
Centre Eric Vonk, Romee, France.
Centre Emanuele Gattinara, Milan, Italy.
Centre Clinic Paoli-Calmettes, Moncalieri, Italy.

Figure 2bis. Grade 3 adverse events occurring in >1 patient during neoadjuvant therapy.

Cycles 1 – 8

Figure 2. Grade 3 adverse events occurring in >1 patient during neoadjuvant therapy.

Cycles 1 – 8

Media, inflammation and necrosis.

Patients were followed up 5 years after enrolment of the trial without evidence of disease recurrence.

Figure 1: Treatment Scheduled in Beverley1.