RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC)

Presenter: N. J. Robert
Presenter’s Affiliation: US Oncology Group
Type of Session: Scientific

Background

● Bevacizumab (B) is a humanized monoclonal antibody which inhibits VEGF, a known central mediator of angiogenesis.

● Two previous large phase III trials, E2100 and AVARO, have demonstrated that B in combination with weekly paclitaxel or docetaxel (D) as 1st-line therapy for MBC has improved progression-free survival (PFS) compared with the respective taxane alone.

● However, there is current a lack of evidence supporting the use of B in combination with other non-taxane agents used at 1st-line treatment for MBC.

● The RIBBON-1 study is a randomized Phase III trial that was designed to investigate the clinical benefit of combining B with various standard 1st-line chemotherapy regimens for MBC.

Materials and Methods

● Eligibility criteria:
  ● Patients with previously untreated histologically confirmed locally recurrent or metastatic HER2 neu negative breast cancer.
  ● Age > 18
  ● ECOG performance status 0 or 1
  ● > 12 months since prior neoadjuvant or adjuvant chemotherapy
  ● No CNS metastases

● Patients were randomized in 2:1 ratio to receive B + chemotherapy or placebo (pl) + chemotherapy.
Prior to randomization, investigators were allowed to choose which chemotherapy they preferred to use. They could choose from capecitabine (Cap) (2000 mg/m² × 14d), taxane (T) (nab-paclitaxel [260 mg/m²] or D [75 or 100 mg/m²], q3wk), or anthracycline (Ant)-based chemotherapy (q3wk).

B or pl was administered at 15 mg/kg q3wk.

If patient’s had disease progression after initial treatment, physicians had the option of starting them on 2nd line chemotherapy + B.

The primary endpoint was PFS as assessed by the investigator.

Secondary endpoints included PFS assessed by and independent review committee (IRC), objective response rate (ORR), overall survival (OS), 1-year survival rate, and safety. At progression, all patients were eligible for B with 2nd line chemotherapy.

The Cap cohort and the pooled T or Ant (T + Ant) cohort were independently powered and analyzed in parallel using two-sided stratified log-rank test

- Cap cohort: 80% power to detect HR=0.75 with planned sample size of 600.
- T + Ant cohort: 90% power to detect HR=0.70 with planned sample size of 600.

Results

- 1237 patients (Cap, 615; T, 307; Ant, 315) from > 200 sites in 22 countries were enrolled on this study between December 2005 and August 2007. Data obtained after July 31, 2008 was not used.
- 206 patients were in the Cap+pl group, 409 patients were in Cap+B group, 207 patients were in the T+Ant+pl group, and 415 patients were in the T+Ant+B group
- Median follow-up was 15.6 months in the Cap cohort and 19.2 months in the T + Ant cohort.
- Patient baseline characteristics were well-balanced between the two arms.
- One-third of patients had died at time of analysis.

Efficacy results for Cap+pl vs. Cap+B:

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<thead>
<tr>
<th></th>
<th>Cap+pl</th>
<th>Cap+B</th>
<th>p-value and HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed PFS</td>
<td>5.7 mo</td>
<td>8.6 mo</td>
<td>p=0.0002</td>
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<td></td>
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<td>HR=0.69</td>
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<tr>
<td>IRC-assessed PFS</td>
<td>6.2 mo</td>
<td>9.8 mo</td>
<td>p=significant</td>
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<tr>
<td>ORR</td>
<td>23.6%</td>
<td>35.4%</td>
<td>p=significant</td>
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<tr>
<td>OS</td>
<td></td>
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<td>No difference</td>
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Efficacy results for T+Ant+pl vs. T+Ant+B:

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<tr>
<th></th>
<th>T+Ant+pl</th>
<th>T+Ant+B</th>
<th>p-value and HR</th>
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<tbody>
<tr>
<td>Investigator-assessed PFS</td>
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<td>IRC-assessed PFS</td>
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<td>OS</td>
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<tr>
<td>Investigator-assessed PFS</td>
<td>8.0 mo</td>
<td>9.2 mo</td>
<td>p=0.0001</td>
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<tr>
<td>IRC-assessed PFS</td>
<td>8.3 mo</td>
<td>10.7 mo</td>
<td>p=significant</td>
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<tr>
<td>ORR</td>
<td>37.9%</td>
<td>51.3%</td>
<td>p=significant</td>
</tr>
<tr>
<td>OS</td>
<td>No difference</td>
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- Safety:
  - Proteinuria and HTN rates were higher in all 3 groups, similar to that seen in bevacizumab previous studies.

**Author’s Conclusions**

- The addition of B to chemotherapy regimens used in 1st line treatment of MBC led to statistically significant improvements in PFS, both assessed by investigator and IRC, and in ORR.
- There was no difference seen in OS with the addition of B.
- The safety profile of this study was comparable to the 2 prior phase III studies done in this area.
- RIBBON-1 provides a third randomized phase III trial demonstrating the efficacy and safety of adding B with 1st line chemotherapy for MBC.
- It also was the 1st phase III trial to test non-taxane chemotherapy with B.

**Clinical/Scientific Implications**

- The results presented for the RIBBON-1 trial confirm the results present previous phase III trials such as E2100 and AVARO, which also examined the benefit of B with chemotherapy for metastatic breast cancer patient with similar patient characteristics
  - Efficacy results were similar between the 3 trials. There was a relative increased in response rate of 20-50% with B treatment seen in all these studies.
  - While the other 2 previous trials provided data for only taxane chemotherapy with B, this trial demonstrated a benefit with adding B with other commonly used chemotherapeutic agents as well. In addition, this trial was placebo-controlled, unlike the E2100 study.
- RIBBON-1 met its primary endpoint of PFS (assessed by both the investigator and IRC) compared to chemotherapy alone. B also increased ORR and was well-tolerated.
- Strengths of the study:
  - Large, contemporaneous population. The patients in this study represented the average patients with metastatic breast cancer seen in clinic.
  - Multiple chemotherapy regimens were allowed which make this study more generalizable to be used in clinics worldwide where various agents are used.
  - An independent review committee was used to assess PFS which helps to eliminate investigator bias.
● Limitations of the study:
  ● This trial was really composed of 2 separate studies conducted in parallel. This makes it difficult to compare between the 2 chemotherapy regimens that were analyzed separately.
  ● Neither chemotherapy group was powered to assess OS. Larger numbers of patients on this trial would be needed to observe a survival benefit.
    ● Additionally, about 50-60% of patients crossed-over to other agents + B in the placebo groups, which is a confounding factor when analyzing survival data.

● From the results of this well-designed Phase III trial, we can conclude from that B is likely an important component for initial chemotherapy for Her2neu negative metastatic breast cancer patients.

● Other interesting questions which should be addressed in future studies include:
  ● Will combination of B with trastuzamab or Her2neu targeted therapies for patients with metastatic Her2neu+ cancers lead to increased efficacy?
  ● Can we combine with B with hormonal treatments such as Tamoxifen or AIs and see clinical benefit?
  ● What is the optimal duration of treatment with B?
  ● Does the choice of chemotherapy matter? Are there differences in chemotherapy effects with B?

● Further study of B with other agents in both breast cancer patients and patients with other cancer type should continue as it is a promising agent that shows potential to be used in various clinical settings.