

Avastin[®] in breast cancer: Summary of clinical data

Worldwide, over one million people are diagnosed with breast cancer every year¹. It is the most frequently diagnosed cancer in women^{1,2}, and the leading cause of cancer death in women¹. About 33% of breast cancer cases are diagnosed after the cancer has spread beyond the primary site to other parts of the body (metastasised)³.

Roche has developed an extensive research and clinical trial programme in order to improve treatment outcomes for patients with breast cancer. Avastin (bevacizumab) is an important therapy for breast cancer and has been shown to double the time breast cancer patients can live without their disease worsening (progression free survival or PFS).

Avastin is an antibody that specifically binds and blocks VEGF (vascular endothelial growth factor). VEGF is the key driver of tumour angiogenesis – an essential process of development and maintenance of blood vessels which is required for a tumour to grow and to spread to other parts of the body. Avastin's precise mode of action helps control tumour growth and metastases with only a limited impact on side effects of chemotherapy.

More than 500,000 patients have been treated with Avastin so far. A comprehensive clinical programme with more than 450 clinical trials is investigating the use of Avastin in various tumour types (including colorectal, breast, lung, brain, gastric, ovarian, prostate and others) and different settings (advanced or early stage disease). Outlined below is key information from clinical trials of Avastin in breast cancer.

E2100

More than 700 patients with previously untreated locally recurrent or metastatic breast cancer (mBC) were enrolled in the E2100 study. Locally recurrent cancer means that the cancer has returned at, or near to, the same place as the original tumour.

Key findings

- Avastin + paclitaxel more than doubled (108%) patients' chances of being alive without disease worsening compared to paclitaxel alone⁴.
- The combination was generally well tolerated, and no new safety signals were observed.

Patients either received Avastin in combination with paclitaxel chemotherapy, or paclitaxel alone. The results showed that Avastin, added to paclitaxel, more than doubled patients' chances of being alive without their disease getting worse compared to those treated with chemotherapy alone⁴. This measure represents a statistically and clinically meaningful outcome. Patients benefited from the combination of Avastin and paclitaxel independent of prior therapies received, disease site, tumour burden or hormone receptor status.

AVADO

Key findings

- Up to 64% increase in patients' chances of being alive without disease worsening compared to docetaxel alone.
- Up to an unprecedented two thirds of patients (64%) experienced major shrinkage of their tumour.
- The addition of Avastin did not impact on, or add to, the known toxicities of docetaxel, thus not increasing the toxicity of the treatment.

The AVADO trial investigated the benefits of adding Avastin to a different chemotherapy, docetaxel, in over 700 previously untreated patients HER2-negative locally recurrent or metastatic breast cancer. HER2 stands for Human Epidermal growth factor Receptor 2, a receptor (or protein) which when over-expressed on breast cancer cells indicates a distinct, fast growing form of breast cancer.

Two Avastin doses were used, 7.5mg/kg and 15mg/kg every three weeks, respectively. Results showed that treatment with Avastin based therapy significantly increased patients' chances of PFS, compared to chemotherapy alone⁵. Although the study was not designed to compare the two doses, the 15mg/kg every 3 weeks dose (breast cancer standard dose) consistently showed a tendency towards greater effectiveness, without increasing the rate of the adverse events.

The study confirmed that patients benefit from combining Avastin with taxane based chemotherapy*, (first proven in the E2100 study) regardless of their particularities: different prior regimens, tumour burden, or hormone receptor status.

RIBBON-1, RIBBON-2 and RIBBON-3

The RIBBON-1 and RIBBON-2 studies are assessing the benefit of Avastin in combination with a wide range of chemotherapies in patients with mBC. The key difference between the trials is that patients in RIBBON-1 have not received previous treatment for their metastatic disease (first line therapy), whereas those in RIBBON-2 have done so (second line therapy). The most common chemotherapy regimens received by patients in the trials are Xeloda[®] (capecitabine), anthracycline based chemotherapy** or taxane based chemotherapy.

The aims of both RIBBON-1 and RIBBON-2 are to determine the efficacy and safety of Avastin when combined with a broad range of common chemotherapies as treatment for mBC. A further study, RIBBON-3, will investigate Avastin in multiple stages of mBC.

The first analysis of the RIBBON-1 trial demonstrated that the study met its primary endpoint of increasing the time that women lived without their cancer getting worse, compared to chemotherapy alone. Further data from the RIBBON-1 trial will be presented at the American Society of Clinical Oncology (ASCO) 2009 Annual Meeting.

MO19391

This ongoing trial is investigating the safety of Avastin in over 2,000 patients recruited in 37 countries with untreated, locally recurrent*** or mBC. All participants are being treated with Avastin in combination with taxane based chemotherapy.

MO19391 is primarily evaluating the safety profile of Avastin in a large patient population. It is also investigating the impact of Avastin on the time it takes for the disease to worsen following initiation of treatment, and duration of patient life (overall survival, OS).

The initial analysis of the MO19391 data confirmed that Avastin based therapy was well tolerated by patients and Avastin related side effects are consistent with those reported in previous trials. In addition, Avastin based therapy delivered a median time from the start of treatment to worsening of disease of almost 10 months⁶. The analysis confirms the efficacy and safety of Avastin when administered in combination with various chemotherapies in the treatment of first line mBC. Further data from the MO19391 trial will be presented at the American Society of Clinical Oncology (ASCO) 2009 Annual Meeting.

AVEREL

The AVEREL trial is evaluating the efficacy and safety of Avastin in combination with Herceptin[®] (trastuzumab) and docetaxel chemotherapy, compared with Herceptin and docetaxel treatment alone. Patients in AVEREL have locally recurrent or metastatic HER2-positive breast cancer and have not received prior treatment for their mBC (first line therapy).

HER2-positive breast cancer tends to be a more aggressive form of breast cancer, accounting for approximately 20 – 30% of breast cancer cases⁷. This is the first study to evaluate the combination of two biologic therapies in the treatment of advanced HER2-positive breast cancer. The AVEREL study is ongoing and data will be reported at a future scientific meeting.

Upcoming clinical trials of Avastin in earlier stage (non metastatic) breast cancer

The potential of Avastin is also being assessed in patients with earlier stage breast cancer, when Avastin based therapy is given directly after the surgical removal of a patient's tumour(s). This method of treatment is often referred to as adjuvant therapy. These trials are of specific interest because they are assessing the ability of Avastin to amend the risk of tumour recurrence and, consequently, to increase the chance of a cure for breast cancer.

E5103

The E5103 trial examines Avastin's efficacy as an adjuvant therapy in combination with an anthracycline and taxane based chemotherapy regimen in patients who have undergone surgery. The E5103 trial was initiated following results an earlier trial (E2104), which demonstrated that Avastin

was well tolerated and had a good safety profile when combined with an anthracycline and taxane based chemotherapy regimen.

BEATRICE

The BEATRICE study is investigating the efficacy of Avastin immediately following surgery in combination with various chemotherapies. This trial is taking place with patients who have a form of breast cancer called triple negative breast cancer. This is usually a more aggressive and difficult to treat form of the disease as it does not tend to respond to standard therapies. In this trial patients receive adjuvant treatment with either Avastin in combination with standard chemotherapy, or standard chemotherapy alone.

BETH

The BETH trial is set to investigate the benefits of Avastin in HER2-positive breast cancer patients, after they have had their tumour(s) surgically removed. Patients will receive Avastin together with Herceptin in combination with standard chemotherapies. This is another example of combining biologic therapies, this time in the adjuvant setting.

Summary

Avastin in combination with chemotherapy has demonstrated significant benefit to patients with mBC, doubling the time patients live without their disease getting worse. The studies have also demonstrated that Avastin can be combined with a wide range of chemotherapies, which allows greater flexibility for physicians to optimise patient care. In addition, Avastin is well tolerated by patients and does not add to the side effects usually associated with chemotherapy such as hair loss, nausea and vomiting.

Current international clinical trials are exploring the benefits of Avastin in patients with earlier stage breast cancer, in the adjuvant setting. These studies offer hope for patients with breast cancer and may demonstrate Avastin's benefits to even more patients.

* Taxane based chemotherapy refers to a class of chemotherapy drugs derived from the Yew tree. Taxane based chemotherapies include paclitaxel and docetaxel.

** Anthracycline based chemotherapies refers to a class of chemotherapy drugs derived from bacteria. Anthracycline based chemotherapies include doxorubicin and epirubicin.

*** Locally recurrent refers to cancer that has come back at, or near, the same place as the original tumour.

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To download images and videos relating to Avastin and colorectal cancer please visit: www.thenewsmarket.com

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