

San Antonio NEWSLETTER

Highlights from the San Antonio Breast Cancer Symposium, December 2008

The Danish professor and chief physician Henning Mouridsen looked conspicuously content when presenting the latest outcome of the BIG 1-98 at the San Antonio Breast Cancer Symposium (SABCS). We caught him briefly to make him elaborate on how crucial the BIG 1-98 study really is.

15 minutes sharp. That was the time slot Henning Mouridsen had to lecture for 10,000 oncologists and practitioners, at the San Antonio Breast Cancer Symposium on Tuesday morning 13th. December 2008. Not much time to present a study that has been running for years, one could argue.

The BIG 1-98 study is a multinational Phase III double-blind, randomized multicenter trial conducted in 27 countries and involving more than 8000 postmenopausal women with early breast cancer and hormone receptor-positive tumours.



BIG 1-98:

THE BEST NEWS IN A LONG TIME

In 2005, this clinical trial proved that Femar when taken over a 5 year period was superior to tamoxifen in preventing breast cancer recurrence. The latest 2008 update even continues to confirm significant reduction in recurrence and suggests a 13% reduction in deaths. The comparison of these two treatment programs is attenuated, because one quarter of the patients on tamoxifen crossed over to Femar after the early results was presented in 2005. The improved survival benefit has not been observed in other trials comparing 5 years of Tamoxifen to other aromatase inhibitors.

In short the 2008 update points at three conclusions:

- Femar showed reduced risk of death by 13% (p=0,08), despite inclusion of patients switching from tamoxifen to Femar therapy
- In a separate censored analysis excluding the patients switching to Femar, even showed a 19% reduction in risk of death
- Long-term follow-up data from the major independent BIG 1-98 trial reinforces that starting on Femar is the optimal treatment strategy versus tamoxifen

A MILESTONE

Henning Mouridsen, age 69, has more than 30 years of experience with breast cancer behind him and an obvious reason to be pleased with the result – first of all on behalf of the all the patients who can look forward to improved treatment but also on behalf of the International Breast Cancer Study Group that has coordinated the study. For Henning Mouridsen personally, the study can be seen as a great completion of an outstanding career.

“The study is based on the fact that tamoxifen has been the standard treatment for 20 years. The question was simple: Is 5 years Femar superior to 5 years tamoxifen as initial therapy? And the results are really impressive. We have never seen anything like it”, says Henning Mouridsen, and continues:

“These data represent an important milestone in the treatment of women with breast cancer. For the first time ever, we are seeing suggested survival benefits with aromatase inhibitor therapy over a five year period compared to tamoxifen taken in the same number of years. The potential reduction in the risk of death seen with Femar in the adjuvant setting may be a positive result of Femar’s early and sustained reduction in the risk of recurrence and distant metastases.”

THIS WILL BENEFIT THOUSANDS OF WOMEN

But, can these results be transferred to other aromatase inhibitors?

“That is a very relevant question. But for me there is no doubt. Results from one aromatase inhibitor can not be transferred to others because they are likely to be very different in effect. Other things points at the fact that Femar is more efficient than anastrozol. We know it is more efficient to prevent what it was initially designed to do – preventing production of the female hormone oestrogen in the body. We can only make an indirect comparison. With anastrozol we have found a 3% reduction of risk of death after 100 months, while we with Femar after 76 months, find a reduction that is at least 13%”.

How will you describe the importance of these results?

“This is the first time that we find indications of improved survival as a result of using aromatase inhibitors. That is extremely important and it will benefit thousands of women all over the world. I would dare to say that this is the most encouraging result within the treatment of postmenopausal women with early breast cancer in 10 years”, says Henning Mouridsen.

How does it feel to have been part of this trial from a personal point of view?

“It is and has been great to be part of an international group that has produced such progress in just 10 years. It’s amazing to have this very positive message to the patients. From a professional point of view this has been very satisfying”.

Has anything surprised you along the way?

“Yes. Honestly, I have been very surprised that the results turned out so positive. Normally, I’m very moderate in my reactions but this is different. On the other hand, it’s important to stress that we still have a long way to go”.

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STRONGER BONES AND LESS RISK OF RECURRENCE

Outi Pajja (MD, PhD.) has been the principal investigator in Finland for the ZO-FAST and the E-ZO-FAST studies, investigating the outcome of treating patients with: 1. an aromatase inhibitor, letrozole, with an upfront bisphosphonate treatment, zoledronic acid twice a year, or 2. an aromatase inhibitor, letrozole, with a delayed bisphosphonate treatment. We met her to talk about the study and the interesting, and even surprising findings.

It's well known that aromatase inhibitors, as a class effect, decrease mineral density in bones and thereby may lead to osteoporosis in postmenopausal women.

In all three studies, the ZO-FAST, E-ZOFAST and in the American 'sister-study' Z-FAST, there are two different treatment arms. One is looking at patients, who get an aromatase inhibitor (letrozole) and a bisphosphonate (Zometa) side by side. In the other arm the treatment with bisphosphonate is delayed until the point where bone mineral density may decrease or the patients suffer from a clinical or subclinical fracture. The bisphosphonate is being infused twice a year. The design of the European and the American studies are basically the same, but with small differences.



HAND IN HAND

What did the study find?

"We found that Zometa will preserve the bone mineral density and even increase it – which is quite unusual for postmenopausal women. At the same time we have seen a significant decrease in disease recurrence after 36 months treatment in the Zometa experimental arm. That seems to be a very positive and encouraging "side effect". Actually, we are talking of a 40 percent reduction in disease recurrence – that's a lot. At present it seems like these two drugs go hand in hand".

What was your goal with this investigation?

"It was to look at bone density. The disease recurrence came as a positive add on – that it actually did influence the disease recurrence and perhaps even later the survival rate".

STANDARD TREATMENT SOONER OR LATER

What will this mean to the patients?

"Basically, I think the patients want to preserve their bones

and keep their good health and I think both things are well within reach. But it will take some time before this combined treatment will be implemented into clinical practice. We will need a bit more patience and wait for the results from the American Z-FAST study. When we get to combine these results I'll hope it will help to confirm, what we have seen so far. When the studies are finished we have included about 3000 patients. I believe the results will give momentum so hopefully sooner or later this might become standard treatment, because we may be able to prevent bone fracture and pain. Figuratively speaking, this will also lead to an improved quality of life for the patients".

Is there a chance that women with postmenopausal breast cancer can develop superior bone health, unlike the women who have not been treated for breast cancer or osteoporosis?

"Yes. Absolutely, there is a possibility for that, the increase in bone mineral density is not minor".



FOCUS ON THE LONG TERM PERSPECTIVE

As principal investigator at the BIG 1-98 study in Sweden, this was naturally the study, associate professor, Stig Holmberg focused at on the SABCS. We asked for his personal view on the conclusions of the study and their impact.

Over the last 10 years, Stig Holmberg, has been involved in several studies investigating the efficiency of aromatase inhibitors and among them is the BIG 1-98. From the beginning the new drugs was used on patients in an advanced stage, with no comprehension of how the drugs could be used adjuvant. Stig Holmberg is a surgeon at Sahlgrenska

Sjukhuset in Göteborg where they are responsible for all the stages of the cancer therapy for the 600 new breast cancer patients who are diagnosed every year. In Sweden it is tradition that the surgeon follows the patient through the adjuvant part of the treatment. This explains Stig Holmberg's interest in the field although he is a surgeon.

"I'm here because of BIG 1-98, but also because of all the other presentations on aromatase inhibitors. One of my specific interests is the challenges related to resistance against tamoxifen but also against aromatase inhibitors, explains Stig Holmberg.

WE HAVE A WIN-WIN SITUATION

Is resistance an issue with letrozole ?

"Resistance always becomes an issue a long the way. But, what I find really interesting is that through BIG 1-98 we developed new strategies for endocrine treatment and how to cheat the cancer cells. By using tamoxifen and aromatase inhibitors like letrozole, in sequence, we have created even better treatment options. Through the next study – SOLE – we hope to show effect of five years extended treatment as we know recurrence occurs late. What we are about to investigate is the use of endocrine treatment in a long term perspective – 10 years maybe. Additionally, we will work with sequential treatment, perhaps pause it and then change the environment of the cancer cell. It is likely that extended treatment can be based on letrozole alone, but with intermissions. This will create a win-win situation as the patient will have fewer problems with adverse effects and it is likely to affect compliance as well."

CHANGES IN TREATMENT

How significant do you find the results of the BIG 1-98?

"The use of aromatase inhibitors has been controversial in Sweden as we have not been able to show better survival rates. But the new findings will, surely, impact the treatment strategies. In the high risk group we already use aromatase inhibitors upfront. I am confident; it is in the intermediate group we will see the biggest changes. They will be started on letrozole in the future. In Sweden we do not always use adjuvant treatment in the low risk group".

What will this mean to the patients?

"To day patients are very enthusiastic. They want more than we can offer through medication. The fact is that a fair number of patients will never experience recurrence and that the treatment is actually overtreatment. As a physician arguments will be based on the fact that the difference between the treatments is modest and many will therefore stick to the well known tamoxifen. The physicians look at the absolute difference which is around 2-3 percent while the patients look at the relative difference that is 20 percent. They will demand the new treatment and they will get it".

One of several breaking news at the San Antonio Breast Cancer Symposium was data from the international AZURE trial demonstrating Zometas effect on reducing tumour sizes. We talked about the latest results and other aspects of the Zometa study with doctor Henrik Lindman from Uppsala in Sweden.

NEW OPTIONS IN BREAST CANCER TREATMENT

Earlier this year the Austrian study ABCSG-12 - presented at the American Society of Clinical Oncology's annual meeting - showed that Zometa can, positively, reduce the recurrence risk of breast cancer in premenopausal women with early-stage breast cancer. At SABCS in December further positive results from studies involving Zometa appeared. New data from the international AZURE trial demonstrate that adding a Zometa injection to standard chemotherapy prior to breast cancer surgery can reduce the size of breast tumours. This is more efficient than chemotherapy alone in women with early-stage disease.

In Sweden doctor, Henrik Lindman, has followed the studies and latest results, carefully. Henrik Lindman is responsible for the breast cancer section at the Oncology Clinic at Akademiska Sjukhuset in Uppsala.

"The AZURE-study has shown that use of Zometa in combination with chemotherapy reduces the size of tumours. This is highly interesting news as it has been discussed widely, the last 10 years, whether bisfosfonates like Zometa could have an clinical relevant anti-tumour effect or not. For a long time the general opinion was that these finding could be just coincidences, however today we have to reconsider.

The pragmatic solution

"This subgroup analysis of AZURE is not a large study; nevertheless, it does show significant differences for patients with tumours when given Zometa. Besides this, the ZO-FAST study concluded the same as the Austrian ABCS. My take is that this will lead to a discussion, back home in Sweden, regarding future treatment. I envisage that we will find a pragmatic solution by prescribing Zometa for patients who also receive aromatase inhibitors and offer them these infusions every six months. My query is whether this treatment has matured yet, to become standard treatment".

"Today, Zometa is used when breast cancer metastases are developed; but in this connection we have not seen survival benefits. However, when Zometa is used at the early stages of breast cancer it may have other effects on the cancer cells", Henrik Lindman explains and continues:

"The discussion in Sweden will focus on how Zometa should be used onwards particular in the areas which the drug was not designed to treat, originally - e.g. prevention of osteoporosis. Additionally, we will investigate whether other bisphosphonates has the same effects as Zometa".



This newspaper is based on presentation from the San Antonio Breast Cancer Symposium, Texas, December 10-14 2008, an independent scientific congress. All interviews are performed on location with Nordic and international experts.

For further information about products and substances mentioned in this newspaper, please consult the product SPC (summary of product characteristics) for the respective country.

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A NEW TOOL IN THE TOOLBOX

Dr. Kim Blackwell, Breast Oncologist at the Duke Comprehensive Cancer Center in Durham North Carolina, has personal views on the BIG 1-98 trial presented at the SABCS.

The BIG 1-98 trial has attracted a lot of attention at this symposium. What is your opinion on the trial?

"It's a step forward. Now we know that using letrozole actually results in meaningful benefits when used up front and its use leads to improved outcome for patients, generally. It is always great to see a survival advantage. It's interesting that within breast cancer we are obsessed about survival advantages, and it is great to see when it happens, but if you look outside oncology there is little to no drugs which have an approved survival advantage. Look at lipid drugs e.g. millions of people get lipid drugs and the outcome measure is prevention of heart attacks, and has nothing to do with survival. You either look at the number of bypass surgeries done, or you look at the effect of beta blockers. The outcome is clearly not survival and if you look at almost any other drug they don't have survival as endpoints.

But what is your point then?

It's great that we saw a survival advantage, in BIG 1-98, but to me that was not a must. In the days when drugs were seriously toxic, you really had to balance the toxicity with the survival rate and ultimately survival was a good measure. Now, especially in curable early stage breast cancer, it's comparable to having had a heart attack. It is a horrible medical event, but in general patients go on to live, so the goal is how much longer can you prolong them from having another heart attack? It is very similar to what we see with

breast cancer occurrences and the fact that there was this survival advantage, for women in the tamoxifen experiment, who received the better drug, is pretty important. The point is that it is great to see a survival advantage, it's just not clear to me, why we cling to a higher standard when these are oral medications with toxic effects".

EVERYBODY TALKS ABOUT THE COSTS

"I am not trying to minimize the survival benefit. But if I was a breast cancer patient and I knew that one pill versus and other pill had an advantage of preventing my breast cancer from returning and additionally, knew that it was associated with, what I consider threatening side effects like seen with tamoxifen, that would be it for me. But the good thing about the BIG 1-98 and the Attack-study is that people always argue over costs. For the patients, prevention of breast cancer recurrence and reducing serious side effects is baseline. On a population based level the cost of recurrence is much greater than the additional costs - we saw that in the NICE-report last fall. But no one talks about the cost of recurrence. Everybody talks about the cost of a drug. It's one thing if a drug costs more and is a less efficient drug in terms of the disease but these drugs (aromatase inhibitors) and particularly, letrozole, has shown to prevent distant recurrence in the first two years, and the cost of distant recurrence is far greater than any cost - I mean that is what the NICE-report says - keeping a woman alive with ER positive metastatic breast cancer, on average they live 4-5 years, which is great, but the cost to that woman, to her family and to the society is much greater than the increased cost of treating a 100 patients with a slightly more expensive drug. Does that make sense? The conclusion to me is that the BIG 1-98 is a great study and at least now I know which tool to reach for in the toolbox".

Anna von Wachenfeldt, chief physician, Södersjukhuset, Stockholm



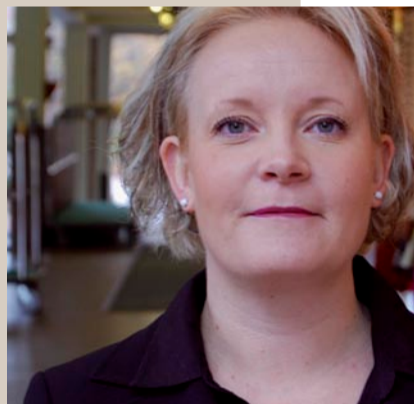
"The symposium was as always well organized and very educating. I bring home one special learning and that's the possibility to start with letrozole and switch to tamoxifen after two and a half years as it is suggested in the BIG 1-98 study. That is both from a economical and side effect point of view good news that I will integrate in my practise".

Per Karlsson, chief physician, Sahlgrenska Sjukhuset, Göteborg



"My primary goal at this symposium has been to update my knowledge on the whole field of breast cancer. I have been screening what goes on and the aromatase inhibitors have had first priority. Both BIG 1-98 and ZO-FAST seem to be very interesting studies".

Pia Vihinen, Medical Oncologist, Department of Oncology and Radiotherapy, Turku University Hospital.



"I have been here several times before and it is always a very well organised meeting giving a good opportunity to meet the experts personally. It's often more rewarding than just reading about results. Most important to bring home are the conclusions from the study comparing an aromatase inhibitor to tamoxifen. I have also joined some basic cancer courses that has been very good education.

