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Quick Pulse

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RESULTS OF NOVARTIS'S FEMARA BIG-1-98 TRIAL

The results of the two five-year continuous therapy arms (Arms 1 and 2) of the ongoing BIG-1-98 trial of Novartis's Femara (letrozole) were reported at the St. Gallen Primary Therapy of Early Breast Cancer conference on January 26, 2005. BIG-1-98 was conducted by IBCSG, with support from Novartis. BIG-1-98 is a four-arm study investigating continuous and sequential therapy with:

- **Arm 1:** Continuous therapy with Femara for five years.
- **Arm 2:** Continuous therapy with tamoxifen for five years.
- **Arm 3:** Two years of tamoxifen followed by three years of Femara.
- **Arm 4:** Two years of Femara followed by three years of tamoxifen.

At the San Antonio Breast Cancer Symposium, doctors said they would be looking to see if BIG-1-98 shows Femara confers disease-free survival (DFS) improvement greater than that seen for AstraZeneca's Arimidex (anastrozole) in the ATAC trial (2.4%), and in line with sequential therapy with Pfizer's Aromasin (exemestane) in the IES trial (4.7%). If so, they said they would conclude that Femara is a more potent drug. The expectation was that BIG-1-98 would report DFS improvement of ~3%-4%. Actually, it was 2.6%.

Currently, Femara is approved by the FDA only for use in breast cancer patients who have completed a five-year course of tamoxifen. Novartis announced it will file with global regulatory authorities in the latter part of 2Q05 for approval of use in adjuvant treatment of breast cancer. Novartis predicted Femara would become a "blockbuster" drug by 2008, with sales of at least $1 billion a year.

BIG-1-98 showed Femara superior to tamoxifen on DFS, time to recurrence, and time to distant recurrence. However, the effect on DFS was only in node-positive women, not node-negative women.

- Prof. Ian Smith, of Royal Marsden Hospital, London, U.K., a BIG-1-98 Steering Committee member, said, "It is interesting. To my mind, it was a little surprising that there was no effect on node-negative patients so far. My personal view – that I shared with the statistician who is thinking about it – is that it could be that because of the crossover at two years and the data subsequently censored, the great majority of node-negative patients would not relapse in two years. Node-negative tends to be associated with late relapses. So, it could be due to censoring. I think it would be surprising not to find some gain in node-negative patients with longer follow-up."
- Diane Young, VP and Global Head of Clinical Development for Novartis Oncology, said, "We do know that Femara is more potent than anastrozole and has greater estrogen suppression, and that might explain why in BIG, the gain seems to be greater in the high risk population…The bottom line is to be

very careful on how much to interpret by comparing the two trials (BIG and ATAC)."

BIG-1-98 also continues to fuel questions about cardiac safety (MI, severe CHF, arrhythmias, CABG, and aneurysms) as well as bone loss associated with Femara. Prof. Smith said, "The (cardiovascular event) numbers are small...I'm not certain the results are completely different from other trials…The conclusions made by the presenter yesterday (at the formal presentation) was that these CV and cerebrovascular events mean we need to go back and look at all of these trials. There may or may not be an issue…It may be that tamoxifen has a small edge in protecting against CV events. We don't know that. We do know it lowers cholesterol levels, which AIs (aromatase inhibitors) don't do. But women don't go on these drugs to lower cholesterol."

In making comparisons of the BIG-1-98 results to the results of the ATAC trial of Arimidex, Novartis officials cautioned that ATAC used a different definition of DFS, and the timeframe was not exactly the same. A Novartis official commented, "You have to be very cautious making a direct comparison of ATAC and BIG-1-98, but there does appear to be an advantage to BIG-1-98."

BIG-1-98 Results

Measurement	Femara n=4,003	Tamoxifen n=4,007	Femara risk reduction vs. tamoxifen	p-value
Primary endpoint: DFS	84.0%	81.4%	19%	.003
OS	---	---	14%	Nss
SDFS	---	---	17%	---
DFS without second primary *	---	---	21%	---
Time to distant recurrence	---	---	27%	.006
Time to recurrence **	---	---	28%	---
DFS in node-positive patients	---	---	29%	---
DFS in node-negative patients	---	---	1%	---
Sites of first failure				
DFS events	8.8%	10.7%	--	.004
Local	0.5%	0.9%	---	.047
Contralateral breast	0.4%	0.7%	---	.125
Distant	4.4%	5.8%	---	.006
Death without recurrence	1.4%	0.9%	---	.077
Deaths	4.1%	4.8%	---	.176
Adverse events				
At least one serious adverse events	587 patients	643 patients	---	---
Bone fractures	5.8% (228 patients)	4.1% (162 patients)	---	.0006
Bone fracture rate	2.2	1.5	---	---
Endometrial biopsies	1.9%	7.2%	---	---
Invasive endometrial cancer	0.2%	0.4%	---	.078
CVA/TIA	1.2%	1.1%	---	Nss
Thromboembolic events	0.8%	2.0%	---	---
Other Grade 3-5 CV events	3.6%	2.5%	---	---
Deaths due to stroke	7 patients	1 patient	---	---
Cardiac deaths	26 patients	13 patients	---	---

*** This compares to a 22% reduction with Arimidex in the ATAC trial.**
**** This compares to a 27% reduction with Arimidex in the ATAC trial.**

Overall, median follow-up in BIG-1-98 was 35.5 months, and the primary core follow-up was 25.8 months. About 1,100 patients completed five years of therapy. DFS, overall survival (OS), and systemic disease-free survival (SDFS) all favored Femara.

Novartis concluded:

- Data at 26 months already show significant overall benefit in DFS across all postmenopausal women with early hormone receptor-positive breast cancer (19%; p=0.003); especially reducing spread to distant sites of the body (27%; p=0.006).
- Femara demonstrated the most significant advantage in DFS vs. tamoxifen in women at greatest risk of recurrence.
- Femara is now the only treatment shown to significantly reduce risk of recurrence both as initial therapy post-surgery and also following standard tamoxifen.

Novartis also reported:

➢ The crossover data from BIG-1-98 is not likely to be available for at least a couple of years.

➢ Global Femara sales were $386 million in 2004, up from $227 million in 2003.

➢ In the G-6 countries (U.S., Japan, Germany, France, U.K., and Italy), there were 1.2 million breast cancer patients in 2004, of which ~880,000 were adjuvant.

➢ Additional combination studies are planned or ongoing, including Femara plus:

- Novartis's RAD-001 (everolimus).
- Novartis's Zometa (zoledronic acid) to prevent bone loss in breast cancer patients treated with aromatase inhibitors. One-year results of the Zo-FAST/Z-FAST trials – which have a primary endpoint of lumbar BMD at 12-months – are expected at ASCO 2005.
- Genentech's Herceptin (trastuzumab).
- Genentech's Tarceva (erlotinib).
- Johnson & Johnson's Zarnestra (tipifarnib, R-115777).

Other interesting points that came up relating to the BIG-1-98 results:

- *David Epstein, President, Novartis Oncology and CEO, Novartis Specialty Medicines:* "What was unexpected was the magnitude of the benefit in distant DFS. That, in its own right, would predict eventually there will be a survival benefit.
- *Prof. Smith:* "This raises the issue in our mind that is there something about a short duration of tamoxifen that might sensitize the estrogen receptor, so that, in the end, the AI – and it appears to be a generic effect – might be more active in the long-run? The difficulty with that strategy is if you wait two years as in the IES trial, then you've lost some patients who relapsed. That strategy means a few patients started on tamoxifen would get worse, but for the greater benefit of everyone later on. The Big-1-98 has crossover arms in it as well, so eventually we may answer that."
- *Prof. Smith on how BIG-1-98 will change his use of AIs:* "With higher risk patients, I would be cautious about starting tamoxifen because you will lose some in two years…Personally, it seems that while we wait for the Big-1-98 data, we might want to start another trial. So, I would say either start an AI right away or I'd like to see another trial of Femara up-front or of short duration tamoxifen followed by Femara, but I'd like the tamoxifen to be pretty short."
- *Prof. Smith on Femara and hypercholesterolemia:* "This is the kind of data that if you just look at it, it could be a concern, but I don't think it should be. Almost all the rise was Grade 1. And patients with breast cancer are much more worried about dying of breast cancer than something else. These are issues (CV and cholesterol) that need to be teased out of all three big trials before we draw conclusions."
- *Prof. Smith, asked what clinicians will be looking for to differentiate the AIs:* "There is no biological reason that (there should be a detrimental effect) to continuing an AI (past five years). And we know the continuing risk of breast cancer is a big problem…The question is, 'Does short-term (five year) AI therapy give the maximum protection? Or will you get further protection by going to 10 years of AI therapy?…There is the potential for women to be on these drugs (AIs) for 10 years or longer. And the drive will come from patients. They will not want to stop (the AI) unless there is a good reason to do so. Most women in my practice don't want to stop tamoxifen until they hear there is a potential adverse effect."

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