

Once-Promising Arzoxifene Flunks Phase III Trial

BY BRUCE JANCIN

SAN ANTONIO — Arzoxifene, a once-promising selective estrogen-receptor modulator, experienced a fatal meltdown in a phase III trial involving nearly 10,000 women.

Arzoxifene was being developed for prevention of both fractures and breast cancer in postmenopausal women with osteoporosis or osteopenia.

But the 9,354-patient randomized, double-blind, placebo-controlled, multinational GENERATIONS trial has put an end to that, Dr. Trevor Powles said at the San Antonio Breast Cancer Symposium.

The breast cancer prevention portion of GENERATIONS went well: After 48 months of follow-up, arzoxifene reduced the incidence of invasive breast cancer by 56%, compared with placebo, and reduced estrogen-receptor-positive invasive breast cancer by 70% (see chart).



Arzoxifene also significantly reduced the incidence of vertebral fractures by 41% after 36 months of follow-up in GENERATIONS participants, who were aged 60-85 years at enrollment.

But there was a deal breaker: the selective estrogen-receptor modulator (SERM) produced no significant reduction in nonvertebral fractures.

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DR. POWLES

“This is disappointing because as an antiosteoporosis drug we really need to have a SERM that would not only reduce vertebral fractures, but nonvertebral fractures as well,” explained Dr. Powles, a medical oncologist who is professor emeritus at the Institute of Cancer Research, London.

Moreover, arzoxifene was associated with increased rates of venous thromboembolism, endometrial polyps, leg cramps, hot flashes, and cholelithiasis, while offering no better protection against cardiovascular events than did placebo.

Arzoxifene Reduces Risk For Vertebral, But Not Other Fractures

	Arzoxifene (n=4,678)	Placebo (n=4,676)	Risk Reduction	P Value
All breast cancers	22	53	58%	< .001
Invasive breast ca	19	43	56%	.002
Invasive ER+ breast cancer	9	30	70%	.001
Vertebral fractures	80	134	41%	.001
Nonvertebral fractures	203	208	none	.71

Note: Based on a study of 9,354 postmenopausal women with osteoporosis.
Source: Dr. Powles

“The overall benefit/risk profile of arzoxifene does not represent a meaningful advancement in the treatment of osteoporosis, so further development of this drug will not take place. It's obviously disappointing, given that so much time and effort has been put into a major trial with good preclinical and early clinical data,” he said.

The investigators are still puzzling over how the earlier studies could have been so misleading.

Arzoxifene is a benzothiophene SERM, like raloxifene, which is approved in postmenopausal women for the treatment and prevention of osteoporosis as

well as for invasive breast cancer risk reduction in such women who are at high risk for the cancer or who have osteoporosis.

In early clinical studies, arzoxifene had greater effects on bone mineral density and bone turnover markers than did raloxifene.

Moreover, in the GENERATIONS trial arzoxifene resulted in increased bone density at nonvertebral sites as well as in the spine.

GENERATIONS was funded by Eli Lilly & Co.

Dr. Powles disclosed that he has no relevant financial relationships. ■

Denosumab Bests Zoledronic Acid for Bone Metastases

BY BRUCE JANCIN

SAN ANTONIO — Denosumab proved superior to zoledronic acid in delaying or preventing complications from bone metastases in breast cancer patients in a large phase III clinical trial.

Denosumab also showed significantly less toxicity than did zoledronic acid (Zometa), the current standard treatment for bone metastases.

Particularly noteworthy was the substantially lower rate of renal toxicity with denosumab; there is no need to monitor serum creatinine in patients on denosumab, unlike with the bisphosphonate, Dr. Alison Stopeck noted at the San Antonio Breast Cancer Symposium.

Denosumab is an investigational fully humanized monoclonal antibody targeting RANK ligand (RANKL), the primary mediator of osteoclast formation, function, and survival.

Metastatic cancer cells stimulate RANKL activity, resulting in increased bone resorption and destruction, explained Dr. Stopeck of the University of Arizona Cancer Center, Tucson.

She reported on 2,046 breast cancer patients with confirmed bone metastases.

Participants were randomized double-blind to denosumab at 120 mg given once monthly by subcutaneous injection or to 4 mg of zoledronic acid given intravenously on an individualized dosing schedule governed by serum creatinine level in accord with the product labeling.

The primary study end point was the

time to the first on-study skeletal-related event (SRE), consisting of fracture, radiation to bone for pain control, surgery, or spinal cord compression.

There was a highly significant 18% relative risk reduction favoring denosumab. The median time to the first SRE was 26.5 months in the zoledronic acid arm; it has not yet been reached in the denosumab arm.

At 36 months of follow up, 30.7% of patients on denosumab and 36.5% on zoledronic acid had experienced at least one SRE, for a 16% relative reduction with the RANKL inhibitor.

The difference between the two therapies grew in magnitude over time: The relative risk reduction favoring denosumab was 5.6% at 12 months and 11.5% at 18 months, Dr. Stopeck continued.

A total of 608 SREs occurred in the zoledronic acid group, compared with 474 with denosumab, a 23% reduction.

The time to experiencing moderate or severe pain was a secondary study outcome—and the most important end point of all from most patients' perspectives.

A score greater than 4 on the 11-point validated Brief Pain Inventory occurred for the first time at a median 64 days in the zoledronic acid group compared with 88 days in the denosumab arm, translating to a 23% advantage favoring the investigational agent ($P = .009$).

Flu-like acute phase reactions in con-

junction with administration of therapy occurred in 27.3% of patients in the zoledronic acid arm compared with 10.4% on denosumab.

Adverse events related to renal toxicity occurred in 8.5% of the zoledronic acid group and 4.9% with denosumab; severe renal toxicity occurred in 1.5% of the zoledronic acid-treated patients compared to 0.2% of those on denosumab.

Osteonecrosis of the jaw (ONJ) occurred in 1.4%

of patients on zoledronic acid and a statistically similar 2.0% of those on denosumab.

More than 80% of cases of ONJ were associated with dental extractions, poor oral hygiene, or use of a dental appliance.

Dr. Theresa Guise, professor of medicine at Indiana University, Indianapolis, commented that it wasn't clear prior to this trial whether ONJ was an adverse event limited to bisphosphonate therapy. These data indicate that it is more globally a side effect associated with inhibiting bone resorption.

Dr. Stopeck said that, interestingly, some cases of ONJ in denosumab-treated patients have turned out to be reversible.

She speculated that this may be a function of the monoclonal antibody's limited duration of activity in bone, in contrast to the bisphosphonates, which

remain present in bone for years.

There is great interest in testing denosumab in the adjuvant setting in patients with early stage breast cancer because of theoretic reasons that RANKL inhibition should curb development of breast cancer, according to Dr. Stopeck.

Asked how she will incorporate denosumab into her own clinical practice if the agent receives marketing approval for the treatment of bone metastases, Dr. Stopeck replied, “I'm going to incorporate it rather quickly, assuming the price isn't exorbitant, since it shows better efficacy, it's easier to give by subcutaneous injection, I don't have to monitor the serum creatinine, and it has less toxicity.”

In October, the Food and Drug Administration held up Amgen's application for marketing approval for denosumab pending more information.

In an interview, a company spokesperson said Amgen plans to resubmit to the FDA, and file for marketing approval in Europe sometime in 2010, armed with these updated data from the breast cancer trial, the findings from another phase III trial involving patients with various solid organ cancers or multiple myeloma, and the results of a third phase III trial in men with prostate cancer, which is expected to report results in the first quarter of 2010.

Collectively, the three studies total roughly 6,000 cancer patients. ■

Disclosures: Dr. Stopeck serves as a consultant to Amgen and Novartis and is on the speakers bureau for Novartis, which markets zoledronic acid.