WILL SOM230 BE EFFECTIVE IN TREATING DUCTAL CARCINOMA IN SITU? A PROOF OF PRINCIPLE TRIAL


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BACKGROUND

232,620 new cases of breast cancer are expected in the U.S. in 2011 (39,870 of these will die). Blockade of estrogen action can prevent breast cancer in up to 50% of women with abnormal hyperplasia, and reduce invasive breast cancer in patients with ductal carcinoma in situ (DCIS) after surgery and chemotherapy. More effective treatments might improve outcomes and have more far-reaching effects.

BIOLIGICAL BACKGROUND

We have found that blocking the action of IGF-1, not only blocks the action of estrogen, but also that of progesterone (3). Therefore, blockade of IGF-1 action might also inhibit actions of IGF-1 that are independent of estrogen and progesterone. These might include IGF-1 induced proliferation of breast cells in the absence of estrogen and effects of IGF-1 on survival of cancer cells.

PHARMACOLOGICAL BACKGROUND

For treatment, we have chosen a multitargeted receptor tyrosine kinase inhibitor, SOM230 (patent pending), that inhibits IGF-1 action by: (1) reducing growth hormone secretion from the pituitary gland, and (2) by directly inhibiting IGF-1 receptors (4) and inhibiting IGF-1 production.

We have previously shown that metastatic breast tumors of mammary gland from hypophysectomized, oophorectomized rat treated with Sgh-1 (left), BGH-SOM (middle), and BGH-SOM + excess IGF-I (right). Celled presented Sgh-1-induced formation of terminal buds and buds in the mammary gland (4), but the inhibition by SOM230 was overriding by additional IGF-I.

FINDINGS

We were awarded a DOD Synergistic Idea award (2006) entitled Breast Cancer Chemoprevention by SOM230, an IGF-I Action Inhibitor. Inhibition of a proof of principal trial. It was designed to determine whether inhibition of IGF-I action by the somatostatin analog, SOM230, would inhibit cell proliferation and stimulate apoptosis in typical or typical hyperplastic lesions in situ (DCIS).

• We have not yet published our findings. Therefore, we are limited in how much we can report.
• We treated 13 women carrying a typical hyperplasia of the breast in situ with 10 days of SOM230 significantly inhibited cell proliferation and increased apoptosis as that in rats.
• One woman with DCIS was treated inadvertently. Results can be seen below.

BC097854 - “WILL SOM230 BE EFFECTIVE IN TREATING DUCTAL CARCINOMA IN SITU? A PROOF-OF-PRINCIPLE CLINICAL TRIAL”

We hypothesize that blockade of IGF-I action by SOM230 will, in principle, be effective in treating ductal carcinoma in situ (DCIS), by inhibiting cell proliferation and stimulating apoptosis, thus allowing ducts and pre-malignant hyperplastic lesions.

SPECIFIC AIM 1: To determine whether SOM230 will inhibit cell proliferation and angio genesis, and stimulate apoptosis in tissue samples from excision biopsies in comparison to core biopsies from women with ER positive DCIS. Also to assess the effects of SOM230 on phosphorylated IGF-I and IRS-1.

SPECIFIC AIM 2: To determine whether treatment with SOM230 for 19.5 days will reduce in vitro growth of breast tumor cell lines with specific features by morphogenesis and dynamic contrast enhanced MRI (DCE-MRI).

SPECIFIC AIM 3: To determine whether the early effects of SOM230 on serum insulin and glucose will alake by 20 days of treatment.

PROTOCOL: We will enroll 24 women with DCIS, with stratification by tumor grade (low or high). Each of these grades will be assessed by including 12 patients in each group. This will also permit evaluation of the group as a whole. In addition to histological endpoints, we will attempt to correlate the tissue results with physiological and tumor volume endpoints by DCE-MRI ( Aim 2). and also must carry out an independent blinded evaluation of whether during continued use of this drug, glucose abnormalities resolve, as these have in previous studies on other disorders ( Aim 3).

SOM230 is in the process of developing a pharmaco-genetic model to assess vascular permeability of pre-malignant and invasive breast cancer by MRI. This will provide a crucial distinction between vascular permeability of normal breast cells and the pathological cells of the tumor. Our model will permit measuring blood flow relative to the aorta vs. tumor. This dual information will allow for better outcome evaluation of this drug in different populations.

CURRENT PROGRESS: During the last 7 months we obtained approvals from the New York University School of Medicine IRB, CTU, NY Cancer Center PRMC, Berlin Breast Cancer PRMC, and the FDA. We also had approval in advance to start enrollment in June 2011 by the FDA and IDA.

We have a Research Coordinator and a Research Scientist. We have developed the DBS entry program and CRIS and set up new protocols for immunostaining and Western blotting.

BC103983 - “EFFECT OF PASIRETIDE IN BREAST CANCER PREVENTION IN BRCA1 DEFICIENCY”

A basic science expansion grant has been recommended for funding by the DoD.

We have recently discovered a novel model of BRCA1 deficiency with an extreme phenotype, which is associated with BRCA1 loss of function mutations. We now wish to apply this model to determine whether pasireotide is effective in treating development of the phenotype and tumor formation.

BRCA1 plays a central role in DNA damage response, regulating cell cycle checkpoints and genomic instability. Moreover, several high-profile publications have shown that BRCA1 loss or mutation affects the mammary epithelial hierarchy, which in turn affects the rate and type of cancer that develops. Our studies will assess whether we can reverse this process through inhibition of tumor phenotype via inhibition of proliferation but also restores genomic stability and normal distribution of cell cycle checkpoints. Our in vitro and in vivo studies are critical for assessing the impact that breast cancer prevention in BRCA1 mutation patients can be achieved by blocking a key role of IGF-I.

SUMMARY

1. We have found that IGF-1 is essential for mammary development and underlies the actions of estrogen and progesterone.
2. Inhibition of IGF-1 by various means, including a multitargeted somatostatin analog, SOM230 (patent pending), prevents mammary development and hyperplasia by inhibiting cell proliferation and stimulating apoptosis.
3. In a proof of principle trial in 13 women with atypical hyperplasia, we found that administration of SOM230 significantly inhibited cell proliferation and increased apoptosis.
4. The medication was generally well tolerated but had a side effect of moderate hyperglycemia due to insulin inhibition.
5. We are now actively recruiting volunteers with DCIS for our present clinical trial.
6. We have developed a novel mouse model of BRCA1 deficiency to determine whether IGF-I action will prevent the phenotype and tumor development. Also. IGF-I blockade whether IGF-I blockade will reduce carcinogenic and genomic instability.

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REFERENCE


SIDE EFFECTS: Side effects included moderate hyperglycemia due to inhibition of IGF-I action. This graph shows the relationship between serum glucose and insulin before, during and after 20 days of treatment. There was also a reduction in serum IGF-I levels within the normal range, which also returned to baseline after stopping drug.

Mean Age: 67 Years
Mean Height: 67 Inches
Mean Weight: 150 Lbs.

Mature Fastening Serum Glucose and Insulin Levels

SOM230 vs. TAMOXIFEN: Although we did not do a direct comparison of the effectiveness of SOM230 vs. tamoxifen, we tested the effects of very high doses of both medications on their ability to prevent or reverse GH and E2-induced hyperplasia and baseline rate (hypophysectomized and oophorectomized at 21 days of age). We found that although tamoxifen did not appear to be as effective as SOM230 in inhibiting GH and E2-induced hyperplasia, it did not enhance the action of SOM230 indicates that SOM230 is as effective as tamoxifen (5).

The figure below shows cell proliferation (Ki67) in a mammary gland from a hypophysectomized, oophorectomized rat treated with Sgh-1 (left), BGH-SOM (middle), and BGH-SOM + excess IGF-I (right). Cell presented Sgh-1-induced formation of terminal buds and buds in the mammary gland (4), but the inhibition by SOM230 was overriding by additional IGF-I. (5)