HORMONE RECEPTOR STATUS

Hormone receptor status is a major factor in planning treatment for breast cancer. Some breast cancer cells grow with the help of estrogen and/or progesterone (female hormones that are produced in the body). These tumor cells have special proteins, called hormone receptors, on their surface. When hormones attach to hormone receptors, the cancer cells with these receptors grow. Breast cancers with hormone receptors are called hormone-receptor positive (or estrogen/progesterone receptor-positive) and can be treated with hormone therapies. Only cancers with hormone receptors will respond to hormone therapies, which will be discussed later. Those that do not have receptors (and cannot be treated with hormone therapies) are called hormone-receptor negative (or estrogen/progesterone receptor-negative). Hormone receptor status is determined by testing the tissue removed during a biopsy.

Breast cancers that are estrogen receptor-positive also tend to be progesterone receptor-positive. Cancers that are estrogen receptor-negative tend to be progesterone receptor-negative. Sometimes, a breast cancer is positive for estrogen receptors, but negative for progesterone receptors. Because current hormone therapies are designed to treat estrogen receptor-positive cancers, these cases are treated the same way as breast cancers that are positive for both hormone receptors. Hormone therapies can stop tumor growth (in hormone receptor-positive cancers) by preventing cancer cells from getting the estrogen they need to grow.

Hormone receptor status is also related to recurrence (the return of cancer after treatment). Hormone receptor-positive tumors have a slightly lower chance of recurrence than hormone receptor-negative tumors at five years after diagnosis. However, this difference decreases and over time makes no difference.

HER2/NEU (ERBB2) STATUS

HER2/neu (human epidermal growth factor receptor 2), also called ErbB2, is a protein that appears on the surface of some breast cancer cells. This protein is an important part of the pathway for cell growth and survival. HER2-positive status (also called HER2/neu over-expression) is found in about 20 percent of all breast cancers. These breast cancers tend to be more aggressive and have a poorer prognosis than HER2/neu-negative cancers. However, it is not clear whether HER2/neu status is an independent risk factor for these traits. HER2/neu-positive cancers also tend to be estrogen receptor-negative and have poorly differentiated cells, both of which lead to poorer prognosis. HER2/neu-positive cancers can benefit from trastuzumab (Herceptin) therapy, which directly targets the HER2/neu receptor. This type of therapy is not used for cancers that are HER2-negative. On the other hand, HER2/neu-positive cancers do not respond as well to tamoxifen as HER2/neu-negative cancers do. Therefore, knowing HER2/neu status helps guide your chemotherapy regimen. All tumors should be tested for HER2/neu status. While HER2 status is an important marker for therapy options, it is unclear at this time whether or not it is an independent predictor of prognosis or survival.

Two common ways to determine HER2/neu status in clinical practice are: 1) immunohistochemistry (IHC) testing which detects the amount of HER2/neu protein in the cancer calls and 2) fluorescence in situ hybridization (FISH) testing which detects the number of copies of the HER2/neu gene in the cancer cells.

years of tamoxifen.

Like anatrozole, taking letrozole can lead to bone thinning and weakening and a higher-than-average risk of broken bones and is not recommended for women with osteoporosis. Other common side effects of Femara are bone and joint pain, fatigue, dizziness, drowsiness, higher cholesterol , hot flashes, weight gain, nausea and vomiting. Anastrozole would be favored over Letrozole, and it has the same negative effects as Anastrozole compared to Tamoxifen. Letrozole would also be a favored treatment following Tamoxifen treatment.

Table 12. SWOT Analysis of Letrozole

Strengths	Weaknesses	Opportunities	Threats
• Less toxic than tamoxifen • Preferred therapy for postmenopausal women after surgery • Oral	• More expensive than tamoxifen • Less is known about long term side effects • Usually given following tamoxifen • Not to be used in women with osteoporosis	• Can be given for an additional 5 year following tamoxifen for 5 years	• Other AI's

EXEMESTANE

Exemestane is approved by the FDA to treat post-menopausal women diagnosed with hormone-receptor-positive, early-stage breast cancer after they've taken tamoxifen for 2 to 3 years to reduce the risk of the cancer coming back and post-menopausal women diagnosed with advanced-stage or metastatic hormone-receptor-positive breast cancer.

The large IES (Intergroup Exemestane Study) trial was started in 1998 and compared switching to Aromasin after taking tamoxifen for 2 to 3 years to staying on tamoxifen for 5 years. The results have shown that switching to Aromasin for 2 to 3 years AFTER taking tamoxifen 2 to 3 years (for a total of 5 years of hormonal therapy medicine) was better than staying on tamoxifen for 5 years for increasing the time before the cancer comes back in those who experience a recurrence, reducing the risk of a new cancer developing in the other breast for post-menopausal women diagnosed with hormone-receptor-positive, early-stage breast cancer.

Taking Aromasin can lead to bone thinning and weakening and a higher-than-average risk of broken bones. Other common side effects of Aromasin are bone and joint pain, hot flashes, fatigue, headache, insomnia, increased sweating.

Table 24. SWOT Analysis of Sunitinib

Strengths	Weaknesses	Opportunities	Threats
• For 1L Breast Cancer Treatment • Oral • Already approved for other oncology indications	• EGFR is common pathway of other drugs • Adverse Effects can be severe	• 1L • Also investigating HER2+ • Also investigating Triple-Negative BC	• Compete with chemotherapy • Other therapy with the same MOA

Sunitinib is already approved for RCC treatment, and is currently in phase 3 trials for advanced breast cancer, but is also being investigated in HER2-positive and triple-negative breast cancer, both of which are difficult to treat. Sunitinib may have utility in this market; however, there are other drugs in the pipeline that affect a similar portion of the pathway, specifically pazopanib and IMC-1121B. The current phase 3 study is scheduled for completion in January 2012 and would not be expected to be approved until 2013 at least.

PAZOPANIB (VOTRIENT)

Pazopanib is the hydrochloride salt of a small molecule inhibitor of multiple protein tyrosine kinases with potential antineoplastic activity. Pazopanib selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R), which may result in inhibition of angiogenesis in tumors in which these receptors are upregulated. Pazopanib is the generic name for Votrient, manufactured by GSK approved by the FDA in October of 2009 for second-line treatment of metastatic RCC. The majority of adverse events were mild to moderate, the most common (incidence ≥ 20%) being diarrhea, hypertension, hair color change, nausea, anorexia, and vomiting. Liver enzymes are also altered and should be monitored carefully.

phase 1 data with pazopanib showed partial responses and stabilization of disease in patients with solid tumors. A phase 2 trial compared the combination of lapatinib and pazopanib with lapatinib alone as first-line therapy in HER2-positive metastatic breast cancer. This combination was used to exploit the blockade of both EGFR and VEGF pathways. Response rates of 44% (14 patients) were seen with combination therapy and 30% (nine patients) with lapatinib alone. The most common toxic effects of the combination treatment were diarrhea, rash, nausea, and increased liver enzymes. One patient had an asymptomatic decline in left ventricular ejection fraction and was removed from the study. This was the first phase 2 trial investigating lapatinib with pazopanib, and further studies are warranted to better understand the potential for this combination to reduce recurrence rates and overcome trastuzumab resistance by blocking multiple downstream pathways.

There are 2 studies no longer recruiting patients consisting of a phase 2, open-label, randomized, multicenter trial of pazopanib in combination with lapatinib compared to lapatinib alone as first-line therapy in subjects with advanced or mBC with ErbB2 fluorescence in situ hybridization (FISH) positive tumors (140 patients) and a phase 2 study of pazopanib in patients with recurrent and/or metastatic invasive breast carcinoma (20 patients).