BREAST CANCER

BY CYNTHIA BORDA

Despite advances in breast cancer treatments, this is still an area of unmet need. Significant opportunities exist in this market, especially for products that are targeted and that have fewer side effects.

Pink Ribbons of Opportunity

Tremendous progress has been made in treating breast cancer. Survival rates have increased because of earlier diagnosis and new therapies, including hormonal products and biologics. Still, about 40,000 patients die every year from breast cancer, and the estimated lifetime risk of breast cancer has gone up gradually over the past several decades. The National Cancer Institute estimates that, based on current rates, 13.2% of women born today (1 in 8 women) will be diagnosed with breast cancer at some time in their lives.

These statistics indicate that there is still substantial unmet need and opportunities for companies that can bring safe and effective products to the market that also have fewer side effects.

The breast cancer therapeutics market — which consists of chemotherapeutics, hormonal therapies, and biologics — is expanding in both Europe and the United States because of new applications for existing therapeutics, new products in the pipeline, and the expected increase in breast cancer incidence, say consultants with Frost & Sullivan. At present there is only one biologic available for treating breast cancer, but Frost analysts expect this area to grow rapidly as novel monoclonal antibody therapeutics with improved efficacy and reduced side effects are approved.

There is much that needs to be done in breast cancer, says Paolo Paoletti, M.D., senior VP of the oncology medicine development center at GlaxoSmithKline.

"We need to answer questions, including what are the new generation of agents; why does cancer still proliferate in some patients when standard treatments are effective for others; why and how resistance to treatment is acquired and how can we predict which patients will respond to specific treatments; and what new targets need to be identi-

Demonstrating advocacy for the cause and educating women are keys to creating successful drugs and brands in the future.

GRETCHEN GOFFE
GSW Worldwide

We have researchers around the world looking at breast cancer cell lines, their signaling pathways, and the molecules that regulate these pathways. This research helps us focus on developing personalized medicines.

DAVID EPSTEIN
Novartis Oncology

fied," he says. "We owe a lot to chemotherapy, but if we could develop a strategy for targeted agents to be used in combination with or in sequence and avoid chemotherapy or develop less toxic chemotherapies, that would be ideal."

At Novartis, which fields a diverse team in the area of cancer development and discovery, the R&D focus is on identifying a novel target, quickly validating it, designing a molecule to interact with it, and then matching the medicine to the right patient.

"For example, we have genomic technicians and biomarker development groups, along with researchers who look at breast cancer cell-lines, signaling pathways, and the molecules that regulate these pathways," says David Epstein, president and CEO of Novartis Oncology. "The focus is now an individualized approach."

Paul Plourd, M.D., senior director of oncology at AstraZeneca Pharmaceuticals LP, says research has to move toward finding personalized treatments through surrogate markers.

"Hopefully, this revolutionary event will happen in the next few years," he says. "With more personalized treatments, drugs will work better for each patient."

Personalization goes beyond treatments; it also needs to extend to how products are marketed and how patients are educated.

"When marketing to women, the prevailing thought is that an emotional element needs to be included; but information about breast cancer that is overly emotional can cause women to tune out," says Gretchen Goffe, VP of planning at GSW Worldwide and principal partner of Pink Tank, a specialty group focused on marketing to women. "Women often don't see breast cancer as a personal risk. Women who have a family history of breast cancer are more motivated to have yearly check ups and pursue other forms of preventive care, but women who don't have a family history have a 'roulette wheel' attitude. They know breast cancer will hit somebody, but odds are it won't be them."

Ms. Goffe says marketers who are able to personalize the risk for women will have an advantage. She says education, dialogue, and advocacy are important for a successful marketing program.

40,000 PATIENTS DIE EVERY YEAR FROM BREAST CANCER.

"Women are caregivers and place a high value on communications that demonstrate caring," she says. "Marketing programs based on advocacy and education — and not self-promotion — are more likely to generate loyalty for a product among women. These are women who want a brand to be an advocate for them. Brands that can provide an educational outlet where women can get specific answers to their questions are the ones that are going to win in this space."

A Market Breakdown

The world breast cancer therapeutics market is expected to be $10.21 billion in 2011 up from $5.29 billion in 2004, according to an August 2005 report by Frost & Sullivan. The United States, at 43%, accounts for the biggest share of the market, followed by Europe, 28%, and the rest of the world, 29%.

But Frost & Sullivan consultants say the market poses considerable challenges, including: significant toxicity associated with chemotherapy regimes; lack of efficacy associated with breast cancer therapies; similar products within each therapeutic class, which is creating variations in prescribing habits; the high cost of bringing an oncology product to the market deters new market entrants; lack of patient-reimbursement strategies for biopharmaceutical products; and the saturation of the aromatase inhibitor market deters further research in this area.

In addition to surgery and radiation, current treatments for breast cancer include chemotherapies, monoclonal antibodies, hormonal therapies, as well as biologic agents.

CHEMOTHERAPIES — There are several regimens of chemotherapy but the most common are some combination of doxorubicin, an antineoplastic agent; cyclophosphamide, an alkylating agent; methotrexate, an antimetabolite; fluorouracil, an antimetabolite; docetaxel, an antineoplastic; and paclitaxel, an antineoplastic. Other chemotherapy drugs used for treating women with advanced breast cancer include vinorelbine, an antineoplastic; gemcitabine, an antimetabolite; and capecitabine, an antimetabolite.

MONOCLONAL ANTIBODIES — The only monoclonal antibody currently available is the humanized monoclonal antibody to the HER2 receptor known as Herceptin

Factors Impacting the Breast Cancer Market

Market Drivers

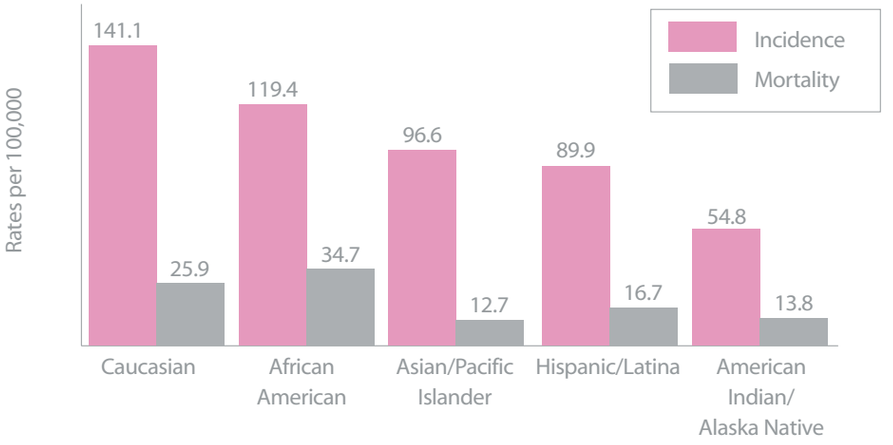
- Significant funding and publicity facilitates breast cancer research and development
- Drive toward personalized medicine reveals a new future for cancer therapy
- Application of existing therapeutics for new indications and preventive measures

Market Restraints

- Market dominance of major players deters market entrants
- Lack of consensus over best course of treatment
- Spending limits on cancer therapeutics

Source: Frost & Sullivan, San Antonio.
For more information, visit frost.com.

Breast Cancer Incidence and Death by Race and Ethnicity, U.S. 1998-2002



Source: American Cancer Society, Washington, D.C. For more information, visit cancer.org.

Breast Cancer Facts

- In the United States, breast cancer is the most common nonskin cancer and the second leading cause of cancer-related deaths in women.
- Based on current rates, 13.2% of women born today will be diagnosed with breast cancer at some time in their lives.
- Estimated lifetime risk of breast cancer has gone up gradually over the past several decades.
- Although the breast cancer diagnosis rate has increased, there has been a steady drop in the overall breast cancer death rate since the early 1990s.
- While the incidence rate is lower for African Americans than Caucasians, the mortality rate is high.
- It is estimated that about $8.1 billion is spent in the United States each year on the treatment of breast cancer.

Source: National Cancer Institute, Bethesda, Md.
For more information, visit cancer.gov.

(trastuzumab) marketed by Genentech Inc. About 25% of women have a mutation of the HER2 gene, which is marked by aggressive tumors and a greater likelihood of recurrence, poorer prognosis, and decreased survival compared with women with HER2-negative breast cancer.

This product is specific to breast cancer patients who overexpress the HER2 gene. This overexpression can cause cells to divide, multiply, and grow more rapidly than normal. Herceptin is a targeted treatment that binds to HER2 receptors on tumor cells and thus can inhibit tumor cell growth.

Herceptin was approved in September 1998 for use in combination with paclitaxel as a first-line therapy after diagnosis of HER2-positive metastatic breast cancer and as a single agent in second- and third-line therapy for these patients after other therapies have failed.

"Herceptin has transformed the care of these women since it was approved," says David Schenkein, M.D., VP of clinical oncology and hematology at Genentech. "The HER2 gene is related to a more aggressive cancer, and these patients have less chance of survival."

More recently, four large trials showed a 50% reduction in the risk of recurrence of breast cancer, and this additional indication is currently before the FDA for approval. Genentech has recently filed a supplemental biologics license application (sBLA) with the FDA for Herceptin in combination with chemotherapy to treat early-stage HER2-positive breast cancer in the adjuvant setting. The FDA's action date for this approval is mid-November.

Top-selling Herceptin had U.S. sales in 2005 of $721 million and is the leading breast cancer therapeutic in terms of prescriptions as well, according to IMS Health.

"In real-time prescription data, we are seeing how Herceptin is gaining importance," says Michel Azoulay, engagement manager at IMS Health.

According to data from TNS Healthcare, among the breast cancer therapeutics Herceptin has the highest percentage of brand commitment with physicians. A TNS Healthcare physician survey revealed that 26% of physicians that prescribe Herceptin are committed to it. Sanofi-Aventis' Taxotere ranks next in terms of brand commitment, at 7%, followed by Roche's Xeloda, at 5%. All other products had minimal commitment levels.

Additionally, 97% of the physicians surveyed claim they prescribe Herceptin, followed by Taxotere at 88%, and Xeloda at 86%.

"Commitment, measured through our Conversion Model, segments prescribers according to their commitment to the brand and nonprescribers according to their likelihood of converting to the brand," says Paul Boyce, VP, client services, at TNS Healthcare. "Conversion Model also identifies the right actions to influence the behaviors of each group. It is important to note that commitment differs from behavioral loyalty. Physicians could have high loyalty (e.g., prescribe high numbers or high share) for a particular brand, but may not be committed. They might exhibit the behavioral loyalty because of a lack of competitive options or formulary restrictions, but once a competitor arrives or formulary access changes, they could quickly change their prescribing habits. Prescription volume of physicians who are committed, however, won't change as dramatically when such market events occur, as they have a bond with the brand."

THE BREAST CANCER MARKET IS EXPECTED TO BE $10.21 BILLION IN 2011.

The top three factors driving the high level of Herceptin commitment are placement within guidelines and protocols, patient quality of life, and health insurance coverage or reimbursement.

"Herceptin's uniqueness as a 'smart drug' plays a large role in its current position within our model," Mr. Boyce says.

We owe a lot to chemotherapy, but if we can devise a strategy for developing targeted agents or less intense chemotherapies, that would be ideal.

DR. PAOLO PAOLETTI
GlaxoSmithKline

HORMONE THERAPIES — AstraZeneca's Nolvadex (tamoxifen) was the first well-known hormone therapy for patients who have estrogen-expressing tumors. The product works by competing for estrogen-receptor sites. While estrogen may not actually cause breast cancer, it may stimulate its growth, feeding the cancer. With estrogen blocked, the cancer cells that need it may not grow.

"When Nolvadex reached the market in 1978 it was the only option available to women who suffered from this type of subcancer," Dr. Plourd says.

In June 2006, Nolvadex lost its patent protection, and numerous generic versions are now available on the market.

AstraZeneca is now focusing its efforts on Arimidex (anastrozole), an aromatase inhibitor (AI). According to IMS, Arimidex had U.S. sales of $447 million in 2005.

AIs, which work by inhibiting the production of estrogen outside of the ovaries, have become increasingly popular in the treatment of estrogen-expressing tumors because they present fewer side effects.

Arimidex is the first hormonal treatment for initial adjuvant treatment (treatment following surgery with or without radiation) of postmenopausal women with hormone receptor-positive early breast cancer.

Arimidex also is indicated for the treatment of locally advanced or metastatic breast cancer, and it was the first hormonal treatment of its kind to be approved by the FDA for treatment of advanced breast cancer in postmenopausal women. It has also been approved for treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

"Arimidex has the greatest amount of data behind it, with more than 68 months of follow-up studies," Dr. Plourd says. "Current studies are being undertaken by a U.S. cooperative group looking at noninvasive breast cancer (DCIS) patients taking Arimidex versus tamoxifen. And there is an ongoing prevention study in Europe."

Other brands in this class are: Pfizer Inc.'s Aromasin (exemestane) and Novartis Pharmaceuticals Corp.'s Femara (letrozole).

According to Frost & Sullivan, AstraZeneca's Arimidex and Novartis' Femara were among the top five breast cancer products, based on market share, in 2004. Arimidex captured 15.2% of the total worldwide breast cancer market, and Femara had a 7.2% market share. These products, along with Taxotere (which has 24.2% of the market), Zoladex (9.4%), and Herceptin (9%), contribute 65% to the total sales in this therapeutic segment.

Arimidex is not the only compound undergoing further examination; Femara also is being investigated for additional indications.

"Femara versus tamoxifen is being studied as part of the BIG-1-98 trial, which is the largest adjuvant trial ever undertaken to evaluate Femara's efficacy in decreasing the risk of cancer spreading," Mr. Epstein says. "We are finding that women who are node positive or who have had prior chemotherapy have a higher chance of breast cancer recurrence and that there is a striking benefit in taking Femara compared with tamoxifen. Finally, there are extended-adjuvant trials showing a 40% decrease in cancer recurrence in women taking Femara after having taken tamoxifen for five years."

HERCEPTIN IS THE LEADING BREAST CANCER THERAPEUTIC BY SALES.

Aromasin is the sixth-leading breast cancer drug worldwide and has been proven to be effective in preventing recurrence following surgery, according to the report by Frost & Sullivan.

Another estrogen blocker is Faslodex (fulvestrant), also an AstraZeneca product. Faslodex is a once-monthly injection, which is currently approved for treating advanced metastatic breast cancer.

Faslodex works on both tamoxifen-resistant and estrogen-sensitive receptors. Studies are now being conducted in early breast cancer and in combination.

BIOLOGIC THERAPIES — Protein kinase inhibitors are small-molecule tyrosine kinase inhibitors of the HER1 receptor. Efficacy for these inhibitors has been demonstrated in patients with advanced lung and pancreatic cancers. Several products are now being evaluated in breast cancer, usually in combination with chemotherapy. Iressa (gefitinib), Tarceva (erlotinib), and Tykerb (lapitinib) are three that have gained some attention.

AstraZeneca's Iressa is an epidermal growth factor receptor (EGFR) inhibitor. It is a once-daily 250-mg oral medication and is indicated for the treatment of advanced non-small cell lung cancer (NSCLC). It has been approved for the treatment of advanced NSCLC in 28 countries, including the United States, Japan, Australia, and Canada.

Iressa has been designed to block the activation of an intracellular signaling pathway implicated in cancer cell proliferation and survival in a variety of common tumors, including NSCLC, head and neck, breast, and colorectal cancers. AstraZeneca is conducting Phase II trials of Iressa for treating breast cancer.

Genentech's Tarceva is a small-molecule human epidermal growth factor type 1/epidermal growth factor receptor (HER1/EGFR) inhibitor. It was approved in November 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Genentech is conducting a Phase II trial of Tarceva in combination with the standard treatment of letrozole in postmenopausal women with metastatic breast cancer.

GlaxoSmithKline is conducting a global multicenter Phase II trial to evaluate Tykerb for the treatment of ErbB2-overexpressing (HER2+) breast cancer that has metastasized to the brain. Tykerb is an orally bioavailable small molecule that potently inhibits two receptors, ErbB2 and ErbB1, and is currently

Our research focus is on pathways that are critical to unraveling new therapies. For breast cancer, it is finding the right drug and ensuring patients receive it at the right time.

DR. DAVID SCHENKEIN
Genentech

in development as a first-line treatment for ErbB2-overexpressing breast cancer.

"Patients on the combination therapy were twice as likely to experience a stop in the progression of the disease," Dr. Paoletti says. "The results were so overwhelming and clinically relevant that, based on interim analysis, the independent data monitor committee asked for the study to be halted and all patients be offered the combination."

There have been other exciting clinical outcomes for Tykerb.

"Tykerb has shown activity in patients whose cancer has progressed during and after treatment with Herceptin," Dr. Paoletti says. "Herceptin works outside the cell, and Tykerb works inside the cell, so if a receptor mutates outside the cell, Tykerb will still create a response inside the cell. Tykerb may also cross the blood-brain barrier, where Herceptin does not, which is an important distinction. Studies at Harvard have observed a decrease in the number of brain metastasis in some patients and an improvement in stabilizing the disease."

Another promising class is antiangiogenic agents, which suppress vascular endothelial growth factor (VEGF)-induced activation in vascular endothelial cells and inhibit tumor-associated angiogenesis or growth. Agents that are currently indicated for other disease states are being studied in breast cancer.

Genentech's Avastin (bevicizumab) and Genaera Corp.'s Evizon (squalamine) are two antiangiogenic agents being studied. Evizon is approved for the treatment of choroidal neovascularization associated with age-related macular degeneration.

Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

"The Eastern Clinical Oncology Group (ECOG) conducted a study with more than 700 women with metastatic disease," Dr. Schenkein says. "Included in the trial were patients who were HER2-negative and HER2-positive for whom Herceptin was not appropriate. These patients were given Avastin and paclitaxel, and results showed a 52% reduction in risk of progression. These data are now in front of the FDA and we are beginning studies in the adjuvant setting."

In development is EntreMed's Panzem NCD, which is part of a next generation of antimitoic cancer drugs that bind to tubulin and work through multiple cellular pathways. It is in a Phase Ib study in combination with paclitaxel.

Another potential breast cancer drug in development is GPC Biotech's lead product, satraplatin, an oral drug that is a member of the platinum family of compounds. It is in Phase II trials to treat metastatic breast cancer and other cancers, as well as in combination with radiation therapy and other drugs.

Additionally, Dr. Azoulay says other products in development to watch include those that target HER2, such as canertinib (CI-1033) from Pfizer, and compounds from Takeda (TAK-165) and Novartis (AEE-788). ✦

NEW BREAST CANCER THERAPIES WILL LIKELY BE MORE TARGETED.

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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