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BREAST CANCER THERAPIES MARKETS

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1. Overview

1.1 About This Report

Breast cancer therapies are entering a new era as game-changers emerge for each of the major breast cancer patient populations. New market entrants must possess drug profiles and a savvy clinical development program to overcome such barriers to entry as a stringent regulatory environment and the incursion of cost containment within oncology. This TriMark Publications report provides comprehensive information on major and minor shapers of the breast cancer drug treatment landscape. The study includes detailed discussions on the impact of critical factors, such as genericization, patent cliffs, drug shortages, reimbursement, predictive testing and personalized medicine, to help current and contemplative drug sponsors navigate the breast cancer pharmacotherapeutic market. Moreover, this report contains a detailed analysis of each of the seven main modalities of breast cancer therapies, *i.e.*, hormone therapy, surgery, radiation, molecular targeted therapy, chemotherapy, hormone treatment and targeted drug therapy. Additionally, this study examines prescribing trends and the arrival of the first biosimilar agents and electronic records in post-marketing surveillance.

1.2 Scope of This Report

The following information details developments and anticipated impact in breast cancer treatments that are expected to shape this market space. Key factors converging on this landscape include: new entrants (and exits) among commercially-available drug treatments; genericization of a number of commonly used agents; improved treatment selection, markers and genomic tests; high regulatory hurdles; the encroachment of cost containment practices into the once-shielded field of oncology. This study covers:

- Current guidelines and best practices.
- R&D pipeline; up-to-date published and presented key data towards approvals and new indications.
- Insights into drug performance in ongoing clinical trials.
- Expert opinion clinical intelligence on emerging agents and trends in care.
- Oncology stakeholder/drug sponsors' marketing, franchise and R&D strategy.
- Product-specific case studies of marketing, regulatory and other challenges in entering (and remaining) in the breast cancer pharma market.
- Unmet medical needs across breast cancer patient subpopulations.
- Research advances in biomarkers and the disease state at-large.

The reader should consult other TriMark Publications reports at www.trimarkpublications.com for detailed discussions of important individual market segments related to cancer diagnostics and therapeutics markets, such as *Cancer Diagnostic Testing World Markets*, *Biomarker Technology Platforms for Cancer Diagnoses and Therapies*, *Cancer Cell Therapy Markets*, *Cancer Therapeutics Markets*, *Companion Diagnostics in Personalized Medicine and Cancer Therapy*, *Cytology and HPV Testing World Markets and Molecular Diagnostics in Cancer Testing*.

1.3 Objectives

The main objectives addressed by this report are to:

- Understand, in-depth, breast cancer pharmacotherapies; their classes, mechanisms of action, utility, market positions and strengths—and weaknesses—within the future of breast cancer market.
- Build command of knowledge of the expected game changers within the ER+, Her2+ or triple negative breast cancer markets for the current decade.
- Gauge the extent to which novel factors are poised to calibrate uptake of these new "stars".
- Assess the composite of breast cancer drug market entrants, exits, and combination treatments to address current unmet medical needs of management of breast cancer.
- Monitor key developments in R&D, including clinical development programs' ongoing trials and target indications.
- Compare and contrast the portfolios of key stakeholders in the breast cancer market, present and future.
- Foresee market opportunities afforded by expansion of indications.

- Frame breast cancer pharmacotherapy options within current guidelines and standards of care.
- Gain perspective through expert opinion insights and clinical insights and intelligence.
- Characterize the raising regulatory bar for oncology, and, understand that the oncology space will not remain cossetted from cost containment measures.
- Anticipate the impact of drug shortages for generic chemotherapies, time the entrance and impact of biosimilars and understand how electronic records are reshaping postmarketing surveillance.

Key questions addressed in this report:

- Which entrants are poised to be the blockbusters that will reshape the breast cancer market?
- What is the extent of the relative and composite impact of the novel drivers for this oncology market?
- What forces and barriers exist for maximal uptake of new entrants?
- How are trends in prescribing recrafting best practices for the management of breast cancer, especially early and late stage disease?
- Which of the leading players are best positioning their portfolios and companies within the burgeoning breast cancer marketspace?

1.4 Methodology

The author of this report holds a Ph.D. in physiology. Trained at the University of California and seasoned with many decades of experience as a pharmaceutical industry analyst, the author also has had first-hand experience with drug development, product launches and medical communications. Company-specific information is obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additional sources of information include non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities, such as the United States Department of Health and Human Services (HHS), the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Where possible and practicable, the most recent data available have been used.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information or omission or for the results obtained by the use of such information. Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this report.

Primary Sources

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that it publishes annually. TriMark extracts relevant data and analytics from its research as part of this data collection.

Secondary Sources

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases and other published information as part of its secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations.

TriMark Publications Report, Research and Data Acquisition Structure

The general sequence of research and analysis activity prior to the publication of every report in TriMark Publications includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly-available data and proprietary databases.

- Formulating a study outline with the assigned writer, including important items, as follows:

    - Market and product segment grouping, and evaluating their relative significance.
    - Key competitors' evaluations, including their relative positions in the business and other relevant facts. to prioritize diligence levels and assist in designing a primary research strategy.
    - End-user research to evaluate analytical significance in market estimation.
    - Supply chain research and analysis to identify any factors affecting the market.
    - New technology platforms and cutting-edge applications.

- Identifying the key technology and market trends that drive or affect these markets.

- Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.

- Completing a confirmatory primary research assessment of the report's findings with the assistance of expert panel partners from the industry being analyzed.

1.5 Drugs Covered in This Report

Breast Cancer Drugs (Marketed)

- Abiraterone acetate (Zytiga®).
- Albumin-bound paclitaxel (Abraxane™).
- Amrubicin.
- Anastrozole (Arimidex®).
- Bevacizumab (Avastin®).
- Capecitabine (Xeloda®).
- Cetuximab (Erbitux®).
- Dasatinib (Sprycel®).
- Docetaxel, generic.
- Docetaxel (Taxotere®).
- Doxorubicin liposomal (Doxil®).
- Eribulin (Halaven™).
- Erlotinib (Tarceva®).
- Everolimus (Afinitor®).
- Exemestane (Aromasin®).
- Fadrozole (Afema®).
- Fluoxymesterone.
- Fulvestrant (Faslodex®).
- Gemcitabine, generic.
- Gemcitabine (Gemzar®).
- Goserelin (Zoladex®).
- Irinotecan (Campotsar®).
- Ixabepilone (Ixempra®).
- Lapatinib (Tykerb®).
- Letrozole (Femara®).

- Leuprorelin depot (Carcinil®).
- Lobaplatin.
- Mitoxantrone (Novantrone®).
- Oxaliplatin (Eloxatin®).
- Paclitaxel—generic.
- Pazopanib (Votrient®).
- Pemetrexed (Alimta®).
- Pralatrexate (Folotyn®).
- Raloxifene (Evista®).
- Sorafenib (Nexavar®).
- Tamoxifen.
- Testosterone cypionate.
- Testosterone propionate.
- Toremifene.
- Trabectedin.
- Trastuzumab (Herceptin®).
- Trilostane.
- Triptorelin.
- Vinflunine.
- Vinorelbine (Navelbine®).
- Vorinostat (Zolinza®).

Breast Cancer Drugs (In Development)

- ABI 008.
- AE 37.
- Afatinib (Tomtovok®).
- Afimoxifene (TamoGel®).
- Apatinib.
- ARC 100.
- Axitinib.
- AZD 4547.
- AZD 8931.
- Bavituximab.
- Bosutinib.
- Breast cancer vaccine—Quantum Immunologics.
- Cancer vaccine—BN ImmunoTherapeutics/National Cancer Institute.
- Cancer vaccine E75—Galena Biopharma.
- Cancer vaccine MUC—Memorial Sloan-Kettering Cancer Center.
- Cediranib.
- Cixutumumab.
- Dovitinib.
- EndoTAG 1.
- Entinostat.
- Enzastaurin.
- Ganitumab.
- Glembatumumab vedotin.
- HER2-antigen specific cancer immunotherapeutic.
- Herceptin® SC, Hyaluronidase/trastuzumab.
- Icrucumab.
- IMP 321.
- Indibulin.
- Iniparib.

- KW 2450.
- Liposome encapsulated paclitaxel.
- Litronesib.
- MEDI 573.
- MetMAb.
- Motesanib.
- MVA-BN-HER2 AutoVac.
- N-Acetyl GM3 vaccine.
- Neratinib.
- N-Glycolyl GM3 cancer vaccine.
- Oblimersen (Genasense).
- Orantinib.
- Paclitaxel liposomal—Sun Pharma Research Company.
- Paclitaxel nanosomal—Intas.
- Panobinostat.
- Pertuzumab (Omnitarg®).
- Pixantrone.
- PTC 299.
- Racotumomab.
- Ramucirumab.
- Ridaforolimus (MK-8669).
- Rucaparib phosphate.
- Sagopilone.
- Satraplatin.
- Tesetaxel.
- Tivozanib.
- Trastuzumab biosimilar.
- Trastuzumab emtansine (T-DM1).
- TVAX cancer vaccine—TVAX Biomedical.
- Varlitinib.

1.6 Summary of Major Findings

The breast cancer market is developing in tandem with rapidly evolving cancer therapeutics. A huge, unmet need remains for curative therapies; there is a robust pipeline of agents—from reformulations to innovations. Many will likely provide additional tools to "throw at" particularly stubborn (advanced) tumors, in hopes of forestalling, if not eliminating, the cancer. The breast cancer market has been increasing over the recent decades, and this trend shows no signs of abating. This dynamic is being driven by several pivotal developments. First, wider integration of breast cancer screening within the U.S., European Union (E.U.) and developing nations allows identification of more cancers that would have eluded detection. Early diagnosis—the ability to find the cancer in its more vulnerable, and therefore more medically manageable stages—dramatically increases survival.

Many of the revealed tumors, however, may be slow or non-growing masses that do not pose a health threat. Currently, the science of accurately categorizing a tumor as harmful or not—and applied treatment accordingly—is inexact. Lifestyle changes are also believed to be key determinants of increased rates of breast cancer as seen in developing countries. Specific examples include lower conception rates, fewer births and less breastfeeding; other lifestyle choices include: being overweight, alcohol consumption and diet. Longer lifespan indirectly leads to increased breast cancers; as this greater longevity is enjoyed, there is more time for the development of cancers. Estimating the future breast cancer market recognizes that stronger economies, better access to healthcare, extended lifespan and trends towards smaller families are key impetuses for a growing market in developing countries.

Based on the [redacted], in [redacted] for the U.S., an estimated [redacted] new cases of invasive breast cancer will be diagnosed among women and [redacted] additional cases of *in situ* breast cancer. Approximately ~[redacted] women are expected to die from breast cancer. Estimates drawn by the American Cancer Society for [redacted] include [redacted] women diagnosed with breast cancer annually worldwide, with ~[redacted] succumbing from the disease. Of the [redacted] new diagnoses, half are expected to come from developed countries. It is estimated that $[redacted] was spent worldwide on the treatment of new breast cancer cases in [redacted]. While a number of chemotherapies have come off patent and lower cost generic options have become available, a number of high cost marketed drugs remain. Taken together with several highly anticipated new entrants that are expected to price $[redacted] per course of treatment, the potential for extended use of certain treatments in the adjuvant setting, and trends in standard of care towards more frequent tumor typing and re-testing, cost per patient, will incur increasingly high expenditures. British nationalized healthcare system's National Institute for Health and Clinical Excellence (NICE) and some regulatory bodies have already begun reviewing candidates not just based on safety and efficacy, but also on measures of value and potential to extend life.

Drugs in development for the treatment of breast cancer number in the hundreds. Some of these drugs represent improved formulations that tweak current interventions into more efficacious drugs. Even more use nanotechnology and adducts to minimize side effects. The vast majority of drugs in development, however, represent not chemotherapies, the once bastion of cancer treatment, but targeted agents that address aberrant growth systems at work in breast cancers. Our growing knowledge of the number and variety of growth pathways of breast tumors is being translated into new drug targets, and, new drugs. These possibilities have not yet been exhausted, as a fundamental premise of cancer biology is that tumors do not represent single entities. Rather, cancer cells acquire the mastery to subjugate any number of these metabolic options, and, often, exploit several at once. The inherent genetic instability of a cancer makes it increasingly adept at mutating, through which advantages to their growth, survival and metastatic potential is accomplished. As tumors progress, this "adaptability" makes growth pathway switching and treatment resistance increasingly rapid and absolute. Accordingly, medical management of late-stage tumors is characterized by poor prognosis, primary treatment objectives of slowing the tumor, and repeated drug switching in the face of treatment failure.

Treatment of estrogen receptor (ER)+ or progesterone (PR)+ tumors, which represent the majority of breast cancers, especially through improved early diagnosis, are well served by current anti-hormone therapies. Emerging agents that help block estrogen, progesterone, and most recently, testosterone growth pathways are in development. Perhaps most interesting, however, is demonstrated benefits of bisphosphonate, such as zoledronic acid, used in antihormone regimens. The most significant game-changer in the management of ER/PR+ tumors, with impressive efficacy data, is expected to be Novartis' Afinitor (mTOR inhibitor; everolimus). Already demonstrated to possess a good safety and tolerability record in existing indications, Afinitor is familiar to oncologists and rapid uptake and adoption may be expected. Everolimus is registered with U.S. and E.U. regulators and launch is expected in [redacted]. Ongoing large-scale trials in the Her2neu+ patient population is expected to prove fruitful and result in additional indications.

The most anticipated game-changer in the breast cancer space is the [redacted] entrance of Roche's T-DM1, which will likely cannibalize Herceptin, and Omnitarg/pertuzumab, Roche/Genentech's new add-on Her2-neu-blocker that has shown superior efficacy to Herceptin alone. These will join GSK's Tykerb and Herceptin (SOC) as important options for the Her2+ patient population. Investigators working with T-DM1 and pertuzumab report a drug profile expected to support regulatory approval, as well as anticipated wide incorporation into patient care by physicians at major institutions and in community oncology practices. Roche is expected to dominate the Her2+ breast cancer market with its portfolio of targeted Her2 agents. This represents one of the first dual antibody treatments and will likely arrive at market with a considerable price tag.

Important trends in care for the coming decade look likely to include increased tumor type testing. This is being facilitated by evidence that testing and re-biopsy upon treatment failure can improve outcomes. Equally influential is the successful introduction of new marker tests. Research advances in understanding the previously elusive Her2 receptor structure-function relationships will allow improved discernment of patient candidates-including those with Herceptin-resistant tumors. These insights are melding with use of currently accepted genotyping tools, such as Genomic Health, Inc.'s OncoType DX and Agendia's MammoPrint BC tests.

These and other diagnostic, treatment selection and prognostic tests will expand inclusion of newly identified genes of interest. Indeed, any number of biotech companies has marker tests in development; alliances are actively being formed between these developers and centers with patient sample sets that could be used for validation.

A second trend in care, per expert sources, may be the decreased aggressive treatment of early stage cancers. Mortality data on >[redacted] patients over four decades suggests that there is no rationale for heavy treatment of tumors with a hormone receptor and metabolic phenotype indicative of a non-worrisome mass. Incorporated as SOC for advanced mBC, Avastin's large-scale trial data released in [redacted] failed to validate the initial promised for the drug, missing critical overall survival endpoints. In [redacted], the FDA revoked Avastin's conditional indication for use in mBC. This is expected to open gaps for alternate targeted therapies for treatment-refractory mBC, including alternate anti-angiogenesis compounds, such as Eli Lilly's ramucirumab.

The two most recent chemotherapies to become generic were gemcitabine (Gemzar in [redacted]) and docetaxel (Taxotere in [redacted]). Xeloda (Roche; capecitabine) faces patent expiry in [redacted], although Roche Legal has launched a strong effort to defend this patent for several years to come. The introduction of generics has been an unintended catalyst of the drug shortages now threatening drug access, albeit from a new quarter.

Early stage drugs may help shape the treatment landscape of breast cancer by the end of the decade. Though iniparib proved disappointing in its Phase III TNBC clinical evaluation (Sanofi-Aventis), research is encouraging on alternate PARP inhibitor (poly (ADP-ribose) polymerase inhibitor) candidates, such as Clovis Oncology's rucaparib phosphate, an early stage, potential first-in-class PARP inhibitor. This class could prove an important option for the TNBC (triple negative breast cancer) patient population, an often young patient group for whom there remains a huge unmet medical need. PARP inhibitors are also being actively evaluated in the clinical setting as chemosensitizers. Vaccines are in early development and are not expected in the short-term, but represent the best chance of achieving higher cure rates.

