Changing the Landscape for People Living with Metastatic Breast Cancer

Metastatic Breast Cancer
MBCalliance
together we are stronger than the disease

Metastatic Breast Cancer Landscape Analysis: Research Report

October 2014

Second Edition

MBC Alliance members:

From bottom right: Katherine Crawford-Gray, MBC Alliance Project Director; Christine Benjamin, SHARE; Elly Cohen, BreastCancerTrials.org; Jo Dulay, Genentech; Janine Guglielmino, Living Beyond Breast Cancer; Jane Levy, Cancer*Care*; Elyse Spatz Caplan, Novartis Oncology; Michael Zincone, Pfizer; Musa Mayer, AdvancedBC.org; Julissa Viana, Cara Thompson, Celgene Corporation; Margaret (Peg) Mastrianni, Breast Cancer Research Foundation; Christine Wilson, Triple Negative Breast Cancer Foundation; Shirley Mertz, Metastatic Breast Cancer Network, Stacy Lewis, Young Survival Coalition; Katherine O'Brien, Virginia (Ginny) Knackmuhs, Metastatic Breast Cancer Network; Megan McCann, Young Survival Coalition; Catherine Ormerod, Living Beyond Breast Cancer; Lisa Schlager, Facing Our Risk of Cancer Empowered (FORCE); Kimberly Sabelko, Susan G. Komen; Marc Hurlbert, Avon Foundation for Women; Virginia (Ginny) Mason, Inflammatory Breast Cancer Research Foundation; Hayley Dinerman, Triple Negative Breast Cancer Foundation; Diane Rose, FORCE; Susan Brown, Susan G. Komen; Allison Harvey, Cancer Support Community; Stephanie Reffey, Susan G. Komen; Kerry Gruninger, SHARE; Jane Perlmutter, Consultant; Amy Bonoff, Dr. Susan Love Research Foundation

Photographer: Yasmeen Anderson Photography

Members absent from photo as of March 2014:
Christine Verini, Eisai; Kelly P. Hodges , Sisters Network® Inc.; Hope Wohl, Breastcancer.org; Elda Railey, Mary Lou Smith, Research Advocacy Network

Metastatic Breast Cancer

MBCalliance

together we are stronger than the disease

Our Vision

MBC Alliance members are driven by a vision to transform and improve the lives of people living with metastatic breast cancer.

Our Mission

The MBC Alliance unifies the efforts of its members to improve the lives of and outcomes for those living with metastatic breast cancer and their families through increasing awareness and education about the disease and advancing policy and strategic coordination of research funding specifically focused on metastasis that has the potential to extend life, enhance quality of life, and ultimately to cure.

AdvancedBC.org
Cancer Action Network
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BreastCancerTrials.org
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CANCERcare
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Eli Lilly
Inflammatory
Breast Cancer
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Triple Negative Breast Cancer Foundation
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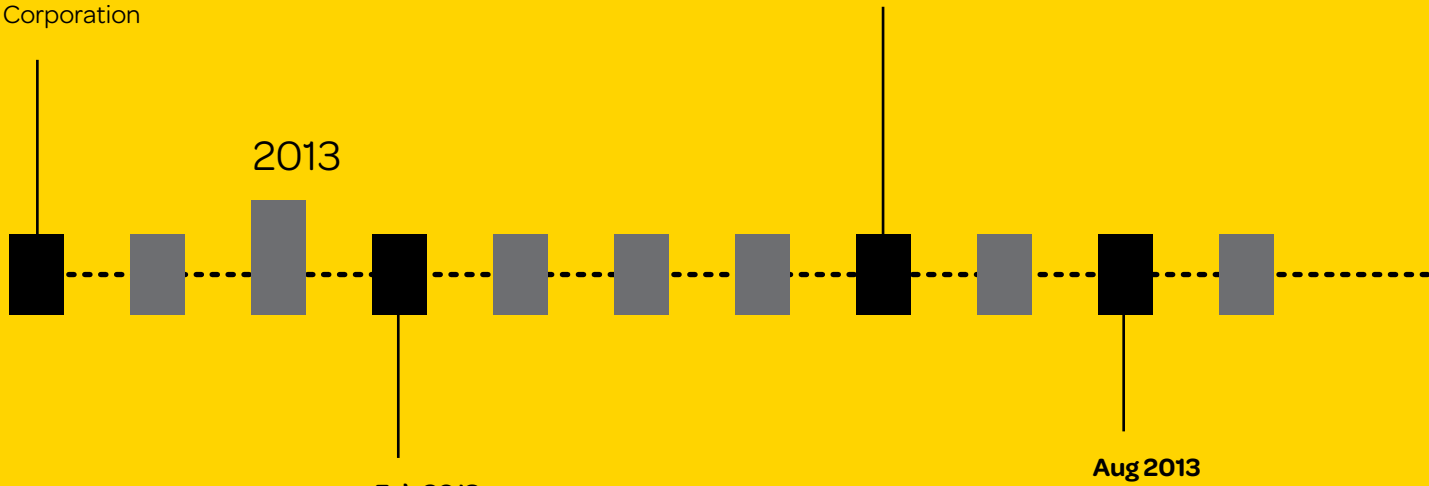
Nueva Vida
AdvancedBC.org
Avon Foundation for Women
Breast Cancer Research Foundation
CancerCare
Metastatic Breast Cancer Network
Pfizer
SHARE
Young Survival Coalition
Patient
Advocate
Foundation
FORCE

MBC Alliance

Nov 2012

Breast cancer nonprofits join MBC advocates to discuss how to increase MBC awareness and improve the lives of people living with MBC; all agree that through collaboration, far more can be achieved than by individual organizations; MBC Alliance is formed with support from Celgene Corporation



Feb 2013

Early members are AdvancedBC.org, Cancer Support Community, FORCE, Living Beyond Breast Cancer, Metastatic Breast Cancer Network, Research Advocacy Network, SHARE, Susan G. Komen, Triple Negative Breast Cancer Foundation, and Young Survival Coalition

Jun 2013

Mission and goals are adopted; governance approaches are considered; landscape analysis is identified as first initiative; Breastcancer.org, Breast Cancer Research Foundation, Genentech, and Pfizer join

Aug 2013

Avon Foundation for Women becomes the Alliance's administrative home with Dr. Marc Hurlbert as project leader

Oct 2013

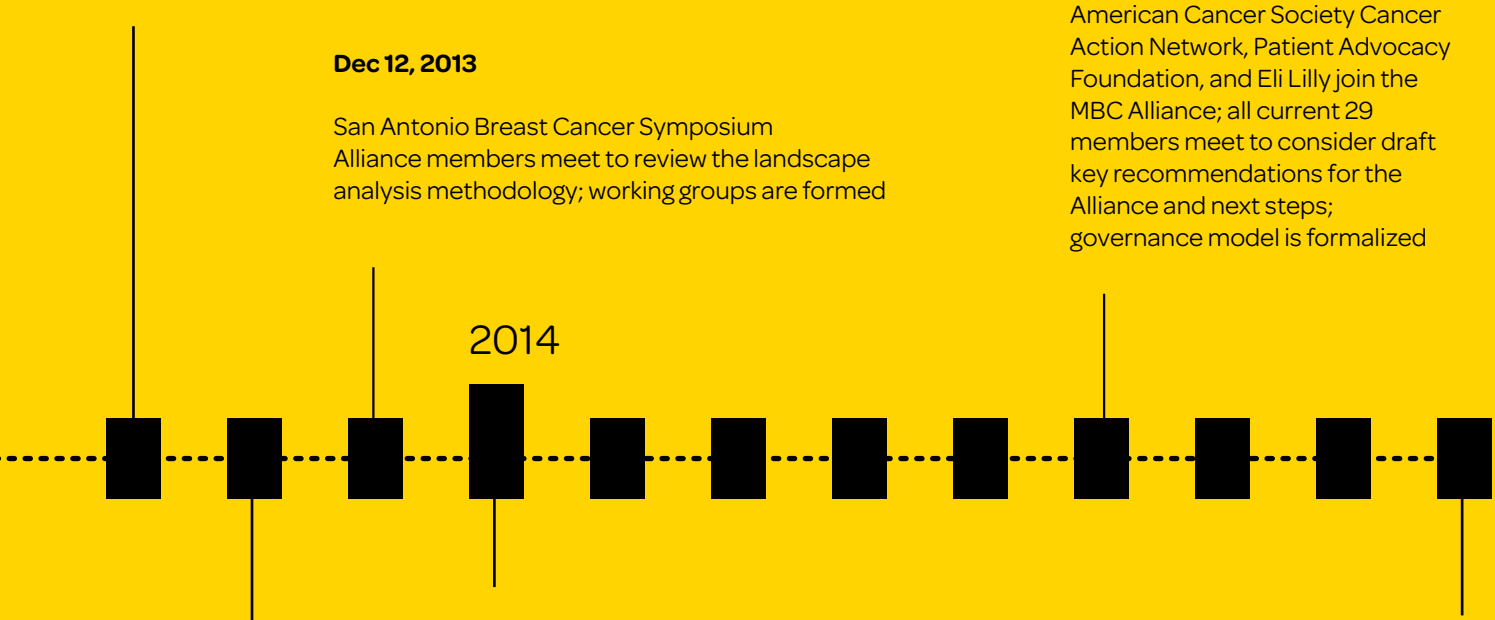
MBC Alliance launches on National Metastatic Breast Cancer Awareness Day; members now include Cancer*Care*, Dr. Susan Love Research Foundation, Sisters Network Inc., Eisai and Novartis

Dec 12, 2013

San Antonio Breast Cancer Symposium Alliance members meet to review the landscape analysis methodology; working groups are formed

Jun - Aug 2014

American Cancer Society Cancer Action Network, Patient Advocacy Foundation, and Eli Lilly join the MBC Alliance; all current 29 members meet to consider draft key recommendations for the Alliance and next steps; governance model is formalized



Jan - May 2014

Landscape analysis work continues; membership reaches 26 with the addition of BreastCancerTrials.org, Inflammatory Breast Cancer Research Foundation, Nueva Vida, Sharsheret, and Triple Step Toward the Cure

Oct 2014

Results of the landscape analysis are released along with actions for the MBC Alliance through 2016

Nov 2013

MBC Alliance project director is appointed; work begins on the landscape analysis; all members meet for the first time

Executive Summary

Why present another report about breast cancer?
Few would dispute that breast cancer has a higher profile than other types of cancer. Since the establishment of National Breast Cancer Awareness Month in the mid 1980s, a tremendous effort has been invested in messaging aimed at screening for early stage breast cancer, while celebrating those who survive diagnosis and treatment.

40,000 women and men still die of breast cancer every year in the US.

The dominance of the "breast cancer survivor" identity masks the reality that patients treated for early stage breast cancer can experience metastatic recurrence. The focus on survivorship obscures the fact that, in spite of decades of breast cancer awareness and research funding, **40,000 women and men *still* die of breast cancer every year in the United States (US)** [1] **with metastasis the cause of virtually all deaths from breast cancer.**

Metastatic breast cancer originates in the breast and then spreads to other parts of the body, such as bones, liver, lungs, or brain.

Metastatic breast cancer (MBC), also referred to as stage IV breast cancer, is an incurable, albeit treatable, progressive cancer that originates in the breast and then spreads to other parts of the body, such as bones, liver, lungs, or brain.

While some progress with research and new treatments has been made in reducing mortality rates from breast cancer, median survival after an MBC diagnosis is 3 years—and this has not increased meaningfully in more than 20 years[2]. Despite these statistics, research funding for MBC accounts for only 7% of the total breast cancer research investment.

While treatable, MBC remains incurable.

Currently, data are not collected on how many people experience a recurrence of early stage breast cancer as MBC or the number of people living with the disease. We have only estimates of how many women diagnosed with early stage breast cancer will experience a recurrence. For unknown reasons, their breast cancer returns after a few months or as long as up to 20 years or more after initial diagnosis. It is also *estimated* that at least 150,000 people of all ages and all racial and ethnic groups are living with MBC in the US[3].

Public messaging about the "cure" and survivorship is so pervasive that people diagnosed at stage IV with MBC can be stigmatized by the perception that they've failed to take care of themselves or undergo annual screening. With breast cancer organizations' main focus on detection and screening of early stage breast cancer, MBC patients and their caregivers face real challenges in finding MBC-specific support and information from these organizations. Further, many MBC patients persist in believing a cure is likely, and health care professionals do not always have the time and skill to discuss treatment options when the prognosis is poor.

A lack of awareness about MBC and how it differs from early stage breast cancer; little research funding to combat this unique and deadly disease; a lack of accurate statistics on incidence, prevalence, and survival; and difficulty in finding information and support services essential for people living with MBC—these are the issues that have defined the work of the Metastatic Breast Cancer Alliance (MBC Alliance) over the past year.

The MBC Alliance

Many patient advocate groups have been working to change the landscape of MBC. In 2012, representatives of breast cancer organizations joined with MBC patient advocates to discuss ways to change the persistent lack of understanding about MBC and how organizations could work together to provide better information and support services to people living with MBC. All agreed that more could be achieved through working together than could be achieved by working alone. Assistance for these early steps was provided by Celgene Corporation.

On October 13, 2013 (National Metastatic Breast Cancer Awareness Day), the MBC Alliance of 16 nonprofits and 5 pharmaceutical corporations was launched. Over the past year, the Alliance has experienced growth in its membership as new advocates and industry partners realized the Alliance's potential to create positive change and impact individual lives. Currently, there are 29 member organizations.

Recognizing the valuable current and future contributions of each member to the MBC field, the Alliance is committed in its approach not to duplicate efforts of its members. Collaboration and learning from others is vital if the Alliance is to have real impact in improving the lives of people living with MBC.

Landscape Analysis of MBC

As its first initiative, the Alliance undertook a landscape analysis to assess gaps, duplication, and opportunities in MBC research, patient information and support services, and public awareness to capitalize on identified opportunities, and identify the ways Alliance members could work together to meet the unique needs of those living with MBC.

Aspects of the MBC landscape examined by advocates and experts with knowledge and experience specific to the area of investigation were:

1. Scientific research, including clinical trials, focused on MBC
2. Quality of life of MBC patients and their families and caregivers
3. Information and support services provided by MBC Alliance members
4. Epidemiology of MBC: Challenges with population-based statistics
5. Public awareness of MBC.

5 Areas of MBC investigation:

Scientific Research
Quality of Life
Information and Support Services
Epidemiology
Challenges
Public Awareness.

Methods

The Alliance collected and reviewed multiple sources of data and information for the landscape analysis:

- Scientific research—a first time effort to analyze information on breast cancer treatment trials recruiting MBC patients in the US and information on breast cancer and MBC research grants awarded by most of the major cancer and biomedical research funding organizations. Interviews were conducted with 59 key opinion leaders with scientific expertise relevant to MBC research.
- Quality of life for MBC patients, and their families and caregivers—more than 150 published, peer reviewed articles relevant to the experience and needs of people living with the disease and 13 MBC surveys from 2006–2014 were analyzed.
- Information and support services specific to MBC—Alliance members were interviewed about their efforts in research, patient advocacy, patient education and support, and community awareness. Collateral materials, including surveys and research reports and information about services and support relevant to MBC, were collected from Alliance members. Member organizations' print and web-based materials were analyzed, and a short survey on telephone information/helplines was conducted.
- Epidemiology—the literature was reviewed to identify shortcomings in currently available population-based statistics relating to MBC.
- Public awareness of MBC—over the course of work of the landscape analysis, discussions among advocates, patients, and industry members at MBC Alliance meetings highlighted the need to educate the public about MBC. Members helped to compile information on common misconceptions around MBC and brainstormed actions for the Alliance to increase understanding.

Key Findings

MBC Scientific Research

More funds need to be directed to MBC research. MBC-focused research made up only 7% of the $15-billion invested in breast cancer research from 2000 to 2013 by the major governmental and nonprofit funders from North America and the United Kingdom. Specific scientific areas are understudied. The field of MBC research is relatively small.

- MBC research grants are focused on the metastasis steps of invasion and metastatic colonization, with far fewer studying intravasation and circulation, arrest and extravasation, or metabolic deregulation. Why these gaps exist in funding and research focused on these areas of the biology of metastasis need further exploration.
- The distribution of funding across stages of MBC research (basic, translational, clinical, and cancer control) has not changed over the past decade, with most funding going to support basic research. There is a paucity of research in MBC cancer control, outcomes, and survivorship.
- Research on mechanisms of disease in cell lines and animal models is usually focused on tissue taken from early stage, primary breast cancer, and not metastatic tumors. In addition, clinical trial endpoints such as tumor shrinkage may not have relevance to tumor spread or metastasis.
- More research is needed to understand all the steps of metastasis to develop new treatments for the multiple types of MBC and to understand how best to improve the quality and duration of the lives of women and men in whom breast cancer becomes metastatic.
- Barriers to clinical trials include too many "me-too" trials in industry and the academic "reward" system for single investigators conducting single-institution phase II trials. To accelerate MBC clinical research, these barriers must be broken down by the conduct of multi-institution, multi-investigator trials.

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Barriers to clinical trials include too many "me-too" trials in industry and the academic "reward" system for single investigators conducting single-institution phase II trials.

There is a paucity of research in MBC cancer control, outcomes, and survivorship.

Quality of Life for MBC Patients and their Families

Patients with MBC have unique emotional, physical, and psychosocial needs, and these have not changed over the last decade of academic research and patient surveys. The needs of minority and poor populations living with MBC have not been fully addressed in research or patient surveys.

Some estimates are that as many as one third of MBC patients suffer from mood disorders such as major depression and anxiety, and one quarter experience mild depression.

Fatigue is by far the most common physical symptom reported by MBC patients, occurring in 80% or more of those undergoing treatment.

Better communication among patients, caregivers and providers and better access to supportive and palliative care are needed.

- Emotional distress, experienced by a majority of MBC patients, is associated with increasing physical symptoms. Depression and anxiety are common, yet patients receiving mental health services are a minority; many methods exist for addressing psychosocial distress, most of which are underutilized.
- Most patients initially report adequate emotional support from friends, family, and community, but many feel isolated by the experience of the disease; social stigma is felt by half of MBC patients, especially within the breast cancer community.
- Individualized information about MBC is a critical factor for informed participation in treatment decision making. Information also plays an important role in coping by reducing uncertainty, lack of control, and distress.
- Many MBC patients do not receive adequate information from health care providers (HCPs) to enable them to understand the disease and its treatments so they can make informed decisions. Patients' understanding of the nature of the disease and goals of treatment is often poor; many believe they will be cured. Limitations of time and resources in busy oncology practices may result in poor patient–doctor dialogue, including one-way "doctor-knows-best" communication. MBC patients also report confusion about reliable sources of information.
- Most MBC patients suffer multiple symptoms of disease and side effects of treatment that disrupt their lives—most common are fatigue, pain, and sleep problems. Despite this, half of patients say they are not routinely asked about their symptoms and express concern about "bothering" their doctors.
- Financial hardship is a common issue for families dealing with MBC, and many patients do not realize they will likely qualify for Social Security Disability benefits or Medicare. Even, if eligible, the 2-year waiting period for Medicare represents a financially vulnerable time; many file for bankruptcy and face lower standards of living. Other practical needs may include transportation to treatment, home, shopping and child care, disability and insurance applications, and work-related issues, among others.
- A significant number of MBC patients report they are not receiving the help they need to address their physical symptoms, side effects from treatment, and emotional distress. Better communication among patients, caregivers and providers and better access to supportive and palliative care are clearly needed.
- Action and initiatives based on the findings from surveys of patients' needs, and other research, are lacking.

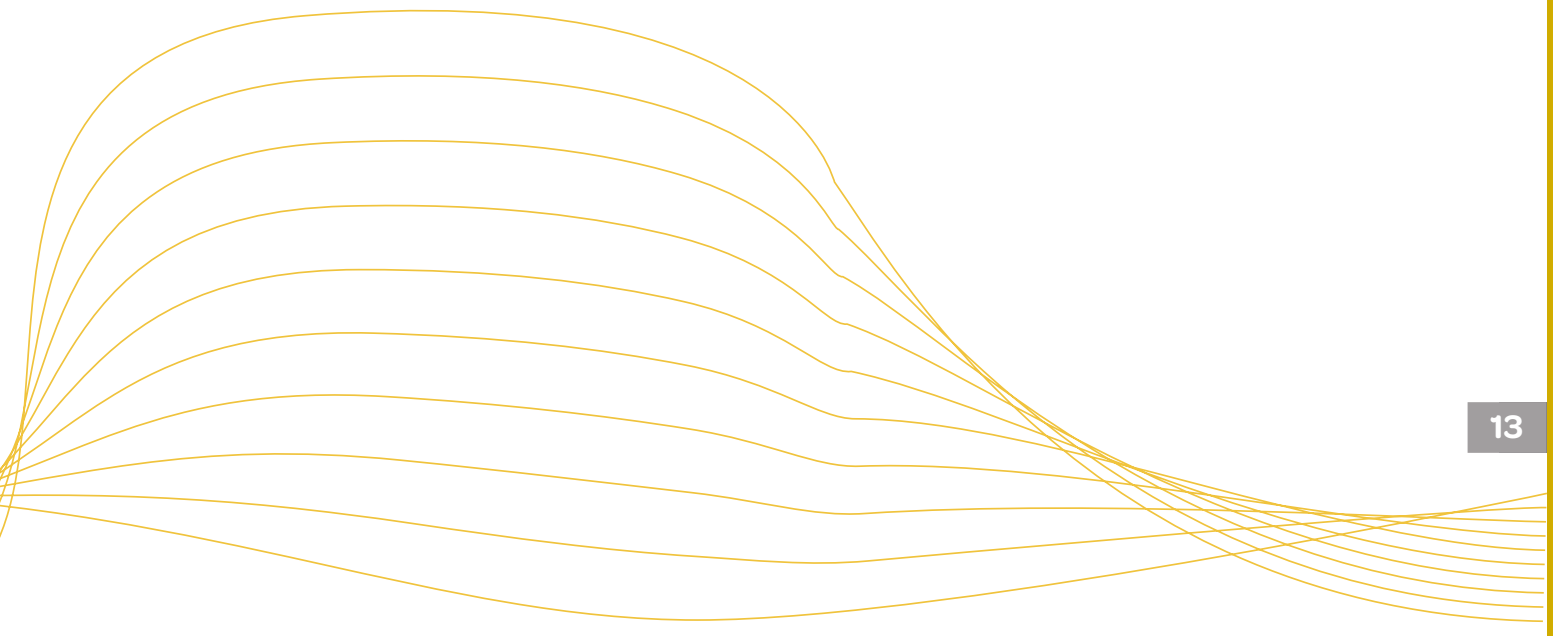
MBC Patient Information and Support Services

Alliance members, and others, need to improve consistency of information about MBC across agencies; better quantify the numbers of people living with MBC they are serving; understand what services are most often accessed; and expand reach into all communities regardless of socioeconomic status, gender, race, culture or geography.

- Quantitative data on the demographics and numbers of MBC patients accessing programs and services are not consistently collected. As a result, it is not known how patients use the tools, how the programs and services can be optimized, and which patients are not being reached.
- The majority of organizations report that their programs and services are underutilized, surmising that patients don't know about them, do not consider the programs to be suited to their needs, or are seeking information and support in other places.
- Many Alliance members provide high-quality information and support services to MBC patients and their families. However, the information provided requires that patients have relatively high health literacy and be Internet savvy. Organizations must consider how to reach other subgroups of the MBC patient population. Because Alliance members offer so much general information, it is difficult for individual patients to find what they need.
- Persistent gaps in MBC information on members' sites and in print include detailed information on the latest treatments; monitoring of treatment, including for side effects and quality of life; palliation; and advanced directives and end-of-life care. Information on how MBC is diagnosed could be improved, and there is a dearth of information on new drugs in clinical research.
- Alliance member websites do not address MBC facts sufficiently to inform the MBC patient populations or even caregivers and early stage breast cancer patients. More content and community can be created by enhancing current information, using a modern design, and adding tools for social networking.

Information and support are not distinct from one another. MBC patients find information to be supportive and seek information from their support systems; thus, services for MBC patients should refer to both.

Nearly half of MBC patients surveyed say they find the information they need difficult to locate and confusing, and that what they do find doesn't fully address their needs.



Epidemiology of MBC

Better epidemiologic data are needed on the numbers of early stage breast cancer patients who experience a recurrence and metastasis and on outcomes and length of survival after a metastatic diagnosis. Only modest improvements in survival after a metastatic diagnosis have been observed, and not in all populations.

Data are not collected on how many people experience a recurrence of early stage breast cancer as MBC, or the number of people living with the disease.

Today, an estimated 3.1 million women living in the US have a history of breast cancer, but we have no way of knowing how many of these people are actually living with MBC.

- Over the past few decades, the duration of survival after metastatic diagnosis has increased modestly—by a matter of months, not years. Hospital-based studies generally report a larger survival benefit than population-based studies.
- The modest increase in survival has been observed mainly in ER+ (estrogen receptor positive/hormone sensitive) MBC and/or HER2+ (human epidermal growth factor receptor 2–positive) MBC and is attributable to the wide use of targeted therapies. No survival benefit has been found in triple-negative MBC.
- The disparity in survival between black women with MBC and non-Hispanic white women with MBC appears to be increasing. It is unclear how much of the observed disparity in outcome is related to access to care and socioeconomic concerns and how much is related to the greater incidence of triple-negative MBC among black women.
- The prevalence and incidence of patients with MBC is unknown. Also unknown is whether the number of recurrent MBC patients is increasing, decreasing, or staying the same. Without this information, we cannot accurately and effectively demonstrate the need for services or plan and fund the application of services.
- Disease trajectories, outcomes, and patient experiences for the different subtypes of MBC have not been well characterized.
- Many critical questions regarding the optimal treatment of MBC remain unresolved. It is imperative that the use, effectiveness, and impact of MBC treatments on the overall MBC population be understood.
- Despite existing research, we have no accurate estimate of how long MBC patients are likely to live. The factors underlying observed variability in median survival across studies are unknown. Among the potential factors are differences in access to newer drugs (especially targeted therapies) and multiple lines of treatment, access to careful follow-up and expert palliative care to preserve optimal quality of life, and the presence of co-morbidities.
- Despite research demonstrating poorer outcomes for disadvantaged, underinsured populations overall, the true impact is unknown of socioeconomic factors on what treatments and care are available for MBC patients and, in turn, how this may affect duration of survival and quality of life.

Public Awareness of MBC

A greater understanding of what MBC is and how it differs from early stage breast cancer is needed among patients, their families and HCPs, researchers, and the public.

- The focus on "fighting" and "beating" breast cancer has led to the creation and dominance of a breast cancer "survivor" identity, which masks the reality that women who have had early stage breast cancer can develop metastatic disease.
- The focus on screening and survivorship can stigmatize patients who experience a recurrence or are diagnosed at stage IV—they may be perceived to be at fault for the cancer's progression.
- The effects of public and professional misconceptions or lack of understanding about MBC can negatively influence decisions made by patients and their doctors regarding treatment and quality of life.
- More can be done to build the understanding of HPCs about how to discuss treatments and quality of life, including palliation with their patients.

"The deaths of 108 people today from MBC will not make the nightly news. If they did, most of the public might be surprised, but then conclude that these women and men probably did not get a mammogram early enough, or fight the disease hard enough."
Shirley Mertz, SABCS 2013

Analysis to Action

This landscape analysis has provided the Alliance with a foundation of shared knowledge of the MBC landscape and pointed us to some critical gaps/needs to be addressed. Collectively, we are now better informed about the areas of scientific research for further exploration, the need to accelerate improvement in quality of life, the gaps in information and support services that require resources, and the current state and limitations of the epidemiology of MBC.

One of the forces that drove breast cancer and MBC advocate organizations to join in an Alliance was the need to build understanding about the different types of MBC and how it differs from early stage breast cancer, not just for people living with the disease and their HCPs, but also researchers, policy makers, and the general public.

In moving forward, MBC Alliance members agree that pivotal to resolving gaps/needs is an effort to build greater understanding in all our future endeavors.

The power of the Alliance lies in our collective experience, resources, and spheres of influence. Guiding our approach to future work is a commitment to not duplicate efforts of individual organizations in the Alliance, and to collaboration to ensure we learn from each other's experience and research. As our work is resource intensive and time consuming, we will be thoughtful in committing our assets and will develop an evaluation framework as part of our planning for 2015–2016.

We have identified a series of actions for our next phase of work over 2015 and 2016. These actions require sustained commitment of multiple stakeholders and MBC Alliance members stand ready to contribute time and energy to this work.

We look forward to reporting on our progress in 2015.

MISSION

Unify the efforts of members to improve the lives of and outcomes for those living with metastatic breast cancer and their families through increasing awareness and education about the disease and advancing policy and strategic coordination of research funding specifically focused on metastasis that has the potential to extend life, enhance quality of life, and ultimately cure.

advance research

GOAL 1

Advance research focused on extending life, enhancing quality of life, and ultimately ending death from MBC

MBC Alliance Think Tanks (2015)
Convene small think tanks of experts and advocates to investigate the data from the landscape analysis and prioritize research gaps.

MBC Summit (2016)
Convene summit of scientists and medical experts from the private and public sectors, along with patients to identify collaborative approaches for metastatic research.

Clinical Trials
Advocate for new trial designs incorporating new end points.

Assess feasibility of establishing a national tissue registry of paired primary and MBC tissue and blood for use by all researchers.

improve knowledge + access

GOAL 2

Improve knowledge by ensuring all patients and their caregivers know how to and can access the care and services they need from a responsive and well-informed health care system

Knowledge and Information Sharing
Facilitate stronger collaboration and sharing amongst Alliance members and other stakeholders with webinars, town halls, and newsletters to improve and extend services for people living with MBC.

MBC Information Project
Investigate with partners the potential to create an independent, up-to-date collection of evidence-based and trusted MBC information.

Empower Project
Building on the work of Alliance members, investigate how to better address information gaps for patients and caregivers, with a focus on underserved communities, as well as physicians.

Potentially pilot new decision-making tools with small groups of health professionals and patients with the aim of strengthening communication between patients and HCPs.

increase understanding

GOAL 3

Increase understanding of MBC and how it differs from early stage breast cancer among those diagnosed, their families, HCPs, researchers, and health policy experts

Public Awareness
Develop with communications researchers main messages that educate people about MBC and how it differs from early stage breast cancer.

Explore how to best leverage the communication capacity of Alliance members to implement a MBC public awareness campaign.

Epidemiology Pilot Project
Collaborating with other agencies and registries, initiate a pilot study designed to achieve more accurate data about the prevalence and disease course of MBC.

Abbreviations:
HCPs = health care providers
MBC = metastatic breast cancer

Table of Contents

Foreword

The slogan of the Metastatic Breast Cancer Alliance (MBC Alliance)—*together we are stronger than the disease*—is not an empty claim. Each year approximately 40,000 women and men will die of metastatic breast cancer (MBC) in the United States. This number has remained unchanged for over a decade. Given the devastating toll this disease takes, the MBC Alliance members—29 cancer, breast cancer, and MBC advocacy organizations, individuals, and industry partners—have come together to transform and improve the lives of people living with MBC. This collaboration is truly the "first of its kind" for breast cancer, with all advocate and industry members committed to working together, openly sharing resources and information.

Since the MBC Alliance's public launch on October 13, 2013, we have been conducting a comprehensive landscape analysis of the needs of people living with MBC and the available information and support services. We have also been looking at funding of MBC research, the analysis of which will help to identify the needs and gaps for future funding.

This is exciting work! In inquiring whether the psychosocial and quality of life needs of MBC patients are being met, we have looked at what gaps exist in information and support available to those living with MBC today and how we can improve our own organizations and programs. We have also conducted a comprehensive assessment of MBC research that has been funded since the year 2000, spanning basic research, clinical trials, epidemiology, and quality of life and psychosocial research.

The purpose of the analysis is to learn from recent patient surveys, comprehensive research-gap analysis, and our own new analysis of the literature, clinical trials, and grant funding in order to develop actions that MBC Alliance members and others can implement to improve outcomes for people with MBC.

It is an honor for me to lead the MBC Alliance as it launches. The Avon Foundation for Women is able to provide a much-needed "neutral place" for the Alliance's early work. I am delighted that the Avon Foundation will be working alongside MBC Alliance members to begin tackling some of the challenges and implementing the critical actions highlighted in this report.

Marc Hurlbert, PhD
Project Leader, MBC Alliance Landscape Analysis
Executive Director, Breast Cancer Crusade, Avon Foundation for Women

Acknowledgments

The MBC Alliance is grateful to the many organizations and individuals who volunteered their time, particularly the women and men living with MBC who shared their personal experiences and advice.

The landscape analysis in Chapter 2 reflects the contributions of key opinion leaders including scientists, medical teams, advocates, journalists, policy makers, other stakeholders, and various consultants.

Special thanks to Elly Cohen and Susan Colen for analyzing currently active MBC clinical trials and to Lynne Davies and the International Cancer Research Partnership (ICRP) for helping with the funded grants analysis.

Special thanks also to Musa Mayer for her work in researching quality of life and epidemiology.

Sincere thanks to Celgene Corporation, Genentech, Eisai, Eli Lilly, Novartis Oncology, and Pfizer for providing financial support for the Alliance in 2013 and 2014. Also, thank you to the Avon Foundation for Women—the administrative home for the Alliance.

The landscape analysis was overseen by a steering committee and working group structure comprised of representatives of member organizations.

Steering Committee

Musa Mayer, AdvancedBC.org; Marc Hurlbert, Avon Foundation for Women; Cara Thompson, Celgene Corporation; Virginia (Ginny) Knackmuhs, Shirley Mertz, Metastatic Breast Cancer Network; Kelly P. Hodges, Sisters Network Inc.; Kimberly Sabelko (replacing Stephanie Reffey), Susan G. Komen

Working Groups

Information and Services

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Governance

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Corrine Ellsworth Beaumont, PhD (http://corrinebeaumont.com)

Acronyms and Other Terms

advanced breast cancer	includes both metastatic breast cancer and locally advanced breast cancer (stage III) and locally recurrent breast cancer
Akt	a serine/threonine-specific protein kinase
BRCA mutation	mutation in the tumor-suppressor gene *BRCA1* or *BRCA2,* associated with hereditary breast cancer
CSO	Common Scientific Outline (www.icrpartnership.org/CSO.cfm)
de novo MBC	breast cancer that is metastatic at the time of *first* diagnosis
ER–	estrogen receptor negative/hormone insensitive breast cancer
ER+	estrogen receptor positive/hormone sensitive breast cancer
ErbB	epidermal growth factor receptor (protein family)
gHRAsp	Grants in the Health Research Alliance Shared Portfolio (www.ghrasp.org),
HCPs	HCPs
HER2	human epidermal growth factor receptor 2
hormone-sensitive MBC	MBC where tumor growth is promoted by estrogen and/or progesterone
HRA	Health Research Alliance
ICRP	International Cancer Research Partnership
incidence	Rate of occurrence of new cases in the population (measure risk of developing a disease)
IOM	Institute of Medicine
KOL	key opinion leader
MBC	metastatic breast cancer
MBC Alliance	Metastatic Breast Cancer Alliance (also called the Alliance)
mTOR	mechanistic target of rapamycin (serine/threonine protein kinase)
NCI	National Cancer Institute
PDQ	Physician Data Query
PI3K	phosphatidylinositide 3-kinase
prevalence	proportion of cases in the population (measures how widespread the disease is)
RECIST	Response Evaluation Criteria in Solid Tumors
SEER	Surveillance, Epidemiology, and End Results program of the National Cancer Institute (NCI)
stage IV breast cancer	another term for metastatic breast cancer
TBCRC	Translational Breast Cancer Research Consortium
TN MBC	triple-negative (hormone insensitive and HER2-negative) metastatic breast cancer
TNBC	triple-negative (hormone insensitive) breast cancer
US	United States


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CHAPTER 1: INTRODUCTION

Metastatic breast cancer (MBC), also known as stage IV, is an incurable, albeit treatable, progressive cancer that originates in the breast and then spreads or metastasizes to other parts of the body such as bones, liver, lungs, or brain.

MBC is the cause of virtually all deaths from breast cancer. For people diagnosed with MBC, managing the disease becomes part of their daily life. Patients change treatments as drugs cease to work and the cancer progresses. Psychologically, the emotional distress of an MBC diagnosis can be worse than that of diagnoses of early stage breast cancer[4]. Public messaging about the "cure" and survivorship is so pervasive that people diagnosed at stage IV with MBC can be stigmatized by the perception that they've failed to take care of themselves or undergo annual screening. The challenges patients and their caregivers face in finding MBC-specific support and information from the organizations focusing on early stage breast cancer can exacerbate feelings of loneliness and isolation.

Driven by a desire to address the unique needs of those living with MBC, advocate organizations have joined forces as the Metastatic Breast Cancer Alliance (MBC Alliance) to address these challenges. The MBC Alliance brings together some of the most active advocates for patients with breast cancer, the 3 largest private funders of breast cancer research in the US, and 6 pharmaceutical corporations. The Alliance was publicly launched on MBC Awareness Day—October 13, 2013—when it announced its first initiative, a landscape analysis that sought to:

- Assess gaps, duplication, and opportunities in MBC research, patient information and support services, and public awareness to capitalize on identified opportunities, and
- Identify the ways in which Alliance members could work together to meet the unique needs of those living with MBC.

We are pleased to present the following body of work, which is the outcome of research undertaken over the past year by the MBC Alliance. Patient advocates and experts with knowledge and experience specific to the area of investigation examined various aspects of the MBC landscape:

- Scientific research, including clinical trials, focused on MBC
- Quality of life of MBC patients and their families and caregivers
- Information and support services provided by MBC Alliance members
- Epidemiology of MBC: Challenges with population-based statistics
- Public Awareness of MBC.

Chapter 2 reviews the landscape of scientific research with a distillation of data from clinical trials, funded biomedical research grants, and interviews with key opinion leaders (KOLs).

Chapter 3 provides a comprehensive review of the available quality of life literature and psychosocial research of patients living with MBC. This section shares learning about psychological distress, emotional support, and the communication issues with HCPs.

Chapter 4 describes internal research of Alliance members' information and support services to better understand gaps and opportunities for improving the quality of life for people living with MBC.

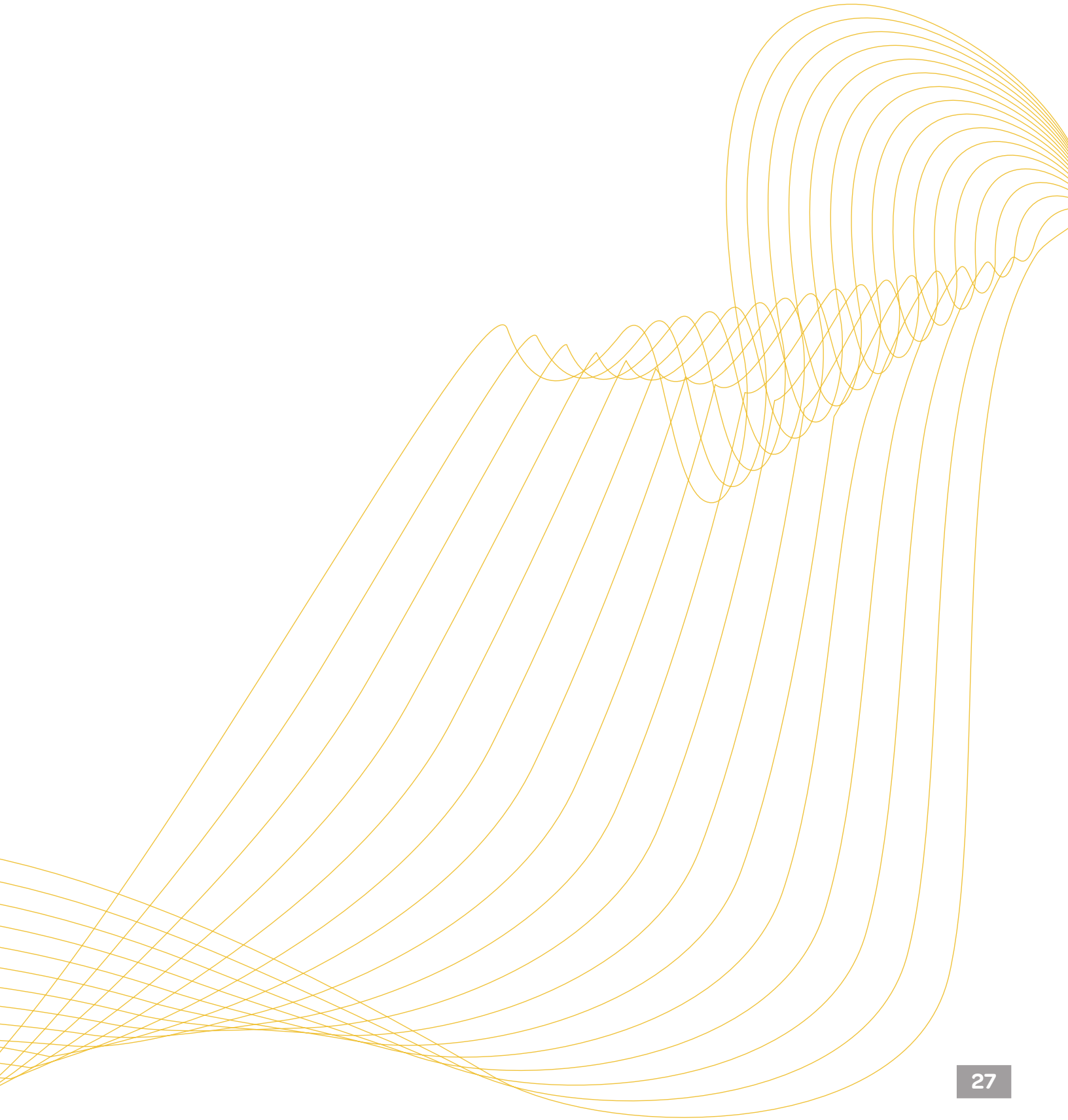
Chapter 5 investigates the limitations around accurate epidemiologic statistics collected or the lack thereof for patients with MBC, such as National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registries that capture only incidence, initial treatment, and mortality.

Chapter 6 looks at the lack of understanding about MBC, which has very real implications for patients. A greater understanding of what MBC is and how it differs from early stage breast cancer is needed among caregivers and HCPs, insurers, policy makers, researchers, and other key stakeholders, including people living with MBC and those with breast cancer.

The main findings from our research will lay a solid foundation for the Alliance's work over 2015 and 2016. In the final chapter of this report, Chapter 7, we outline actions for 2015–2016 that align with our 3 goals:

1. Advance research focused on extending life, enhancing quality of life, and ultimately ending death from MBC.
2. Improve knowledge and access by ensuring all MBC patients and their caregivers know how to and can access the care and services they need from a responsive and well-informed health care system.
3. Increase understanding of MBC and how it differs from early stage breast cancer among those diagnosed, their families, HCPs, researchers, and health policy experts.

We look forward to reporting on our progress in 2015.



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CHAPTER 2: LANDSCAPE ANALYSIS OF MBC RESEARCH

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Avon Foundation for Women, [2]BreastCancerTrials.org, [3]Susan G. Komen, [4]AdvancedBC.org, [5]National Cancer Institute,[6]California Breast Cancer Research Program, [7]National Breast Cancer Foundation (Australia), [8]Inflammatory Breast Cancer Research Foundation, and [9]International Cancer Research Partnership

Abstract

One part of the MBC Alliance's mission is to advocate for and support research focusing on extending life, enhancing quality of life, and ultimately ending death from the disease. To inform these efforts we conducted a landscape analysis of MBC research by analyzing active clinical trials and previously funded research grants and conducting interviews with KOLs. ***Methods:*** We used a mixed-methods approach that included quantifying numbers of clinical trials and funded research grants and qualitative interviews with KOLs. We captured relevant aspects of the clinical trials and research grants for categorization and also assigned both trials and grants into the Hallmarks of Cancer framework[5] or Steps of Metastasis framework [6], where feasible. ***Results: Clinical trials.*** We identified 224 clinical trials actively recruiting MBC patients through the NCI Physician Data Query (PDQ) dataset: 169 trials of targeted therapies, 35 chemotherapy trials, and 20 trials focusing on specific organ sites. Most (162) of the 169 trials of targeted therapies for MBC addressed 7 of the 10 hallmarks of cancer, including 95 trials of drugs that target sustained proliferative signaling and 27 trials of drugs that target immune escape mechanisms. Among the 169 targeted therapy trials there were 17 phase III trials, 54 phase II trials, and 96 phase I or phase I/II trials (note phase was not listed for 2 trials). We also identified 118 new drugs, vaccines, or combinations thereof being tested as targeted therapies, including 26 drugs targeting the PI3K/Akt/mTOR pathway, 20 targeting the epidermal growth factor receptor (ErbB) family, and 10 targeting hormone receptors. ***Grants.*** A search of 2 databases housing research grants from the majority of the cancer research funding organizations around the world revealed 20,800 funded research grants relevant to breast cancer, totaling $15.0 billion. Of these, we identified 2281 grants (11%), specifically relevant to MBC totalling $1.07 billion (7.1%). The majority of MBC grants focused on either invasion (36%, n=815) or metastatic colonization (29%, n=670); several other grants focused on multiple steps in metastasis (10%, n=238), whereas others could not be assigned to a specific step (13%, n=295). The grants relevant to MBC are predominantly basic research (69%), with some

translational research (24%), clinical research (6%), and cancer control research (1%). The percentage of grants in either database addressing particular research areas did not vary substantially from 2000 through 2013. ***KOL interviews.*** We interviewed 59 KOLs in the MBC space. Four main themes arose from these interviews: (1) the need for a tissue bank that matches primary tumors with metastatic tumors, (2) the need to standardize metastatic preclinical models, (3) the need to redesign clinical trials for MBC to measure new endpoints (beyond MBC tumor shrinkage and Response Evaluation Criteria in Solid Tumors [RECIST] scale) and to coordinate the trials across multiple investigators and institutions, and (4) the need to diversify clinical R&D funds to invest in promising new targets, noting there are too many "me too" drugs, such as PI3K. **Conclusions:** We were able to successfully categorize most targeted therapies in clinical trials according to the hallmarks of cancer, and research grants could be categorized according to the steps of metastasis. In addition, the data gathered from funded research grants and clinical trials was consistent overall with the research needs identified by KOLs. The next steps are to better understand why gaps in certain areas exist and develop strategies to address those gaps.

Introduction

One of 3 mission areas of the Alliance is to advance research focused on extending life, enhancing quality of life, and ultimately ending death from MBC. To determine how best to advocate for research in MBC, the Alliance conducted a landscape analysis of MBC research in addition to separate assessments of patient needs and quality of life (see **Chapter 3**) and information and services available for patients (see **Chapter 4**).

The Alliance's research landscape analysis is an effort to identify gaps in and opportunities for MBC research by analyzing currently active clinical trials and information on previously funded biomedical research grants as well as by interviewing KOLs in the MBC space. By understanding and reporting on MBC research gaps and opportunities, Alliance members and others can advocate for, and potentially fund, the MBC research that is most needed.

The Alliance believes this exercise of reviewing and categorizing MBC research and understanding key expert opinions will enable us to target our own efforts and to inform the larger cancer community. Our goal is to advance research more rapidly and help accelerate the development of new treatments that extend the life span of, while maintaining a high quality of life for, people living with MBC.

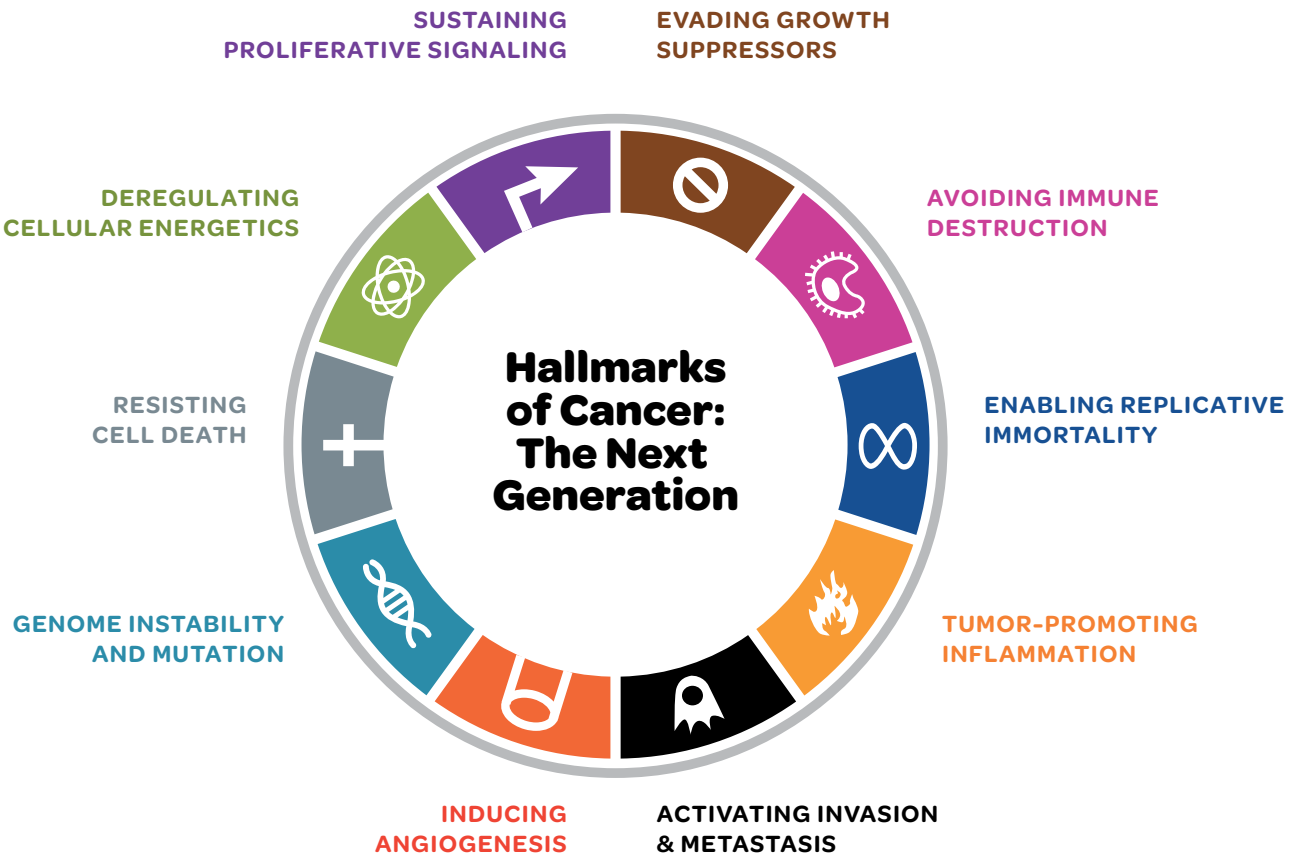
Methods

We used a mixed-methods approach to our landscape analysis of MBC research, including both quantitative aspects (classification and quantification of clinical trials and grants) and qualitative aspects (KOL interviews). The Alliance used 2 leading frameworks about cancer development and metastasis (**Figure 1** and **Figure 2**) in order to categorize and group MBC research information. The Hallmarks of Cancer framework, recently updated by Hanahan and Weinberg, includes 8 hallmarks of cancer and 2 enabling characteristics that describe biological capabilities acquired during the multistep development of human tumors and takes into account the tumor microenvironment[5]. The second framework, the "Steps in Metastasis," describes the mechanistic insights of tumor metastasis[6, 7]. This framework describes the steps necessary for tumor metastasis—including invasion outside of the primary tumor and into nearby tissues, entering of the lymphatics or bloodstream (called intravasation), surviving, avoiding immune attack and eventually arresting the circulation, entering a new organ site (called extravasation), and then growing in the new organ (called metastatic colonization)[6]. These frameworks encompass understanding the period of tumor dormancy, the need for angiogenesis, and tumor–host cell interactions. Clinical trials were assigned to the Hallmarks of Cancer framework, when applicable, and funded research grants were assigned to the Steps in Metastasis framework, where sufficient information was available in research summaries for this purpose.

Clinical Trials Analysis

We extracted clinical trials information on all phase I, II, and III breast cancer treatment trials that were recruiting patients with MBC in the United States (US) in April and May 2014 from the NCI PDQ database, which imports information on all cancer trials registered in ClinicalTrials.gov. We also included trials in solid tumors if they were tagged for breast cancer and therapeutic trials that targeted patients with BRCA mutations (associated with hereditary breast cancer), regardless of metastatic status. We manually categorized these trials (into a single category, even if potentially applicable to > 1) according to whether their interventions were a targeted therapy, chemotherapy, or therapy directed at a specific metastatic site such as brain, liver, or bone. Targeted therapies were defined as agents that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") involved in the growth, progression, and spread of cancer[8]. The targeted-therapy trials were further manually assigned to the Hallmarks of Cancer framework[5]. For each study, we also captured the investigational agent and its biological target (where appropriate), required tumor biomarkers, and trial phase. We reviewed the list in August 2014 to note trials that were no longer recruiting patients, as noted in **Appendix 1**.

Figure 1: Hallmarks of Cancer Framework by Hanahan and Weinberg[5] Used for Trials

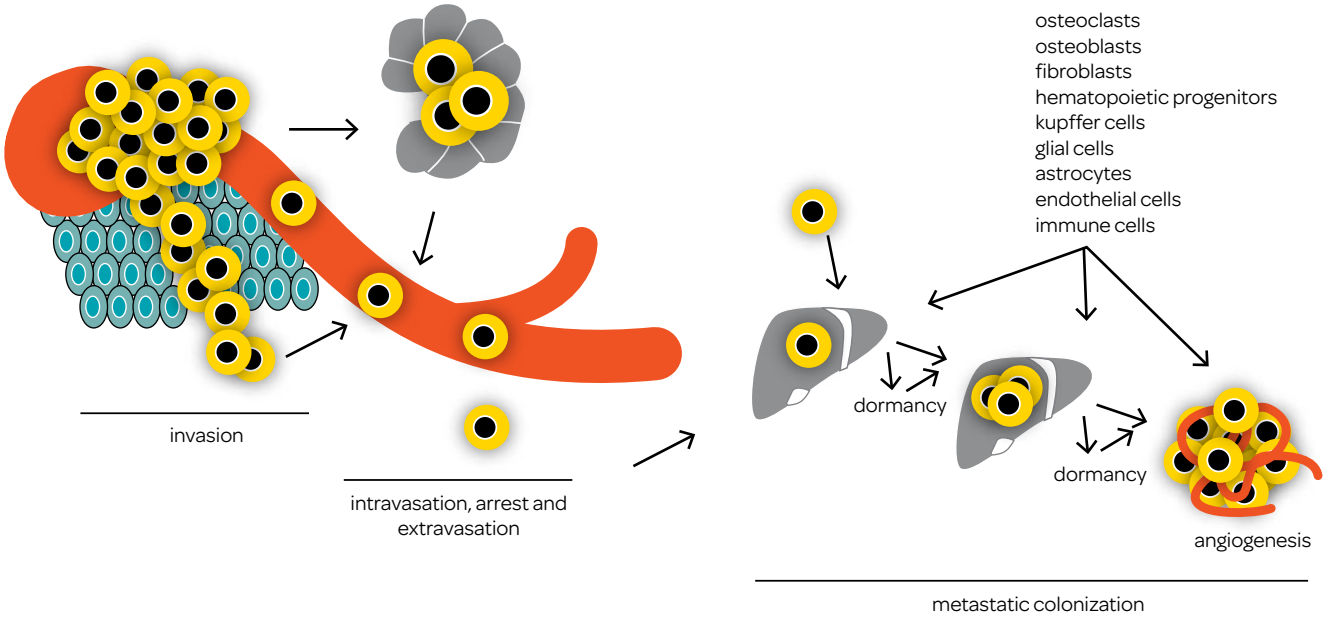


Funded Research Grants Analysis

Information on research grants awarded by most major cancer and biomedical research funding organizations was extracted from 2 databases: the International Cancer Research Partnership (ICRP) database and the Health Research Alliance (HRA) database.

Established in 2000, the ICRP is a unique alliance of cancer research funding organizations working together to enhance global collaboration and strategic coordination of research[9]. The ICRP aims to improve access to information about cancer research being conducted and enable cancer funding organizations to maximize the impact of their independent efforts for the benefit of researchers and cancer patients worldwide. The ICRP includes organizations from Australia, Canada, France, Japan, the Netherlands, United Kingdom, and US. ICRP member organizations share funding information in a common format (known as the Common Scientific Outline [CSO]) to facilitate the pooling and evaluation of data across organizations[10-12]. The database includes grants from both government and private, nonprofit cancer research funding organizations from within the ICRP member countries, including the US National Institutes of Health. (For a complete list of ICRP members and CSO codes, see www.icrpartnership.org.)

Figure 2: Steps in Metastasis Framework by Steeg[6], Used For Grants



Abbreviations: BH3 = pro-apoptotic member of the Bcl-2 protein family; anti-CTLA4 mAb = anti–cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody; EFGR = another term for ErbB, the epidermal growth factor receptor protein family, , HGF/c-Met = hepatocyte growth factor/MET proto-oncogene, receptor tyrosine kinase; PARP = poly-ADP ribose polymerase, VEGF = vascular endothelial growth factor.

The HRA was established in 2005 as an alliance that fosters collaboration among nonprofit, nongovernmental funders to support health research and training across a continuum of biomedical science applications that advance health. The HRA also has a shared grants database called Grants in the Health Research Alliance Shared Portfolio (gHRAsp, www.ghrasp.org), which has been previously described[13]. Importantly, gHRAsp includes funded grant information from cancer funders that are not part of the ICRP, including Breast Cancer Research Foundation, and large foundations that are not cancer specific, including the Burroughs Wellcome Fund, Doris Duke Charitable Foundation, Howard Hughes Medical Institute, and others. (For a complete list of HRA members, see www.healthra.org.)

Research grants were extracted from the ICRP and HRA databases using combinations of keywords (breast cancer and metastasis, metastatic, metastases, metasta*, advanced or stage IV) followed by manual validation to ascertain their relatedness to MBC, creating a MBC Grants Dataset. Duplicate grants were removed (e.g., grants from the American Cancer Society, Avon, and Komen that were in both databases). For grants in the ICRP database, we limited our analysis to those identified as having at least 50% relevance to breast cancer (vs. relevance to many or all cancers). We then manually reviewed a random sample (n=100) of grants in the MBC Grants Dataset to validate our search and data extraction strategies. The abstracts of the grants within the random sample confirmed to be relevant to MBC were then used to manually classify each grant in the full MBC Grants Dataset according to the categories in **Table 1**; key information on targets and therapies under study was extracted. A team of 8 volunteer coders manually assigned the grants in the MBC Grants Dataset to the metastatic stage corresponding to key parts of the Steps in Metastasis framework and Hallmarks of Cancer framework. These assignments were reviewed and validated by 2 additional coders who reviewed the entire dataset. Grants were also categorized by model system or study type as preclinical research, technologic development, or therapy/intervention. The research stage (basic, translational, clinical, or cancer control research) was assigned by mapping the framework assignments to CSO codes. These assignments were manually validated.

We extracted the grant information into a large spreadsheet with multiple pivot tables and analyzed the number of grants and dollar amount of funding in each category over time. We also developed a comprehensive list of molecular targets, pathways, and therapies identified in abstracts of the funded grants.

Table 1. Classification Schemes Used for Research Grants

Main Category	Subcategory
Metastatic stage (from Steps in Metastasis framework)	• Invasion [5, 6] • Intravasation & circulation [6] • Arrest & extravasation [6] • Immune surveillance/escape [5, 6] • Metastatic colonization [6] • Metabolic deregulation [5] • Other • Not specified/not relevant
Research stage (from CSO codes)	1. Basic 2. Translational 3. Clinical 4. Cancer control 5. Other
Model System or Study Type	• Preclinical research (model system/cell line/gene hunt) • Technologic developments (diagnostic/prognostic/imaging) • Therapy/intervention
Molecular Target	• Free text (e.g., MAPK, CDK6)
Pathway	Free text (e.g., name of signalling pathway)
Therapy/Intervention	Free text (e.g., name of drug, therapy,or diagnostic tool)

Abbreviations: CDK6 = cyclin-dependent kinase 6, CSO = Common Scientific Outline, MAPK = mitogen-activated protein kinases.

Interviews with Key Opinion Leaders

The qualitative part of our research landscape analysis included interviews with experts from various sectors relevant to MBC research, including advocacy and nonprofit organizations, academic and medical institutions, government agencies, pharmaceutical and biotechnology organizations, professional societies, and clinical trials cooperative groups (a complete list can be found in **Appendix 2**).

All Alliance members were asked to suggest experts they believed we should interview, including members of their organization's medical and scientific advisory boards or external scientists believed to be leaders in metastatic research. In addition, we identified experts to be interviewed from those listed as the principal investigator on multiple awards from the MBC Grants Dataset. The experts interviewed had expertise in basic laboratory research, clinical trial design and execution, health care and research policy, patient-reported outcomes, and quality of life research.

Seven questions were asked of each KOL interviewed:

1. What exciting scientific opportunities do you see for advancing our understanding of metastasis?
2. What do you think is the most promising target for developing new therapeutics aimed at metastasis?
    a. Cancer stem cells in tumors
    b. Cell invasion from the breast
    c. Tumor dormancy
    d. Tumor cell avoidance of immune surveillance ("immune escape")
    e. End-organ microenvironment
    f. Cell signaling and proliferation
    g. Other
3. What gaps or roadblocks exist that hinder advances in MBC research?
4. What role do you see for markers or circulating tumor cells, circulating tumor DNA, or other?
    a. Companion diagnostics (for new agents)
5. Can you describe MBC clinical trials you are involved with conducting?
    a. Challenges in designing and conducting trials for MBC
    b. Current pipeline of trials or products planned for MBC trials
6. Are there other aspects of MBC research we should discuss?
7. Whom else should we interview?

Each interview was conducted by 2 Alliance staff. Each interview was recorded and the interviewee was de-identified. All responses and interviewer notes were manually logged in a spreadsheet. The final spreadsheet was reviewed by 2 Alliance staff to identify and extract common topics: any topic noted by 3 or more respondents is included in the results section.

Results

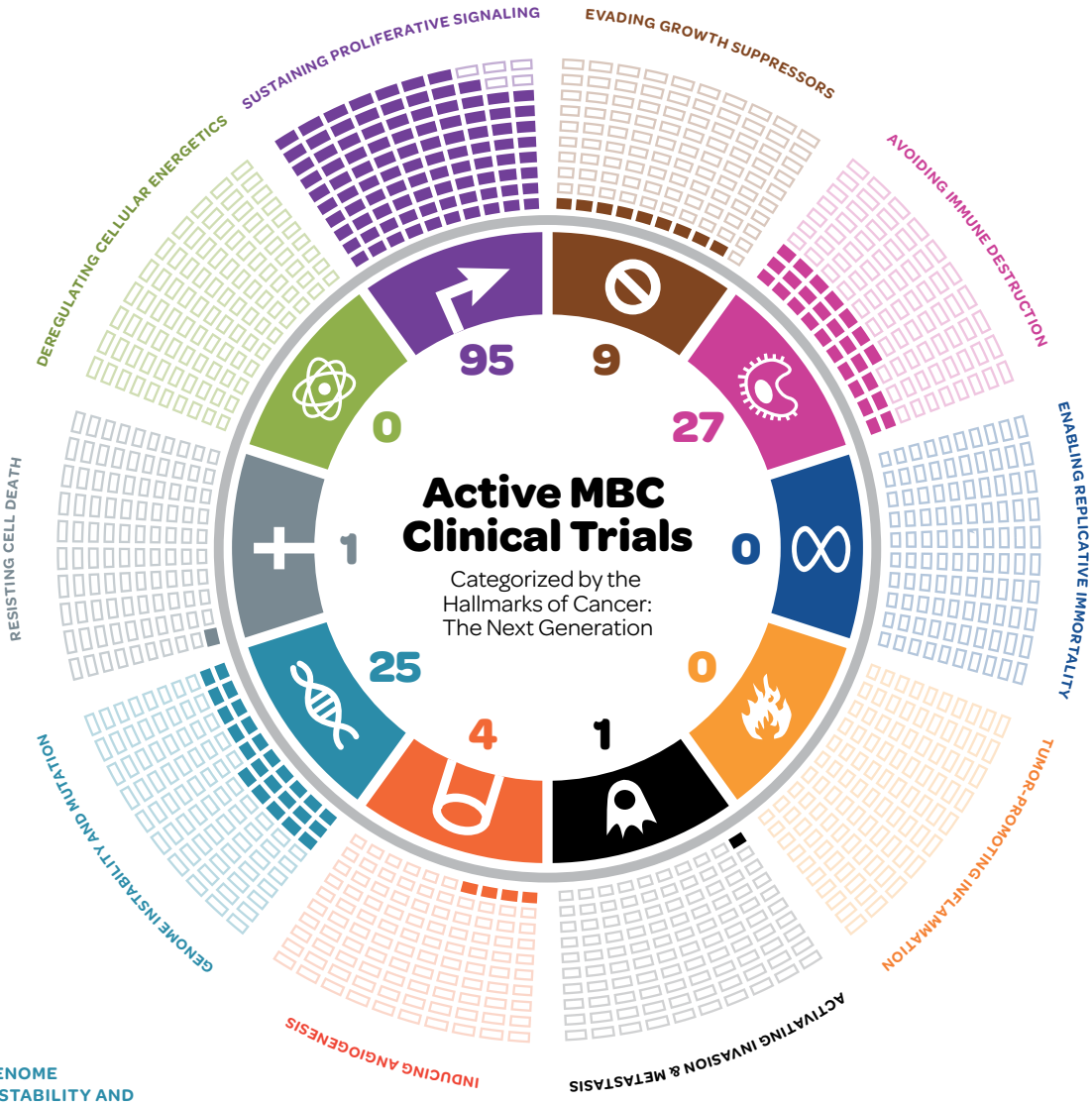
Clinical Trials

We identified 224 trials actively recruiting MBC patients in the US from the NCI's PDQ dataset: 169 testing targeted therapies, 35 testing chemotherapies, and 20 that were targeted to a specific metastatic tumor at a new organ site (e.g., brain, bone, liver, lung) (see **Table 2**). On August 1, 2014, we reviewed the status of each of the 224 trials on Clinicaltrials.gov to see whether they were still active and identified 2 trials that had completed enrollment and are no longer recruiting, 2 that were terminated, and 8 that had a trial status updated to "unknown". We kept all 12 of these in the data analysis but noted recent trials in **Appendix 1**.

Trials of Targeted Therapies

We found that 162 of the 169 targeted therapy clinical trials could be assigned to the Hallmarks of Cancer framework (see **Figure 3**). However, some molecular targets and some drugs may have an effect on more than 1 hallmark pathway and thus could be assigned to more than 1 framework category. **Table 2** summarizes the trials by hallmark category and phase (I, II, or III). There are 95 trials of drugs that target 8 molecular pathways involved in sustaining proliferative signaling, 27 trials testing drugs that target mechanisms of immune escape, 25 trials of drugs that target 2 pathways related to genomic instability and mutation, 1 trial in the hallmark of resisting cell death, 1 in the hallmark of activating invasion and metastasis, 4 trials assigned to the hallmark of inducing angiogenesis, and 9 in the hallmark of evading growth suppressors. The remaining 7 trials of the 169 total were categorized under "other"; 4 targeted heat-shock proteins and 3 could not be assigned to a target. Altogether, the 169 trials for targeted therapies included 74 phase I, 22 phase I/II, 54 phase II, and 17 phase III trials. Note that phase was not listed for 2 targeted therapy clinical trials.

Figure 3: 162 MBC Clinical Trials Assigned to the Hallmarks of Cancer Framework



ACTIVE CLINICAL TRIAL DETAILS

Note: 37 additional trials not targeted or could not be assigned to a hallmark

GENOME INSTABILITY AND MUTATION
PARP inhibitors
HDAC inhibitors*
Minor groove of DNA inhibitor (PM01183)

RESISTING CELL DEATH
IAP (inhibit apoptosis proteins) (LCL161)

DEREGULATING CELLULAR ENERGETICS
DIG-HIF1 being studied in early BC. Phase II

INDUCING ANGIOGENESIS
VEGF inhibitors

ACTIVATING INVASION AND METASTASIS
TGF-b inhibitor (fresolimumab)

TUMOR-PROMOTING INFLAMMATION
Inflammation remains of key interest in BC

ENABLING REPLICATIVE IMMORTALITY
GRN163L trial halted in MBC in 2013
Other telomerase inhibitors in trials for hematologic cancers

SUSTAINING PROLIFERATIVE SIGNALING
PI3/Akt/mTOR
JAK
Notch
ERB receptors
Hormone-mediated
PTEN
RAF/MEK/ERK/ALK
Other

EVADING GROWTH SUPPRESSORS
CDK inhibitors
Agents:
Palbociclib
LEE011
Y2835219

AVOIDING IMMUNE DESTRUCTION
18 vaccine
7 immunomodulators

*does not relate to "Genome Instability and Mutation" hallmark but instead is a modulator of transcription that is not easily fit into any one of the hallmark categories.

Abbreviations: BC = breast cancer; BH3 = pro-apoptotic member of the Bcl-2 protein family; anti-CTLA4 mAb = anti–cytotoxic T-lymphocyte associated protein 4 monoclonal antibody; CDK = cyclin-dependent kinase; DNA = deoxyribonucleic acid; EFGR, ERB = another term for ErbB, the epidermal growth factor receptor protein family; HDAC = histone deacetylase; HGF/c-Met = hepatocyte growth factor/MET proto-oncogene, receptor tyrosine kinase; JAK = Janus kinase family; MBC = metastatic breast cancer; Notch = family of proteins involved in intracellular signaling; PARP = poly-ADP ribose polymerase; PTEN = phosphatase and tensin homolog; RAF/MEK/ERK/ALK = a key cellular signaling pathway; TGF-b = transforming growth factor beta; VEGF = vascular endothelial growth factor.

Table 2: Trial Phase and Number of Drugs Studied in the 224 MBC Clinical Trials

Trial Category	No. of Trials	No. of Drugs under Study*	No. of Phase I	No. of Phase I/II	No. of Phase II	No. of Phase III
Targeted Trials Assigned to Hallmark of Cancer Category (n=162)						
1. Sustaining Proliferative Signaling (n=95)						
Total	95	69	41	7	38	9
PI3/Akt/mTOR	37	26	17	4	13	3
JAK	2	1	0	1	1	0
Notch	3	2	3	0	0	0
RAF/MEK/ERK/ALK	4	4	2	0	2	0
IGF	1	1	0	1	0	0
ERB receptors	29	20	11	0	13	5
Hormone-mediated	13	10	6	0	6	1
PTEN Mutation	1	1	1	0	0	0
Other	5	4	1	1	3	0
2. Evading Growth Suppressors (n=9)						
Cyclin-Dependent Kinase Inhibitors	9	3	3	2	1	3
3. Inducing Angiogenesis (n=4)						
VEGF Signaling Inhibitors	4	4	3	0	0	1
4. Resisting Cell Death (n=1)						
IAP (Inhibit apoptosis proteins)	1	1	1	0	0	0
5. Enabling Replicative Immortality (n=0)						
Telomerase Inhibitors	0	0	0	0	0	0
6. Genome Instability and Mutation (n=25)						
Total	25	10	11	6	4	4
PARP Inhibitors	16	5	8	3	3	2
HDAC Inhibitors	8	4	3	3	0	2
Other	1	1	0	0	1	0

Table continued next page

Trial Category	No. of Trials	No. of Drugs under Study*	No. of Phase I	No. of Phase I/II	No. of Phase II	No. of Phase III
Targeted Trials Assigned to Hallmark of Cancer Category (n=162)						
7. Tumor-Promoting Inflammation (n=0)	0	0	0	0	0	0
Selective Anti-inflammatory Agents	0	0	0	0	0	0
8. Deregulating Cellular Energetics (n=0)	1	1	1	0	0	0
9. Activating Invasion and Metastasis (n=1)						
10. Avoiding Immune Destruction (n=27)	27**	25	12	5	8	0
Total	18	18	8	4	4	0
Vaccines	9	7	4	1	4	0
Immunomodulators						
11. Other Targeted Trials (n=7)	7	5	2	2	3	0
Total	4	2	1	1	2	0
Heat Shock Protein	3	3	1	1	1	0
Other						
Trials of Nontargeted Therapies (n=35)	35	37	15	4	13	3
Total	4	4	2	1	1	0
Cancer Stem Cells	28	30	12	3	11	2
Chemotherapy	3	3	1	0	1	1
Surgery/Other	0	0	0	0	0	0
Supportive Care						
Site-Specific Trials (n=20)	20**	20	1	4	11	1
Total	17	17	1	3	9	1
Brain	1	1	0	0	1	0
Bone	1	1	0	0	1	0
Liver	1	1	0	1	0	0
Liver/Lung	1	1	0	0	1	0

Abbreviations: Akt = a serine/threonine-specific protein kinase; ErB = another term for ErbB, the epidermal growth factor receptor protein family; HDAC = histone deacetylase; IAP = inhibitors of apoptosis protein family; IGF = insulin-like growth factor; JAK = Janus kinase family; Notch = family of proteins involved in intracellular signaling; PARP = poly-ADP ribose polymerase; PTEN = phosphatase and tensin homolog; RAF/MEK/ERK/ALK = a key cellular signaling pathway; VEGF = vascular endothelial growth factor.

* Some agents are being tested in multiple trials; other trials are testing combinations of drugs.

**Six trials did not list the phase.

We then reviewed all targeted therapy trials and found 118 new drugs, vaccines, or new combinations of drugs being tested. **Appendix 3** lists the drug, or combination of drugs (if applicable), molecular targets, and biomarkers/cancer subtype being tested in these clinical trials according to the hallmarks of cancer categories.

TNBC Trials

We also conducted an analysis of trials based on enrollment by biomarker status. There were 16 trials specifically recruiting patients with triple-negative breast cancer (TNBC), 42 with hormone receptor-positive breast cancer, and 40 with HER2-positive breast cancer. Patients with TNBC were also potentially eligible for 10 trials enrolling patients with BRCA-positive breast cancer and 19 trials for patients with HER2-negative breast cancer (see **Table 3**). Similarly, patients with hormone-positive cancer were potentially eligible for 14 trials enrolling patients with HER2-negative breast cancer for which hormone receptor status was not a criterion. Of the 42 trials for hormone receptor-positive breast cancer, 30 excluded patients with HER2-positve disease. An additional 79 trials did not specify biomarker status including those for targeted therapy and chemotherapy as well as studies evaluating treatment for site-specific metastases to liver, brain, and bone.

Table 3: Characteristics of 124 MBC Trials Potentially Recruiting TNBC Patients

	Total	Phase I or I/II	Phase II	Phase II or II/III	Pilot or No Phase
Biomarker Specified					
TNBC Only	16	7	6	3	0
HER2–	19	11	7	1	0
BRCA	10	5	4	1	0
SubTotal	**45**	**23**	**17**	**5**	**0**
No Biomarker Specified					
Targeted Therapy	47	38	8	0	1
Chemotherapy	18	11	7	0	0
Brain Mets	9	0	5	1	3
Liver Mets	2	1	1	0	0
Bone Mets	1	0	1	0	0
Other	2	0	1	1	0
SubTotal	**79**	**50**	**23**	**2**	**4**

Abbreviations: BRCA = mutation in the tumor-suppressor gene BRCA1 or BRCA2 associated with hereditary breast cancer, HER2 = human epidermal growth factor receptor 2, Mets = metastases, TNBC = triple-negative breast cancer.

Trials from the Translational Breast Cancer Research Consortium

In addition to reviewing actively recruiting trials from the NCI PDQ database, we reviewed both ongoing and completed clinical trials from the Translational Breast Cancer Research Consortium (TBCRC) that were related to MBC[14]. The TBCRC was founded in 2005 and has been funded, in part, by Alliance members: Breast Cancer Research Foundation, Susan G. Komen, and the Avon Foundation. The TBCRC is a collaborative, multi-institution, academic group that conducts innovative and high-impact clinical trials for breast cancer. The TBCRC is composed of 17 clinical sites, 5 core subcommittees, and working groups. Collectively, these groups work together to foster trial development and enrollment in a collegial environment that enhances cross-institutional collaborations. The activity of the TBCRC is of interest because it is an exemplary model of collaboration, accelerating clinical research related to breast cancer and MBC. The collaboration includes 19 leading academic medical centers and principal investigators launching joint trials, recruiting patients together, and sharing valuable tissue sources and samples.

Upon analysis, we found that, of the 30 multicenter clinical trials conducted since the inception of the TBCRC in 2005, 15 (50%) either targeted or included MBC patients (see **Table 4**). Of these 15 trials, 12 were either not yet fully active or closed to accrual. Because our dataset only includes trials that were active or recruiting patients in April and May 2014, these 12 trials are not included, although the 3 active TBCRC trials are included. Across all 15 MBC trials from TBCRC, 17 new drugs or combinations of drugs have been or are being tested.

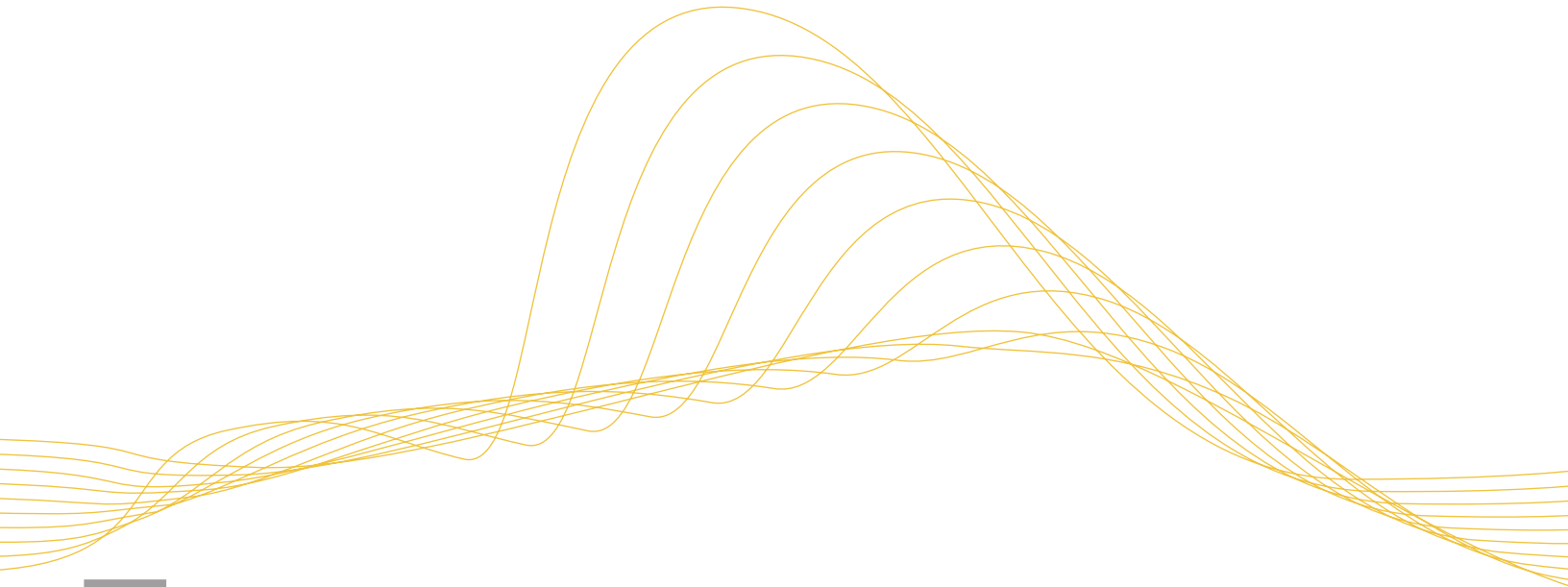


Table 4: MBC Trials Conducted by the Translational Breast Cancer Research Consortium

Trial #	Status	Trial Description	Trial Presentations
TBCRC 019	Closed to Accrual	An Open Label, Randomized, Phase II Trial of Abraxane™ (Paclitaxel Albumin-Bound Particles for Injectable Suspension), with or without Tigatuzumab (a Humanized Monoclonal Antibody Targeting Death Receptor 5) (CS-1008) in Patients with Metastatic, Triple Negative (ER, PR, and HER-2 Negative) Breast Cancer	2013 SABCS Poster (Poster # P1-04-01); 2013 ASCO Poster (Abstract # 1052); 2011 ASCO Trials in Progress Poster (Abstract # TPS128)
TBCRC 018	Closed to Accrual	A Phase II Study of the PARP Inhibitor, Iniparib (BSI-201), in Combination with Chemotherapy to Treat Triple Negative Breast Cancer Brain Metastasis	2014 Breast Cancer Research and Treatment Manuscript (PMID: 25001612); 2013 ASCO Poster Discussion Session (Abstract # 515); 2011 ASCO Trials in Progress Poster (Abstract # TPS127)
TBCRC 015	Closed to Accrual	Investigation of Genetic Determinants of Capecitabine Toxicity	N/A
TBCRC 013	Closed to Accrual	A Prospective Analysis of Surgery in Patients Presenting with Stage IV Breast Cancer	2013 SABCS Poster (Poster # P2-18-09); 2013 ASCO Oral Presentation (Abstract # 507)
TBCRC 011	Closed to Accrual	Bicalutamide for the Treatment of Androgen Receptor Positive (AR(+)), Estrogen Receptor Negative, Progesterone Receptor Negative (ER(-)/PR(-)) Metastatic Breast Cancer Patients: A Phase II Feasibility Study	2013 Clinical Cancer Research Manuascript (PMID: 23965901); 2012 SABCS Poster (Poster # P6-05-02); 2012 ASCO Oral Presentation (Abstract # 1006); 2011 ASCO Trials in Progress Poster (Abstract # TPS122)
TBCRC 010	Closed to Accrual	Phase I/II Study of Dasatinib in Combination with Zoledronic Acid for the Treatment of Breast Cancer Bone Metastasis	N/A
TBCRC 009	Closed to Accrual	A Phase II Study of Cisplatin or Carboplatin for Triple-Negative Metastatic Breast Cancer and Evaluation of p63/p73 as a Biomarker of Response	2014 ASCO Oral Presentation (Abstract #1020); 2012 SABCS Poster Discussion Session (Poster Discussion # PD-09-03); 2012 Cancer Research Manuscript (PMID: 23135909); 2011 ASCO Poster Discussion Session (Abstract # 1025)
TBCRC 007	Closed to Accrual	MPA Revisited: A Phase II Study of Anti-Metastatic, Anti-Angiogenic Therapy in Postmenopausal Patients with Hormone Receptor Negative Breast Cancer.	2010 ASCO Poster (Abstract # 1074)
TBCRC 003	Active	A Phase 2 Study of Lapatinib in Combination with Trastuzumab in Patients with HER2-Positive, Metastatic Breast Cancer	2014 ASCO Poster Highlights Session (Abstract # 536); 2011 SABCS Poster (Poster # P2-09-07); 2011 2-ASCO Poster Discussion Sessions (Abstract # 527 & 528); 2010 ASCO Trials in Progress Poster (Abstract # TPS132)
TBCRC 001	Closed to Accrual	Phase II Trial of Cetuximab Alone and in Combination with Carboplatin in ER-Negative, PR-Negative, HER2-nonoverexpressing Metastatic Breast Cancers	2014 Science Signaling Manuscript (PMID: 24667376); 2012 JCO Manuscript (PMID: 22665533); 2009 SABCS Poster; 2008 Molecular Markers Poster (Abstract # 2); 2008 ASCO Oral Presentation (Abstract # 1009); 2007 SABCS Poster Discussion Session (Poster # 307)

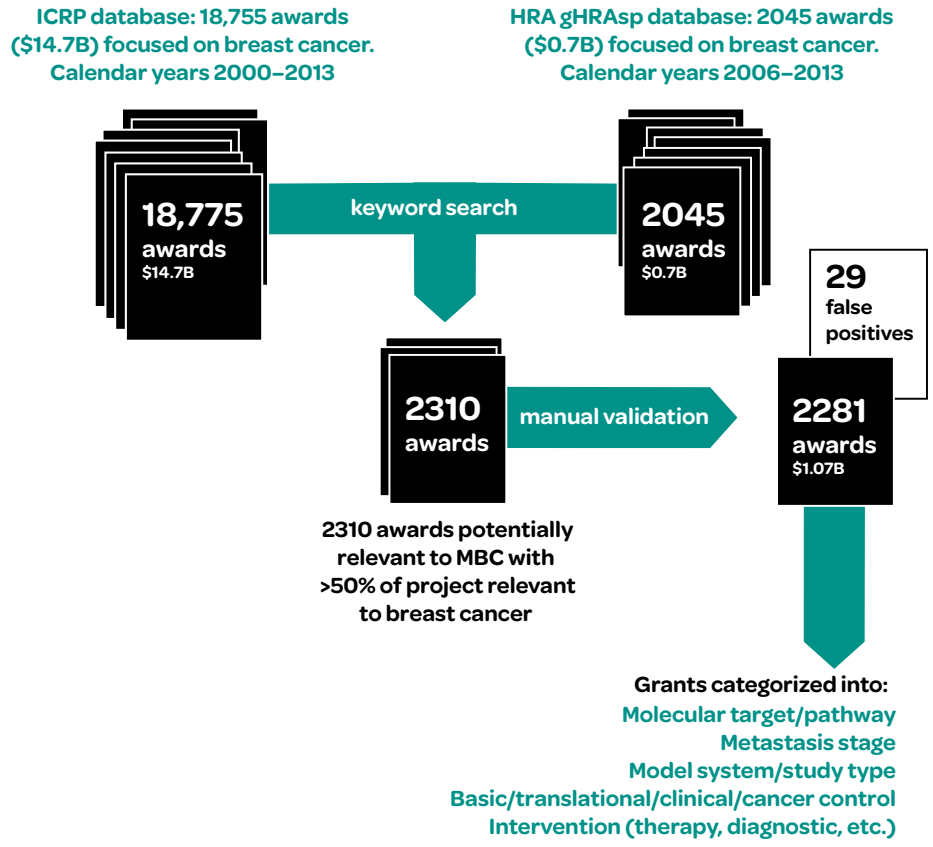
Abbreviations: ASCO American Society of Clinical Oncology, SABCS = San Antonio Breast Cancer Symposium

Grants Analysis

Identification of MBC-Relevant Awards

As of June 1, 2014, the ICRP database contained 18,755 grants that were active between the years of 2000 and 2013 and had been identified as being related to breast cancer studies; the HRA gHRAsp database contained 2045 grants that were active between the years of 2006 and 2013 and were related to breast cancer (see **Figure 4**). Using combinations of keywords (e.g., "metastasis, metastatic, advanced") that would select for grants potentially relevant to MBC, the ICRP database yielded 2237 records and the HRA database yielded 73 records. We then manually reviewed a random sample of these grants to validate our search and data extraction strategy. Only 29 records were identified as being false positives—meaning that manual review of the record determined that it was irrelevant to MBC (around 1%). Thus, the keyword search strategy was effective in identifying relevant grants from both databases. The search yielded an MBC Grants dataset of 2281 grants totaling $1.07 billion. Examples of how grants were further categorized into the metastasis stage are given in **Appendix 4**.

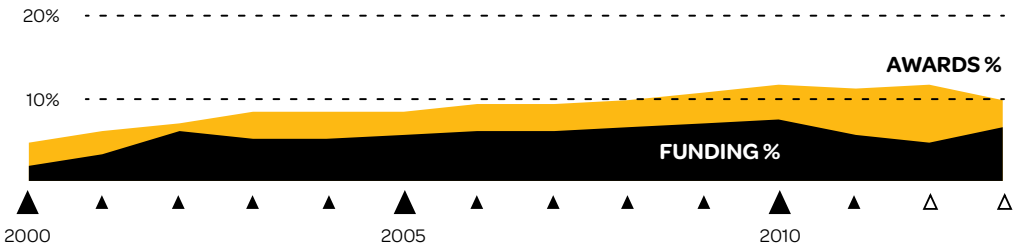
Figure 4: MBC Grants Dataset



Of the 20,800 breast cancer research grants totaling $15 billion US that were extracted from the ICRP and HRA databases, 2281, or 11%, were identified as being relevant to MBC research. Those 2281 grants totaled $1.1 billion US, or 7.1% of the total investment. Funding for MBC research grew gradually over time, from 2% of the breast cancer research funding in 2000 to a peak of 9% in 2010 (**Figure 5**). In addition, the numbers of active MBC projects in a given year grew from 6% of the total number of breast cancer projects in 2000 to 15% in 2012. Note that the data for 2012 and 2013 are incomplete, as data from all ICRP and all HRA members have not been finalized for those years.

The largest sources of MBC research funding identified from the MBC Grant Dataset were (from greatest to least dollar value of funding over time) as follows: the Department of Defense Congressionally Directed Medical Research Programs, NCI/National Institutes of Health, Canadian Cancer Research Alliance, Susan G. Komen, United Kingdom's National Cancer Research Institute, National Breast Cancer Foundation (Australia), California Breast Cancer Research Program, American Cancer Society, Breast Cancer Research Foundation, Dutch Cancer Society (KWF), Avon Foundation, French National Cancer Institute, and the American Institute for Cancer Research. Note the Canadian Cancer Research Alliance and the United Kingdom's National Cancer Research Institute are not direct funders of research; rather they are umbrella organizations that aggregate and collate national data from many individual funding organizations.

Figure 5: Number and Amount of MBC Awards as a Function of Overall Breast Cancer Funding

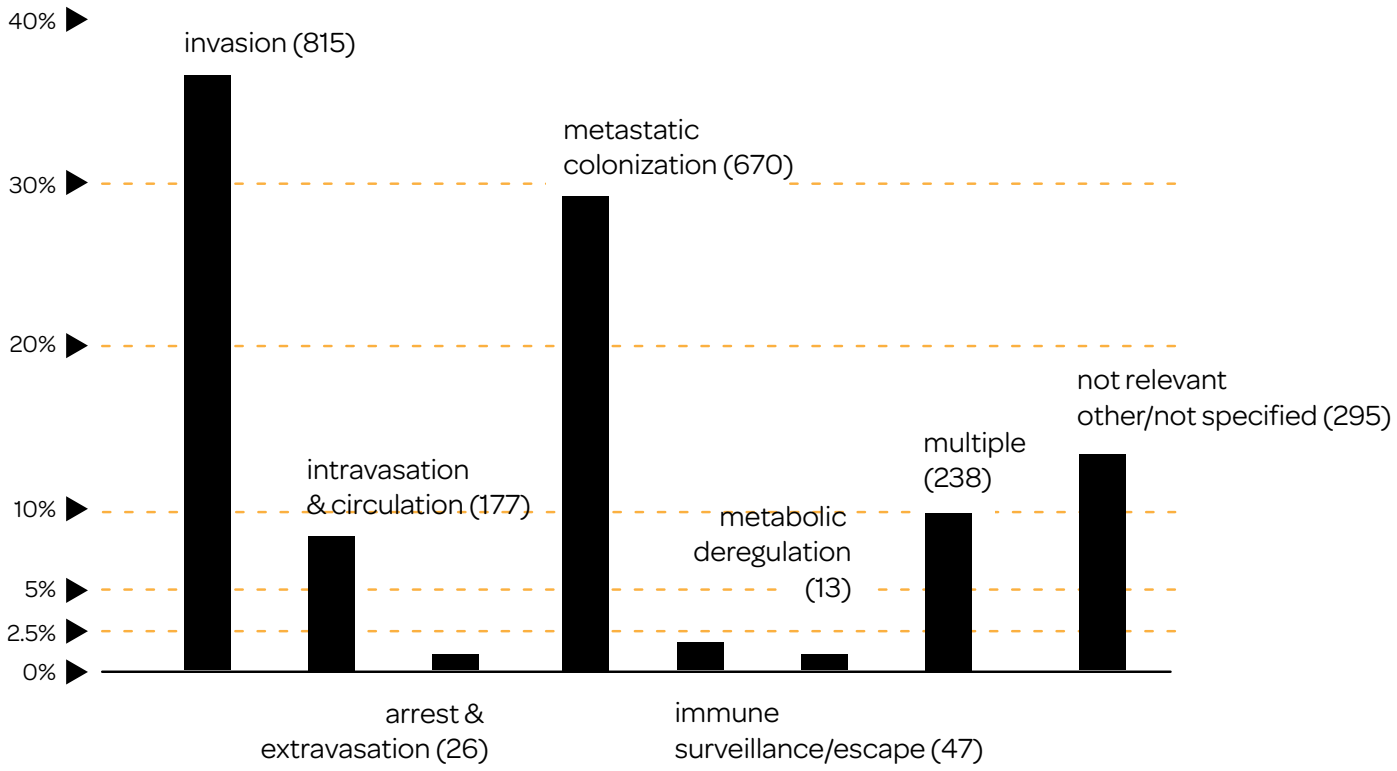


Black: funding for MBC research (% of total). Orange: active MBC projects (%).
Note that the data for 2012 and 2013 are incomplete, as data from all ICRP and all HRA members have not been finalized for those years.

Details of MBC Grants Dataset from 2000–2013

Each record in the MBC Grants dataset was analyzed and assigned to 1 or more steps of metastasis. As shown in **Figure 6**, 815 grants (36%) were investigating aspects of invasion, 670 (29%) were looking at metastatic colonization, 177 (8%) were studying intravasation and circulation, 47 (2%) focused on immune surveillance/escape, 26 (1%) were investigating arrest and extravasation, and 13 (1%) were studying metabolic deregulation. A total of 295 awards (13%) could not be categorized into a metastatic stage and were classified as "other"; and 238 (10%) were classified into more than 1 metastatic stage. These percentages did not vary substantially from year to year from 2000 through 2013.

Figure 6: Grants Categorized by Steps in Metastatic Process

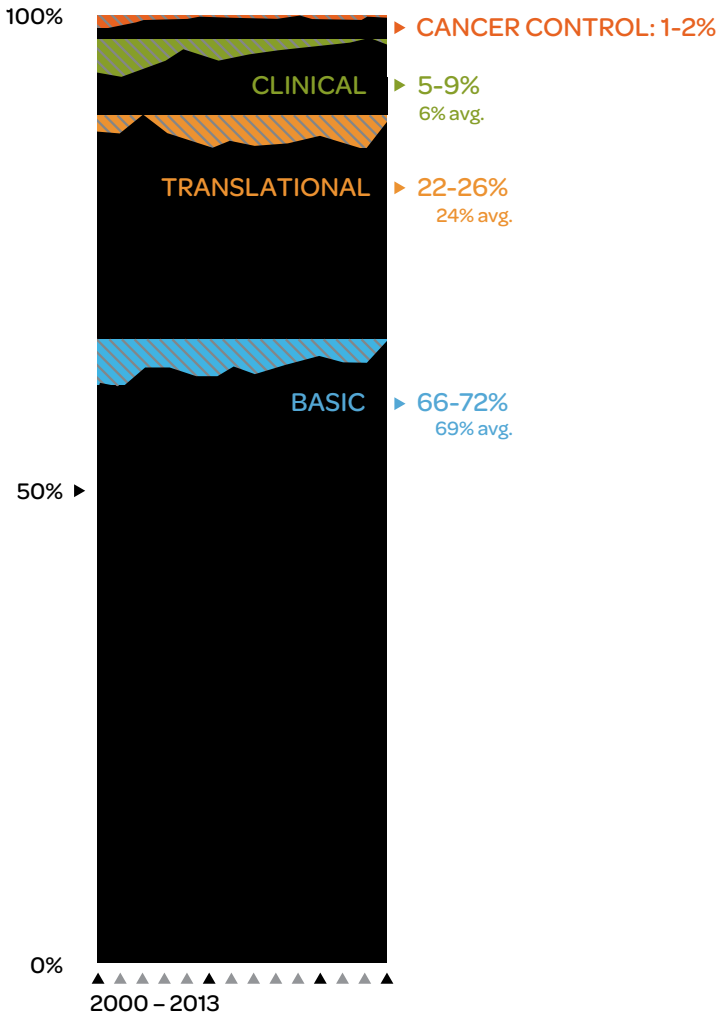


As seen in **Figure 7**, the MBC Grants Dataset was composed predominantly of basic research grants (69%), 24% represented translational research, and vastly smaller percentages were grants for clinical research (6%) and cancer control research (1%). These percentages did not vary substantially across the time studied.

Only 41 grants in the MBC Grants Dataset were related to MBC survivorship and outcomes research (includes projects both wholly and partly related to survivorship and outcomes research). A review of these grants revealed that they are focused on bone pain, behavioral–psychological factors, and treatment side effects relevant to MBC.

Information on the molecular targets, cellular pathways, and therapies being studied was also extracted and captured from the MBC Grants Dataset. As **Appendix 3** shows, a wide range of molecular targets are being pursued (estimated at >200).The most common targets in those projects with a clinical focus are ErbB/HER, vascular endothelial growth factor (VEGF) pathway family, bone/osteolysis pathways, hormone receptors, and immune system (general).

Figure 7: Stages of Research in the MBC Research Grants from 2000–2013



The MBC Grants Dataset can be categorized in a variety of ways. For example, the numbers of awards over time investigating specific molecular targets can be separated according to whether the model system or study type is preclinical (using a model system, using cell lines, or is a "gene hunt"), technologic (involves developing a diagnostic or prognostic tool or imaging technique), or is aimed at developing a therapy or intervention. For example, here we show this assessment for research related to integrins and cadherins (**Figure 8a**) and cytokines and chemokines (**Figure 8b**).

Figure 8a: MBC Research Grants Studying Integrins and Cadherins from 2000 - 2013

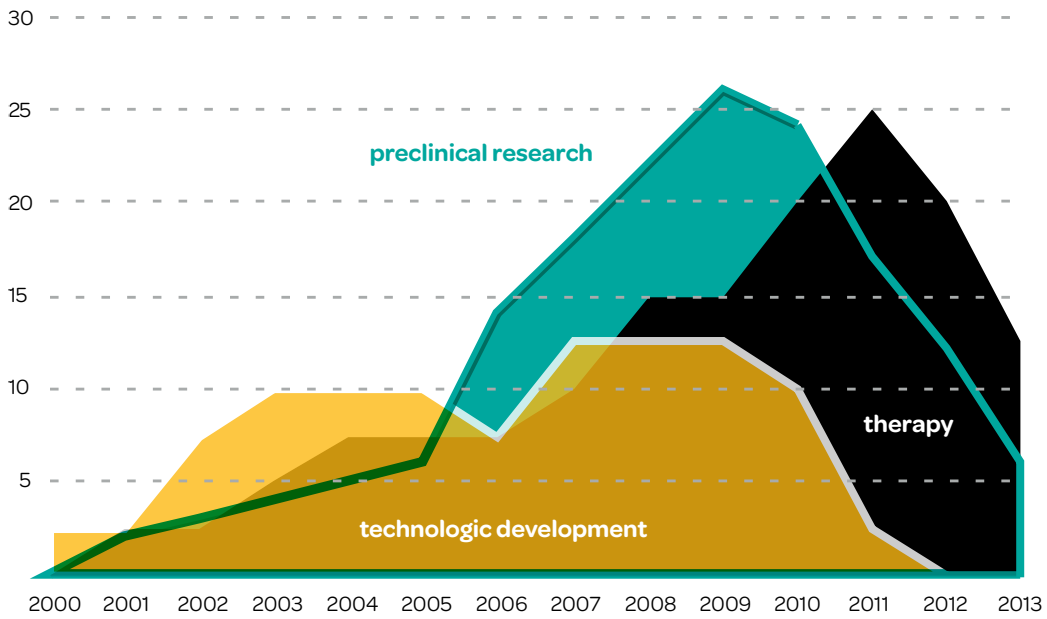
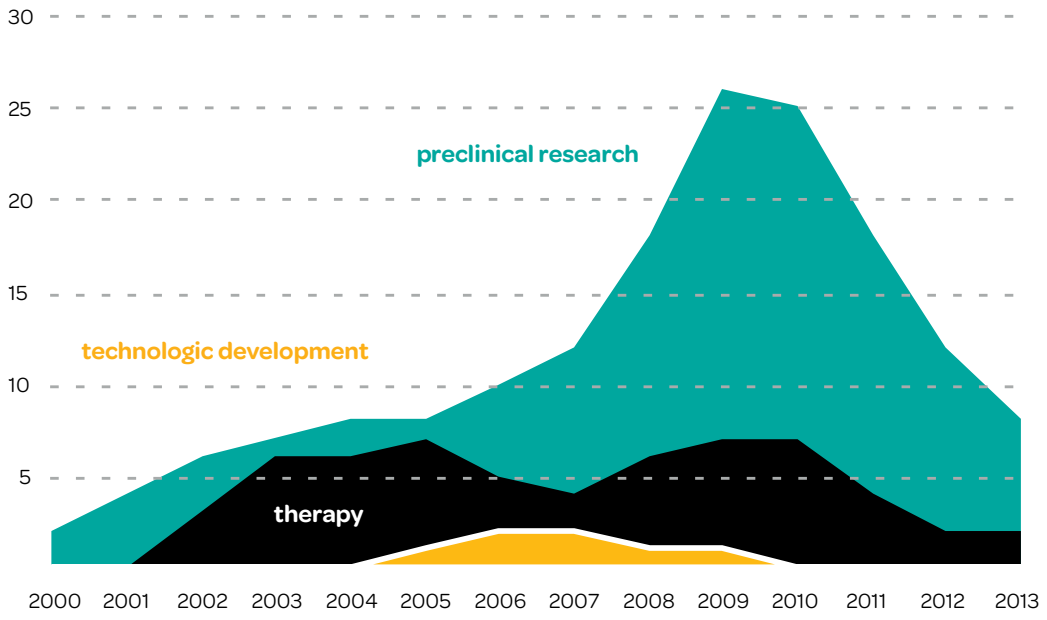


Figure 8b: MBC Research Grants Studying Cytokines and Chemokines from 2000- 2013



Key Opinion Leader Interviews

We interviewed 59 KOLs representing the breast cancer patient advocacy, academic, government, pharmaceutical industry, and nonprofit sectors. The goal of these interviews was to gain input on urgent priorities, gaps, and opportunities in MBC research. We identified our list of interviewees from the leadership of our own Alliance member organizations and from the MBC Grants Dataset by identifying those scientists who were listed as principal investigator on 6 or more grants. A complete list of the KOLs interviewed is in **Appendix 2**.

Many of the experts cautioned against specifically focusing on the list of 7 questions we had developed, noting that not all possible or exciting target areas were listed. However, the questions did elicit informative responses. The recurring themes that emerged from the 3 or more respondents are summarized in **Table 5**.

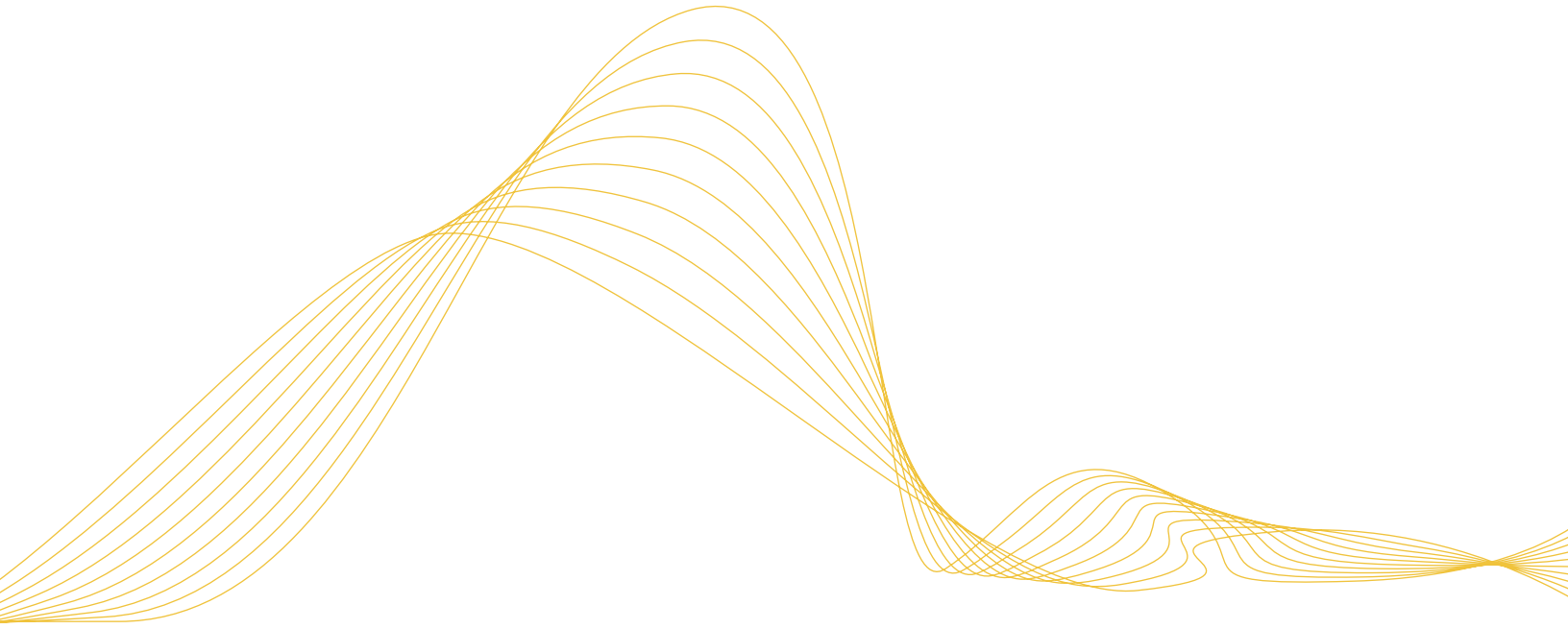


Table 5: Interviews with Key Opinion Leaders

Question	Representative Responses
What exciting scientific opportunities do you see for advancing our understanding of metastasis?	**Basic biology** • A deeper understanding of the biology of the steps of metastasis is needed to make improved, targeted treatments • For ER+ breast cancer, we need to understand more about late relapse and how best to treat it **Translational and clinical research:** • Significant preclinical literature points to our ability to prevent or slow metastasis, but not shrink overt metastatic tumors; to translate this we need drug-combination experiments and new clinical trials design • Developing more effective treatments for TNBC and IBC and controlling brain metastases are the biggest unmet medical need today related to MBC • For HER2+ breast cancer, we need to develop the safest long-term regimens for controlling the disease

What do you think is the most promising target for developing new therapeutics aimed at metastasis?	• The many targeted therapies in phase II and III MBC trials are among the most exciting (see Table 2). Still many more opportunities to identify new targets and combinations of targets are in the research stages
	• The therapeutics farthest along in drug development are CDK4/6 inhibitors, PARP inhibitors for BRCA carriers with breast cancer, and HSP90 inhibitors
	• All areas of new therapeutics outlined in your questions below are important; caution against picking only 1 or 2 as priority areas
	• We need to understand all of these as they relate to MBC
	  ◦ Cancer stem cells
	  ◦ Cell invasion
	  ◦ Cell signalling and proliferation as it relates to MBC
	  ◦ Tumor dormancy
	  ◦ Immune system
	  ◦ End organ microenvironment and the signals between the end organ and metastatic cell

What gaps, or roadblocks exist that hinder advances in MBC research?	**Research funding** • MBC research has been underfunded (approximately <5% of breast cancer funding) • Overall cancer research is also underfunded (0.1% of the Federal budget.). Other areas receive more funding including the military, farm subsidies, education, and others **Matched tissue samples** • To advance MBC research, better access to tissue is needed, including the primary tumor, metastatic tumor, and interval blood samples collected and banked between the primary and development of the recurrent, metastatic tumor • MBC tissue from different populations needs to be studied (e.g., MBC in younger, premenopausal women vs. MBC in older women) **Model systems** • The previously available laboratory models for MBC research were discouraging, but in 2013 and 2014, several laboratories have demonstrated interesting MBC models • MBC models need to be validated and standardized across laboratories **Academic-initiated clinical trials** • Academics have not focused enough on MBC (in basic research, clinical trials, or cooperative groups), although focus is rapidly shifting to MBC as a priority • MBC research is complicated, costly and time consuming (e.g., early BC studies in animals can be 2 or 3 months, MBC animal studies can take up to 9 months to run a single set of animal experiments) • Lack of academic involvement has resulted in MBC trials being led by the pharmaceutical industry and business interests, including correlative science studies **Epidemiology** • Need to better understand the epidemiology of MBC: How many patients have a recurrence? What are their treatments and responses? How long do they survive?

What role do you see for markers or circulating tumor cells (CTCs)?	• Clinical utility of CTCs and ctDNA remains unproven, but they are useful tools for the research setting and can be prognostic in some clinical settings, however we still do not understand whether they are biologically useful • What do CTCs/ctDNA represent? Are they from primary tumors? From metastatic tumors? Both? • The source of these cells or ctDNA now in circulation is unknown
Can you describe the challenges in designing and conducting clinical trials for MBC?	**Endpoints** • New clinical trial designs are needed that address endpoints beyond tumor shrinkage and the RECIST scale; consider time to secondary metastasis or time to first metastasis in early breast cancer • Consider how many patients had lesion growth or shrinkage, how many had a secondary metastatic site develop; and consider progression-free survival studies in early metastatic disease • Quality of life measures need to be a part of all clinical trials **Drugs/experimental therapeutics** • Preclinical studies show that several agents can prevent or slow metastasis; need to translate these findings into clinical trial design • Current drugs in solid tumors do not work very well; there is too much industry influence driving clinical trials, which has trickled down into academia; progression-free survival and other endpoints are meaningless if the drugs do not significantly extend life span and quality of life • There is duplication in clinical research; for example, too many "me-too" drugs are being developed in industry (e.g., PI3K inhibitors) **Recruitment for MBC trials in the US is challenging; patients need easier access to trial information—should review the steps the United Kingdom took to triple the number of cancer patients on trials from 4% to 12%** • In general, screening is not aimed at early detection of metastasis, largely because in the past there were few treatment options; it is worth reconsidering this approach • There are too many solo investigators who design, execute, complete and publish single-center phase II trials; most likely this is required for promotion of clinical investigators; the reward system in academia needs to change to reward multicenter, multi-investigator, collaborative phase II trials

Are there other aspects of MBC research we should discuss?	• In vitro models of MBC are insufficient; we need reproducible in vivo models of MBC • Need a better understanding of the natural history of MBC • Need to understand whether a metastatic cell is truly a cancer or aggressive cell; for example, in pancreatic cancer there are "metastatic" cells that are from non-cancerous hyperplasia (equivalent to DCIS or ADH in the breast)—that is, they have become metastatic but are not yet designated a cancer cell; whether this same phenomenon happens in breast hyperplasia is unknown • Reproducibility is key; several labs share cell lines and animal models of MBC that other labs have used incorrectly, thus drawing incorrect conclusions in their research publications • Important to look at the whole person, not just the primary tumor or metastatic site; for example, we now know that giving prophylactic antibiotics during chemotherapy may result in worse outcomes, because the patient's microbiome is disturbed; need to study what role the microbiome has in health, immune function, response to therapy, etc.

Abbreviations: ADH = atypical ductal hyperplasia, BC= breast cancer, CDK4/6 = cyclin-dependent kinase 4/6, CTC = circulating tumor cells, ctDNA = circulating tumor DNA, DCIS = ductal carcinoma in situ, ER+ = estrogen receptor positive breast cancer, HER2+ = human epidermal growth factor receptor2–positive breast cancer, HSP90 = heat shock protein 90, IBC = inflammatory breast cancer, MBC = metastatic breast cancer, PARP = poly-ADP ribose polymerase, PI3K = phosphatidylinositide 3-kinase, RECIST = Response Evaluation Criteria in Solid Tumors, TNBC = triple negative breast cancer.

Discussion

The MBC Alliance analyzed the MBC research landscape, including 224 clinical trials actively recruiting MBC patients and 2281 funded grants totaling $1.07 billion US. Using the hallmarks of cancer[5] and the steps in metastasis[6] as frameworks, we were able to identify well supported areas as well as some neglected areas in MBC research. For example, no targeted therapy trials were identified for 3 of the 10 hallmarks of cancer: enabling replicative immortality, tumor-promoting inflammation, and deregulating cellular energetics. Furthermore, few MBC research grants were focused on understanding some of the steps of metastasis, including intravasation and circulation, immune escape, arrest and extravasation, and metabolic deregulation. In addition, we found that MBC research is underfunded, accounting for only 7% of the breast cancer funding identified in our analysis from 2000 to 2013.

Interviews with experts in the field suggested that laboratory models that appropriately mimic the steps of metastasis need to be refined and standardized across laboratories and that more laboratories need to access and study metastatic tissue in comparison to primary tumors. These suggestions were supported in the published literature [15-17]. Experts also called for updates in clinical trials for MBC, including new trial designs with time-to-new metastasis as an endpoint, and the need for multicenter, collaborative phase II trials [17,18].

Through our analysis, we found that there are 118 unique drugs or drug combinations being studied in 169 clinical trials of targeted therapies that address 7 of the 10 hallmarks of cancer currently being tested. Of note, more than 40% of the targeted therapy trials are in the latter stages of development (17 phase III, 54 phase II), which suggests they are nearing clinical applicability. MBC appears to be well studied in clinical trials in comparison to other cancers; as of August 2014, the numbers of active trials included 376 trials for any breast cancer, 57 trials for metastatic small-cell lung cancer, 220 trials for metastatic non–small cell lung cancer, and 116 trials for metastatic pancreatic cancer. However, it should be noted that clinical trials for breast cancer nearly always start in the MBC setting before being tested in early settings.

The Alliance believes that categorizing MBC clinical trials according to the hallmarks of cancer is important for MBC research, especially since the simplistic view of a "war" on cancer and the hope for a single "magic bullet" treatment has evolved—combination therapy is now routine [19,20]. A multipronged approach is essential, because cancer is a dynamic, heterogeneous system with a complex network of interrelations that vary between and across cells as well as over time within each cell[19,21]. For example, it is now clear that cancers can initially resist the targeting of a hallmark by activating other cellular mechanisms within that hallmark. A second pattern of resistance is to rely on other hallmark capabilities to overcome deficiencies; for example, a cancer could resist angiogenesis inhibitors by becoming more invasive and metastatic[22-24]. Thus, the use of categorization schemes, such as the hallmarks of cancer, can provide strategic guidance for clinical approaches that will target multiple hallmarks simultaneously and avoid these common mechanisms of therapeutic resistance.

Several KOLs noted that it is challenging to recruit patients to MBC trials and it can thus take a long time to complete accrual (e.g., 2 years to recruit 600 MBC patients)[17,25]. Although one barrier is the low percentage of cancer patients that participate in clinical trials in general, this can be mitigated. Groups in the United Kingdom faced a similarly low rate of enrollment into cancer trials and increased the rate from approximately 4% to 12% of cancer patients within just a few years through a coordinated and managed approach to clinical research and by integrating research networks with community cancer service networks in their socialized

healthcare system [26]. Another commonly cited barrier is the challenge of presenting information about clinical trials and eligibility requirements to patients in an easily searchable and understandable fashion. The Alliance member BreastCancerTrials.org is one resource for identifying trials patients may be eligible to join. Although this site is considerably user-friendly, it could provide a more customized user experience. For example, searching would be simpler if dashboards and search results were provided by tumor type (see **Table 3** for an example for TNBC). In addition, the ability to export search data to other websites frequently visited by MBC patients would simplify the search process for patients and increase participation in these clinical trials.

The academic and pharmaceutical industries were also identified by KOLs as barriers to progress in MBC clinical trials. Specifically, in both academia and the pharmaceutical industry, there is too much focus on "me-too" drugs—drugs designed to target the same molecules (e.g., PI3K inhibitors) —rather than focusing on new drugs or drug targets. In addition, academia places too much emphasis on single investigator/single institution trials. To successfully accelerate MBC clinical research, these barriers must be broken down and multi-institution, multi-investigator trials that focus on new drugs or new drug combinations must become the norm. The MBC Alliance is poised to act on the recommendations of KOLs in this area through its experience with the TBCRC, which has been collaboratively funded by 3 Alliance members (Breast Cancer Research Foundation, Komen, and Avon), as well as by leveraging existing relationships with many of the leading pharmaceutical and biotechnology companies that are active Alliance partners and members.

Although our study of previously funded research shows that only 7.1% of breast cancer research investments has been directed towards understanding metastasis, several new initiatives could quickly begin to fill gaps, including the Ludwig Institute for Cancer Research's $540-million investment in 6 centers to fast-track research to bring new treatments for metastatic cancers [27], the Breast Cancer Research Foundation's $27-million Founder's Fund with a focus on MBC [28], and the National Breast Cancer Coalition's MBC Artemis project[29]. Breast Cancer Research Foundation raised millions in memory of Evelyn Lauder after her death in 2011 and is directing the funds to projects focused on understanding the biology of MBC. Breast Cancer Research Foundation's Founder's Fund is coordinating the efforts of leading clinical and laboratory sites across North America and Europe over a 3-to-5-year period that started in early 2014 and will include the prospective collection, banking and analysis of primary and metastatic tumors from 1300 patients.

In conclusion, using publicly available research databases, we have abstracted information from approximately 2281 funded research grants and 224 clinical trials related to MBC. We have assembled comprehensive lists of the molecular targets, cellular pathways, and therapeutics under study for MBC that will enable us to better coordinate, manage, and advocate on behalf of MBC research.

Our next steps as an Alliance are to understand why these gaps in MBC research exist and launch new programs to fill these gaps. For example, why are intravasation, arrest and extravasation, and immune escape understudied? Are there adequate model systems to study these steps of metastasis? Are there adequate numbers of scientists working on understanding the multiple steps in the metastatic process? What are the bottlenecks to further understanding these metastatic processes? Identifying and understanding these gaps will enable the MBC Alliance to work to effectively advocate for funding to fill them.


3

CHAPTER 3: ANALYSIS OF QUALITY OF LIFE RESEARCH ON LIVING WITH MBC

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Abstract

Targeted treatment options and advances in supportive care are transforming MBC from a terminal illness with short survival into a disease many patients can live with over long periods. This lengthened survival of MBC patients has had an impact on quality of life research. ***Methods:*** Over 150 published, peer-reviewed research articles relevant to the experiences and needs of people with advanced cancers, including quantitative and qualitative studies of patients living with MBC and their families, were read and reviewed to summarize research findings about the reality of living with MBC. In addition, 13 MBC patient surveys were analysed. ***Results:*** The research base around MBC quality of life issues is extensive, permitting summary of findings into 6 categories: psychosocial distress; emotional support; information about the disease, its treatment, and resources; communication and decision making about care; relief of physical symptoms; and practical concerns: work, health insurance, and finances. Sources of emotional support, individual and group psychotherapy, and counseling, as well as adequate information about the disease, its treatments, and methods to alleviate symptoms and side effects have been shown to be useful in helping patients to cope with and adapt to MBC. However, MBC patients are typically not well informed in areas required for decision making about their care, and patient–clinician communication can be difficult to navigate. MBC symptoms and side effects of continuous treatment interfere with daily life and cause fatigue, sleeping difficulties, and pain as well as emotional distress for most patients; supportive and palliative care is often insufficient. Financial hardship is a fact of life for many families affected by MBC. ***Conclusions:*** The quality of life issues for patients with MBC and their caregivers are well understood; however, resources and intent to address them are still lacking.

Targeted treatment options and advances in supportive care are transforming MBC from a terminal illness associated with short survival, into a disease some patients are living with over longer periods of time.

Introduction

As patients live longer with MBC, quality of life becomes an increasingly important focus. Targeted treatment options and advances in supportive care are transforming MBC from a terminal illness associated with short survival into a disease many patients are living with over longer periods of time. Although median survival is still widely cited in the range of 2 to 4 years, many patients with ER+ and HER2+ MBC are living much longer. The most recent published data from SEER registries report 5-year survival of newly diagnosed de novo MBC (breast cancer that is already metastatic at the time of *first* diagnosis) to be 24.3% (ranging from 13.7% for black women over 50 years of age to 32.9% for white women under 50 years of age)[30]. Because of trends toward longer survival, some have used the word "chronic" to apply to MBC, but many patients and advocates take exception to this overly-optimistic term, believing that it trivializes the nature of what remains a deadly disease.

The lengthened survival of MBC patients has had an impact on quality of life research. Psychosocial researchers are now concerned with more than just end-of-life issues, and "palliative care" has been repurposed earlier in the course of disease, to be initiated with metastatic diagnosis[31].

Background on Quality of Life Research

Quality of life is a multidimensional concept, consisting of physical, emotional, social, and cognitive functioning, including the impact of disease symptoms and treatment side effects [32]. Over the past decade, MBC patients' voices are being heard more frequently through support and advocacy organizations, through surveys, and in quality of life research that increasingly incorporates patient-reported outcomes.

Oncology researchers and key opinion leaders have issued a strong call for treating the patient as a whole person, rather than merely as a disease or a cluster of symptoms.

Historically, the field of psycho-oncology, which addresses the mental, social, and emotional burden of cancer, has been hindered by long-standing societal attitudes relating to not only fear of cancer, especially metastatic disease, but also the stigma associated with mental illness[33]. Beginning in the 1970s, behavioral medicine began to develop models of how patients cope with and adapt to living with serious physical illness and disability and to quantify psychosocial issues so that they could be reliably measured. This paved the way to broader use of symptom assessment, studies of unmet patient needs, and screening for psychosocial distress—not only in research but also in standards of care for patients. For example, National Comprehensive Cancer Network guidelines now recommend the incorporation into standard care of an instrument that measures "distress," a term chosen because it is believed to be less stigmatizing than terms like "depression" and "anxiety" associated with mental illness[34].

In 2007, an Institute of Medicine (IOM) panel examined psychosocial issues for cancer patients and issued recommendations[35], noting the presence of anxiety and depression, the lack of information available to patients to help them manage their illness, and an absence of resources to address these issues. Better communication between patients and providers, routine assessment of needs, patient engagement, and development of care plans were among the IOM recommendations.

Over the past 2 decades, a number of quality of life assessment tools and patient-reported outcome measures have been widely used and validated, and about one third of phase III clinical trials in MBC, according to 1 report[36], now incorporate quality of life measures. This has been strongly encouraged by US regulators, who have determined that valid quality of life endpoints can serve as meaningful indicators of clinical benefit when assessing drug efficacy and safety. In 2009, the US Food and Drug Administration issued guidance for industry for incorporating patient-reported outcome measures into drug registration trials[37]. As in other areas of medicine, in oncology, researchers and KOLs have issued a strong call for treating the patient as a whole person, rather than merely as a disease or a cluster of symptoms. However, cost constraints and sobering recent assessments demonstrate that there is still a very long way to go before what has been learned is widely applied [38].

Methods of the Quality of Life Landscape Analysis

Over 150 published, peer-reviewed research articles relevant to the experiences and needs of people with advanced cancers, including quantitative and qualitative studies of patients living with MBC and their families, were reviewed. The intent of this literature review was not to examine the methods used to measure quality of life but rather to summarize some of the more important recent research findings about the reality of living with MBC. Results of 13 surveys completed by 7939 respondents living with MBC were reviewed (see **Appendix 5**). The surveys are from 2006–2014; most were designed by breast cancer organizations, usually with the financial support of pharmaceutical partners or research grants (see **Table 6**).

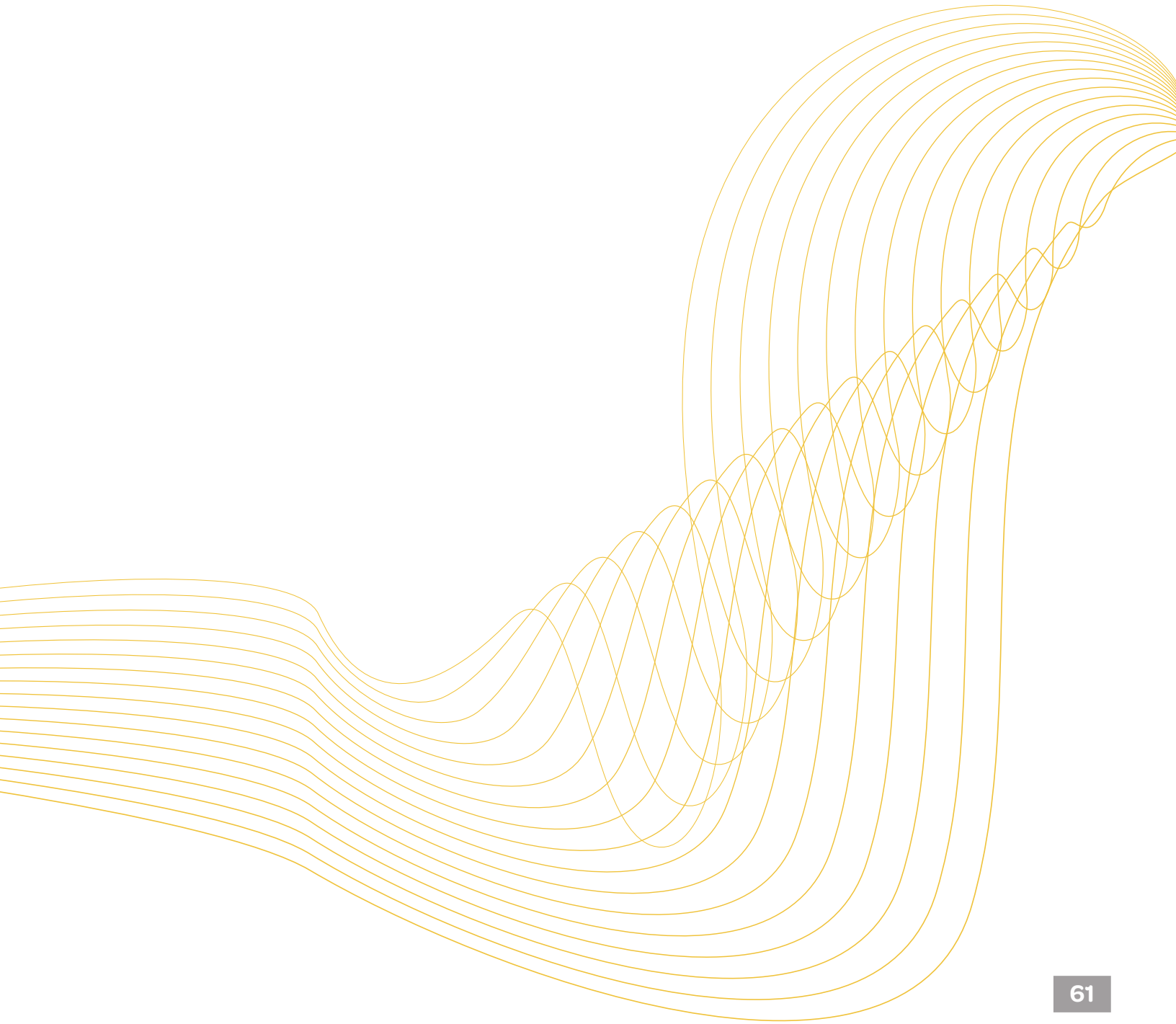
Table 6: 13 Surveys Completed by Respondents Living With MBC

Date	Survey Name	Sponsor
2006	Silent Voices: Advanced (Metastatic) Breast Cancer Needs Assessment Survey	Living Beyond Breast Cancer
2009, 2010	BRIDGE Survey: Identifying the Unmet Needs of the MBC Community	Pfizer with various support organizations
2011	A pan-European Survey of Patients with MBC	Eisai; Imperial College, London
2011	Key Support and Lifestyle Needs of MBC Patients	METAvivor
2011	Preferences of Patients with MBC	Research Advocacy Network (RAN), Department of Defense, Breast Cancer Research Program Center of Excellence
2011	HER2+ MBC Patient Experiences on Treatment in the Biologic Era	Genentech with various support organizations
2012	Metastatic Breast Cancer in Canada: The Lived Experience of Patients and Caregivers	Canadian Breast Cancer Network and RETHINK Breast Cancer
2012	Informational Needs and QOL in 1st Year MBC	Dana Farber Embrace Trial
2012	Impact of Toxicity on Patient Treatment Choices for MBC	RAN, Genentech
2013	Count Us, Know Us, Join Us International Survey	Novartis with various breast cancer organizations and Harris Interactive
2013	Control of Symptoms and Side Effects in MBC	AdvancedBC.org
2013	Surveying Young Women with MBC	Young Survival Coalition
2014	Cancer Experience Registry	Cancer Support Community

MBC = Metastatic Breast Cancer, QOL = Quality of Life

The survey data have some limitations. Two of the larger surveys had an international focus, 1 involving face-to-face interviews with patients referred by their oncologists in both developed and developing countries. Otherwise, the 13 surveys may not have captured data representative of the entire MBC population. First, all but 1 survey was completed online. Consequently, the demographic information collected reflects Internet users, who tend to be affluent, educated, and white [116]—and data from population-based registries show that poor and black patients have worse breast cancer outcomes[30]. And because these surveys were promoted in online patient MBC communities, it is likely that some motivated patients responded to more than 1 survey. Finally, overall, the survey respondents had a mean age of 55 years (younger than the median age of invasive breast cancer diagnosis in the US, 61 years)[30], were well educated, had health insurance, were married or partnered, and were predominantly white, and nearly half had children still living at home.

Not available for review and analysis are the upcoming results from the Novartis Oncology "Make Your Dialogue Count" survey in the US, conducted during the summer of 2014. This survey included 234 caregivers, along with 359 women living with MBC and 252 licensed oncologists to better understand potential gaps in treatment goals among patients and oncologists, experiences dealing with treatment side effects, and related emotional dynamics. Survey responses will be reported in December 2014 at the San Antonio Breast Cancer Symposium.



Results of the Quality of Life Landscape Analysis

The following 6 interrelated aspects of living with MBC are covered in the analysis:

1. Psychosocial distress

Psychological health is a major focus of quality of life assessment, and for good reason. As one researcher points out: "When a person has incurable disease, optimizing quality of life and meeting the woman's psychosocial and information needs must be central to excellent care"[39]. Yet studies have shown that the majority of patients with MBC experience significant emotional distress[40-42]. Some estimates are that as many as one third of MBC patients suffer from mood disorders such as major depression and anxiety, and one quarter experience mild depression[39, 42-44]. The scores on validated quality of life tests are much worse among MBC patients than in the overall population or even among patients with other serious illnesses[4]. Even more troubling, professional follow-up and mental health referrals for MBC patients from providers are often lacking[45].

Researchers have applied differing theoretical constructs to examine sources of emotional distress. An analysis of 26 quantitative and qualitative studies of MBC patients[46] found uncertainty and lack of control to be an overarching theme. Other sources of distress were fear of disease progression and death, grief over impending losses, worry over the impact on family members, and the sense of the disease as a "ticking time bomb," with patients waiting for treatment to fail and the MBC to progress.

The theme of loss is pervasive, from the loss of femininity, sexuality, and attractiveness to loss of roles in family and community to loss of dignity and independence as the disease progresses. Many women with MBC mourn the loss of their ability to actively care for their families and experience acute anguish about leaving their children without mothers and their spouses without partners. Those who are nurturers may find the pain their cancer inflicts on the people they love hard to bear.

The theme of loss is pervasive, from the loss of femininity, sexuality, and attractiveness to loss of roles in family and community to loss of dignity and independence as the disease progresses.

Surveys also confirm that MBC patients have significant emotional distress and indicate that access to mental health services is often either lacking or is not pursued by patients who could benefit[57]. Although most surveyed patients believe they are coping well[58], a substantial minority report symptoms of depression and anxiety, which often go untreated. Emotional distress tends to worsen with disease progression, as symptoms and side effects increase[57].

Patients and family members struggle with anticipatory grief and making end-of-life plans, often feeling alone[59]. Loss of control is part of the distress most patients feel[46]. A patient's sense of control can be enhanced in a number of ways: by becoming well-informed about the illness and its treatments; through immersion in meaningful tasks, including continuation of work that offers satisfaction and financial support; through realistic planning for the future; by seeking social support; and by caring for one's family. Many patients speak of having discovered a new sense of meaning, having a new appreciation of how their time is precious, cherishing time with their loved ones, and looking forward to significant events.

In examining different coping strategies, studies indicate that patients' attempts to cope by avoidance turn out to be far more distressing than direct and active discussion and problem solving, a finding in many serious diseases[47].

Numerous studies have found that better emotional functioning is strongly linked with fewer physical symptoms[48-52]. These multiple symptoms interact with one another in unknown ways. As one notable example, 56 consecutive newly diagnosed MBC patients in one hospital-based study[51], when scored for health-related quality of life and coping capacity using a series of validated measures, reported "multiple, concurrent and interrelated" symptoms, with two thirds reporting 10 to 23 symptoms. In another study, clusters of symptoms tended to be associated with one another: for example, fatigue, drowsiness, nausea, decreased appetite, and breathlessness[53].

Access to mental health services is often either lacking or is not pursued by patients who could benefit.

Adjustment to illness, write Brennan et al.[54], involves "ongoing psychological processes that occur over time as the individual, and the individuals in their social world, manage, learn from, and adapt to the multitude of changes which have been precipitated by the illness and its treatment." Fortunately, many patients and families become quite knowledgeable about MBC and how to live with the disease. Time passing since recurrence or diagnosis can moderate psychosocial distress[55]. Coping and adjustment are extremely complex processes, however, and not all MBC patients are equally resilient.

Longer-term adaptation after MBC diagnosis has not been widely studied. However, in 1 survey, nearly half of patients with HER2+ breast cancer surviving more than 6 years after MBC diagnosis still reported symptoms of anxiety and depression, despite decreased physical symptoms[56].

In surveys, most patients' overall satisfaction with their HCPs is good, and they generally believe they are coping well despite the challenges they face[57,58,60]. They attribute the coping to their own resilience and spiritual beliefs and to the kindness and generosity of others[61]. A number of small qualitative studies across diverse socioeconomic and racial populations of women with MBC have reported that maintaining hope is a critical factor in coping[62].

Emotional distress tends to worsen with disease progression, as symptoms and side effects increase.

Psychiatrist David Kissane describes the challenge of living with MBC as a confrontation of existential suffering[63]. Feelings of hopelessness and futility, loss of faith and transcendence, loneliness, shame, fear of dependency, profound sadness, and death anxiety are all part of a universal and fundamentally human struggle as patients deal with their mortality. Each challenge contains within it the seeds of transformation and adaptive adjustment. And "physicians can do much," says Kissane, "to nurture courage and maintain each person's sense of meaning, value, and purpose."

In conclusion, interventions for anxiety and depression in MBC patients represent a crucial service that health care workers can add to the patients' and families' own set of coping tools. Appropriate referrals to mental health professionals, for medical and nonmedical treatment and other interventions, are important, whether the referral is for pharmacological, behavioral, or psychological intervention or some combination thereof. An extensive literature exists on the efficacy of various methods of helping cancer patients confront psychosocial issues, symptoms of disease, and side effects of treatment. Sources of emotional support, individual and group psychotherapy and counseling, as well as adequate information about the disease, its treatments, and methods to alleviate symptoms and side effects have all been shown to be useful in helping patients to cope with and adapt to their disease[64].

2. Emotional Support

For MBC patients, emotional support from family, friends, community, other people living with MBC, and HCPs plays a crucial role in decreasing psychosocial distress. Research across many diseases indicates that emotional support is strongly associated with improving health outcomes and even extending life. Between married and single patients with MBC who feel hopeless, the single patients are more vulnerable to depression[65].

In surveys, MBC patients generally report receiving adequate emotional support from friends, family, community sources, and HCPs. However, survey respondents are more likely than other MBC patients to be partnered and have sufficient financial and social resources, and they may therefore be less isolated overall.

Emotional support is strongly associated with improving health outcomes and even extending life.

Chronic, debilitating illness such as MBC often leads to increasing social withdrawal[66]. Sometimes described as "a marathon, not a sprint," life with MBC involves challenges that last for months and years, not days and weeks. Over time, sources of support can erode. Friends and family may not comprehend the toll that continuous treatment takes or the inevitability of disease progression. Even patients who feel well supported initially or in times of medical crisis may find that support from friends, family, and community tends to wane with time and as the disease progresses[57, 61].

Nearly half of surveyed MBC patients report a sense of stigma, of feeling like outcasts or feeling isolated, especially within the larger social context of the breast cancer community. Symbolized by ubiquitous pink ribbons, support for patients with early breast cancer is highly visible and widespread[58-60]. MBC patients can feel silenced by the "triumphant, happy and healthy" rhetoric of breast cancer organizations[67].

Access to online peer support is important to many MBC patients who are Internet users. Surveys and studies have reported great benefit from contact with other MBC patients[3, 58, 59]. Most MBC patients say they highly value information and support from patients like themselves and that it helps them to cope and to feel less alone. However, few of these patients' HCPs recommend support groups or other contact with peers[57].

A cost of spending time with other MBC patients is the inevitable disease progression, which may be perceived as "too depressing" and may heighten emotional distress to the point where the sense of camaraderie and support is outweighed by grief and fear[68, 69]. Studies of hospital-based groups do not tend to be nearly as positive regarding peer support as are studies of online support groups[70, 71].

Surveys indicate that although almost all patients value emotional support, the preferred form of that support varies greatly: from meeting individually with mental health professionals, to participating in in-person support groups (whether professionally led or not), to semi-anonymous interactions with online patient communities. In addition, relatively few MBC patients report being involved with these sources of support, suggesting that many are either not aware of organized professional and peer support or simply prefer to rely on informal support networks within their families and communities[3]. There are certainly some patients who cope in isolation, either by choice, by circumstance, or because of cultural beliefs; some view their disease as shameful or as a punishment[62].

Support for partners or spouses also matters to MBC patients, who are often keenly aware of the impact of their illness on their families. Some studies indicate that spouses may suffer more emotional distress than patients, perhaps because of feelings of uncertainty, hopelessness, and helplessness. Moreover, spouses are likely to receive significantly less emotional support from family and friends than patients[62]. Not surprisingly, mutual spousal support plays a key role in coping with MBC for both partners[52, 72].

3. Information

Most MBC patients say they highly value information and support from patients like themselves and that it helps them cope and to feel less alone.

In 2013, an IOM committee reviewing the current state of cancer care described a system in crisis and issued an urgent call for change[38]. Patient engagement in healthcare decision-making was identified as a top priority. Such engagement cannot occur, according to the IOM, without patients being adequately informed: "The cancer care team should provide patients and their families with understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of the total and out-of-pocket costs of cancer care." Moreover, the committee stipulated that this information should be personalized, leading to care plans that reflect the patient's needs, values, and preferences, considering palliative care needs and psychosocial support across the entire continuum of cancer care.

Information is perceived as a primary need by about 75% of MBC patients, as reported in several large surveys, regardless of nationality[44, 59, 73]. The role of information in helping patients and families cope has also been well documented in the health care literature[74]. Information that facilitates decision making about treatment may help patients cope with uncertainty and loss of control, thus reducing anxiety and depression[46]. Information-seeking

is an important component of self-efficacy, enabling patients to regain a sense of control.

In 1 survey, feeling informed was statistically associated with lower levels of anxiety, depression, and fatigue as patients reported a greater sense of control, despite uncertainty[3].

At least three quarters of surveyed patients say they seek information about MBC and treatment options "very frequently"[3, 59], a finding confirmed in face-to-face interviews with a broader, international patient population[60]. Information on coping with and managing side effects and symptoms is also strongly desired by most patients. Almost all MBC patients surveyed say that being informed about treatments and the progression of disease helps their quality of life[61].

Nearly half of MBC patients surveyed say they find the information they need difficult to locate and confusing and that what they do find does not fully address their needs. In fact, informational needs of patients change throughout the course of MBC. There are significant times when patients and family members seek information from HCPs and elsewhere: initial MBC diagnosis, treatment failure, symptom crisis, disease progression, and end of life. Patients also vary in their response to the information formats available—websites and webinars, teleconferences, videos, print materials, meetings, presentations, and conferences. Thus, information is probably best delivered in several of these formats. In addition, the type of information sought varies. For example, young MBC patients express concerns related to genetic testing, fertility, dating, children, career, and other issues and want resources and support dedicated to their specific needs[59]. In addition, information and support are not distinct from one another. MBC patients find information to be supportive and seek information from their support systems; thus, services for MBC patients should offer both[3].

Information is perceived as a primary need by about 75% of MBC patients.

Feeling informed is associated with lower levels of anxiety, depression, and fatigue as patients reported a greater sense of control, despite uncertainty.

Access to information is not only associated with patients' ability to cope but also affects clinical trial enrollment. Surveys show that MBC patients who seek out information are more likely than others to participate in clinical trials[60, 61]. Patients are often motivated to participate in trials because they believe that access to new treatments is vital to extending life; treatment choices may be limited by cost, insurance coverage, and delays in trial completion. However, patients say they are rarely informed about new treatments or clinical trials available and even more rarely about those beyond their hospital or oncology practice[61]. When they do enroll in clinical trials, MBC patients most commonly cite encouragement from their HCPs as the reason for their participation[75].

4. Communication and Decision Making

Busy oncologists do not always have the time, skills, or inclination to offer details in a form that patients or family members can easily grasp, especially when treatment choices are unclear and the prognosis may be poor.

MBC patients strongly desire better communication with their health care providers.

It would seem obvious that realistic goals and expectations of treatment, specifics about the potential harms and benefits of cancer therapies, and timely feedback regarding scans and other tests to ascertain current disease status would all be essential components of informed decision making for MBC patients. Nevertheless, research indicates that patients are often not well informed in any of these areas. Many MBC patients persist in believing a cure is likely, when it is not. According to 1 study[76], two thirds of patients with metastatic cancers were not informed of the likely impact of a given treatment on their quality of life, and nearly one third were unaware of the uncertainty around the described benefit.

One problem with patient–clinician communication is that, although almost all patients say they wish to receive all possible information around their diagnosis, good or bad, not all truly wish to know the details[77]. The available research strongly suggests that patients are less anxious and depressed when their role in making treatment decisions is congruent with their wishes, suggesting that communication of at least patients' desires is critical.

Busy oncologists do not always have the time, skills, or inclination to offer details in a form that patients or family members can easily grasp, especially when treatment choices are unclear and the prognosis may be poor. According to one review, "time constraints in busy clinics, and physicians' belief that they know the amount and kind of information that is best for their patients to receive, may contribute to consultations that are physician-directed and physician-dominated, leaving patients with unmet communication needs and feelings of dissatisfaction"[78]. Some research suggests that even when communication is clear, patients and families may overestimate the likely prognosis and benefits from treatments, which may in turn interfere with good decision making. This is especially likely to occur toward the end of life, when an approach that emphasizes palliative care may enhance quality of life and even extend survival.

A recent, large survey of MBC patients[61] demonstrates the magnitude of the problem, even in an educated, insured, and advantaged population. The survey found that nearly all patients received information about their type of cancer but two thirds did not receive any guidance or tools to assist in decision making. As a consequence, nearly half of those who didn't write down their questions before consultation with their physician felt unprepared to make treatment decisions.

Surveys indicate that MBC patients strongly desire better communication with their HCPs. They would like to feel cared for and respected as persons, not just patients, and to have their concerns heard and the challenges they face understood. Areas much in need of improvement are continuity and coordination of care; patient-friendly office procedures and hours, including less waiting time, timely test results, and better access to staff when the office is closed. Also needed are higher-quality patient education and disclosure to facilitate treatment decision making, more time with providers to address patient concerns, and referrals to second opinions and specialists[57, 79].

An overwhelming majority of surveyed patients with MBC are either currently undergoing an anticancer treatment or are in the process of changing treatments after disease progression. When asked, very few survey participants say they prefer to "live out the time they have peacefully, without treatment"[3, 57].

When asked, MBC patients have many concerns about the treatment they receive, some of which could be addressed through better communication with HCPs. They express frustration at the trial-and-error nature of treatment, seek less toxicity, and are eager for biomarkers predictive of treatment benefit. When asked about the risk-to-benefit "trade-off" of treatment, MBC patients show a willingness to tolerate significant toxicity in exchange for possible benefit, such as longer survival or even a modest delay in progression of their disease[79-81]. However, symptom severity is also of concern to them, and treatment choices may vary by stage of life—for example, whether or not children are still at home[80].

We did not review the extensive literature on communication issues with physicians, patients, and families surrounding end-of-life choices, as the focus of our analysis is living with MBC. But it is never too soon for MBC patients to establish lines of frank and open communication with their treating physicians, as a full discussion of the goals of treatment is central to quality of cancer care as well as quality of life.

People diagnosed with MBC would like to feel cared for and respected as persons, not just patients, and to have their concerns heard and the challenges they face understood.

5. Relief of Physical Symptoms

For most MBC patients, symptoms and side effects of treatment disrupt daily life and interfere with normal activities.

Since the goal of MBC treatment is to control the disease for as long as possible while preserving functional status and quality of life, a major task for the health care team is palliating symptoms that may interfere with daily life, causing emotional distress, and the fatigue, sleeping difficulties, pain, and many other symptoms typically experienced. As mentioned previously, physical symptoms are intertwined with psychosocial distress. As the disease progresses, symptoms tend to become more debilitating and interfere more with normal functioning, resulting in greater distress. One consecutively sampled community-based study[82] found significant physical impairments in almost all 163 MBC patients, yet only one third were receiving appropriate remediation with occupational or physical therapy. Racial and socioeconomic disparities in provision of care were clearly present.

Physical symptoms of MBC may be generalized, such as fatigue or insomnia, or organ-specific, according to the site of tumor-cell spread. Organ-specific examples include dyspnea (breathlessness), which may be associated with lung metastases or pleural effusion, and anemia, which may be related to bone marrow metastases or to low red blood cell counts from chemotherapy.

The prevalence of chronic pain in patients with metastatic cancers is estimated at 70–90% and is among the most distressing physical symptoms[83]. Pain may be associated with tumors exerting pressure on or displacing nerves. A common source of pain is bone metastases, although bone-modifying agents have significantly decreased bone pain and fractures in recent years. Some drugs used to control the cancer cause worrisome and in some cases permanent side effects, such as taxane-related peripheral neuropathy.

Nausea and vomiting may be related to involvement of the gastrointestinal tract, such as liver or peritoneal metastases or ascites, or to brain or other central nervous system metastasis or side effects from chemotherapy or other anticancer agents. Significant progress has been made in developing supportive medications that can decrease the frequency and severity of nausea and vomiting.

Fatigue is by far the most common physical symptom reported by MBC patients, occurring in 80% or more of those undergoing treatment[84], as confirmed in patient surveys[57]. Fatigue is frequently associated with depression or anxiety as well as with treatment toxicities and MBC itself[4]. Other contributing factors may include tumor burden, pain, difficulty sleeping, anemia, poor diet, inactivity, and other coexisting conditions[51, 85-88]. Fatigue is also one of the most difficult symptoms to treat[89].

Up to 75% of patients with advanced cancer have problems either falling or staying asleep, with a lesser number meeting the strict criteria for insomnia[90]. In a recent survey, more than half of surveyed patients report difficulty sleeping, gastrointestinal issues, pain, and problems with memory, organization, and concentration. Nearly half of patients report hot flashes, neuropathy, changes in weight, sexual and self-image issues, and emotional upset and stress[57].

Not surprisingly, MBC patients also say that living with the disease and undergoing continuous treatment has a significant impact on quality of life. For most, symptoms and side effects of treatment disrupt daily life and interfere with normal activities. As the disease progresses and symptoms intensify, treatments become even more disruptive, and emotional distress increases.

The past 2 decades have seen major improvements in supportive care, but many MBC patients fail to receive adequate palliation for their symptoms that could improve their quality of life.

Nearly half of patients say their providers don't ask them about the symptoms and side effects they are having, leaving it up to them to ask for help when they need it[57, 61]. Yet nearly as many worry about "bothering" their doctors, or express concern about being seen as "complainers," and are hesitant to bring up their concerns, especially about topics such as emotional distress and sexuality. One large survey found that 35% of MBC patients seen in comprehensive cancer centers, and 50% seen in community oncology practices, did not mention sources of distress to their providers[57, 59, 61]. Clearly, communication difficulties exist on both sides of the physician–patient relationship.

The past 2 decades have seen major improvements in supportive care, but many MBC patients fail to receive adequate palliation for their symptoms that could improve their quality of life. Very few patients are referred to palliative care or pain specialists during their treatment. In fact, only one quarter of patients are given a symptom checklist as part of their routine office visits, as recommended by National Comprehensive Cancer Network guidelines[57].

A common perspective among oncologists is that "managing symptoms to maintain an optimum quality of life is the major goal of care in the metastatic setting because all therapy is palliative"[64]. However, the emphasis on palliation as the primary goal in MBC may not conform to the cancer-controlling strategies many oncologists discuss with their patients, nor may it reflect patient wishes, as detailed in surveys where MBC patients clearly prioritize remote chances of treatment efficacy even at the cost of significant toxicity[81]. The dynamic tension underlying this "treat or palliate" duality of choice runs throughout the literature on metastatic cancer and plays an important role in disputes about health care policy and allocation of resources. However, treatment and palliation need not be in conflict but may instead represent different points on the continuum of care during the course of the disease, driven by the wishes of an informed patient in consultation with the treatment team.

6. Practical Issues: Work, Insurance, Finances

The practical issues MBC patients and their families face are monumental. Surveys reveal that financial hardship is a fact of life for many families, driven by inability to work, for both patient and family caregiver; travel expenses; and high out-of-pocket co-payment and treatment costs[58, 59, 61].

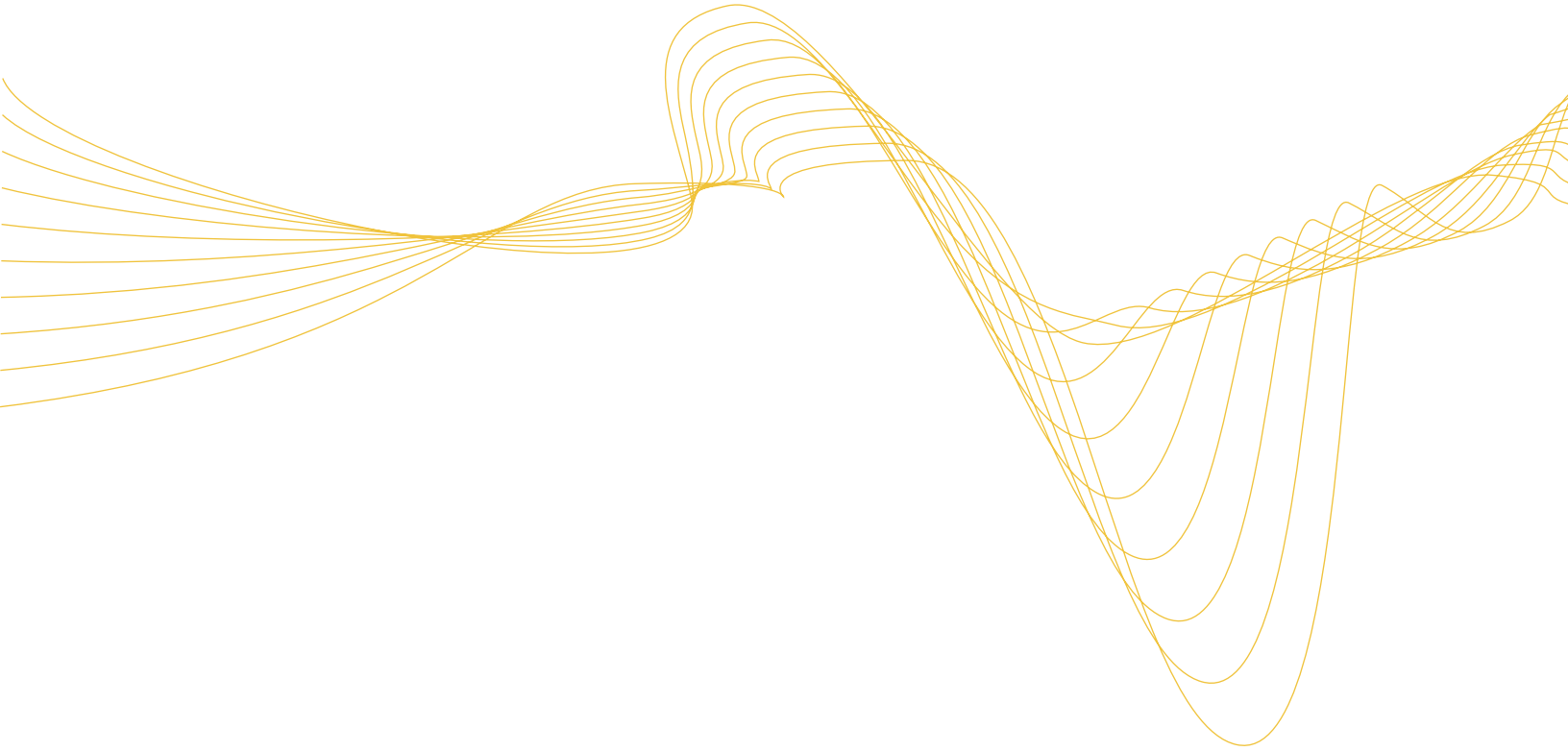
The practical issues MBC patients and their families face are monumental.

Merely having health insurance may fail to insulate patients from the financial impact of expensive and ongoing treatments[91]. In patients with early stage breast cancer, compliance with treatment decreases as the amount of co-payment increases, suggesting that patients may be forced to choose between treatment and other expenses[92]. As the cost of new treatments escalates to levels far exceeding the annual income of most families, it's easy to imagine patients having to make difficult choices, especially during the 2-year lapse between Social Security Disability determination and Medicare coverage, when many families' savings are depleted[93]. High rates of bankruptcy have been documented, particularly among MBC patients under 65 years of age, in a population-based study[94].

Despite the challenges they face, most people with MBC and their families demonstrate considerable resilience, adaptation, and courage as they continue to live with the disease.

The majority of MBC patients are in the workforce at the time of diagnosis. Within the first year of treatment, at least half have quit or lost their jobs, which often results in greater financial problems and a lower standard of living than before diagnosis[57, 61, 95]. Most patients report being unaware of available resources that help address financial need. For example, one quarter of the MBC patients completing an online survey in the US were not aware that MBC patients with a certain amount of work history qualify for Social Security Disability benefits. Although few of the more advantaged patients who completed the surveys had to forgo treatment because of financial circumstances, many missed vacations, celebrations, and social events and depleted their savings[58, 95].

Other practical needs that MBC patients report as problematic include accessing transportation to health care facilities; managing the home, child care, and shopping; getting help with applications for disability or insurance benefits; obtaining medical referrals; and finding help with work-related issues, such as Americans with Disabilities Act protections and medical leave[3].



Conclusions

Despite the challenges they face, most people with MBC and their families demonstrate considerable resilience, adaptation, and courage as they continue to live with the disease[96]. But what they do, they cannot do alone. They need everyone involved in breast cancer advocacy and support calling for improved treatment and services.

Although cures cannot yet be offered to MBC patients, health care and support organizations already know how to guide patients and their families toward better quality of life. This review demonstrates that the research is clear, but the application is poor. We know how to help patients cope, how to inform them, and how to perform the services they need. But the resources to do so and the broader recognition of those needs are still lacking.


4

Chapter 4: MBC Information and Support Services—an Analysis of MBC Alliance Member Efforts

Katherine Crawford-Gray[2]

[2]*Metastatic Breast Cancer Alliance*

Abstract

Information and support services are essential in helping patients manage common aspects of living with MBC. ***Methods:*** Staff and volunteers of 16 nonprofits were interviewed to identify gaps and duplications in member services. The most recently available Form 990s, as well as research reports, surveys, scientific roundtables, posters, and services were also reviewed for MBC-specific content. Information and support services provided on the websites of the nonprofits, as well as 5 pharmaceutical members, were assessed for quality, breadth, and depth of MBC information. Member websites were also assessed for attractiveness to the user, 13 aspects of MBC information, evidence supporting the MBC information provided, recency of updates, ease of navigation, and use of social media tools. Thirteen organizations were sent an online survey about helpline/hotline services. Finally, 10 publicly available surveys and 4 proprietary reports provided by Alliance members were reviewed. ***Results:*** While the majority of the nonprofit members focus on meeting the information and support needs of the breast cancer community, not enough attention is paid to the MBC patient populations. Print and electronic material provided by the Alliance members requires that patients have relatively high health literacy and be Internet savvy. There are no dedicated helpline services for MBC patients; conferences and in-person networking events tend to be in large cities. Opportunities to create community through social media are very limited. Nonprofits report their services are underutilized and there is a lack of data collected on who is using the services. Gaps in information from members include lack of detailed information on the latest treatments, quality of life, palliation, and advanced directives and end-of-life care. ***Conclusions:*** Alliance members provide some level of high-quality information and support services to MBC patients and their families. However, because Alliance members offer so much general information, it is difficult for individual patients to find what they need. Organizations must consider how to reach other subgroups of the MBC patient population.

Introduction

Information and support services are essential in helping patients manage common aspects of living with MBC. MBC patients experience psychosocial distress, particularly depression and anxiety; require emotional support from family, friends, community, and other people with the disease; need information to help facilitate and empower decision making around treatment and end of life; deserve relief of physical symptoms, both during treatment and end of life; and must resolve practical issues with work, insurance, and finance. (These issues are addressed in detail in **Chapter 3**.)

The literature review in **Chapter 3** finds that, despite a greater knowledge and recognition of these quality of life issues over the past 2 decades, they persist—and addressing them remains a challenge for advocate organizations.

Another part of this landscape analysis was to better understand the breadth and depth of information and support services provided by MBC Alliance members, which are some of the most active advocate organizations in the US. The analysis will help the Alliance to identify gaps, duplications, and opportunities to most effectively leverage its collective resources, power, and influence to improve the quality of life of people living with MBC.

Scope of Alliance Membership

The MBC Alliance currently includes 23 nonprofit organizations working in cancer, breast cancer, and MBC. The 23 nonprofit members vary greatly in scope of mission but share a desire to improve quantity and quality of life of MBC patients and their families. Collectively, Alliance members raise $750 million annually in philanthropic support for cancer. Each offers various educational and patient support services, including information and support services for MBC patients and their families.

The 6 industry members of the Alliance all develop and market drugs to treat MBC. Representatives from the patient advocacy departments have actively participated alongside the advocate organizations in the research and review process for the landscape analysis.

We know that MBC Alliance members are only 1 part, albeit a crucial part, of the landscape serving patients and caregivers living with MBC. Public and community hospitals, health care systems, university medical centers, grassroots organizations, and many others undertake very valuable work across the country. The services provided outside of the MBC Alliance are not covered in this analysis.

Methods

We interviewed executive, program, and/or volunteer leadership of 16 nonprofits and 5 pharmaceutical members of the Alliance to identify the major gaps and duplications in services across the Alliance in meeting the needs of MBC patients, recommend strategies for how the organizations can better work together to reduce gaps, and identify areas ripe for collaboration. A table of interviewees is provided in **Appendix 6**.

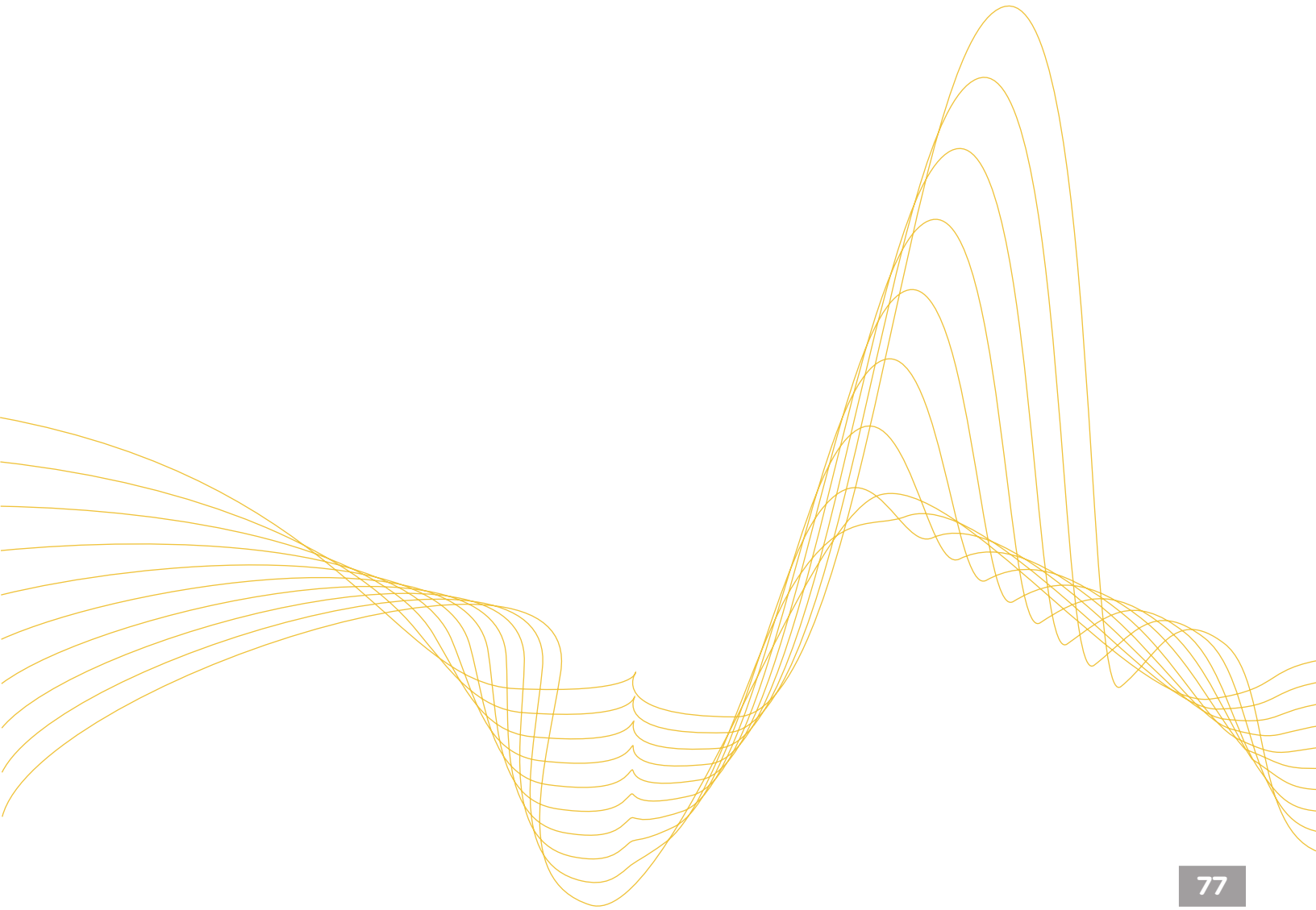
Information about each organization was collected from their respective websites and most recently available Form 990. Additionally, collateral specific to MBC was reviewed, including research reports, surveys, scientific roundtables, posters, and services such as conferences, networks, support lines, counseling, and peer-to-peer group support.

Websites of Alliance members, including pharmaceutical members, were assessed for attractiveness to the user, amount of MBC information, evidence supporting the MBC information provided, recency of updates, ease of navigation, and use of social media tools. The quality of MBC-specific content was assessed to identify to what extent, and at what

level, the websites offered information in 13 areas: diagnosis, current treatment options, latest research and new treatments, symptoms and side effects, monitoring treatment, clinical trials, complementary medicine, pain management, communication, psychological and social support, parenting issues, hospice and end of life care, and advance directives. Print materials (excluding those from pharmaceutical members) were appraised for the extent and quality of MBC content. Videos and webinars were not assessed. Thirteen organizations were sent an online survey to capture information about helpline/hotline services; 8 organizations completed the survey. The survey participants are provided in **Appendix 7**.

A top-line review of 10 publicly available surveys and 4 proprietary reports provided by Alliance members was undertaken to identify continuing themes, recent trends, and new gaps in information.

Preliminary findings were discussed with Alliance members in a meeting in New York City on March 3-4, 2014.



Results

Profile of MBC Alliance Members

The Alliance members are as diverse as the people they serve.

The majority of the nonprofit members focus on meeting the information and support needs of the breast cancer community. Within this group, several Alliance members specialize in supporting women with particular types of breast cancer (Inflammatory Breast Cancer Research Foundation, Triple Negative Breast Cancer Research Foundation, and Triple Step Toward the Cure). A small number of members support and/or advocate for people with any type of cancer (American Cancer Society Cancer Action Network, Cancer*Care*, Cancer Support Community, Patient Advocate Foundation). Two Alliance members—AdvancedBC.org and the Metastatic Breast Cancer Network—focus exclusively on MBC (**Figure 9**).

Figure 9: MBC Alliance Members by Cancer Focus

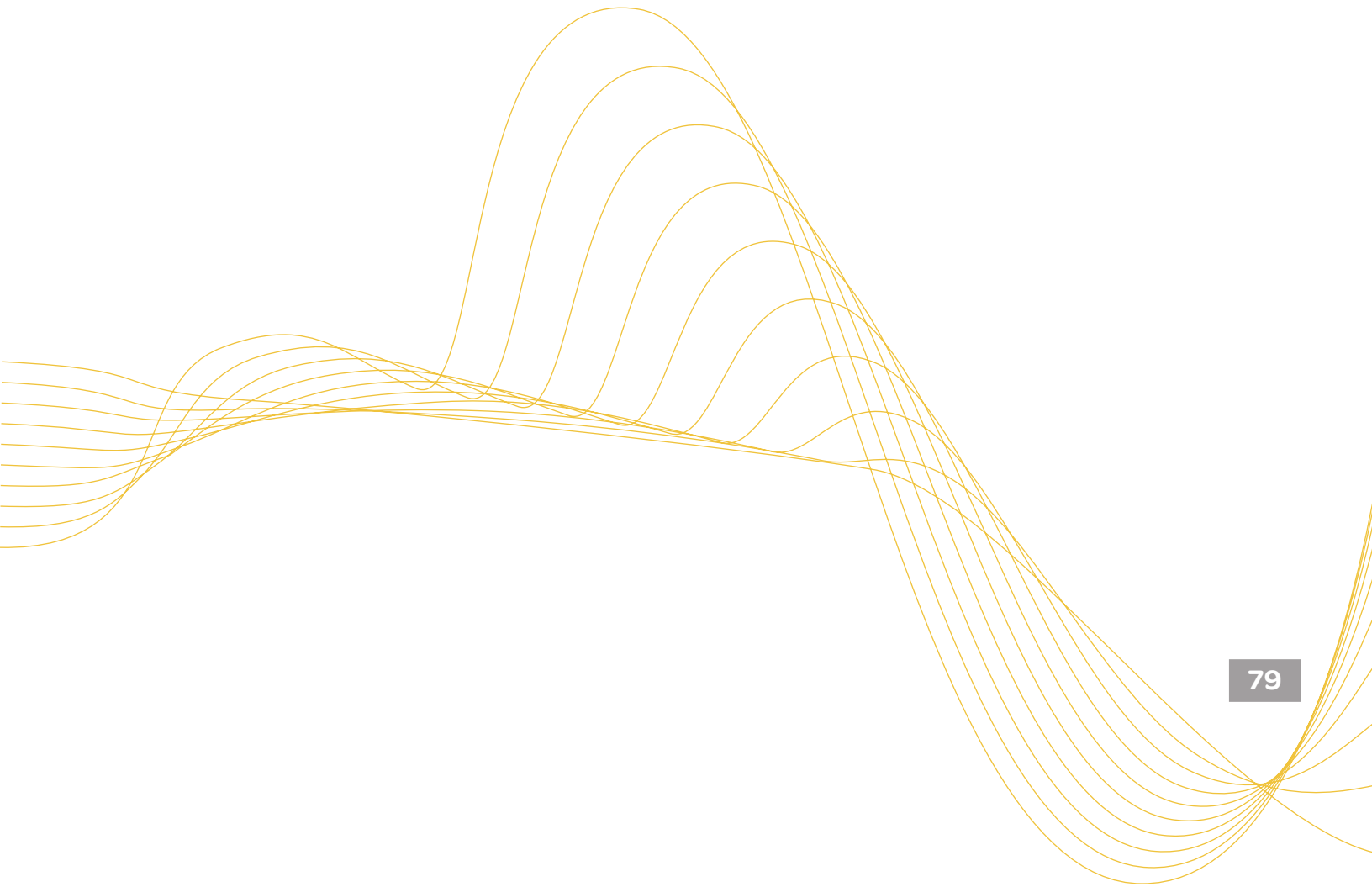
* Breast and Ovarian cancer

Δ These 16 organizations were interviewed as part of the landscape analysis.

Some members work for particular target populations, such as patients with hereditary risk (FORCE [Facing Our Risk of Cancer Empowered]), black patients (Sisters Network Inc.), Latina/o patients (Nueva Vida), Jewish patients (Sharsheret), and young patients (Young Survival Coalition).

Some members have an online presence only; others have a more extensive reach. Susan G. Komen, for example, works at both the national and local levels through its headquarters and national network of more than 100 local affiliates. (Note that, for the most part, Komen reported MBC-related information and activities of its headquarters rather than the local affiliates, for which the data are not complete.) Other participating Alliance members were Avon Foundation for Women and Breast Cancer Research Foundation; these 2, in addition to Komen, are among the largest private funders of breast cancer research in the US. In contrast, many Alliance members have relatively limited resources; those with the most revenue typically have the broadest focus on breast cancer. The 2 organizations focused solely on MBC are the least resourced.

There is considerable variability among members as to where they direct their resources. As noted, some nonprofits are active on a number of fronts, including research, patient support and education and policy advocacy, whereas others are more focused in the scope of their activities. Each member organization offers various educational and/or patient support services, with almost all including information and support services for MBC patients and their families. Of the advocate organizations providing information and support services to people living with MBC, education is the largest area of investment.



Tables 7a and 7b provide a snapshot of the breadth of information and support services provided by advocate members.

Table 7a: MBC Information and Support Activities of MBC Alliance Members

Organization	MBC Goals	Patient Advocacy	Research	Policy	Patient Education	Patient Support	Awareness	Clinical Trials / Registries	Scientific Contribution
AdvancedBC.org	✓	✓	✓	✓	✓	✓	✓	✓	
American Cancer Society Cancer Action Network		✓		✓					
Avon Foundation for Women	✓		✓						✓
Breastcancer.org		✓	✓		✓	✓	✓	✓	
BreastCancerTrials.org							✓	✓	✓
Breast Cancer Research Foundation	✓		✓				✓	✓	✓
Cancer Support Community					✓	✓	✓	✓	✓
Cancer*Care*					✓	✓			
Dr. Susan Love Research Foundation		✓			✓	✓	✓	✓	
FORCE		✓	✓		✓	✓	✓	✓	
Inflammatory Breast Cancer Research Foundation			✓		✓			✓	✓
Living Beyond Breast Cancer					✓	✓	✓	✓	
Metastatic Breast Cancer Network	✓	✓	✓		✓	✓	✓	✓	
Nueva Vida					✓	✓			
Patient Advocate Foundation		✓			✓	✓	✓		
Research Advocacy Network			✓						
SHARE	✓	✓		✓	✓	✓	✓	✓	
Sharsheret		✓	✓	✓	✓	✓	✓		
Sisters Network, Inc.									
Susan G. Komen	✓		✓		✓	✓	✓	✓	✓
Triple Negative Breast Cancer Research Foundation		✓			✓	✓		✓	
Triple Step for the Cure		✓			✓	✓			
Young Survival Coalition	✓	✓	✓		✓	✓			

detail

Abbreviations:

FORCE= Facing Our Risk of Cancer Empowered

SHARE= Self-Help for women with Breast or Ovarian Cancer

Table 7b: MBC Patient Support Provided by MBC Alliance Members

Patient Support Organization	Print	Teleconference	Support Groups	Radio/ Podcasts	TV/ YouTube	Chat	Message Boards	Facebook	Twitter	Blog	Helpline	Social Media App	Financial Assistance	Conference / Networking
AdvancedBC.org	✓													
Breastcancer.org	✓			✓		✓	✓			✓				
Cancer Support Community	✓	✓	✓			✓					✓	✓	✓	
Cancer*Care*	✓	✓	✓	✓							✓		✓	
Dr. Susan Love Research Foundation	✓			✓				✓	✓	✓				
FORCE		✓					✓				✓			
Living Beyond Breast Cancer	✓	✓	✓	✓	✓						✓			✓
Metastatic Breast Cancer Network	✓		✓		✓			✓	✓	✓				✓
Nueva Vida	✓	✓				✓								
Patient Advocate Foundation													✓	
SHARE	✓	✓	✓	✓	✓			✓	✓	✓	✓			✓
Sharsheret	✓	✓	✓		✓	✓					✓			
Susan G. Komen	✓						✓				✓			✓
Triple Negative Breast Cancer Research Foundation	✓						✓							
Triple Step Towards the Cure													✓	
Young Survival Coalition	✓		✓	✓		✓	✓	✓	✓	✓				✓

Definitions

Patient Advocacy - Use of health plans/mediation/arbitration; supporting patients to become advocates

Research - supporting MBC research; surveys; convened round tables

Policy - providing MBC policy forums

Patient Education - information to patients and their caregivers that will alter their health behaviours or improve their health status

Awareness - about MBC for the wider community; for families

Clinical Trials/Registries - providing information about clinical trials; maintaining registries

Scientific Contribution - MBC funded research

*current as of June, 2014

Information and Patient Support

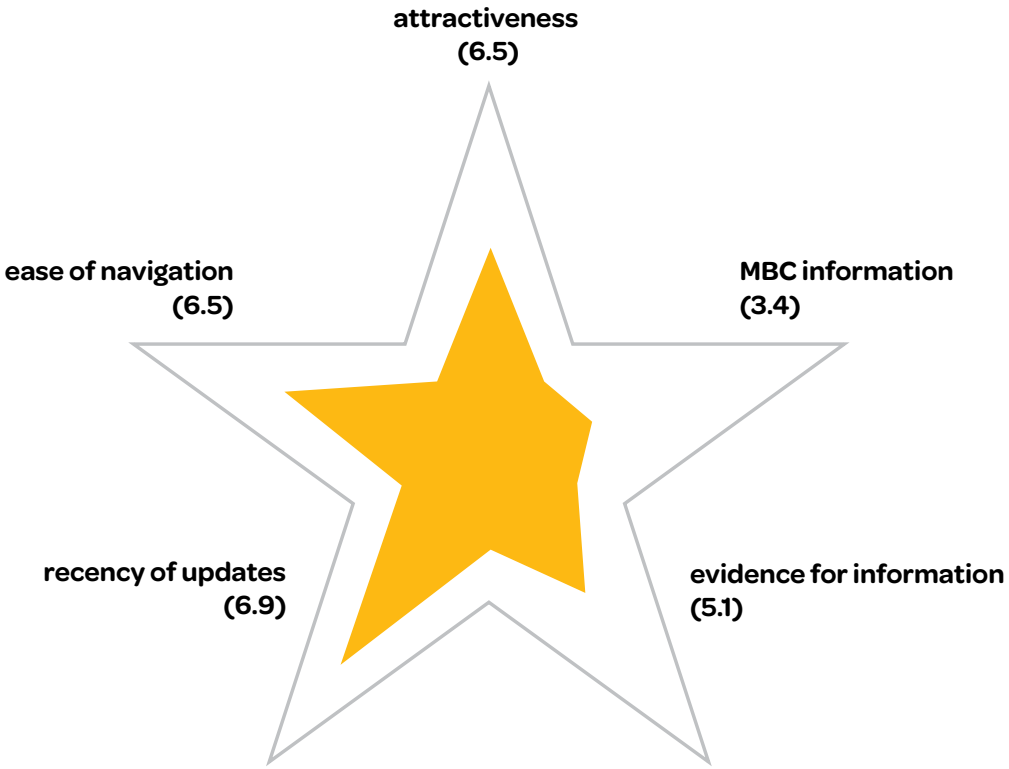
For MBC patients, information and support are often one and the same. The 2 main sources of information for MBC patients are electronic and print. Other "live" sources include conferences, telephone helplines, and webinars.

Between 2006 and 2013, the Alliance's advocate members developed a variety of educational materials about MBC. This information is featured on 12 websites as well as in over 40 print documents, 8 posters, 8 telephone and 7 online support groups, nearly 40 blog posts, 17 videos/television clips, more than 20 first-person stories, 19 webinars, and 78 conferences and workshops. Industry members among them have 5 unbranded disease-based programs and 6 disease-state programs.

Websites

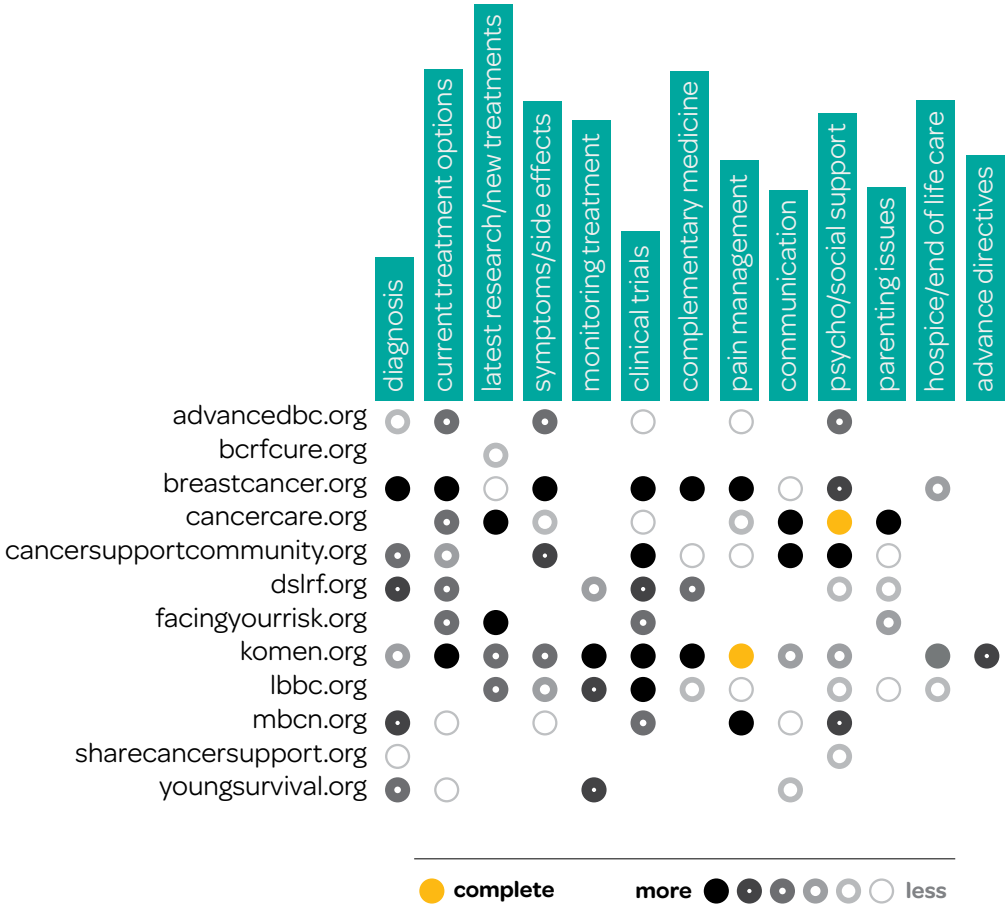
Websites are a main source of information. **Figure 10** shows findings on the usability of advocacy member websites. On the scale of 1 to 10, the overall mean across the 16 members was 5.7, with overall means for the individual score categories—attractiveness, ease of navigation, MBC information, evidence for the information given, and recency of updates—from 3.4 to 6.9. Some sites offer multiple languages and 1 allowed users to create customized pages. Most of the sites are not modern or designed with the end user in mind.

Figure 10: Usability of Advocacy Member Websites (on of a scale of 10, with 10 being the best and 0 being the worst)



On MBC advocate member websites, not enough attention is paid to the MBC patient populations or even to informing caregivers and early stage breast cancer patients about MBC facts. Opportunities exist to create more specific MBC content, social networking, and up-to-date information and to design more user-friendly websites. Regarding breadth of information, no single website among the Alliance members' sites provided MBC information and support, such as webinars and chat rooms, across all the desired topics, even when PDFs available on the sites were considered. Most topics are covered by fewer than 50% of the websites. Of the websites that do provide information on MBC, the depth and breadth of coverage varies (see **Figure 11a**).

Figure 11a: Breadth and Depth of MBC Information in Advocate Member Websites



Excludes Avon Foundation for Women, Research Advocacy Network, and Sisters Network Inc., which do not provide MBC information on their websites.

Most Alliance member websites provide information about clinical trials and encourage patients to discuss options with their health care team to enroll in trials. Some websites also provide services that match clinical trials to patients. For example, BreastCancerTrials.org (which joined the Alliance in March 2014) encourages patients to enroll in clinical trials as a routine care option. However, enrollment in clinical trials remains low owing to multiple factors, including lack of encouragement from physicians, the inconvenience of trial participation, fear of receiving a placebo, and difficulty meeting inclusion criteria[97].

Unbranded disease based websites:

advancedbreast cancercommunity.org

facesofMBC.org

pledgetofightforward.org

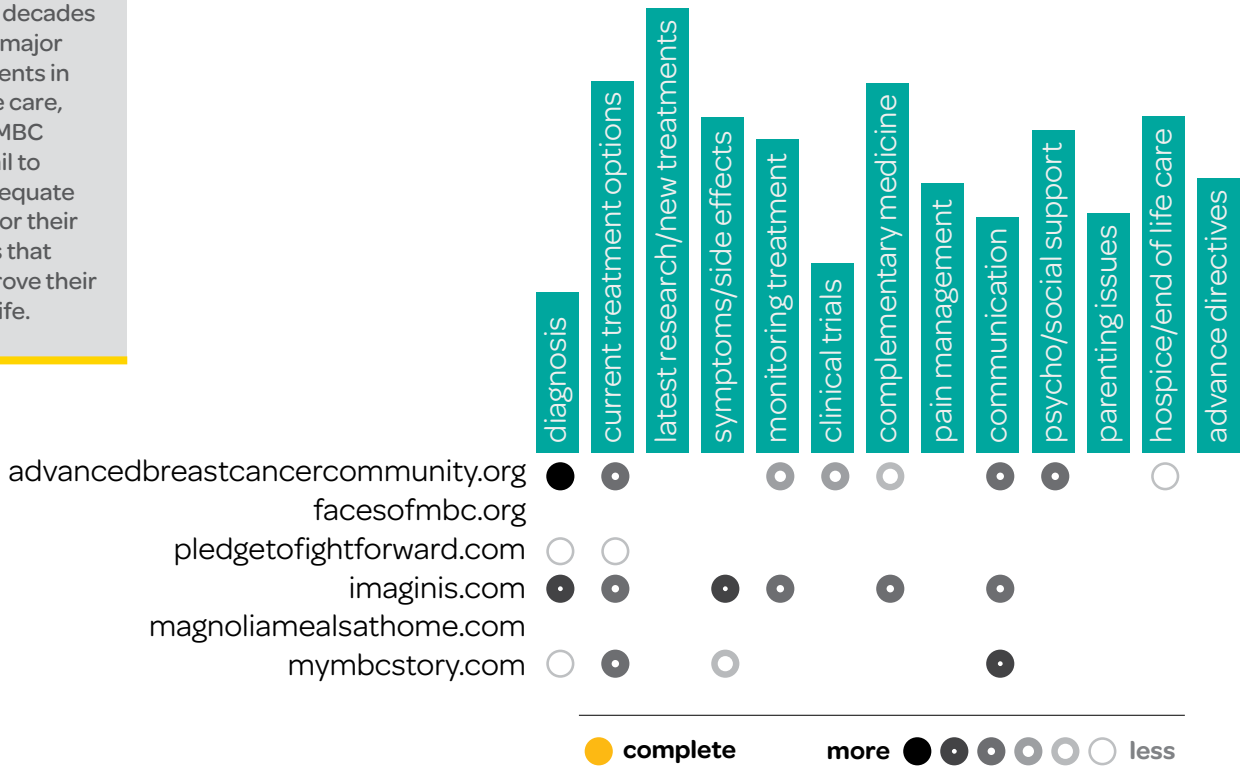
imaginis.com

myMBCstory.com

The 5 unbranded disease-based websites of our industry members are primarily designed as "sharing platforms" for patients, supporting social elements such as viewable comments and chat rooms. Those that do provide information, such as www.advancedbreastcancercommunity.org, tend to focus on diagnosis, current treatment options, and communication. Most sites provide links to patient MBC advocacy organizations and funder sites. In general, the websites lack overall cohesion, MBC content, and a well-organized links section. There appears to be no commitment to consistently update the sites. These issues leave the user wondering "Why am I here?" The breadth and depth of MBC information is shown in **Figure 11b**.

The past 2 decades have seen major improvements in supportive care, but many MBC patients fail to receive adequate palliation for their symptoms that could improve their quality of life.

Figure 11b: Breadth and Depth of MBC Information in Industry Member Unbranded Disease-Based Websites



A more complete source of MBC information and support for patients is housed in the disease-state websites (branded by drug name) of each pharmaceutical company. Here, content includes MBC disease information, treatment information specific to the marketed drug, support tools for patients such as treatment planners, questions for HCPs, links to community groups and discussion boards, as well as financial support for treatment.

Social Media

Beyond its potential for fundraising, social media provides powerful tools for educating a large population about the disease[9]. It also reduces isolation by creating engagement. Most MBC Alliance members use social media, although few provide MBC-specific communications (see **Figure 12**). Unlike traditional online communities, social media support for cancer patients allows members to be seen by their own personal social network and by the public[10]. This aids in increasing the visibility of MBC among the public. Six in 10 cell-phone owners access the Internet on their cell phones, with blacks and Hispanics more likely to do so than whites[98]. However, MBC Alliance members provide few mobile websites or smartphone apps. These, along with forums, chat rooms, and social media tools catering to the smartphone portion of the MBC population, would provide another avenue of support to patients.

Notable Discussion Boards

Breastcancer.org*

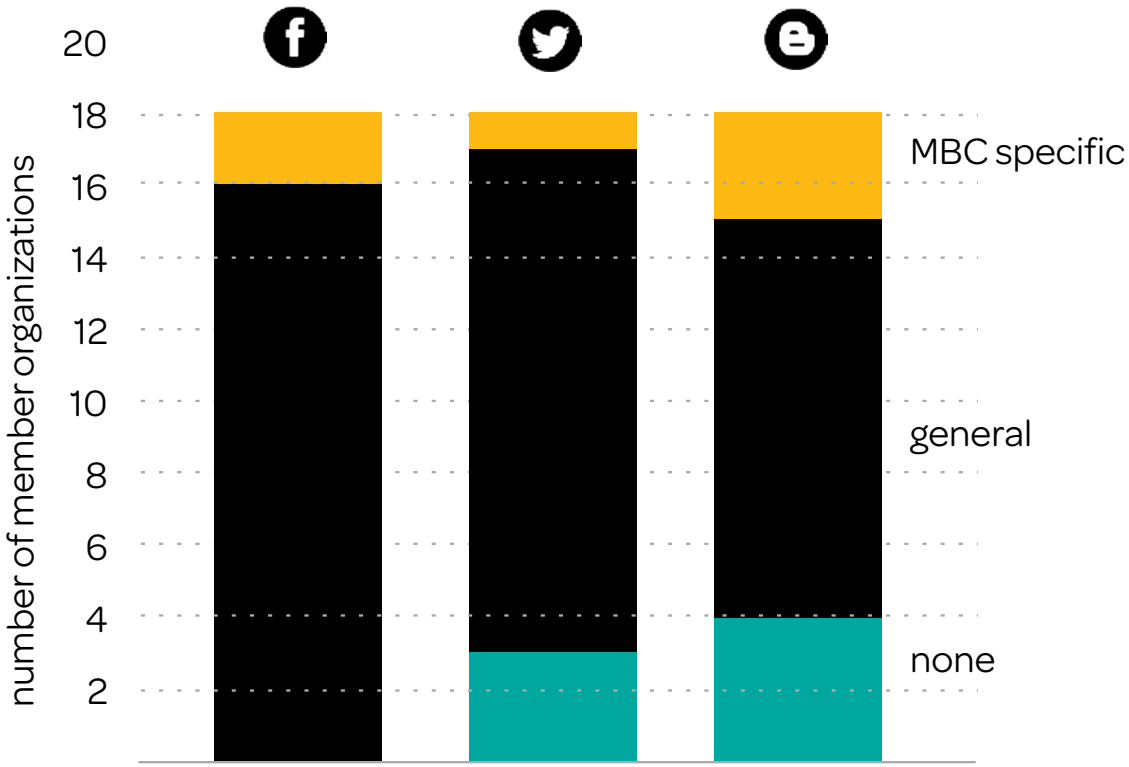
BCMets.org

Inspire

TNBC Foundation

* just for Stage IV caregivers/family

Figure 12: Social Media Focus of Advocate Members



Notable MBC publications:
Guide for the Newly Diagnosed – Metastatic Breast Cancer, LBBC & MBCN, 2014
Frankly Speaking About Cancer: Metastatic Breast Cancer Series, Cancer Support Community, 2013
Metastatic Navigator, YSC, 2010
Managing Practical Concerns Raised by MBC, Cancer*Care*, 2013

Notable MBC Specific Conferences and networking events:
- LBBC - Annual
- MBCN – Annual
- SHARE - Regular networking events on MBC topics

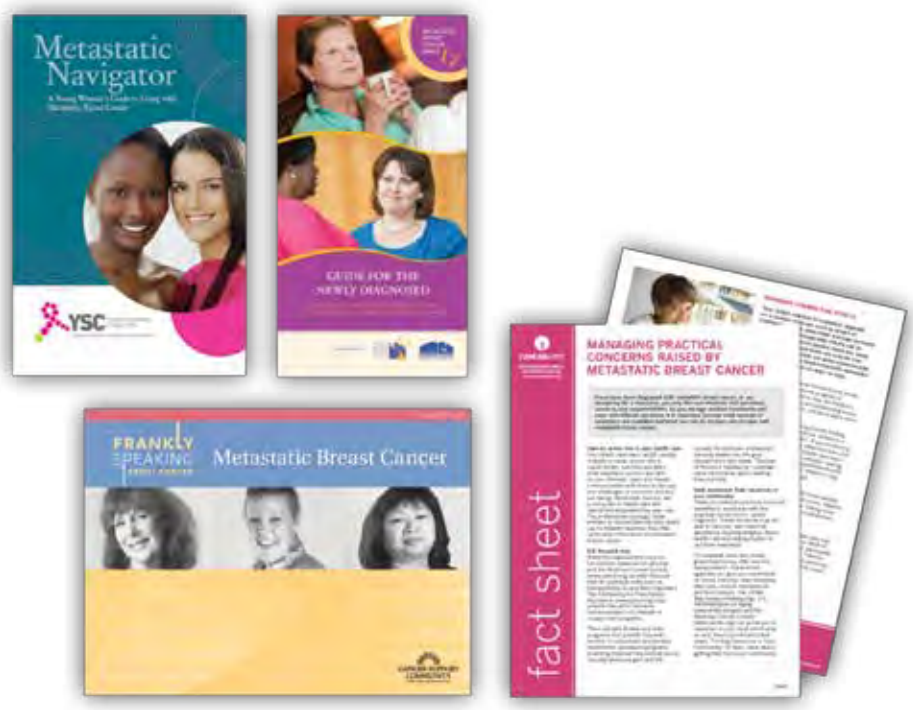
Notable support groups:
MBC Retreats: A Journey of Courage and Hope for Couples by Johns Hopkins Hospital is supported through Avon Foundation for Women

Metastatic Breast Cancer Network provides a list of known in person groups at http://mbcn.org/support#in-person-groups-for-mbc

Print Materials

As with web content, there is a scarcity of MBC information across print materials of individual Alliance members. The print materials tend to be of high quality, but few focus exclusively on the needs of people living with MBC (see **Figure 13**). Specific information provided by Alliance members in print and online tends to be complex, requiring a tenth-grade reading level for a basic understanding. Information about drug therapy is even more difficult to understand. This is a concern because of estimates that 1 in 5 patients have poor literacy and 89% of patients prefer visual materials to nonvisual material; wordy educational materials may not be read.

Figure 13: Print Publications of Alliance Members Specific to MBC



Conferences, Webinars, Support Groups, and Telephone Resources

In-person support is vital for some MBC patients to help reduce feelings of isolation and allow for identification with others. Conferences, retreats, in-person support groups and other networking opportunities specifically for MBC patients help participants feel part of a community. Many breast cancer conferences do include MBC programs, but they could have more content. Conferences tend to be located in large cities, and some MBC patients find it hard to travel during treatment periods. Living Beyond Breast Cancer and Metastatic Breast Cancer Network have annual conferences specifically for MBC patients and caregivers. Information about in-person support groups is hard to find.


Photo: Living Beyond Breast Cancer's 2014 Eighth Annual Conference for Women with Metastatic Breast Cancer

Webinars are another important source of information and often cover new research and treatments. Organizations such as Living Beyond Breast Cancer and SHARE (Self-Help for Women with Breast or Ovarian Cancer) have webinars on results of MBC studies from major symposia, such as the American Society of Clinical Oncology meeting and the San Antonio Breast Cancer Symposium. Programs on practical matters in living with MBC, such as financial issues, are also available in this format, which allows for replay.

Nearly half of Alliance member organizations provide telephone support services, all of which assist MBC patients in some capacity, even if just to refer them to other telephone helplines. Few telephone support services focus specifically on MBC patients; the ones that do include those by the Cancer Support Community, Living Beyond Breast Cancer, Susan G. Komen, and SHARE. Data collected on the use of helpline services by MBC patients is very limited. Most have live counselors during business hours and, at other times, callbacks within 24 hours.

Nearly half the services use professional counselors; the rest use breast cancer survivors as counselors. Some helplines provide follow-up calls and/or matched mentors. All the helplines have Spanish-speaking counselors; several have counselors and/or translators available in other languages. Challenges for helplines include how to broaden awareness and utilization of services, how to retain well-trained counselors (especially for MBC patients), and how to manage technological problems with the telephone system.

Helplines to assist MBC patients:

CancerSuportCommunity
1-888-793-9355

Living Beyond Breast Cancer
888-753-LBBC (5222)

Susan G. Komen
1-877 GO KOMEN

SHARE
866-891-2392

Information for HCPs

Alliance members provide information and support to educate patients about their cancer and treatment options, which helps to empower patients in their conversation with health care professionals. However, oncologists and general practitioners often face their own obstacles in their communication with MBC patients. Information developed by Alliance members could be very helpful to providers, so both parties have a shared basis on which to discuss diagnosis and treatment. Web and print materials of members are not currently geared toward assisting providers in these tasks.

Discussion

"There is a lack of of information on new drugs, current clinical research, advanced directives, end of life care, and monitoring treatment." MBCA Landscape Analysis - web content analysis, Pamela Miller 2014.

Providing accurate, up to date, comprehensive, and relevant (to the person seeking it) information and support services on MBC is challenging. Over time, patients move from diagnosis into a series of treatments until medicines and therapies no longer work. Over the course of their disease, information needs change, usually prompted by a change in treatment or life circumstances. Patients seek information about their disease subtype and their demographic. Caregivers have different information needs as well.

This analysis found that Alliance advocate members provide high quality information and support services to MBC patients and their families. However, information provided by the Alliance members requires that patients have relatively high health literacy and be Internet savvy. Organizations must consider how to reach these people and other subgroups of the MBC patient population. Unfortunately, quantitative data on the demographics and numbers of people who are accessing the programs and services is not consistently collected. As a result, the profiles and needs of the patients who are and who are not accessing the information and support are unknown.

While the disease-state websites of industry partners is comprehensive, the information is hard to find for patients not using the product/drug. There is a duplication of patient support tools across the websites such as treatment planners, discussion guides, accessing community groups. Similar to the advocate organizations, data are not collected on the patient using the websites. Without understanding who the user is and what types of information they seek and value, it is difficult to know how to make the sites more useful.

Notable end of life sources:

Cancercare.org: Caregiving at the End of Life (2011)

Susan G. Komen on Advanced Directives ww5.komen.org/uploadedFiles/Content_Binaries/806-03161.pdf

The majority of nonprofits report that their programs and services are underutilized. This may be because people are not aware of the advocacy organizations and where to find information or are finding support in other places. Because members offer so much general information, it is difficult for individual patients to find what they need.

Persistent gaps in information include detailed information on the latest treatments; monitoring of treatment, including for side effects and quality of life; palliation; and advanced directives and end-of-life care. Information on how people are diagnosed with MBC could be improved, and there is a dearth of information on new drugs in clinical research.

MBC Alliance members recognize that there are a number of opportunities to use our collective resources to extend the quality and reach of our information and patient support services. A next step is to understand more clearly who is and who is not using the support services and tools, how the services are being used, and how they can be improved to better meet the needs of people living with MBC. Through a collaborative effort, we will work to offer better support to address MBC patients' unique needs and empower them to be informed partners in their treatment decision making.


5

Chapter 5: Epidemiology of MBC—Challenges with Population-Based Statistics

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[1]*AdvancedBC.org,*

Abstract

To advocate most effectively for a population of patients, they must be accurately described and the course of the disease must be well characterized. Accurate epidemiologic statistics are currently lacking for the MBC population. ***Methods:*** We reviewed the availability of epidemiologic data related to MBC and the nature of those data. ***Results:*** The NCI SEER registries collect only incidence at first diagnosis, initial treatment, and mortality. Recurrent cancer is not tracked; the data on MBC are limited. While creative methods have been used to estimate the number of new cases of MBC and the number of those currently living with the disease, more accurate estimates of MBC incidence and prevalence do not currently exist. The modest increase in duration of MBC survival that has been documented over the past few decades has been observed primarily in ER+ and/or HER2+ MBC and appears to be attributable to the wide use of targeted therapies. During this time frame, the disparity between survival among black women with MBC and non-Hispanic white women with MBC has been increasing. ***Conclusions:*** Accurate epidemiologic information is needed to accurately and effectively demonstrate the need for services and plan and fund the application of services.

To advocate for a population of patients, they must be accurately described and the course of the disease must be well characterized.

Why Do Accurate Statistics Matter?

To advocate most effectively for a population of patients, they must be accurately described and the course of the disease must be well characterized. Accurate epidemiologic statistics are currently lacking for the MBC population.

Epidemiologic studies are needed to inform discussions about the size and characteristics of the MBC patient population as well as the numbers and types of resources and services needed. A true picture of the number of new cases each year and the number of people living with MBC could encourage drug development. Studies should also include analysis of trends in incidence and length of survival for future planning and investigations of the natural history of MBC to allow for evaluation of the impact of new interventions.

Of particular concern for advocates is having a realistic picture of the impact of emerging research on the issues that matter most to patients. For example, new drugs for MBC represent a source of hope that patients can live longer or even be cured. But do these drugs actually extend life or just increase health care costs? Do they improve quality of life?

Other related research questions include: How many new cases of MBC are diagnosed each year? How representative of the whole MBC population are patients in clinical trials? Does delaying cancer progression mean that overall survival is improved? What problems do MBC patients have with obtaining treatment, given existing co-payment and treatment access programs, and what impact does this have on MBC survival? Currently there are no population-based data-collection systems that can answer these questions.

Data from the NCI SEER Registries

Since 1973, the SEER registries of the NCI have been collecting population-based information on cancer cases and the initial course of treatment. These registries include 9 states, 5 metropolitan areas, and the Alaskan Native Tumor Registry. Together they represent about 28% of the entire US population, broadened in the past 20 years to offer a truly representative cross-section of the country with regard to our ethnic, immigrant, racial, educational, and socioeconomic diversity. Analyzing SEER data enables researchers and policy makers to monitor cancer trends and gather data on incidence, the extent of disease at diagnosis, initial therapy, mortality, and survival.

An estimated 3.1 million women in the US have a history of invasive breast cancer. We have no way of knowing how many of these people are actually living with MBC.

Unfortunately, because only incidence, initial treatment, and mortality are captured in the SEER registries, and recurrent cancer is not tracked, the data on all metastatic cancers, including MBC are limited.

Incidence

The actual number of new cases of MBC diagnosed each year is unknown. This is because SEER only records the 5% of newly diagnosed breast cancer patients who have de novo MBC. However, most patients with MBC were first diagnosed at earlier stages of breast cancer that then recurs, months to years later[30]. An estimated 20% to 30% of early stage breast cancer patients will develop MBC sooner or later. The SEER registries do not capture this much larger percentage. As a result, the actual annual incidence of MBC remains unknown.

Prevalence

The prevalence of breast cancer is increasing. Today, an estimated 3.1 million women living in the US already have a history of invasive breast cancer, and in 2014, an estimated 232,670 women will be newly diagnosed [99]. However, we have no way of knowing how many of these people are actually living with MBC as a chronic, progressive, and ultimately fatal disease or how many are "cured" of the disease, meaning they will go on to die of other causes. After early stage breast cancer is treated, it can lie dormant for as many as 20 or more years, with no way of determining whether it is actually cured or in a temporary state where there is "no evidence of disease." This complicates the already challenging assessment of MBC prevalence. Neither the total number of people living with MBC nor its burden in society can currently be determined.

Creative methods have therefore been used to estimate the prevalence of MBC. The duration of survival of patients with MBC (itself an estimate based on data from clinical trials involving highly selected patients), multiplied by the annual number of breast cancer deaths, has been used to approximate MBC prevalence. Estimating survival duration is complicated by significant variability related to the type of MBC and the treatment received. With good access to care and favorable tumor biology, some MBC patients can live for a decade or more. Using more sophisticated techniques, Australian biostatisticians have modeled the prevalence of MBC using the New South Wales cancer registry, estimating the prevalence as 3 to 4 times the number of annual deaths from breast cancer[100]. This approach is based on the fact that at least 90% of breast cancer deaths occur as a result of complications related to MBC.

Treatment Options

In large part, MBC remains incurable because the cancer is able to acquire resistance to each treatment given, as mutations occur and some cancer cells die but other more deadly ones remain and reproduce. Thus, MBC is controlled through the use of sequential "lines" of treatment that work in different ways.

Targeted therapies focus on genes that play dominant "driver" roles in the growth of ER+ and/or HER2+ MBC. Use of drugs that successfully target these key drivers controls cancer growth and extends survival. Sooner or later, however, MBC almost always acquires resistance to a given treatment, and a treatment change is necessary. Beyond tamoxifen, aromatase inhibitors (Arimidex, Femara and Aromasin) and fulvestrant (Faslodex) have offered further lines of treatment for MBC patients with ER+ disease. Trastuzumab (Herceptin) has slowed the spread of this aggressive form of MBC in the 25% of patients whose cancer is HER2+. Continued use of drugs targeting HER2 throughout treatment results in better control of HER2+ MBC. Newer agents targeting the HER2 pathway need to be studied further but may extend survival, as indicated in a recent small study showing a median survival of 45 months in patients with HER2+ MBC [101].

It's important to ask whether all MBC patients whose cancers are ER+ and/or HER2+ have equal access to the multiple lines of expensive targeted treatments appropriate for their subtypes and to the supportive follow-up care now considered standard that can greatly improve quality of life. Cytotoxic chemotherapies in combination with HER2-directed treatments are important to those patients with HER2+ breast cancer. Chemotherapy is the sole effective approach so far in triple-negative (TN) MBC treatment. Over the past 2 decades, newer chemotherapy agents have undergone reformulation and refinement to improve tolerability and therefore improve quality of life as well, even if they do not significantly extend survival. Improved tolerability is especially important for patients with TN MBC, for whom chemotherapy remains the only treatment option. These kinds of quality of life improvements are not reflected in studies that look at survival alone..

Survival

It has been suggested that outcomes of those with de novo MBC could be used to model duration of survival for all patients with MBC, because mortality data for de novo MBC patients are captured in the SEER registries.

However, de novo MBC patients are not necessarily representative of the entire MBC population. This is shown in a study[102] comparing the outcomes of de novo and recurrent MBC patients by analyzing an MD Anderson Cancer Center database of MBC patients who received chemotherapy from 1992 to 2007. Overall, patients with recurrent MBC had a 1.75 increased risk of death (median survival, 27 months) compared with de novo MBC patients (median survival, 39 months). In the recurrent MBC group, several factors predicted longer survival: initial diagnosis at stage I, presence of HER2+ disease, low-grade tumors, no prior chemotherapy, and a longer disease-free interval after adjuvant treatment. It should be noted that survival was longer for patients who were white (vs. other race or ethnic group), premenopausal (vs. postmenopausal), had ER+ MBC (vs. other types), or had only 1 (vs. >1) bone metastasis.

One reason for the difference in survival may be that the patients with de novo MBC had not been exposed to any breast cancer treatments at the time of diagnosis, and consequently had not acquired resistance to therapy, leading to better and longer responses to treatment as compared with the recurrent MBC patients.

Survival Benefit of New Treatments

It is generally believed that, as new treatments have been introduced for MBC, the duration of survival in the MBC population has increased. A number of studies have examined this hypothesis, with data from 1975 through 2008. Some studies have involved de novo cases from SEER and other registries; others, hospital-based populations with available recurrence and outcome data. Typically, the studies have examined successive periods over a number of years to see whether duration of survival has improved over time (see **Table 8**).

Over the past few decades, the duration of survival after a diagnosis of MBC has increased modestly—by months, not years.

Dawood et al. examined survival among more than 15,000 patients with de novo MBC in the SEER registries from 1988 to 2003[103]. They found modestly improved median survival over time (from 20 months to 27 months) among non-Hispanic white women, but not in black women, whose median survival remained constant at 17 months. SEER data for many types of cancer have revealed disparities between non-Hispanic white and black populations.

Chia et al. examined data for 2150 MBC patients referred to the British Columbia Cancer Agency from 1991 through 2001, a decade during which 7 new MBC treatments became available in Canada[104]. At the earliest time point, median survival was only 14 months, but it increased to 22 months by the end of the decade.

Giordano et al.[105] analyzed data from the MD Anderson Cancer Center database for patients with recurrent breast cancer from 1974 to 2000. The median survival was 15 months for the earliest cohort to 58 months for the most recent cohort. However, the sample included women with locally advanced recurrence, which has a better prognosis than distant metastatic disease.

Ruiterkamp et al. studied 8000 patients with de novo MBC in the Netherlands Cancer Registry diagnosed between 1995 and 2008, finding an improvement in median survival from 17 to 23 months, with the largest increase occurring among patients under 50 years of age[106]. An earlier (2007) population-based study in northern Holland by Ernst et al.[107] found similar results: an increase in median survival from 18 months in 1975 to 21 months in 2002.

Finally, Andre et al.[108] analyzed 724 consecutively enrolled patients with de novo MBC, from 3 French cancer centers, diagnosed between 1987 and 2000. Overall, the median survival improved over time from 23 to 29 months. Among patients with ER+ MBC, median survival improved from 28 months to 45 months, whereas patients with hormone-insensitive MBC (TNBC or ER– MBC), median survival was unchanged.

The apparent lack of a survival benefit seen in the Andre et al. study with the use of new cytotoxic chemotherapy agents in TN or ER– MBC was confirmed by Pal et al., who analyzed 274 patients with de novo MBC patients in the City of Hope, California, registry between 1985 and 2004, to ascertain the possible contribution of newer chemotherapy agents[109]. The authors concluded that, although overall survival had improved slightly over 20 years, "the contribution of conventional cytotoxic agents to this improvement is minimal."

Overall, these studies suggest that improvements in survival duration are due to targeted treatments for hormonally sensitive and HER2+ breast cancers. Of note, the survival estimates in these studies could reflect not only evolution of available care but also changes in imaging, earlier detection of metastatic disease, and changes in the definition of distant metastases.

Table 8. Changes in Median Survival of MBC Over Time, According to Study

Authors, Year	Population	Database	Time Frame	Median Survival Change over Time
Dawood et al. 2008 [103]	>15,000 de novo MBC	NCI SEER Registries, US	1988–2003	▶ Increase from 20 months to 27 months among non-Hispanic white women ▶ No change (from 17 months) among black women
Chia et al. 2007 [104]	2150 MBC patients	British Columbia Cancer Agency, Canada	1991–2001	Increase from 14 months to 22 months
Giordano et al. 2004 [105]	834 patients with recurrent MBC*	MD Anderson Cancer Center, US	1974–2000	Increase from 15 months to 58 months
Ruiterkamp et al. 2011 [106]	8000 patients with de novo MBC	Netherlands Cancer Registry	1995–2008	Increase from 17 months to 23 months
Ernst et al. 2007 [107]	1089 patients with de novo MBC	South-East Netherlands Registry	1975–2002	Increase from 18 months to 21 months
Andre et al. 2004 [108]	724 patients with de novo MBC	3 French cancer centers	1987–2000	Increase from 23 to 29 months overall ▶ Increase from 28 months to 45 months among patients with ER+ MBC ▶ No change among those with ER– MBC

Abbreviations: ER = estrogen receptor, MBC = metastatic breast cancer, NCI = National Cancer Institute, SEER = Surveillance, Epidemiology, and End Results program, US = United States.

* Sample included patients with locally advanced relapse.

Disease-Free Interval

Patients with de novo MBC are used in studies of prognosis, despite the difficulty of extrapolating results from this population to the entire MBC population, because the disease-free interval—the time between the initial diagnosis and the metastatic diagnosis—doesn't exist in this subgroup and need not be considered. Because the length of time before breast cancer recurs has been confirmed as an independent predictive factor known to impact duration of survival, studies relying on these data can be misleading.

Tevaarwerk et al.[110] demonstrated the effect of the disease-free interval in their 2013 analysis of long-term patient outcomes across 11 phase 3 adjuvant chemotherapy trials completed by the Eastern Cooperative Oncology Group over approximately 30 years (1978–2010). In this study of 13,785 breast cancer patients who received adjuvant chemotherapy, 3447 patients (25%) developed distant MBC; the overall median survival after relapse was 20 months. The factor that best predicted duration of survival was disease-free interval, which was 2.44 times higher among patients with relapse 6 or more years after initial diagnosis as compared with those with relapse after 3 or fewer years. By contrast, TN or ER– tumors (vs. ER+ tumors), any involved lymph nodes (vs. none), and black race (vs. other) were much weaker (but statistically significant) predictors of survival.

Modest increase in survival has been observed mainly in ER+ and/or HER2+ MBC and is attributable to the wide use of targeted therapies. No survival benefit has been found in TN MBC.

In fact, when this study's results were stratified to take disease-free interval into account, the increased survival benefit over time all but disappeared—except among ER– MBC patients who had relapse within 5 years after adjuvant treatment. The exception was probably due to the approval of trastuzumab (Herceptin) in 1998.

Summary

Recent studies on duration of survival of de novo and recurrent MBC generally demonstrate 3 findings:

The disparity between survival among black women with MBC and non-Hispanic white women with MBC appears to be increasing as treatments improve.

- Over the past few decades, the duration of survival after metastatic diagnosis has increased modestly—by a matter of months, not years. Hospital-based studies generally report a larger survival benefit than population-based studies.
- The modest increase in survival has been observed mainly in ER+ and/or HER2+ MBC and is attributable to the wide use of targeted therapies. No survival benefit has been found in TN MBC.
- The disparity between survival among black women with MBC and non-Hispanic white women with MBC appears to be increasing. According to SEER data, non-Hispanic white patients with de novo MBC have a survival benefit that is not found in black patients. It is unclear how much of the observed disparity in outcome is related to access to care and related socioeconomic concerns and how much is related to the greater incidence of TN MBC among black women.

Conclusions

Information about the epidemiology of MBC is currently lacking.

- **Prevalence and incidence of MBC.** The prevalence and incidence of patients with MBC is unknown. Also unknown is whether the number of recurrent MBC patients is increasing, decreasing, or staying the same. Without this information, we cannot accurately and effectively demonstrate the need for services or plan and fund the application of services.
- **Disease course by population and MBC subtype.** Disease trajectories, outcomes, and patient experiences for the different subtypes of MBC have not been well characterized.
- **Impact of MBC treatment.** Many critical questions regarding the optimal treatment of MBC remain unresolved. It is imperative that the use, effectiveness, and impact of MBC treatments on the overall MBC population be understood.
- **Length and variability of MBC survival.** Despite existing research, we have no accurate estimate of how long MBC patients are likely to live. The factors underlying observed variability in median survival across studies are unknown. Among the potential factors are differences in access to newer drugs (especially targeted therapies) and multiple lines of treatment, access to careful follow-up and expert palliative care to preserve optimal quality of life, and the presence of co-morbidities.
- **MBC disparities.** Despite research demonstrating poorer outcomes for disadvantaged, underinsured populations overall, we don't know the true impact of socioeconomic factors on what treatment and care are available for MBC patients and, in turn, how this may affect duration of survival and quality of life.

For the past 30 years, the breast cancer community has been a leader in patient support, advocacy, and research. Advocates have a pivotal role to play in the planning and implementation of future research. The MBC Alliance can continue to lead the way by helping policy makers and other MBC stakeholders to establish the blueprints for collection of epidemiologic data that will allow patients with MBC to be followed, to be visible, and to finally count.


6

Chapter 6: Public Education: Building Awareness of MBC

Katherine Crawford-Gray[1]

[1]*Metastatic Breast Cancer Alliance*

Abstract

Breast cancer campaigns have heightened public awareness yet have propagated unexpected misinformation. ***Methods:*** We informally explored various aspects of misinformation around MBC. ***Results:*** The most persistent myths relate to the breast cancer "survivor," which masks the reality that a proportion of women who have had early breast cancer will eventually develop metastatic disease. Further, the promotion of the "survivor" can stigmatize patients whose breast cancer progresses. The majority of adults in a recent survey reported they know little to nothing about MBC, that breast cancer in the advanced stages is curable, and that breast cancer progresses because patients did not take the right medicines or preventative measures. ***Conclusions:*** There is an opportunity for the Alliance to help ensure the facts about MBC are brought into the public awareness; to do so, a broad communication strategy should be informed by MBC patient advocates and developed drawing on Alliance member's collective experience, resources and spheres of influence.

Discussion

The Alliance aims to build an understanding of MBC, and how it differs from early stage breast cancer, among those diagnosed, their families, HCPs, researchers, and health policy experts.

The past 30 years of breast cancer campaigns have been successful in shining the light on the disease, the importance of early detection, and the methods of screening. And yet with this heightened public awareness of "survivorship" has come unexpected misinformation. A 2014 Pfizer-sponsored study of more than 2000 adults in the general public found that 72% believed breast cancer in the advanced stages is curable if diagnosed early; 50% believe that breast cancer progresses because patients did not take the right medicine or preventative measures, and more than 60% said they knew little to nothing about MBC[111].

The focus on fighting and beating breast cancer has led to the creation and dominance of the breast cancer "survivor"—an identity central to various public fundraising events, celebrity endorsements, and calls to action. This "survivor" identity masks the reality that 20-30% of women who have had early breast cancer will eventually develop metastatic disease[112].

Campaigns with a focus on "the cure" distract from a research agenda to increase the quality and quantity of life for MBC patients. Drives based on "beating cancer" and survivorship also deny the fact that women who have early breast cancer can develop metastatic disease. Further, the promotion of the survivor stigmatizes patients whose breast cancer progresses; they are seen or may even see themselves at fault for the cancer's progression, and ultimately failing to win the battle for survival.

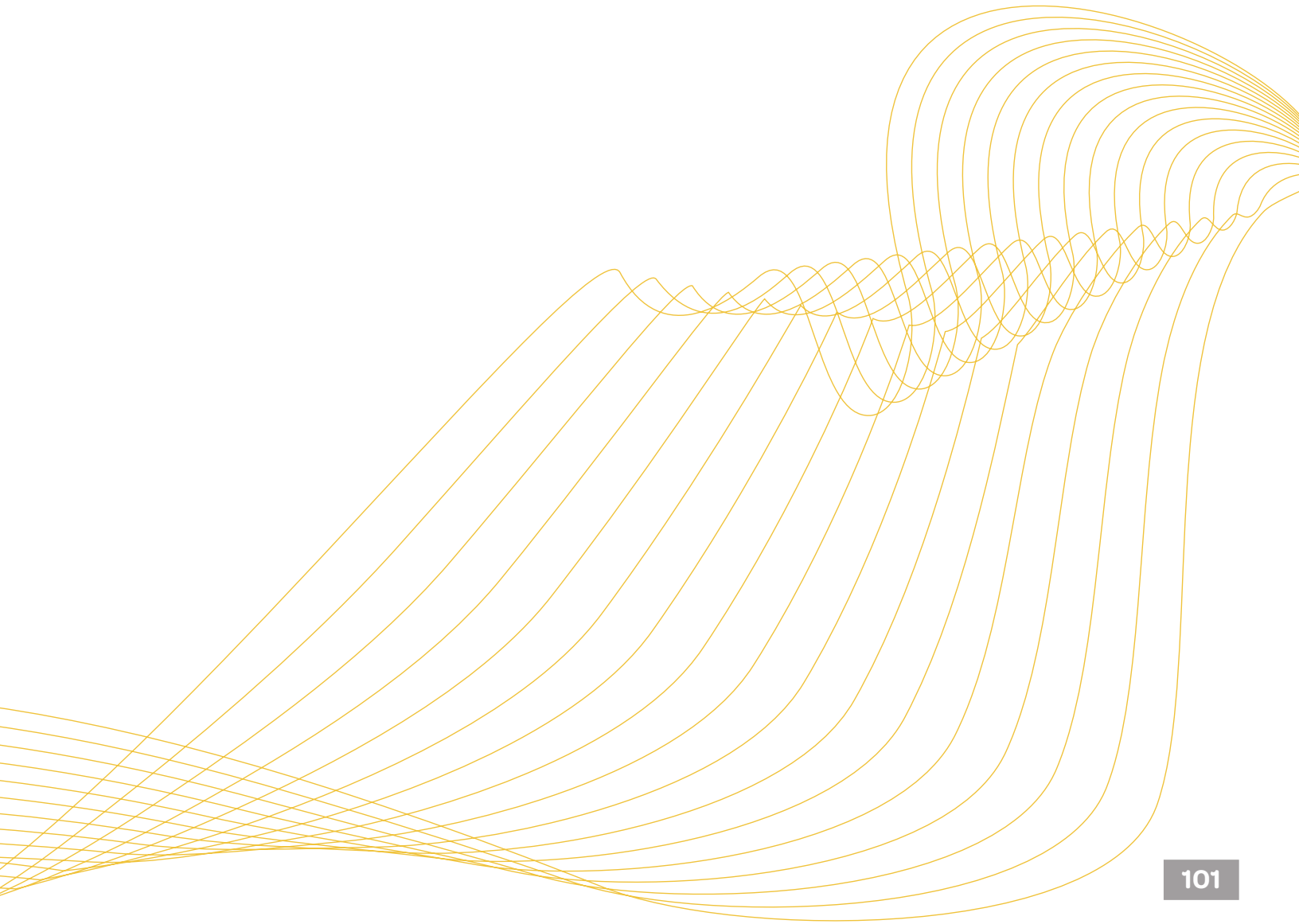
> "We did nothing wrong. Our medical team did nothing wrong. Metastatic breast cancer happens...at any time...regardless of your age, whether you did chemo[therapy], radiation, had a mastectomy, had a bilateral mastectomy, ate well, took vitamins, exercised regularly, prayed, had positive thoughts, had negative thoughts, got regular mammograms, did self exams religiously, had a tiny stage 1 primary tumor, or a stage 0 primary tumor, or a stage 3 primary tumor, or never even had primary breast cancer. It doesn't matter." — MBCN website www.mbcn.org

Nearly half of surveyed MBC patients report a sense of stigma, of feeling like outcasts or feeling isolated, especially within the larger social context of the breast cancer community.

Effects of stigmas and myths cannot be overstated. A global survey on perspectives about cancer determined that myths and stigma present significant challenges to cancer control, have a silencing effect, and affect individuals' behavior in seeking out support and making treatment and quality of life decisions[113]. According to researchers, key aspects of stigma are secrecy, myths and misinformation, social rejection and isolation, and shame, self-blame and low self-esteem[114]. These key elements are hallmarks of the MBC experience, within the breast cancer community and in the community at large. "When misfortune strikes, it is a natural human tendency to search for a reason," wrote psycho-oncologist Jimmie Holland. "The ready explanation is often 'he must have brought it on himself.' By blaming the victim, we get a false sense of security that we can prevent events that are beyond our control"[115].

How can we, as an alliance of individual members, begin to challenge the myths and stigmas that cause fear in the breast cancer community and the larger public, resulting in financial, social, and emotional distress for people living with MBC? How do we reduce the isolation that many people with MBC feel? How can the Alliance focus its resources on educating different groups about MBC and the importance of helping those with MBC to live longer and better?" To address the lack of understanding of MBC, the Alliance will draw on our collective experience, resources, and spheres of influence. The following principles will guide our future efforts to build understanding across all spheres of MBC, including scientific and quality of life research, epidemiology, and information and support services:

- Our actions must be led by advocates and informed by research and evaluation if we are to change the landscape for people living with MBC.
- The Alliance will not duplicate efforts of individual member organizations of the Alliance.
- We value learning from other cancers and other diseases, so we can apply best practices to our work.
- People living with MBC come from diverse backgrounds; differing cultural values and belief systems must inform the provision of information and support services, as well as public education about the disease, treatments, and quality of life.
- Collaboration is essential. Advocate organizations and industry members of the Alliance will work together to learn from each other's experience and research.
- As our work is resource intensive and time consuming, we will be thoughtful in how we commit our assets to future campaigns.
- Developing an evaluation framework that goes beyond counting pamphlets, banners, press releases, radio announcements, and Facebook posts is an exciting challenge for the Alliance and one that will be a major part of our planning for 2015–2016.



7

Chapter 7: Analysis to Action

The analysis undertaken by the MBC Alliance over the past year has prepared a solid foundation of shared knowledge across the MBC landscape. Collectively, Alliance members are now better informed about the areas of scientific research needing further exploration, gaps in information and support services that require resources, the need to accelerate improvement in quality of life, and increasing evidence-based public education about MBC.

Actions for the next phase of work for the Alliance have been prepared based on the research from this landscape analysis and the many discussions with patient advocates and breast cancer organizations.

We have identified a series of actions for our next phase of work over 2015 and 2016. These actions are aligned with our goals of advancing research, increasing understanding, and improving knowledge and awareness of MBC. They require sustained commitment of multiple stakeholders and MBC Alliance members stand ready to contribute time and energy to this work.

We look forward to reporting on our progress in 2015.

Actions for the next phase, next page.

GOALS, ACTIONS

advance research

GOAL 1

Advance research focused on extending life, enhancing quality of life, and ultimately ending death from MBC

MBC Alliance Think Tanks (2015)
Convene small think tanks of experts and advocates to investigate the data from the landscape analysis and prioritize research gaps.

MBC Summit (2016)
Convene summit of scientists and medical experts from the private and public sectors, along with patients to identify collaborative approaches for metastatic research.

Clinical Trials
Advocate for new trial designs incorporating new end points.

Assess feasibility of establishing a national tissue registry of paired primary and MBC tissue and blood for use by all researchers.

improve knowledge + access

GOAL 2

Improve knowledge by ensuring all patients and their caregivers know how to and can access the care and services they need from a responsive and well-informed health care system

Knowledge and Information Sharing
Facilitate stronger collaboration and sharing amongst Alliance members and other stakeholders with webinars, town halls, and newsletters to improve and extend services for people living with MBC.

MBC Information Project
Investigate with partners the potential to create an independent, up-to-date collection of evidence-based and trusted MBC information.

Empower Project
Building on the work of Alliance members, investigate how to better address information gaps for patients and caregivers, with a focus on underserved communities, as well as physicians.

Potentially pilot new decision-making tools with small groups of health professionals and patients with the aim of strengthening communication between patients and HCPs.

increase understanding

GOAL 3

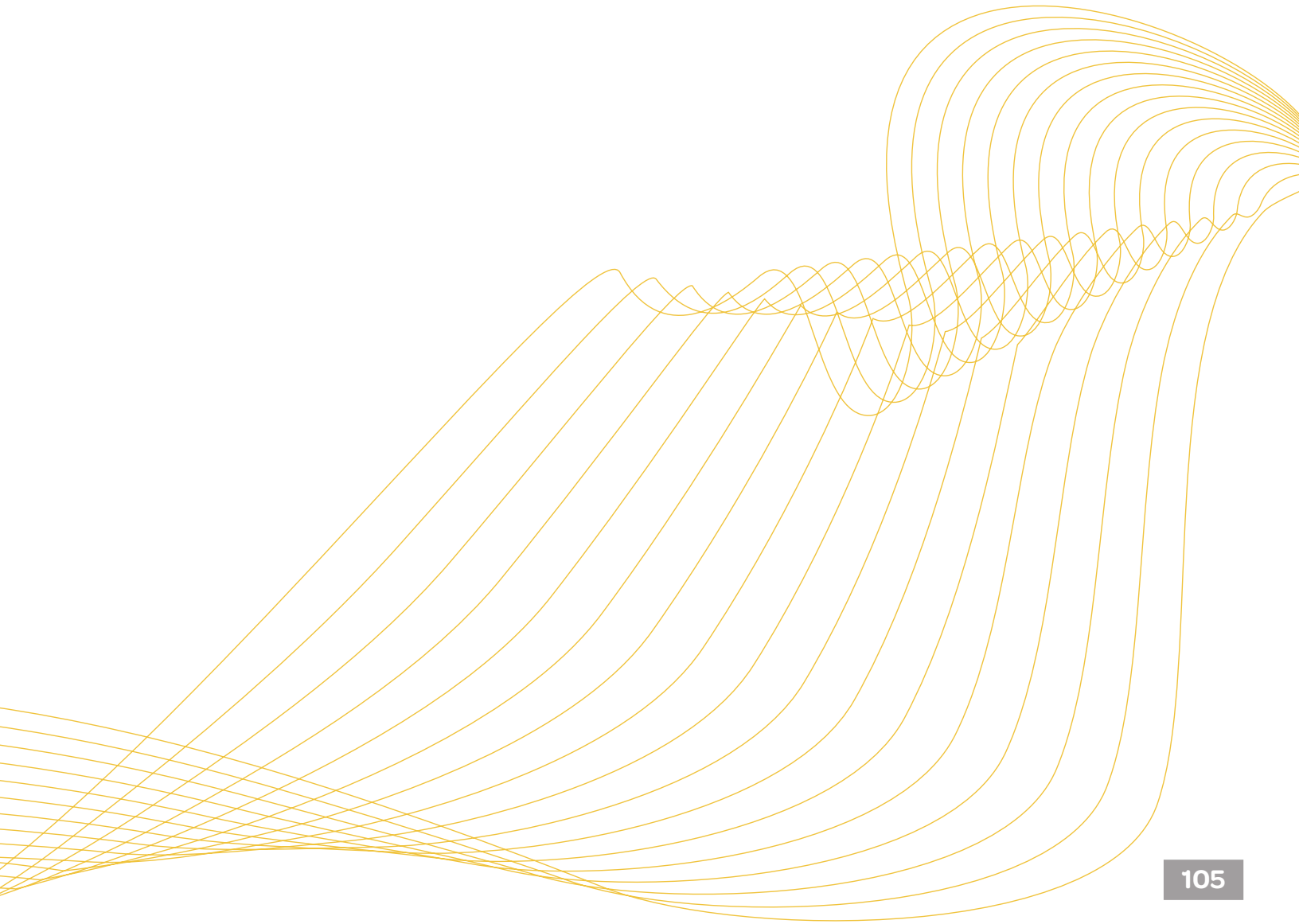
Increase understanding of MBC and how it differs from early stage breast cancer among those diagnosed, their families, HCPs, researchers, and health policy experts

Public Awareness
Develop with communications researchers main messages that educate people about MBC and how it differs from early stage breast cancer.

Explore how to best leverage the communication capacity of Alliance members to implement a MBC public awareness campaign.

Epidemiology Pilot Project
Collaborating with other agencies and registries, initiate a pilot study designed to achieve more accurate data about the prevalence and disease course of MBC.

Abbreviations:
HCPs = Health Care Providers
MBC = metastatic breast cancer



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Appendices

Appendix 1: Clinical Trials Analyzed

Appendix 2: Key Opinion Leader Interviewees

Appendix 3: Molecular Pathways, Cellular Targets and Therapies Being Studied in the MBC Grants Dataset

Appendix 4: Examples of How Grants in the MBC Grants Dataset Were Further Categorized into the Metastasis Stage

Appendix 5: 13 Surveys Completed by 7939 Respondents Living with MBC

Appendix 6: Executive, Program and/or Volunteer Leadership Interview

Appendix 7: Survey Participants in Help/Hotlines Survey

Appendix 1: Clinical Trials Analyzed

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
1. Sustaining Proliferative Signaling					
PI3/Akt/mTOR	BKM120	PI3	TripleNegative		SOLTI Breast Cancer Research Group
	BKM120	PI3	HER2-	BKM120/paclitaxel vs. BKM120/placebo	Novartis
	BKM120	PI3	Hormone+_HER2-	Fulvestrant	Novartis
	BKM120	PI3	Hormone+_HER2-	Fulvestrant	Novartis
	BKM120	PI3	All	Capecitabine	Novartis
	BKM120, olaparib	PI3K	TripleNegative		Dana-Farber/Harvard Cancer Center
	GDC-0032	PI3	Hormone+	Fulvestrant	Genentech
	GDC-0032	PI3	HER2-	Docetaxel or paclitaxel	Genentech
Active, not recruiting	GDC-0941	PI3	Hormone+_HER2-	Paclitaxel	Genentech
	GDC-0941	P13	TripleNegative	Cisplatin	Vanderbilt-Ingram Cancer Center
	BAY80-6946	PI3	All	Paclitaxel	Bayer
	AZD8186	PI3	TripleNegative		AstraZeneca
Suspended as of 8/1	Triciribine	Akt	HER2-		Cahaba
	Trametinib, GSK2141795	Akt	TripleNegative		National Cancer Institute
	BYL719	PI3	Hormone+_HER2-	Letrozole	Vanderbilt-Ingram Cancer Center
	BYL719, AMG479	PI3K, IGF1, and IGF2	Hormone+		Novartis, Amgen
	BYL719, BGJ398	PI3	All		Novartis
	BYL719	PI3	Hormone+	Letrozole or exemestane	Sloan Kettering
	BYL719	PI3	N/A	Paclitaxel	Novartis
	LDE225, BKM120	PI3K, Hedgehog	All		Novartis
	LY3023414	PI3/mTOR	All		Eli Lilly
	PF-05212384	PI3/mTOR	All	Docetaxel (ER+), cisplatin (triple negative), dacomitinib (HER2+)	Pfizer
	AZD2014	mTOR	Hormone+	Fulvestrant	AstraZeneca
	MGAH22	mTOR	HER2-		MacroGenics
	Everolimus	mTOR	HER2+	Lapatinib	University of Kansas
	Everolimus	mTOR	Hormone+_HER2-	Letrozole	Novartis
	Everolimus	mTOR	Hormone+_HER2-	Trastuzumab	Emory University
	Everolimus	mTOR	Hormone+_HER2-	Fulvestrant	Eastern Cooperative Oncology Group (ECOG)
	Everolimus/exemestane	mTOR	Hormone+	Compared to everolimus alone or capecitabine	Novartis
	Everolimus/fulvestrant or everolimus/fulvestrant/anastrozole	mTOR	Hormone+	Compared to fulvestrant alone	SWOG collaboration with Novartis and AstraZeneca
	Everolimus/letrozole/ lapatinib	mTOR	Hormone+_HER2-		University of Maryland
	CC-223	mTOR	All		Celgene
Unknown as of 8/1	Sirolimus (rapamycin)	mTOR	HER2+	Hercpetin	Yale Cancer Center

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
	Temsirolimus, Metformin	mTOR	All		MD Anderson Cancer Center
	Everolimus, trametinib, temozolomide and ABT-888, or MK-1775	mTOR, MEK, PARP, Wee1	All		National Cancer Institute
	Temsirolimus, neratinib	mTOR, HER2	HER2+		Puma Biotechnology
	LGK974	Wnt pathway (Porcupine)	TripleNegative		Novartis
JAK	Ruxolitinib	IL6/JAK/Stat pathway	All		Dana-Farber/Harvard Cancer Center
Active, not recruiting	Ruxolitinib	JAK	All		Dana-Farber/Harvard Cancer Center
Notch	BMS-906024	Pan-Notch	TripleNegative		Bristol-Myers Squibb
	BMS-906024	Pan-Notch	TripleNegative	Chemotherapy	Bristol-Myers Squibb
	PF-03084014	Notch	All	Docetaxel	Pfizer
RAF/MEK/ERK					
ALK	Crizotinib/pazopanib/ pemetrexed	ALK/VEG	N/A		MD Anderson Cancer Center
	X-396	ALK	ALK+		Xcovery
	Pazopanib	VEGFR	Hormone+	Letrozole or anastrozole	GlaxoSmithkline
Active, not recruiting	Cabozantinib (XL184)	VEGFR2, c-Met	TripleNegative		Dana-Farber/Harvard Cancer Center
ErbB	Erlotinib/metformin	ERB1 (EGFR)	TripleNegative		Astellas Pharma/Komen
	Erlotinib	ERB1 (EGFR)	TripleNegative	Chemotherapy and bevacizumab	University of Washington
	Panitumumab	ERB1 (EGFR)	HER2-	Nab-pacliatxel, carboplatin, pluorouracil, epirubicin, cyclophosphamide	Celgene/MD Anderson Cancer Center
	Trastuzumab/lapatinib	ErB1/ErB2 (HER2R)	HER2+		GlaxoSmithKline
	Trastuzumab/lapatinib	ErB2 (HER2R)	HER2+	Combinations with capecitabine and cyclophosphamide	University of Southern California
	Trastuzumab, pertuzumab	HER2	HER2+		Genentech, Susan G. Komen, GlaxoSmithKline
	Trastuzumab, lapatinib	HER2	HER2+		GlaxoSmithKline, Genentech
	Lapatinib	HER2	Hormone+_HER2-		University of Kansas
Completed as of 8/1	High-dose lapatinib	ErB2 (HER2R)	HER2+		University of California, San Francisco
	AdHER2/neu dendritic cell vaccine	ERB2	HER2+		National Cancer Institute
	ONT-380, T-DM1	ERB2	HER2+		Oncothyreon
	ONT-380	ERB2	HER2+	Capecitabine and/or trastuzumab	Oncothyreon
	Pertuzumab	ErB2	HER2+	Protein-bound paclitaxel/trastuzumab	City of Hope
	Pertuzumab, trastuzumab, paclitaxel	ErB2	HER2+		Memorial Sloan Kettering
	Pertuzumab/trastuzumab	ErB2	HER2+		Genentech
	Pertuzumab, trastuzumab, and eribulin	ErB2	HER2+		Dana-Farber/Harvard Cancer Center
	PF-05280014	ErB2	HER2+	Paclitaxel	Pfizer
	MGAH22	ErB2	HER2+		Macrogenics

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
	LJM716	ErB2	HER2+	Trastuzumab	Novartis
	TDM, protein-bound paclitaxel, lapatinib	ERB2	HER2+		Methodist Hospital System
	Neratinib	ErB2	HER2-		Washington University, St. Louis
	212Pb-TCMC-Trastuzumab	ErB2 and ER	HER2+	Trastuzumab	AREVA Med
	AI, Lapatinib, trastuzumab	ErB2	HER2+_Hormone+		National Cancer Institute
	Afatinib (BIBW 2992)	ErB1/ErB2	HER2+	Vinorelbine	Boehringer Ingelheim
	Afatinib (BIBW 2992)	ErB1/ErB2	HER2+		Boehringer Ingelheim
	Afatinib (BIBW 2992)	ErB1/ErB2	HER2+	Alone or with vinorelbine	Boehringer Ingelheim
	Afatinib (BIBW 2992)	ErB1/ErB2	HER2+		Boehringer Ingelheim
	Neratinib vs. lapatinib	ErB1/ErB2	HER2+	Capecitabine	Puma Biotechnology
Active, not recruiting	MM-121	ErB3	Hormone+_HER2-		Merrimack Pharmaceuticals
IGF Receptors	IGF-Methotrexate	IGF	All		University Illinois/IGF Oncology
Hormone-mediated	Endoxifen	Estrogen Receptor	Hormone+		National Cancer Institute
	Z-endoxifen HCl	Estrogen Receptor	Hormone+		National Cancer Institute
	Anostrazole + targeted therapies	Estrogen Receptor	Hormone+	Everolimus, sorafenib, erlotinib, fulvestrant, or bevacizumab	MD Anderson Cancer Center
	ARN-810	Estrogen Receptor	Hormone+_HER2-		Seragon Pharmaceuticals
	Enzalutamide	Androgen Receptor	TripleNegative		Medivation/Astellas Pharma
	Enzalutamide	Androgen Receptor	Hormone+_HER2-	Exemestane	Medivation
	Enzalutamide	Androgen receptor	All		Astellas Pharma
	Orteronel	Androgen receptor	Androgen+		Sarah Cannon Research Institute
	Orteronel	CYP17A1/Androgen	Hormone+		University of Wisconsin
	Cabergoline	Prolactin Receptor	Prolactin+		Northwestern University
	Exemestane/cyclophosphamide	Estrogen Rec/ ImmuneCells	Hormone+_HER2-		New York University
	Anastrazole vs. fulvestrant	Estrogen Receptor	Hormone+		
	Tamoxifen	Estrogen Receptor	Hormone+	Biomarker analysis CYP2D6	ECOG
PTEN Mutation	GSK2636771	PTEN Mutation	TripleNegative		GlaxoSmithKline
Other	Tetrathiomolybdate	Copper	All		Weill Cornell Medical College
	MORAb-066	TissueFactor antigen	All		Morphotek
	ENMD-2076	Unspecified tyrosine kinase	TripleNegative		EntreMed
	Dovitinib	FGFR	HER2+		Novartis/MD Anderson Cancer Center
Active, not recruiting	Dovitinib	FGFR3	Hormone+_HER2-	Aromatase inhibitor	Georgetown University

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
2. Evading Growth Suppressors					
Cyclin-Dependent Kinases	Palbociclib	CDK-4/6	All		University of Pennsylvania
	Palbociclib	CDK-4/6	All	Paclitaxel	University of Pennsylvania
	Palbociclib	CDK-4/6	Hormone+_HER2-	Fulvestrant	Pfizer
Active, not recruiting	Palbociclib	CDK-4/7	Hormone+_HER2-	Letrozole	Pfizer
Active, not recruiting	LY2835219	CDK-4/6	All		Eli Lilly
	LY2835219	CDK-4/6	Hormone+_HER2-	Standard Hermone Therapy or everolimus/ exemestane	Eli Lilly
	LEE011	CDK-4/6	Hormone+_HER2-	Exemestane and everolimus	Novartis
	LEE011	CDK-4/6	Hormone+_HER2-	Letrozole	Novartis
	LEE011 and BYL719	CDK-4/6 & PI3	Hormone+_HER2-	Letrozole	Novartis
SubTotal					
3. Inducing Angiogenesis					
VEGF Signaling	Bevacizumab	VEGF	HER2-		
Unknown as of 8/1	Sorafenib	VEGF	All	Capecitabine	Yale Cancer Center
	Apatanib (YN968D)	VEGF	All		LSK BioPharma
	Pazopanib	VEGF	All	Paclitaxel/ carboplatin	Rutgers University
4. Resisting Cell Death					
IAP (Inhibit apoptosis proteins)	LCL161	IAP	All	Paclitaxel	Novartis
5. Enabling Replicative Immorality	**NOT IN TRIALS FOR MBC**				
6. Genome Instability and Mutation					
PARP Inhibitors	Veliparib	PARP	BRCA+	Temozolomide vs. carboplatin/ paclitaxel	AbbVie
	Veliparib	PARP	TripleNegative	Doxorubicin	National Cancer Institute/ Montiforie Medical Center
	Veliparib	PARP	All	Paclitaxel/paraplatin chemotherapy	National Cancer Institute/ University of Pittsburgh
Active, not recruiting	Veliparib	PARP	BRCA+	With/without carboplatin	National Cancer Institute
	Veliparib	PARP	HER2-	Paclitaxel/paraplatin chemotherapy	National Cancer Institute/ University of Pittsburgh
	Veliparib	PARP	Hormone+_HER2-	Carboplatin	National Cancer Institute
Active, not recruiting	Veliparib	PARP	BRCA+		AbbVie
	Veliparib	PARP	All	Radiation	University of Michigan Comprehensive Cancer Center
Active, not recruiting	Veliparib/cyclophosphamide	PARP	BRCA+	With/without doxorubicin	National Cancer Institute
	BMN 673	"PARP	BRCA+	Various Chemo agents	BioMarin
"	BRCA+	Various chemotherapeutic agents	BioMarin		BioMarin
	BMN 673	"PARP	BRCA+		NCI
	AZD2281 (Olaparib)	PARP	BRCA+	Carboplatin	NCI
"	BRCA+		BioMarin	With/without Carboplatin	NCI

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
	BMN 673	PARP	BRCA+		National Cancer Institute
	AZD2281 (olaparib)	PARP	BRCA+	Carboplatin	National Cancer Institute
	AZD2281 (olaparib)	PARP	All	With/without carboplatin	National Cancer Institute
	Rucaparib	PARP	BRCA+		Clovis Oncology
	Niraparib	PARP	HER2-		TESARO
HDAC Inhibitors	Vorinostat	HDAC			
Unknown as of 8/1	Vorinostat	HDAC	All	Capecitabine	Yale Cancer Center/Merck
	Vorinostat	HDAC	All	Paclitaxel, carboplatin	National Cancer Institute
	Etinostat	HDAC	HER2+	Lapatinib	National Cancer Institute/MD Anderson Cancer Center
	Romidepsin	HDAC		Protein-bound paclitaxel	Thomas Jefferson University/ Celgene
	Romidepsin	HDAC	All		National Cancer Institute
	Entinostat	HDAC	Hormone+_HER2-	Exemestane	National Cancer Institute
	Entinostat	HDAC	Hormone+_HER2-	Exemestane	National Cancer Institute
Other	PM01183	Minor groove of DNA	BRCA+		PharmaMar
Subtotal					
7. Tumor Promoting Inflammation	**NOT IN TRIALS FOR MBC**				
8. Deregulating Cellular Energetics	**NOT IN TRIALS FOR MBC**				
9. Activating Invasion and Metastasis					
	Fresolimumab (GC1008)	TGF-Beta	All	Radiotherapy	New York University
10. Avoiding Immune Destruction					
Vaccines	AntiHER2/antiCD3-activated T Cells	HER2, CD3	HER2-	Cyclophophamide	
	AdHER2/neu dendritic cell vaccine	ERB2	HER2+		National Cancer Institute
	HER2 peptide-based Vaccine	ERB2	HER2+		University of Washington
	Dendritic cell vaccine with oncofetal antigen/ iLRP	Tumor antigen OFA/iLRP	All		Southern Cancer Center
	Designer T cells	CEA	CEA+		Roger Williams Medical Center
	HER2neu DNA Vaccine	ERB2	HER2+		Sloan Kettering
	HER2 ICD Peptide Vaccine	ERB2	HER2+	Trastuzumab/ polysaccharide-K	University of Washington
Active, not recruiting	Mammaglobin-A DNA Vaccine	Mammaglobin-A	All		Washington University, St. Louis
	ONT-10	MUC1	All		Oncothyreon
	cMet RNA chimeric antigen receptor (CAR) T cells	Tumor antigens	All		Abramson Cancer Center, University of Pennsylvania
	FANG vaccine (bi-shRNAfurin and GMCSF autologous tumor cells)	Tumor antigens	All		Gradalis, Inc.
	OPT-822/OPT-821	Globo H	All	cyclophosphamide	OBI Pharma, Inc.
	hTERT/survivin multipeptide vaccine	hTERT	All	basiliximab, GM-CSF and Prevnar	Abramson Cancer Center, University of Pennsylvania

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
Active, not recruiting	Rintatolimod/HER2 Peptide Vaccine	ERB2	HER2+	GM-CSF vs. Ampligen as adjuvant	University of Washington
	Chimeric (trastuzumab-like/pertuzumab-like) HER-2 B-cell peptide vaccine	ERB2	HER2+		Ohio State Comprehensive Cancer Center
	Allogeneic GM-CSF–secreting breast cancer vaccine/trastuzumab	Tumor antigens	Hormone+_HER2-	cyclophosphamide	Sidney Kimmel Cancer Center
Active, not recruiting	Genetically modified lymphocytes	NY-ESO-1	All	Proleukin, cyclophosphamide, fludarabine	National Cancer Institute
	HER2 VRP	ERB2	HER2+		Duke University
Immunomodulators	Imiquimod	TLR7 (Toll-like receptor 7)	All	Radiation	National Cancer Institute
Terminated as of 8/1	Natural killer cells	Immunotherapy	All	Chemotherapy	Investigator-initiated
	NLG919	IDO Pathway	All		NewLink Genetics
	Indoximod	IDO Pathway	Hormone+_HER2-	Docetaxel	NewLink Genetics
Active, not recruiting	Agatolimod	TLR9	HER2+	Trastuzumab	Pfizer
	CC-122	Pleiotropic pathway	All		Celgene
	MK-3475	PD-1 (programmed death 1)	TripleNegative		Merck
	PLX3397	CSF-1 receptor (Fms)	All	Paclitaxel	Plexxikon
	Cyroablation (procedure)	Immune system	Hormone+_HER2-		John Wayne Cancer Institute at Saint John's Health Center
Other					
Heat Shock Protein (Hsp)	Ganetespib	Hsp90	HER2+		Synta Pharmaceuticals
	Ganetespib	Hsp90	Hormone+_HER2-	Fulvestrant	Dana-Farber/Harvard Cancer Center
	Ganetespib	Hsp90	All	Paclitaxel, trastuzumab	New York University
	SNX-5422	Hsp90	HER2+		Esanex Incorporated
Other	Dasatinib	BCR-ABL tyrosine kinase	All	Paclitaxel	Sloan Kettering
	PF-06647263	Not disclosed	All		Pfizer
	Multiple drugs	Mutlple targets	All		National Cancer Institute
Subtotal Targeted					
Non-Targeted Therapies					
Cancer Stem Cells	BBI608	Cancer stem cells	All	Paclitaxel	Boston Biomedical
	POL6326	CXCR4 receptors	Hormone+_HER2-	Eribulin	Polyphor
	Chloroquine	Cancer stem cells	All	Paclitaxel, docetaxel, nab-paclitaxel, or ixabepilone	Methodist Hospital Houston
	Vantictumab	Cancer stem cells	HER2-	Paclitaxel	OncoMed Pharmaceuticals
Arginine	ADI-PEG 20	Arginine	HER2-	Doxorubicin	Polaris Group
Chemotherapy					
Active, not recruiting	Pemetrexed		All		

	Study Drug(s)	Target	Biomarkers/ Subtype	Combination	Sponsor
	Eribulin	N/A	All		University of Washington
	Eribulin	N/A	Hormone+_HER2-		Dana-Farber/Harvard Cancer Center
	Eribulin	N/A	HER2-		Eisai
	Eribulin/cyclophosphamide	N/A	All		University of California, San Francisco
	Eribulin/carboplatin	N/A	All		Eisai
	Capecitabine/digoxin	N/A	All		Western Regional Medical Center
	FdCyd (5-fluoro-2'-deoxcytidine) and THU (tetrahydrouridine)	N/A	All		National Cancer Institute
	Protein-bound paclitaxel	N/A	All		City of Hope
	Protein-bound paclitaxel/Anakinra (anti-inflammatory)	N/A	HER2-		Baylor Research Institute
Completed as of 8/1	Protein-bound paclitaxel/Lapatinib	N/A	All		University of California, San Francisco
	Protein-bound paclitaxel vs. IG-001	N/A	All		IGDRASOL
Unknown as of 8/1	Tesetaxel	N/A	HER2-		Genta
Unknown as of 8/1	Tesetaxel/capecitabine	N/A	HER2-		Genta
	ThermoDox (doxorubicin enhanced with lysolipid thermally sensitive liposomes)	Chemotherapy	All	Hyperthermia therapy	Celsion
Completed as of 8/1	Heated cisplatin	Chemotherapy	All	Surgery	St. Luke's-Roosevelt Hospital Center
	FOLFOX (folinic acid, fluorouracil, oxaliplatin)/ hepatic infusion	Liver metastases	All		Western Regional Medical Center
Unknown as of 8/1	Oral eniluracil + 5-fluorouracil + leucovorin	N/A	All		
	MM-398/irinotecan	N/A	Solid Tumor	Tracer for MRI imaging	Merrimack Pharmaceuticals
	IMMU-132/irinotecan	N/A	All		Immunomedics
	Azacitidine	N/A	HER2-	Protein-bound paclitaxel	University of Utah
	Nab-paclitaxel	N/A	TripleNegative	With gemcitabine/ carboplatin vs. gemictabine/ carboplatin alone	Celgene
Unknown as of 8/1	Doxorubicin/heat treatment	N/A	All		National Center for Research Resources (NCRR)
	Ixabepilone and stereotactic radiation	N/A	TripleNegative		University of Texas Southwestern
	EC1456	Folate receptors	TripleNegative		Endocyte
	TAS-114	Pyramidine metabolism	All	Capecitabine	Taiho Oncology
	Lurbinectedin (PM01183)	DNA binding	All	Paclitaxel with or without bevacizumab	PharmaMar
	MM-302	ERB2	HER2+	With/without traztuzumab or cyclophosphamide	Merrimack Pharmaceuticals
Other					
Unknown as of 8/1	Whole body hyperthermia	Heat	All	Fluorouracil, doxorubicin	University of Texas
	Surgery	N/A	All	Radiation	National Cancer Institute

Appendix 2: Key Opinion Leader Interviewees

First name	Last name	Area	Organization Name
Robin	Anderson	International	Peter MacCallum Cancer Centre, Melbourne, Australia
Fabrice	Andre	International	INSERM (Institut National de la Santé et de la Recherche Médicale)
Carlos	Arteaga	Professional Society	American Association for Cancer Research
Dietmer	Berger	Pharmaceutical/Biotech	Genentech Biooncology
Amy	Bonoff	Advocate	Dr. Susan Love Research Foundation
Powel	Brown	Academic	University Texas MD Anderson Cancer Center
David	Cameron	International	Edinburgh Cancer Research Centre, Scotland
Lewis	Chodosh	Academic	University of Pennsylvania
Elly	Cohen	Clinical Trials	BreastCancerTrials.org
John	Condeelis	Academic	Albert Einstein College of Medicine
Nancy	Davidson	Academic	University of Pittsburgh Medical Center
Mika	Derynck	Pharmaceutical/Biotech	Genentech Biooncology
Karen	Durham	Advocate	Susan G. Komen
Matthew	Ellis	Professional Society/Academic	Baylor College of Medicine, TX
Lesley	Fallowfield	International	University of Sussex
Sandy	Finestone	Advocate	Susan G. Komen
Margaret	Frame	International	Edinburgh Cancer Research Centre, UK
Amy	Fulton	Academic	University of Maryland
Patricia	Ganz	Academic	UCLA (University of California, Los Angeles)
Paul	Goss	Nonprofit Organization	MGH, Boston
Pat	Haugen	Advocate	National Breast Cancer Coalition
Dan	Hayes	Professional Society	Cooperative Groups
Rachel	Hazan	Academic	Albert Einstein College of Medicine
Kate	Horwitz	Academic	University of Colorado Denver
Cliff	Hudis	Professional Society	American Society of Clinical Oncology (ASCO)
Yibin	Kang	Academic	Princeton University
Mhel	Kavanaugh-Lynch	Government	California Breast Cancer Research Program
Celina	Kleer	Academic	University of Michigan
Maria	Koehler	Pharmaceutical/Biotech	Pfizer
Susan	Love	Nonprofit Organization	Dr. Susan Love Research Foundation
Andrea	Mastro	Academic	Pennsylvania State University
Sofia	Merajver	Academic	University of Michigan
William	Muller	Academic	McGill University, Canada
Christine	Norton	Advocate	National Breast Cancer Coalition
Larry	Norton	Nonprofit Organization/ Academic	Breast Cancer Research Foundation/Memorial Sloan Kettering Cancer Center
Morag	Park	Academic	Rosalind and Morris Goodman Cancer Research Centre, McGill University, Canada
Joe	Pearlberg	Pharmaceutical/Biotech	Sanofi
Lynne	Penberthy	Government	National Cancer Institute
Martine	Piccart	International	Universite Libre de Bruxelles
Andrew	Reynolds	International	Breakthrough Breast Cancer Research Center, London
Elizabeth	Robinson	International	Breakthrough Breast Cancer Research Center, London
Julia	Rowland	Government	National Cancer Institute
Pepper	Schedin	Academic	Oregon Health & Science University
Robert	Schneider	Academic	New York University School of Medicine
Peter	Siegel	Academic	McGill University, Canada
George	Sledge	Nonprofit Organization	Susan G. Komen

First name	Last name	Area	Organization Name
Iain	Smith	International	Royal Marsden Hospital, London, UK
Kate	Sommer	Advocate	Susan G. Komen
Pat	Steeg	Government	National Cancer Institute
Steven	Stein	Pharmaceutical/Biotech	Novartis Oncology
Alicia	Subasinghe	Clinical Trials	PhRMA (Pharmaceutical Research and Manufacturers of America)
Sara	Sukumar	Academic	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Andrew	Tutt	International	Breakthrough Breast Cancer Research Center, London
Ralph	Weichselbaum	Academic	University of Chicago
Danny	Welch	Academic	University of Kansas
Debbie	Winn	Government	National Cancer Institute
Antonio	Wolff	Clinical Trials	TBCRC (Translational Breast Cancer Research Consortium)
Dihau	Yu	Academic	University of Texas MD Anderson Cancer Center
Ming	Zhang	Academic	Northwestern University

Appendix 3: Molecular Pathways, Cellular Targets and Therapies Being Studied in the MBC Grants Dataset

A grant with a focus on **invasion**

Title:
The ezrin signaling network as a potential novel marker for breast cancer metastasis

Ezrin, a plasma membrane cytoskeleton linker, is required for cell survival and morphogenesis. It has been found that over-expression of ezrin frequently occurs in invasive human breast cancer and is required for cell motility and invasion of carcinoma cells. Studies indicate that ezrin acts co-operatively with Src in the disruption of cell-cell contacts and increased cell scattering and motility – characteristic of a transformed phenotype. Over-activation of Src and ezrin also causes increased activation of the receptor tyrosine kinase Met, a proto-oncogene that is frequently overexpressed in patients with high risk of metastatic disease. This transdisciplinary project will focus on determining the role of Src/ezrin/Met activation (referred to as the Src/ezrin signalling network) at specific stages of human breast cancer metastasis, and correlating the Src ezrin signalling network with tumour stage and grade as a possible predictor and/or treatment target for human breast cancer metastasis.

Metastasis stage (Steeg)	Invasion and motility
Hanahan/Weinberg	Activating invasion & metastasis
Research stage	Understanding (basic) Translational
Pathway	Ezrin, Src, Met
Therapy/intervention	none

A grant with a focus on **intravasation**

Title:
Microfluidic 3D Scaffold Assay for Cancer Cell Migration and Intravasation

DESCRIPTION (provided by applicant): Migration through extra-cellular matrix (ECM) and intravasation across a cellular barrier comprise the initial, rate-limiting steps of cancer metastasis. Physiologically relevant and well-controlled models that mimic the in vivo tumor microenvironment will enable better understanding of the initial steps of metastasis and evaluation of potential therapy efficacy. In vivo models have physiological relevancy, yet inherently lack a high level of control. In vitro cancer migration models have high levels of control, yet lack critical components of the tumor microenvironment. We propose a new technology, a microfluidic migration and intravasation assay (MIA). The MIA replicates essential components of the in vivo tumor microenvironment, including a 3D ECM and a vasculature, while providing tight control of biochemical and biophysical parameters. To further establish the MIA, we propose to use it to investigate a specific biophysical factor - interstitial flow - which has not previously been studied in the context of metastatic disease. The objective of the proposed work is to evaluate the metastatic potential of cancerous cells by developing the MIA and identifying novel extent of invasion metrics (Specific Aim 1), and applying them to study the influence of interstitial flow on cancer cell metastasis (Specific Aim 2). The MIA will have an input channel for the cancer cells, a 3D collagen gel to simulate native ECM, and an endothelial cell (EC) layer adherent to the gel in a second channel. The configuration will permit migration of cancer cells either from the input channel or within the gel towards the second channel. Optimized gel parameters will present appropriate chemotactic gradients and physical parameters simulating a tumor microenvironment and inducing cancer cell migration. The EC layer will mimic the in vivo vascular barrier allowing observation of cancer cell intravasation. Optical access from two vantage points will permit real time observation of cancer cell migration and intravasation. The optical access combined with image processing techniques will quantify cancer cell morphological and migratory parameters, leading to identification of novel extent of invasion metrics that will quantify the metastatic potential of cancer cells. Finally, we will leverage the microfluidic capability of the MIA to induce interstitial flow across the gel, and quantify the effects of this biophysical parameter on cancer cell invasion. Taken together, the two aims establish the MIA as an excellent platform for quantitative research of molecular mechanisms governing cancer cell invasion. For example, therapies capitalizing on altered vascular morphology near tumors would clearly benefit from using the MIA as a development platform, as the system provides a characterized EC layer in conjunction with a well-controlled system. Future development will enable the MIA to serve as a cancer cell diagnostic device and a high throughput drug development tool. Cancer spreads and invades through a process called metastasis, often resulting in patient death. The metastasis process is not well understood, since there is a shortage of well-controlled models that realistically represent the tumor microenvironment and its blood supply. This application seeks to develop a well-controlled and realistic tumor environment model to aid cancer metastasis research and eventually provide a platform to more efficiently develop and evaluate cancer therapies.

Metastasis stage (Steeg)	Invasion and motility
Hanahan/Weinberg	Activating invasion & metastasis
Research stage	Understanding (basic) Translational
Pathway	n/a
Therapy/intervention	diagnostic/prognostic/research tool

A grant with a focus on Metastatic **colonization**

Title:
Use of a Novel Embryonic Mammary Stem Cell Gene Signature to Improve Human Breast Cancer Diagnostics and Therapeutic Decision Making

Background: Most of the morbidity and mortality from breast cancer stems from the failure to adequately control metastases using existing chemotherapies. Metastatic colonization of secondary sites is an important rate-limiting step in the progression of metastatic disease. The role of the cell adhesion molecule E-cadherin in initiating tumor invasion and dissemination is well-established. However, recent findings of E-cadherin expression in metastatic foci originating from E-cadherin-negative primary tumors suggest that E-cadherin re-expression may play a role in metastatic colonization. In fact, our laboratory has found that co-culture of E-cadherin-negative metastatic breast cancer cells with hepatocytes induces E-cadherin re-expression and that these induced adhesion molecules can bind with those on hepatocytes to activate the canonical ERK and Akt cell survival pathways. Objective/Hypothesis: We will test the hypothesis that metastatic breast carcinoma cells require E-cadherin re-expression to integrate and subsequently to confer a survival advantage in the liver, a common site of breast cancer metastases. Specific Aims: (1) Determine whether breast cancer cells upregulate E-cadherin expression within a metastatic niche. (2) Determine whether E-cadherin re-expression endows resistance to chemotherapy. Impact: This proposal aims to fill a gap in our understanding of the pathogenesis of breast cancer metastasis. The molecular basis of metastatic progression is still poorly understood, and not much is known or being studied about metastases to the liver. The work in the proposal is relevant because it not only advances what is currently known about metastasis, but also identifies a putative target that can be used clinically. Further, the skills learned under this training award can be directly applied to investigating other molecules of interest believed to be involved in cancer progression.

Metastasis stage (Steeg)	Metastatic colonizationy
Hanahan/Weinberg	Activating invasion & metastasis
Research stage	Understanding (basic)
Pathway	E-cadherin
Therapy/intervention	n/a

A grant with a focus on Immune surveillance/escape

Title:
Blocking breast cancer cell Type I IFN signalling prevents immune recognition and allows metastatic progression to bone.

Breast cancer is rarely curable once it has spread to bone. Our recent studies have revealed that cancer cells growing in bone suppress an immune defence pathway called the Type I interferon (IFN) pathway, and that restoration of this pathway blocks cancer spread. In this project, I aim to identify the immune responses that are specifically activated when cancer cells produce Type I IFN and test if restoration of such responses is critical in blocking the spread of breast cancer to bone. This project will reveal the role of the Type I IFN immune pathway in activating the immune system and preventing breast cancer spread and may discover new therapeutic avenues for treating advanced breast cancer patients.

Metastasis stage (Steeg)	Immune surveillance/escape
Hanahan/Weinberg	Activating invasion & metastasis Avoiding Immune Destruction
Research stage	Understanding (basic)
Pathway	Type I IFN
Therapy/intervention	n/a

Appendix 4: Examples of How Grants in the MBC Grants Dataset Were Further Categorized into the Metastasis Stage

Molecular pathways and targets (CY 2000 - 2013)

Includes any awards active over this thirteen year period

Awards are categorized into Basic, Translational or Clinical, based on their CSO profile

Where possible, pathways/targets have been grouped into categories

Basic research awards	
Pathway (Group)	Total
Other	22.0%
Multiple	12.5%
Bone/osteolysis pathways	6.7%
Pathway not specified	4.9%
Angiogenic pathways	4.6%
Integrins, Cadherins etc.	3.4%
TGF	3.3%
cytokines and chemokines	2.9%
Stem cells	1.8%
Hypoxia factors	1.5%
matrix metalloproteinases	1.5%
Rho family GTPases	1.4%
VEGF pathway family	1.4%
Erb/Her	1.4%
Immune system (general)	1.3%
Src + family	1.0%
NF Kappa B pathway	1.0%
hormone receptors	1.0%
microRNAs (miRNAs)	1.0%
Six family genes	0.8%
FAK	0.8%
Twist	0.8%
STAT	0.7%
receptor tyrosine kinase	0.6%
Cell surface glycoproteins	0.6%
cytoskeleton	0.6%
Protein kinases	0.5%
Ras pathway	0.5%
HGF/MET	0.5%
Collagen	0.5%
MUC1	0.5%
stress pathways	0.5%
FGF signalling	0.5%
brain metastases	0.5%
Ephrins	0.4%
Wnt signalling	0.4%
insulin receptor substrate (IRS)	0.4%
metastasis suppressor genes	0.4%

Translational research awards	
Molecular Target (Group)	Total
Other	23.4%
0_No specific target	16.4%
Multiple	7.4%
Integrins, Cadherins etc.	3.9%
Erb/Her	3.1%
cytokines and chemokines	3.0%
Bone/osteolysis pathways	2.7%
Stem cells	2.5%
TGF	2.1%
matrix metalloproteinases	2.0%
VEGF pathway family	1.8%
(blank)	1.8%
angiogenesis factor	1.7%
Circulating tumour cells (CTC)	1.4%
Hypoxia factors	1.4%
NF Kappa B pathway	1.2%
hormone receptors	1.0%
Interleukins	0.9%
urokinase (uPA-R) pathway	0.9%
Immune system (general)	0.9%
EGF pathway	0.8%
cysteine proteases	0.8%
tumor necrosis family (TNF) superfamily	0.8%
Fibroblast activation protein (FAP)	0.7%
IGF signalling	0.7%
COX	0.7%
Ephrins	0.7%
HSP	0.6%
NK cells	0.6%
p38 pathway	0.5%
Galectins	0.5%
Rho family GTPases	0.5%
Cell surface glycoproteins	0.5%
ID-2/ID-1	0.4%
MUC1	0.4%
AKT PKB signalling	0.4%
FAK	0.4%
PTHrP	0.4%

Clinical research awards	
Molecular Target (Group)	Total
Other	24%
0_No specific target	17%
Multiple	11%
Erb/Her	6%
hormone receptors	5%
VEGF pathway family	3%
(blank)	3%
IGF signalling	3%
Bone/osteolysis pathways	3%
HGF/MET	2%
urokinase (uPA-R) pathway	2%
angiogenesis factor	2%
Immune system (general)	2%
thymidylate synthase	2%
p53 pathway	2%
Integrins, Cadherins etc.	1%
Src + family	1%
cytokines and chemokines	1%
COX	1%
Stem cells	1%
HSP	1%
TGF	1%
Ras pathway	1%
PI3 kinase	1%
disintegrin family	1%
breast tumor suppressors	1%
Circulating tumour cells (CTC)	1%
MUC1	0%
matrix metalloproteinases	0%
minor fatty acids	0%
ID-2/ID-1	0%
tumor necrosis family (TNF) super-family	0%
Rho family GTPases	0%
FGF signalling	0%
Fibroblast activation protein (FAP)	0%
prolactin (PRL)	0%
transcription factor	0%
proteases	0%

Basic research awards		Translational research awards		Clinical research awards	
lysine oxidase (LOX)	0.4%	tumor associated macrophages (TAMs)	0.4%	receptor tyrosine kinase	0%
PAR	0.4%	TWIST transcription factos	0.4%	EGF pathway	0%
SLUG/SNAIL	0.3%	PGE2 receptors	0.3%	nuclear protooncoproteins	0%
Actin	0.3%	HLA	0.3%	FAK	0%
Abl Kinases	0.3%	S100 family of Ca2+-binding proteins	0.3%	tumor suppressor genes	0%
p53 pathway	0.3%	TF Signaling	0.3%	Interleukins	0%
BRCA	0.3%	Src + family	0.3%	HOX family transcription factors	0%
HDAC	0.3%	transcription factor	0.3%	metastasis suppressor genes	0%
HOX homeobox factors	0.3%	p53 pathway	0.3%	immunophilin proteins	0%
AKT	0.3%	immunophilin proteins	0.3%	PTHrP	0%
Phosphoinsitide signaling	0.3%	anthrax toxin receptor 2 (CMG2)	0.3%	telomeres	0%
COX	0.3%	Plasminogen signalling	0.3%	SDF-1	0%
Fibroblast activation protein (FAP)	0.3%	Retinoids	0.3%	G-protein coupled receptors	0%
SDF-1	0.3%	telomeres	0.3%	Ezrin	0%
adhesion molecules	0.2%	PI3 kinase	0.2%	HDAC	0%
IBC	0.2%	Vitamin D pathway	0.2%	tumor associated macrophages (TAMs)	0%
sympathetic nervous system (SNS) signalling	0.2%	Hedgehog	0.2%	SIX family genes	0%
tumor necrosis family (TNF) superfamily	0.2%	bcl-2 family	0.2%	Hypoxia factors	0%
Oncostatin M	0.2%	tumor homing peptides	0.2%	G protein coupled receptors	0%
PTEN	0.2%	src kinase substrate	0.2%	Vitamin D pathway	0%
p21 activated kinase (PAK)	0.2%	Ras pathway	0.2%	lysophospholipid family	0%
Crk family	0.2%	autocrine motility factor (AMF)	0.2%	Cell surface glycoproteins	0%
telomeres	0.2%	STAT	0.2%	scaffolding adapters	0%
tumor microenvironment	0.2%	endoglycosidases	0.2%	HLA	0%
p38 pathways	0.2%	Notch pathway	0.2%	claudins	0%
brain	0.2%	disintegrin family	0.2%	tumor homing peptides	0%
TF Signaling	0.2%	SDF-1	0.2%	Plasminogen signalling	0%
ezrin	0.2%	sialylation	0.2%	Retinoids	0%
map kinases	0.2%	tubulin binding agent	0.2%	autocrine motility factor (AMF)	0%
transcription factor	0.2%	metastasis suppressor genes	0.2%	Cystatin M	0%
Interleukins	0.2%	receptor tyrosine kinase	0.2%	Ubiquitin ligases	0%
ALDH	0.2%	HDAC	0.2%	NF Kappa B pathway	0%
serine protease	0.2%	Thrombospondins	0.2%	SLUG/SNAIL	0%
IGF signalling	0.2%	G-protein coupled receptors	0.2%	STAT	0%
Plasminogen signalling	0.2%	miRNAs	0.2%	p21-activated kinase (Pak1)	0%
HSP	0.2%	protein tyrosine kinase	0.2%	TF Signaling	0%
Leptin	0.2%	lysine oxidase (LOX)	0.1%	BCRP	0%
Hedgehog	0.2%	indoles	0.1%	metastasis associated (MTA)	0%
Notch pathway	0.2%	breast tumor suppressors	0.1%	NK cells	0%
liver	0.2%	Protein-tyrosine kinases (PTKs)	0.1%	miRNAs	0%
SATB1	0.2%	Sphingosines	0.1%	anthrax toxin receptor 2 (CMG2)	0%
Neuropilin	0.2%	metastasis associated (MTA)	0.1%	sialylation	0%
ADAM	0.2%	lysophospholipid family	0.1%	endoglycosidases	0%
tumor suppressor genes	0.2%	proteases	0.1%	Galectins	0%

Basic research awards	
Tetraspanins	0.2%
urokinase (uPA-R) pathway	0.2%
anoikis	0.2%
CCN	0.2%
PRL	0.2%
MEKK	0.2%
14-3-3 family proteins	0.2%
Ubiquitin ligases	0.1%
PELP1	0.1%
ID-2/ID-1	0.1%
Dlc	0.1%
Thrombospondins	0.1%
Protein-tyrosine kinases (PTKs)	0.1%
Androgen receptor pathway	0.1%
Cell cycle proteins	0.1%
Cathepsin C	0.1%
metastasis associated (MTA)	0.1%
Heparan Sulfate	0.1%
Galectins	0.1%
Cystatin M	0.1%
tubulin detyrosination	0.1%
lipogenesis	0.1%
miRNAs	0.1%
activity-based protein profiling (ABPP)	0.1%
sialylation	0.1%
KGF	0.1%
DNA repair pathways	0.1%
TNBC	0.1%
Chemotaxis	0.1%
tumor associated macrophages (TAMs)	0.1%
proteases	0.1%
Annexin II	0.1%
Cholesterol	0.1%
cysteine proteases	0.1%
DecR	0.1%
Vit D	0.1%
TbetaRIII	0.1%
breast tumor suppressors	0.1%
PI3 kinase	0.1%
Retinoids	0.0%
anthrax toxin receptor 2 (CMG2)	0.0%
Circulating tumour cells (CTC)	0.0%
SERPINs	0.0%

Translational research awards	
FGF signalling	0.1%
HGF/MET	0.1%
Ezrin	0.1%
SIX family genes	0.1%
SLUG/SNAIL	0.1%
minor fatty acids	0.1%
Androgen receptor pathway	0.1%
tumor suppressor genes	0.0%
HOX family transcription factors	0.0%
HMGA	0.0%
fibrinolysis	0.0%
prolactin (PRL)	0.0%
B-crystallin	0.0%
Wnt/Dishevelled signaling	0.0%
pepducins	0.0%
serine proteinases	0.0%
claudins	0.0%
Ubiquitin ligases	0.0%
podocalyxin	0.0%
proteoglycans	0.0%
Cystatin M	0.0%
p21-activated kinase (Pak1)	0.0%
Maspin	0.0%
BCRP	0.0%
Crk family	0.0%
thymidylate synthase	0.0%
G protein coupled receptors	0.0%
nuclear protooncoproteins	0.0%
scaffolding adapters	0.0%
Grand Total	100.0%

Clinical research awards	
Ephrins	0%
AKT PKB signalling	0%
serine proteinases	0%
Notch pathway	0%
fibrinolysis	0%
lysine oxidase (LOX)	0%
tubulin binding agent	0%
Androgen receptor pathway	0%
bcl-2 family	0%
p38 pathway	0%
Crk family	0%
Maspin	0%
src kinase substrate	0%
indoles	0%
podocalyxin	0%
proteoglycans	0%
Sphingosines	0%
PGE2 receptors	0%
Thrombospondins	0%
TWIST transcription factos	0%
Hedgehog	0%
cysteine proteases	0%
Wnt/Dishevelled signaling	0%
pepducins	0%
HMGA	0%
S100 family of Ca2+-binding proteins	0%
B-crystallin	0%
Protein-tyrosine kinases (PTKs)	0%
protein tyrosine kinase	0%
Grand Total	100%

Basic research awards	
EGF pathway	0.0%
HLA	0.0%
CEA family	0.0%
MYC	0.0%
LABC	0.0%
antioxidants	0.0%
ERK Pathway	0.0%
CNS	0.0%
antiapoptotic chaperone proteins	0.0%
(blank)	0.0%
lobular carcinoma	0.0%
Grand Total	100.0%

Translational research awards	

Clinical research awards	

Appendix 5: 13 Surveys Completed by 7939 Respondents Living with MBC

Survey Name	Date	Sponsor	Method	N	Needs Assess.	QOL \S/SE	Work	Psycho-social	Support/ Coping	Finance/Insurance	Tx Choices	Tx Info	Med. Comm.	Med. Satis.	Stigma	Clinical Trials
Silent Voices: Advanced (Metastatic) Breast Cancer Needs Assessment Survey [1, 2]	2006	Living Beyond Breast Cancer	Online and, later,on paper	618	✓	✓		✓	✓		✓	✓	✓	✓		✓
BRIDGE Survey: Identifying the Unmet Needs of the MBC Community [3, 4]	2009, 2010	Pfizer, with various support organizations	Interviews; Harris Inter-active, in 13 countries	1342	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓
A pan-European Survey of Patients with MBC [5]	2011	Eisai; Imperial College, London	Online	230							✓	✓	✓	✓		
Key Support and Lifestyle Needs of MBC Patients [6]	2011	METAvivor	Online	789		✓	✓	✓	✓	✓					✓	
Preferences of Patients with MBC [7,8]	2011	Research Advocacy Network (RAN), Department of Defense, Breast Cancer Research Program Center of Excellence	Online	400		✓					✓					
HER2+ MBC Patient Experiences on Treatment in the Biologic Era [9]	2011	Genentech with various support organizations	Online	185		✓	✓					✓				
Metastatic Breast Cancer in Canada: The Lived Experience of Patients and Caregivers [10]	2012	Canadian Breast Cancer Network and RETHINK Breast Cancer	Online	87		✓	✓			✓	✓					
Informational Needs and QOL in 1st Year MBC [11]	2012	Dana Farber Embrace Trial	On paper	52	✓	✓		✓				✓				
Impact of Toxicity on Patient Treatment Choices for MBC [12]	2012	RAN, Genentech	Online	551		✓					✓					
Count Us, Know Us, Join Us International Survey [13]	2013	Novartis with various breast cancer organizations and Harris Interactive	Online International	1273	✓		✓	✓	✓	✓		✓			✓	
Control of Symptoms and Side Effects in MBC [14]	2013	AdvancedBC.org	Online	585	✓	✓		✓	✓		✓	✓	✓	✓	✓	
Surveying Young Women with MBC [15]	2013	Young Survival Coalition	Online	329	✓	✓	✓	✓	✓			✓	✓	✓		
Cancer Experience Registry [16, 17]	2014	Cancer Support Community	Online	909 so far		✓	✓	✓		✓			✓			✓

Needs Assess. = needs assessment for services
QOL S/SE = Quality of life, symptoms, and side effects
Work = employment, disability, financial support
Psychosocial = emotional distress, mental health services
Finance/Insurance = financial issues and health insurance coverage
Support/Coping = sources of emotional support/coping mechanisms
Tx Choices = treatment decision making, access issues
Tx Info = information seeking, patient education
Med. Comm.= communication and relationship with health care providers
Stigma = experience of social isolation, avoidance, stigma
Clinical Trials = clinical trials participation

[1] Mayer, M., Grober, S.E., Caplan, E. *Silent Voices: Women with advanced (metastatic) breast cancer share their needs and preferences for information, support and practical resources.* 2006: Living Beyond Breast Cancer website.

[2] Mayer M., *Lessons learned from the metastatic breast cancer community.* Semin Oncol Nurs, 2010. Aug26(3):pp.195-202.

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[6] Corneliussen-James, D. *International survey identifies key support and lifestyle needs of metastatic breast cancer (MBC) patients in ABC1: Advanced Breast Cancer First International Consensus Conference.* 2011: Lisbon, Portugal.

[7] Smith, M.L., White, C.B., Railey, E., Storniolo, A.M., Sledge, G.W., *Metastatic Breast Cancer Drugs: Using Conjoint Analysis to Examine Attributes of Paclitaxel and Capecitabine in 2012 ASCO Annual Meeting.* 2012, Journal of Clinical Oncology: Chicago, IL.

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[12] White C.B., Smith, M.L., Abidoye, D., Lalla, D., *Impact of toxicity on patient treatment choices for metastatic breast cancer* in 2012 ASCO Annual Meeting. 2012, Journal of Clinical Oncology: Chicago, IL.

[13] Harris Interactive, Novartis Oncology. *Count Us, Know Us, Join Us Advanced Breast Cancer Survey in ABC2: Advanced Breast Cancer Second Consensus Conference.* 2013: Lisbon, Portugal.

[14] Mayer M, Grober S.E., *Patient Perspectives on Control of Symptoms and Side Effects of Metastatic Breast Cancer in ABC2: Advanced Breast Cancer Second Consensus Conference.* 2013: Lisbon, Portugal.

[15] Rowe, J., *Surveying Young Women with Metastatic Breast Cancer to Create Interventions with Impact in ABC2: Advanced Breast Cancer Second Consensus Conference.* 2013: Lisbon, Portugal.

[16] Buzaglo, J., *Cancer Experience Registry: Metastatic Breast Cancer, Update to the National Advisory Council, in Cancer Support Community.* 2014: Washington D.C.

[17] Buzaglo, J., Morris, A., Gayer, C., Miller. M., *Work-related impact of metastatic breast cancer: Results from the Cancer Experience Registry in 7th Biennial Cancer Survivorship Research Conference.* 2014: Atlanta, GA.

Appendix 6: Executive, Program and/or Volunteer Leadership Interviews

AdvancedBC.org	Musa Mayer, Patient and Research Advocate
Avon Foundation for Women	Marc Hurlbert, Executive Director
Breast Cancer Research Foundation (BCRF)	Peg Mastrianni, Chief Program Officer
Breastcancer.org	Melissa Bollman-Jenkins, Community Manager Claire Nixon, Managing Editor Hope Wohl, Chief Executive Officer Michele McLaughlin-Zwiebel, Director, Programs and Content
Cancer*Care*	Jane Levy, Director of Patient Assistance Programs
Cancer Support Community (CSC)	Joanne Buzaglo, Vice President, Research and Training
Dr. Susan Love Research Foundation (DSLRF)	Karla Lancaster, Research Project Manager Susan Love, Founder
Facing Our Risk of Cancer Empowered (FORCE)	Sue Friedman, Executive Director Diane Rose, Director of Volunteer Programs Lisa Schlager, Vice President, Community Affairs and Public Policy
Living Beyond Breast Cancer (LBBC)	Catherine Ormerod, Vice President, Programs and Partnerships Janine Guglielmino, Director, Programs and Strategic Initiatives Jean Sachs, Chief Executive Officer Arin Ahlum Hanson, Manager, Young Women's Initiative
Metastatic Breast Cancer Network (MBCN)	Ginny Knackmuhs, Vice President Shirley Mertz, President
Research Advocacy Network (RAN)	Elda Railey, Co-founder Mary Lou Smith, Co-founder
SHARE (Self-Help for Women with Breast or Ovarian Cancer)	Christine Benjamin, Breast Cancer Program Director Ivis Sampayo, Senior Director, Programs
Sisters Network Inc.	Kelly Hodges, National Program Director
Susan G. Komen	Susan Brown, Managing Director Jacqueline McKnight, Scientific Programs Specialist Jeremy Patch, Community Health Analyst
Triple Negative Breast Cancer Foundation (TNBCF)	Hayley Dinerman, Executive Director
Young Survival Coalition (YSC)	Stacy Lewis, Chief Program Officer Megan McCann, Senior Manager, National Programs

Appendix 7: Survey Participants in Help/Hotlines Survey

1. AdvancedBC.org
2. American Cancer Society
3. Breast Cancer Research Foundation
4. Cancer Support Community
5. Facing Our Risk of Cancer Empowered
6. Living Beyond Breast Cancer
7. Metastatic Breast Cancer Network
8. Research Advocacy Network
9. SHARE
10. Sisters Network Inc.
11. Susan G. Komen
12. Triple Negative Breast Cancer Foundation
13. Young Survival Coalition

Metastatic Breast Cancer
MBCalliance

together we are stronger than the disease

People living with metastatic breast cancer and patient advocates at the Metastatic Breast Cancer Network 2013 Annual Conference

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