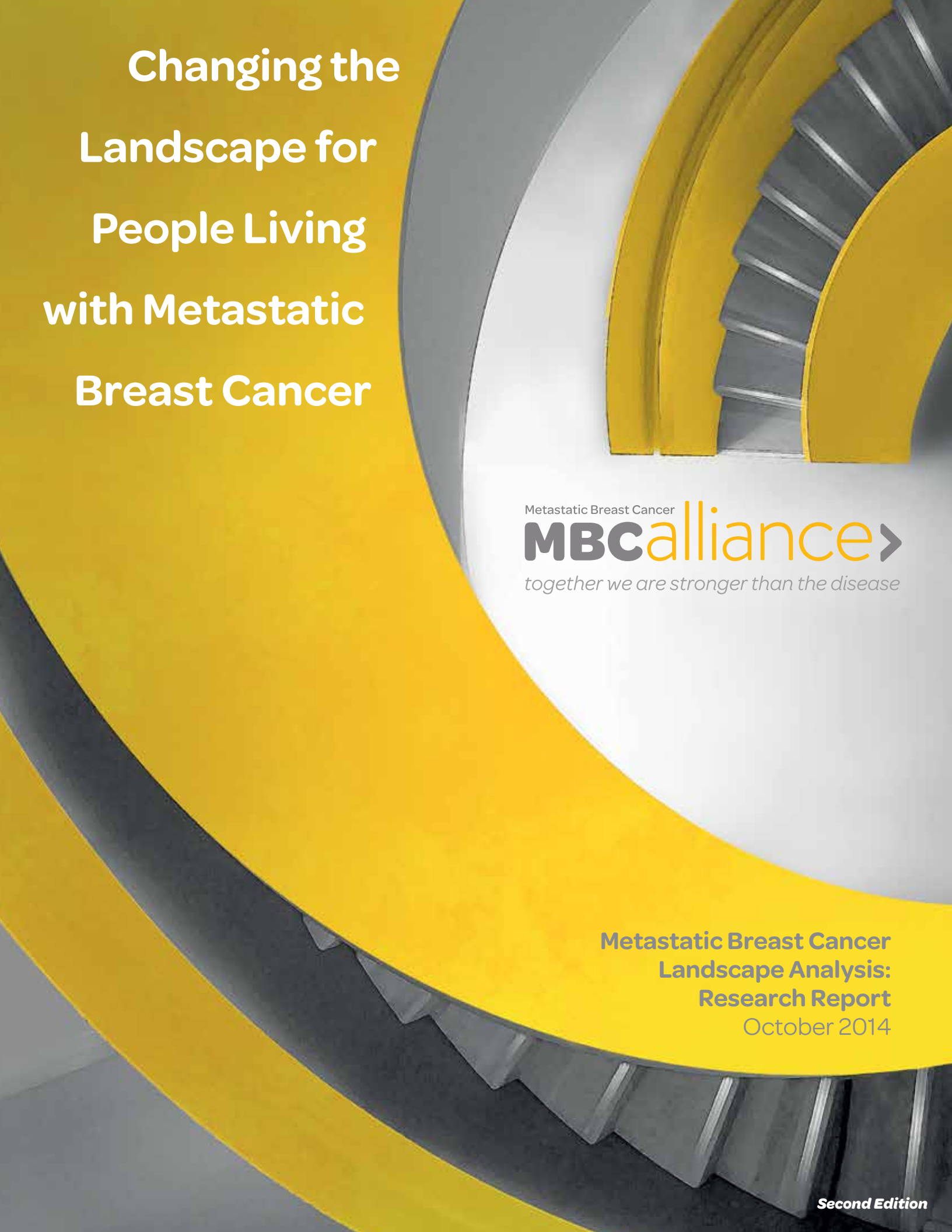
Changing the Landscape for People Living with Metastatic Breast Cancer



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

AVON Foundation for Women

BREASTCANCER.ORG
REAL. ANSWERS.

BCRF

BreastCancerTrials.org
find a trial that's right for you

CANCERcare

CANCER SUPPORT COMMUNITY

Celgene

Dr. Susan Love RESEARCH FOUNDATION

Eisai

Lilly | ONCOLOGY

FORCE EMPOWERED

Genentech

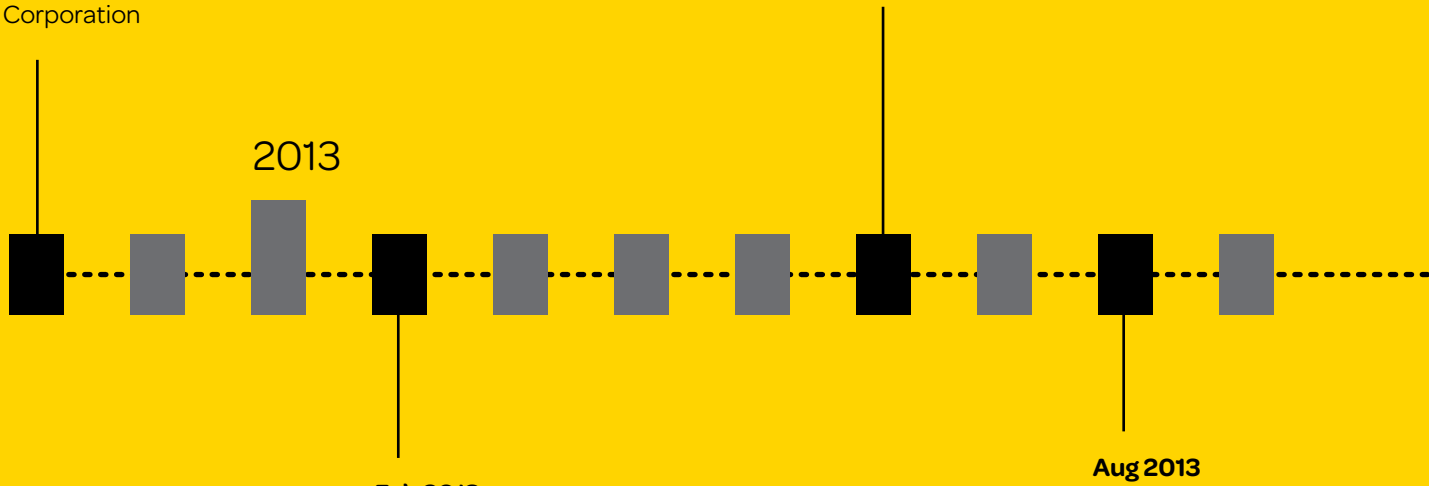
INFLAMMATORY BREAST CANCER


Eli Lilly
Inflammatory
Breast Cancer
Research Foundation
Breastcancer.org
Living Beyond
Breast Cancer
Celgene Corporation
Eisai
Novartis Oncology
Sharsheret
Triple Negative Breast Cancer Foundation
ACS CAN
Cancer Support Community
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

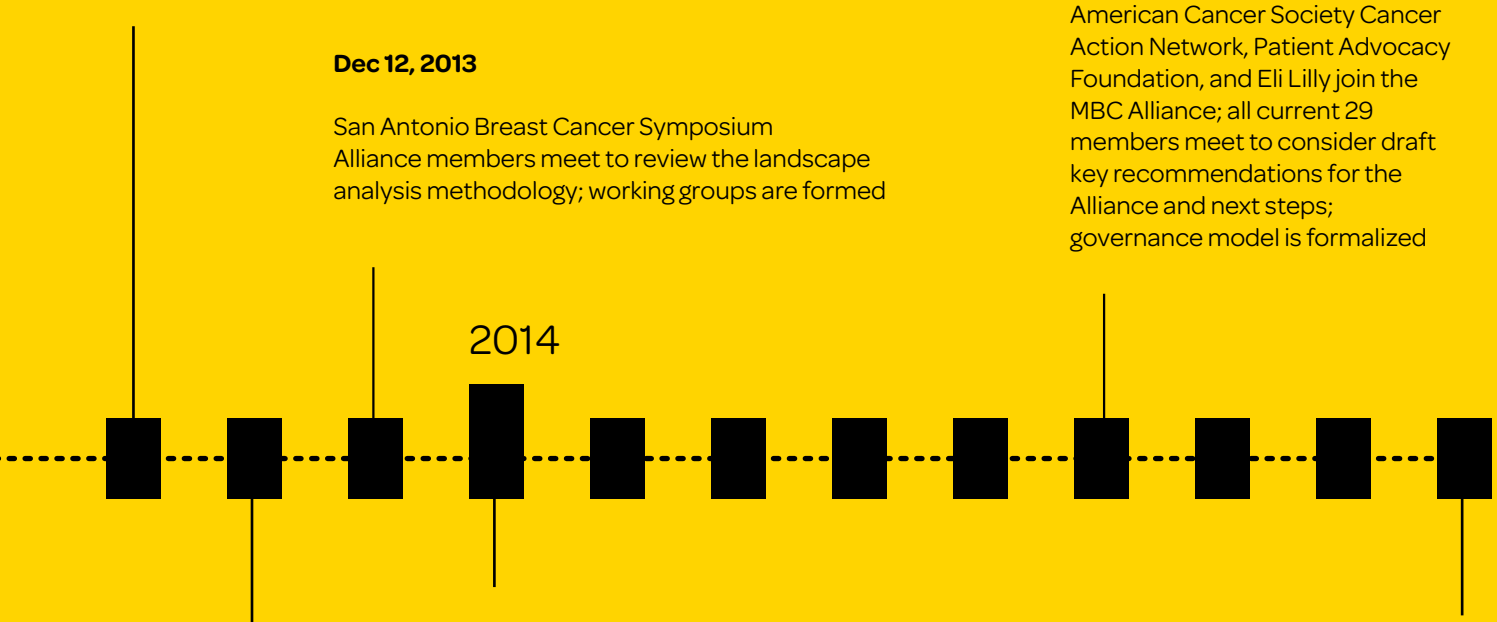
MBC Alliance launches on National Metastatic Breast Cancer Awareness Day; members now include Cancer*Care*, Dr. Susan Love Research Foundation, Sisters Network Inc., Eisai and Novartis

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

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

2

http://dayton.hq.nasa.gov/IMAGES/LARGE/GPN-2000-000663.jpg

CHAPTER 2: LANDSCAPE ANALYSIS OF MBC RESEARCH

Marc Hurlbert[1], Elly Cohen[2], Susan Colen[2], Stephanie Reffey[3], Kari Wojtanik[3], Musa Mayer[4], Samantha Finstad[5] Katie McKenzie[6], Alison Butt[7], Ginny Mason[8], and Lynne Davies[9]

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.

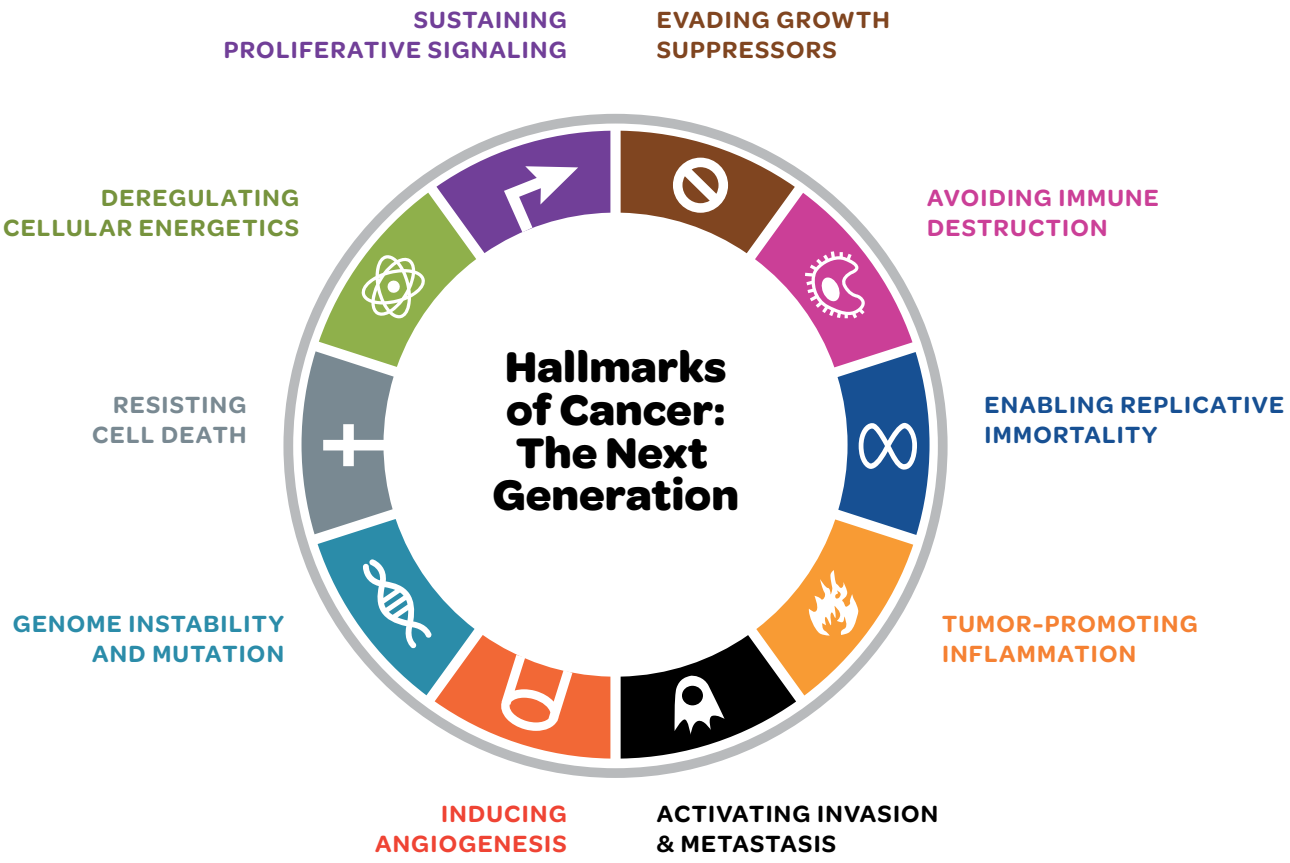
Methods

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

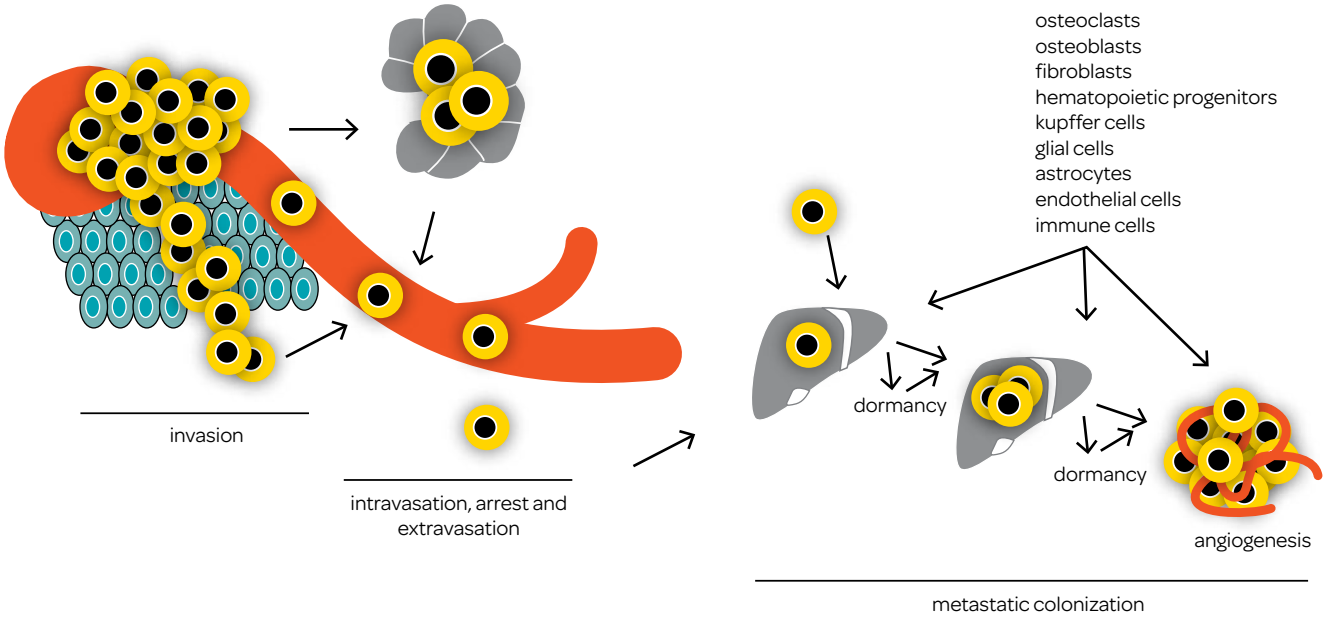


Funded Research Grants Analysis

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

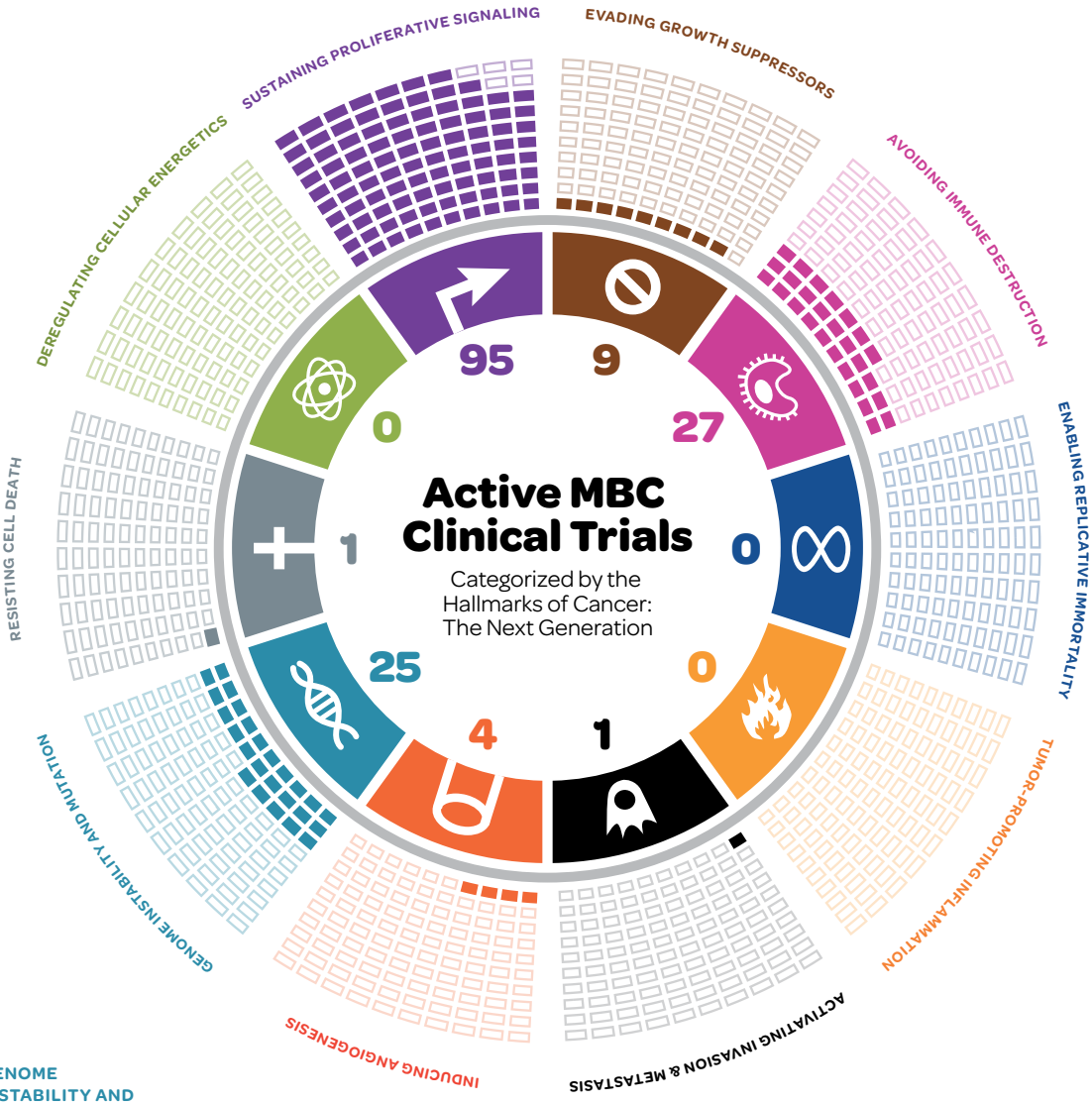
Clinical Trials

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.

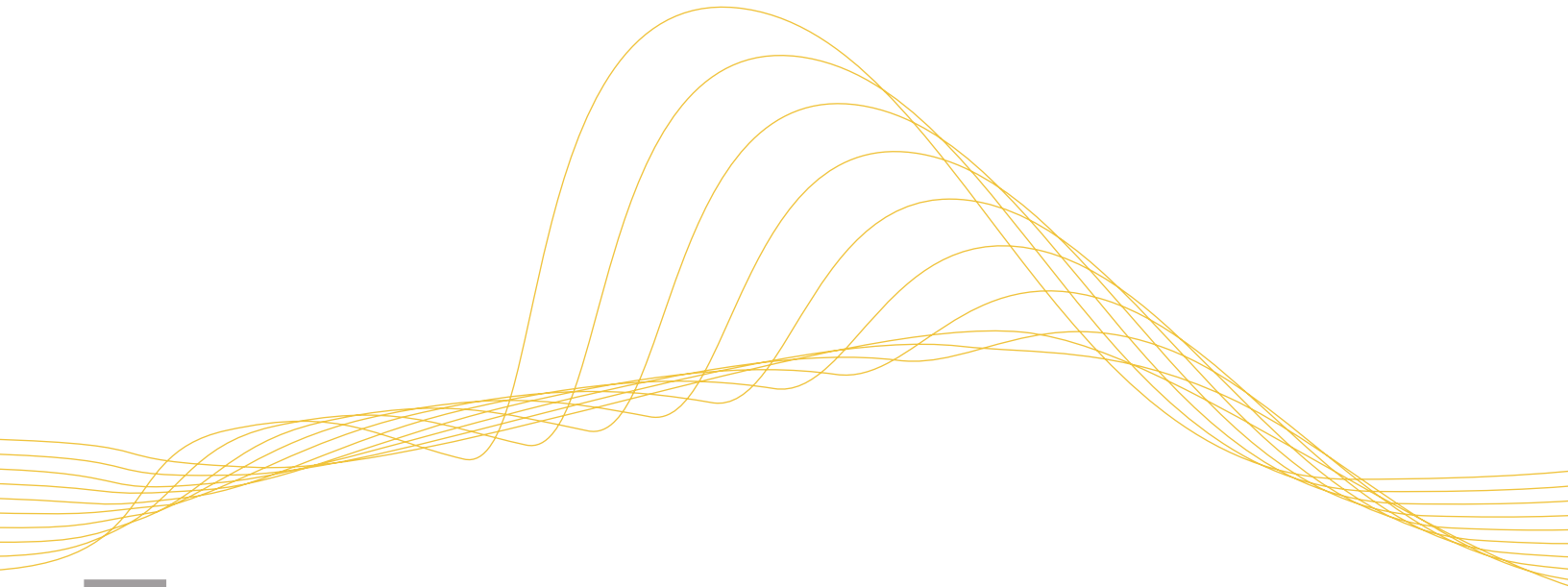


Table 4: MBC Trials Conducted by the Translational Breast Cancer Research Consortium

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)

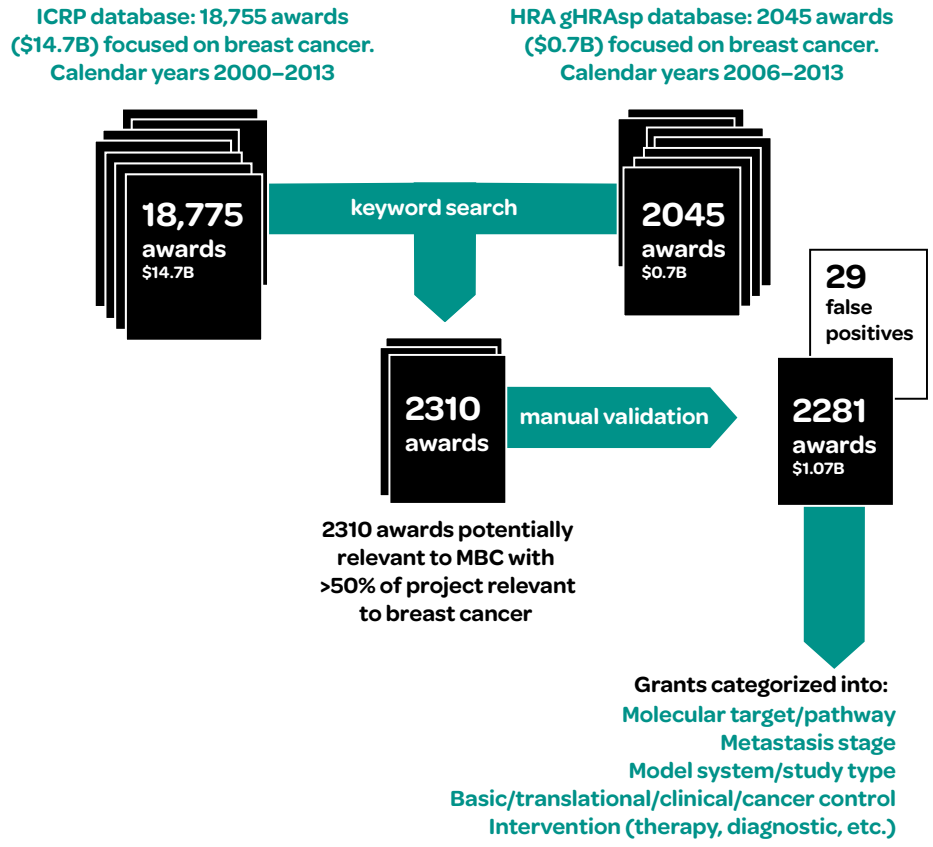
Abbreviations: ASCO American Society of Clinical Oncology, SABCS = San Antonio Breast Cancer Symposium

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**.

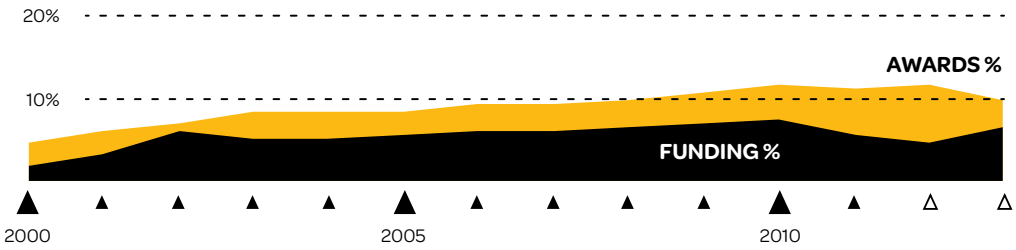
Figure 4: MBC Grants Dataset



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

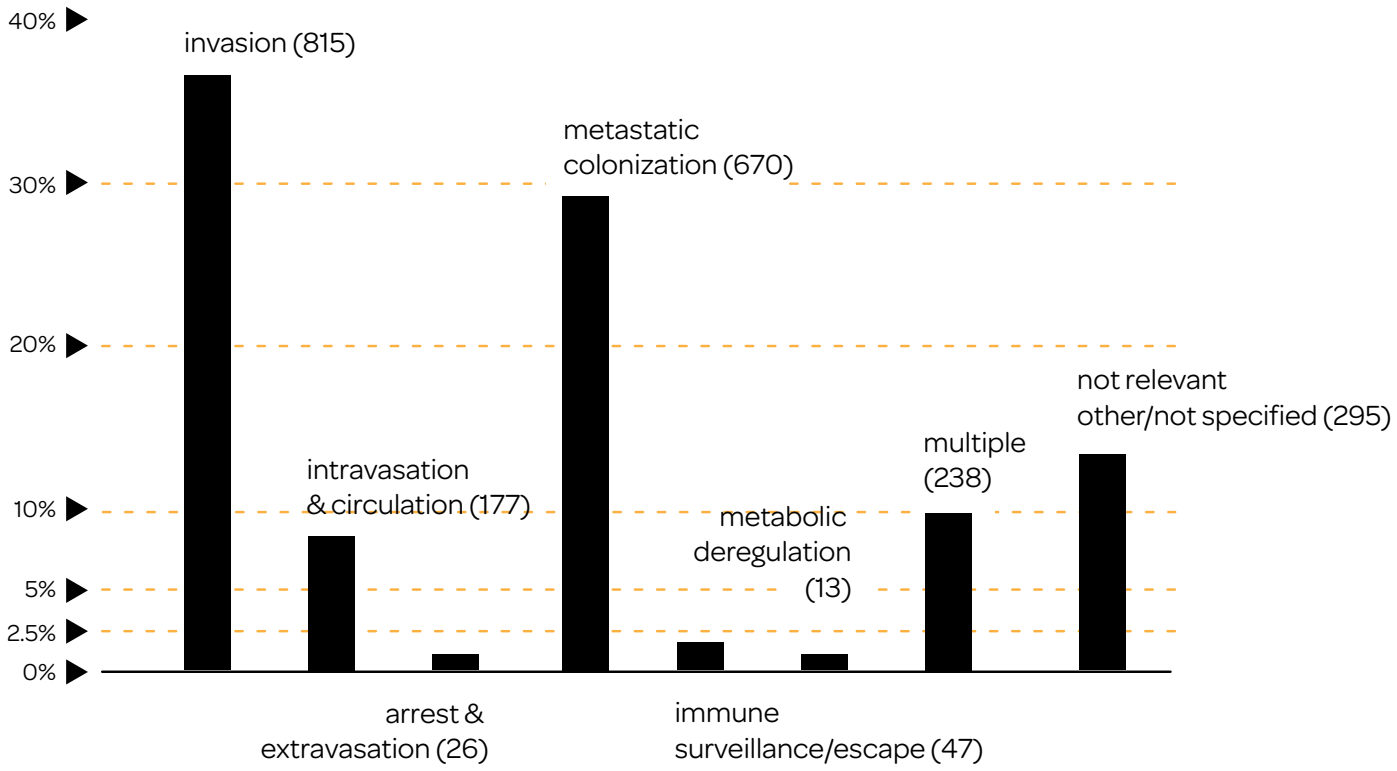


Black: funding for MBC research (% of total). Orange: active MBC projects (%).
Note that the data for 2012 and 2013 are incomplete, as data from all ICRP and all HRA members have not been finalized for those years.

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

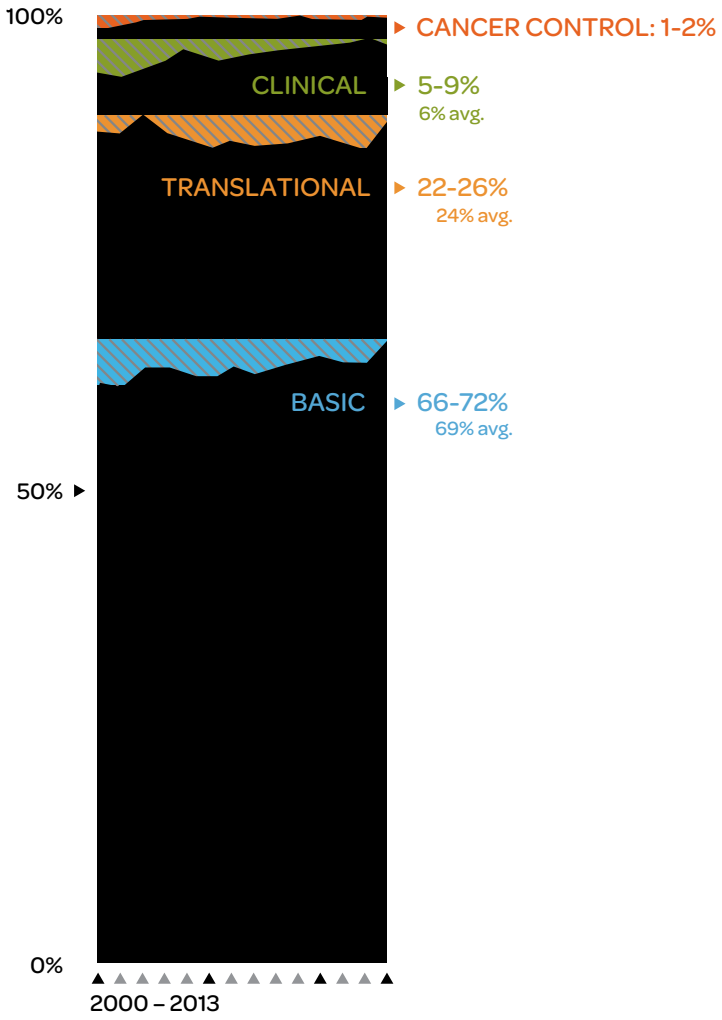


As seen in **Figure 7**, the MBC Grants Dataset was composed predominantly of basic research grants (69%), 24% represented translational research, and vastly smaller percentages were grants for clinical research (6%) and cancer control research (1%). These percentages did not vary substantially across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

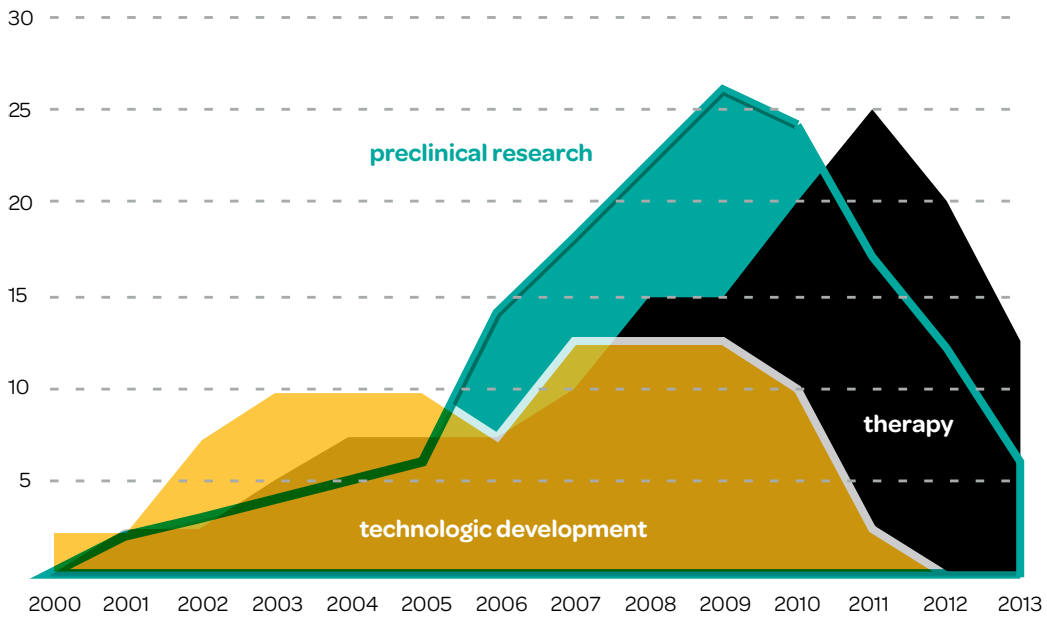
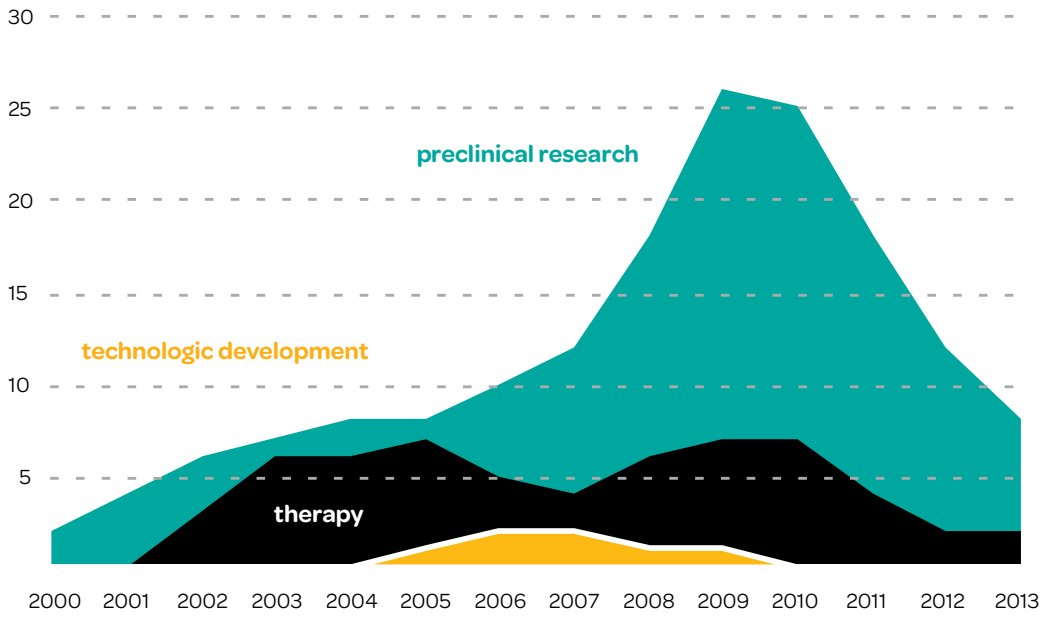


Figure 8b: MBC Research Grants Studying Cytokines and Chemokines from 2000- 2013



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**.

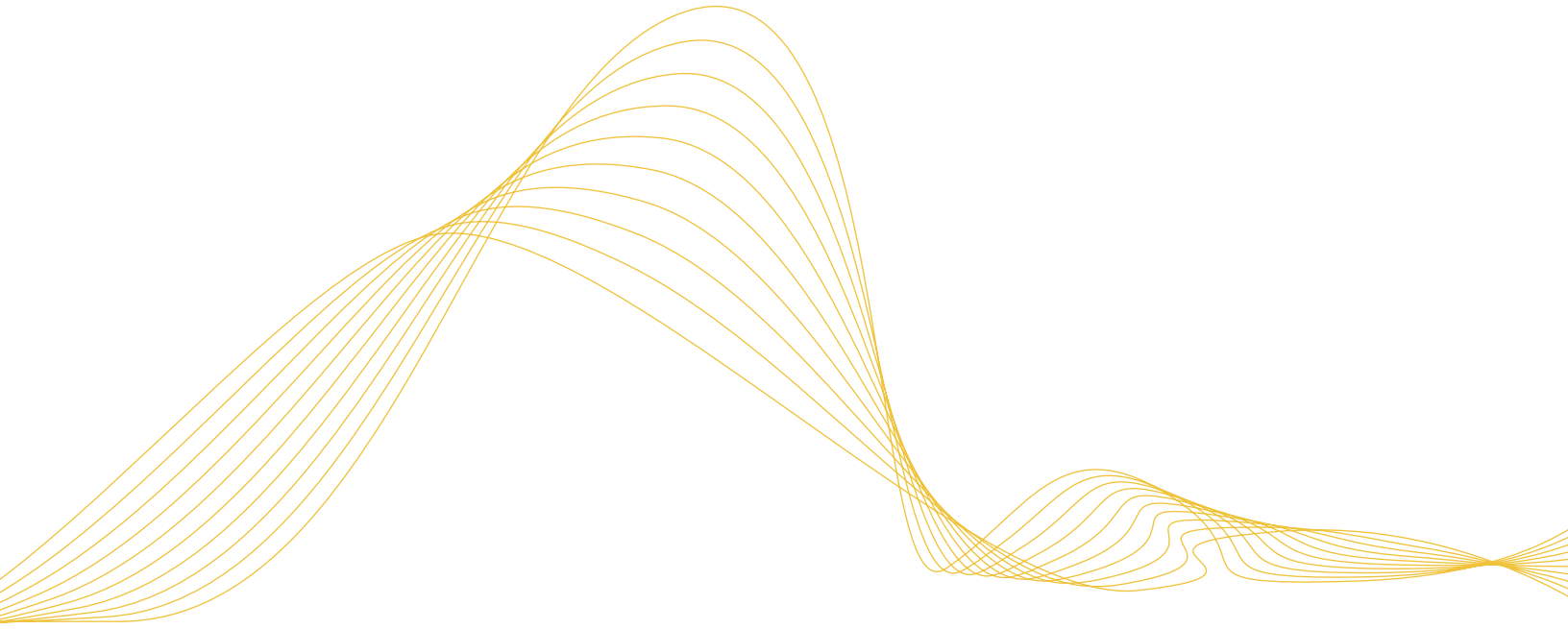


Table 5: Interviews with Key Opinion Leaders

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.

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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		Translational research awards		Clinical 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%				

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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