CHAPTER 2: LANDSCAPE ANALYSIS OF MBC RESEARCH

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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.

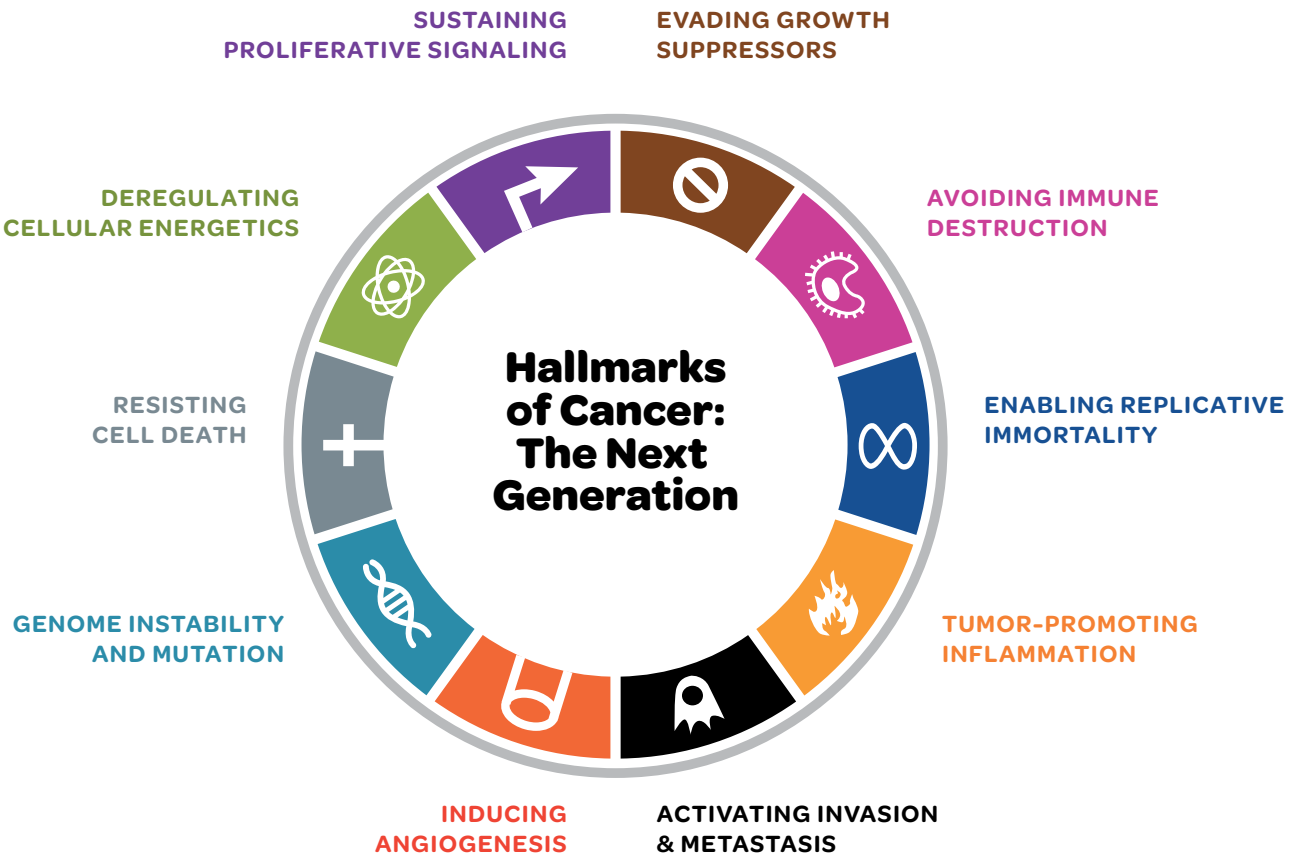
Methods

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

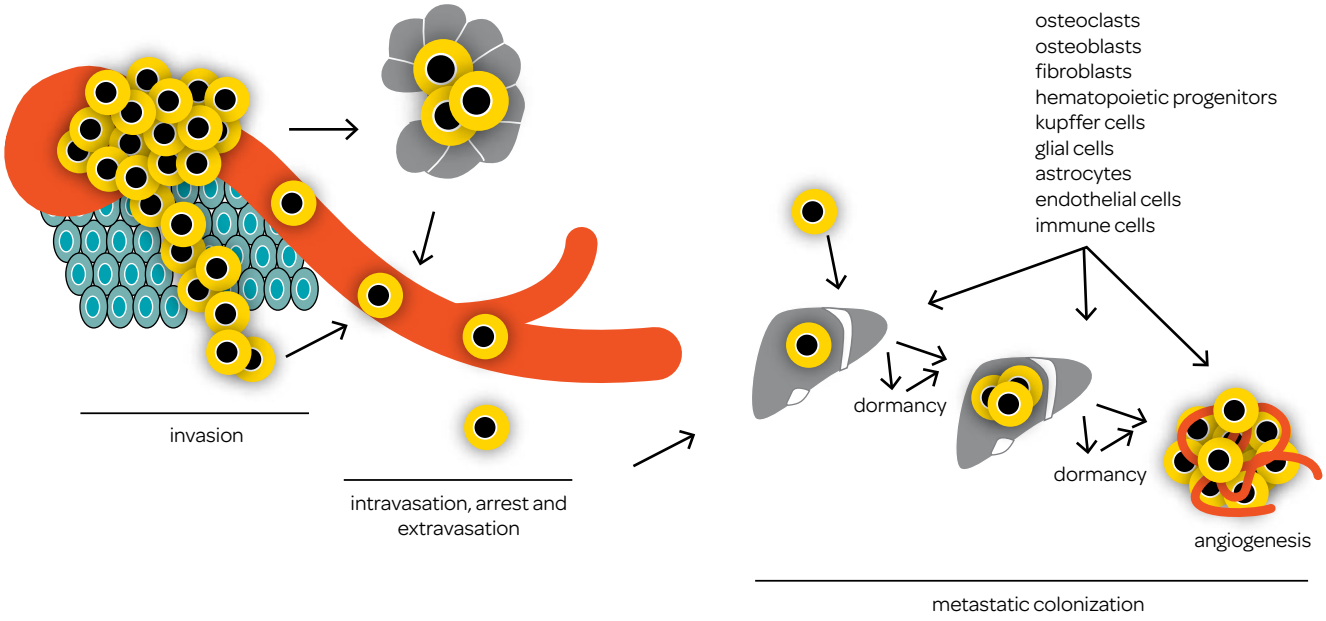


Funded Research Grants Analysis

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

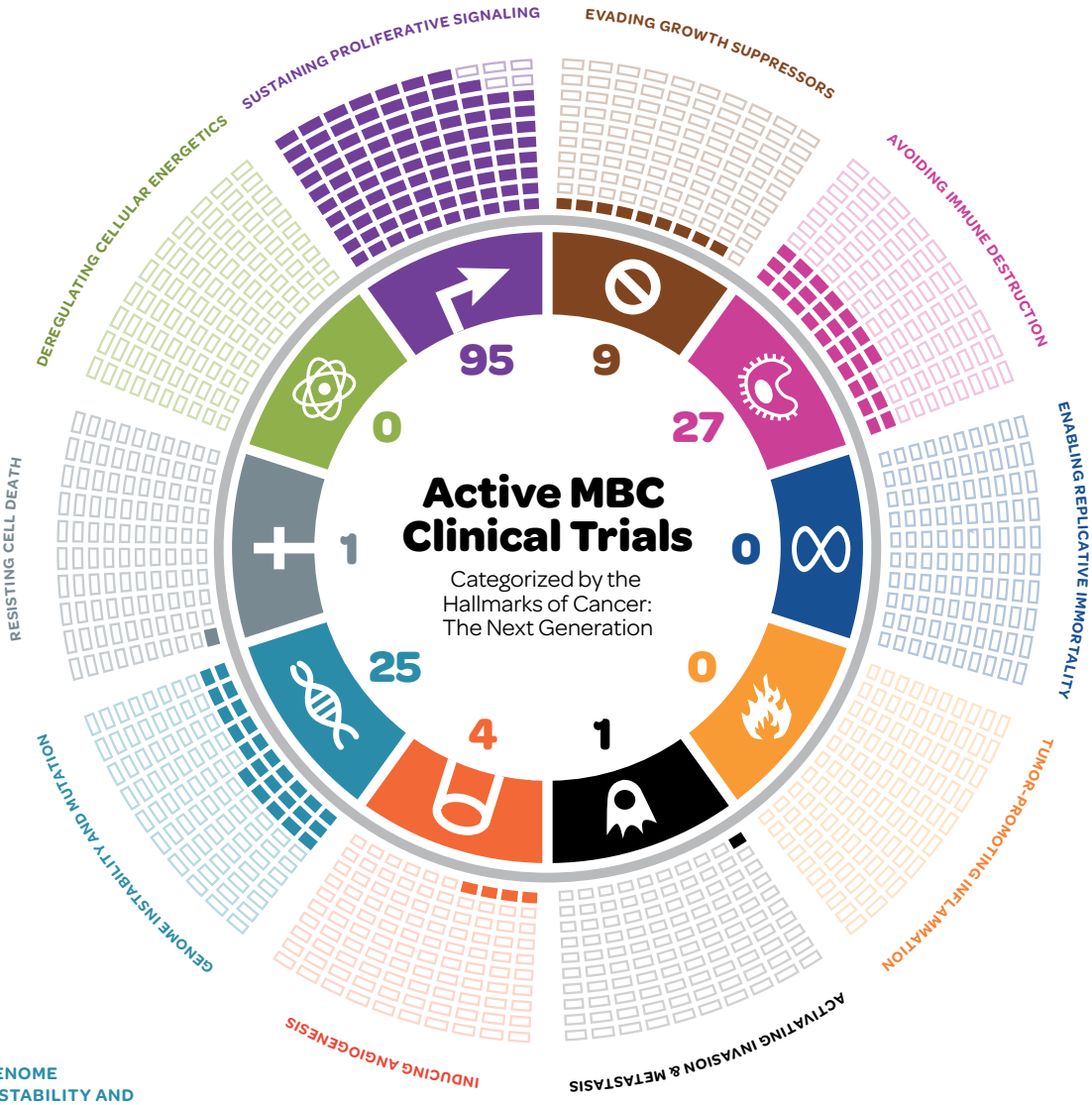
Clinical Trials

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.

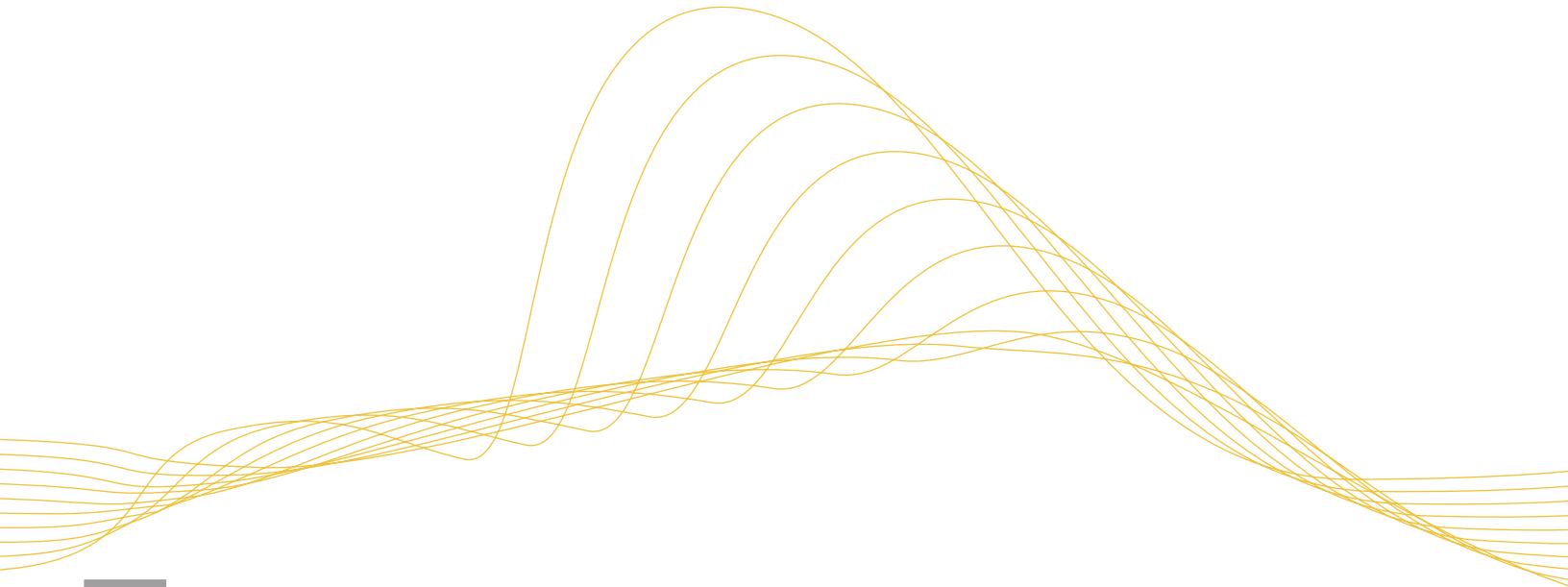


Table 4: MBC Trials Conducted by the Translational Breast Cancer Research Consortium

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)

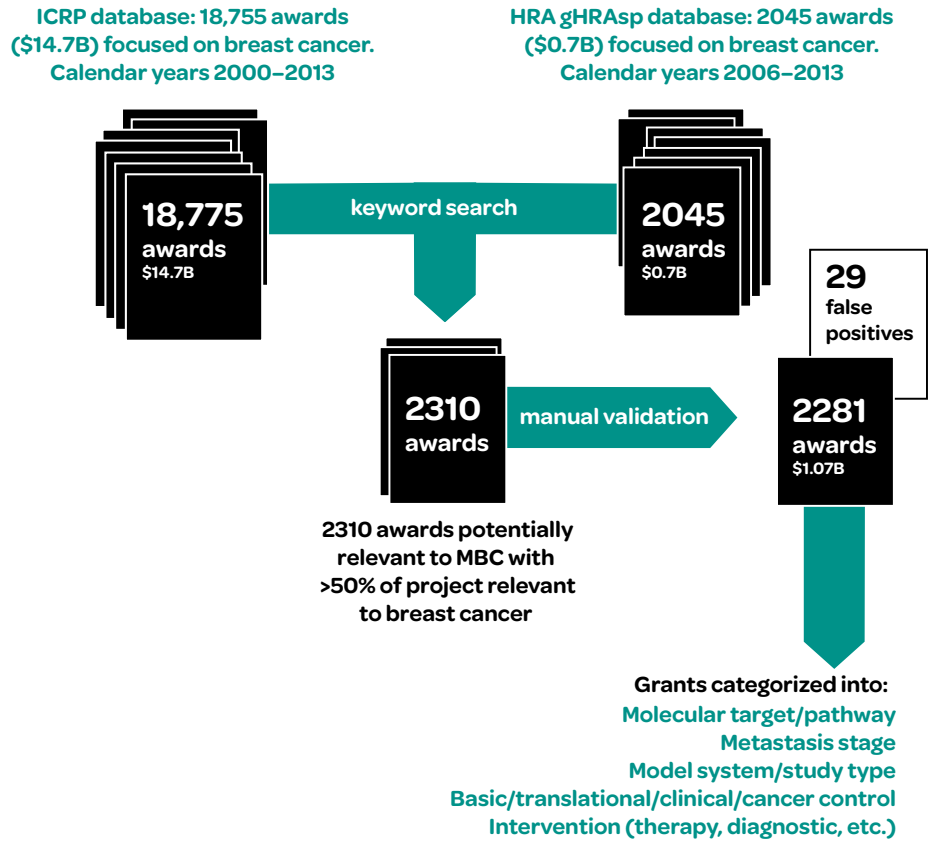
Abbreviations: ASCO American Society of Clinical Oncology, SABCS = San Antonio Breast Cancer Symposium

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**.

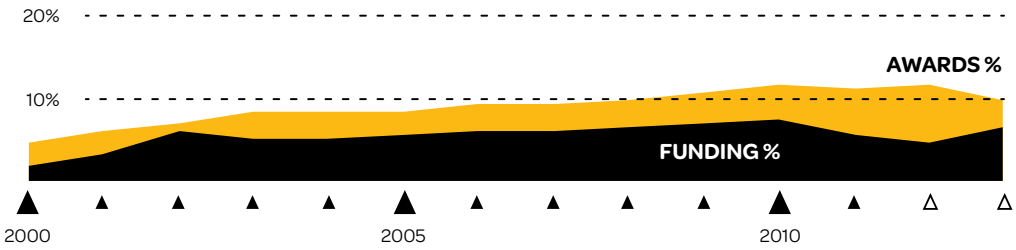
Figure 4: MBC Grants Dataset



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

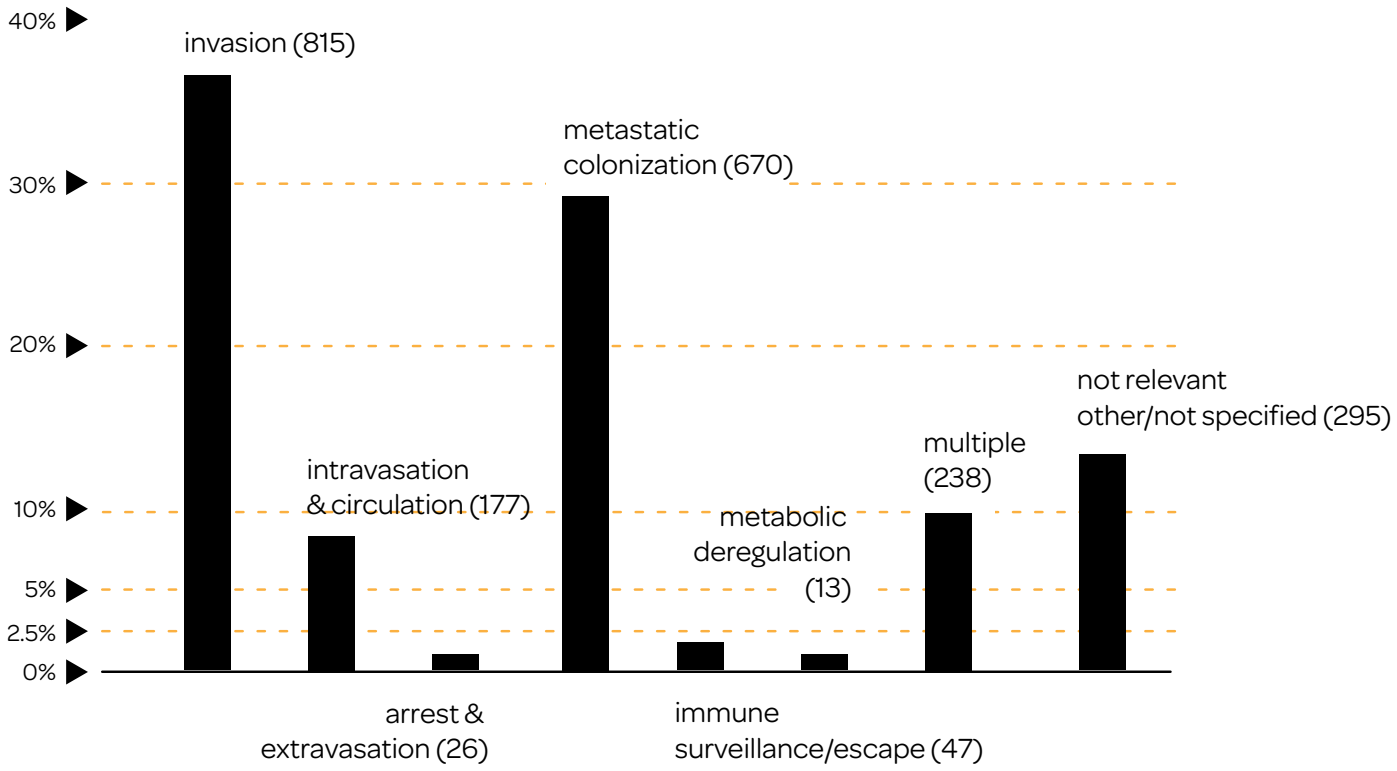


Black: funding for MBC research (% of total). Orange: active MBC projects (%).
Note that the data for 2012 and 2013 are incomplete, as data from all ICRP and all HRA members have not been finalized for those years.

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

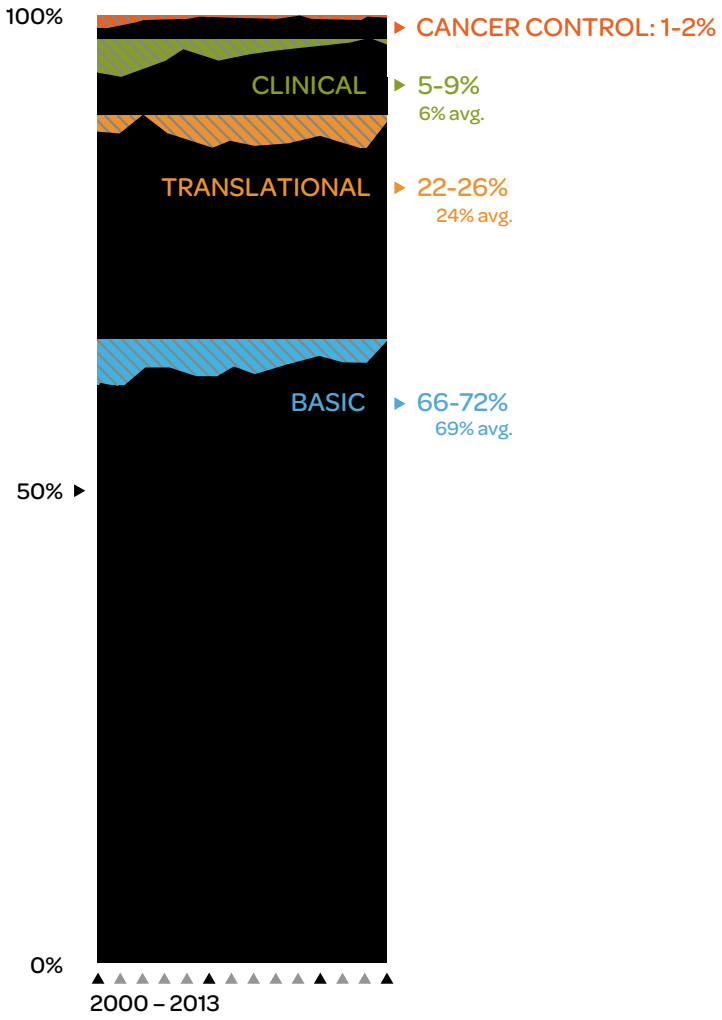


As seen in **Figure 7**, the MBC Grants Dataset was composed predominantly of basic research grants (69%), 24% represented translational research, and vastly smaller percentages were grants for clinical research (6%) and cancer control research (1%). These percentages did not vary substantially across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

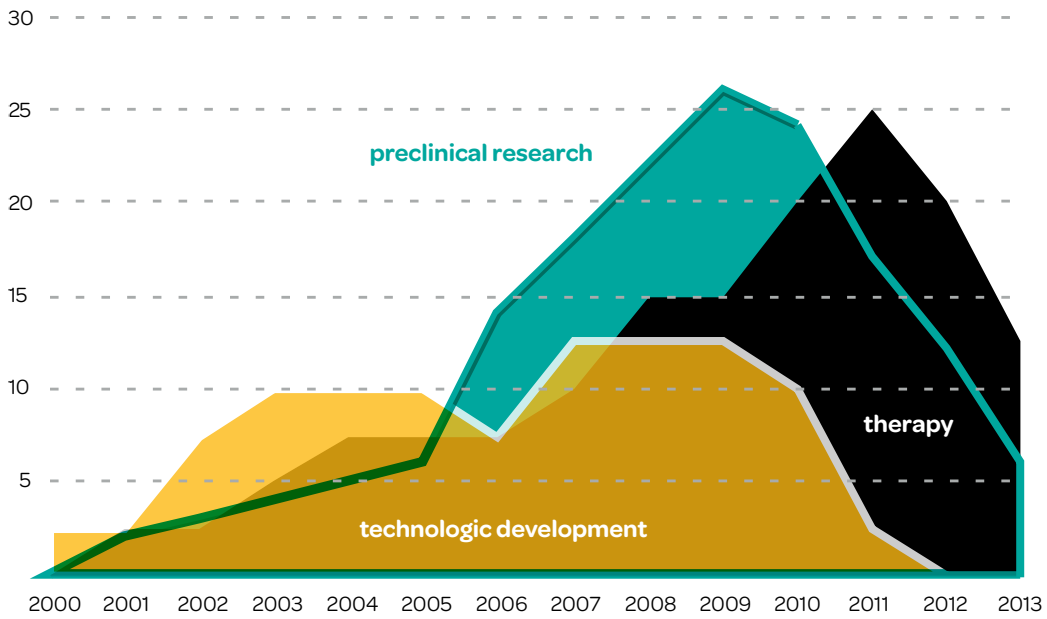
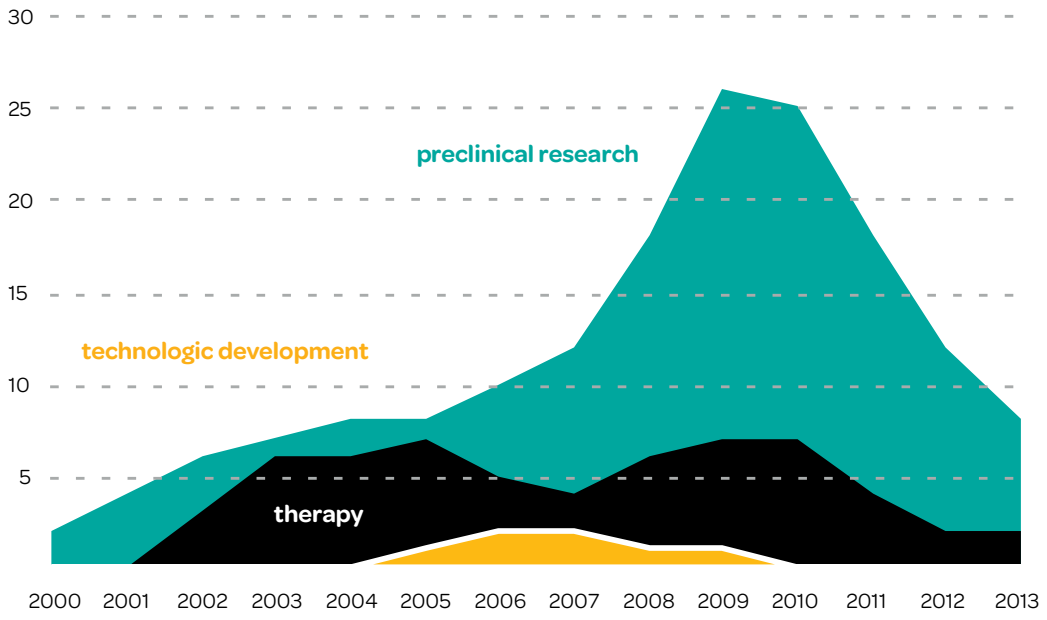


Figure 8b: MBC Research Grants Studying Cytokines and Chemokines from 2000- 2013



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**.

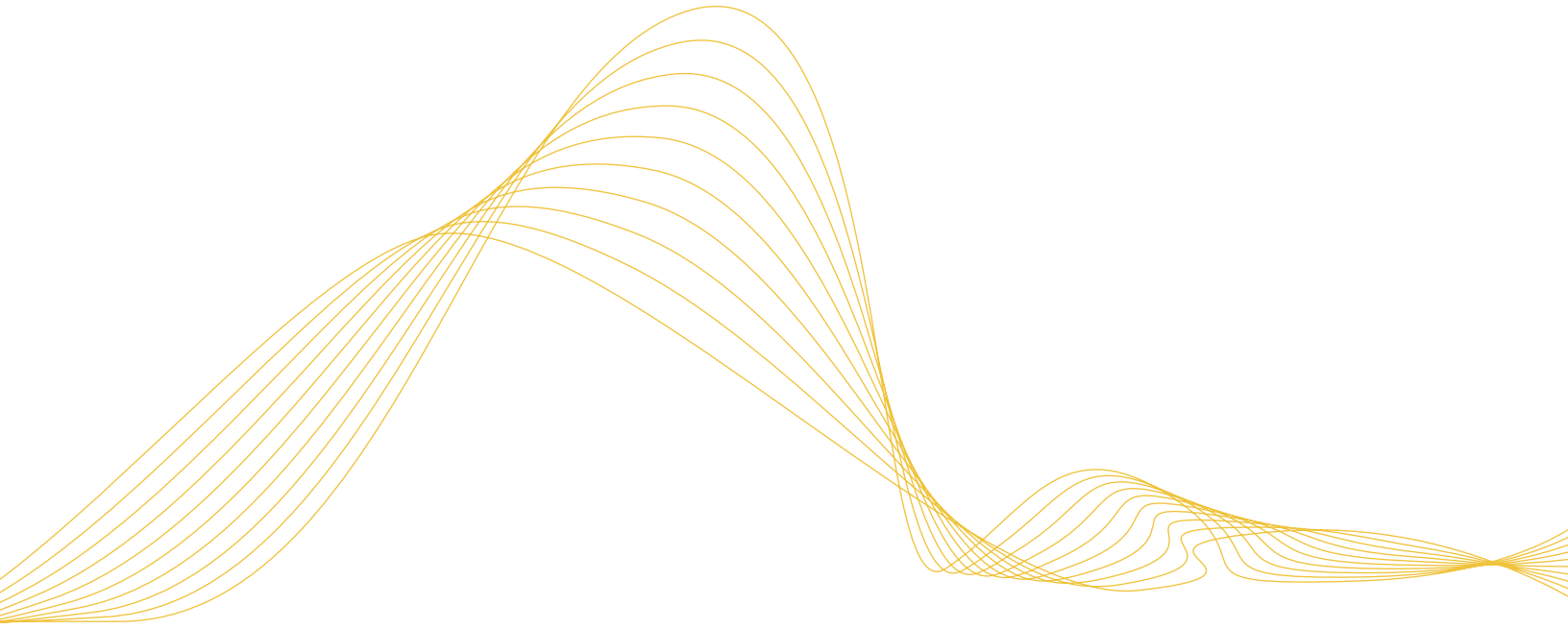


Table 5: Interviews with Key Opinion Leaders

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.

References

1. Society, A.C., *American Cancer Society. Breast Cancer Facts & Figures 2013-2014. Atlanta: American Cancer Society, Inc.* . 2013.

2. Pal, S.K., *Lack of survival benefit in metastatic breast cancer with newer chemotherapy agents: The City of Hope cancer experience.* Journal of Clinical Oncology, 2008. 26(Supplement).

3. Mayer, M. and S.E. Grober, *Silent Voices: Women with Advanced (Metastatic) Breast Cancer Share Their Needs and Preferences for Information, Support, and Practical Resources*. 2006: Living Beyond Breast Cancer website.

4. Kroenke, K., et al., *The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients.* J Pain Symptom Manage, 2010. 40(3): p. 327-41.

5. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation.* Cell, 2011. 144(5): p. 646-74.

6. Steeg, P.S., *Tumor metastasis: mechanistic insights and clinical challenges.* Nat Med, 2006. 12(8): p. 895-904.

7. Fidler, I.J., *The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited.* Nat Rev Cancer, 2003. 3(6): p. 453-8.

8. Institute, N.C., *National Cancer Institute Fact Sheet: Targeted Cancer Therapies*. 2014.

9. ICRP. *International Cancer Research Partnership*. Available *from: http://www.icrpartnership.org/.*

10. ICRP, Cancer Research Funding from an International Perspective, L. Davies, Editor. 2012, International Cancer Research Partnership.

11. O'Toole, L., P. Nurse, and G. Radda, An analysis of cancer research funding in the UK. Nat Rev Cancer, 2003. 3(2): p. 139-43.

12. Nurse, P., et al., Cancer research: joint planning for the future. Ann Oncol, 2003. 14(11): p. 1593-4.

13. Myers, E.R., et al., Similarities and differences in philanthropic and federal support for medical research in the United States: an analysis of funding by nonprofits in 2006-2008. Acad Med, 2012. 87(11): p. 1574-81.

14. TBCRC. Translational Breast Cancer Research Consortium. Available from: http://pub.emmes.com/study/bcrc/.

15. Eccles, S.A., et al., Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. Breast Cancer Res, 2013. 15(5): p. R92.

16. Criscitiello, C., et al., *Biopsy confirmation of metastatic sites in breast cancer patients: clinical impact and future perspectives.* Breast Cancer Res, 2014. 16(2): p. 205.

17. Sleeman, J. and P.S. Steeg, *Cancer metastasis as a therapeutic target.* Eur J Cancer, 2010. 46(7): p. 1177-80.

18. Steeg, P.S., *Perspective: The right trials.* Nature, 2012. 485(7400): p. S58-9.

19. Hanahan, D., *Rethinking the war on cancer.* Lancet, 2014. 383(9916): p. 558-63.

20. Sledge, G.W., et al., *A dickens tale of the treatment of advanced breast cancer: the past, the present, and the future.* Am Soc Clin Oncol Educ Book, 2012: p. 28-38.

21. Floor, S.L., et al., *Hallmarks of cancer: of all cancer cells, all the time?* Trends Mol Med, 2012. 18(9): p. 509-15.

22. Hu, J., et al., *Antitelomerase therapy provokes ALT and mitochondrial adaptive mechanisms in cancer.* Cell, 2012. 148(4): p. 651-63.

23. Bergers, G. and D. Hanahan, *Modes of resistance to anti-angiogenic therapy.* Nat Rev Cancer, 2008. 8(8): p. 592-603.

24. Bottsford-Miller, J.N., R.L. Coleman, and A.K. Sood, *Resistance and escape from antiangiogenesis therapy: clinical implications and future strategies.* J Clin Oncol, 2012. 30(32): p. 4026-34.

25. Dogan, S., F. Andre, and M. Arnedos, *Issues in clinical research for metastatic breast cancer.* Curr Opin Oncol, 2013. 25(6): p. 625-9.

26. Stead, M., et al., *Strengthening clinical cancer research in the United Kingdom.* Br J Cancer, 2011. 104(10): p. 1529-34.

27. Research, L.C., *Ludwig Cancer Research bestows half a billion in new funding to six eminent U.S. research institutions* 2014.

28. Foundation, B.C.R., *Founder's Fund*. 2014.

29. Visco, F., *Breast Cancer Deadline 2020 3rd Annual Progress Report*. 2014.

30. Howlader N, N.A., Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014*, N.A. Howlader N, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). Editor. 2014.

31. McCorkle, R., et al., *Self-management: Enabling and empowering patients living with cancer as a chronic illness.* CA Cancer J Clin, 2011. 61(1): p. 50-62.

32. Karamouzis, M.V., G. Ioannidis, and G. Rigatos, *Quality of life in metastatic breast cancer patients under chemotherapy or supportive care: a single-institution comparative study.* Eur J Cancer Care (Engl), 2007. 16(5): p. 433-8.

33. Holland, J.C., *History of psycho-oncology: overcoming attitudinal and conceptual barriers.* Psychosom Med, 2002. 64(2): p. 206-21.

34. Network, N.C.C. *NCCN Distress Thermometer for Patients. National Comprehensive Cancer Network website.* 2014 August 11, 2014]; Available from: http://www.nccn.org/patients/resources/life_with_cancer/pdf/nccn_distress_thermometer.pdf.

35. Adler, N.E., et al., *Cancer Care for the Whole Patient*, A.E.K. Page, Editor. 2007: Institute of Medicine, National Academies.

36. Tatla, R., et al., *A review of clinical endpoints and use of quality-of-life outcomes in phase III metastatic breast cancer clinical trials* in *Thirty-Fifth Annual CTRC-AACR San Antonio Breast Cancer Symposium*. 2012, Cancer Research San Antonio, TX. p. P2-12-07.

37. Office of Communications, D.o.D.I., Food and Drug Administration, *Gudiance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. 2009, Food and Drug Administration: FDA Website.

38. Levit, L., et al., *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*. 2013, National Academy of Science: Institute of Medicine, The National Academies.

39. Aranda, S., et al., *Mapping the quality of life and unmet needs of urban women with metastatic breast cancer.* Eur J Cancer Care (Engl), 2005. 14(3): p. 211-22.

40. Caplette-Gingras, A. and J. Savard, *Depression in women with metastatic breast cancer: a review of the literature.* Palliat Support Care, 2008. 6(4): p. 377-87.

41. Turner, J., et al., *Psychosocial impact of newly diagnosed advanced breast cancer.* Psychooncology, 2005. 14(5): p. 396-407.

42. Grabsch, B., et al., *Psychological morbidity and quality of life in women with advanced breast cancer: a cross-sectional survey.* Palliat Support Care, 2006. 4(1): p. 47-56.

43. Kissane, D.W., et al., *Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis.* Aust N Z J Psychiatry, 2004. 38(5): p. 320-6.

44. Seah, D.S., et al., *Informational needs and psychosocial assessment of patients in their first year after metastatic breast cancer diagnosis*, in *San Antonio Breast Cancer Symposium*. 2012, Cancer Research: San Antonio, TX.

45. Hall, A., L. Fallowfield, and R. A'Hern, *When Breast Cancer Recurs: A 3-Year Prospective Study of Psychological Morbidity.* The Breast Journal, 1996. 2(3): p. 197-203.

46. Warren, M., *Uncertainty, lack of control and emotional functioning in women with metastatic breast cancer: a review and secondary analysis of the literature using the critical appraisal technique.* Eur J Cancer Care (Engl), 2010. 19(5): p. 564-74.

47. Kashdan, T.B. and J. Rottenberg, *Psychological flexibility as a fundamental aspect of health.* Clin Psychol Rev, 2010. 30(7): p. 865-78.

48. Fulton, C., *Patients with metastatic breast cancer: their physical and psychological rehabilitation needs.* Int J Rehabil Res, 1999. 22(4): p. 291-301.

49. Kershaw, T., et al., *Coping strategies and quality of life in women with advanced breast cancer and their family caregivers.* Psychology and Health, 2004. 19(S1): p. 139-155.

50. Luoma, M.L. and L. Hakamies-Blomqvist, *The meaning of quality of life in patients being treated for advanced breast cancer: a qualitative study.* Psychooncology, 2004. 13(10): p. 729-39.

51. Kenne Sarenmalm, E., et al., *Coping with recurrent breast cancer: predictors of distressing symptoms and health-related quality of life.* J Pain Symptom Manage, 2007. 34(1): p. 24-39.

52. Northouse, L.L., G. Dorris, and C. Charron-Moore, *Factors affecting couples' adjustment to recurrent breast cancer.* Soc Sci Med, 1995. 41(1): p. 69-76.

53. Cheung, W.Y., L.W. Le, and C. Zimmermann, *Symptom clusters in patients with advanced cancers.* Support Care Cancer, 2009. 17(9): p. 1223-30.

54. Brennan, J., *Adjustment to cancer - coping or personal transition?* Psychooncology, 2001. 10(1): p. 1-18.

55. Oh, S., et al., *Quality of life of breast cancer survivors after a recurrence: a follow-up study.* Breast Cancer Res Treat, 2004. 87(1): p. 45-57.

56. Mayer, M., et al., *Assessment of burden of illness of women with HER2+ metastatic breast cancer: The results of a community-based survey*, in *ASCO Annual Meeting*. 2011, Journal of Clinical Oncology: Chicago, IL.

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

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

59. Rowe, J., *Surveying young women with metastatic breast cancer to create interventions with impact.* , in *ABC2: Advanced Breast Cancer Second Consensus Conference*. 2013: Lisbon, Portugal.

60. Mayer, M., et al., *Living with metastatic breast cancer: a global patient survey.* Community Oncology, 2010. 7(9): p. 406-413.

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

62. Willis, K., et al., *The Experience of Living With Metastatic Breast Cancer-A Review of the Literature.* Health Care Women Int, 2014: p. 1-29.

63. Kissane, D.W., *The relief of existential suffering.* Arch Intern Med, 2012. 172(19): p. 1501-5.

64. Irvin, W., Jr., H.B. Muss, and D.K. Mayer, *Symptom management in metastatic breast cancer.* Oncologist, 2011. 16(9): p. 1203-14.

65. Brothers, B.M. and B.L. Andersen, *Hopelessness as a predictor of depressive symptoms for breast cancer patients coping with recurrence.* Psychooncology, 2009. 18(3): p. 267-75.

66. Charmaz, K., *Good Days, Bad Days: The self in chronic illness and time.* Vol. 1. 1991: Rutgers University Press. 324.

67. Bell, K. and S. Ristovski-Slijepcevic, *Metastatic cancer and mothering: being a mother in the face of a contracted future.* Med Anthropol, 2011. 30(6): p. 629-49.

68. Griffiths, K.M., A.L. Calear, and M. Banfield, *Systematic review on Internet Support Groups (ISGs) and depression (1): Do ISGs reduce depressive symptoms?* J Med Internet Res, 2009. 11(3): p. e40.

69. Lieberman, M.A., et al., *Electronic support groups for breast carcinoma: a clinical trial of effectiveness.* Cancer, 2003. 97(4): p. 920-5.

70. Eysenbach, G., et al., *Health related virtual communities and electronic support groups: systematic review of the effects of online peer to peer interactions.* BMJ, 2004. 328(7449): p. 1166.

71. Goodwin, P.J., et al., *The effect of group psychosocial support on survival in metastatic breast cancer.* N Engl J Med, 2001. 345(24): p. 1719-26.

72. Northouse, L.L., D. Laten, and P. Reddy, *Adjustment of women and their husbands to recurrent breast cancer.* Res Nurs Health, 1995. 18(6): p. 515-24.

73. Mayer, M., *Lessons learned from the metastatic breast cancer community.* Semin Oncol Nurs, 2010. 26(3): p. 195-202.

74. Lazarus, R.S., *Coping theory and research: past, present, and future.* Psychosom Med, 1993. 55(3): p. 234-47.

75. Fallowfield, L., et al., *Identifying Barriers Preventing Clinical Trials Enrollment: Results of a Global Survey of Patients with Metastatic Breast Cancer*, in *AACR Annual Conference*. 2009: Denver, CO.

76. Gattellari, M., et al., *When the treatment goal is not cure: are cancer patients equipped to make informed decisions?* J Clin Oncol, 2002. 20(2): p. 503-13.

77. Jenkins, V., L. Fallowfield, and J. Saul, *Information needs of patients with cancer: results from a large study in UK cancer centres.* Br J Cancer, 2001. 84(1): p. 48-51.

78. Hack, T.F., et al., *The communication goals and needs of cancer patients: a review.* Psychooncology, 2005. 14(10): p. 831-45; discussion 846-7.

79. Harding, V., et al., *'Being there' for women with metastatic breast cancer: a pan-European patient survey.* Br J Cancer, 2013. 109(6): p. 1543-8.

80. Smith, M.L., et al., *Preferences of patients with metastatic breast cancer.*, in *2011 ASCO Annual Meeting*. 2011, Journal of Clinical Oncology: Chicago, IL.

81. Smith, M.L., et al., *Examining patient choices for metastatic breast cancer drugs.* , in *2012 ASCO Annual Meeting*. 2012, Journal of Clinical Oncology: Chicago, IL.

82. Cheville, A.L., et al., *Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer.* J Clin Oncol, 2008. 26(16): p. 2621-9.

83. Portenoy, R.K. and P. Lesage, *Management of cancer pain.* Lancet, 1999. 353(9165): p. 1695-700.

84. Butt, Z., et al., *Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy.* J Natl Compr Canc Netw, 2008. 6(5): p. 448-55.

85. Hwang, S.S., et al., *Multidimensional independent predictors of cancer-related fatigue.* J Pain Symptom Manage, 2003. 26(1): p. 604-14.

86. Bennett, B., et al., *Fatigue and psychological distress--exploring the relationship in women treated for breast cancer.* Eur J Cancer, 2004. 40(11): p. 1689-95.

87. Stone, P., *The measurement, causes and effective management of cancer-related fatigue.* Int J Palliat Nurs, 2002. 8(3): p. 120-8.

88. Palesh, O.G., et al., *A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer.* Biol Psychol, 2007. 75(1): p. 37-44.

89. Carroll, J.K., et al., *Pharmacologic treatment of cancer-related fatigue.* Oncologist, 2007. 12 Suppl 1: p. 43-51.

90. Fiorentino, L. and S. Ancoli-Israel, *Insomnia and its treatment in women with breast cancer.* Sleep Med Rev, 2006. 10(6): p. 419-29.

91. Jagsi, R., et al., *Long-term financial burden of breast cancer: experiences of a diverse cohort of survivors identified through population-based registries.* J Clin Oncol, 2014. 32(12): p. 1269-76.

92. Neugut, A.I., et al., *Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early stage breast cancer.* J Clin Oncol, 2011. 29(18): p. 2534-42.

93. Zafar, S.Y., et al., *The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience.* Oncologist, 2013. 18(4): p. 381-90.

94. Ramsey, S., et al., *Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis.* Health Aff (Millwood), 2013. 32(6): p. 1143-52.

95. Buzaglo, J., et al., *Work-related impact of metastatic breast cancer: Results from the Cancer Experience Registry.*, in *7th Biennial Cancer Survivorship Research Conference*. 2014: Atlanta, GA.

96. Yang, H.C., et al., *Surviving recurrence: psychological and quality-of-life recovery.* Cancer, 2008. 112(5): p. 1178-87.

97. English, R.A., Y. Lebovitz, and R.B. Giffin, *Transforming Clinical Trials in the United States: Challenges and Opportunities. A workshop summary.* 2010.

98. Duggan, M., *Pew Research Internet Project, Cell Phone Activities 2013: Additional Demographics*, in *Pew Research Internet Project*. 2013: Pew Research.

99. DeSantis, C.E., et al., *Cancer treatment and survivorship statistics, 2014.* CA Cancer J Clin, 2014. 64(4): p. 252-71.

100. Clements, M.S., et al., *Estimating prevalence of distant metastatic breast cancer: a means of filling a data gap.* Cancer Causes Control, 2012. 23(10): p. 1625-34.

101. Fiteni, F., et al., *Long-term survival of patients with HER2 metastatic breast cancer treated by targeted therapies.* , in *Thirty-Fifth Annual CTRC-AACR San Antonio Breast Cancer Symposium*. 2012, Cancer Research: San Antonio, TX.

102. Dawood, S., et al., *Survival differences among women with de novo stage IV and relapsed breast cancer.* Ann Oncol, 2010. 21(11): p. 2169-74.

103. Dawood, S., et al., *Trends in survival over the past two decades among white and black patients with newly diagnosed stage IV breast cancer.* J Clin Oncol, 2008. 26(30): p. 4891-8.

104. Chia, S.K., et al., *The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer.* Cancer, 2007. 110(5): p. 973-9.

105. Giordano, S.H., et al., *Is breast cancer survival improving?* Cancer, 2004. 100(1): p. 44-52.

106. Ruiterkamp, J., et al., *Improved survival of patients with primary distant metastatic breast cancer in the period of 1995-2008. A nationwide population-based study in the Netherlands.* Breast Cancer Res Treat, 2011. 128(2): p. 495-503.

107. Ernst, M.F., et al., *Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002.* Breast, 2007. 16(4): p. 344-51.

108. Andre, F., et al., *Breast cancer with synchronous metastases: trends in survival during a 14-year period.* J Clin Oncol, 2004. 22(16): p. 3302-8.

109. Pal, S.K., et al., *Impact of modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer.* BMC Cancer, 2012. 12: p. 435.

110. Tevaarwerk, A.J., et al., *Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years.* Cancer, 2013. 119(6): p. 1140-8.

111. Pfizer, *Breast Cancer Survey*. 2014: ASCO Meeting.

112. O'Shaughnessy, J., *Extending survival with chemotherapy in metastatic breast cancer.* Oncologist, 2005. 10 Suppl 3: p. 20-9.

113. Neal, C., *Cancer Stigma and Silence Around the World.* 2007.

114. Else-Quest, N.M., et al., *Perceived stigma, self-blame, and adjustment among lung, breast and prostate cancer patients*. Psychol Health, 2009. 24 (8): 949-64.

115. Holland, J.C., et al., *The human side of cancer: living with hope, coping with uncertainty*. Oncology, 2001. 15:8.

116. HINTS Health Information National Trends Survey: HINTS 4, Cycle 3 (2013) demographics. http://hints.cancer.gov/topic.aspx?section=Demographics. Accessed September 29, 2014.

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